1.0 Title Page

Clinical Study Protocol M15-566

A Phase 2 Multiple Dose, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ABBV-8E12 in Subjects with Early Alzheimer's Disease

Incorporating Administrative Change 1, 2, and 3 (US Only) and Amendments 1, 2, and 3

AbbVie Investigational Product:	ABBV-8E12
Date:	02 October 2020
EudraCT Number:	2016-001634-10
Development Phase:	2
Study Design:	This is a Phase 2, multiple-dose, randomized, double-blind, placebo-controlled, study evaluating the efficacy and safety of ABBV-8E12 in subjects with Early Alzheimer's Disease
Investigators:	Multicenter Trial: Investigator Information is on file at AbbVie
Sponsor:	AbbVie
Sponsor/Emergency Contact:	[redacted] Phone: [redacted] Fax: Neuroscience Development 1 North Waukegan Road North Chicago, IL 60064

The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	18 May 2016
Administrative Change 1	18 August 2016
Administrative Change 2	12 May 2017
Administrative Change 3	12 February 2018
Amendment 1	19 March 2018
Amendment 2	15 November 2018

The purpose of this amendment is to:

- Update Section 3.2 Benefits and Risks to include language for the coronavirus disease-19 (COVID-19) pandemic.

  Rationale: *To include study subjects infected with SARS-Cov2 (COVID-19).*
- Update Section 5.1 Overall Study Design and Plan: Description to remove sites in Japan from the study.

  Rationale: *Sites in Japan were planned for enrollment, but did not occur.*
- Update Section 5.3.1.1 Study Procedures [Physical Examination, Neurological Examination, Vital Signs, 12-Lead Electrocardiogram (ECG), Abnormal Findings, Lumbar Puncture (LP), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) Tau Imaging, Retinal Imaging for Amyloid, and Digital Clock Drawing Test (dCDT)] to include language for the COVID-19 pandemic.

  Rationale: *To describe alternative processes that may be needed because of the COVID-19 pandemic.*
- Update Section 5.3.1.2 Collection and Handling of Biomarker and Pharmacogenetic Research Samples [Apolipoprotein E (APOE) Pharmacogenetic Sample; Optional Pharmacogenetic Research Samples] to include language for the COVID-19 pandemic.

Rationale: *To describe alternative processes that may be needed because of the COVID-19 pandemic.*

- Update Section 5.4.1 Discontinuation of Individual Subjects to include language for the COVID-19 pandemic.

  Rationale: *To describe alternative processes that may be needed because of the COVID-19 pandemic.*

- Update Section 5.5.1 Treatments Administered to include language for the COVID-19 pandemic.

  Rationale: *To describe alternative processes that may be needed because of the COVID-19 pandemic.*

- Update Section 6.1.5 Adverse Event Reporting to include language for the COVID-19 pandemic.

  Rationale: *To describe alternative processes that may be needed because of the COVID-19 pandemic.*

- Update Section 8.1.7.1 Tabulations and Summary Statistics to include summary of data for all subjects

  Rationale: *To include a summary of all data collected from subjects in Cohorts 1 and 2.*

- Update Section 9.2 Ethical Conduct of the Study to include language for the COVID-19 pandemic.

  Rationale: *To describe alternative processes that may be needed because of the COVID-19 pandemic.*

- Update Section 9.3 Subject Information and Consent to include language for the COVID-19 pandemic.

  Rationale: *To describe alternative processes that may be needed because of the COVID-19 pandemic.*

- Update Section 11.0 Data Quality Assurance to include language for the COVID-19 pandemic.

  Rationale: *To describe alternative processes that may be needed because of the COVID-19 pandemic.*

- Update footnote at Appendix C Study Activities to accommodate tau PET due to scheduling conflicts.

Rationale: *To schedule tau PET as close as possible to Weeks 44 (Dose 12) and 96 visits.*

An itemized list of all changes made to this protocol under this amendment can be found in Appendix E.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M15-566
Name of Study Drug: ABBV-8E12	**Phase of Development:** 2
Name of Active Ingredient: ABBV-8E12	**Date of Protocol Synopsis:** 02 October 2020
Protocol Title: A Phase 2 Multiple Dose, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ABBV-8E12 in Subjects with Early Alzheimer's Disease	

Objectives:

The primary objectives of this study are:

- To assess the efficacy of ABBV-8E12 in slowing disease progression (cognitive and functional impairment) in subjects with Early Alzheimer's Disease (AD) as measured by the Clinical Dementia Rating – Sum of Boxes (CDR-SB).
- To assess the long-term safety of ABBV-8E12 for up to 96 weeks in subjects with Early AD.

The secondary objectives of this study are:

- To assess the pharmacokinetics of ABBV-8E12 in subjects with Early AD.
- To assess the efficacy of ABBV-8E12 in slowing cognitive and functional impairment in subjects with Early AD as measured by the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale (14-Item) Cognition Portion (ADAS-Cog-14), Repeatable Battery for Assessment of Neuropsychological Status (RBANS), 24-Item Alzheimer's Disease Cooperative Study/Activities of Daily Living Scale Adapted for Patients with Mild Cognitive Impairment (ADCS-MCI-ADL-24), Functional Activities Questionnaire (FAQ) and University of California San Diego Performance Based Skills Assessment, Brief Version (UPSA-Brief).
- To assess the global impact of ABBV-8E12 on cognition, function and behavior as measured by Alzheimer's Disease Cooperative Study Clinical Global Impression of Change for Mild Cognitive Impairment (ADCS-CGIC-MCI).

The exploratory objectives of this study are:

- To assess the effect of ABBV-8E12 on cerebrospinal fluid (CSF) and plasma tau protein.
- To assess the effect of ABBV-8E12 on potential CSF and plasma biomarkers of disease progression.
- To assess the efficacy of ABBV-8E12 in slowing the rate of regional and/or whole brain atrophy in subjects with Early AD as measured by volumetric magnetic resonance imaging (vMRI).
- To assess any signals or trends for efficacy of ABBV-8E12 in removing tau deposits or slowing the accumulation and spread of tau deposits in the brain as measured by tau positron emission tomography (PET) in a subset of subjects.
- To generate additional data for the correlation between retinal amyloid imaging and amyloid PET imaging in a subset of subjects.
- To characterize the performance of a digital clock drawing test (dCDT) in measuring cognitive function and assess its correlation with other clinical rating scales and biomarkers in a subset of subjects.

Investigators: Multicenter
Study Sites: Up to 80 global sites
Study Population: Adult (55 – 85 years old) subjects with early AD.
Number of Subjects to be Enrolled: Approximately 400
Methodology: This Phase 2 multiple dose, multicenter, multinational, randomized, double-blind, placebo-controlled study is designed to evaluate the efficacy and safety of ABBV-8E12 in subjects with Early AD. Subjects will be allowed to use medications to treat symptoms related to AD, if on a stable dose for at least 12 weeks prior to randomization. The study will consist of a screening period of up to 12 weeks, a 96-week double-blind treatment period and a follow-up period of approximately 20 weeks following the last study drug administration (for those subjects who prematurely discontinue from treatment, decline to participate in or do not qualify for extended treatment). At the end of the treatment period, eligible subjects who completed the 96-week treatment period may enter a planned separate extension study for extended treatment. All activities for these subjects will be outlined in a separate extension study protocol. Approximately 400 subjects with Early AD between 55 to 85 years of age will be eligible to participate in the study according to the selection criteria. Upon completion of screening and baseline procedures, eligible subjects will be randomized to one of the 3 ABBV-8E12 dose arms (300 mg, 1000 mg or 2000 mg) or placebo in a 1:1:1:1 ratio. Doses will be administered every 4 weeks via IV infusion. This study will utilize a Data Monitoring Committee (DMC). The DMC will consist of at least 2 non-AbbVie clinicians, at least 1 non-AbbVie statistician, and at least 1 external pharmacokineticist. The DMC will review unblinded safety data and make recommendations based on the emerging safety profile of ABBV-8E12 and on the results of the interim efficacy analyses. The DMC membership, responsibilities and operating logistics will be documented in a charter that will be finalized prior to the first DMC review meeting. Safety and tolerability will be monitored throughout the study. The first 48 subjects enrolled into the study will be represented as Cohort 1 in this protocol while the subjects enrolled subsequently to Cohort 1 will be represented as Cohort 2. More frequent pharmacokinetic sampling and safety monitoring by the DMC will be conducted for Cohort 1 subjects. Eligible subjects will be enrolled into the Treatment Period of the study on Day 1 and receive their first infusion of study drug. Subjects will return to the study site every 4 weeks for their study drug infusion, blood collection, study procedures and assessments as outlined in the Study Activities Table. Subjects will be observed on-site for at least 2 hours following each of the first 4 infusions of study drug and for at least 30 minutes after the end of infusion of all doses thereafter. In addition, Cohort 1 subjects will return to the study site 5 and 15 days after both the first and fourth infusion of study drug for collection of additional safety assessments and pharmacokinetic samples.

Methodology (Continued):

In addition to blinded safety data monitoring by the sponsor, the first four mandatory safety DMC reviews of unblinded safety data will take place after the 12th, 24th, 36th and 48th subject have been administered their second dose and results for the MRI scheduled at approximately 2 weeks after their second dose are available. The data set will consist of all of the available safety and pharmacokinetic data in the study, including the data of any subjects from Cohort 2 who have received at least one dose of study drug.

Additional safety DMC reviews will occur after a total of approximately 100, 200, 300 and 400 subjects are randomized.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

- Male or female and age is between 55 and 85 years, inclusive, at Screening Visit 1.
- Subject who meets the National Institute on Aging and the Alzheimer's Association (NIA-AA) clinical criteria for mild cognitive impairment or probable AD, and has:
  - Clinical Dementia Rating (CDR)-Global Score of 0.5 at Screening Visit 1
  - Mini-Mental State Examination (MMSE) score of 22 to 30, inclusive, at Screening Visit 1
  - Repeatable Battery for the Assessment of Neuropsychological Status-Delayed Memory Index (RBANS – DMI) score of 85 or lower
- Subject has a positive amyloid PET scan.
- Subject has a Modified Hachinski Ischemic Scale (MHIS) score of ≤ 4.
- The subject has an identified, reliable study partner (e.g., family member), who has frequent contact with the subject and who will provide information as to the subject's cognitive and functional abilities.
- If using medications to treat symptoms related to AD, doses must be stable for at least 12 weeks prior to randomization.

Main Exclusion:

- Subject has any contraindications or inability to tolerate brain magnetic resonance imaging (MRI), PET scans or lumbar puncture (Cohort 1 only).
- Subject has evidence of any other clinically significant neurological disorder other than Early AD including but not limited to Parkinson's disease, vascular dementia, significant cerebrovascular abnormalities, frontal-temporal dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, history of significant head trauma followed by persistent neurologic deficits or known structural brain abnormalities.
- Subject has a screening MRI scan, interpreted by a radiologist with evidence of infection, infarction (including multiple lacunas in a critical memory structure), or other focal lesions.
- In the opinion of the investigator, the subject has any clinically significant or uncontrolled medical or psychiatric illness, or has had an infection requiring medical intervention in the past 30 days.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued): • Subject has had a myocardial infarction, unstable angina, stroke, transient ischemic attack or required intervention for any of these conditions (e.g., coronary artery bypass graft, percutaneous coronary intervention via cardiac catheterization, thrombolytic therapy) within 6 months of Screening Visit 1.	
Investigational Product:	ABBV-8E12 (300 mg/15 mL) ABBV-8E12 (1000 mg/10 mL)
Doses:	Doses will be given every 4 weeks. Dose 1: 300 mg Dose 2: 1000 mg Dose 3: 2000 mg Doses may be modified after evaluation by the data monitoring committee of the safety, tolerability and available pharmacokinetic data.
Mode of Administration:	IV infusion
Reference Therapy:	Placebo (0.9% Sodium Chloride Injection/Solution for Infusion)
Doses:	Doses will be given every 4 weeks.
Mode of Administration:	Intravenous (IV) Infusion
Duration of Treatment: 96 Weeks	
Criteria for Evaluation: **Efficacy:** **Clinical Assessments:** • Clinical Dementia Rating sum of boxes (CDR-SB) • Repeatable Battery for Assessment of Neuropsychological Status (RBANS) • University of California's Performance Based Skills Assessment, Brief Version (UPSA-Brief) • Mini Mental State Examination (MMSE) • Alzheimer's Disease Assessment Scale (ADAS-Cog-14) • Functional Activities Questionnaire (FAQ) • Neuropsychiatric Inventory (NPI) • 24-item Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for patients with mild cognitive impairment (ADCS-MCI-ADL-24) • Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change for Mild Cognitive Impairment (ADCS-CGIC-MCI)	

Criteria for Evaluation (Continued):

Pharmacokinetic:

The concentration of ABBV-8E12 will be determined in serum and CSF samples collected in the study.

Values for the following pharmacokinetic parameters will be estimated using non-compartmental methods: maximum observed serum concentration (C_{max}), the time to C_{max} (peak time, T_{max}), the area under the concentration time curve (AUC) over the dosing interval after the first and the fourth doses; the observed serum concentration at the end of a dose interval (C_{trough}) after all doses.

A mixed-effect modeling approach will be used to estimate the population central value and the empirical Bayesian estimates of the individual values for ABBV-8E12 clearance (CL) and volume of distribution (V).

The concentration of ABBV-8E12 in CSF will be summarized after the fourth dose and after the final dose if administered at least 3 months after the previous LP for subjects in Cohort 1. LPs will be optional for subjects in Cohort 2, and the concentration of ABBV-8E12 in these CSF samples will be summarized, if available.

Additional parameters may be calculated if useful in the interpretation of the data.

Immunogenicity:

Anti-drug antibodies will be determined in serum for assessment of immunogenicity.

Biomarkers and Pharmacogenetics:

Exploratory research to assess effects of ABBV-8E12 on potential biomarkers of disease progression will be conducted. Blood sampling, CSF sampling and MRIs for volumetric analysis will be done at designated time points throughout the study in order to obtain the data. Tau PET scans will be collected in a subset of the subjects. Also, retinal optical images will be obtained in a subset of subjects, and data from a digital clock drawing test as a measure of cognitive function will be collected from a subset of subjects. The potential biomarkers for which data will be obtained from all subjects will include, but are not limited to, the following: tau, amyloid beta 40 and 42, and neurofilament light chain (NFL) plasma concentrations; volumetric MRI measures for whole brain, hippocampus and lateral ventricles; tau PET standardized uptake value ratio (SUVR) for hippocampus, entorhinal area, frontal, parietal, temporal, and occipital lobes.

The CSF concentration of total tau and free tau will be determined to assess binding of ABBV-8E12 to tau.

Apolipoprotein E (APOE) allele status will be determined for each subject and analyzed as a factor contributing to the subject's response to treatment. Optional pharmacogenetic research samples will also be collected.

Tau PET imaging will be used to assess the amount of tau burden and the ability of ABBV-8E12 to slow the accumulation and spread of tau deposits in the brain for subjects at participating sites. The amount of tau deposits in a given region will be assessed by calculating a SUVR. Due to the exploratory nature of these PET imaging endpoints, analyses will be performed for multiple brain regions, which will include, but not necessarily be limited to, 4 composite meta-regions that correspond to anatomical definitions of Braak stages III, IV, V, and VI. Additional variables will be assessed.

Criteria for Evaluation (Continued):

Safety:

Adverse event monitoring (including infusion and allergic reactions), vital signs, physical examination, neurologic examination, electrocardiogram (ECG), laboratory tests, Columbia-Suicide Severity Rating Scale (C-SSRS) and MRI assessments.

Subjects will be monitored closely for the occurrence of adverse events (AEs) and serious AEs (SAEs), including infusion/allergic reactions, both during and after the IV infusion up to the final follow-up visit, at a minimum of approximately 20 weeks from the date of the last dose of study drug. Monitoring will occur according to the protocol-defined Study Activities Table and will include but not be limited to AEs, vital signs, complete neurologic exam and MRIs. The DMC will be in place to provide recommendations during the study.

Statistical Methods:

Efficacy:

The efficacy variables will be the change from baseline up to the Week 96 observation on the CDR-SB score, ADAS-Cog-14 total score, RBANS total score, MMSE total score, NPI total score, ADCS-MCI-ADL-24 total score, FAQ score, UPSA-Brief and ADCS-CGIC-MCI scores. The primary efficacy variable will be the change from baseline up to the Week 96 on the CDR-SB score. The primary efficacy analysis is to compare each ABBV-8E12 dose group with placebo using a likelihood-based, mixed-effects model repeated measures (MMRM) analysis of the change from baseline for each post-baseline observation using all observed data. The model will include fixed, categorical effects for treatment, site, visit, and treatment-by-visit interaction, and baseline-by-visit interaction with continuous fixed covariate for the corresponding baseline score. The primary comparison will be the contrast between each ABBV-8E12 dose group and placebo at the Week 96 Visit using two-sided tests. A group-sequential graphical approach will be used to handle multiplicity of primary and secondary efficacy endpoints for multiple ABBV-8E12 doses and multiple analyses. The treatment group difference at earlier visits will be assessed as secondary. An unstructured (co)variance structure will be used to model the within-patient errors. Satterthwaite's approximation will be used to estimate denominator degrees of freedom and the Type III sum-of-squares for the Least Square (LS) means will be used to estimate treatment group differences. This MMRM analysis will be applied to each efficacy variable with repeated measurements.

Statistical Methods (Continued):

Pharmacokinetic:

The concentration data at the end of the first four dose intervals in Cohort 1 will be summarized to investigate the change in serum concentration with repeated dosing. The logarithmic transformation will be used if appropriate. The model will have effects for dose level, week and the interaction of dose level and week. For measures of exposure, an analysis of covariance will be performed on dose normalized parameters of Cohort 1. It is anticipated that the logarithmic transformation will be employed. Subjects will be classified by dose level. Body weight will be a covariate, and there may be other covariates. The hypothesis of dose proportionality will be tested within the framework of the model by testing the hypothesis of no difference between the highest and lowest doses. Population pharmacokinetic analyses will be performed using a non-linear mixed-effect modeling approach with the nonlinear mixed effect modeling (NONMEM) software (version VII, or higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies and Cohort 1 of this study. Apparent CL and V of ABBV-8E12 will be the pharmacokinetic parameters of major interest in the NONMEM analyses.

CSF concentration data after the fourth dose and the final dose in Cohort 1 and Cohort 2 (if available) will be tabulated and summarized by dose level.

Immunogenicity:

The anti-drug antibody (ADA) titers will be tabulated by dose level and summarized as appropriate.

Biomarker:

For CSF total tau and free tau concentrations and for their ratio, and for CSF NFL concentration, an analysis of covariance (ANCOVA) will be performed for each scheduled time of evaluation after treatment begins. The model will have classification of subjects by treatment. The covariate in these analyses will be the baseline value, except that for the analysis on the ratio of free tau and total tau concentrations, the covariate will be the baseline total tau concentration measurement. An MMRM analysis will be performed for plasma/serum concentration variables, vMRI variables, and tau PET variables for the scheduled measurements during treatment (ending at Week 96). For these analyses, the baseline value will be a covariate. Hypothesis testing on the effects of ABBV-8E12 doses will be done within the framework of the model. The primary tests will be a test on trend with dose (with placebo considered a dose level) and a test on the difference between the highest dose and placebo. The data will be transformed if there is a meaningful departure from the assumption of normality.

For some biomarker variables, the relationship to disease progression and response to treatment will be explored with disease state represented by the efficacy variable CDR-SB score and perhaps by some other variables. The exploration on the relationship with disease progression will include an analysis of data of only the subjects treated with placebo.

Statistical Methods (Continued):

Safety:

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting treatment-emergent adverse events will be tabulated by MedDRA System Organ Class (SOC) and Preferred Term (PT) with a breakdown by treatment group. Tabulations will also be provided in which the number of subjects reporting an adverse event (MedDRA term) is additionally broken down by rating (mild, moderate or severe) and by whether possibly related to study drug. The number and percent of subjects experiencing treatment-emergent SAEs (including deaths) and adverse events leading to premature discontinuation of the study drug will be tabulated according to the MedDRA SOC and preferred term by treatment group. Treatment group differences between each ABBV-8E12 dose group and placebo will be analyzed using Fisher's exact test. Differences between each ABBV-8E12 dose group and placebo in change from baseline to minimum, maximum and final clinical laboratory evaluation, vital sign observation and ECG parameters will be analyzed by a one-way analysis of variance (ANOVA) with treatment as the main effect.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

α	alpha
Aβ	amyloid
AD	Alzheimer's Disease
ADA	Anti-drug antibody
ADAS-Cog-14	Alzheimer's Disease Assessment Scale (14-Item) Cognition portion
ADCS-CGIC-MCI	Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change for Mild Cognitive Impairment
ADCS-MCI-ADL-24	24-item Alzheimer's Disease Cooperative Study/Activities of Daily Living Scale Adapted for Patients with Mild Cognitive Impairment
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APOE	Apolipoprotein E
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATEMS	AbbVie Temperature Excursion Management System
AUC	Area under the concentration time curve
BMI	Body mass index
BUN	Blood urea nitrogen
C2N	C2N Diagnostics Company
CBD	Corticobasal degeneration
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CDT	Clock drawing test
CFR	Code of Federal Regulations
CL	Clearance
C_{max}	Maximum observed serum concentration
CNS	Central nervous system
COVID-19	Coronavirus disease-2019
CPK	Creatine phosphokinase

CRA	Clinical research associate
CRF	Case report form
CS	Clinically significant
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Observed serum drug concentration at the end of a dose interval
dCDT	Digital clock drawing test
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSUR	Developmental Safety Update Report
DTP	Direct-to-Patient
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
ERAC	Exposure-Response Analysis Center
eTIV	Estimated total intracranial volume
FAQ	Functional Activities Questionnaire
GAM	Generalized additive method
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
iADLs	Instrumental Activities in Daily Living
IBRC	Internal Biomarker Review Committee
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IERC	Internal Executive Review Committee
IgG4	Immunoglobulin G4

IMP	Investigational Medicinal Product
IND	Investigational New Drug Application
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IVR	Interactive Voice-Response (system)
IWR	Interactive Web-Response (system)
LP	Lumbar puncture
LS	Least square
MCHC	Mean corpuscular hemoglobin concentration
MCI	Mild cognitive impairment
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MHIS	Modified Hachinski Ischemic Scale
MMA	Methylmalonic acid
MMRM	Mixed-effects model repeated measures
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
N/A	Not applicable
NCS	Not clinically significant
NFL	Neurofilament light chain
NIA-AA	National Institute on Aging and the Alzheimer's Association
NOAEL	No observed adverse effects level
NONMEM	Nonlinear mixed effect modeling
NPI	Neuropsychiatric Inventory
PCR	Polymerase chain reaction
PCS	Potentially clinically significant
PD	Premature discontinuation
PET	Positron emission tomography
PIN	Personal identification number
PK	Pharmacokinetic
PRN	As needed

PSP	Progressive supranuclear palsy
PT	Preferred Term
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
RBANS-DMI	Repeatable Battery for Assessment of Neuropsychological Status-Delayed Memory Index
RBC	Red blood cell count
RNA	Ribonucleic acid
RSI	Reference Safety Information
SAD	Single-ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDAC	Statistical and Data Analysis Center
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
SUV	Standardized uptake value
SUVR	Standardized uptake value ratio
T4	Thyroxine
TA MD	Therapeutic Area Medical Director
TEAE	Treatment-emergent adverse event
T_{max}	Time to peak (maximum) observed serum concentration
TSH	Thyroid-stimulating hormone
UPSA Brief	University of California San Diego Performance Based Skills Assessment, Brief Version
V	Volume of distribution
vMRI	Volumetric magnetic resonance imaging
WBC	White blood cell count
WHO	World Health Organization

Definition of Terms

Visit Window	Treatment Visits on Days 5, 15, 89 and 99 must be scheduled within ± 2 days (these visits apply to Cohort 1 subjects only). Visits on all other days during the treatment period may be scheduled within ± 4 days.
Study Drug Infusion	Study drug will be administered every 4 weeks for 96 weeks (24 infusions)
Treatment Period	Period of time to complete Day 1 through Week 96 or premature discontinuation.
Post-treatment Follow-up Period	Beginning at the time of completion of the Treatment Period and continues up to 16 weeks, OR, if eligible, a planned separate extension study. Subjects will only enter the Post-treatment Follow-up Period in this study if they prematurely discontinue from treatment, do not qualify for, or decline to participate in the planned separate extension study.

2.0 Table of Contents

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3.0 Introduction

Alzheimer's Disease

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease among the elderly population and the most common cause of dementia. The latest figures estimate that over 46 million people are living with dementia worldwide.[1] AD is pathologically defined by the extracellular accumulation of amyloid (Aβ), intracellular accumulation of tau, neuronal and synaptic loss, brain atrophy, and neuroinflammation. The disease is clinically characterized by cognitive deterioration, progressive impairment of activities of daily living, and a variety of neuropsychiatric and behavioral disturbances. Many lines of evidence from laboratories and clinics worldwide support the concept that an imbalance between production and clearance of $A\beta_{1-42}$ is a very early and often initiating factor in AD many years or even decades before the onset of symptoms. Once Aβ begins building up in the brain, a number of downstream events occur that probably play important roles in damaging axons, dendrites, synapses, intracellular signaling, synaptic transmission, and ultimately cell death. In particular, the aggregation and accumulation of tau appears to play a critical role and unlike accumulation of amyloid, correlates well with clinical disease progression.

At present, approved pharmacological therapy for AD consists of symptomatic treatment with either cholinesterase inhibitors (donepezil, rivastigmine, galantamine) in the mild to moderate stages of the disease, or with an N-methyl-d-aspartate receptor antagonist (memantine) in the more severe stage. These drugs provide only modest effects on cognitive function and activities of daily living in some patients. Thus, even if patients receive the ideal therapy available today, the effect would not be long lasting and the patient's condition would eventually return to basal levels after a certain period of time.[2,3] For this reason, a huge demand and unmet medical need exist for the development of disease-modifying drugs for AD with the direct impact on the biology of the disease, which if possible, will change the course of the disease and reduce its associated burdens. While the best targets for such treatments remain to be determined, it is hypothesized that accumulation of Aβ into plaques in the brain is an early event in AD that is followed by

abnormal spreading of extracellular tau and tau's deposition into intracellular tangles.[4] There are several anti-Aβ antibody therapies currently in clinical trials, with several completing Phase III.[5,6] Results from the anti-Aβ trials suggest that due to the early role of Aβ in AD, the antibody therapy needs to be administered before the onset of symptoms or at the earliest stages of cognitive impairment. Since tau is generally thought to play a role at later stages of disease progression, there is a potential that an anti-tau therapeutic would be efficacious even when administered to patients who may be already showing clinical symptoms of AD.

ABBV-8E12

ABBV-8E12 is a humanized IgG4 monoclonal antibody against human microtubule-associated protein tau. It targets soluble extracellular tau in the brain, which has been implicated in the development and spreading of tau pathology. Neurofibrillary tangles, a characteristic pathologic feature in AD and other neurological disorders such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), are formed inside of neurons by aggregated and post-translationally modified tau. Based on preclinical evidence, ABBV-8E12 may be able to block soluble tau aggregates, or seeds, from propagating between cells and thereby decrease the spreading of tau pathology in brains with tauopathy.

Preclinical Efficacy

In preclinical studies, the mouse version of the ABBV-8E12 antibody (HJ8.5) that recognizes the same epitope was found to specifically block tau seeding activity from brain lysates of P301S transgenic mice in vitro.[7] The P301S animal is a transgenic mouse model that carries a mutated human tau gene that leads to early onset frontotemporal dementia in humans. In vivo, 3 months of treatment with HJ8.5 as a continuous intracerebroventricular infusion was associated with potent reductions in tau pathology, as evidenced by biochemical, histopathological, and functional/behavioral measures. A similar study to assess the effects of peripherally (intraperitoneal) administered HJ8.5 found that weekly intraperitoneal injections of HJ8.5 were highly effective at reducing

insoluble tau in the brain, reducing cortical and hippocampal atrophy, and improving sensorimotor function.[8]

Nonclinical Safety

ABBV-8E12 binds to human tau but not to tau protein from preclinical toxicology species (i.e., rhesus/cynomolgus monkey, canine, rabbit, rat or mouse). Therefore, there is no pharmacologically relevant species in which to conduct toxicology studies to support safety of ABBV-8E12. To assess toxicity in non-relevant species, a 4-week study in wild-type mice was conducted at doses up to 250 mg/kg for 4 weeks via weekly intravenous (IV) injections. There were no adverse effects at any dose level and the no adverse effects level (NOAEL) was 250 mg/kg. It provided a margin of 3-fold over projected exposures at the highest dose of 2000 mg planned in this study.

A detailed discussion of the preclinical toxicology and pharmacology can be found in the Investigator's Brochure.[9]

Clinical Experience

Prior to the regular Investigational New Drug (IND) submission, treatment was initiated under an Expanded Access IND (United States) for one patient with PSP, and subsequently for one patient with CBD under a compassionate use treatment protocol (Germany).

The PSP patient received 20 monthly infusions (highest dose 25 mg/kg), then died for reasons unrelated to study drug due to PSP complications. The CBD patient who had a strong history of suicidal ideation and premeditation that preceded compassionate treatment with ABBV-8E12, received 3 monthly infusions (1 at 7.5 mg/kg, 2 at 15 mg/kg), but died due to suicide 10 days after the second 15 mg/kg infusion. No evidence of imaging abnormalities or other evidence of drug-related toxicity was detected in these 2 patients.

Single Dose Study

The single-ascending dose (SAD) study (Study C_2N-8E12-WW-104) investigated 5 dose levels (2.5 mg/kg, 7.5 mg/kg, 15 mg/kg, 25 mg/kg and 50 mg/kg) in 30 patients with PSP (n = 23 on ABBV-8E12, n = 7 on placebo).

Three serious adverse events (SAEs) were reported in this study. In the 15 mg/kg dose group, one subject reported an SAE of a subdural hematoma resulting from a fall that was assessed as possibly related to study drug by the investigator. The sponsor judged the SAE to be unlikely related to study drug, and likely related to the underlying PSP disease. In the 25 mg/kg dose group, one subject was hospitalized due to a severe increase in agitation, anxiety, and perseverative behavior; the subject was discontinued from the study after being unable to participate following the SAE. The investigator and sponsor assessed that the worsening symptoms may represent progression of the patient's underlying disease, but that the study drug cannot be ruled out as a contributing factor, so the event was therefore assessed as possibly drug related. In the 50 mg/kg dose group, 1 subject was hospitalized for evaluation and treatment of hypertension. This SAE was assessed by the investigator as moderate in severity, resolved without sequelae, and unrelated to study drug.

No subject experienced a systemic hypersensitivity reaction or injection site reaction, and there were no clinically relevant patterns of adverse events (AEs) or abnormal laboratory findings observed. Based on available anti-drug antibody (ADA) data in Study C_2N-8E12-WW-104, no ADAs have been detected in post-dose samples on Day 14 and Day 28.

The plasma pharmacokinetic data from Study C_2N-8E12-WW-104 indicate dose-proportional increases in area under the concentration time curve (AUC) from 2.5 to 50 mg/kg. The mean time to maximum plasma concentration (T_{max}) ranged from 0.3 hours to 4.6 hours, and half-life ranged from 27 to 37 days.

Cerebrospinal fluid (CSF) concentrations increased with dose, and the CSF/plasma ABBV-8E12 ratio ranged from 0.181% to 0.385%.

3.1 Differences Statement

This is the first study in which ABBV-8E12 will be administered to subjects with Early AD and in which ABBV-8E12 will be administered for an extended treatment period of up to 96 weeks.

3.2 Benefits and Risks

ABBV-8E12 was administered under Protocol C_2N-8E12-WW-104 to 23 subjects with PSP in single doses up to 50 mg/kg with no clinically concerning safety findings.

In addition, 2 subjects received multiple doses of ABBV-8E12, one under an Expanded Access IND, Protocol C_2N-8E12-EA-001 (United States) and the other under a single named trial application, Study C_2N-8E12-DE-003 (Germany). Treatment appeared to be well tolerated. One subject received 20 monthly doses up to 25 mg/kg and one subject received 3 monthly doses up to 15 mg/kg.

No preclinical toxicology data are available in pharmacologically relevant species. No adverse effects at any dose level were detected in the wild-type mouse toxicology study. Evidence of efficacy demonstrated in preclinical studies and safety data from clinical studies obtained to date provide rationale for continuing assessment of efficacy and safety in the current study.

The benefit-risk profile will be further defined in this trial.

In consideration of the coronavirus disease (COVID-19) pandemic, the benefits and risks to subjects participating in this study have been re-evaluated. Based on the limited information to date, no additional risk is anticipated for study participants infected with SARS-Cov2 during the COVID-19 pandemic, due to the mechanism of action of ABBV-8E12.

4.0 Study Objectives

The primary objectives of this study are:

- To assess the efficacy of ABBV-8E12 in slowing disease progression (cognitive and functional impairment) in subjects with Early AD as measured by the Clinical Dementia Rating-Sum of Boxes (CDR-SB).
- To assess the long-term safety of ABBV-8E12 for up to 96 weeks in subjects with Early AD.

The secondary objectives of this study are:

- To assess the pharmacokinetics of ABBV-8E12 in subjects with Early AD.
- To assess the efficacy of ABBV-8E12 in slowing cognitive and functional impairment in subjects with Early AD as measured by the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale (14-Item) Cognition Portion (ADAS-Cog-14), Repeatable Battery for Assessment of Neuropsychological Status (RBANS), 24-Item Alzheimer's Disease Cooperative Study/Activities of Daily Living Scale Adapted for Patients with Mild Cognitive Impairment (ADCS-MCI-ADL-24), Functional Activities Questionnaire (FAQ), University of California San Diego Performance Based Skills Assessment, Brief Version (UPSA-Brief), and Neuropsychiatric Inventory (NPI).
- To assess the global impact of ABBV-8E12 on cognition, function and behavior as measured by Alzheimer's Disease Cooperative Study Clinical Global Impression of Change for Mild Cognitive Impairment (ADCS-CGIC-MCI).

The exploratory objectives of this study are:

- To assess the effect of ABBV-8E12 on CSF and plasma tau protein.
- To assess the effect of ABBV-8E12 on potential CSF and plasma biomarkers of disease progression.

- To assess the efficacy of ABBV-8E12 in slowing the rate of regional and/or whole brain atrophy in subjects with Early AD as measured by volumetric magnetic resonance imaging (vMRI).
- To assess any signals or trends for efficacy of ABBV-8E12 in removing tau deposits or slowing the accumulation and spread of tau deposits in the brain as measured by tau positron emission tomography (PET) in a subset of subjects
- To generate additional data for the correlation between retinal amyloid imaging and amyloid PET imaging in a subset of subjects.
- To characterize the performance of a digital clock drawing test (dCDT) in measuring cognitive function and assess its correlation with other clinical rating scales and biomarkers in a subset of subjects.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This Phase 2 multiple dose, multicenter, multinational, randomized, double-blind, placebo-controlled study is designed to evaluate the efficacy and safety of ABBV-8E12 in subjects with Early AD. Subjects will be allowed to use medications to treat symptoms related to AD, if on a stable dose for at least 12 weeks prior to randomization. The study will consist of a screening period of up to 12 weeks, a 96-week double-blind treatment period and a follow-up period of approximately 20 weeks following the last study drug administration (for those subjects who prematurely discontinue from treatment, decline to participate in or do not qualify for extended treatment). At the end of the treatment period, eligible subjects who completed the 96-week treatment period may enter a planned separate extension study for extended treatment. All activities for these subjects will be outlined in a separate extension study protocol.

Approximately 400 subjects with Early AD between 55 to 85 years of age will be eligible to participate in the study according to the selection criteria described in Section 5.2. Upon completion of screening and baseline procedures, eligible subjects will be randomized to one of the 3 ABBV-8E12 dose arms (300 mg, 1000 mg or 2000 mg) or

placebo in a 1:1:1:1 ratio. Doses will be administered every 4 weeks via IV infusion. Refer to Section 5.5.1 for details on infusion times.

This study will utilize a Data Monitoring Committee (DMC). The DMC will consist of at least 2 non-AbbVie clinicians, at least 1 non-AbbVie statistician, and at least 1 external pharmacokineticist. The DMC will review unblinded safety data and make recommendations based on the emerging safety profile of ABBV-8E12 and on the results of the interim efficacy analyses. The DMC membership, responsibilities and operating logistics will be documented in a charter that will be finalized prior to the first DMC review meeting.

Safety and tolerability will be monitored throughout the study.

The first 48 subjects enrolled into the study will be represented as Cohort 1 in this protocol while the subjects enrolled subsequently to Cohort 1 will be represented as Cohort 2. More frequent pharmacokinetic (PK) sampling and safety monitoring by the DMC will be conducted for Cohort 1-subjects (Table 1).

Eligible subjects will be enrolled into the Treatment Period of the study on Day 1 and receive their first infusion of study drug. Subjects will return to the study site every 4 weeks for their study drug infusion, blood collection, study procedures and assessments as outlined in the Study Activities Table (Appendix C). Subjects will be observed on-site for at least 2 hours following each of the first 4 infusions of study drug and for at least 30 minutes after the end of infusion of all doses thereafter. In addition, Cohort 1 subjects will return to the study site 5 and 15 days after both the first and fourth infusion of study drug for collection of additional safety assessments and PK samples.

In addition to blinded safety data monitoring by the sponsor, the first four mandatory DMC reviews of unblinded safety data will take place after the 12^{th}, 24^{th}, 36^{th} and 48^{th} subject have been administered their second dose and results for the magnetic resonance imaging (MRI) scheduled at approximately 2 weeks after their second dose are available. The data set will consist of all of the available safety and pharmacokinetic data in the

study, including the data of any subjects from Cohort 2 who have received at least one dose of study drug.

Additional safety DMC reviews will occur after a total of approximately 100, 200, 300 and 400 subjects are randomized.

A schematic of the study design is shown in Figure 1.

Figure 1. Study Schematic

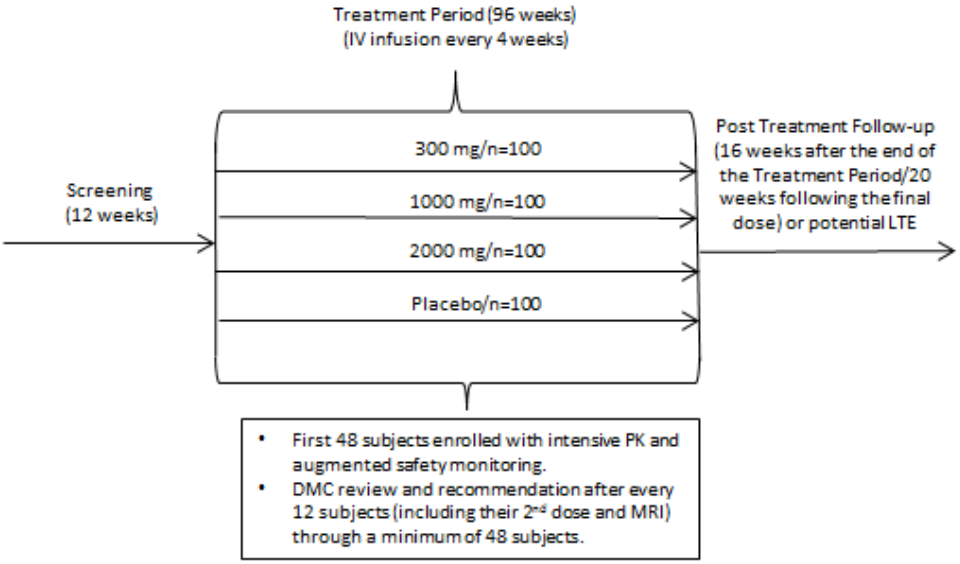


Table 1. Safety and PK Procedures for Cohort 1

	Screening	Cohort 1, Doses 1 – 4							
	Visit 1	Dose 1			Dose 2	Dose 3	Dose 4		
Weeks of Study Drug Exposure	**N/A**	**0**	**0**	**2**	**4**	**8**	**12**	**12**	**14**
	Days –56 to –8	**Day 1**	**Days 5 and 15**		**Day 29**	**Day 57**	**Day 85**	**Days 89 and 99**	
Neurological Exam	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X[a]	X	X	X	X	X[a]		
Clinical Laboratory Tests	X	X			X	X	X		
Amyloid PET Scan	X								
MRI	X				X[b]		X[b]		
Lumbar Puncture/CSF Sample Collection	X						X[c]		
PK Sample Collection		X[d]	X	X	X	X	X[d]	X	X
ADA Sample Collection		X[e]		X	X[e]	X[e]	X[e]	X	X
C-SSRS	X	X	X	X	X	X	X	X	X
AE/ConMed Review	X	X	X	X	X	X	X	X	X

ADA = anti-drug antibody; AE = adverse event; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; MRI = magnetic resonance imaging; N/A = not applicable; PET = positron emission tomography; PK = pharmacokinetic

Visits on Days 5, 15, 89 and 99 must be scheduled within ± 2 days. Visits on all other days may be scheduled within ± 4 days.

a. Pre-dose and within 15 minutes after the end of the infusion and prior to the PK sample collection.

b. The MRI will be scheduled approximately 2 weeks following the dose and results must be available prior to the next scheduled dose.

c. The lumbar puncture will be performed approximately 14 days after the fourth dose.

d. Prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion), immediately after the end of the infusion (within 15 minutes) and 1 and 2 hours after the end of the infusion.

e. Prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion).

Detailed information regarding the regimens/treatments administered and assignment of the subjects to the treatment groups can be found in Section 5.5.3.

This study was designed to enroll approximately 400 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with

ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

5.2 Selection of Study Population

Subjects will undergo screening procedures within 12 weeks prior to initial study drug administration. Adult male and female subjects who meet the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

Subjects who have signed informed consent and did not randomize because they did not complete the study-specific procedures during the Screening Period or did not meet all entry criteria will be considered Screen Failures. The reason(s) for screen failure will be recorded in the source documents and will be captured in the electronic case report form (eCRF). Subjects who screen fail may be re-screened on a case-by-case basis after consulting the AbbVie Therapeutic Area Medical Director (TA MD) for approval.

5.2.1 Inclusion Criteria

A subject will be eligible for study participation if he/she meets the following criteria:

1. Subject must be able to understand the nature of the study and has the opportunity to have any questions answered. The subject has voluntarily signed the Independent Review Board (IRB)/Independent Ethics Committee (IEC) approved Informed Consent, prior to the conduct of any study procedures (including any changes occurring in the subject's current therapeutic regimen). If based on the investigator's judgment at any point during the study the subject does not have an adequate capacity to provide consent, then the informed consent must be obtained by a person who has the legal right to act on behalf of the subject following local regulations.
2. Male or female and age is between 55 and 85 years, inclusive, at Screening Visit 1.

3. Subject who meets the National Institute on Aging and the Alzheimer's Association (NIA-AA) clinical criteria for mild cognitive impairment or probable AD,[10] and has:
   - Clinical Dementia Rating (CDR)-Global Score of 0.5 at Screening Visit 1
   - Mini-Mental State Examination (MMSE) score of 22 to 30, inclusive, at Screening Visit 1
   - Repeatable Battery for the Assessment of Neuropsychological Status-Delayed Memory Index (RBANS-DMI) score of 85 or lower
4. Subject has a positive amyloid PET scan.
5. Subject has a Modified Hachinski Ischemic Scale (MHIS) score of ≤ 4.
6. Subject has an identified, reliable study partner (e.g., family member), who has frequent contact with the subject and who will provide information as to the subject's cognitive and functional abilities. The study partner has voluntarily signed the IEC/IRB approved Study Partner Informed Consent, prior to the conduct of any study procedures.
7. If female, subject must be postmenopausal defined as:
   - Age ≥ 55 years with no menses for 12 or more months without an alternative medical cause.

     OR
   - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
8. If the male subject is sexually active with female partner(s) of childbearing potential, he must agree, from Study Day 1 through 20 weeks after the last dose of study drug to practice the protocol specified contraception (Section 5.2.4) and must refrain from sperm donation.
9. If using medications to treat symptoms related to AD, doses must be stable for at least 12 weeks prior to randomization.

Rationale for the Inclusion Criteria

1	In accordance with the harmonized Good Clinical Practice (GCP)
7 – 8	The effects of ABBV-8E12 on pregnancy are currently unknown
2 – 6, 9	To select subject population appropriate for this study

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Subject has any visual, auditory or other impairment that in the Investigator's opinion would preclude collection of outcome measures.
2. Subject has any contraindication to or inability to tolerate brain MRIs (e.g., a pacemaker or any other implanted device or condition that would preclude proximity to a strong magnetic field).
3. Subject has any contraindication to or inability to tolerate a PET scan (includes current or recent participation in any procedures involving radioactive agents such that the total radiation dose exposure to the subject in any given year would exceed the local country limits of annual and total dose).
4. Subject enrolled in Cohort 1 has any contraindications to or inability to tolerate lumbar punctures (e.g., use of anticoagulant medications such as warfarin and inability to temporarily cease use of such therapy for a limited duration surrounding lumbar punctures).
5. Subject has evidence of any other clinically significant neurological disorder other than Early AD, including but not limited to:
    - Parkinson's disease
    - vascular dementia
    - significant cerebrovascular abnormalities
    - frontal-temporal dementia

- Huntington's disease
- normal pressure hydrocephalus
- brain tumor
- progressive supranuclear palsy
- seizure disorder
- subdural hematoma
- multiple sclerosis
- history of significant head trauma followed by persistent neurologic deficits
- known structural brain abnormalities

6. Subject has a screening MRI scan, interpreted by a radiologist with evidence of infection, infarction (including multiple lacunas in a critical memory structure), or other focal lesions.
7. Subject has a history of or currently has schizophrenia, schizoaffective disorder or bipolar disorder according to DSM-V or ICD-10 criteria.
8. In the opinion of the investigator, the subject has any clinically significant or uncontrolled medical or psychiatric illness, or has had an infection requiring medical intervention in the past 30 days.
9. Subject has significant current suicidal ideation within one year prior to Screening as evidenced by answering "yes" to questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) completed at Screening or a history of suicidal attempts within the last 2 years.
10. Subject has a positive screen for drugs of abuse or marijuana at Screening Visit.
11. Subject has a current diagnosis or history of drug or alcohol abuse (by DSM-V criteria) within 24 months prior to screening visit.
12. Subject has had a myocardial infarction, unstable angina, stroke, transient ischemic attack or required intervention for any of these conditions (e.g., coronary artery bypass graft, percutaneous coronary intervention via cardiac catheterization, thrombolytic therapy), within 6 months of Screening Visit 1.

13. Subject has a history or evidence of a malignancy within the 2 years prior to Screening Visit 1. Subjects with some indolent malignancies (e.g., basal cell carcinoma or squamous cell carcinoma) or malignancies considered to be cured or not actively treated with anti-cancer therapy or radiotherapy may be permitted to enroll with the permission of the AbbVie TA MD.
14. Subject has a positive test result for hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCV Ab) or known history of Human Immunodeficiency Virus (HIV) infection.
15. Subject has had surgery under general anesthesia within 3 months prior to Screening or has a planned major surgical procedure scheduled during the period when the subject would be participating in this study. The subject may subsequently be considered for the study following full recuperation from the surgical procedure.
16. Receipt of an investigational product within a time period equal to 5 half-lives, if known, or within 6 weeks (for small molecules) or 6 months (for monoclonal antibodies or other biologics) prior to study drug administration.
17. Subject has any history of prior receipt of active immunotherapy directed against tau or amyloid.
18. Subject is taking specific exclusionary psychoactive medications or any other exclusionary medications as defined in Section 5.2.3.1.
19. Subject has an abnormally low vitamin B_{12} (cobalamin), abnormal thyroxine (T4) or an abnormally high thyroid-stimulating hormone (TSH) at Screening that is considered clinically significant by the investigator.
20. The investigator considers subject, for any reason, as an unsuitable candidate to receive ABBV-8E12 or unable or unlikely to comply with the dosing schedule or study evaluations.

Rationale for Exclusion Criteria

1, 5 – 15, 19, 20	These criteria were selected to ensure the appropriate subject population
2 – 4	To ensure the safety of the subjects
16 – 18	These products may interfere with the pharmacokinetics of the study drug

5.2.3 Prior and Concomitant Therapy

If a subject reports taking any over-the-counter or prescription medications, vitamins and/or herbal supplements or if administration of any medication becomes necessary from 30 days prior to Screening through the end of the study, the name of the medication, dosage information including dose, route and frequency, date(s) of administration including start and end dates, and reason for use must be recorded. The AbbVie TA MD must be notified if administration of any prohibited medication is reported during the study.

Permitted medications include (but are not limited to) the following:

- Cholinesterase inhibitors and memantine are permitted if the dose is stable for 12 weeks prior to randomization and no change is expected during the study.
- Use of estrogen and estrogen-like compounds is allowed if the dose has been stable for 4 weeks prior to randomization.
- Use of sedative/benzodiazepines (other than those listed in the prohibited medications Table 2) is allowed if the dose has been low and stable for 4 weeks prior to randomization.
- Use of narcotic analgesics is allowed if the dose has been low and stable for 4 weeks prior to randomization: (e.g., codeine, hydrocodone, meperidine, oxycodone, propoxyphene, and tramadol).

These medications should remain stable for the duration of the study unless a change in regimen is medically necessary.

All concomitant medications, including any change in dose must be recorded with the reason for use, dates of administration, dosages and frequency in the eCRF.

5.2.3.1 Prohibited Therapy

Unless approved by the Investigator in consultation with the AbbVie TA MD, subjects should not receive the following medications (not a comprehensive list) described in Table 2.

Table 2. Prohibited Medications

Anticoagulants (Exclusionary for Lumbar Punctures*)	
Generic Name:	Brand Name:
Vitamin K antagonists	Warfarin, Acenocoumarol, Phenprocoumon
Enoxaparin sodium	Lovenox
Dabigatran	Pradaxa
Rivaroxaban	Xarelto
Apixaban	Eliquis
Edoxaban	Lixiana
Heparin	
***Some subjects may be able to temporarily cease use of anticoagulant therapy in the limited duration surrounding lumbar punctures.**	
Neuroleptics: Prohibited Within 4 Weeks Prior to Screening and Throughout the Duration of the Study	
Generic Name:	Brand Name:
Chlorpromazine	Thorazine
Fluphenazine	Prolixin
Loxapine	Loxitane
Perphenazine	Etrafon, Trilafon
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Clozapine	Clozaril
Haloperidol	Haldol (allowed if dose stable for 4 weeks prior to screening)

Table 2. Prohibited Medications (Continued)

Anticholinergic Agents: Prohibited Within 4 Weeks Prior to Screening and Throughout the Duration of the Study	
Generic Name:	Brand Name:
Amantadine	Symmetrel
Benztropine	Cogentin
Cyproheptadine	Periactin
Dicyclomine	Bentyl
Diphenhydramine	Benadryl, Sominex 2
Diphenoxylate with Atropine	Lomotil
Hydroxyzine	Vistaril, Atarax
Hyoscyamine	Levsin
Meclizine	Antivert, Bonine
Prochlorperazine	Compazine
Trihexyphenidyl	Artane
Trimethobenzamide	Tigan
Antiparkinsonian Medications: Prohibited Within 4 Weeks Prior to Screening and Throughout the Duration of the Study	
Generic Name:	Brand Name:
Bromocriptine	Parlodel
Deprenyl/Selegiline	Eldepryl
Levodopa	Sinemet
Pergolide	Permax
Pramipexole	Mirapex
Sedatives/Benzodiazepines: Prohibited Within 4 Weeks Prior to Screening and Throughout the Duration of the Study	
Generic Name:	Brand Name:
Chlordiazepoxide	Librium
Clonazepam	Klonopin
Diazepam	Valium
Flurazepam	Dalmane
Meprobamate	Miltown
Triazolam	Halcion
Antihypertensive Agents with Frequent Central Nervous System (CNS) Side Effects: Prohibited Within 4 Weeks Prior to Screening and Throughout the Duration of the Study	
Generic Name:	Brand Name:
Clonidine	Catapres

Note: Brand names may vary by country/region.

In general, dose changes or administration of additional medications with psychotropic effects (including opiates) on an as-needed (i.e., PRN) basis is prohibited. In the exceptional case, low doses of anxiolytic/hypnotic agents, antipsychotic or opiate containing medications are permitted in the interest of patient safety or emergent symptom control; however, ongoing use of PRN medications should be discussed with the AbbVie TA MD. If a subject requires PRN use of a medication with psychotropic effects, subject efficacy scales must not be administered within 48 hours of a PRN medication administration. Depending on the time of dose administration, the next study visit should be rescheduled to assure an interval of at least 48 hours between PRN medication administration and psychometric assessments. Each case of PRN medication administration must be documented with the reason for use, dates of administration, and dosages in the eCRF. Regularly scheduled medications administered to a subject on a daily basis should not be delayed, and administration times should not be altered due to cognitive assessments.

The AbbVie TA MD should be contacted if there are any questions regarding concomitant and prior therapy(ies), or prohibited medications.

5.2.4 Contraception Recommendations and Pregnancy Testing

Pregnancy testing will not be required in this study.

If female, subject must be postmenopausal defined as:

- Age > 55 years with no menses for 12 or more months without an alternative medical cause.
- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

If male, subject must be surgically sterile (vasectomy with medical assessment confirming surgical success) or have a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), OR if sexually active

with female partner(s) of childbearing potential must agree from Study Day 1 through 20 weeks after the last dose of study drug to practice contraception with:

- Condom use.
- True abstinence: Refraining from heterosexual intercourse-when this is in line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods by the female partner and withdrawal are not acceptable).
- Additionally, male subject agrees not to donate sperm from Study Day 1 through 20 weeks after the last dose of study drug.

5.3 Efficacy, Pharmacokinetic, Biomarker, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C.

5.3.1.1 Study Procedures

Study visits may be impacted due to the COVID-19 pandemic may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures. Additional details are provided in the subsequent sections of this protocol. Every effort should be made to ensure the safety of subjects and onsite staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, the updates below on how to proceed should be followed.

Identification of Study Partner

To be eligible for screening, each subject must have a study partner (e.g., family member or friend), who has frequent contact with the subject (a minimum of 10 hours per week)

and who will provide information as to the subject's cognitive and functional abilities. The designated study partner must be sufficiently familiar with the subject (as determined by the investigator) to provide accurate data. The site must obtain the name and contact information of the study partner and the source documents must record the study partner's consent to satisfy the responsibility of the study partner in this study.

Medical History

For all subjects, a complete medical history, including subject's history of cognitive impairment and any medications taken for AD or MCI, will be obtained at Screening. In addition, history of alcohol and tobacco use will be obtained from each subject. The medical history will be updated on Day 1. The updated medical history on Day 1 will serve as the baseline for clinical assessment.

Ongoing concomitant medication (prescription or over-the-counter, including vitamins and herbal supplements) use and any medication stopped within 30 days prior to screening and any monoclonal antibodies or other biologics within 6 months prior to the study drug administration will also be recorded.

Hepatitis Screen

HBsAg and HCV Ab tests will be performed at Screening. The hepatitis test panel will be performed by a certified laboratory.

Physical Examination

Physical examinations will be performed as indicated in the Study Activities Table (Appendix C). A symptom-directed physical examination will be performed when necessary. The last physical examination performed at screening prior to the first dose will serve as the baseline physical examination for clinical assessment. Any significant physical examination findings after dosing begins will be recorded as adverse events.

Height will be measured at Screening; the subject will not wear shoes.

Body weight will be measured as indicated in the Study Activities Table (Appendix C). The subject will wear lightweight clothing and no shoes during weighing.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event physical examinations may not be performed due to study modifications related to the COVID-19 pandemic, these examinations should be completed at the next onsite visit.

Neurological Examination

A neurological examination will be performed at the times indicated in the Study Activities Table. The neurological exam performed on Day 1 will serve as the baseline for clinical assessment. Symptoms identified during the Screening Period will not be recorded as adverse events; however, new symptoms or current symptoms that change in severity or frequency after the first day of study drug will be recorded as adverse events.

The neurological examination will assess:

- Mental Status – assessment of orientation, speech, and memory
- Cranial nerves – assessment of cranial nerves II-XII
- Motor system – brief assessment of tone and strength, tremors
- Sensory system – brief survey for light touch and temperature
- Reflexes – assessment of deep tendon reflexes and plantar responses (Babinski sign)
- Coordination – assessment of upper and lower extremities, including assessment for tremor
- Gait – assessment of tandem gait
- Station – assessment of posture and stability

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event neurological examinations may not be performed due to study modifications related to the COVID-19 pandemic, these examinations should be completed at the next onsite visit.

Vital Signs

Body temperature, blood pressure and pulse will be measured at the times indicated in the Study Activities Table (Appendix C). The vital signs measurements just prior to dosing on Study Day 1 will serve as the baseline measurements for clinical assessment.

Blood pressure and pulse rate will be measured after the subject has been sitting for at least 5 minutes. For visits in which both vital signs and blood sample(s) are collected, vital signs should be obtained prior to any blood collection.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event vital signs may not be obtained due to study modifications related to the COVID-19 pandemic, these measurements should be obtained at the next onsite visit.

12-Lead Electrocardiogram (ECG)

A 12-lead resting ECG will be obtained as indicated in the Study Activities Table. For visits in which both ECGs and blood sample(s) are collected, ECGs should be obtained prior to any blood collection. ECGs will be recorded after the subject has been supine for at least 5 minutes. The subject should be instructed to remain completely stationary during the recording, without talking, laughing, deep breathing or swallowing during the time of recording (10 seconds). The ECG measurements obtained on Day 1 will serve as the baseline for clinical assessment.

The ECGs will be read by a qualified local physician for an immediate safety assessment and also by the central reader who will provide a full report to the site within 3 business days.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event 12-lead ECG may not be performed due to study modifications related to the COVID-19 pandemic, this procedure should be completed at the next onsite visit.

Local ECG Reading:

A qualified physician at the study site will interpret and document his/her global interpretation on the ECG tracing, based on the following conventions, as appropriate:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

This physician will sign and date the ECG tracings. Each ECG should be reviewed by the physician before the study drug administration to ensure the tracing is interpretable and no acute, medically serious condition is present. The investigator's (or physician designee's) initial interpretation of the ECG will be the basis of any decisions related to the study conduct and treatment of the study subjects (e.g., eligibility at baseline, AE assessment, etc.).

Central ECG Reading:

Site personnel will transmit ECG data to an ECG central laboratory for central processing and reading by a qualified cardiologist (central reader) who, also blinded by study drug assignment, will independently review each ECG. QT interval corrected for heart rate (QTc) will be determined using Fridericia's correction method (QTcF). The central ECG laboratory's data will be entered into the database. The central reader will also provide the interpretation of the ECG (i.e., "Normal" or "Abnormal"). The central ECG laboratory will send the ECG report to the site within 3 business days. The Investigator (or physician designee) will review the central reader's report/assessment and document his/her review by signing and dating the central ECG laboratory report. The investigator should review and reconcile if necessary his/her interpretation of the ECG

(normal/abnormal) with the central ECG laboratory in case of relevant divergent assessments and reconcile as he/she determines is appropriate.

ECGs will be collected as single ECGs as follows:

Cohort 1 Subjects:

- **Screening**
- **Day 1 (Dose 1)**
  - Pre-dose (just prior to the start of infusion) and within 15 minutes after the end of infusion prior to the PK sample collection)
- **Days 5 and 15**
  - Collection should be scheduled as close as possible to the corresponding time of the post infusion collection on Day 1.
- **Days 29 and 57 (Doses 2 and 3)**
  - Pre-dose (just prior to the start of infusion)
- **Day 85 (Dose 4)**
  - Pre-dose (just prior to the start of infusion) and within 15 minutes after the end of infusion (prior to the PK sample collection)
- **Weeks 24, 36, 48, and 72 (Doses 7, 10, 13 and 19 respectively)**
  - Pre-dose (just prior to the start of infusion)
- **Week 96 (Study Completion Visit)**
- **Follow-up (Week 104)**

Cohort 2 Subjects:

- **Screening**
- **Day 1 (Dose 1)**
  - Pre-dose (just prior to the start of infusion) and approximately within 15 minutes after the end of infusion).
- **Days 29, 57, 85 and Weeks 24, 36, 48, and 72 (Doses 2, 3, 4, 7, 10, 13 and 19 respectively)**

- Pre-dose (just prior to the start of infusion).

- **Week 96 (Study Completion Visit)**
- **Follow-up (Week 104)**

Urine Screens for Drugs of Abuse

Urine specimens will be collected at times indicated in the Study Activities Table (Appendix C) to test for drugs of abuse by the central laboratory chosen for the study. Any subject testing positive for cocaine metabolites, phencyclidine, opiates, barbiturates, benzodiazepines, marijuana metabolites, amphetamines, or methadone prior to randomization, will be excluded from the study, unless the detected drug has been appropriately prescribed by a physician. Additional drug screens may be obtained at the discretion of the investigator. With the exception of subjects who are regularly taking opiates for pain control, any subjects testing positive during the study will be considered for premature discontinuation in consultation with the AbbVie TA MD.

Subjects should be instructed to abstain from drinking any alcoholic beverages for 24 hours prior to each visit.

Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 3 at the time points designated in the Study Activities Table (Appendix C).

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

Table 3. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Bands (if detected) Lymphocytes Monocytes Basophils (if detected) Eosinophils (if detected) Platelet count (estimate not acceptable) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin concentration (MCHC) Prothrombin time (PT) Activated partial thromboplastin time (aPTT) PT/INR (Prothrombin Time/International Normalized Ratio)	Blood urea nitrogen (BUN) Creatinine Total bilirubin Albumin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphate Uric acid Cholesterol Total protein Glucose Triglycerides Bicarbonate/CO_2 Chloride Thyroid Stimulating Hormone (TSH)* Thyroxine (T4)* Vitamin B12 (cobalamin)*	Specific gravity Ketones Ph Protein Glucose Blood Microscopic examination, if dipstick results are positive
		CSF Basic Labs**
		RBC, WBC with differential Total Protein Albumin Glucose
		Reference Tests if Vitamin B12 is Under the Lower Limit of Normal Range
		Methylmalonic Acid (MMA) Homocysteine
		Hepatitis Tests*
		Hepatitis B surface antigen (HBsAg) Hepatitis C virus antibody (HCV Ab) • Any positive HCV Ab test must be confirmed by a positive Hepatitis-C Viral ribonucleic acid (RNA) polymerase chain reaction (PCR) Qualitative test for HCV

* Screening only.

** Done locally according to the local laboratory specifications and capabilities.

Abnormal Findings

For any laboratory test value outside the reference range that the investigator considers to be clinically significant:

- The investigator will repeat the test to verify the out-of-range value.
- The investigator will follow the out-of-range value to a satisfactory clinical resolution.
- A laboratory test value that requires a subject to be discontinued from the study or requires a subject to receive treatment will be recorded as an adverse event.

For all laboratory abnormalities the investigator will determine if they indicate a new disease process, an exacerbation or worsening of an existing condition, or require further action to be taken and therefore need to be reported as adverse events. Accordingly, for any values outside of the reference range, the Investigator will indicate on the report if the result is clinically significant (CS) or not clinically significant (NCS). If a laboratory abnormality meets criteria for a potentially clinically significant (PCS) laboratory value, as defined in Appendix D, the investigator must either report an associated adverse event or document in source the reason(s) the finding was not considered an adverse event.

Any laboratory value that remains abnormal at Premature Discontinuation/End of Study and was judged to be clinically significant will be followed according to accepted medical standards until resolution of the abnormality.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event clinical laboratory tests may not be performed due to study modifications related to the COVID-19 pandemic, these tests should be completed at the next onsite visit.

If laboratory tests cannot be performed, study drug may be administered to subjects if the investigator has reviewed all prior laboratory results and confirms there are no safety concerns.

Lumbar Puncture (LP)

Lumbar punctures are required for subjects enrolled in Cohort 1 and are optional for subjects enrolled in Cohort 2. For all Cohort 1 subjects and subjects agreeing to LPs in Cohort 2, LPs to collect CSF will be performed at time points indicated in the Study Activities Table (Appendix C). Subjects will undergo a LP during Screening (preferably after all other entry criteria have been satisfied and after MRI and PET scan and any time prior to Day 1), after the 4th dose and after the final dose if administered at least 3 months after the previous LP. A sample of CSF will be collected according to the CSF Collection Manual provided to the study site by the sponsor. Computed tomography (CT)/fluoro-guided lumbar puncture can be used at the discretion of the local clinical site staff. Basic neurochemical CSF analyses will be performed locally according to the local laboratory capabilities at the applicable clinical site after each lumbar puncture/CSF collection. These measures may include cell counts (red blood cell [RBC] and white blood cell [WBC] with differential), total protein, albumin and glucose. Other CSF measurements (e.g., ABBV-8E12 concentration, tau and other exploratory biomarkers) will be analyzed by the applicable designated laboratory.

Headaches occur commonly following withdrawal of CSF. Subjects may be treated with the following, such as: IV hydration, IV caffeine administration, bed-rest and analgesics. Uncommonly a blood patch (injection of some of the subject's blood to patch the CSF leak) may be needed. Potential but rare risks of lumbar puncture include infection, damage to nerves in the back, and bleeding into the CSF space. The risk of these is much less than 1%.[11]

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event lumbar puncture may not be performed due to study modifications related to the COVID-19 pandemic, this procedure should be completed at the next onsite visit.

Magnetic Resonance Imaging (MRI)

For all subjects, a Magnetic Resonance Imaging (MRI) will be obtained at time points indicated in the Study Activities Table (Appendix C) and interpreted by a radiologist or neurologist. Subjects will be queried to assure they do not have specific contraindications for MRI. The Screening MRI should be completed after all other relevant screening procedures (except for the Amyloid PET and LP) have been completed and reviewed by the investigator.

The Screening MRI assessment will rule out the presence of any intracranial masses that might preclude the subject from undergoing a lumbar puncture and exclude focal or diffuse processes that could interfere with the diagnosis of AD or MCI, including signal abnormalities on FLAIR or T2 weighted images consistent with infectious, vascular, neoplastic or other degenerative processes. The 3D T1 weighted sequences will also be acquired for volumetric analysis that will enable a quantitative assessment of the whole and regional brain volume.

On-treatment safety MRI analysis will be performed at the time points indicated in the Study Activities Table. On-treatment volumetric MRI analysis will be performed at the time points indicated in the Study Activities Table (Appendix C) starting from Week 28.

The MRI scan should be done prior to the LP otherwise at least a 3-day window between the LP and the MRI appointment is necessary. Details of the MRI procedures will be described in the MRI Procedures Manual provided by the Sponsor.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event MRI may not be performed due to study modifications related to the COVID-19 pandemic, this procedure should be completed at the next onsite visit.

Positron Emission Tomography (PET) Amyloid Imaging

For all subjects without an acceptable historical amyloid positive PET scan, an amyloid PET scan will be obtained at Screening. The acceptability of the historical PET scan will

be determined by the central reader. Even though amyloid is not a target for ABBV-8E12, amyloid imaging is included for subject selection to increase the diagnostic and prognostic accuracy in the early stages of AD. It allows for a better differential diagnosis of cognitive impairment and identification of individuals that are at increased risk of progressive cognitive decline.

Subjects will be queried to assure they do not have specific contraindications for PET such as a history of radiation therapy within the past year, or a history of receiving radiation for research purposes within the past year. The amyloid PET scan should be completed after all other relevant screening procedures including screening MRI scan have been completed and reviewed by the investigator.

If the LP and PET scan are done on the same day, the LP should be completed prior to the PET scan; otherwise there should be at least 12 hours between the LP and the PET scan. Details of PET procedures will be described in the Amyloid PET Procedures Manual provided by the Sponsor.

Positron Emission Tomography (PET) Tau Imaging

Tau PET imaging will be conducted only at sites selected to participate by AbbVie based on scientific, technical and logistical considerations. For all eligible subjects, tau PET imaging will be conducted at Screening, after completion of Weeks 44 (Dose 12) and 96 as indicated in the Study Activities Table (Appendix C). Subjects who did not complete tau PET imaging during the screening period may still have tau PET imaging performed at subsequent visits.

Tau deposition in the brain, unlike amyloid, tracks closely with the cognitive decline of AD. Preclinical data suggest that ABBV-8E12 decreases tau seeding activity in vitro and overall tau pathology in vivo. Tau PET imaging will be used to assess any signals or trends of ABBV-8E12 to slow the accumulation (amount) and extent (spread) of tau deposits in the brain or potentially remove existing tau deposits

The tau PET scan at Screening should be carried out no longer than 12 weeks prior to administration of the first dose.

If the LP and tau PET scan are done on the same day, the LP should be completed prior to the tau PET scan; otherwise there should be at least 12 hours between the LP and the tau PET scan. Details of tau PET procedures will be described in the tau PET Procedures Manual provided by the Sponsor.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event the tau PET scan may not be performed due to study modifications related to the COVID-19 pandemic, this procedure should be completed at the next onsite visit.

Retinal Imaging for Amyloid

Non-invasive retinal imaging is currently utilized to screen for a number of retinal diseases and is widely available. Recently, retinal imaging has shown some utility in detecting trace amounts of beta amyloid in the retinal epithelial layer. Retinal Aβ plaques have been identified in postmortem eyes from AD patients and in amyloid over-expressing transgenic mice. Preliminary data suggest amyloidogenic densities can be detected in the retina of early AD patients. An exploratory retinal imaging test designed to detect trace amounts of amyloid may be conducted only at sites selected to participate by AbbVie based on scientific, technical and logistical considerations. For all eligible subjects at participating sites, the retinal imaging test will be obtained during screening or within a 6-month window of initial randomization data. An additional blood sample will also be collected. This assessment will examine the relationship between retinal amyloid imaging and brain amyloid PET imaging results. Only retinal imaging for amyloid will be conducted. One eye drop will be administered in each eye for dilation. As a result, the retinal imaging test should not be carried out prior to cognitive testing if scheduled on the same day. If the retinal imaging test is scheduled during planned blood and CSF collections, the retinal imaging test should be completed after biofluid sampling. Details for the retinal imaging procedure will be provided in a separate manual and will be conducted by trained site personnel.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event the retinal scan may not be performed due to study modifications related to the COVID-19 pandemic, this procedure should be completed at the next onsite visit.

Diagnostic Tools and Rating Scales

Prior to the start of the study, designated raters will be certified in the use of all scales used in this study. The objective of this certification/training is to establish uniformity across sites in the administration, interpretation and scoring of these rating instruments. Raters who cannot participate in pre-study certification/training or raters who become involved in the study after training at the investigator's meeting will not be permitted to perform any study-specified ratings until they have satisfactorily completed an individualized certification/training program designed by the central trainers, approved by AbbVie and supervised by the investigator or his/her designee. It is the responsibility of the investigator to ensure that the raters at his/her site are appropriately trained and certified in the use of selected rating scales. Every effort must be made by the investigative sites to ensure that each subject is rated by the same rater throughout their participation in the study.

AbbVie, in conjunction with the rater training vendor, will determine the minimum rater qualifications for each of the rating scales. All raters must meet these qualifications prior to participation in the training process. The qualifications of the raters will be verified through the training vendor. Individual exceptions to these requirements must be approved by the Sponsor via the training vendor. The order of the administration of scales at each visit should be consistent throughout the study.

Administration of selected scales will be audio recorded (as permitted by local regulations) to allow for central review of the data to ensure consistency and reliability.

Assessments will be performed at the times indicated in Table 4.

Table 4. Diagnostic Tools and Scale Administration Timing

	Recommended Order of Administration	Approximate Administration Time[a] (Minutes)	Patient/ Study Partner	Screening Day –84 – Day –8	Day –7 to Day 1 (Prior to Infusion)[b]	Week 12	Week 24	Week 36	Week 48	Week 72	Week 96
CDR	1	45 – 75	Both	X	X		X		X	X	X
RBANS	2	25	Patient	X	X		X		X	X	X
UPSA – Brief	3	10 – 15	Patient		X				X		X
ADAS-Cog-14	4	30 – 60	Patient		X		X		X	X	X
MMSE	5	10 – 15	Patient	X	X		X		X	X	X
ADCS-CGIC-MCI	6	10 – 15	Both		X				X		X
C-SSRS[c]	7	5 – 20	Patient	X	X		X		X	X	X
FAQ	d	6 – 10	Study partner		X		X		X	X	X
NPI	d	15	Study partner		X		X		X	X	X
ADCS-MCI-ADL-24	d	30 – 45	Study partner		X				X		X
MHIS (I)	d	5	N/A clinician assessed	X							
Digital clock drawing	d	5	Patient	X	X	X	X	X	X	X	X

ADAS-Cog-14 = Alzheimer's Disease Assessment Scale (14-Item) Cognition portion; ADCS-CGIC-MCI = Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change for Mild Cognitive Impairment; ADCS-MCI-ADL-24 = 24-item Alzheimer's Disease Cooperative Study/Activities of Daily Living Scale Adapted for Patients with Mild Cognitive Impairment; CDR = Clinical Dementia Rating; C-SSRS = Columbia-Suicide Severity Rating Scale; FAQ = Functional Activities Questionnaire; MHIS = Modified Hachinski Ischemic Scale; MMSE = Mini-Mental State Examination; N/A = not applicable; NPI = Neuropsychiatric Inventory; RBANS = Repeatable Battery for Assessment of Neuropsychological Status; UPSA Brief = University of California San Diego Performance Based Skills Assessment, Brief Version

a. Breaks should be taken as necessary.

b. Assessments will be done once during this time frame and can be administered on any day, but all must be done on the same day.

c. The C-SSRS will be done at each visit throughout the study (see Study Activities Table Appendix C for all time points).

d. Scale may be administered/assessed at any time during the visit.

I – Administered during Screening to assess inclusion criteria only.

The diagnostic tools and rating scales include the following:

Clinical Dementia Rating (CDR)[12]

The Clinical Dementia Rating (CDR) is a numeric scale used to quantify the severity of symptoms of dementia. A qualified health professional will assess a patient's cognitive and functional performance in six areas: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The CDR scale gives a score from 0 – 3 for each of the six areas. The sum of these six areas, the CDR sum of boxes (CDR-SB) score can range from 0 – 18.

Using a scoring algorithm, a CDR global score (range from 0 – 3) will be generated. The subject must have a CDR global score of 0.5 at Screening to be eligible for study participation. The CDR-SB score will be calculated at each time point. The CDR will be administered to both the patient and the study partner at the times indicated in Table 4.

Alzheimer's Disease Assessment Scale (14-Item) Cognition Portion; (ADAS-Cog-14)[13]

The ADAS-Cog was designed to assess the cognitive impairments most common in AD. The ADAS-Cog is a subscale of the ADAS, which focuses on cognitive functioning and memory.

The ADAS-Cog-14 includes the original 11 items from the ADAS-Cog-11 [1. Spoken language ability, 2. Comprehension of spoken language, 3. Recall of test instructions, 4. Word-findings difficulty in spontaneous speech, 5. Following commands, 6. Naming objects and fingers, 7. Constructional praxis, 8. Ideational praxis, 9. Orientation, 10. Word-recall task, 11. Word-recognition task] and includes three additional tasks [12. Number cancellation task, 13. Delayed word recall task, 14. Executive functioning], for increased sensitivity in MCI patients. The total score of the 14-item ADAS-cog ranges from 0 to 90, with a higher score representing greater impairment. The ADAS-Cog-14 will be administered to the patient at the times indicated in Table 4.

Mini Mental State Exam (MMSE)[14,15]

The MMSE is a brief, 30-point questionnaire, administered by a trained rater, which provides a quantitative measure of cognitive status in adults and is widely used to screen for cognitive impairment and to estimate the severity of cognitive impairment at a given point in time in AD subjects. The subject must have a score of 22 to 30, inclusive at Screening to be eligible for study participation. Lower scores indicate greater impairment. The MMSE will be administered to the patient at the times indicated in Table 4.

Functional Activities Questionnaire (FAQ)[16,17]

The FAQ measures level of assistance (functional disability) needed for carrying out instrumental activities in daily living (iADLs). The FAQ score ranges from 0 – 30 and consists of 10 items (each scored from 0 – 3), which measure a specific iADL in the past 4-weeks: [1) writing checks, paying bills, keeping financial records; 2) assembling tax or business records; 3) shopping alone; 4) playing a game of skill; 5) making coffee or tea; 6) preparing a balanced meal; 7) keeping track of current events; 8) attending to and understanding a television program, book, or magazine; 9) remembering appointments, family occasions, medications; and 10) traveling out of the neighborhood.]. Performance in each category is rated from 0 – 3 as follows: 0 – normal; 1 – has difficulty, but does by self; 2 – requires assistance; or 3 – dependent. The FAQ will be administered to the study partner by a trained interviewer. Higher scores indicate a greater requirement of assistance. The FAQ will be administered to the study partner at the times indicated in Table 4.

Neuropsychiatric Inventory (NPI)[18-20]

The NPI was developed to assess the presence of psychopathology in subjects with AD and other dementias. The scale is based on responses from the study partner and should be administered in the absence of the subject. The NPI is used to assess changes in the subject's behavior that have occurred in a defined period of time (4 weeks). The NPI assesses 12 behavioral domains on the dimensions of frequency and severity. Frequency

is rated on a scale where 0 = absent, 1 = occasionally, 2 = often, 3 = frequently, 4 = very frequently. Severity is rated on a scale where 0 = absent, 1 = mild, 2 = moderate, 3 = severe. For each of the domains, 3 scores will be obtained: frequency, severity, and total (product of frequency and severity; ranges from 0 to 12). A total NPI score can be calculated by summing the domain total scores (ranges from 0 to 144 with a lower score desirable). The reliability, content validity and concurrent validity of the inventory has been established, and it has been shown to be sensitive to treatment effects. The NPI will be administered to the study partner at the times indicated in Table 4.

24-Item Alzheimer's Disease Cooperative Study/Activities of Daily Living Scale Adapted for Patients with Mild Cognitive Impairment (ADCS-MCI- ADL-24)[21-23]

The ADCS-MCI-ADL-24 is a 24-item, study partner-based assessment of activities of daily living designed specifically for AD patients and is completed by a trained rater. The scale assesses functional activities such as cooking, household chores, shopping, keeping appointments, social interactions and hobbies. Items are assessed according to whether they were performed in the past 4 weeks and, if so, some items are further assessed as to whether they were performed independently, with supervision, or with physical help. Scores on the ADCS-ADL-MCI range from 0 to 69, where higher score indicates greater capability to carry out activities of daily living. The scale has good test-retest reliability, was designed for use across severities of AD, and has been demonstrated to detect drug effects in clinical trials. The ADCS-MCI-ADL-24 will be administered to the study partner at the times indicated in Table 4.

Alzheimer's Disease Cooperative Study Clinical Global Impression of Change for Mild Cognitive Impairment (ADCS-CGIC-MCI)[24,25]

The instrument covers four major domains: 1. General condition, 2. Cognition, 3. Behavior, and 4. Social and daily functioning. Scoring is based on a 7-point Likert Scale: 1, marked improvement; 2, moderate improvement; 3, minimal improvement; 4, no change; 5, minimal worsening; 6, moderate worsening; 7, marked worsening. Higher score indicates greater worsening.

At baseline, the clinician interviews the subject and study partner about baseline status for later reference. At baseline only, clinical information about the subject may be used, including medical history, physical and neurological examination, and other ratings done at screening. At interval assessments, the subject is interviewed first, followed by the informant. After completing the worksheets, the clinician records his/her clinical impression of change from baseline on the 7-item scale, referring only to his/her own baseline information when making the assessment, without consulting other study personnel and blinded to possible medication or adverse effects. The instrument has 5-items for baseline and 4-items for the post-baseline assessment. The ADCS-CGIC-MCI will be administered to both the patient and the study partner at the times indicated in Table 4.

Modified Hachinski Ischemic Scale (MHIS)[26,27]

The MHIS is a brief clinical scale used to distinguish vascular dementia from non-vascular dementia by assessing the presence of concurrent vascular risk factors, focal neurological symptoms or signs suggestive of prior stroke, or a history of strokes. An experienced clinician will assess the MHIS for all subjects. Subjects must have a score ≤ 4 to be eligible for study participation. The MHIS will be administered at the times indicated in Table 4.

Repeatable Battery for Assessment of Neuropsychological Status (RBANS)[28]

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a 25-minute, standardized neurocognitive battery with North American population-based normative data. The RBANS measures five neurocognitive domains, with age-based scaling. Twelve subtests measure cognitive decline or improvement across the following domains:

1. Immediate Memory – List Learning and Story Memory,
2. Visuospatial/Constructional – Figure Copy and Line Orientation,
3. Language – Picture naming and Semantic Fluency,

4. Attention – Digit Span and Coding, and
5. Delayed Memory – List Recall, List Recognition, Story Memory, and Figure Recall.

The RBANS has been shown to be effective at both detecting and characterizing dementia of different etiologies. The Delayed Memory domain has been shown to be particularly sensitive to discriminating mild cognitive impairment (MCI) due to AD from controls, and also is predictive of cerebral amyloid burden. The RBANS has been translated into over 25 different languages, with extensive clinical validity data from a wide variety of geographic regions. The RBANS will be administered to the patient at the times indicated in Table 4.

University of California's Performance Based Skills Assessment, Brief Version (UPSA – Brief)[29]

The UPSA-Brief is a performance-based instrument which uses a series of tasks and role-play scenarios to evaluate a person's functional capacity in two areas of basic living skills (i.e., financial skills and communication skills). The UPSA-Brief will be administered to the patient at the times indicated in Table 4.

Columbia-Suicide Severity Rating Scale[30]

The C-SSRS is a systematically administered instrument developed to track suicidal adverse events across a treatment study. The instrument is designed to assess suicidal behavior and ideation, track and assess all suicidal events, as well as the lethality of attempts. Additional features assessed include frequency, duration, controllability, reason for ideation, and deterrents. The C-SSRS is considered a low-burden instrument as it typically takes less than 5 minutes to administer. The C-SSRS questionnaire will be administered at the time points indicated in the Study Activities Table (Appendix C).

Any subject noted to have suicidal ideation with plan within the prior month, either via answering "yes" to questions 4 or 5 to the suicidal ideation portion of the C-SSRS or via

clinical interview, will be evaluated immediately by the study physician. The AbbVie TA MD will also be informed. Appropriate steps will be taken to protect the subject, including but not limited to possible discontinuation from the study and referral for appropriate psychiatric care. Any such subject at Screening or on Day 1 will also be excluded from the study.

Digital Clock Drawing Test (dCDT)

The clock drawing test (CDT) is a well-established tool that assesses an individual's cognitive function and has been studied extensively in patients with various neurological disorders, including AD.[31] In this study, a digitized ballpoint pen will be used to capture data points as subjects complete both the Command and Copy conditions of the CDT and associated software will be used to analyze the entire drawing process and final output. Preliminary data suggest that this approach may allow for the early detection of subtle nuances in cognitive performance beyond successful task completion as assessed in the traditional CDT.[32]

The dCDT will be conducted only at sites selected to participate by AbbVie based on scientific, technical, and logistical considerations. For all eligible subjects, the test will be conducted by trained personnel at the Screening, Baseline, Week 12, Week 24, Week 36, Week 48, Week 72, and Week 96 visits as indicated in the Study Activities Table (Appendix C) and Table 4. While it is ideal to have the dCDT administered starting with the Screening visit for all participating subjects, those who did not complete the test at Screening may do so at the subsequent visits. Details for the administration procedure will be provided in a separate manual.

The results of all screening and evaluations at the time of the first study drug administration must be within clinically acceptable limits, upon review by the investigator before a subject can be administered study drug. Subjects will not be enrolled in the study if laboratory or other screening results are unacceptable. Subjects who meet the inclusion criteria and do not meet any of the exclusion criteria will proceed to randomization (Section 5.5.3). Patients who do not proceed to randomization may be asked to provide

an optional consent for sponsor to retain clinical and biomarker screening data for exploratory research.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If scale administration is not performed due to study modifications related to the COVID-19 pandemic, the scale(s) should be completed at the next onsite visit. Should a virtual visit be conducted, the investigator should refer to the table below for scales that may be administered remotely.

Scale	May be Administered Via Phone or Video Conference
ADAS-Cog-14	No
ADCS-CGIC-MCI	Yes
ADCS-MCI-ADL-24	Yes
CDR	Yes
C-SSRS	Yes
dCDT	No
FAQ	Yes
MMSE	No
NPI	Yes
RBANS	No
UPSA – Brief	No

ADAS-Cog-14 = Alzheimer's Disease Assessment Scale (14-Item) Cognition Portion; ADCS-CGIC-MCI = Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change for Mild Cognitive Impairment; ADCS-MCI-ADL-24 = 24-item Alzheimer's Disease Cooperative Study/Activities of Daily Living Scale Adapted for Patients with Mild Cognitive Impairment; CDR = Clinical Dementia Rating; C-SSRS = Columbia-Suicide Severity Rating Scale; dCDT = Digital clock drawing test; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; RBANS = Repeatable Battery for Assessment of Neuropsychological Status; USPA Brief = University of California San Diego Performance Based Skills Assessment, Brief Version

5.3.1.2 Collection and Handling of Biomarker and Pharmacogenetic Research Samples

Blood and CSF Biomarker Samples

Blood and CSF samples will be collected as outlined in the Study Activities Table (Appendix C) and may be utilized to evaluate known and/or novel disease-related or drug-related biomarkers. The biomarker rationale will be discussed in the Biomarker Research Variables Section (Section 5.3.6).

All biomarker samples should be collected, processed, labeled and shipped as outlined in the study-specific laboratory manual, which will be provided separately.

AbbVie (or people or companies working with AbbVie) will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on ABBV-8E12, or drugs of this class, or AD or related conditions continues, but for no longer than 20 years from the end of the study, or per local requirement.

Blood samples (10 mL) will be collected at Screening and (20 mL) prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion) at the time points indicated in the Study Activities Table (Appendix C). Blood samples collected at Week 96 (Study Completion/PD Visit) may be collected at any time during that visit.

CSF samples (~24 mL) will be collected by lumbar puncture at the time points indicated in the Study Activities Table (Appendix C). CSF samples collected at Week 14 will be approximately 14 days following the fourth dose. In Cohort 2, CSF sample collection is optional.

Apolipoprotein E (APOE) Pharmacogenetic Sample

One (required) 4 mL whole blood sample will be collected from each subject at study Day 1 for APOE pharmacogenetic analysis. This sample will not be used for any testing other than APOE genotypes.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event blood and optional CSF biomarker samples may not be collected due to study modifications related to the COVID-19 pandemic, these samples should be obtained at the next onsite visit.

Optional Pharmacogenetic Research Samples

Subjects will have the option to provide additional samples for pharmacogenetic research. Subjects may still participate in the main study even if they decide not to participate in this optional research.

AbbVie (or people or companies working with AbbVie) will store the optional pharmacogenetic research samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on ABBV-8E12 (or drugs of this class) or AD and related conditions continues, but for no longer than 20 years after study completion. The procedure for obtaining and documenting informed consent for exploratory research samples is discussed in Section 9.3.

Optional whole blood samples (6.5 mL) for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) isolation will be collected at Screening, Day 1, Day 85, Week 36, Week 48, Week 72 and Week 96 (Completion/PD) Visit from each consenting subject at the time points indicated in the Study Activities Table (Appendix C).

All pharmacogenetic samples (mandatory and optional) should be collected, processed, labeled and shipped as outlined in the study-specific laboratory manual, which will be provided separately.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event optional pharmacogenetic research samples may not be collected due to study modifications related to the COVID-19 pandemic, these samples should be obtained at the next onsite visit.

5.3.1.3 Confinement

No overnight confinement will be required for this study.

5.3.1.4 Meals and Dietary Requirements

No meals will be provided as part of this study and there are no dietary requirements or restrictions for this study.

5.3.2 Drug and Anti-Drug Antibody Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Specific instructions for collection of blood samples and subsequent preparation and storage of the serum samples for the pharmacokinetic assays of ABBV-8E12 will be provided by the central laboratory, the Sponsor, or its designee.

Blood Samples for ABBV-8E12 Assay

Blood samples, approximately 3 mL for ABBV-8E12 analysis will be collected by venipuncture as follows:

For Subjects Enrolled in Cohort 1

- **Day 1 (Dose 1)**
  - Prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion), immediately after the end of the infusion (within 15 minutes) and 1 and 2 hours after the end of the infusion.
- **Days 5 and 15**
- **Days 29 and 57 (Doses 2 and 3)**
  - Prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion).
- **Day 85 (Dose 4)**
  - Prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion), immediately after the end of the infusion (within 15 minutes) and 1 and 2 hours after the end of the infusion.

- **Days 89 and 99**
- **Weeks 16, 24, 36, 48, and 72 (Doses 5, 7, 10, 13 and 19, respectively)**
  - Prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion).
- **Week 96 (Study Completion/PD Visit)**
  - Sample may be collected anytime during the day.
- **Weeks 104 and 112 (Post-Treatment Follow-up Period)**
  - Sample may be collected anytime during the day.

For Subjects Enrolled in Cohort 2

- **Days 1, 29, 85 and Weeks 24, 36, 48, and 72 (Doses 1, 2, 4, 7, 10, 13 and 19, respectively)**
  - Prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion)
- **Week 96 (Study Completion/PD Visit)**
  - Sample may be collected anytime during the day
- **Weeks 104 and 112 (Post-Treatment Follow-Up Period)**
  - Sample may be collected anytime during the day.

Blood Samples for ABBV-8E12 Anti-Drug Antibodies (ADA) Assays

Blood samples, approximately 3 mL for ABBV-8E12 ADA analysis will be collected by venipuncture as follows:

For Subjects Enrolled in Cohort 1:

- **Days 1, 29, 57, 85 and Weeks 16, 24, 36, 48, and 72 (Doses 1, 2, 3, 4, 5, 7, 10, 13 and 19, respectively)**
  - Prior to the start of the infusion (0 hour, approximately 30 minutes prior to the start of the infusion).
- **Days 15, 89 and 99**
- **Week 96 (Study Completion/PD Visit)**

- Sample may be collected anytime during the day.

- **Weeks 104 and 112 (Post-Treatment Follow-Up Period)**
  - Sample may be collected anytime during the day.

For Subjects Enrolled in Cohort 2:

- **Days 1, 29, 85 and Weeks 24, 36, 48, and 72 (Doses 1, 2, 4, 7, 10, 13 and 19, respectively)**
  - Prior to the start of the infusion (0 hour, approximately 30 minutes prior to the start of the infusion).
- **Week 96 (Study Completion/PD Visit)**
  - Sample may be collected anytime during the day.
- **Weeks 104 and 112 (Post-Treatment Follow-Up Period)**
  - Sample may be collected anytime during the day.

CSF Samples for ABBV-8E12 Assay

CSF collection in subjects enrolled in Cohort 1 is required and CSF collection in subjects enrolled in Cohort 2 is optional.

CSF samples will be collected as outlined in the Study Activities Table (Appendix C) by LP. The collection time and procedures of CSF samples can be found in the Lumbar Puncture section of Study Procedures Section (Section 5.3.1.1). As described in the Collection and Handling of Biomarker and Pharmacogenetic Research Samples Section (Section 5.3.1.2), CSF samples (~24 mL) collected at Week 14 will be approximately 14 days following the fourth dose.

5.3.2.2 Measurement Methods

Analysis of Serum and CSF Samples

Serum and CSF concentrations of ABBV-8E12 and relative titers of ABBV-8E12 ADA in serum will be determined using validated methods at the Bioanalysis Department at AbbVie. Any additional analytes may be analyzed using non-validated methods. Serum

samples collected for ABBV-8E12 and ABBV-8E12 ADA analysis may be used for future assay development or validation activities. ABBV-8E12 ADA samples upon request may be used for the analysis of neutralizing ADAs.

5.3.3 Efficacy Variables

The primary efficacy variable is CDR-SB score; the primary efficacy measurement will be the change from baseline up to final evaluation at Week 96/PD of the CDR-SB score.

Secondary efficacy variables include the ADAS-Cog-14 total score, RBANS total score, MMSE total score, FAQ score, NPI total score, ADCS-ADL-MCI total score, UPSA-B and ADCS-CGIC score. The secondary efficacy variables obtained from these measures are detailed in Section 8.0.

5.3.4 Safety Variables

The following safety evaluations will be performed and safety information will be collected during the study: adverse event monitoring (including infusion and allergic reactions), vital signs, physical examination, neurological examination, ECG, laboratory tests, C-SSRS and MRI assessments.

5.3.5 Pharmacokinetic Variables

Values for the following pharmacokinetic parameters of ABBV-8E12 will be estimated using non-compartmental methods: maximum observed serum concentration (C_{max}), the time to C_{max} (peak time, T_{max}), the area under the concentration time curve (AUC) over the dosing interval after the first and the fourth doses; the observed serum concentration at the end of a dose interval (C_{trough}) after all doses.

A mixed-effect modeling approach will be used to estimate the population central value and the empirical Bayesian estimates of the individual values for ABBV-8E12 clearance (CL) and volume of distribution (V).

The concentration of ABBV-8E12 in CSF will be summarized after the fourth dose and after the final dose if administered at least 3 months after the previous LP for subjects in Cohort 1. LPs will be optional for subjects in Cohort 2, and the concentration of ABBV-8E12 in these CSF samples will be summarized, if available.

Additional parameters may be calculated if useful in the interpretation of the data.

5.3.6 Biomarker and Pharmacogenetic Research Variables

5.3.6.1 Biomarker Research Variables

CSF and Plasma Concentration Variables

CSF samples will be assayed for neurofilament light chain (NFL), free tau and total tau, and the ratio of free tau concentration to total tau concentration will also be statistically analyzed. The assessments on free tau and the ratio of free tau to total tau will be done to investigate the binding of ABBV-8E12 to CSF tau. Plasma samples will be assayed for tau and NFL to understand the relationship to disease progression and response to treatment. Plasma samples may also be analyzed for plasma Abeta 40 and Abeta 42 to study relationship with amyloid PET positivity.

CSF and blood samples may be analyzed for biochemical or macromolecular factors (e.g., amyloid beta) related to the pharmacodynamics and safety of ABBV-8E12. Additional CSF, plasma and/or serum evaluations may include analyzing biomarkers related to the pathway(s) targeted by the study drug or believed to be related to the disease or to drug response. Biomarker samples may also be used for non-genetic exploratory research to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures or develop assays. In addition, the information learned from analyzing these samples may be used to investigate factors impacting response to treatment, scientific questions related to various disease where ABBV-8E12 may be investigated, or in the development of new therapies. The results of biomarker testing may not be reported in the clinical study report.

Volumetric MRI

Baseline vMRI measurements and measurements on change from baseline in vMRI measurements for MRIs from Week 28 through Week 96 will be obtained. Measurements will be obtained for whole brain, hippocampus and lateral ventricles. Measurements may be obtained for additional regions.

Tau PET Imaging

The amount of tau deposits in a given region will be assessed by calculating a standardized uptake value ratio (SUVR) of each region. The SUVR is a ratio between the standardized uptake values (SUV) of a target brain region relative to that of cerebellar cortex, which is considered as the reference tissue devoid of tau. The SUV is calculated by normalizing the concentration of radioactivity in the region (KBq/mL) to the injected dose (BMq) and the subject's body weight (kg). Due to the exploratory nature of these PET imaging endpoints, analyses will be performed for multiple brain regions, which will include, but not necessarily be limited to, 4 composite meta-regions that correspond to anatomical definitions of Braak stages III, IV, V, and VI. Additional variables (e.g., proportion of voxels within a target region that have a SUVR greater than a pre-determined cutoff value) that reflect the extent or spread of tau pathology will be assessed.

Retinal Amyloid Imaging

Retinal optical images will be collected from each eye for a subset of subjects and subjected to image analysis. Retinal imaging will be conducted during screening or within a 6 month window of randomization date. The results of the retinal imaging test will be compared to amyloid PET imaging results, may be pooled with additional external data and reported in a separate addendum study report.

Digital Clock Drawing Test

Data from a dCDT as a measure of cognitive function will be obtained from a subset of subjects. In addition to assessing the performance of the treatments with respect to this instrument, the correlation of dCDT measures with other clinical rating scales and

biomarkers will be assessed. Results for dCDT will be reported in a separate addendum study report.

5.3.6.2 Pharmacogenetic Research Variables

APOE allele status will be determined for each subject and analyzed as a factor contributing to the subject's response to study treatment. The APOE genotype results may be analyzed as part of a multi-study assessment of APOE and response to ABBV-8E12 treatment. The results may also be used for the development of diagnostic tests related to ABBV-8E12, or other drugs in development for AD or related conditions. The APOE genotype results may not be included in the study summary.

The optional pharmacogenetic DNA and RNA samples may be analyzed for known and novel genetic (DNA), epigenetic (DNA), and transcription (RNA) factors contributing to AD or the subject's response to ABBV-8E12, in terms of pharmacokinetics, efficacy, tolerability and safety. Such genetic factors may include genes and genetic expression for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, or other genes believed to be related to AD or drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in AD or the response to ABBV-8E12 or drugs of this class. The samples may also be used for the development of diagnostic tests related to ABBV-8E12 or other drugs for AD or related disorders. The results of any pharmacogenetic analyses that are done may not be reported in the study summary.

5.3.7 Immunogenicity

Anti-drug antibody (ADA) levels will be determined for the assessment of immunogenicity.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol.

Subjects with the following adverse events will be considered for treatment discontinuation:

- Severe or life-threatening allergic reactions will require the immediate interruption of ABBV-8E12 treatment, permanent discontinuation from further treatment and initiation of appropriate medical therapy and follow-up.
- Life-threatening drug related adverse events of nervous system will require discontinuation from further treatment with ABBV-8E12, initiation of appropriate medical therapy and follow-up.

All moderate and severe symptomatic neurological abnormalities and treatment-emergent MRI findings will be reported to AbbVie TA MD and subjects will be considered for discontinuation from treatment and may be permitted to continue in the study only after a management plan is discussed with the AbbVie TA MD.

Subjects with unexpected worsening of cognitive impairment or dementia will be reported to AbbVie TA MD and considered for discontinuation from treatment and may be permitted to continue in the study only after a management plan is discussed with the AbbVie TA MD.

Subjects at risk of suicide as indicated by answering yes to question 4 or 5 on the C-SSRS and/or determined by the investigator to be at risk of suicide should be discontinued from participation in the study and referred for appropriate follow-up care.

In the event that a subject withdraws or is discontinued from the study, the primary reason for discontinuation and any other reason(s) for the discontinuation from the study will be recorded and a physical examination, neurological examination, body weight, vital signs measurement, ECG, laboratory analyses, C-SSRS and an assessment of adverse events will be performed as soon as possible after discontinuation from the study. Additional blood samples for drug measurement may be collected at the time of discontinuation from subjects who are discontinued due to adverse events; the clock time, time in relation to dose, and date the sample was taken will be recorded.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Subjects who miss multiple study drug doses due to the COVID-19 pandemic may continue participation with approval from the TA MD.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

A DMC will review unblinded safety data during the study. Depending on the outcome of these evaluations, the DMC may make a recommendation to discontinue the entire study or stop enrollment in a single dose group prior to enrollment of the planned sample size.

The entire study will be discontinued if it is determined by AbbVie in consultation with the DMC that the continued exposure of subjects to study drug represents a significant safety risk. Enrollment to a single dose group will be discontinued if it is determined by AbbVie in consultation with the DMC that the continued exposure of subjects to that dose of study drug represents a significant safety risk. Alternatively, a recommendation may be made to reduce the dose in a single dose group.

5.5 Treatments

5.5.1 Treatments Administered

ABBV-8E12 will be given by IV infusion. Subject weight will be obtained prior to study drug administration to determine the appropriate infusion rate as shown in the table below.

Subject's Weight in kg	Infusion Rate*
26.0 – 34.9 kg (inclusive)	2.1 mL/min or 126 mL/hr
35.0 – 44.9 kg (inclusive)	2.8 mL/min or 168 mL/hr
45.0 – 59.9 kg (inclusive)	3.6 mL/min or 216 mL/hr
60.0 – 89.9 kg (inclusive)	4.8 mL/min or 288 mL/hr
90.0 kg and over	7.2 mL/min or 432 mL/hr

* Continue infusion until bag is empty.

Study drug will be administered by IV infusion, preferably in the morning but should be around the same time at each visit as follows:

Study Drug	Formulation
Placebo (0.9% Sodium Chloride Injection/Solution for Infusion)	IV infusion every 4 weeks for 96 weeks (Total of 24 infusions)
ABBV-8E12 300 mg	
ABBV-8E12 1000 mg	
ABBV-8E12 2000 mg	

Doses may be modified after evaluation by the data monitoring committee of the safety, tolerability and available pharmacokinetic data.

The start and stop time of each study drug infusion will be recorded to the nearest minute. The start of study drug infusion occurs from ABBV-8E12 initiation up until the administration of the complete dose (including flush). The Pharmacy Manual may be referred to for detailed instructions.

Home Healthcare Service Due to the COVID-19 Pandemic

Subjects may be offered the option of home healthcare visits provided by a study nurse or third-party vendor based on the subject's suitability as assessed by the investigator and following the subject's written consent. This option can only be offered in countries and sites that comply with local regulatory and IEC/IRB requirements for home healthcare. Any prerequisite submissions or notifications to the site IEC/IRB and local competent health authority should be made and approved prior to the implementation of home infusions.

5.5.2 Identity of Investigational Product

Information about the ABBV-8E12 and placebo products to be used in this study is presented in Table 5.

Table 5. Identity of Investigational Product

Investigational Product	Mode of Administration	Formulation	Strength
ABBV-8E12	Infusion	Solution for infusion in a vial	300 mg/15 mL 1000 mg/ 10 mL
Placebo	Infusion	0.9% Sodium Chloride Injection/Solution for infusion, 250 mL	N/A

N/A = not applicable

0.9% Sodium Chloride Injection/Solution for Infusion will be administered to those subjects not receiving active ABBV-8E12 and as a vehicle for administration of ABBV-8E12. 0.9% Sodium Chloride Injection/Solution for Infusion will be supplied with commercially available material in either bags or bottles, locally sourced by the sites.

However, if mandated by local regulation, or in the case of exceptional circumstances when sites are unable to procure on their own, AbbVie may supply 0.9% Sodium Chloride Injection/Solution for Infusion if necessary.

5.5.2.1 Packaging and Labeling

ABBV-8E12 will be provided in a glass vial as solution for infusion. One vial will be packaged per carton. Each vial and carton will be labeled with the information necessary per country requirement. Labels must remain affixed to the vial and carton. All blank spaces on the label will be completed by the site staff prior to dispensing to the subjects.

The commercially sourced 0.9% Sodium Chloride Injection/Solution for Infusion will not be labeled as an Investigational Medicinal Product (IMP) prior to the handling by the unblinded pharmacist or qualified designee. Instead, after addition of ABBV-8E12 to the 0.9% Sodium Chloride Injection/Solution for Infusion to be administered in the active arm, it will be labeled with a blinded dispensing label by the unblinded pharmacist or qualified designee as required. 0.9% Sodium Chloride Injection/Solution for Infusion without addition of ABBV-8E12, to be administered in the placebo arm, will be labeled with a blinded dispensing label by the unblinded pharmacist or qualified designee as well. Labels must remain affixed to the material.

If an IMP label on the 0.9% Sodium Chloride Injection/Solution for Infusion is mandated by local agencies, labels may be applied on the overwrap and will be removed by unblinded pharmacist prior to administration.

5.5.2.2 Storage and Disposition of Study Drugs

ABBV-8E12 must be stored at 2° to 8°C/36° to 46°F, must be protected from light and **must not be frozen** at any time.

0.9% Sodium Chloride Injection/Solution for Infusion should be stored per the locally approved commercial label, Summary of Product Characteristics (SmPC) or clinical study label.

A storage temperature log is to be maintained to document proper storage conditions. The refrigerator temperature must be recorded on each business day. All temperature excursions lasting longer than 30 minutes must be reported to the Sponsor immediately using the AbbVie Temperature Excursion Management System (ATEMS). Study medication should be quarantined and not dispensed until AbbVie (ATEMS) deems the medication as acceptable.

Investigational products are for investigational use only, and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under conditions specified on the label until dispensed for subject use or returned to AbbVie or representative.

5.5.2.3 Preparation/Reconstitution of Dosage Form

The preparation of blinded doses will be performed by the unblinded site pharmacist or qualified designee. The prepared IP (placebo and ABBV-8E12) infusion bags should be covered by the blinding bags before dispensation. Written instructions for the preparation of ABBV-8E12 solutions for infusion will be provided as separate document from the protocol.

5.5.3 Method of Assigning Subjects to Treatment Groups

Prior to enrolling subjects, each site will be provided with a user manual as well as a telephone number and user instructions for the Interactive Voice-Response/Interactive Web-Based (IVR/IWB) system. Each user will receive a code number that will be used in combination with a personal identification number (PIN) to access the system by telephone and a unique username and confidential password to access the system through the internet.

As subjects are screened for the study, the IVR/IWB system will assign each subject a unique 5 digit subject number. The first digit will be 2, the second and third digits will be the site number (01, 02, etc.) and the fourth and fifth digits will be assigned in ascending numerical order at each site.

At the Day 1 visit, each subject will be randomly assigned to a double-blind treatment group through the IVR/IWB system after the site verifies that the subject is eligible to participate in the study. The first dose of study drug will be administered after randomization at the same visit. The randomization schedule will be computer-generated and implemented in IVR/IWB system before the start of the study by the AbbVie Statistical Department.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the dose for this study is discussed in Section 5.6.4. Each subject will be randomized to one of four cohorts as described in Section 5.5.1. ABBV-8E12 will be administered every 4 weeks via IV infusion at the research site in the morning.

5.5.5 Blinding

Placebo solution will be essentially identical in volume to the ABBV-8E12 solution. The Investigator, study site personnel (except the unblinded pharmacist) and the subject will remain blinded to the treatment throughout the course of the study. The study sponsor will remain blinded; however, a pharmacokineticist will be provided individual pharmacokinetic data from Cohort 1 after 48 weeks of treatment. Subject identification numbers will be changed for the pharmacokinetic analysis to maintain the sponsor blind.

ABBV-8E12 and 0.9% Sodium Chloride Injection/Solution for Infusion (if applicable) will be delivered to the unblinded pharmacist or qualified designee in an open-label format. The unblinded pharmacist or qualified designee will prepare the dosing of ABBV-8E12 (in a blinded manner) following the available preparation instructions as appropriate based on the subject's assigned treatment group. For blinding purposes, identical commercial 0.9% Sodium Chloride Injection/Solution for Infusion bag or bottle will be used in the placebo and ABBV-8E12 arms at each site. The unblinded pharmacist or qualified designee will place a blinding bag over the infusion bag or bottle before dispensation following the written instructions provided as a separate document from the protocol.

For investigational product monitoring, there will be an unblinded clinical research associate (CRA) for verification of unblinded documentation. The unblinding procedure for the unblinded pharmacist/designee and the unblinded CRA will be defined in a separate study-specific document.

The IVR system will be programmed with blind-breaker instructions. The study blind for a subject may be broken, if, in the opinion of the investigator, it is in the subject's best interest to know the study drug assignment.

AbbVie must be notified before breaking the blind, unless identification of the study drug is required for a medical emergency, i.e., situation in which the knowledge or the specific blinded treatment will affect the immediate management of the subject's conditions (e.g., antidote is available). AbbVie must then be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be recorded in the source documentation and on the eCRF, as applicable.

Unblinding of Data for the Data Monitoring Committee (DMC)

In order to ensure that the DMC will be fully informed, the DMC will be unblinded in its assessment of safety and efficacy data. The DMC will have full access to all data as needed for safety assessment and all data included in interim efficacy analyses. SAS data sets blinded with respect to treatment assignment will be sent to an external statistical center by AbbVie. The study randomization schedules will be sent to an external statistical center under separate cover. The external statistician will generate closed reports that will include unblinded information. While the studies are ongoing, only the DMC and the external statistical center will have access to the closed reports. An AbbVie Internal Executive Review Committee (IERC) may request access to closed reports if the discontinuation of the study, major modifications to the study design, or Phase 3 initiation is recommended by the DMC as outlined in the DMC charter. All other AbbVie personnel will remain blinded to the treatment assignment. The AbbVie Primary Contact for the DMC and the AbbVie IERC members will not be involved in any aspects of the trial or its management.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol. Subjects will be supervised at the time of study drug administration.

5.5.7 Drug Accountability

The investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt or similar document. A current (running) and accurate inventory of study drug will be kept by the investigator and will include shipping invoices and the date on which study drug is administered to the subject. An overall accountability of the study drug will be performed and verified by an unblinded AbbVie monitor throughout the study and at the study site closeout visit. Written instructions for IP accountability requirements will be provided in a separate document from the protocol. Upon completion or termination of the study, all original containers (containing used study drug or containing unused study drug) will be destroyed at site, according to instructions from AbbVie and according to local regulations. For those sites where local destruction of unused study drug is not feasible, sites will return the original containers of unused study drug to AbbVie according to instructions from AbbVie and according to local regulations. Labels must remain attached to the containers.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This study is designed to assess the safety and efficacy of ABBV-8E12 in subjects with Early AD for up to 96 weeks. The inclusion of placebo administration and the double blind feature of the study will provide unbiased assessments. There is no anticipated risk to subjects in the placebo group because participating in the study will not prevent subjects from taking approved medications for the treatment of AD. The parallel-group

design with placebo control will provide a well-controlled unbiased assessment of the effect of ABBV-8E12 on clinical outcome measures and potential neuroimaging and CSF biomarkers that are associated with AD disease activity. Toxicity management in the parallel group design is described in Section 6.1.6.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical and clinical procedures will be utilized in this study. On-treatment safety evaluations (neurological examinations, adverse event monitoring, ECGs) are scheduled at more frequent intervals for the first 48 subjects enrolled (Cohort 1) to promptly detect potential emerging safety signals.

Overall, choice of instruments to measure key domains of function, cognition, behavior and caregiver distress has been guided by published data on their use in MCI and AD patients. These instruments have shown to be sensitive to the change in Early AD and MCI patients over a period of time.

5.6.3 Suitability of Subject Population

The target population is aimed to be still clinically very mildly affected but demonstrating observable disease burden that can be captured and monitored throughout the trial duration. Confirmation of amyloid load on PET imaging will increase the diagnostic accuracy in the early stages of AD and together with onset of clinical symptoms will increase probability of cognitive decline due to initiation of tau spreading. Several neuropathological studies suggested that at the onset of clinical symptoms tau spreading and aggregation has been already initiated but is still an ongoing and potentially interruptible process.

5.6.4 Selection of Doses in the Study

The doses chosen for the study were determined based on the safety and tolerability of the SAD study in patients with PSP that included single doses of ABBV-8E12 ranging from 2.5 to 50 mg/kg. All doses have been administered without notable treatment-related adverse effects or any evidence of safety findings. In the 15 mg/kg dose group,

one subject reported an SAE of a subdural hematoma resulting from a fall that was assessed as possibly related to study drug by the investigator due to a temporal relationship with dosing. The sponsor judged the SAE to be unlikely related to study drug, and likely related to the underlying PSP disease. In the 25 mg/kg dose group, one subject was hospitalized due to a severe increase in agitation, anxiety, and perseverative behavior. The subject had a prior history of anxiety and agitation during stressful events, such as medical procedures. The investigator assessed the event as possibly drug related. In the 50 mg/kg dose group, one subject was hospitalized due to hypertensive cerebrovascular disease, which was a pre-existing condition for this subject. The investigator assessed this event as not study drug related.

The highest dose, 2000 mg administered IV, is approximately 2-fold lower than the highest dose administered in the SAD study in patients with PSP (50 mg/kg based on a body weight of 80 kg). This dose is also approximately equal to the maximal dose (25 mg/kg) administered every 4 weeks for 7 months to the 1 subject with PSP in the Expanded Access protocol.

The subject with PSP in the Expanded Access protocol began treatment at 1 mg/kg and received a total of 20 monthly ABBV-8E12 infusions. The dosing regimen escalated in the following manner: 1 mg/kg for Month 1, 2.5 mg/kg for Month 2, 7.5 mg/kg for Month 3, 15 mg/kg for Months 4 – 11, 20 mg/kg for Months 12 – 13, and 25 mg/kg for Months 14 – 20. Preliminary pharmacokinetic analysis estimated that half-life was approximately 13 to 21 days, and the accumulation ratio was around 1.7. In the ongoing SAD study in patients with PSP, available pharmacokinetic data from the 2.5 mg/kg to 25 mg/kg dose groups indicate dose proportional increases in exposure. The plasma half-life ranged from 17 to 24 days. CSF concentrations measured 14 days after ABBV-8E12 administration from the 2.5 mg/kg and 7.5 mg/kg dose groups increased with dose and the estimated CSF:plasma ratio was approximately 0.38%.

In the 4-week preclinical mouse toxicology study, the highest dose tested was 250 mg/kg and the corresponding C_{max} and $AUC_{0\text{-}168h}$ were 3050 µg/mL and 298,000 hr•µg/mL (on Day 22) after 4 doses administered weekly. Assuming the pharmacokinetics of

ABBV-8E12 is linear, the steady-state pharmacokinetic profiles were simulated at 300, 1000, and 2000 mg following monthly administration of ABBV-8E12 based on the pharmacokinetic data from the 25 mg/kg dose group up to Day 56 in the ongoing SAD study in patients with PSP. The predicted safety margin at the dose levels of 300, 1000, and 2000 mg is approximately 18-, 6- and 3-fold, respectively, for both C_{max} and AUC. In addition, the predicted AUC for a 1000 mg dose administered over 4 months and for a 2000 mg dose administered over 2 months is no greater than the AUC following a single 50 mg/kg dose predicted from the ongoing SAD study in patients with PSP.

Based on pharmacokinetics from the SAD study, it is possible to estimate the percent of tau in CSF that is bound by ABBV-8E12. For this calculation, it is assumed that the CSF concentration for humanized antibodies is 0.2% of the plasma concentration and that the concentration of tau in CSF is 400 pg/mL. Based on the K_D of ABBV-8E12 determined in vitro, 300 mg will lead to approximately 30% – 55% of tau in CSF being bound by the antibody at predicted C_{trough} and C_{max} values. Similar modeling was performed with 1000 and 2000 mg ABBV-8E12 and estimated that the average tau binding over the 28 day period ranges from approximately 60% – 80% and 75% – 90%, respectively.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.6. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record

any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specific criteria for potentially clinically significant (PCS) laboratory values defined in Appendix D and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event within 24 hours of the site being made aware of the serious adverse event:

Death of Subject	An event that results in the death of a subject.
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.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. 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 subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. 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.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.2 Adverse Event Severity

The investigator will use the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.1.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.

No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

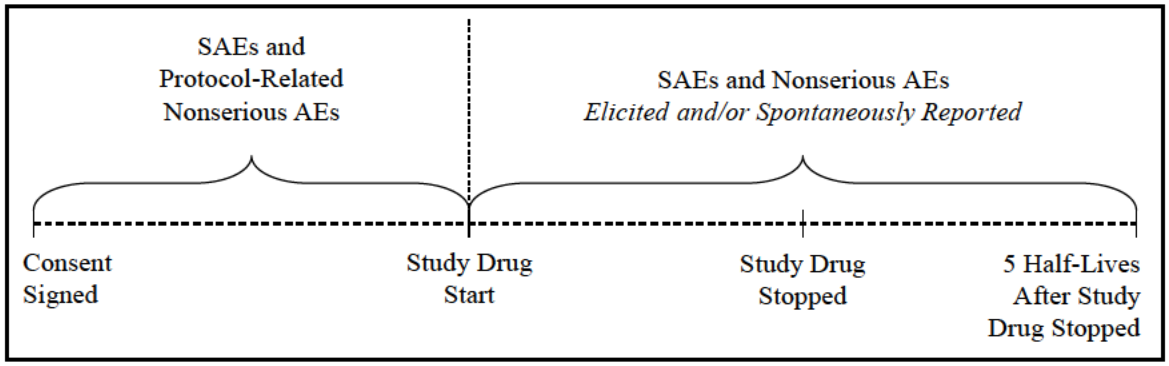
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 20 weeks following discontinuation of study drug administration have elapsed (approximately 5 half-lives) will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) RAVE® system. Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE is not operable can be Emailed (this is the preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

For safety concerns, contact the Neuroscience Safety Team at:

Neuroscience Safety Team
Dept. R48S, Bldg. AP32
1 North Waukegan Road
North Chicago, IL 60064

Office: +1 (847) 938-4191
Email: SafetyManagement_Neuroscience@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director:

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Telephone Contact Information:
Office:
Mobile:
Email: [redacted]

In emergency situations involving study subjects when the primary AbbVie TA MD is not available by phone, please contact the 24-hour **AbbVie Medical Escalation Hotline** where your call will be re-directed to a designated AbbVie TA MD.

Phone: +1 (973) 784-6402

AbbVie will be responsible for Suspected Unexpected Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a Development Safety Update Report (DSUR) reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

Serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., International Council on Harmonization [ICH]

Expedited Reports or any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

The investigator should capture COVID-19 infections as AEs. If the event meets the criteria for a serious adverse event (SAE), reporting directions as described in Section 6.1 should be followed.

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or AEs (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as AEs. If the event meets the criteria for a serious adverse event (SAE), then the SAE reporting directions per the protocol and above should be followed. The following COVID-19 related supplemental eCRFs should be completed (for both serious and non-serious events):

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

6.1.6 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the investigator.

A drug-related toxicity is an adverse event or laboratory value outside of the reference range that is judged by the investigator or AbbVie as a "reasonable possibility" of being

related to the study drug (Section 6.1.3). A toxicity is deemed "clinically significant" based on the medical judgment of the investigator. The following guidelines should be used for study drug-related toxicity management.

Potential Drug-Related Toxicities

No potential drug related toxicities were identified from preclinical or clinical studies conducted to date. Examples of safety concerns that could be hypothetically associated with ABBV-8E12 and safety concerns associated with monoclonal antibodies, in general, are summarized below.

On-Target Toxicities

The brain appears to be the only organ to express tau at significant levels. Tau is an intracellular protein mainly expressed in neurons, although lower levels can be found in astrocytes and oligodendrocytes. ABBV-8E12 is directed against extracellular tau and no function of extracellular tau has been reported. No cellular uptake of mouse version of ABBV-8E12 antibody bound to tau aggregates was detected in preclinical studies.[7] The likelihood of adverse on-target side effects of an anti tau immunotherapy is therefore anticipated to be low.

Non-Specific Off-Target Toxicities

Potential toxicities resulting from the non-human origin of ABBV-8E12 include allergic reactions or infusion reactions, including anaphylaxis or anaphylactoid reactions, flu-like symptoms, including fever, fatigue or loss of appetite, rash. ABBV-8E12 is lacking the Fc effector function activity and therefore Fc-mediated antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity is not expected. In addition, ABBV-8E12 exhibited a favorable in vitro immunosafety profile. No infusion reactions have occurred in the single dose PSP clinical study or the Expanded Access protocol.

6.1.6.1 Allergic Reactions Management

Subjects will be closely monitored for treatment-related adverse events, including allergic reactions, during the infusion. For the 4 initial ABBV-8E12 infusions, subjects should be monitored on site until 2-hours post-infusion. For subsequent infusions, subjects should be monitored on site until at least 30 minutes after the end of infusion. Longer observation periods and more frequent vital sign checks may be required in subjects who experience infusion reactions.

Severe or life-threatening allergic reactions require the immediate interruption of ABBV-8E12 treatment and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.

Moderate allergic reactions will also require the interruption of ABBV-8E12 treatment. Once symptoms have resolved, the next scheduled infusion is allowed with a 50% reduction of the infusion rate.

6.1.6.2 Management of Adverse Events of the Nervous System

Subjects will be closely monitored for adverse events suggesting neurotoxicity. Drug related adverse event is an adverse that is judged by the investigator or AbbVie as a "reasonable possibility" of being related to the study drug.

Life-threatening drug related adverse events of the nervous system will require discontinuation from further treatment with ABBV-8E12 and prompt notification of AbbVie TA MD. Appropriate medical therapy will be initiated and subjects will be followed up until the resolution.

Subjects with moderate and severe drug related adverse events of the nervous system, symptomatic neurological abnormalities and treatment-emergent MRI findings and

subjects with unexpected worsening of cognitive impairment or dementia will be considered for discontinuation and may be permitted to continue in the study only after a management plan is discussed with the AbbVie TA MD.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product or packaging issues.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation is identified after a subject has been enrolled, the principal investigator is responsible for notifying IEC/IRB regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s):

Primary Contact:

[redacted]
AbbVie Deutschland GmbH & Co. KG
Knollstr. 50
67061 Ludwigshafen
Germany

Office: [redacted]
Email:

Alternate Contact:

[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Email:

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

General Considerations

Unless otherwise specified, when a total score of an efficacy or safety scale is calculated from a set of individual items, the total score will be considered missing if any of the

individual items are missing. Study sites that do not enroll at least two subjects to each treatment group who have non-missing observations of CDR-SB score after randomization will be combined using an algorithm that will be described in the Statistical Analysis Plan (SAP).

8.1.1 Analysis Data Sets

Intent-to-Treat Data Set

The intent-to-treat (ITT) data set will include all randomized subjects who take at least one dose of study drug. The data from the ITT data set will be analyzed by the treatment group assigned at the time of randomization, even if the subject does not receive the correct treatment, is not compliant with the protocol or does not follow through with the study until completion. All efficacy analyses will be conducted on the ITT data set unless otherwise specified.

Safety Data Set

The safety data set will include all randomized subjects who take at least one dose of study drug. For this analysis data set, actual treatment received will be used instead of treatment assignment at the time of randomization. All safety analyses will be conducted on the safety data set unless otherwise specified.

8.1.2 Disposition, Demographics, and Other Baseline Characteristics

Subject Disposition

The number and percentage of subjects contributed by each country and site will be summarized for each treatment group and for all treatment groups combined for the safety data set.

The number and percentage of subjects who prematurely discontinue study drug will be summarized by treatment group and overall for the safety data set for the primary reason as well as for all reasons collected. In the summary, the number and percentage of

subjects who discontinue due to any reason as well as due to each specific primary reason will be presented. Subjects may report multiple reasons for prematurely discontinuing study drug, but the primary reason for discontinuation will be indicated in the eCRF and used to infer treatment group difference in subject's disposition. Two-sided Fisher's exact tests will be used to perform pairwise comparisons between each ABBV-8E12 dose group and placebo with respect to the proportion of who discontinue for any reason and for each reason reported as primary.

Demographic and Other Baseline Characteristics

Demographics will be summarized for the ITT data set and the safety dataset unless otherwise specified. Treatment group differences will be evaluated using overall tests. No pairwise comparisons between treatment groups will be performed for demographic and baseline characteristics variables unless the overall *P* value is ≤ 0.050.

For continuous demographic variables including age, weight, height, body mass index (BMI), descriptive statistics (number of subject with non-missing data, mean, standard deviation, median, and minimum and maximum) will be provided for each treatment group and for all treatment groups combined. The overall treatment differences will be tested using one-way analysis of variance (ANOVA).

For categorical demographic variables including gender and race, number and percentage of subjects in each category will be provided for each treatment group and for all treatment groups combined. Fisher's exact test will be carried out to assess the overall comparability of treatment groups based on two-sided tests.

Efficacy and clinical measures taken at baseline (CDR-SB score, scores for the ADAS-Cog-14, MMSE, FAQ, UPSA-Brief, NPI, RBANS, ADCS-MCI-ADL-24 and ADCS-CGIC-MCI) will be summarized for the ITT data set only. One-way ANOVA will be used to assess the overall comparability of treatment groups for all measurements.

Medical History

Medical history data, including subject's history of Early AD or MCI, will be summarized for the safety data sets using body systems and conditions/diagnoses as captured on the eCRF.

Previous and Concomitant Medications

Prior and concomitant medications will be coded by the most recent World Health Organization (WHO) Drug dictionary, and will be summarized by treatment group for the safety data set. No statistical testing will be performed. A subject who reports two or more uses of medication that belong to the same category defined by WHO Drug will be counted only once for that WHO category.

8.1.3 Efficacy Analyses

All efficacy analyses will be conducted on the ITT data set unless otherwise specified. Data collected more than 45 days after the last dose of the study drug will not be included in efficacy analyses. Unless otherwise specified, for all efficacy analyses, "baseline" refers to the last non-missing observation prior to the first dose of study drug and "final" refers to the last non-missing observation after the first dose of study drug and no more than 45 days after the last dose of study drug. Pairwise comparisons between each ABBV-8E12 dose group and the placebo group will be performed using two-sided tests. A group-sequential graphical approach[33,34] will be applied for multiplicity control for multiple comparisons due to multiple endpoints, multiple ABBV-8E12 doses, and multiple interim analyses and final analysis. The overall family-wise error rate will be controlled within 5%. The detailed hypotheses testing procedure and multiplicity control method for the interim analyses and final analysis will be pre-specified in the SAP and the DMC Charter, which will be finalized and signed off before the first efficacy interim analysis of this trial.

8.1.3.1 Primary Efficacy Analysis

The primary efficacy variable will be the change from baseline up to the Week 96 on the CDR-SB score. The primary efficacy analysis is to compare each ABBV-8E12 dose group with placebo in using a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each post-baseline observation using all observed data. The model will include fixed, categorical effects for treatment, site, visit, treatment-by-visit interaction, and baseline-by-visit interaction with continuous fixed covariates for baseline score. The primary comparison will be the contrast between each ABBV-8E12 dose group and placebo at the Week 96 Visit using two-sided tests. The treatment group difference at earlier visits will be assessed as secondary. An unstructured (co)variance structure will be used to model the within-patient errors. Satterthwaite's approximation will be used to estimate denominator degrees of freedom and the Type III sum-of-squares for the least squares (LS) means will be used to estimate treatment group differences.

8.1.3.2 Secondary Efficacy Analysis

Secondary Efficacy Analysis of the Primary Efficacy Variable

The change from baseline to each post-baseline observation on the CDR-SB scores will be summarized. The change from baseline to final observation up to Week 96 on the CDR-SB score will be analyzed by an analysis of covariance (ANCOVA) model with treatment and study site as the main effects and the baseline CDR-SB score as covariate.

Analyses for Secondary Efficacy Variables

The other secondary efficacy variables include ADAS-Cog-14 total score, scores of MMSE, NPI and ADCS-MCI-ADL-24 and scores of FAQ, UPSA-Brief, RBANS and ADCS-CGIC-MCI.

The change from baseline score on each secondary efficacy variable (with the exception of ADCS-CGIC-MCI) will be summarized and analyzed using the similar MMRM model described for the primary efficacy analysis. The change from baseline to final observation

up to Week 96 for each secondary efficacy variable (with the exception of ADCS-CGIC-MCI) will also be analyzed using an ANCOVA model with treatment and study site as the main effects and the baseline value of analyzed variable as a covariate.

The ADCS-CGIC-MCI score at each visit up to Week 96 will be summarized and analyzed using an MMRM model with fixed, categorical effects for treatment, site, visit and treatment-by-visit interaction. The final ADCS-CGIC-MCI score up to Week 96 will be analyzed using an ANCOVA model with treatment and study site as the main effects.

The analyses will be performed in the ITT data set.

8.1.4 Subgroup Analysis of CDR-SB Score

To examine whether gender, age group, study site, country/geographic region or other baseline variables have an impact on response to treatment, subgroup analyses on CDR-SB score will be conducted on change from baseline to last observations up to Week 96. Subgroup analyses will be performed using an ANCOVA model with the terms of treatment, site, subgroup variable, the treatment-by-subgroup variable interaction, and baseline score as a covariate. The subgroup analysis for country/region will be performed using the same model but with the study site nested within geographic region. The hypothesis that consistent response to treatment across strata of a subgroup variable will be tested at the significance level of 0.100 by examining the P value of the treatment-by-subgroup interaction term in the ANCOVA model specified above. The statistical comparison of each ABBV-8E12 dose group with placebo within each stratum will be performed when the statistical significance of the treatment-by-subgroup interaction term is achieved at 0.100 level. The subgroup analysis will be conducted in the ITT data set.

8.1.5 Biomarker Research Analyses

CSF Concentration Variables

An ANCOVA will be performed on CSF concentrations for total tau, free tau, the ratio of free tau concentration to total tau concentration, and NFL for each scheduled time of evaluation during treatment (fourth dose interval and Week 96). For the analysis for the

fourth dose interval, an analysis will be performed for the data of Cohort 1 alone and also for all available data. The observations will be classified by treatment. The baseline value (last value before the first dose of study drug) will be the covariate except for the analysis on the ratio of the free tau and total tau concentrations, in which case the covariate will be the baseline total tau concentration measurement. If the probability distribution for a variable appears to have considerable non-symmetry (skewness coefficient > 0.75 in magnitude), a transformation will be sought so that the transformed variable has an approximately normal distribution. Within the framework of the ANCOVA the means of the four treatments (with adjustment for baseline) will be estimated. For each ABBV-8E12 dose level, the results of the test of the hypothesis of no difference between the dose and placebo will be reported. Also, with the motivation to have a test with good power if the dose response curve is a monotonic function of dose, a test will be performed on a contrast in the four treatment means. With μ_0, μ_1, μ_2 and μ_3 denoting the means for placebo, the 300 mg treatment, the 1000 mg treatment and 2000 mg treatment, respectively, the hypothesis that $-3\mu_0 - \mu_1 + \mu_2 + 3\mu_3 = 0$ will be tested at significance level 0.05 against the two-sided alternative hypothesis. The tests on the effects of the 1000 mg dose and the 300 mg dose will not be formally considered unless the statistic on the effect of the 2000 mg dose or the statistic on the contrast in the four means is significant at level 0.050.

Other CSF concentration variables of interest will be analyzed using methodology like that described for the analysis of total tau concentration.

Serum/Plasma Concentration Variables

Descriptive statistics will be provided for plasma concentrations of total tau and NFL. For each of these variables, an MMRM analysis will be performed on the data from the scheduled times of measurement. The model will include the baseline value as a covariate, have classification of subjects by treatment, an effect for time (classification) and will include an effect for the interaction of treatment and time of measurement. The initial model will also allow the regression coefficient for the baseline value to vary with time (an effect for interaction of time and the baseline value), but this feature will be

removed from the model if the statistic on this interaction is not significant at level 0.100. Within the framework of this model, the mean across the scheduled times of measurement and the mean for each individual time will be estimated for each treatment. Also, tests on differences of effect among the dose levels (with placebo considered a dose level) will be performed within the framework of the model. The primary tests will be on trend with dose (with placebo considered a dose level) and on the difference between the highest dose and placebo.

For total tau and NFL, the relationship to disease progression and response to treatment will be explored with disease state represented by CDR-SB score and perhaps by other variables of interest. The exploration on the relationship with disease progression will include an analysis of data from only the subjects treated with placebo.

Descriptive statistics and some or all of the analyses described here may be provided for other variables.

vMRI Variables

Descriptive statistics will be provided for the baseline value, for each scheduled time after that and for the changes from baseline. An analysis will be performed like that described for plasma NFL concentration, but with estimated total intracranial volume (eTIV) as a covariate in addition to the baseline value. The regression coefficient for eTIV will not vary with time, as may be allowed for the vMRI baseline value. An appropriate structure for the covariance matrix will be selected.

For each of whole brain, hippocampus and lateral ventricles, the relationship with the primary efficacy variable CDR-SB score, and possibly other efficacy variables, will be explored. The exploration will include an analysis of data from only the subjects treated with placebo. This may also be done for other regions.

Tau PET Scan Variables

For each region of the brain for which SUVR values are obtained, a joint analysis will be performed for the two scheduled times of evaluation during treatment (Week 44 and Week 96). The analysis will be like that described for plasma NFL concentration. For SUVR of selected regions, the relationship with the primary efficacy variable CDR-SB score will be explored. The exploration will include an analysis of data from only the subjects treated with placebo. This may be done also for other tau PET variables.

Consideration of Missing Values

The possibility of bias associated with missing data of subjects who prematurely discontinue treatment for reasons possibly related to study drug will be addressed.

8.1.6 Safety Analyses

All safety analysis will be performed on the safety data set unless otherwise specified. Comparisons between each ABBV-8E12 dose group and placebo will be performed with two-sided test at the significance level of 0.05, if applicable. Pairwise comparisons for each ABBV-8E12 dose group versus placebo will be evaluated.

All safety assessments that are taken no more than 20 weeks after the last dose of study drug will be included in the safety evaluation for subjects who complete the double-blind Treatment Period or PD and do not roll over to the planned extension study. If subjects enroll in the planned extension study, their safety information collected before the first dose of the planned extension study will be included in the safety evaluation for the double-blinded period.

Study Drug Exposure and Compliance

The number of doses on study drug will be summarized by treatment group and all treatment groups combined. The number and percentage of subjects with at least 90% compliance with study drug (i.e., complete 90% of scheduled doses) will be summarized by treatment group and all treatment groups combined.

Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any adverse event that begins or worsens in severity on or after the first study drug dose date and no more than 20 weeks after the last study drug dose date.

Unless otherwise specified, the treatment group differences in continuous safety variables (e.g., change from baseline to final observation on laboratory tests) will be assessed using an ANOVA model with the term of treatment, and the treatment group differences in binary safety variables will be evaluated using a Fisher's exact test.

8.1.6.1 Analysis of Adverse Events

Adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects who report TEAEs will be tabulated by MedDRA system organ class (SOC) and preferred term (PT) for each treatment group, overall ABBV-8E12 and all treatment groups combined. Treatment group differences between each ABBV-8E12 dose group and placebo will be analyzed using Fisher's exact test.

The number and percent of subjects experiencing treatment-emergent SAEs (including deaths) and adverse events leading to premature discontinuation of study drug will be tabulated by MedDRA SOC and PT for each treatment group, overall ABBV-8E12 dose groups, and all treatment groups combined. Treatment group differences between each ABBV-8E12 dose group and placebo will be analyzed using Fisher's exact test.

8.1.6.2 Analysis of Laboratory Tests

Change from baseline to each double-blind visit value and to the minimum, maximum and final double-blind value will be presented for each continuous hematology, chemistry and urinalysis parameter. Treatment differences between each ABBV-8E12 dose group and placebo in change from baseline to minimum, maximum and final clinical laboratory evaluation will be analyzed using one-way ANOVA with treatment as the main effect.

For each treatment group, shift tables will be generated showing the number and percentage of subjects with low, normal, high and missing values at baseline and final observation based on the reference ranges provided by each laboratory.

The number and percentage of subjects in each treatment group who have values meeting predefined criteria for potentially clinically significant values (definitions will be provided in the SAP) at any time after the first dose of study drug and no more than 20 weeks after the last dose of study drug or before the first dose in the planned extension study will be summarized separately for hematology and chemistry variables.

8.1.6.3 Analysis of Vital Signs and Weight

Vital sign variables include pulse, systolic blood pressure, diastolic blood pressure, body temperature, weight, and body mass index (BMI).

Change from baseline to each double-blind visit value and to the minimum, maximum and final double-blind value will be presented for each vital sign and weight variable and analyzed using one-way ANOVA with treatment as the main effect.

The number and percentage of subjects in each treatment group who have values meeting predefined criteria for potentially clinically significant values (definitions will be provided in the SAP) at any time after the first dose of study drug and no more than 20 weeks after the last dose of study drug or before the first dose in the planned extension study will be summarized.

8.1.6.4 Analysis of ECG Variables

ECG variables include heart rate, PR, QRS, QT and QTcF intervals. Change from baseline to final double-blind value will be presented for each ECG parameters and analyzed by a one-way ANOVA with treatment as the main effect.

The number and percentage of subjects in each treatment group who have values meeting predefined criteria for potentially clinically significant values (defined in the SAP and DMC charter) at any time after the first dose of study drug will be summarized.

8.1.6.5 Analysis of C-SSRS

Number and percentage of subjects in the following categories will be summarized for each treatment group by visit and for the entire study:

- Answered 'Yes' to each C-SSRS item
- Had suicidal ideation (defined as answering 'Yes' to one or more suicidal ideation items)
- Had suicidal ideation only (defined as answering 'Yes' to one or more suicidal ideation items and answering 'No' to all suicidal behavior items)
- Had suicidal behavior (defined as answering 'Yes' to one or more suicidal behavior items)
- Had suicidal ideation or behavior (defined as answering 'Yes' to one or more suicidal ideation or behavior items

8.1.7 Pharmacokinetics

8.1.7.1 Tabulations and Summary Statistics

For the data of Cohort 1, serum concentrations of ABBV-8E12 and pharmacokinetic parameter values will be tabulated for each subject and each dose level, and summary statistics will be computed for each sampling time and each parameter by dose level. Also, for the serum concentration data of all subjects (Cohort 1 and Cohort 2), summary statistics will be provided for each scheduled time of sampling with breakdown by dose level.

CSF concentration data after the fourth dose and the final dose will be tabulated and summarized by dose level for Cohort 1. A summary of data for all subjects (Cohort 1 and Cohort 2) will also be included noting that CSF sample collection was optional for subjects in Cohort 2 per Amendment 1 of the protocol.

8.1.7.2 Model and Tests

Unless stated otherwise, hypothesis tests will be performed at significance level 0.05.

Change in Concentration with Repeated Dosing

The concentration data at the end the first four dose intervals in Cohort 1 will be summarized to investigate change in serum concentration with repeated dosing. That is, the pre-dose ABBV-8E12 serum concentration data for the second through the fourth doses and the concentration at the end of the fourth dose interval will be summarized. A MMRM analysis will be performed. The logarithmic transformation will be used unless the data show that the logarithm has substantial non-symmetry (e.g., magnitude of skewness coefficient > 1.0) while untransformed concentration or another transformation has an approximately symmetric distribution. The model will have effects for dose level, week and the interaction of dose level and week. The concentration central value (back transformation of the LS mean of the transformed data) versus time curves for the three dose levels will be plotted on the same graph. As a part of the investigation, hypothesis tests will be performed on the three changes in the mean (of the transformation) from the first three time points to the last time point. Within the framework of the repeated measures analysis model, a test will be performed on the hypothesis of no interaction between the highest and lowest dose levels with time point. If this hypothesis is not rejected at level 0.05, the tests on the three mean changes will be performed on the time point main effects. Otherwise, the tests will be performed for each dose level separately within the framework of the model.

A corresponding exploratory analysis over a longer period of time may also be performed on the pre-dose data of Cohorts 1 and Cohort 2 combined, beginning with Week 4 (Dose 2) and ending with Week 72 (Dose 19), but restricted to the planned times of sampling of Cohort 2. The emphasis will be estimation of any longer term trends that may be suggested by the data.

Dose Proportionality

An analysis will be performed on dose normalized C_{max}, dose-normalized AUC and dose-normalized C_{trough} of the first and fourth dose intervals. The logarithmic transformation will be employed for C_{max} and AUC and will likely be used for C_{trough}. An ANCOVA will

be performed for each exposure variable for each of the first and fourth dose intervals, with the greater emphasis on the fourth dose interval. Subjects will be classified by dose level, and body weight will be a covariate. Other variables such as age and sex that might explain some of the variability among subjects will be considered. A necessary condition for such a variable to be included in the final model is that the regression coefficient be significant at level 0.10. The dependence among explanatory variable candidates will also be considered when selecting the final model. Within the framework of the final model, the hypothesis of no difference between the means of the highest and lowest doses will be tested.

Accumulation Ratio

An analysis will be performed to estimate the accumulation ratio for C_{max} and AUC from the first dose interval to the fourth dose interval. For each of C_{max} and AUC, a one-way ANOVA with classification by dose level will be performed on the change in the logarithm from first dose interval to the fourth dose interval. If the test statistic on the dose level effect is significant at level 0.10, the estimate of the accumulation ratio will be provided for each dose level within the framework of the analysis of variance by exponentiation of the mean change in the logarithm (the geometric mean). Along with the point estimate, a 95% confidence interval will be provided by exponentiation of 95% confidence limits for the mean change in the logarithm. If the test statistic on dose level effect is not significant at level 0.10, a single estimate of the accumulation ratio will be given by exponentiation of the average of the mean changes for the three dose levels, with a 95% confidence interval also provided.

8.1.7.3 Missing Values and Model Violations

The possibility of bias from missing data of subjects who prematurely discontinue for reasons possibly related to study drug will be addressed.

It is anticipated that in a majority of cases of a missing individual concentration value in the first or fourth dose interval, estimates for pharmacokinetic variables (C_{max}, AUC, etc.) will be determined without replacing missing individual concentration values, but simply

using the available data. However, if a missing individual concentration value results in a value of a pharmacokinetic parameter that may be too low or too high to a meaningful degree, the value of the pharmacokinetic parameter will tentatively be considered missing. In this case, a value for the missing individual concentration may be imputed so that an appropriate value of the pharmacokinetic parameter can be included in the analysis. The imputed value will be obtained using appropriate methodology that takes into account the individual characteristics of the subject. Also, if the concentration value at the beginning or end of the dose interval is missing, a value must be imputed in order for a value of AUC to be determined.

Transformation of variables in order to avoid a meaningful degree of non-normality in the probability distributions is discussed in Section 8.1.5. If an adequate transformation is not found for a variable, then a non-parametric analysis may be performed.

8.1.7.4 Population Pharmacokinetic and Exposure-Response Analysis

Data from this study may be combined with data from other studies for the population pharmacokinetic and exposure-response analyses. Population pharmacokinetic and exposure-response analyses of only data from this study may not be conducted. The following general methodology will be used for the population pharmacokinetic and exposure-response analyses.

Population pharmacokinetic analyses will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the nonlinear mixed effect modeling (NONMEM) software (version VII, or higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies and Cohort 1 of this study. Apparent CL and volume of distribution (V) of ABBV-8E12 will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters may be fixed if useful in the analysis.

The evaluation criteria described below will be used to examine the performance of different models.

- The objective function of the best model is significantly smaller than the alternative model(s).
- The observed and predicted concentrations from the preferred model are more randomly distributed across the line of unity (a straight line with zero intercept and a slope of one) than the alternative model(s).
- Visual inspection of model fits, standard errors of model parameters and change in inter-subject and intra-subject error.

Once an appropriate base pharmacokinetic model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM. The relationship between these conditional estimates of CL and V values and potentially physiologically relevant or clinically meaningful covariates (such as subject age, sex, body weight, concomitant medications, laboratory markers of hepatic or renal function, etc.) will be explored using either stepwise forward selection method, or generalized additive method (GAM), or another suitable regression/smoothing method at a significance level of 0.05. After identification of all relevant covariates, a stepwise backward elimination of covariates from the full model will be employed to evaluate the significance (at $P < 0.005$, corresponding to a decrease in objective function > 7.88 for one degree of freedom) of each covariate in the full model.

Linear or non-linear relationships of primary pharmacokinetic parameters with various covariates will be explored.

Relationships between exposure and clinical observations (primary efficacy variable) will be explored. Exposure-response relationships for secondary efficacy variables and/or some safety measures of interest may also be explored. Initially, the time-course of placebo response will be modeled. Subsequently the relationship between exposure (e.g., population pharmacokinetic model predicted average concentrations or AUC or

trough concentrations of the individual model-predicted pharmacokinetic profiles, or some other appropriate measure of exposure) and drug effect will be explored after accounting for the time-course of placebo response. Several classes of models (e.g., linear, log-linear, exponential, E_{max}, sigmoid E_{max}, etc.) will be evaluated to characterize the exposure-response relationship based on the observed data.

Additional analyses will be performed if useful and appropriate.

The possibility of bias from missing data of subjects who prematurely discontinue due to an adverse event will be addressed.

8.1.8 Immunogenicity

The ADA titers will be tabulated by dose level and summarized as appropriate.

Additional analyses will be performed if useful and appropriate.

8.1.9 Data Monitoring Committee (DMC)

A DMC will be employed for this study. The DMC will be responsible for providing assessments of safety at regular intervals and will be conducting efficacy data reviews during the efficacy interim analyses. The independent external Statistical and Data Analysis Center (SDAC) and Exposure-Response Analysis Center (ERAC) will be outside AbbVie organizations with experience in producing statistical reports that will be facilitating DMC meetings, conducting the analysis and preparing reports for the DMC. The DMC will provide recommendations about continuing, modifying, or stopping the trial for safety reasons or efficacy reasons. The DMC membership and responsibilities will be documented in the DMC charter. After each DMC meeting, the chair of the DMC will communicate its recommendations to the designated AbbVie Primary Contact or AbbVie IERC representative, as described in the DMC charter. The AbbVie Primary Contact or the IERC representative will triage the recommendations to either the AbbVie Study Team if the recommendation can be implemented without unblinded data review or the IERC if unblinded data review is required.

8.1.10 Interim Analysis

Interim analyses will be performed in this study to evaluate safety, target engagement, and efficacy of ABBV-8E12 treatment in the Early AD population. Assessment of safety and efficacy data at interim will be conducted by the DMC. Assessment of target engagement will be conducted by the AbbVie Internal Biomarker Review Committee (IBRC).

Safety Interim Reviews

The first four mandatory safety DMC reviews of unblinded safety data will take place after the 12th, 24th, 36th and 48th subject have been administered their second dose and results for the MRI scheduled at approximately 2 weeks after their second dose are available. The data set will consist of all of the available safety and pharmacokinetic data in the study, including the data of any subjects from Cohort 2 who have received at least one dose of study drug when the data is cut. Additional safety DMC reviews will occur after a total of approximately 100, 200, 300, and 400 subjects are randomized and every 6 months thereafter until the study has completed. Additional unplanned safety DMC reviews can occur at the discretion of the DMC and/or AbbVie.

The DMC chair will make recommendations to the AbbVie Primary Contact (who is not involved in the conduct of the trial) regarding continuing, modifying or terminating the trial due to safety concerns in accordance with the DMC charter.

Interim analysis for Target Engagement

An assessment of target engagement analysis for the first 48 Cohort 1 subjects will be conducted by the IBRC. Biomarkers for target engagement will be defined as including both target binding (CSF free tau, CSF total tau, and plasma tau) and pharmacodynamic activity (CSF and plasma NFL). An AbbVie internal biomarker team not involved in the study conduct and firewalled from the study team will perform detailed analysis on target engagement and provide the results to the IBRC. This interim analysis results will guide the decision if an early futility analysis should be conducted. Details of the target engagement analysis will be described in a separate biomarker analysis plan.

Efficacy Interim Analyses

Efficacy interim analyses will be performed. The DMC will be responsible for the interim efficacy reviews. The DMC will make recommendations to the sponsor IERC representative regarding initiating of Phase 3 development, continuing the study to completion or terminating the study based on interim analysis results.

Futility stopping rules for the efficacy and decision rules for initiating phase 3 will be implemented in the efficacy interim analyses. Details of interim analyses will be described in the SAP and DMC charter.

8.2 Determination of Sample Size

Approximately 400 Early AD subjects (100 subjects/group) will be enrolled and randomized into three ABBV-8E12 dose groups and placebo with 1:1:1:1 randomization ratio. This sample size has about 80% power to detect an ABBV-8E12 treatment effect size (vs. placebo) of 0.45 for both the high dose and the middle dose and 0.28 for the low dose on CDR-SB score changes from baseline up to Week 96 using one-sided test at the 2.5% significance level-with Bonferroni method to adjust multiplicity.[35] This power assessment was based on the assumption that 25% subjects do not have post-baseline data and the calculation was conducted using Cytel EAST version 6.4.

8.3 Randomization Methods

Approximately 400 subjects will be enrolled into the study and randomized through the IVR/IWB system in a 1:1:1:1 ratio to one of the 3 ABBV-8E12 doses or placebo at the Day 1 Visit after the site verifies that the subject is eligible to participate in the study. The first dose of study drug will be administered after randomization at the same visit. Subject randomization will be stratified by site.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to International Conference on Harmonization (ICH) GCP.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in an effort to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., contact by phone or virtual site visits), alternative locations (e.g., use of infusion centers), and the shipping of IP and/or supplies directly to subjects. In all cases, these alternative measures must be

permitted by local regulations and the IEC/IRB. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazards.

9.3 Subject Information and Consent

Prior to the initiation of any screening or study-specific procedures, the investigator or his/her representative will explain the nature of the study to the subject, their study partner, and the subject's representative (if applicable), and answer all questions regarding this study. Each informed consent will be reviewed, signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. An informed consent statement will also be reviewed, signed and dated, by the subject's study partner prior to beginning any study related screening activities. A copy of each informed consent will be given to the subject and their study partner and each original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

In the event a subject withdraws consent to participate from the study, stored biomarker and optional pharmacogenetic research samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research using these samples, the subject may request that their samples be withdrawn. Once AbbVie receives the request, remaining biomarker and optional pharmacogenetic research samples will be destroyed. If the subject changes his/her consent, and the samples have already been tested, those results will still remain as part of the overall research data.

An informed consent, approved by an IEC/IRB, must be voluntarily signed and dated before samples are collected for optional pharmacogenetic research. The nature of the testing should be explained and the subject given an opportunity to ask questions. The informed consent must be signed before the samples are collected and any testing is performed. If the subject does not consent to provide samples for the pharmacogenetic exploratory research, it will not impact their participation in the study.

Due to the COVID-19 pandemic, protocol modifications in addition to those outlined in this protocol may become necessary. If this situation arises, verbal consent may be added to the informed consent already included in this protocol. Verbal consent would need to be obtained prior to making adaptations or substantial changes in study conduct in accordance with local regulations.

10.0 Source Documents, Data Collection and Electronic Case Report Forms

10.1 Source Documents

Source documents are defined as original documents, data, and records. These may include hospital records, clinical and office charts, laboratory data/information, subject diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Source document data may be transcribed as required. Data collected during this study must be recorded to the appropriate source document.

The investigator/institution will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Data Collection/Electronic Case Report Forms

Electronic case report forms (eCRFs) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The case report form (CRF) data for this study are being collected with an electronic data capture

(EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of Internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

Prior to enrolling any subject in the study, an initiation meeting will be held with AbbVie personnel, the investigator(s), and the study coordinators/project manager(s). This

meeting will include a detailed discussion and review of the protocol and essential documents, performance of study procedures, CRF completion and specimen collection methods.

The AbbVie monitor will monitor the study site throughout the study according to a monitoring plan. Source document review will be made against entries in RAVE and a quality assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. During the study, an ongoing review of the data will be conducted by a physician or representative at AbbVie. Computer logic will be run to identify inconsistent study data. Any necessary corrections will be made to the database via the appropriate change process.

During the COVID-19 pandemic, remote source document review of data may be employed if permitted by the local regulatory authority, the IEC/IRB, and the study site.

12.0 Use of Information

All information concerning ABBV-8E12 and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of ABBV-8E12. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The investigator will maintain a confidential subject identification code list of all subjects enrolled in the study, including each subject's name, subject number, address, phone number and emergency contact information. This list will be maintained at the study site with other study records under adequate security and restricted access, and will not be retrieved by AbbVie.

Any research that may be done using research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from research may be provided to investigators and used in scientific publications or presented at medical conventions. Research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory coordinating investigator from the investigators who participate in each multicenter study. Selection criteria for this signatory investigator will be based on level of participation, and significant knowledge of the clinical research, investigational drug, and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

The end of study is defined as the date of the last subject's last visit.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for ABBV-8E12.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Phase 2 Multiple Dose, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ABBV-8E12 in Subjects with Early Alzheimer's Disease
Protocol Date:	02 October 2020

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Program Development
		Medical Writing
		Statistics
		Statistics
		Pharmacokinetics
		Neuroscience

Appendix C. Study Activities

	Screening	Treatment Period[a] (Year 1)																
	Visit 1	Visit 2	Dose 1		Dose 2	Dose 3	Dose 4			Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13
Weeks of Study Drug Exposure	N/A	N/A	0	0 2	4	8	12	12	14	16	20	24	28	32	36	40	44	48
	Day –84 to –8	Day –7 to –1[c]	Day 1[c]	Days 5[d], 15[c,d]	Day 29[c]	Day 57[c]	Day 85[c]	Days 89[d], 99[d]		Day 113[c]	Day 141[c]	Day 169[c]	Day 197[c]	Day 225[c]	Day 253[c]	Day 281[c]	Day 309[c]	Day 337[c]
Informed Consent and Study Partner identification	X																	
Medical/early AD History	X																	
Drug Screen (Urine) and Hepatitis Screen	X																	
Weight & Height[e]	X		X		X	X	X			X	X	X	X	X	X	X	X	X
Physical Exam	X											X						X
Neurological Exam	X		X	C1	X	X	X	C1		X	X	X			X			X
Vital Signs	X		X	C1	X	X	X	C1		X	X	X	X	X	X	X	X	X
12-Lead ECG[f]	X		X	C1	X	X	X					X			X			X
Clinical Laboratory Tests	X		X		X	X	X			X	X	X			X			X
Randomization[g]			X															
Administer IV Study Drug			X		X	X	X			X	X	X	X	X	X	X	X	X
Amyloid PET Scan	X																	
Tau PET Scan[o]	X																X[p]	
Retinal Imaging Scan	X																	
MRI	X				X[h]		X[h]						X[h]				X[h]	

	Screening	Treatment Period[a] (Year 1)																	
	Visit 1	Visit 2	Dose 1			Dose 2	Dose 3	Dose 4			Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13
Weeks of Study Drug Exposure	**N/A**	**N/A**	**0**	**0**	**2**	**4**	**8**	**12**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
	Day –84 to –8	**Day –7 to –1[c]**	**Day 1[c]**	**Days 5[d], 15[c,d]**		**Day 29[c]**	**Day 57[c]**	**Day 85[c]**	**Days 89[d], 99[d]**		**Day 113[c]**	**Day 141[c]**	**Day 169[c]**	**Day 197[c]**	**Day 225[c]**	**Day 253[c]**	**Day 281[c]**	**Day 309[c]**	**Day 337[c]**
Lumbar Puncture/CSF Sample Collection[r]	X							X[i]											
APOE Pharmacogenetic Sample			X																
Optional Pharmacogenetic Sample (DNA and RNA)[j]	X		X					X								X			X
Biomarker Plasma and Serum Sample	X		X					X								X			X
Blood Samples for ABBV-8E12 Assay[k]			X	C1		X	C1	X	C1		C1		X			X			X
ADA Sample[k]			X	C1[l]		X	C1	X	C1		C1		X			X			X
Diagnostic Tools and Rating Scales[m]	X	X						X[q]					X			X[q]			X
Columbia Suicide Severity Rating Scale	X		X	C1		X	X	X	C1		X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	C1		X	X	X	C1		X	X	X	X	X	X	X	X	X
Adverse Event Monitoring[n]	X	X	X	C1		X	X	X	C1		X	X	X	X	X	X	X	X	X

	Treatment Period[a] (Year 2)												Post-Treatment Follow-Up Period[a,b]	
	Dose 14	**Dose 15**	**Dose 16**	**Dose 17**	**Dose 18**	**Dose 19**	**Dose 20**	**Dose 21**	**Dose 22**	**Dose 23**	**Dose 24**	**Completion Visit/PD**	**Week 104**	**Week 112**
Weeks of Study Drug Exposure	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**N/A**	**N/A**
	Day 365[c]	**Day 393[c]**	**Day 421[c]**	**Day 449[c]**	**Day 477[c]**	**Day 505[c]**	**Day 533[c]**	**Day 561[c]**	**Day 589[c]**	**Day 617[c]**	**Day 645[c]**	**Day 673[c]**	**Days 729**	**Day 785**
Physical Exam						X						X		
Neurological Exam			X			X			X			X	X	
Weight & Height[e]	X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[f]						X						X	X	
Clinical Laboratory Tests			X			X			X			X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X			
MRI					X[h]							X		
Tau PET Scan[o]												X[p]		
Lumbar Puncture/CSF[r]												X		
Optional Pharmacogenetic Sample (DNA and RNA)[j]						X						X		
Biomarker Plasma and Serum Sample						X						X		
Blood Samples for ABBV-8E12 Assay[k]						X						X	X	X
ADA Sample[k]						X						X	X	X
Diagnostic Tools and Rating Scale[m,q]						X						X		
Columbia Suicide Severity Rating Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	

	Treatment Period[a] (Year 2)												Post-Treatment Follow-Up Period[a,b]	
	Dose 14	**Dose 15**	**Dose 16**	**Dose 17**	**Dose 18**	**Dose 19**	**Dose 20**	**Dose 21**	**Dose 22**	**Dose 23**	**Dose 24**	**Completion Visit/PD**	**Week 104**	**Week 112**
Weeks of Study Drug Exposure	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**N/A**	**N/A**
	Day 365[c]	**Day 393[c]**	**Day 421[c]**	**Day 449[c]**	**Day 477[c]**	**Day 505[c]**	**Day 533[c]**	**Day 561[c]**	**Day 589[c]**	**Day 617[c]**	**Day 645[c]**	**Day 673[c]**	**Days 729**	**Day 785**
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Monitoring[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

C1 – Cohort 1 subjects only, Procedures should be conducted at approximately the same time as they would be conducted on the days of dosing.

a. Visits on Days 5, 15, 89 and 99 must be scheduled within ± 2 days of the scheduled date. Visits on all other days may be scheduled within ± 4 days of the scheduled date.

b. Post-Treatment Visits to occur approximately 8 and 16 weeks after the Completion or Premature Discontinuation (PD) visit.

c. Assessments on Day –7 to –1 will be done once during this time frame and can be administered on any day, but all should be done on the same day. Assessments may also be completed on Day 1, but must be completed prior to the start of the study drug infusion. At visits after Day 1 rating scales may be completed on any day within the visit window prior to the visit, but all rating scales should be completed on the same day.

d. Only subjects enrolled in Cohort 1 will be required to return to the clinical site 5 and 15 days after doses 1 and 4.

e. Height collected at Screening Visit 1 only. On dosing days, weight will be collected prior to the start of the infusion.

f. A detailed description for the timing of 12-Lead Single ECGs can be found in Section 5.3.1.1.

g Randomization should be completed just prior to the first dose administration.

h. The MRI will be scheduled approximately 2 weeks following the dose and results must be available prior to the next scheduled dose.

i. The lumbar puncture will be performed approximately 14 days after the fourth dose.

j. The optional Pharmacogenetic DNA and RNA samples require consent. Verify consent prior to sample collection.

k. A detailed description of the collection time points can be found in Section 5.3.2.1.

l. ADA sample for Cohort 1 will only be collected on Day 15.

m. See Table 4 for additional information on Diagnostic Tools and Rating Scales.

n. A detailed description for procedures involving adverse event assessments can be found in Section 6.0.

o. Tau PET scan obtained only for subjects at sites selected to participate in the tau imaging assessment.

p. Tau PET should be scheduled as close as possible to Weeks 44 (Dose 12) and 96 visits.

q. On Weeks 12 and 36, only digital clock drawing test will be performed.

r. The lumbar punctures at Screening Visit 1, Weeks 12 and 96 are optional for subjects in Cohort 2.

Appendix D. Potentially Clinically Significant (PCS) Laboratory Value

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Hematology						
Activated partial thromboplastin time (aPTT) prolonged	1	**> upper limit of normal (ULN)**	> ULN – 1.5 × ULN	> 1.5 – 2.5 × ULN	> 2.5 × ULN; hemorrhage	--
Anemia (Hemoglobin decreased)	2	**< 100 g/L (i.e., < 10 g/dL, < 6.2 mmol/L)**	< LLN – 100 g/L (i.e., < LLN – 10 g/dL, < LLN – 6.2 mmol/L)	< 100 – 80 g/L (i.e., < 10 – 8 g/dL, < 6.2 – 4.9 mmol/L)	< 80 g/L (i.e., < 8 g/dL, < 4.9 mmol/L); transfusion indicated	Life-threatening consequences; urgent intervention indicated
Hemoglobin increased	3	**> 40 g/L above ULN**	Increase in > 0 – 20 g/L above ULN **or** above baseline if baseline is above ULN	Increase in > 20 – 40 g/L above ULN **or** above baseline if baseline is above ULN	Increase in > 40 g/L above ULN **or** above baseline if baseline is above ULN	--
International normalized ratio (INR) increased	1	**> ULN**	> 1 – 1.5 × ULN **or** > 1 – 1.5 times above baseline if on anticoagulation	> 1.5 – 2.5 × ULN **or** > 1.5 – 2.5 times above baseline if on anticoagulation	> 2.5 × ULN **or** > 2.5 times above baseline if on anticoagulation	--
Leukocytosis (WBC increased)	3	**> 100 × 10^9/L (i.e., > 100,000/mm^3)**	--	--	> 100 × 10^9/L (i.e., > 100,000/mm^3)	Clinical manifestations of leukostasis; urgent intervention indicated
Lymphocyte count decreased	3	**< 0.5 × 10^9/L (i.e., < 500/mm^3)**	< LLN – 0.8 × 10^9/L (i.e., < LLN – 800/mm^3)	< 0.8 – 0.5 × 10^9/L (i.e., < 800 – 500/mm^3)	< 0.5 – 0.2 × 10^9/L (i.e., < 500 – 200/mm^3)	< 0.2 × 10^9/L (i.e., < 200/mm^3)
Lymphocyte count increased	3	**> 20 × 10^9/L (i.e., > 20,000/mm^3)**	--	> 4 – 20 × 10^9/L (i.e., > 4000 – 20,000/mm^3)	> 20 × 10^9/L (i.e., > 20,000/mm^3)	--

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophil count decreased	3	**< 1 × 10^9/L (i.e., < 1000/mm^3)**	< LLN – 1.5 × 10^9/L (i.e., < LLN – 1500/mm^3)	< 1.5 – 1 × 10^9/L (i.e., < 1500 – 1000/mm^3)	< 1– 0.5 × 10^9/L (i.e., < 1000 – 500/mm^3)	< 0.5 × 10^9/L (i.e., < 500/mm^3)
Platelet count decreased	2	**< 75 × 10^9/L (i.e., < 75,000/mm^3)**	< LLN – 75 × 10^9/L (i.e., < LLN – 75,000/mm^3)	< 75 – 50 × 10^9/L (i.e., < 75,000 – 50,000/mm^3)	< 50 – 25 × 10^9/L (i.e., < 50,000 – 25,000/mm^3)	< 25 × 10^9/L (i.e., < 25,000/mm^3)
White blood cell decreased	3	**< 2 × 10^9/L (i.e., < 2000/mm^3)**	< LLN – 3 × 10^9/L (i.e., < LLN – 3000/mm^3)	< 3 – 2 × 10^9/L (i.e., < 3000 – 2000/mm^3)	< 2 – 1 × 10^9/L (i.e., < 2000 – 1000/mm^3)	< 1 × 10^9/L (i.e., < 1000/mm^3)
Chemistry						
Blood bilirubin increased	2	**> 1.5 × ULN**	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 10 × ULN	> 10 × ULN
Cholesterol high	4	**> 12.92 mmol/L (i.e., > 500 mg/dL)**	> ULN – 7.75 mmol/L (i.e., > ULN – 300 mg/dL)	> 7.75 – 10.34 mmol/L (i.e., > 300 – 400 mg/dL)	> 10.34 – 12.92 mmol/L (i.e., > 400 – 500 mg/dL)	> 12.92 mmol/L (i.e., > 500 mg/dL)
Creatinine increased	2	**> 1.5 × ULN**	> ULN – 1.5 × ULN or > 1 – 1.5 × baseline	> 1.5 – 3 × ULN or > 1.5 – 3 × baseline	> 3 – 6 × ULN or > 3 × baseline	> 6 × ULN
Gamma-Glutamyl Transpeptidase (GGT) increased	2	**> 2.5 × ULN**	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
		Corrected Serum Calcium of:				
Hypercalcemia	3	**> 3.1 mmol/L (i.e., > 12.5 mg/dL)**	> ULN – 2.9 mmol/L (i.e., > ULN – 11.5 mg/dL)	> 2.9 – 3.1 mmol/L (i.e., > 11.5 – 12.5 mg/dL)	> 3.1 – 3.4 mmol/L (i.e., > 12.5 – 13.5 mg/dL)	> 3.4 mmol/L (i.e., > 13.5 mg/dL)
		Ionized Calcium				
		> 1.6 mmol/L	> ULN – 1.5 mmol/L	> 1.5 – 1.6 mmol/L; symptomatic	> 1.6 – 1.8 mmol/L; hospitalization indicated	> 1.8 mmol/L; life-threatening consequences
			Fasting Glucose Value			
Hyperglycemia	3	**> 13.9 mmol/L (i.e., > 250 mg/dL)**	> ULN – 8.9 mmol/L (i.e., > ULN – 160 mg/dL)	> 8.9 – 13.9 mmol/L (i.e., > 160 – 250 mg/dL)	> 13.9 – 27.8 mmol/L; (i.e., > 250 – 500 mg/dL) hospitalization indicated	> 27.8 mmol/L (i.e., > 500 mg/dL); life-threatening consequences
Hyperkalemia	3	**> 6 mmol/L**	> ULN – 5.5 mmol/L	> 5.5 – 6 mmol/L	> 6 – 7 mmol/L; hospitalization indicated	> 7 mmol/L; life-threatening consequences
Hypermagnesemia	3	**> 1.23 mmol/L (i.e., > 3 mg/dL)**	> ULN – 1.23 mmol/L (i.e., > ULN – 3 mg/dL)	--	> 1.23 – 3.30 mmol/L (i.e., > 3 – 8 mg/dL)	> 3.30 mmol/L consequences (i.e., > 8 mg/dL); life-threatening
Hypernatremia	3	**> 155 mmol/L**	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L; hospitalization indicated	> 160 mmol/L; life-threatening consequences

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Hypertriglyceridemia	3	**> 5.7 mmol/L (i.e., > 500 mg/dL)**	1.71 – 3.42 mmol/L (i.e., 150 – 300 mg/dL)	> 3.42 – 5.7 mmol/L (i.e., > 300 – 500 mg/dL)	> 5.7 – 11.4 mmol/L (i.e., > 500 – 1000 mg/dL)	> 11.4 mmol/L (i.e., > 1000 mg/dL); life-threatening consequences
Hyperuricemia (Uric Acid Increased)	4	**> 0.59 mmol/L (i.e., > 10 mg/dL)**	> ULN – 0.59 mmol/L (10 mg/dL) without physiologic consequences	--	> ULN – 0.59 mmol/L (10 mg/dL) with physiologic consequences	> 0.59 mmol/L (i.e., > 10 mg/dL); life-threatening
Hypoalbuminemia	3	**< 20 g/L**	< LLN – 30 g/L	< 30 – 20 g/L	< 20 g/L	Life-threatening consequences; urgent intervention indicated
		Corrected Serum Calcium				
Hypocalcemia	3	**< 1.75 mmol/L (i.e., < 7 mg/dL)**	< LLN – 2 mmol/L (i.e., < LLN – 8 mg/dL)	< 2 – 1.75 mmol/L (i.e., < 8 – 7 mg/dL)	< 1.75 – 1.5 mmol/L (i.e., < 7 – 6 mg/dL)	< 1.5 mmol/L (i.e., < 6 mg/dL)
		Ionized Calcium				
		< 0.9 mmol/L	< LLN – 1 mmol/L	< 1 – 0.9 mmol/L; symptomatic	< 0.9 – 0.8 mmol/L; hospitalization indicated	< 0.8 mmol/L; life-threatening consequences
Hypoglycemia	3	**< 2.2 mmol/L (i.e., < 40 mg/dL)**	< LLN – 3 mmol/L (i.e., < LLN – 55 mg/dL)	< 3 – 2.2 mmol/L (i.e., < 55 – 40 mg/dL)	< 2.2 – 1.7 mmol/L (i.e., < 40 – 30 mg/dL)	< 1.7 mmol/L (i.e., < 30 mg/dL); life-threatening consequences; seizures
Hypokalemia	3	**< 3 mmol/L**	< LLN – 3 mmol/L	< LLN – 3 mmol/L; symptomatic; intervention indicated	< 3 – 2.5 mmol/L; hospitalization indicated	< 2.5 mmol/L; life-threatening consequences

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Hypomagnesemia	3	**< 0.4 mmol/L (i.e., < 0.9 mg/dL)**	< LLN – 0.5 mmol/L (i.e., < LLN – 1.2 mg/dL)	< 0.5 – 0.4 mmol/L (i.e., < 1.2 – 0.9 mg/dL)	< 0.4 – 0.3 mmol/L (i.e., < 0.9 – 0.7 mg/dL)	< 0.3 mmol/L (i.e., < 0.7 mg/dL); life-threatening consequences
Hyponatremia	3	**< 130 mmol/L**	< LLN – 130 mmol/L	--	< 130 – 120 mmol/L	< 120 mmol/L; life-threatening consequences
Hypophosphatemia	3	**< 0.6 mmol/L (i.e., < 2 mg/dL)**	< LLN – 0.8 mmol/L (i.e., < LLN – 2.5 mg/dL)	< 0.8 – 0.6 mmol/L (i.e., < 2.5 – 2 mg/dL)	< 0.6 – 0.3 mmol/L (i.e., < 2 – 1 mg/dL)	< 0.3 mmol/L (i.e., < 1 mg/dL); life-threatening consequences
Enzymes						
Alanine aminotransferase (ALT) increased	2	**> 3 × ULN**	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Alkaline phosphatase increased	2	**> 2.5 × ULN**	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Aspartate aminotransferase (AST) increased	2	**> 3 × ULN**	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Creatine Phosphokinase (CPK) increased	3	**> 5 × ULN**	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 10 × ULN	> 10 × ULN

Adapted from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010)

Appendix E. Protocol Amendment: List of Changes

The summary of changes can be found in Section 1.1.

Specific Protocol Changes

Section 1.2 Synopsis
Subsection Methodology:
Fifth paragraph
Delete: last sentence

Japanese subjects enrolled in Cohort J1 will follow safety and pharmacokinetic sample collection procedures of Cohort 1; however, the lumbar puncture will be optional for Cohort J1 subjects.

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Add:

COVID-19	Coronavirus disease-2019
DTP	Direct-to-Patient
IBRC	Internal Biomarker Review Committee
IERC	Internal Executive Review Committee

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Delete:

IRC	Independent Review Committee

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Abbreviation "MMA" previously read:

MMA	Methylmalonic acide

Has been changed to read:

MMA	Methylmalonic acid

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Delete:

Sub-IRC	Sub-team of Internal Review Committee

Section 3.2 Benefits and Risks
Add: new last paragraph

In consideration of the coronavirus disease (COVID-19) pandemic, the benefits and risks to subjects participating in this study have been re-evaluated. Based on the limited information to date, no additional risk is anticipated for study participants infected with SARS-Cov2 during the COVID-19 pandemic, due to the mechanism of action of ABBV-8E12.

Section 5.1 Overall Study Design and Plan: Description
Fifth paragraph
Delete: last sentence

Japanese subjects enrolled in Cohort J1 will follow safety and PK sample collection procedures of Cohort 1; however, the lumbar puncture will be optional for Cohort J1 subjects.

Table 1. Safety and PK Procedures for Cohort 1 and Cohort J1
Table title previously read:

Safety and PK Procedures for Cohort 1 and Cohort J1

Has been changed to read:

Safety and PK Procedures for Cohort 1

Table 1. Safety and PK Procedures for Cohort 1 and Cohort J1
Header row, column "Cohort 1 and Cohort J1, Doses 1 – 4" previously read:

Cohort 1 and Cohort J1, Doses 1 – 4

Has been changed to read:

Cohort 1, Doses 1 – 4

Table 1. Safety and PK Procedures for Cohort 1 and Cohort J1
Week of study drug exposure "Lumbar Puncture/CSF Sample Collection[f]" previously read:

Lumbar Puncture/CSF Sample Collection[f]

Has been changed to read:

Lumbar Puncture/CSF Sample Collection

Table 1. Safety and PK Procedures for Cohort 1 and Cohort J1
Delete: table note "f."

Lumbar puncture will be optional for Cohort J1.

Section 5.2.1 Inclusion Criteria
Criterion 3, first paragraph previously read:

Subject who meets the National Institute on Aging and the Alzheimer's Association (NIA-AA) clinical criteria for mild cognitive impairment or probable AD,[35] and has:

Has been changed to read:

Subject who meets the National Institute on Aging and the Alzheimer's Association (NIA-AA) clinical criteria for mild cognitive impairment or probable AD,[10] and has:

Section 5.2.1 Inclusion Criteria
Criterion 6, last sentence previously read:

The study partner has voluntarily signed the IRB/IEC approved Study Partner Informed Consent, prior to the conduct of any study procedures.

Has been changed to read:

The study partner has voluntarily signed the IEC/IRB approved Study Partner Informed Consent, prior to the conduct of any study procedures.

Section 5.3.1.1 Study Procedures
Add: new first paragraph

Study visits may be impacted due to the COVID-19 pandemic may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures. Additional details are provided in the subsequent sections of this protocol. Every effort should be made to ensure the safety of subjects and onsite staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, the updates below on how to proceed should be followed.

Section 5.3.1.1 Study Procedures
Subsection Physical Examination
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event physical examinations may not be performed due to study modifications related to the COVID-19 pandemic, these examinations should be completed at the next onsite visit.

Section 5.3.1.1 Study Procedures
Subsection Neurological Examination
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event neurological examinations may not be performed due to study modifications related to the COVID-19 pandemic, these examinations should be completed at the next onsite visit.

Section 5.3.1.1 Study Procedures
Subsection Vital Signs
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event vital signs may not be obtained due to study modifications related to the COVID-19 pandemic, these measurements should be obtained at the next onsite visit.

Section 5.3.1.1 Study Procedures
Subsection 12-Lead Electrocardiogram (ECG)
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event 12-lead ECG may not be performed due to study modifications related to the COVID-19 pandemic, this procedure should be completed at the next onsite visit.

Section 5.3.1.1 Study Procedures
Subsection Abnormal Findings
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event clinical laboratory tests may not be performed due to study modifications related to the COVID-19 pandemic, these tests should be completed at the next onsite visit.

If laboratory tests cannot be performed, study drug may be administered to subjects if the investigator has reviewed all prior laboratory results and confirms there are no safety concerns.

Section 5.3.1.1 Study Procedures
Subsection Lumbar Puncture (LP)
First paragraph, first and second sentence previously read:

Lumbar punctures are required for subjects enrolled in Cohort 1 and are optional for subjects enrolled in Cohort 2 and Cohort J1. For all Cohort 1 subjects and subjects agreeing to LPs in Cohort 2 and Cohort J1, LPs to collect CSF will be performed at time points indicated in the Study Activities Table (Appendix C).

Has been changed to read:

Lumbar punctures are required for subjects enrolled in Cohort 1 and are optional for subjects enrolled in Cohort 2. For all Cohort 1 subjects and subjects agreeing to LPs in Cohort 2, LPs to collect CSF will be performed at time points indicated in the Study Activities Table (Appendix C).

Section 5.3.1.1 Study Procedures
Subsection Lumbar Puncture (LP)
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event lumbar puncture may not be performed due to study modifications related to the COVID-19 pandemic, this procedure should be completed at the next onsite visit.

Section 5.3.1.1 Study Procedures
Subsection Magnetic Resonance Imaging (MRI)
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event MRI may not be performed due to study modifications related to the COVID-19 pandemic, this procedure should be completed at the next onsite visit.

Section 5.3.1.1 Study Procedures
Subsection Positron Emission Tomography (PET) Tau Imaging
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event the tau PET scan may not be performed due to study modifications related to the COVID-19 pandemic, this procedure should be completed at the next onsite visit.

Section 5.3.1.1 Study Procedures
Subsection Positron Emission Tomography (PET) Tau Imaging
Heading "Retinal Imaging for Amyloid"
Subheading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new subheading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event the retinal scan may not be performed due to study modifications related to the COVID-19 pandemic, this procedure should be completed at the next onsite visit.

Table 4. Diagnostic Tools and Scale Administration Timing
Abbreviation "UPSA - Brief" previously read:

UPSA - Brief = University of California San Diego Performance Based Skills Assessment, Brief Version

Has been changed to read:

UPSA Brief = University of California San Diego Performance Based Skills Assessment, Brief Version

Section 5.3.1.1 Study Procedures
Subsection Diagnostic Tools and Rating Scales
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If scale administration is not performed due to study modifications related to the COVID-19 pandemic, the scale(s) should be completed at the next onsite visit. Should a virtual visit be conducted, the investigator should refer to the table below for scales that may be administered remotely.

Scale	May be Administered Via Phone or Video Conference
ADAS-Cog-14	No
ADCS-CGIC-MCI	Yes
ADCS-MCI-ADL-24	Yes
CDR	Yes
C-SSRS	Yes
dCDT	No
FAQ	Yes
MMSE	No
NPI	Yes
RBANS	No
UPSA – Brief	No

ADAS-Cog-14 = Alzheimer's Disease Assessment Scale (14-Item) Cognition Portion; ADCS-CGIC-MCI = Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change for Mild Cognitive Impairment; ADCS-MCI-ADL-24 = 24-item Alzheimer's Disease Cooperative Study/Activities of Daily Living Scale Adapted for Patients with Mild Cognitive Impairment; CDR = Clinical Dementia Rating; C-SSRS = Columbia-Suicide Severity Rating Scale; dCDT = Digital clock drawing test; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; RBANS = Repeatable Battery for Assessment of Neuropsychological Status; USPA Brief = University of California San Diego Performance Based Skills Assessment, Brief Version

Section 5.3.1.2 Collection and Handling of Biomarker and Pharmacogenetic Research Samples
Subsection Apolipoprotein E (APOE) Pharmacogenetic Sample
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event blood and optional CSF biomarker samples may not be collected due to study modifications related to the COVID-19 pandemic, these samples should be obtained at the next onsite visit.

Section 5.3.1.2 Collection and Handling of Biomarker and Pharmacogenetic Research Samples
Subsection Optional Pharmacogenetic Research Samples
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event optional pharmacogenetic research samples may not be collected due to study modifications related to the COVID-19 pandemic, these samples should be obtained at the next onsite visit.

Section 5.4.1 Discontinuation of Individual Subjects
Subsection COVID-19 Pandemic-Related Acceptable Protocol Modifications
Add: new subsection title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Subjects who miss multiple study drug doses due to the COVID-19 pandemic may continue participation with approval from the TA MD.

Section 5.5.1 Treatments Administered
Second paragraph previously read:

Study drug will be administered by IV infusion in the morning (if possible) at each visit as follows:

Has been changed to read:

Study drug will be administered by IV infusion, preferably in the morning but should be around the same time at each visit as follows:

Section 5.5.1 Treatments Administered
Last paragraph, last sentence previously read:

Refer to the Pharmacy Manual for detailed instructions.

Has been changed to read:

The start of study drug infusion occurs from ABBV-8E12 initiation up until the administration of the complete dose (including flush). The Pharmacy Manual may be referred to for detailed instructions.

Section 5.5.1 Treatments Administered
Subsection Home Healthcare Service Due to the COVID-19 Pandemic
Add: new subsection title and text

Home Healthcare Service Due to the COVID-19 Pandemic

Subjects may be offered the option of home healthcare visits provided by a study nurse or third-party vendor based on the subject's suitability as assessed by the investigator and following the subject's written consent. This option can only be offered in countries and sites that comply with local regulatory and IEC/IRB requirements for home healthcare. Any prerequisite submissions or notifications to the site IEC/IRB and local competent health authority should be made and approved prior to the implementation of home infusions.

Table 5. Identity of Investigational Product
Previously read:

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
ABBV-8E12	Infusion	Solution for infusion in a vial	300 mg/15 mL 1000 mg/ 10 mL	AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany
Placebo	Infusion	0.9% Sodium Chloride Injection/Solution for infusion, 250 mL	N/A	Various* (See below)

N/A = not applicable

* Can be sourced from approved marketed products from various commercial manufacturers depending on availability.

Has been changed to read:

Investigational Product	Mode of Administration	Formulation	Strength
ABBV-8E12	Infusion	Solution for infusion in a vial	300 mg/15 mL 1000 mg/ 10 mL
Placebo	Infusion	0.9% Sodium Chloride Injection/Solution for infusion, 250 mL	N/A

N/A = not applicable

Section 5.5.2.2 Storage and Disposition of Study Drugs
Third paragraph, third sentence previously read:

Malfunctions or any temperature excursion must be reported to the Sponsor immediately using the AbbVie Temperature Excursion Management System (ATEMS).

Has been changed to read:

All temperature excursions lasting longer than 30 minutes must be reported to the Sponsor immediately using the AbbVie Temperature Excursion Management System (ATEMS).

Section 5.5.5 Blinding
Subsection Unblinding of Data for the Data Monitoring Committee (DMC)
Seventh sentence previously read:

An AbbVie Independent Review Committee (IRC) may request access to closed reports if the discontinuation of the study, major modifications to the study design, or Phase 3 initiation is recommended by the DMC as outlined in the DMC charter.

Has been changed to read:

An AbbVie Internal Executive Review Committee (IERC) may request access to closed reports if the discontinuation of the study, major modifications to the study design, or Phase 3 initiation is recommended by the DMC as outlined in the DMC charter.

Section 5.5.5 Blinding
Subsection Unblinding of Data for the Data Monitoring Committee (DMC)
Last sentence previously read:

The AbbVie Representative and the AbbVie IRC members will not be involved in any aspects of the trial or its management.

Has been changed to read:

The AbbVie Primary Contact for the DMC and the AbbVie IERC members will not be involved in any aspects of the trial or its management.

Section 5.6.2 Appropriateness of Measurements
First paragraph, last sentence previously read:

On-treatment safety evaluations (neurological examinations, adverse event monitoring, ECGs) are scheduled at more frequent intervals for the first 48 subjects enrolled (Cohort 1) and for subjects enrolled in Cohort J1 to promptly detect potential emerging safety signals.

Has been changed to read:

On-treatment safety evaluations (neurological examinations, adverse event monitoring, ECGs) are scheduled at more frequent intervals for the first 48 subjects enrolled (Cohort 1) to promptly detect potential emerging safety signals.

Section 6.1.5 Adverse Event Reporting
Subsection COVID-19 Pandemic-Related Acceptable Protocol Modifications
Add: new subsection title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

The investigator should capture COVID-19 infections as AEs. If the event meets the criteria for a serious adverse event (SAE), reporting directions as described in Section 6.1 should be followed.

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or AEs (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as AEs. If the event meets the criteria for a serious adverse event (SAE), then the SAE reporting directions per the protocol and above should be followed. The following COVID-19 related supplemental eCRFs should be completed (for both serious and non-serious events):

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

Section 7.0 Protocol Deviations
Contact Information previously read:

Primary Contact:	Alternate Contact:
[redacted]	[redacted]
AbbVie 1 North Waukegan Road North Chicago, IL 60064	AbbVie 1 North Waukegan Road North Chicago, IL 60064
Office: Mobile: Fax: Email: [redacted]	Office: Mobile: Fax: Email: [redacted]

Has been changed to read:

Primary Contact:	Alternate Contact:
[redacted]	[redacted]
AbbVie Deutschland GmbH & Co. KG Knollstr. 50 67061 Ludwigshafen Germany	AbbVie 1 North Waukegan Road North Chicago, IL 60064
Office: Email: [redacted]	Office: Email: [redacted]

Section 8.1.7.1 Tabulations and Summary Statistics
Previously read:

For the data of Cohort 1 and Cohort J1, serum concentrations of ABBV-8E12 and pharmacokinetic parameter values will be tabulated for each subject and each dose level, and summary statistics will be computed for each sampling time and each parameter by dose level. Also, for the serum concentration data of all subjects (Cohort 1, Cohort J1, and Cohort 2), summary statistics will be provided for each scheduled time of sampling with breakdown by dose level.

CSF concentration data after the fourth dose and the final dose will be tabulated and summarized by dose level for Cohort 1 and for Cohort J1 and Cohort 2, if available (collection in Cohort J1 and Cohort 2 is optional).

Has been changed to read:

For the data of Cohort 1, serum concentrations of ABBV-8E12 and pharmacokinetic parameter values will be tabulated for each subject and each dose level, and summary statistics will be computed for each sampling time and each parameter by dose level. Also, for the serum concentration data of all subjects (Cohort 1 and Cohort 2), summary

statistics will be provided for each scheduled time of sampling with breakdown by dose level.

CSF concentration data after the fourth dose and the final dose will be tabulated and summarized by dose level for Cohort 1. A summary of data for all subjects (Cohort 1 and Cohort 2) will also be included noting that CSF sample collection was optional for subjects in Cohort 2 per Amendment 1 of the protocol.

Section 8.1.9 Data Monitoring Committee (DMC)
Sixth and seventh sentence previously read:

After each DMC meeting, the chair of the DMC will communicate its recommendations to the designated AbbVie Contact, as described in the DMC charter. The AbbVie Contact will triage the recommendations to either the AbbVie Study Team if the recommendation can be implemented without unblinded data review or the Independent Review Committee (IRC) if unblinded data review is required.

Has been changed to read:

The DMC membership and responsibilities will be documented in the DMC charter. After each DMC meeting, the chair of the DMC will communicate its recommendations to the designated AbbVie Primary Contact or AbbVie IERC representative, as described in the DMC charter. The AbbVie Primary Contact or the IERC representative will triage the recommendations to either the AbbVie Study Team if the recommendation can be implemented without unblinded data review or the IERC if unblinded data review is required.

Section 8.1.10 Interim Analysis
First paragraph, last sentence previously read:

Assessment of target engagement will be conducted by an AbbVie sub-team of Internal Review Committee (sub-IRC).

Has been changed to read:

Assessment of target engagement will be conducted by the AbbVie Internal Biomarker Review Committee (IBRC).

Section 8.1.10 Interim Analysis
Subsection Safety Interim Reviews
Last paragraph previously read:

The DMC chair will make recommendations to the AbbVie Contact (who is not involved in the conduct of the trial) regarding continuing, modifying or terminating the trial due to safety concerns in accordance with the DMC charter.

Has been changed to read:

The DMC chair will make recommendations to the AbbVie Primary Contact (who is not involved in the conduct of the trial) regarding continuing, modifying or terminating the trial due to safety concerns in accordance with the DMC charter.

Section 8.1.10 Interim Analysis
Subsection Interim analysis for Target Engagement
First sentence previously read:

An assessment of target engagement analysis for the first 48 Cohort 1 subjects will be conducted by the sub-IRC.

Has been changed to read:

An assessment of target engagement analysis for the first 48 Cohort 1 subjects will be conducted by the IBRC.

Section 8.1.10 Interim Analysis
Subsection Interim analysis for Target Engagement
Third sentence previously read:

An AbbVie internal biomarker team not involved in the study conduct and firewalled from the study team will perform detailed analysis on target engagement and provide the results to sub-IRC.

Has been changed to read:

An AbbVie internal biomarker team not involved in the study conduct and firewalled from the study team will perform detailed analysis on target engagement and provide the results to the IBRC.

Section 8.1.10 Interim Analysis
Subsection Efficacy Interim Analyses
First paragraph, last sentence previously read:

The DMC will make recommendations to the sponsor representative regarding initiating of Phase 3 development, continuing the study to completion or terminating the study based on interim analysis results.

Has been changed to read:

The DMC will make recommendations to the sponsor IERC representative regarding initiating of Phase 3 development, continuing the study to completion or terminating the study based on interim analysis results.

Section 8.3 Randomization Methods
Last sentence previously read:

Subject randomization will be stratified by site except in Japan where all sites together will be treated as one "pseudo site" for randomization.

Has been changed to read:

Subject randomization will be stratified by site.

Section 9.2 Ethical Conduct of the Study
Add: new last paragraph

In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in an effort to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., contact by phone or virtual site visits), alternative locations (e.g., use of infusion centers), and the shipping of IP and/or supplies directly to subjects. In all cases, these alternative measures must be permitted by local regulations and the IEC/IRB. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazards.

Section 9.3 Subject Information and Consent
Last paragraph, first sentence previously read:

An informed consent, approved by an IRB/IEC, must be voluntarily signed and dated before samples are collected for optional pharmacogenetic research.

Has been changed to read:

An informed consent, approved by an IEC/IRB, must be voluntarily signed and dated before samples are collected for optional pharmacogenetic research.

Section 9.3 Subject Information and Consent
Add: new last paragraph

Due to the COVID-19 pandemic, protocol modifications in addition to those outlined in this protocol may become necessary. If this situation arises, verbal consent may be added to the informed consent already included in this protocol. Verbal consent would need to be obtained prior to making adaptations or substantial changes in study conduct in accordance with local regulations.

Section 11.0 Data Quality Assurance
Add: new last paragraph

During the COVID-19 pandemic, remote source document review of data may be employed if permitted by the local regulatory authority, the IEC/IRB, and the study site.

15.0 Reference List
Add: new Reference 10

Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment 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. 2011;7(3):270-9.

15.0 Reference List
Delete: Reference 35

Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment 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. 2011;7(3):270-9.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Clinical
		Medical Writing
		Statistics
		Pharmacokinetics
		Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical Program Development
		Medical Writing
		Statistics
		Statistics
		Pharmacokinetics
		Neuroscience

Appendix C. Study Activities
Table note "p." previously read:

Tau PET should be scheduled as close as possible after Weeks 44 (Dose 12) and 96 visits.

Has been changed to read:

Tau PET should be scheduled as close as possible to Weeks 44 (Dose 12) and 96 visits.