1.0 Title Page

Clinical Study Protocol M15-570

An Extension Study of ABBV-8E12 in Early Alzheimer's Disease

Incorporating Amendments 1 and 2

AbbVie Investigational Product:	ABBV-8E12
Date:	20 October 2020
EudraCT Number:	2018-000268-26
Development Phase:	2
Study Design:	This is a Phase 2 extension of Study M15-566 evaluating the long-term safety and tolerability of ABBV-8E12 in subjects with early Alzheimer's disease
Investigators:	Multicenter trial: Investigator information is on file at AbbVie
Sponsor:	AbbVie
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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	09 April 2018
Amendment 1	24 January 2019

The purpose of this amendment is to:

- Update Section 3.0 Introduction Clinical Experience to remove studies.

  Rationale: *Study M15-562 and Study M15-563 have been completed and the PSP program is discontinued.*
- Update Section 3.2 Benefits and Risks to include language for the coronavirus disease-19 (COVID-19) pandemic.

  Rationale: *To describe alternative processes that may be needed because of the COVID-19 pandemic.*
- Update Section 5.1 Overall Study Design and Plan: Description to specify timing in schedule of activities.

  Rationale: *To clarify the timing of the Day 1 visit of Study M15-570 in relation to Study M15-566 for study sites to follow.*
- Update Section 5.2.2 Exclusion Criteria to add a rationale for the exclusion criteria.

  Rationale: *to allow the TA MD to delegate responsibility.*
- Update Section 5.3.1.1 Study Procedures [Physical Examination, Neurological Examination, Vital Signs, 12-Lead Electrocardiogram (ECG), Abnormal Findings, Optional Lumbar Puncture, Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET) Tau Imaging] 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 5.3.1.1 Study Procedures, Table 2 to specify optional tests.

Rationale: *To clarify procedures that are not required if using Study M15-566 Week 96 visit for Baseline.*

- Update Section 5.3.1.1 Study Procedures [Positron Emission Tomography (PET) Tau Imaging] to specify timing in schedule of activities.

  Rationale: *To clarify the timing of the tau PET scan for Day 1/Baseline for study sites to follow.*

- Update Section 5.3.1.1 Study Procedures to remove procedures.

  Rationale: *To remove retinal imaging for amyloid and digital measures of cognition, actigraphy, and sleep because sleep and activity platforms will not be investigated.*

- Update Section 5.3.1.1 Study Procedures, Table 3 to specify timing of scales.

  Rationale: *To confirm that the 24-item Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for patients with Mild Cognitive Impairment (ADCS-MCI-ADL-24), EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L), and Columbia-Suicide Severity Rating Scale (C-SSRS) can be administered/assessed at any time during the visit. This change was also created to align with Study M15-566.*

- Update Section 5.3.1.1 Study Procedures, EuroQuality of Life-5-level (EQ-5D-5L) to add language describing the scale.

  Rationale: *To clarify the version of the scale.*

- Update Section 5.3.1.2 Collection and Handling of Biomarker and Pharmacogenetic Research Samples (Blood and Optional CSF Biomarker Samples; 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 5.3.2.1 Collection of Samples for Analysis (Optional CSF Samples for ABBV-8E12 Assay) 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 5.3.6.1 Biomarker Research Variables, Volumetric MRI to include language reflecting analysis.

  Rationale: *To clarify the analysis and algin with the planned data analysis as described in Study M15-566 and the current SAP.*

- Update Section 5.3.6.1 Biomarker Research Variables to remove language.

  Rationale: *To remove retinal imaging for amyloid because this will not be investigated.*

- 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 specify timing of drug administration.

  Rationale: *To clarify when study drug should be administered.*

- 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 5.5.2 Identity of Investigational Product, Table 4 to add additional strength of study drug

  Rationale: *To clarify the additional strength of 2000 mg/20 mL of ABBV-8E12*

- 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 8.1.1 Analysis Data Sets, Data Set for Safety Analyses to remove language pertaining to analysis.

  Rationale: *Removed because the cumulative safety data analysis will not be conducted for this study. It will be considered in future aggregate safety analyses***.**

- Update Section 8.1.1 Analysis Data Sets, Data Set for Biomarkers to include language pertaining to analysis.

  Rationale: *To clarify the analysis in relation to Study M15-566.*

- Update Section 8.1.4 Safety Analysis to include language pertaining to analyses.

  Rationale: *Language replaced due to a change in statistical analysis plans.*

- Update Section 8.1.4.2 Analysis of Adverse Events to include language pertaining to analyses.

  Rationale: *Language replaced due to a change in statistical analysis plans.*

- Update Section 8.1.5 Biomarker Analyses to include language pertaining to analysis.

  Rationale: *Language replaced to reflect a part of the change in the method of analysis.*

- Update Section 8.1.5 Biomarker Analyses, Volumetric MRI Variables to include language pertaining to analysis.

  Rationale: *Language replaced to clarify the method of analysis.*

- 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 Section 15.0 Reference List to replace reference.

Rationale: *The new reference establishes the validity and reliability of using the EuroQuality of Life-5-level (EQ-5D-5L) Proxy Version 1 in the Alzheimer's disease population. It also compares the self-report and proxy-based version.*

Other revisions were made to ensure consistency within the protocol and to provide further clarifications of study design and processes.

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:** M15-570
Name of Study Drug: ABBV-8E12	**Phase of Development:** 2
Name of Active Ingredient: ABBV-8E12	**Date of Protocol Synopsis:** 20 October 2020
Protocol Title: An Extension Study of ABBV-8E12 in Early Alzheimer's Disease	
Objectives: The primary objective of this study is to assess the long-term safety and tolerability of ABBV-8E12 in subjects with early Alzheimer's disease (AD). The secondary objective of this study is to assess the pharmacokinetics (PK) of ABBV-8E12 in subjects with early AD. The exploratory objectives of this study are: • To assess the long-term efficacy of ABBV-8E12 in slowing disease progression in subjects with early AD. • To assess the long-term effect of ABBV-8E12 on a range of disease-related and drug-related biomarkers in subjects with early AD.	
Investigators: Multicenter	
Study Sites: Up to 80 global sites	
Study Population: Adult subjects with early AD who completed Study M15-566	
Number of Subjects to be Enrolled: Approximately 400	
Methodology: Study M15-570 is a Phase 2 extension of the multiple dose, multicenter, multinational, randomized, double-blind, placebo-controlled study, Study M15-566, and is designed to evaluate the long-term safety and tolerability of ABBV-8E12 in subjects with early AD. The study will consist of a 5-year treatment period and a follow-up period of approximately 20 weeks following the last study drug administration. All subjects who complete the Treatment Period in Study M15-566 will be eligible to participate in this study according to the selection criteria. Upon completion of baseline study procedures, eligible subjects will receive ABBV-8E12 via intravenous (IV) infusion on Day 1 of Study M15-570 as follows: • Subjects who received placebo in Study M15-566 will receive 2000 mg ABBV-8E12 in Study M15-570; • Subjects who received 300 mg ABBV-8E12 in Study M15-566 will receive 1000 mg ABBV-8E12 in Study M15-570; and • Subjects who received 1000 mg or 2000 mg ABBV-8E12 in Study M15-566 will continue on the same dose in Study M15-570. Note: if any changes are made to alter Study M15-566 with regards to the treatment arms due to safety, efficacy, or other reasons, a corresponding change will be implemented in Study M15-570. This change may include, but is not limited to, adding or dropping treatment arm(s).	

Methodology (Continued):

Subjects will receive study drug infusion every 4 weeks and undergo other study procedures and assessments as outlined in the Study Activities table (Appendix C). Subjects will continue to receive treatment either until one of the discontinuation criteria is met, the sponsor discontinues the study, or the subject completes the 5-year treatment period of Study M15-570. Refer to Section 5.4 for detailed description of discontinuation criteria.

Day 1 visit of Study M15-570 will be approximately 4 weeks but no more than 8 weeks after the Week 92 visit of Study M15-566. Should this window be longer than 8 weeks, the subject may be considered for participation in Study M15-570 only with the approval of the AbbVie Therapeutic Area Medical Director (TA MD) or designee. The investigators and subjects will remain blinded to the treatment assignments in Study M15-566 and will be blinded to the dose level of ABBV-8E12 in Study M15-570.

Safety will be closely monitored during the study conduct. The study will also utilize an external data monitoring committee (DMC), which will review accumulating study data and make recommendations based on the emerging safety profile of ABBV-8E12. The DMC membership, responsibilities, operating logistics, and timing of reviews will be documented in a charter that will be finalized prior to the first DMC review meeting.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

- 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 institutional review board (IRB)/independent ethics committee (IEC) approved informed consent, prior to the conduct of any extension study-specific procedures (including any changes occurring in the subject's current therapeutic regimen). In the absence of subject's ability to provide the informed consent, the informed consent must be obtained by a person who has the legal right to act on behalf of the subject following local regulations.
- Subject completed the 96-week treatment period of Study M15-566.
- In the investigator's opinion, subject was compliant during participation in Study M15-566.
- Subject has an identified, reliable study partner (e.g., caregiver, family member, social worker, or friend; preferably the same person for the duration of the study) who has frequent contact with the subject (at least 10 hours per week) and who will provide information as to the subject's cognitive and functional abilities. The study partner has voluntarily signed the IRB/IEC approved study partner informed consent, prior to the conduct of any extension study-specific procedures.
- 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).
- 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.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion:

- The subject has any significant change in his/her medical condition since participation in Study M15-566 that could interfere with the subject's participation in Study M15-570, could place the subject at increased risk, or could confound interpretation of study results. The investigator must re-evaluate the subject for continuing participation and consider relevant factors including:
  - interim development of any clinically significant neurological, hematological, autoimmune, endocrine, cardiovascular, neoplastic, renal, hepatic, metabolic, psychiatric, pulmonary, gastrointestinal, or other major disorder
  - interim development of contraindication to or inability to tolerate brain MRI or PET scans
- More than 8 weeks have elapsed since the subject received his/her last dose of study drug in Study M15-566 (i.e., Week 92 visit in Study M15-566). In certain cases, subject may be eligible to enroll after approval by the TA MD or designee.
- Subject is concurrently enrolled in another interventional clinical study (with the exception of Study M15-566) involving a therapeutic agent.
- Subject is considered by the investigator, for any reason, to be an unsuitable candidate to receive ABBV-8E12 or the subject is considered by the investigator to be unable or unlikely to comply with the dosing schedule or study evaluations.

Investigational Product:	ABBV-8E12 (vial of 1000 mg/10 mL and vial of 2000 mg/20 mL)
Doses:	Dose 1: 1000 mg Dose 2: 2000 mg Doses will be given every 4 weeks. Doses may be modified after evaluation by the DMC of the safety, tolerability, and available PK data.
Mode of Administration:	IV infusion
Reference Therapy:	Not applicable
Doses:	Not applicable
Mode of Administration:	Not applicable

Duration of Treatment: 5 years

Criteria for Evaluation:

Safety:

Adverse event monitoring, vital signs, physical examination, neurologic examination, electrocardiogram (ECG), laboratory tests, Columbia-suicide severity rating scale (C-SSRS), MRI, and immunogenicity assessments will be conducted.

Subjects will be monitored closely for the occurrence of AEs and serious adverse events (SAEs) 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 (Appendix C). The DMC will be in place to provide recommendations during the study.

Criteria for Evaluation (Continued):

Efficacy:

Clinical Assessments:

- Clinical Dementia Rating - Sum of Boxes (CDR-SB)
- Repeatable Battery for Assessment of Neuropsychological Status (RBANS)
- 24-item AD Cooperative Study/Activities of Daily Living scale adapted for patients with mild cognitive impairment (ADCS-MCI-ADL-24)
- EuroQuality of Life-5-level (EQ-5D-5L) Proxy Version 1

Pharmacokinetics:

Values for the following pharmacokinetic parameters will be estimated using mixed-effect modeling approach: clearance (CL) and volume of distribution (V). Additional parameters may be calculated if useful in the interpretation of the data. Pharmacokinetic data from this study may be combined with data from other ABBV-8E12 studies for pharmacokinetic analyses. Additional parameters may be calculated if useful in the interpretation of the data.

Immunogenicity:

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

Biomarkers and Pharmacogenetics:

Exploratory research to assess effects of ABBV-8E12 on potential disease-related and drug-related biomarkers will be conducted. Blood sampling, optional CSF sampling and MRIs for volumetric analysis will be done at designated time points throughout the study in order to obtain the data. Also, tau PET scans will be collected in a subset of the subjects. The potential CSF and plasma biomarkers will include, but are not limited to, the following: tau and NFL concentrations; volumetric MRI measures for whole brain, hippocampus, temporal lobes 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.

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. The values of other variables may be determined. 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.

Statistical Methods:

Safety:

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting treatment-emergent AEs will be tabulated by MedDRA system organ class (SOC) and preferred term (PT) with a breakdown by treatment sequence. Tabulations will also be provided in which the number of subjects reporting an AE (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 SAE (including deaths) and AEs leading to premature discontinuation of the study drug will be tabulated according to the MedDRA SOC and preferred term by treatment sequence. Treatment sequence differences between each ABBV-8E12 dose group will be analyzed using Fisher's exact test. Differences between each ABBV-8E12 dose group 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.

Efficacy:

All efficacy analyses of comparisons will be performed with a 2-sided test at the significance level of 0.050 unless otherwise specified. All efficacy assessments that are taken no more than 45 days after the last dose of study drug will be included in the efficacy analyses.

The analysis of efficacy variables will be performed on the Study M15-570 ITT data set. The analysis model is a likelihood-based, mixed effects model repeated measures (MMRM) analysis at Study M15-570 Baseline and each post-baseline observation using all observed data. This MMRM analysis will be applied to each efficacy variable with repeated measurements. Details of the analysis will be described in the statistical analysis plan (SAP).

If applicable, delayed-start analysis will be conducted on the change from Baseline of Study M15-566 up to Week 96 in Study M15-570 on CDR-SB score. An MMRM analysis model will be used. Details of the analysis will be specified in the SAP.

Pharmacokinetics:

For ABBV-8E12 serum concentration data, descriptive statistics will be provided for each scheduled time of measurement with a breakdown by treatment sequence.

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

Population PK analyses will be performed using the actual sampling time relative to the last administered dose. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (Version 7, or higher version). The structure of the starting PK model will be based on the PK analysis of data from previous studies. Apparent CL and apparent V of ABBV-8E12 will be the PK parameters of major interest in the NONMEM analyses. If necessary, other parameters may be fixed if useful in the analysis.

Immunogenicity:

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

Statistical Methods (Continued):

Biomarkers:

For each variable, descriptive statistics will be provided for each scheduled time of measurement with a breakdown by group as defined by treatment in Study M15-566 and treatment in Study M15-570, i.e.,:

- ABBV-8E12 1000 mg in Study M15-566, continuing the same in Study M15-570
- ABBV-8E12 2000 mg in Study M15-566, continuing the same in Study M15-570
- ABBV-8E12 300 mg in Study M15-566, ABBV-8E12 1000 mg in Study M15-570
- Placebo in Study M15-566, ABBV-8E12 2000 mg in Study M15-570.

For the CSF concentrations of total and free tau and their ratio and for the plasma concentrations of total tau and NFL, an MMRM analysis will be performed for scheduled measurements after study drug administration of Study M15-570 begins.

The model for the MMRM analysis performed for the tau variables and plasma NFL will include classification by treatment sequence and by time of measurement. There will be an effect for the interaction of treatment and time of measurement. Except for the ratio of CSF free tau concentration to CSF total concentration, the baseline value will be a covariate. For the ratio of CSF free to total tau, the value for baseline total tau concentration will be a covariate if this variable is found to be a significant covariate for the ratio in Study M15-566. The subjects in each treatment sequence will be viewed as a random sample, and an appropriate structure for the covariance matrix of the measurements of a subject will be selected.

For volumetric MRI variables, descriptive statistics will be provided for the baseline value and the change from baseline for each of the scheduled times of measurement. For each variable, an MMRM analysis will be performed for the changes from baseline. The analysis will be much like that described for plasma total tau concentration, but with estimated total intracranial volume (eTIV) as a covariate in addition to the baseline value.

For each region of the brain for which SUVR values are obtained from PET scans, an analysis like that described for plasma total tau concentration will be performed.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

Aβ	Amyloid
AD	Alzheimer's disease
ADA	Anti-drug antibody
ADCS-MCI-ADL-24	24-item Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for patients with mild cognitive impairment
ADL	activities of daily living
AE	Adverse event
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AUC	Area under the concentration time curve
BMI	Body mass index
C_2N	C_2N diagnostics company
CBD	Corticobasal degeneration
CDR	Clinical dementia rating
CDR-SB	Clinical Dementia Rating Sum of Boxes
CL	Clearance
C_{max}	Maximum observed serum concentration
CNS	Central nervous system
COVID-19	Coronavirus disease - 2019
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
CTE	chronic traumatic encephalopathy
C_{trough}	Observed serum drug concentration at the end of a dose interval
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DTP	Direct-to-patient
EC	Ethics committee

ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
E_{max}	Maximum effect
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels Health State Instrument
ERAC	Exposure-response analysis center
eTIV	Estimated total intracranial volume
GAM	generalized additive method
GCP	Good clinical practice
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/IWB	Interactive Voice-Response/Interactive Web-Based
K_D	Dissociation constant
LP	Lumbar puncture
MCI	Mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
NCS	Not clinically significant
NFL	Neurofilament light chain
NONMEM	nonlinear mixed effect modeling
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
QTc	QT interval corrected
QTcF	Fridericia-corrected QT interval
RBANS	Repeatable battery for assessment of neuropsychological status
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
TA MD	Therapeutic area medical director
TEAE	Treatment-emergent Adverse Event
US	United States
V	Volume of distribution
V/F	apparent volume of distribution
VAS	visual analogue scale
vMRI	Volumetric magnetic resonance imaging
WBC	White blood cell count
WHO	World Health Organization
WHO DRUG	World Health Organization Drug Dictionary

Definition of Terms

Treatment Visit Window	Visits during the Treatment Period may be scheduled within ± 4 days.
Study Drug Infusion	Study drug will be administered every 4 weeks for 5 years (65 infusions)
Treatment Period	Period of time to complete Day 1 through Week 260 or premature discontinuation (PD).
Post treatment Follow-up Period	Begins at the time of completion of the Treatment Period and continues up to 20 weeks. Subjects can also enter the Post treatment Follow-up Period in this study if they prematurely discontinue from treatment.

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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 (ADL), and a variety of neuropsychiatric and behavioral disturbances. The aggregation and accumulation of tau appears to play a critical role in AD and, unlike accumulation of Aβ, 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 ADL 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] Results from trials of anti-Aβ antibody therapies 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 that may be already showing clinical symptoms of AD.

ABBV-8E12

ABBV-8E12 is a humanized immunoglobulin G4 (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 tau-associated neurodegenerative disorders.

A detailed discussion of the ABBV-8E12 preclinical and nonclinical data can be found in the Investigator's Brochure.[4]

Clinical Experience

Compassionate-Use Protocols

Prior to the regular Investigational New Drug Application (IND) submission, treatment was initiated under an Expanded Access IND (United States [US]) for one patient with PSP, and subsequently for one patient with CBD under a compassionate-use treatment protocol (Germany). ABBV-8E12 was later administered to one patient with chronic traumatic encephalopathy (CTE) under an expanded access investigator-initiated protocol (US).

The PSP patient received 20 monthly infusions (highest dose 25 mg/kg), then died for reasons unrelated to study drug from 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 from 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. The CTE patient has received 15 infusions of ABBV-8E12 ranging from 2.5 to 25 mg/kg.

Phase 1 Single Ascending 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: subdural hematoma resulting from a fall (15 mg/kg dose group), hospitalization due to a severe increase in agitation, anxiety, and perseverative behavior (25 mg/kg dose group), and hospitalization for hypertension (50 mg/kg dose group).

No subject experienced a systemic hypersensitivity reaction or injection site reaction, and there were no clinically relevant patterns of adverse event (AE) 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.

Phase 2 Multiple-Dose Study in Subjects with AD

Study M15-566 is an ongoing Phase 2, randomized, multicenter, double-blind, placebo-controlled, multiple-dose trial in which 3 dose levels of ABBV-8E12 are being evaluated (300, 1000 and 2000 mg). A total of approximately 400 subjects (300 on ABBV-8E12 and 100 on placebo) are planned to participate in this study.

3.1 Differences Statement

Study M15-570 is the second study in which ABBV-8E12 will be administered to subjects with early AD after Study M15-566. ABBV-8E12 will be administered for an extended treatment period of up to 5 years compared with up to 96 weeks in Study M15-566. All subjects in Study M15-570 will be on active treatment (ABBV-8E12 1000 or 2000 mg), whereas Study M15-566 is a placebo-controlled study.

3.2 Benefits and Risks

There is a significant demand and unmet medical need for the development of disease-modifying drugs for AD. The aggregation and accumulation of tau appears to play a critical role in AD and correlates well with clinical disease progression. ABBV-8E12 may block tau seeds from propagating between cells and, therefore, may slow disease progression, thus providing a viable treatment option for patients with early AD.

The safety profile of ABBV-8E12 to date has been favorable and no clinically relevant patterns of adverse events or abnormal laboratory findings have been observed. Further, no ADAs were detected in post-dose samples in a SAD study in subjects with PSP. Risks include infusion reactions and possibly life-threatening allergic reactions; however, no systemic hypersensitivity or injection site reactions have been reported to date.

Evidence of efficacy demonstrated in preclinical studies and safety data from clinical studies obtained to date provide rationale for continuing assessment of safety and efficacy of ABBV-8E12. The benefit-risk profile of ABBV-8E12 will be further defined in this trial as well as the ongoing Study M15-566.

In consideration of the coronavirus disease 2019 (COVID-19) pandemic, the benefits and risks to subjects participating in this study have been re-evaluated. Based on the limited information to date and due to the mechanism of action of ABBV-8E12, no additional risk is anticipated for study participants infected with SARS-Cov2 during the COVID-19 pandemic.

4.0 Study Objectives

The primary objective of this study is to assess the long-term safety and tolerability of ABBV-8E12 in subjects with early AD.

The secondary objective of this study is to assess the pharmacokinetics (PK) of ABBV-8E12 in subjects with early AD.

The exploratory objectives of this study are:

- To assess the long-term efficacy of ABBV-8E12 in slowing disease progression in subjects with early AD.
- To assess the long-term effect of ABBV-8E12 on a range of disease-related and drug-related biomarkers in subjects with early AD.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This Phase 2 extension of a multiple dose, multicenter, multinational, randomized, double-blind study is designed to evaluate the long-term safety and tolerability of ABBV-8E12 in subjects with early AD. The study will consist of a 5-year treatment period and a follow-up period of approximately 20 weeks following the last study drug administration.

All subjects who complete the Treatment Period in Study M15-566 will be eligible to participate in this study according to the selection criteria. Upon completion of baseline study procedures, eligible subjects will receive ABBV-8E12 via intravenous (IV) infusion on Day 1 of Study M15-570 as follows:

- Subjects who received placebo in Study M15-566 will receive 2000 mg ABBV-8E12 in Study M15-570;
- Subjects who received 300 mg ABBV-8E12 in Study M15-566 will receive 1000 mg ABBV-8E12 in Study M15-570; and
- Subjects who received 1000 mg or 2000 mg ABBV-8E12 in Study M15-566 will continue on the same dose in Study M15-570.

Note: if any changes are made to alter Study M15-566 with regards to the treatment arms due to safety, efficacy, or other reasons, a corresponding change will be implemented in Study M15-570. This change may include, but is not limited to, adding or dropping treatment arm(s).

Subjects will receive study drug infusion every 4 weeks and undergo other study procedures and assessments as outlined in the Study Activities table (Appendix C). Subjects will continue to receive treatment until one of the discontinuation criteria is met, the sponsor discontinues the study, or the subject completes the 5-year treatment period of Study M15-570. Refer to Section 5.4 for detailed description of discontinuation criteria.

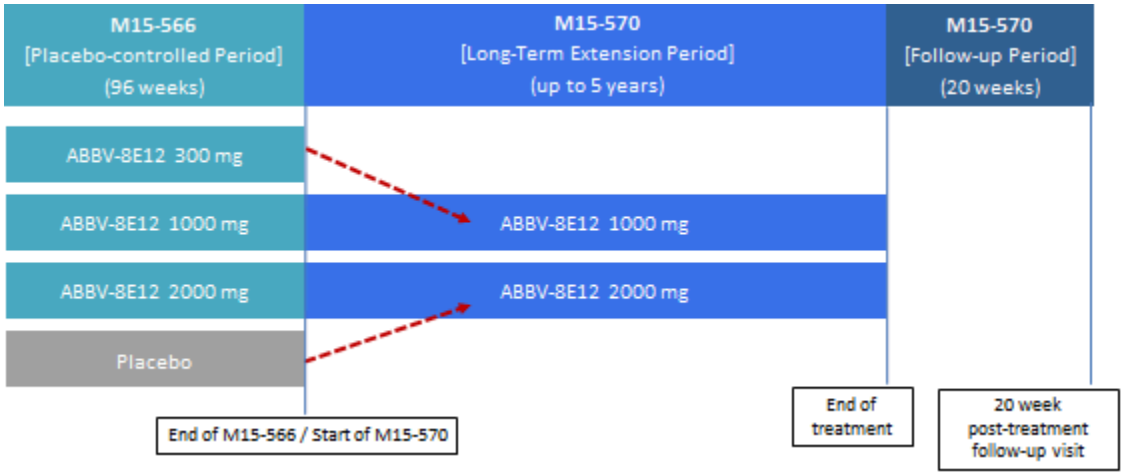
Day 1 visit of Study M15-570 (day of the first dose of Study M15-570) will be approximately 4 weeks but no more than 8 weeks after the Week 92 visit of Study M15-566. Should this window be longer than 8 weeks, the subject may be considered for participation in Study M15-570 only with the approval of the therapeutic area medical director (TA MD) or designee. The investigators and subjects will remain blinded to the treatment assignments in Study M15-566 and will be blinded to the dose level of ABBV-8E12 in Study M15-570.

For subjects who do not have extended interruptions in study drug administration between Study M15-566 and Study M15-570 (i.e., the duration between the last dose of study drug in Study M15-566 and the first dose of study drug in Study M15-570 is no more than 8 weeks), certain procedures that were performed at the Week 96 Visit in Study M15-566 do not need to be repeated for the Day 1 Visit in Study M15-570.

Safety will be closely monitored during the study conduct. The study will also utilize an external data monitoring committee (DMC), which will review accumulating study data and make recommendations based on the emerging safety profile of ABBV-8E12. The DMC membership, responsibilities, operating logistics, and timing of reviews will be documented in a charter that will be finalized prior to the first DMC review meeting.

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

Figure 1. Study Schematic



Detailed information regarding the regimens/treatments administered and assignment of the subjects to the treatment sequences can be found in Section 5.5.1 and Section 5.5.3.

5.2 Selection of Study Population

All subjects with early AD who complete Study M15-566, meet all inclusion criteria, and do not meet any exclusion criteria will be eligible for enrollment.

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 institutional review board (IRB)/independent ethics committee (IEC) approved informed consent, prior to the conduct of any extension study-specific procedures (including any changes occurring in the subject's current therapeutic regimen). In the absence of subject's ability to provide the informed consent, 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. Subject completed the 96-week treatment period of Study M15-566.
3. In the investigator's opinion, subject was compliant during participation in Study M15-566.
4. Subject has an identified, reliable study partner (e.g., caregiver, family member, social worker, or friend; preferably the same person for the duration of the study) who has frequent contact with the subject (at least 10 hours per week) and who will provide information as to the subject's cognitive and functional abilities. The study partner has voluntarily signed the IRB/IEC approved study partner informed consent, prior to the conduct of any extension study-specific procedures.
5. 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).
6. 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.

Rationale for the Inclusion Criteria

1	In accordance with the harmonized Good Clinical Practice (GCP)
2 – 4	To select subject population appropriate for this study
5 – 6	The effects of ABBV-8E12 on pregnancy are currently unknown.

5.2.2 Exclusion Criteria

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

1. The subject has any significant change in his/her medical condition since participation in Study M15-566 that could interfere with the subject's participation in Study M15-570, could place the subject at increased risk, or could confound interpretation of study results. The investigator must re-evaluate the subject for continuing participation and consider relevant factors including:
   - interim development of any clinically significant neurological, hematological, autoimmune, endocrine, cardiovascular, neoplastic, renal, hepatic, metabolic, psychiatric, pulmonary, gastrointestinal, or other major disorder
   - interim development of contraindication to or inability to tolerate brain MRI or positron emission tomography (PET) scan
2. More than 8 weeks have elapsed since the subject received his/her last dose of study drug in Study M15-566 (i.e., Week 92 visit in Study M15-566). In certain cases, subject may be eligible to enroll after approval by the TA MD or designee.
3. Subject is concurrently enrolled in another interventional clinical study (with the exception of Study M15-566) involving a therapeutic agent.
4. Subject is considered by the investigator, for any reason, to be an unsuitable candidate to receive ABBV-8E12 or the subject is considered by the investigator to be unable or unlikely to comply with the dosing schedule or study evaluations.

Rationale for Exclusion Criteria

1	To ensure the safety of the subjects
2	To allow the TA MD to delegate responsibility
2, 4	To select subject population appropriate for this study
3	These products may interfere with the PK 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 medically

necessary at any point during 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 in the electronic case report form (eCRF).

The AbbVie TA MD should be contacted with any questions regarding concomitant or prior therapy(ies).

5.2.3.1 Prohibited Therapy

There are no prohibited medications for this long-term extension study. All concomitant medications, including any change in dose, must be recorded as described in Section 5.2.3.

Anticoagulants may be exclusionary for optional lumbar punctures (LPs). Some subjects may be able to temporarily cease use of anticoagulant therapy in the limited duration surrounding the optional LP procedures.

Regularly scheduled or as needed (PRN) use of medications with psychotropic effects (some examples in Table 1, not a comprehensive list) should be considered in the context of the cognitive assessments and avoided when medically not necessary, so as not to confound interpretation of the assessments. 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 should not be administered within 48 hours of a PRN medication administration.

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.

Subject should be discontinued from the study if she/he starts receiving an approved disease-modifying therapy for AD or a biologic medication for the treatment of AD. Refer to Section 5.4.1 for other discontinuation criteria.

The AbbVie TA MD should be contacted if there are any questions regarding concomitant and prior medications.

Table 1. Medications That Require Special Consideration

Anticoagulants (May Be Exclusionary for Optional Lumbar Punctures*)	
Generic Name:	Brand Name:
Vitamin K antagonists	Warfarin, Acenocoumarol, Phenprocoumon
Enoxaparin sodium	Lovenox
Dabigatran	Pradaxa
Rivaroxaban Apixaban	Xarelto
Edoxaban	Eliquis
Heparin	Lixiana
***Some subjects may be able to temporarily cease use of anticoagulant therapy in the limited duration surrounding optional lumbar punctures.**	
Neuroleptics:	
Generic Name:	Brand Name:
Chlorpromazine	Thorazine
Fluphenazine	Prolixin
Loxapine	Loxitane
Perphenazine	Etrafon, Trilafon
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Clozapine	Clozaril
Haloperidol	Haldol
Anticholinergic Agents:	
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

Table 1. Medications That Require Special Consideration (Continued)

Antiparkinsonian Medications:	
Generic Name:	Brand Name:
Bromocriptine	Parlodel
Deprenyl/Selegiline	Eldepryl
Levodopa	Sinemet
Pergolide	Permax
Pramipexole	Mirapex
Sedatives/Benzodiazepines:	
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:	
Generic Name:	Brand Name:
Clonidine	Catapres

Note: Brand names may vary by country/region.

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

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 and 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 this study, each subject must have a study partner (e.g., caregiver, family member, social worker, or friend; preferably the same person for the duration of the study), 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. In exceptional cases when the study partner is not available to accompany the subject to an applicable study visit, he/she may provide the information regarding subject's cognitive and/or functional abilities by telephone. For subjects that prematurely discontinue the study, safety and efficacy assessments may be conducted remotely (for example, via telephone), where applicable.

Medical History Update

For all subjects, an update to the medical history (from that obtained in Study M15-566), including subject's history of cognitive impairment and any medications taken for AD or mild cognitive impairment (MCI), will be obtained on Day 1. The updated medical history on Day 1 will serve as the baseline for clinical assessment.

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 Baseline 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 AEs.

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 (Appendix C). The neurological exam performed on Day 1 will serve as the baseline for clinical assessment. Symptoms identified during Day 1 will be recorded as AEs for Study M15-566; however, new symptoms or current symptoms that change in severity or frequency after Day 1 of study drug administration will be recorded as AEs for Study M15-570.

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 (Appendix C). 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 (NCS)

- 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 (QTc) for heart rate will be determined using Fridericia-corrected QT interval (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 follows:

- Day 1 (Dose 1):
  - Pre-dose (within approximately 15 minutes before infusion begins)
  - Post-dose (within approximately 15 minutes after sodium chloride flush is completed)
- Weeks 12, 24, 52, 104, 156, and 208:
  - Pre-dose (within approximately 15 minutes before infusion begins)

- Week 260 (Study Completion / Premature Discontinuation Visit):
  - May be done at any time during the visit

Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 2 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 2. 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 mean corpuscular hemoglobin concentration Prothrombin time (PT)[c] Activated partial thromboplastin time[c] PT/INR (prothrombin time/international normalized ratio)[c]	Blood urea nitrogen Creatinine Total bilirubin Albumin Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphate Uric acid Cholesterol Total protein Glucose Triglycerides Bicarbonate/CO_2 Chloride Thyroid Stimulating Hormone (TSH)[a] Thyroxine (T4)[a] Vitamin B12 (cobalamin)[a]	Specific gravity Ketones Ph Protein Glucose Blood Microscopic examination, if dipstick results are positive
		CSF Basic Labs with Optional LPs[b]
		RBC, WBC with differential Total Protein Albumin Glucose
		Reference Tests if Vitamin B12 is Under the Lower Limit of Normal Range
		Methylmalonic Acid Homocysteine

CSF = Cerebrospinal fluid; INR = international normalized ratio; LP = Lumbar puncture; PT = Preferred term; RBC = Red blood cell count; T4 = Thyroxine; TSH = Thyroid stimulating hormone; WBC = White blood cell count

a. Optional. Not required if using Study M15-566 Week 96 visit for Baseline.

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

c. Only in subjects who undergo LPs.

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 AE.

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 AEs. Accordingly, for any values outside of the reference range, the investigator will indicate on the report if the result is clinically significant (CS) or 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 AE or document in source the reason(s) the finding was not considered an AE.

Any laboratory value that remains abnormal at premature discontinuation (PD)/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.

Optional Lumbar Puncture

LPs to collect cerebrospinal fluid (CSF) are optional procedures in Study M15-570. Subjects may still participate in the study even if they decide not to participate in this optional sample collection.

For all subjects who agree, LPs will be performed at time points indicated in the Study Activities table (Appendix C). 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 LP 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 LP/CSF collection. These measures may include cell counts (Red blood cell count [RBC] and white blood cell count [WBC] with differential), total protein, albumin, and glucose. Other CSF measurements (e.g., ABBV-8E12 concentration, tau, and other 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, bedrest, 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 LP include infection, damage to nerves in the back, and bleeding into the CSF space. The risk of these is much less than 1%.[5]

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

For all subjects, a 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.

MRI assessment at Day 1 will be used as baseline for evaluating changes during the study. Signal abnormalities on FLAIR or T2 weighted images will be evaluated to determine the presence of 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 starting from Baseline.

The MRI scan should be done prior to the optional LP, if applicable. 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 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 time points indicated in the Study Activities table (Appendix C). Subjects who did not complete tau PET imaging through Study M15-566 and at Study M15-570 Day 1/Baseline will have tau PET imaging performed at subsequent visits only after discussion with the TA MD or designee.

Tau deposition in the brain, unlike Aβ, tracks closely with the cognitive decline of AD. Preclinical data suggests 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 for Day 1/Baseline should be carried out prior to administration of the first dose.

If the optional 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 obtained at the next onsite visit with the exception of Day 1/Baseline, which should be obtained prior to the administration of the first dose.

Diagnostic Tools and Rating Scales

Raters 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. The objective of this certification/training is to establish uniformity across sites in the administration, interpretation and scoring of these rating instruments. 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(s), 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(s). Individual exceptions to these requirements must be approved by the sponsor via the training vendor. The recommended order of administration is Clinical Dementia Rating (CDR) followed by 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) and EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L) may be administered/assessed at any subsequent time during the visit. The timing and arrangements for the rating scales are presented in Table 3. The order of the administration of scales at each visit should be consistent throughout the study.

Table 3. Diagnostic Tools and Scale Administration Timing

Scale[a]	Recommended Order of Administration	Approximate Administration Time[b] (Minutes)
CDR	1	45 – 75
RBANS	2	25
ADCS-MCI-ADL-24	c	30 – 45
EQ-5D-5L	c	5
C-SSRS	c	5 – 20

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; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels Health State Instrument; RBANS = Repeatable battery for assessment of neuropsychological status

a. See Study Activities table in Appendix C for all time points.

b. Breaks should be taken as necessary.

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

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 the Study Activities table (Appendix C).

The diagnostic tools and rating scales include the following:

Clinical Dementia Rating (CDR)[6]

The CDR is a numeric scale used to quantify the severity of symptoms of dementia. A qualified health professional will assess a subject'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 to 3 for each of the 6 areas. The sum of these six areas, the CDR sum of boxes (Clinical Dementia Rating Sum of Boxes [CDR-SB]) score can range from 0 to 18.

The CDR-SB score will be calculated at each time point. The CDR will be administered to both the subject and the study partner at the times indicated in the Study Activities table (Appendix C).

24-Item Alzheimer's Disease Cooperative Study/Activities of Daily Living Scale Adapted for Patients with Mild Cognitive Impairment (ADCS-MCI-ADL-24)[7-10]

The ADCS-MCI-ADL-24 is a 24-item study partner-based assessment of ADL designed specifically for MCI patients and is completed by a trained rater. The scale assesses functional activities such as grooming, 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 ADL. 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 the Study Activities table (Appendix C).

Repeatable Battery for Assessment of Neuropsychological Status (RBANS)[11]

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 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 subject at the times indicated in the Study Activities table (Appendix C).

EuroQuality of Life-5-level (EQ-5D-5L)[12,13]

The EuroQuality of Life-5-level (EQ-5D-5L) Proxy Version 1 measures overall health status. The caregiver (the proxy) will rate the patient's health status in their (the proxy's) opinion. The scale contains a descriptive system comprised of 5 dimensions [(1) mobility, (2) self-care, (3) usual activities, (4) pain/discomfort, and (5) anxiety/depression]. These health states get scored on 5 levels of severity [(1) no problems, (2) slight problems, (3) moderate problems, (4) severe problems, and (5) unable to/extreme problems] and a visual analog scale (VAS) to evaluate current health state from 0 (worst imaginable) to 100 (best imaginable). The descriptive profile can be converted into a value (EQ-Index) which ranges from 0 (death) to 1 (perfect health), with negative values indicating health states considered worse than death. The EQ-5D-5L Proxy Version 1 will be administered at the times indicated in the Study Activities table (Appendix C).

Columbia-Suicide Severity Rating Scale[14]

The C-SSRS is a systematically administered instrument developed to track suicidal AEs 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 may also be excluded from the study based on the clinical judgment of the investigator.

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 reference the table below for scales that may be administered remotely.

Scale	May be Administered Via Phone or Video Conference
ADCS-MCI-ADL-24	Yes
CDR	Yes
C-SSRS	Yes
EQ-5D-5L	Yes
RBANS	No

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; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels Health State Instrument; RBANS = Repeatable Battery for Assessment of Neuropsychological Status

5.3.1.2 Collection and Handling of Biomarker and Pharmacogenetic Research Samples

Blood and Optional CSF Biomarker Samples

Blood and CSF samples will be collected at the times specified 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 5.3.6.1).

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 scheduled on a day of dosing will be collected prior to the start of the infusion. Blood samples collected at Year 5 (Study Completion)/PD Visit may be collected at any time during that visit. Optional CSF samples will be collected by optional LP at the time points indicated in the Study Activities table (Appendix C).

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 or per local requirement. 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 from each consenting subject at the time points indicated in the Study Activities table (Appendix C). All pharmacogenetic samples 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 PK assays of ABBV-8E12 will be provided by the central laboratory, the sponsor, or its designee. The schedule for collection of blood samples is summarized in Appendix C.

Blood Samples for ABBV-8E12 Assay

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

- **Day 1 and Weeks 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 and 240**

- Prior to the start of the infusion.

- **Week 260 (Study Completion)/PD Visit**
  - Sample may be collected anytime during the day.
- **20 weeks post last dose (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:

- **Day 1 and Weeks 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240**
  - Prior to the start of the infusion.
- **Week 260 (Study Completion)/PD Visit**
  - Sample may be collected anytime during the day.
- **20 weeks post last dose (Post-Treatment Follow-Up Period)**
  - Sample may be collected anytime during the day.

Optional CSF Samples for ABBV-8E12 Assay

CSF samples will be collected at times specified in the Study Activities table (Appendix C) by LP. Information on the optional LP procedure can be found in the Lumbar Puncture section of Study Procedures section (Section 5.3.1.1).

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event blood samples for ABBV-8E12/ADA assays and the optional CSF for the ABBV-8E12 assay may not be performed due to study modifications related to the COVID-19 pandemic, these samples should be obtained at the next onsite visit.

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 ADA.

5.3.3 Efficacy Variables

Exploratory efficacy measures are described in Section 5.3.1.1 along with other study procedures and will be derived from assessments of CDR, RBANS, ADCS-MCI-ADL-24, and EQ-5D-5L.

5.3.4 Safety Variables

The following safety evaluations will be performed and safety information will be collected during the study: Adverse event monitoring, vital signs, physical examination, neurological examination, ECG, laboratory tests, C-SSRS, and MRI assessments, and immunogenicity as determined by ADA responses in blood.

5.3.5 Pharmacokinetic Variables

Values for the following PK parameters will be estimated using a mixed-effect modeling approach: clearance (CL) and volume of distribution (V). Additional parameters may be calculated if useful in the interpretation of the data. Pharmacokinetic data from this study may be combined with data from other ABBV-8E12 studies for PK analyses.

5.3.6 Biomarker and Pharmacogenetic Research Variables

5.3.6.1 Biomarker Research Variables

Optional CSF and Plasma Concentration Variables

CSF samples will be assayed for free 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 tau. CSF samples will also be analyzed for neurofilament light chain (NFL). Plasma samples will be assayed for total tau and NFL to understand the relationship to disease progression and response to treatment.

CSF and blood samples may also be analyzed for biochemical or macromolecular factors (e.g., Aβ 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 main clinical study report, but may be described in a separate biomarker addendum.

Volumetric MRI

Baseline volumetric MRI (vMRI) measurements and measurements on change from baseline in vMRI measurements will be obtained. The value itself for a given visit will be obtained by adding the baseline value to the value for change from baseline. Measurements will be obtained for whole brain, hippocampus, temporal lobes, and lateral ventricles. Measurements may be obtained for additional regions. The baseline measurement will be the same as the baseline measurement for Study M15-566, that is,

the last measurement obtained before the first study drug administration of Study M15-566.

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). Additional variables (e.g., proportion of voxels within a target region that have a SUVR greater than a predetermined cutoff value) that reflect the extent or spread of tau pathology might also be assessed. 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.

5.3.6.2 Pharmacogenetic Research Variables

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 PK, 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

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 AE or noncompliance with the protocol.

The subject will be discontinued from the study if any of the following occur:

- Subject starts receiving an approved disease-modifying therapy for AD or a biologic medication for the treatment of AD.
- Subject develops unacceptable toxicity.
- Female subject becomes pregnant.
- Investigator decides it is in the subject's best interest to discontinue.
- Subject is noncompliant with the protocol based on the investigator or medical monitor assessment.
- Subject withdraws consent.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.

Subjects with the following AEs 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 AEs 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 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 AEs 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 AEs; 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 AE 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 AE is achieved.

For subjects who prematurely discontinue the study for reasons other than withdrawal of consent safety and efficacy assessments may be conducted remotely (for example, via telephone), where applicable.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

For subjects who miss 3 or more study drug doses due to the COVID-19 pandemic, the TA MD should be contacted to discuss continuation in the study.

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 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 every 4 weeks ± 4 days. 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 (inclusive)	Infusion Rate*
26.0 – 34.9 kg	2.1 mL/min or 126 mL/hr
35.0 – 44.9 kg	2.8 mL/min or 168 mL/hr
45.0 – 59.9 kg	3.6 mL/min or 216 mL/hr
60.0 – 89.9 kg	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. Any subject weight between whole numbers should be rounded down to the lower number (i.e., select lower infusion rate/longer infusion time).

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	Infusion
ABBV-8E12 1000 mg ABBV-8E12 2000 mg	IV infusion every 4 weeks ± 4 days for 5 years (Total of 65 infusions)

Doses may be modified after evaluation by the DMC of the safety, tolerability, and available PK data or in accordance with changes made in Study M15-566.

The start and stop time of each study drug infusion will be recorded to the nearest minute. 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 IRB/IEC requirements for home healthcare. Any prerequisite submissions or notifications to the site IRB/IEC 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 products to be used in this study is presented in Table 4.

Table 4. Identity of Investigational Product

Investigational Product	Mode of Administration	Formulation	Strength
ABBV-8E12	Infusion	Solution for infusion in a vial	1000 mg/10 mL
ABBV-8E12	Infusion	Solution for infusion in a vial	2000 mg/20 mL

0.9% Sodium Chloride Injection/Solution for Infusion will be administered 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 study, it will be labeled with a blinded dispensing label by the unblinded pharmacist or qualified designee as required. 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 AbbVie. Study drug should be quarantined and not dispensed until AbbVie (or temperature excursion management system) deems drug as acceptable. Study drug should be quarantined and not dispensed until AbbVie (or temperature excursion management system) deems drug as acceptable.

Investigational products (IPs) 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 doses will be performed by the unblinded site pharmacist or qualified designee. Written instructions for the preparation of ABBV-8E12 solutions for infusion will be provided as a Pharmacy Manual separate 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 enrolled in the study, the IVR/IWB system will retain the unique 5-digit subject number from Study M15-566. The first digit will be 2, the second and third digits will be the site number (00, 01, 02, etc.) and the fourth and fifth digits will be assigned in ascending numerical order at each site.

Subjects in this study will receive ABBV-8E12 as follows:

- Subjects who received placebo in Study M15-566 will receive 2000 mg ABBV-8E12 in Study M15-570;
- Subjects who received 300 mg ABBV-8E12 in Study M15-566 will receive 1000 mg ABBV-8E12 in Study M15-570; and
- Subjects who received 1000 mg or 2000 mg ABBV-8E12 in Study M15-566 will continue on the same dose in Study M15-570.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the doses for this study is discussed in Section 5.6.4. Each subject will receive ABBV-8E12 as described in Section 5.5.3. ABBV-8E12 will be administered every 4 weeks via IV infusion, preferably in the morning.

5.5.5 Blinding

The investigator and study site personnel (except the unblinded pharmacist) will remain blinded to the treatment throughout the course of the study.

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 sequences. For IP monitoring, there will be an unblinded AbbVie monitor for verification of unblinded documentation. The unblinding procedure for the unblinded pharmacist/designee and the unblinded AbbVie monitor will be defined in a separate study-specific document.

The IVR/IWR 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

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 for safety assessment. SAS data sets blinded with respect to treatment assignment will be sent to an external statistical center by AbbVie. The randomization schedules of Study M15-570 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. The AbbVie Internal Executive Review Committee (IERC) may request access to closed reports if the DMC recommends that the study be discontinued or that the study design undergo major modifications, as outlined in the DMC charter. All other AbbVie personnel will remain blinded to the treatment

assignment. The AbbVie Primary Contact 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 Pharmacy Manual separate 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 primarily designed to assess the long-term safety and tolerability of ABBV-8E12 in subjects with early AD when administered for up to 5 years. Toxicity management in the parallel group design is described in Section 6.1.6.

5.6.2 Appropriateness of Measurements

Standard PK, statistical, and clinical procedures will be utilized in this study. On-treatment safety evaluations (neurological examinations, AE monitoring, ECGs) are scheduled 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 selection criteria are intended to identify suitable subjects from those who participated in Study M15-566 and have the potential to benefit from treatment and not be exposed to undue risk.

5.6.4 Selection of Doses in the Study

The doses chosen for the study (1000 mg and 2000 mg) were selected based on the 2 highest doses used in Study M15-566, which were determined based on available safety and tolerability data from the SAD study in subjects with PSP (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.

The highest dose in Studies M15-566 and M15-570, 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.

In the 4-week preclinical mouse toxicology study, the highest dose tested was 250 mg/kg and the corresponding maximum observed serum concentration (C_{max}) and area under the concentration time curve $(AUC)_{0\text{-}168h}$ were 3050 µg/mL and 298,000 hr•µg/mL (on

Day 22) after 4 doses administered weekly. Assuming the PK of ABBV-8E12 is linear, the steady-state PK profiles were simulated at 1000 and 2000 mg following monthly administration of ABBV-8E12 based on the PK 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 1000 and 2000 mg is approximately 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 PK 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 dissociation constant (K_D) of ABBV-8E12 determined in vitro, it is estimated that the average tau binding in CSF by the antibody at predicted C_{trough} and C_{max} values over the 28-day period ranges from approximately 60% to 80% for 1000 mg and 75% to 90%, for 2000 mg ABBV-8E12 doses.

This study will enable further exploration of the safety profile of ABBV-8E12 at the 1000 mg and 2000 mg dose levels.

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 IP must be reported to the sponsor (Section 6.2.2). For AEs, 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 AEs on a routine basis throughout the study. The investigator will assess and record any AE in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the AE to study drug, and any action(s) taken. For SAEs considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "Other" cause of the event. For AEs to be considered intermittent, the events must be of similar nature and severity. Adverse event, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All AEs will be followed to a satisfactory conclusion.

Subjects should be monitored for at least 30 minutes after the end of study drug infusions. Longer observation periods and more frequent vital sign checks may be required in subjects who experience infusion reactions.

6.1.1 Definitions

6.1.1.1 Adverse Event

An AE 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 AE 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 preexisting condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from

the study, necessitate therapeutic medical intervention, meet protocol specific criteria for PCS laboratory values defined in Appendix D and/or if the investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a preexisting condition and the surgery/procedure has been preplanned prior to study entry. However, if the preexisting 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 AE.

6.1.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to AbbVie as a SAE within 24 hours after the site becomes aware of the SAE:

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 SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form (CRF).

6.1.2 Adverse Event Severity

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

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subject's usual activities.
Severe	The AE 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 AE to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

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.

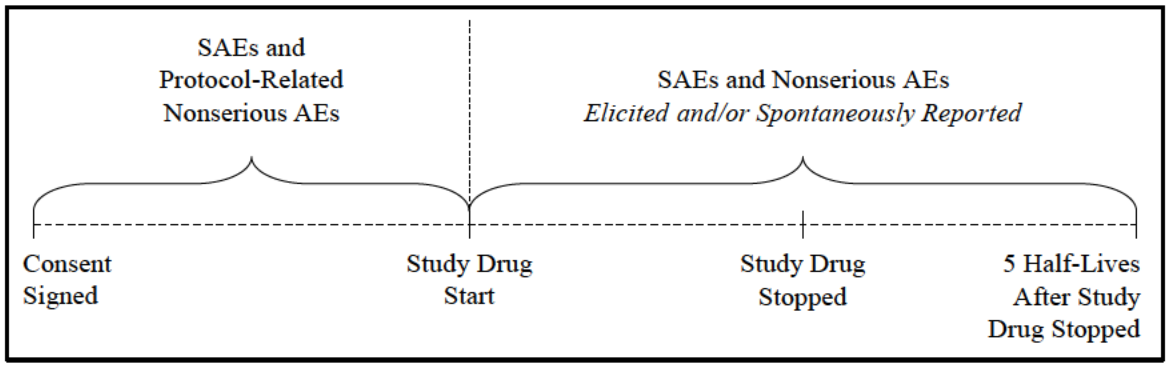
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the SAE.

6.1.4 Adverse Event Collection Period

All AEs 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, SAEs and protocol-related nonserious AEs 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



AE = adverse event; SAE = serious adverse event

6.1.5 Adverse Event Reporting

In the event of a SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours after the site becomes aware of the SAE by entering the SAE data into the electronic data capture (EDC) RAVE® system. SAEs 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 after the site becomes aware of the SAE.

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]
1 North Waukegan Road
North Chicago, IL 60064

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

In emergency situations involving study subjects when the primary 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's Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a 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.

SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible ethics committees (ECs) 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 AEs and laboratory abnormalities that occur during the study must be evaluated by the investigator.

A drug-related toxicity is an AE 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.[8] 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 AEs, including allergic reactions, during the infusion. 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. Moderate infusion reactions resolving with supportive care should be discussed with the TA MD, and a reduction of the infusion rate for future administrations can be considered.

6.1.6.2 Management of Adverse Events of the Nervous System

Subjects will be closely monitored for AEs suggesting neurotoxicity. Drug related AE 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 AEs 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 AEs 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 IP must be reported to the sponsor within 1 business day 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 AEs 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 contacts:

Primary Contact:		Alternate Contact:	
[redacted]		[redacted]	
Office: Email:	[redacted]	Mobile: Email:	[redacted]

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

Efficacy assessment will be an exploratory objective in this study. The data analyses will be grouped by assigned treatment sequences/groups in Studies M15-566/M15-570: 300/1000 mg, 1000/1000 mg, placebo/2000 mg, and 2000/2000 mg. If the one-sided unadjusted *P* value is ≤ 0.100 for the difference in treatment effect between ABBV-8E12 2000 mg and placebo at Week 96 in Study M15-566, a delayed-start analysis will be

conducted. The 2000/2000 mg group will be the early start group, and placebo/2000 mg will be the delayed-start group for the delayed-start analysis. Details of the analysis plan will be specified in the statistical analysis plan (SAP).

8.1.1 Analysis Data Sets

Data Sets for Efficacy Analyses

Two data sets will be created for the efficacy analysis: an intent-to-treat (ITT) data set and a delayed-start data set.

ITT Data Set: The Study M15-570 ITT data set consists of all subjects who received any dose of study drug in Study M15-570. All efficacy analyses will be conducted on the ITT data set using data from Study M15-570 alone unless otherwise specified.

Delayed-Start Data Set: The delayed-start analysis data set includes all subjects from the Study M15-566 ITT data set who received placebo or ABBV-8E12 2000 mg in Study M15-566 regardless of whether they enroll in Study M15-570 or not. For the delayed-start analysis, efficacy data from both Studies M15-566 and M15-570 will be included.

Data Set for Safety Analyses

The safety data set will consist of all subjects who received any dose of study drug in Study M15-570. For safety analyses, the actual treatment received will be used instead of the treatment assignment at enrollment.

Data Set for Biomarkers

The subjects of the data set for biomarkers will be all subjects who have biomarker data for at least one scheduled visit later than Visit 1 of Study M15-570. The data of a subject included for the analysis of a biomarker variable will include the baseline value of Study M15-566, which will also be the baseline value for Study M15-570, and all the data of Study M15-570 after Day 1 (day of the first dose of Study M15-570).

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 sequence and for all treatment sequence combined for the safety data set.

The number and percentage of subjects who prematurely discontinue study drug will be summarized by treatment sequence and overall for 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 sequence difference in subject's disposition.

Demographic and Other Baseline Characteristics

Demographics will be summarized for the ITT data set unless otherwise specified. Treatment sequence differences will be evaluated using overall tests. No pairwise comparisons between treatment sequences 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 sequence and for all treatment sequences combined. The overall treatment sequence 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 sequence and for all treatment sequences combined. Fisher's exact test will be carried out to assess the overall comparability of treatment sequences based on two-sided tests.

Efficacy and clinical measures taken at baseline (CDR-SB score, RBANS, ADCS-MCI-ADL-24, and EQ-5D-5L) will be summarized for the ITT data set only. One-way ANOVA will be used to assess the overall comparability of treatment sequences for all measurements.

Medical History

Medical history data, including subject's history of early AD or MCI, will be summarized for the safety data set 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 sequence 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 of comparisons will be performed with a 2-sided test at the significance level of 0.050 unless otherwise specified. All efficacy assessments that are taken no more than 45 days after the last dose of study drug will be included in the efficacy analyses.

Analyses of the efficacy variables CDR-SB score, ADCS-MCI-ADL-24 total score, RBANS total scores, and EQ-5D-5L score will be performed on the Study M15-570 ITT data set. The analysis model is a likelihood-based, mixed model repeated measures (MMRM) analysis at Study M15-570 Baseline and each post-baseline observation using all observed data. This MMRM analysis will be applied to each efficacy variable with repeated measurements. Details of the analysis will be described in the SAP.

The delayed-start analysis will be conducted on the change from Baseline of Study M15-566 up to Week 96 in Study M15-570 on CDR-SB score. An MMRM analysis model will be used. Details of the analysis will be specified in the SAP.

8.1.4 Safety Analyses

Comparisons between treatment sequences (Study M15-566 and Study M15-570) of interest will not be performed.

All other safety assessments that are taken no more than 45 days after the last dose of study drug will be included in the safety evaluation of the Treatment Period, and all safety assessments that are taken more than 45 days but not more than 20 weeks after the last dose of study drug will be included in the safety evaluation for the Post-treatment Follow-up Visit.

8.1.4.1 Study Drug Exposure and Compliance

The number of doses of study drug will be summarized by treatment sequence and overall subjects. The number and percentage of subjects with at least 90% compliance with study drug dosing (i.e., complete 90% of scheduled doses for each subject) will be summarized by treatment sequences and overall subjects. No comparisons between treatment sequences will be performed.

8.1.4.2 Analysis of Adverse Events

The safety data set will be used for the AE summary.

Adverse event will be coded using the most current version of the MedDRA. The number and percentage of subjects who report treatment-emergent adverse events (TEAEs) will be tabulated by the SOC and preferred term for the treatment sequences specified in Section 8.0. No comparisons between treatment sequences will be performed.

The number and percentage of subjects who experienced treatment emergent SAEs (including deaths) and AEs leading to PD of study drug will be tabulated by the MedDRA

SOC and preferred term for treatment sequences specified in Section 8.0. No comparisons between treatment sequences will be conducted for AE summaries.

A TEAE is defined as any AE that begins or worsens in severity on or after the date of the first dose of study drug and no more than 20 weeks after the date of the last study dose.

8.1.4.3 Analysis of Laboratory Tests

Analysis will be performed on the safety data set for laboratory tests. Change from Baseline to each visit value and to the minimum, maximum, and final value will be presented for each continuous hematology, chemistry, and urinalysis parameter. Treatment differences between treatment sequence in change from Baseline to minimum, maximum, and final clinical laboratory evaluation will be analyzed using a 1-way ANOVA with treatment sequence as the main effect.

For each treatment sequence, 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. Laboratory observations will be categorized as normal, low, or high relative to the reference (normal) range associated with the laboratory that performed the assay. Details will be specified in the SAP.

The number and percentage of subjects in each treatment sequence who have values meeting predefined criteria for PCS (Appendix D) at any time after the first dose of study drug and no more than 20 weeks after the last dose of study drug will be summarized separately for hematology and chemistry variables. No comparisons between treatment sequences will be performed for PCS analysis.

8.1.4.4 Analysis of Vital Signs and Weight

Analysis will be performed on the safety data set for vital signs and weight. Vital sign variables for this study will be pulse rate, systolic blood pressure, diastolic blood pressure, body temperature, weight, and BMI.

Change from Baseline to each visit value and to the minimum, maximum, and final value will be presented for each vital sign and weight variable and analyzed using a 1-way ANOVA with treatment sequence as the main effect.

The number and percentage of subjects in each treatment sequence who have values meeting predefined criteria for PCS (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 will be summarized. No comparisons between treatment sequences will be conducted.

8.1.4.5 Analysis of ECG Variables

Analysis of ECG variables will be performed on the safety data set. ECG variables for this study will be heart rate, PR, QRS, QT, and QTcF intervals. Change from Baseline to final value will be presented for each ECG parameter and analyzed using a 1-way ANOVA with treatment sequence as the main effect.

The number and percentage of subjects in each treatment sequence who have values meeting predefined criteria for PCS (definitions will be provided in the SAP) at any time after the first dose of study drug will be summarized.

8.1.4.6 Analysis of C-SSRS

Analysis of C-SSRS will be performed on the safety data set. The number and percentage of subjects in the following categories will be summarized for each treatment sequence 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), and

- Had suicidal ideation or behavior (defined as answering "Yes" to one or more suicidal ideation or behavior items).

8.1.5 Biomarker Analyses

For plasma concentration variables, CSF concentration variables, volumetric MRI variables, and tau PET variables identified in Section 5.3.6.1, descriptive statistics will be provided for each scheduled time of measurement with a breakdown by group as defined by treatment in Study M15-566 and treatment in this study. That is, the 4 treatment sequences are as follows:

- ABBV-8E12 1000 mg in Study M15-566, continuing the same in Study M15-570.
- ABBV-8E12 2000 mg in Study M15-566, continuing the same in Study M15-570.
- ABBV-8E12 300 mg in Study M15-566, ABBV-8E12 1000 mg in Study M15-570.
- Placebo in Study M15-566, ABBV-8E12 2000 mg in Study M15-570.

The scheduled times of measurement will include the baseline measurement. The baseline measurement will be the same as the baseline measurement for Study M15-566, that is, the last measurement obtained before the first study drug administration of Study M15-566.

For CSF free tau, total tau, the ratio of free tau to total tau, and plasma total tau and NFL, a MMRM analysis will be performed for the planned times of assessment after the first dose of study drug administration in Study M15-570. The model will include classification by treatment (one of the 4 treatment sequences described above) and by time of measurement. There will be an effect for the interaction of treatment and time of measurement. Except for the ratio of CSF free tau concentration to CSF total tau concentration, the baseline value will be a covariate. For the ratio of CSF free to total tau, the total tau baseline concentration will be a covariate if this variable is found to be a

significant covariate for the ratio in Study M15-566. The subjects in each treatment sequence will be viewed as a random sample, and an appropriate structure for the covariance matrix of the measurements of a subject will be selected.

Volumetric MRI Variables

For each MRI variable, descriptive statistics will be provided for the baseline values, the values at the scheduled times of measurement after study drug administration in Study M15-570 begins, and changes from baseline at the scheduled times of measurement. An MMRM analysis will be performed on the changes from baseline. The analysis will be much like that described for plasma total tau concentration, but with estimated total intracranial volume (eTIV) as a covariate in addition to the baseline value. An appropriate structure for the covariance matrix will be selected. For each of whole brain, hippocampus, temporal lobes, lateral ventricles and possibly other brain regions, the relationship with the primary efficacy variable CDR-SB, and possibly other efficacy variables, will be explored.

Tau PET Scan Variables

For each region of the brain for which SUVR values (i.e., tau load density) are obtained, an analysis like that described for plasma total tau concentration will be performed. This analysis may also be performed on other variables for which values are determined, including measurements of extent or spread of tau load in the brain.

For the SUVR of selected regions, the relationship with the primary efficacy variable CDR-SB will be explored. This may be done also for other tau PET variables.

8.1.6 Pharmacokinetics and Exposure-Response Analyses

8.1.6.1 Tabulations and Summary Statistics

For ABBV-8E12 serum concentration data, descriptive statistics will be provided for each scheduled time of measurement with a breakdown by treatment sequence as defined in Section 8.1.5.

8.1.6.2 Population Pharmacokinetic and Exposure-Response Analysis

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

Population PK analyses will be performed using the actual sampling time relative to the last administered dose. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the nonlinear mixed effect modeling (NONMEM) software (Version 7, or higher version). The structure of the starting PK model will be based on the PK analysis of data from previous studies. Apparent CL and apparent V of ABBV-8E12 will be the PK 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.

1. The objective function of the best model is significantly smaller than the alternative model(s).
2. 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 1) than the alternative model(s).
3. Visual inspection of model fits, standard errors of model parameters and change in inter-subject and intra-subject error.

Once an appropriate base PK 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 apparent clearance or apparent oral clearance and V/F 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) will be explored using either a stepwise forward selection method, or a generalized additive method (GAM), or another suitable regression/smoothing method at a significance level of 0.050. 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 nonlinear relationships of primary PK parameters with various covariates will be explored.

Relationships between exposure, biomarker, and clinical observations (efficacy or safety variables of interest) may be explored. Initially, the time-course of placebo response will be modeled. Subsequently the relationship between exposure (e.g., population PK model predicted average concentrations or AUC or trough concentrations of the individual model-predicted PK 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, maximum effect [E_{max}], sigmoid E_{max}) will be evaluated to characterize the exposure-response relationship based on the observed data.

Additional analyses will be performed if useful and appropriate.

8.1.7 Immunogenicity

The ADA titers will be summarized as appropriate with a breakdown by treatment (treatments as defined in Section 8.1.5).

8.1.8 Safety Interim Analysis

The DMC for Study M15-566 will serve as the DMC for Study M15-570. The DMC will be responsible for providing assessments of safety at regular intervals. An independent

statistical and data analysis center (SDAC) and an Exposure-Response Analysis Center (ERAC) external to AbbVie and with experience in producing statistical reports, 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. After each DMC meeting, the chair of the DMC will communicate its recommendations to the designated AbbVie Primary Contact, as described in the DMC charter. The AbbVie Primary Contact will triage the recommendations to either the AbbVie study team if the recommendation can be implemented without unblinded data review or the Internal Executive Review Committee (IERC) if unblinded data review is required. The DMC, IERC, SDAC, and ERAC membership and responsibilities will be documented in the DMC charter.

8.1.9 Preliminary Efficacy Analysis

No formal interim efficacy analyses are planned for this study. Other planned preliminary and exploratory analyses will be described in detail in the SAP.

8.2 Determination of Sample Size

The sample size for this study is dependent on the number of subjects who complete Study M15-566 and are qualified for enrollment into Study M15-570. Approximately 400 subjects will be randomized in Study M15-566; the number of subjects who enroll in Study M15-570 will be less than or equal to the total number of subjects enrolled in Study M15-566.

8.3 Randomization Methods

Not applicable. Refer to Section 5.5.3 for method of assigning subjects to treatment groups.

9.0 Ethics

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

Good clinical practice 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 ICH GCP.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Council for Harmonisation (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 IRB/IEC. 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 study-related 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 activities. A copy of each complete, signed, and dated informed consent will be given to the subject and their study partner and each original will be placed in the subject's study 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 IRB/IEC, must be voluntarily signed and dated before optional pharmacogenetic samples are collected. 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 the optional samples, 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 inspections, 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 CRF data for this study are being collected with an 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 Code of Federal Regulations 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 investigators, and the study coordinators/project managers. 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 IRB/IEC, 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: An Extension Study of ABBV-8E12 in Early Alzheimer's Disease

Protocol Date: 20 October 2020

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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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]	Neuroscience
		Clinical Program Development
		Statistics
		Statistics
		Pharmacokinetics
		Medical Writing

Appendix C. Study Activities

	Year 1													
Dose	**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**	**Dose 14**
Visits & Procedures[a]	**Day 1/ Baseline**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**
Subject/study partner ICF[b]	X													
Medical history update[c]	X													
Treatment assignment	X													
Physical examination	X[d]													X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination	X[d]			X			X							X
12-lead ECG	X[d]			X			X							X
Clinical laboratory tests	X[d]			X			X						X	
Brain MRI	X[d]			X			X						X	
Optional LP/CSF collection	X[d]												X	
Tau PET[f]	X[d]												X	
Blood sample for ABBV-8E12 assay	X[d]			X			X						X	
ADA sample	X[d]			X			X						X	
Plasma and serum biomarker sample	X[d]			X			X						X	
Optional PG DNA and RNA sample[g]	X[d]			X			X						X	

	Year 1													
Dose	**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**	**Dose 14**
Visits & Procedures[a]	**Day 1/ Baseline**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDR[h]	X[d]						X						X	
RBANS[h]	X[d]												X	
ADCS-MCI-ADL-24[h]	X[d]													X
EQ-5D-5L[h]	X													X
C-SSRS[e,h]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications review[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Year 2												
Dose	**Dose 15**	**Dose 16**	**Dose 17**	**Dose 18**	**Dose 19**	**Dose 20**	**Dose 21**	**Dose 22**	**Dose 23**	**Dose 24**	**Dose 25**	**Dose 26**	**Dose 27**
Visits & Procedures[a]	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 104**
Subject/study partner ICF[b]													
Medical history update[c]													
Treatment assignment													
Physical examination													X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination					X						X		
12-lead ECG													X
Clinical laboratory tests					X						X		
Brain MRI					O						X		
Optional LP/CSF collection											X		
Tau PET[f]											X		
Blood sample for ABBV-8E12 assay					X						X		
ADA sample					X						X		
Plasma and serum biomarker sample					X						X		
Optional PG DNA and RNA sample[g]					X						X		
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
CDR[h]					X						X		

	Year 2												
Dose	**Dose 15**	**Dose 16**	**Dose 17**	**Dose 18**	**Dose 19**	**Dose 20**	**Dose 21**	**Dose 22**	**Dose 23**	**Dose 24**	**Dose 25**	**Dose 26**	**Dose 27**
Visits & Procedures[a]	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 104**
RBANS[h]											X		
ADCS-MCI-ADL-24[h]													X
EQ-5D-5L[h]													X
C-SSRS[e,h]					X						X		X
Concomitant medications review[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Year 3												
Dose	**Dose 28**	**Dose 29**	**Dose 30**	**Dose 31**	**Dose 32**	**Dose 33**	**Dose 34**	**Dose 35**	**Dose 36**	**Dose 37**	**Dose 38**	**Dose 39**	**Dose 40**
Visits & Procedures[a]	**Wk 108**	**Wk 112**	**Wk 116**	**Wk 120**	**Wk 124**	**Wk 128**	**Wk 132**	**Wk 136**	**Wk 140**	**Wk 144**	**Wk 148**	**Wk 152**	**Wk 156**
Subject/study partner ICF[b]													
Medical history update[c]													
Treatment assignment													
Physical examination													X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination				X						X			
12-lead ECG													X
Clinical laboratory tests										X			
Brain MRI				O						X			
Optional LP/CSF collection													
Tau PET[f]										X			
Blood sample for ABBV-8E12 assay				X						X			
ADA sample				X						X			
Plasma and serum biomarker sample				X						X			
Optional PG DNA and RNA sample[g]				X						X			
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
CDR[h]				X						X			

	Year 3												
Dose	**Dose 28**	**Dose 29**	**Dose 30**	**Dose 31**	**Dose 32**	**Dose 33**	**Dose 34**	**Dose 35**	**Dose 36**	**Dose 37**	**Dose 38**	**Dose 39**	**Dose 40**
Visits & Procedures[a]	**Wk 108**	**Wk 112**	**Wk 116**	**Wk 120**	**Wk 124**	**Wk 128**	**Wk 132**	**Wk 136**	**Wk 140**	**Wk 144**	**Wk 148**	**Wk 152**	**Wk 156**
RBANS[h]										X			
ADCS-MCI-ADL-24[h]													X
EQ-5D-5L[h]													X
C-SSRS[e,h]				X						X			X
Concomitant medications review[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Year 4												
Dose	**Dose 41**	**Dose 42**	**Dose 43**	**Dose 44**	**Dose 45**	**Dose 46**	**Dose 47**	**Dose 48**	**Dose 49**	**Dose 50**	**Dose 51**	**Dose 52**	**Dose 53**
Visits & Procedures[a]	**Wk 160**	**Wk 164**	**Wk 168**	**Wk 172**	**Wk 176**	**Wk 180**	**Wk 184**	**Wk 188**	**Wk 192**	**Wk 196**	**Wk 200**	**Wk 204**	**Wk 208**
Subject/study partner ICF[b]													
Medical history update[c]													
Treatment assignment													
Physical examination													X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination			X						X				
12-lead ECG													X
Clinical laboratory tests									X				
Brain MRI			O						X				
Optional LP/CSF collection													
Tau PET[f]									X				
Blood sample for ABBV-8E12 assay			X						X				
ADA sample			X						X				
Plasma and serum biomarker sample			X						X				
Optional PG DNA and RNA sample[g]			X						X				
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
CDR[h]			X						X				

	Year 4												
Dose	**Dose 41**	**Dose 42**	**Dose 43**	**Dose 44**	**Dose 45**	**Dose 46**	**Dose 47**	**Dose 48**	**Dose 49**	**Dose 50**	**Dose 51**	**Dose 52**	**Dose 53**
Visits & Procedures[a]	**Wk 160**	**Wk 164**	**Wk 168**	**Wk 172**	**Wk 176**	**Wk 180**	**Wk 184**	**Wk 188**	**Wk 192**	**Wk 196**	**Wk 200**	**Wk 204**	**Wk 208**
RBANS[h]									X				
ADCS-MCI-ADL-24[h]													X
EQ-5D-5L[h]													X
C-SSRS[e,h]			X						X				X
Concomitant medications review[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Year 5													
Dose	**Dose 54**	**Dose 55**	**Dose 56**	**Dose 57**	**Dose 58**	**Dose 59**	**Dose 60**	**Dose 61**	**Dose 62**	**Dose 63**	**Dose 64**	**Dose 65**	**Wk 260/ Study Completion PD Visit**	**20 Wk Post-Last Dose[i] Follow-Up Visit**
Visits & Procedures[a]	**Wk 212**	**Wk 216**	**Wk 220**	**Wk 224**	**Wk 228**	**Wk 232**	**Wk 236**	**Wk 240**	**Wk 244**	**Wk 248**	**Wk 252**	**Wk 256**		
Subject/study partner ICF[b]														
Medical history update[c]														
Treatment assignment														
Physical examination													X	
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Neurological examination		X						X					X	X
12-lead ECG													X	
Clinical laboratory tests								X					X	X
Brain MRI		O						X					X	X
Optional LP/CSF collection													X	
Tau PET[f]													X	
Blood sample for ABBV-8E12 assay		X						X					X	X
ADA sample		X						X					X	X
Plasma and serum biomarker sample		X						X					X	X
Optional PG DNA and RNA sample[g]		X												X

	Year 5													
Dose	**Dose 54**	**Dose 55**	**Dose 56**	**Dose 57**	**Dose 58**	**Dose 59**	**Dose 60**	**Dose 61**	**Dose 62**	**Dose 63**	**Dose 64**	**Dose 65**	**Wk 260/ Study Completion PD Visit**	**20 Wk Post-Last Dose[i] Follow-Up Visit**
Visits & Procedures[a]	**Wk 212**	**Wk 216**	**Wk 220**	**Wk 224**	**Wk 228**	**Wk 232**	**Wk 236**	**Wk 240**	**Wk 244**	**Wk 248**	**Wk 252**	**Wk 256**		
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X		
CDR[h]		X						X					X	X
RBANS[h]								X					X	
ADCS-MCI-ADL-24[h]													X	
EQ-5D-5L[h]													X	X
C-SSRS[e,h]		X						X					X	X
Concomitant medications review[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

O = Optional; Wk = Week

a. Study drug will be administered on Day 1/Baseline visit, and then every 4 weeks thereafter until 1 of the discontinuation criteria is met, until the sponsor discontinues the study, or until the study reaches completion. Visits during the Treatment Period may be scheduled within ± 4 days. All dosing visits may be completed over 2 consecutive days at the discretion of the investigator with the second day to include the start and end of the infusion.

b. Subject informed consent, or as applicable, legally authorized representative informed consent and subject assent, and study partner informed consent must be obtained prior to any Study M15-570 specific procedures being completed.

c. Review medical history to confirm subject does not meet exclusion criteria prior to enrollment.

d. Not required if procedure was conducted during the Week 96 visit in Study M15-566. A repeat assessment/procedure may be required based on discussion with the TA MD or designee if subject is enrolling outside the 8 week window from the Week 92 visit in Study M15-566.

e. Vital signs, body weight, C-SSRS, concomitant medications review and AE assessment to be completed to administration of infusion.

f. Subjects who did not complete tau PET imaging through Study M15-566 and at Study M15-570 Day 1/Baseline will have tau PET imaging performed at subsequent visits only after discussion with TA MD or designee. Tau PET imaging will only be collected for subjects at sites selected to participate in the tau PET assessment.

g. Optional pharmacogenetic DNA and RNA samples require consent. Verify consent prior to sample collection.

h. The recommended order of administration is CDR followed by RBANS. When applicable, ADCS-MCI-ADL-24, EQ-5D-5L, and C-SSRS may be subsequently administered/assessed in any order.

i. Post-treatment follow-up to occur approximately 20 weeks after the last dose.

Note: For subjects who prematurely discontinue the study, safety and efficacy assessments may be conducted remotely (for example, via telephone), where applicable.

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	**> 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	--
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 leucostasis; 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)

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Hematology (continued)						
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)	--
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 × UL Nor > 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
Chemistry (continued)						
		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
Chemistry (continued)						
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

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry (continued)						
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
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 is listed in Section 1.1.

Specific Protocol Changes

Section 1.2 Synopsis
Previously read:

AbbVie Inc.	**Protocol Number:** M15-570
Name of Study Drug: ABBV-8E12	**Phase of Development:** 2
Name of Active Ingredient: ABBV-8E12	**Date of Protocol Synopsis:** 24 January 2019
Protocol Title: An Extension Study of ABBV-8E12 in Early Alzheimer's Disease	
Objectives: The primary objective of this study is to assess the long-term safety and tolerability of ABBV-8E12 in subjects with early Alzheimer's disease (AD). The secondary objective of this study is to assess the pharmacokinetics (PK) of ABBV-8E12 in subjects with early AD. The exploratory objectives of this study are: • To assess the long-term efficacy of ABBV-8E12 in slowing disease progression in subjects with early AD. • To assess the long-term effect of ABBV-8E12 on a range of disease-related and drug-related biomarkers in subjects with early AD.	
Investigators: Multicenter	
Study Sites: Up to 80 global sites	
Study Population: Adult subjects with early AD who completed Study M15-566	
Number of Subjects to be Enrolled: Approximately 400	
Methodology: Study M15-570 is a Phase 2 extension of the multiple dose, multicenter, multinational, randomized, double-blind, placebo-controlled study, Study M15-566, and is designed to evaluate the long-term safety and tolerability of ABBV-8E12 in subjects with early AD. The study will consist of a 5-year treatment period and a follow-up period of approximately 20 weeks following the last study drug administration. All subjects who complete the Treatment Period in Study M15-566 will be eligible to participate in this study according to the selection criteria. Upon completion of baseline study procedures, eligible subjects will receive ABBV-8E12 via intravenous (IV) infusion on Day 1 of Study M15-570 as follows: • Subjects who received placebo in Study M15-566 will receive 2000 mg ABBV-8E12 in Study M15-570; • Subjects who received 300 mg ABBV-8E12 in Study M15-566 will receive 1000 mg ABBV-8E12 in Study M15-570; and • Subjects who received 1000 mg or 2000 mg ABBV-8E12 in Study M15-566 will continue on	

the same dose in Study M15-570. Note: if any changes are made to alter Study M15-566 with regards to the treatment arms due to safety, efficacy, or other reasons, a corresponding change will be implemented in Study M15-570. This change may include, but is not limited to, adding or dropping treatment arm(s).
Methodology (Continued): Subjects will receive study drug infusion every 4 weeks and undergo other study procedures and assessments as outlined in the Study Activities table (Appendix C). Subjects will continue to receive treatment either until one of the discontinuation criteria is met, the sponsor discontinues the study, or the subject completes the 5-year treatment period of Study M15-570. Refer to Section 5.4 for detailed description of discontinuation criteria. Day 1 visit of Study M15-570 will be at least 4 weeks but no more than 8 weeks after the last dosing visit (Week 92) of Study M15-566. Should this window be longer than 8 weeks, the subject may be considered for participation in Study M15-570 only with the approval of the AbbVie Therapeutic Area Medical Director (TA MD). The investigators and subjects will remain blinded to the treatment assignments in Study M15-566 and will be blinded to the dose level of ABBV-8E12 in Study M15-570. Safety will be closely monitored during the study conduct. The study will also utilize an external data monitoring committee (DMC), which will review accumulating study data and make recommendations based on the emerging safety profile of ABBV-8E12. The DMC membership, responsibilities, operating logistics, and timing of reviews will be documented in a charter that will be finalized prior to the first DMC review meeting.
Diagnosis and Main Criteria for Inclusion/Exclusion: **Main Inclusion:** • 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 institutional review board (IRB)/independent ethics committee (IEC) approved informed consent, prior to the conduct of any extension study-specific procedures (including any changes occurring in the subject's current therapeutic regimen). In the absence of subject's ability to provide the informed consent, the informed consent must be obtained by a person who has the legal right to act on behalf of the subject following local regulations. • Subject completed the 96-week treatment period of Study M15-566. • In the investigator's opinion, subject was compliant during participation in Study M15-566. • Subject has an identified, reliable study partner (e.g., caregiver, family member, social worker, or friend; preferably the same person for the duration of the study) who has frequent contact with the subject (at least 10 hours per week) and who will provide information as to the subject's cognitive and functional abilities. The study partner has voluntarily signed the IRB/IEC approved study partner informed consent, prior to the conduct of any extension study-specific procedures. • If female, subject must be postmenopausal defined as: o Age ≥ 55 years with no menses for 12 or more months without an alternative medical cause. OR o Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

• 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.	
Diagnosis and Main Criteria for Inclusion/Exclusion (Continued): **Main Exclusion:** • The subject has any significant change in his/her medical condition since participation in Study M15-566 that could interfere with the subject's participation in Study M15-570, could place the subject at increased risk, or could confound interpretation of study results. The investigator must re-evaluate the subject for continuing participation and consider relevant factors including: o interim development of any clinically significant neurological, hematological, autoimmune, endocrine, cardiovascular, neoplastic, renal, hepatic, metabolic, psychiatric, pulmonary, gastrointestinal, or other major disorder o interim development of contraindication to or inability to tolerate brain MRI or PET scans • More than 8 weeks have elapsed since the subject received his/her last dose of study drug in Study M15-566 (i.e., Week 92 visit in Study M15-566). In certain cases, subject may be eligible to enroll after approval by the TA MD. • Subject is concurrently enrolled in another interventional clinical study (with the exception of Study M15-566) involving a therapeutic agent. • Subject is considered by the investigator, for any reason, to be an unsuitable candidate to receive ABBV-8E12 or the subject is considered by the investigator to be unable or unlikely to comply with the dosing schedule or study evaluations.	
Investigational Product:	ABBV-8E12 (1000 mg/10 mL)
Doses:	Dose 1: 1000 mg Dose 2: 2000 mg Doses will be given every 4 weeks. Doses may be modified after evaluation by the DMC of the safety, tolerability, and available PK data.
Mode of Administration:	IV infusion
Reference Therapy:	Not applicable
Doses:	Not applicable
Mode of Administration:	Not applicable
Duration of Treatment: 5 years	
Criteria for Evaluation: **Safety:** Adverse event monitoring, vital signs, physical examination, neurologic examination, electrocardiogram (ECG), laboratory tests, Columbia-suicide severity rating scale (C-SSRS), MRI, and immunogenicity assessments will be conducted. Subjects will be monitored closely for the occurrence of AEs and serious adverse events (SAEs) 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 (Appendix C). The DMC will be in place to provide recommendations during the study.

Criteria for Evaluation (Continued):

Efficacy:

Clinical Assessments:

- Clinical Dementia Rating - Sum of Boxes (CDR-SB)
- Repeatable Battery for Assessment of Neuropsychological Status (RBANS)
- 24-item AD Cooperative Study/Activities of Daily Living scale adapted for patients with mild cognitive impairment (ADCS-MCI-ADL-24)
- EuroQuality of Life-5-level (EQ-5D-5L)
- Digital measures of cognition, actigraphy, and sleep (for subjects enrolled at participating sites)

Pharmacokinetics:

Values for the following pharmacokinetic parameters will be estimated using mixed-effect modeling approach: clearance (CL) and volume of distribution (V). Additional parameters may be calculated if useful in the interpretation of the data. Pharmacokinetic data from this study may be combined with data from other ABBV-8E12 studies for pharmacokinetic analyses. Additional parameters may be calculated if useful in the interpretation of the data.

Immunogenicity:

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

Biomarkers and Pharmacogenetics:

Exploratory research to assess effects of ABBV-8E12 on potential disease-related and drug-related biomarkers will be conducted. Blood sampling, optional CSF sampling and MRIs for volumetric analysis will be done at designated time points throughout the study in order to obtain the data. Also, tau PET scans will be collected in a subset of the subjects. Retinal images will be obtained in a subset of subjects. The potential CSF and plasma biomarkers will include, but are not limited to, the following: tau and NFL 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.

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. The values of other variables may be determined. 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.

Statistical Methods:

Safety:

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting treatment-emergent AEs will be tabulated by MedDRA system organ class (SOC) and preferred term (PT) with a breakdown by treatment sequence. Tabulations will also be provided in which the number of subjects reporting an AE (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 SAE (including deaths) and AEs leading to premature discontinuation of the study drug will be tabulated according to the MedDRA SOC and preferred term by treatment sequence. Treatment sequence differences between each ABBV-8E12 dose group will be analyzed using Fisher's exact test. Differences between each ABBV-8E12 dose group 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.

Efficacy:

All efficacy analyses of comparisons will be performed with a 2-sided test at the significance level of 0.050 unless otherwise specified. All efficacy assessments that are taken no more than 45 days after the last dose of study drug will be included in the efficacy analyses.

The analysis of efficacy variables will be performed on the Study M15-570 ITT data set. The analysis model is a likelihood-based, mixed effects model repeated measures (MMRM) analysis at Study M15-570 Baseline and each post-baseline observation using all observed data. This MMRM analysis will be applied to each efficacy variable with repeated measurements. Details of the analysis will be described in the statistical analysis plan (SAP).

If applicable, delayed-start analysis will be conducted on the change from Baseline of Study M15-566 up to Week 96 in Study M15-570 on CDR-SB score. An MMRM analysis model will be used. Details of the analysis will be specified in the SAP.

Pharmacokinetics:

For ABBV-8E12 serum concentration data, descriptive statistics will be provided for each scheduled time of measurement with a breakdown by treatment sequence.

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

Population PK analyses will be performed using the actual sampling time relative to the last administered dose. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (Version 7, or higher version). The structure of the starting PK model will be based on the PK analysis of data from previous studies. Apparent CL and apparent V of ABBV-8E12 will be the PK parameters of major interest in the NONMEM analyses. If necessary, other parameters may be fixed if useful in the analysis.

Immunogenicity:

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

Statistical Methods (Continued):

Biomarkers:

For each variable, descriptive statistics will be provided for each scheduled time of measurement with a breakdown by group as defined by treatment in Study M15-566 and treatment in Study M15-570, i.e.,:

- ABBV-8E12 1000 mg in Study M15-566, continuing the same in Study M15-570
- ABBV-8E12 2000 mg in Study M15-566, continuing the same in Study M15-570
- ABBV-8E12 300 mg in Study M15-566, ABBV-8E12 1000 mg in Study M15-570
- Placebo in Study M15-566, ABBV-8E12 2000 mg in Study M15-570.

For the CSF concentrations of total and free tau and their ratio and for the plasma concentrations of total tau and NFL, an MMRM analysis will be performed to compare the effects of the 1000 and 2000 mg doses of ABBV-8E12 for scheduled measurements after the baseline assessment until Week 260. The data set will contain the data of the first 2 groups identified above. The data set will also include the data of the last group (those receiving placebo in Study M15-566 and ABBV-8E12 2000 mg in Study M15-570) beginning with Week 120 of Study M15-570, but with a shift in time by 96 weeks for the purposes of this analysis so that the shifted time indicates the length of time on ABBV-8E12 past 96 weeks. Thus, for this analysis, the Week 192 data of the last group will be considered the same as Week 96 data of the first 2 groups. Data of the last group of Week 96 and earlier will not be included for this analysis.

The model for the MMRM analysis performed for the tau variables and plasma NFL will include classification by ABBV-8E12 dose and by time of measurement. There will be an effect for the interaction of ABBV-8E12 dose and time of measurement. Except for the ratio of CSF free tau concentration to CSF total concentration, the baseline value will be a covariate. For the ratio of CSF free to total tau, the value for baseline total tau concentration will be a covariate if this variable is found to be a significant covariate for the ratio in Study M15-566. The model will also have an effect to distinguish between subjects who were assigned to ABBV-8E12 treatment in Study M15-566 and those who were assigned to placebo in Study M15-566. The subjects in each treatment sequence will be viewed as a random sample, and an appropriate structure for the covariance matrix of the measurements of a subject will be selected.

For volumetric MRI variables, descriptive statistics will be provided for the baseline value and the change from baseline for each of the scheduled times of measurement. For each variable, an MMRM analysis will be performed for the changes from baseline. The model will be much like that described for plasma total tau concentration, but with estimated total intracranial volume (eTIV) as a covariate in addition to the baseline value.

For each region of the brain for which SUVR values are obtained from PET scans, an analysis like that described for plasma total tau concentration will be performed.

Has been changed to read:

AbbVie Inc.	**Protocol Number:** M15-570
Name of Study Drug: ABBV-8E12	**Phase of Development:** 2
Name of Active Ingredient: ABBV-8E12	**Date of Protocol Synopsis:** 20 October 2020
Protocol Title: An Extension Study of ABBV-8E12 in Early Alzheimer's Disease	
Objectives: The primary objective of this study is to assess the long-term safety and tolerability of ABBV-8E12 in subjects with early Alzheimer's disease (AD). The secondary objective of this study is to assess the pharmacokinetics (PK) of ABBV-8E12 in subjects with early AD. The exploratory objectives of this study are: • To assess the long-term efficacy of ABBV-8E12 in slowing disease progression in subjects with early AD. • To assess the long-term effect of ABBV-8E12 on a range of disease-related and drug-related biomarkers in subjects with early AD.	
Investigators: Multicenter	
Study Sites: Up to 80 global sites	
Study Population: Adult subjects with early AD who completed Study M15-566	
Number of Subjects to be Enrolled: Approximately 400	
Methodology: Study M15-570 is a Phase 2 extension of the multiple dose, multicenter, multinational, randomized, double-blind, placebo-controlled study, Study M15-566, and is designed to evaluate the long-term safety and tolerability of ABBV-8E12 in subjects with early AD. The study will consist of a 5-year treatment period and a follow-up period of approximately 20 weeks following the last study drug administration. All subjects who complete the Treatment Period in Study M15-566 will be eligible to participate in this study according to the selection criteria. Upon completion of baseline study procedures, eligible subjects will receive ABBV-8E12 via intravenous (IV) infusion on Day 1 of Study M15-570 as follows: • Subjects who received placebo in Study M15-566 will receive 2000 mg ABBV-8E12 in Study M15-570; • Subjects who received 300 mg ABBV-8E12 in Study M15-566 will receive 1000 mg ABBV-8E12 in Study M15-570; and • Subjects who received 1000 mg or 2000 mg ABBV-8E12 in Study M15-566 will continue on the same dose in Study M15-570. Note: if any changes are made to alter Study M15-566 with regards to the treatment arms due to safety, efficacy, or other reasons, a corresponding change will be implemented in Study M15-570. This change may include, but is not limited to, adding or dropping treatment arm(s).	

Methodology (Continued):

Subjects will receive study drug infusion every 4 weeks and undergo other study procedures and assessments as outlined in the Study Activities table (Appendix C). Subjects will continue to receive treatment either until one of the discontinuation criteria is met, the sponsor discontinues the study, or the subject completes the 5-year treatment period of Study M15-570. Refer to Section 5.4 for detailed description of discontinuation criteria.

Day 1 visit of Study M15-570 will be approximately 4 weeks but no more than 8 weeks after the Week 92 visit of Study M15-566. Should this window be longer than 8 weeks, the subject may be considered for participation in Study M15-570 only with the approval of the AbbVie Therapeutic Area Medical Director (TA MD) or designee. The investigators and subjects will remain blinded to the treatment assignments in Study M15-566 and will be blinded to the dose level of ABBV-8E12 in Study M15-570.

Safety will be closely monitored during the study conduct. The study will also utilize an external data monitoring committee (DMC), which will review accumulating study data and make recommendations based on the emerging safety profile of ABBV-8E12. The DMC membership, responsibilities, operating logistics, and timing of reviews will be documented in a charter that will be finalized prior to the first DMC review meeting.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

- 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 institutional review board (IRB)/independent ethics committee (IEC) approved informed consent, prior to the conduct of any extension study-specific procedures (including any changes occurring in the subject's current therapeutic regimen). In the absence of subject's ability to provide the informed consent, the informed consent must be obtained by a person who has the legal right to act on behalf of the subject following local regulations.
- Subject completed the 96-week treatment period of Study M15-566.
- In the investigator's opinion, subject was compliant during participation in Study M15-566.
- Subject has an identified, reliable study partner (e.g., caregiver, family member, social worker, or friend; preferably the same person for the duration of the study) who has frequent contact with the subject (at least 10 hours per week) and who will provide information as to the subject's cognitive and functional abilities. The study partner has voluntarily signed the IRB/IEC approved study partner informed consent, prior to the conduct of any extension study-specific procedures.
- 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).
- 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.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion:

- The subject has any significant change in his/her medical condition since participation in Study M15-566 that could interfere with the subject's participation in Study M15-570, could place the subject at increased risk, or could confound interpretation of study results. The investigator must re-evaluate the subject for continuing participation and consider relevant factors including:
  - interim development of any clinically significant neurological, hematological, autoimmune, endocrine, cardiovascular, neoplastic, renal, hepatic, metabolic, psychiatric, pulmonary, gastrointestinal, or other major disorder
  - interim development of contraindication to or inability to tolerate brain MRI or PET scans
- More than 8 weeks have elapsed since the subject received his/her last dose of study drug in Study M15-566 (i.e., Week 92 visit in Study M15-566). In certain cases, subject may be eligible to enroll after approval by the TA MD or designee.
- Subject is concurrently enrolled in another interventional clinical study (with the exception of Study M15-566) involving a therapeutic agent.
- Subject is considered by the investigator, for any reason, to be an unsuitable candidate to receive ABBV-8E12 or the subject is considered by the investigator to be unable or unlikely to comply with the dosing schedule or study evaluations.

Investigational Product:	ABBV-8E12 (vial of 1000 mg/10 mL and vial of 2000 mg/20 mL)
Doses:	Dose 1: 1000 mg Dose 2: 2000 mg Doses will be given every 4 weeks. Doses may be modified after evaluation by the DMC of the safety, tolerability, and available PK data.
Mode of Administration:	IV infusion
Reference Therapy:	Not applicable
Doses:	Not applicable
Mode of Administration:	Not applicable

Duration of Treatment: 5 years

Criteria for Evaluation:

Safety:

Adverse event monitoring, vital signs, physical examination, neurologic examination, electrocardiogram (ECG), laboratory tests, Columbia-suicide severity rating scale (C-SSRS), MRI, and immunogenicity assessments will be conducted.

Subjects will be monitored closely for the occurrence of AEs and serious adverse events (SAEs) 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 (Appendix C). The DMC will be in place to provide recommendations during the study.

Criteria for Evaluation (Continued):

Efficacy:

Clinical Assessments:

- Clinical Dementia Rating - Sum of Boxes (CDR-SB)
- Repeatable Battery for Assessment of Neuropsychological Status (RBANS)
- 24-item AD Cooperative Study/Activities of Daily Living scale adapted for patients with mild cognitive impairment (ADCS-MCI-ADL-24)
- EuroQuality of Life-5-level (EQ-5D-5L) Proxy Version 1

Pharmacokinetics:

Values for the following pharmacokinetic parameters will be estimated using mixed-effect modeling approach: clearance (CL) and volume of distribution (V). Additional parameters may be calculated if useful in the interpretation of the data. Pharmacokinetic data from this study may be combined with data from other ABBV-8E12 studies for pharmacokinetic analyses. Additional parameters may be calculated if useful in the interpretation of the data.

Immunogenicity:

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

Biomarkers and Pharmacogenetics:

Exploratory research to assess effects of ABBV-8E12 on potential disease-related and drug-related biomarkers will be conducted. Blood sampling, optional CSF sampling and MRIs for volumetric analysis will be done at designated time points throughout the study in order to obtain the data. Also, tau PET scans will be collected in a subset of the subjects. The potential CSF and plasma biomarkers will include, but are not limited to, the following: tau and NFL concentrations; volumetric MRI measures for whole brain, hippocampus, temporal lobes 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.

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. The values of other variables may be determined. 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.

Statistical Methods:

Safety:

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting treatment-emergent AEs will be tabulated by MedDRA system organ class (SOC) and preferred term (PT) with a breakdown by treatment sequence. Tabulations will also be provided in which the number of subjects reporting an AE (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 SAE (including deaths) and AEs leading to premature discontinuation of the study drug will be tabulated according to the MedDRA SOC and preferred term by treatment sequence. Treatment sequence differences between each ABBV-8E12 dose group will be analyzed using Fisher's exact test. Differences between each ABBV-8E12 dose group 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.

Efficacy:

All efficacy analyses of comparisons will be performed with a 2-sided test at the significance level of 0.050 unless otherwise specified. All efficacy assessments that are taken no more than 45 days after the last dose of study drug will be included in the efficacy analyses.

The analysis of efficacy variables will be performed on the Study M15-570 ITT data set. The analysis model is a likelihood-based, mixed effects model repeated measures (MMRM) analysis at Study M15-570 Baseline and each post-baseline observation using all observed data. This MMRM analysis will be applied to each efficacy variable with repeated measurements. Details of the analysis will be described in the statistical analysis plan (SAP).

If applicable, delayed-start analysis will be conducted on the change from Baseline of Study M15-566 up to Week 96 in Study M15-570 on CDR-SB score. An MMRM analysis model will be used. Details of the analysis will be specified in the SAP.

Pharmacokinetics:

For ABBV-8E12 serum concentration data, descriptive statistics will be provided for each scheduled time of measurement with a breakdown by treatment sequence.

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

Population PK analyses will be performed using the actual sampling time relative to the last administered dose. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (Version 7, or higher version). The structure of the starting PK model will be based on the PK analysis of data from previous studies. Apparent CL and apparent V of ABBV-8E12 will be the PK parameters of major interest in the NONMEM analyses. If necessary, other parameters may be fixed if useful in the analysis.

Immunogenicity:

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

Statistical Methods (Continued):

Biomarkers:

For each variable, descriptive statistics will be provided for each scheduled time of measurement with a breakdown by group as defined by treatment in Study M15-566 and treatment in Study M15-570, i.e.,:

- ABBV-8E12 1000 mg in Study M15-566, continuing the same in Study M15-570
- ABBV-8E12 2000 mg in Study M15-566, continuing the same in Study M15-570
- ABBV-8E12 300 mg in Study M15-566, ABBV-8E12 1000 mg in Study M15-570
- Placebo in Study M15-566, ABBV-8E12 2000 mg in Study M15-570.

For the CSF concentrations of total and free tau and their ratio and for the plasma concentrations of total tau and NFL, an MMRM analysis will be performed for scheduled measurements after study drug administration of Study M15-570 begins.

The model for the MMRM analysis performed for the tau variables and plasma NFL will include classification by treatment sequence and by time of measurement. There will be an effect for the interaction of treatment and time of measurement. Except for the ratio of CSF free tau concentration to CSF total concentration, the baseline value will be a covariate. For the ratio of CSF free to total tau, the value for baseline total tau concentration will be a covariate if this variable is found to be a significant covariate for the ratio in Study M15-566. The subjects in each treatment sequence will be viewed as a random sample, and an appropriate structure for the covariance matrix of the measurements of a subject will be selected.

For volumetric MRI variables, descriptive statistics will be provided for the baseline value and the change from baseline for each of the scheduled times of measurement. For each variable, an MMRM analysis will be performed for the changes from baseline. The analysis will be much like that described for plasma total tau concentration, but with estimated total intracranial volume (eTIV) as a covariate in addition to the baseline value.

For each region of the brain for which SUVR values are obtained from PET scans, an analysis like that described for plasma total tau concentration will be performed.

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

COVID-19	Coronavirus disease - 2019
DTP	Direct-to-patient
IERC	Internal Executive Review Committee

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

CRA	Clinical research associate
IRC	independent review committee

Section 3.0 Introduction
Subsection Clinical Experience
Heading "Phase 2 Multiple-Dose Study in Subjects with PSP"
Delete: heading title and text

Phase 2 Multiple-Dose Study in Subjects with PSP

Study M15-562 is an ongoing Phase 2, randomized, multicenter, double-blind, placebo-controlled, multiple-dose trial in which 2 dose levels of ABBV-8E12 are being evaluated (2000 and 4000 mg). A total of 330 subjects (220 on ABBV-8E12 and 110 on placebo) are planned to participate in this study.

Section 3.0 Introduction
Subsection Clinical Experience
Heading "Phase 2 Extension of Multiple-Dose Study in Subjects with PSP"
Delete: heading title and text

Phase 2 Extension of Multiple-Dose Study in Subjects with PSP

Study M15-563 is an ongoing extension study of the Phase 2 Study M15-562 in which 2 dose levels of ABBV-8E12 are being evaluated (2000 and 4000 mg). Subjects who complete the treatment period in Study M15-562 and meet all entry criteria are eligible to participate in Study M15-563. All subjects will be assigned to receive ABBV-8E12 (2000 or 4000 mg) in 1:1 ratio.

Section 3.2 Benefits and Risks
Add: new last paragraph

In consideration of the coronavirus disease 2019 (COVID-19) pandemic, the benefits and risks to subjects participating in this study have been re-evaluated. Based on the limited

information to date and due to the mechanism of action of ABBV-8E12, no additional risk is anticipated for study participants infected with SARS-Cov2 during the COVID-19 pandemic.

Section 4.0 Study Objectives
Second paragraph previously read:

The secondary objective of this study is to assess the pharmacokinetic (PK) of ABBV-8E12 in subjects with early AD.

Has been changed to read:

The secondary objective of this study is to assess the pharmacokinetics (PK) of ABBV-8E12 in subjects with early AD.

Section 5.1 Overall Study Design and Plan: Description
Fifth paragraph, first and second sentence previously read:

Day 1 visit of Study M15-570 (day of the first dose of Study M15-570) will be at least 4 weeks but no more than 8 weeks after the last dosing visit (Week 92) of Study M15-566. Should this window be longer than 8 weeks, the subject may be considered for participation in Study M15-570 only with the approval of the therapeutic area medical director (TA MD).

Has been changed to read:

Day 1 visit of Study M15-570 (day of the first dose of Study M15-570) will be approximately 4 weeks but no more than 8 weeks after the Week 92 visit of Study M15-566. Should this window be longer than 8 weeks, the subject may be considered for participation in Study M15-570 only with the approval of the therapeutic area medical director (TA MD) or designee.

Section 5.2.2 Exclusion Criteria
Criterion 2, last sentence previously read:

In certain cases, subject may be eligible to enroll after approval by the TA MD.

Has been changed to read:

In certain cases, subject may be eligible to enroll after approval by the TA MD or designee.

Section 5.2.2 Exclusion Criteria
Subsection Rationale for Exclusion Criteria
Previously read:

1	To ensure the safety of the subjects
2, 4	To select subject population appropriate for this study
3	These products may interfere with the PK of the study drug.

Has been changed to read:

1	To ensure the safety of the subjects
2	To allow the TA MD to delegate responsibility
2, 4	To select subject population appropriate for this study
3	These products may interfere with the PK of the study drug.

Section 5.3.1.1 Study Procedures
Add: new first paragraph

Study visits may be impacted due to the COVID-19 pandemic and 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.

Table 2. Clinical Laboratory Tests
Add: new abbreviation "T4" and "TSH"

T4 = Thyroxine; TSH = Thyroid stimulating hormone

Table 2. Clinical Laboratory Tests
Table note "a." previously read:

Baseline only.

Has been changed to read:

Optional. Not required if using Study M15-566 Week 96 visit for Baseline.

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 Optional Lumbar Puncture
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
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 Tau Imaging
First paragraph, last sentence previously read:

Subjects who did not complete tau PET imaging at Day 1/Baseline will have tau PET imaging performed at subsequent visits only after discussion with the TA MD.

Has been changed to read:

Subjects who did not complete tau PET imaging through Study M15-566 and at Study M15-570 Day 1/Baseline will have tau PET imaging performed at subsequent visits only after discussion with the TA MD or designee.

Section 5.3.1.1 Study Procedures
Subsection Positron Emission Tomography Tau Imaging
Third paragraph previously red:

The tau PET scan at Baseline should be carried out prior to administration of the first dose.

Has been changed to read:

The tau PET scan for Day 1/Baseline should be carried out prior to administration of the first dose.

Section 5.3.1.1 Study Procedures
Subsection Positron Emission Tomography 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 obtained at the next onsite visit with the exception of Day 1/Baseline, which should be obtained prior to the administration of the first dose.

Section 5.3.1.1 Study Procedures
Subsection Retinal Imaging for Amyloid
Delete: subsection title and text

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 Aβ in the retinal epithelial layer. Retinal Aβ plaques have been identified in postmortem eyes from AD patients and in Aβ overexpressing transgenic mice. Preliminary data suggests amyloidogenic densities can be detected in the retina of early AD patients. An exploratory retinal imaging test designed to detect trace amounts of Aβ 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 conducted at time points indicated in the Study Activities table (Appendix C). Only retinal imaging for Aβ 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 optional 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.

Section 5.3.1.1 Study Procedures
Subsection Digital Measures of Cognition, Actigraphy, and Sleep
Delete: subsection title and text

Digital Measures of Cognition, Actigraphy, and Sleep

Measures of cognition, actigraphy, and sleep will be conducted in a subset of sites selected to participate by AbbVie based on scientific, technical, and logistical considerations. Details of sensor use and other digital measures will be described in a separate lab manual.

Table 3. Diagnostic Tools and Scale Administration Timing
Table note "c." previously read:

When applicable, scale may be subsequently administered/assessed in any order prior to study drug administration.

Has been changed to read:

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

Section 5.3.1.1 Study Procedures
Subsection Diagnostic Tools and Rating Scales
Heading "EuroQuality of Life-5-level (EQ-5D-5L)[12,13]"
Previously read:

The EuroQuality of Life-5-level (EQ-5D-5L) contains a health state descriptive part comprising 5 items, scored from 1 (no problems or symptoms) to 5 (serious problems or symptoms); a question about change in health state in the preceding 12 months, and a visual analog scale (VAS) to evaluate current health state (from 0, worst imaginable, to 100, best imaginable). The descriptive profile can be converted into a value (EQ-Index) which ranges from 0 (death) to 1 (perfect health), with negative values indicating health states considered worse than death. It is administered to the subject by a clinician and takes approximately 8 minutes to complete. The EQ-5D-5L will be administered to the subject at the times indicated in the Study Activities table (Appendix C).

Has been changed to read:

The EuroQuality of Life-5-level (EQ-5D-5L) Proxy Version 1 measures overall health status. The caregiver (the proxy) will rate the patient's health status in their (the proxy's) opinion. The scale contains a descriptive system comprised of 5 dimensions [(1) mobility, (2) self-care, (3) usual activities, (4) pain/discomfort, and (5) anxiety/depression]. These health states get scored on 5 levels of severity [(1) no problems, (2) slight problems, (3) moderate problems, (4) severe problems, and (5) unable to/extreme problems] and a visual analog scale (VAS) to evaluate current health state from 0 (worst imaginable) to 100 (best imaginable). The descriptive profile can be converted into a value (EQ-Index) which ranges from 0 (death) to 1 (perfect health), with negative values indicating health states considered worse than death. The EQ-5D-5L Proxy Version 1 will be administered at the times indicated in the Study Activities table (Appendix C).

Section 5.3.1.1 Study Procedures
Subsection Diagnostic Tools and Rating Scales
Heading "Columbia-Suicide Severity Rating Scale[14]"
Subheading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new subheading 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 reference the table below for scales that may be administered remotely.

Scale	May be Administered Via Phone or Video Conference
ADCS-MCI-ADL-24	Yes
CDR	Yes
C-SSRS	Yes
EQ-5D-5L	Yes
RBANS	No

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; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels Health State Instrument; RBANS = Repeatable Battery for Assessment of Neuropsychological Status

Section 5.3.1.2 Collection and Handling of Biomarker and Pharmacogenetic Research Samples
Subsection Blood and Optional CSF Biomarker 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 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 5.3.2.1 Collection of Samples for Analysis
Subsection Optional CSF Samples for ABBV-8E12 Assay
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 samples for ABBV-8E12/ADA assays and the optional CSF for the ABBV-8E12 assay may not be performed due to study modifications related to the COVID-19 pandemic, these samples should be obtained at the next onsite visit.

Section 5.3.3 Efficacy Variables
Previously read:

Exploratory efficacy measures are described in Section 5.3.1.1 along with other study procedures and will be derived from assessments of CDR, RBANS, ADCS-MCI-ADL-24, EQ-5D-5L, and digital measures of cognition, actigraphy, and sleep.

Has been changed to read:

Exploratory efficacy measures are described in Section 5.3.1.1 along with other study procedures and will be derived from assessments of CDR, RBANS, ADCS-MCI-ADL-24, and EQ-5D-5L.

Section 5.3.6.1 Biomarker Research Variables
Subsection Volumetric MRI
Second sentence previously read:

Measurements will be obtained for whole brain, hippocampus, and lateral ventricles.

Has been changed to read:

The value itself for a given visit will be obtained by adding the baseline value to the value for change from baseline. Measurements will be obtained for whole brain, hippocampus, temporal lobes, and lateral ventricles.

Section 5.3.6.1 Biomarker Research Variables
Subsection Volumetric MRI
Fourth, fifth, and sixth sentence previously read:

Measurement of changes from baseline will be obtained for two different definitions of baseline. One definition of the baseline is the same as that for Study M15-566, the last measurement prior to the first dose of the study. For the other definition, the baseline MRI will be that for the extension study itself, the last MRI of Study M15-566 or one done on Day 1 of this study, as explained in Section 5.1.

Has been changed to read:

The baseline measurement will be the same as the baseline measurement for Study M15-566, that is, the last measurement obtained before the first study drug administration of Study M15-566.

Section 5.3.6.1 Biomarker Research Variables
Subsection Retinal Amyloid Imaging
Delete: subsection title and text

Retinal Amyloid Imaging

Retinal optical images will be collected from each eye at the time points indicated in the Study Activities table (Appendix C) and subjected to image analysis. The results of the

retinal imaging test will be compared to Aβ PET imaging results and reported in a separate addendum study report.

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

For subjects who miss 3 or more study drug doses due to the COVID-19 pandemic, the TA MD should be contacted to discuss continuation in the study.

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
Third and fourth paragraph previously read:

The start and stop time of each study drug infusion will be recorded to the nearest minute. Refer to the Pharmacy Manual for detailed instructions.

Home infusion visits may be available depending on local regulations, logistical, and procedural considerations, and the investigator's assessment of the subject's suitability. These considerations and other relevant information will be detailed in a separate manual describing this provision.

Has been changed to read:

The start and stop time of each study drug infusion will be recorded to the nearest minute. 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 IRB/IEC requirements for home healthcare. Any prerequisite submissions or notifications to the site IRB/IEC and local competent health authority should be made and approved prior to the implementation of home infusions.

Table 4. Identity of Investigational Product
Previously read:

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
ABBV-8E12	Infusion	Solution for infusion in a vial	1000 mg/10 mL	AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany

Has been changed to read:

Investigational Product	Mode of Administration	Formulation	Strength
ABBV-8E12	Infusion	Solution for infusion in a vial	1000 mg/10 mL
ABBV-8E12	Infusion	Solution for infusion in a vial	2000 mg/20 mL

Section 5.5.5 Blinding
Second paragraph, second and third sentence previously read:

For IP 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.

Has been changed to read:

For IP monitoring, there will be an unblinded AbbVie monitor for verification of unblinded documentation. The unblinding procedure for the unblinded pharmacist/designee and the unblinded AbbVie monitor will be defined in a separate study-specific document.

Section 5.5.5 Blinding
Subsection Unblinding of Data for the Data Monitoring Committee
Second sentence previously read:

The DMC will have full access to all data PRN for safety assessment.

Has been changed to read:

The DMC will have full access to all data for safety assessment.

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

An AbbVie internal review committee (IRC) may request access to closed reports if the DMC recommends that the study be discontinued or that the study design undergo major modifications, as outlined in the DMC charter.

Has been changed to read:

The AbbVie Internal Executive Review Committee (IERC) may request access to closed reports if the DMC recommends that the study be discontinued or that the study design undergo major modifications, as outlined in the DMC charter.

Section 5.5.5 Blinding
Subsection Unblinding of Data for the Data Monitoring Committee
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 and the AbbVie IERC members will not be involved in any aspects of the trial or its management.

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:

[redacted]

Office:
Email: [redacted]

Alternate Contact:

[redacted]

Office:
Mobile:
Fax:
Email: [redacted]

Has been changed to read:

Primary Contact:	Alternate Contact:
[redacted]	[redacted]
Office: [redacted]	Mobile: [redacted]
Email:	Email:

Section 8.1.1 Analysis Data Sets
Subsection Data Sets for Safety Analyses
Subsection title previously read:

Data Sets for Safety Analyses

Has been changed to read:

Data Set for Safety Analyses

Section 8.1.1 Analysis Data Sets
Subsection Data Sets for Safety Analyses
First paragraph
Delete: last sentence

There are two safety data sets: a stand-alone data set and a cumulative data set.

Section 8.1.1 Analysis Data Sets
Subsection Data Sets for Safety Analyses
Delete: second and third paragraph

Stand-Alone Data Set: The stand-alone data set is the primary data set for safety analyses, and will contain data from Study M15-570 only, regardless of the treatment received in Study M15-566. Baseline for the stand-alone data set will be the last observation on or

before the first dose of ABBV-8E12 in Study M15-570. If no Baseline is recorded in Study M15-570, the last value in Study M15-566 will be used as the Baseline.

Cumulative Data Set: The cumulative data set will consist of data from both Study M15-566 and Study M15-570. It is the secondary data set for safety analyses. For subjects who were in the placebo group in Study M15-566, their safety data from Study M15-566 will not be included in the cumulative data set but their safety data from Study M15-570 will be included. For subjects who were in the placebo group in Study M15-566, Baseline will be the last observation prior to the first dose of study drug in Study M15-570. For subjects who were in ABBV-8E12 treatment sequences in Study M15-566, Baseline for the cumulative data set will be their Baseline in Study M15-566.

Section 8.1.1 Analysis Data Sets
Subsection Data Set for Biomarkers
Add: new subsection title and text

Data Set for Biomarkers

The subjects of the data set for biomarkers will be all subjects who have biomarker data for at least one scheduled visit later than Visit 1 of Study M15-570. The data of a subject included for the analysis of a biomarker variable will include the baseline value of Study M15-566, which will also be the baseline value for Study M15-570, and all the data of Study M15-570 after Day 1 (day of the first dose of Study M15-570).

Section 8.1.2 Disposition, Demographics, and Other Baseline Characteristics
Subsection Subject Disposition
First paragraph previously read:

The number and percentage of subjects contributed by each country and site will be summarized for each treatment sequence and for all treatment sequence combined for the stand-alone data set.

Has been changed to read:

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

Section 8.1.2 Disposition, Demographics, and Other Baseline Characteristics
Subsection Subject Disposition
Second paragraph, first sentence previously read:

The number and percentage of subjects who prematurely discontinue study drug will be summarized by treatment sequence and overall for stand-alone data set for the primary reason as well as for all reasons collected.

Has been changed to read:

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

Section 8.1.2 Disposition, Demographics, and Other Baseline Characteristics
Subsection Demographic and Other Baseline Characteristics
Last paragraph, first sentence previously read:

Efficacy and clinical measures taken at baseline (CDR-SB score, RBANS, ADCS-MCI-ADL-24, EQ-5D-5L, and exploratory measures of cognition, actigraphy, and sleep) will be summarized for the ITT data set only.

Has been changed to read:

Efficacy and clinical measures taken at baseline (CDR-SB score, RBANS, ADCS-MCI-ADL-24, and EQ-5D-5L) will be summarized for the ITT data set only.

Section 8.1.2 Disposition, Demographics, and Other Baseline Characteristics
Subsection Medical History
Previously read:

Medical history data, including subject's history of early AD or MCI, will be summarized for the stand-alone data set using body systems and conditions/diagnoses as captured on the eCRF.

Has been changed to read:

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

Section 8.1.2 Disposition, Demographics, and Other Baseline Characteristics
Subsection Previous and Concomitant Medications
First sentence previously read:

Prior and concomitant medications will be coded by the most recent World Health Organization (WHO) Drug dictionary, and will be summarized by treatment sequence for the stand-alone data set.

Has been changed to read:

Prior and concomitant medications will be coded by the most recent World Health Organization (WHO) Drug dictionary, and will be summarized by treatment sequence for the safety data set.

Section 8.1.3 Efficacy Analyses
Second paragraph, first sentence previously read:

Analyses of the efficacy variables CDR-SB score, ADCS-MCI-ADL-24 total score, RBANS total scores, EQ-5D-5L score, and the relevant cognition, actigraphy, and sleep variables will be performed on the Study M15-570 ITT data set.

Has been changed to read:

Analyses of the efficacy variables CDR-SB score, ADCS-MCI-ADL-24 total score, RBANS total scores, and EQ-5D-5L score will be performed on the Study M15-570 ITT data set.

Section 8.1.4 Safety Analyses
First, second, and third paragraph previously read:

Comparisons between treatment sequences (Studies M15-566/M15-570) of interest will be performed with a 2-sided test at the significance level of 0.050 unless otherwise specified. 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.

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

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

Has been changed to read:

Comparisons between treatment sequences (Study M15-566 and Study M15-570) of interest will not be performed.

Section 8.1.4.2 Analysis of Adverse Events
First paragraph previously read:

The stand-alone data set will be the primary data set for the AE summary. Analyses that will be performed on the cumulative data set include the following: Adverse event overview, AE incidence by Medical Dictionary for Regulatory Activities (MedDRA)

system organ class (SOC) and preferred term (PT), AE incidence in descending frequency by overall subjects, and SAE incidence by SOC and PT.

Has been changed to read:

The safety data set will be used for the AE summary.

Section 8.1.4.2 Analysis of Adverse Events
Second paragraph, second sentence previously read:

The number and percentage of subjects who report TEAEs will be tabulated by the SOC and preferred term for the treatment sequences specified in Section 8.0.

Has been changed to read:

The number and percentage of subjects who report treatment-emergent adverse events (TEAEs) will be tabulated by the SOC and preferred term for the treatment sequences specified in Section 8.0.

Section 8.1.4.2 Analysis of Adverse Events
Add: new last paragraph

A TEAE is defined as any AE that begins or worsens in severity on or after the date of the first dose of study drug and no more than 20 weeks after the date of the last study dose.

Section 8.1.4.3 Analysis of Laboratory Tests
First paragraph, first sentence previously read:

Analysis will be performed on the stand-alone data set for laboratory tests.

Has been changed to read:

Analysis will be performed on the safety data set for laboratory tests.

Section 8.1.4.4 Analysis of Vital Signs and Weight
First paragraph, first sentence previously read:

Analysis will be performed on the stand-alone data set for vital signs and weight.

Has been changed to read:

Analysis will be performed on the safety data set for vital signs and weight.

Section 8.1.4.5 Analysis of ECG Variables
First paragraph, first sentence previously read:

Analysis of ECG variables will be performed on the stand-alone data set.

Has been changed to read:

Analysis of ECG variables will be performed on the safety data set.

Section 8.1.4.6 Analysis of C-SSRS
First sentence previously read:

Analysis of C-SSRS will be performed on the stand-alone data set.

Has been changed to read:

Analysis of C-SSRS will be performed on the safety data set.

Section 8.1.5 Biomarker Analyses
Second, third, and fourth paragraph previously read:

The scheduled times of measurement will include the baseline measurement. For subjects who were treated with ABBV-8E12 in Study M15-566 and continuing the same treatment in Study M15-570, the baseline measurement will be the same as it was in Study M15-566, the last measurement prior to the first dose of the study. For the 2 groups whose treatment in this study is a change from the treatment in Study M15-566, the baseline value will be that for the extension study itself, the last measurement of Study M15-566 or the predose measurement on Day 1 of Study M15-570, as explained in Section 5.1. The descriptive statistics for a given time will provide information for both the data of the given time and the changes from Baseline, except for the vMRI variables, for which only a value for the change from Baseline will be available.

For the CSF concentrations of total and free tau and their ratio and for the plasma concentrations of total tau and NFL, an MMRM analysis for scheduled measurements after the baseline assessment until Week 260 will be performed to compare the effects of the 1000 and 2000 mg doses of ABBV-8E12. The data set will contain the data of the first 2 groups identified above. The data set will also include data of the last group (those receiving placebo in Study M15-566, ABBV-8E12 2000 mg in Study M15-570) beginning with Week 120 of Study M15-570, but with a shift in time by 96 weeks for the purposes of this analysis so that the shifted time indicates the length of time on ABBV-8E12 past 96 weeks. Thus, for this analysis, the Week 192 data of the last group will be considered the same as Week 96 data of the first 2 groups. The Week 120 data of the last group will be considered the same as Week 24 data of the first 2 groups. Data of the last group of Week 96 and earlier will not be included for this analysis.

The model for the MMRM analysis performed for the tau variables and plasma NFL will include classification by ABBV-8E12 dose and by time of measurement. There will be an effect for the interaction of ABBV-8E12 dose and time of measurement. Except for the ratio of CSF free tau concentration to CSF total concentration, the baseline value will be a covariate. For the ratio of CSF free to total tau, the total tau baseline concentration will be a covariate if this variable is found to be a significant covariate for the ratio in Study M15-566. The model will also have an effect to distinguish between subjects who were assigned to ABBV-8E12 treatment in Study M15-566 and those who were assigned to placebo in Study M15-566. The subjects in each treatment sequence will be viewed as a random sample and an appropriate structure for the covariance matrix of the measurements of a subject will be selected.

Has been changed to read:

The scheduled times of measurement will include the baseline measurement. The baseline measurement will be the same as the baseline measurement for Study M15-566, that is, the last measurement obtained before the first study drug administration of Study M15-566.

For CSF free tau, total tau, the ratio of free tau to total tau, and plasma total tau and NFL, a MMRM analysis will be performed for the planned times of assessment after the first dose of study drug administration in Study M15-570. The model will include classification by treatment (one of the 4 treatment sequences described above) and by time of measurement. There will be an effect for the interaction of treatment and time of measurement. Except for the ratio of CSF free tau concentration to CSF total tau concentration, the baseline value will be a covariate. For the ratio of CSF free to total tau, the total tau baseline concentration will be a covariate if this variable is found to be a significant covariate for the ratio in Study M15-566. The subjects in each treatment sequence will be viewed as a random sample, and an appropriate structure for the covariance matrix of the measurements of a subject will be selected.

Section 8.1.5 Biomarker Analyses
Subsection Volumetric MRI Variables
Previously read:

Descriptive statistics will be provided for the baseline value and the change from baseline for volumetric MRI variables for each of the scheduled times of measurement. For each variable, an MMRM analysis will be performed for the changes from baseline. The model will be much like that described for plasma total tau concentration, but with estimated total intracranial volume (eTIV) as a covariate in addition to the baseline value. An appropriate structure for the covariance matrix will be selected. For each of whole brain, hippocampus, lateral ventricles and possibly other brain regions, the relationship with the primary efficacy variable CDR-SB, and possibly other efficacy variables, will be explored.

Has been changed to read:

For each MRI variable, descriptive statistics will be provided for the baseline values, the values at the scheduled times of measurement after study drug administration in Study M15-570 begins, and changes from baseline at the scheduled times of measurement. An MMRM analysis will be performed on the changes from baseline. The analysis will be much like that described for plasma total tau concentration, but with

estimated total intracranial volume (eTIV) as a covariate in addition to the baseline value. An appropriate structure for the covariance matrix will be selected. For each of whole brain, hippocampus, temporal lobes, lateral ventricles and possibly other brain regions, the relationship with the primary efficacy variable CDR-SB, and possibly other efficacy variables, will be explored.

Section 8.1.8 Safety Interim Analysis
Fifth, 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 internal review committee (IRC) if unblinded data review is required. The DMC, IRC, SDAC, and ERAC membership and responsibilities will be documented in the DMC charter.

Has been changed to read:

After each DMC meeting, the chair of the DMC will communicate its recommendations to the designated AbbVie Primary Contact, as described in the DMC charter. The AbbVie Primary Contact will triage the recommendations to either the AbbVie study team if the recommendation can be implemented without unblinded data review or the Internal Executive Review Committee (IERC) if unblinded data review is required. The DMC, IERC, SDAC, and ERAC membership and responsibilities will be documented in the DMC charter.

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 IRB/IEC. 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
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 IRB/IEC, and the study site.

Section 15.0 Reference List
Item 13 previously read:

Schrag A, Selai C, Quinn N, et al. Measuring quality of life in progressive supranuclear palsy. In: Jenkinson C, Peters M, Bromberg M, editors. Quality of Life Measurement in Neurodegenerative and Related Conditions. Cambridge: Cambridge University Press; 2011. P. 52-9.

Has been changed to read:

Jönsson L, Andreasen N, Kilander L, et al. Patient- and proxy-reported utility in Alzheimer disease using the EuroQoL. Alzheimer Dis Assoc Disord. 2006;20(1):49-55.

Appendix B. List of Protocol Signatories

Previously read:

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

Has been changed to read:

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

Appendix C. Study Activities
Previously read:

	Year 1													
Dose	**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**	**Dose 14**
Visits & Procedures[a]	**Day 1/ Baseline**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**
Subject/study partner ICF[b]	X													
Medical history update[c]	X													
Treatment assignment	X													
Physical examination	X[d]													X
Retinal imaging scan[e]														
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination	X[d]			X			X							X
12-lead ECG	X[d]			X			X							X
Clinical laboratory tests	X[d]			X			X						X	
Brain MRI	X[d]			X			X						X	
Optional LP/CSF collection	X[d]												X	
Tau PET[g]	X[d]												X	
Blood sample for ABBV-8E12 assay	X[d]			X			X						X	
ADA sample	X[d]			X			X						X	
Plasma and serum biomarker sample	X[d]			X			X						X	

	Year 1													
Dose	**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**	**Dose 14**
Visits & Procedures[a]	**Day 1/ Baseline**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**
Optional PG DNA and RNA sample[h]	X[d]			X			X						X	
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDR[i]	X[d]						X						X	
RBANS[i]	X[d]												X	
ADCS-MCI-ADL-24[i]	X[d]													X
EQ-5D-5L[i]	X													X
C-SSRS[f,i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Digital measurements of cognition, actigraphy, and sleep[j]	X[j]					X[j]						X[j]		
Concomitant medications review[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Year 2												
Dose	**Dose 15**	**Dose 16**	**Dose 17**	**Dose 18**	**Dose 19**	**Dose 20**	**Dose 21**	**Dose 22**	**Dose 23**	**Dose 24**	**Dose 25**	**Dose 26**	**Dose 27**
Visits & Procedures[a]	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 104**
Subject/study partner ICF[b]													
Medical history update[c]													
Treatment assignment													
Physical examination													X
Retinal imaging scan[e]		X											
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination					X						X		
12-lead ECG													X
Clinical laboratory tests					X						X		
Brain MRI					X						X		
Optional LP/CSF collection											X		
Tau PET[g]											X		
Blood sample for ABBV-8E12 assay					X						X		
ADA sample					X						X		
Plasma and serum biomarker sample					X						X		
Optional PG DNA and RNA sample[h]					X						X		
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Year 2												
Dose	**Dose 15**	**Dose 16**	**Dose 17**	**Dose 18**	**Dose 19**	**Dose 20**	**Dose 21**	**Dose 22**	**Dose 23**	**Dose 24**	**Dose 25**	**Dose 26**	**Dose 27**
Visits & Procedures[a]	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 104**
CDR[i]					X						X		
RBANS[i]											X		
ADCS-MCI-ADL-24[i]													X
EQ-5D-5L[i]													X
C-SSRS[f,i]					X						X		X
Digital measurements of cognition, actigraphy, and sleep[j]				X[j]						X[j]			
Concomitant medications review[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[f]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Year 3												
Dose	**Dose 28**	**Dose 29**	**Dose 30**	**Dose 31**	**Dose 32**	**Dose 33**	**Dose 34**	**Dose 35**	**Dose 36**	**Dose 37**	**Dose 38**	**Dose 39**	**Dose 40**
Visits & Procedures[a]	**Wk 108**	**Wk 112**	**Wk 116**	**Wk 120**	**Wk 124**	**Wk 128**	**Wk 132**	**Wk 136**	**Wk 140**	**Wk 144**	**Wk 148**	**Wk 152**	**Wk 156**
Subject/study partner ICF[b]													
Medical history update[c]													
Treatment assignment													
Physical examination													X
Retinal imaging scan[e]													
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination				X						X			
12-lead ECG													X
Clinical laboratory tests										X			
Brain MRI				X						X			
Optional LP/CSF collection													
Tau PET[g]										X			
Blood sample for ABBV-8E12 assay				X						X			
ADA sample				X						X			
Plasma and serum biomarker sample				X						X			
Optional PG DNA and RNA sample[h]				X						X			
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Year 3												
Dose	**Dose 28**	**Dose 29**	**Dose 30**	**Dose 31**	**Dose 32**	**Dose 33**	**Dose 34**	**Dose 35**	**Dose 36**	**Dose 37**	**Dose 38**	**Dose 39**	**Dose 40**
Visits & Procedures[a]	**Wk 108**	**Wk 112**	**Wk 116**	**Wk 120**	**Wk 124**	**Wk 128**	**Wk 132**	**Wk 136**	**Wk 140**	**Wk 144**	**Wk 148**	**Wk 152**	**Wk 156**
CDR[i]				X						X			
RBANS[i]										X			
ADCS-MCI-ADL-24[i]													X
EQ-5D-5L[i]													X
C-SSRS[f,i]				X						X			X
Digital measurements of cognition, actigraphy, and sleep[j]			X[j]						X[j]				
Concomitant medications review[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[f]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Year 4												
Dose	**Dose 41**	**Dose 42**	**Dose 43**	**Dose 44**	**Dose 45**	**Dose 46**	**Dose 47**	**Dose 48**	**Dose 49**	**Dose 50**	**Dose 51**	**Dose 52**	**Dose 53**
Visits & Procedures[a]	**Wk 160**	**Wk 164**	**Wk 168**	**Wk 172**	**Wk 176**	**Wk 180**	**Wk 184**	**Wk 188**	**Wk 192**	**Wk 196**	**Wk 200**	**Wk 204**	**Wk 208**
Subject/study partner ICF[b]													
Medical history update[c]													
Treatment assignment													
Physical examination													X
Retinal imaging scan[e]													
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination			X						X				
12-lead ECG													X
Clinical laboratory tests									X				
Brain MRI			X						X				
Optional LP/CSF collection													
Tau PET[g]									X				
Blood sample for ABBV-8E12 assay			X						X				
ADA sample			X						X				
Plasma and serum biomarker sample			X						X				
Optional PG DNA and RNA sample[h]			X						X				
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Year 4												
Dose	**Dose 41**	**Dose 42**	**Dose 43**	**Dose 44**	**Dose 45**	**Dose 46**	**Dose 47**	**Dose 48**	**Dose 49**	**Dose 50**	**Dose 51**	**Dose 52**	**Dose 53**
Visits & Procedures[a]	**Wk 160**	**Wk 164**	**Wk 168**	**Wk 172**	**Wk 176**	**Wk 180**	**Wk 184**	**Wk 188**	**Wk 192**	**Wk 196**	**Wk 200**	**Wk 204**	**Wk 208**
CDR[i]			X						X				
RBANS[i]									X				
ADCS-MCI-ADL-24[i]													X
EQ-5D-5L[i]													X
C-SSRS[f,i]			X						X				X
Digital measurements of cognition, actigraphy, and sleep[i]		X[i]						X[i]					
Concomitant medications review[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[f]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Year 5													
Dose	**Dose 54**	**Dose 55**	**Dose 56**	**Dose 57**	**Dose 58**	**Dose 59**	**Dose 60**	**Dose 61**	**Dose 62**	**Dose 63**	**Dose 64**	**Dose 65**	**Wk 260/ Study Completion PD Visit**	**20 Wk Post-Last Dose[k] Follow-Up Visit**
Visits & Procedures[a]	**Wk 212**	**Wk 216**	**Wk 220**	**Wk 224**	**Wk 228**	**Wk 232**	**Wk 236**	**Wk 240**	**Wk 244**	**Wk 248**	**Wk 252**	**Wk 256**		
Subject/study partner ICF[b]														
Medical history update[c]														
Treatment assignment														
Physical examination													X	
Retinal imaging scan[e]													X	
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Neurological examination		X						X					X	X
12-lead ECG													X	
Clinical laboratory tests								X					X	X
Brain MRI		X						X					X	X
Optional LP/CSF collection													X	
Tau PET[g]													X	
Blood sample for ABBV-8E12 assay		X						X					X	X
ADA sample		X						X					X	X
Plasma and serum biomarker sample		X						X					X	X

	Year 5													
Dose	**Dose 54**	**Dose 55**	**Dose 56**	**Dose 57**	**Dose 58**	**Dose 59**	**Dose 60**	**Dose 61**	**Dose 62**	**Dose 63**	**Dose 64**	**Dose 65**	**Wk 260/ Study Completion PD Visit**	**20 Wk Post-Last Dose[k] Follow-Up Visit**
Visits & Procedures[a]	**Wk 212**	**Wk 216**	**Wk 220**	**Wk 224**	**Wk 228**	**Wk 232**	**Wk 236**	**Wk 240**	**Wk 244**	**Wk 248**	**Wk 252**	**Wk 256**		
Optional PG DNA and RNA sample[h]		X						X					X	
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X		
CDR[i]		X						X					X	X
RBANS[i]								X					X	
ADCS-MCI-ADL-24[i]													X	
EQ-5D-5L[i]													X	X
C-SSRS[f,i]		X						X					X	X
Digital measurements of cognition, actigraphy, and sleep[j]	X[j]						X[j]					X[j]		
Concomitant medications review[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Wk = Week

a. Study drug will be administered on Day 1/Baseline visit, and then every 4 weeks thereafter until 1 of the discontinuation criteria is met, until the sponsor discontinues the study, or until the study reaches completion. Visits during the Treatment Period may be scheduled within ± 4 days. All dosing visits may be completed over 2 consecutive days at the discretion of the investigator with the second day to include the start and end of the infusion.

b. Subject informed consent, or as applicable, legally authorized representative informed consent and subject assent, and study partner informed consent must be obtained prior to any Study M15-570 specific procedures being completed.

c. Review medical history to confirm subject does not meet exclusion criteria prior to enrollment.

d. Not required if procedure was conducted during the Week 96 visit in Study M15-566. A repeat assessment/procedure may be required based on discussion with the TA MD if more than 4 weeks have passed since the Week 96 visit.

e. Exploratory eye test for AD pathology may be conducted at participating sites and will be performed at Weeks 60 and 260 or Premature Discontinuation.

f. Vital signs, body weight, C-SSRS, concomitant medications review and AE assessment to be completed prior to administration of infusion.

g. Subjects who did not complete tau PET imaging at Day 1/Baseline will have tau PET imaging performed at subsequent visits only after discussion with TA MD. Tau PET imaging will only be collected for subjects at sites selected to participate in the tau PET assessment.

h. Optional pharmacogenetic DNA and RNA samples require consent. Verify consent prior to sample collection.

i. The recommended order of administration is CDR followed by RBANS. When applicable, ADCS-MCI-ADL-24, EQ-5D-5L, and C-SSRS may be subsequently administered/assessed in any order prior to study drug administration.

j. Start of collection period for digital measures of cognition, actigraphy, and sleep. Detailed instructions and other considerations will be provided in a separate manual.

k. Post-treatment follow-up to occur approximately 20 weeks after the Completion or Premature Discontinuation (PD) visit.

Note: for subjects who prematurely discontinue the study, safety and efficacy assessments may be conducted remotely (for example, via telephone), where applicable.

Has been changed to read:

	Year 1													
Dose	**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**	**Dose 14**
Visits & Procedures[a]	**Day 1/ Baseline**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**
Subject/study partner ICF[b]	X													
Medical history update[c]	X													
Treatment assignment	X													
Physical examination	X[d]													X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination	X[d]			X			X							X
12-lead ECG	X[d]			X			X							X
Clinical laboratory tests	X[d]			X			X						X	
Brain MRI	X[d]			X			X						X	
Optional LP/CSF collection	X[d]												X	
Tau PET[f]	X[d]												X	
Blood sample for ABBV-8E12 assay	X[d]			X			X						X	
ADA sample	X[d]			X			X						X	
Plasma and serum biomarker sample	X[d]			X			X						X	
Optional PG DNA and RNA sample[g]	X[d]			X			X						X	

	Year 1													
Dose	**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**	**Dose 14**
Visits & Procedures[a]	**Day 1/ Baseline**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDR[h]	X[d]						X						X	
RBANS[h]	X[d]												X	
ADCS-MCI-ADL-24[h]	X[d]													X
EQ-5D-5L[h]	X													X
C-SSRS[e,h]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications review[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Year 2												
Dose	**Dose 15**	**Dose 16**	**Dose 17**	**Dose 18**	**Dose 19**	**Dose 20**	**Dose 21**	**Dose 22**	**Dose 23**	**Dose 24**	**Dose 25**	**Dose 26**	**Dose 27**
Visits & Procedures[a]	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 104**
Subject/study partner ICF[b]													
Medical history update[c]													
Treatment assignment													
Physical examination													X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination					X						X		
12-lead ECG													X
Clinical laboratory tests					X						X		
Brain MRI					O						X		
Optional LP/CSF collection											X		
Tau PET[f]											X		
Blood sample for ABBV-8E12 assay					X						X		
ADA sample					X						X		
Plasma and serum biomarker sample					X						X		
Optional PG DNA and RNA sample[g]					X						X		
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
CDR[h]					X						X		

	Year 2												
Dose	**Dose 15**	**Dose 16**	**Dose 17**	**Dose 18**	**Dose 19**	**Dose 20**	**Dose 21**	**Dose 22**	**Dose 23**	**Dose 24**	**Dose 25**	**Dose 26**	**Dose 27**
Visits & Procedures[a]	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 104**
RBANS[h]											X		
ADCS-MCI-ADL-24[h]													X
EQ-5D-5L[h]													X
C-SSRS[e,h]					X						X		X
Concomitant medications review[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Year 3												
Dose	**Dose 28**	**Dose 29**	**Dose 30**	**Dose 31**	**Dose 32**	**Dose 33**	**Dose 34**	**Dose 35**	**Dose 36**	**Dose 37**	**Dose 38**	**Dose 39**	**Dose 40**
Visits & Procedures[a]	**Wk 108**	**Wk 112**	**Wk 116**	**Wk 120**	**Wk 124**	**Wk 128**	**Wk 132**	**Wk 136**	**Wk 140**	**Wk 144**	**Wk 148**	**Wk 152**	**Wk 156**
Subject/study partner ICF[b]													
Medical history update[c]													
Treatment assignment													
Physical examination													X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination				X						X			
12-lead ECG													X
Clinical laboratory tests										X			
Brain MRI				O						X			
Optional LP/CSF collection													
Tau PET[f]										X			
Blood sample for ABBV-8E12 assay				X						X			
ADA sample				X						X			
Plasma and serum biomarker sample				X						X			
Optional PG DNA and RNA sample[g]				X						X			
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
CDR[h]				X						X			

	Year 3												
Dose	**Dose 28**	**Dose 29**	**Dose 30**	**Dose 31**	**Dose 32**	**Dose 33**	**Dose 34**	**Dose 35**	**Dose 36**	**Dose 37**	**Dose 38**	**Dose 39**	**Dose 40**
Visits & Procedures[a]	**Wk 108**	**Wk 112**	**Wk 116**	**Wk 120**	**Wk 124**	**Wk 128**	**Wk 132**	**Wk 136**	**Wk 140**	**Wk 144**	**Wk 148**	**Wk 152**	**Wk 156**
RBANS[h]										X			
ADCS-MCI-ADL-24[h]													X
EQ-5D-5L[h]													X
C-SSRS[e,h]				X						X			X
Concomitant medications review[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Year 4												
Dose	**Dose 41**	**Dose 42**	**Dose 43**	**Dose 44**	**Dose 45**	**Dose 46**	**Dose 47**	**Dose 48**	**Dose 49**	**Dose 50**	**Dose 51**	**Dose 52**	**Dose 53**
Visits & Procedures[a]	**Wk 160**	**Wk 164**	**Wk 168**	**Wk 172**	**Wk 176**	**Wk 180**	**Wk 184**	**Wk 188**	**Wk 192**	**Wk 196**	**Wk 200**	**Wk 204**	**Wk 208**
Subject/study partner ICF[b]													
Medical history update[c]													
Treatment assignment													
Physical examination													X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination			X						X				
12-lead ECG													X
Clinical laboratory tests									X				
Brain MRI			O						X				
Optional LP/CSF collection													
Tau PET[f]									X				
Blood sample for ABBV-8E12 assay			X						X				
ADA sample			X						X				
Plasma and serum biomarker sample			X						X				
Optional PG DNA and RNA sample[g]			X						X				
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
CDR[h]			X						X				

	Year 4												
Dose	**Dose 41**	**Dose 42**	**Dose 43**	**Dose 44**	**Dose 45**	**Dose 46**	**Dose 47**	**Dose 48**	**Dose 49**	**Dose 50**	**Dose 51**	**Dose 52**	**Dose 53**
Visits & Procedures[a]	**Wk 160**	**Wk 164**	**Wk 168**	**Wk 172**	**Wk 176**	**Wk 180**	**Wk 184**	**Wk 188**	**Wk 192**	**Wk 196**	**Wk 200**	**Wk 204**	**Wk 208**
RBANS[h]									X				
ADCS-MCI-ADL-24[h]													X
EQ-5D-5L[h]													X
C-SSRS[e,h]			X						X				X
Concomitant medications review[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Year 5													
Dose	**Dose 54**	**Dose 55**	**Dose 56**	**Dose 57**	**Dose 58**	**Dose 59**	**Dose 60**	**Dose 61**	**Dose 62**	**Dose 63**	**Dose 64**	**Dose 65**	**Wk 260/ Study Completion PD Visit**	**20 Wk Post-Last Dose[i] Follow-Up Visit**
Visits & Procedures[a]	**Wk 212**	**Wk 216**	**Wk 220**	**Wk 224**	**Wk 228**	**Wk 232**	**Wk 236**	**Wk 240**	**Wk 244**	**Wk 248**	**Wk 252**	**Wk 256**		
Subject/study partner ICF[b]														
Medical history update[c]														
Treatment assignment														
Physical examination													X	
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Neurological examination		X						X					X	X
12-lead ECG													X	
Clinical laboratory tests								X					X	X
Brain MRI		O						X					X	X
Optional LP/CSF collection													X	
Tau PET[f]													X	
Blood sample for ABBV-8E12 assay		X						X					X	X
ADA sample		X						X					X	X
Plasma and serum biomarker sample		X						X					X	X
Optional PG DNA and RNA sample[g]		X												X

	Year 5													
Dose	**Dose 54**	**Dose 55**	**Dose 56**	**Dose 57**	**Dose 58**	**Dose 59**	**Dose 60**	**Dose 61**	**Dose 62**	**Dose 63**	**Dose 64**	**Dose 65**	**Wk 260/ Study Completion PD Visit**	**20 Wk Post-Last Dose[i] Follow-Up Visit**
Visits & Procedures[a]	**Wk 212**	**Wk 216**	**Wk 220**	**Wk 224**	**Wk 228**	**Wk 232**	**Wk 236**	**Wk 240**	**Wk 244**	**Wk 248**	**Wk 252**	**Wk 256**		
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X		
CDR[h]		X						X					X	X
RBANS[h]								X					X	
ADCS-MCI-ADL-24[h]													X	
EQ-5D-5L[h]													X	X
C-SSRS[e,h]		X						X					X	X
Concomitant medications review[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

O = Optional; Wk = Week

a. Study drug will be administered on Day 1/Baseline visit, and then every 4 weeks thereafter until 1 of the discontinuation criteria is met, until the sponsor discontinues the study, or until the study reaches completion. Visits during the Treatment Period may be scheduled within ± 4 days. All dosing visits may be completed over 2 consecutive days at the discretion of the investigator with the second day to include the start and end of the infusion.

b. Subject informed consent, or as applicable, legally authorized representative informed consent and subject assent, and study partner informed consent must be obtained prior to any Study M15-570 specific procedures being completed.

c. Review medical history to confirm subject does not meet exclusion criteria prior to enrollment.

d. Not required if procedure was conducted during the Week 96 visit in Study M15-566. A repeat assessment/procedure may be required based on discussion with the TA MD or designee if subject is enrolling outside the 8 week window from the Week 92 visit in Study M15-566.

e. Vital signs, body weight, C-SSRS, concomitant medications review and AE assessment to be completed to administration of infusion.

f. Subjects who did not complete tau PET imaging through Study M15-566 and at Study M15-570 Day 1/Baseline will have tau PET imaging performed at subsequent visits only after discussion with TA MD or designee. Tau PET imaging will only be collected for subjects at sites selected to participate in the tau PET assessment.

g. Optional pharmacogenetic DNA and RNA samples require consent. Verify consent prior to sample collection.

h. The recommended order of administration is CDR followed by RBANS. When applicable, ADCS-MCI-ADL-24, EQ-5D-5L, and C-SSRS may be subsequently administered/assessed in any order.

i. Post-treatment follow-up to occur approximately 20 weeks after the last dose.

Note: For subjects who prematurely discontinue the study, safety and efficacy assessments may be conducted remotely (for example, via telephone), where applicable.