Statistical Programming Plan for

Study M15-570

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

Date: 30 July 2021

Version 2.0

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1.0 Purpose and Scope

This statistical programming plan (SPP) provides details to further elaborate some statistical methods as outlined in the statistical analyses plan (SAP) version 2.0 for M15-570 study. The document describes analysis conventions to guide the statistical programming work. The analysis will be completed by AbbVie Data and Statistical Sciences for tilavonemab (ABBV-8E12) Study Protocol M15-570.

2.0 Study-Specific Programming Guidelines

2.1 Definition of Analysis Sets

Data Set for Safety Analyses

The safety data set will contain data from Study M15-570 only, regardless of the treatment received in Study M15-566. Baseline for the safety data set will be the last observation before the first dose of tilavonemab 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.

2.2 Analysis Conventions

2.2.1 Statistical Significance

Unless otherwise specified, statistical tests will be two-sided for efficacy and safety analyses at 0.05 level.

2.2.2 Visit Definitions

Definition of Rx Day (Days Relative to the First Dose of Study Drug)

Rx Day is calculated for each time point as the number of days between the day of the first dose of study drug and the specific time point. For dates before the first dose date of study drug, Rx day = date of time point – first dose date; for dates on or after the first dose date of study drug, Rx day = date of time point – first dose date + 1. Thus, Rx Day is a negative value when the time point of interest is prior to the first study drug dose day; Rx Day is a positive value when

the time point of interest is on or after the first study drug dose day. There is no Rx Day 0. With this defined algorithm, the day of the first dose of study drug will be Rx Day 1.

RxEnd Day is calculated for each post-treatment time point as the number of days between the day of the last dose of study drug and the specific time point: RxEnd Day = date of time point – last dose date. With this defined algorithm, the day of the last dose of study drug will be RxEnd Day 0.

Definition of Baseline and Final Observation

For primary efficacy analyses on the ITT data set and for safety analyses on the safety data set of the Treatment Period, "baseline" shall refer to the last non-missing observation prior to the first dose of study drug of Study M15-570.

- If the duration between Day 1 of Study M15-570 and the last dose (Week 92) of Study M15-566 is less than or equal to 45 days and no M15-570 Day 1 visit data, vital sign, laboratory, MRI, and questionnaire data at visit Week 96 of Study M15-566 will be used as the baseline for Study M15-570. If M15-570 Day 1 visit data are available, Day 1 visit data will be used as the baseline.

- If the duration between Day 1 of M15-570 and the last dose (Week 92) of Study M15-566 is larger than 45 days, Day 1 visit data of Study M15-570 of vital sign, laboratory, MRI, and questionnaire data will be the baseline. If M15-570 Day 1 visit data are not available, the last available data from M15-566 will be used as the baseline.

- Day 1 visit data of M15-570 will always be the baseline of Study M15-570 for all other data (Adverse Event, ECG) and will not be impacted by the duration between Day 1 visit of Study M15-570 and Week 92 visit of Study M15-566.

For all safety analyses, "final" for the Treatment Period shall refer to the last non-missing observation in the Treatment Period but no more than 45 days after the last dose of the study drug for safety variables. The "final" for the post-treatment follow-up period for safety variables

shall refer to the last non-missing observation greater than 45 days but no more than 20 weeks after the last dose of study drug.

Definition of Analysis Windows

To perform longitudinal data analysis, observations that are obtained after the first day of study drug administration will be assigned to an analysis "Week" associated with the Rx Days that are corresponding to the observations. Unless otherwise specified, efficacy observations and safety observations no more than 45 days after the last dose of study drug will be included in analyses for the treatment period. Safety observations later than 45 days, but no more than 20 weeks, after the last dose of study drug will be included for the post-treatment follow-up period safety analysis. The intervals presented below for each scheduled visit (Rx Days X through Y) include both Rx Days X and Y. The nominal day for each scheduled post-baseline visit is 7 times "X" where "X" is visit week number. For example, the nominal day for Week 12 visit is 7*12=84.

For measurements that are planned to be collected at Weeks 12, 24, 48, 72, 96, 144, 192, 240, and 260, i.e. clinical laboratory tests, observations will be mapped to an analysis "Week" according to the following windows defined by Rx day.

Week 12	Rx Days 2 through 126
Week 24	Rx Days 127 through 252
Week 48	Rx Days 253 through 420
Week 72	Rx Days 421 through 588
Week 96	Rx Days 589 through 840
Week 144	Rx Days 841 through 1176
Week 192	Rx Days 1177 through 1512
Week 240	Rx Days 1513 through 1750
Week 260	Rx Days > 1750

For measurements that are planned to be collected at Weeks 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240 and 260, i.e. Brain MRI, observations will be mapped to an analysis "Week" according to the following windows defined by Rx day.

Week 12	Rx Days 2 through 126
Week 24	Rx Days 127 through 252

Week 48	Rx Days 253 through 420
Week 72	Rx Days 421 through 588
Week 96	Rx Days 589 through 756
Week 120	Rx Days 757 through 924
Week 144	Rx Days 925 through 1092
Week 168	Rx Days 1093 through 1260
Week 192	Rx Days 1261 through 1428
Week 216	Rx Days 1429 through 1596
Week 240	Rx Days 1597 through 1750
Week 260	Rx Days > 1750

For measurements that are planned to be collected at Weeks 4, 4n (n=2, 3, …12), 52, 72, 96, 104, 120, 144, 156, 168, 192, 208, 216, 240 and 260, i.e. body weight and C-SSRS, observations will be mapped to an analysis "Week" according to the following windows defined by Rx day.

Week 4	Rx Days 2 through 42
Week 4n	Rx Days 7*((n-1)*4+2)+1 through 7*(n*4+2)
Week 52	Rx Days 351 through 434
Week 72	Rx Days 435 through 588
Week 96	Rx Days 589 through 700
Week 104	Rx Days 701 through 756
Week 120	Rx Days 757 through 924
Week 144	Rx Days 925 through 1050
Week 156	Rx Days 1051 through 1134
Week 168	Rx Days 1135 through 1260
Week 192	Rx Days 1261 through 1400
Week 208	Rx Days 1401 through 1484
Week 216	Rx Days 1485 through 1596
Week 240	Rx Days 1597 through 1750
Week 260	Rx Days > 1750

For safety assessments that are planned to be collected during post-treatment follow-up period, observations will be mapped to an analysis "Week" according to the following windows defined by RxEnd day.

Post-Treatment Week 20	45< RxEnd Days ≤140

If more than 1 observation is included in a visit time window, the non-missing observation closest to the nominal day will be used in analyses. If more than 1 observation occurs on the same day, the average will be calculated and used in analyses.

3.0 Version History

Table 1 SPP Version History Summary

Version	Date of Approval	Summary
1.0	10 Feb 2021	Initial version
2.0	30 Jul 2021	• Removed contents related to efficacy, biomarker analysis, PK analysis, and some safety sections to align with update SAP v2.0 for abbreviated CSR • Update TOC for abbreviated CSR

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1.0 Title Page

Statistical Analysis Plan

Study M15-570

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

Date: 29 July 2021

Version 2.0

1.1 List of Abbreviations and Definition of Terms

AD	Alzheimer's Disease
AE	Adverse event
ALT	Alanine aminotransferase
APOE	Apolipoprotein E
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
INR	International normalized ratio
MCHC	Mean corpuscular hemoglobin concentration
MCI	Mild cognitive impairment
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MHIS	Modified Hachinski Ischemic Scale
MRI	Magnetic resonance imaging
NFL	Neurofilament light
PCS	Potentially clinically significant
PD	Premature discontinuation
PET	Positron emission tomography
PK	Pharmacokinetic
PT	Preferred Term
RBC	Red blood cell count
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class

SUV	Standardized uptake value
SUVR	Standardized uptake value ratio
TEAE	Treatment-emergent adverse event
vMRI	Volumetric magnetic resonance imaging
WBC	White blood cell count

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3.0 Introduction

This analysis plan describes the statistical analyses to be completed by AbbVie Data and Statistical Science for ABBV-8E12 Study Protocol M15-570, that incorporates one amendment (original Protocol: 09 April 2018; Amendment 1: 24 January 2019; Amendment 2: 20 October 2020).

This statistical analysis plan (SAP) provides details to further elaborate statistical methods as outlined in the protocol and describes analysis conventions to guide the statistical programming work. Population pharmacokinetic and exposure-response analysis for this study will be conducted separately and are not included in this SAP. The SAP v2.0 is updated to provide details of analysis for the abbreviated CSR.

Analyses will be performed using SAS version 9.3 or higher (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 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.

4.2 Study Design

This Phase 2 extension of a multiple dose, multicenter, multinational, 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 (Table 2). 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.

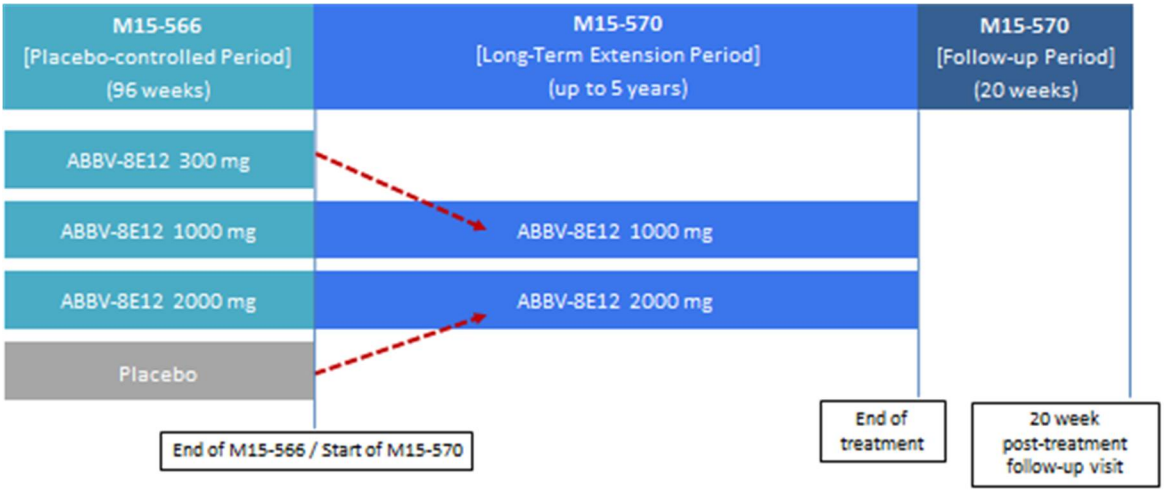
Day 1 visit of Study M15-570 (day of the first dose of Study M15-570) will be at least 4 weeks but no more than 8 weeks after the last dosing visit (Week 92) of Study M15-566. Should this window be longer than 8 weeks, the subject may be considered for participation in Study M15-570 only with the approval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



4.3 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. Enrollment of Study M15-566 has been completed with 453 subjects randomized. The number of subjects who enroll in Study M15-570 could be up to 453.

4.4 Interim Analyses

Interim Efficacy Analysis

No interim analysis will be performed due to early termination of the study.

Safety Reviews

The DMC for Study M15-566 will serve as the DMC for Study M15-570. Before database lock of Study M15-566, DMC safety reviews of Study M15-570 data will follow the same schedule as the Study M15-566 DMC safety review meetings (i.e., data from both studies will be reviewed jointly depending on the pre-specified Study M15-566 review time points). The database snapshots will be taken for the safety interim reviews.

Once the database is locked for Study M15-566, there will be no further planned DMC reviews for Study M15-570.

4.5 Safety Variables

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

4.6 Biomarker and Pharmacogenetic Research Variables

4.6.1 Biomarker Research Variables

Plasma and Optional CSF Concentration Variables

CSF samples will be assayed for free and total tauA value for the ratio of free tau concentration to total tau concentration could be determined The assessments on free tau and the ratio of free tau to total tau could 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.

Volumetric MRI

Baseline volumetric MRI (vMRI) measurements and measurements on change from baseline in vMRI measurements will be obtained. 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. Measurements will be obtained for whole brain, hippocampus, and lateral ventricles. Measurements may be obtained for additional regions.

Tau PET Imaging

The amount of tau deposits in a given region will be assessed by calculating a standardized uptake value ratio (SUVR) of each region. The SUVR is a ratio between the standardized uptake values (SUV) of a target brain region relative to that of cerebellar

cortex, which is considered as the reference tissue devoid of tau. The SUV is calculated by normalizing the concentration of radioactivity in the region (KBq/mL) to the injected dose (BMq) and the subject's body weight (kg). 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, values will be obtained 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.

5.0 Analysis Populations and Analysis Data Set

Data Sets for Safety Analyses

Safety Data Set: The Safety Data Set will contain data from Study M15-570 only, regardless of the treatment received in Study M15-566. Baseline for the Safety 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.

6.0 Demographics, Baseline Characteristics, Subject History, and Previous/Concomitant Medications

The data analysis will be conducted on Safety Data Set and among treatment groups defined as Studies M15-566/M15-570: 300/1000 mg, 1000/1000 mg, placebo/2000 mg, and 2000/2000 mg.

6.1 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized for each treatment group.

- Gender (male/female)
- Race (white, black, American Indian/Alaska native, Native Hawaiian or other Pacific Islander, Asian, Other, Multi-Race)

- Education (high school or above, lower than high school)
- Ethnicity (Hispanic or Latino)
- Age (years)
- Age group (<65, ≥ 65)
- Weight for all subjects (kg)
- Weight for all male subjects (kg)
- Weight for all female subjects (kg)
- Height (cm)
- Body mass index (BMI, kg/m^2)
- Body mass index category (kg/m^2) (< 25, ≥ 25)
- APOE allele status (ε2ε2, ε2ε3, ε2ε4, ε3ε3, ε3ε4, ε4ε4)
- Baseline cholinesterase inhibitors (AChEI) medication or memantine use (AChEI includes donepezil, rivastigmine, and galantamine)

6.2 Medical History

Medical history data for this study is transferred from Study M15-566 and will be conducted on Safety Data Set. The conditions/diagnoses recorded in medical/surgery history eCRF will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). Data will be summarized and presented using system organ classes (SOCs) and preferred terms (PTs). The SOC will be presented in alphabetical order and the PTs will be presented in alphabetical order within each SOC. The number and percentage of subjects with a particular SOC and PT will be summarized for each treatment group and overall. Subjects reporting more than one PT within a SOC will be counted only once for that SOC.

The following disease history variables will be summarized for each treatment group, and overall subjects.

- Age at onset of symptoms of cognitive impairment (years)
- Age when first diagnosed as having MCI due to AD or AD (years)

- Years since onset of symptoms of cognitive impairment (Date of Day 1 – Date of onset)
- Years since MCI due to AD or AD diagnosis (Date of Day 1 – Date of diagnosis)
- Family history of AD (None, biological mother, biological father, full sibling, biological child)
- Years of formal education

Categorical variables will be summarized with the number and percentage of subjects in each category. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum, and maximum).

6.3 Previous and Concomitant Medications

Previous medications are defined as all medications with a start date before the first study drug infusion of M15-570, regardless of the end date of these mediations. Concomitant medications are defined as all medications, other than study drug, taken during the treatment period (i.e., from the first day of study drug administration through 45 days after the last day of study drug administration). Concomitant medication use for AD or MCI will be summarized into two categories: taken both at baseline and post-baseline, not taken at baseline but taken post-baseline. Previous and concomitant medications will be coded using the World Health Organization (WHO) dictionary and will be summarized by generic name and Anatomical Therapeutic Chemical (ATC) classification system level 3. The number and percentage of subjects who take at least 1 medication and who take at least 1 dose of each specific medication in the following categories will be summarized for each treatment group and overall subjects.

- Previous AD or MCI medication: donepezil, rivastigmine, galantamine, tacrine, memantine, investigational medicine or other.
- Previous antipsychotic/neuroleptic medications
- Previous anticholinergic medications

- Previous sedatives/benzodiazepines
- Previous Parkinsonian medications
- Concomitant antipsychotic/neuroleptic medications
- Concomitant anticholinergic medications
- Concomitant sedatives/benzodiazepines
- Concomitant Parkinsonian medications
- Concomitant AChEIs (donepezil, rivastigmine, galantamine) or memantine for cognitive impairment.

7.0 Subject Disposition

For subjects who are enrolled in the study, the number and percentage of subjects in each enrollment disposition category (enrolled but not treated, prematurely discontinued and completed) will be summarized for each treatment group and overall subjects.

The number and percentage of subjects who prematurely discontinued study drug or prematurely discontinued from the study will be summarized by reason (primary or any reason) for each treatment group and overall subjects.

In addition, the following additional summaries will be presented for all enrolled subjects:

- The number and percentage of subjects who are enrolled at each site.
- The number and percentage of subjects who prematurely discontinued at each site.

8.0 Study Drug Exposure and Compliance

Study drug exposure will be summarized for each treatment group and overall subjects. Duration of exposure is calculated as the last study drug administration date minus the first study drug administration date + 30. Total subject years of exposure is calculated by summing the duration of exposure across all subjects and dividing this sum by 365 (1 year will be considered to be 365 days). The number and percentage of subjects who have

taken a total of infusions ≤ 6, 7 to 12, 13 to 18, 19 to 24, 25 to 30, 31 to 36, 37 to 42, 43 to 48, 49 to 54, 55 to 60, and ≥ 61 will be summarized. In addition, duration of exposure will be summarized with descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum and maximum duration, and total years).

To evaluate impact of Coronavirus Disease 2019 (COVID-19) pandemic on study drug compliance, expected infusions (completers are expected to have 65 infusions, prematurely discontinued subjects are expected to have expected number of infusions based on discontinuation visit date) and infusions missed due to COVID-19 pandemic will be summarized for each treatment group and Overall (mean, minimum, maximum of expected infusions; mean, minimum, maximum of missed infusions, mean of the percentage of missed infusions relative to expected number of infusions will be tabulated) across all countries and by country.

At each scheduled dosing visit, the investigator will document whether the subject has received the entire dose infusion or not and the volume administered will be recorded in the eCRF if the entire dose is not administered. The percentage of the assigned dose administered will be calculated at each visit. The mean of this percentage across infusions for each subject will be obtained. The descriptive statistics (number of non-missing observations, minimum, mean, median, standard deviation, maximum) based on each subject's mean volume percentage of study drug infusion will be summarized for each treatment group and overall subjects.

9.0 Efficacy Analysis

9.1 General Considerations

No efficacy analysis will be performed for this study due to early termination of the study.

10.0 Safety Analysis

10.1 General Considerations

No comparisons between treatment groups (Studies M15-566/M15-570) of interest will be performed unless otherwise specified.

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.

The Safety Data Set will be the data set for all safety data analyses.

10.2 Analysis of Adverse Events

All adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event (TEAE) is defined as any adverse event that begins or worsens in severity on or after the first study drug dose date and no more than 20 weeks after the last study drug dose date.

10.2.1 Adverse Event Overview

The number and percentage of subjects experiencing one or more adverse events in the following adverse event categories will be summarized for each treatment group and overall subjects.

- Any TEAE
- Any TEAE that was rated reasonable possibility of being related to study drug by the investigator
- Any severe TEAE
- Any serious TEAE
- Any TEAE that led to discontinuation of study drug

- Any fatal TEAE
- All deaths

10.2.2 Adverse Event Incidence

TEAE incidence will be summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs). The system organ classes will be presented in alphabetical order and the preferred terms will be presented in the alphabetical order within each system organ class. Subjects reporting more than one adverse event for a given MedDRA PT will be counted only once for that term. Subjects reporting more than one adverse event within a SOC will be counted only once for the SOC total. Subjects reporting more than one adverse event will be counted only once in the overall adverse event total.

The number and percentage of subjects experiencing one or more TEAEs will be summarized by PT for each treatment group and overall subjects. The PTs will be presented by decreasing frequency in overall subjects.

The number and percentage of subjects experiencing one or more adverse events in the following adverse event categories will be summarized by primary SOC and PT for each treatment group and overall subjects.

- Any TEAE
- Any serious TEAE
- Any TEAE that led to discontinuation of study drug
- Any TEAE assessed by the investigator to be Reasonable Possibility of Being Related to study drug

The number of subjects experiencing one or more TEAEs will also be summarized by maximum severity category (mild, moderate, severe and unknown) and primary SOC and PT for each treatment group and overall subjects. Subjects reporting more than one TEAE for a given PT will be counted only once for that term in the most severe category

reported. If a subject has an adverse event with unknown severity, then the subject will be counted in the severity category of "unknown" even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Severe" category.

The number of subjects experiencing one or more TEAEs will also be summarized by maximum relationship category (Reasonable Possibility of Being Related, No Reasonable Possibility of Being Related and Unknown), as assessed by the investigator, and primary SOC and PT for each treatment group and overall subjects. Subjects reporting more than one TEAE for a given PT will be counted only once for that term in the most related category reported. If a subject has an adverse event with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is that if a subject has another occurrence of the same adverse event with a relationship assessment of "Reasonable Possibility of Being Related." In this case, the subject will be counted under the "Reasonable Possibility of Being Related."

10.2.3 Listing of Adverse Events

The following additional summaries of adverse events will be prepared.

- List of subject numbers associated with each PT for all TEAEs
- List of subject numbers associated with each PT for all TEAEs assessed by the investigator as Reasonable Possibility of Being Related.
- Listing of all serious adverse events
- Listing of all adverse events that led to discontinuation of study drug
- Listing of all fatal adverse events
- Listing of all deaths

10.3 Analysis of Laboratory Tests

The laboratory tests with continuous values that will be analyzed are described in Table 1.

Table 1. Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Bands (if detected) Lymphocytes Monocytes Basophils (if detected) Eosinophils (if detected) Platelet count (estimate not acceptable) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin concentration (MCHC) Prothrombin time (PT) Activated partial thromboplastin time (aPTT) PT/INR (Prothrombin Time/International Normalized Ratio)	Blood urea nitrogen (BUN) Creatinine Total bilirubin Albumin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphate Uric acid Cholesterol Total protein Glucose Triglycerides Bicarbonate/Carbon Dioxide (CO_2) Chloride	Specific gravity pH

10.3.1 Potentially Clinically Significant Laboratory Values

Criteria for potentially clinically significant (PCS) values have been predefined for selected laboratory variables as outlined in Appendix A. For each variable, a summary of the number and percentage of subjects in each treatment group who have at least one double-blind observation that meets the PCS criteria and is more extreme than their baseline value will be provided at any time in the entire study. A listing will also be prepared that will include, for each variable, all observations for each subject that met the PCS criteria for that variable at any time during the study.

10.4 Analysis for Other Safety Variables

10.4.1 Columbia-Suicide Severity Rating Scale (C-SSRS)

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

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

10.4.2 Summary of MRI Safety Evaluations

MRI safety evaluations will be summarized by treatment sequences placebo/2000mg, 2000/2000mg, 300/1000mg, and 1000/1000mg based on MRI evaluations in the double blinded period. The summaries include number and percentage of subjects with presence and severity of baseline and post baseline MRI findings of cerebral edema, microhemorrhages, and severe white matter disease as defined by a score of 3 on Age-Related White Matter Changes (ARWMC) scale and other structural abnormalities. Descriptive statistics (mean, median, minimum, maximum) of number of new microhemorrhages or new lesions in the double-blinded period will be presented. Listing of subjects with post-baseline MRI findings will be provided.

11.0 Pharmacokinetic Analysis

No pharmacokinetic analysis will be performed for this study due to early termination of the study.

12.0 Biomarker Analysis

No biomarker analysis will be performed for this study due to early termination of the study.

13.0 Summary of Changes

Changes in the planed analyses from the latest version of the protocol (Protocol Amendment 2) have been incorporated into Statistical Analysis Plan version 2.0.

Efficacy analysis, PK analysis, and biomarker analysis sections and some safety analyses were removed in SAP version 2.0.

Table 2. 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
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	
Optional PG DNA and RNA sample[h]	X[d]			X			X						X	

Table 2. Study Activities (Continued)

	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[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

Table 2. Study Activities (Continued)

	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		

Table 2. Study Activities (Continued)

	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**
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
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

Table 2. Study Activities (Continued)

	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			

Table 2. Study Activities (Continued)

	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**
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
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

Table 2. Study Activities (Continued)

	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				

Table 2. Study Activities (Continued)

Dose	Year 4												
	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**
Administer IV study drug[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
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

Table 2. Study Activities (Continued)

Dose	Year 5													
	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

Table 2. Study Activities (Continued)

Dose	Year 5													
	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.

Table 2. Study Activities (Continued)

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.

Appendix A. Potentially Clinically Significant (PCS) Laboratory Value

Clinical Laboratory Tests	Very Low (VL)	Very High (VH)
Hematology		
Activated partial thromboplastin time	NA	> ULN
Hemoglobin	< 100 g/L (6.2 mmol/L)	> 40 g/L above ULN
Prothrombin Intl. Normalized Ratio	NA	> ULN
Leukocytes	$< 2 \times 10^9$/L	$> 100 \times 10^9$/L
Lymphocyte	$< 0.5 \times 10^9$/L	$> 20 \times 10^9$/L
Neutrophil	$< 1 \times 10^9$/L	NA
Platelets	$< 75 \times 10^9$/L	NA
Chemistry		
Bilirubin	NA	> 1.5 × ULN
Cholesterol	NA	> 12.92 mmol/L (500 mg/dL)
Creatinine	NA	> 1.5 × ULN
Calcium (corrected serum)	< 1.75 mmol/L (7.0 mg/dL)	> 3.1 mmol/L (12.5 mg/dL)
Glucose (fasting)	< 2.2 mmol/L (40 mg/dL)	> 13.9 mmol/L (250 mg/dL)
Potassium	< 3.0 mmol/L	> 6.0 mmol/L
Triglycerides	NA	> 5.7 mmol/L (500 mg/dL)
Uric acid	NA	> 590 umol/L (10 mg/dL)
Albumin	< 20 g/L	NA
Sodium	< 130 mmol/L	> 155 mmol/L
Phosphate	< 0.6 mmol/L (2.0 mg/dL)	NA
Enzymes		
Alanine aminotransferase (ALT)	NA	> 3 × ULN
Alkaline phosphatase	NA	> 2.5 × ULN
Aspartate aminotransferase (AST)	NA	> 3 × ULN

NA = not applicable; ULN = upper limit normal

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

Appendix B. Criteria for Potentially Clinically Significant Vital Sign and Weight Values

Vital Signs	Very Low (VL)	Very High (VH)
Systolic Blood Pressure (SBP) (mmHG)	≤ 90 and decreased ≥ 30 from baseline	≥ 180 and increased ≥ 40 from baseline
Diastolic Blood Pressure (DBP) (mmHG)	≤ 50 and decreased ≥ 20 from baseline	≥ 105 and increased ≥ 30 from baseline
Pulse (bpm)	≤ 45 and decreased ≥ 30 from baseline	≥ 120 and increased ≥ 30 from baseline
Temperature (C)	≥ 1.1 decrease from baseline	> 38.5 or increase ≥ 1.1 from baseline
Weight (kg)	Decreased ≥ 7% from baseline	Increased ≥ 7% from baseline

Appendix C. Criteria for Potentially Clinically Significant ECG Values

ECG Parameters	Significant Values
QTcF Interval (msec)	> 499
QTcF Interval Increased from Baseline (msec)	> 60