1.0 Title Page

Statistical Analysis Plan

Study M15-566

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

Date: 19 May 2020

Version 3.0

1.1 List of Abbreviations and Definition of Terms

AD	Alzheimer's Disease
ADA	Anti-drug-antibody
ADAS-Cog-14	Alzheimer's Disease Assessment Scale (14-Item) Cognition portion
ADCS-CGIC-MCI	Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change for Mild Cognitive Impairment
ADCS-MCI-ADL-24	24-item Alzheimer's Disease Cooperative Study/Activities of Daily Living Scale Adapted for Patients with Mild Cognitive Impairment
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APOE	Apolipoprotein E
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
BMI	Body mass index
BUN	Blood urea nitrogen
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-Sum of Boxes
C_{max}	Maximum observed serum concentration
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Observed serum drug concentration at the end of a dose interval
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
ERAC	Exposure-Response Analysis Center
eTIV	Estimated total intracranial volume
FAQ	Functional Activities Questionnaire
FWER	Family wise error rate
IBRC	Internal Biomarker Review Committee

IERC	Internal Executive Review Committee
INR	International normalized ratio
ITT	Intent-to-treat
LS	Least square
MCHC	Mean corpuscular hemoglobin concentration
MCI	Mild cognitive impairment
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MHIS	Modified Hachinski Ischemic Scale
MI	Multiple imputation
MMRM	Mixed-effects model repeated measures
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NFL	Neurofilament light
NPI	Neuropsychiatric Inventory
PCS	Potentially clinically significant
PD	Premature discontinuation
PET	Positron emission tomography
PK	Pharmacokinetic
PT	Preferred Term
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
RBC	Red blood cell count
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDAC	Statistical and Data Analysis Center
SOC	System Organ Class
SUV	Standardized uptake value
SUVR	Standardized uptake value ratio
TEAE	Treatment-emergent adverse event
T_{max}	Time to peak (maximum) observed serum concentration
vMRI	Volumetric magnetic resonance imaging
WBC	White blood cell count

2.0 Table of Contents

List of Tables

List of Figures

List of Appendices

3.0 Introduction

This analysis plan describes the statistical analyses to be completed by AbbVie Clinical Statistics and Programming for ABBV-8E12 Study Protocol M15-566, that incorporates two amendments (original Protocol; Administrative Change 1; Administrative Change 2; Administrative Change 3 (US-only); Amendment 1, Amendment 2).

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.

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 objectives of this study are:

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

The secondary objectives of this study are:

- To assess the pharmacokinetics of ABBV-8E12 in subjects with Early AD.
- To assess the efficacy of ABBV-8E12 in slowing cognitive and functional impairment in subjects with Early AD as measured by the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale (14-Item) Cognition Portion (ADAS-Cog-14), Repeatable Battery for Assessment of

Neuropsychological Status (RBANS), 24-Item Alzheimer's Disease Cooperative Study/Activities of Daily Living Scale Adapted for Patients with Mild Cognitive Impairment (ADCS-MCI-ADL-24), Functional Activities Questionnaire (FAQ) and University of California San Diego Performance Based Skills Assessment, Brief Version (UPSA-Brief), and Neuropsychiatric Inventory (NPI).

- To assess the global impact of ABBV-8E12 on cognition, function and behavior as measured by Alzheimer's Disease Cooperative Study Clinical Global Impression of Change for Mild Cognitive Impairment (ADCS-CGIC-MCI).

The exploratory objectives of this study are:

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

4.2 Study Design

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

Approximately 400 subjects with Early AD between 55 to 85 years of age will be eligible to participate in the study according to the selection criteria described in protocol Section 5.2. Upon completion of screening and baseline procedures, eligible subjects will be randomized to one of the 3 ABBV-8E12 dose arms (300 mg, 1000 mg or 2000 mg) or placebo in a 1:1:1:1 ratio. Doses will be administered every 4 weeks via IV infusion.

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

Safety and tolerability will be monitored throughout the study. The first 48 subjects enrolled into the study will be represented as Cohort 1 in this protocol while the subjects enrolled subsequently to Cohort 1 will be represented as Cohort 2. The protocol Amendment 2 states that Japanese subjects enrolled in J1 would follow safety and PK

sample collection procedures of Cohort 1. However, the enrollment of the study has completed without enrolling Japanese subjects. Therefore, J1 is not described in this SAP. More frequent pharmacokinetic (PK) sampling and safety monitoring by the DMC will be conducted for Cohort 1 subjects (Table 1).

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

In addition to blinded safety data monitoring by the sponsor, the first four mandatory DMC safety reviews of unblinded safety data will take place after the 12th, 24th, 36th and 48th subject have been administered their second dose and results for the MRI scheduled at approximately 2 weeks after their second dose are available. The dataset will consist of all of the available safety and pharmacokinetic data in the study, including the data of any subjects from Cohort 2 who have received at least one dose of study drug. Additional DMC safety reviews will occur after a total of approximately 100, 200, 300 and 400 subjects are randomized and every 6 months thereafter until the study completion.

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

Figure 1. Study Schematic

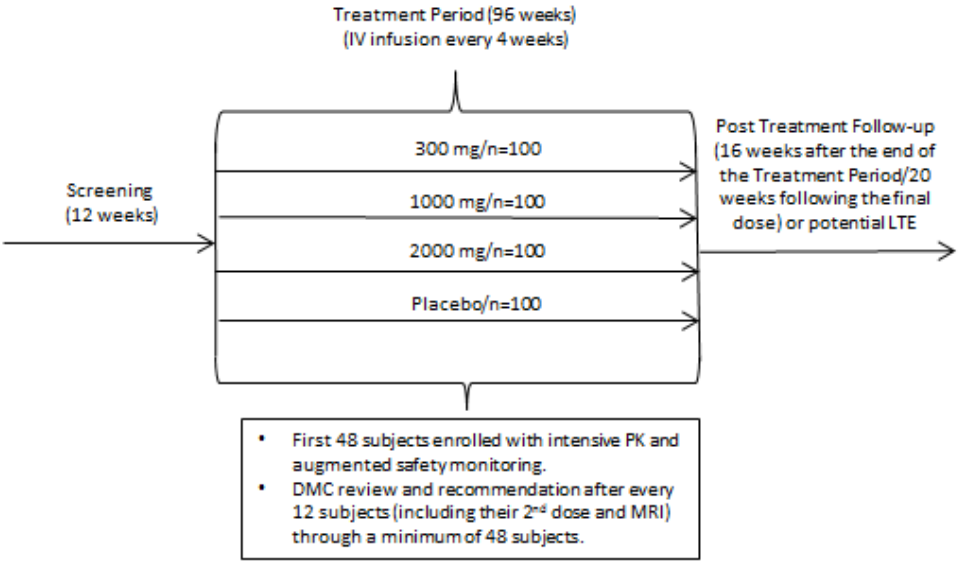


Table 1. Safety and PK Procedures for Cohort 1

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

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

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

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

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

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

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

Table 2. Study Activities

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

Table 2. Study Activities (Continued)

	Screening	Treatment Period[a] (Year 1)																
	Visit 1	Visit 2	Dose 1			Dose 2	Dose 3	Dose 4			Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13
Weeks of Study Drug Exposure	N/A	N/A	0	0	2	4	8	12	12	14	16	20	24	28	32	36	40	44	48
	Day –84 to –8	Day –7 to –1[c]	Day 1[c]	Days 5[d], 15[c,d]		Day 29[c]	Day 57[c]	Day 85[c]	Days 89[d], 99[d]		Day 113[c]	Day 141[c]	Day 169[c]	Day 197[c]	Day 225[c]	Day 253[c]	Day 281[c]	Day 309[c]	Day 337[c]
Amyloid PET Scan	X																		
Tau PET Scan[o]	X																	X[p]	
Retinal Imaging Scan	X																		
MRI	X					X[h]		X[h]						X[h]				X[h]	
Lumbar Puncture/CSF Sample Collection[r]	X							X[i]											
APOE Pharmacogenetic Sample			X																
Optional Pharmacogenetic Sample (DNA and RNA)[j]	X		X					X								X			X
Biomarker Plasma and Serum Sample	X		X					X								X			X

Table 2. Study Activities (Continued)

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

Table 2. Study Activities (Continued)

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

Table 2. Study Activities (Continued)

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

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

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

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

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

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

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

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

Table 2. Study Activities (Continued)

g Randomization should be completed just prior to the first dose administration.
h. The MRI will be scheduled approximately 2 weeks following the dose and results must be available prior to the next scheduled dose.
i. The lumbar puncture will be performed approximately 14 days after the fourth dose.
j. The optional Pharmacogenetic DNA and RNA samples require consent. Verify consent prior to sample collection.
k. A detailed description of the collection time points can be found in Section 5.3.2.1 in the protocol.
l. ADA sample for Cohort 1 will only be collected on Day 15.
m. See Table 3 for additional information on Diagnostic Tools and Rating Scales.
n. A detailed description for procedures involving adverse event assessments can be found in Section 6.0 in the protocol.
o. Tau PET scan obtained only for subjects at sites selected to participate in the tau imaging assessment.
p. Tau PET should be scheduled as close as possible after Weeks 44 (Dose 12) and 96 visits.
q. On Weeks 12 and 36, only digital clock drawing test will be performed.
r. The lumbar punctures at Screening Visit 1, Weeks 12 and 96 are optional for subjects in Cohort 2.

Table 3. Diagnostic Tools and Scale Administration Timing

	Recommended Order of Administration	Approximate Administration Time[a] (Minutes)	Patient/Study Partner	Screening Day –56 – Day –8	Day –7 to Day 1 (Prior to Infusion)[b]	Week 12	Week 24	Week 36	Week 48	Week 72	Week 96
CDR	1	45 – 75	Both	X	X		X		X	X	X
RBANS	2	25	Patient	X	X		X		X	X	X
UPSA – Brief	3	10 – 15	Patient		X				X		X
ADAS-Cog-14	4	30 – 60	Patient		X		X		X	X	X
MMSE	5	10 – 15	Patient	X	X		X		X	X	X
ADCS-CGIC-MCI	6	10 – 15	Both		X				X		X
C-SSRS[c]	7	5 – 20	Patient	X	X		X		X	X	X
FAQ	d	6 – 10	Study partner		X		X		X	X	X
NPI	d	15	Study partner		X		X		X	X	X
ADCS-MCI-ADL-24	d	30 – 45	Study partner		X				X		X
MHIS[I]	d	5	N/A clinician assessed	X							
Digital clock drawing	d	5	Patient	X	X	X	X	X	X	X	X

a. Breaks should be taken as necessary.

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

c. The C-SSRS will be done at each visit throughout the study (see Table 2 Study Activities for all time points).

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

I. Administered during Screening to assess inclusion criteria only.

4.3 Sample Size

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

4.4 Interim Analysis

DMC safety reviews, interim analysis for target engagement, and interim efficacy analyses will be performed in this study. Assessment of safety and efficacy data at interims will be performed by the DMC.

Except for interim analysis for target engagement, an independent Statistical and Data Analysis Center (SDAC) and an independent Exposure-Response Analysis Center (ERAC) which are organizations outside AbbVie with experience in producing statistical reports will be responsible for generating and providing unblinded statistical tables, figures, and listings to the DMC for the interim reviews. To maintain the integrity of the trial, a specific data access plan with a strict firewall will be in place to protect the unblinded data and the details will be described in the DMC charter and the Interim Unblinding Plan.

Safety Reviews

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

study drug when the data is cut. Additional DMC safety reviews will occur after a total of approximately 100, 200, 300 and 400 subjects are randomized and then approximately every six months thereafter until the study completion. Additional unplanned DMC safety reviews can occur at the discretion of the DMC and/or AbbVie.

The DMC will communicate their recommendations to the AbbVie Primary Contact (who is not involved in the conduct of the trial) regarding continuing, modifying or terminating the trial due to safety concerns in accordance with the DMC charter. More details of safety reviews will be specified in the DMC Charter.

Interim Analysis for Target Engagement

An assessment of target engagement analysis for the first 48 Cohort 1 subjects will be conducted by an AbbVie Internal Biomarker Review Committee (IBRC). Biomarkers for target engagement will include both target binding and pharmacodynamic activity biomarkers. An AbbVie internal team will perform detailed analysis on target engagement. This interim analysis results will guide the decision if an early futility analysis (Interim analysis 1) should be conducted. Details of the target engagement analysis will be described in a separate biomarker analysis plan.

Interim Efficacy Analyses

Three potential interim efficacy analyses could be performed when approximately 8 subjects/group, 35 subjects/group (or 45% information) and 55 subjects/group (or 75% information) complete Week 96 visit, respectively. The number of subjects at each interim analysis is subject to change based on observed dropout rate at interim. Information fractions will be used to determine the number of subjects for each interim analysis.

The first interim efficacy analysis will be optional and for futility review only depending on interim target engagement and pharmacodynamic biomarker analysis results from Cohort 1 subjects. The DMC will be informed by the IBRC chair regarding if the first efficacy review for futility is going to be conducted or not, and if conducted, the futility

criteria for the first interim efficacy analysis will be selected by the IBRC based on interim target engagement biomarker analysis results.

At the second and the third interim efficacy analyses, the DMC will make recommendations to trigger AbbVie Internal Executive Review Committee (IERC) review if pre-specified futility criteria or criteria for acceleration of Phase 3 development are met. The IERC is a group of executive R&D leaders responsible for reviewing important data from ongoing studies in order to make strategic and operational decisions. The IERC operates under its own standing charter which describes membership and IERC operations. The IERC will make one of the decisions listed below:

- Continue Study M15-566 as is (no sponsor unblinding)
- Terminating Study M15-566 due to futility
- Accelerate Phase 3 programs and continue Study M15-566 as is

If none of pre-specified criteria is met, the IERC will not review interim efficacy data.

Two-sided tests will be applied at interim efficacy analyses. A group-sequential graphical approach will be used to handle multiplicity of comparing multiple ABBV-8E12 doses to placebo at interim analyses and final analysis. Details of multiplicity control are specified in Section 10.7 of the SAP.

4.5 Efficacy Variables

The primary efficacy variable is the CDR-SB score change from baseline at Week 96.

Secondary efficacy variables include the ADAS-Cog-14 total score and subscale scores, RBANS total scale score and subtest scores, MMSE total score, FAQ total score, NPI total score, ADCS-MCI-ADL-24 total score, UPSA-Brief score and ADCS-CGIC-MCI scores. The descriptions of the secondary efficacy variables are detailed in protocol Section 5.0. The key secondary efficacy variables are ADAS-Cog-14 total score and FAQ total score.

4.6 Safety Variables

The following safety variables will be analyzed for the study: adverse event, vital signs, C-SSRS, laboratory tests, ECG, and MRI safety evaluations.

4.7 Pharmacokinetic Variables

Values for the following pharmacokinetic parameters of ABBV-8E12 in Cohort 1 will be determined using non-compartmental methods: maximum observed serum concentration (C_{max}), the time to C_{max} (peak time, T_{max}), and the area under the concentration time curve (AUC) for the first and the fourth dose intervals. For all subjects, the observed serum concentration at the end of a dose interval (C_{trough}) will be obtained prior to study drug infusion on the days of dosing specified in Table 2 in all subjects.

4.8 Biomarker and Pharmacogenetic Research Variables

4.8.1 Biomarker Research Variables

Data to conduct research on disease-related and drug-related biomarkers will be obtained from blood and CSF samples, volumetric MRI, and tau PET imaging. The biomarkers to be analyzed will include, but are not limited to, the following:

- CSF samples will be assayed for free tau and total tau and plasma samples for total tau to investigate tau binding of ABBV-8E12. In addition to a statistical analysis of tau concentrations, an analysis will be performed for the ratio of CSF free tau concentration to total tau concentration. A statistical analysis will also be carried out for plasma total tau concentration.
- CSF and plasma samples will be analyzed for NFL and perhaps for other biochemical or macromolecular factors related to the pharmacodynamics of ABBV-8E12.
- Volumetric brain MRI will be performed at about 2 weeks after each of the doses scheduled for Weeks 28, 44 and 68 and at the Week 96 visit (end of the last dose interval) to assess regional volume change for the hippocampus, lateral ventricles, temporal lobes, and whole brain volume change. Change of volume in other regions may also be explored.

- For each of several regions of the brain, the amount of tau deposits will be assessed with the standardized uptake value ratio (SUVR) obtained from tau PET imaging. An SUVR is computed as the ratio of a target region value to a reference region value. Priority will be given to SUVR computed with the inferior part of the cerebellar gray matter as the reference region. SUVR values will be determined for four composite meta- regions of interest (ROI) that correspond to anatomical definitions of Braak stages I, II, III, IV, V, and VI. Individual ROIs that make up these composite meta-ROIs are listed in detail in the Imaging Review Charter. The SUVR value for a composite meta-region will be a weighted average of the SUVR values for the individual ROIs of the composite meta-region. In addition to SUVR computed using the inferior part of the cerebellar gray matter as the reference region, SUVR will also be computed using the following three reference regions: subcortical white matter, pons and the whole cerebellum. If the analysis for a composite region gives evidence of an effect by 8E12, then an analysis will be performed for each individual ROI of the composite region. An additional set of output metrics will be generated. These metrics will include Extent (tau positive fraction) defined as the number of tau positive voxels in a region divided by the total number of voxels in that region. Details of the quantitative analyses of tau PET scans, including the calculation of SUVR and amplitude/extent of SUVRs can be found in the Imaging Review Charter.

4.8.2 Pharmacogenetic Research Variables

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

5.0 Analysis Populations and Analysis Datasets

Intent-to-Treat (ITT) Dataset

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

Safety Dataset

The safety dataset will include all randomized subjects who receive any dose of study drug infusion. For this analysis dataset, actual treatment received will be used instead of treatment assignment at the time of randomization. All safety analyses will be conducted on the safety dataset unless otherwise specified.

5.1 Variables Used for Stratification of Randomization

Subject randomization is stratified by study site.

6.0 Analysis Conventions

6.1 Statistical Significance

Unless otherwise specified, statistical tests will be two-sided for efficacy and safety analyses. The null hypotheses for efficacy will be rejected at the pre-specified significance level with the overall Type I family wise error rate (FWER) to be controlled at the two-sided 5% level. *P* values will be rounded to five decimal points for primary and key secondary variables included in the FWER control and rounded to three decimal points for other analyses before assessing statistical significance. All efficacy analyses will be conducted on the ITT dataset and all safety analyses will be conducted on the safety dataset unless otherwise specified.

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

Rx End 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:
Rx End Day = date of time point – last dose date. With this defined algorithm, the day of the last dose of study drug will be Rx End Day 0.

Definition of Baseline and Final Observation

Unless otherwise specified, for all efficacy analyses and for all safety analyses of the double-blind Treatment Period, "baseline" shall refer to the last non-missing observation prior to the first dose of study drug and "final" for the double-blind Treatment Period shall refer to the last non-missing observation but no more than 45 days after the last dose of the study drug for both efficacy variables and 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.

Randomization and study drug administration are the last activities of Day 1 Visit after the site completes other study procedures and verifies that the subject is eligible to participate in the study. From the definition of "baseline," it is clear that the baseline for a specific measurement is the last non-missing observation taken up to the Day 1 Visit (the

Randomization Visit). At the computation level, the value of "baseline" for an efficacy or safety assessment is determined using the Rx Day associated with the visit. Namely, baseline value is determined by taking the last non-missing observation obtained before the time of first dosing on Rx Day 1. If an SAE occurs on the first dosing day, the event will be reported as a post-baseline event and the related safety assessments will be considered post-baseline data as well.

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 double-blind 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 visit is defined in "Days of Study Activities" row in Table 2.

For measurements that are planned to be collected during the double-blind treatment period at Weeks 24, 48, 72 and 96, i.e., CDR, RBANS, ADAS-Cog-14, MMSE, FAQ and NPI, observations will be mapped to an analysis "week" according to the following windows defined by Rx day.

- Week 24 Rx Days 2 through 252
- Week 48 Rx Days 253 through 420
- Week 72 Rx Days 421 through 588
- Week 96 Rx Days > 588

For measurements that are planned to be collected during the double-blind treatment period at Weeks 48 and 96, i.e., UPSA-Brief, ADCS-CGIC-MCI and ADCS-MCI-ADL-

24, observations will be mapped to an analysis "week" according to the following windows defined by Rx day.

- Week 48 Rx Days 2 through 504
- Week 96 Rx Days > 504

For measurements that are planned to be collected during the double-blind treatment period at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 and 96, i.e., body weight, observation will be mapped to an analysis "week" according to the following windows defined by Rx day.

- Week 4 Rx Days 2 through 42
- Week 8 Rx Days 43 through 70
- Week 12 Rx Days 71 through 98
- Week 16 Rx Days 99 through 126
- Week 20 Rx Days 127 through 154
- Week 24 Rx Days 155 through 182
- Week 28 Rx Days 183 through 210
- Week 32 Rx Days 211 through 238
- Week 36 Rx Days 239 through 266
- Week 40 Rx Days 267 through 294
- Week 44 Rx Days 295 through 322
- Week 48 Rx Days 323 through 350
- Week 52 Rx Days 351 through 378
- Week 56 Rx Days 379 through 406
- Week 60 Rx Days 407 through 434
- Week 64 Rx Days 435 through 462
- Week 68 Rx Days 463 through 490
- Week 72 Rx Days 491 through 518
- Week 76 Rx Days 519 through 546

- Week 80 Rx Days 547 through 574
- Week 84 Rx Days 575 through 602
- Week 88 Rx Days 603 through 630
- Week 92 Rx Days 631 through 658
- Week 96 Rx Days > 658

For measurements that are planned to be collected during the double-blind treatment period at Weeks 2, 4, 8, 12, 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, and 96, i.e., vital signs and C-SSRS, observations will be mapped to an analysis "week" according to the following windows defined by Rx day.

- Week 2 Rx Days 2 through 21 (Cohort 1 subjects)
- Week 4 Rx Days 22 through 42 (Cohort 1 subjects)
  Rx Days 2 through 42 (Cohort 2 subjects)
- Week 8 Rx Days 43 through 70
- Week 12 Rx Days 71 through 91 (Cohort 1 subjects)
  Rx Days 71 through 98 (Cohort 2 subjects)
- Week 14 Rx Days 92 through 105 (Cohort 1 subjects)
- Week 16 Rx Days 106 through 126 (Cohort 1 subjects)
  Rx Days 99 through 126 (Cohort 2 subjects)
- Week 20 Rx Days 127 through 154
- Week 24 Rx Days 155 through 182
- Week 28 Rx Days 183 through 210
- Week 32 Rx Days 211 through 238
- Week 36 Rx Days 239 through 266
- Week 40 Rx Days 267 through 294
- Week 44 Rx Days 295 through 322
- Week 48 Rx Days 323 through 350
- Week 52 Rx Days 351 through 378
- Week 56 Rx Days 379 through 406

- Week 60 Rx Days 407 through 434
- Week 64 Rx Days 435 through 462
- Week 68 Rx Days 463 through 490
- Week 72 Rx Days 491 through 518
- Week 76 Rx Days 519 through 546
- Week 80 Rx Days 547 through 574
- Week 84 Rx Days 575 through 602
- Week 88 Rx Days 603 through 630
- Week 92 Rx Days 631 through 658
- Week 96 Rx Days > 658

For measurements that are planned to be collected during the double-blind treatment period at Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84 and 96, i.e., clinical laboratory tests, observations will be mapped to an analysis "week" according to the following windows defined by Rx day.

- Week 4 Rx Day 2 through 42
- Week 8 Rx Day 43 through 70
- Week 12 Rx Days 71 through 98
- Week 16 Rx Day 99 through 126
- Week 20 Rx Days 127 through 154
- Week 24 Rx Days 155 through 210
- Week 36 Rx Days 211 through 294
- Week 48 Rx Days 295 through 378
- Week 60 Rx Days 379 through 462
- Week 72 Rx Days 463 through 546
- Week 84 Rx Days 547 through 630
- Week 96 Rx Days > 630

For measurements that are planned to be collected during the double-blind treatment period at Weeks 2, 4, 8, 12, 24, 36, 48, 72 and 96, i.e., ECG, observation will be mapped to an analysis "week" according to the following windows defined by Rx day.

- Week 2 Rx Days 2 through 21 (Cohort 1 subjects)
- Week 4 Rx Days 22 through 42 (Cohort 1 subjects)
  Rx Days 2 through 42 (Cohort 2 subjects)
- Week 8 Rx Days 43 through 70
- Week 12 Rx Days 71 through 126
- Week 24 Rx Days 127 through 210
- Week 36 Rx Days 211 through 294
- Week 48 Rx Days 295 through 420
- Week 72 Rx Days 421 through 588
- Week 96 Rx Days > 588

For vital sign measurements, C-SSRS, ECG, clinical laboratory tests, and MRI that are planned to be collected during the post-treatment follow-up period at Weeks 104, observations will be mapped to an analysis "week" according to the following windows defined by Rx End day.

- Post-Treatment Week 8 Rx End Days > 45

For measurements that are planned to be collected during double-blind treatment period on Weeks 6, 14, 30, 46, 70 and 96, i.e., MRI observation will be mapped to an analysis "week" according to the following windows defined by Rx day.

- Week 6 Rx Days 2 through 70
- Week 14 Rx Days 71 through 154
- Week 30 Rx Days 155 through 266
- Week 46 Rx Days 267 through 406
- Week 70 Rx Days 407 through 581

- Week 96 Rx Days > 581

If more than 1 observation is included in a visit time window, the observation that is closed to the nominal day of the visit will be used in the analysis. If two observations have the same distance to the nominal day of the visit, the last non-missing observation will be used in analyses. If more than 1 observation occurs on the same day, the average will be calculated and used in analyses.

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

7.1 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized for each treatment group, for the combination of all ABBV-8E12 dose groups ("ABBV-8E12 Overall") and for the combination of all treatment groups ("Total Subjects") for the safety dataset.

- 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 (BMI, kg/m^2) (< 25, ≥ 25)
- APOE allele status (ε2ε2, ε2ε3, ε2ε4, ε3ε3, ε3ε4, ε4ε4)

- Baseline AD medication use: AChEI (donepezil, rivastigmine, galantamine) and memantine

Alcohol and tobacco uses will be summarized for each treatment group, ABBV-8E12 Overall and Total Subjects for the safety dataset. For alcohol use, the number and percentage of subjects who are drinkers, ex-drinkers and non-drinkers (defined as those who have never been a drinker) will be presented. For the tobacco use, the number and percentage of users, ex-users and non-users (defined as those who have never been a user) will be presented. A subject reporting multiple use categories for the different types of tobacco (cigarette, pipe, cigar and chewing tobacco) will be counted in the tobacco user category.

The following baseline efficacy variables will be summarized for each treatment group, ABBV-8E12 Overall and Total Subjects for the ITT dataset.

- CDR-SB score
- ADAS-Cog-14 total score and subscale scores
- FAQ total score
- UPSA-Brief score
- ADCS-MCI-ADL-24 total score
- RBANS total scale score and subtest scores
- MMSE total score
- NPI total score
- ADCOMS score

ADCOMS score is a composite score which is a weighted linear combination of the remaining individual scale items from ADAS-cog, MMSE, and CDR-SB scales. The weights for items are listed below.[3]

Scale	Item name	Weights
ADAS-cog	Delayed word recall	0.008
	Orientation	0.017
	Word recognition	0.004
	Word finding difficulty	0.016
MMSE	Orientation time	0.042
	Drawing	0.038
CDR-SB	Personal care	0.054
	Community affairs	0.109
	Home and hobbies	0.089
	Judgement and problem solving	0.069
	Memory	0.059
	Orientation	0.078

Categorical variables will be summarized by the number and percentage of subjects in each category and Fisher's exact test will be carried out to assess the comparability between treatment groups. No comparisons of treatment groups will be performed for alcohol and tobacco uses. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum and maximum) and no comparisons between treatment groups will be performed.

7.2 Medical History

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, ABBV-8E12 Overall and Total Subjects for the safety dataset. Subjects reporting more than one PT within a SOC will be counted only once for that SOC. No comparison among treatment groups will be performed.

The following MCI due to AD or AD history variables will be summarized for each treatment group, ABBV-8E12 Overall and Total Subjects for the safety dataset.

- 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). No comparisons of treatment groups will be performed.

7.3 Previous and Concomitant Medications

Previous medications are defined as all medications with a start date before the first study drug infusion date. 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, ABBV-8E12 Overall and Total 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 cholinesterase inhibitors (donepezil, rivastigmine, galantamine) or memantine for cognitive impairment.

No comparisons of treatment groups will be performed.

8.0 Subject Disposition

The number of subjects who are screened will be summarized and screen failures will be summarized in Total Subjects and by each reason for screen failures.

For subjects who are randomized in the study, the number and percentage of subjects in each randomization disposition category (randomized but not treated, prematurely discontinued and completed) will be summarized for each treatment group, ABBV-8E12 Overall and Total 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, ABBV-8E12 Overall and Total Subjects.

In addition, the following additional summaries will be presented for all randomized 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.

9.0 Study Drug Exposure and Compliance

Summaries of study drug exposure and compliance will be prepared for the safety dataset.

Study drug exposure will be summarized for each ABBV-8E12 treatment group, ABBV-8E12 Overall. 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 1, 2, 3, 4 - 6, 7 - 9, 10 - 12, 13 - 15, 16 - 18, 19 - 21, 22 - 24, > 24 infusions of study drug will be summarized. No comparisons of treatment groups will be performed for this summary. 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 subject-years).

To evaluate impact of COVID-19 pandemic on study drug compliance, expected infusions (completers are expected to have 24 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 ABBV-8E12 treatment group and ABBV-8E12 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 for ABBV-8E12 groups, 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 ABBV-8E12 treatment group and ABBV-8E12 Overall.

10.0 Efficacy Analysis

10.1 General Considerations

All efficacy analyses will be conducted on the intent-to-treat dataset unless otherwise specified. Data collected more than 45 days after the last dose of the study drug will not be included in efficacy analyses.

10.2 Primary Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to Week 96 visit on the CDR--SB score. The primary analysis population will be subjects in the ITT dataset and the primary analysis will be a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline to each post-baseline assessment up to and including Week 96. The model will include fixed, categorical effects for treatment, site, visit, baseline score-by-visit and treatment-by-visit interactions, with continuous fixed covariate for baseline score. The primary comparison will be the contrast between each ABBV-8E12 dose group and placebo group at Week 96. Contrasts between each ABBV-8E12 dose group and placebo at Weeks 24, 48, 72, and overall across the treatment period will be obtained and will be considered as secondary. An unstructured (co)variance structure will be used to model the within-patient errors. The same (co)variance structure will also be used for all MMRM analyses for secondary efficacy variables. Satterthwaite's approximation will be used to estimate denominator degrees of freedom.

The following statistics will be presented on the statistical table of MMRM analysis for change from baseline to each visit (Weeks 24, 48, 72, and 96): descriptive statistics

(number of non-missing observations, mean, standard deviation, minimum and maximum) for each treatment group. Within group LS mean and standard error will be presented for each treatment group. LS mean, standard error, 95% confidence interval and two-sided *P* values for comparisons between each ABBV-8E12 dose group and placebo at each post-baseline visit will also be presented. The LS mean, standard error, 95% confidence interval and two-sided *P* values of treatment difference comparing each ABBV-8E12 dose group with placebo across the treatment period will be included in the output as well.

10.3 Secondary Efficacy Analysis

10.3.1 Analysis of Secondary Efficacy Variables

The secondary efficacy variables include:

- ADAS-Cog-14 total score and subscale scores
- FAQ total score
- ADCS-CGIC-MCI clinical global impression, cognition, behavior and functional abilities scores
- UPSA-Brief score
- ADCS-MCI-ADL-24 total score
- RBANS total scale score and subtest scores
- MMSE total score
- NPI total score
- ADCOMS

ADAS-Cog-14 total score and FAQ total score are key secondary efficacy variables and the Week 96 comparisons for each ABBV-8E12 dose vs placebo will be included in the multiplicity adjustment for the overall FWER control. Other secondary efficacy variables will not be included in the multiplicity adjustment for the overall FWER control. The MMRM method used for the primary efficacy analysis will be applied to analyze the change from the baseline to each post-baseline assessment up to and including Week 96 for these secondary variables with the exception of ADCS-CGIC-MCI scores for which

the dependent variable is ADCS-CGIC-MCI score itself. The model will include fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interactions, with continuous fixed covariate for baseline score in the model. For the MMRM analysis of ADCS-CGIC-MCI scores, there is no baseline score and no baseline score-by-visit interaction in the model. The comparison will be the contrast between each ABBV-8E12 dose group and placebo group at each post-baseline visit.

The following statistics will be presented in the statistical table of MMRM analysis for change from baseline to each post-baseline visit: descriptive statistics (number of non-missing observations, mean, standard deviation, minimum, and maximum) for each treatment group. Within group LS mean and standard error for each post-baseline visit will be presented for each treatment group. LS mean, standard error, 95% confidence interval and two-sided *P* values of treatment difference comparing each ABBV-8E12 dose group with placebo will also be presented for each post-baseline visit. The LS mean, standard error, 95% confidence interval and two-sided *P* values of treatment difference comparing each ABBV-8E12 dose group with placebo across the treatment period will be included in the output. P-values after considering multiplicity adjustment for the primary and key secondary variables will be presented in a separate table.

10.4 Additional Efficacy Analysis

10.4.1 Sensitivity analysis of CDR-SB score

Sensitivity analyses of CDR-SB score change from baseline will be conducted in ITT dataset in the final analysis. Subjects who are randomized and dosed but failed to meet all inclusion criteria or met any exclusion criteria will be excluded from these analyses. In addition, the impact of COVID-19 on data collection in Study M15-566 should be considered as well. The following sensitivity analyses on CDR-SB score may be conducted:

- Sensitivity analysis I: excluding subjects from ABBV-8E12 groups who missed more than two doses than expected (subjects who complete Week 96

visit and receive less than 22 doses, subjects who are prematurely discontinued and receive more than two doses less than expected before the discontinue visit date) or received less than 80% amount dosage than the assigned amount for more than two doses during the double-blind period.

- Sensitivity analysis II: include all subjects who have available CDR-SB score change from baseline regardless how many doses are missed or under-dosed or records are more than 45 days after the last dosing.

The MMRM analysis will be applied for these analyses and similar output will be generated for the sensitivity analyses of CDR-SB score. No multiplicity adjustment is needed for these analyses.

Sensitivity analysis will also be conducted on the CDR-SB score to evaluate the impact of missing data on the primary efficacy results. Details of sensitivity analysis for missing data are specified in Section 10.6 of the SAP.

10.4.2 Listing of Randomized Subjects not Included in the Primary Efficacy Analysis

A listing of the randomized subjects that were not included in the primary efficacy analysis will be prepared. The listing will include the reason(s) the subject was not included (did not receive study drug, had no baseline observation, and/or had no post-baseline observation within 45 days after the last dose of study drug).

10.5 Combination of Sites with Fewer than 2 Subjects per Treatment Group

When "site" is included as a factor in a statistical model, sites that do not have at least 2 subjects per treatment group for the ITT dataset will be combined within each country as follows.

1. Divide the sites into 2 groups with Group 1 including all sites that have at least 2 subjects per treatment group and Group 2 including all remaining sites. Sort each group in ascending order by total sample size and investigator number.

2. Starting at the top of the Group 2 list (i.e., the first site with the smallest sample size), combine the minimum number of sites required to achieve a pseudo-site that has at least 2 subjects per treatment group. Continue this process until all Group 2 sites have been grouped into pseudo-sites.
3. If there is a site (or sites) left after Step 2, combine this site (or sites) with the last pseudo-site that is created. For the situation where there is no previous pseudo-site exists, combine this site (or sites) with the first site on the sorted Group 1 list.

The naming of the pseudo-sites will be given by xxx99901, xxx99902, etc., where xxx is the country code.

The combined pseudo-sites will be used in all statistical models that include the "Site" as a factor. However, the original site identification will be used in all summaries of subject disposition or discontinuation by Study Site and in all data listings. In the summaries of the number and percentage of subjects contributed by each site in each treatment group for the ITT dataset, the name of pseudo-sites will also be displayed.

10.6 Handling of Missing Data for Efficacy Assessments and Sensitivity Analysis of the Primary Efficacy Endpoint

Missing Items for a Rating Scale

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

Missing Visit Data

Before conducting any imputation of missing data, patterns of missing data for the primary endpoint CDR-SB score in placebo and three ABBV-8E12 arms will be assessed. Observed mean changes from baseline in CDR-SB score will be summarized over time for different missing patterns of longitudinal data (discontinued before Week 24 assessment, discontinued after Week 24 assessment, discontinued after Week 48

assessment, discontinued after Week 48 assessment, discontinued after Week 72, completer). Number of subjects and percentage of subjects for each missing pattern will be summarized as well.

To evaluate robustness of the primary efficacy results on CDR-SB score changes from baseline, sensitivity analysis will be conducted using a multiple imputation (MI) method assuming a missing pattern that is mostly monotonic in this study and missing at random (MAR). The COVID-19 pandemic is interfering with the conduct of ongoing Study M15-566, with potential impact on treatment duration and the data collection, analysis and interpretation of clinical trial data. The probability of having missed visits and missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic can be reasonably assumed to be unrelated to the unobserved values conditional on the observed data. Therefore, for the purpose of statistical analysis, it is reasonable to assume that these missing data are MAR and the MMRM analysis model that is based on MAR assumption is appropriate.

Sensitivity analysis will be conducted only if at least one ABBV-8E12 dose is statistically significant different from placebo after multiplicity adjustment for the primary endpoint in the primary efficacy analysis.

Sensitivity analysis using MI will be conducted in the following three steps:

1. Use Monte Carlo Markov Chain (MCMC) methodology from PROC MI to impute the intermittent missing data so that a monotone missing pattern can be obtained for treatment group
2. Impute missing data to create 20 complete datasets including observed CDR-SB change from baseline scores for subjects with scores for all 4 visits as well as observed and imputed change from baseline scores for subjects with missing visits using the MI method

3. Analyze each imputed dataset generated in Step 1 with the same analysis model for the primary efficacy analysis of the primary endpoint and keep analysis results for each imputed dataset
4. Combine analysis results across imputed datasets.

The MI method will be used to impute missing data at various visits overtime. The MI method will be applied separately for each ABBV-8E12 dose arm and placebo arm. Multivariate regression models will be used to impute CDR-SB missing data for different visits. To impute missing values for CDR-SB score for Visit X, variables included in the imputation model are baseline CDR-SB score, CDR-SB score before discontinuation at Visit X, investigator sites. A mean vector and variance covariance matrix based on all available cases will be used for the imputation. If the monotonic missing pattern is not satisfied, the MCMC method will be used to create monotonic missing pattern by filling missing values between visits where data are observed. Imputed CDR-SB score needs satisfy the range requirement for the scale (integer and half integer value between 0 and 18. If an imputed value is not in the range, it will be rounded down to 18 if greater than 18 or rounded up to 0 if less than 0). The MI will be implemented using PROC MI in SAS 9.4. In Step 3, PROC MIANALYZE procedure will be used to combine MMRM analysis results based on 20 imputed datasets.

10.7 Handling of Multiplicity

Pairwise comparisons between each ABBV-8E12 dose group and the placebo group will be performed using two-sided tests. A group-sequential graphical approach[4,5] will be applied for multiplicity control for multiple comparisons due to multiple endpoints, multiple ABBV-8E12 doses and multiple interim analyses (IA) and final analysis. The overall family-wise error rate (FWER) will be controlled at the two-sided 5% level.

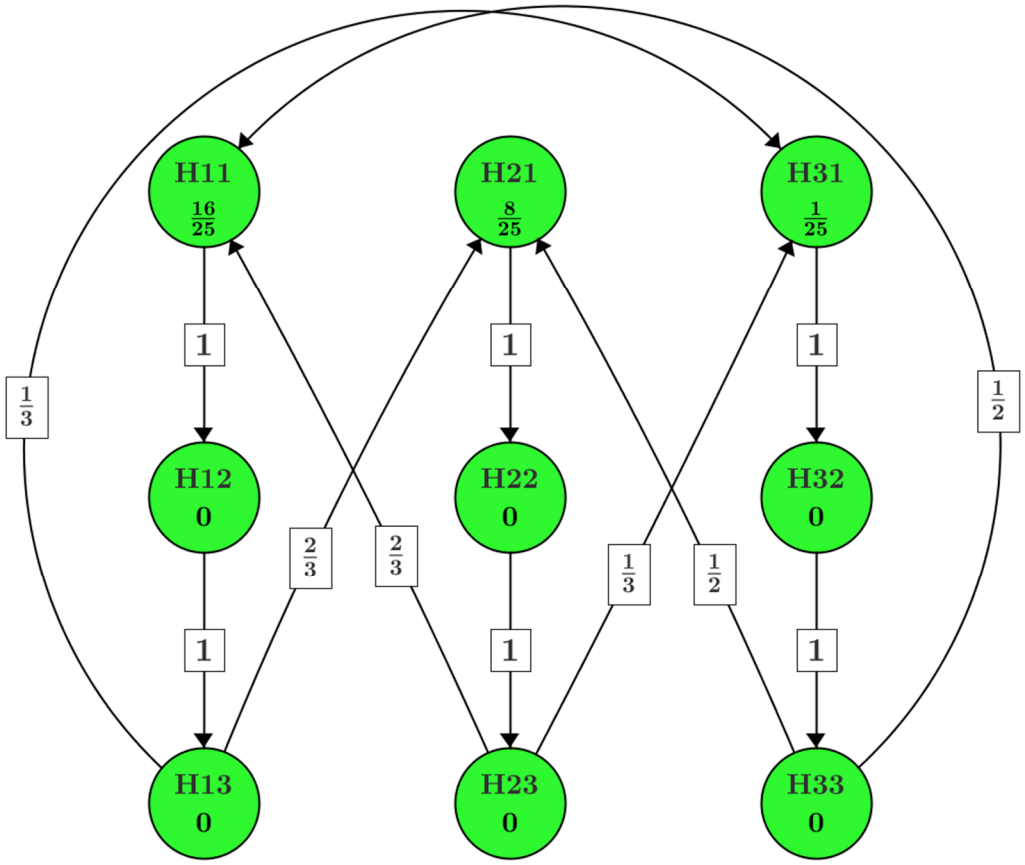
The primary endpoint and two ranked key secondary efficacy endpoints will be included for the FWER control in this study. These endpoints are presented in Table 4. The initial alpha allocation to the primary hypotheses for three doses and alpha propagation among

hypotheses are presented in Figure 2. The ranked secondary endpoints hypotheses for a dose can be tested only if the primary endpoint hypothesis is rejected for that dose. The primary endpoint hypothesis is the gatekeeper for testing the key secondary endpoints hypotheses and a higher ranked endpoint hypothesis is the gatekeeper for testing the lower ranked endpoint hypothesis for each dose. O'Brien-Fleming (OBF) p-value boundaries will be used for all endpoints' hypotheses testing at interim and final analyses. The detailed group-sequential graphical testing procedure is described below. A summary table for multiplicity adjustment will be prepared. The table will include rejection boundary for each hypothesis at each analysis, observed p-value for testing each hypothesis at each analysis.

Table 4. Hypotheses Included in the Group-sequential Graphical Procedure

Hypothesis Family	Endpoint	Comparative Hypotheses	Notation of Hypotheses
Primary family	CDR-SB score change from baseline at Week 96	ABBV-8E12 2000 mg vs. placebo	H11
		ABBV-8E12 1000 mg vs. placebo	H21
		ABBV-8E12 300 mg vs. placebo	H31
Secondary family	ADAS-Cog-14 total score change from baseline at Week 96	ABBV-8E12 2000 mg vs. placebo	H12
		ABBV-8E12 1000 mg vs. placebo	H22
		ABBV-8E12 300 mg vs. placebo	H32
	FAQ total score change from baseline at Week 96	ABBV-8E12 2000 mg vs. placebo	H13
		ABBV-8E12 1000 mg vs. placebo	H23
		ABBV-8E12 300 mg vs. placebo	H33

Figure 2. An Initial Graph for Alpha Allocation and Propagation



Note: Numbers inside each circle is the amount of alpha allocated initially for each hypothesis. Numbers in rectangle boxes on arrow lines are weights for alpha propagation among hypotheses.

The steps to perform hypotheses testing procedure is summarized below:

- Step 0: Set I = {H11, H21, H31, H12, H22, H32, H13, H23, H33}. Initial alpha allocation weights w = (16/25, 8/25, 1/25) and corresponding alpha level (0.032, 0.016, 0.002) for CDR-SB change from baseline at Week 96 will be allocated to 2000 mg, 1000 mg and 300 mg doses (H11, H21, H31), respectively. Zero alpha is allocated initially to all secondary endpoints' hypotheses. Initial propagation weights (g) between hypotheses are assigned and listed in Figure 2. The p-value (two-sided) initial OBF rejection boundaries for 3 analyses (IA2, IA3, and final analyses) for the primary

endpoint are calculated using pre-allocated alpha levels with information fractions of 45%, 75% and 100% for IA2, IA3 and final analysis, respectively. The initial P-value boundaries for CDR-SB change from baseline at Week 96 are presented in Table 5. Initial OBF P-value rejection boundaries for all secondary endpoints are set to be (0.0, 0.0, 0.0) because no alpha is allocated for any secondary endpoint hypothesis.

Table 5. Initial OBF P-Value Boundaries for CDR-SB Change from Baseline at Week 96

	IA2	IA3	Final
ABBV-8E12 2000 mg (H11): alpha = 0.032			
OBF two-sided p-value boundary	0.00106	0.01126	0.02816
Cumulative alpha spending	0.00106	0.01166	0.032
ABBV-8E12 1000 mg (H21): alpha = 0.016			
OBF two-sided p-value boundary	0.00026	0.00472	0.01438
Cumulative alpha spending	0.00026	0.00482	0.016
ABBV-8E12 300 mg (H31): alpha = 0.002			
OBF two-sided p-value boundary	0.00001	0.00034	0.00188
Cumulative alpha spending	0.00001	0.00034	0.002

- Stage k (k = IA2, IA3, Final):

  Step 1: obtain Week 96 p-values for the primary and key secondary endpoints.

  Step 2: compare p-values in step 1 against the boundaries for analysis at Stage k. If one or more hypotheses are rejected, go to Step 3. Otherwise, go to Step 5.

  Step 3: update the graph (Figure 2) using the method proposed by Bretz et al. (2009).[6] If none of hypothesis is rejected, then go to Step 5 without updating the boundaries and Figure 2. The following are steps to update the graph with updated alpha allocation weights for each hypothesis and alpha propagation weights among hypotheses:

- $I \rightarrow I\backslash\{i\}$, i.e., update Set I after the i^{th} hypothesis is rejected and excluded from Set I.
- $w_j \rightarrow w_j + w_i g_{ij}, j \in I$; 0, otherwise. w_j is updated alpha allocation weight for hypothesis j, w_i is alpha allocation weight for hypothesis i, g_{ij} is the alpha propagation weight from hypotheses i to j.
- $g_{ih} = (g_{ih}+g_{ji}g_{ih})/(1-g_{ji}g_{ij}), j,h \in I, j \neq h, g_{ji}g_{ij} < 1$; 0, otherwise. g_{ji} is the alpha propagation weight from hypotheses j to i, g_{ih} is the alpha propagation weight from hypotheses i to h.

Step 4: calculate new OBF p-value boundaries for all endpoints with updated significant levels obtained in Step 3 and go to Step 2.

Step 5: go to next stage (k + 1) and go to Step 1 or stop the testing.

10.8 Efficacy Subgroup Analysis

To examine whether gender, age group (< 65 vs ≥ 65 years old), APOE4 carrier status (carrier vs non-carrier), baseline AD medication use (use vs no use. AD medications are defined in Section 7.1), baseline amyloid PET level (baseline centiloid value < median vs ≥ median), and geographical region [North America (US and Canada) vs other countries] have an impact on response to treatment, subgroup analyses on CDR-SB change score will be conducted using an ANCOVA model with the terms of treatment, subgroup variable, site (site is nested within a region for geographical region subgroup analysis), the treatment-by-subgroup variable interaction, and baseline score as a covariate. The hypothesis that consistent response to treatment across strata of a subgroup variable will be tested at the significance level of 0.100 by examining the *P* value of the treatment-by-subgroup interaction term in the ANCOVA model specified above. The statistical comparison of each ABBV-8E12 dose group with placebo within each subgroup stratum will be performed when the statistical significance of the treatment-by-subgroup interaction term is achieved at 0.100 level. The subgroup analysis will be conducted on the ITT dataset.

11.0 Safety Analysis

11.1 General Considerations

All safety analyses will be performed on the safety dataset. Unless otherwise specified, treatment group differences in safety parameters are evaluated using two-sided test at the significance level of 0.050. When statistical tests are performed, the comparisons will be between each ABBV-8E12 dose and placebo. With the exception of adverse events, all safety assessments that are taken no more than 45 days after the last dose of study drug infusion will be included in the safety evaluation of the Double-blind Treatment Period. All safety assessments that are taken more than 45 days but no more than 20 weeks after the last dose of study drug infusion will be included in the safety evaluation for the Post-Treatment Follow-Up Period.

11.2 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.

11.2.1 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, ABBV-8E12 Overall. No comparisons of treatment groups will be performed.

- Any TEAE
- Any TEAE that was rated as having 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

11.2.2 Adverse Event Incidence

Treatment emergent adverse event (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 the 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, ABBV-8E12 Overall. The PTs will be presented by decreasing frequency in ABBV-8E12 Overall.

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, ABBV-8E12 Overall. No comparisons of treatment groups will be performed.

- Any TEAE
- Any serious TEAE
- Any TEAE that led to discontinuation of study drug
- Any TEAE assessed by the investigator to have 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, ABBV-8E12 Overall. 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" unless 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. No comparisons of treatment groups will be performed.

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, ABBV-8E12 Overall. 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," unless the 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." No comparisons between treatment groups will be performed.

11.2.3 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 having 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

11.3 Analysis of Laboratory Tests

Analyses will be performed on the following continuous laboratory variables:

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

11.3.1 Analysis of Mean Changes for Laboratory Tests

Analyses of mean change from baseline to each double-blind visit value and to the minimum, maximum and final double-blind value will be presented for each continuous hematology, chemistry and urinalysis variable. Analyses of mean change from final double-blind value to final post-treatment value will also be presented for each continuous hematology, chemistry and urinalysis variable.

For each mean change analysis, the mean and median change will be presented for each treatment group. The mean change for each ABBV-8E12 dose group will also be compared to the mean change for the placebo group using an ANOVA with treatment as

the factor. *P* values and 95% confidence intervals will be calculated based on pairwise contrasts within the ANOVA.

11.3.2 Shifts Between Normal and Abnormal for Laboratory Tests

Laboratory observations will be categorized as normal, low, or high relative to the reference (normal) range associated with the laboratory that performed the assay. For each hematology and chemistry variable with a reference range, shift tables will be prepared for shifts from baseline to lowest, highest and final value during the entire study for each treatment group and ABBV-8E12 overall. No comparisons of treatment groups will be performed. The tables will present:

- The numbers and percentages of subjects with low or normal observations at baseline who have a high observation at any post-baseline visit
- The numbers and percentages of subjects with normal or high observations at baseline who have a low observations at any post-baseline visit
- The numbers and percentages of subjects with low or normal observations at baseline who have a high observation at the final visit
- The numbers and percentages of subjects with normal or high observations at baseline who have a low observations at the final visit

11.3.3 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. A listing will also be prepared that will include, for each variable, all observations for each subject that meet the PCS criteria for that variable at any time during the study. No comparisons of treatment groups will be performed.

11.4 Analysis of Vital Signs and Weight

Vital sign variables include: diastolic blood pressure, systolic blood pressure and pulse rate and body temperature. Weight variables include weight and BMI.

11.4.1 Vital Sign and Weight Mean Changes

Diastolic blood pressure, systolic blood pressure and pulse will be analyzed separately. Analyses of mean change from baseline to each double-blind visit value and to the minimum, maximum and final double-blind value will be presented for each vital sign and weight variable. Analyses of mean change from final double-blind value to final post-treatment value will also be presented for each vital sign and weight variable.

For each mean change analysis, the mean and median change will be presented for each treatment group. The mean change for each ABBV-8E12 dose group will also be compared to the mean change for the placebo group using an ANOVA with treatment as the factor. *P* values and 95% confidence intervals will be calculated based on pairwise contrasts within the ANOVA.

11.4.2 Potentially Clinically Significant Vital Sign and Weight Values

Criteria for potentially clinically significant values have been predefined for selected vital sign and weight 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. 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. No comparisons of treatment groups will be performed.

11.5 Analysis of Electrocardiogram (ECG) Variables

Electrocardiogram (ECG) variables include: heart rate (HR), PR interval, QRS interval, uncorrected QT interval, and QT interval corrected for heart rate using Fridericia's formula (QTcF).

11.5.1 ECG Mean Changes

Analyses of mean change from baseline to each double-blind visit value and to the minimum, maximum and final double-blind value will be presented for each ECG variable. Analyses of mean change from final double-blind value to final post-treatment value will also be presented for each ECG variable.

For each mean change analysis, the mean and median change will be presented for each treatment group. The mean change for each ABBV-8E12 dose group will also be compared to the mean change for the placebo group using an ANOVA with treatment as the factor. *P* values and 95% confidence intervals will be calculated based on pairwise contrasts within the ANOVA.

11.5.2 Potentially Clinically Significant ECG Values

Criteria for potentially clinically significant values have been predefined for selected ECG variables as outlined in Appendix C. 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. Listings will also be prepared to include all observations for each variable for each subject that meet the PCS criteria for that variable at any time during the study. No comparisons of treatment groups will be performed.

11.6 Analysis for Other Safety Variables

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

Number and percentage of subjects in the following categories will be summarized for each treatment group and ABBV-8E12 Overall 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)

11.6.2 Analysis of CSF Lab Parameters

CSF variables include RBC and WBC with differential, total protein, albumin, glucose. Summary (number of non-missing observations, minimum, mean, median, standard deviation, maximum) of mean change from baseline to Week 12 (Cohort 1 subjects only) and mean change from baseline to final double-blind value will be presented for each CSF variable.

11.6.3 Summary of MRI Safety Evaluations

MRI safety evaluations will be summarized and compared between each ABBV-8E12 dose and placebo 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-blind period will be presented. Listing of subjects with post-baseline MRI findings will be provided. No comparison will be performed for MRI safety summary.

12.0 Pharmacokinetic Analysis

12.1 Determination of Values of Pharmacokinetic Parameters

C_{max} for a dose interval will be the maximum observed concentration after the beginning of infusion of the dose and before the beginning of infusion of the next dose. T_{max} will be the time of C_{max} relative to the beginning of infusion. The values of C_{max} and T_{max} will be considered missing if there is no measurement from a sample obtained before 3 hours after the end of infusion.

AUC for a dose interval will be obtained using straight lines between adjacent concentrations for times before 4 hours after the end of infusion. An exponential curve will be used between the last time point of measurement before 4 hours after the end of infusion and the first time point of measurement after 4 hours after the end of infusion, and an exponential curve will be used between adjacent time points of measurement in the dose interval that come after this. Actual times relative to the beginning of infusion will be used in the calculation of AUC.

The scheduled length of the first and fourth dose intervals is 672 hours. If the actual length of a dose interval differs from the scheduled length by more than an hour, a value for the ABBV-8E12 concentration at the scheduled end of the dosing interval (672 hours after the start of infusion of the dose at the beginning of the dose interval) will be imputed. In this case, the AUC will be calculated using the imputed value at the scheduled end of the dosing interval. The imputed value will be obtained from interpolation with, or extrapolation of, the exponential curve defined by the last two concentration measurements in the dosing interval.

For the first dose interval, the concentration at the beginning of infusion of the dose will be assumed to be 0 even if the scheduled pre-dose blood sample is mistakenly obtained after the beginning of infusion. For the fourth dose interval, the concentration of the pre-dose sample will be used as the concentration at the beginning of infusion of the dose provided that the blood sample is obtained in the 30 minute interval before the beginning of infusion. If the blood sample is obtained earlier than 30 minutes before the beginning

of infusion, for the calculation of AUC the concentration at the beginning of infusion will be C_{obs} X $e^{-\beta t}$, where C_{obs} is the reported measurement for the pre-dose concentration, β is the rate constant determined from the exponential curve defined by the last two concentrations in the third dose interval and t the length of the time interval between the pre-dose blood sample and the beginning of infusion. If the pre-dose sample for the fourth dose interval is mistakenly obtained after the beginning of infusion of the dose, a value for the concentration at the beginning of the dose interval (beginning of infusion) must be imputed unless the sample was obtained within a very few minutes of the beginning of infusion (< 15 minutes). The other subjects in the same treatment group who have values for the concentrations at the beginning of the fourth dose interval, the beginning of the third dose interval and the end of the fourth dose interval may be used to obtain a linear regression model for the concentration at the beginning of the fourth dose interval, with the concentrations at the beginning of the third dose interval and the end of the fourth dose interval as explanatory (predictor) variables. The missing value may be replaced by the predicted value from the regression model.

12.2 Tabulations and Summary Statistics

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

CSF concentration data after the fourth dose and the final dose will be tabulated and summarized by dose level.

Summary statistics will consist of: number of observations (n), mean, standard deviation, coefficient of variation as a percentage (quotient of standard deviation and mean, multiplied by 100), minimum, median and maximum. In addition, the geometric mean will be given for C_{max} and AUC.

12.3 Model and Tests

Unless stated otherwise, hypothesis tests will be performed at significance level 0.050.

Change in Concentration with Repeated Dosing

The concentration data of the planned pre-infusion sampling times of Cohort 2 during Weeks 4 through 72 will be analyzed to investigate change in serum concentration over time. The data of Cohort 1 will also be included in this analysis. The logarithmic transformation will be used unless the data show that the logarithm has substantial non-symmetry (e.g., magnitude of skewness coefficient > 1.0) while untransformed concentration or another transformation has an approximately symmetric distribution. A MMRM analysis will be performed. The model will have fixed effects for dose level, classification by time and the interaction of dose level and time. The subjects will be viewed as a random sample, and an appropriate structure will be selected for the covariance matrix of the observations from a subject. The concentration central value (back transformation of the estimate of the mean of the transformed data) versus time curves for the three dose levels will be plotted on the same graph.

Dose Proportionality

Analyses to address the issue of dose proportionality will be performed on the data of Cohort 1. An analysis will be performed on each of dose normalized C_{max} and dose-normalized AUC for each of the first and fourth dose intervals. An analysis will also be performed on dose-normalized C_{trough} at Week 16. The logarithmic transformation will be employed for C_{max} and AUC and will likely be used for C_{trough}. An analysis of covariance (ANCOVA) will be performed for each exposure variable, with the greater emphasis on the fourth dose interval. Subjects will be classified by dose level, and body weight will be a covariate. Other variables such as age and sex that might explain some of the variability among subjects will be considered. Except for body weight, a necessary condition for a variable to be included as a covariate in the final model is that the regression coefficient be significant at level 0.100. The dependence among explanatory variable candidates will

also be considered when selecting the final model. Within the framework of the final model, the hypothesis of no difference between the means of the highest and lowest doses will be tested. If this hypothesis is rejected, corresponding tests will be conducted for the comparison of the middle dose to the lowest and highest doses.

12.4 Missing Values and Model Violations

The possibility of bias from missing data of subjects who prematurely discontinue for reasons possibly related to study drug will be addressed. If it is concluded that there may be a bias of meaningful magnitude as a result of premature discontinuation, a value may be imputed for the missing pharmacokinetic parameter or missing concentrations, Sensitivity analyses might be carried out with the missing value replaced over a range of values.

In some cases of a missing individual concentration value, values of pharmacokinetic variables (C_{max}, AUC, etc.) will be determined without replacing missing individual concentration values, but simply using the available data. However, if a missing individual concentration value results in a value of a pharmacokinetic parameter that may be too low or too high to a meaningful degree, the value of the pharmacokinetic parameter will tentatively be considered missing. In this case, a value for the missing individual concentration may be imputed so that an appropriate value of the pharmacokinetic parameter can be included in the analysis. The imputed value will be obtained using appropriate methodology that takes into account the individual characteristics of the subject. Also, if the concentration value at the beginning or end of the dose interval is missing, a value must be imputed in order for a value of AUC to be determined.

An imputed value will be obtained using appropriate methodology that takes into account the individual characteristics of the subject. The data set from which the value is imputed will be restricted to that of subjects whose data could be considered a random sample from the probability distribution applicable to the subject with the missing data. Ordinarily, the data set from which the imputed value is obtained would be that of the treatment group to which the subject with the missing value is a member, or some

appropriate subset of the treatment group, using only subjects who do not have missing values of their own that would make them unsuitable for the purpose.

As stated in Section 12.4, it is expected that the logarithmic transformation will be used for dose-normalized AUC and dose-normalized C_{max} and is likely to be used for pre-infusion concentration (or C_{trough}). The primary purpose of a transformation will be to have a random variable with an approximately symmetric probability distribution, but an approximately symmetric distribution with apparently very heavy tails (e.g., kurtosis coefficient, as defined in the SAS Procedure Univariate, exceeding 9) would also be of concern. If an adequate transformation is not found for a variable, then a non-parametric analysis may be performed.

13.0 Analysis of Biomarker Research Variables

Descriptive Statistics

Descriptive statistics will be provided for each variable by treatment and scheduled time of measurement. The statistics will consist of: number of observations (n), mean, standard deviation, coefficient of variation as a percentage (quotient of standard deviation and mean, multiplied by 100), minimum, median and maximum. If the logarithmic transformation is employed for the analysis of a variable, the geometric mean will also be reported.

Transformation of Variables for Analysis

If the probability distribution for a variable appears to have considerable non-symmetry (e.g., skewness coefficient > 1.00 in magnitude), a transformation will be sought that has an approximately normal distribution. If a transformation is employed for the analysis, estimates of central values on the original scale (back transformation of SAS least squares means) will be provided. If the logarithmic transformation is used, the comparison of a pair of treatments (usually with placebo as the reference treatment) will be in terms of the ratio of central values.

Analysis of CSF Concentration Variables

An ANCOVA model will be used to evaluate CSF concentrations for total tau, free tau and the ratio of free tau concentration to total tau concentration for each scheduled time of evaluation during treatment (fourth dose interval and Week 96). For the analysis for the fourth dose interval, an analysis will be performed for the data of Cohort 1 alone and also for all available data. The observations will be classified by treatment. The baseline value for total tau and free tau (last value before the first dose of study drug) will be the covariate in the case of total tau and free tau, but for the analysis on the ratio the covariate will be the baseline total tau concentration measurement. If the probability distribution for a variable appears to have considerable non-symmetry (skewness coefficient > 0.75 in magnitude), a transformation will be sought so that the transformed variable has an approximately normal distribution. For each ABBV-8E12 dose level, the results of the test of the hypothesis of no difference between the dose and placebo will be reported. Also, with the motivation to have a test with good power if the dose response curve is a monotonic function of dose, a test will be performed on a contrast in the four treatment means. With μ_0, μ_1, μ_2 and μ_3 denoting the means for placebo, the 300 mg treatment, the 1000 mg treatment and 2000 mg treatment, respectively, the hypothesis that $-3\mu_0 - \mu_1 + \mu_2 + 3\mu_3 = 0$ will be tested at significance level 0.050 against the two-sided alternative hypothesis. The tests on the effects of the 1000 mg dose and the 300 mg dose will not be formally considered unless the statistic on the effect of the 2000 mg dose or the statistic on the contrast in the four means is significant at level 0.050.

CSF NFL concentration will be analyzed as described above for CSF total tau concentration. The same will be done for other CSF concentration variables for which data are reported, provided that the proportion of measurements that are outside the limits of quantification and the magnitude of the lower limit do not make a conventional analysis of covariance inappropriate.

Analysis of Serum/Plasma Concentration Variables

An analysis will be performed for plasma total tau concentration and for plasma NFL concentration. If the data are reported for other plasma concentration variables, an analysis like that described for plasma total tau concentration will be performed, provided that the proportion of measurements that are outside the limits of quantification and the magnitude of the lower limit do not make the methodology inappropriate.

A MMRM analysis will be performed on the data from scheduled times of measurement. The model will include the baseline value as a covariate, have classification of subjects by treatment, an effect for time (classification) and will include an effect for the interaction of treatment and time of measurement. The initial model will also allow the regression coefficient for the baseline value to vary with time (an effect for interaction of time and the baseline value), but this feature will be removed from the model if the statistic on this interaction is not significant at level 0.100. The subjects of each treatment group will be viewed as a random sample, and an appropriate structure for the covariance matrix of the measurements of a subject will be selected. Within the framework of this model, the mean across the scheduled times of measurement will be estimated for each treatment. Also, tests on differences of effect among the dose levels (with placebo considered a dose level) will be performed within the framework of the model. Tests on the dose level main effects will be performed as described for dose level effects in the analysis of covariance for CSF free tau concentration and CSF total tau concentration. These same tests will be provided for each time of measurement in the framework of the MMRM model, and the tests for the individual times will be given the greater attention if the statistic on the interaction of treatment and time of measurement is significant at level 0.100.

Analysis of Volumetric MRI Variables

For volumetric MRI variables, descriptive statistics will be provided for the baseline value, for each scheduled time after that and for the changes from baseline. An MMRM analysis will be performed like that described for plasma NFL concentration, but with an additional covariate, estimated total intracranial volume (eTIV), in the model. The

regression coefficient for eTIV will not vary with time, as may be allowed for the vMRI baseline value.

Analysis of Tau PET Scan Variables

For each region of the brain for which SUVR values are obtained, a joint analysis will be performed for the two scheduled times of evaluation during treatment (Week 44 and Week 96). The analysis will be like that described for plasma NFL concentration with some additional assumptions made. The model will be that of a MMRM analysis even though there are only two times of measurement. The baseline value will be a covariate, with the regression coefficient assumed to be the same for the two times of measurement. Compound symmetry will be assumed for the covariance matrix of the error terms of the two times of measurement. If data are reported for other continuous variables that reflect the extent of tau pathology, a similar approach will be used for their analysis.

Consideration of Premature Discontinuations

The possibility of bias from missing data of subjects who prematurely discontinue for reasons possibly related to study drug will be addressed. If it is concluded that there may be a bias of meaningful magnitude as a result of premature discontinuation, sensitivity analyses may be carried out. Also, some imputation of missing values for subjects who prematurely discontinue might be done.

Relationship with Disease State

For some of the exploratory biomarker variables, an analysis will be performed to explore the relationship to disease state/progression. Disease state will be represented by CDR-SB score, and explorations may be carried out on the relationship between the biomarker variables and other measures of disease level. The biomarker variables will include, but not necessarily be limited to, plasma total tau concentration, plasma NFL concentration, and the vMRI measures for whole brain, hippocampus, temporal lobe and lateral ventricles. The relationship between change in CDR-SB score and change in biomarker will be explored.

The schedule of visits for which the biomarker measurements are obtained are not the same as the schedule of visits on which the CDR-SB assessments are done. For plasma concentration variables and vMRI variables, respectively, the visits defining the bivariate observations composing the data sets on which the analyses will be performed are shown in the two tables that follow. Although there were times of evaluation before Week 48 for both plasma concentration biomarkers and CDR-SB, there was no pair of visits before Week 48 for which the blood sample for the biomarkers and the CDR-SB evaluation were judged to be close enough in time to form an acceptable bivariate observation.

Bivariate Observations for CDR-SB and Plasma Concentration Variable		
Observation	**Visit for CDR-SB Score**	**Visit for Plasma Concentration**
1	Week 48	Week 48
2	Week 72	Week 72
3	Week 96	Week 96

Bivariate Observations for CDR-SB and vMRI		
Observation	**Visit for CDR-SB Score**	**Visit for vMRI Measurement**
1	Week 24	Week 28
2	Week 48	Week 44
3	Week 72	Week 68
4	Week 96	Week 96

For each biomarker variable, the bivariate data of CDR-SB and the biomarker variable for each combination of treatment and time of observation will be plotted. With each plot Spearman's rank correlation coefficient and the p-value for the test of independence will be provided. An investigation of the relationship of CDR-SB with the biomarker variable for all of the times of observation jointly will be carried out in the framework of a MMRM analysis with decrease from baseline in CDR-SB score as the response variable and with change from baseline in the biomarker variable as a covariate (explanatory variable) that changes with time. If a transformation is used for the analysis of the biomarker variable itself, that same transformation will be used for the biomarker variable in this analysis; that is, the covariate will be the change from baseline in the value of the

transformed variable. The model will include classification by time of observation, which can also be thought of as the visit at which the CDR-SB evaluation was done. The model will include classification by treatment and the interaction of treatment and time. The initial model will have interaction of the covariate with treatment, allowing the regression coefficient of the covariate to depend upon treatment. This interaction effect will be removed from the model if the statistic on the interaction is not significant at level 0.100 in the analysis with the final choice of the structure for the covariance matrix of the error term, as discussed in the paragraph that follows.

The initial model will impose no restrictions on the covariance matrix for the error term (using Option UN with the SAS REPEATED statement). A simpler structure for the covariance matrix will be considered, with the correlation coefficients for all pairs of times assumed to be the same while imposing no restrictions on the variances for the several times (using Option CSH with the SAS REPEATED statement). An approximate test of the hypothesis that the covariance matrix with the more complex model is same as the covariance matrix with the simpler model will be performed. The approximate test will be that based upon the difference in the values of –2log (likelihood) for the two models, using the chi-square approximation for the null distribution, with degrees of freedom being the difference in the number of parameters required for the two structures of the covariance matrix. If the test statistic is not significant at level 0.050, the simpler model will be tentatively adopted. In that case, the compound symmetry structure (default option with the SAS REPEATED statement) will be considered. The approximate test for the comparison of the two models will again be performed. The compound symmetry model will be adopted only if the test statistic is not significant at level 0.050. If the computational algorithm does not satisfactorily converge with a particular structure assumed for the covariance matrix, that structure will not be adopted, and only the simpler structure(s) will be considered.

If the final model contains an effect for the interaction of treatment and covariate, the estimate for each of the four regression coefficients and for the average of the four regression coefficients will be provided. For each of the four regression coefficients

and for their average, a two-tailed test of the hypothesis that the regression coefficient (or the average) = 0 will be performed at significance level 0.050. This will serve as a test of the hypothesis that the correlation coefficient between the CDR-SB change from baseline and the biomarker change from baseline is 0. If the final model does not contain an effect for the interaction of treatment and covariate (a common regression coefficient for all four treatments), this hypothesis test will be performed on the single regression coefficient and will apply to placebo and all three ABBV-8E12 treatments.

To give further confidence in the assessment of the relationship of the biomarker variables with disease state and progression in the absence of treatment with ABBV-8E12, a MMRM analysis will be performed on the data set restricted to subjects on the placebo treatment. The model and analysis will be simpler than that described above in that there will be no effects involving treatment. In particular, there will be only a single regression coefficient.

14.0 Summary of Changes

Changes in the planed analyses from the latest version of the protocol (Protocol Amendment 1, Administrative Change 1, Administrative Change 2, Administrative Change 3, and Amendment 2) have been incorporated into Statistical Analysis Plan version 1.0.

In Statistical Analysis Plan version 2.0, changes of interim analysis (Section 4.4) and impact of COVID-19 on statistical analysis (Section 10.4 and Section 10.6) have been incorporated. In Section 13.0, tau PET variables have been removed from the biomarkers specified for the exploration of relationship with disease state as represented by CDR-SB since the number of subjects with tau PET data is now expected to be substantially smaller than was anticipated.

In Statistical Analysis Plan version 3.0, Braak stage I and II were included in Section 4.8.1. Analysis window definitions for vMRI, tau PET, CSF, and NFL were

removed in Section 6.2. Sensitivity analysis in Section 10.6 was updated. Baseline amyloid centiloid value criterion for a subgroup analysis was updated in Section 10.8.

15.0 Reference List

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4. Xi D, Tamhane AC. Allocating recycled significance levels in group sequential procedures for multiple endpoints. Biom J. 2015;57(1):90-107.
5. Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. Statistics in Biopharmaceutical Research. 2013;5(4):311-20.
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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)
Urate	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