1.0 Title Page

Statistical Analysis Plan

Study M15-562

A Randomized, Double-Blind, Placebo-Controlled Multiple Dose Study to Assess Efficacy, Safety, Tolerability, and Pharmacokinetics of ABBV-8E12 in Progressive Supranuclear Palsy

Date: 23 Oct 2018

Version 1.0

1.1 List of Abbreviations and Definition of Terms

Abbreviations

AD	Axial Diffusivity
ADA	Anti-Drug-Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration Time Curve
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CL	Clearance
C_{max}	Maximum Observed Serum Concentration
COMT	Catechol-O-Methyltransferase
CPK	Creatine Phosphokinase
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
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
CTT	Color Trails Test
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DTI	Diffusion Tensor Imaging
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

EQ-5D	EuroQol-5D
ERAC	Exposure-Response Analysis Center
ES	Effective Size
FA	Fractional Anisotropy
FLAIR	Fluid Attenuated Inversion Recovery
FWER	Family Wise Error Rate
GABA	Gamma-Aminobutyric Acid
GEE	Generalized Estimation Equation
GGT	Gamma-Glutamyl Transpeptidase
HbsAg	Hepatitis B Surface Antigen
HR	Heart Rate
IA	Interim Analysis
ITT	Intent-to-Treat
INR	International Normalized Ratio
LFT	Letter Fluency Test
LLN	Lower Limit of Normal
LP	Lumbar Puncture
LTE	Long-term Extension
LS	Least Square
MAPT	Microtubule Associated Protein Tau
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MCMC	Monte Carlo Markov Chain
MD	Mean Diffusivity
MMRM	Mixed-effect Model Repeated-Measures
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NFL	Neurofilament Light Protein
NNIPPS-PPS	Natural History and Neuroprotection in Parkinson Plus Syndromes-Parkinson Plus Scale
PCS	Potentially Clinically Significant
PGI-C	Patient Global Impression of Change
PK	Pharmacokinetic
PSP	Progressive Supranuclear Palsy
PSP-QoL	Progressive Supranuclear Palsy Health Related Quality of Life Scale

PSPRS	Progressive Supranuclear Palsy Rating Scale
PT	Prothrombin Time
PT/INR	Prothrombin Time/International Normalized Ratio
PTT	Partial Thromboplastin Time
PTs	Preferred Terms
QRS	ECG QRS Complex
QT	Measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTcF	QT corrected for heart rate using Fridericia's Method
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
RBC	Red Blood Cell
RD	Radial Diffusivity
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SDAC	Statistical and Data Analysis Center
SEADL	Schwab and England Activities of Daily Living Scale
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
T_{max}	Peak Time
ULN	Upper Limit of Normal
UPDRS	Unified Parkinson's Disease Rating Scale
VAS	Visual Analog Scale
WBC	White Blood Cell
WHO	World Health Organization

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 Pipeline Statistics and Programming for ABBV-8E12 Study Protocol M15-562, that incorporates the original protocol and three amendments (original Protocol, Amendment 1, Amendment 2, Amendment 2.01 [US only], Amendment 2.02 [Germany only], Amendment 3, Amendment 3.01 [Germany Only], Amendment 3.02 [Japan Only], Amendment 2.01.01 [US only], Amendment 4).

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, if performed, 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 in subjects with progressive supranuclear palsy as measured by the PSP Rating Scale (PSPRS).
- To assess the long term safety and tolerability of ABBV-8E12 for up to 52 weeks in subjects with progressive supranuclear palsy.

The secondary objectives of this study are:

- To assess the pharmacokinetics of multiple doses of ABBV-8E12 in subjects with progressive supranuclear palsy.

- To assess the efficacy of ABBV-8E12 in slowing disease progression and functional impairment in subjects with progressive supranuclear palsy as measured by secondary endpoints.
- To assess the efficacy of ABBV-8E12 in slowing regional and/or whole brain atrophy in subjects with progressive supranuclear palsy as measured by volumetric magnetic resonance imaging (MRI).

The exploratory objectives of this study are:

- To assess the efficacy of ABBV-8E12 in slowing disease progression and functional impairment in subjects with progressive supranuclear palsy as measured by exploratory endpoints.
- To assess the effect of ABBV-8E12 on cerebrospinal fluid (CSF) free/total tau protein levels.
- To assess the effect of ABBV-8E12 on potential CSF biomarkers of disease progression.

4.2 Study Design

This Phase 2, randomized, double-blind, placebo-controlled, multiple dose, multicenter study will consist of a screening period of up to 8 weeks (56 days), a 52 week double-blind treatment period, and a post-treatment follow-up period of approximately 20 weeks following last study drug administration (including those subjects who prematurely discontinue from treatment, decline to participate in or do not qualify for participation in a long term extension [LTE] study). The study is planned to be conducted at approximately 60 sites in the US and outside of the US. Approximately 330 subjects who are at least 40 years of age with PSP will be eligible to participate in the study according to the selection criteria.

Upon completion of screening and baseline procedures, eligible subjects will be randomized to one of the two ABBV-8E12 dose arms (2000 mg or 4000 mg) or placebo in a 1:1:1 ratio. Subjects will enter the Treatment Period of the study on Day 1 and receive their first infusion of study drug. During the first 4 weeks, subjects will have

3 study drug infusions; the first on Day 1, the second on Day 15, and then on Day 29; thereafter, subjects will return to the study site every 28 Days for their the schedules for study drug infusion, blood collection, study procedures and assessments as outlined in the Study Activities Table (Table 1 and Table 2). This dosing schedule (with one additional dose delivered on Day 15) is intended to enable subjects to reach steady-state levels of ABBV-8E12 in plasma as soon as reasonably possible in order to maximize the potential benefit to subjects during the treatment period. This study will utilize a Data Monitoring Committee (DMC) consisting of 4 external clinicians, 1 external statistician and 1 external pharmacokineticist. The DMC will review unblinded safety and efficacy data and make recommendations to the Sponsor based on the totality of available clinical data. The DMC memberships, responsibilities and operating logistics will be documented in a charter that will be prepared prior to the first DMC review meeting.

The first 30 subjects enrolled into the study in countries not including Japan will be represented as Cohort 1 in this protocol while the first 9 Japanese subjects enrolled into the study will compose Cohort J1. Subjects enrolled subsequent to Cohort 1 and Cohort J1 will be represented as Cohort 2. Augmented safety and pharmacokinetic monitoring including additional study visits, more frequent neurological exams, vital signs, blood collections for safety labs, an additional lumbar puncture and MRI, and additional monitoring by the DMC will be performed in Cohorts 1 and J1.

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

Figure 1. Study Schematic

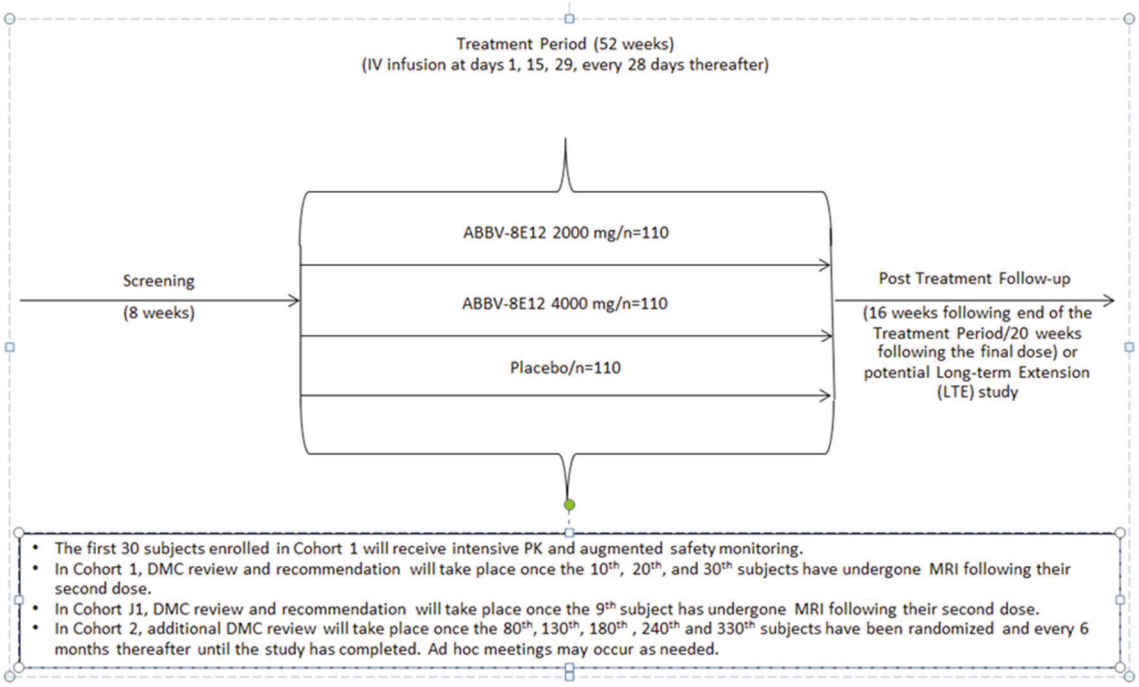


Table 1. Safety and PK Procedures for Cohort 1 and Cohort J1

	Screening		Cohort 1 and Cohort J1, Doses 1 – 5										
	Visit 1	Visit 2	Dose 1				Dose 2	Dose 3	Dose 4	Dose 5			Dose 6
Weeks of Study Drug Exposure	N/A	N/A	0	0	0	0	2	4	8	12	13	14	16
	Days –56 to –8	Days –56 to –8	Day 1	Day 2[j,k]	Day 3[j]	Day 5	Day 15	Day 29	Day 57	Day 85	Day 89	Day 99	Day 113
Physical Exam[a]	X		X	X	X								
Neurological Exam	X		X	X	X	X	X	X	X	X		X	
Orthostatic Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X		X[b]			X[c]	X[b]	X[d]	X[d]	X[b]			
Clinical Laboratory Tests	X		X				X[j]	X	X	X			
MRI	X						X[e]			X			
Lumbar Puncture/ CSF Sample Collection	X											X[f]	
PK Sample Collection			X[g]			X	X[g]	X	X	X[g]	X	X	X
ADA Sample Collection			X[h]				X[h]	X[h]	X[h]	X[h]	X	X	X
C-SSRS	X	X	X			X	X	X	X	X	X	X	X
AE/ ConMed Review	X	X	X	X	X	X	X	X	X	X	X	X	X
24 hour confinement[i]			X										

a. Additional symptom-driven physical exams can be performed as needed.

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

c. Collection should be scheduled as close as possible to the corresponding time of the post infusion PK collection on Day.

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

Table 1. Safety and PK Procedures for Cohort 1 and Cohort J1 (Continued)

e. For subjects in Cohort 1 and Cohort J1, an MRI will be performed within 2 weeks following the second dose and results must be available prior to the next scheduled dose.
f. The lumbar puncture will be performed approximately 14 days after the fifth dose.
g. 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.
h. Prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion).
i. A 24-hour confinement will be required following the first dose in Cohort J1.
j. Cohort J1 subjects only.
k. Cohort J1 Day 2 assessments will be performed only in subjects discharged on Day 2.

Note: 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.

Table 2. Study Activities

	Screening[a]		Treatment Period[b]											
			Dose 1				Dose 2	Dose 3	Dose 4	Dose 5			Dose 6	Dose 7
Weeks of Study Drug Exposure	**Days –56 to –8**		**Week 0**	**Week 0**	**Week 0**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 13**	**Week 14**	**Week 16**	**Week 20**
Activities[c]	**Visit 1**	**Visit 2**	**Day 1**	**Day 2[u]**	**Day 3**	**Day 5**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 89**	**Day 99**	**Day 113**	**Day 141**
Subject/Study Partner Informed Consent[d]	X													
Medical History[e]	X	X	X											
Physical Examination[e,f]	X		X	J1	J1									
Orthostatic Vital Signs[e,g]	X	X	X	J1	J1	C1/J1	X	X	X	X	C1/J1	C1/J1	X	X
Body Weight and Height[h]	X	X	X				X	X	X	X			X	X
Pregnancy Test (Females only) Urine (u) Serum (s)[i]	S	U	U							U				
Urine Drug Screen	X													
HbsAg, HCV Ab Tests	X													
Neurological Exam[e]	X		X	J1	J1	C1/J1	X	X	X	X		C1/J1		
12-Lead ECG[e,j]	X		X			C1/J1	C1/J1	X	X	X				

Table 2. Study Activities (Continued)

	Screening[a]		Treatment Period[b]											
			Dose 1				Dose 2	Dose 3	Dose 4	Dose 5			Dose 6	Dose 7
Weeks of Study Drug Exposure	**Days –56 to –8**		**Week 0**	**Week 0**	**Week 0**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 13**	**Week 14**	**Week 16**	**Week 20**
Activities[c]	**Visit 1**	**Visit 2**	**Day 1**	**Day 2[u]**	**Day 3**	**Day 5**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 89**	**Day 99**	**Day 113**	**Day 141**
Clinical Laboratory Tests[e]	X		X				J1	C1/J1	C1/J1	X				
Brain MRI[e,k,l]	X						C1/J1			X				
Lumbar Puncture (LP)/CSF Collection[e,m,n]	X											C1/J1		
Pharmacogenetic MAPT Sample			X											
Serum Plasma Biomarkers	X									C1/J1				
Blood PK Sample			X			C1/J1	X	X	C1/J1	X	C1/J1	C1/J1	C1/J1	
Optional Exploratory Pharmacogenetic DNA and RNA Sample[o]			X							X				
Serum Antibodies (ADA)			X				C1/J1	X	C1/J1	X	C1/J1	C1/J1	C1/J1	
Randomization[p]			X											
Administer IV Study Drug			X				X	X	X	X			X	X

Table 2. Study Activities (Continued)

	Screening[a]		Treatment Period[b]											
			Dose 1				Dose 2	Dose 3	Dose 4	Dose 5			Dose 6	Dose 7
Weeks of Study Drug Exposure	**Days –56 to –8**		**Week 0**	**Week 0**	**Week 0**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 13**	**Week 14**	**Week 16**	**Week 20**
Activities[c]	**Visit 1**	**Visit 2**	**Day 1**	**Day 2[u]**	**Day 3**	**Day 5**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 89**	**Day 99**	**Day 113**	**Day 141**
PSP Rating Scale (PSPRS)	1		1							1				
CGI-S	2	5	2						5	2				5
CGI-C									6	3				6
SEADL	3		3							4				
UPDRS Part II	4		4							5				
RBANS		1							1					1
Color Trails Test (CTT)														
Parts 1 & 2		2							2					2
Letter Fluency Test (LFT)		3							3					3
NNIPPS-PPS[#]		4							4					4
MMSE[q]	X													
PGI-C[r]										X				
PSP-QoL[r]	X		X							X				
Euro-QoL-5D (EQ-5D)[r]		X							X					X
C-SSRS[r]	X	X	X			C1/J1	X	X	X	X	C1/J1	C1/J1	X	X

Table 2. Study Activities (Continued)

	Screening[a]		Treatment Period[b]											
			Dose 1				Dose 2	Dose 3	Dose 4	Dose 5			Dose 6	Dose 7
Weeks of Study Drug Exposure	**Days –56 to –8**		**Week 0**	**Week 0**	**Week 0**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 13**	**Week 14**	**Week 16**	**Week 20**
Activities[c]	**Visit 1**	**Visit 2**	**Day 1**	**Day 2[u]**	**Day 3**	**Day 5**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 89**	**Day 99**	**Day 113**	**Day 141**
Concomitant Medication	X	X	X	J1	J1	C1/J1	X	X	X	X	C1/J1	C1/J1	X	X
Adverse Event Assessment[s]	X	X	X	J1	J1	C1/J1	X	X	X	X	C1/J1	C1/J1	X	X
24-hour confinementt			J1											

Table 2. Study Activities (Continued)

	Treatment Period[b]									
	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13	Dose 14			
Weeks of Study Drug Exposure	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**	**Week 60**	**Week 68**
Activities[c]	**Day 169**	**Day 197**	**Day 225**	**Day 253**	**Day 281**	**Day 309**	**Day 337**	**Completion/ Premature Discontinuation**	**Post-Treatment Follow-Up**	**Post Treatment Follow-Up**
Physical Examination[f]	X							X		
Orthostatic Vital Signs[g]	X	X	X	X	X	X	X	X	X	X
Body Weight	X	X	X	X	X	X	X	X		
Pregnancy Test (Females only) Urine (u) Serum (s)[i]	U						U	S		
Neurological Exam	X			X				X	X	
12-Lead ECG[j]	X			X				X	X	
Clinical Laboratory Tests	X						X	X		
Administer IV Study Drug	X	X	X	X	X	X	X			
Brain MRI[k,l]	X							X		
Lumbar Puncture (LP)/CSF Collection[m,n]								X		
Serum Plasma Biomarkers		X					X	X		
Optional Exploratory Pharmacogenetic DNA and RNA Sample[o]				X				X		
Blood PK Levels	X			X				X	X	X
Serum Antibodies (ADA)	X			X				X	X	X

Table 2. Study Activities (Continued)

	Treatment Period[b]									
	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13	Dose 14			
Weeks of Study Drug Exposure	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**	**Week 60**	**Week 68**
Activities[c]	**Day 169**	**Day 197**	**Day 225**	**Day 253**	**Day 281**	**Day 309**	**Day 337**	**Completion/ Premature Discontinuation**	**Post-Treatment Follow-Up**	**Post Treatment Follow-Up**
PSP Rating Scale (PSPRS)	1			1				1		
CGI-S	2		5	2			5	2		
CGI-C	3		6	3			6	3		
SEADL	4			4				4		
UPDRS Part II	5			5				5		
RBANS			1				1			
Color Trails Test (CTT) Parts 1 & 2			2				2			
Letter Fluency Test (LFT)			3				3			
NNIPPS-PPS[#]			4				4			
PGI-C[r]	X			X				X		
PSP-QoL[r]	X			X				X		
Euro-QoL-5D (EQ-5D)[r]			X				X			
C-SSRS[r]	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment[s]	X	X	X	X	X	X	X	X	X	X
24-hour confinement[t]										

Table 2. Study Activities (Continued)

a. All screening assessments are to be completed within –56 to –8 days prior to initial study drug administration (Day 1). Refer to Table 7 in the protocol for a pre-defined order of administration that should occur during each visit. Screening visit assessments may be completed on a single date or multiple visit days. Screening is complete when all screening assessments are complete or subject screen fails. If screening assessments are completed on a single date, the scales for Screening Visit 1 (SV1) will be performed in the recommended order in this table, followed by the recommended order of scales for Screening Visit 2 (SV2). Also, the CGI-S and the C-SSRS will only be performed once.

b. 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. The scheduled date for each study visit will be based on the number of days from the beginning of the treatment period on study Day 1, as indicated in the Study Activities table.

c. Audio recordings/central review of the administration/assessment of selected scales may be conducted.

d. Study-related assessments, procedures or activities may not occur prior to subject completing the signed informed consent process. If at any time during the study, a subject experiences diminished decision-making capacity, a legally authorized representative (LAR) is necessary when an informed consent must be obtained.

e. Update medical and/or neurological history with any findings prior to randomization.

f. Additional symptom-driven physical examinations can be performed as needed.

g. All systolic and diastolic blood pressure and pulse rate measurements are to be measured as part of an orthostatic assessment. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.

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

i. All females of child-bearing potential must have a negative serum pregnancy test performed at screening and Premature Discontinuation. A negative urine pregnancy test result is required prior to any radiological procedures involving exposure to radiation.

j. A detailed description for ECG parameters and schedule can be found in Section 5.3.1.1 in the protocol.

k. Brain MRI scans will be without contrast and will include 3D T1 structural imaging, FLAIR, diffusion-weighted imaging, PD/T2, T2*, and diffusion tensor imaging including subcortical regions. The additional MRI for subjects in Cohort 1 and Cohort J1 following Dose 2 will be performed within 2 weeks following the second dose and results must be available prior to the next scheduled dose. The time window for the MRI procedure at each protocol-required time points is ± 7 days.

l. If sedation is required it should occur after all scales and cognitive testing have been performed or, if this is not possible, at least 48 hours before the testing.

m. Coagulation and complete blood cell (CBC) results must be reviewed by the investigator before the LP. During Cohort 2, some subjects who are not able to undergo LP may be admitted with permission of the AbbVie Medical Director, and these subjects will not be required to undergo LP during the study.

n. LP must be performed greater than 3 months from previous LP.

o. Samples are optional. Verify consent was obtained prior to sample collection.

Table 2. Study Activities (Continued)

p. Randomization should be completed just prior to the first dose administration.
q. MMSE administered during Screening to assess inclusion criteria only.
r. Scale may be administered/assessed at any time during the visit with the exception of during the scheduled time of infusion.
s. A detailed description for procedures involving adverse event assessments can be found in Section 6.1.1 in the protocol.
t. A 24-hour confinement will be required following the first dose in Cohort J1.
u. Cohort J1 Day 2 assessments will be performed only in subjects discharged on Day 2.
The NNIPPS-PPS will not be administered in Japan.

Note: Activities labeled as "C1" and/or "J1" are to be completed for Cohort 1 and/or Cohort J1 only. Unscheduled visits can be performed as clinically indicated.

4.3 Sample Size

Approximately 330 PSP subjects (110 subjects/group) will be enrolled and randomized into two ABBV-8E12 dose groups and the placebo group with 1:1:1 randomization ratio. This sample size has ~90% power to detect an ABBV-8E12 effect size (vs. placebo) of 0.56 for the high dose and 0.28 effect size for the low dose on the PSPRS total score changes from baseline at Week 52 using the Bonferroni method to control for multiplicity due to multiple comparisons between two doses and placebo at the two-sided 5% significant level. A no data rate of 25% at Week 52 is assumed in this sample size calculation using East version 6.3.1 (Cytel).

In Japan, a total of 24 subjects (8 subjects/arm) randomized will have 80% probability to detect the consistent treatment effect among three regions (Japan, North America including US/Canada, and European countries including Australia assuming 7%, 54%, and 39% of the total 330 PSP subjects are randomized in three regions, respectively). This calculation is based on Method 2[1] and assumes that the significance level for comparison of each ABBV-8E12 dose vs. placebo is two-sided 2.5% and the dropout rate is 25% in all regions.

4.4 Interim Analyses

Regular interim safety analyses and two preplanned interim futility analyses will be performed in this study. Assessment of safety and efficacy data at interims will be performed by the DMC. An independent statistical and data analysis center (SDAC) will be responsible for generating and providing unblinded statistical tables, figures, and listings to the DMC for the interim review. An independent exposure-response analysis center (ERAC) will provide exposure-response analysis services to the DMC. 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.

Safety Interim Analyses

The DMC will evaluate the available unblinded safety data and communicate their recommendations to the AbbVie Contact. In addition to blinded safety data monitoring by the Sponsor, the first three mandatory DMC reviews of unblinded safety data will take place after the 10th, 20th, and 30th subjects in Cohort 1 have been administered their second dose and results for the MRI scheduled at approximately 2 weeks after their second dose are available. For Cohort J1, an additional mandatory DMC review will take place after the 9th subject enrolled in Japan has received their second dose and results for the Day 15 safety labs and the MRI performed within 2 weeks after their second dose, are available. Only after the DMC recommends continuing enrollment into the study without modification, will Japanese subjects be enrolled into Cohort 2. 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 reviews of available safety data will occur after a total of approximately 80, 130, and 180, 240, and 330 subjects are randomized and every 6 months thereafter until the study has completed.

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

Futility Interim Analyses

Two pre-planned interim efficacy analyses for futility will be performed. The DMC will communicate their recommendations to AbbVie Contact who will share recommendations to the Sponsor. The DMC will make recommendation to the Sponsor to stop the trial for futility or to continue the study without modification. The study will not be stopped because of positive results at the interim futility analyses and administrative α spending at each interim analysis will be 0.00001. Futility interim analyses will be conducted on PSPRS total score changes from baseline.

Mixed Model Repeated Measure (MMRM) analysis on PSPRS total score change from the baseline up to Week 52 using observed data will be conducted in the futility interim analyses.

Rules for Interim Futility Analyses

A simulation study was conducted to determine the timing and decision making thresholds for futility interim analyses (see details of the simulation report in the DMC Charter).

The timing of futility interim analysis was determined based on the need to have sufficient information available to make a decision with reasonable confidence. Two futility interim analyses are planned for this trial. The first futility interim is planned to occur when approximately 60 subjects (20 subjects/group) have completed 52 Week visit; the second futility interim is planned to occur when approximately 120 subjects (40 subjects/group) have completed 52 Week visit (see projected timing on Table 1 in simulation report in the DMC Charter).

At both futility interim analyses, if observed effect sizes at Week 52 for both doses are below the threshold, the DMC will make the recommendation to terminate the study due to futility.

Details of interim futility analyses plan will be described in the DMC charter for this study.

4.5 Efficacy Variables

The primary efficacy variable will be the change from baseline to the Week 52 assessment in the PSP Rating Scale (PSPRS) total score to assess the effect of ABBV-8E12 in slowing disease progression.

Secondary efficacy variables include the changes from baseline of Unified Parkinson's Disease Rating Scale (UPDRS) Part II score, Clinical Global Impression of Severity and

Change (CGI-S, CGI-C) score, the Schwab and England Activities of Daily Living Scale (SEADL) score, PSP-Quality of Life (PSP-QoL) total score, PSP Staging System and time to loss of ability to walk independently as measured by PSPRS item 26, PSPRS domain scores, and regional (midbrain, frontal lobes, and third ventricle) and whole brain atrophy as measured by volumetric MRI.

Exploratory efficacy variables include the Natural History and Neuroprotection in Parkinson Plus Syndromes-Parkinson Plus Scale (NNIPPS-PPS) total score and dimensional scores, Patient Global Impression of Change (PGI-C) score, Letter Fluency Test (LFT) score, Repeatable Battery for Assessment of Neuropsychological Status (RBANS) total scale score and subtest scores, Color Trails Test (CTT) (Parts 1 and 2) completion time, EuroQoL-5D (EQ-5D) summary index score. Exploratory quantitative MRI measures may additionally be evaluated; including diffusion tensor imaging (DTI) derived fractional anisotropy (FA) and diffusivity measures [radial diffusivity (RD), mean diffusivity (MD), and axial diffusivity (AD)] to assess changes in microstructural integrity.

4.6 Safety Variables

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

4.7 Pharmacokinetic Variables

Values for the following pharmacokinetic parameters will be determined using non-compartmental methods: maximum observed serum concentration (C_{max}), the time to C_{max} (peak time, T_{max}), the area under the concentration time curve (AUC) over the dosing interval after the first and the fifth doses in Cohort 1 and Cohort J1; and the observed serum concentration at the end of a dose interval (C_{trough}) in all subjects.

4.8 Biomarker and Pharmacogenetic Research Variables

4.8.1 Biomarker Research Variables

Blood and CSF samples will be collected to conduct research to investigate disease-related and drug-related biomarkers. The biomarkers to be analyzed may include, but are not limited to, the following:

- CSF and serum/plasma samples will be assayed for free/total tau to demonstrate tau binding of ABBV-8E12.
- CSF or serum/plasma samples may be analyzed for biochemical or macromolecular factors (e.g., NFL) related to the pharmacodynamics and safety of ABBV-8E12.

Exploratory evaluations from samples may include analyzing biomarkers related to the pathway(s) targeted by the study drug or believed to be related to the disease or to drug response. Analysis of these exploratory biomarkers will be described in a separate biomarker document.

The information learned from analyzing these data may be used to investigate factors impacting response to treatment, scientific questions related to PSP, support development of ABBV-8E12, or in the development of new therapies. Furthermore, given the exploratory nature of these data the results may not be included in the clinical study report (CSR).

4.8.2 Pharmacogenetic Research Variables

MAPT haplotype status may be determined for each subject and analyzed as a factor contributing to the subject's response to study treatment. The MAPT haplotype results may be analyzed as part of a multi-study assessment of MAPT 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 PSP or related conditions. The MAPT haplotype results may not be included in the CSR.

Optional pharmacogenetic samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. The samples may be analyzed as part of a multi-study assessment of factors influencing the subjects' response to the study drug (or drugs of the same or similar class) or the development and progression of the subjects' disease or related conditions. The samples may also be used to develop new diagnostic tests, therapies, research methods or technologies. The results from these analyses are exploratory in nature and may not be included in the CSR.

5.0 Analysis Populations

5.1 Analysis Datasets

Intent-to-Treat (ITT) Dataset

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

5.2 Variables Used for Stratification of Randomization

Subject randomization is stratified by study site except for Japanese subjects who are randomly assigned to three groups with 1:1:1 ratio within Japan.

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 (including type I error rate spent in interim analyses). *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. Multiplicity adjustment will be carried out to control the overall FWER rate in this study.

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

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

Definition of Baseline and Final Observation

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 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 the 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 a baseline for a specific measurement is the last non-missing observation taken up to and on 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-blinded 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 schedule visit (Rx Days X through Y) include both Rx Days X and Y. The nominal day for each scheduled visit is defined in "Activities" row in Table 2.

For measurements that are planned to be collected during double-blind treatment period at Weeks 12, 24, 36, and 52, i.e., PSPRS, SEADL, PGI-C, PSP-QoL and UPDRS Part II, observations will be mapped to an analysis "week" according to the following windows defined by Rx day.

- Week 12 Rx Days 2 through 126
- Week 24 Rx Days 127 through 210
- Week 36 Rx Days 211 through 308
- Week 52 Rx Days > 308

For measurements that are planned to be collected during double-blind treatment period at Weeks 8, 20, 32, and 48, i.e., RBANS, Color Trails Test (Parts 1 & 2), letter fluency, EQ-5D, and NNIPPS-PPS, observations will be mapped to an analysis "week" according to the following windows defined by Rx day.

- Week 8 Rx Days 2 through 98
- Week 20 Rx Days 99 through 182
- Week 32 Rx Days 183 through 280
- Week 48 Rx Days > 280

For measurements that are planned to be collected during double-blind treatment period at Weeks 8, 12, 20, 24, 32, 36, 48 and 52, i.e., CGI-S and CGI-C, observations will be mapped to an analysis "week" according to the following windows defined by Rx day.

- Week 8 Rx Days 2 through 70
- Week 12 Rx Days 71 through 112
- Week 20 Rx Days 113 through 154
- Week 24 Rx Days 155 through 196
- Week 32 Rx Days 197 through 238

- Week 36 Rx Days 239 through 294
- Week 48 Rx Days 295 through 350
- Week 52 Rx Days > 350

For measurements that are planned to be collected during double-blind treatment period at Weeks 1, 2, 4, 8, 12, 13, 14, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52, i.e., vital sign and C-SSRS observations will be mapped to an analysis "week" according to the following windows defined by Rx day. The first 30 randomized subjects represent Cohort 1 and the rest randomized subjects represent Cohort 2.

- Week 1 Rx Days 2 through 10 (Cohort 1 and Cohort J1 only)
- Week 2 Rx Days 11 through 22 (Cohort 1 and Cohort J1 subjects)
  Rx Days 2 through 22 (Cohort 2 subjects)
- Week 4 Rx Days 23 through 42
- Week 8 Rx Days 43 through 70
- Week 12 Rx Days 71 through 87 (Cohort 1 and Cohort J1 subjects)
  Rx Days 71 through 98 (Cohort 2 subjects)
- Week 13 Rx Days 88 through 94 (Cohort 1 and Cohort J1 only)
- Week 14 Rx Days 95 through 105 (Cohort 1 and Cohort J1 only)
- Week 16 Rx Days 106 through 126 (Cohort 1 and Cohort J1 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 > 350

For measurements that are planned to be collected during double-blind treatment period at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, i.e., body weight observations will be mapped to an analysis "week" according to the following windows defined by Rx day.

- Week 2 Rx Days 11 through 21
- Week 4 Rx Days 22 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 > 350

For measurements that are planned to be collected during double-blind treatment period at Weeks 2, 4, 8, 12, 24, 48, and 52, i.e., clinical laboratory tests will be mapped to an analysis "week" according to the following windows defined by Rx day.

- Week 2 Rx Day 2 through 21 (Cohort J1 only)
- Week 4 Rx Day 22 through 42 (Cohort J1 only)
  Rx Day 2 through 42 (Cohort 1 only)
- Week 8 Rx Day 43 through 70 (Cohort 1 and Cohort J1 only)
- Week 12 Rx Days 71 through 126 (Cohort 1 and Cohort J1 subjects)
  Rx Days 2 through 126 (Cohort 2 subjects)

- Week 24 Rx Days 127 through 252
- Week 48 Rx Days 253 through 350
- Week 52 Rx Days > 350

For measurements that are planned to be collected during double-blind treatment period at Weeks 1, 2, 4, 8, 12, 24, 36 and 52, i.e., ECG observations will be mapped to an analysis "week" according to the following windows defined by Rx day.

- Week 1 Rx Days 2 through 10 (Cohort 1 and Cohort J1 only)
- Week 2 Rx Days 11 through 21 (Cohort 1 and Cohort J1 only)
- Week 4 Rx Days 22 through 42 (Cohort 1 and Cohort J1 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 308
- Week 52 Rx Days > 308

For measurements that are planned to be collected during double-blind treatment period at Weeks 2, 12, 24, and 52, i.e., brain volumetric MRI observations will be mapped to an analysis "week" according to the following windows defined by Rx day.

- Week 2 Rx Days 2 through 49 (Cohort 1 and Cohort J1 only)
- Week 12 Rx Days 50 through 126 (Cohort 1 and Cohort J1 subjects)
  Rx Days 2 through 126 (Cohort 2 subjects)
- Week 24 Rx Days 127 through 266
- Week 52 Rx Days > 266

For vital sign measurements and C-SSRS assessments that are planned to be collected during post-treatment follow-up period on Weeks 60 and 68, observations will be mapped to an analysis "week" according to the following windows defined by RxEnd day.

- Post-Treatment Week 12 RxEnd Days 46 through 112
- Post-Treatment Week 20 RxEnd Days > 112

For ECG measurements that are planned to be collected during post-treatment follow-up period at Weeks 60, observations will be mapped to an analysis "week" according to the following windows defined by RxEnd day.

- Post-Treatment Week 12 RxEnd Days > 45

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 both 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)
- 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)

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 intent-to-treat dataset.

- PSPRS total and domain scores
- SEADL score
- UPDRS Part II score
- RBANS scale score
- Color trails test (Parts 1 and 2) completion time
- Letter Fluency Test score
- NNIPPS-PPS total and dimension scores
- CGI-S score
- PSP-QoL total and subscale core and Visual Analog Scale (VAS) scores
- EQ-5D index score and VAS score

Categorical variables will be summarized by the number and percentage of subjects in each category. No comparisons of treatment groups will be performed for alcohol and nicotine uses. Continuous variables will be summarized with descriptive statistics

(number of non-missing observations, mean, standard deviation, median, minimum and maximum). 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 any condition/diagnosis and condition/diagnosis in 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 progressive supranuclear palsy disease 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 PSP (years)
- Age when first diagnosed as having PSP (years)
- Years since onset of PSP symptoms (Date of Day 1 – Date of onset)
- Years since PSP diagnosis (Date of Day 1 – Date of diagnosis)
- Family history of PSP (None, biological mother, biological father, full sibling, biological child)

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 administration 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). 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.

- Previous medications for PSP (CMCAT = "PROGRESSIVE SUPRANUCLEAR PALSY MEDICATIONS") will be summarized by the following categories:
  - Antipsychotic medication
  - Antidepressants
  - Medications for Parkinsonian symptoms (including levodopa/carbidopa, dopamine agonists, monoamine oxidase inhibitors, COMT inhibitors, and amantadine).
  - Anti-dementia drugs (CMCLAS3 = ANTI-DEMENTIA DRUGS): cholinesterase inhibitors (donepezil, rivastigmine, galantamine) or memantine for cognitive impairment.
  - Selective benzodiazepines and gamma-aminobutyric acid (GABA) agonists (zolpidem, zaleplon, eszopiclone, alprazolam, clonazepam and lorazepam for sleep and anxiety).
  - Other medications
- Other previous medications
- Concomitant medications for PSP (CMCAT = "PROGRESSIVE SUPRANUCLEAR PALSY MEDICATIONS") will be summarized by the same categories as previous medications for PSP.

- Other concomitant medications

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 failure.

For subjects who are randomized in the study, the number and percentage of subjects in each randomization disposition category (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. The treatment group differences in the percentage of subjects who discontinued for any reason as well as for each specific reason as the primary will be assessed using Fisher's exact test.

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 treatment group, ABBV-8E12 Overall, and Total Subjects. Duration of exposure is calculated as the last study drug administration date minus the first study drug administration date + 30. Total subject

years of exposure is calculated by summing the duration of exposure across all subjects and dividing this sum by 365 (1 year will be considered to be 365 days). The number and percentage of subjects who have taken a total of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 doses 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).

At each scheduled dosing visit, the investigator will document whether the subject has received the entire infusion and the volume administered will be recorded in the eCRF if the entire dose is not administered. The percentage of the assigned dose administered will be calculated at each visit. The mean of this percentage across infusions for each subject will be obtained. The descriptive statistics (number of non-missing observations, minimum, mean, median, standard deviation, maximum) based on each subject's mean volume percentage of study drug infusion will be summarized for each treatment group, ABBV-8E12 Overall and Total Subjects.

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 52 visit on the PSPRS total 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 52. The model will include fixed, categorical effects for treatment, site, visit, baseline score-by-visit and treatment-by-visit interactions, with continuous fixed

covariates for baseline score. The primary comparison will be the contrast between each ABBV-8E12 dose group and placebo group at Week 52. Contrasts between each ABBV-8E12 dose group and placebo at Weeks 12, 24, and 36 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. If this analysis fails to converge, compound symmetry (co)variance structures will be tested. 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 12, 24, 36, and 52): descriptive statistics (number of non-missing observations, mean, standard deviation, minimum and maximum) for each treatment group. LS mean and standard error within group will be presented for each treatment group. LS mean, standard error, 95% confidence interval and two-sided nominal *P* value 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 nominal *P* value of treatment difference comparing each ABBV-8E12 dose group with placebo across the treatment period will be included in the output as well.

In addition, a histogram will be generated to describe the proportion of subjects in each PSPRS response category for each treatment group. The 1-point interval response categories are defined based on PSPRS total score change from the baseline to final starting from the minimum to the maximum of the change score (e.g., …; $-5 <$ to ≤ -4; $-4 <$ to ≤ -3; $-3 <$ to ≤ -2; $-2 <$ to ≤ -1; $-1 <$ to ≤ 0; $0 <$ to ≤ 1; $1 <$ to ≤ 2; $2 <$ to ≤ 3; ….).

10.3 Secondary Efficacy Analyses

10.3.1 Analysis of Secondary Efficacy Variables

The secondary efficacy variables include change from baseline in the following score:

- Unified Parkinson's Disease Rating Scale (UPDRS) Part II score
- Clinical Global Impression of Change (CGI-C) score (the score itself indicate change)
- Midbrain atrophy measured by volumetric MRI change from baseline
- Schwab and England Activities of Daily Living Scale (SEADL) score
- Clinical Global Impression of Severity (CGI-S) score
- PSP Quality of Life (PSP-QoL) total, subscales and VAS scores
- PSPRS domain scores
- Regional atrophy measured by volumetric MRI – third ventricle, frontal lobes, superior cerebellar peduncle, brainstem, whole brain
- PSP Staging System (PSP-SS) (composite of dysphagia and gait items from PSPRS) score
- Time to loss of ability to walk independently as measured by PSPRS item 26, which is the Rx day of the first time when the post-baseline item 26 score is 3 or 4.

UPDRS Part II score, CGI-C score, SEADL score and the midbrain atrophy measured by volumetric MRI are key secondary efficacy variables, and the Week 52 contrasts for these variables for ABBV-8E12 doses vs placebo will be included in the multiplicity adjustment for the overall FWER control. Volumetric MRI atrophy variables (third ventricle, frontal lobes, superior cerebellar peduncle, brainstem, whole brain), PSP-QoL total score and subscale and VAS scores, PSPRS domain scores, CGI-S score, PSP-SS score and time to loss of ability to walk analysis (measured by PSPRS item 26) 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 52 for all secondary variables except time to loss of ability to walk independently as measured by PSPRS item 26. The model will include fixed, categorical effects for treatment, site, visit, baseline score-by-visit and treatment-by-visit interaction, with continuous fixed covariate for baseline score and the 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. For

CGI-C analysis, the dependent variable is the CGI-C score itself, baseline CGI-S score will be used in the MMRM model as a covariate and no baseline score-by-visit interaction in the model. For the volumetric MRI variables, the model will have a second covariate, a measure of head size (i.e., estimated pseudo total intracranial volume).

The following statistics will be presented on 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. LS mean and standard error within group 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 overall LS mean, standard error, 95% confidence interval and two-sided raw *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.

Responder analysis will be conducted for CGI-C variable. The responses of "Very much improved," "Much improved," "Minimally improved" and "No change" on the CGI-C will be defined as responders. Repeated measure analysis of responders over time on CGI-C responder status will be conducted using a generalized estimation equation (GEE) model with a logit link function to compare the probability of being a responder between each ABBV-8E12 dose and placebo. The model will include fixed, categorical effects for treatment, site, visit and treatment-by-visit interaction in the model using exchangeable working correlation structure. The odds ratio and corresponding 95% confidence interval will be provided for each ABBV-8E12 dose vs placebo at each visit. This responder analysis will not be included in multiplicity adjustment for FWER.

The time to loss of ability to walk independently as measured by PSPRS item 26 will be analyzed using log-rank test to compare median time to loss of ability to walk between placebo and ABBV-8E12 arms.

If both doses are statistically significant on the primary endpoint (PSPRS total score change from baseline at Week 52) after multiplicity adjustment, the contrast between pooled two ABBV-8E12 doses vs. placebo will also be obtained from the MMRM or GEE models for the primary and all secondary efficacy variables.

10.3.2 Analysis of Exploratory Efficacy Variables

The exploratory efficacy variables include the following:

- Natural History and Neuroprotection in Parkinson Plus Syndromes-Parkinson Plus Scale (NNIPPS-PPS) total score and dimensional scores
- Patient Global Impression of Change (PGI-C) score
- Letter Fluency Test (words per minute) score
- Repeatable Battery for Assessment of Neuropsychological Status (RBANS) total scale score and subtest scores
- Color Trails Test (Parts 1 and 2) completion time
- EuroQuality of Life (EQ-5D-3L) summary index score and VAS score
- Exploratory quantitative MRI measures including diffusion tensor imaging (DTI) derived fractional anisotropy (FA) and diffusivity measures [radial diffusivity (RD), mean diffusivity (MD), and axial diffusivity (AD)]

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 the last visit of these exploratory variables with the exception of PGI-C for which the dependent variable is the PGI-C score itself. The model will include fixed, categorical effects for treatment, site, visit and treatment-by-visit interaction, with continuous fixed covariate for baseline score and the baseline score-by-visit interaction in the model. There is no baseline score and baseline score-by-visit interaction in the MMRM model for PGI-C analysis. 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 on 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. LS mean and standard error within group will be presented for each treatment group. LS mean, standard error, 95% confidence interval and two-sided norminal *P* values of treatment difference comparing each ABBV-8E12 dose group with placebo will also be presented for each post-baseline visit. No multiplicity adjustment will be conducted for multiple comparisons of exploratory efficacy variables.

Responder analysis will be conducted for PGI-C variable. The responses of "Very much improved," "Much improved," "Minimally improved" and "No change" on the PGI-C will be defined as responders. Repeated measure analysis of responders over time on PGI-C responder status will be conducted using a GEE model with a logit link function to compare probability of being a responder between each ABBV-8E12 dose and placebo. The model will include fixed, categorical effects for treatment, site, visit and treatment-by-visit interaction using an exchangeable working correlation structure in the model. The odds ratio and corresponding 95% confidence interval will be provided for each dose group at each visit. This responder analysis will not be included in multiplicity adjustment for FWER.

10.4 Additional Efficacy Analysis

10.4.1 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 no more than 45 days after the last dose of study drug).

10.4.2 Combination of Sites with Fewer Than 2 Subjects per Treatment Group

When "site" is included as a factor in a statistical model for the interim or final analyses, Japan is considered as one site because randomization is stratified by country for Japan. In countries other than Japan, 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.

10.5 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 a total or domain score of an efficacy measure is calculated from a set of individual items, the total or domain score will be considered missing if any of the individual items are missing. When an average score is obtained from a set of individual items, it will be calculated from the non-missing items. Missing items will be imputed specifically for the following scales:

- UPDRS Part II: if no more than 15% of items are missing for an assessment, i.e., if 1 item has missing answer, the missing item will be imputed using the mean of non-missing items' scores for the assessment. If 2 or more items are missing for an assessment, the items' score will not be imputed and UPDRS Part II score is missing.
- NNIPPS-PPS:
  - Total score: if no more than 15% of all items are missing for an assessment, i.e., if less than or equal to 12 items are missing, each item score is imputed using the mean value of the same item from subjects of the same treatment group whose data are not missing for the item at the same visit. NNIPPS-PPS total score will be calculated based on this imputation but dimensional scores will not be calculated from this imputation. If more than 12 items of NNIPPS-PPS for an assessment for a subject are missing, then those items will not be imputed and the NNIPPS-PPS total score will be missing. Dimensional scores without any missing items will not be missing.
  - Dimensional score: if no more than 15% items for a dimension is missing, then each item score is imputed using the mean value of the same item from subjects of the same treatment group whose data are not missing for the item at the same visit. If more than 15% of all items for the dimension are missing, then those items will not be imputed and the dimensional score will be missing. After the imputation of this step, dimensional scores

will be calculated and used in dimensional score analysis, total score will not be calculated based on this imputation.

- PSP-QoL
  - Missing VAS score will not be imputed.
  - Total score: If no more than 15% of the 45 items, i.e., less than or equal to 6 items are missing for an assessment, each item score is imputed using the mean value of the same item from subjects of the same treatment group whose data are not missing for the item at the same visit. If more than 6 items of PSP-QoL for an assessment for a subject are missing, then those items will not be imputed and the PSP-QoL total score will be missing. After the imputation in this step, subscale scores won't be calculated and only the total score will be added up and used in total score analysis.
  - Subscale score: if no more than 15% of all items are missing in a subscale, each item score is imputed using the mean value of the same item from subjects of the same treatment group whose data are not missing for the item at the same visit. If more than 15% of all items for a subscale are missing, then those items will not be imputed and the subscale score will be missing. After the imputation of this step, subscale scores will be calculated and used in subscale score analysis, the total score will not be calculated based on this imputation.

Missing Visit Data

Before conducting any imputation of missing visit data, patterns of missing data for the primary endpoint PSPRS total score changes in placebo and two ABBV-8E12 arms will be assessed. Observed mean changes from baseline in PSPRS total score will be summarized over time for different missing patterns of longitudinal data (discontinued after Week 12 assessment, discontinued after Week 24 assessment, discontinued after Week 36 assessment, completer). Number and percentage of subjects for each missing pattern will be summarized as well.

10.5.1 Sensitivity analysis accounting for missing data

To evaluate robustness of the primary efficacy results on PSPRS total score changes from baseline, sensitivity analysis of PSPRS total score changes will be conducted using a multiple imputation (MI) assuming monotonic missing in this study. Sensitivity analysis will be conducted only if at least one ABBV-8E12 dose is statistically significant different from the placebo with multiplicity adjustment in the primary efficacy endpoint analysis.

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

1. Using Monte Carlo Markov Chain (MCMC) methodology from PROC MI to impute the intermittent missing data to achieve a monotone missing pattern by treatment group;
2. Impute missing data to create 20 complete datasets including observed completers and imputed data for PSPRS total score changes from baseline 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 multiple imputation (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 PSPRS total score missing data for different visits. To impute missing values for PSPRS total score for Visit X, variables included in the impute model are baseline PSPRS total score, PSPRS total score before discontinuation at Visit X, investigator site. 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 PSPRS total score needs satisfy the range requirement for the scale

(0 to 100). The MI will be implemented using PROC MI in SAS 9.4. In Step 3, SAS PROC MIANALYZE procedure will be used to combine MMRM analysis results based on 20 imputed datasets.

The following analysis results will be presented for the sensitivity analysis with multiple imputations: LS mean difference between ABBV-8E12 doses and placebo, standard error, 95% confidence interval of LS mean difference at Week 52 based on imputed data including observed data and p-values comparing ABBV-8E12 doses against placebo. Parameters based on imputed dataset will be combined estimation across 20 imputed datasets using Rubin's rules.

Tipping-point sensitivity analysis using multiple imputations to impute missing data will also be performed to evaluate robustness of primary analysis results for PSPRS total score changes from baseline if missing data deviate from the missing at random (MAR) assumption. A total of 20 imputed datasets will be generated using MI for each shift parameter. The shift parameter k indicates the percentage of treatment group difference (Δ) between ABBV-8E12 and placebo for PSPRS total score change obtained in the primary MMRM analysis that is not maintained for the MI sensitivity analysis. For each k, the imputation will be carried out by subtracting $k*\Delta$ from imputed missing data for those treated subjects in ABBV-8E12 groups after dropout. The imputation will be conducted with corresponding visit specific $k*\Delta$ for missing data after dropout. The values of k range from 0% to 100% or higher in 10% increments. The first value of k that reverses the study conclusion is considered the tipping point. The treatment group differences and associated p-values from tipping point analysis for each value of k will be presented.

The tipping point analysis will be conducted in the following steps:

1. Using Monte Carlo Markov Chain (MCMC) methodology from SAS PROC MI by treatment group to impute the intermittent missing data to a monotone missing pattern;

2. Using a standard multiple imputation approach from SAS PROC MI to impute data from monotone missing data;
3. For subjects who have missing data in the ABBV-8E12 groups, a shift which is equal to k*Δ will be subtracted for imputed values in Step 2 after the dropout, with k described in the above. For subjects in the placebo group, no shift will be performed for missing data after dropout;
4. Using MMRM model for the primary efficacy endpoint analysis to analyze the observed data along with the imputed data from Step 3 for PSPRS total score change from baseline;
5. Obtaining the overall results using PROC MIANALYZE for each shift parameter k using Rubin's rules.

The following analysis results will be presented by the shift parameter k for the tipping point analysis: LS mean difference between ABBV-8E12 doses and placebo, standard error, 95% confidence interval of LS mean difference at Week 52 based on imputed data including observed data and p-values comparing ABBV-8E12 doses against placebo.

10.6 Handling of Multiplicity

Pairwise comparisons between each ABBV-8E12 dose group and the placebo group will be performed with two-sided tests. Hochberg procedure[2] will be used for the efficacy analysis to handle multiplicity of comparisons between multiple ABBV-8E12 doses and placebo at the pre-specified significance level at the interim analysis ($\alpha = 0.00001$ at each futility interim analysis), which is described in the DMC Charter.

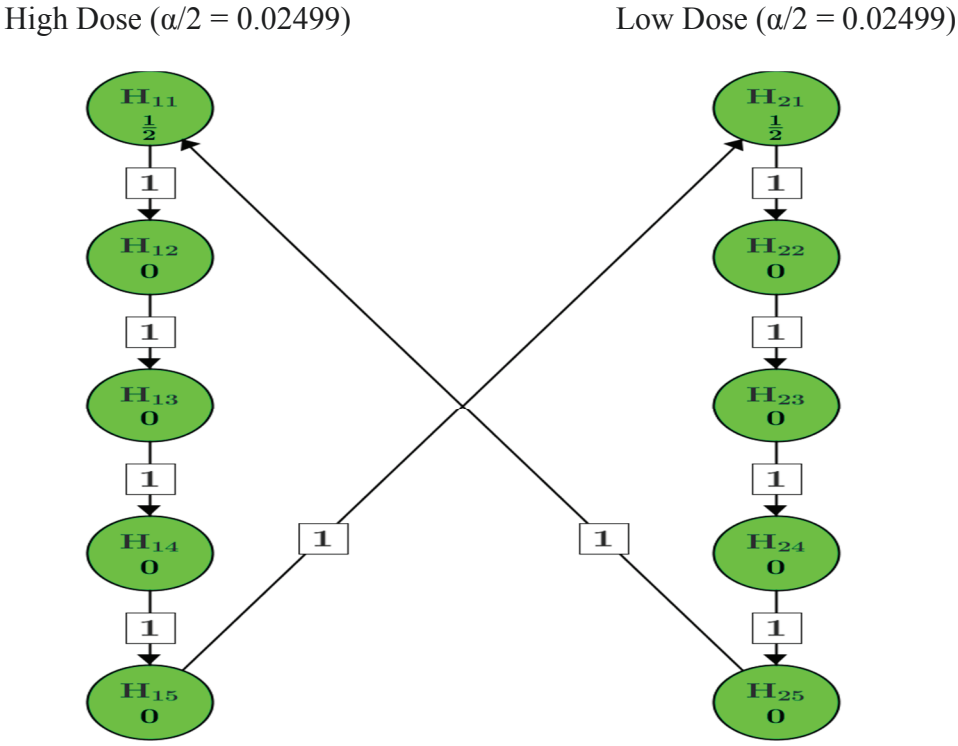
For the final analysis, a graphic approach[3] will be used to control overall family wise error rate due to multiple comparisons for primary and key secondary efficacy endpoints for multiple ABBV-8E12 doses. The overall α for the final analysis is 0.04998 after accounting for α spending at interim futility analyses. This α will be split equally between two dose groups to test the efficacy endpoints in the primary and key secondary families within each dose level at Week 52. The order of efficacy endpoints to be tested is PSPRS

total score change at Week 52, UPDRS-II score change at Week 52, CGI-C score at Week 52, midbrain atrophy measured by volumetric MRI change from baseline at Week 52, SEADL score change at Week 52 (Table 3). The primary endpoint will be tested first followed by the secondary endpoints and α could be propagated between two doses and two families of hypotheses testing based on the graphic approach (Figure 2). In the graph, the arrows specify the α transfer paths. Once an endpoint is rejected (i.e., deemed significant) at its assigned significance level, its significance level will be transferred to subsequent endpoint(s) following the arrow(s). If more than one arrow originates from an endpoint, the significance level for this endpoint (once rejected) will be split between multiple subsequent endpoints following the arrows. The numbers on the arrows denote the weights for transferring and (possibly) splitting significance levels. Specifically, the weight 1 denotes 100% transfer of significance level. The number underneath of each hypothesis is the original weight for α splitting assigned to the hypothesis. The overall type I error rate for this trial will be controlled at the two-sided 5% level. Nominal P values and multiplicity adjusted P values for all variables listed in Table 3 will be presented in a table.

Table 3. Hypotheses Testing Order in The Graphical Testing Approach

Efficacy Endpoints Family	Ordered Efficacy Endpoints	Hypotheses	
		The High Dose (4000 mg) vs. Placebo	The Low Dose (2000 mg) vs. Placebo
Primary family	PSPRS total score change from baseline at Week 52	H_{11}	H_{21}
Secondary family	UPDRS Part II score change from baseline at Week 52	H_{12}	H_{22}
	CGI-C score at Week 52	H_{13}	H_{23}
	Midbrain atrophy measured by volumetric MRI change from baseline at Week 52	H_{14}	H_{24}
	SEADL score change from baseline at Week 52	H_{15}	H_{25}

Figure 2. A graph for multiplicity adjustment of multiple hypotheses



10.7 Efficacy Subgroup Analysis

To examine whether gender, age group (≤ 65 vs > 65 year old), disease severity (≤ vs > median of PSPRS baseline total score which is rounded to the closest multiple of 5. E.g., if the median is 38.5 then the median cut off will be 40.), and geographical region (North America including US and Canada, European countries plus Australia, and Japan) have an impact on response to treatment, subgroup analyses on PSPRS total score will be conducted on change from baseline to final. Subgroup analyses will be performed using an ANCOVA model with the terms of treatment, subgroup variable, site (site nested within a region will be used for subgroup analysis by geographical region), 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. 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 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 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. Analysis of adverse events will also be conducted by geographical region (North America including US and Canada, European countries plus Australia, and Japan).

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

TEAE incidence will be summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs). The system organ classes will be presented in alphabetical order and the preferred terms will be presented in 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.

- 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" even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Severe" category. 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," even if the subject has another occurrence of the same event with a relationship present. The only exception is that if a subject has another occurrence of the same adverse event with a relationship assessment of "Reasonable Possibility of Being Related." In this case, the subject will be counted under the "Reasonable Possibility of Being Related." 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

The laboratory tests are described in the following table.

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, urinalysis, and vital sign variables.

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, chemistry and urinalysis 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. Shift tables will also be prepared by geographical region. 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 met the PCS criteria for that variable at any time during the study. PCS analysis for laboratory values will also be prepared by geographical region. No comparisons of treatment groups will be performed.

11.4 Analysis of Vital Signs and Weight

Vital sign variables include: diastolic blood pressure (DBP), systolic blood pressure (SBP) and pulse rate at supine and standing positions, orthostatic diastolic blood pressure, orthostatic systolic blood pressure, orthostatic pulse rate, and body temperature. The calculations of orthostatic vital sign values are:

- Orthostatic SBP (mmHg) = Standing SBP – Supine SBP
- Orthostatic DBP (mmHg) = Standing DBP – Supine DBP
- Orthostatic Pulse Rate (bpm) = Standing Pulse Rate – Supine Pulse Rate.

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 for each position of measurement. 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 each post-treatment visit will also be presented for vital sign 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 B. 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. PCS analysis for vital sign and weight will also be conducted by geographical region. 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 met the PCS criteria for that variable at any time during the study. PCS analysis for ECG values will also be conducted by geographical region. 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 Safety Parameters

CSF safety variables include RBC and WBC with differential, total protein, albumin, glucose and IgG. Analyses of mean change from baseline to Week 14 (Cohort 1 subjects only) and mean change from baseline to final double-blind value will be presented for each CSF safety 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.

11.6.3 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 the number and percentage of subjects pertaining cerebral edema, micro- and macro-haemorrhages, white matter hyperintensities (ARWMC score) across visits; number and percentage of subjects with presence and increasing severity of cerebral edema; number and percentage of subjects with new micro- and macro-haemorrhage lesions; number and percentage of subject with white matter hyperintensities change (ARWMC score) from previous time point. Descriptive statistics (mean, median, minimum, maximum) of number of new micro- and macro-hemorrhages or new lesions, as well as changes in ARWMC score in the double-blinded period will be presented.

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 fifth dose intervals is 336 hours and 672 hours, respectively. 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 (336 hours or 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 fifth 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 the 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 fifth 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 fifth 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 data of other subjects in the same treatment group who have values for the concentrations at the beginning of the fifth dose interval, the beginning of the fourth dose interval and the end of the fifth dose interval may be used to obtain a linear regression model for the concentration at the beginning of the fifth dose

interval, with the concentrations at the beginning of the fourth dose interval and the end of the fifth 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 (Cohort 1 and Cohort 2), summary statistics will be provided for each scheduled time of sampling with breakdown by dose level.

CSF concentration data after the fifth dose (for subjects in Cohort 1) 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 (Days 15, 29 and 85 plus Weeks 24 and 36) will be analyzed to investigate change in serum concentration over time. The data of Cohort 1 and Cohort J1 will also be included in this analysis except for Day 29. 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, geographical region (as identified in Section 10.7), classification by time, interaction of dose level and time and the interaction or region 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. If the statistic on the interaction of region and time is not significant at level 0.050, that term will be removed from the model. The concentration central value estimate versus time curves for the two dose levels will be plotted on the same graph, with the estimate of the central value for a dose level at a given time being the back transformation of the SAS least squares mean for the transformed data.

Dose Proportionality

Analyses to address the issue of dose proportionality will be performed on the combined data of Cohort 1 and Cohort J1. An analysis will be performed on each of dose normalized C_{max} and dose-normalized AUC for each of the first dose interval (2 weeks in length) and the dose interval beginning at Day 85 (4 weeks in length). 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 dose interval that begins at Day 85. Subjects will be classified by dose level and geographical region, and body weight will be a covariate. The initial model will include a term for the interaction of dose level and region, but this term will be removed from the model if the statistic for it is not significant at level 0.050. Other variables such as age and sex that might explain some of the variability among subjects will be considered. A necessary condition for such a variable to be included in the final model is that the regression coefficient be significant at level 0.100. 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 two doses (main effects for the two doses) will be tested. If the statistic on the interaction of dose level and region is significant at level 0.050, the test will be performed for each region separately within the framework of the final model.

Comparison of the Geographical Regions with Respect to Drug Exposure Variables

The data set for this analysis will be the same as that for the analysis to address the issue of dose proportionality. Because Cohort 1 and Cohort J1 have no data from Canada, European countries or Australia, the analysis provides a comparison of the Japan region to the North America region (US). The model will be the same as the final model for the analysis on dose proportionality with the one exception that body weight will not be included as a covariate. Assuming that the logarithmic transformation is employed, the estimates of the central values for the four combinations of region and dose level (on the original scale and without dose normalization) will be provided by exponentiation of the corresponding SAS least squares means, followed by multiplication of the respective dose levels.

Within the framework of the final model, the hypothesis of no difference between the means of the two regions (main effects for the two regions) will be tested. The estimate of the ratio of the central values (a composite value for the two dose levels) of the two regions will be provided by exponentiation of the difference of the SAS least squares means for the two regions. If the statistic on the interaction of dose level and region is significant at level 0.050, the test will be performed for each dose level separately within the framework of the final model, and the corresponding estimate of the ratio of region central values provided by exponentiation of the difference of least squares means for the two regions for the given dose level.

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 dataset 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 dataset 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.

Transformation of variables in order to avoid a meaningful degree of non-normality in the probability distributions is discussed in Section 12.3. 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 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.

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. A corresponding analysis will be performed on plasma total tau concentration and on other plasma tau variables for which data are reported. The observations will be classified by treatment and geographical region (as identified in Section 10.7). The initial model will have a term for the interaction of treatment and region. 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. The term for the interaction of treatment and region will be removed if the statistic for this term is not significant at level 0.050. Within the framework of the analysis of covariance model, the hypothesis of no difference between main effects of the higher ABBV-8E12 dose and placebo will be tested at significance level 0.05. If this hypothesis is rejected, the hypothesis of no difference between the lower ABBV-8E12 dose and placebo will then be tested at significance level 0.050. The SAS least squares means corresponding to the treatment main effects (a composite estimate for the three regions) will be provided. If the term for the interaction of treatment and region is retained in the final model, the testing procedure described for the main treatment effects will be carried out for each region, and the SAS least squares means will be provided for all the combinations of region and treatment.

For the analysis of a tau concentration variable, the conditions on the time that a sample is obtained in order for a measurement to be included in an analysis for a planned time are

given in the table below. If a measurement qualifies for more than one of the times, it will be used only for the time that is nearest the actual time of the sample (in terms of Rx Day).

Scheduled Time	Conditions on Time of Blood or CSF Sample
Week 12 (Cohort 1 and Cohort J1 only)	Rx Day 71 – 99, after at least four doses, between 21 and 35 days after the last previous dose
Week 14 (Cohort 1 and Cohort J1 only)	Rx Day 85 – 113, after at least four doses, between 7 and 21 days after the last previous dose
Week 24	Rx Day 141 – 197, after at least six doses, between 21 and 35 days after the last previous dose
Week 28	Rx Day 169 – 225, after at least seven doses, between 21 and 35 days after the last previous dose
Week 48	Rx Day 281 or later, after at least 10 doses, 21 to 35 days after the last previous dose administered
Week 52	Rx Day 281 or later, after at least 11 doses, 21 to 35 days after the last previous dose administered

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, estimates of central values on the original scale (back transformation of SAS least squares means) will be provided in place of the SAS least squares means referred to above. If the logarithmic transformation is used, the comparison of the treatments will be in terms of the ratio of central values.

If data are reported for CSF NFL concentration, serum or plasma NFL concentration, other continuous variables, or count variables that can be appropriately analyzed as a continuous variable (perhaps after transformation), then descriptive statistics will be provided and an analysis like that described for the tau concentration variables will be performed. If data for other types of variables are reported, appropriate descriptive statistics and analyses will be provided.

The association between the variables referred to here as biomarkers and measures of clinical efficacy will be explored.

14.0 Summary of Changes

There are some changes in the planned analyses from the protocol (original protocol, protocol Amendment 1, Amendment 2, Amendment 3, Amendment 4) to Statistical Analysis Plan version 1.0. The multiplicity adjustment method using Dunnet's test at interim analyses have changed to using Hochberg procedure in Amendment 3 and in the current SAP. Detailed multiplicity adjustment method is added in protocol Amendment 3 and is reflected in Section 10.6 for multiplicity method change in the SAP. The sample size increase from 180 (in protocols prior to Amendment 3) to 330 (Amendment 3) and including Japan in Study M15-562 are reflected in the current SAP. These changes are reflected in Section 4.3. Analysis of the primary efficacy variables and safety variables analysis by geographical region are included in Section 10.7 and Section 11.0 of the current SAP, respectively.

15.0 Reference List

1. "Basic Principles on Global Clinical Trials" (YAKUSHOKUSHINSA Notification No. 0928010 dated on September 28, 2007, issued by Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health Labour and Welfare).
2. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988;75(4):800-2.
3. Bretz F, Maurer W, Brannath W, et al. A graphical approach to sequentially rejective multiple test procedures. Stat Med. 2009;28(4):586-604.
4. Westfall PH, Krishen A. Optimally weighted, fixed-sequence, and gatekeeping multiple testing procedures. J Stat Plan Infer. 2001;99:25-40.

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

Note: 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
Orthostatic SBP (Hypotension) (mmHg)	Decrease of ≥ 30 in SBP (supine to standing)	NA
Orthostatic DBP (Hypotension) (mmHg)	Decrease of ≥ 20 in DBP (supine to standing)	NA
Orthostatic pulse (bpm)	NA	Increase ≥ 30 bpm (supine to standing)
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