1.0 Title Page

Clinical Study Protocol 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

Incorporating Administrative Changes 1 and 2 (US Only), Amendments 1, 2, 2.01 (US Only), 2.01.01 (US Only), 2.02 (Germany Only), 2.02.01 (Germany Only), 3, 3.01 (Germany Only), 3.02 (Japan Only), 4, and 5

AbbVie Investigational Product:	ABBV-8E12
Date:	13 December 2018
EudraCT Number:	2016-001635-12
Development Phase:	2
Study Design:	This is a Phase 2, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, tolerability, immunogenicity, and pharmacokinetics of repeated dose administration of ABBV-8E12 in subjects with progressive supranuclear palsy (PSP).
Investigators:	Multicenter Trial: Investigator Information is on file at AbbVie
Sponsor:	AbbVie
Sponsor/Emergency Contact:	[redacted] Medical Director Neuroscience Development AbbVie Inc. 1 N Waukegan Road [redacted] North Chicago, IL 60064 Phone: Fax: Mobile: [redacted] Email: [redacted]

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

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	06 July 2016
Amendment 1	18 August 2016
Amendment 2	31 October 2016
Administrative Change 1	12 May 2017
Amendment 2.01 (US Only)	27 June 2017
Administrative Change 2 (US Only)	20 March 2018
Amendment 2.01.01 (US Only)	27 March 2018
Amendment 2.02 (Germany Only)	21 August 2017
Amendment 2.02.01 (Germany Only)	27 October 2017
Amendment 3	26 January 2018
Amendment 3.01 (Germany Only)	30 January 2018
Amendment 3.02 (Japan Only)	22 February 2018
Amendment 4	19 October 2018

The purpose of this amendment is to:

- Update Section 5.3.1.1, Study Procedures, and Appendix C, Study Activities, to add Progressive Supranuclear Palsy (PSP) clinical features during the Screening Period.

  Rationale: *To gather more specific data regarding PSP signs and symptoms prior to enrollment in the trial.*

- Update Appendix C, Study Activities, to add telephone contacts at Weeks 12, 24, 36, and 52 for subjects who prematurely discontinue.

  Rationale: *To learn about the condition of subjects since their premature discontinuation from the study.*

Appendix B was revised to update the protocol signatories for this amendment.

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M15-562
Name of Study Drug: ABBV-8E12	**Phase of Development:** 2
Name of Active Ingredient: ABBV-8E12	**Date of Protocol Synopsis:** 13 December 2018
Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Multiple Dose Study to Assess Efficacy, Safety, Tolerability, and Pharmacokinetics of ABBV-8E12 in Progressive Supranuclear Palsy (PSP)	
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 (PK) 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) and plasma tau protein levels. • To assess the effect of ABBV-8E12 on potential CSF and plasma biomarkers of disease progression.	
Investigators: Multicenter	
Study Sites: Approximately 60 multinational sites.	
Study Population: Adult male and female subjects with possible or probable progressive supranuclear palsy who meet all the inclusion criteria and who do not meet any exclusion criteria.	
Number of Subjects to be Enrolled: Approximately 330	

Methodology:

The study will consist of a screening period of up to 8 weeks, a 52-week double-blind treatment period and a post-treatment follow-up period of approximately 20 weeks following the 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). At the end of the treatment period, eligible subjects who completed the 52-week treatment period may enter a separate LTE study for extended treatment. Upon completion of screening and baseline procedures, eligible subjects will be randomized to one of the 2 ABBV-8E12 dose arms (2000 mg or 4000 mg) or placebo in a 1:1:1 ratio.

The study will consist of 3 Cohorts.

Region	Cohort 1*	Cohort J1**	Cohort 2***
Global (not including Japan)	First 30 subjects enrolled[#]	NA	n = ~276
Japan	NA	First 9 subjects enrolled[#]	n = ~15

* Cohort 1: Augmented safety and PK assessments in the first 30 subjects enrolled into the global study from countries other than Japan.

** Cohort J1: Augmented safety and PK assessments in the first 9 subjects enrolled into the study from Japan.

*** Cohort 2: All other subjects enrolled in the global study not participating in Cohort 1 or Cohort J1.

\# Augmented safety and pharmacokinetic assessments 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 Data Monitoring Committee (DMC) will be performed in Cohort 1 and Cohort J1.

Eligible subjects will be enrolled into 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 at Day 15, and the third at Day 29. Thereafter, subjects will return to the study site every 28 days for their study drug infusion, blood collection, study procedures and assessments. Subjects will be observed on-site for at least 2 hours following each of the first 4 infusions of study drug and for at least 30 minutes after the end of infusion of all doses thereafter.

Subjects in Cohort J1 will be enrolled at least 2 days apart and will be confined for a minimum of 24 hours following their first infusion. Subjects will have another study visit to be assessed for safety 2 days after the first infusion. From the second to the fourth infusion, Cohort J1 subjects will be observed on-site for at least 2 hours following each infusion of study drug.

Subjects in Cohort 2 will be observed on-site for at least 2 hours following each of the first 4 infusions of study drug. Following the 4th infusion, all subjects in all cohorts will be observed on-site for at least 30 minutes after the end of the infusion.

This study will utilize a DMC consisting of at least 2 external clinicians, at least 1 external statistician, and at least 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.

Methodology (Continued):

Safety and tolerability will be monitored throughout the study, specifically including conditions associated with infusions in general, and infusion reactions. The first 39 subjects enrolled into the study will be represented as Cohort 1 (30 subjects) and Cohort J1 (9 subjects) in this protocol, while the subjects enrolled subsequently to Cohort 1 and Cohort J1 will be represented as Cohort 2. More frequent PK sampling and safety monitoring by the DMC will be conducted for Cohort 1 and Cohort J1 subjects.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion Criteria:

- Male or female subject with age 40 years or greater at the time of signed consent.
- Meets the following criteria for possible or probable progressive supranuclear palsy (Steele-Richardson-Olszewski Syndrome):
  - gradually progressive disorder, with age at disease onset greater than or equal to 40 years
  - either or both of the following two items are met:
    1. vertical supranuclear gaze palsy
    2. slowing of vertical saccades AND postural instability with falls within the first 3 years of PSP symptoms
- Presence of PSP symptoms for less than 5 years. For the purpose of this inclusion criterion, a PSP symptom will be defined as any neurological, cognitive or behavior symptom consistent with known symptoms of PSP, occurring newly and subsequently progressing during the clinical course in the absence of another identifiable cause.
- Subject is able to walk 5 steps with minimal assistance (stabilization of one arm or use of cane/walker).
- Subject has an identified, reliable, study partner (e.g., caregiver, family member, social worker, or friend), who has frequent contact with the subject (at least 10 hours per week) and who can accompany the subject to study visits to provide information as to the subject's functional abilities. The study partner has voluntarily signed the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved Informed Consent, prior to the conduct of any study procedures.

Main Exclusion Criteria:

- Male or female subject weighing less than 44 kg (97 lbs.) at screening will be excluded.
- Mini-Mental State Examination (MMSE) score less than 15 at screening, or cognitive impairment that in the Investigator's opinion would preclude collection of outcome measures.
- Any contraindication or inability to tolerate brain magnetic resonance imaging (MRI) (e.g., a pacemaker or any other implanted device or condition that would preclude proximity to a strong magnetic field).
- During enrollment of Cohort 1 and Cohort J1, any contraindication or inability to tolerate lumbar punctures (e.g., use of anticoagulant medications such as warfarin) are exclusionary. During enrollment of Cohort 2, subjects who are not able to undergo lumbar puncture may be admitted with permission of the AbbVie Medical Director, and these subjects will not be required to undergo lumbar puncture during the study.
- Subject resides at a skilled nursing or dementia care facility, or admission to such a facility is planned during the study period.

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

Main Exclusion (Continued):

- Evidence of any neurological disorder that could explain signs of PSP, including:
  - Signs of idiopathic Parkinson's disease (e.g., severe asymmetric parkinsonian signs, clinically significant tremor at rest, or prominent and sustained response to levodopa therapy)
  - Signs of multiple system atrophy (MSA) (e.g., prominent early cerebellar limb ataxia or unexplained symptomatic autonomic dysfunction)
  - Signs of Lewy body disease (e.g., hallucinations or delusions unrelated to dopaminergic therapy or other illness)
  - Probable Alzheimer disease according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria
  - History of repeated strokes with stepwise progression of parkinsonian features
  - History of major stroke
  - History of severe or repeated head injury
  - History of encephalitis
  - History of neuroleptic use (with the exception of clozapine or quetiapine) for a prolonged period of time or within the past 6 months
  - Oculogyric crises
  - Street-drug–related parkinsonism
  - Known history of autosomal dominant PSP due to a Microtubule Associated Protein Tau (*MAPT*) mutation
  - Known history of an autosomal dominant mutation associated with Frontotemporal Lobar Degeneration (FTLD) (e.g., an autosomal dominant mutation in *C9ORF72* or *GRN*)
  - Significant other neurological disease on MRI that could account for PSP symptoms
- Evidence of any clinically significant neurological disorder other than PSP, including but not limited to significant cerebrovascular abnormalities, vascular dementia, motor neuron disease or Amyotrophic Lateral Sclerosis (ALS), Huntington's disease, normal pressure hydrocephalus, brain tumor, seizure disorder, multiple sclerosis, or known structural brain abnormalities.
- The subject has a history of or currently has schizophrenia, schizoaffective disorder or bipolar disorder according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) or International Classification of Diseases (ICD)-10 criteria.
- Subject has had a significant illness or infection requiring medical intervention in the past 30 days.
- Any clinically significant hematological, autoimmune, endocrine, cardiovascular, neoplastic, renal, gastrointestinal, or other disorder that, in the Investigator's opinion, could interfere with the subject's participation in the study, place the subject at increased risk, or confound interpretation of study results.
- Any history of prior receipt of active immunotherapy directed against tau.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued): **Main Exclusion (Continued):** • Subject has received an investigational product (other than ABBV-8E12, also known as C_2N-8E12) within a time period equal to 5 half-lives, if known, or within 6 weeks (for small molecules) or 6 months (for monoclonal antibodies or other biologics) prior to study drug administration. • Current enrollment in another interventional clinical study involving a therapeutic agent. • Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive ABBV-8E12 or that the subject is unable or unlikely to comply with the dosing schedule or study evaluations.	
Investigational Product:	ABBV-8E12 (300 mg/15 mL)[#] ABBV-8E12 (1000 mg/10 mL) # Dosage formulation will not be used in Japan and Spain.
Doses:	Doses will be given at Day 1, Day 15, Day 29, and every 28 Days thereafter. Cohort 1 and Cohort J1: • Dose 1: 2000 mg • Dose 2: 4000 mg Cohort 2 (expanded enrollment): • Dose 1: 2000 mg • Dose 2: 4000 mg Doses may be decreased after the evaluation by the DMC of available safety, tolerability and PK data.
Mode of Administration:	Intravenous (IV) infusion
Reference Therapy:	Placebo (0.9% Sodium Chloride Injection/Solution for Infusion)
Doses:	Doses will be given at Day 1, Day 15, Day 29, and every 28 days thereafter.
Mode of Administration:	IV Infusion
Duration of Treatment: 52 Weeks	
Criteria for Evaluation: **Efficacy:** **Clinical and Cognitive Assessments:** **Primary:** • PSP Rating Scale (PSPRS) **Key Secondary:** • Unified Parkinson's Disease Rating Scale (UPDRS) Part II • Clinical Global Impression of Change (CGI-C) • Midbrain atrophy as measured by volumetric MRI • Schwab and England Activities of Daily Living Scale (SEADL)	

Criteria for Evaluation (Continued):

Efficacy (Continued):

Clinical and Cognitive Assessments (Continued):

Additional secondary:

- Clinical Global Impression of Severity (CGI-S)
- PSP Quality of Life Scale (PSP-QoL)
- PSPRS domain scores
- Volumetric MRI of third ventricle, whole brain, frontal lobes, superior cerebellar peduncle, and brainstem
- PSP Staging System (PSP-SS) (composite of dysphagia and gait items from PSPRS)
- Time to loss of ability to walk independently as measured by PSPRS item 26

Exploratory

- Natural History and Neuroprotection in Parkinson Plus Syndromes-Parkinson Plus Scale (NNIPPS-PPS) (not conducted in Japan)
- Patient Global Impression of Change (PGI-C)
- Letter fluency test (LFT) score
- Repeatable Battery for Assessment of Neuropsychological Status (RBANS)
- Color Trails Test (CTT) (Parts 1 and 2) score
- EuroQuality of Life (EQ-5D) index score and Visual Analog Scale (VAS)
- 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] to assess changes in pathophysiology
- Additional brain regions that are not listed under secondary assessments may be measured by volumetric MRI
- CSF and plasma tau and neurofilament (NFL) biomarkers

Pharmacokinetics:

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

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

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

The concentration of ABBV-8E12 in CSF will be summarized after the fifth dose and after the final dose if administered at least 3 months after the previous LP for subjects in Cohort 1 and Cohort J1, and after final dose for subjects in Cohort 2.

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

Criteria for Evaluation (Continued):

Immunogenicity:

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

Biomarkers:

CSF and Plasma Biomarkers:

- Tau and NFL in CSF and plasma
- Additional exploratory CSF and plasma-based pharmacodynamics (PD) analyses may be conducted based on sample availability

Imaging Biomarkers:

- Regional and/or whole brain volume derived from MRI
- Fractional anisotropy and diffusivity measures in brain regions of interest derived from diffusion tensor imaging

Safety:

Adverse events (AE) and serious adverse events (SAE) will be monitored throughout the dosing period and for at least 20 weeks after the last dose. Safety evaluations will include the following: monitoring of adverse events (including infusion and allergic reactions), vital signs, physical examination, complete neurologic exam, cognitive assessments, Columbia-Suicide Severity Rating Scale (C-SSRS), laboratory abnormalities, electrocardiogram (ECG), brain magnetic resonance imaging (MRI) including fluid attenuated inversion recovery (FLAIR), and immunogenicity as determined by anti-drug antibody responses in blood.

Statistical Methods:

Efficacy:

The efficacy variables will be the change from baseline to Week 52 for each efficacy assessment. The primary efficacy variable is the change on the PSPRS total score from baseline to Week 52. The primary analysis is to compare each ABBV-8E12 dose group with placebo for all subjects in the study (including subjects in Cohort 1, Cohort J1, and Cohort 2) using a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the PSPRS total score change from baseline for each post-baseline observation using all observed data. The model will include fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with a continuous fixed covariate for baseline PSPRS total score. The primary comparison will be the contrast between each ABBV-8E12 dose group and placebo at the Week 52 Visit using a graphic approach to control for multiplicity for primary and key secondary variables across 2 ABBV-8E12 doses. The treatment group differences at earlier visits will be assessed as the secondary. An unstructured (co)variance structure will be used to model the within-subject errors. Satterthwaite's approximation will be used to estimate denominator degrees of freedom, and the Type III sum-of-squares for the Least Square (LS) means will be used to estimate treatment group differences. This MMRM analysis will be applied to each efficacy variable with repeated measurements.

Statistical Methods (Continued):

Pharmacokinetic:

The change in serum concentration across time will be considered in an analysis of C_{trough} data, with the logarithmic transformation used if appropriate. The pre-infusion concentration data for Days 15, 29 and 85, plus Weeks 24 and 36 will be analyzed with a MMRM model. For measures of exposure, an analysis of covariance will be performed on dose normalized parameters of Cohort 1 and Cohort J1. It is anticipated that the logarithmic transformation will be employed. Subjects will be classified by dose level and region, and the initial model will contain an effect for the interaction of dose level and region. Body weight will be a covariate. The model may have other covariates. The hypothesis of dose proportionality will be tested within the framework of the model.

Population pharmacokinetic analyses will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (version VII, or higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies and Cohort 1 and Cohort J1 of this study. Apparent CL and apparent volume of distribution (V) of ABBV-8E12 will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis.

CSF concentration data after the fifth dose (for subjects in Cohort 1 and Cohort J1) and the final dose will be summarized by dose level.

Immunogenicity:

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

Biomarker:

An ANCOVA model will be used to evaluate CSF concentrations for total tau, free tau, and NFL for each scheduled time of evaluation during treatment. Corresponding analyses on plasma measurements of total tau and NFL will be performed. The observations will be classified by treatment and region, and the initial model will have an effect for the interaction of treatment and region. The baseline value for total tau and free tau 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. Within the framework of the analysis of covariance the means of the three treatments (with adjustment for baseline) will be estimated. The hypothesis of no difference between the higher ABBV-8E12 dose and placebo will be tested at significance level 0.050. If this hypothesis is rejected, the hypothesis on no difference between the lower ABBV-8E12 dose and placebo will then be tested at significance level 0.050.

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 data for other variables are reported, descriptive statistics will be provided and appropriate analyses performed.

Statistical Methods (Continued):

Safety:

Adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting treatment-emergent adverse events will be tabulated by MedDRA System Organ Class (SOC) and Preferred Term with a breakdown by treatment group. Tabulations will also be provided by rating of severity (mild, moderate, and severe) and by whether possibly related to study drug. The number and percent of subjects experiencing treatment-emergent serious adverse events (including deaths) and adverse events leading to premature discontinuation of the study drug will be tabulated according to the MedDRA SOC and preferred term by treatment group. Treatment group differences between each ABBV-8E12 dose group and placebo will be analyzed by Fisher's exact test. Differences between each ABBV-8E12 treatment group and placebo for mean laboratory, vital signs and ECG variables will be analyzed by a one-way analysis of variance (ANOVA) with treatment as the main effect. The number and percentage of laboratory test values and measurements on vital signs that are potentially clinically significant, according to predefined criteria, will be tabulated as well. Proportion of subjects who have suicidal behavior, suicidal ideation only, and suicidal behavior or ideation from the C-SSRS assessment will be summarized by treatment group.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

AD	Alzheimer's Disease
ADA	Anti-Drug-Antibody
AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AP	Atypical Parkinsonism
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATEMS	AbbVie Temperature Excursion Management System
AUC	Area Under the Concentration Time Curve
B12	Cobalamin
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBD	Corticobasal Degeneration
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CL	Clearance
C_{max}	Maximum Observed Serum Concentration
CO_2	Carbon Dioxide
COMT	Catechol-O-Methyltransferase
CPK	Creatine Phosphokinase
CPPM	Clinical Pharmacology and Pharmacometrics
CRA	Clinical Research Associate
CRF	Case Report Form
CS	Clinically Significant
CSF	Cerebrospinal Fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events

C_{trough}	Observed serum drug concentration at the end of a dose interval
CTT	Color Trails Test
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSS	Data and Statistical Sciences
DTI	Diffusion Tensor Imaging
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EQ-5D	EuroQol-5D
ERAC	Exposure-Response Analysis Center
FA	Fractional Anisotropy
Fc	Fragment Crystallizable
FLAIR	Fluid Attenuated Inversion Recovery
FSH	Follicle-Stimulating Hormone
FTLD	Frontotemporal Lobar Degeneration
GABA	Gamma-Aminobutyric Acid
GAM	Generalized Additive Method
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GRN	Progranulin
HbsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HCV Ab	Hepatitis C Virus Antibody
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICD	International Classification of Diseases
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgG4	Subclass of IgG Antibody
IMP	Investigational Medicinal Product

IND	Investigational New Drug Application
INR	International Normalized Ratio
IP	Intraperitoneal
IRB	Institutional Review Board
IRC	Internal Review Committee
ITT	Intent-to-Treat
IU/L	International Units/Liter
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IV	Intravenous
IVR/IWB	Interactive Voice-Response/Interactive Web-Based (system)
k_D	Dissociation Constant
LAR	Legally Authorized Representative
LFT	Letter Fluency Test
LLN	Lower Limit of Normal
LP	Lumbar Puncture
LS	Least Square
LTE	Long-term Extension
MAPT	Microtubule Associated Protein Tau
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MD	Mean Diffusivity
MedDRA	Medical Dictionary for Regulatory Activities
MMA	Methylmalonic Acid
MMRM	Mixed-effect Model Repeated-Measures
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
MSA	Multiple System Atrophy
NCS	Not Clinically Significant
NFL	Neurofilament
NFTs	Neurofibrillary Tangles
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NINDS-SPSP	National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy

NNIPPS-PPS	Natural History and Neuroprotection in Parkinson Plus Syndromes-Parkinson Plus Scale
NOAEL	No Observed Adverse Effect Level
PCR	Polymerase Chain Reaction
PCS	Potentially Clinically Significant
PD	Pharmacodynamics
PGI-C	Patient Global Impression of Change
PIN	Personal Identification Number
PK	Pharmacokinetic
PPS	Pharmacovigilance and Patient Safety
PR	Measure of the time between the start of the P wave and the end of the R wave in the heart's electrical cycle
PRN	As Needed
PSP	Progressive Supranuclear Palsy
PSP-QoL	Progressive Supranuclear Palsy Health Related Quality of Life Scale
PSPRS	Progressive Supranuclear Palsy Rating Scale
PSP-SS	PSP Staging System
PT	Prothrombin Time
PT/INR	Prothrombin Time/International Normalized Ratio
PTT	Partial Thromboplastin Time
QRS	Measure of the time between the start of the Q wave and the end of the S wave in the heart's electrical cycle
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
QTc	Corrected QT
QTcF	QT corrected for heart rate using Fridericia's Method
RA	Regulatory Affairs
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
RBC	Red Blood Cell count
RD	Radial Diffusivity
RNA	Ribonucleic acid
RSI	Reference Safety Information
SAD	Single-Ascending Dose
SAP	Statistical Analysis Plan
SDAC	Statistical and Data Analysis Center

SAE	Serious Adverse Event
SEADL	Schwab and England Activities of Daily Living Scale
SmPC	Summary of Product Characteristics
SNRIs	Serotonin-Norepinephrine Reuptake Inhibitors
SOC	System Organ Class
SSRIs	Selective Serotonin Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reactions
SV1	Screening Visit 1
SV2	Screening Visit 2
T4	Thyroxine
TA MD	Therapeutic Area Medical Director
TEAE	Treatment-Emergent Adverse Event
TIA	Transient Ischemic Attack
T_{max}	Peak Time
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States
V	Volume of distribution
VAS	Visual Analog Scale
WBC	White Blood Cell count
WHO	World Health Organization
WOCBP	Women of Childbearing Potential
WPM	Words Per Minute

Definition of Terms

Visit Window	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. Refer to Section 5.3.2.1 for acceptable PK and ADA windows.
Study Drug Infusion	Study drug will be administered at Day 1, Day 15, Day 29, and every 28 Days thereafter
Scale Order	Certain scales follow a pre-defined order of administration. Refer to Table 7 for recommended sequence.

Study Drug Infusion Visit	A Study Drug Infusion Visit (i.e., defined as a study visit when study drug is administered) is deemed complete when all assessments per the Study Activities Table (Appendix C) are complete. The visit may be completed over 2 consecutive days, with the second day to include the start and end of the infusion.

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3.0 Introduction

Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP, also known as Steele-Richardson-Olszewski Syndrome) is a progressive neurodegenerative disorder, with an estimated annual incidence of 5 – 7 per 100,000.[1] Within the United States (US), the disease affects approximately 20,000 individuals. There is no apparent geographical, ethnic, gender, or racial disparity in PSP frequency. PSP can initially present with clinical symptoms similar to other brain disorders, including idiopathic Parkinson's disease. For this reason, correct diagnosis of PSP is sometimes delayed, often taking place 1 to 3 years after the initial onset of clinical symptoms. Symptom onset is most often between the ages of 50 to 70 years, and although the clinical course is variable, the typical survival from time of symptom onset is 5 to 9 years.[2] Though some heterogeneity in clinical presentation exists, the most common and initially described PSP syndrome, now referred to as Steele-Richardson-Olszewski Syndrome, presents with symptoms including prominent postural instability and axial rigidity leading to falls, supranuclear gaze palsy causing range of vision impairment, frontal-subcortical cognitive impairment, and dysphagia leading to aspiration. The course of disease is progressive and uniformly fatal.[3]

Pathologically, PSP is characterized by the abnormal accumulation of hyperphosphorylated, insoluble aggregates of tau protein in neurons and glia in the brainstem, cerebellum, basal ganglia, and cerebral cortex.[3] The degree and distribution of tau aggregation in PSP is strongly correlated with PSP symptomatology during life.[4] The National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy (NINDS-SPSP) research criteria which describe Steele-Richardson-Olszewski Syndrome are highly predictive of underlying PSP pathology.[5] Neuronal loss in various regions of the brain accompanies neurofibrillary tangles (NFTs) that are composed of tau aggregates. Multiple neurotransmitter abnormalities arise as well, including those affecting specific dopaminergic, cholinergic, GABAergic, and noradrenergic systems.

There are no currently approved treatments for PSP.[6] The negative outcomes of therapeutic efficacy studies in PSP preclude recommending an evidence-based standard therapy.[7] In the absence of any effective disease modifying or neuroprotective therapies, PSP represents an urgent unmet medical need.

ABBV-8E12

ABBV-8E12 is a humanized monoclonal subclass of the IgG antibody (IgG4) against human microtubule-associated protein tau. It is a recombinant glycoprotein produced in Chinese hamster ovary cells. It targets soluble extracellular tau in the brain, which has been implicated in the development and spreading of tau pathology. Neurofibrillary tangles, a characteristic pathologic feature in PSP and several other neurological disorders including corticobasal degeneration (CBD) and Alzheimer's disease (AD), are formed inside of neurons by aggregated and post-translationally modified tau. Based on preclinical evidence, ABBV-8E12 may be able to block soluble tau aggregates, or seeds, from propagating between cells, and thereby decrease the spreading of tau pathology in neurodegenerative disorders associated with tau.

Preclinical Efficacy

In preclinical studies, the mouse version of the antibody (HJ8.5) was found to specifically block tau seeding activity from brain lysates of P301S transgenic mice in vitro.[8] The P301S animal is a transgenic mouse model that carries a mutated human tau gene that leads to early onset frontotemporal dementia in humans. In vivo, 3 months of treatment with HJ8.5 as a continuous intracerebroventricular infusion was associated with potent reductions in tau pathology, as evidenced by biochemical, histopathological, and functional/behavioral measures. A similar study to assess the effects of peripherally (intraperitoneal, IP) administered HJ8.5, found that weekly IP injections of HJ8.5 was highly effective at reducing insoluble tau in the brain, reducing cortical and hippocampal atrophy, and improving sensorimotor function.[9]

Nonclinical Safety

ABBV-8E12 binds to human tau but not to tau protein from preclinical toxicology species (i.e., rhesus/cynomolgus monkey, canine, rabbit, rat or mouse). Therefore, there is no pharmacologically relevant species in which to conduct toxicology studies to support safety of ABBV-8E12. To assess toxicity in non-relevant species, a 4-week study in wild-type mice was conducted at doses up to 250 mg/kg for 4 weeks via weekly intravenous (IV) injections. There were no adverse effects at any dose level and the no observed adverse event level (NOAEL) was 250 mg/kg. Based on predictions from the 2.5 and 7.5 mg/kg groups in the single ascending dose (SAD) study, this is predicted to provide a margin of 1.4-fold over projected exposures at the highest dose of 4000 mg planned in this study.

A detailed discussion of the preclinical toxicology and pharmacology can be found in the Investigator's Brochure (IB).[10]

Clinical Experience

Prior to this study, treatment with ABBV-8E12 was initiated under an Expanded Access Investigational New Drug (IND) in the US for one patient with PSP, and subsequently treatment with ABBV-8E12 was initiated for one patient with CBD under a single named trial application in Germany.

The PSP patient received 20 monthly infusions (highest dose 25 mg/kg for the last 7 infusions), then died from PSP complications unrelated to study drug. The CBD patient received 3 monthly infusions (1 at 7.5 mg/kg, 2 at 15 mg/kg), but died due to suicide 10 days after the second 15 mg/kg infusion. The CBD patient had a strong history of suicidal ideation and premeditation that preceded compassionate treatment with ABBV-8E12. No evidence of imaging abnormalities or other evidence of drug-related toxicity was detected in these 2 patients.

Single Dose Study

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

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

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

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

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

3.1 Differences Statement

Study M15-562 Phase 2 study is the first randomized, placebo controlled clinical trial to evaluate efficacy, safety, tolerability, and pharmacokinetics (PK) of multiple doses of ABBV-8E12 in subjects with PSP. The study features enhanced PK and safety assessments in Cohort 1, Cohort J1 and all subjects will be enrolled for an extended treatment period of up to 52 weeks. The initial Phase 1 clinical study (Study C_2N-8E12-WW-104) is a randomized, double-blind, placebo controlled, SAD study in PSP patients at doses ranging from 2.5 mg/kg to 50 mg/kg and the results of the study indicate that ABBV-8E12 is generally well tolerated up to the highest tested dose of 50 mg/kg without notable treatment-related adverse effects or any clinically concerning safety findings.

3.2 Benefits and Risks

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

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

ABBV-8E12 recognizes human tau and does not bind to tau from other species. Off-target toxicity of ABBV-8E12, up to 250 mg/kg/week, was assessed in a 4-week mouse toxicity study. No adverse effects at any dose level were detected. Evidence of efficacy demonstrated in preclinical studies and safety data from clinical studies obtained to date provide a strong rationale for continuing assessment of safety and efficacy in the current study.

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

4.0 Study Objective

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

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

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 around the world. Approximately 330 subjects will participate in the study.

At the end of the treatment period, eligible subjects who completed the 52 week treatment period may enter a separate LTE study for extended treatment. All activities for the LTE study will be outlined in a separate extension study protocol.

Eligible subjects will be enrolled into 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 at Day 15, and the third at Day 29; thereafter, subjects will return to the study site every 28 Days for their study drug infusion, blood collection, study procedures and assessments as outlined in the Study Activities Table (Appendix C). This dosing schedule (with one additional dose delivered at Day 15) will enable rapid attainment of steady-state drug levels in plasma to maximize the likelihood of demonstrating a treatment effect. Subjects will be observed on-site for at least 2 hours following each of the first 4 infusions of study drug and for at least 30 minutes after the end of infusion of all doses thereafter.

Refer to Section 5.5.1 for details on infusion times.

Approximately 330 subjects with PSP matching the selection criteria described in Section 5.2, will be eligible to enter the study double-blind treatment period. 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. Doses will be administered via IV infusion at Day 1,

Day 15, Day 29, and every 28 days thereafter through dose 14 at Week 48. Refer to Section 5.5.1 for details on infusion times.

Safety and tolerability will be monitored throughout the study.

The study will consist of 3 Cohorts (Table 1).

Table 1. Description of Cohorts

Region	Cohort 1*	Cohort J1**	Cohort 2***
Global (not including Japan)	First 30 subjects enrolled#	NA	n = ~276
Japan	NA	First 9 subjects enrolled#	n = ~15

* Cohort 1: Augmented safety and PK assessments in the first 30 subjects enrolled into the global study from countries other than Japan.

** Cohort J1: Augmented safety and PK assessments in the first 9 subjects enrolled into the study from Japan.

*** Cohort 2: All other subjects enrolled in the global study not participating in Cohort 1 or Cohort J1.

Augmented safety and pharmacokinetic assessments 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 Data Monitoring Committee (DMC) will be performed in Cohort 1 and Cohort J1.

Eligible subjects will be enrolled into 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 the third on Day 29; thereafter, subjects will return to the study site every 28 Days for their study drug infusion, blood collection, study procedures and assessments as outlined in the Study Activities Table (Appendix C). This dosing schedule (with one additional dose delivered at Day 15) will enable rapid attainment of steady-state drug levels in plasma to maximize the likelihood of demonstrating a treatment effect. Subjects will be observed on-site for at least 2 hours following each of the first 4 infusions of study drug and for at least 30 minutes after the end of infusion of all doses thereafter. Subjects randomized in Cohort 1 and Cohort J1 will return to the study site on Day 5, Day 15, Day 89, Day 99, and Day 113 for collection of additional safety assessments and PK samples listed in Table 4 (Safety and PK Procedures for Cohort 1 and Cohort J1).

Subjects in Cohort J1 will be confined for a minimum of 24 hours following their first infusion. For subjects expecting to be discharged on the second day (Day 2), the Investigator will assess safety to determine discharge. Subjects will have another study visit 2 days after the first infusion (Day 3), either while in the hospital or as an outpatient to assess safety. From their second to fourth infusion, Cohort J1 subjects will be observed on-site for at least 2 hours following each infusion of study drug.

Subjects in Cohort 2 will be observed on site for at least 2 hours following each of the first 4 infusions of study drug. Following the 4th infusion, all subjects will be observed on-site for at least 30 minutes after the end of infusion of all doses (Table 2).

Investigators will monitor for AEs, including conditions associated with infusions in general, and infusion reactions. Subjects experiencing AEs, including infusion reactions, may need to be observed for longer periods and undergo additional assessments at the Investigator's discretion.

Additionally, subjects enrolled in Cohort J1 (first 9 subjects) will be randomized at least 2 days apart from each other. During this 2-day interval the Investigator will assess for clinically relevant adverse events. In this context, the term "clinically relevant" adverse events refers to severe or life threatening adverse events potentially related to study drug, for example: infusion-related allergic or hypersensitivity reactions, or neurologic AEs such as a seizure. AbbVie will confirm that the Investigator has reviewed the safety of the most recently enrolled subject into Cohort J1, and will ensure the safety of the product prior to allowing the next subject to be randomized into Cohort J1.

In Japan, sites must contact AbbVie prior to randomizing any subject into Cohort J1 and AbbVie will notify sites when Cohort J1 is fully enrolled. A DMC meeting will occur to review the safety of subjects enrolled in Cohort J1, and only after the DMC has recommended to continue enrollment into the study without modification, will Japanese subjects be enrolled into Cohort 2. Henceforth, no further restriction to randomization will apply.

Table 2. Safety Observation Period Following Infusions

Cohort	Infusion 1	Infusions 2, 3, and 4	Infusion 5 and Onwards
Cohort 1*	Observed on-site for at least 2 hours	Observed on-site for at least 2 hours	Observed on site for at least 30 minutes
Cohort J1	Confined for a minimum of 24 hours and safety confirmation 2 days post 1st infusion	Observed on-site for at least 2 hours	Observed on site for at least 30 minutes
Cohort 2	Observed on-site for at least 2 hours	Observed on-site for at least 2 hours	Observed on site for at least 30 minutes

* Cohort 1: The first 30 subjects enrolled into the global study from countries other than Japan.

DMC Review of Interim Safety Data

This study will utilize a DMC consisting of at least 2 external clinicians, at least 1 external statistician, and at least 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.

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 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. The dataset reviewed will include 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.

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 has recommended to continue enrollment into the study without modification, will Japanese subjects be enrolled into Cohort 2.

Additional DMC reviews of available safety data will occur after a total of approximately 80, 130, 180, 240, and 330 subjects are randomized and every 6 months thereafter until the study has completed. Ad hoc meetings may occur as needed.

Doses may be decreased after the evaluation by the DMC of available safety, tolerability and PK data.

Long-Term Extension Study:

If ABBV-8E12 is safe and well tolerated in the current study, a long-term extension study will be developed and implemented under a separate protocol.

Post-Treatment Follow-Up:

All subjects who would not enter the separate long-term extension study for extended treatment (including subjects who prematurely discontinue from treatment, or would decline to participate in or would not qualify for the long-term extension study) will enter the Post-treatment Follow-up Period within this study.

A schematic of the study design is shown in Figure 1. A table of sample size and dosing groups is provided in Table 3.

Figure 1. Study Schematic

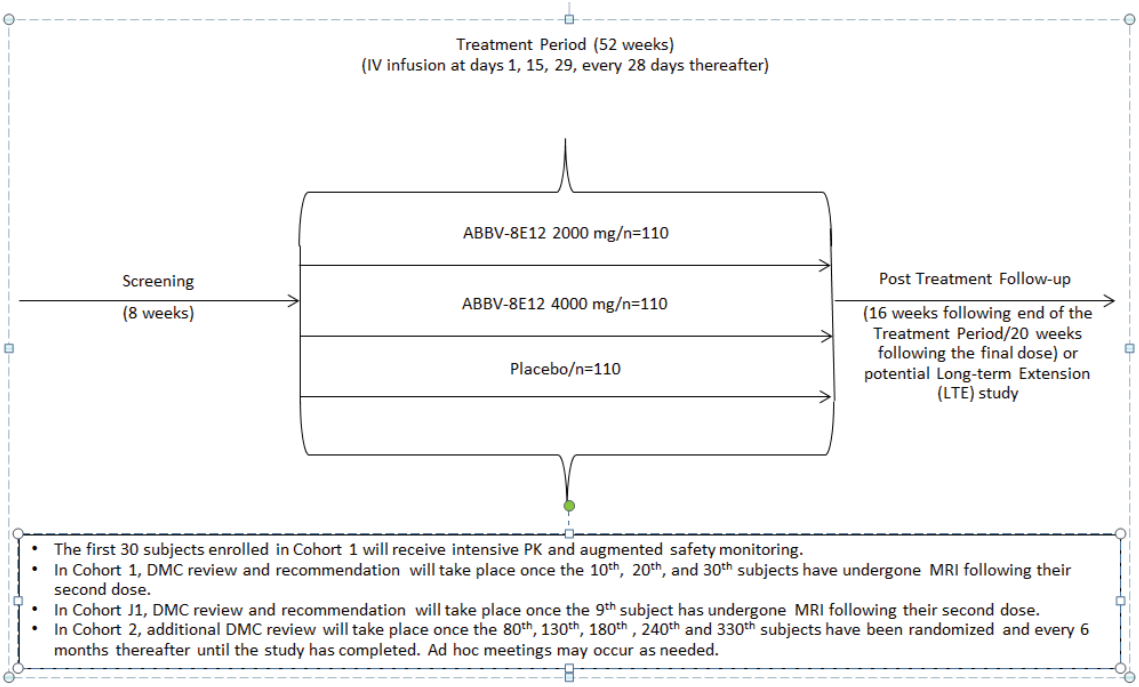


Table 3. Sample Size

Treatment Group	N = 330	Treatment Duration
Placebo	n = 110	IV infusion on Day 1, Day 15, Day 29, and then every 28 days for 52 weeks (Total of 14 infusions)
ABBV-8E12 2000 mg	n = 110	
ABBV-8E12 4000 mg	n = 110	

Safety and PK procedures for Cohort 1 and Cohort J1 are presented in Table 4.

Table 4. Safety and PK Procedures for Cohort 1 and Cohort J1

	Screening		Cohort 1 and Cohort J1, Doses 1 – 6										
	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										

This table describes the frequency of safety and PK procedures for Cohort 1and Cohort J1 through Day 113. Refer to Appendix C for complete list of required study procedures at each visit.

Table 4. Safety and PK Procedures for Cohort 1 and Cohort J1 (Continued)

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

a. 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).
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.

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

This study was designed to randomize approximately 330 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects have been randomized, there is a possibility that additional subjects in screening will not be randomized.

5.2 Selection of Study Population

Subjects will undergo screening procedures within 8 weeks prior to initial study drug administration. Adult male and female subjects who meet the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

Subjects who have signed informed consent and did not randomize because they did not complete the study-specific procedures during the Screening Period or did not meet all entry criteria will be considered Screen Failures. The reason(s) for screen failure will be

recorded in the source documents and will be captured in the electronic case report form (eCRF). Subjects who screen fail may be re-screened on a case-by-case basis after consulting the AbbVie Therapeutic Area Medical Director (TA MD) for approval.

Prior to enrolling a subject into Cohort J1, the Investigator/study staff must contact AbbVie to obtain approval. AbbVie will notify sites when Cohort J1 has been fully enrolled and will also notify sites when enrollment into Cohort 2 for Japanese subjects may commence.

5.2.1 Inclusion Criteria

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

1. Subject must be able to understand the nature of the study and has had the opportunity to have any questions answered. The subject has voluntarily signed the Independent Ethics Committee (IEC)/Independent Review Board (IRB) approved Informed Consent, prior to the conduct of any study procedures (including any changes occurring in the subject's current therapeutic regimen). In the absence of subject's ability to provide the informed consent, the informed consent must have been signed by a person who has the legal right to act on behalf of the subject following national laws. In Germany, where the subject's legally authorized representative (LAR) is not permitted to sign the IEC/IRB approved Informed Consent form on behalf of the subject, evaluation by an independent psychiatrist will be sought if the investigator who is evaluating the subject for inclusion in the study doubts the subject's cognitive ability to independently provide informed consent.
2. Male or female subject with age 40 years or greater at the time of signed consent.
3. Meets the following criteria for possible or probable PSP (Steele-Richardson-Olszewski Syndrome):
    - gradually progressive disorder, with age at disease onset greater than or equal to 40 years

- either or both of the following two items are met: (Refer to Section 5.3.1.1, Neurological Examination, for a description of assessment techniques):
    1. vertical supranuclear gaze palsy
    2. slowing of vertical saccades AND postural instability with falls within the first 3 years of PSP symptoms

4. Presence of PSP symptoms for less than 5 years. For the purpose of this inclusion criterion, a PSP symptom will be defined as any neurological, cognitive or behavior symptom consistent with known symptoms of PSP, occurring newly and subsequently progressing during the clinical course in the absence of another identifiable cause.
5. Subject is able to walk 5 steps with minimal assistance (stabilization of one arm or use of cane/walker).
6. Subject has an identified, reliable, study partner (e.g., caregiver, family member, social worker, or friend), who has frequent contact with the subject (at least 10 hours per week) and who can accompany the subject to study visits to provide information as to the subject's functional abilities. The study partner has voluntarily signed the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved Informed Consent, prior to the conduct of any study procedures.
7. If female, the subject may not be pregnant or breastfeeding.
8. If female and of non-childbearing potential, the subject must be either postmenopausal (defined as age $\geq$ 55 years with no menses for 12 or more months without an alternative medical cause) or permanently surgically sterile (bi-lateral oophorectomy, bilateral salpingectomy or hysterectomy). If female and of childbearing potential, the subject must agree to practice at least one of the following methods of birth control throughout the study and for 20 weeks after study completion:
    - Total abstinence from intercourse;

- Vasectomized partner(s);
- Intrauterine device (IUD);
- Using oral, injected,* or implanted* methods of hormonal contraceptives (oral, parenteral or transdermal) for at least 3 months prior to randomization and the partner should also use a barrier method (e.g., condom) with spermicidal* foam/gel/film/cream/suppository during this study and for 20 weeks after study completion.

9. All female subjects of childbearing potential must have negative result of a serum pregnancy test performed at screening and a negative urine pregnancy test result is required prior to any radiological procedures.

10. If male and sexually active with female partner(s) of childbearing potential, subject must agree, from Study Day 1 through 20 weeks after the last dose of study drug, to practice the protocol specified contraception (Refer to Section 5.2.4).

* Not approved in Japan.

Rationale for the Inclusion Criteria

1	In accordance with the harmonized Good Clinical Practice (GCP)
2 – 7	To select subject population appropriate for this study
8 – 10	The effects of ABBV-8E12 on pregnancy are currently unknown

5.2.2 Exclusion Criteria

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

1. Male or female subject weighing less than 44 kg (97 lbs.) at screening will be excluded.

2. Mini-Mental State Examination (MMSE) score less than 15 at screening, or cognitive impairment that in the Investigator's opinion would preclude collection of outcome measures. In Germany, for all subjects with an MMSE score of 24 or less

at the time of study entry, an evaluation by an independent psychiatrist will also be requested. If, in the opinion of the independent psychiatrist, subject is unable to provide consent independently, the subject will not be enrolled in the study.

3. Any contraindication or inability to tolerate brain MRIs (e.g., a pacemaker or any other implanted device or condition that would preclude proximity to a strong magnetic field).
4. During enrollment of Cohort 1 and Cohort J1, any contraindication or inability to tolerate lumbar punctures (LP) (e.g., use of anticoagulant medications such as warfarin) are exclusionary. During enrollment of Cohort 2, 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.
5. Subject resides at a skilled nursing or dementia care facility, or admission to such a facility is planned during the study period.
6. Evidence of any neurological disorder that could explain signs of PSP, including:
   a. Signs of idiopathic Parkinson's disease (e.g., severe asymmetric parkinsonian signs, clinically significant tremor at rest, or prominent and sustained response to levodopa therapy)
   b. Signs of multiple system atrophy (MSA) (e.g., prominent early cerebellar limb ataxia or unexplained symptomatic autonomic dysfunction)
   c. Signs of Lewy body disease (e.g., hallucinations or delusions unrelated to dopaminergic therapy or other illness)
   d. Probable Alzheimer's disease according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria
   e. History of repeated strokes with stepwise progression of parkinsonian features
   f. History of major stroke
   g. History of severe or repeated head injury
   h. History of encephalitis

i. History of neuroleptic use (with the exception of clozapine or quetiapine) for a prolonged period of time or within the past 6 months

j. Oculogyric crises

k. Street-drug-related parkinsonism

l. Known history of autosomal dominant PSP due to a microtubule associated protein tau *(MAPT)* mutation

m. Known history of an autosomal dominant mutation associated with frontotemporal lobar degeneration (FTLD) (e.g., an autosomal dominant mutation in *C90RF72* or *GRN*)

n. Significant other neurological disease on MRI that could account for PSP symptoms

7. Evidence of any clinically significant neurological disorder other than PSP, including but not limited to significant cerebrovascular abnormalities, vascular dementia, motor neuron disease or amyotrophic lateral sclerosis (ALS), Huntington's disease, normal pressure hydrocephalus, brain tumor, seizure disorder, multiple sclerosis, or known structural brain abnormalities.

8. The subject has a history of or currently has schizophrenia, schizoaffective disorder or bipolar disorder according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) or International Classification of Diseases (ICD)-10 criteria.

9. In the opinion of the investigator, the subject has any clinically significant uncontrolled psychiatric illness.

10. Subject has significant current suicidal ideation within one year prior to screening as evidenced by answering "yes" to questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) completed at screening or a history of suicidal attempts within the last 2 years.

11. Positive screen for drugs of abuse or marijuana at screening visit.

12. Current diagnosis or history of drug or alcohol abuse (by DSM-V criteria) within 24 months prior to screening visit.
13. Subject has had a significant illness or infection requiring medical intervention in the past 30 days.
14. Subject has a positive test result for hepatitis B surface antigen (HbsAg) or hepatitis C virus antibody (HCV Ab), or a known history of Human Immunodeficiency Virus (HIV) infection.
15. The subject has a history or evidence of a malignancy within the 2 years prior to the screening visit. Subjects with some indolent malignancies (e.g., basal cell carcinoma or squamous cell carcinoma of the skin) may be permitted to enroll with the permission of the AbbVie Medical Director.
16. Subject has had a myocardial infarction, advanced chronic heart failure, unstable angina, stroke, transient ischemic attack (TIA), clinically significant conduction abnormalities, or required intervention for any of these conditions (e.g., coronary artery bypass graft, percutaneous coronary intervention via cardiac catheterization, or thrombolytic therapy), within 1 year of screening.
17. Any clinically significant hematological, autoimmune, endocrine, cardiovascular, neoplastic, renal, gastrointestinal, or other disorder that, in the Investigator's opinion, could interfere with the subject's participation in the study, place the subject at increased risk, or confound interpretation of study results.
18. Subject has a planned major surgical procedure scheduled during the period when the subject would be participating in this study. The subject may subsequently be considered for the study following full recuperation from the surgical procedure.
19. History of serious adverse reaction to ABBV-8E12 or other monoclonal antibodies or biologics.
20. Subject has received an investigational product (other than ABBV-8E12, also known as C_2N 8E12) within a time period equal to 5 half-lives, if known, or within

6 weeks (for small molecules) or 6 months (for monoclonal antibodies or other biologics) prior to study drug administration.

21. Subject is using any exclusionary medications as defined in Section 5.2.3.1.
22. Subject has any history of prior receipt of active immunotherapy directed against tau.
23. Current enrollment in another interventional clinical study involving a therapeutic agent.
24. Male subject who is considering fathering a child or donating sperm during the study or for approximately 20 weeks after the last dose of study drug.
25. Subject considered by the investigator, for any reason, an unsuitable candidate to receive ABBV-8E12 or unable or unlikely to comply with the dosing schedule or study evaluations.

Rationale for Exclusion Criteria

1, 2, 5 – 17, 22, 25	These criteria were selected to ensure the appropriate subject population
3, 4, 18, 23	To ensure the safety of the subjects
19 – 21	These products may interfere with the pharmacokinetics of the study drug
24	The effects of ABBV-8E12 on pregnancy are currently unknown

5.2.3 Prior and Concomitant Therapy

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

All allowable concomitant medications must be at a stable dose for at least 30 days prior to the subject's screening visit, and it is anticipated that no change in dose will be required during the study treatment period. All medications should remain at stable doses for the duration of the study unless a change in regimen is medically necessary. All concomitant medications, including any change in dose must be recorded with the reason for use, dates of administration, dosages and frequency in the eCRF.

Permitted medications include the following:

- Ramelteon, trazodone, amitriptyline and mirtazapine for sleep.
- Selective benzodiazepines and gamma-aminobutyric acid (GABA) agonists, zolpidem, zaleplon, eszopiclone, alprazolam, clonazepam and lorazepam for sleep and anxiety.
- Selective neuroleptics, clozapine or quetiapine for the treatment of psychotic symptoms.
- Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), buspirone, mirtazapine or trazodone for anxiety or depression.
- Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) or memantine for cognitive impairment.
- Medications for Parkinsonian symptoms (including levodopa/carbidopa, dopamine agonists, monoamine oxidase inhibitors, Catechol-O-Methyltransferase (COMT) inhibitors, or amantadine).

5.2.3.1 Prohibited Therapy

Unless approved by the Investigator in consultation with the Sponsor, subjects should not receive the following medications (not a comprehensive list) described in Table 5.

Table 5. Prohibited Medications

Anticoagulants (Exclusionary for Lumbar Puncture)
Examples
Vitamin K antagonists
Dabigatran
Enoxaparin sodium
Rivaroxaban
Apixaban
Heparin
Neuroleptics*: Prohibited within 30 days prior to screening and throughout the duration of the study
Examples
Chlorpromazine
Fluphenazine
Loxapine
Perphenazine
Thioridazine
Thiothixene
Trifluoperazine
Haloperidol
Benzodiazepines/Gamma-Aminobutyric Acid (GABA) agonists*: Prohibited within 30 days prior to screening and throughout the duration of the study, such as:
Examples
Chlordiazepoxide
Diazepam
Midazolam
Flurazepam
Temazepam
Meprobamate
Triazolam

* Excluding the selected compounds mentioned in Section 5.2.3.

Additional recommendations are the following:

Drugs commonly known to cause excessive sedation, orthostatic hypotension or increased risk for falls should be avoided, if possible.

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

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

5.2.4 Contraception Recommendations and Pregnancy Testing

If female, subject must be either postmenopausal defined as:

- Age > 55 years with no menses for 12 or more months without an alternative medical cause.
- Age < 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 40 IU/L.

  OR

- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

  OR

- Practicing at least one of the following methods of birth control, for at least 3 months prior to randomization through at least 20 weeks after the last dose of study drug:
  - Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal,* transdermal*) associated with the inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
  - Progestogen-only hormonal contraception (oral, injectable,* implantable*) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
  - Bilateral tubal occlusion/ligation.
  - Vasectomized partner(s) and is the sole sexual partner of the woman of childbearing potential (WOCBP) trial participant.
  - IUD.
  - Intrauterine hormone-releasing system (IUS).
  - Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 1 month prior to Study Day 1.
  - Male or female condom with or without spermicide.
  - Cap, diaphragm or sponge with spermicide.*
  - A combination of male condom with cap, diaphragm or sponge with spermicide* (double barrier method).
  - True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

* Not approved in Japan.

If male, subject must be surgically sterile (vasectomy with medical assessment confirming surgical success) or have a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), OR if sexually active with female partner(s) of childbearing potential must agree from Study Day 1 through 20 weeks after the last dose of study drug to practice contraception with:

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

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

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

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

5.3.1.1 Study Procedures

Identification of Study Partner

To be eligible for screening, each subject must have an identified, reliable, study partner (e.g., caregiver, family member, social worker, or friend), who has frequent contact with the subject (at least 10 hours per week) and who will accompany the subject to study visits to provide information as to the subject's functional abilities. In the exceptional case the study partner is not available to accompany the subject to a visit he/she may provide the information regarding subject's functional abilities by telephone. The designated study partner must be sufficiently familiar with the subject (as determined by

the investigator) to provide accurate data and be willing to be the study partner for the duration of the study. The site investigator must consider the study partner to be able to perform all of these functions. The site must obtain the name and contact information of the study partner and the source documents must record the study partner's consent to satisfy the responsibility of the study partner in this study.

Medical History

For all subjects, a complete medical history, including subject's history of PSP and any medications taken for symptoms related to PSP, will be obtained at screening. In addition, history of alcohol and tobacco use will be obtained from each subject. The medical history will be updated on Day 1. The updated medical history on Day 1 will serve as the baseline for clinical assessment.

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

PSP Clinical Features[32]

A detailed assessment of PSP signs and symptoms present at Screening will be collected and include the following:

- Ocular motor dysfunction
- Postural instability
- Akinesia
- Cognitive dysfunction

Physical Examination

Physical examinations will be performed as indicated in the Schedule of Study Activities in Appendix C. A symptom-directed physical examination will be performed when necessary. The physical examination performed on Day 1 prior to the first dose will serve

as the baseline physical examination for clinical assessment. Any significant physical examination findings after dosing will be recorded as adverse events.

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

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

Vital Signs

Body temperature and measurements for orthostatic vital signs assessment will be obtained at the times indicated in the Schedule of Study Activities in Appendix C. All systolic and diastolic blood pressure and pulse rate measurements are to be measured while the subject is supine (after 3 to 5 minutes) followed by measurements while standing (after 2 minutes). Study staff should make efforts to measure with the same arm and method, including recording of the arm and method in the subject's source documentation.

The vital signs measurements just prior to dosing on Study Day 1 will serve as the baseline measurements for clinical assessment.

For visits in which both vital signs and blood sample(s) are collected, vital signs should be obtained prior to any blood collection.

Urine Screens for Drugs of Abuse

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

opiates for pain control, any subjects testing positive during the study will be considered for premature discontinuation in consultation with the AbbVie Medical Director.

Hepatitis Screen

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

Neurological Examination

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

The neurological examination will assess:

- Mental Status – assessment of orientation, speech, and memory
- Cranial nerves – assessment of cranial nerves II-XII. This will include an assessment of supranuclear gaze palsy and slowing of vertical saccades
    - Vertical supranuclear palsy will be established by neurological examination demonstrating a greater than 50% limitation of the range of voluntary gaze in the vertical plane, which is overcome by reflexive vestibular stimulation
    - Slowing of vertical saccades may be assessed by either of the two following methods:
        - Slowing of vertical saccades may be established by neurological examination of saccades toward a target held greater than 20 degrees from the position of primary gaze in the vertical plane. Slowing of vertical saccades will be defined as present when ocular movement is slow enough for the examiner to see its progress, rather than just its

initial and final positions. A delay in initiation of saccades is not considered slowing.

- Slowing of vertical saccades may be established using quantitative measurements of saccades, such as infrared oculography of adequate spatial and temporal resolution to resolve multiple saccades.

- Motor system – brief assessment of tone and strength, tremors
- Sensory system – brief assessment of light touch and temperature sensation
- Reflexes – assessment of deep tendon reflexes and plantar responses (Babinski sign)
- Coordination – assessment of upper and lower extremities, including assessment for tremor
- Gait – assessment of tandem gait (if clinically indicated and safe)
- Station – assessment of posture and stability as defined by the following:
  - If clinically indicated and safe, postural instability may be assessed by determining the impairment of postural reflexes on neurological examination (i.e., retropulsion with or without unaided recovery after a backward pull) in the absence of any other medical cause to explain this impairment (e.g., primary sensory deficit, vestibular dysfunction, pontine infarction, cerebellar syndrome, prominent upper or lower motor neuron signs).

12-Lead Electrocardiogram (ECG)

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

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

Local ECG Reading:

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

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

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

Central ECG Reading:

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

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

ECGs will be collected as single ECGs as follows:

Cohort 1 and Cohort J1 Subjects:

- **Screening**
  - May be done at any time during the visit.
- **Day 1 (Dose 1)**
  - Pre-dose (just prior to pre-infusion PK sample collection and the start of infusion) and within 15 minutes after the end of infusion prior to the PK sample collection
- **Day 5**
  - Collection should be scheduled as close as possible to the corresponding time of the post infusion collection on Day 1.
- **Day 15 (Dose 2)**
  - Pre-dose (just prior to the start of infusion) and within 15 minutes after the end of infusion prior to the PK sample collection
- **Days 29 and 57 (Doses 3 and 4)**
  - Pre-dose (just prior to the start of infusion)
- **Day 85 (Dose 5)**
  - Pre-dose (just prior to the start of infusion) and within 15 minutes after the end of infusion (prior to the PK sample collection)
- **Weeks 24 and 36 (Doses 8 and 11)**
  - Pre-dose (just prior to the start of infusion)
- **Week 52: (Study Completion/Premature Discontinuation Visit)**
  - May be done at any time during the visit.
- **Week 60: (Post-Treatment Follow-up Visit)**
  - May be done at any time during the visit.

Cohort 2 Subjects:

- **Screening**
  - May be done at any time during the visit.
- **Days 1, 29, 57, 85, and Weeks 24, and 36 (Doses 1, 3, 4, 5, 8, and 11)**
  - Pre-dose (just prior to the start of infusion)
- **Week 52 (Study Completion/Premature Discontinuation Visit)**
  - May be done at any time during the visit.
- **Week 60 (Post-Treatment Follow-up Visit)**
  - May be done at any time during the visit.

Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 6 at the time points designated in the Table 4 (Safety and PK Procedures for Cohort 1 and Cohort J1) and Study Activities Table (Appendix C).

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

Table 6. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Bands (if detected) Lymphocytes Monocytes Basophils (if detected) Eosinophils (if detected) Platelet count (estimate not acceptable)[a] Mean corpuscular volume (MCV) Mean corpuscular hemoglobin concentration (MCHC) Prothrombin time (PT) Activated partial thromboplastin time (aPTT)[b] PT/INR (Prothrombin Time/International Normalized Ratio)[b]	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 Thyroid Stimulating Hormone (TSH)[c] Thyroxine (T4)[c] Vitamin B12 (cobalamin)[c] Pregnancy test[d]	Specific gravity Ketones pH Protein Glucose Blood Urine pregnancy test[e,f] Microscopic examination, if dipstick results are positive
		CSF Basic Labs[f]
		RBC, WBC with differential Total Protein Albumin Glucose
		Reference Tests if Vitamin B12 is Under the Lower Limit of Normal Range
		Methylmalonic Acid (MMA) Homocysteine[c]
		Hepatitis[c]
		HbsAg HCV Ab -Any positive HCV Ab test must be confirmed by a positive Hepatitis-C Viral RNA (polymerase chain reaction [PCR]) Qualitative test for HCV

a. Platelet count results to be reviewed by investigator before the LP.

b. Coagulation results to be reviewed by the investigator before the LP.

c. Screening Visit only.

d. For all females of child-bearing potential; a serum pregnancy test will be performed at the screening visit and Premature Discontinuation.

e. For all females of child-bearing potential; a negative urine pregnancy test result is required prior to any radiological procedures.

f. To be done at local laboratory. If local laboratory is unable to perform, samples may be sent to the Central Laboratory for analyses of Total Protein, Albumin, and Glucose only.

Abnormal Findings

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

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

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

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

Magnetic Resonance Imaging (MRI)

For all subjects, a Magnetic Resonance Imaging (MRI) of the brain will be obtained at time points indicated in the Study Activities Table (Appendix C) and interpreted by a radiologist or neurologist. The subjects will be positioned supine on the MRI bed and their head will be positioned within a head coil with appropriate foam padding to decrease movement during the scan and to standardize the orientation of the head. The subjects will then be positioned within the MRI scanner for imaging. The screening MRI should

be completed after all other relevant screening procedures (except LP) have been completed and reviewed by the investigator.

The screening MRI assessment will be used to rule out the presence of any intracranial masses that might preclude the subject from undergoing a lumbar puncture, and exclude focal or diffuse processes that could indicate a clinically significant neurologic disorder other than PSP, including signal abnormalities on fluid attenuated inversion recovery (FLAIR) or T2 weighted images consistent with infectious, vascular, neoplastic or other degenerative processes. The 3D T1 weighted sequences will also be acquired for volumetric analysis that will enable a quantitative assessment of whole brain volume and regional brain volume.

All or a subset of the following brain MRI imaging sequence types will be performed:

- T1 weighted
- Diffusion weighted imaging
- T2 weighted FLAIR
- PD/T2 weighted
- T2* weighted
- Diffusion tensor imaging

The above listed imaging sequences may be adapted, sequences may be dropped or additional imaging sequences may be included based on feasibility. The duration of each imaging session is not expected to exceed 60 minutes. Details of the MRI procedures will be described in the MRI Procedures Manual provided by the Sponsor. The 3D T1 weighted sequences will also be acquired for volumetric analysis that will enable a quantitative assessment of whole brain volume and regional brain volume.

Scans at all protocol-required time points, including at screening, that are of poor quality (e.g., due to subject motion during the scan, inadequate coverage of the brain, improper positioning of the head, use of incorrect scan or geometry parameters or noisy image) as determined by the MRI technologist at the imaging center or reviewing radiologist or

Sponsor will be repeated at the earliest possible time but within 15 days of the protocol-required time point to obtain a scan of good quality.

On-treatment MRIs will be performed at the time points indicated in the Study Activities Table (Appendix C). The time window for the MRI procedure at each protocol-required time point is ±7 days.

Sedation is not recommended but is allowed. Subjects who might need sedation should discuss this with the principal investigator prior to the imaging procedure. 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.

The MRI technician is responsible for performing brain MRI scans at all protocol-required time points.

Lumbar Puncture (LP)

For all subjects, LPs to collect cerebrospinal fluid (CSF) will be performed at time points indicated in the Study Activities Table (Appendix C).

Subjects in Cohort 1 and Cohort J1 will undergo a LP at the following time points:

- Screening – To be done after all other entry criteria have been satisfied.
- Day 99
- Premature Discontinuation or Week 52 (Completion Visit/Premature Discontinuation) – if at least 3 months after the previous LP.

Subjects in Cohort 2 will undergo a LP at the following time points.

- Screening – To be done after all other entry criteria have been satisfied.
- Premature Discontinuation or Week 52 (Completion/Premature Discontinuation Visit) – if at least 3 months after the previous LP.

A sample of CSF will be collected according to the Collection and Processing of CSF Samples manual provided to the study site by the Sponsor. If sampling is not successful or is standard of care for the institution, other methods including CT/fluoro guided or ultrasound guided lumbar puncture can be used at the discretion of the local clinical site staff. CSF clinical labs will be analyzed locally at the applicable clinical site after each lumbar puncture/CSF collection. These measures include cell counts (red blood cell [RBC] and white blood cell [WBC] with differential), total protein, albumin, and glucose (Refer to Table 6 for Clinical Laboratory Tests). If the local laboratory is unable to perform some of the CSF measurements, samples may be sent to the Central Laboratory for analyses of Total Protein, Albumin, and Glucose only. Other CSF measurements (e.g., ABBV-8E12 concentration, tau and other exploratory biomarkers) will be analyzed by the applicable designated laboratory or at AbbVie.

Cohort 2 subjects who are not able to undergo a LP may be enrolled with permission of the AbbVie Medical Director without the requirement of a LP during the study.

Headaches may occur following withdrawal of CSF. Subjects may be treated with the following: IV hydration, IV caffeine administration, bed-rest and analgesics. Uncommonly a blood patch (injection of some of the subject's blood to patch the CSF leak) may be needed. Potential but rare risks of lumbar puncture include infection, damage to nerves in the back, and bleeding into the CSF space. The risk of these is much less than 1%.[11] Institutional policy and investigator discretion should be followed to provide the appropriate post-lumbar puncture observation period, and to provide information to the patient on possible side effects and limitations on strenuous physical activity and driving.

Diagnostic Tools and Rating Scales

Prior to the start of the study, designated raters will be certified in the use of all scales used in this study. The objective of this certification/training is to establish uniformity across sites in the administration, interpretation and scoring of these rating instruments. Raters who cannot participate in pre-study certification/training or raters who become

involved in the study after training at the investigator's meeting will not be permitted to perform any study-specified ratings until they have satisfactorily completed an individualized certification/training program designed by the central trainers, approved by AbbVie and supervised by the investigator or his/her designee. It is the responsibility of the investigator to ensure that the raters at his/her site are appropriately trained and certified in the use of selected rating scales. Every effort must be made by the investigative sites to ensure that each subject is rated by the same rater for each scale throughout their participation in the study.

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

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

Assessments will be performed at the times indicated in Table 7.

Table 7. Diagnostic Tools and Scale Order and Duration of Administration

Diagnostic Tools and Scales[a,b]	Approx. Duration (min.)	Patient (P)/ Study Partner (SP)	Screening Days –56 to –8		Week 0 Day 1[c]	Week 8 Day 57	Week 12 Day 85	Week 20 Day 141	Week 24 Day 169	Week 32 Day 225	Week 36 Day 253	Week 48 Day 337	Completion/ Premature Discontinuation Week 52
			Visit 1	Visit 2									
PSPRS	10	P and SP	1		1		1		1		1		1
CGI-S	40 – 60	P and SP	2	5	2	5	2	5	2	5	2	5	2
CGI-C	1	P and SP				6	3	6	3	6	3	6	3
SEADL	5 – 10	P	3		3		4		4		4		4
UPDRS Part II	10	P	4		4		5		5		5		5
RBANS	25	P		1		1		1		1		1	
CTT (Parts 1 & 2)	5 – 10	P		2		2		2		2		2	
Letter Fluency Test (wpm)	1	P		3		3		3		3		3	
NNIPPS-PPS*	30 – 45	P and SP		4		4		4		4		4	
MMSE[d]	10 – 15	P	X										
PGI-C[e]	1 – 2	P					X		X		X		X
PSP-QoL[e]	30	P	X		X		X		X		X		X
EuroQoL-5D (EQ-5D)[e]	8	P		X		X		X		X		X	
C-SSRS[e,f]	< 5	P	X	X	X	X	X	X	X	X	X	X	X

Table 7. Diagnostic Tools and Scale Order and Duration of Administration (Continued)

CTT = Color Trails Test; WPM = words per minute

* NNIPPS will not be administered in Japan.

a. Numbering listed in the table provides a pre-defined order of administration that should occur during each visit.

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

c. Assess prior to randomization and the first dose of study drug.

d. MMSE will be administered during Screening to assess inclusion criteria only.

e. Scale may be administered/assessed at any time during the visit with the exception of the scheduled infusion time.

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

The diagnostic tools and rating scales include the following:

PSP Rating Scale (PSPRS)[12] (Primary Endpoint)

The 28-item PSPRS was initially constructed in 1992 by Golbe in consultation with numerous colleagues, and was developed over a 10-year period. Content validity was established by interviewing patients who met the published diagnostic criteria for PSP, typically every 3 – 4 months. Patient and study partner together were asked to assign a value to each PSP item. When the patient did not concur with study partner observations, the interviewer encouraged discussion between the two parties and assigned a value to that particular item using clinical judgment. Study data for patients were collected from baseline through study completion, or participant death. Only the data of patients who presented with PSP symptoms and who subsequently developed PSP were included in the psychometric analysis. All interviewed patients were taking medication for PSP-related symptoms. However, the PSPRS has been widely used in clinical studies.[7,13-15]

The PSPRS contains 28 items comprised of 6 domains: daily activities (7 items), mentation (4 items), bulbar (2 items), ocular motor (4 items), limb motor (6 items), and gait/midline (5 items). Six items are graded 0 to 2 and 22 items are graded 0 to 4. The PSPRS total score is the sum of item scores and ranges from 0 to 100. It is administered to the subject and the Study Partner by a clinician and takes approximately 10 minutes to complete, as reported in Table 7.

Schwab and England Activities of Daily Living Scale (SEADL)[16] (Secondary Endpoint)

The SEADL scale will be used as a means of assessing the subject's ability to perform daily activities. The Schwab England Activities of Daily Living (SEADL) scale was developed by Schwab and England in 1957 and consists of ten items intended to evaluate the daily life activities of a patient. The SEADL is composed of two sections: the first is a self-report questionnaire in which patients grade their own daily life activities, such as dressing, using the toilet, resting, eating, and social activities (subjective assessment), and the second is an assessment of motor functions, such as postural balance, speaking, rigidity, and tremors, conducted by a clinician (objective assessment). It is a percentage

scale divided into deciles, and the results are reported between 0% (bedridden) and 100% (healthy). It is administered to the subject by a clinician and takes approximately 5 – 10 minutes to complete, as reported in Table 7.

Unified Parkinson's Disease Rating Scale (UPDRS) (Secondary Endpoint)

The Unified Parkinson's Disease Rating Scale (UPDRS)[17] is an Investigator-used rating tool to follow the longitudinal course of Parkinson's disease. The UPDRS assessment will be performed by an approved, trained rater. To be qualified by the Sponsor and the rater vendor, all raters must have participated in the Rater Training and have a current, valid Rater Certificate.

The UPDRS is made up of the following sections:

- Part I – Mentation, Behavior, and Mood
- *Part II – Activities of Daily Living
- Part III – Motor Examination
- Part IV – Complications of Therapy (including dyskinesias)
- Part V – Modified Hoehn and Yahr Staging

* Only Part II will be administered in this study.

It is administered to the subject by a clinician and takes approximately 10 minutes to complete, as reported in Table 7.

Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Change (CGI-C) (Secondary Endpoint)

The CGI-S is a clinician's rating of disease severity. The CGI-S rates severity of illness on a 7-point scale, using a range of responses from 1 (normal) through to 7 (the most severely ill). This rating is based upon observed and reported symptoms, behavior, and function in the past 7 days. The CGI-C rates improvement by 7 categories: very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse. These assessments are administered to the subject by a

clinician. The CGI-S takes approximately 40 to 60 minutes to complete and the CGI-C takes approximately 1 minute to complete, as reported in Table 7.

PSP-Quality of Life (PSP-QoL)[18] (Secondary Endpoint)

The PSP-QoL is a validated patient-reported outcome measure, specifically designed to assess the quality of life of patients with PSP. There are 45 items and two subscales: physical and mental impact. Items are scored from 0 (no problem) to 4 (extreme problems). The total subscale sum scores are linearly converted into a 0 to 100 scale. The PSP-QoL, with a 4-week time frame, can be completed by the patients or study partners. The PSP-QoL form includes a visual analog scale (VAS) about the patient's satisfaction with overall life. It takes 30 minutes to complete. The PSP-QoL was developed specifically for PSP and displays good psychometric properties. A panel of experts in movement disorders determined that content validity was good. Internal construct validity was verified through a moderate correlation between the two subscales. Convergent and discriminant validity was supported by correlations between the PSP-QoL subscales and other measures (EuroQol-5D [EQ-5D] and the Hospital Anxiety and Depression Scale), with no differences by gender. PSP-QoL is administered to the subject by a clinician and takes approximately 30 minutes to complete, as reported in Table 7.

Repeatable Battery for Assessment of Neuropsychological Status (RBANS)[19] (Exploratory Endpoint)

The RBANS is a 25-minute, standardized neurocognitive battery with North American population-based normative data. The RBANS measures five neurocognitive domains, with age-based scaling. Twelve subtests measure cognitive decline or improvement across the following domains:

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

5. Delayed Memory – List Recall, List Recognition, Story Memory, and Figure Recall.

The RBANS has been shown to be effective at both detecting and characterizing dementia of different etiologies. The RBANS has been translated into over 25 different languages, with extensive clinical validity data from a wide variety of geographic regions. It is administered to the subject by a clinician and takes approximately 25 minutes to complete, as reported in Table 7.

Color Trails Test (CTT) (Parts 1 and 2)[20] (Exploratory Endpoint)

The Color Trails Test (CTT) (Parts 1 and 2) involves numbered circles that are printed with vivid pink or yellow backgrounds that are perceptible to color-blind individuals. For Part 1, the respondent uses a pencil to rapidly connect circles numbered 1 – 25 in sequence. For Part 2, the respondent rapidly connects numbered circles in sequence, but alternates between pink and yellow. The length of time to complete each trial is recorded, along with qualitative features of performance indicative of brain dysfunction, such as near-misses, prompts, number sequence errors, and color sequence errors. The clinician administering this test will need a stopwatch to record the length of time for the completion of each part. It is administered to the subject by a clinician and takes approximately 5 – 10 minutes to complete, as reported in Table 7.

Letter Fluency Test (LFT)[21] (Exploratory Endpoint)

This is a phonemic fluency task, requiring subjects to generate as many words as they can that start with a given letter over a 60 second interval. This study will employ two trials per administration, involving different letters. The score is the total number of correct words generated over the two trials. It will be administered to the subject by a clinician and will take approximately 1 minute for each of the two trials to complete, as reported in Table 7.

Natural History and Neuroprotection in Parkinsons Plus Syndromes-Parkinson Plus Scale (NNIPPS-PPS)[22] (Exploratory Endpoint)

The NNIPPS-PPS is a validated rating scale used to assess disease severity and progression in patients with PSP and MSA. The NNIPPS-PPS contains 83 items, comprised of 11 domains: functional disability (ADLs), mental function (cognition, mood, and behavior), motor disability (rigidity and bradykinesia), tremor, oculomotor function, cerebellar signs, pyramidal signs, dysautonomia, bulbar/pseudobulbar symptoms, myoclonus, and dystonia. Responses are graded according to their severity. It is administered by a clinician and takes approximately 30 – 45 minutes to complete, as reported in Table 7.

The NNIPPS-PPS will not be administered in Japan.

Patient Global Impression of Change (PGI-C)[23] (Exploratory Endpoint)

Subjects will evaluate the change in their PSP-related symptoms since initiation of study drug by choosing one of seven responses. The PGI-C is a 7-point response scale. The subject will be asked by the Investigator or qualified designee to rate their change in status using the following 7-point scale:

1 = Very much improved, 2 = Much improved, 3 = Minimally improved, 4 = No change, 5 = Minimally worse, 6 = Much worse, 7 = Very much worse.

The responses of "Very much improved," "Much improved," "Minimally improved" and "No change" on the PGI-C will be used to define responders. It is administered to the subject by a clinician and takes approximately 1 – 2 minutes to complete, as reported in Table 7.

EuroQuality of Life (EQ-5D)[24] (Exploratory Endpoint)

The EQ-5D contains a health state descriptive part comprising five items, scored from 1 (no problems or symptoms) to 3 (serious problems or symptoms); a question about change in health state in the preceding 12 months, and a VAS to evaluate current health

state (from 0, worst imaginable, to 100, best imaginable). The descriptive profile can be converted into a value (EQ-Index) which ranges from 0 (death) to 1 (perfect health), with negative values indicating health states considered worse than death. It is administered to the subject by a clinician and takes approximately 8 minutes to complete, as reported in Table 7.

Mini-Mental State Exam (MMSE)[25]

The MMSE is a brief, 30-point questionnaire that provides a quantitative measure of cognitive status in adults and is widely used to screen for cognitive impairment and to estimate the severity of cognitive impairment at a given point in time. The MMSE total score ranges from 0 to 30, with lower score indicating greater impairment. The subject must have a score of greater than 15, inclusive, at screening to be eligible for study participation. It is administered to the subject by a trained rater and takes approximately 10 – 15 minutes to complete, as reported in Table 7.

Columbia-Suicide Severity Rating Scale (C-SSRS)[26]

The C-SSRS is a systematically administered instrument developed to track suicidal adverse events across a treatment study. The instrument is designed to assess suicidal behavior and ideation, track and assess all suicidal events, as well as the lethality of attempts. Additional features assessed include frequency, duration, controllability, reason for ideation, and deterrents. The C-SSRS is considered a low-burden instrument as it takes less than 5 minutes to administer. It is administered to the subject by a clinician and takes less than 5 minutes to complete, as reported in Table 7.

Any subject noted to have suicidal ideation with plan within the prior month, either via answering "yes" to questions 4 or 5 to the suicidal ideation portion of the C-SSRS or via clinical interview, will be evaluated immediately by the study physician. The AbbVie Medical Director will also be informed. Appropriate steps will be taken to protect the subject, including but not limited to possible discontinuation from the study and referral for appropriate psychiatric care. Any such subject at screening or on Day 1 will also be excluded from the study.

5.3.1.2 Collection and Handling of Biomarker and Pharmacogenetic Research Samples

Biomarker Samples

Blood and CSF samples will be collected as outlined in the Study Activities Table (Appendix C) and may be utilized to evaluate known and/or novel disease-related or drug-related biomarkers. The biomarker rationale will be discussed in the Biomarker Research Variables Section (Section 5.3.6.1).

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

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

Blood samples (approximately 11 mL) will be collected prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion) at the time points indicated in the Study Activities Table (Appendix C). Blood samples collected at Week 52 (Study Completion/Premature Discontinuation Visit) may be collected at any time during that visit.

CSF samples (18 – 20 mL) will be collected by lumbar puncture.

MAPT Pharmacogenetic Sample

One (required) 4 mL whole blood sample will be collected from each subject at study Day 1 for microtubule associated protein tau (MAPT) haplotype and progranulin (GRN) pharmacogenetic analysis. This sample will not be used for any testing other than MAPT haplotyping and genetic analysis of GRN mutations.

Optional Pharmacogenetic Exploratory Research Samples

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

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

Optional whole blood pharmacogenetic samples for Deoxyribonucleic Acid (DNA) and Ribonucleic acid (RNA) isolation will be collected from each subject who consents to provide samples for exploratory research. Optional whole blood samples (6.5 mL) for DNA and RNA isolation will be collected at the following time points:

- Day 1 (Dose 1)
- Day 85 (Dose 5)
- Week 36 (Dose 11)
- Week 52: (Completion/Premature Discontinuation Visit)

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

5.3.1.3 Confinement

Subjects in Cohort J1 will be required to be confined for a minimum of 24 hours following their first dose. The Investigator will assess the subject for safety prior to discharge to determine that the subject can be discharged. If a subject is suspected of

having any abnormality during the medical examination prior to discharge, additional testing, including the extension of the confinement, will be considered.

5.3.1.4 Meals and Dietary Requirements

There are no dietary requirements or restrictions for this study.

5.3.2 Drug and Anti-Drug Antibody Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

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

Blood Samples for ABBV-8E12 Assay

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

For Subjects Enrolled in Cohort 1 and Cohort J1 (*See Below for Allowable PK Windows)

- **Day 1 (Dose 1)**
  - Prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion), immediately after the end of the infusion (within 15 minutes) and 1 and 2 hours after the end of the infusion.
- **Day 5**
  - Sample may be collected at any time during the visit.
- **Day 15 (Dose 2)**
  - Prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion), immediately after the end of the infusion (within 15 minutes) and 1 and 2 hours after the end of the infusion.
- **Days 29 and 57 (Doses 3 and 4)**
  - Sample may be collected at any time during the visit.

- **Day 85 (Dose 5)**
  - Prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion), immediately after the end of the infusion (within 15 minutes) and 1 and 2 hours after the end of the infusion.
- **Days 89 and 99**
  - Sample may be collected at any time during the visit.
- **Weeks 16, 24, and 36 (Doses 6, 8, and 11, respectively)**
  - Prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion).
- **Week 52 (Study Completion/Premature Discontinuation Visit)**
  - Sample may be collected anytime during the day.
- **Weeks 60 and 68 (Post-Treatment Follow-up Period)**
  - Sample may be collected anytime during the day.

***Cohort 1 and Cohort J1 Allowable PK Windows**

On Days 1, 15, and 85 and at Weeks 16, 24, and 36, the PK samples collected prior to infusion should be collected within 30 minutes of the start of infusion. For 1-hour post-dose samples (Days 1, 15, and 85), the allowable PK window is ± 6 minutes, and for 2-hour post-dose samples (Days 1, 15, and 85), the allowable PK window is ± 12 minutes. The allowable window is ± 2 days for samples scheduled on Days 5, 89, and 99, and ± 4 days for samples scheduled on other study days.

For Subjects Enrolled in Cohort 2 (*See Below for Allowable PK Windows)

- **Days 1, 29, 85, and Weeks 24 and 36 (Doses 1, 3, 5, 8, and 11, respectively)**
  - Prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion).
- **Day 15 (Dose 2)**
  - 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.

- **Week 52: (Study Completion/Premature Discontinuation Visit)**
  - Sample may be collected anytime during the day.
- **Weeks 60 and 68 (Post-Treatment Follow-up Period)**
  - Sample may be collected anytime during the day.

***Cohort 2 Allowable PK Windows**

On Days 1, 15, 29, and 85 and at Weeks 24 and 36, the PK samples collected prior to infusion should be collected within 30 minutes of the start of infusion. For 1-hour post-dose sample (Day 15), the allowable PK window is ± 6 minutes, and for 2-hour post-dose samples (Day 15), the allowable PK window is ± 12 minutes. For the samples scheduled for Weeks 52, 60, and 68, the allowable window is ± 4 days.

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

Blood samples, approximately 3 mL for ABBV-8E12 ADA analysis will be collected by venipuncture. The collection schedule for ADA will be the same for subjects who previously did or did not participate in the Single-Ascending Dose Study (Study C_2N-8E12-WW-104). The schedule for ABBV-8E12 ADA collection is as follows:

For Subjects Enrolled in Cohort 1 and Cohort J1 (*See Below for Allowable ADA Windows)

- **Days 1, 15, 29, 57, 85, and Weeks 16, 24, and 36 (Doses 1, 2, 3, 4, 5, 6, 8, and 11, respectively)**
  - Prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion).
- **Days 89 and 99**
  - Sample may be collected anytime during the day.
- **Week 52: (Study Completion/Premature Discontinuation Visit)**
  - Sample may be collected anytime during the day.
- **Weeks 60 and 68: Post-Treatment Follow-up Period**

- Sample may be collected anytime during the day.

***Cohort 1 and Cohort J1 Allowable ADA Windows**

On Days 1, 15, 29, 57, 85, and Weeks 16, 24, and 36, the ADA samples collected prior to infusion should be collected within 30 minutes of the start of infusion. Blood samples may be collected within ± 2 days on Days 89, and 99, and ± 4 days on other study days.

For Subjects Enrolled in Cohort 2 (*See Below for Allowable ADA Windows)

- **Days 1, 29, 85, and Weeks 24 and 36 (Doses 1, 3, 5, 8, and 11, respectively)**
  - Prior to the start of the infusion (0 hour, no more than 30 minutes prior to the start of the infusion).
- **Week 52: (Study Completion/Premature Discontinuation Visit)**
  - Sample may be collected anytime during the day.
- **Weeks 60 and 68: Post-Treatment Follow-up Period**
  - Sample may be collected anytime during the day.

***Cohort 2 Allowable ADA Windows**

On Days 1, 29, 85, and Weeks 24, and 36, the ADA samples collected prior to infusion should be collected within 30 minutes of the start of infusion. Blood samples may be collected within ± 4 days on other study days.

CSF Samples for ABBV-8E12 Assay

CSF samples will be collected as outlined in the Study Activities Table (Appendix C-Assessment referred to as LP).

The collection time and procedures of CSF samples can be found in the Lumbar Puncture section of Study Procedures Section (Section 5.3.1.1).

As described in the Collection and Handling of Biomarker and Pharmacogenetic Research Samples Section (Section 5.3.1.2), CSF samples (18 – 20 mL) will be collected by lumbar puncture.

5.3.2.2 Measurement Methods

Analysis of Serum and CSF Samples

Serum concentrations and relative titers of ABBV-8E12 ADA will be determined using validated methods at the Bioanalysis Department at AbbVie. CSF concentrations of ABBV-8E12 will be analyzed using qualified or validated methods. Any additional analytes may be analyzed using non-validated methods either at AbbVie or by outside vendors or collaborators. Serum samples collected for ABBV-8E12 and ABBV-8E12 ADA analysis may be used for future assay development or validation activities. ABBV-8E12 ADA samples may be used for the analysis of neutralizing anti-drug antibodies.

5.3.3 Efficacy Variables

The primary efficacy variable will be the mean change from Baseline at Day 1 pre-dose 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 measures include the SEADL, UPDRS Part II, CGI-S, CGI-C, and PSP-QoL, and PSP Staging System and time to loss of ability to walk independently as measured by PSPRS item 26, as well as regional (midbrain, third ventricle, frontal lobes, superior cerebellar peduncle, brainstem) and whole brain atrophy as measured by volumetric MRI.
- Exploratory efficacy variables include the RBANS, Color Trails Test (Parts 1 and 2), Letter Fluency Test, NNIPPS-PPS, PGI-C, and EuroQoL-5D (EQ-5D). 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] to assess changes in pathophysiology and additional regions as measured by volumetric MRI.

Analysis of the secondary and exploratory efficacy variables obtained from these measures is detailed in Section 8.0.

5.3.4 Safety Variables

The following safety evaluations will be performed during the study: adverse event monitoring (including infusion and allergic reactions), vital signs, physical examination, complete neurological exam, cognitive assessments, C-SSRS, laboratory abnormalities, ECG, MRI including FLAIR, and immunogenicity as determined by ADA responses in blood.

5.3.5 Pharmacokinetic Variables

Values for the following pharmacokinetic parameters will be estimated using non-compartmental methods: maximum observed serum concentration (C_{max}), the time to C_{max} (peak time, T_{max}), the area under the concentration time curve (AUC) over the dosing interval after the first and the fifth doses in Cohort 1 and Cohort J1; and the observed serum concentration at the end of a dose interval (C_{trough}, concentration prior to infusion on a day of dosing) in both Cohort 1, Cohort J1, and Cohort 2.

The concentration of ABBV-8E12 in CSF will be summarized after the fifth dose and after the final dose if administered at least 3 months after the previous LP for subjects in Cohort 1 and Cohort J1, and after final dose for subjects in Cohort 2.

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

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

5.3.6 Biomarker and Pharmacogenetic Research Variables

5.3.6.1 Biomarker Research Variables

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 plasma samples will be assayed for tau to demonstrate tau binding of ABBV-8E12 and for neurofilament to examine effects on neurodegeneration.
- CSF or plasma samples may be analyzed for biochemical or macromolecular factors related to the pharmacodynamics and safety of ABBV-8E12.

Exploratory evaluations from blood and CSF 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.

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 study summary.

5.3.6.2 Pharmacogenetic Research Variables

MAPT H1/H2 haplotype status may be determined for each subject and analyzed as a factor contributing to the subject's response to study treatment. The MAPT H1/H2 haplotype results may be analyzed as part of a multi-study assessment of MAPT and response to ABBV-8E12 treatment. Testing for GRN haploinsufficiency polymorphisms will also be conducted as patients with these mutations typically have low progranulin serum levels and are less likely to have tau brain pathology. 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 and progranulin results may not be included in the study summary.

Optional 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 with the study report.

5.3.7 Immunogenicity

ADA levels will be determined for the assessment of immunogenicity.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

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

Severe allergic reactions or other adverse events that require the immediate interruption of ABBV-8E12 treatment will be taken into consideration by the AbbVie Medical Director for permanent discontinuation from further treatment and initiation of appropriate medical therapy and follow-up.

Any treatment-emergent, clinically significant, symptomatic neurological abnormalities and treatment-emergent MRI findings will be reported to the AbbVie Medical Director and subjects will be considered for discontinuation from treatment if clinically indicated.

Subjects at risk of suicide as indicated by answering yes to question 4 or 5 on the C-SSRS and/or determined by the investigator to be at risk of suicide, should be promptly referred

for appropriate follow-up care. Subjects determined to be at ongoing risk of suicide should be discontinued from study participation.

If for any reason the subject becomes unable to continue treatment with ABBV-8E12, undergo protocol required procedures, or otherwise continue to participate in the study, discontinuation should be discussed with the AbbVie Medical Director.

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

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

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the study, the administration of study drug to that subject must be discontinued immediately. The investigator must report a pregnancy within 1 working day of the site being aware to one of the AbbVie representatives listed in Section 6.1.5 or Section 7.0.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended

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

The DMC may evaluate the results of interim efficacy evaluation(s) and may make a recommendation to discontinue the entire study if the study is deemed to be futile. The DMC will review unblinded safety data during the study. Depending on the outcome of these evaluations, the DMC may make a recommendation to discontinue the entire study or stop enrollment in a single dose group prior to enrollment of the planned sample size. The entire study will be discontinued if it is determined by AbbVie in consultation with the DMC that the continued exposure of subjects to study drug represents a significant safety risk. Enrollment to a single dose group will be discontinued if it is determined by AbbVie in consultation with the DMC that the continued exposure of subjects to that dose of study drug represents a significant safety risk. Alternatively, a recommendation may be made to adjust the dose in one or both dose groups.

5.5 Treatments

5.5.1 Treatments Administered

For subjects randomized to the treatment arms, the solution contained in the study vial(s) of ABBV-8E12 will be diluted in the 0.9% Sodium Chloride Injection/Solution for Infusion. Subject weight will be obtained prior to study drug administration to determine the appropriate infusion rate as shown in the table below. Written instructions for the preparation of ABBV-8E12 solutions for infusion will be provided as a separate document from the protocol.

Subject's Weight in kg/lbs.	Infusion Rate**
*44 – 49 kg (97 – 109 lbs., inclusive)	3.5 mL/min or 210 mL/hr
50 – 58 kg (110 – 128 lbs., inclusive)	4.0 mL/min or 240 mL/hr
59 kg and over (129 lbs. and over)	4.7 mL/min or 282 mL/hr

* Subjects weighing less than 44 kg (97 lbs.) will be excluded from enrollment (refer to exclusion criteria, Section 5.2.2, Exclusion Criterion 1).

** Continue infusion until bag is empty.

Study continuation for subjects whose weight falls below 44 kg (97 lbs.) during the course of their participation will be discussed with the AbbVie Medical Director and adjustment of the infusion time or potential discontinuation from the study will be considered.

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

Study Drug	Formulation
Cohort 1/Cohort J1 Placebo (0.9% Sodium Chloride Injection/Solution for Infusion) ABBV-8E12 2000 mg ABBV-8E12 4000 mg	IV infusions at Day 1, Day 15, and Day 29, then every 28 days for 52 weeks (Total of 14 infusions)
***Cohort 2** Placebo (0.9% Sodium Chloride Injection/Solution for Infusion) ABBV-8E12 2000 mg ABBV-8E12 4000 mg	IV infusions at Day 1, Day 15, and Day 29, then every 28 days for 52 weeks (Total of 14 infusions)

(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).

* Doses may be decreased after the evaluation by the DMC of available safety, tolerability and PK data.

The start and stop time of each study drug infusion will be recorded to the nearest minute.

5.5.2 Identity of Investigational Product

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

Table 8. Identity of Investigational Product

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
ABBV-8E12	Infusion	Solution for infusion in a vial	300 mg/15 mL[#] 1000 mg/10 mL	AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany
Placebo	Infusion	0.9% Sodium Chloride Injection/Solution for Infusion, 500 mL	N/A	Various* (See below)

Dosage formulation will not be used in Japan and Spain.

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

0.9% Sodium Chloride Injection/Solution for Infusion will be administered to those subjects not receiving active ABBV-8E12 and as a vehicle for administration of ABBV-8E12. 0.9% Sodium Chloride Injection/Solution for Infusion will be supplied with commercially available material in either bags or bottles, locally sourced by the sites. However, if mandated by local regulation, or in the case of exceptional circumstances when sites are unable to procure on their own, AbbVie may supply 0.9% Sodium Chloride Injection/Solution for Infusion if necessary.

5.5.2.1 Packaging and Labeling

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

The commercially sourced 0.9% Sodium Chloride Injection/Solution for Infusion will not be labeled as an Investigational Medicinal Product (IMP) prior to the handling by the unblinded pharmacist or qualified designee. Instead, after addition of ABBV-8E12 to the 0.9% Sodium Chloride Injection/Solution for Infusion to be administered in the active

arm, it will be labeled with a blinded dispensing label by the unblinded pharmacist or qualified designee as required. 0.9% Sodium Chloride Injection/Solution for Infusion without addition of ABBV-8E12, to be administered in the placebo arm, will be labeled with a blinded dispensing label by the unblinded pharmacist or qualified designee as well. Labels must remain affixed to the material.

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

5.5.2.2 Storage and Disposition of Study Drug

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

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

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

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

5.5.2.3 Preparation/Reconstitution of Dosage Form

The preparation of blinded doses will be performed by the unblinded pharmacist or qualified designee. Placebo doses, consisting of 0.9% Sodium Chloride Injection/Solution for Infusion bags or bottles, will be essentially identical in volume to the active doses. Written instructions for the preparation of ABBV-8E12 solutions for infusion will be outlined in the Pharmacy Manual.

5.5.3 Method of Assigning Subjects to Treatment Groups

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

As subjects are screened for the study, the IVR/IWB system will assign each subject a unique 5 digit subject number. The first digit will be 1, the second and third digits will be the site number (01, 02, etc.) and the fourth and fifth digits will be assigned in ascending numerical order at each site.

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

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the dose for this study is discussed in Section 5.6.4. Each subject will be randomized to one of three dose groups as described in Section 5.5.1. ABBV-8E12 will be administered via IV infusion; if possible this will be performed in the morning.

AbbVie will inform all sites in Japan when Cohort J1 is open for enrollment in the IVR/IWB system. The IVR/IWB system will be programmed such that Subject 2 through Subject 9 may only be enrolled at least 48 hours after the prior subject was enrolled into Cohort J1. This 48-hour pause is to allow adequate time for the Investigator to assess safety of the last subject and to allow AbbVie adequate time to review the safety of the subjects enrolled into Cohort J1. Sites must contact AbbVie prior to enrolling any subject into Cohort J1 and AbbVie will notify sites when Cohort J1 is fully enrolled.

Cohort 2 in Japan will be opened in the IVR/IWB for enrollment only after Cohort J1 has been fully enrolled, following the DMC review of the Cohort J1 safety data, and after the DMC recommendation for the study to proceed without modifications, thus allowing AbbVie to commence enrolling Japanese subjects into Cohort 2. AbbVie will notify all sites when Cohort 2 is open for enrollment in Japan.

5.5.5 Blinding

Subjects in the placebo group will be administered 0.9% Sodium Chloride Injection/Solution for Infusion that is essentially identical in volume to the ABBV-8E12 solution. Written instructions for preparation of ABBV-8E12 solutions for infusion and blinding procedures will be outlined in the Pharmacy Manual. An unblinded pharmacist or qualified designee will be used for receiving and preparing of the blinded doses across the treatment groups. The Investigator, study site personnel (except the unblinded pharmacist or qualified designee) and the subject will remain blinded to the treatment assignment throughout the course of the study. The study Sponsor will remain blinded.

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

For investigational product monitoring, there will be an unblinded Clinical Research Associate (also referred to as a Pharmacy CRA) for verification of unblinded preparation documentation. The unblinded Pharmacy CRA will be a separate individual than the blinded CRA to ensure blinding is maintained. The unblinding procedure for the unblinded pharmacist/qualified designee and the unblinded Pharmacy CRA will be in a separate study-specific document.

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

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

Unblinding of Data for the Data Monitoring Committee (DMC)

In order to ensure that the DMC will be fully informed, the DMC will be unblinded in its assessment of safety and efficacy data. The DMC will have full access to all data as needed for safety assessment. SAS® data sets blinded with respect to treatment assignment will be sent to an external Statistical and Data Analysis Center (SDAC) and Exposure-Response Analysis Center (ERAC) by AbbVie. The study randomization will be sent to the SDAC and ERAC under separate cover. The SDAC and ERAC will generate a Closed Report that includes unblinded information for DMC. Review of the Closed Report will be limited to the DMC and, if necessary, an Internal Review Committee (IRC) from the Sponsor who may need to consult with the DMC in order to formulate a decision based on the DMC's recommendations. Detailed communication plan between DMC and IRC will be specified in the DMC Charter.

5.5.6 Treatment Compliance

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

5.5.7 Drug Accountability

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

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This study is designed to assess the efficacy, safety, and tolerability of ABBV-8E12 in subjects with PSP for up to 52 weeks. The inclusion of placebo administration and the double blind nature of the study will provide unbiased assessments. The parallel-group design with placebo control will provide a well-controlled unbiased assessment of the effect of ABBV-8E12 on clinical outcome measures and potential neuroimaging and CSF

biomarkers that are associated with PSP disease activity. Toxicity management in the parallel group design is described in Section 6.1.7.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study.

The PSPRS was developed to evaluate the severity and progression of PSP symptoms.

The PSPRS has been widely used in the scientific literature to evaluate PSP symptoms and has adequate reliability and validity.[12] The SEADL, UPDRS Part II, RBANS, NNIPPS-PPS, and PSP-QoL are currently accepted and validated methods of evaluating subjects with PSP. All safety assessments are standard measures used in pharmaceutical research.

On-treatment safety evaluations are scheduled at more frequent intervals for the subjects enrolled in Cohort 1 and Cohort J1 to promptly detect emerging safety signals.

5.6.3 Suitability of Subject Population

The research diagnostic criteria for possible and probable progressive supranuclear palsy developed by the National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy (NINDS-SPSP) have been well validated and are highly predictive of underlying PSP pathology.[5] The selection criteria are intended to identify subjects who have the potential to benefit from treatment would not be exposed to undue risk. The selection of subjects who are otherwise in general good health is standard for pharmacokinetic studies, promotes compliance and reduces variability.

5.6.4 Selection of Doses in the Study

Cohort 1 and Cohort J1

Dose levels of 2000 mg and 4000 mg have been selected for Cohort 1 and Cohort J1 based on available safety, tolerability and pharmacokinetic data from two patients with

tauopathies that received ABBV-8E12 under an expanded access IND (US; 20 monthly infusions; maximum dose of 25 mg/kg for the last 7 months) and a compassionate use trial application (Germany; 3 monthly infusions; maximum dose of 15 mg/kg for the last 2 months) as well as preliminary safety, tolerability and pharmacokinetic data from the ongoing SAD study (Study C_2N-8E12-WW-104) in patients with PSP, which is exploring the safety, tolerability, and pharmacokinetics of single doses of ABBV-8E12 ranging from 2.5 mg/kg to 50 mg/kg. In both compassionate-use protocols, the ABBV-8E12 infusions were well tolerated without any observed signs or symptoms of antibody-related toxicity.

Study C_2N-8E12-WW-104 has been completed and ABBV-8E12 has been generally well tolerated up to the highest tested dose of 50 mg/kg without notable treatment-related adverse effects or any clinically concerning safety findings.

The actual doses administered in the SAD study were based on the subject's body weight, and the range of actual doses at the 50 mg/kg group was 2625 mg to 4760 mg.

The planned doses to be administered in this study are 2000 mg and 4000 mg, and these fixed-doses were determined based on an 80-kg person at the 2 highest doses administered in ongoing SAD study with patients with PSP (25 mg/kg and 50 mg/kg). In the SAD study, mean body weight of the 23 patients with PSP who received ABBV-8E12 was 74.8 kg, consistent with weights observed in previous studies[7,27] in patients with PSP.

Based on modeling and simulations of all pharmacokinetic data in the SAD study, exposures following single dose of fixed-dose 4000 mg are expected to be comparable to the observed exposures at the 50 mg/kg group in the SAD study, and exposure variability following a fixed-dose regimen is predicted to be similar to a weight-based regimen.

In the 4-week preclinical mouse toxicology study, that assessed off-target toxicity of ABBV-8E12, the highest dose tested was 250 mg/kg and the corresponding C_{max} and $AUC_{0\text{-}168h}$ were 3050 µg/mL and 298,000 hr•µg/mL (on Day 22) after 4 weeks of dosing. Assuming the pharmacokinetics of ABBV-8E12 is linear, the steady-state pharmacokinetic profiles were simulated at 2000 and 4000 mg following monthly

administration of ABBV-8E12 based on the available pharmacokinetic data in the ongoing SAD study in patients with PSP. The predicted safety margin at the dose levels of 2000 and 4000 mg is approximately 3- and 1.4-fold, respectively, for both C_{max} and AUC. There is no pharmacologically relevant species in which to conduct toxicology studies to support safety of ABBV-8E12.

Overall, based on available safety and tolerability data and pharmacokinetic projections, it is expected that ABBV-8E12 should be well tolerated within the dose range to be administered in the planned Phase 2 study. In order to minimize any potential risk associated with higher drug exposure following the administration of a fixed dose in an individual subject with low weight compared to the weight-based dosing regimen in Study C_2N-8E12-WW-104 and/or the risk associated with higher drug exposure after multiple dosing, augmented safety, and pharmacokinetic monitoring in the initial cohorts of 39 subjects (Cohort 1 and Cohort J1) will be conducted in the Phase 2 study. Subjects in Cohort 1 and Cohort J1 will have additional study visits, and more frequent neurological exams, vital signs, safety labs, and lumbar punctures. Additionally, safety oversight will be provided by a Data Monitoring Committee.

Reductions in free CSF tau may be a target engagement marker that is associated with efficacy, as such, based on the pharmacokinetic data from the SAD study and the dissociation constant (k_D) of ABBV-8E12 determined in vitro, 2000 mg and 4000 mg are predicted to lead to approximately 75% to 90% and 85% to 95% of tau in CSF being bound by the antibody, respectively, at predicted C_{trough} and C_{max} values. Assuming 70% binding of tau by the 2000 mg dose, it is likely that lower doses would not provide sufficient binding to achieve near maximal efficacy and doses higher than 4000 mg of ABBV-8E12 would not lead to significantly higher percentage of tau binding and as such the 4000 mg dose has the greatest likelihood of being maximally effective. Since PSP is a rare and rapidly progressing disorder with no currently approved treatments and there is a limited pool of potential study participants, there is a strong rationale to initially allocate subjects to doses that are likely to demonstrate maximum or near maximum efficacy.

Cohort 2

Doses in Cohort 2 will not exceed the highest dose administered in Cohort 1 and Cohort J1, and dose-response and exposure-response relationships in CSF total and free tau levels (observed and change from baseline) will be evaluated to support dose selection in Cohort 2, if appropriate.

Doses may be decreased after evaluation of the safety, tolerability, and available pharmacokinetic data by the DMC.

6.0 Complaints

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

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

6.1 Medical Complaints

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

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

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

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

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

6.1.1.2 Serious Adverse Events

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

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

6.1.2 Adverse Event Severity

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

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

6.1.3 Relationship to Study Drug

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

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

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

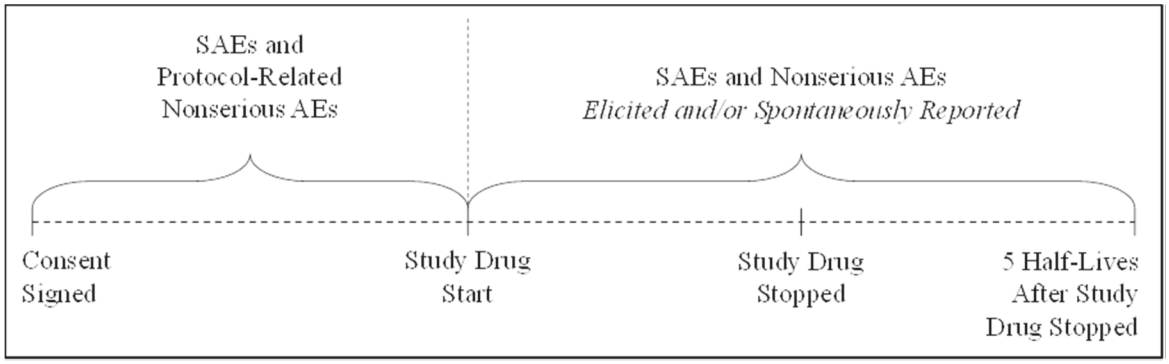
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

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

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

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

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

Email: [redacted]

FAX to: [redacted]

For safety concerns, contact the Neuroscience Safety Team at:

Neuroscience Safety Team
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office:
Email: [redacted]

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

Primary AbbVie Medical Director:

[redacted]
Medical Director
Neuroscience Development
AbbVie Inc.
1 N Waukegan Road
[redacted]
North Chicago, IL 60064

Telephone Contact Information:
Phone:
Cell:
Email: [redacted]

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

Phone: [redacted]

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

Serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible ethics committees and regulatory agencies as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., International Council on Harmonisation [ICH] Expedited

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

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued from the study drug (Section 5.4.1).

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 Toxicity Management

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

A drug-related toxicity is an adverse event or laboratory value outside of the reference range that is judged by the investigator or AbbVie as a "reasonable possibility" of being related to the study drug (Section 6.1.3). Toxicity is deemed "clinically significant" based on the medical judgment of the investigator. The following guidelines should be used for study drug-related toxicity management.

Potential Drug-Related Toxicities

No potential drug related toxicities were identified from preclinical or clinical studies conducted to date. Examples of safety concerns that could be hypothetically associated

with ABBV-8E12 and safety concerns associated with monoclonal antibodies, in general, are summarized below.

On-Target Toxicities

The brain appears to be the only organ to express tau at significant levels. Tau is an intracellular protein mainly expressed in neurons, although lower levels can be found in astrocytes and oligodendrocytes. ABBV-8E12 is directed against extracellular tau and no function of extracellular tau has been reported. No cellular uptake of the mouse version of ABBV-8E12 antibody bound to tau aggregates was detected in preclinical studies.[28] The likelihood of adverse on-target side effects of an anti tau immunotherapy is therefore anticipated to be low.

Non-Specific Off-Target Toxicities

Potential toxicities resulting from the non-human origin of ABBV-8E12 include allergic reactions or infusion reactions, including anaphylaxis or anaphylactoid reactions, flu-like symptoms, including fever, fatigue or loss of appetite, or rash. ABBV-8E12 is lacking the Fragment Crystallizable (Fc) effector function activity and therefore Fc-mediated antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity is not expected. In addition, ABBV-8E12 exhibited a favorable in vitro immune-safety profile. No infusion reactions have occurred in the single dose PSP clinical study or in the Expanded Access protocol (Studies C_2N-8E12-EA-001 and C_2N-8E12-DE-003).

Allergic Reactions Management

Subjects will be closely monitored for treatment-related adverse events, including allergic reactions, during the infusion. For their first 4 ABBV-8E12 infusions, subjects should be monitored on site until 2 hours post-infusion. For subsequent infusions, subjects should be monitored on site until at least 30 minutes after the end of infusion. Subjects in Cohort J1 will be confined for a minimum of 24 hours following their first infusion. The Investigator will assess safety 2 days after the first infusion, either while in hospital or as an outpatient. From their second to fourth infusion, Cohort J1 subjects will be observed

on-site for at least 2 hours following each infusion of study drug. Subjects in Cohort 2 will be observed on-site for at least 2 hours following each of the first 4 infusions of study drug. Following the 4th infusion, all subjects should be monitored on-site for at least 30 minutes after the end of infusion. Longer observation periods and more frequent vital sign checks may be required in subjects who experience infusion reactions. In general, Infusion reactions are more frequently observed during the first infusion and within 24 hours from the start of administration, especially within the first 2 hours.[29] Please refer to Table 2, Safety Observation Period Following Infusions, for a summary of the observation periods following infusions.

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

Moderate infusion reactions resolving with supportive care should be discussed with the TA MD, and a reduction of the infusion rate for future administrations can be considered.

6.1.7.1 Management of Adverse Events of the Nervous System

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

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

Clinically significant treatment-emergent neurological abnormalities or MRI findings will prompt notification of the AbbVie Medical Director; subjects will be considered for

discontinuation if clinically indicated, and may be permitted to continue in the study only after a management plan is discussed with the AbbVie Medical Director.

6.1.8 Collection of Data Regarding Known Complications of the Disease Under Study

Natural progression of PSP (including new or worsening neurological symptoms and signs) is expected in the subjects. Disease progression will be assessed at pre-determined intervals throughout the treatment period by standardized criteria (such as the PSPRS, SEADL, UPDRS Part II, CGI-S, NNIPPS-PPS) and recorded on the corresponding case report form (CRF) pages for purposes or risk/benefit determinations. Therefore, "disease progression" or other similar verbatim terms related to disease status SHOULD NOT be recorded on the AE CRF pages. Similarly, since falls are a core component and defining feature of PSP (Steele-Richardson-Olszewski Syndrome), falls will not be recorded as AEs unless they lead to other injury or represent a change in frequency or character from pre-randomization falls.

Similarly, the slow progression of pre-existing disease-related signs and symptoms clearly associated with the disease during the treatment period will not be reported as AEs unless these signs and symptoms are judged by the Investigator to have become unusually severe or accelerated, or if the Investigator suspects the deterioration of disease-related signs and symptoms to be potentially related to the investigational drug. If there is any uncertainty about the worsening of an AE being due solely to the disease under the treatment protocol, it should be reported as an AE or SAE as appropriate.

Discontinuation from this treatment protocol because of progression or deterioration of the disease should be recorded on the protocol Termination CRF page as discontinuation due to "disease progression" and NOT as discontinuation due to an AE.

6.2 Product Complaint

6.2.1 Definition

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

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

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

6.2.2 Reporting

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

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

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

7.0 Protocol Deviations

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

Primary Contact:

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

Office: [redacted]
Mobile:
Email:

Alternate Contact:

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

Mobile: [redacted]
Email:

[redacted]
Clinical Project Manager
AbbVie
3-5-27, Mita, Minato-ku
Tokyo, Japan 108-6302

Office: [redacted]
Fax:
Email:

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

General Considerations

Unless otherwise specified, when a total score of an efficacy or safety scale is calculated from a set of individual items, the total score will be considered missing if any of the individual items are missing. When an average score is obtained from a set of individual items, it will be calculated from the non-missing items.

8.1.1 Analysis Data Sets

Intent-to-Treat Data Set

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

Safety Data Set

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

8.1.2 Disposition, Demographics, and Other Baseline Characteristics

Subject Disposition

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

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

Demographic and Other Baseline Characteristics

Demographics will be summarized for the intent-to-treat data set and the safety data set unless otherwise specified. Treatment group differences will be evaluated using overall tests. No pairwise comparisons between treatment groups will be performed unless the overall P value is ≤ 0.050.

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

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

Efficacy and clinical measures at baseline (PSPRS total score, SEADL score, UPDRS Part II score, CGI-S score, CGI-C score, PSP-QoL subscale scores and VAS, RBANS score, Color Trails Test (Parts 1 and 2) scores, Letter fluency test score, NNIPPS-PPS total score, EQ-5D index score and VAS, and MMSE total score) will be summarized for the intent-to-treat data set only. One-way ANOVA will be used to assess the overall comparability of treatment groups for all measurements.

Medical History

Medical history data, including subject's history of early PSP, will be summarized for the safety data set using body systems and conditions/diagnoses as captured on the eCRF and coded per Medical Dictionary for Regulatory Activities (MedDRA) guidelines.

Previous and Concomitant Medications

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

8.1.3 Efficacy Analyses

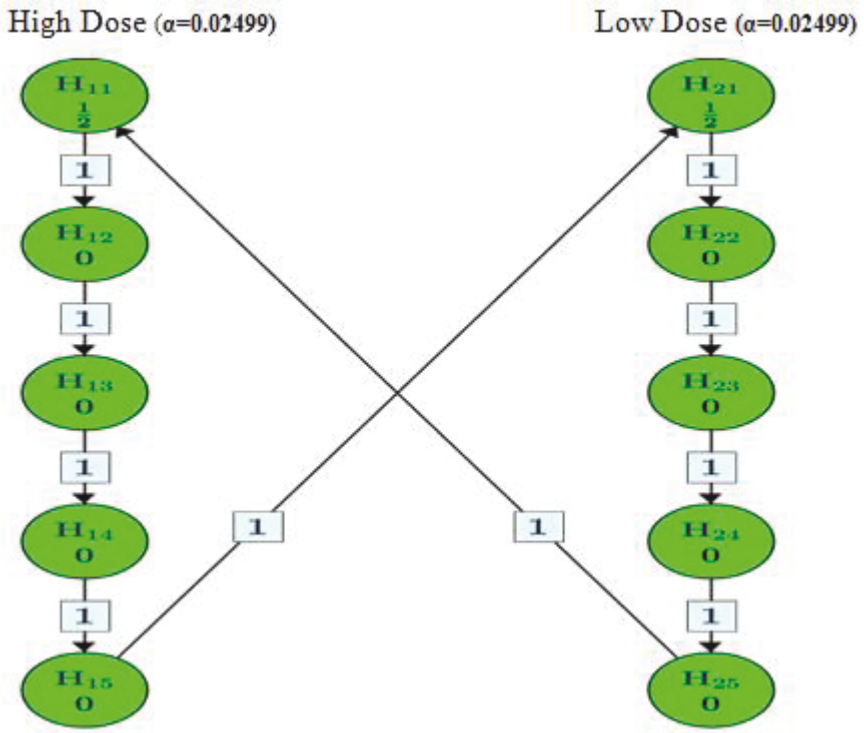
All efficacy analyses will be conducted on the intent-to-treat data set unless otherwise specified. Data collected more than 45 days after the last dose of the study drug will not be included in efficacy analyses. Unless otherwise specified, for all efficacy analyses, "baseline" refers to the last non-missing observation prior to the first dose of study drug and "final" refers to the last non-missing observation after the first dose of study drug and no more than 45 days after the last dose of study drug administration. Pairwise

comparisons between each ABBV-8E12 dose group and the placebo group will be performed with two-sided tests. Hochberg procedure[27] 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. For the final analysis, a graphic approach[30] will be used to propagate alpha (α) among hypotheses testing and 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 adjusting for interim futility analyses. The α will be split equally between two dose groups to test the primary and key secondary endpoints at Week 52 within each dose level. The order of efficacy endpoints to be tested will be the same within each dose level (Table 9). 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 3). 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). The numbers on the arrows denote the weights for transferring and (possibly) splitting the significance level. The overall type I error rate for this trial will be controlled at the two-sided 5% level. The detailed hypotheses testing procedure and the details of analyses methods will be pre-specified in the Statistical Analysis Plan (SAP) which will be finalized and signed off before the first futility interim analysis of this trial.

Table 9. Hypotheses Testing Order in the Graphical Testing Approach

Efficacy Endpoints Family	Ordered Efficacy Endpoints	Hypotheses: The High Dose (4000 mg) vs. Placebo	Hypotheses: 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}
	Volumetric MRI change from baseline at Week 52 – Midbrain	H_{14}	H_{24}
	SEADL score change from baseline at Week 52	H_{15}	H_{25}

Figure 3. A Graph for Multiplicity Adjustment of Multiple Hypotheses



8.1.3.1 Primary Efficacy Analysis

The primary efficacy variable will be the change from baseline to Week 52 on the PSPRS total score. The primary efficacy analysis will utilize a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each post-baseline and compare each ABBV-8E12 dose group with the placebo group. The model, which uses all observed data, will include fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score. The primary comparison will be the contrast between each ABBV-8E12 dose group and placebo at Week 52. The treatment group differences at earlier visits will be assessed as secondary. An unstructured (co)variance structure will be used to model the within-subject errors. Satterthwaite's approximation will be used to estimate denominator degrees of freedom and the Type III sum-of-squares for the Least Square (LS) means will be used to estimate treatment group differences.

8.1.3.2 Secondary Efficacy Analysis

Secondary Efficacy Analysis of the Primary Efficacy Variable

The change from baseline to each post-baseline observation on the PSPRS total score will be summarized. The change from baseline to final observation on the PSPRS total score will be analyzed by an analysis of covariance (ANCOVA) model with treatment and study site as the main effects and the baseline PSPRS total score as a covariate in the ITT data set. Missing data could occur due to loss of follow-up or early termination during the treatment period in the trial. To consider different missing data mechanisms, sensitivity analyses will be conducted on PSPRS total score after imputation of missing data. Detailed sensitivity statistical analysis plan will be described in the SAP.

Analyses for Secondary and Exploratory Efficacy Variables

The key secondary efficacy variables include:

- Unified Parkinson's Disease Rating Scale (UPDRS) Part II score

- Clinical Global Impression of Change (CGI-C) score
- Midbrain atrophy as measured by volumetric MRI
- the Schwab and England Activities of Daily Living Scale (SEADL) score

Other secondary efficacy variables include:

- Clinical Global Impression of Severity (CGI-S)
- PSP-Quality of Life (PSP-QoL) score
- PSPRS domain scores
- Regional (third ventricle, frontal lobes, superior cerebellar peduncle, brainstem) and whole brain atrophy as measured by volumetric MRI.
- PSP Staging System (PSP-SS) (composite of dysphagia, gait, and sitting down items from PSPRS)
- Time to loss of ability to walk independently as measured by PSPRS item 26

Exploratory efficacy variables include:

- Natural History and Neuroprotection in Parkinson Plus Syndromes-Parkinson Plus Scale (NNIPPS-PPS) total score (not conducted in Japan),
- Patient Global Impression of Change (PGI-C) score,
- Letter Fluency Test (LFT) score,
- Repeatable Battery for Assessment of Neuropsychological Status (RBANS) score,
- Color Trails Test (CTT) (Parts 1 and 2) score,
- EuroQoL-5D (EQ-5D) index score and Visual Analog Scale (VAS),
- 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] to assess changes in pathophysiology.
- Additional brain regions that are not listed under secondary assessments may be measured by volumetric MRI.

The change from baseline score on each secondary and exploratory efficacy variable if appropriate (with the exception of CGI-C and PGI-C scores) will be summarized and analyzed using the similar MMRM model described for the primary efficacy analysis. The analyses will be performed in the ITT data set.

CGI-C scores at each post-baseline visit will be analyzed using an MMRM model, including fixed, categorical effects for treatment, site, visit, and treatment-by-visit interaction, with continuous fixed covariates for baseline CGI-S.

PGI-C scores at each post-baseline visit will be analyzed using an MMRM model, including fixed, categorical effects for treatment, site, visit, and treatment-by-visit interaction.

8.1.4 Subgroup Analysis of PSPRS Total Score

To examine whether gender, age group, study site, country/region or other baseline variables have an impact on response to treatment, subgroup analyses on PSPRS total score will be conducted on change from baseline to last observations up to Week 52. Subgroup analyses will be performed using an ANCOVA model with the terms of treatment, site, subgroup variable, the treatment-by-subgroup variable interaction, and baseline score as a covariate. The subgroup analysis for country/region will be performed using the same model but with the study site nested within country/region. The hypothesis that consistent response to treatment across strata of a subgroup variable will be tested at the significance level of 0.100 by examining the *P* value of the treatment-by-subgroup interaction term in the ANCOVA model specified above. The statistical comparison of each ABBV-8E12 dose group with placebo within each 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 in the ITT data set.

8.1.5 Biomarker Analyses

An ANCOVA model will be used to evaluate CSF concentrations for total tau, free tau, and NFL for each scheduled time of evaluation during treatment. Corresponding analyses on plasma measurements of total tau and NFL will be performed. The observations will be classified by treatment and region, and the initial model will have an effect 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. If the test statistic on the interaction of treatment and region is not significant at level 0.050, the effect for interaction will be removed from the model. Within the framework of the analysis of covariance the means of the three treatments (with adjustment for baseline) will be estimated. The hypothesis of no difference between the 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. If the statistic on the interaction of treatment and region is significant at level 0.050, the tests for the comparison of the ABBV-8E12 dose levels to placebo will also be performed for each region within the framework of the final model.

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. If the logarithmic transformation is used, the comparison of the treatments will be in terms of the ratio of central values.

If data for other variables are reported, descriptive statistics will be provided and appropriate analyses performed. The association between the variables referred to here as biomarkers and measures of clinical efficacy will be explored.

8.1.6 Safety Analyses

All safety analyses will be performed on the safety data set unless otherwise specified. Comparisons between each ABBV-8E12 dose group and placebo will be performed with two-sided test at the significance level of 0.050, if applicable. All safety assessments that are taken no more than 20 weeks after the last dose of study drug administration will be included in the safety evaluation of the Double-blind Treatment Period, and all safety assessments that are taken 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.

Study Drug Exposure and Compliance

The number of doses on study drug will be summarized by treatment group and all treatment groups combined. The number and percentage of subjects with at least 90% compliance with study drug dosing will be summarized by treatment group and all treatment groups combined.

Adverse Events

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

All other safety assessments that are taken no more than 20 weeks after the last dose of study drug will be included in the safety evaluation of the Double-blind Treatment Period, and all safety assessments that are taken 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.

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

8.1.6.1 Analysis of Adverse Events

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

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

8.1.6.2 Analysis of Laboratory Tests

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

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

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

8.1.6.3 Analysis of Vital Signs and Weight

Vital sign variables include pulse rate, systolic blood pressure, and diastolic blood pressure, body temperature, weight, and BMI. Pulse rate and blood pressure variables will include measurement in the supine position, measurement in the standing position and the orthostatic change (from supine to standing).

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

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

8.1.6.4 Analysis of ECG Variables

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

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

8.1.6.5 Analysis of C-SSRS

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

- Answered 'Yes' to each C-SSRS item
- Had suicidal ideation (defined as answering 'Yes' to one or more suicidal ideation items)

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

8.1.7 Pharmacokinetics

8.1.7.1 Tabulations and Summary Statistics

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

CSF concentration data after the fifth dose (for subjects in Cohort 1 and Cohort J1) and the final dose will be tabulated and summarized by dose level.

8.1.7.2 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, classification by time and the interaction of dose level and time. The subjects will be viewed as a random sample, and an appropriate structure will be selected for the covariance matrix of the observations from a subject. The concentration central value (back transformation of the estimate of the mean of the transformed data) versus time curves for the two dose levels will be plotted on the same graph.

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 region, and the initial model will contain an effect for the interaction of dose level and region. Body weight will be a covariate. Other variables such as age and sex that might explain some of the variability among subjects will be considered for inclusion as covariates. 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. If the test statistic for interaction of dose level and region is not significant at level 0.100 for at least one of the three exposure variables for the dose interval beginning at Day 85, the effect for interaction will be removed from the model for all variables for both dose intervals. For each of the two dose intervals for each variable, the hypothesis of no difference between the dose level main effects will be tested (a composite assessment across the regions) within the framework of the final model. If the final model contains an effect for interaction of dose level and region and if the test statistic on interaction is

significant at level 0.100, the hypothesis of no difference between the dose levels will be tested for each region within the framework of the final model.

8.1.7.3 Missing Values and Model Violations

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

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.

Transformation of variables in order to avoid a meaningful degree of non-normality in the probability distributions is discussed in Section 8.1.7.2. If an adequate transformation is not found for a variable, then a non-parametric analysis may be performed.

8.1.7.4 Population Pharmacokinetic and Exposure-Response Analysis

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

Population pharmacokinetic analyses will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (version VII, or higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies and Cohort 1 and Cohort J1 of this study. Apparent CL and volume of distribution (V) of ABBV-8E12 will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters may be fixed if useful in the analysis.

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

The objective function of the best model is significantly smaller than the alternative model(s).

The observed and predicted concentrations from the preferred model are more randomly distributed across the line of unity (a straight line with zero intercept and a slope of one) than the alternative model(s).

Visual inspection of model fits, standard errors of model parameters and change in inter-subject and intra-subject error.

Once an appropriate base pharmacokinetic model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM. The relationship between these conditional estimates of CL and V values and potentially physiologically relevant or clinically meaningful covariates (such as subject age, sex, body weight, concomitant medications, laboratory markers of hepatic or renal function, etc.) will be explored using either stepwise forward selection method, or generalized additive method (GAM), or another suitable regression/smoothing method at a significance level of 0.050. After identification of all relevant covariates, a stepwise backward elimination of covariates from the full model will be employed to evaluate the

significance (at $P < 0.005$, corresponding to a decrease in objective function > 7.88 for one degree of freedom) of each covariate in the full model.

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

Relationships between exposure and clinical observations (primary efficacy variable) will be explored with Cohort 1, Cohort J1, and Cohort 2 data combined. Exposure-response relationships for secondary efficacy variables and/or some safety measures of interest may also be explored. Initially, the time-course of placebo response will be modeled. Subsequently the relationship between exposure (e.g., population pharmacokinetic model predicted average concentrations or AUC or trough concentrations of the individual model-predicted pharmacokinetic profiles, or some other appropriate measure of exposure) and drug effect will be explored after accounting for the time-course of placebo response. Several classes of models (e.g., linear, log-linear, exponential, E_{max}, sigmoid E_{max}, etc.) will be evaluated to characterize the exposure-response relationship based on the observed data.

Additional analyses will be performed if useful and appropriate.

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

8.1.8 Immunogenicity

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

Additional analyses will be performed if useful and appropriate.

8.1.9 Data Monitoring Committee (DMC)

This study will utilize a DMC consisting at least 2 external clinicians, at least 1 external statistician, and at least 1 external pharmacokineticist. The DMC will review unblinded

safety and efficacy data and make recommendations to AbbVie based on the totality of available trial data. An independent Statistical and Data Analysis Center (SDAC) and Exposure-Response Analysis Center (ERAC) will provide service to the DMC. Unblinded data will be kept by the SDAC and ERAC that will be conducting the analysis and preparing unblinded reports for the DMC and will not be released to the study team or study sites. The DMC will provide recommendations about continuing, modifying, or stopping the trial for safety or efficacy reasons. The DMC membership and responsibilities will be documented in the DMC charter. After each DMC meeting, the chair of the DMC will communicate its recommendations to the designated AbbVie Point of Contact, as described in the DMC charter. The AbbVie Representative will triage the recommendations to either the AbbVie Study Team if the recommendation can be implemented without unblinded data review or the AbbVie Internal Review Committee (IRC) if unblinded data review is required. The AbbVie IRC will consist of a group of senior individuals representing, at a minimum, the Therapeutic Area (TA), Pharmacovigilance and Patient Safety (PPS), Regulatory Affairs (RA), Clinical Pharmacology and Pharmacometrics (CPPM), and Data and Statistical Sciences (DSS), who are not directly involved in the conduct of this clinical trial. Members of IRC have technical depth to competently make decisions based on DMC recommendations to either (a) terminate the study or (b) implement significant unplanned protocol modifications.

8.1.10 Interim Analyses

Regular interim safety analyses and preplanned interim futility evaluation(s) will be performed in this study. Assessment of safety and efficacy data at interim(s) will be performed by the DMC.

Safety Interim Analyses

The DMC will evaluate the available unblinded safety data and communicate their recommendations to the AbbVie Point of Contact. The first three mandatory DMC reviews of unblinded safety data will take place after the 10^{th}, 20^{th}, and 30^{th} 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. An additional mandatory DMC review for Japanese subjects will take place after the 9th subject enrolled in Japan (Cohort J1) has been administered their second dose and results for the Day 15 Safety labs and MRI performed within 2 weeks after their second dose, are available for comparison with previous DMC review results as Cohort J1 patients' safety assessment. The data set will consist of all of the available safety and pharmacokinetic data in the study, including the data of any subjects from Cohort 2 who have received at least one dose of study drug. Additional DMC reviews of available safety data will occur after a total of approximately 80, 130, 180, 240, and 330 subjects are randomized and every 6 months thereafter until the study has completed. Ad hoc meetings may occur as needed.

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. Details of safety interim analyses will be specified in the DMC Charter.

Futility Interim Analyses

Preplanned futility interim analyses may be performed. The SDAC will be responsible for generating and providing unblinded statistical tables, figures, and listings to the DMC for the interim review for futility. The DMC will communicate their recommendations to stop the trial for futility or to continue the study without modification to the AbbVie Contact who will share it with the IRC only. The study will not be stopped because of positive results at the interim analyses and the α to be administratively spending at each interim analysis will be 0.00001. DMC recommendations will not be communicated to the study team, study investigators, or any parties outside of the Sponsor. 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.

Details of futility interim analyses plan will be described in the DMC charter and the SAP.

8.2 Determination of Sample Size

Approximately 330 PSP subjects (110 subjects/group) will be enrolled and randomized to two ABBV-8E12 dose groups and the placebo group with 1:1:1 randomization ratio. This sample size has at least 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 of multiple comparisons between two doses and placebo at the two-sided 5% significance level. This sample size calculation was performed 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[31] 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.

9.0 Ethics

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

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

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

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

Prior to the initiation of any screening or study-specific procedures, the investigator or his/her representative will explain the nature of the study to the subject, their study partner, and legally authorized representative (LAR) (if applicable), and answer all questions regarding this study.

In Germany, if the investigator screening the subject has doubts about subject's cognitive capability, evaluation by an independent psychiatrist will be conducted to assess subject's ability to provide consent independently. Additionally, for all subjects with an MMSE score of 24 or less at the time of study entry, an evaluation by an independent psychiatrist will also be requested. If, in the opinion of the independent psychiatrist, subject is unable to provide consent independently, the subject will not be enrolled in the study.

Each informed consent will be reviewed, signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. An informed consent statement will also be reviewed, signed and dated, by the subject's study partner prior to beginning any study related screening activities. A copy of each informed consent will be given to the subject and their study partner and each original will be placed in the subject's medical record. An entry must also be made

in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

If at any time during the study, a subject experiences diminished decision-making capacity, an informed consent must be obtained from an LAR. In Germany, where the subject's LAR is not permitted to sign the IEC/IRB approved Informed Consent form on behalf of the subject, evaluation by an independent psychiatrist will be sought if the investigator who is evaluating the subject for inclusion in the study doubts the subject's cognitive ability to independently provide informed consent.

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

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

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

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

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

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

10.2 Case Report Forms

Electronic case report forms (eCRFs) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

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

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person

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

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

11.0 Data Quality Assurance

Prior to enrolling any subject in the study, an initiation meeting will be held with AbbVie personnel, the investigator(s), and the study coordinators/project manager(s). This meeting will include a detailed discussion and review of the protocol and essential documents, performance of study procedures, case report form completion and specimen collection methods.

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

12.0 Use of Information

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

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

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

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

Any research that may be done using research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results

will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from research may be provided to investigators and used in scientific publications or presented at medical conventions. Research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

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

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

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

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

14.0 Investigator's Agreement

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

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Multiple Dose Study to Assess Efficacy, Safety, Tolerability, and Pharmacokinetics of ABBV-8E12 in Progressive Supranuclear Palsy
Protocol Date:	13 December 2018

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator

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

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

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not making any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Clinical
		Statistics
		Pharmacokinetics
		Clinical
		Bioanalysis

Appendix C. 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									
PSP Clinical Features	X													
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				
Clinical Laboratory Tests[e]	X		X				J1	C1/J1	C1/J1	X				
Brain MRI[e,k,l]	X						C1/J1			X				

	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**
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
PSP Rating Scale (PSPRS)	1		1							1				
CGI-S	2	5	2						5	2				5
CGI-C									6	3				6
SEADL	3		3							4				

	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**
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
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 confinement[t]			J1											
Telephone Contact[v]										X				

	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
PSP Rating Scale (PSPRS)	1			1				1		
CGI-S	2		5	2			5	2		

	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**
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]										
Telephone Contact[v]	X			X				X		

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 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.
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.
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.

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.
v. Only applicable to subjects who prematurely discontinue. Verify consent was obtained prior to making contact.
The NNIPPS-PPS will not be administered in Japan.
Notes: 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.

Appendix D. Potentially Clinically Significant (PCS) Laboratory Value

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

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Hematology (continued)						
Lymphocyte count increased	3	**> 20× 10^9/L (i.e., > 20,000/mm^3)**	--	> 4 – 20× 10^9/L (i.e., > 4000 – 20,000/mm^3)	> 20× 10^9/L (i.e., > 20,000/mm^3)	--
Neutrophil count decreased	3	**< 1 × 10^9/L (i.e., < 1000/mm^3)**	< LLN – 1.5 × 10^9/L (i.e., < LLN – 1500/mm^3)	< 1.5 – 1 × 10^9/L (i.e., < 1500 – 1000/mm^3)	< 1– 0.5 × 10^9/L (i.e., < 1000 – 500/mm^3)	< 0.5 × 10^9/L (i.e., < 500/mm^3)
Platelet count decreased	2	**< 75 × 10^9/L (i.e., < 75,000/mm^3)**	< LLN – 75× 10^9/L (i.e., < LLN – 75,000/mm^3)	< 75 – 50 × 10^9/L (i.e., < 75,000 – 50,000/mm^3)	< 50 – 25 × 10^9/L (i.e., < 50,000 – 25,000/mm^3)	< 25 × 10^9/L (i.e., < 25,000/mm^3)
White blood cell decreased	3	**< 2× 10^9/L (i.e., < 2000/mm^3)**	< LLN – 3× 10^9/L (i.e., < LLN – 3000/mm^3)	< 3 – 2 × 10^9/L (i.e., < 3000 – 2000/mm^3)	< 2 – 1 × 10^9/L (i.e., < 2000 – 1000/mm^3)	< 1 × 10^9/L (i.e., < 1000/mm^3)
Chemistry						
Blood bilirubin increased	2	**> 1.5 × ULN**	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 10 × ULN	> 10 × ULN
Cholesterol high	4	**> 12.92 mmol/L (i.e., > 500 mg/dL)**	> ULN – 7.75 mmol/L (i.e., > ULN – 300 mg/dL)	> 7.75 – 10.34 mmol/L (i.e., > 300 – 400 mg/dL)	> 10.34 – 12.92 mmol/L (i.e., > 400 – 500 mg/dL)	> 12.92 mmol/L (i.e., > 500 mg/dL)
Creatinine increased	2	**> 1.5 × ULN**	> ULN – 1.5 × ULN or > 1 – 1.5 × baseline	> 1.5 – 3 × ULN or > 1.5 – 3 × baseline	> 3 – 6 × ULN or > 3 × baseline	> 6 × ULN
Gamma-Glutamyl Transpeptidase (GGT) increased	2	**> 2.5 × ULN**	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN

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

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

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

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

Appendix E. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 5.3.1.1 Study Procedures
Subsection PSP Clinical Features[32]
Add: new subsection title and text

PSP Clinical Features[32]

A detailed assessment of PSP signs and symptoms present at Screening will be collected and include the following:

- Ocular motor dysfunction
- Postural instability
- Akinesia
- Cognitive dysfunction

Section 15.0 Reference List
Add: new Reference 32

Hoglinger GU, Respondek G, Stamelou M, et al. Clinical diagnosis of progressive supranuclear palsy: The Movement Disorder Society Criteria. Mov Disord. 2017;32(6):853-64. Available from: doi: 10.1002/mds.26987.

Appendix B. List of Protocol Signatories

Previously read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Clinical
		Statistics
		Pharmacokinetics
		Clinical
		Bioanalysis

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Statistics
		Pharmacokinetics
		Clinical
		Bioanalysis

Appendix C. Study Activities
First table
Add: new activity "PSP Clinical Features" and "Telephone Contact[v]"

	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 Clinical Features	X													
Telephone Contact[v]										X				

Appendix C. Study Activities
Second table
Add: new activity "Telephone Contact[v]"

	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**
Telephone Contact[v]	X			X				X		

Appendix C. Study Activities
Second table
Add: new table note "v."

Only applicable to subjects who prematurely discontinue. Verify consent was obtained prior to making contact.