1.0 Title Page

Clinical Study Protocol M15-563

An Extension Study of ABBV-8E12 in Progressive Supranuclear Palsy (PSP)

Incorporating Administrative Change 1, Amendment 1, and Amendment 2

AbbVie Investigational Product:	ABBV-8E12
Date:	21 February 2019
EudraCT Number:	2017-001590-16
Development Phase:	2
Study Design:	Phase 2 extension of Study M15-562 to assess the long-term safety, tolerability, and efficacy of ABBV-8E12 in subjects with progressive supranuclear palsy (PSP)
Investigators:	Multicenter Trial: Investigator Information is on file at AbbVie
Sponsor:	AbbVie
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The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	19 May 2017
Amendment 1	29 March 2018

The purpose of this amendment is to:

- Update Section 5.2.1, Inclusion Criteria, to remove the need for subjects to sign an assent form.

  Rationale: *To align with Study M15-562 and clarify that subject assent is not required.*
- Update Section 5.3.1.1.9, 12-Lead Electrocardiogram, to remove the requirement for postdose ECG on Day 1.

  Rationale: *To align with Study M15-562.*
- Update Section 5.3.1.1.11, Magnetic Resonance Imaging, to remove the requirement that study entry MRI must be completed after other relevant procedures have been completed.

  Rationale: *To align Study M15-563 as an extension study to Study M15-562.*
- Update Section 5.3.1.1.11, Magnetic Resonance Imaging, to add that if a subject cannot undergo MRI for clinical reasons, the AbbVie TA MD should be consulted for approval.

  Rationale: *To reduce subject burden.*
- Update Section 5.3.1.1.12, Lumbar Puncture, to add that subjects who are unable to undergo an LP may be enrolled with permission of the AbbVie TA MD without the requirement of an LP during the study.

  Rationale: *To align with Study M15-562 procedures.*
- Update Section 5.3.1.1.13, Diagnostic Tools and Rating Scales, to add a Treatment Satisfaction Questionnaire for Medication, PSP Caregiver Questionnaires, and the BioStamp nPoint device.

Rationale: *To collect additional data related to the subject's caregiver. To collect data related to subject's movement.*

- Update Section 5.5.1, Treatments Administered, to align the infusion rates in this extension study with those of the parent study (Study M15-562).

  Rationale: *To maintain consistency and reduce subject burden.*

- Update Section 5.5.2.2, Storage and Disposition of Study Drug, to clarify the requirements for reporting temperature excursions.

  Rationale: *To clarify temperature reporting procedures.*

- Update Section 6.2.2, Reporting, to correct the time frame for which product complaints must be reported.

  Rationale: *To align with Sponsor updates.*

- Update Appendix C, Study Activities, to align with changes above as appropriate.

  Rationale: *To be consistent with the study design throughout the protocol.*

- Update Section 5.1, Overall Study Design and Plan: Description, to add a digital BioStamp substudy.

  Rationale: *To assess the utility of BioStamp digital sensor to monitor body position and gait.*

An itemized list of all changes made to this protocol under this amendment is located in Appendix E.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M15-563
Name of Study Drug: ABBV-8E12	**Phase of Development:** 2
Name of Active Ingredient: ABBV-8E12	**Date of Protocol Synopsis:** 21 February 2019
Protocol Title: An Extension Study of ABBV-8E12 in Progressive Supranuclear Palsy (PSP)	
Objectives: The primary objectives of this study are: • To assess the long-term safety and tolerability of ABBV-8E12 in subjects with PSP. • To assess the long-term efficacy of ABBV-8E12 in slowing disease progression in subjects with PSP as measured by the PSP Rating Scale (PSPRS). The secondary objectives of this study are: • To assess the long-term efficacy of ABBV-8E12 in slowing disease progression and functional impairment in subjects with PSP as measured by secondary endpoints. • To assess the pharmacokinetics of ABBV-8E12 in subjects with PSP. • To assess the long-term efficacy of ABBV-8E12 in slowing regional and/or whole brain atrophy in subjects with PSP as measured by volumetric magnetic resonance imaging (MRI). The exploratory objectives of this study are: • To assess the long-term efficacy of ABBV-8E12 in slowing disease progression and functional impairment in subjects with PSP as measured by exploratory endpoints. • To assess the long-term effect of ABBV-8E12 on cerebrospinal fluid (CSF) and plasma tau protein levels. • To assess the long-term effect of ABBV-8E12 on other potential CSF and plasma biomarkers of disease progression. • To assess body position and gait in a subset of participating subjects using BioStamp digital sensors.	
Investigators: Multicenter	
Study Sites: Approximately 60 multinational sites.	
Study Population: Adult male and female subjects with possible or probable PSP who complete Study M15-562, meet all inclusion criteria, and do not meet any exclusion criteria.	
Number of Subjects to be Enrolled: Up to the number of subjects enrolled in Study M15-562.	
Methodology: Study M15-563 is a long-term extension of the Phase 2, double-blind study, Study M15-562. Subjects who completed the 52-week Treatment Period in Study M15-562 will be eligible for enrollment into Study M15-563. All subjects in Study M15-563 will receive ABBV-8E12 as follows: 1) subjects who received placebo in Study M15-562 will be randomized, in a 1:1 ratio, to 1 of 2 ABBV-8E12 doses (2000 or 4000 mg); and 2) subjects who received ABBV-8E12 2000 or 4000 mg in Study M15-562 will continue on the same dose. Investigators and subjects will remain blinded to the treatment assignments in Study M15-562 and will be blinded to the dose level of ABBV-8E12 in Study M15-563.	

Methodology (Continued):

Subjects who enroll in Study M15-563 from Study M15-562 will complete baseline procedures and receive their first infusion of study drug on Day 1 of Study M15-563. Subjects will receive 3 infusions of study drug during the first 4 weeks of Study M15-563, the first on Day 1, the second on Day 15 (subjects who received placebo in Study M15-562 will receive ABBV-8E12 on Day 15 of Study M15-563, and subjects who received ABBV-8E12 in Study M15-562 will receive placebo on Day 15 of Study M15-563 to maintain the blind in Study M15-562), and the third on Day 29. After Day 29, subjects will receive study drug infusions every 28 days and will continue to receive ABBV-8E12 until one of the discontinuation criteria is met, until the study is discontinued by the Sponsor, or until the study reaches completion. Subjects will be observed on-site for at least 30 minutes after the end of study drug infusions. Subjects will return to the site approximately 20 weeks after their last dose for a post-treatment Follow-up Visit.

Safety and tolerability will be monitored throughout the study. Blood samples will be collected for pharmacokinetic and anti-drug antibodies (ADAs) assessments every 3 months during the first 6 months and every 6 months thereafter. Lumbar puncture will be performed every 6 months during the first year, then once a year thereafter; it is optional every 6 months in years 2 through 5. Volumetric MRI will be performed every 3 months in the first 6 months, then every 6 months thereafter. In a subset of subjects (up to 50) at participating sites, subjects will be assigned digital sensor BioStamp units to be worn for 1-week epochs starting on Day 1, Day 29 (Week 4), Day 57 (Week 8), and Day 85 (Week 12).

A Data Monitoring Committee (DMC) will review unblinded safety data and make recommendations to the Sponsor based on the totality of available clinical data. The DMC memberships, responsibilities, and operating logistics are documented in a DMC charter.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion Criteria:

- Subject completed the 52-week treatment period of Study M15-562.
- In the opinion of the Investigator, subject was compliant during participation in Study M15-562.
- 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.
- Subject voluntarily signed the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved Informed Consent Form, prior to the conduct of any study procedures, or, where applicable (i.e., countries other than Germany*) for a given subject, the subject's legally authorized representative (LAR) signed the IEC/IRB approved Informed Consent form on behalf of the subject, prior to the conduct of any procedures. *For 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.

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

Main Exclusion Criteria:

- Subject weighs less than 44 kg (97 lbs.) at time of study entry.
- Subject has any contraindication or inability to tolerate brain MRI (e.g., a pacemaker or any other implanted device or condition that would preclude proximity to a strong magnetic field).
- Subject has any significant change in his/her medical condition that could interfere with the subject's participation in the study, could place the subject at increased risk, or could confound interpretation of study results. The Investigator must re-evaluate the subject for continuing participation and consider any factors including the interim development of any clinically significant neurological, hematological, autoimmune, endocrine, cardiovascular, neoplastic, renal, hepatic, metabolic, psychiatric, pulmonary, gastrointestinal, or other major disorder.
- More than 8 weeks have elapsed since the subject received his/her last dose of study drug in Study M15-562.
- Subject is concurrently enrolled in another interventional clinical study involving a therapeutic agent.
- Subject is considered by the investigator, for any reason, to be an unsuitable candidate to receive ABBV-8E12 or the subject is considered by the investigator to be unable or unlikely to comply with the dosing schedule or study evaluations.

Investigational Product:	ABBV-8E12 (vials of 300 mg/15 mL and 1000 mg/10 mL)
Doses:	Doses will be administered on Day 1, Day 15 (placebo for subjects who received ABBV-8E12 in Study M15-562), Day 29, and every 28 days thereafter. • Dose level 1: 2000 mg • Dose level 2: 4000 mg Doses may be decreased after evaluation by the DMC of available safety, tolerability, and pharmacokinetic data.
Mode of Administration:	Intravenous infusion

Duration of Treatment: Subjects may continue study treatment until any of the criteria for discontinuation have been met, until the study is discontinued by the sponsor, or until the study reaches completion. Planned treatment duration is up to 5 years.

Discontinuation Criteria:

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

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

Criteria for Evaluation:

Efficacy:

Clinical and Cognitive Assessments:

Primary:

- PSPRS

Key Secondary:

- Unified Parkinson's Disease Rating Scale (UPDRS) Part II
- Clinical Global Impression of Change (CGI-C)
- Schwab and England Activities of Daily Living Scale (SEADL)

Additional Secondary:

- Clinical Global Impression of Severity (CGI-S)
- Patient Global Impression of Change (PGI-C)
- PSP Staging System (PSP-SS) (composite of items from PSPRS)
- Time to loss of ability to walk independently as measured by PSPRS item 26

Exploratory:

- Time to death
- EuroQuality of Life (EQ-5D)
- Letter Fluency Test (words per minute)
- Repeatable Battery for Assessment of Neuropsychological Status (RBANS)
- Color Trails Test (Parts 1 and 2)
- Natural History and Neuroprotection in Parkinson Plus Syndromes-Parkinson Plus Scale (NNIPPS-PPS) (not applicable in Japan)
- Frequency of hospitalizations related to PSP

Pharmacokinetics:

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

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 at each collection time point.

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

Immunogenicity:

ADAs will be determined in serum for assessment of immunogenicity.

Criteria for Evaluation (Continued):

Biomarkers:

CSF and Plasma Biomarkers:

- Tau in CSF and plasma
- Additional exploratory CSF and plasma-based pharmacodynamic 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

Digital Biomarkers:

- BioStamp sensor motor outcomes including posture, gait, and step count

Safety:

Adverse events and serious adverse events (SAEs) will be monitored throughout the dosing period and for approximately 20 weeks after the last dose. Safety evaluations will consist of 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, ECG, brain MRI including fluid attenuated inversion recovery (FLAIR), and immunogenicity as determined by ADA responses in blood.

Statistical Methods:

Efficacy:

All subjects who receive any infusion of ABBV-8E12 in Study M15-563 and have at least one efficacy evaluation after dosing will be assessed for efficacy. The analysis will be grouped by treatment sequences in Studies M15-562/M15-563: 2000/2000 mg, 4000/4000 mg, placebo/2000 mg, and placebo/4000 mg. The primary efficacy variable is the PSPRS total score. The primary analysis model is a likelihood-based, mixed-effect model, repeated measures (MMRM) analysis of the PSPRS total score at Study M15-563 Baseline and each post-baseline observation using all observed data. The model will include fixed, categorical effects for treatment, site, visit, and treatment-by-visit interaction. 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. The differences for placebo/2000 mg vs 2000/2000 mg and for placebo/4000 mg vs 4000/4000 mg at Study M15-563 Baseline and at the end of Study M15-563 Treatment Period will be presented together with a 95% confidence interval. This MMRM analysis will be applied to each efficacy variable with repeated measurements.

Statistical Methods (Continued):

Pharmacokinetics:

Summary statistics of serum concentration data for all subjects will be provided for each scheduled time of sampling with a breakdown by dose level and by whether treatment in Study M15-562 was with ABBV-8E12 or placebo.

Population pharmacokinetic analyses will be performed using the actual sampling time relative to the last administered dose. Pharmacokinetic data from this study may be combined with data from other ABBV-8E12 studies in the population pharmacokinetic analyses. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (version 7, or higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies. CL and 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.

CSF concentration data will be summarized by treatment.

Immunogenicity:

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

Biomarkers:

Descriptive statistics will be provided for each scheduled time of measurement with a breakdown by dose level and by whether treatment in Study M15-562 was with ABBV-8E12 or placebo. For CSF and plasma concentrations of tau and for volumetric MRI variables, a repeated means analysis will be performed with classification by dose level and by time of assessment. An effect for the interaction of dose level and time will be included. The model will include covariates for level at Baseline, and for volumetric MRI variables, a measure of head size will be a covariate. The data set will include the data for Week 76 and later for the subjects assigned to placebo in Study M15-562, but with a shift in time to reflect that these subjects began treatment with ABBV-8E12 only on Day 1 of this study. The model will have an effect to distinguish between assignment to ABBV-8E12 and placebo in Study M15-562. Digital substudy endpoints will be handled in a separate scientific report.

Safety:

Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events will be tabulated by MedDRA System Organ Class (SOC) and Preferred Term with a breakdown by treatment sequence in Studies M15-562/M15-563: 2000/2000 mg, 4000/4000 mg, placebo/2000 mg, and placebo/4000 mg. Tabulations will also be provided by rating of severity (mild, moderate, and severe) and by whether possibly related to study drug. The number and percentage of subjects experiencing treatment-emergent SAEs (including deaths) and adverse events leading to premature discontinuation of study drug will be tabulated according to the MedDRA SOC and preferred term by treatment group. The number and percentage of subjects with laboratory test values and measurements on vital signs that are potentially clinically significant, according to predefined criteria, will be tabulated as well. The percentage of subjects who have suicidal behavior, suicidal ideation only, and suicidal behavior or ideation from the C-SSRS assessment will be summarized by treatment sequence.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ADA	anti-drug-antibody
ANOVA	analysis of variance
ATEMS	AbbVie Temperature Excursion Management System
AUC	area under the concentration time curve
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
COMT	catechol-*O*-methyltransferase
CRA	clinical research associate
CRF	case report form
CS	clinically significant
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTT	Color Trails Test
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DTI	diffusion tensor imaging
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
E_{max}	maximum effect
EQ-5D	EuroQol-5D
ERAC	exposure-response analysis center
Fc	fragment crystallizable
FLAIR	fluid attenuated inversion recovery
FSH	follicle-stimulating hormone
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice

IB	investigator brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IgG4	subclass of IgG antibody
IMP	investigational medicinal product
IP	intraperitoneal
IRB	institutional review board
IRC	internal review committee
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVR/IWB	interactive voice-response/interactive web-based (system)
LAR	legally authorized representative
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measures
MRI	magnetic resonance imaging
NCS	not clinically significant
NFTs	neurofibrillary tangles
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
PCS	potentially clinically significant
PGI-C	Patient Global Impression of Change
PK	pharmacokinetic(s)
PRN	as needed
PSP	Progressive Supranuclear Palsy
PSPRS	Progressive Supranuclear Palsy Rating Scale
PSP-SS	Progressive Supranuclear Palsy Staging System
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
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
RBC	red blood cell
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
SNRIs	serotonin-norepinephrine reuptake inhibitors
SOC	system organ class
SSRIs	selective serotonin reuptake inhibitors
SUSAR	suspected unexpected serious adverse reactions
TA MD	therapeutic area medical director
TEAE	treatment-emergent adverse event
UPDRS	Unified Parkinson's Disease Rating Scale
V	volume of distribution
WBC	white blood cell
WOCBP	women of childbearing potential

Definition of Terms

Visit Window	Visits must 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 on 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 3 for recommended sequence.

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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 to 7 per 100,000.[1] Within the US, the disease affects approximately 20,000 individuals. No geographical, ethnic, gender, or racial disparity in PSP frequency is apparent. 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] Although 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 that 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.

No treatments for PSP are currently approved.[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 immunoglobulin G 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. NFTs, a characteristic pathologic feature in PSP and several other neurological disorders including corticobasal degeneration (CBD) and Alzheimer's disease, are formed inside of neurons by aggregated and post-translationally modified tau. Based on preclinical evidence, ABBV-8E12 may be able to block tau 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]

Preclinical 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 effect level (NOAEL) was 250 mg/kg.

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

Clinical Experience

Compassionate-Use Protocols

Treatment with ABBV-8E12 was administered to 1 patient with PSP under an expanded access protocol in the United States (Study C_2N-8E12-EA-001) and to 1 patient with CBD under a single named patient compassionate-use plan in Germany (Study C_2N-8E12-DE-003). ABBV-8E12 is currently being administered to 1 patient with chronic traumatic encephalopathy (CTE) under an expanded access, investigator-initiated protocol in the US (Study C16-344).

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 9 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. The CTE patient has received multiple infusions of ABBV-8E12 from 2.5 to 25 mg/kg.

Phase 1 Single Ascending Dose Study

Study C_2N-8E12-WW-104 is a single-ascending dose (SAD) trial in 30 subjects with PSP in which 5 dose levels of ABBV-8E12 (2.5 mg/kg, 7.5 mg/kg, 15 mg/kg, 25 mg/kg, and 50 mg/kg) were evaluated. Twenty-three subjects received ABBV-8E12, and 7 subjects received placebo.

Three serious adverse events (SAEs) were reported:

- One subject (15 mg/kg group) experienced an SAE of subdural hematoma resulting from a fall that was assessed by the investigator as possibly related to study drug; the sponsor judged the SAE to be unlikely related to study drug, and likely related to the underlying PSP.
- One subject (25 mg/kg group) was hospitalized due to a severe increase in agitation, anxiety, and perseverative behavior, and 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 subject's underlying disease, but that study drug cannot be ruled out as a contributing factor, so the event was therefore assessed as possibly drug related.
- One subject (50 mg/kg group) 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 no clinically relevant patterns of adverse events or abnormal laboratory findings were observed. Based on available anti-drug antibody (ADA) data in Study C_2N-8E12-WW-104, no ADAs were detected in postdose samples on Day 14 or Day 28.

Pharmacokinetic data from Study C_2N-8E12-WW-104 indicate dose-proportional increases in area under the concentration time curve (AUC) and in the maximum observed serum concentration (C_{max}) from 2.5 to 50 mg/kg. Half-life ranged from 27 to 37 days.

The mean peak ABBV-8E12 concentration (T_{max}) was attained at a range of 0.3 to 4.6 hours after dosing. ABBV-8E12 cerebrospinal fluid (CSF) to plasma concentration ratios ranged from 0.181% to 0.385% with no clear trend across dose levels.

Phase 2 Multiple-Dose Study in Subjects with PSP

Study M15-562 is an ongoing Phase 2, randomized, multicenter, double-blind, placebo-controlled, multiple-dose trial in which 2 dose levels of ABBV-8E12 are being evaluated (2000 and 4000 mg). A total of 378 subjects are planned.

3.1 Differences Statement

Study M15-563 is a Phase 2, multicenter, long-term extension of Phase 2 Study M15-562. Study M15-562 is a randomized, placebo-controlled clinical study to evaluate efficacy, safety, tolerability, immunogenicity, and pharmacokinetics (PK) of multiple doses of ABBV-8E12 in subjects with PSP. The Treatment Period in Study M15-563 is up to 5 years compared with up to 52 weeks in Study M15-562. Subjects who complete the 52-week treatment period in Study M15-562 and meet all entry criteria will be eligible to enroll in Study M15-563. All subjects in Study M15-563 will be on active treatment (ABBV-8E12 2000 or 4000 mg), whereas Study M15-562 is placebo-controlled.

3.2 Benefits and Risks

Patients with PSP suffer serious debilitating symptoms that affect gait and balance, vision, swallowing and speaking, and cognition. The disease is characterized by tau aggregation and is ultimately fatal. No approved treatment exists.

ABBV-8E12, a humanized monoclonal antibody that is being developed for the treatment of PSP, may block tau seeds from propagating between cells, and therefore, may slow disease progression, thus providing a viable treatment option for patients with PSP. The safety profile of ABBV-8E12 to date has been favorable, and no clinically relevant patterns of adverse events or abnormal laboratory findings have been observed. Further, no ADAs were detected in postdose samples in an SAD study in subjects with PSP.

Risks include infusion reactions and possibly life-threatening allergic reactions; however, no systemic hypersensitivity or injection site reactions have been reported to date. Subjects will be monitored closely during clinical trials for the occurrence of these events, study drug will be withdrawn immediately in the case of allergic reaction, and appropriate medical therapy will be provided for any adverse event.

Evidence of efficacy demonstrated in preclinical studies and safety data from clinical studies obtained to date provide a strong rationale for continuing the assessment of safety and efficacy of ABBV-8E12. The benefit-risk profile of ABBV-8E12 will be further defined in Study M15-562, which is ongoing, and in Study M15-563, which is described herein.

4.0 Study Objectives

The primary objectives of this study are:

- To assess the long-term safety and tolerability of ABBV-8E12 in subjects with PSP.
- To assess the long-term efficacy of ABBV-8E12 in slowing disease progression in subjects with PSP as measured by the PSP Rating Scale (PSPRS).

The secondary objectives of this study are:

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

The exploratory objectives of this study are:

- To assess the long-term efficacy of ABBV-8E12 in slowing disease progression and functional impairment in subjects with PSP as measured by exploratory endpoints.
- To assess the long-term effect of ABBV-8E12 on CSF and plasma tau protein levels.
- To assess the long-term effect of ABBV-8E12 on other potential CSF and plasma biomarkers of disease progression.
- To assess body position and gait in a subset of participating subjects using BioStamp digital sensors.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

Overview

Study M15-563 is a long-term extension of Study M15-562, a Phase 2, randomized, multiple-dose, multicenter study in subjects with PSP. Subjects who completed the 52-week Treatment Period in Study M15-562 and meet all entry criteria will be eligible for enrollment into Study M15-563. Study M15-562 was designed to randomize 378 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, the number of subjects who will participate in Study M15-563 will be up to the number of subjects enrolled in Study M15-562 (the actual number of subjects who enroll in Study M15-563 will depend on the number of subjects from Study M15-562 who are eligible and consent to rollover). The study will be conducted at approximately 60 multinational sites.

Study M15-563 will consist of a treatment period of up to 5 years and a post-treatment follow-up visit approximately 20 weeks after the last dose of study drug (including subjects who prematurely discontinue treatment). All subjects will receive ABBV-8E12 as follows: 1) subjects who received placebo in Study M15-562 will be randomized, in a

1:1 ratio, to 1 of 2 ABBV-8E12 doses (2000 or 4000 mg); and 2) subjects who received ABBV-8E12 2000 or 4000 mg in Study M15-562 will continue on the same dose. Refer to Section 5.5.3 for detailed information on randomization. Investigators and subjects will remain blinded to the treatment assignments in Study M15-562 and will be blinded to the dose level of ABBV-8E12 in Study M15-563.

Subjects from Study M15-562 will complete baseline procedures and receive the first infusion of study drug on Day 1 of Study M15-563. For subjects who do not have interruptions in study drug administration between Study M15-562 and Study M15-563 (i.e., the duration between the last dose of study drug in Study M15-562 and the first dose of study drug in Study M15-563 is no more than 45 days), procedures that were performed at the Week 52 Visit in Study M15-562 do not need to be repeated for the Day 1 Visit in Study M15-563. Week 52 procedures from Study M15-562 cannot be used to satisfy the Day 1 requirements for Study M15-563 if more than 45 days (but less than 8 weeks) have elapsed since the subject's last dose of study drug in Study M15-562; in that case, Day 1 activities for Study M15-563 must be performed.

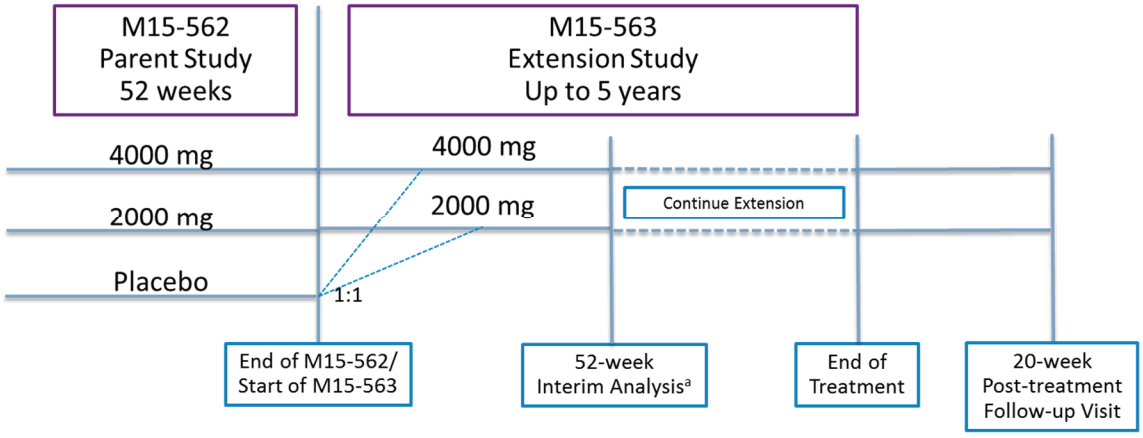
Study drug will be infused 3 times during the first 4 weeks: on Days 1, 15, and 29. Subjects who received placebo in Study M15-562 will receive ABBV-8E12 on Day 15 in Study M15-563, and subjects who received ABBV-8E12 in Study M15-562 will receive placebo on Day 15 in Study M15-563 (to maintain the blind in Study M15-562). After Day 29 of Study M15-563, study drug will be administered every 28 days until one of the discontinuation criteria is met, until the study is discontinued by the sponsor, or until the study reaches completion. The rate of infusion for each subject will be based upon that subject's most recently obtained weight and will range from 3.5 to 4.7 mL/min (210 to 282 mL/hr) (refer to Section 5.5.1 for details on infusion rates). Subjects will be observed on-site for at least 30 minutes after the end of study drug infusions.

Study drug will be administered and study procedures will be performed as shown in Appendix C. Safety and tolerability will be monitored throughout the study. Blood samples will be collected for pharmacokinetic and anti-drug antibodies (ADA) assessments every 3 months during the first 6 months, and every 6 months thereafter.

Lumbar puncture will be performed every 6 months during the first year, then once a year thereafter; it is optional every 6 months in years 2 through 5. Volumetric MRI will be performed every 3 months during the first 6 months, then every 6 months thereafter. In a subset of subjects (up to 50) at participating sites, subjects will be assigned digital sensor BioStamp units to be worn for 1 week epochs starting on Day 1, Day 29 (Week 4), Day 57 (Week 8), and Day 85 (Week 12).

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

Figure 1. Study Schematic



a. Additional interim analyses may be performed.

DMC Review of Safety Data

A Data Monitoring Committee (DMC) will review unblinded safety data and make recommendations to the Sponsor based on the totality of available clinical data. The DMC memberships, responsibilities, and operating logistics are documented in a DMC charter. The DMC consists of at least 2 external clinicians, at least 1 external statistician, and at least 1 external pharmacokineticist.

The data set reviewed by the DMC will consist of all available safety and pharmacokinetic data in the study, including data from any subjects who have received at least 1 dose of study drug.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

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

1. The subject voluntarily signed the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved Informed Consent form, prior to the conduct of any study procedures, or, where applicable (i.e., countries other than Germany*) for a given subject, the subject's legally authorized representative (LAR) signed the IEC/IRB approved Informed Consent form on behalf of the subject, prior to the conduct of any procedures. *For 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.
2. The subject completed the 52-week treatment period in Study M15-562.
3. In the opinion of the investigator, the subject was compliant during participation in Study M15-562.
4. The 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 regarding the subject's functional abilities.
5. If female, the 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 of > 40 IU/L.

  OR

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

  OR

  a woman of childbearing potential (WOCBP) practicing at least 1 protocol-specified method of birth control (refer to Section 5.2.4), starting on Study Day 1 through at least 20 weeks after the last dose of study drug.

6. If a male subject is sexually active, he must agree from Study Day 1 through at least 20 weeks after the last dose of study drug, to practice protocol specified contraception (refer to Section 5.2.4).

7. Female subjects of childbearing potential must have a negative urine pregnancy test result on Day 1.

Rationale for the Inclusion Criteria

1	In accordance with the harmonized Good Clinical Practice (GCP)
2 – 4	To select subject population appropriate for this study
5 – 7	The effects of ABBV-8E12 on pregnancy are currently unknown

5.2.2 Exclusion Criteria

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

1. The subject weighs less than 44 kg (97 lbs) at study entry.

2. The subject has any contraindication or inability to tolerate brain MRI (e.g., a pacemaker or any other implanted device or condition that would preclude proximity to a strong magnetic field).

3. The subject has any significant change in his/her medical condition that could interfere with the subject's participation in the study, could place the subject at increased risk, or could confound interpretation of study results. The Investigator must re-evaluate the subject for continuing participation and consider any factors including the interim development of any clinically significant neurological, hematological, autoimmune, endocrine, cardiovascular, neoplastic, renal, hepatic, metabolic, psychiatric, pulmonary, gastrointestinal, or other major disorder.
4. More than 8 weeks have elapsed since the subject received his/her last dose of study drug in Study M15-562.
5. The subject is concurrently enrolled in another interventional clinical study involving a therapeutic agent.
6. The subject is considered by the investigator, for any reason, to be an unsuitable candidate to receive ABBV-8E12 or the subject is considered by the investigator to be unable or unlikely to comply with the dosing schedule or study evaluations.
7. The subject is female and is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 20 weeks after the last dose of study drug.
8. The subject is male and is considering fathering a child or donating sperm during the study or for approximately 20 weeks after the last dose of study drug.

Rationale for Exclusion Criteria

1, 2, 4 – 6	To ensure the appropriate subject population
3	To ensure the safety of the subjects
7, 8	The effects of ABBV-8E12 on pregnancy are currently unknown

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

The AbbVie therapeutic area medical director (TA MD) should be contacted with any questions regarding concomitant or prior therapy(ies), or prohibited medications.

5.2.3.1 Concomitant Therapy

All concomitant medications should remain at stable doses for the duration of the study unless a change in regimen is medically necessary; any change in dose must be recorded.

The following medications are permitted:

- Ramelteon, trazodone, amitriptyline, and mirtazapine for sleep; low doses of clozapine and quetiapine are also permitted for sleep.
- Selective benzodiazepines and gamma-aminobutyric acid (GABA) agonists, zolpidem, zaleplon, eszopiclone, alprazolam, clonazepam, and lorazepam for sleep and anxiety.
- Atypical antipsychotics, clozapine (≤ 300 mg [consult AbbVie TA MD for doses > 300 mg]) 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).

5.2.3.2 Prohibited Therapy

Subjects should not receive the medications listed in Table 1 unless approved by the Investigator in consultation with the Sponsor. This list is not comprehensive.

Table 1. Prohibited Medications

Anticoagulants (exclusionary for lumbar puncture)
Examples
Vitamin K antagonists
Dabigatran
Enoxaparin sodium
Rivaroxaban
Apixaban
Heparin
Neuroleptics:[a] prohibited throughout the duration of the study
Examples
Chlorpromazine
Fluphenazine
Loxapine
Perphenazine
Thioridazine
Thiothixene
Trifluoperazine
Haloperidol
Benzodiazepines/GABA agonists:[a] prohibited throughout the duration of the study
Examples
Chlordiazepoxide
Diazepam
Midazolam
Flurazepam
Temazepam
Meprobamate
Triazolam

GABA = gamma-aminobutyric acid

a. Excluding the selected compounds mentioned in Section 5.2.3.1.

Additional recommendations are as follows:

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 (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 subject safety or emergent symptom control; however, ongoing use of PRN medications should be discussed with the AbbVie TA MD. If a subject requires PRN use of a medication with psychotropic effects, subject efficacy scales 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 electronic case report form (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.

5.2.4 Contraception Recommendations

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 an 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 (per local regulation), on Day 1 (or earlier) 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 Day 1.
  - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Day 1.
  - Bilateral tubal occlusion/ligation.
  - Vasectomized partner(s) and is the sole sexual partner of the woman of childbearing potential trial participant.
  - Intrauterine device (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 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).

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 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 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

5.3.1.1.1 Identification of Study Partner

To be eligible for enrollment, 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. It is preferable that the same person act as the subject's study partner for the duration of the study.

5.3.1.1.2 Medical History Update

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

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

5.3.1.1.3 Physical Examination

Symptom-driven physical examinations will be performed at the times indicated in the Study Activities Table (Appendix C). Additional symptom-directed physical examinations 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.

5.3.1.1.4 Orthostatic Vital Signs

Body temperature and orthostatic vital signs (blood pressure and pulse rate) will be measured at the times indicated in the Study Activities Table (Appendix C).

Supine blood pressure and pulse rate measurements should be followed by measurements while standing (after 2 minutes). Study staff should make efforts to measure on the same arm and with the same method, including recording of the arm and method in the subject's source documentation.

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

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

5.3.1.1.5 Vital Signs

Body temperature and vital signs will be measured at the times indicated in the Study Activities Table (Appendix C).

Blood pressure and pulse rate are to be measured while the subject has been sitting for at least 5 minutes. Study staff should make efforts to measure on the same arm and with the same method, including recording of the arm and method in the subject's source documentation.

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

5.3.1.1.6 Body Weight

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

5.3.1.1.7 Pregnancy Testing

WOCBP must have a negative urine pregnancy test result on Day 1. Pregnancy testing should be performed during treatment at the times indicated in the Study Activities Table (Appendix C), including at the last dose of study drug and for at least 20 weeks after the last dose of study drug. WOCBP must also have a negative urine pregnancy test result prior to any radiological procedures.

5.3.1.1.8 Neurological Examination

A neurological examination will be performed at the times indicated in the Study Activities Table (Appendix C). The neurological exam performed on Day 1 will serve as the baseline for clinical assessment. Symptoms identified on Day 1 will be recorded as adverse events for Study M15-562; new symptoms or current symptoms that change in severity or frequency after Day 1 will be recorded as adverse events for Study M15-563.

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).

5.3.1.1.9 12-Lead Electrocardiogram

Procedure

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

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

ECGs will be collected as single ECGs as follows:

- **Day 1 (Dose 1)**
  - Pre-dose (just prior to pre-infusion PK sample collection and the start of infusion)

- **Weeks 12, 24, 52, 104, 156, 208, and 260**
  - Pre-dose (just prior to the start of infusion, when applicable [no dose at Week 260])

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 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, adverse event assessment).

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 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.

5.3.1.1.10 Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests listed in Table 2 at the times indicated in the Study Activities Table (Appendix C).

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

Table 2. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	BUN	Specific gravity
Hemoglobin	Creatinine	Ketones
RBC count	Total bilirubin	pH
WBC count	Albumin	Protein
Neutrophils	AST	Glucose
Bands (if detected)	ALT	Blood
Lymphocytes	ALP	Microscopic examination, if dipstick results are positive
Monocytes	Sodium	
Basophils (if detected)	Potassium	**CSF Basic Laboratory Tests[c]**
Eosinophils (if detected)	Calcium	
Platelet count (estimate not acceptable)[a]	Inorganic phosphate	RBC, WBC with differential
MCV	Uric acid	Total protein
MCHC	Cholesterol	Albumin
PT	Total protein	Glucose
aPTT[b]	Glucose	
PT/INR[b]	Triglycerides	
	Bicarbonate/CO_2 chloride	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CSF = cerebrospinal fluid; CO_2 = carbon dioxide; INR = international normalized ratio; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell

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

b. Coagulation results to be reviewed by the investigator before lumbar puncture.

c. To be done at the local laboratory. 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.

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.

5.3.1.1.11 Magnetic Resonance Imaging

Volumetric MRI of the brain will be obtained for all subjects at the times indicated in the Study Activities Table (Appendix C) and interpreted by a radiologist or neurologist. Subjects will be positioned supine on the MRI bed and their heads 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 Day 1 MRI assessment will be used to rule out the presence of any intracranial masses 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
- Proton density/T2 weighted
- T2* weighted
- Diffusion tensor imaging (DTI)

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 study entry, 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. If a subject cannot undergo MRI due to clinical reasons, the AbbVie TA MD should be consulted for approval.

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.

5.3.1.1.12 Lumbar Puncture

Lumbar punctures to collect CSF will be performed on all subjects at the times indicated in the Study Activities Table (Appendix C). Lumbar puncture on Day 1 and lumbar puncture at completion (Week 260) or premature discontinuation should only be done if at least 3 months have elapsed since the previous lumbar puncture.

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 laboratory tests will be analyzed locally at the applicable clinical site after each lumbar puncture/CSF collection. These measures include cell counts (RBC and WBC with differential), total protein, albumin, and glucose (Refer to Table 2 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.

Subjects who are not able to undergo an LP may be enrolled with permission of the AbbVie TA MD without the requirement of an 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 subject on possible side effects and limitations on strenuous physical activity and driving.

5.3.1.1.13 Diagnostic Tools and Rating Scales

Overview

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 to ensure consistency and reliability. Assessments will be performed at the times indicated in Table 3 and in the Study Activities Table (Appendix C).

Table 3. Diagnostic Tools and Scale Order, and Duration of Administration

Diagnostic Tools and Scales[a,b]	Approx. Duration (min)	S/SP	Treatment Period												20 Weeks Post Last Dose F/U
			Year 1				Year 2		Year 3		Year 4		Year 5		
			Day 1[c]	Wk 12	Wk 24	Wk 52	Wk 76	Wk 104	Wk 128	Wk 156	Wk 180	Wk 208	Wk 232	Wk 260 Completion/ Premature D/C	
PSPRS	10	S and SP	1	1	1	1	1	1	1	1	1	1	1	1	1
CGI-S	40 – 60	S and SP	2	2	2	2	2	2	2	2	2	2	2	2	2
CGI-C	1	S and SP	3	3	3	3	3	3	3	3	3	3	3	3	3
SEADL	2	S	4	4	4	4	4	4	4	4	4	4	4	4	4
UPDRS Part II	10	S	5	5	5	5	5	5	5	5	5	5	5	5	5
RBANS	25	S				6		6		6		6		6	
CTT Parts 1 & 2	5 – 10	S				7		7		7		7		7	
Letter Fluency Test (wpm)	1	S				8		8		8		8		8	
NNIPPS-PPS[d]	30 – 45	S and SP				9		9		9		9		9	
PGI-C[e]	1 – 2	S	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D[e]	8	S	X			X		X		X		X		X	
C-SSRS (at every visit)[f]	< 5	S	X	X	X	X	X	X	X	X	X	X	X	X	X
BioStamp nPoint[g]		S	X	X											
PSP Caregiver Questionnaires	25	SP	X		X	X	X	X	X	X	X	X	X	X	X
TSQM-9	5	S	X		X	X	X	X	X	X	X	X	X	X	X

Table 3. Diagnostic Tools and Scale Order, and Duration of Administration (Continued)

Approx = approximately; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; CTT = Color Trails Test; D/C = discontinuation; EQ-5D = EuroQol-5D; F/U = follow-up; min = minutes; NNIPPS-PPS = National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy; PGI-C = Patient Global Impression of Change; RBANS = Repeatable Battery for Assessment of Neuropsychological Status; S = subject; SEADL = Schwab and England Activities of Daily Living Scale; SP = study partner; TSQM-9 = Treatment Satisfaction Questionnaire for Medication; UPDRS = Unified Parkinson's Disease Rating Scale; Wk = week; wpm = words per minute

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. The NNIPPS-PPS will not be administered in Japan.
e. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.
f. Scale may be administered/assessed at any time during the visit with the exception of the scheduled infusion time.
g. BioStamp nPoint will also be administered at Weeks 4 and 8.

The diagnostic tools and rating scales are as follows:

PSP Rating Scale[12]

The 28-item PSPRS was initially constructed in 1992 by Dr. Lawrence 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 to 4 months. Subject 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 2 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 3.

The PSP staging system (PSP-SS) used as an endpoint in this study was developed by Dr. Golbe and it emphasizes dysphagia and postural instability, the 2 features of PSP most likely to lead to life-threatening complications.[16] All the items used to devise the staging system are derivable from the PSPRS. The staging system uses the following items from the PSPRS: dysphagia for solids, dysphagia for liquids, gait and sitting down, each graded from 0 to 4. Only the first is obtained by history, the others by examination. The PSP-SS contains 6 stages defined by the total scores of the 4 items: Stage 0: total 0, Stage 1: total 1 – 4, Stage 2: 5 – 8, Stage 3: 9 – 12, Stage 4: 13 – 15, Stage 5: 16. This

PSP-SS was formulated for ease of use as well as criterion validity against the PSPRS and time.

Clinical Global Impression of Severity and Change

The Clinical Global Impression of Severity **(**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 Clinical Global Impression of change (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 and take approximately 40 to 60 minutes to complete, as reported in Table 3.

Schwab and England Activities of Daily Living Scale[17]

The Schwab and England Activities of Daily Living Scale **(**SEADL) scale will be used as a means of assessing the subject's ability to perform daily activities. The SEADL scale was developed by Schwab and England in 1957 and consists of 10 items intended to evaluate the daily life activities of a patient. The SEADL is composed of 2 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 2 minutes to complete, as reported in Table 3.

Unified Parkinson's Disease Rating Scale[18]

The Unified Parkinson's Disease Rating Scale (UPDRS) 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 3.

Repeatable Battery for Assessment of Neuropsychological Status[19]

The Repeatable Battery for Assessment of Neuropsychological Status (RBANS) is a 25-minute, standardized neurocognitive battery with North American population-based normative data. The RBANS measures five neurocognitive domains, with age-based scaling. Twelve subtests measure cognitive decline or improvement across the following domains:

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

The RBANS has been shown to be effective at both detecting and characterizing dementia of different etiologies. The RBANS has been translated into over 25 different languages, with extensive clinical validity data from a wide variety of geographic regions. It is administered to the subject by a clinician and takes approximately 25 minutes to complete, as reported in Table 3.

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

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 to 10 minutes to complete, as reported in Table 3.

Letter Fluency Test[21]

The Letter Fluency Test 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 2 trials per administration, involving different letters. The score is the total number of correct words generated over the 2 trials. It will be administered to the subject by a clinician and will take approximately twice 1 minute to complete, as reported in Table 3.

Natural History and Neuroprotection in Parkinson Plus Syndromes-Parkinson Plus Scale[22]

The Natural History and Neuroprotection in Parkinson Plus Syndromes-Parkinson Plus Scale (NNIPPS-PPS) is a validated rating scale used to assess disease severity and

progression in patients with PSP and Multiple System Atrophy (MSA). The NNIPPS-PPS contains 83 items, comprised of 11 domains: functional disability (activities of daily living [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 to 45 minutes to complete, as reported in Table 3. This scale will not be administered in Japan.

Patient Global Impression of Change[23]

Subjects will evaluate the change in their PSP-related symptoms since initiation of study drug by choosing 1 of 7 responses. The Patient Global Impression of Change (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 to 2 minutes to complete, as reported in Table 3.

EuroQuality of Life[24,25]

The EuroQuality of Life (EQ-5D) contains a health state descriptive part comprising 5 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 visual analog scale (VAS) to evaluate current health state (from 0, worst imaginable, to 100, best imaginable). The descriptive profile can be converted into a value (EQ-Index) which ranges from 0 (death) to 1 (perfect health), with negative values indicating health states

considered worse than death. It is administered to the subject by a clinician and takes approximately 8 minutes to complete, as reported in Table 3.

Columbia-Suicide Severity Rating Scale[26]

The Columbia-Suicide Severity Rating Scale (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. It is administered to the subject by a clinician and takes less than 5 minutes to complete, as reported in Table 3.

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

BioStamp nPoint (for subjects participating in the substudy only)[27]

BioStamp nPoint is an FDA 510(k)-cleared medical device designed to collect medical grade, clinical quality biometric, physiologic, and other electronic clinical outcome assessment (eCOA) data in a clinical trial setting. The system processes raw data into recognizable clinical metrics including heart rate, activity and posture classification, surface electromyography (sEMG), and sleep metrics. The sensors are multi-modal, multi-location, rechargeable, and reusable. BioStamp data are processed and stored in a secure cloud that can be synchronized with third-party electronic data capture (EDC) and clinical trial management (CTM) systems.

Three BioStamp sensor locations (left precordial chest, anterior thigh, and small of back) will be used in the study, and will capture information on heart rate, sleep, and measures of motor activity including posture, gait, and step count. Subjects will be trained during a clinic visit how to use the system including how to apply and remove sensors and how to upload data. Detailed laboratory manuals will be provided to participating sites.

PSP Caregiver Questionnaires[28,29]

The PSP caregiver questionnaire assesses the burden of caregivers, their work productivity, and health resource use, as well as quality of life. The questionnaire consists of both questions specifically developed for this study as well as validated scales. Caregivers will complete the following sections of the questionnaire at scheduled visits during the study:

- Caregiver Information: This section gathers caregiver's basic demographic information such as age, gender, ethnicity, and household information. It takes approximately 2 minutes to complete.
- Caring for Someone with PSP: This section contains a list of questions to capture the relationship between the caregiver and the person with PSP, the living arrangement, and the amount of time spent on caring. In addition, it measures how frequently the caregiver helps with daily activities. It takes approximately 5 minutes to administer this section.
- Caregiver Work Productivity and Status: Caregiver Work Productivity is measured by (Work Productivity and Activity Impairment Questionnaire [WPAI]). The WPAI caregiver version is a validated 6-question instrument to measure impairments in work and activities. The first 4 questions measure employment status and hours missed from work, and the last 2 questions measure the impact of caregiving on work productivity and daily activities on a 0 - 10 scale. In addition to WPAI, there are 2 additional questions measuring the caregiver's work status and if the reason of unemployment is related to caregiving. It takes approximately 5 minutes to administer the questionnaire.
- Caregiver Healthcare Resource Use: This section assesses the caregiver's general health as well as their health resource use in terms of number of

physician, ER visits, hospitalization, and length of stay for each hospitalization. It takes approximately 5 minutes to administer this section.

- Caregiver Quality of Life (carers quality-of-life questionnaire for PSP [PQoL Carers]): PQoL Carers is a QoL instrument for carers of people with atypical parkinsonism (AP), including PSP and MSA. The 26-item instrument was generated from in-depth interviews with carers of patients with AP and a thorough review of the existing literature and consultation with movement disorder experts. The items are scored from 0 (no problem) to 4 (extreme problems). It is a concise instrument with adequate psychometric qualities. Convergent and concurrent validity was supported by correlations of PQoL Carers with the patient's health status and QoL measures such as The Parkinson's Disease Questionnaire-39 (PDQ-39) and EQ-5D, as well as carers' measures, such as Caregiver Burden Inventory (CBI) and carer EQ-5D. The discriminant validity of the scale was demonstrated through its capacity to differentiate between carers with varying levels of self-reported health. It takes approximately 8 minutes to administer the questionnaire.

Treatment Satisfaction Questionnaire for Medication[30]

The Treatment Satisfaction Questionnaire for Medication (TSQM-9) assesses patient satisfaction with medication in 3 domains: effectiveness (3 items), convenience (3 items), and global satisfaction (3 items). Each item is scored on a 7- or 5-point Likert scale. The total score in each domain is converted to a score between 0 and 100, with higher scores indicating greater satisfaction with treatment. It takes approximately 5 minutes to complete the questionnaire.

5.3.1.2 Collection and Handling of Biomarker and Pharmacogenetic Research Samples

5.3.1.2.1 Biomarker Samples

Blood and CSF samples will be collected at the times indicated in the Study Activities Table (Appendix C) and may be used to evaluate known and/or novel disease-related or

drug-related biomarkers. The biomarker rationale is discussed in the Section 5.3.6.1 (Biomarker Research Variables).

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). CSF samples (18 to 20 mL) will be collected by lumbar puncture. Details for collection and processing are provided in a separate laboratory manual.

5.3.1.2.2 Pharmacogenetic 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 samples (6.5 mL) for DNA and RNA isolation will be collected at the times indicated in the Study Activities Table (Appendix C).

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

5.3.1.3 Confinement

No confinement will be required for this study.

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.

5.3.2.1.1 Blood Samples for ABBV-8E12 Assay

Blood samples (approximately 3 mL) for ABBV-8E12 analysis will be collected by venipuncture at the times indicated in the Study Activities Table (Appendix C) as follows:

- **Day 1 (Dose 1)**
  - Prior to the start of the infusion (0 hour), immediately after the end of the infusion (within 15 minutes) and 1 and 2 hours after the end of the infusion
- **Weeks 12, 24, 52, 76, 104, 128, 156, 180, 208, 232, and 260**
  - Prior to the start of the infusion (0 hour), when applicable (no dose at Week 260)
- **Post-Treatment Follow-up Visit (20 weeks after last dose)**
  - Sample may be collected any time during the visit

PK samples collected prior to infusion (0 hour) should be collected no more than 30 minutes prior to the start of infusion. The allowable PK window for 1-hour postdose

samples is ± 6 minutes, and the allowable PK window for 2-hour postdose samples is ± 12 minutes. The allowable window for samples scheduled for the post-treatment Follow-Up Visit is ± 4 days.

5.3.2.1.2 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 at the times indicated in the Study Activities Table (Appendix C) as follows:

- **Day 1 (Dose 1)**
  - Prior to the start of the infusion (0 hour)
- **Weeks 12, 24, 52, 76, 104, 128, 156, 180, 208, 232, and 260**
  - Prior to the start of the infusion (0 hour), when applicable (no dose at Week 260)
- **Post-Treatment Follow-up Visit (20 weeks after last dose)**
  - Sample may be collected any time during the visit

The ADA samples collected prior to infusion (0 hour) should be collected no more than 30 minutes prior to the start of infusion. Blood samples may be collected within ± 4 days for the post-treatment Follow-up Visit.

5.3.2.1.3 CSF Samples for ABBV-8E12 Assay

CSF samples (assessment referred to as lumbar puncture) will be collected at the times indicated in the Study Activities Table (Appendix C).

The collection time and procedures of CSF samples are located in the lumbar puncture section of Study Procedures Section (Section 5.3.1.1.12).

5.3.2.2 Measurement Methods

Serum concentrations and relative titers in serum 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

5.3.3.1 Primary Variable

The primary efficacy variable will be the PSPRS total score to assess the effect of ABBV-8E12 in slowing disease progression.

5.3.3.2 Secondary Variables

Key secondary efficacy measures are as follows:

- UPDRS Part II
- CGI-C
- SEADL

Additional secondary efficacy measures are as follows:

- CGI-S
- PGI-C
- PSP-SS (composite of items from PSPRS)
- Time to loss of ability to walk independently as measured by PSPRS item 26

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

5.3.3.3 Exploratory Variables

Exploratory efficacy measures are as follows:

- Time to death
- EQ-5D
- Letter Fluency Test (words per minute)
- RBANS
- CTT (Parts 1 and 2)
- NNIPPS-PPS (not applicable in Japan)
- Frequency of hospitalizations related to PSP

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

5.3.4 Safety Variables

Adverse events and SAEs will be monitored throughout the dosing period and for approximately 20 weeks after the last dose. Safety evaluations will consist of the following: monitoring of adverse events (including infusion and allergic reactions), vital signs, physical examination, complete neurologic exam, cognitive assessments, C-SSRS, laboratory abnormalities, ECG, brain MRI including FLAIR, and immunogenicity as determined by ADA responses in blood.

5.3.5 Pharmacokinetic Variables

The concentration of ABBV-8E12 will be determined in serum and CSF samples collected in the study. Data from this study may be combined with data from other ABBV-8E12 studies for pharmacokinetic analyses.

A mixed-effect modeling approach will be used to estimate the population central value and obtain 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 at each collection time point.

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 Biomarkers:
  - Tau in CSF and plasma
  - Additional exploratory CSF and plasma-based pharmacodynamic 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 DTI
- Digital Biomarkers:
  - BioStamp sensor motor outcomes including posture, gait, and step count

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.

Digital substudy endpoints will be handled in a separate scientific report.

5.3.6.2 Pharmacogenetic Research Variables

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.

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

- Subject starts receiving an approved therapy for PSP.
- Subject develops unacceptable toxicity.
- Female subject becomes pregnant.
- Investigator decides it is in the subject's best interest to discontinue.
- Subject is noncompliant with the protocol based on the investigator or medical monitor assessment.
- Subject withdraws consent.

- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.

Severe allergic reactions or other adverse events that require the immediate interruption of ABBV-8E12 treatment will be taken into consideration by the AbbVie TA MD 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 TA MD 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 TA MD.

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, lumbar puncture, administration and completion of scales/questionnaires, C-SSRS, a serum pregnancy test (WOCBP only), 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 collected 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.

Subjects who prematurely discontinue from the study can be contacted by telephone for periodic updates at the times shown in Appendix C providing that consent for this contact was obtained prior to contact being made.

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 will review 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.

5.5 Treatments

5.5.1 Treatments Administered

The solution contained in the study vial(s) of ABBV-8E12 must be diluted with 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 in a document that is separate from the protocol.

Subject's Weight in kg/lbs	Infusion Rate[b]
44 – 49 kg (97 – 109 lbs, inclusive)[a]	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

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

b. Continue infusion until bag is empty.

Study continuation for subjects whose weight falls below 44 kg (97 lbs.) during their participation will be discussed with the AbbVie TA MD and adjustment of the infusion rate 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
ABBV-8E12 2000 mg	IV infusions at Day 1, Day 15, and Day 29, then every 28 days for up to 5 years
ABBV-8E12 4000 mg	
Placebo[a]	

a. Subjects who received active drug in Study M15-562 will receive placebo on Day 15 to maintain the blind in Study M15-562; this is the only time point at which placebo will be dosed.

Note: Visits may be scheduled within ± 4 days.

Doses may be decreased after evaluation by the DMC of available safety, tolerability, and pharmacokinetic 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 products to be used in this study is presented in Table 4.

Table 4. Identity of Investigational Product

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
ABBV-8E12	Infusion	Solution for infusion in a vial	300 mg/15 mL and 1000 mg/10 mL	AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany
Placebo	Infusion	0.9% NaCl injection/solution for infusion 500 mL	N/A	Various[a]

NaCl = sodium chloride

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

The 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 exceptional circumstances when sites are unable to procure 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 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, it will be labeled with a dispensing label by the unblinded pharmacist or qualified designee as required. The 0.9% sodium chloride injection/solution without addition of ABBV-8E12, to be administered as placebo, 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.

The 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 temperature excursion must be reported to the Sponsor immediately using the AbbVie Temperature Excursion Management System (ATEMS). Study drug should be quarantined and not dispensed until ATEMS deems the drug 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 active doses. Written instructions for the preparation of ABBV-8E12 solutions for infusion will be provided 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 enrolled in the study, the subject number from Study M15-562 will be rolled over to the IVR/IWB system for Study M15-563. Each subject has 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 who received placebo in Study M15-562 will be randomly assigned to either ABBV-8E12 2000 or 4000 mg 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. Subjects who received ABBV-8E12 in Study M15-562 will remain on the same dose in Study M15-563.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the doses for this study is discussed in Section 5.6.4. Each subject who received placebo in Study M15-562 will be randomized to either ABBV-8E12 2000 or 4000 mg as described in Section 5.5.3. Subjects who received ABBV-8E12 in Study M15-562 will remain on the same dose in Study M15-563. ABBV-8E12 will be administered via IV infusion; if possible this will be performed in the morning.

5.5.5 Blinding

Study M15-563 is a long-term extension study. Investigators, study site personnel (except the unblinded pharmacist or qualified designee), subjects, and the sponsor will remain blinded to the treatment assignments in Study M15-563 to maintain the blind in Study M15-562.

A 0.9% sodium chloride injection/solution that is essentially identical in volume to the ABBV-8E12 solution will be administered on Day 15 to subjects who received ABBV-8E12 in Study M15-562. Written instructions for the preparation of ABBV-8E12 solutions for infusion will be provided as a separate document from the protocol. Identical commercial 0.9% sodium chloride injection/solution for infusion bag or bottle will be used for the placebo doses at each site.

An unblinded pharmacist or qualified designee will receive and prepare the blinded doses. 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 doses of ABBV-8E12 (in a blinded manner) following the available preparation instructions as appropriate based on the subject's assigned treatment.

For investigational product monitoring, an unblinded clinical research associate (also referred to as a pharmacy clinical research associate [CRA]) will be appointed for verification of unblinded preparation documentation. The unblinded pharmacy CRA will be a different 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 provided in a separate study-specific document.

The IVR/IWB system will be programmed with blind-breaker instructions.

To ensure that the DMC will be fully informed, the DMC will be unblinded in its assessment of safety 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 independent Statistical and Data Analysis Center (SDAC) and an independent exposure-response analysis center (ERAC) by AbbVie. The study randomization will be sent to the SDAC and ERAC under separate cover. The SDAC will generate a closed report that includes unblinded information for the 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 to formulate a decision based on the DMC's recommendations. A detailed communication plan between the 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 AbbVie monitor throughout the study and at the study site closeout visit. Written instructions for investigational product accountability

requirements will be provided as a separate document from the protocol. Upon completion or termination of the study, all original containers (containing used study drug or containing unused study drug) will be destroyed at the 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 safety, tolerability, efficacy, and PK of ABBV-8E12 in subjects with PSP for up to 5 years. There is a delayed-start group[31] (the placebo group for Study M15-562) and an early-start group (the ABBV-8E12 2000 and 4000 mg groups for Study M15-562) in Study M15-563. The combined data from Study M15-562 and Study M15-563 will enable the evaluation of a disease modification effect of ABBV-8E12 utilizing a delayed-start analysis. Toxicity management is described in Section 6.1.7.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be used 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, and NNIPPS-PPS are currently accepted and validated methods of evaluating subjects with PSP. All safety assessments are standard measures used in pharmaceutical research.

5.6.3 Suitability of Subject Population

The research diagnostic criteria for possible and probable PSP 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.

5.6.4 Selection of Doses in the Study

Dose levels for Study M15-563 (2000 and 4000 mg) were selected based on the doses used in Study M15-562, which were selected based on available safety, tolerability, and pharmacokinetic data from 2 patients with tauopathies who received ABBV-8E12 under an expanded access protocol (US [20 monthly infusions; maximum dose of 25 mg/kg for the last 7 months]) and a compassionate use trial (Germany [3 monthly infusions; maximum dose of 15 mg/kg for the last 2 months]) as well as safety, tolerability, and pharmacokinetic data from the SAD study (Study C_2N-8E12-WW-104) in subjects with PSP, in which the safety, tolerability, and PK of single doses of ABBV-8E12 ranging from 2.5 to 50 mg/kg were evaluated. The NOAEL was 250 mg/kg/week based on a 4-week preclinical GLP toxicology study in C57BL/6 mice, and the corresponding mean C_{max} and $AUC_{0\text{-}168h}$ were 3050 µg/mL and 298,000 µg•hr/mL (on Day 22) after 4 doses administered weekly. The predicted safety margins are approximately 3- and 1.4-fold for both C_{max} and AUC at the dose levels of 2000 and 4000 mg in humans, based on predictions from a 2-compartment PK model developed with the PK data from Study C_2N-8E12-WW-104.

ABBV-8E12 infusions were well tolerated without any observed signs or symptoms of antibody-related toxicity in both compassionate-use protocols. Dosing and follow-up have been completed in all dose groups in Study C_2N-8E12-WW-104, and ABBV-8E12 was 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 in Study C_2N-8E12-WW-104. The actual doses administered in the SAD study were based

on the subject's body weight, and the range of actual doses in the 50 mg/kg group was 2625 to 4760 mg.

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 SAEs 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 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 an SAE within 24 hours of the site being made aware of the SAE:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.

Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

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

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

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

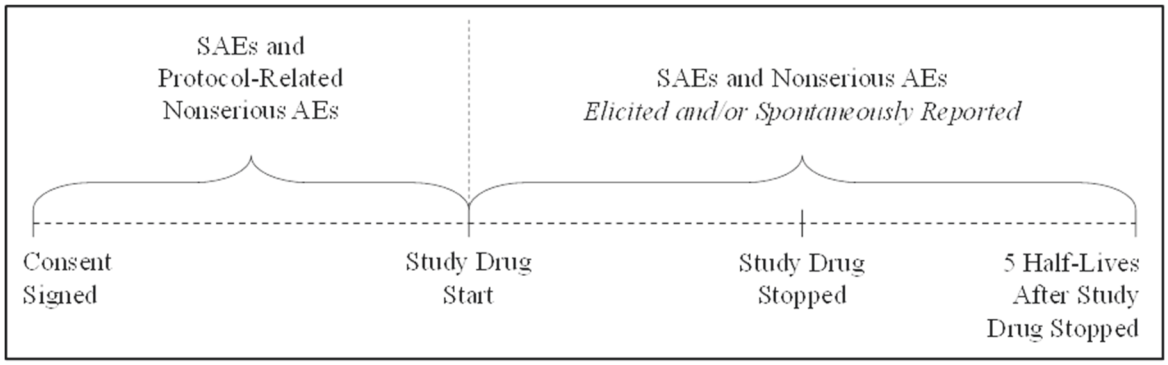
6.1.4 Adverse Event Collection Period

All 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, SAEs 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 an SAE, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) RAVE® system. SAEs that occur prior to the site having access to the RAVE® system or if RAVE is not operable should be documented on the SAE non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of being made aware of the SAE.

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: [redacted]
Email:

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

Primary TA MD:

[redacted]
Medical Director
Neuroscience Development
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

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

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 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 Development Safety Update Report 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.

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. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, is considered an SAE 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.

6.1.7.1 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.

6.1.7.2 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.[32] The likelihood of adverse on-target side effects of an anti tau immunotherapy is therefore anticipated to be low.

6.1.7.3 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).

6.1.7.4 Allergic Reactions Management

Subjects will be closely monitored for treatment-related adverse events, including allergic reactions, during the infusion. Subjects should be monitored on site for at least 30 minutes after the end of study drug infusions. Longer observation periods and more frequent vital sign checks may be required in subjects who experience infusion reactions.

Severe or life-threatening allergic reactions require the immediate interruption of ABBV-8E12 treatment and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, IV antihistamines,

bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.

Moderate 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.

6.1.7.5 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 event 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 TA MD. 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 TA MD; 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 TA MD.

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 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 adverse event CRF pages. Similarly, since falls are a core component and defining feature of PSP (Steele-Richardson-Olszewski Syndrome), falls will not be recorded as

adverse events unless they lead to other injury or represent a change in frequency or character before enrollment in this study.

Similarly, the slow progression of pre-existing (before enrollment in this study) disease-related signs and symptoms clearly associated with the disease during the treatment period will not be reported as adverse events 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 adverse event being due solely to the disease under the treatment protocol, it should be reported as an adverse event 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 adverse event.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (refer to 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 1 business day of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with 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 IEC/IRB, regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s):

Primary Contact:	Alternate Contact:
[redacted] Study Project Manager AbbVie 1 North Waukegan Road North Chicago, IL 60064	[redacted] Study Project Manager II AbbVie 1 North Waukegan Road North Chicago, IL 60064
Office: Not applicable Mobile: [redacted] Fax: Email:	Office: [redacted] Mobile: 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

The data analysis will be grouped by assigned treatment sequences/group in Studies M15-562/M15-563: 2000/2000 mg, 4000/4000 mg, placebo/2000 mg, and placebo/4000 mg. If the treatment effect between each ABBV-8E12 dose and placebo is statistically significant at Week 52 in Study M15-562, the 2000/2000 mg and 4000/4000 mg groups could be combined as the early-start ABBV-8E12 treatment group, and the placebo/2000 mg and placebo/4000 mg groups could be combined as the delayed-start group for the delayed-start analysis. Details of the analyses will be specified in the statistical analysis plan (SAP).

Data Sets for Efficacy Analyses

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

ITT Data Set: The Study M15-563 ITT data set consists of all subjects who received any dose of study drug in Study M15-563. This is the primary efficacy analysis set for this

study. All efficacy analyses for Study M15-563 alone will be conducted on the ITT set unless otherwise specified.

Delayed-Start Data Set: The delayed start analysis data set includes efficacy data from both Studies M15-562 and M15-563. All subjects from Study M15-562 ITT data set will be included, regardless if they enroll in Study M15-563 or not. Subjects who complete Study M15-562 and rollover to Study M15-563 but have a gap of more than 8 weeks between study drug infusions before enrolling into Study M15-563 will be excluded from this analysis set.

Data Sets for Safety Analyses

The safety data sets will consist of all subjects who received any dose of study drug in Study M15-563. For the safety analyses, the actual treatment received will be used instead of the treatment assignment at the time of randomization. There are 2 safety datasets: a Stand-Alone safety data set and a cumulative safety data set as described below.

Stand-Alone Data Set: The stand-alone data set is the primary data set for the safety analysis, and will contain data from Study M15-563 only, regardless of the treatment received in Study M15-562. Baseline will be the last observation on or before the first dose of ABBV-8E12 in Study M15-563. If no Baseline is recorded in Study M15-563, the last value in Study M15-562 will be used as the Baseline.

Cumulative Data Set: The cumulative data set will consist of data from both Study M15-562 and Study M15-563. It is the secondary data set for safety analyses. For subjects who were in the placebo group in Study M15-562, their safety data from Study M15-562 will not be included in the cumulative data sets but their safety data from Study M15-563 will be included. For Study M15-562 placebo subjects, Baseline will be the last observation prior to the first dose of study drug in Study M15-563. For subjects who were in ABBV-8E12 treatment groups in Study M15-562, Baseline for the safety analyses will be their Baseline in Study M15-562.

8.1 Statistical and Analytical Plans

8.1.1 Efficacy Analyses

All efficacy analyses of comparisons will be performed with a 2-sided test at the significance level of 0.05 unless otherwise specified. All efficacy assessments that are taken no more than 45 days after the last dose of study drug will be included in the efficacy analysis.

The primary efficacy variable is the PSPRS total score in the Study M15-563 ITT analysis. The primary analysis model is a likelihood-based, mixed-effect model, repeated measures (MMRM) analysis of the PSPRS total score at Study M15-563 Baseline and each post-baseline observation using all observed data. The model will consist of fixed, categorical effects for treatment, site, visit, and treatment-by-visit interaction. An unstructured (co)variance structure will be used to model 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. The differences for placebo/2000 mg vs 2000/2000 mg and for placebo/4000 mg vs 4000/4000 mg at Study M15-563 Baseline and at the end of the Study M15-563 Treatment Period will be presented with a 95% confidence interval. Contrasts of treatment effects for other visits will be conducted as well. This MMRM analysis will be applied to each efficacy variable with repeated measurements. Details of the analysis will be described in the SAP.

The delayed-start analysis will be conducted on the change from Baseline in Study M15-562 up to Week 52 in Study M15-563 on the PSPRS total score. An MMRM analysis model will be used. The model will consist of fixed, categorical effects for treatment, site, visit, and treatment-by-visit interaction, with continuous fixed covariates for baseline PSPRS total score and the baseline score-by-visit interaction. An unstructured (co)variance structure will be used to model within-subject errors. Satterthwaite's approximation will be used to estimate denominator degrees of freedom, and the Type III sum-of-squares for the LS means will be used to estimate treatment

group differences. The primary comparisons will be the contrasts between an ABBV-8E12 dose group and the placebo group at Week 52 in both Study M15-562 and Study M15-563, and non-inferiority analysis of treatment effects at Week 52 between the 2 studies. If only one of the ABBV-8E12 dose groups in Study M15-562 is statistically significantly different from placebo at Week 52, the delayed-start analysis will be conducted only for that dose. If treatment effects at Week 52 in Study M15-562 are statistically significant for both ABBV-8E12 doses (based on the primary analysis defined in the Study M15-562 SAP), the combined early-start groups and the combined delayed-start groups will be used for the delayed-start analysis. If neither ABBV-8E12 dose is statistically significantly different from the placebo at Week 52 in Study M15-562, the delayed-start analysis will not be conducted. No multiplicity adjustment will be made for the delayed-start analysis based on combined groups or a selected ABBV-8E12 dose. Details of the analysis will be specified in the SAP.

The analysis on secondary and exploratory efficacy variables will be detailed in the SAP.

8.1.2 Safety Analyses

Comparisons between treatment groups (Studies M15-562/M15-563) of interest will be performed with a 2-sided test at the significance level of 0.05 unless otherwise specified.

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 analysis of variance (ANOVA) model with treatment group as the main effect, and the treatment group differences in binary safety variables will be evaluated using Fisher's exact test.

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

All other safety assessments that are taken no more than 45 days after the last dose of study drug will be included in the safety evaluation of the Treatment Period, and all safety

assessments that are taken more than 45 days but not more than 20 weeks after the last dose of study drug will be included in the safety evaluation for the Post-treatment Follow-up Visit.

8.1.2.1 Study Drug Exposure and Compliance

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

8.1.2.2 Analysis of Adverse Events

The Stand-Alone data set will be the primary data set for adverse event summaries. Analyses that will be performed on the cumulative data set are as follows: adverse event overview, adverse event incidence by system organ class (SOC) and preferred term, adverse event incidence in descending frequency by overall subjects, and SAE incidence by SOC and preferred term.

Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects who report TEAEs will be tabulated by the MedDRA SOC and preferred term for treatment groups specified in Section 8.0. No comparisons between treatment groups will be performed.

The number and percentage of subjects who experienced treatment-emergent SAEs (including deaths) and adverse events leading to premature discontinuation of study drug will be tabulated by the MedDRA SOC and preferred term for treatment groups specified in Section 8.0. No comparisons between treatment groups will be conducted for adverse event summaries.

8.1.2.3 Analysis of Laboratory Tests

Analyses will be performed on the Stand-Alone data set for laboratory tests. Change from Baseline to each visit value and to the minimum, maximum, and final value will be presented for each continuous hematology, chemistry, and urinalysis parameter. Treatment differences between treatment group in change from Baseline to minimum, maximum, and final clinical laboratory evaluation will be analyzed using a one-way ANOVA with treatment group 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. Details will be specified in the SAP.

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

8.1.2.4 Analysis of Vital Signs and Weight

Vital sign variables for this study will be pulse rate, systolic blood pressure, diastolic blood pressure, body temperature, weight, and body mass index (BMI). Pulse rate and blood pressure will be measured in both supine and standing positions; orthostatic change (from supine to standing) will also be measured.

Change from Baseline to each visit value and to the minimum, maximum, and final value will be presented for each vital sign and weight variable and analyzed using a one-way ANOVA with treatment group as the main effect. The number and percentage of subjects in each treatment group who have values meeting predefined criteria for PCS (definitions will be provided in the SAP) at any time after the first dose of study drug and no more

than 20 weeks after the last dose of study drug will be summarized. No comparisons between treatment groups will be conducted.

8.1.2.5 Analysis of ECG Variables

ECG variables for this study will be heart rate, PR, QRS, QT, and QTcF intervals. Change from Baseline to final value will be presented for each ECG parameter and analyzed using a one-way ANOVA with treatment group as the main effect. The number and percentage of subjects in each treatment group who have values meeting predefined criteria for PCS at any time after the first dose of study drug will be summarized.

8.1.2.6 Analysis of C-SSRS

The 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.

8.1.3 Biomarker Analyses

For CSF and plasma concentrations of tau and for volumetric MRI variables, descriptive statistics will be provided for each scheduled time of measurement with a breakdown by groups defined by treatment in Study M15-562 and treatment in this study. That is, the treatments of the 4 groups are as follows:

- ABBV-8E12 2000 mg in Study M15-562, continuing the same in Study M15-563
- ABBV-8E12 4000 mg in Study M15-562, continuing the same in Study M15-563
- Placebo in Study M15-562, ABBV-8E12 2000 mg in Study M15-563
- Placebo in Study M15-562, ABBV-8E12 4000 mg in Study M15-563

The scheduled time of measurement will include the baseline measurement. For subjects who were treated with ABBV-8E12 in Study M15-562, the baseline measurement will be the same as it was in Study M15-562. For subjects whose treatment was placebo in Study M15-562, the baseline value will be the predose measurement on Day 1 of Study M15-563. The descriptive statistics for a given time will provide information for both the data of the given time and the changes from Baseline.

For CSF and plasma concentrations of tau, an MMRM analysis will be performed to compare the effects of the 2000 and 4000 mg doses of ABBV-8E12. The data set will contain the data of the first 2 groups identified above. The data set will also include the data of the last 2 groups beginning with Week 76 of Study M15-563, but with a shift in time by 52 weeks for the purposes of this analysis so that the shifted time indicates the length of time on ABBV-8E12 past 52 weeks. Thus, for this analysis, the Week 104 data of the last 2 groups will be considered the same as Week 52 of the first 2 groups.

The model for the MMRM analysis performed for the tau variables will include classification by ABBV-8E12 dose and by time of measurement. There will be an effect for the interaction of ABBV-8E12 dose and time of measurement. The baseline value will be a covariate. The model will also have an effect to distinguish between subjects who were assigned to ABBV-8E12 treatment in Study M15-562 and those who were assigned to placebo in Study M15-562. The subjects in each treatment group will be viewed as a random sample, and an appropriate structure for the covariance matrix of the measurements of a subject will be selected.

For volumetric MRI variables, descriptive statistics as described for the CSF tau concentrations will be provided. An MMRM analysis corresponding to that described for the tau variables will be performed; however, the 2 models will differ with respect to covariates. For the volumetric MRI variables, the baseline value and a measure of head size (e.g., intracranial volume) will be covariates.

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

Digital substudy endpoints will be handled in a separate scientific report.

8.1.4 Pharmacokinetic and Exposure-Response Analyses

For ABBV-8E12 serum concentration data, descriptive statistics will be provided for each scheduled time of measurement with a breakdown by groups defined by treatment in Study M15-562 and treatment in this study. That is, the treatments in the 4 groups are as defined in Section 8.1.3.

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 data from this study only 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 the last administered dose. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (Version 7, or higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies. Apparent CL and apparent 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.

1. The objective function of the best model is significantly smaller than the alternative model(s).
2. The observed and predicted concentrations from the preferred model are more randomly distributed across the line of unity (a straight line with zero intercept and a slope of 1) than the alternative model(s).
3. Visual inspection of model fits, standard errors of model parameters and change in inter-subject and intra-subject error.

Once an appropriate base 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/F and V/F values and potentially physiologically relevant or clinically meaningful covariates (such as subject age, sex, body weight, concomitant medications, laboratory markers of hepatic or renal function) will be explored using either a stepwise forward selection method, or a generalized additive method (GAM), or another suitable regression/smoothing method at a significance level of 0.05. After identification of all relevant covariates, a stepwise backward elimination of covariates from the full model will be employed to evaluate the significance (at $P < 0.005$, corresponding to a decrease in objective function > 7.88 for one degree of freedom) of each covariate in the full model.

Linear or nonlinear relationships of primary pharmacokinetic parameters with various covariates will be explored.

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

Additional analyses will be performed if useful and appropriate.

8.2 Interim analysis

Regular interim safety analyses will be performed and preplanned interim efficacy evaluation(s) may be performed. Assessment of safety and efficacy data at interim(s) will be conducted by the DMC.

8.2.1 Safety Interim Analyses

Safety data will be reviewed by the DMC based on interim safety review schedules for Study M15-563. A detailed timeline of the safety interim analysis will be provided in a DMC charter.

8.2.2 Efficacy Interim Analysis

An efficacy interim analysis may be conducted when the last subject completes Week 52 assessments in Study M15-563. Additional efficacy interim analyses may be conducted as needed. A delayed-start analysis will be conducted and details of the delayed-start analysis will be specified in the SAP.

8.3 Determination of Sample Size

The sample size for this study is dependent on the number of subjects who complete Study M15-562 and are qualified for enrollment into Study M15-563. A total of 378 subjects will be randomized in Study M15-562; and the number of subjects who enroll in Study M15-563 will be up to the number of subjects enrolled in Study M15-562.

9.0 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

GCP requires that the clinical protocol, any protocol amendments, the IB, 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 for Harmonisation (ICH) GCP.

Any SAEs 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., ICH Expedited Reports, and 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.

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 study-specific procedures, the investigator or his/her representative will explain the nature of the study to the subject, their study partner, and the subject's LAR (if applicable), and answer all questions regarding this study. Each informed consent will be reviewed, signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. For 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. An informed consent statement will also be reviewed, signed and dated, by the subject's study partner prior to beginning any study related activities. A copy of each 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.

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 optional 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. This may include hospital records, clinical and office charts, laboratory data/information, subjects' 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. Data collected during this study must be recorded to the appropriate source document. The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

The investigator(s)/institution(s) 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

eCRFs must be completed for each subject enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an EDC system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific eCRFs will comply with Title 21 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

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

The AbbVie monitor will monitor the study site throughout the study according to a monitoring plan. Source document review will be made against entries in RAVE and a quality assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. During the study, an ongoing review of the data will be conducted by a physician or representative at AbbVie.

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

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/designated person and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator/designated person and AbbVie. The investigator/designated person 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/designated person must retain any records related to the study according to local requirements. If the investigator/designated person is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory coordinating investigator from the investigators who participate in each multicenter study. Selection criteria for this signatory investigator will be based on level of participation, and significant knowledge of the clinical research, investigational drug, and study protocol. The signatory investigator for the study will

review and sign the final study report in accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

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

14.0 Investigator's Agreement

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

Protocol Title:	An Extension Study of ABBV-8E12 in Progressive Supranuclear Palsy (PSP)
Protocol Date:	21 February 2019

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
		Clinical
		Statistics
		Statistics
		Pharmacokinetics
		Neuroscience Development
		Bioanalysis
		Medical Writing

Appendix C. Study Activities

Visits & Procedures[b]	Treatment Period[a]																20 Wks Post Last Dose F/U
	Year 1																
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13	Dose 14	Dose 15		
	Day 1	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365		
	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	D/C	
Subject/study partner ICF[c]	X																
Medical history update[d]	X																
Randomization	X																
Physical examination	X																
Symptom-driven physical examination[e]								X							X	X	X
Orthostatic vital signs[f,g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs[g]																X	X
Body weight (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP)[h]	U				U			U							U	S	U
Neurological examination	X				X			X							X	X	X
12-lead ECG	X				X			X							X	X	
Clinical laboratory tests	X				X			X							X	X	
Brain MRI[i]	X				X			X							X	X	X
LP/CSF collection[j]	X							X							X	X	X

Visits & Procedures[b]	Treatment Period[a]																20 Wks Post Last Dose F/U
	Year 1																
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13	Dose 14	Dose 15		
	Day 1	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365		
	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	D/C	
Blood PK sample	X				X			X							X	X	X
ADA Sample collection	X				X			X							X	X	X
Plasma biomarkers	X				X			X							X	X	X
CSF biomarkers	X							X							X	X	X
Optional exploratory PGx DNA and RNA blood sample	X				X			X							X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PSPRS	1				1			1							1	1	1
CGI-S	2				2			2							2	2	2
CGI-C	3				3			3							3	3	3
SEADL	4				4			4							4	4	4
UPDRS Part II	5				5			5							5	5	5
RBANS															6	6	
CTT Parts 1 & 2															7	7	
Letter Fluency Test (wpm)															8	8	
NNIPPS-PPS[k]															9	9	
PGI-C[l]	X				X			X							X	X	X

Visits & Procedures[b]	Treatment Period[a]																
	Year 1																
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13	Dose 14	Dose 15		
	Day 1	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365		
	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	D/C	20 Wks Post Last Dose F/U
EQ-5D[l]	X														X	X	
C-SSRS[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BioStamp Digital[n]	X		X	X	X												
PSP Caregiver Questionnaires	X							X							X	X	X
TSQM-9	X							X							X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone contact[o]	X				X			X							X	X	X

AE = adverse event; ICF = informed consent form; LP = lumbar puncture; PK = pharmacokinetic; PGx = pharmacogenetic; S = serum; U = urine

a. Study drug will be administered on Days 1, 15, and 29, then every 28 days thereafter until 1 of the discontinuation criteria is met, until the Sponsor discontinues the study, or until the study reaches completion. For those Visits that include both study drug infusion and other activities, the Visits may be completed over 2 consecutive days with the second day to include the start and end of the infusion.

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

c. Subject informed consent, or as applicable, legally authorized representative informed consent, and study partner informed consent must be obtained prior to Study M15-563 Day 1 dosing.

d. Review medical history to confirm subject does not meet exclusion criteria prior to randomization.

e. Additional symptom-driven physical examinations may be performed as needed.

f. All supine and standing blood pressure and pulse rate measurements are to be measured as part of an orthostatic assessment.

g. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.
h. For all females of childbearing potential, a negative urine pregnancy test result is also required prior to any radiological procedures.
i. If a subject cannot undergo MRI due to a clinical reason, the AbbVie TA MD should be consulted for approval.
j. Subjects who are not able to undergo an LP may be enrolled with permission of the AbbVie TA MD without the requirement of an LP during the study.
k. The NNIPPS-PPS will not be administered in Japan.
l. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.
m. Scale may be administered/assessed at any time during the visit with the exception of the scheduled infusion time.
n. Device to be worn for 7 days.
o. Only applicable to subjects who prematurely discontinue. Verify consent was obtained prior to making contact.

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

Visits & Procedures[b]	Treatment Period[a]														20 Wks Post Last Dose F/U
	Year 2														
	Dose 16	Dose 17	Dose 18	Dose 19	Dose 20	Dose 21	Dose 22	Dose 23	Dose 24	Dose 25	Dose 26	Dose 27	Dose 28	D/C	
	Day 393	Day 421	Day 449	Day 477	Day 505	Day 533	Day 561	Day 589	Day 617	Day 645	Day 673	Day 701	Day 729		
	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96	Wk 100	Wk 104		
Symptom-driven physical examination[c]						X							X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP)[e]						U							U	S	U
Neurological examination						X							X	X	X
12-lead ECG													X	X	
Clinical laboratory tests													X	X	
Brain MRI[f]						X							X	X	X
LP/CSF collection						X							X	X	X
Blood PK sample						X							X	X	X
ADA Sample collection						X							X	X	X
Plasma biomarkers													X	X	X
CSF biomarkers						X							X	X	X
Optional exploratory PGx DNA and RNA sample													X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X		
PSPRS						1							1	1	1

Visits & Procedures[b]	Treatment Period[a]														20 Wks Post Last Dose F/U
	Year 2														
	Dose 16	Dose 17	Dose 18	Dose 19	Dose 20	Dose 21	Dose 22	Dose 23	Dose 24	Dose 25	Dose 26	Dose 27	Dose 28	D/C	
	Day 393	Day 421	Day 449	Day 477	Day 505	Day 533	Day 561	Day 589	Day 617	Day 645	Day 673	Day 701	Day 729		
	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96	Wk 100	Wk 104		
CGI-S						2							2	2	2
CGI-C						3							3	3	3
SEADL						4							4	4	4
UPDRS Part II						5							5	5	5
RBANS													6	6	
CTT Parts 1 & 2													7	7	
Letter Fluency Test (wpm)													8	8	
NNIPPS-PPS[g]													9	9	
PGI-C[h]						X							X	X	X
EQ-5D[h]													X	X	
C-SSRS[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PSP Caregiver Questionnaires						X							X	X	X
TSQM-9						X							X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone contact[j]						X							X	X	X

AE = adverse event; LP = lumbar puncture; PK = pharmacokinetic; PGx = pharmacogenetic; S = serum; U = urine

a. Study drug will be administered on Days 1, 15, and 29, then every 28 days thereafter until 1 of the discontinuation criteria is met, until the Sponsor discontinues the study, or until the study reaches completion. For those Visits that include both study drug infusion and other activities, the Visits may be completed over 2 consecutive days with the second day to include the start and end of the infusion.
b. Audio recordings/central review of the administration/assessment of selected scales may be conducted.
c. Additional symptom-driven physical examinations may be performed as needed.
d. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.
e. For all females of childbearing potential, a negative urine pregnancy test result is also required prior to any radiological procedures.
f If a subject cannot undergo MRI due to a clinical reason, the AbbVie TA MD should be consulted for approval.
g. The NNIPPS-PPS will not be administered in Japan
h. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.
i. Scale may be administered/assessed at any time during the visit with the exception of the scheduled infusion time.
j. Only applicable to subjects who prematurely discontinue. Verify consent was obtained prior to making contact.

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

Visits & Procedures[b]	Treatment Period[a]														20 Weeks Post Last Dose F/U
	Year 3														
	Dose 29	Dose 30	Dose 31	Dose 32	Dose 33	Dose 34	Dose 35	Dose 36	Dose 37	Dose 38	Dose 39	Dose 40	Dose 41		
	Day 757	Day 785	Day 813	Day 841	Day 869	Day 897	Day 925	Day 953	Day 981	Day 1009	Day 1037	Day 1065	Day 1093		
	Wk 108	Wk 112	Wk 116	Wk 120	Wk 124	Wk 128	Wk 132	Wk 136	Wk 140	Wk 144	Wk 148	Wk 152	Wk 156	D/C	
Symptom-driven physical examination[c]						X							X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP)[e]						U							U	S	U
Neurological examination						X							X	X	X
12-lead ECG													X	X	
Clinical laboratory tests													X	X	
Brain MRI[f]						X							X	X	X
LP/CSF collection						X							X	X	X
Blood PK sample						X							X	X	X
ADA Sample collection						X							X	X	X
Plasma biomarkers													X	X	X
CSF biomarkers						X							X	X	X
Optional exploratory PGx DNA and RNA sample													X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X		
PSPRS						1							1	1	1

Visits & Procedures[b]	Treatment Period[a]														20 Weeks Post Last Dose F/U
	Year 3														
	Dose 29	Dose 30	Dose 31	Dose 32	Dose 33	Dose 34	Dose 35	Dose 36	Dose 37	Dose 38	Dose 39	Dose 40	Dose 41		
	Day 757	Day 785	Day 813	Day 841	Day 869	Day 897	Day 925	Day 953	Day 981	Day 1009	Day 1037	Day 1065	Day 1093		
	Wk 108	Wk 112	Wk 116	Wk 120	Wk 124	Wk 128	Wk 132	Wk 136	Wk 140	Wk 144	Wk 148	Wk 152	Wk 156	D/C	
CGI-S						2							2	2	2
CGI-C						3							3	3	3
SEADL						4							4	4	4
UPDRS Part II						5							5	5	5
RBANS													6	6	
CTT Parts 1 & 2													7	7	
Letter Fluency Test (wpm)													8	8	
NNIPPS-PPS[g]													9	9	
PGI-C[h]						X							X	X	X
EQ-5D[h]													X	X	
C-SSRS[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PSP Caregiver Questionnaires						X							X	X	X
TSQM-9						X							X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone contact[j]						X							X	X	X

AE = adverse event; LP = lumbar puncture; PK = pharmacokinetic; PGx = pharmacogenetic; S = serum; U = urine

a. Study drug will be administered on Days 1, 15, and 29, then every 28 days thereafter until 1 of the discontinuation criteria is met, until the Sponsor discontinues the study, or until the study reaches completion. For those Visits that include both study drug infusion and other activities, the Visits may be completed over 2 consecutive days with the second day to include the start and end of the infusion.
b. Audio recordings/central review of the administration/assessment of selected scales may be conducted.
c. Additional symptom-driven physical examinations may be performed as needed.
d. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.
e. For all females of childbearing potential, a negative urine pregnancy test result is also required prior to any radiological procedures.
f. If a subject cannot undergo MRI due to a clinical reason, the AbbVie TA MD should be consulted for approval.
g. The NNIPPS-PPS will not be administered in Japan
h. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.
i. Scale may be administered/assessed at any time during the visit with the exception of the scheduled infusion time.
j. Only applicable to subjects who prematurely discontinue. Verify consent was obtained prior to making contact.

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

Visits & Procedures[b]	Treatment Period[a]														20 Weeks Post Last Dose F/U
	Year 4														
	Dose 42	Dose 43	Dose 44	Dose 45	Dose 46	Dose 47	Dose 48	Dose 49	Dose 50	Dose 51	Dose 52	Dose 53	Dose 54		
	Day 1121	Day 1149	Day 1177	Day 1205	Day 1233	Day 1261	Day 1289	Day 1317	Day 1345	Day 1373	Day 1401	Day 1429	Day 1457		
	Wk 160	Wk 164	Wk 168	Wk 172	Wk 176	Wk 180	Wk 184	Wk 188	Wk 192	Wk 196	Wk 200	Wk 204	Wk 208	D/C	
Symptom-driven physical examination[c]						X							X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP)[e]						U							U	S	U
Neurological examination						X							X	X	X
12-lead ECG													X	X	
Clinical laboratory tests													X	X	
Brain MRI[f]						X							X	X	X
LP/CSF collection						X							X	X	X
Blood PK sample						X							X	X	X
ADA Sample collection						X							X	X	X
Plasma biomarkers													X	X	X
CSF biomarkers						X							X	X	X
Optional exploratory PGx DNA and RNA sample													X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X		
PSPRS						1							1	1	1

Visits & Procedures[b]	Treatment Period[a]														20 Weeks Post Last Dose F/U
	Year 4														
	Dose 42	Dose 43	Dose 44	Dose 45	Dose 46	Dose 47	Dose 48	Dose 49	Dose 50	Dose 51	Dose 52	Dose 53	Dose 54		
	Day 1121	Day 1149	Day 1177	Day 1205	Day 1233	Day 1261	Day 1289	Day 1317	Day 1345	Day 1373	Day 1401	Day 1429	Day 1457		
	Wk 160	Wk 164	Wk 168	Wk 172	Wk 176	Wk 180	Wk 184	Wk 188	Wk 192	Wk 196	Wk 200	Wk 204	Wk 208	D/C	
CGI-S						2							2	2	2
CGI-C						3							3	3	3
SEADL						4							4	4	4
UPDRS Part II						5							5	5	5
RBANS													6	6	
CTT Parts 1 & 2													7	7	
Letter Fluency Test (wpm)													8	8	
NNIPPS-PPS[g]													9	9	
PGI-C[h]						X							X	X	X
EQ-5D[h]													X	X	
C-SSRS[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PSP Caregiver Questionnaires						X							X	X	X
TSQM-9						X							X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone contact[j]						X							X	X	X

AE = adverse event; LP = lumbar puncture; PK = pharmacokinetic; PGx = pharmacogenetic; S = serum; U = urine

a. Study drug will be administered on Days 1, 15, and 29, then every 28 days thereafter until 1 of the discontinuation criteria is met, until the Sponsor discontinues the study, or until the study reaches completion. For those Visits that include both study drug infusion and other activities, the Visits may be completed over 2 consecutive days with the second day to include the start and end of the infusion.
b. Audio recordings/central review of the administration/assessment of selected scales may be conducted.
c. Additional symptom-driven physical examinations may be performed as needed.
d. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.
e. For all females of childbearing potential, a negative urine pregnancy test result is also required prior to any radiological procedures.
f. If a subject cannot undergo MRI due to a clinical reason, the AbbVie TA MD should be consulted for approval.
g. The NNIPPS-PPS will not be administered in Japan.
h. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.
i. Scale may be administered/assessed at any time during the visit with the exception of the scheduled infusion time.
j. Only applicable to subjects who prematurely discontinue. Verify consent was obtained prior to making contact.

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

Visits & Procedures[b]	Treatment Period[a]														
	Year 5														
	Dose 55	Dose 56	Dose 57	Dose 58	Dose 59	Dose 60	Dose 61	Dose 62	Dose 63	Dose 64	Dose 65	Dose 66/ Final	No Dose	D/C	20 Weeks Post Last Dose F/U
	Day 1485	Day 1513	Day 1541	Day 1569	Day 1597	Day 1625	Day 1653	Day 1681	Day 1709	Day 1737	Day 1765	Day 1793	Day 1821		
	Wk 212	Wk 216	Wk 220	Wk 224	Wk 228	Wk 232	Wk 236	Wk 240	Wk 244	Wk 248	Wk 252	Wk 256	Wk 260		
Symptom-driven physical examination[c]						X							X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP)[e]						U							S	S	U
Neurological examination						X							X	X	X
12-lead ECG													X	X	
Clinical laboratory tests													X	X	
Brain MRI[f]						X							X	X	X
LP/CSF collection						X							X	X	X
Blood PK sample						X							X	X	X
ADA Sample collection						X							X	X	X
Plasma biomarkers													X	X	X
CSF biomarkers						X							X	X	X
Optional exploratory PGx DNA and RNA sample													X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X	X			

Visits & Procedures[b]	Treatment Period[a]														
	Year 5														
	Dose 55	Dose 56	Dose 57	Dose 58	Dose 59	Dose 60	Dose 61	Dose 62	Dose 63	Dose 64	Dose 65	Dose 66/ Final	No Dose	D/C	20 Weeks Post Last Dose F/U
	Day 1485	Day 1513	Day 1541	Day 1569	Day 1597	Day 1625	Day 1653	Day 1681	Day 1709	Day 1737	Day 1765	Day 1793	Day 1821		
	Wk 212	Wk 216	Wk 220	Wk 224	Wk 228	Wk 232	Wk 236	Wk 240	Wk 244	Wk 248	Wk 252	Wk 256	Wk 260		
PSPRS						1							1	1	1
CGI-S						2							2	2	2
CGI-C						3							3	3	3
SEADL						4							4	4	4
UPDRS Part II						5							5	5	5
RBANS													6	6	
CTT Parts 1 & 2													7	7	
Letter Fluency Test (wpm)													8	8	
NNIPPS-PPS[g]													9	9	
PGI-C[h]						X							X	X	X
EQ-5D[h]													X	X	
C-SSRS[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PSP Caregiver Questionnaires						X							X	X	X
TSQM-9						X							X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visits & Procedures[b]	Treatment Period[a]														
	Year 5														
	Dose 55	Dose 56	Dose 57	Dose 58	Dose 59	Dose 60	Dose 61	Dose 62	Dose 63	Dose 64	Dose 65	Dose 66/ Final	No Dose	D/C	20 Weeks Post Last Dose F/U
	Day 1485	Day 1513	Day 1541	Day 1569	Day 1597	Day 1625	Day 1653	Day 1681	Day 1709	Day 1737	Day 1765	Day 1793	Day 1821		
	Wk 212	Wk 216	Wk 220	Wk 224	Wk 228	Wk 232	Wk 236	Wk 240	Wk 244	Wk 248	Wk 252	Wk 256	Wk 260		
Telephone contact[j]						X							X	X	X

AE = adverse event; LP = lumbar puncture; PK = pharmacokinetic; PGx = pharmacogenetic; S = serum; U = urine

a. Study drug will be administered on Days 1, 15, and 29, then every 28 days thereafter until 1 of the discontinuation criteria is met, until the Sponsor discontinues the study, or until the study reaches completion. For those Visits that include both study drug infusion and other activities, the Visits may be completed over 2 consecutive days with the second day to include the start and end of the infusion.

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

c. Additional symptom-driven physical examinations may be performed as needed.

d. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.

e. For all females of childbearing potential, a negative urine pregnancy test result is also required prior to any radiological procedures.

f. If a subject cannot undergo MRI due to a clinical reason, the AbbVie TA MD should be consulted for approval.

g. The NNIPPS-PPS will not be administered in Japan.

h. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.

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

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

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

Appendix D. Potentially Clinically Significant (PCS) Laboratory Values

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 leukostasis; 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
		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)

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry (Continued)						
		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
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

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry (Continued)						
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
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

CTCAE v4.0 Term	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry (Continued)						
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

LLN = lower limit of normal; ULN = upper limit of normal

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

Appendix E. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.0 Title Page
"Sponsor/Emergency Contact:" previously read:

Sponsor/Emergency Contact:	[redacted] Medical Director Neuroscience Development AbbVie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen Germany	Phone: Fax: [redacted]

Has been changed to read:

Sponsor/Emergency Contact:	[redacted] Medical Director Neuroscience Development [redacted] 1 North Waukegan Road North Chicago, IL 60064	Phone: Fax: Cell: [redacted]

Section 1.2 Synopsis
Subsection Objectives:
Third paragraph
Add: new last bullet

To assess body position and gait in a subset of participating subjects using BioStamp digital sensors.

Section 1.2 Synopsis
Subsection Methodology:
Third paragraph
Add: new last sentence

In a subset of subjects (up to 50) at participating sites, subjects will be assigned digital sensor BioStamp units to be worn for 1-week epochs starting on Day 1, Day 29 (Week 4), Day 57 (Week 8), and Day 85 (Week 12).

Section 1.2 Synopsis
Subsection Diagnosis and Main Criteria for Inclusion/Exclusion:
Heading "Main Inclusion Criteria:"
Last bullet, first sentence previously read:

Subject voluntarily signed the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved Informed Consent Form, prior to the conduct of any study procedures, or, where applicable (i.e., countries other than Germany*) for a given subject, the subject's legally authorized representative (LAR) signed the IEC/IRB approved Informed Consent form on behalf of the subject and the subject signed the IEC/IRB approved assent form, prior to the conduct of any procedures.

Has been changed to read:

Subject voluntarily signed the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved Informed Consent Form, prior to the conduct of any study procedures, or, where applicable (i.e., countries other than Germany*) for a given subject, the subject's legally authorized representative (LAR) signed the IEC/IRB approved Informed Consent form on behalf of the subject, prior to the conduct of any procedures.

Section 1.2 Synopsis
Subsection Criteria for Evaluation:
Heading "Digital Biomarkers:"
Add: new heading and text

Digital Biomarkers:

- BioStamp sensor motor outcomes including posture, gait, and step count

Section 1.2 Synopsis
Subsection Statistical Methods:
Heading "Biomarkers:"
Add: new last sentence

Digital substudy endpoints will be handled in a separate scientific report.

Section 1.2 Synopsis
Subsection Statistical Methods:
Heading "Safety:"
First sentence previously read:

Adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA).

Has been changed to read:

Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

Section 3.0 Introduction
Subsection Clinical Experience
Heading "Phase 2 Multiple-Dose Study in Subjects with PSP"
Last sentence previously read:

A total of 330 subjects (220 on ABBV-8E12 and 110 on placebo) are planned.

Has been changed to read:

A total of 378 subjects are planned.

Section 4.0 Study Objectives
Third paragraph
Add: new last bullet

To assess body position and gait in a subset of participating subjects using BioStamp digital sensors.

Section 5.1 Overall Study Design and Plan: Description
Subsection Overview
First paragraph, third sentence previously read:

Study M15-562 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.

Has been changed to read:

Study M15-562 was designed to randomize 378 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Section 5.1 Overall Study Design and Plan: Description
Subsection Overview
Fourth paragraph, fourth sentence previously read:

The rate of infusion for each subject will be based upon that subject's most recently obtained weight and will range from 2.0 to 2 .7 mL/min (125 to 166 mL/hr) (refer to Section 5.5.1 for details on infusion rates).

Has been changed to read:

The rate of infusion for each subject will be based upon that subject's most recently obtained weight and will range from 3.5 to 4.7 mL/min (210 to 282 mL/hr) (refer to Section 5.5.1 for details on infusion rates).

Section 5.1 Overall Study Design and Plan: Description
Subsection Overview
Last paragraph
Add: new last sentence

In a subset of subjects (up to 50) at participating sites, subjects will be assigned digital sensor BioStamp units to be worn for 1 week epochs starting on Day 1, Day 29 (Week 4), Day 57 (Week 8), and Day 85 (Week 12).

Section 5.2.1 Inclusion Criteria
Criterion 1
First sentence previously read:

The subject voluntarily signed the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved Informed Consent form, prior to the conduct of any study procedures, or, where applicable (i.e., countries other than Germany*) for a given subject, the subject's legally authorized representative (LAR) signed the IEC/IRB approved Informed Consent form on behalf of the subject and the subject signed the Independent IEC/IRB approved assent form, prior to the conduct of any procedures.

Has been changed to read:

The subject voluntarily signed the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved Informed Consent form, prior to the conduct of any study procedures, or, where applicable (i.e., countries other than Germany*) for a given subject, the subject's legally authorized representative (LAR) signed the IEC/IRB approved Informed Consent form on behalf of the subject, prior to the conduct of any procedures.

Section 5.3.1.1.9 12-Lead Electrocardiogram
Subsection Procedure
Third paragraph
First bullet, sub-bullet previously read:

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)

Has been changed to read:

Pre-dose (just prior to pre-infusion PK sample collection and the start of infusion)

Section 5.3.1.1.11 Magnetic Resonance Imaging
First paragraph
Delete: last sentence

The study entry MRI should be completed after all other relevant study entry procedures (except lumbar puncture) have been completed and reviewed by the investigator.

Section 5.3.1.1.11 Magnetic Resonance Imaging
Second paragraph, first sentence previously read:

The Day 1 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.

Has been changed to read:

The Day 1 MRI assessment will be used to rule out the presence of any intracranial masses 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.

Section 5.3.1.1.11 Magnetic Resonance Imaging
Sixth paragraph
Add: new last sentence

If a subject cannot undergo MRI due to clinical reasons, the AbbVie TA MD should be consulted for approval.

Section 5.3.1.1.12 Lumbar Puncture
First paragraph, last sentence previously read:

The lumbar puncture on Day 1 must be done after all other entry criteria have been satisfied, and the lumbar puncture at completion (Week 260) or premature discontinuation should only be done if at least 3 months have elapsed since the previous lumbar puncture.

Has been changed to read:

Lumbar puncture on Day 1 and lumbar puncture at completion (Week 260) or premature discontinuation should only be done if at least 3 months have elapsed since the previous lumbar puncture.

Section 5.3.1.1.12 Lumbar Puncture
Add: new third paragraph

Subjects who are not able to undergo an LP may be enrolled with permission of the AbbVie TA MD without the requirement of an LP during the study.

Table 3. Diagnostic Tools and Scale Order, and Duration of Administration
Previously read:

Diagnostic Tools and Scales[a,b]	Approx. Duration (min)	S/SP	Treatment Period												20 Weeks Post Last Dose F/U
			Year 1				Year 2		Year 3		Year 4		Year 5		
			Day 1[c]	Wk 12	Wk 24	Wk 52	Wk 76	Wk 104	Wk 128	Wk 156	Wk 180	Wk 208	Wk 232	Wk 260 Completion/ Premature D/C	
PSPRS	10	S and SP	1	1	1	1	1	1	1	1	1	1	1	1	1
CGI-S	40 – 60	S	2	2	2	2	2	2	2	2	2	2	2	2	2
CGI-C	1	S	3	3	3	3	3	3	3	3	3	3	3	3	3
SEADL	2	S	4	4	4	4	4	4	4	4	4	4	4	4	4
UPDRS Part II	10	S	5	5	5	5	5	5	5	5	5	5	5	5	5
RBANS	25	S				6		6		6		6		6	
CTT Parts 1 & 2	5 – 10	S				7		7		7		7		7	
Letter Fluency Test (wpm)	1	S				8		8		8		8		8	
NNIPPS-PPS[d]	30 – 45	S and SP				9		9		9		9		9	
PGI-C[e]	1 – 2	S	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D[e]	8	S	X			X		X		X		X		X	
C-SSRS (at every visit prior to infusion)	< 5	S	X	X	X	X	X	X	X	X	X	X	X	X	X

Approx = approximately; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; CTT = Color Trails Test; D/C = discontinuation; EQ-5D = EuroQol-5D; F/U = follow-up; min = minutes; NNIPPS-PPS = National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy; PGI-C = Patient Global Impression of Change; RBANS = Repeatable Battery for Assessment of Neuropsychological Status; S = subject; SEADL = Schwab and England Activities of Daily Living Scale; SP = study partner; UPDRS = Unified Parkinson's Disease Rating Scale; Wk = week; wpm = words per minute

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. The NNIPPS-PPS will not be administered in Japan.
e. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.

Has been changed to read:

Diagnostic Tools and Scales[a,b]	Approx. Duration (min)	S/SP	Treatment Period												20 Weeks Post Last Dose F/U
			Year 1				Year 2		Year 3		Year 4		Year 5		
			Day 1[c]	Wk 12	Wk 24	Wk 52	Wk 76	Wk 104	Wk 128	Wk 156	Wk 180	Wk 208	Wk 232	Wk 260 Completion/ Premature D/C	
PSPRS	10	S and SP	1	1	1	1	1	1	1	1	1	1	1	1	1
CGI-S	40 – 60	S and SP	2	2	2	2	2	2	2	2	2	2	2	2	2
CGI-C	1	S and SP	3	3	3	3	3	3	3	3	3	3	3	3	3
SEADL	2	S	4	4	4	4	4	4	4	4	4	4	4	4	4
UPDRS Part II	10	S	5	5	5	5	5	5	5	5	5	5	5	5	5
RBANS	25	S				6		6		6		6		6	
CTT Parts 1 & 2	5 – 10	S				7		7		7		7		7	
Letter Fluency Test (wpm)	1	S				8		8		8		8		8	
NNIPPS-PPS[d]	30 – 45	S and SP				9		9		9		9		9	
PGI-C[e]	1 – 2	S	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D[e]	8	S	X			X		X		X		X		X	
C-SSRS (at every visit)[f]	< 5	S	X	X	X	X	X	X	X	X	X	X	X	X	X
BioStamp nPoint[g]		S	X	X											
PSP Caregiver Questionnaires	25	SP	X		X	X	X	X	X	X	X	X	X	X	X
TSQM-9	5	S	X		X	X	X	X	X	X	X	X	X	X	X

Approx = approximately; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; CTT = Color Trails Test; D/C = discontinuation; EQ-5D = EuroQol-5D; F/U = follow-up; min = minutes; NNIPPS-PPS = National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy; PGI-C = Patient Global Impression of Change; RBANS = Repeatable Battery for Assessment of Neuropsychological Status; S = subject; SEADL = Schwab and England Activities of Daily Living Scale; SP = study partner; TSQM-9 = Treatment Satisfaction Questionnaire for Medication; UPDRS = Unified Parkinson's Disease Rating Scale; Wk = week; wpm = words per minute

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. The NNIPPS-PPS will not be administered in Japan.

e. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.

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

g. BioStamp nPoint will also be administered at Weeks 4 and 8.

Section 5.3.1.1.13 Diagnostic Tools and Rating Scales
Subsection Schwab and England Activities of Daily Living Scale
Subsection title previously read:

Schwab and England Activities of Daily Living Scale

Has been changed to read:

Schwab and England Activities of Daily Living Scale[17]

Section 5.3.1.1.13 Diagnostic Tools and Rating Scales
Subsection BioStamp nPoint (for subjects participating in the substudy only)[27]
Add: new subsection title and text

BioStamp nPoint (for subjects participating in the substudy only)[27]

BioStamp nPoint is an FDA 510(k)-cleared medical device designed to collect medical grade, clinical quality biometric, physiologic, and other electronic clinical outcome assessment (eCOA) data in a clinical trial setting. The system processes raw data into recognizable clinical metrics including heart rate, activity and posture classification, surface electromyography (sEMG), and sleep metrics. The sensors are multi-modal, multi-location, rechargeable, and reusable. BioStamp data are processed and stored in a secure cloud that can be synchronized with third-party electronic data capture (EDC) and clinical trial management (CTM) systems.

Three BioStamp sensor locations (left precordial chest, anterior thigh, and small of back) will be used in the study, and will capture information on heart rate, sleep, and measures of motor activity including posture, gait, and step count. Subjects will be trained during a clinic visit how to use the system including how to apply and remove sensors and how to upload data. Detailed laboratory manuals will be provided to participating sites.

Section 5.3.1.1.13 Diagnostic Tools and Rating Scales
Subsection PSP Caregiver Questionnaires[28,29]
Add: new subsection title and text

PSP Caregiver Questionnaires[28,29]

The PSP caregiver questionnaire assesses the burden of caregivers, their work productivity, and health resource use, as well as quality of life. The questionnaire consists of both questions specifically developed for this study as well as validated scales. Caregivers will complete the following sections of the questionnaire at scheduled visits during the study:

- Caregiver Information: This section gathers caregiver's basic demographic information such as age, gender, ethnicity, and household information. It takes approximately 2 minutes to complete.
- Caring for Someone with PSP: This section contains a list of questions to capture the relationship between the caregiver and the person with PSP, the living arrangement, and the amount of time spent on caring. In addition, it measures how frequently the caregiver helps with daily activities. It takes approximately 5 minutes to administer this section.
- Caregiver Work Productivity and Status: Caregiver Work Productivity is measured by (Work Productivity and Activity Impairment Questionnaire [WPAI]). The WPAI caregiver version is a validated 6-question instrument to measure impairments in work and activities. The first 4 questions measure employment status and hours missed from work, and the last 2 questions measure the impact of caregiving on work productivity and daily activities on a 0 - 10 scale. In addition to WPAI, there are 2 additional questions measuring the caregiver's work status and if the reason of unemployment is related to caregiving. It takes approximately 5 minutes to administer the questionnaire.
- Caregiver Healthcare Resource Use: This section assesses the caregiver's general health as well as their health resource use in terms of number of physician, ER visits, hospitalization, and length of stay for each hospitalization. It takes approximately 5 minutes to administer this section.

- Caregiver Quality of Life (carers quality-of-life questionnaire for PSP [PQoL Carers]): PQoL Carers is a QoL instrument for carers of people with atypical parkinsonism (AP), including PSP and MSA. The 26-item instrument was generated from in-depth interviews with carers of patients with AP and a thorough review of the existing literature and consultation with movement disorder experts. The items are scored from 0 (no problem) to 4 (extreme problems). It is a concise instrument with adequate psychometric qualities. Convergent and concurrent validity was supported by correlations of PQoL Carers with the patient's health status and QoL measures such as The Parkinson's Disease Questionnaire-39 (PDQ-39) and EQ-5D, as well as carers' measures, such as Caregiver Burden Inventory (CBI) and carer EQ-5D. The discriminant validity of the scale was demonstrated through its capacity to differentiate between carers with varying levels of self-reported health. It takes approximately 8 minutes to administer the questionnaire.

Section 5.3.1.1.13 Diagnostic Tools and Rating Scales
Subsection Treatment Satisfaction Questionnaires for Medication[30]
Add: new subsection title and text

Treatment Satisfaction Questionnaire for Medication[30]

The Treatment Satisfaction Questionnaire for Medication (TSQM-9) assesses patient satisfaction with medication in 3 domains: effectiveness (3 items), convenience (3 items), and global satisfaction (3 items). Each item is scored on a 7- or 5-point Likert scale. The total score in each domain is converted to a score between 0 and 100, with higher scores indicating greater satisfaction with treatment. It takes approximately 5 minutes to complete the questionnaire.

Section 5.3.1.2.1 Biomarker Samples
Last paragraph
Add: new last sentence

Details for collection and processing are provided in a separate laboratory manual.

Section 5.3.6.1 Biomarker Research Variables
Add: new last bullet and sub-bullet

- Digital Biomarkers:
  - BioStamp sensor motor outcomes including posture, gait, and step count

Section 5.3.6.1 Biomarker Research Variables
Add: new last paragraph

Digital substudy endpoints will be handled in a separate scientific report.

Section 5.4.1 Discontinuation of Individual Subjects
Add: new last paragraph

Subjects who prematurely discontinue from the study can be contacted by telephone for periodic updates at the times shown in Appendix C providing that consent for this contact was obtained prior to contact being made.

Section 5.5.1 Treatments Administered
First table previously read:

Subject's Weight in kg/lbs	Infusion Rate[b]
44 – 49 kg (97 – 109 lbs, inclusive)[a]	2.0 mL/min or 125 mL/hr
50 – 58 kg (110 – 128 lbs, inclusive)	2.3 mL/min or 142 mL/hr
59 kg and over (129 lbs and over)	2.7 mL/min or 166 mL/hr

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

b. Continue infusion until bag is empty.

Has been changed to read:

Subject's Weight in kg/lbs	Infusion Rate[b]
44 – 49 kg (97 – 109 lbs, inclusive)[a]	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

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

b. Continue infusion until bag is empty.

Section 5.5.2.2 Storage and Disposition of Study Drug
Third paragraph, third and fourth sentence previously read:

Malfunctions or any temperature excursion must be reported to the Sponsor immediately using the AbbVie Temperature Excursion Management System (ATEMS). Study drug should be quarantined and not dispensed until AbbVie (ATEMS) deems the drug as acceptable.

Has been changed to read:

Malfunctions or temperature excursion must be reported to the Sponsor immediately using the AbbVie Temperature Excursion Management System (ATEMS). Study drug should be quarantined and not dispensed until ATEMS deems the drug as acceptable.

Section 6.1.5 Adverse Event Reporting
"Primary TA MD:" previously read:

[redacted]
Medical Director
Neuroscience Development
AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

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

Has been changed to read:

[redacted]
Medical Director
Neuroscience Development
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

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

Section 6.1.7.5 Management of Adverse Events of the Nervous System
First paragraph, last sentence previously read:

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.

Has been changed to read:

A drug related adverse event is an event that is judged by the investigator or AbbVie to have a "reasonable possibility" of being related to the study drug.

Section 6.2.2 Reporting
First paragraph, first sentence previously read:

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.

Has been changed to read:

Product Complaints concerning the investigational product must be reported to the Sponsor within 1 business day of the study site's knowledge of the event via the Product Complaint form.

Section 8.1.2.2 Analysis of Adverse Events
Second paragraph, first sentence previously read:

Adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA).

Has been changed to read:

Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

Section 8.1.3 Biomarker Analyses
Add: new last paragraph

Digital substudy endpoints will be handled in a separate scientific report.

Section 8.2.2 Efficacy Interim Analysis
Add: new second sentence

Additional efficacy interim analyses may be conducted as needed.

Section 8.3 Determination of Sample Size
Last sentence previously read:

Approximately 330 subjects will be randomized in Study M15-562; and the number of subjects who enroll in Study M15-563 will be up to the number of subjects enrolled in Study M15-562.

Has been changed to read:

A total of 378 subjects will be randomized in Study M15-562; and the number of subjects who enroll in Study M15-563 will be up to the number of subjects enrolled in Study M15-562.

Section 15.0 Reference List
Add: new Reference 17, 27, 28, 29, 30

17. Schwab RS, England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson MC, eds. Third symposium on Parkinson's disease. Edinburgh. Livingston. 1969:152-7.

27. Adams JL, Dinesh K, Xiong M, et al. Multiple wearable sensors in Parkinson and Huntington disease individuals: a pilot study in clinic and at home. Digit Biomark. 2017;1:52-63.

28. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4(5):353-65.

29. Pillas M, Selai C, Quinn NP, Lees A, et al. Development and validation of a carers quality-of-life questionnaire for parkinsonism (PQoL Carers). Qual Life Res. 2016;25(1): 81–8.

30. Bharmal M, Payne K, Atkinson MJ, et al. Validation of an abbreviated treatment satisfaction questionnaire for medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes. 2009;7:36.

Appendix B. List of Protocol Signatories

Previously read:

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

Has been changed to read:

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

Appendix C. Study Activities
Previously read:

Visits & Procedures[b]	Treatment Period[a]																20 Wks Post Last Dose F/U
	Year 1																
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13	Dose 14	Dose 15		
	Day 1	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365		
	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	D/C	
Subject/study partner ICF[c]	X																
Medical history update[d]	X																
Randomization	X																
Physical examination	X																
Symptom-driven physical examination[e]								X							X	X	X
Orthostatic vital signs[f,g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs[g]																X	X
Body weight (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP)[h]	U				U			U							U	S	U
Neurological examination	X				X			X							X	X	X
12-lead ECG	X				X			X							X	X	
Clinical laboratory tests	X				X			X							X	X	
Brain MRI	X				X			X							X	X	X
LP/CSF collection	X							X							X	X	X

Visits & Procedures[b]	Treatment Period[a]																20 Wks Post Last Dose F/U
	Year 1																
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13	Dose 14	Dose 15		
	Day 1	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365		
	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	D/C	
Blood PK sample	X				X			X							X	X	X
ADA Sample collection	X				X			X							X	X	X
CSF and plasma biomarkers	X				X			X							X	X	X
Optional exploratory PGx DNA and RNA blood sample	X				X			X							X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PSPRS	1				1			1							1	1	1
CGI-S	2				2			2							2	2	2
CGI-C	3				3			3							3	3	3
SEADL	4				4			4							4	4	4
UPDRS Part II	5				5			5							5	5	5
RBANS															6	6	
CTT Parts 1 & 2															7	7	
Letter Fluency Test (wpm)															8	8	
NNIPPS-PPS[il]															9	9	
PGI-C[j]	X				X			X							X	X	X
EQ-5D[j]	X														X	X	

Visits & Procedures[b]	Treatment Period[a]																
	Year 1																
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13	Dose 14	Dose 15		
	Day 1	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365		
	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	D/C	20 Wks Post Last Dose F/U
C-SSRS (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BioStamp																	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; ICF = informed consent form; LP = lumbar puncture; PK = pharmacokinetic; PGx = pharmacogenetic; S = serum; U = urine

a. Study drug will be administered on Days 1, 15, and 29, then every 28 days thereafter until 1 of the discontinuation criteria is met, until the Sponsor discontinues the study, or until the study reaches completion. For those Visits that include both study drug infusion and other activities, the Visits may be completed over 2 consecutive days with the second day to include the start and end of the infusion.

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

c. Subject informed consent, or as applicable, legally authorized representative informed consent and subject assent, and study partner informed consent must be obtained prior to Study M15-563 Day 1 dosing.

d. Review medical history to confirm subject does not meet exclusion criteria prior to randomization.

e. Additional symptom-driven physical examinations may be performed as needed.

f. All supine and standing blood pressure and pulse rate measurements are to be measured as part of an orthostatic assessment.

g. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.

h. For all females of childbearing potential, a negative urine pregnancy test result is also required prior to any radiological procedures.

i. The NNIPPS-PPS will not be administered in Japan.

j. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.

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

Visits & Procedures[b]	Treatment Period[a]														20 Wks Post Last Dose F/U
	Year 2														
	Dose 16	Dose 17	Dose 18	Dose 19	Dose 20	Dose 21	Dose 22	Dose 23	Dose 24	Dose 25	Dose 26	Dose 27	Dose 28	D/C	
	Day 393	Day 421	Day 449	Day 477	Day 505	Day 533	Day 561	Day 589	Day 617	Day 645	Day 673	Day 701	Day 729		
	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96	Wk 100	Wk 104		
Symptom-driven physical examination[c]						X							X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP)[e]						U							U	S	U
Neurological examination						X							X	X	X
12-lead ECG													X	X	
Clinical laboratory tests													X	X	
Brain MRI						X							X	X	X
LP/CSF collection						O							X	X	X
Blood PK sample						X							X	X	X
ADA Sample collection						X							X	X	X
CSF and plasma biomarkers													X	X	X
Optional exploratory PGx DNA and RNA sample													X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X		
PSPRS						1							1	1	1
CGI-S						2							2	2	2

Visits & Procedures[b]	Treatment Period[a]														20 Wks Post Last Dose F/U
	Year 2														
	Dose 16	Dose 17	Dose 18	Dose 19	Dose 20	Dose 21	Dose 22	Dose 23	Dose 24	Dose 25	Dose 26	Dose 27	Dose 28		
	Day 393	Day 421	Day 449	Day 477	Day 505	Day 533	Day 561	Day 589	Day 617	Day 645	Day 673	Day 701	Day 729		
	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96	Wk 100	Wk 104	D/C	
CGI-C						3							3	3	3
SEADL						4							4	4	4
UPDRS Part II						5							5	5	5
RBANS													6	6	
CTT Parts 1 & 2													7	7	
Letter Fluency Test (wpm)													8	8	
NNIPPS-PPS[f]													9	9	
PGI-C[g]						X							X	X	X
EQ-5D[g]													X	X	
C-SSRS (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; LP = lumbar puncture; O = optional; PK = pharmacokinetic; PGx = pharmacogenetic; S = serum; U = urine

a. Study drug will be administered on Days 1, 15, and 29, then every 28 days thereafter until 1 of the discontinuation criteria is met, until the Sponsor discontinues the study, or until the study reaches completion. For those Visits that include both study drug infusion and other activities, the Visits may be completed over 2 consecutive days with the second day to include the start and end of the infusion.

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

c. Additional symptom-driven physical examinations may be performed as needed.

d. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.

e. For all females of childbearing potential, a negative urine pregnancy test result is also required prior to any radiological procedures.

f. The NNIPPS-PPS will not be administered in Japan

g. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.

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

Visits & Procedures[b]	Treatment Period[a]														20 Weeks Post Last Dose F/U
	Year 3														
	Dose 29	Dose 30	Dose 31	Dose 32	Dose 33	Dose 34	Dose 35	Dose 36	Dose 37	Dose 38	Dose 39	Dose 40	Dose 41		
	Day 757	Day 785	Day 813	Day 841	Day 869	Day 897	Day 925	Day 953	Day 981	Day 1009	Day 1037	Day 1065	Day 1093		
	Wk 108	Wk 112	Wk 116	Wk 120	Wk 124	Wk 128	Wk 132	Wk 136	Wk 140	Wk 144	Wk 148	Wk 152	Wk 156	D/C	
Symptom-driven physical examination[c]						X							X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP)[e]						U							U	S	U
Neurological examination						X							X	X	X
12-lead ECG													X	X	
Clinical laboratory tests													X	X	
Brain MRI						X							X	X	X
LP/CSF collection						O							X	X	X
Blood PK sample						X							X	X	X
ADA Sample collection						X							X	X	X
CSF and plasma biomarkers													X	X	X
Optional exploratory PGx DNA and RNA sample													X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X		
PSPRS						1							1	1	1
CGI-S						2							2	2	2

Visits & Procedures[b]	Treatment Period[a]														20 Weeks Post Last Dose F/U
	Year 3														
	Dose 29	Dose 30	Dose 31	Dose 32	Dose 33	Dose 34	Dose 35	Dose 36	Dose 37	Dose 38	Dose 39	Dose 40	Dose 41		
	Day 757	Day 785	Day 813	Day 841	Day 869	Day 897	Day 925	Day 953	Day 981	Day 1009	Day 1037	Day 1065	Day 1093		
	Wk 108	Wk 112	Wk 116	Wk 120	Wk 124	Wk 128	Wk 132	Wk 136	Wk 140	Wk 144	Wk 148	Wk 152	Wk 156	D/C	
CGI-C						3							3	3	3
SEADL						4							4	4	4
UPDRS Part II						5							5	5	5
RBANS													6	6	
CTT Parts 1 & 2													7	7	
Letter Fluency Test (wpm)													8	8	
NNIPPS-PPS[f]													9	9	
PGI-C[g]						X							X	X	X
EQ-5D[g]													X	X	
C-SSRS (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; LP = lumbar puncture; O = optional; PK = pharmacokinetic; PGx = pharmacogenetic; S = serum; U = urine

a. Study drug will be administered on Days 1, 15, and 29, then every 28 days thereafter until 1 of the discontinuation criteria is met, until the Sponsor discontinues the study, or until the study reaches completion. For those Visits that include both study drug infusion and other activities, the Visits may be completed over 2 consecutive days with the second day to include the start and end of the infusion.

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

c. Additional symptom-driven physical examinations may be performed as needed.

d. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.

e. For all females of childbearing potential, a negative urine pregnancy test result is also required prior to any radiological procedures.

f. The NNIPPS-PPS will not be administered in Japan

g. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.

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

Visits & Procedures[b]	Treatment Period[a]														20 Weeks Post Last Dose F/U
	Year 4														
	Dose 42	Dose 43	Dose 44	Dose 45	Dose 46	Dose 47	Dose 48	Dose 49	Dose 50	Dose 51	Dose 52	Dose 53	Dose 54		
	Day 1121	Day 1149	Day 1177	Day 1205	Day 1233	Day 1261	Day 1289	Day 1317	Day 1345	Day 1373	Day 1401	Day 1429	Day 1457		
	Wk 160	Wk 164	Wk 168	Wk 172	Wk 176	Wk 180	Wk 184	Wk 188	Wk 192	Wk 196	Wk 200	Wk 204	Wk 208	D/C	
Symptom-driven physical examination[c]						X							X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP)[e]						U							U	S	U
Neurological examination						X							X	X	X
12-lead ECG													X	X	
Clinical laboratory tests													X	X	
Brain MRI						X							X	X	X
LP/CSF collection						O							X	X	X
Blood PK sample						X							X	X	X
ADA Sample collection						X							X	X	X
CSF and plasma biomarkers													X	X	X
Optional exploratory PGx DNA and RNA sample													X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X		
PSPRS						1							1	1	1
CGI-S						2							2	2	2

Visits & Procedures[b]	Treatment Period[a]														20 Weeks Post Last Dose F/U
	Year 4														
	Dose 42	Dose 43	Dose 44	Dose 45	Dose 46	Dose 47	Dose 48	Dose 49	Dose 50	Dose 51	Dose 52	Dose 53	Dose 54		
	Day 1121	Day 1149	Day 1177	Day 1205	Day 1233	Day 1261	Day 1289	Day 1317	Day 1345	Day 1373	Day 1401	Day 1429	Day 1457		
	Wk 160	Wk 164	Wk 168	Wk 172	Wk 176	Wk 180	Wk 184	Wk 188	Wk 192	Wk 196	Wk 200	Wk 204	Wk 208	D/C	
CGI-C						3							3	3	3
SEADL						4							4	4	4
UPDRS Part II						5							5	5	5
RBANS													6	6	
CTT Parts 1 & 2													7	7	
Letter Fluency Test (wpm)													8	8	
NNIPPS-PPS[f]													9	9	
PGI-C[g]						X							X	X	X
EQ-5D[g]													X	X	
C-SSRS (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; LP = lumbar puncture; O = optional; PK = pharmacokinetic; PGx = pharmacogenetic; S = serum; U = urine

a. Study drug will be administered on Days 1, 15, and 29, then every 28 days thereafter until 1 of the discontinuation criteria is met, until the Sponsor discontinues the study, or until the study reaches completion. For those Visits that include both study drug infusion and other activities, the Visits may be completed over 2 consecutive days with the second day to include the start and end of the infusion.

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

c. Additional symptom-driven physical examinations may be performed as needed.

d. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.

e. For all females of childbearing potential, a negative urine pregnancy test result is also required prior to any radiological procedures.

f. The NNIPPS-PPS will not be administered in Japan.

g. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.

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

Visits & Procedures[b]	Treatment Period[a]														
	Year 5														
	Dose 55	Dose 56	Dose 57	Dose 58	Dose 59	Dose 60	Dose 61	Dose 62	Dose 63	Dose 64	Dose 65	Dose 66/ Final	No Dose	D/C	20 Weeks Post Last Dose F/U
	Day 1485	Day 1513	Day 1541	Day 1569	Day 1597	Day 1625	Day 1653	Day 1681	Day 1709	Day 1737	Day 1765	Day 1793	Day 1821		
	Wk 212	Wk 216	Wk 220	Wk 224	Wk 228	Wk 232	Wk 236	Wk 240	Wk 244	Wk 248	Wk 252	Wk 256	Wk 260		
Symptom-driven physical examination[c]						X							X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP)[e]						U							S	S	U
Neurological examination						X							X	X	X
12-lead ECG													X	X	
Clinical laboratory tests													X	X	
Brain MRI						X							X	X	X
LP/CSF collection						O							X	X	X
Blood PK sample						X							X	X	X
ADA Sample collection						X							X	X	X
CSF and plasma biomarkers													X	X	X
Optional exploratory PGx DNA and RNA sample													X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X	X			
PSPRS						1							1	1	1

Visits & Procedures[b]	Treatment Period[a]														
	Year 5														
	Dose 55	Dose 56	Dose 57	Dose 58	Dose 59	Dose 60	Dose 61	Dose 62	Dose 63	Dose 64	Dose 65	Dose 66/ Final	No Dose	D/C	20 Weeks Post Last Dose F/U
	Day 1485	Day 1513	Day 1541	Day 1569	Day 1597	Day 1625	Day 1653	Day 1681	Day 1709	Day 1737	Day 1765	Day 1793	Day 1821		
	Wk 212	Wk 216	Wk 220	Wk 224	Wk 228	Wk 232	Wk 236	Wk 240	Wk 244	Wk 248	Wk 252	Wk 256	Wk 260		
CGI-S						2							2	2	2
CGI-C						3							3	3	3
SEADL						4							4	4	4
UPDRS Part II						5							5	5	5
RBANS													6	6	
CTT Parts 1 & 2													7	7	
Letter Fluency Test (wpm)													8	8	
NNIPPS-PPS[f]													9	9	
PGI-C[g]						X							X	X	X
EQ-5D[g]													X	X	
C-SSRS (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; LP = lumbar puncture; O = optional; PK = pharmacokinetic; PGx = pharmacogenetic; S = serum; U = urine

a. Study drug will be administered on Days 1, 15, and 29, then every 28 days thereafter until 1 of the discontinuation criteria is met, until the Sponsor discontinues the study, or until the study reaches completion. For those Visits that include both study drug infusion and other activities, the Visits may be completed over 2 consecutive days with the second day to include the start and end of the infusion.

b. Audio recordings/central review of the administration/assessment of selected scales may be conducted.
c. Additional symptom-driven physical examinations may be performed as needed.
d. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.
e. For all females of childbearing potential, a negative urine pregnancy test result is also required prior to any radiological procedures.
f. The NNIPPS-PPS will not be administered in Japan.
g. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.

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

Has been changed to read:

Visits & Procedures[b]	Treatment Period[a]																20 Wks Post Last Dose F/U
	Year 1																
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13	Dose 14	Dose 15		
	Day 1	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365		
	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	D/C	
Subject/study partner ICF[c]	X																
Medical history update[d]	X																
Randomization	X																
Physical examination	X																
Symptom-driven physical examination[e]								X							X	X	X
Orthostatic vital signs[f,g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs[g]																X	X
Body weight (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP)[h]	U				U			U							U	S	U
Neurological examination	X				X			X							X	X	X
12-lead ECG	X				X			X							X	X	
Clinical laboratory tests	X				X			X							X	X	
Brain MRI[i]	X				X			X							X	X	X
LP/CSF collection[j]	X							X							X	X	X

Visits & Procedures[b]	Treatment Period[a]																20 Wks Post Last Dose F/U
	Year 1																
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13	Dose 14	Dose 15		
	Day 1	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365		
	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	D/C	
Blood PK sample	X				X			X							X	X	X
ADA Sample collection	X				X			X							X	X	X
Plasma biomarkers	X				X			X							X	X	X
CSF biomarkers	X							X							X	X	X
Optional exploratory PGx DNA and RNA blood sample	X				X			X							X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PSPRS	1				1			1							1	1	1
CGI-S	2				2			2							2	2	2
CGI-C	3				3			3							3	3	3
SEADL	4				4			4							4	4	4
UPDRS Part II	5				5			5							5	5	5
RBANS															6	6	
CTT Parts 1 & 2															7	7	
Letter Fluency Test (wpm)															8	8	
NNIPPS-PPS[k]															9	9	
PGI-C[l]	X				X			X							X	X	X

Visits & Procedures[b]	Treatment Period[a]																
	Year 1																
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13	Dose 14	Dose 15		
	Day 1	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365		
	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	D/C	20 Wks Post Last Dose F/U
EQ-5D[l]	X														X	X	
C-SSRS[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BioStamp Digital[n]	X		X	X	X												
PSP Caregiver Questionnaires	X							X							X	X	X
TSQM-9	X							X							X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone contact[o]	X				X			X							X	X	X

AE = adverse event; ICF = informed consent form; LP = lumbar puncture; PK = pharmacokinetic; PGx = pharmacogenetic; S = serum; U = urine

a. Study drug will be administered on Days 1, 15, and 29, then every 28 days thereafter until 1 of the discontinuation criteria is met, until the Sponsor discontinues the study, or until the study reaches completion. For those Visits that include both study drug infusion and other activities, the Visits may be completed over 2 consecutive days with the second day to include the start and end of the infusion.

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

c. Subject informed consent, or as applicable, legally authorized representative informed consent, and study partner informed consent must be obtained prior to Study M15-563 Day 1 dosing.

d. Review medical history to confirm subject does not meet exclusion criteria prior to randomization.

e. Additional symptom-driven physical examinations may be performed as needed.

f. All supine and standing blood pressure and pulse rate measurements are to be measured as part of an orthostatic assessment.

g. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.
h. For all females of childbearing potential, a negative urine pregnancy test result is also required prior to any radiological procedures.
i. If a subject cannot undergo MRI due to a clinical reason, the AbbVie TA MD should be consulted for approval.
j. Subjects who are not able to undergo an LP may be enrolled with permission of the AbbVie TA MD without the requirement of an LP during the study.
k. The NNIPPS-PPS will not be administered in Japan.
l. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.
m. Scale may be administered/assessed at any time during the visit with the exception of the scheduled infusion time.
n. Device to be worn for 7 days.
o. Only applicable to subjects who prematurely discontinue. Verify consent was obtained prior to making contact.

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

Visits & Procedures[b]	Treatment Period[a]														20 Wks Post Last Dose F/U
	Year 2														
	Dose 16	Dose 17	Dose 18	Dose 19	Dose 20	Dose 21	Dose 22	Dose 23	Dose 24	Dose 25	Dose 26	Dose 27	Dose 28	D/C	
	Day 393	Day 421	Day 449	Day 477	Day 505	Day 533	Day 561	Day 589	Day 617	Day 645	Day 673	Day 701	Day 729		
	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96	Wk 100	Wk 104		
Symptom-driven physical examination[c]						X							X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP)[e]						U							U	S	U
Neurological examination						X							X	X	X
12-lead ECG													X	X	
Clinical laboratory tests													X	X	
Brain MRI[f]						X							X	X	X
LP/CSF collection						X							X	X	X
Blood PK sample						X							X	X	X
ADA Sample collection						X							X	X	X
Plasma biomarkers													X	X	X
CSF biomarkers						X							X	X	X
Optional exploratory PGx DNA and RNA sample													X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X		
PSPRS						1							1	1	1

Visits & Procedures[b]	Treatment Period[a]														20 Wks Post Last Dose F/U
	Year 2														
	Dose 16	Dose 17	Dose 18	Dose 19	Dose 20	Dose 21	Dose 22	Dose 23	Dose 24	Dose 25	Dose 26	Dose 27	Dose 28	D/C	
	Day 393	Day 421	Day 449	Day 477	Day 505	Day 533	Day 561	Day 589	Day 617	Day 645	Day 673	Day 701	Day 729		
	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96	Wk 100	Wk 104		
CGI-S						2							2	2	2
CGI-C						3							3	3	3
SEADL						4							4	4	4
UPDRS Part II						5							5	5	5
RBANS													6	6	
CTT Parts 1 & 2													7	7	
Letter Fluency Test (wpm)													8	8	
NNIPPS-PPS[g]													9	9	
PGI-C[h]						X							X	X	X
EQ-5D[h]													X	X	
C-SSRS[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PSP Caregiver Questionnaires						X							X	X	X
TSQM-9						X							X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone contact[j]						X							X	X	X

AE = adverse event; LP = lumbar puncture; PK = pharmacokinetic; PGx = pharmacogenetic; S = serum; U = urine

a. Study drug will be administered on Days 1, 15, and 29, then every 28 days thereafter until 1 of the discontinuation criteria is met, until the Sponsor discontinues the study, or until the study reaches completion. For those Visits that include both study drug infusion and other activities, the Visits may be completed over 2 consecutive days with the second day to include the start and end of the infusion.
b. Audio recordings/central review of the administration/assessment of selected scales may be conducted.
c. Additional symptom-driven physical examinations may be performed as needed.
d. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.
e. For all females of childbearing potential, a negative urine pregnancy test result is also required prior to any radiological procedures.
f If a subject cannot undergo MRI due to a clinical reason, the AbbVie TA MD should be consulted for approval.
g. The NNIPPS-PPS will not be administered in Japan
h. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.
i. Scale may be administered/assessed at any time during the visit with the exception of the scheduled infusion time.
j. Only applicable to subjects who prematurely discontinue. Verify consent was obtained prior to making contact.

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

Visits & Procedures[b]	Treatment Period[a]														20 Weeks Post Last Dose F/U
	Year 3														
	Dose 29	Dose 30	Dose 31	Dose 32	Dose 33	Dose 34	Dose 35	Dose 36	Dose 37	Dose 38	Dose 39	Dose 40	Dose 41		
	Day 757	Day 785	Day 813	Day 841	Day 869	Day 897	Day 925	Day 953	Day 981	Day 1009	Day 1037	Day 1065	Day 1093		
	Wk 108	Wk 112	Wk 116	Wk 120	Wk 124	Wk 128	Wk 132	Wk 136	Wk 140	Wk 144	Wk 148	Wk 152	Wk 156	D/C	
Symptom-driven physical examination[c]						X							X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP)[e]						U							U	S	U
Neurological examination						X							X	X	X
12-lead ECG													X	X	
Clinical laboratory tests													X	X	
Brain MRI[f]						X							X	X	X
LP/CSF collection						X							X	X	X
Blood PK sample						X							X	X	X
ADA Sample collection						X							X	X	X
Plasma biomarkers													X	X	X
CSF biomarkers						X							X	X	X
Optional exploratory PGx DNA and RNA sample													X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X		
PSPRS						1							1	1	1

Visits & Procedures[b]	Treatment Period[a]														20 Weeks Post Last Dose F/U
	Year 3														
	Dose 29	Dose 30	Dose 31	Dose 32	Dose 33	Dose 34	Dose 35	Dose 36	Dose 37	Dose 38	Dose 39	Dose 40	Dose 41		
	Day 757	Day 785	Day 813	Day 841	Day 869	Day 897	Day 925	Day 953	Day 981	Day 1009	Day 1037	Day 1065	Day 1093		
	Wk 108	Wk 112	Wk 116	Wk 120	Wk 124	Wk 128	Wk 132	Wk 136	Wk 140	Wk 144	Wk 148	Wk 152	Wk 156	D/C	
CGI-S						2							2	2	2
CGI-C						3							3	3	3
SEADL						4							4	4	4
UPDRS Part II						5							5	5	5
RBANS													6	6	
CTT Parts 1 & 2													7	7	
Letter Fluency Test (wpm)													8	8	
NNIPPS-PPS[g]													9	9	
PGI-C[h]						X							X	X	X
EQ-5D[h]													X	X	
C-SSRS[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PSP Caregiver Questionnaires						X							X	X	X
TSQM-9						X							X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone contact[j]						X							X	X	X

AE = adverse event; LP = lumbar puncture; PK = pharmacokinetic; PGx = pharmacogenetic; S = serum; U = urine

a. Study drug will be administered on Days 1, 15, and 29, then every 28 days thereafter until 1 of the discontinuation criteria is met, until the Sponsor discontinues the study, or until the study reaches completion. For those Visits that include both study drug infusion and other activities, the Visits may be completed over 2 consecutive days with the second day to include the start and end of the infusion.
b. Audio recordings/central review of the administration/assessment of selected scales may be conducted.
c. Additional symptom-driven physical examinations may be performed as needed.
d. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.
e. For all females of childbearing potential, a negative urine pregnancy test result is also required prior to any radiological procedures.
f. If a subject cannot undergo MRI due to a clinical reason, the AbbVie TA MD should be consulted for approval.
g. The NNIPPS-PPS will not be administered in Japan
h. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.
i. Scale may be administered/assessed at any time during the visit with the exception of the scheduled infusion time.
j. Only applicable to subjects who prematurely discontinue. Verify consent was obtained prior to making contact.

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

Visits & Procedures[b]	Treatment Period[a]														20 Weeks Post Last Dose F/U
	Year 4														
	Dose 42	Dose 43	Dose 44	Dose 45	Dose 46	Dose 47	Dose 48	Dose 49	Dose 50	Dose 51	Dose 52	Dose 53	Dose 54		
	Day 1121	Day 1149	Day 1177	Day 1205	Day 1233	Day 1261	Day 1289	Day 1317	Day 1345	Day 1373	Day 1401	Day 1429	Day 1457		
	Wk 160	Wk 164	Wk 168	Wk 172	Wk 176	Wk 180	Wk 184	Wk 188	Wk 192	Wk 196	Wk 200	Wk 204	Wk 208	D/C	
Symptom-driven physical examination[c]						X							X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP)[e]						U							U	S	U
Neurological examination						X							X	X	X
12-lead ECG													X	X	
Clinical laboratory tests													X	X	
Brain MRI[f]						X							X	X	X
LP/CSF collection						X							X	X	X
Blood PK sample						X							X	X	X
ADA Sample collection						X							X	X	X
Plasma biomarkers													X	X	X
CSF biomarkers						X							X	X	X
Optional exploratory PGx DNA and RNA sample													X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X		
PSPRS						1							1	1	1

Visits & Procedures[b]	Treatment Period[a]														20 Weeks Post Last Dose F/U
	Year 4														
	Dose 42	Dose 43	Dose 44	Dose 45	Dose 46	Dose 47	Dose 48	Dose 49	Dose 50	Dose 51	Dose 52	Dose 53	Dose 54		
	Day 1121	Day 1149	Day 1177	Day 1205	Day 1233	Day 1261	Day 1289	Day 1317	Day 1345	Day 1373	Day 1401	Day 1429	Day 1457		
	Wk 160	Wk 164	Wk 168	Wk 172	Wk 176	Wk 180	Wk 184	Wk 188	Wk 192	Wk 196	Wk 200	Wk 204	Wk 208	D/C	
CGI-S						2							2	2	2
CGI-C						3							3	3	3
SEADL						4							4	4	4
UPDRS Part II						5							5	5	5
RBANS													6	6	
CTT Parts 1 & 2													7	7	
Letter Fluency Test (wpm)													8	8	
NNIPPS-PPS[g]													9	9	
PGI-C[h]						X							X	X	X
EQ-5D[h]													X	X	
C-SSRS[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PSP Caregiver Questionnaires						X							X	X	X
TSQM-9						X							X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone contact[j]						X							X	X	X

AE = adverse event; LP = lumbar puncture; PK = pharmacokinetic; PGx = pharmacogenetic; S = serum; U = urine

a. Study drug will be administered on Days 1, 15, and 29, then every 28 days thereafter until 1 of the discontinuation criteria is met, until the Sponsor discontinues the study, or until the study reaches completion. For those Visits that include both study drug infusion and other activities, the Visits may be completed over 2 consecutive days with the second day to include the start and end of the infusion.
b. Audio recordings/central review of the administration/assessment of selected scales may be conducted.
c. Additional symptom-driven physical examinations may be performed as needed.
d. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.
e. For all females of childbearing potential, a negative urine pregnancy test result is also required prior to any radiological procedures.
f. If a subject cannot undergo MRI due to a clinical reason, the AbbVie TA MD should be consulted for approval.
g. The NNIPPS-PPS will not be administered in Japan.
h. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.
i. Scale may be administered/assessed at any time during the visit with the exception of the scheduled infusion time.
j. Only applicable to subjects who prematurely discontinue. Verify consent was obtained prior to making contact.

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

Visits & Procedures[b]	Treatment Period[a]														
	Year 5														
	Dose 55	Dose 56	Dose 57	Dose 58	Dose 59	Dose 60	Dose 61	Dose 62	Dose 63	Dose 64	Dose 65	Dose 66/ Final	No Dose	D/C	20 Weeks Post Last Dose F/U
	Day 1485	Day 1513	Day 1541	Day 1569	Day 1597	Day 1625	Day 1653	Day 1681	Day 1709	Day 1737	Day 1765	Day 1793	Day 1821		
	Wk 212	Wk 216	Wk 220	Wk 224	Wk 228	Wk 232	Wk 236	Wk 240	Wk 244	Wk 248	Wk 252	Wk 256	Wk 260		
Symptom-driven physical examination[c]						X							X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP)[e]						U							S	S	U
Neurological examination						X							X	X	X
12-lead ECG													X	X	
Clinical laboratory tests													X	X	
Brain MRI[f]						X							X	X	X
LP/CSF collection						X							X	X	X
Blood PK sample						X							X	X	X
ADA Sample collection						X							X	X	X
Plasma biomarkers													X	X	X
CSF biomarkers						X							X	X	X
Optional exploratory PGx DNA and RNA sample													X	X	
Administer IV Study Drug	X	X	X	X	X	X	X	X	X	X	X	X			

Visits & Procedures[b]	Treatment Period[a]														
	Year 5														
	Dose 55	Dose 56	Dose 57	Dose 58	Dose 59	Dose 60	Dose 61	Dose 62	Dose 63	Dose 64	Dose 65	Dose 66/ Final	No Dose	D/C	20 Weeks Post Last Dose F/U
	Day 1485	Day 1513	Day 1541	Day 1569	Day 1597	Day 1625	Day 1653	Day 1681	Day 1709	Day 1737	Day 1765	Day 1793	Day 1821		
	Wk 212	Wk 216	Wk 220	Wk 224	Wk 228	Wk 232	Wk 236	Wk 240	Wk 244	Wk 248	Wk 252	Wk 256	Wk 260		
PSPRS						1							1	1	1
CGI-S						2							2	2	2
CGI-C						3							3	3	3
SEADL						4							4	4	4
UPDRS Part II						5							5	5	5
RBANS													6	6	
CTT Parts 1 & 2													7	7	
Letter Fluency Test (wpm)													8	8	
NNIPPS-PPS[g]													9	9	
PGI-C[h]						X							X	X	X
EQ-5D[h]													X	X	
C-SSRS[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PSP Caregiver Questionnaires						X							X	X	X
TSQM-9						X							X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visits & Procedures[b]	Treatment Period[a]														
	Year 5														
	Dose 55	Dose 56	Dose 57	Dose 58	Dose 59	Dose 60	Dose 61	Dose 62	Dose 63	Dose 64	Dose 65	Dose 66/ Final	No Dose	D/C	20 Weeks Post Last Dose F/U
	Day 1485	Day 1513	Day 1541	Day 1569	Day 1597	Day 1625	Day 1653	Day 1681	Day 1709	Day 1737	Day 1765	Day 1793	Day 1821		
	Wk 212	Wk 216	Wk 220	Wk 224	Wk 228	Wk 232	Wk 236	Wk 240	Wk 244	Wk 248	Wk 252	Wk 256	Wk 260		
Telephone contact[j]						X							X	X	X

AE = adverse event; LP = lumbar puncture; PK = pharmacokinetic; PGx = pharmacogenetic; S = serum; U = urine

a. Study drug will be administered on Days 1, 15, and 29, then every 28 days thereafter until 1 of the discontinuation criteria is met, until the Sponsor discontinues the study, or until the study reaches completion. For those Visits that include both study drug infusion and other activities, the Visits may be completed over 2 consecutive days with the second day to include the start and end of the infusion.

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

c. Additional symptom-driven physical examinations may be performed as needed.

d. An attempt should be made to obtain all vital sign measurements at the same time of day and using the same arm.

e. For all females of childbearing potential, a negative urine pregnancy test result is also required prior to any radiological procedures.

f. If a subject cannot undergo MRI due to a clinical reason, the AbbVie TA MD should be consulted for approval.

g. The NNIPPS-PPS will not be administered in Japan.

h. Scale may be administered/assessed at any time during the visit, after the other procedures are completed, with the exception of the scheduled infusion time.

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

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

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