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PROTOCOL NUMBER: 251PP301 / NCT03068468

PHASE OF DEVELOPMENT: 2b

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Intravenously Administered BIIB092 in Participants with Progressive Supranuclear Palsy

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Protocol 251PP301 was approved by:

[redacted] 4 Feb 2019

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Biogen may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

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1. SYNOPSIS

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Intravenously Administered BIIB092 in Participants with Progressive Supranuclear Palsy
Protocol Number:	251PP301
Version Number:	7
Name of Study Treatment:	BIIB092
Study Phase:	2b
Study Indication:	Progressive Supranuclear Palsy
Study Rationale:	The neuropathological hallmark of Progressive Supranuclear Palsy (PSP) is the presence of tau pathology in characteristic subcortical and cortical brain regions. N-terminal tau is implicated in mediating the transcellular spreading of this tau pathology in PSP. Based on the available preclinical and clinical data, BIIB092 (formerly known as BMS-986168 and IPN007) is expected to prevent spreading of tau pathology by binding and reducing unbound N-terminal tau in brain interstitial fluid, thereby delaying the progression of clinical signs and symptoms of PSP. The purpose of this study is to demonstrate the efficacy of BIIB092 in the treatment of PSP and characterize its safety/tolerability profile.
Study Objective(s) and Endpoints:	The primary objectives of the study are to: 1) Evaluate the efficacy of BIIB092 and 2) Assess the safety and tolerability of BIIB092. The primary endpoints that relate to these objectives are: 1) Change from baseline in the total PSP Rating Scale (PSPRS) score at Week 52 in participants treated with BIIB092 relative to the change in the total PSPRS score in participants treated with placebo and 2) Frequency of deaths, serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, and Grade 3 & 4 laboratory abnormalities. Key secondary objectives and endpoints are as follows: • To evaluate the efficacy of BIIB092, compared to placebo, as measured by a change from baseline in the Movement Disorder

Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II at Week 52.

The impact of BIIB092 on the MDS-UPDRS Part II will be evaluated relative to the change from baseline at Week 52 of the BIIB092-treated participants to that of the placebo-treated participants.

- To evaluate the efficacy of BIIB092, compared to placebo, as measured by the Clinical Global Impression of Change (CGI-C) at Week 52.

  The impact of BIIB092 on the CGI-C scale score will be evaluated at Week 52 in the BIIB092-treated participants and compared to that of the placebo-treated participants.

- To evaluate the efficacy of BIIB092, compared to placebo, as measured by a change from baseline in the Repeatable Battery for the Assessment of Neuropsychological Disease Severity (RBANS) total score at Week 52.

  The impact of BIIB092 on the RBANS scale will be evaluated relative to the change from baseline at Week 52 in the BIIB092-treated participants to that of the placebo-treated participants.

- To assess the impact of BIIB092 on quality of life, relative to placebo, as measured by change from baseline on the Progressive Supranuclear Palsy Quality of Life scale (PSP-QoL) at Week 52.

  The impact of BIIB092 on the PSP-QoL scale will be evaluated relative to the change from baseline at Week 52 in the BIIB092-treated participants to that of the placebo-treated participants.

Other secondary objectives and endpoints are as follows:

- To assess the efficacy of BIIB092, relative to placebo, as measured by a change from baseline at Week 48 (Week 52 for Clinical Global Impression of Severity [CGI-S]) on the following instruments:
  - Schwab and England Activities of Daily Living (SEADL) Scale
  - CGI-S
  - Phonemic Fluency Test
  - Letter-Number Sequencing (LNS) Test
  - Color Trails Test
  - Montreal Cognitive Assessment (MoCA)

  The impact of BIIB092 on the instruments mentioned above will be evaluated relative to the change from baseline at Week 48 (Week 52

for CGI-S) in the BIIB092-treated participants to that of the placebo-treated participants.

- To assess the immunogenicity of BIIB092.

  Immunogenicity of BIIB092 will be measured by assessment of the presence or absence of anti-BIIB092 antibodies in serum.

- To assess the efficacy of BIIB092, relative to placebo, as measured by absolute and percent change from baseline of brain volumes, as determined by magnetic resonance imaging (MRI), at Week 52 in the following regions:

  – Ventricles

  – Whole brain

  – Midbrain

  – Pons

  – Superior cerebellar peduncle

  – Third ventricle

  – Frontal lobe

  The impact of BIIB092 on brain volumes, as determined by MRI in the regions mentioned above, will be evaluated relative to the change from baseline at Week 52 in the BIIB092-treated participants to that of the placebo-treated participants.

Tertiary objectives and endpoints are listed in Section 4.

Extension Objective(s)	The primary objective of the open-label extension period is to assess the long-term safety and tolerability of BIIB092 in participants with PSP based on the numbers and percentages of deaths and of participants with SAEs and AEs. The secondary objective is to assess the long-term efficacy of BIIB092 in these participants based on clinical and health-outcomes measures.
Study Design:	Randomized, double-blind, placebo-controlled, parallel-group study with an open-label extension period. This study includes an optional substudy to measure quantitative movement assessments (QMAs) using wearable sensors. The QMAs will measure gait, postural instability, motor function, and falls in a subset of study participants participating in the long-term extension period.
Study Location:	Approximately 98 sites are planned globally.

Number of Planned Participants:	Approximately 459 participants will be randomly assigned, in a 2:1 ratio, to receive BIIB092 or placebo (306 participants in the BIIB092 treatment group and 153 in the placebo group). Anticipating a dropout rate of approximately 25% (based on previous clinical studies in participants with PSP), approximately 345 participants (230 participants in the BIIB092 treatment group and 115 participants in the placebo group) are expected to complete the study through Week 52. Using a two-sided, two-sample t-test, with an alpha level set at 0.05, this sample size will provide 80% power to detect a difference of 3.2 points in the change in PSPRS total score from baseline to Week 52 for BIIB092 relative to placebo, assuming a common standard deviation of 9.95 in the change in PSPRS total score from baseline to Week 52.
Study Population:	This study will be conducted in male and female participants with probable or possible PSP. Women of childbearing potential (WOCBP) and sexually active fertile men with partners who are WOCBP must use highly effective birth control in Study 251PP301. Detailed criteria are described in Section 6.
Treatment Groups:	Study treatment includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed in the following table.

Study Treatment for 251PP301

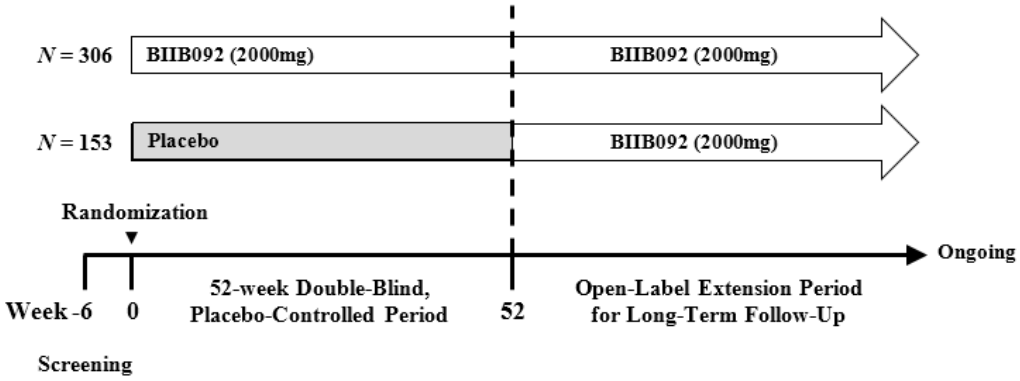
Medication	Potency	IP/Non-IP
BIIB092[a]	50 mg/mL	IP
Placebo[b] (0.9% Sodium Chloride)	N/A	IP

IP = investigational product

[a] Study treatment supplies may be labeled as BIIB092 or BMS-986168. The two study treatment names refer to an identical study treatment substance.

[b] 5% dextrose injection can be used if sodium chloride is not available.

Study Schematic:



In the 52-week double-blind treatment period of the study, approximately 459 participants in total will be randomly assigned, in a 2:1 ratio, to receive 2000 mg of BIIB092 or placebo (306 participants in the BIIB092 treatment group and 153 in the placebo group) administered by intravenous (IV) infusion approximately once every 4 weeks (Q4W) up to a total of 13 times, with the last dose of the double-blind study treatment administered at Week 48.

At Week 52, participants completing the double-blind treatment period may choose to continue into the open-label extension period of the study. The first dose of 2000 mg of BIIB092 of the open-label extension period will be administered to all participants by intravenous (IV) infusion at Week 52. All participants will be dosed with 2000 mg of BIIB092 by IV infusion approximately once Q4W throughout the duration of the open-label extension period of the study. The duration of participation in the open-label extension period of treatment will vary depending on the date of enrollment of the participant in the study. The open-label extension period is expected to continue until BIIB092 is commercially available, the development program is terminated, or the study is terminated at the discretion of the Sponsor, whichever comes first.

Duration of Treatment and Follow-up:	The study will consist of a 52-week double-blind treatment period followed by an open-label extension period for long-term follow-up.

2. SCHEDULE OF ACTIVITIES

Table 1: Screening Procedural Outline

Procedure	Screening Visit[a]	Notes
Eligibility Assessments		
Informed Consent	X	Participant is considered enrolled only when a protocol-specific informed consent is signed.
Informed Consent for Caregiver	X	Caregiver is defined as that person who accompanies participant to study visits and has frequent contact with participant of at least 3 hours per week at one time or at different times. Only one caregiver can be designated for participant at a given time. At a minimum, caregiver should personally attend the following study visits: Screening; Baseline; Weeks 12, 24, 36, 48, 52; and Early Discontinuation. Although caregiver assessments cannot be conducted by telephone, caregiver should be available for telephone consultation regarding information on AEs and SAEs when not otherwise attending a scheduled visit.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose.
Medical History	X	
Concomitant Medications	X	
Mini Mental Status Examination (MMSE)	X	Score $\geq$ 20 on the MMSE is a criterion for inclusion.
Safety Assessments		
Physical Examination	X	Includes height and weight.
Vital Signs	X	Includes body temperature, respiratory rate, and seated BP and heart rate. BP and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
Neurological Examination (NE)	X	Besides documenting signs of PSP, the NE should focus on any clinical evidence of increased intracranial pressure (e.g., history of headache, vomiting, or visual disturbances, and neurologic signs such as pupillary abnormalities and papilledema) that might contraindicate a lumbar puncture.

Procedure	Screening Visit[a]	Notes
12-Lead Electrocardiogram (ECG)	X	ECG should be recorded after the participant has been supine for at least 5 minutes.
Monitor for Serious Adverse Events (SAEs)	X	Following written consent to participate in the study, all SAEs whether related or not related to study treatment that occur during the screening period, continuously throughout the study, and until 30 days following the last dose should be monitored and recorded.
Laboratory Tests	X	Includes blood and urine samples.
Pregnancy Test	X	WOCBP only (serum or urine - local/site).
Follicle-Stimulating Hormone	X	Required for post-menopausal women < 55 (Refer to Appendix 4).
[redacted]	X	Baseline/Screening Version.
Efficacy Assessments		
Progressive Supranuclear Palsy Rating Scale (PSPRS)	X	
Repeatable Battery for the Assessment of Neuropsychological Disease Severity (RBANS)	X	
Montreal Cognitive Assessment (MoCA)	X	
Phonemic Fluency Test	X	
Letter-Number Sequencing (LNS) Test	X	
Color Trails Test (CTT)	X	Randomization will be stratified by country and screening CTT Part 2 score of either less than or equal to 170 seconds, or greater than 170 seconds.
Magnetic Resonance Imaging (MRI)	X	The MRI should be completed at least 14 days prior to first dose to allow for central assessment of image. A repeat MRI may be requested prior to randomization if protocol standards are not yet met. MRI image quality must be determined to be adequate and local interpretation performed to determine eligibility and to rule out any contraindication to lumbar puncture for participants participating in the [redacted]

Procedure	Screening Visit[a]	Notes
Lumbar Puncture (LP)	X	[redacted] The baseline LP may be performed up to Day -1 to allow recovery before dosing. LP should be performed in the morning (between 08:00 and 12:00 hours) to minimize potential diurnal variation of CSF parameters. Any participant with an AE related to LP should not be dosed until the AE has resolved. Use of low dose ASA or other antiplatelet/anticoagulant medications may be associated with a higher risk of LP complications. At the discretion of the Investigator, if not contraindicated, low dose ASA or other antiplatelet/anticoagulant medications may be discontinued for a short period of time prior to performing the LP. Stop and start dates must be documented on the appropriate Concomitant Medication CRF. CSF may be assessed for BIIB092 concentrations, white and red blood cell counts, protein, glucose, levels of unbound N-terminal tau, total tau, phosphorylated tau, and neurofilament light chain (NfL). Participants should be observed for approximately 2 hours after the LP for AEs. LP can be done in either the decubitus or sitting position, however it is preferred that all LPs for each participant are performed in the same position. The position of the participant during the LP will be recorded. LP may be performed under fluoroscopy or with computed tomography guidance at the discretion of the Investigator.
Pharmacokinetic (PK) Assessment		
CSF PK Sampling	X	Collect at time of LP ([redacted])
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Procedure	Screening Visit[a]	Notes
IRT/Clinical Supplies		
IRT	X	Transaction must be made in IRT as follows: For participant number assignment at the time informed consent is obtained. Prior to dosing for study treatment vial assignments (transaction should be made within 1 day prior to dosing).

AE = adverse event; ASA = acetylsalicylic acid; BP = blood pressure; CRF = case report form; CSF = cerebrospinal fluid; CTT = Color Trails Test; [redacted] ECG = electrocardiogram; IRT = Interactive Response Technology; LNS = Letter-Number Sequencing; LP = lumbar puncture; MMSE = Mini Mental Status Examination; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; NE = neurological examination; NfL = neurofilament light chain; PK = pharmacokinetic; PSP = Progressive Supranuclear Palsy; PSPRS = Progressive Supranuclear Palsy Rating Scale; RBANS = Repeatable Battery for the Assessment of Neuropsychological Disease Severity; SAE = serious adverse event; WOCBP = women of childbearing potential.

[a] Screening procedures may be conducted within 42 days prior to first dose unless otherwise specified.

Table 2: Double-Blind Procedural Outline

Procedure[a]	Week 0 (Day 1)	Weeks 4, 8, 16, 20, 28, 32, 40, 44[b] (±3 days)	Weeks 12, 24, 36 (±3 days)	Week 48 (±3 days)	Week 52 (±3 days)	Early Discontinuation[c],[d]	Notes
Eligibility Assessments							
Concomitant Medications	Review of concomitant medication as per Section 7.7.						
Safety Assessments							
Physical Examination	X		X		X	X	Predose.
Targeted Physical Examination	X	X	X	X	X	X	Postdose. Targeted, problem-focused physical examination performed at clinician's discretion (e.g., to evaluate any AEs).
Neurological Examination (NE)	X				X		Besides documenting signs of PSP, the NE should focus on any clinical evidence of increased intracranial pressure (e.g., history of headache, vomiting, or visual disturbances, and neurologic signs such as pupillary abnormalities and papilledema) that might contraindicate a lumbar puncture.
Physical Measurements	X		X		X	X	Weight only.
Vital Signs	X	X	X	X	X	X	Includes body temperature, respiratory rate, and seated BP and heart rate. BP and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
12-Lead Electrocardiogram (ECG)	X		See notes		X	X	Week 24 only.

Procedure[a]	Week 0 (Day 1)	Weeks 4, 8, 16, 20, 28, 32, 40, 44[b] (±3 days)	Weeks 12, 24, 36 (±3 days)	Week 48 (±3 days)	Week 52 (±3 days)	Early Discontinuation[c,d]	Notes
Assess Infusion Site	X	X	X	X	X	X	
Laboratory Tests	X	See notes	X	X	X	X	Weeks 4 and 8 only.
Pregnancy Test	X	X	X	X	X	X	For WOCBP only (serum or urine - local/site) within 24 hours prior to dosing.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Immunogenicity Assessments							
Serum Anti-BIIB092 Antibody	X	See notes	X	X			Weeks 4 and 8 only. Additional event driven samples may be justified; see Section 14.
Adverse Event Reporting							
Monitor for Non-Serious Adverse Events (NSAEs)	Collection of NSAEs begins at initiation of study treatment and continues throughout the study and until 30 days following the last dose. Participants who discontinue study treatment should have an assessment of AEs 30 days after last dose.[e]						
Monitor for Serious Adverse Events (SAEs)	Following written consent to participate in the study, all SAEs whether related or not related to study treatment that occur during the screening period, continuously throughout the study, and until 30 days following the last dose, should be monitored and recorded. Participants who discontinue study treatment should have an assessment of SAEs 30 days after last dose.[e]						
Efficacy Assessments							
Progressive Supranuclear Palsy Rating Scale (PSPRS)	X		X	X	X	X	
MDS-UPDRS Part II, CGI, RBANS, PSP-QoL	X		X		X	X	
SEADL, Phonemic Fluency, Letter-Number Sequencing, Color Trails Test, MoCA	X		X	X[f]			

Procedure[a]	Week 0 (Day 1)	Weeks 4, 8, 16, 20, 28, 32, 40, 44[b] (±3 days)	Weeks 12, 24, 36 (±3 days)	Week 48 (±3 days)	Week 52 (±3 days)	Early Discontinuation[c,d]	Notes
[redacted]	[redacted]		[redacted]	[redacted]			[redacted]
Magnetic Resonance Imaging (MRI)			See notes		X		Week 24 only.
Lumbar Puncture (LP)					X	X	LP should be performed prior to dosing ([redacted]).
Pharmacokinetic (PK) Assessments							
Blood PK Sampling	See notes	See notes	See notes	See notes	See notes		Weeks 0, 4, 24, and 48: collect predose and at EOI. Weeks 12, 36, and 52: collect predose only.
CSF PK Sampling					X	X	Collect at the time of LP ([redacted]).
[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]					[redacted]	[redacted]	[redacted]
Clinical Study Treatment Supplies							
Randomize	X						Prior to dosing for study treatment vial assignments (call should be made within 1 day prior to dosing).
Dispense Study Treatment	X	X	X	X			Duration of infusion will be at least 1 hour.

AE = adverse event; BP = blood pressure; CSF = cerebrospinal fluid; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; [redacted] ECG = electrocardiogram; EOI = end of infusion; [redacted]

[redacted]; LP = lumbar puncture; MDS-UPDRS = Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; NSAE = non-serious adverse event; PK = pharmacokinetic; MRI = magnetic resonance imaging; NE = neurological examination; PSP = Progressive Supranuclear Palsy; PSPRS = Progressive Supranuclear Palsy Rating Scale; QoL = quality of life; RBANS = Repeatable Battery for the Assessment of Neuropsychological Disease Severity; [redacted]; SAE = serious adverse events; SEADL = Schwab and England Activities of Daily Living scale; [redacted] WOCBP = women of childbearing potential.

[a] Efficacy assessments requiring participant involvement should be completed prior to dosing with study treatment unless otherwise specified in the notes; specific attention should be paid to conducting the Week 24 MRI within 7 days prior to the Week 24 dosing visit. The study visits at Weeks 0, 12, 24, 36, 48, 52, and Early Discontinuation, which involve the conduct of efficacy assessments, may be completed over a period of up to 3 consecutive days.

[b] Weeks 28, 32, 40, and 44 may qualify for a home visit if appropriate. See Section 5.1.4 for details.

[c] Participants who discontinue study treatment during the double-blind period of the study (prior to Week 52) and remain enrolled in the study will be expected to complete scheduled safety and efficacy evaluations at Weeks 12, 24, 36, 48, and 52 until the decision is made to withdraw from the study.

d Early Discontinuation visit procedures should be completed for any participant who discontinues study treatment and also withdraws from the study at any time prior to Week 52. Participants who withdraw from the study should be encouraged to return to the clinic at Week 52 to complete the Week 52 procedures. If the visit cannot be done in person by the participant, the site should attempt a phone call at approximately Week 52 to collect at a minimum vital status (whether the participant is alive or dead) and SAE/AE information on the participant.

[e] This 30-day assessment of AEs/SAEs may be done by phone if no visit occurs.

[f] CGI interviews collected from Week 36 will be used to review all areas of the functioning section (including complex daily activities and basic functions) and will be used to determine whether there have been any changes or additions to the functioning at the Week 48 visit, with both the caregiver and participant independently. This will be used to assign the Week 48 SEADL score.

Table 3: Extension Period Procedural Outline

Procedure	Week 52	Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, and 192[a] (±7 days)	Weeks 64, 88, 112, 136, 160, 184 (±7 days)	Weeks 76, 100, 124, 148, 172, 196 (±7 days)	Early Discontinuation[b]	Notes
Eligibility Assessments						
Concomitant Medications	Review of concomitant medication as per Section 7.7 .					
Safety Assessments						
Physical Examination			See notes	X	X	At Week 64 only.
Targeted Physical Examination		X	X	X	X	Post-dose. Targeted, problem-focused physical examination performed at clinician's discretion (e.g., to evaluate any AEs).
Neurological Examination				See notes		Week 100 only. Besides documenting signs of PSP, the NE should focus on any clinical evidence of increased intracranial pressure (e.g., history of headache, vomiting, or visual disturbances, and neurologic signs such as pupillary abnormalities and papilledema) that might contraindicate a lumbar puncture.
Physical Measurements			X	X	X	Weight only.
Vital Signs		X	X	X	X	

Procedure	Week 52	Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, and 192[a] (±7 days)	Weeks 64, 88, 112, 136, 160, 184 (±7 days)	Weeks 76, 100, 124, 148, 172, 196 (±7 days)	Early Discontinuation[b]	Notes
12-Lead Electrocardiogram (ECG)				X	X	
Assess Infusion site		X	X	X	X	
Laboratory Tests			See notes	X	X	At Week 64 only.
Pregnancy Test		X	X	X	X	For WOCBP only (serum or urine - local/site).
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
Immunogenicity Assessments						
Serum Anti-BIIB092 Antibody[c]				X		Additional event driven samples may be justified; see Section 14.
Adverse Event Reporting						
Monitor for Non-Serious Adverse Events (NSAEs)	Collection of NSAEs begins at initiation of study treatment and continues throughout the study and until 30 days following the last dose. Participants who discontinue study treatment should have an assessment of AEs 30 days after last dose.[d]					
Monitor for Serious Adverse Events (SAEs)	Following written consent to participate in the study, all SAEs whether related or not related to study treatment that occur during the screening period, continuously throughout the study, and until 30 days following the last dose, should be monitored and recorded. Participants who discontinue study treatment should have an assessment of SAEs 30 days after last dose.[d]					
Efficacy Assessments						
Progressive Supranuclear Palsy Rating Scale (PSPRS)			X	X	X	

Procedure	Week 52	Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, and 192[a] (±7 days)	Weeks 64, 88, 112, 136, 160, 184 (±7 days)	Weeks 76, 100, 124, 148, 172, 196 (±7 days)	Early Discontinuation[b]	Notes
MDS-UPDRS Part II, CGI, RBANS, PSP-QoL			See notes	X	X	At Week 64 only.
SEADL, Phonemic Fluency, Letter-Number Sequencing (LNS), Color Trails Test (CTT), MoCA				X		
[redacted]				[redacted]		[redacted]
Magnetic resonance imaging (MRI)				See notes		At Week 100 only.
Lumbar Puncture (LP)				See notes		At Week 100 only ([redacted]).
Pharmacokinetic (PK) Assessments						
Blood PK Sampling[c]		See notes		X		At Week 56 only.
CSF PK Sampling[c]				See notes		At Week 100 only ([redacted]).
[redacted]						
[redacted]			[redacted]	[redacted]		[redacted]
[redacted]				[redacted]		[redacted]

Procedure	Week 52	Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, and 192[a] (±7 days)	Weeks 64, 88, 112, 136, 160, 184 (±7 days)	Weeks 76, 100, 124, 148, 172, 196 (±7 days)	Early Discontinuation[b]	Notes
Clinical Drug Supplies						
Dispense Study Treatment	X	X	X	X		Duration of infusion will be at least 1 hour.

AE = adverse event; CGI = Clinical Global Impression; CSF = cerebrospinal fluid; [redacted] CTT = Color Trails Test; ECG = electrocardiogram; [redacted] LNS = Letter-Number Sequencing; LP = lumbar puncture; MDS-UPDRS = Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; NE = neurological examination; NSAEs = Non-Serious Adverse Events; PK = pharmacokinetic; QoL = quality of life; PSP = Progressive Supranuclear Palsy ; PSPRS = Progressive Supranuclear Palsy Rating Scale; RBANS = Repeatable Battery for the Assessment of Neuropsychological Disease Severity; [redacted] SAEs = serious adverse events; SEADL = Schwab and England Activities of Daily Living scale; [redacted]; WOCBP = women of childbearing potential.

[a] Weeks 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, and 192 may qualify for home visits if appropriate. See Section 5.1.4 for details.

[b] Participants who discontinue study treatment during the open-label extension period of the study (after Week 52) but remain enrolled in the study will be expected to complete scheduled safety and efficacy evaluations at Weeks 64, 76, 88, 100, 112, 124, 136, 148, 160, 172, 184, and 196.

[c] Sample to be collected predose.

[d] This 30-day assessment of AEs/SAEs may be done by phone if no visit occurs.

Table 4: Quantitative Assessment Procedural Outline for the Extension Period Substudy

Quantitative Movement Assessments	Substudy Enrollment in the Open-Label Extension Period		
	Baseline Visit [a]	Three-Month Follow-Up Visit[b]	Six-Month Follow-Up Visit[b]
In-Clinic Assessments			
Orthostatic vitals	X		
Visual acuity	X		
Joint-position test	X		
Strength test for hip flexion and knee extension	X		
Sway	X	X	X
Gait	X	X	X
Timed chair stands	X	X	X
Instrumented push and release test	X	X	X
Toe taps	X	X	X
Wrist rotations	X	X	X
In-Home Assessments			
Falls[c]	X		

QMA = quantitative movement assessments

[a] The QMA substudy baseline visit will start after participants sign the informed consent form and are eligible to enroll in the substudy.

[b] Two follow-up visits will be conducted at 3 and 6 months after the baseline visit of the QMA substudy.

[c] Falls will be assessed in-home for 6 months using wearable sensors to capture and quantify falls.

3. INTRODUCTION

Progressive supranuclear palsy (PSP) is a rare neurodegenerative disorder that leads to death in an average of 7 years following symptom onset [Williams 2005]. The National Institute of Neurological Disorders and Stroke (NINDS), the National Organization for Rare Disorders (NORD), and the European Organisation for Orphan Diseases estimate the prevalence of PSP to be between 3 and 6 per 100,000 persons. Both the NINDS and NORD estimate that there are approximately 20,000 cases of PSP in the United States and 30,000 in the European Union, while there are thought to be approximately 17,000 cases in Japan [Takigawa 2016].

The disease is characterized by progressive aberrations in gait, eye movements, dysphagia, dysarthria, pseudobulbar affect, neuropsychiatric abnormalities, and dementia, as well as difficulties with sleep [Boxer 2017; Nath 2003]. Since the syndrome was first characterized in 1963, it is now recognized that there are a number of different clinical presentations that appear to be linked to the regional distribution and severity of pathology in the brain [Williams 2007]. There is currently no treatment available to stop or slow the progression of this deadly disease.

The neuropathological hallmark of PSP is the presence of neurofibrillary tangles in clinically correlated regions of the brain, including the basal ganglia, diencephalon, brainstem, and cerebellum with restricted involvement of the neocortex [Dickson 2010]. The tangles are composed of tau, an intracellular microtubule-associated protein, of which fragments may also be released into the cerebrospinal fluid (CSF) and interstitial space as N-terminal tau [Bright 2015; Guo 2017]. Tau dysfunction is thought to play a key role in the pathophysiology of PSP, both by causing neuronal dysfunction via tau aggregation into neurofibrillary tangles and by facilitating cell to cell spreading of tau pathology via secreted N-terminal tau.

BIIB092 is a humanized monoclonal antibody (mAb) that binds to amino acid residues 15 to 22 of N-terminal tau, removing it from the CSF. It is hypothesized that BIIB092-mediated depletion of N-terminal tau will inhibit the spread of tau pathology, potentially slowing the progression of PSP. This would be expected to translate into important improvements in function, activities of daily living, health outcomes, and overall quality of life for patients living with PSP.

3.1. Study Rationale

The neuropathological hallmark of PSP is the presence of tau pathology in the form of neurofibrillary tangles in characteristic subcortical and cortical brain regions. N-terminal tau is implicated in mediating the transcellular spreading of this tau pathology in PSP.

BIIB092 has been shown to bind N-terminal tau and suppress CSF concentrations of unbound N-terminal tau (i.e., N-terminal tau that is not bound to BIIB092) in preclinical studies, a single ascending dose (SAD) study in normal healthy volunteers (NHVs) (Study CN002001), and a multiple ascending dose (MAD) study in participants with PSP (Study CN002003). Based on these data, BIIB092 is expected to prevent spreading of tau pathology by binding and reducing unbound N-terminal tau in brain interstitial fluid, suggesting that it has potential utility for the treatment of human tauopathies, such as PSP.

The aim of this study is to demonstrate the efficacy of BIIB092 in delaying the progression of clinical signs and symptoms of PSP and to characterize its safety/tolerability profile.

3.2. Background

BIIB092 (formerly known as BMS-986168 and IPN007) is a humanized mAb of subclass IgG4 that specifically binds the microtubule-associated protein tau. BIIB092 is derived from the murine IgG1 mAb, IPN002, which was produced in response to immunization of mice with aggregated, recombinant full-length human tau (tau isoform 2N4R). The affinity, specificity, and functional activity of the antibody were maintained following humanization. BIIB092 recognizes a linear, amino terminal epitope (including amino acid residues 15 to 22 of full-length human tau) of tau. BIIB092 exhibits high affinity for human and cynomolgus monkey tau, with binding affinities of 7×10^{-10} M and 6.35×10^{-10} M, respectively. The primary site of action of BIIB092 is believed to be the interstitial space between neurons where it binds N-terminal tau, thereby reducing tau-induced neuronal hyperexcitability and tau-mediated spread of tau pathology.

BIIB092 is being developed for the treatment of PSP, a rare neurodegenerative disease associated with tau pathology that results in a progressive movement disorder. There is a significant unmet medical need for safe and effective agents for patients with PSP, as there are currently no approved drugs for its treatment. Existing medical management is focused on reducing symptoms, using drugs approved for various other indications off-label along with dietary supplements. However, it is widely accepted that none of these drugs is particularly effective in treating PSP.

BIIB092 was first introduced into clinical trials in the Phase 1 trials conducted in the United States (US), Study CN002001 in healthy adult volunteers and Study CN002003 in participants with PSP.

Results from the first-in-human study, CN002001, indicate that administration of single doses of up to 4200 mg of BIIB092 in healthy volunteers is well tolerated. Mean suppression of the CSF-unbound N-terminal tau in that study ranged from 67% to 97% at doses ranging from 70 to 4200 mg.

Study CN002003 was a Phase 1b randomized, double-blind, placebo-controlled, MAD study to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of BIIB092 doses of 150, 700, and 2100 mg in participants with PSP. All 3 doses were well tolerated based on results from the dose escalation phase of the study. Treatment with monthly doses of BIIB092 decreased CSF-unbound N-terminal tau by mean values of approximately 90%, 93%, and 96% on Day 29 and 91%, 95%, and 97% on Day 85 at doses of 150, 700, and 2100 mg, respectively.

Study 251PP201 is an ongoing open-label extension study to evaluate the long-term safety and tolerability of multiple doses of BIIB092 in participants with PSP who participated in CN002003.

A more detailed description of the chemistry, pharmacology, and safety of BIIB092 is provided in the Investigator's Brochure.

3.2.1. Research Hypothesis

This study will demonstrate that BIIB092 is effective and safe for the treatment of participants with PSP.

3.3. Benefit/Risk Assessment

The benefit/risk profile of BIIB092 in nonclinical studies, the SAD study in NHVs (Study CN002001), and the MAD study and its associated open-label extension study (Studies CN002003 and 251PP201, respectively) supports further evaluation of the safety, tolerability, immunogenicity, PK, PD response, and clinical efficacy of BIIB092 in participants with PSP.

BIIB092 is a humanized IgG4 isotype antibody that is considered to have a low potential for immunogenicity in humans based on nonclinical studies. There were no adverse effects noted at any dose tested in the pivotal toxicity studies in monkeys. Nonclinical findings were limited to decreases in CSF unbound N-terminal tau consistent with the intended pharmacology of BIIB092. In completed clinical study CN002001, there was no consistent trend showing a potential effect of anti-drug antibody (ADA) on the PK of BIIB092. In completed clinical study CN002003, there was no apparent dose-related trend in the number of subjects with positive immunogenicity results post-treatment.

Studies evaluating the potential for reproductive and developmental toxicity have not been performed for BIIB092.

As of 25 November 2018, an estimated 486 participants have been exposed to BIIB092 across all completed (Studies CN002001 and CN002003) and ongoing clinical studies (Studies 251PP201, 251PP301, and 251AD201). Based on safety data from a completed Phase 1 study in healthy volunteers (Study CN002001) and a completed Phase 1B study in participants with PSP (Study CN002003), the benefit/risk profile of BIIB092 was favorable to support further clinical development.

There is no information available about possible interaction of BIIB092 with other drugs, although no PK interactions are anticipated.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of BIIB092 may be found in the Investigator's Brochure. However, because BIIB092 is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur.

4. STUDY OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
To evaluate the efficacy of BIIB092, compared to placebo, as measured by a change from baseline in the PSP Rating Scale (PSPRS) at Week 52.	The primary efficacy endpoint will be evaluated by comparing the change from baseline in the total PSPRS score at Week 52 in participants treated with BIIB092 relative to the change in the total PSPRS score in participants treated with placebo.
To assess the safety and tolerability of BIIB092, relative to placebo, by measuring the frequency of deaths, SAEs, and AEs leading to discontinuation, and Grade 3 & 4 laboratory abnormalities.	The primary safety endpoint will be evaluated by tabulating the numbers and percentages of deaths and unique participants with SAEs and AEs leading to discontinuation, and Grade 3 & 4 laboratory abnormalities.
Key Secondary	
To evaluate the efficacy of BIIB092, compared to placebo, as measured by a change from baseline in the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II at Week 52.	The impact of BIIB092 on the MDS-UPDRS Part II will be evaluated relative to the change from baseline at Week 52 in the BIIB092-treated participants and compared to that of the placebo-treated participants.
To evaluate the efficacy of BIIB092, compared to placebo, as measured by the Clinical Global Impression of Change (CGI-C) at Week 52.	The impact of BIIB092 on the CGI-C scale score will be evaluated at Week 52 in the BIIB092-treated participants and compared to that of the placebo-treated participants.
To evaluate the efficacy of BIIB092, compared to placebo, as measured by a change from baseline in the Repeatable Battery for the Assessment of Neuropsychological Disease Severity (RBANS) at Week 52.	The impact of BIIB092 on the RBANS scale will be evaluated relative to the change from baseline at Week 52 in the BIIB092-treated participants and compared to that of the placebo-treated participants.
To assess the impact of BIIB092 on quality of life, relative to placebo, as measured by change from baseline on the Progressive	The impact of BIIB092 on the PSP-QoL will be evaluated relative to the change from baseline at Week 52 in the BIIB092-treated

Supranuclear Palsy Quality of Life scale (PSP-QoL) at Week 52.	participants and compared to that of the placebo-treated participants.
Other Secondary	
To assess the efficacy of BIIB092, relative to placebo, as measured by a change from baseline at Week 48 (Week 52 for Clinical Global Impression of Severity [CGI-S]) on the following instruments: • Schwab and England Activities of Daily Living (SEADL) Scale • CGI-S • Phonemic Fluency Test • Letter-Number Sequencing (LNS) Test • Color Trails Test (CTT) • Montreal Cognitive Assessment (MoCA)	The impact of BIIB092 on the following instruments: • SEADL Scale • CGI-S • Phonemic Fluency Test • LNS Test • CTT • MoCA will be evaluated relative to the change from baseline at Week 48 (Week 52 for CGI-S) in the BIIB092-treated participants and compared to that of the placebo-treated participants.
To assess the immunogenicity of BIIB092.	Immunogenicity of BIIB092 will be measured by assessment of the presence or absence of anti-BIIB092 antibodies in serum.
To assess the efficacy of BIIB092, relative to placebo, as measured by absolute and percent change from baseline of brain volumes, as determined by magnetic resonance imaging (MRI), at Week 52 in the following regions: • Ventricles • Whole brain • Midbrain • Pons • Superior cerebellar peduncle • Third ventricle • Frontal lobe	The impact of BIIB092 on brain volumes, as determined by MRI in the following regions: • Ventricles • Whole brain • Midbrain • Pons • Superior cerebellar peduncle • Third ventricle • Frontal lobe will be evaluated relative to the absolute and percent changes from baseline at Week 52 in the BIIB092-treated participants and compared to that of the placebo-treated participants.

Tertiary/Exploratory

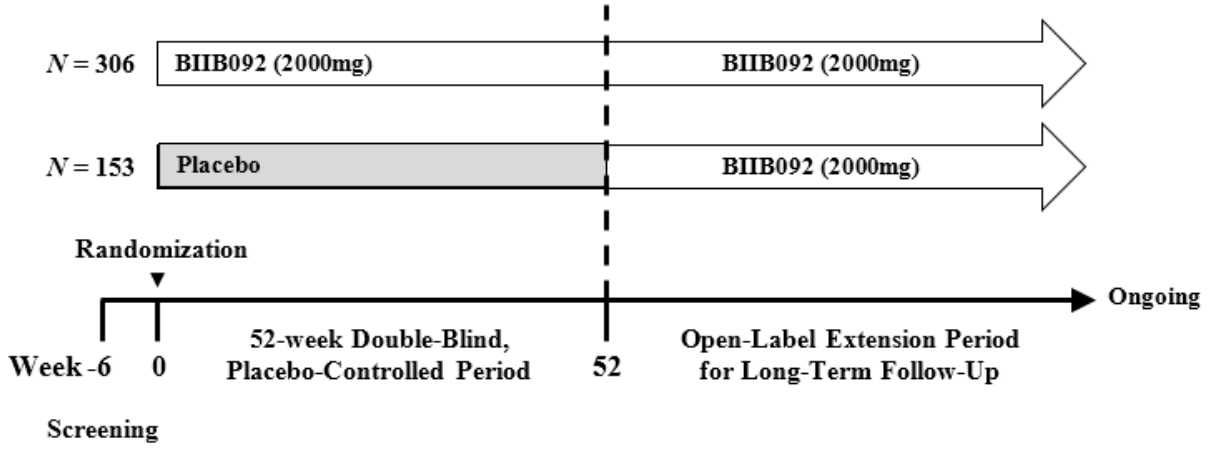
[redacted]	[redacted] • [redacted] • [redacted] • [redacted] • [redacted]
Open-Label Extension Period	
To assess the long-term safety and tolerability of BIIB092 in participants with PSP.	The tertiary endpoint will be incidence of AEs, SAEs, and SAEs accompanied by death.
To assess the long-term efficacy of BIIB092 in participants with PSP.	The tertiary endpoints will be change from baseline over the placebo-controlled period and long-term extension period for clinical and health-outcomes assessments. This study includes an optional substudy to measure quantitative movement assessments (QMAs) using wearable sensors. The QMAs will measure gait, postural instability, motor function, and falls in a subset of participants participating in the long-term extension period.

5. STUDY DESIGN

5.1. Overall Design

The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



This is a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of intravenously administered BIIB092 in participants with PSP with an open-label extension period.

5.1.1. Overall Study Design

The study design schematic is presented in Figure 1. The study will consist of a 52-week double-blind treatment period, which will be followed by a long-term open-label extension period for follow up. Participants will be randomized to receive BIIB092 or placebo. Approximately 459 participants in total will be randomized in a 2:1 ratio to receive BIIB092 or placebo (306 participants active or 153 placebo). In the double-blind treatment period of the study, participants will be dosed approximately once every 4 weeks (Q4W) up to a total of 13 times, with the last dose of study treatment of the double-blind period (Dose 13) administered at Week 48.

At Week 52, participants completing the double-blind treatment period may choose to continue into the open-label extension period of the study. Participants who wish to continue in the open-label extension period will receive the first dose of the open-label study treatment at Week 52. Participants will be dosed approximately once Q4W throughout the duration of the open-label extension period. The duration of the open-label extension period will vary depending on the date of enrollment of the participant in the study. The study is expected to continue until BIIB092 is commercially available, the development program is terminated, or the study is terminated at the discretion of the Sponsor, whichever comes first.

5.1.2. Study Visits

Study visits will be conducted approximately Q4W. Study treatment will be administered and safety, efficacy, and other assessments will be performed (Table 1, Table 2, Table 3, and Table 4). The study will generally be conducted on an outpatient basis unless some procedures would be better performed on an inpatient basis based on the needs of the participant. Participants will be observed and monitored by study personnel for approximately 2 hours after the end of an infusion. Participants with ongoing AEs or SAEs will remain at the site or be sent to an inpatient monitoring facility until the Investigator has determined that these events have resolved or do not require inpatient monitoring.

5.1.3. Study Assessments

- Participants will be closely monitored for safety throughout the study. Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations, including assessments for immunogenicity will be performed. AEs will be closely monitored. Suicidality will also be assessed by completing the [redacted]
- PSP-related signs, symptoms, and quality of life will be assessed using the following clinical assessments: PSPRS, MDS-UPDRS Part II, SEADL scale, CGI-S, CGI-C, MoCA, European Quality of Life (EuroQol) version[redacted] and PSP-QoL and neuropsychological testing (RBANS, phonemic fluency, LNS, and CTT).
- Caregiver burden will also be assessed [redacted]
- Blood will be collected for immunogenicity, PK, PD, and exploratory biomarker analysis from each participant during this study in the double-blind period and in the open-label extension period.
- Structural changes in the brain will be assessed using MRI. It is anticipated that each participant will have total of 4 MRIs over the course of the study, including an MRI during the screening period (up to Day -14) and at Weeks 24, 52, and 100.
- [redacted]
- Participants in the QMA substudy will undergo quantitative assessments of core motor features of PSP using wearable sensors to measure gait, postural instability, motor function, and falls

5.1.4. Home Visits

After Week 24, except for those visits when clinical scales, LPs, or MRI assessments are performed, visits and procedures may be performed in the home as long as appropriate services

are available to perform the required study procedures and adequately monitor for potential safety events. In the double-blind period of the study, Weeks 28, 32, 40, and 44 may qualify for home visits.

In the open-label extension period of the study, Week 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, and 192 visits may qualify for a home visit. However, in the event that the participant experienced a clinically significant infusion reaction during the first 24 weeks of the protocol, the participant should not be administered BIIB092 in the home unless previously approved by the Study Investigator.

5.1.5. Discontinuation of Study Treatment and/or Study Withdrawal

Participants who discontinue study treatment may belong to 1 of the following groups:

- Participants who discontinue study treatment but remain enrolled until the end of the study
- Participants who discontinue study treatment and later withdraw from the study
- Participants who discontinue study treatment and immediately withdraw from the study

Participants who discontinue study treatment during the double-blind period of the study (prior to Week 52) and remain enrolled in the study will be expected to complete the scheduled safety and efficacy evaluations until the end of the study or until the decision is made to withdraw from the study (see Table 2 for schedule of evaluations). SAE collection will be up to 30 days after the last dose of study treatment and will continue for as long as the participant remains enrolled in the study.

Early discontinuation visit procedures should be completed for any participant who discontinues study treatment and also withdraws from the study at any time prior to end of study. All SAEs that occur until 30 days after last dose of study treatment should be monitored and/or recorded. In the double-blind period, participants who withdraw from the study should be encouraged to return to the clinic at Week 52 to complete the Week 52 procedures.

5.2. Substudy Design

This study includes an optional substudy to measure QMAs using wearable sensors. The QMAs will measure gait, postural instability, motor function, and falls in a subset of participants participating in the long-term extension period.

Study participants included in this substudy will be from selected countries, and participants will be required to ambulate independently or with assistive devices. Participants will participate in the QMA substudy for 6 months, with in-clinic assessments of gait, postural instability, and motor function conducted every 3 months. Falls will be assessed continuously in the home using wearable sensors for 6 months to capture and quantify falls. The QMA substudy baseline visit will be conducted after participants sign the informed consent form and are eligible to enroll in the substudy. Two follow-up visits will be conducted at 3 and 6 months after the baseline visit of the QMA substudy. If a participant at a selected site is unwilling to participate in the QMA substudy, they can still participate in the open-label extension study.

5.3. Data Monitoring Committee and Other External Committees

An independent Data Monitoring Committee (DMC) will be established for this study and its activities will be fully described in a DMC Charter. The DMC will be composed of at least 2 independent physicians and 1 independent statistician with experience in neurological clinical trials. In this study, the major tasks of the DMC will be to review unblinded data and monitor the benefit/risk of BIIB092, to assess whether there are unacceptable safety findings after administration of BIIB092 that require modifying or stopping the study, and potentially to adjudicate study treatment-relatedness of SAEs and deaths that are unexpected and/or atypical for participants with PSP.

5.4. Number of Participants

It is anticipated that approximately 459 male and female participants will be dosed in this study. Approximately 459 participants will be randomly assigned, in 2:1 ratio, to receive 2000 mg of BIIB092 or placebo (306 participants active and 153 placebo) administered by intravenous (IV) infusion approximately once Q4W. Randomization will be stratified by country and screening CTT Part 2 score of either less than or equal to 170 seconds or greater than 170 seconds. Anticipating a dropout rate of approximately 25%, approximately 345 participants (230 participants in the BIIB092 treatment group and 115 participants in the placebo group) are expected to complete the study through Week 52.

5.5. End of Study Definition

The date the first participant signs a study-specific informed consent form will be defined as the start of the study. A participant is considered enrolled when the study-specific informed consent form is signed. The date that the last participant completes the last study visit or scheduled procedure shown in Section 2, Schedule of Activities, will be defined as the end of the study.

5.6. Scientific Rationale for Study Design

The double-blind period of the study is intended to determine the efficacy and safety/tolerability of BIIB092. It is anticipated that participants will be randomized in a 2:1 ratio to receive 2000 mg of BIIB092 or placebo, respectively, administered by IV infusion once Q4W for approximately 48 weeks (up to a total of 13 times). The justification for the dose is described in Section 5.7 and based on previous studies evaluating the PK of BIIB092 and PD effects on unbound N-terminal tau levels in CSF. A duration of treatment of up to 52 weeks and comparison with a placebo control are considered adequate and appropriate to evaluate the efficacy of BIIB092 on the primary and secondary endpoints, given the natural history of PSP and the lack of any approved therapies.

The open-label extension period of the study is intended to further characterize the long-term efficacy and safety/tolerability of BIIB092. It is anticipated that all participants in the study, including those randomized to receive placebo in the double-blind period, will receive 2000 mg of BIIB092 administered Q4W by IV infusion throughout the open-label extension period of the study.

The QMA substudy in the open-label extension period is intended to further characterize disease progression with wearable sensors. Postural instability, gait disturbances, and falls are prominent signs of PSP that impact participant outcomes. At present these signs are assessed in the clinic with questionnaires. It is anticipated that advances in wearable sensor technology and analytics could improve quantification of these signs and may provide sensitive measures of disease progression.

5.6.1. Clinical Assessments

All participants will have baseline and periodic, on-treatment measures throughout the study to evaluate PSP symptoms using the PSPRS, MDS-UPDRS Part II, SEADL scale, CGI-S and CGI-C; [redacted]MoCA; PSP-QoL, [redacted], and neuropsychological assessments (RBANS, phonemic fluency, LNS, and CTT). The [redacted]will be performed for all participants. Each participant will have their respective caregiver assessed for caregiver burden and resource utilization using the [redacted]

5.6.2. Rationale for Inclusion of Key Biomarkers

All participants will have blood collected for assessment of serum concentrations of unbound N-terminal tau and exploratory biomarkers determined at baseline and at regular intervals during the study to confirm target engagement.

Where local regulations and institutional approvals allow, a deoxyribonucleic acid (DNA) sample will be prepared to analyze genetic variation in specific genes associated with PSP, genes impacting drug absorption, distribution, metabolism, elimination, and/or neurodegeneration. The impact of genetic variation such as H1 and H2 haplotypes on tau protein levels may also be examined.

All participants will have MRI evaluations at baseline and at Weeks 24, 52, and 100 to assess structural changes in the brain.

[redacted]

5.7. Justification for Dose

The dose of BIIB092 selected for this study is 2000 mg, administered once Q4W.

In the SAD study in NHVs (CN002001), single doses of BIIB092 were well tolerated at all doses tested (i.e., 21 to 4200 mg). A maximum tolerated dose was not identified. Robust suppression of unbound N-terminal tau in CSF (88% to 97%) was observed for at least 4 weeks after a single dose, compared to baseline, in the dose range of 210 to 4200 mg.

The MAD study in participants with PSP (CN002003) assessed three Q4W doses of BIIB092 of 150, 700, and 2100 mg during the dose escalation phase of the study. All three doses were well tolerated in participants with PSP, based on preliminary results from the dose escalation phase of

the study. Treatment with monthly doses of BIIB092 decreased CSF unbound N-terminal tau by mean values of approximately 90%, 93%, and 96% on Day 29 and 91%, 95%, and 97% on Day 85 at doses of 150, 700, and 2100 mg respectively. Additional data on safety, tolerability, PK, and PD of all 3 dose levels is accruing with the open-label extension period of this study.

Emerging PK and unbound N-terminal tau data from Panels 1 and 2 (150 and 700 mg, administered Q4W) of CN002003 were modeled using a semi-mechanistic PK-PD model developed using the NHV data, and re-estimating the model parameters to describe the observed data in participants with PSP. The observed PK-PD profile in participants was well characterized by the PK-PD model based on the estimates of the model parameters in participants as well as the goodness of fit plots.

Using the estimated PK-PD model parameters and the variability around these parameters in participants with PSP, 1000 profiles were simulated and the time course of PK in serum and CSF and PD (unbound N-terminal tau) in CSF were obtained for the 2000 mg dose administered Q4W for a period of 1 year. Unbound N-terminal tau concentrations were converted to percent suppression, relative to each participant's baseline value, prior to summarization based on the simulations. Table 5 shows summary statistics of percent suppression of unbound N-terminal tau relative to baseline levels at 4, 12, 24, and 52 weeks following the 2000 mg Q4W dosing regimen.

Table 5: Summary Statistics of Percent Suppression of Unbound N-terminal Tau Relative to Baseline Following 2000 mg Q4W (Simulated)

Statistic	4 Weeks	12 Weeks	24 Weeks	52 Weeks
Number of simulations	1000	1000	1000	1000
Median	96.46	97.46	97.57	97.58
Minimum	93.87	94.80	94.82	94.82
Maximum	98.25	98.92	99.03	99.04
10th percentile	95.35	96.34	96.43	96.43
90th percentile	97.37	98.25	98.39	98.40

Q4W = once every 4 weeks.

Based on the results of the simulation, ninety percent of all participants who are dosed the 2000 mg Q4W dose are expected to have a percentage suppression of unbound N-terminal tau at 96% or greater at trough. The remaining 10% of participants are expected to have a suppression of approximately 95% and greater.

Whereas the actual level of unbound N-terminal tau suppression in CSF that is associated with efficacy in humans is unknown, it is anticipated that higher levels of unbound N-terminal tau suppression will be associated with greater efficacy. The high level of suppression of unbound N-terminal tau was well tolerated in monkeys and has been well tolerated in both healthy volunteers and participants with PSP.

Overall, a dose of 2000 mg Q4W is expected to be a well tolerated dose in participants with PSP that will achieve and maintain greater than 95% suppression of unbound N-terminal tau in CSF in the vast majority of participants for the entire study period, which is expected to increase the likelihood of demonstrating efficacy with BIIB092.

6. STUDY POPULATION

For entry into the study, the following criteria MUST be met.

6.1. Inclusion Criteria

6.1.1. Signed Written Informed Consent

1. Participants, or a legally authorized representative (where local regulations and institutional practices permit), must have signed and dated an Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal participant care.
2. The investigator must obtain consent consistent with the applicable legal, regulatory, and institutional policy requirements and specifically, taking into account the participant's state of disease progression and its impact on the participant's cognitive and motor abilities.
3. In the event that the study participant is unable to sign and date the informed consent form, a legally authorized representative, permitted to act on behalf of the participant in the context of this study, may provide consent on behalf of the participant.
4. Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study.
5. Participant's caregiver must have signed and dated an IRB-/IEC-approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal participant care.
6. Participant's caregiver must be willing and able to comply with scheduled visits and other requirements of the study. Only one caregiver can be designated for the participant at a given time. At a minimum, the caregiver should personally attend the following study visits: Screening; Baseline; Weeks 12, 24, 36, 48, and 52; and Early Discontinuation. Although caregiver assessments cannot be conducted by telephone, the caregiver should be available for telephone consultation regarding information on AEs and SAEs when not otherwise attending a scheduled visit.

6.1.2. Type of Participant and Target Disease Characteristics

1. Probable or possible PSP defined
   a. Based on the following:
      - A progressive history of postural instability during the first 3 years that symptoms are present

        OR

      - A progressive history of falls during the first 3 years that symptoms are present

b. Based on the following:

   – Vertical supranuclear gaze palsy defined as clear limitation of the range of voluntary gaze in the vertical more than in the horizontal plane, more than expected with age, which is overcome by activation with the vestibulo-ocular reflex (at later stages, the vestibulo-ocular reflex may be lost, or the maneuver prevented by nuchal rigidity).

   OR

   – Slow velocity of vertical saccades (i.e., decreased velocity [and gain] of vertical greater than horizontal saccadic eye movements). Gaze should be assessed by command to a stationary target rather than by pursuit, with the target >20° from the position of primary gaze. Typically, saccadic movement is slow enough for the examiner to see its progress, rather than just its initial and final positions. Deficits are more prominent in the vertical than the horizontal plane. A delay in initiation of saccades is not considered slowing.

c. Age at symptom onset of 40 to 85 years by history, and current age between 41 and 86 years, inclusive, at the time of screening.

d. An akinetic-rigid syndrome.

e. Presence of PSP symptoms for less than or equal to 5 years (determined by the best judgement of the Investigator) at screening.

2. Body weight range of ≥43 kg/95 lbs. to ≤120 kg/265 lbs.
3. Able to ambulate independently or with assistance defined as the ability to take at least 10 steps with a walker (guarding is allowed provided there is no contact) or the ability to take at least 10 steps without a walker or cane with the assistance of another person who can only have contact with one upper extremity.
4. Able to tolerate MRI.
5. Able to perform all protocol-specified assessments and comply with the study visit schedule.
6. Able to comply with neuropsychological evaluation at screening and throughout the 52-week double-blind period of the study (determined by the best judgement of the Investigator).
7. Have reliable caregiver to accompany participant to study visits. Caregiver must be able to read, understand, and speak local language fluently to ensure comprehension of informed consent and informant-based assessments of participant. Caregiver must also have frequent contact with participant (at least 3 hours per week at one time or different times) and be willing to monitor the participant's health and concomitant medications throughout the study. Caregiver must be willing to sign and date an IRB-/IEC- approved written informed consent form in accordance with regulatory and institutional guidelines as appropriate.
8. Score ≥20 on the Mini Mental State Examination (MMSE) at screening.

9. Participant must reside outside a skilled nursing facility or dementia care facility at the time of screening and admission to such a facility must not be planned. Residence in an assisted living facility is allowed.
10. If participant is receiving coenzyme Q10, levodopa/carbidopa, levodopa/benserazide, fava bean extract, a dopamine agonist, catechol-O-methyltransferase inhibitor, amantadine, or other Parkinson's disease medications, the dose must have been stable for at least 60 days prior to baseline and expected to remain stable for the double-blind period of the study.
11. Stable on other chronic medications for at least 30 days prior to baseline.

6.1.3. Age and Reproductive Status

1. Males and females, ages 41 to 86 years, inclusive.
2. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotrophin) within 24 hours prior to the start of study treatment.
3. Women must not be breastfeeding
4. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) BIIB092 plus 5 half-lives of study treatment BIIB092 plus 30 days (duration of ovulatory cycle) for a total of 155 days post-treatment completion.
5. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment(s) BIIB092 plus 5 half-lives of the study treatment plus 90 days (duration of sperm turnover) for a total of 215 days post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.
6. Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (Appendix 4).

6.2. Exclusion Criteria

6.2.1. Medical Conditions

1. Presence of other significant neurological or psychiatric disorders including (but not limited to) Alzheimer's disease (AD), dementia with Lewy bodies; prion disease, Parkinson's disease (which has not subsequently been revised to a diagnosis of PSP); any psychotic disorder; severe bipolar or unipolar depression; seizure; brain tumor or other space-occupying lesion; history of clinically significant stroke (e.g., stroke with

neurological deficit); history of head injury with loss of consciousness for at least 15 minutes within the past 20 years.

2. Diagnosis of amyotrophic lateral sclerosis or other motor neuron disease.
3. Diagnosis of cerebellar ataxia, choreoathetosis, and early symptomatic autonomic dysfunction.
4. History of early, prominent rapid eye movement sleep behavior disorder.
5. History of or screening brain MRI scan indicative of significant abnormality, including, but not limited to, prior hemorrhage or infarct >1 cm^3, ≥3 lacunar infarcts, cerebral contusion, aneurysm, vascular malformation >1 cm^3, subdural hematoma, hydrocephalus, and space-occupying lesion (e.g., abscess or brain tumor).
6. Known history of serum or plasma progranulin level less than one standard deviation below the normal participant mean for the laboratory performing the assay.
7. Known presence of known disease-associated mutation in C9ORF72, GRN, CHMPB2, TBK1, TARBP, or VCP genes or any other frontotemporal lobar degeneration causative genes not associated with underlying tau pathology (individuals with MAPT mutations may participate if they meet all other eligibility criteria).
8. Any major surgery within 4 weeks of screening.
9. History of deep brain stimulator surgery other than sham surgery for deep brain stimulation clinical trial.
10. Inability to be venipunctured and/or tolerate venous access.
11. Contraindication to the MRI examination for any reason.
12. [redacted]
13. History of cancer within 5 years of screening with the exception of fully excised non-melanoma skin cancers or non-metastatic prostate cancer that has been stable for at least 6 months.
14. History of clinically significant hematological, endocrine, cardiovascular, renal, hepatic, gastrointestinal, or neurological disease.
15. Autoimmune disease (quiescent rheumatoid arthritis or controlled diabetes are acceptable).
16. Blood transfusion within 4 weeks of screening.

17. Any vaccination within 30 days prior to screening. Vaccination may be allowed during the study according to guidance issued to study sites by the Sponsor; if necessary, please contact the Medical Monitor for that guidance.
18. Known history of human immunodeficiency virus infection.
19. Recent (within 6 months of study treatment administration) drug or alcohol abuse as defined in Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Diagnostic Criteria for Drug and Alcohol Abuse.
20. Any history of clinically significant suicidal ideation and/or behavior within 1 year of screening as determined by the Investigator.
21. History of a clinically significant medical condition that would interfere with the participant's ability to comply with study instructions, would place the participant at increased risk, or might confound the interpretation of the study results.
22. Any other sound medical, psychiatric, and/or social reason as determined by the Investigator.
23. Current hepatitis C or hepatitis B infection
    - Current hepatitis C virus (HCV) infection (defined as positive HCV antibody and detectable HCV ribonucleic acid [RNA]). Participants with positive HCV antibody and undetectable HCV RNA are eligible to participate in the study (US Centers for Disease Control and Prevention).
    - Current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or hepatitis B core antibody [anti-HBc]). Participants with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive anti-HBc, and positive hepatitis B surface antibody [anti-HBs]) or vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study (US Centers for Disease Control and Prevention).

6.2.2. Prior/Concomitant Therapy

1. Within 4 weeks of screening (first visit) or anticipated during the 52-week double-blind period of the study, concurrent treatment with memantine; acetylcholinesterase inhibitors, antipsychotic agents, or mood stabilizers (e.g., valproate, lithium); or benzodiazepines, with the following exceptions:
    - Low dose lorazepam or other short-acting medications may be used for sedation prior to MRI scans for those participants requiring sedation. At the discretion of the Investigator, 0.5 to 1 mg may be given orally prior to scan with a single repeat dose given if the first dose is ineffective. Neuropsychological testing may not be performed on the same day of lorazepam administration. Participants and caregiver must be informed of risks of lorazepam use prior to administration.
    - Participants who take short-acting benzodiazepines or other hypnotics (e.g., temazepam, zolpidem) for sleep may continue to do so if they have been on a stable dose for 30 days prior to screening.

- Clonazepam may be used for treatment of restless legs syndrome, dystonia, or painful rigidity associated with PSP if the dose has been stable for 60 days prior to screening.
- Quetiapine or clozapine may be permitted if at a stable dose for at least 60 days prior to screening.

2. Receipt of systemic corticosteroids within 30 days prior to baseline.
3. Receipt of an investigational immunomodulator or mAb within 180 days (or 5 half-lives, whichever is longer) prior to screening.
4. Treatment with any other investigational drugs (e.g., salsalate) including placebo or devices within 90 days prior to screening.

6.2.3. Physical and Laboratory Test Findings

1. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population.
2. Clinically significant abnormality on 12-lead ECG prior to study treatment administration, confirmed by repeat.
3. Total bilirubin, alanine aminotransferase (ALT), or aspartate aminotransferase (AST) greater than 2 times the upper limit of normal (ULN), confirmed by repeat. Elevated total bilirubin suspected to be due to Gilbert syndrome should be discussed with the Medical Monitor.
4. Serum creatinine >168 mol/L (1.9 mg/dL), confirmed by repeat.
5. Hematocrit <30%, absolute neutrophil cell count of ≤1500/μL (with the exception of a documented history of a chronic benign neutropenia), or platelet cell count of <120,000/μL, or International normalized ratio (INR) >1.4 or other coagulopathy, confirmed by repeat. (Note: Participants with INR >1.4 due to antiplatelet/anticoagulant medications are eligible.)
6. A clinically significant abnormal thyroid-stimulating hormone test.
7. [redacted]
8. Hemoglobin A1C (HbA1C) >8%, confirmed by repeat.

6.2.4. Allergies and Adverse Drug Reaction

1. History of allergy, hypersensitivity, or serious adverse reaction to mAbs or related compounds.
2. Allergy to any of the components of the study treatment, such as Polysorbate 80.
3. History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).

6.2.5. Other Exclusion Criteria

1. Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Biogen approval is required.)
2. Participants who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3. Lifestyle Restrictions

Participants who are active tobacco smokers should not currently be smoking more than 10 cigarettes per day.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any SAEs.

6.4.1. Retesting During Screening or Lead-In Period

Participant Re-screening: This study permits the re-screening of a participant who screen-failed up to 2 times (i.e., participant was not randomized or treated). If re-screened, the participant must be re-consented. The assessments to be conducted on re-screening will depend upon how much time passed since the previous Screening Visit. Please contact the Medical Monitor for guidance regarding the acceptability of any previous assessments completed.

Retesting of laboratory parameters and/or other assessments within any single screening or lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to Randomization is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7. TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device intended to be administered to a study participant according to the study randomization or treatment allocation.

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) as listed in the following table.

Study Treatment for Study 251PP301		
Medication	**Potency**	**IP/Non-IP**
BIIB092[a]	50 mg/mL	IP
Placebo[b] (0.9% Sodium Chloride)	N/A	IP

IP = investigational product

[a] Study treatment supplies may be labeled as BIIB092 or BMS-986168. The 2 study treatment names refer to an identical drug substance.

[b] The 5% dextrose injection can be used if sodium chloride is not available.

An IP, also known as IMP in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

A rescue medication such as EpiPen or Epi-kit (containing 1 mg/mL of epinephrine) will be dispensed for home care visits, for use in the event of an allergic reaction.

See Table 6 for details regarding study treatments.

Table 6: Study Treatments for Study 251PP301

Product Description[a]	Potency	IP/Non-IMP	Study Period	Packaging/Appearance	Storage Conditions (per label)
BIIB092 Injection, 1000 mg/vial[b]	50 mg/mL	IP	Double-blind	BIIB092 is supplied as a liquid drug product in glass vials containing an extractable dose per the DHA	Store refrigerated 2°C to 8°C Protect from light Do not freeze
BIIB092 Injection, 1000 mg/vial [b]	50 mg/mL	IP	Open-label extension	BIIB092 is supplied as a liquid drug product in glass vials containing an extractable dose per the DHA	Store refrigerated 2°C to 8°C Protect from light Do not freeze
BIIB092 Injection, 2000 mg/vial [b]	50 mg/mL	IP	Open-label extension	BIIB092 is supplied as a liquid drug product in glass vials containing an extractable dose per the DHA	Store refrigerated 2°C to 8°C Protect from light Do not freeze
Placebo (0.9% Sodium Chloride or 5% Dextrose) [c]	0.9% NaCl Or 5% dextrose	IP	Double-blind	Per product label	Per product label

DHA = Directions for Handling and Administration; IMP = investigational medicinal product; IP = investigational product; N/A = not applicable

[a] BIIB092 dosage form and composition are provided in the DHA

[b] BIIB092 is provided open-label to the unblinded pharmacist. After study treatment is prepared by the unblinded pharmacist all other study personnel will remain blinded to the identification of study treatment (BIIB092 vs. placebo) through Week 48.

[c] Placebo is not provided by Biogen and obtained commercially by the site; storage should be in accordance with the product label.

7.1. Treatments Administered

The selection and timing of dose for each participant is as follows (Table 7):

Table 7: Selection and Timing of Dose

Study Treatment	Unit Dose Strength(s)/ Dosage Level(s)	Dosage Formulation Frequency of Administration	Route of Administration
BIIB092	2000 mg	Q4W	IV
Placebo	Matching dose volume at 0.9% NaCl or 5% Dextrose	Q4W	IV

IV = intravenous; Q4W = Once every 4 weeks.

7.2. Method of Treatment Assignment

All participants will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log in information and directions on how to access the IRT. Randomization will be stratified by country and screening CTT Part 2 stratum of a score either less than or equal to 170 seconds or greater than 170 seconds. Randomization will only be stratified by screening CTT Part 2 stratum under the IRT system for protocol Version 1. To promote treatment balance within each country, randomization will be stratified by both country and screening CTT Part 2 when the new IRT system for this protocol is in place.

Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

7.3. Blinding

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the investigational product is critical to the participant's management, the blind for that participant may be broken by the Investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the Investigator should determine that the unblinded information is necessary, i.e., that it will alter the participant's immediate management. In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the participant is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the Investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the participant has made the decision to discontinue from study treatment.

For information on how to unblind in an emergency, consult the IRT manual.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind. The Bioanalytical Sciences section or its designate will be unblinded to the randomized treatment assignments in order to minimize unnecessary analysis of samples from control group participants.

Any request to unblind a participant for non-emergency purposes should be discussed with the Medical Monitor.

7.4. Dosage Modification

There will be no dose escalations or reductions of study treatment allowed.

Participants may be dosed within a ±3-day window for each dosing visit in the double-blind portion of the study after the first dose administered on Day 1 of Week 0. For the open-label extension period of the study, participants may be dosed within a ±7-day window for each dosing visit.

Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, participants should be managed according to Section 14.

Dosing visits should generally not be skipped, only delayed. In the unusual circumstance where an extended delay occurs (e.g., 2 weeks or more), the Investigator should discuss this with the Medical Monitor.

7.5. Preparation/Handling/Storage/Accountability

Study treatment will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice.

BIIB092 is supplied as a liquid drug product in glass vials containing an extractable dose per the Directions for Handling and Administration (DHA). The contents of the BIIB092 label will be in accordance with all applicable regulatory requirements. BIIB092 should not be used after the expiration date.

BIIB092 must be stored refrigerated between 2°C and 8°C with protection from light. Study treatment not supplied by Biogen will be stored in accordance with the package insert.

The product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the DHA. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed, and Biogen should be contacted immediately.

The study treatment should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that study treatment is only dispensed to study participants. The study treatment must be dispensed only from official study sites by authorized personnel according to local regulations.

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, storage, and disposal of the study treatment. The DHA will also describe the masking of the IV bags of study treatment (both BIIB092 and placebo) to maintain the treatment blind. The DHA supersedes all other references (e.g., protocol or Investigator's Brochure).

Investigational product documentation (whether supplied by Biogen or not) must be maintained to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g., required diluents, administration sets).

7.5.1. Retained Samples for Bioavailability/Bioequivalence

Not Applicable.

7.6. Treatment Compliance

Not applicable as treatment is IV infusion.

7.7. Concomitant Therapy

7.7.1. Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study treatment administration and during the study are described below. Medications taken within 4 weeks prior to study treatment administration and during study treatment must be recorded on the case report form (CRF).

1. Prior exposure to BIIB092.
2. Within 4 weeks of screening or anticipated during the 52-week double-blind portion of the study, concurrent treatment with memantine; acetylcholinesterase inhibitors; antipsychotic agents or mood stabilizers (e.g., valproate, lithium); or benzodiazepines, with the following exceptions:
    a. Low dose lorazepam or other short-acting medications may be used for sedation prior to MRI scans for those participants requiring sedation. At the discretion of the Investigator, 0.5 to 1 mg may be given orally prior to scan with a single repeat dose given if the first dose is ineffective. Neuropsychological testing may not be performed on the same day of lorazepam administration. Participants and caregiver must be informed of risks of lorazepam use prior to administration.
    b. Participants who take short-acting benzodiazepines or other hypnotics (e.g., temazepam, zolpidem) for sleep may continue to do so if they have been on a stable dose for 30 days prior to screening.
    c. Clonazepam may be used for treatment of restless legs syndrome, dystonia, or painful rigidity associated with PSP if the dose has been stable for 60 days prior to screening.
    d. Quetiapine or clozapine may be permitted if at a stable dose for at least 60 days prior to screening.
3. Receipt of systemic corticosteroids within 30 days prior to screening.
4. Receipt of an investigational immunomodulator or mAb within 180 days (or 5 half-lives, whichever is longer) prior to screening.
5. Treatment with any other investigational drugs (e.g., salsalate) including placebo or devices within 90 days prior to screening.

No concomitant medications (prescription, over-the-counter, or herbal) should be administered during study unless they are prescribed for treatment of specific clinical events. Any concomitant therapies must be recorded on the CRF.

The Investigator should contact and confirm agreement with the Medical Monitor prior to the administration of any concomitant medications that may be prohibited and/or restricted.

7.7.2. Other Restrictions and Precautions

7.7.2.1. Imaging Restriction and Precautions

The imaging specialist at the study site's MRI facility is responsible for determining if a participant is contraindicated from having this procedure. The following is a list of some common conditions that may preclude the participant from having MRI scans. However, this should not be used as a substitute for local clinical standards of care. The ultimate decision to perform the MRI rests with the site radiologist, the Investigator, and the standard set by the local IRB/IEC:

- A history of claustrophobia
- An MRI-incompatible pacemaker, epicardial pacemaker wires, incompatible cardiac valve prostheses, and MRI-incompatible vascular clips less than 2 months old or MRI-incompatible aneurysm clips of any age
- An MRI-incompatible cochlear implant
- An MRI-incompatible spinal nerve stimulator
- An MRI-incompatible infusion pump
- Metallic fragments in the eyes/orbits or in the vicinity of the brain or major neurovascular structures of the body
- An employment history that involves exposure to welding, unless absence of metallic fragments is documented by X-ray examination as per institutional practice
- Shrapnel at any place in the body

7.8. Treatment After the End of the Study

Sometime after the completion of the double-blind portion of the study, the Investigator may be unblinded to participant's treatment to either BIIB092 or placebo.

Biogen reserves the right to terminate access to Biogen supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of BIIB092 is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government-sponsored or private health program. In all cases, Biogen will follow local regulations.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation From Study Treatment

Participants MUST discontinue study treatment (and non-IP at the discretion of the Investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who discontinue study treatment and remain enrolled in the study will be expected to complete scheduled safety and efficacy evaluations until the decision is made to withdraw from the study.
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Biogen
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness

In the case of pregnancy, the Investigator must immediately notify the Medical Monitor of this event and study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant safety). Please call the Medical Monitor within 24 hours of awareness of the pregnancy. If the Investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the Investigator and the Medical Monitor/designee must occur.

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate CRF page.

8.2. Study Follow-Up

In this study, safety is a key endpoint of the study. Study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study.

Participants who discontinue study treatment and remain in the study will be expected to complete scheduled safety and efficacy tests and assessments until the end of study or withdrawal of consent (see Table 2 and Table 3). Participants who discontinue study treatment and remain in the study should have all AEs collected up to 30 days after the last dose of study treatment. AE collection should continue until the end of study or withdrawal from the study.

At any point after discontinuing study treatment, if the participant makes the decision to withdraw from the study (see Section 8.3), the following should be done:

- Early Discontinuation visit procedures should be completed.
- Participants and/or caregivers should receive a follow-up phone call approximately 30 days after discontinuation of study treatment to collect relevant clinical

information, including, but not limited to, safety data (i.e., AEs, SAEs) and vital status (e.g., ability to ambulate, cognitive disability, speech, dysphagia, dependence on wheelchair for mobility, placement in residential care, and death).

8.3. Withdrawal From the Study

Participants who request to withdraw from the study should complete the Early Discontinuation visit procedures (Table 2 and Table 3). The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the Investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.4. Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the Investigator should be reported and documented in the participant's medical records.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

9.1. Efficacy Assessments

Each of the clinician-reported outcome measures described below will be performed by an appropriately qualified individual, for example a psychometrist or neurologist. The specific requirements will be documented in the procedure manual. The PSPRS and RBANS may be recorded (either audio or video) in order to allow for central review for standardization of test administration where allowable by country and/or local authorities.

Each of the participant-reported outcome measures described below may be administered as clinician-reported outcome measures where allowable by the assessments author/developer meaning that the assessments will be completed by a qualified member of the site staff, who will be reporting information collected from the participant and/or the caregiver as appropriate in order to promote consistent quality, standardization of test, and minimize burden on the study participant and/or caregiver.

These assessments are described below:

PSPRS

The PSPRS [Golbe and Ohman-Strickland 2007] is a quantitative measure of disability in participants with PSP. The PSPRS comprises 28 items in six areas. The available total score ranges from 0 (normal) to 100. Six items are rated on a 3-point scale (0 to 2), and 22 are rated on a 5-point scale (0 to 4). The History/Daily Activities area includes seven items with a total maximum of 24 points, the mentation area four items with 16 points, the bulbar area two items with 8 points, the ocular motor area four items with 16 points, the limb motor area six items with

16 points, and the gait area five items with 20 points. The PSPRS should be conducted by a neurologist.

MDS-UPDRS Part II

The MDS-UPDRS Part II includes 13 items assessing motor aspects of experiences of daily living [Goetz 2007]. These include speech, saliva and drooling, chewing and swallowing, handwriting, doing hobbies and other activities, eating tasks, tremor, dressing, hygiene, turning in bed, getting out of bed, walking and balance, and freezing.

CGI-S and CGI-C

The CGI-S measures the symptomatology of the disease using a 7-point scale. The CGI-C [Guy 1976] scale measures the change in the participant's clinical status from a specific point in time. Using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change. Whenever possible, for any individual participant, this assessment should be done by the same rater throughout the study. The CGI-C should be assessed relative to the CGI at the Week 0 (Day 1) visit as the reference. A version of the CGI that has been modified for use in Participants with PSP will be used in this study [Boxer 2014].

RBANS

The RBANS [Randolph 1998] was developed for the dual purposes of identifying and characterizing abnormal cognitive decline in the older adult. The full battery is composed of 12 subtests.

PSP-QoL

The PSP-QoL [Schrag 2006] is a participant-reported outcome measure developed specifically for assessing the health-related quality of life in people living with PSP. It is a validated 45-item questionnaire and visual analog scale that is comprised of two subscales: physical health state (22 items), which covers mobility, dysarthria, dysphagia, visual disturbances, self-care, and activities of daily living, and mental health state (23 items), which covers emotional, cognitive, and social functioning. Items are given a 5-response option format (0 = no problem to 4 = extreme problem). The subscale results are derived by summing the respective items for that subscale and transforming the scores into a range of 0 to 100, with higher scores indicating a greater impact of the disease on the aspect measured. The scale has high internal consistency in both physical health and mental health subscales (Cronbach's alpha = 0.93 and 0.95, respectively).

SEADL scale

The SEADL scale [Dal Bello-Haas 2011] is a means of assessing a person's ability to perform daily activities in terms of speed and independence through a percentage figure. The rating will be determined by a qualified staff member according to the participant's self-reported functional ability of specific criteria, with 100% indicating total independence and falling to 0% indicating a state of complete dependence.

QMA

QMA evaluates the effect of BIIB092 on motor function during typical daily activities. Participants in the QMA substudy will undergo quantitative assessments of core motor features

of PSP using wearable sensors to measure gait, postural instability, motor function, and falls (see Table 4). Participants will be asked to perform motor tasks while wearing lightweight accelerometers on their neck, feet, lower back, and wrists. Refer to the QMA manual for details of each assessment. The following tests will be performed for QMA:

- Falls: Participants will be asked to wear a necklace-like sensor at home to capture any fall data and quantify the number of falls.
- Sway: A postural sway test will be conducted, where the participant will be asked to remain standing still for 30 seconds while staring at a fixed object on a wall 1 to 4 m away. A foot block will be placed between the participant's feet. Sway jerk, velocity, and frequency dispersion will be determined.
- Gait: Gait speed, stride length, foot strike angle, arm swing range of motion, and turn velocity will be determined.
  - Usual gait: The participant will be asked to walk back and forth over a 7-m distance, at a comfortable speed, for approximately 2 minutes.
  - Dual-task gait: The participant will be asked to walk back and forth over a 7-m distance, at a comfortable speed, while doing a cognitive task, for approximately 1 minute.
- Timed chair stands (TCS): This performance-based measure will evaluate the amount of time it takes for a participant to rise from a chair and sit down.
- Instrumented push and release test: This evaluation is similar to a retropulsion test but with a standardized pull of force. Participants will lean backward into the examiner and will be given a small push and release to quantify postural stepping response.
- Rapid successive movements: Assessment of rapid successive movements consists of 2 tasks. Each task will be performed separately for the left and right limbs. Change in frequency and amplitude of repetitive movements will be determined during each of the following tasks:
  - Toe taps: For this task, both feet will be flat on the floor. Participants will be asked to tap their toe as high and as fast as they can without lifting their heel. The other foot must remain still.
  - Wrist rotations: For this task, the hand is fully extended. Participants will be asked to alternate between having the palm fully up and fully down. This pattern will be repeated as quickly as possible.
- Orthostatic vitals: Resting heart rate and blood pressure will be recorded after the participant has been seated for a few minutes. The participant will then be asked to stand, and blood pressure and heart rate will be recorded within the first 30 seconds and after an additional 3 minutes.
- Visual acuity: A standard printed Snellen eye chart will be used with the participant 6 m away.

- Joint position test: Position sense will be tested by having the participant close their eyes and report if their large toe is “up” or “down” when the examiner manually moves the participant's toe in the respective direction.
- Strength test of hip flexion and knee extension: The participant is tested in the recumbent position on the back. Hip flexion and knee extension strength are given a Medical Research Council (MRC) Grade from 0 to 5 for each side.

Phonemic Fluency

Phonemic fluency is a sensitive test for assessing frontal lobe dysfunction. The participants will be given a letter of the alphabet and asked to name as many words as they can that start with that letter, in 1 minute.

LNS

LNS is a test of working memory which involves ordering a series of up to seven letters and numbers in which the numbers are repeated back first in order starting with the lowest number, then followed by the letters in alphabetical order. For example, 3 - W - 5 should be repeated back as 3 - 5 - W.

CTT

The CTT is a language-free version of the Trail Making Test and was developed to allow for broader cross-cultural assessment. Numbered circles 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 to 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.

MoCA

The MoCA [Nasreddine 2005] was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes.

EuroQol

The EuroQol [Brooks 1996; Rabin and de Charro 2001; The EuroQol Group 1990] is a standardized instrument for use as a measure of health outcome. It assesses health-related quality of life in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The [redacted] version of the instrument will be used to measure health-related quality of life for participants and/or caregivers as appropriate.

[redacted]

[redacted]

9.2. Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2).

9.2.1. Physical Examinations

Refer to the Schedule of Activities.

9.2.2. Vital signs

Refer to the Schedule of Activities.

9.2.3. ECGs

Refer to the Schedule of Activities.

9.2.4. Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Table 8: Laboratory Safety Assessments

Hematology	
Red blood cell count	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Serum Chemistry	
Aspartate aminotransferase	Total protein
Alanine aminotransferase	Albumin
Total bilirubin	Sodium
Direct bilirubin	Potassium
Alkaline phosphatase	Chloride
Lactate dehydrogenase	Calcium
Creatinine	Phosphorus
Blood urea nitrogen	Magnesium
Uric acid	Creatine kinase
Glucose	Thyroid-stimulating hormone[a] - Screening only
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive on the dipstick	
Serology	
Serum for hepatitis C antibody[b], hepatitis B surface antigen (HBsAg; Screening only)	
Other Analyses	
INR (International normalized ratio)	
Prothrombin time	
HbA1C - screening only	

Pregnancy test (women of childbearing potential only: screening, predose, discharge).
Follicle-stimulating hormone (screening only for women only)
[redacted]

[a] Thyroxine and triiodothyronine were tested if thyroid-stimulating hormone result was abnormal.
[b] Hepatitis C antibody RNA was tested if the hepatitis C antibody result was abnormal.

9.2.5. Suicidal Risk Monitoring

BIIB092 is considered to be a central nervous system (CNS)-active study treatment. There has been some concern that some CNS-active study treatments may be associated with an increased risk of suicidal ideation or behavior when given to some participants with certain conditions. Although this study treatment or other similar drugs in this class have not been shown to be associated with an increased risk of suicidal thinking or behavior when given to healthy volunteers or participants with PSP, Biogen considers it important to monitor for such events before and during this clinical study.

Participants being treated with BIIB092 should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing BIIB092 in participants who experience signs of suicidal ideation or behavior.

Families and caregivers of participants being treated with BIIB092 should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the Study Investigator.

Baseline assessment of suicidal ideation and behavior and treatment-emergent suicidal ideation and behavior will be monitored during the study using the [redacted] Refer to Section 9.4 for more information.

9.2.6. Imaging Safety Assessment

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

9.3. Imaging Assessment for the Study

MRI

A central imaging vendor will perform imaging analyses. Image acquisition guidelines and submission processes will be outlined in the Study 251PP301 Imaging Manual to be provided by the core central imaging vendor. Sites will be trained prior to scanning the first study participant.

Brain volumetric measurements will be done using 3D T1-weighted MRI to estimate brain volumes (e.g., ventricles, whole brain, midbrain, pons, superior cerebellar peduncle, third

ventricle, and frontal lobes). Specifically, a three-dimensional MRI sequence with 1.0 x 1.0 x 1.2 mm isotropic voxels will be acquired according to the AD Neuroimaging Initiative recommendation. 1.5 T and 3.0 T MRI scanners will be employed in this study. The volumes of 7 brain structures of particular relevance in PSP (ventricles, whole brain, midbrain, pons, superior cerebellar peduncle, third ventricle and frontal lobes) will be measured. In addition, volumes of additional brain structures will also be measured (e.g., gray/white matter, cerebrum, cerebral cortex, frontal/parietal/temporal/occipital lobes, hippocampus, caudate nucleus, cerebellum, brainstem, medulla oblongata). In addition, fluid attenuation inversion recovery (FLAIR) and T2 sequences will be performed to exclude new pathologies.

All MRI scans will be locally and centrally read. Local reads should be performed to confirm eligibility.

9.4. Other Assessments

[redacted]

10. ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver or surrogate).

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study treatment or the study, or that caused the participant to withdraw before completing the study.

Contacts for SAE reporting are specified in Appendix 3.

10.1. Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment and continue until end of study at the timepoints specified in the Schedule of Activities (Section 2).

Section 6.6 in the Investigator's Brochure represents the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study treatment, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period, continuously throughout the study, and until 30 days following the last dose (see Table 2 and Table 3).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the electronic case report form (eCRF) section.
- All SAEs will be recorded and reported to Sponsor within 24 hours, as indicated in Appendix 3.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of this being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants; however, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study and he/she considers the event reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.
- The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

10.2. Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

10.3. Follow-up of AEs and SAEs

Nonserious AEs should be followed to resolution or stabilization or reported as SAEs if they become serious (see Appendix 3).

Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment, as appropriate.

All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.4).

Further information on follow-up procedures is given in Appendix 3.

10.4. Regulatory Reporting Requirements for SAEs

Prompt notification from the Investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.

An Investigator who receives an Investigator safety report describing SAEs or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

The Sponsor will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws, including European Directive 2001/20/EC and Food and Drug Administration Code of Federal Regulations (CFR) 21 CFR Parts 312 and 320. A (suspected, unexpected serious adverse reaction (SUSAR) is a subset of SAEs and will be reported to the appropriate regulatory authorities and Investigators following local and global guidelines and requirements.

10.5. Pregnancy

Participants should not become pregnant or impregnate their partners for the duration of treatment with study treatment(s) BIIB092 plus 5 half-lives of study treatment BIIB092 plus 30 days for females (duration of ovulatory cycle) or 90 days for males (duration of sperm turnover) for a total of 155 days or 215 days for females and males, respectively. If a female participant becomes pregnant, study treatment must be discontinued immediately.

The Investigator must report a pregnancy occurring in a female participant by faxing or emailing the appropriate form to Biogen within 24 hours of the site staff becoming aware of the pregnancy. Refer to the Study Contact List for complete contact information. The Investigator or site staff must report the outcome of the pregnancy to Biogen. A pregnancy is not considered an AE and should not be recorded on the AE CRF.

Congenital abnormalities and birth defects in the offspring of male or female participants should be reported as an SAE if conception occurred during the study treatment period.

10.6. Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term should be used by the reporting Investigator (e.g., anemia versus low hemoglobin value).

10.7. Potential Drug Induced Liver Injury

Potential drug induced liver injury (DILI) is defined as follows:

Aminotransaminases (ATs), including ALT or AST elevation >3 times ULN

AND

Total bilirubin >2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

All occurrences of potential DILIs, meeting the defined criteria must be reported as SAEs (see Section 10 and Appendix 3 for reporting details).

10.8. Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECG, x-ray filming, or any other potential safety assessment required or not required by protocol should also be recorded as a nonserious AE or SAE, as appropriate, and reported accordingly.

10.9. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the Investigator's Brochure.

10.10. Suspected Unexpected Serious Adverse Reactions

SUSARs are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Appropriate personnel at Biogen will unblind SUSARs for the purpose of regulatory reporting. Biogen will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen will submit SUSARs to Investigators in a blinded fashion.

10.11. Overdose

An overdose is any dose of study treatment administered to a participant or taken by a participant that exceeds the dose assigned to the participant according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed or emailed to Biogen within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Biogen even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed or emailed to Biogen. All study treatment-related dosing information must be recorded on the dosing CRF.

10.12. Medical Emergency

In a medical emergency requiring immediate attention, site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should contact the study's Medical Director. Refer to the Study Contact List for complete contact information.

10.13. Unblinding for Medical Emergency

In a medical emergency when knowledge of the participant's treatment assignment may influence the participant's clinical care, the Investigator may access the participant's treatment assignment by IRT. The Investigator must document the reasons for unblinding in the participant's source documents. The Investigator is strongly advised not to divulge the participant's treatment assignment to any individual not directly involved in managing the medical emergency, or to personnel involved with the analysis and conduct of the study. The Investigator can contact Biogen to discuss such situations.

10.14. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

11. PHARMACOKINETICS

The PK data obtained in this study will be combined with data from other studies in the clinical development program to develop a population PK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of BIIB092 and to determine measures of individual exposure (such as steady-state trough, or time-averaged concentration, or area under the concentration-time curve). Model determined exposures will be used for exposure-response analyses of selected efficacy and safety end points. Results of population PK and exposure-response analyses will be reported separately.

Table 9 lists the sampling schedule to be followed for the assessment of pharmacokinetics in serum and CSF. Further details of blood and CSF collection and processing will be provided to the site in the procedure manual and laboratory manual.

Serum samples will be analyzed for BIIB092 using a validated ligand binding assay. Pharmacokinetic samples collected from a participant who received placebo will not be analyzed.

Table 9: Pharmacokinetic Sampling Schedule

Study Week of Sample Collection	Event	Estimated Time (Relative to start of Infusion of BIIB092) Hour: Min	BIIB092 Blood Sample for Serum	BIIB092 CSF Sample[a]
Week 0 (Day 1)	Predose	00:00	X	X
Week 0 (Day 1)	EOI[b]	01:00	X	
Week 4	Predose	00:00	X	
Week 4	EOI[b]	01:00	X	
Week 12	Predose	00:00	X	
Week 24	Predose	00:00	X	
Week 24	EOI[b]	01:00	X	
Week 36	Predose	00:00	X	
Week 48	Predose	00:00	X	
Week 48	EOI[b]	01:00	X	
Week 52	Predose	00:00	X	X
Week 56	Predose[c]	00:00	X	
Weeks 76, 100, 124, 148, 172, and 196 [d]	Predose	00:00	X	Week 100 only

CSF = cerebrospinal fluid; EOI = end of infusion.
[a] Collect at the time of LP ([redacted])

[b] This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of the infusion). If the end of infusion is delayed to more than the nominal infusion duration, the collection of this sample should also be delayed accordingly.
[c] The scheduled predose sampling at Week 56 is also the Week 52 postdose sampling (672 hours after Week 52 dosing).
[d] Visit intervals of 24 weeks after Week 52 (Weeks 76, 100, 124, 148, 172, and 196).

12. PHARMACODYNAMICS

[redacted]

The final disposition of samples will be conducted per local regulations.

Details on processes for collection and shipment of these samples can be found in the procedure manual.

[redacted] [redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted].

[redacted]

[redacted]

[redacted]

14. IMMUNOGENICITY ASSESSMENTS

A validated immunoassay will be used to assay samples for the presence of, and measure titers of, anti-BIIB092 antibodies in serum on an ongoing basis in Study 251PP301. Samples will be collected during the 52-week double-blind period at Day 1, Week 4, Week 8, Week 12, Week 24, Week 36, and Week 48 (Table 2). In addition, samples will also be collected during the open-label extension period approximately every 24 weeks (Table 3). All samples will be collected predose.

Anti-drug antibody (ADA) titers will be monitored throughout the course of Study 251PP301. If ADAs are observed, analyses will be conducted to assess impacts on safety, pharmacological, and efficacy measures across treated participants with and without ADAs. ADAs may also be assessed for neutralizing activity.

Participants who withdraw from Study 251PP301 with ADA titers that are not stable or are increasing in two consecutive samples leading up to discontinuation will be asked to return for follow-up assessment approximately every 6 weeks for up to 24 weeks for measurement of ADAs and immunological AE assessment until resolved (defined as two sequential samples showing no change or declining levels).

Clinically relevant immune reactions (e.g., hypersensitivity reactions) will be treated according to current standard of care medical practice. Additional samples for immunogenicity assessments referred to as “event driven” samples may be justified on the basis of ≥Grade 3 hypersensitivity reactions. The immunogenicity and corresponding drug exposure (PK) data from these samples will be reported as part of a participant’s overall PK and immunogenicity assessment.

15. OTHER ASSESSMENTS

15.1. PSP phenotypes

Based on participant's medical history, Investigators will be asked to provide the participant's clinical phenotype as outlined in the Movement Disorder Society-PSP criteria [Höglinger 2017].

PSP clinical phenotypes may include the following:

- PSP with predominant Richardson syndrome
- PSP with predominant ocular motor dysfunction
- PSP with predominant postural instability
- PSP with predominant parkinsonism
- PSP with progressive gait freezing
- PSP with predominant frontal presentation
- PSP with predominant speech/language disorder
- PSP with predominant corticobasal syndrome

16. MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Medical resource utilization and health economics data that is associated with medical encounters may be collected in the CRF by the Investigator and study site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and may include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient),
- Duration of hospitalization (total days length of stay, including duration by wards; e.g., intensive care unit),
- Number and character of diagnostic and therapeutic tests and procedures, and
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

17. STATISTICAL CONSIDERATIONS

17.1. Sample Size Determination

Approximately 459 participants will be randomly assigned in a 2:1 ratio to receive BIIB092 or placebo (306 participants in the BIIB092 treatment group and 153 in the placebo group). Anticipating a dropout rate of approximately 25% (based on previous clinical studies in participants with PSP), approximately 345 participants (230 participants in the BIIB092 treatment group and 115 participants in the placebo group) are expected to complete the study through Week 52.

Using a two-sided, two-sample t-test with an alpha level set at 0.05, this sample size will provide 80% power to detect a difference of 3.2 points in the change in PSPRS total score from baseline to Week 52 for BIIB092 relative to placebo, assuming a common standard deviation of 9.95 [Stamelou 2016] in the change in PSPRS total score from baseline to Week 52.

17.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled participants	All participants who signed informed consent and were assigned a participant identification number
Randomized participants	Enrolled participants who received a randomization treatment assignment from the Interactive Response Technology (BIIB092 or placebo)
Treated participants	Enrolled participants who received at least 1 dose of study treatment, i.e., blinded therapy (BIIB092 or placebo) or open-label BIIB092
Intention-to-treat (ITT) participants	Randomized participants who received at least 1 dose of blinded study treatment
Cumulative BIIB092-treated participants	All randomized participants who received at least 1 dose of BIIB092 during the double-blind and/or the open-label period.

Additional analysis populations will be defined in the statistical analysis plan.

17.3. Handling of Missing Data

Missing data patterns will be summarized. Percentage of participants who withdrew from the study over time through Week 52 will be summarized and graphically presented by (1) as randomized treatment group and reason for discontinuation, and (2) as randomized treatment group and disease severity (split by the median of baseline PSPRS). Observed mean change from baseline in the primary endpoint will be summarized and graphically presented by treatment group and dropout pattern over time.

Main analyses using a likelihood-based mixed model approach will based on the assumption of missing at random (MAR). Sensitivity analyses for the primary endpoint will be conducted with missing data imputed by multiple imputation. Specifically, the multiple imputation will be

performed under the following methods under the framework of missing not at random (MNAR):

- Copy Differences from Control (CDC): This pattern mixture model assumes that changes over time in future outcomes in participants who withdraw from all treatment groups are similar to those future changes observed among completers in the control group.
- Jump to Reference (J2R): This pattern mixture model assumes that participants withdrawn from all treatment groups would have had outcomes similar to those that were observed among completers (with similar baseline characteristics) in the control group.

In addition, an analysis of covariance (ANCOVA) sensitivity analysis at Week 52 will be conducted for the primary using the last observation carried forward (LOCF) method adjusted by historical progression; that is, missing PSPRS data will be imputed by assuming historical placebo progression (11.24 points/year) [Stamelou 2016] from the visit of the last observation prior to Week 52.

17.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

17.4.1. Efficacy Analyses

Efficacy analyses will be performed using the intent-to-treat participants. Unless stated otherwise, all tests of treatment effects will be conducted at a two-sided significance level of 0.05. The primary efficacy analyses will be for comparative efficacy of BIIB092 to placebo in the double-blind treatment period (including all data through Week 52 for participants discontinuing study treatment during the double-blind period). Details of the efficacy analyses for the open-label extension period will be provided in the statistical analysis plan.

Endpoint	Statistical Analysis Methods
Primary	Changes from baseline in PSPRS will be analyzed using a restricted maximum likelihood (REML)-based Mixed Model with Repeated Measures (MMRM) approach. The principal analysis of the primary endpoint will be a MMRM model that will include treatment, visit, treatment-by-visit interaction, stratification factors as categorical fixed effects, baseline value of PSPRS as a continuous covariate, and baseline value of PSPRS-by-visit interaction. An unstructured covariance matrix will be used to model the within-participant errors. If this analysis fails to converge, the following structures will be tested in this order: the heterogeneous Toeplitz covariance structure, autoregressive model of order 1, and compound symmetric. The first covariance structure yielding convergence will be used.

Endpoint	Statistical Analysis Methods
	The treatment comparison of BIIB092 to placebo will be based on the difference in least-squares means with a two-sided 95% confidence interval and p-value. Sensitivity analyses for the primary endpoint will include the following analyses: • ANCOVA analysis at Week 52 using LOCF adjusted by historical placebo progression: The ANCOVA model will include treatment, stratification factors as categorical effects, and baseline value of PSPRS as continuous covariate. • MMRM analysis with missing data imputed by the CDC multiple imputation method. The specification of the MMRM model based on the imputed data will be the same as the primary MMRM model. • MMRM analysis with missing data imputed by the J2R multiple imputation method. The specification of the MMRM model based on the imputed data will be the same the primary MMRM model. • Responder analysis in which participants with missing data at Week 52 will be treated as non-responders. • Subscales of the PSPRS will be summarized over time descriptively. • Additional analysis may be performed with details specified in the statistical analysis plan.
Key Secondary	• If the primary analysis finds that participants treated with BIIB092 performed significantly better than placebo, the key secondary endpoints will be analyzed hierarchically in the following order: MDS-UPDRS Part II, CGI-C, RBANS, and PSP-QoL. • The testing procedure will maintain an alpha level of 0.05 at each level of the hierarchy and ensures the preservation of the overall type I error at 0.05.
Non-Key Secondary	• Non-key secondary endpoints will be tested at an uncontrolled alpha level of 0.05 per endpoint. The p-values resulting from these analyses will be considered as nominal and descriptive in nature.
Exploratory	• Will be described in the statistical analysis plan.

17.4.2. Safety Analyses

Safety analyses will be performed by as-treated treatment group for treated participants. Safety endpoints include the frequency and proportion of participants with AEs, SAEs, AEs leading to discontinuations and deaths, and other significant AEs reported on case report forms. Other safety endpoints include laboratory abnormalities, changes in laboratory parameters, changes in vital signs, physical findings, and ECGs.

In general, AE presentations will be by system organ class and preferred term.

The primary safety analyses will be for comparative safety of BIIB092 to placebo in the double-blind treatment period. Safety endpoints will include data up to the start of the open-label extension period for participants who completed the double-blind treatment period and continue into the open-label extension, or up to last dosing date plus 30 days for participants discontinuing study treatment during the double-blind treatment period.

Additional safety analyses will include all events reported through the time of database lock for the cumulative BIIB092-treated participants. Safety endpoints will include data from the first dose of BIIB092 in the study up to the last dose of BIIB092 treatment in the study plus 30 days.

17.4.3. Interim Analysis

An interim analysis for superiority may be performed before the last participant has had the opportunity to complete the Week 52 visit. An alpha spending function approach will be used for the analysis. In order to maintain the treatment blind in the event of this interim analysis, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim superiority analysis. The independent group will present the unblinded interim analysis to the DMC. The aim of this interim analysis is to allow the possibility to demonstrate treatment effect early. The analysis (including the details of the alpha spending approach) will be discussed in the statistical analysis plan.

17.5. Other Analyses

17.5.1. PK and PD Analyses

PK and PD analyses will be described in the statistical analysis plan. The population PK analysis and PD analyses will be presented separately from the main clinical study report.

17.5.2. Immunogenicity Analyses

Immunogenicity analyses will be described in the statistical analysis plan.

17.5.3. Biomarker Analyses

Biomarker analyses will be described in the statistical analysis plan.

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19. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Intravenously Administered BIIB092 in Participants with Progressive Supranuclear Palsy," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____ _____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

20. APPENDICES

APPENDIX 1. ABBREVIATIONS AND TRADEMARKS

Term	Definition
AD	Alzheimer's disease
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
AT	aminotransaminase
BP	blood pressure
CDC	Copy Differences from Control
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CNS	central nervous system
CRF	case report form, paper or electronic
CSF	cerebrospinal fluid
[redacted]	[redacted]
CTA	clinical trial agreement
CTT	Color Trails Test
DHA	Directions for Handling and Administration
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EOI	end of infusion
[redacted]	[redacted]
EuroQol	European Quality of Life
GCP	Good Clinical Practice
HbA1C	hemoglobin A1C
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

HCV	hepatitis C virus
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
Ig	immunoglobulin
IMP	investigational medicinal product
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
J2R	Jump to Reference
LAM	lactation amenorrhea method
LP	lumbar puncture
LNS	Letter-Number Sequencing
LOCF	last observation carried forward method
mAb	monoclonal antibody
MAD	multiple ascending dose
MAPT	microtubule-associated protein tau
MAR	missing at random
MDS-UPDRS	Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale
MMRM	Mixed Model with Repeated Measures
MMSE	Mini Mental State Examination
MNAR	missing not at random
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
MRC	Medical Research Council
N/A	not applicable
NfL	neurofilament light chain
NHV	normal healthy volunteer
NSAE	non-serious adverse event
[redacted]	[redacted]
PD	pharmacodynamic(s)

PK	pharmacokinetic(s)
[redacted]	[redacted]
PSP	progressive supranuclear palsy
PSP-QoL	Progressive Supranuclear Palsy Quality of Life scale
PSPRS	Progressive Supranuclear Palsy Rating Scale
RNA	ribonucleic acid
Q4W	every 4 weeks
QMA	quantitative movement assessment
RBANS	Repeatable Battery for the Assessment of Neuropsychological Disease Severity
[redacted]	[redacted]
SAD	single ascending dose
SAE	serious adverse event
SEADL	Schwab and England Activities of Daily Living
[redacted]	[redacted]
SOP	standard operating procedure
SUSAR	suspected, unexpected serious adverse reaction
TCS	timed chair stands
ULN	upper limit of normal
US	United States
WOCBP	women of childbearing potential

APPENDIX 2. STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the electronic case report form (eCRF) is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

Ethical Requirements

Biogen and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator is responsible for endorsing all data on completed case report forms (CRFs) electronically prior to any Interim lock or Database lock.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, informed consent form (ICF), and other required study documents prior to starting the study. The contract research organization will submit documents on behalf of the investigational sites worldwide in compliance with local regulations.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen.

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

Biogen must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and no less than annually.

At the completion or termination of the study, the study site must submit a close-out letter to the ethics committee and Biogen.

Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject, in accordance with local practice and regulations.

The Investigator must reassess the subject's capacity to provide informed consent periodically over the course of the study. In the event the subject is cognitively intact and loses capacity to provide informed consent, the Investigator must obtain subject assent and consent by the subject's legally authorized representative (in accordance with local laws and regulations) or withdraw the subject from the study.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and ethnicity will be collected during the study (unless the collection is not permitted by applicable law or not approved by the governing ethics committee) and the data will be used during analysis of study results.

A copy of the signed and dated ICF must be given to the subject or the subject's legally authorized representative. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the subject's medical record.

Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

During the study, subjects' race and ethnicity will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). These data will be used in the analysis of the safety and/or pharmacokinetic profile of the study treatment. It is unknown whether the effects of the study treatment are influenced by race or ethnicity.

Study reports will be used for research purposes only. The subject will not be identified by name in CRFs, study-related forms, study reports, or any related publications. Biogen, its partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen) with the subject before the subject makes a decision to participate in the study.

Registration of Study and Disclosure of Study Results

Biogen will register the study and post-study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

Compliance with the Protocol and Protocol Revisions

The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s) the deviation or change will be submitted as soon as possible to the following:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to Biogen.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, Investigators must inform their IRB(s)/IEC(s).

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Source Documents

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of

electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, adverse event (AE) tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

Study Treatment Records

Records for study treatment use of BIIB092 (whether supplied by Biogen, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of Biogen or a Health Authority.

If	Then
Supplied by Biogen (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include the following: • the amount received and placed in storage area • the amount currently in storage area • the label identification number or batch number • the amount dispensed to and returned by each participant, including unique participant identifiers • the amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • the amount destroyed at study site, if applicable • the amount returned to Biogen • samples retained for bioavailability/bioequivalence, if applicable

If	Then
	• dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority form
Sourced by site, and not supplied by Biogen or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The Investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the Standard Operating Procedures (SOPs)/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • dates and initials of person responsible for IP dispensing/accountability, as per the Delegation of Authority Form.

Biogen will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

Case Report Forms

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to serious adverse events (SAEs) and pregnancy, which will be reported on the electronic SAE form and Pregnancy Notification and Outcome form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The Investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the Investigator or qualified physician who is a sub-Investigator and who is delegated this task on the Delegation of Authority form. Sub-Investigators in Japan may not be delegated the CRF approval task for electronic CRFs, review and approval/signature is completed electronically through the Biogen electronic data capture tool. The Investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor training requirements and must only access the Biogen electronic data capture tool using the unique user account provided by Sponsor. User accounts are not to be shared or reassigned to other individuals.

Monitoring

Sponsor representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of Biogen must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents:

In addition, the study may be evaluated by Sponsor internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. Biogen audit reports will be kept confidential.

The Investigator must notify Biogen promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor.

Records Retention

The Investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by Biogen or designee, whichever is longer. The Investigator (or head of the study site in Japan) must contact Biogen prior to destroying any records associated with the study.

Biogen or designee will notify the Investigator (or head of the study site in Japan) when the study records are no longer needed.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator, study site, IRB). Notice of such transfer will be given in writing to Biogen or designee.

Return of Study Treatment

For this study, study treatments (those supplied by Biogen, a vendor or sourced by the Investigator) such as partially used study treatment containers, vials and syringes may be destroyed on site.

If	Then
Study treatments supplied by Biogen (including its vendors)	Any unused study treatments supplied by Biogen can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by Biogen (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply or a specialty pharmacy)	It is the Investigator's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the Investigator's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to Biogen upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the Investigator's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by Biogen (or its vendors). Destruction of non-study treatments sourced by the site, not supplied by Biogen, is solely the responsibility of the Investigator.

Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on one or more of the following criteria:

- Participant recruitment (e.g., among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (e.g., among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to Sponsor. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing Investigator participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

APPENDIX 3. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

Adverse Events

Adverse Event Definition:
An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Serious Adverse Events

Serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in Biogen clinical studies: • a visit to the emergency room or other hospital department <24 hours, that does not result in admission (unless considered an important medical or life- threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)

• medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 10.7 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study treatment is an SAE.

Although pregnancy, overdose, cancer, and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 10.5 for reporting pregnancies).

Any component of a study endpoint that is considered related to study treatment should be reported as SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

Evaluating AEs and SAEs

The causal relationship to study treatment is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:

- Related: An AE will be considered "related" to the use of the IP if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to a positive rechallenge, a reasonable temporal sequence between administration of the IP and the AE, a known response pattern of the suspected product, improvement following discontinuation or dose reduction, a biologically plausible relationship between the product and the AE, or a lack of an alternative explanation for the AE.
- Not related: An AE will be considered "not related" to the use of the IP if there is not a reasonable possibility that the event has been caused by the product under

investigation. Factors pointing toward this assessment include but are not limited to the lack of reasonable temporal relationship between administration of the IP and the AE, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.

Follow-up of AEs and SAEs

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same Investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to Biogen using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

Reporting of SAEs to Sponsor

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to Biogen within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Notification and Outcome Form (electronic or paper forms).
- The preferred method for SAE data reporting collection is through the electronic case report form (eCRF).
- The paper SAE/pregnancy notification and outcome forms are only intended as a back-up option when the eCRF system is not functioning.
    - In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

APPENDIX 4. WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle-stimulating hormone, (FSH) level >40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the Investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is >40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

Any one of the approved methods of contraception listed below is required for the duration of this study and for 155 days after treatment has been discontinued.

Local laws and regulations may require use of alternative and/or additional contraception methods.

Contraceptive methods that are approved for use during and for 155 days after participation in this study are: *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 10.5. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness.

Unacceptable Methods of Contraception

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method (LAM)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

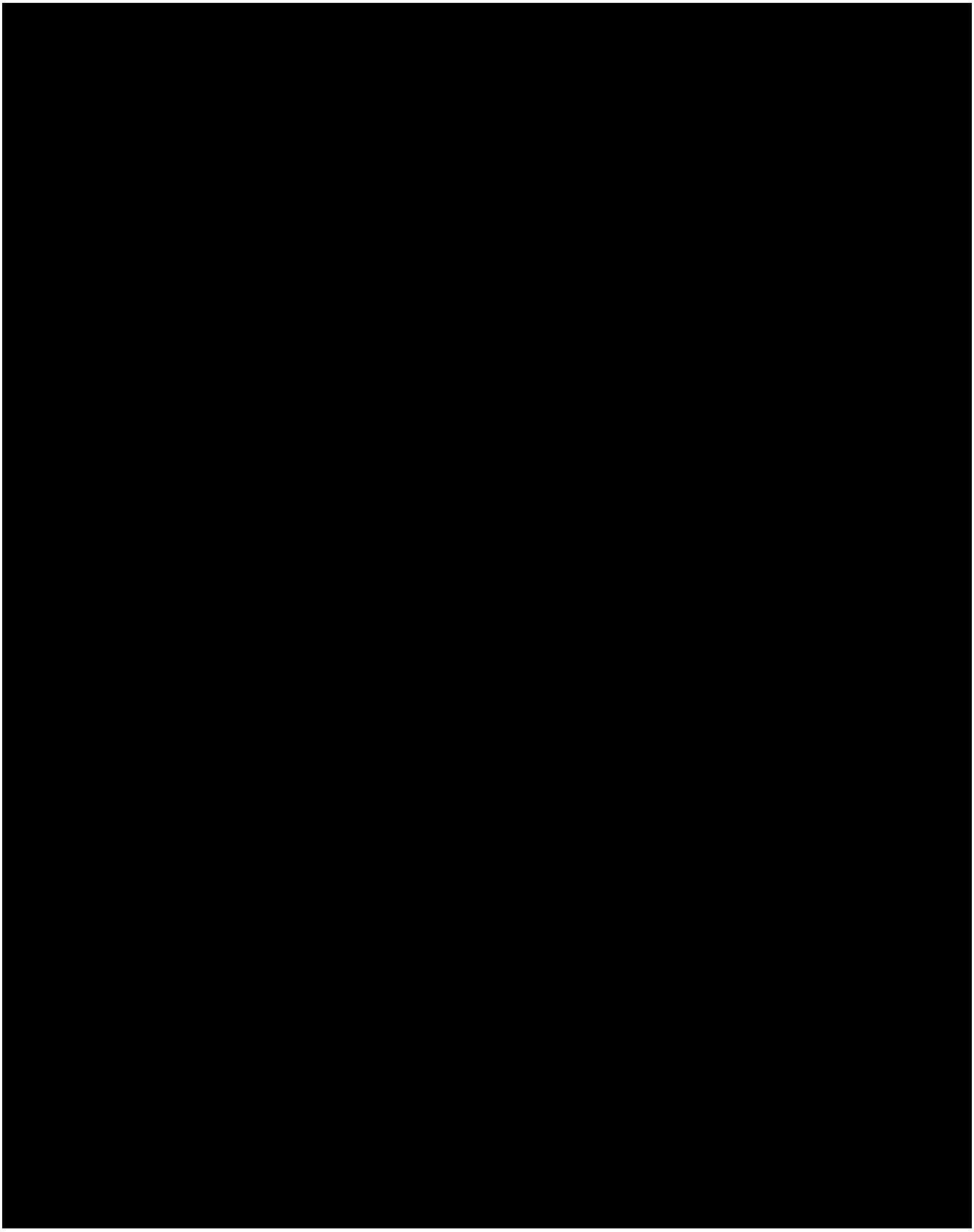
Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

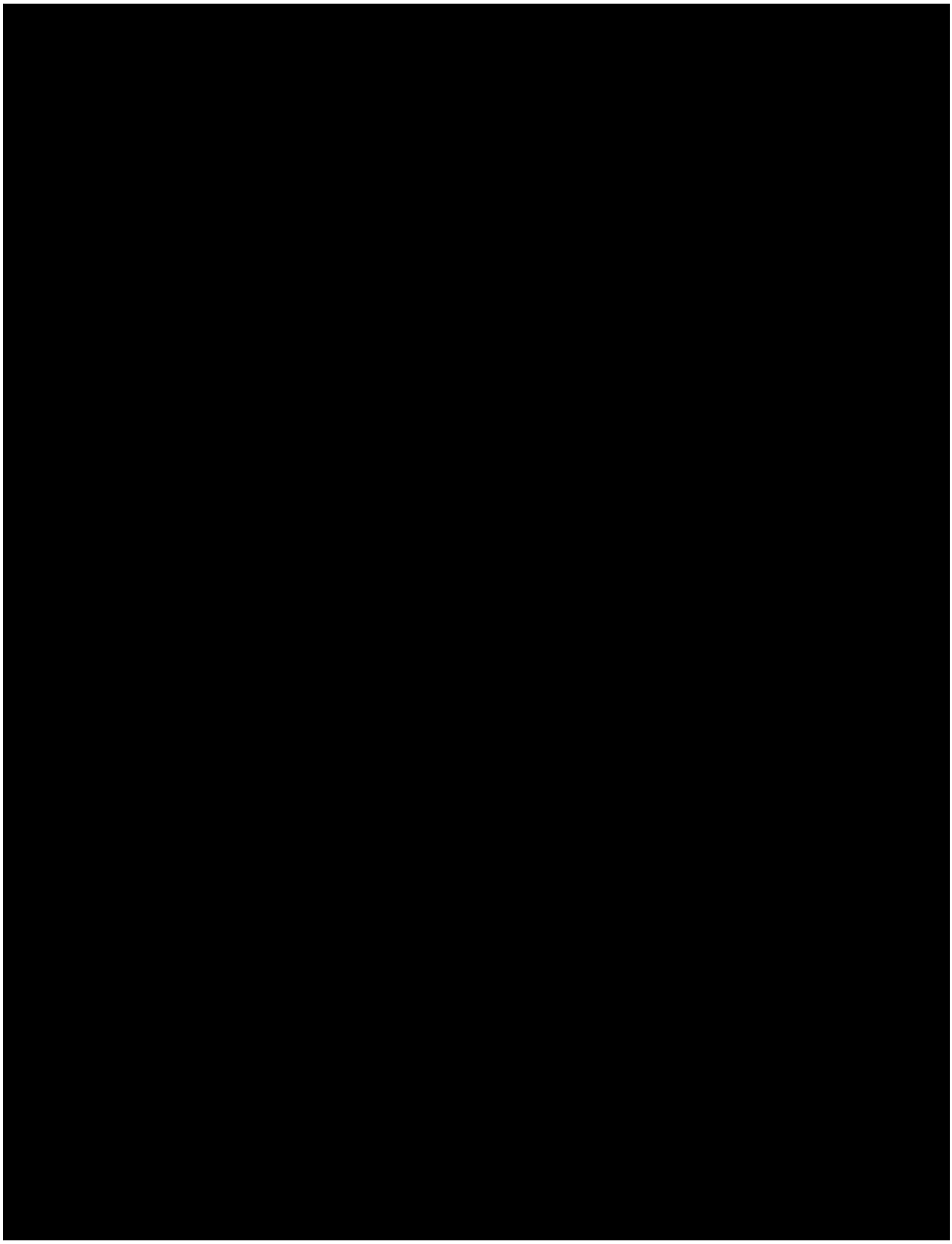
- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the Investigator.

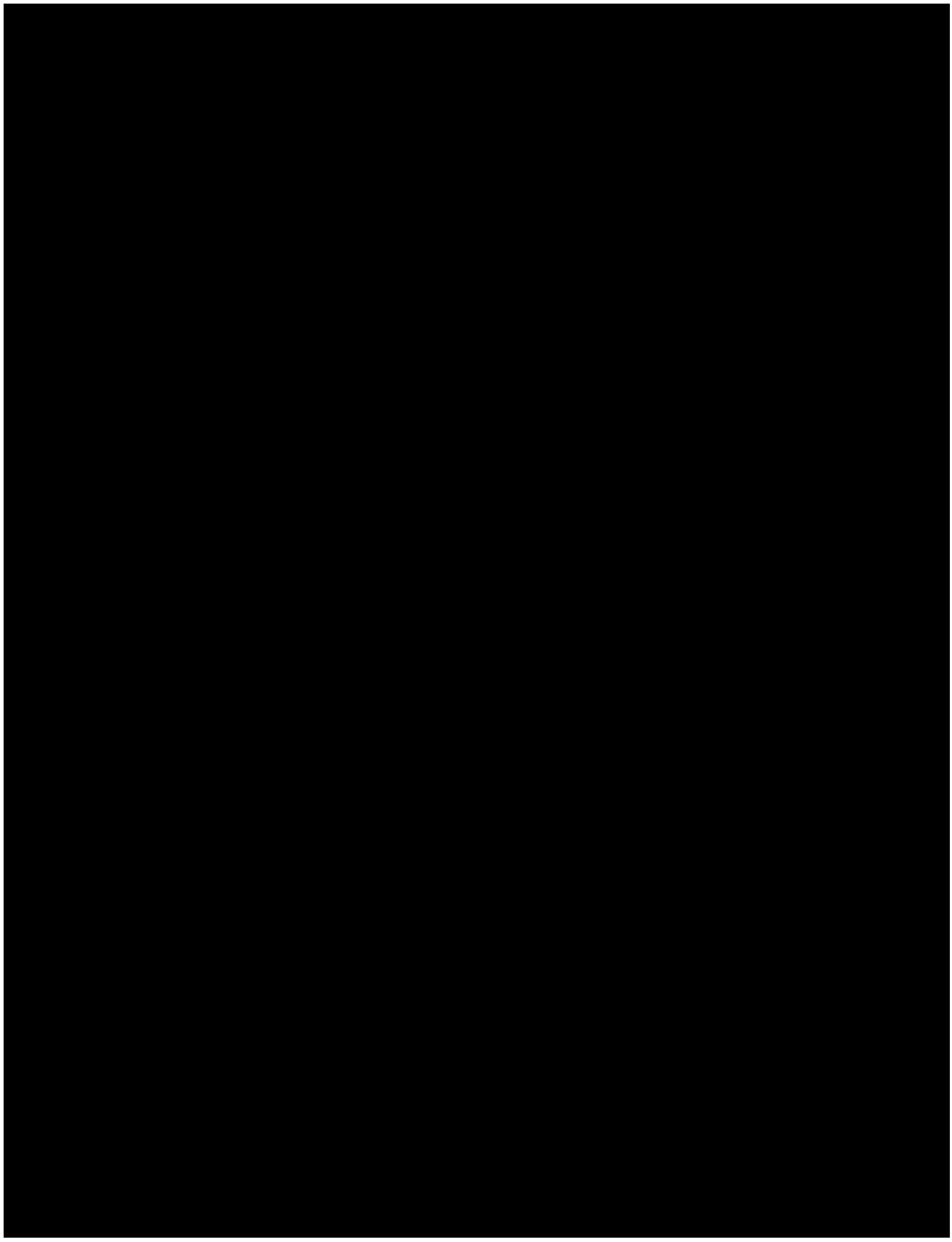
No additional contraceptive measures are required to be used.

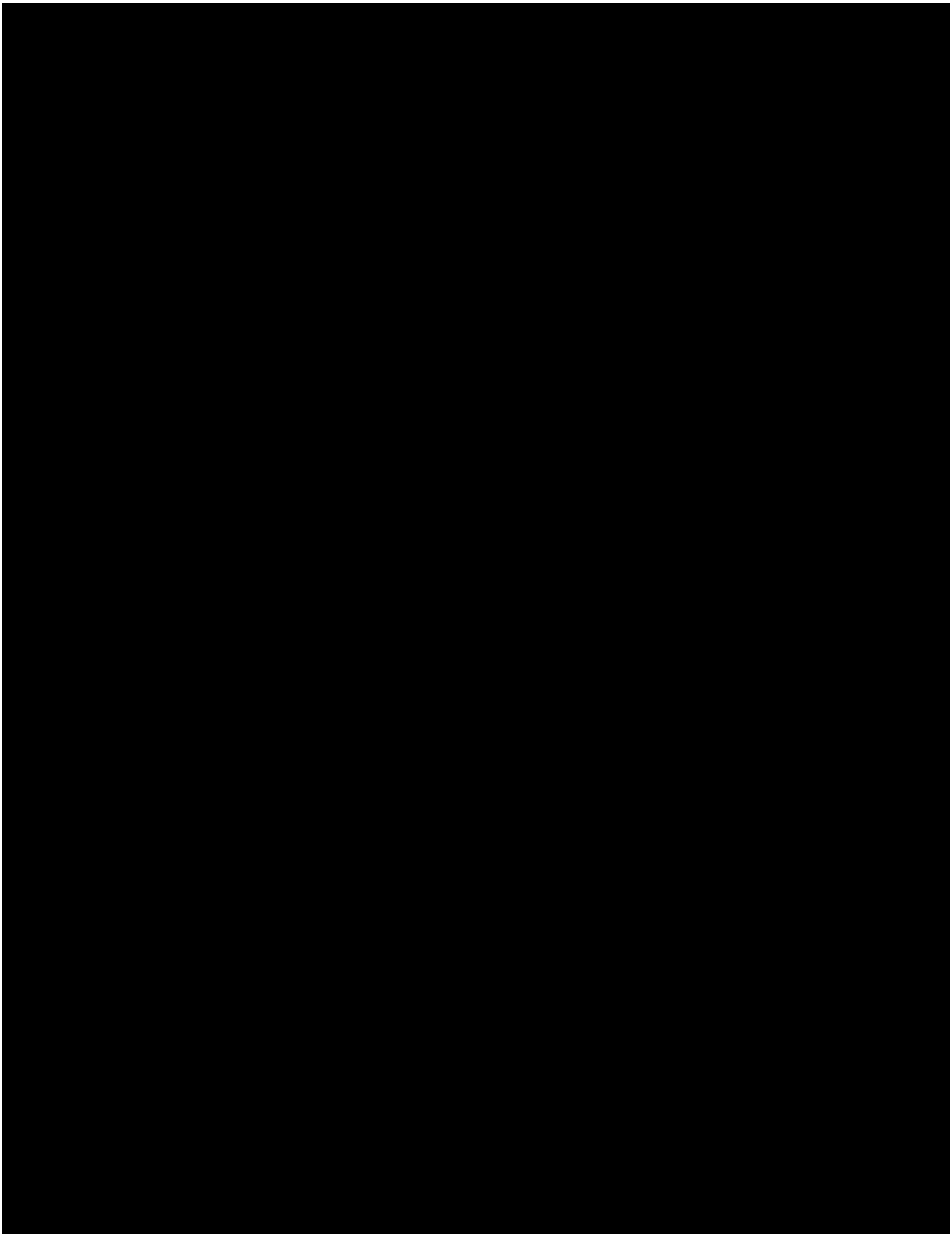
COLLECTION OF PREGNANCY INFORMATION

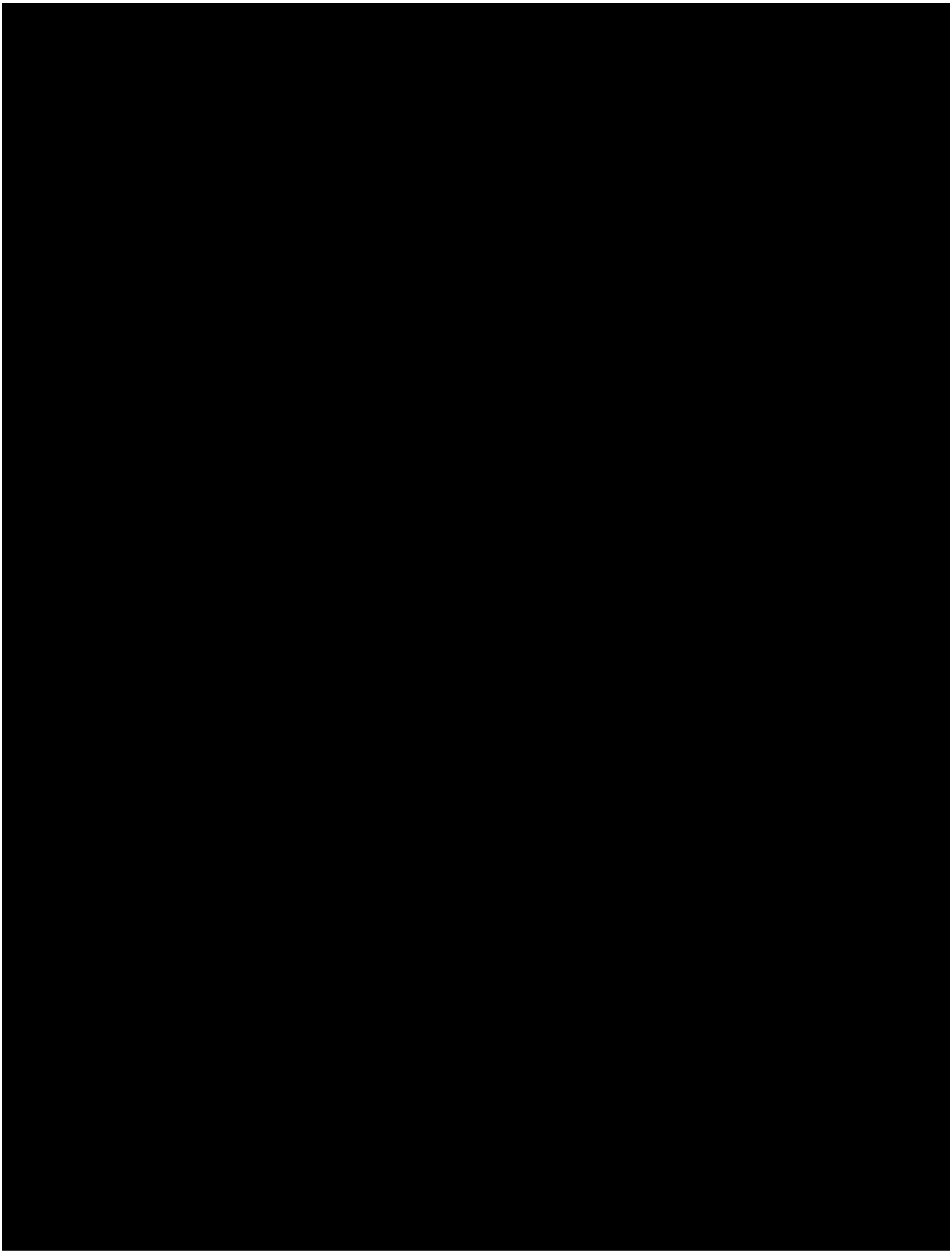
Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Notification and Outcome Form is provided in Section 10.5 and Appendix 3.











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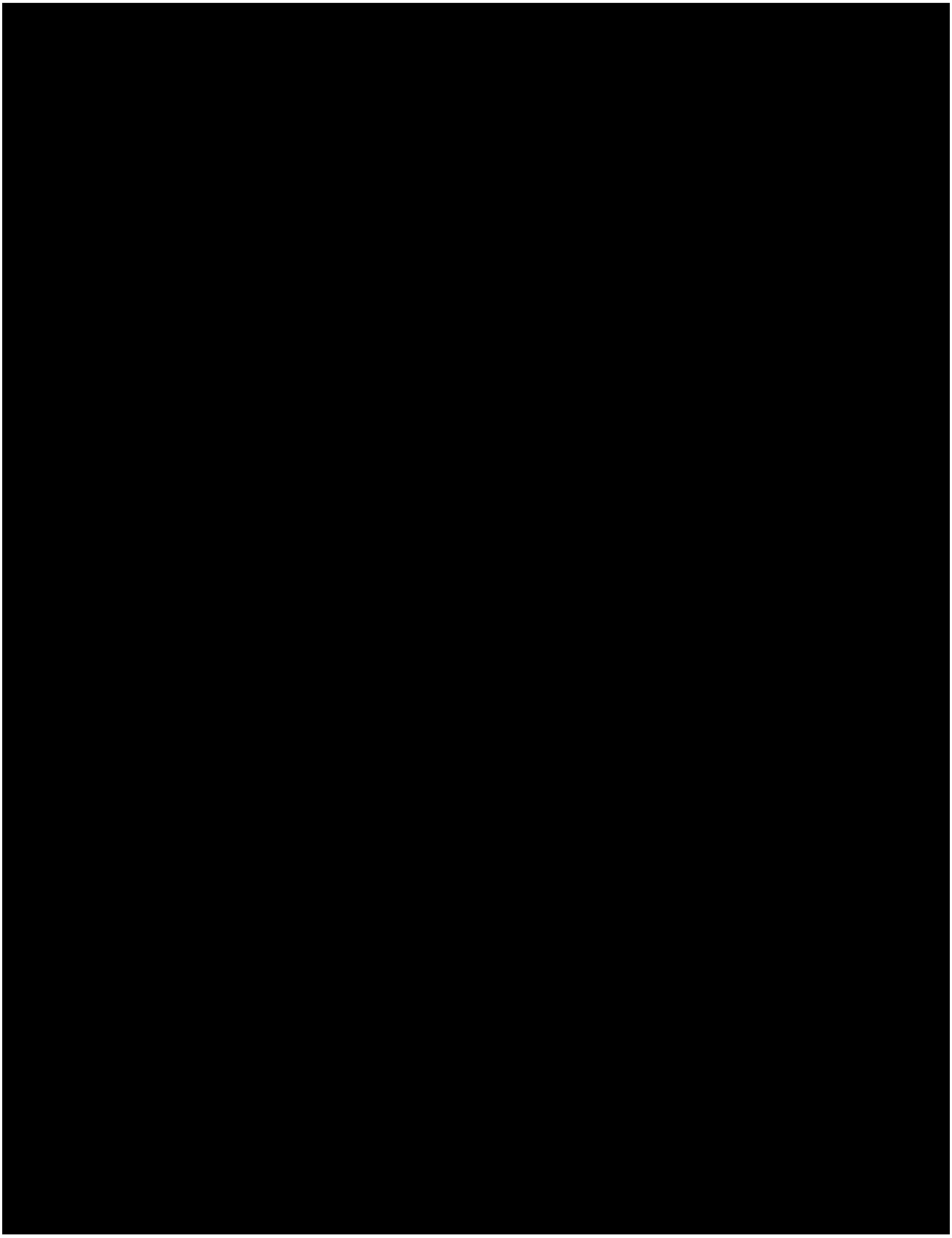

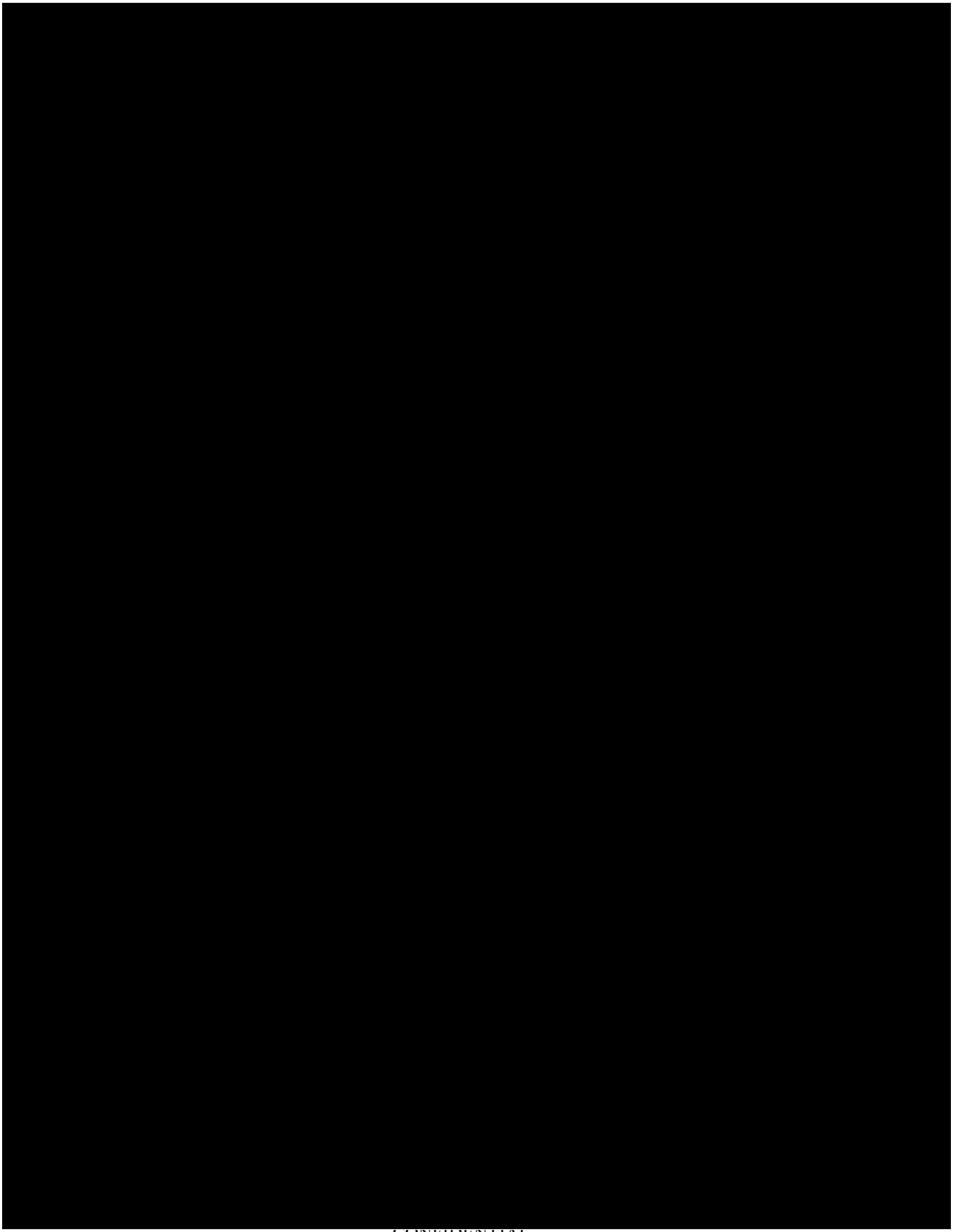

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AMENDMENT SUMMARY

Biogen Protocol 251PP301

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Intravenously Administered BIIB092 in Participants with Progressive Supranuclear Palsy

Version 7

Date: 01 February 2019

EUDRA CT Number: 2016-002554-21

Version 7 of the protocol has been prepared for this amendment, which supersedes Version 6.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 251PP301 was to update the study treatment product provided for use in the open-label extension period, to include the 2000 mg/vial.

Section 7, Treatment (Table 6)

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Now reads:

Table 6: Study Treatments for Study 251PP301

Product Description[a] ~~/ Class and Dosage Form~~	Potency	IP/Non-IMP	Study Period	Packaging/Appearance	Storage conditions (per label)
BIIB092 Injection, 1000 mg/vial [b]	**50 mg/mL**	**IP**	**Double-blind**	**BIIB092 is supplied as a liquid drug product in glass vials containing an extractable dose per the DHA**	**Store refrigerated 2°C to 8°C** **Protect from light** **Do not freeze**
BIIB092 Injection, 1000 mg/vial [b] ~~(50 mg/mL) The composition of the drug product is: 50 mg/mL, BIIB092, histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid, polysorbate 80, and sterile water for injection, pH 6.0~~	50 mg/mL	IP	**Open-Label extension**	~~Clear to very opalescent, colorless to slightly yellow liquid, in which light (few) particulates may be present~~ **BIIB092 is supplied as a liquid drug product in glass vials containing an extractable dose per the DHA**	Store refrigerated 2°C to 8°C Protect from light Do not freeze
BIIB092 Injection, 2000 mg/vial [b]	**50 mg/mL**	**IP**	**Open-Label extension**	**BIIB092 is supplied as a liquid drug product in glass vials containing an extractable dose per the DHA**	**Store refrigerated 2°C to 8°C** **Protect from light** **Do not freeze**
Placebo (0.9% Sodium Chloride or 5% Dextrose)[c]	0.9% NaCl Or 5% Dextrose	IP	**Double-blind**	Per product label	Per product label

DHA = Directions for Handling and Administration; IMP = investigational medicinal product; IP = investigational product; N/A = not applicable.

[a] **BIIB092 dosage form and composition are provided in the DHA.**

[b] BIIB092 is provided open-label to the unblinded pharmacist. After study ~~drug~~ **treatment** is prepared by the unblinded pharmacist all other study personnel will remain blinded to the identification of study ~~drug~~ **treatment** (BIIB092 vs. placebo) through Week 48.

[c] Placebo is not provided by Biogen and obtained commercially by the site; storage should **be** in accordance with the product label.

Rationale: Introduced the larger 2000 mg/vial size of the study treatment. The vial size was increased from the 1000mg/vial dose to the 2000mg/vial dose for the study sites to be able to administer 1 vial of the 2000 mg dose, instead of 2 vials of the 1000mg/dose.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 1, Synopsis

The Synopsis was revised to reflect changes made throughout the protocol.

Section 2, Schedule of Activities (Table 1, Table 2, and Table 3)

Change: Tables were revised to clarify the safety language in the protocol that specifies the timelines during which AEs and SAEs are being collected.

Now reads:

Table 1: Screening Procedural Outline

Procedure	Screening Visit[a]	Notes
Safety Assessments		
Monitor for Serious Adverse Events (SAEs)	X	Following written consent to participate in the study, all SAEs whether related or not related to study ~~drug~~**treatment** that occur during the screening period, ~~until 30 days post discontinuation of dosing or end of treatment~~ **continuously throughout the study, and until 30 days following the last dose should be monitored and recorded.**

Table 2: Double-Blind Procedural Outline

Procedure[a]	Week 0 (Day 1)	Weeks 4, 8, 16, 20, 28, 32, 40, 44[b] (±3 days)	Weeks 12, 24, 36 (±3 days)	Week 48 (±3 days)	Week 52 (±3 days)	Early Discontinuation[c,d],	Notes
Monitor for Non-Serious Adverse Events (NSAEs)	Collection of NSAEs begins at initiation of study ~~drug~~**treatment and continues throughout the study and until 30 days following the last dose.** Participants ~~that~~**who** discontinue ~~early~~**study treatment** should ~~receive a follow-up phone call~~**have an assessment of AEs** 30 days after last dose.[e]						

Procedure[a]	Week 0 (Day 1)	Weeks 4, 8, 16, 20, 28, 32, 40, 44[b] (±3 days)	Weeks 12, 24, 36 (±3 days)	Week 48 (±3 days)	Week 52 (±3 days)	Early Discontinuation[c,d],	Notes
Monitor for Serious Adverse Events (SAEs)	~~See notes~~**Following written consent to participate** in **the study, all SAEs whether related or not related to study treatment that occur during the** screening ~~procedures.~~**period** , **continuously throughout the study, and until 30 days following the last dose should be monitored and recorded**. **Participants who discontinue study treatment should have an assessment of SAEs 30 days after last dose.** [e]						

[e] This 30-day assessment of AEs/SAEs may be done by phone if no visit occurs.

Table 3: Extension Period Procedural Outline

Procedure	**Week 52**	**Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, and 192[a,b]** **(±7 days)** ~~4, 8, 16, 20 week intervals after Week 52[a,b]~~	**Weeks 64, 88, 112, 136, 160, 184[e]** **(±7 days)** ~~12 week intervals after Week 52[e]~~	**Weeks 76, 100, 124, 148, 172, 196[d]** **(±7 days)** ~~24 week intervals after Week 52[d]~~	Early Discontinuation[a]	Notes
Adverse Event Reporting						
Monitor for Non-Serious Adverse Events (NSAEs)	Collection of NSAEs begins at initiation of study ~~drug.~~**treatment and continues throughout the study and until 30 days following the last dose**. Participants ~~that~~**who** discontinue ~~early~~**study treatment** should ~~receive a follow-up phone call~~**have an assessment of AEs** 30 days after last dose.[e]					
Monitor for Serious Adverse Events (SAEs)	~~See notes~~**Following written consent to participate** in **the study, all SAEs whether related or not related to study treatment that occur during the** screening ~~procedures~~**period** , **continuously throughout the study, and until 30 days following the last dose should be monitored and recorded. Participants who discontinue study treatment should have an assessment of SAEs 30 days after last dose.** [e]					

[e] This 30-day assessment of AEs/SAEs may be done by phone if no visit occurs.

Rationale: Clarified the language in the protocol that specifies the timelines during which AEs and SAEs are being collected.

This change also affects Section 5.1.5, Discontinuation of Study treatment and/or Study Withdrawal; and Section 10.1, Time Period and Frequency for Collecting AE and SAE Information

Section 2, Schedule of Activities (Table 2)

Change: The table was revised to remove the dispensation of study treatment during the Week 52 visit in the double-blind period.

Now reads:

Table 2: Double-Blind Procedural Outline

Procedure[a]	**Week 0 (Day 1)**	**Weeks 4, 8, 16, 20, 28, 32, 40, 44**[b] **(±3 days)**	**Weeks 12, 24, 36 (±3 days)**	**Week 48 (±3 days)**	**Week 52 (±3 days)**	**Early Discontinuation**[c,d]	**Notes**
Clinical Drug Supplies							
Dispense Study ~~Drug~~**Treatment**	X	X	X	X	~~X~~		Duration of infusion will be at least 1 hour.

Rationale: Corrected table to be consistent with Study Synopsis and protocol which stated that participants will receive "last dose of the double-blind study treatment administered at Week48".

Section 2, Schedule of Activities (Table 3)

Change: The table was revised to include the dispensation of study treatment during the Week 52 baseline visit in the open-label extension period.

Now reads:

Table 3: Extension Period Procedural Outline

Procedure	**Week 52**	**Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, and 192[a]** **(±7 days)** ~~4, 8, 16, 20 week intervals after Week 52[a,b]~~	**Weeks 64, 88, 112, 136, 160, 184[e]** **(±7 days)** ~~24 week intervals after Week 52[d]~~	**Weeks 76, 100, 124, 148, 172, 196[d]** **(±7 days)** ~~24 week intervals after Week 52[d]~~	Early Discontinuation[b]	Notes
Clinical Drug Supplies						
Dispense Study ~~Drug~~**Treatment**	**X**	X	X	X		Duration of infusion will be at least 1 hour.

Rationale: Clarified that participants who continue in the open-label extension period will receive the first dose of the open-label study treatment at Week 52.

This change also affects Section 5.1.1, Overall Study Design.

Section 3, Introduction

Change: Text introducing tau, tau pathology, PSP disease, and BIIB092 function was updated.

Now reads:

~~BIIB092 (formerly referred to as BMS-986168 and IPN007) is a humanized monoclonal antibody (mAb) of subclass~~ **Progressive supranuclear palsy (PSP) is a rare neurodegenerative disorder that leads to death in an average of 7 years following symptom onset [Williams 2005]. The National Institute of Neurological Disorders and Stroke (NINDS), the National Organization for Rare Disorders (NORD), and the European Organisation for Orphan Diseases estimate the prevalence of PSP to be between 3 and 6 per 100,000 persons. Both the NINDS and NORD estimate that there are approximately 20,000 cases of PSP in the United States and 30,000 in the European Union, while there are thought to be approximately 17,000 cases in Japan [Takigawa 2016].**

The disease is characterized by progressive aberrations in gait, eye movements, dysphagia, dysarthria, pseudobulbar affect, neuropsychiatric abnormalities, and dementia, as well as difficulties with sleep [Boxer 2017, Nath 2003]. Since the syndrome was first characterized

in 1963, it is now recognized that there are a number of different clinical presentations that appear to be linked to the regional distribution and severity of pathology in the brain [Williams 2007]. There is currently no treatment available to stop or slow the progression of this deadly disease.

The neuropathological hallmark of PSP is the presence of neurofibrillary tangles in clinically correlated regions of the brain, including the basal ganglia, diencephalon, brainstem, and cerebellum with restricted involvement of the neocortex [Dickson 2010]. The tangles are composed of tau, an intracellular microtubule-associated protein, of which fragments may also be released into the cerebrospinal fluid (CSF) and interstitial space as N-terminal tau [Bright 2015, Guo 2017]. Tau dysfunction is thought to play a key role in the pathophysiology of PSP, both by causing neuronal dysfunction via tau aggregation into neurofibrillary tangles and by facilitating cell to cell spreading of tau pathology via secreted N-terminal tau.

BIIB092 is a humanized monoclonal antibody (mAb) that binds to amino acid residues 15 to 22 of N-terminal tau, removing it from the CSF. It is hypothesized that BIIB092-mediated depletion of N-terminal tau will inhibit the spread of tau pathology, potentially slowing the progression of PSP. This would be expected to translate into important improvements in function, activities of daily living, health outcomes, and overall quality of life for patients living with PSP.

~~immunoglobulin (Ig) G4 that recognizes human extracellular tau (eTau). It is currently being evaluated as a treatment for Progressive Supranuclear Palsy (PSP).~~

~~Although tau is primarily an intracellular protein, a small amount of tau is secreted. eTau refers to the extracellular, soluble fragments of tau that contain an intact amino terminal and are truncated prior to the beginning of the first microtubule binding domain of tau. eTau produces disruptions in neuronal activity in vitro. eTau is believed to play two roles in the pathophysiology of PSP. First, eTau may cause neuronal dysfunction directly, and second, eTau may be partially responsible for the spreading of tau pathology that is observed in human tauopathies, such as PSP.~~

~~PSP is a neurodegenerative disease characterized by atypical Parkinsonism for which there are no approved or effective treatments. At autopsy, insoluble tau aggregates are found throughout the brain within neurons and glia, most notably in the brainstem, deep cerebellar nuclei, basal ganglia, and neocortex [Dickson 2012; Dickson 2010; Steele 1964]. Symptoms of PSP include early and severe gait instability with falls, greater slowing of vertical than horizontal saccadic eye movements, slowed movement, rigidity of the axial musculature, dysphagia, dysarthria, pseudobulbar affect, neuropsychiatric abnormalities, and dementia [Boxer 2014; Golbe 2014; Steele 1964]. Survival time from symptom onset for PSP patients ranges from 5.3 to 9.7 years with a typical figure of 7.4 years from symptom onset. PSP has a prevalence ranging between 1 to 9 cases per 100,000 individuals. The mean age of diagnosis is around 63 years [Boxer 2014; Golbe, 2014; Nath 2001]. No medications have been approved for PSP. There is a significant~~

~~unmet medical need to develop therapies that can either alleviate or slow the relentless worsening of PSP symptoms.~~

~~In a transgenic mouse tauopathy model, the murine analog of BIIB092 slowed the progression of locomotor impairment and limited the spreading of tau pathology. In non-human primates, BIIB092 reduced cerebrospinal fluid (CSF) concentrations of free eTau. Administration of single doses of BIIB092 is safe and well tolerated in normal healthy volunteers (NHVs). In addition, administration of multiple doses of BIIB092 is safe and well tolerated in participants with PSP. In both NHVs and participants with PSP, BIIB092 reduces CSF concentrations of free eTau in a dose-dependent fashion. These findings suggest that BIIB092 may have utility for the treatment of human tauopathies, such as PSP.~~

Rationale: Clarified the terminology, background, and rationale in using BIIB092 as a treatment for PSP. Clarified that the amino acid residues involved in BIIB092 were corrected from "15 to 24" to "15 to 22".

Section 3.3, Benefit/Risk Assessment

Change: The number of subjects who have been exposed to BIIB092 has been updated.

Now reads:

BIIB092 is a humanized IgG4 isotype antibody that is considered to have a low potential for immunogenicity in humans based on nonclinical studies. There were no adverse effects noted at any dose tested in the pivotal toxicity studies in monkeys. Nonclinical findings were limited to decreases in CSF unbound N-terminal tau consistent with the intended pharmacology of BIIB092. **In completed clinical study CN002001, there was no consistent trend showing a potential effect of anti-drug antibody (ADA) on the PK of BIIB092. In completed clinical study CN002003, there was no apparent dose-related trend in the number of subjects with positive immunogenicity results post-treatment.**

Studies evaluating the potential for reproductive and developmental toxicity have not been performed for BIIB092.

As of ~~July 31, 2017, 114 subjects~~**25 November 2018, an estimated 486 participants** have been exposed to BIIB092 across all completed **(Studies CN002001 and CN002003)** and ongoing clinical studies (Studies ~~CN002001, CN002003,~~ 251PP201, ~~and~~ 251PP301~~).~~**, and 251AD201).** Based on safety data from a completed Phase 1 study in healthy volunteers (Study CN002001) and a completed Phase 1B study in participants with PSP (Study CN002003), the ~~majority of adverse events (AEs) reported to date have been mild to moderate in severity and transient in nature. There have been no deaths or discontinuations due to an AE reported in the program. There have been 4 serious AEs (SAEs) reported in 3 participants in Study CN002003, all of which were considered not related to study drug by the Investigator~~**benefit-risk profile of BIIB092 was favorable to support further clinical development**.

Rationale: Updated the information based on clinical trial exposure and safety data available as of 25 November 2018, to provide the most recent information.

Section 5, Study Design

Change: A substudy was added to assess changes in motor function and related activities of daily living in study participants during the open-label extension period, for long-term follow-up.

Now reads:

Section 5.2. Substudy Design

This study includes an optional substudy to measure QMAs using wearable sensors. The QMAs will measure gait, postural instability, motor function, and falls in a subset of participants participating in the long-term extension period.

Study participants included in this substudy will be from selected countries, and participants will be required to ambulate independently or with assistive devices. Participants will participate in the QMA substudy for 6 months, with in-clinic assessments of gait, postural instability, and motor function conducted every 3 months. Falls will be assessed continuously in the home using wearable sensors for 6 months to capture and quantify falls. The QMA substudy baseline visit will be conducted after participants sign the informed consent form and are eligible to enroll in the substudy. Two follow-up visits will be conducted at 3 and 6 months after the baseline visit of the QMA substudy. If a participant at a selected site is unwilling to participate in the QMA substudy, they can still participate in the open-label extension study.

Rationale: The QMA substudy in the open-label extension period was added to further characterize disease progression with wearable sensors. Postural instability, gait disturbances, and falls are prominent signs of PSP that affect participant outcomes. At present, these signs are assessed in the clinic with questionnaires. It is anticipated that advances in wearable sensor technology and analytics could improve quantification of these signs and may provide sensitive measures of disease progression.

This change also affects: Section 2, Schedule of Activities (Table 4); Section 5.1.3, Study Assessments; Section 5.6, Scientific Rationale for Study Design; Section 9.1, Efficacy Assessments; Appendix 1, Abbreviations and Trademarks

Section 6.1.1, Signed Written Informed Consent

Change: Content was added to detail consent provided by a legally authorized representative when the patient is unable to physically sign the consent form.

Now reads:

6.1.1. Signed Written Informed Consent

1. Participants, or a legally authorized representative (where local regulations and institutional practices permit), must have signed and dated an Institutional Review Board

(IRB)-/Independent Ethics Committee (IEC)-approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal participant care.

2. **The investigator must obtain consent consistent with the applicable legal, regulatory, and institutional policy requirements and specifically, taking into account the participant's state of disease progression and its impact on the participant's cognitive and motor abilities.**

3. **In the event that the study participant is unable to sign and date the informed consent form, a legally authorized representative, permitted to act on behalf of the participant in the context of this study, may provide consent on behalf of the participant.**

Rationale: Clarified the consent procedures for those participants who are able to give consent but who are unable to physically sign a consent form due to progression of disease.

Section 7, Treatment (Section 7.5, Preparation/Handling/Storage/Accountability)

Change: Language regarding the composition, preparation, handling, storage, and accountability of the BIIB092 study treatment was modified to refer to the Directions for Handling and Administration (DHA).

Now reads:

Study treatment will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice.

BIIB092 is supplied as a liquid drug product in glass vials containing an extractable dose per the Directions for Handling and Administration (DHA). The contents of the BIIB092 label will be in accordance with all applicable regulatory requirements. BIIB092 should not be used after the expiration date.

BIIB092 must be stored refrigerated between 2°C and 8°C with protection from light. The placebo will be supplied locally and stored according to the packaging specifications. Study treatment not supplied by Biogen will be stored in accordance with the package insert.

~~The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study Participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.~~

The product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by ~~Biogen.~~ **the**

DHA. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed, and Biogen should be contacted immediately.

The study treatment should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that study treatment is only dispensed to study participants. The study treatment must be dispensed only from official study sites by authorized personnel according to local regulations.

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, storage, and disposal of the study treatment. The DHA will also describe the masking of the IV bags of study treatment (both BIIB092 and placebo) to maintain the treatment blind. The DHA supersedes all other references (e.g., protocol or Investigator's Brochure).

Investigational product documentation (whether supplied by Biogen or not) must be maintained to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g., required diluents, administration sets).

~~Please refer to the current version of the Investigator Brochure and pharmacy manual for complete storage, handling, dispensing and infusion information for BIIB092.~~

~~Further guidance and information for final disposition of unused study treatment are provided in Appendix 2 and the pharmacy manual.~~

Rationale: Clarified that the DHA manual is to be followed as guidance for study site staff regarding handling, preparation, administration, storage, and disposal of the study treatment.

This change also affects Section 7, Table 6.

Section 8, Discontinuation Criteria

Change: This change identifies the discontinuation criteria for the study participants who discontinue study treatment but remain in the study and for the study participants who discontinue study treatment and withdraw early from the study.

Now reads:

8.1 Discontinuation From Study Treatment

Participants MUST discontinue ~~investigational product~~**study treatment** (and non-~~investigational product~~ **IP** at the discretion of the Investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who ~~request to~~ discontinue study treatment ~~will~~**and** remain **enrolled** in the study ~~and must continue to~~ **will** be ~~followed for protocol specified follow-up procedures. The only exception to~~

~~this~~**expected to complete scheduled safety and efficacy evaluations until the decision** is ~~when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information~~**made to withdraw from the study.**

- Any clinical ~~adverse event (~~AE~~),~~**,** laboratory abnormality**,** or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the participant

- Termination of the study by Biogen

- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness

~~Refer to the Schedule of Activities (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.~~

In the case of pregnancy, the Investigator must immediately notify the Medical Monitor of this event~~. In the event a normal healthy female participant becomes pregnant during a clinical trial, the~~ **and** study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant safety). Please call the Medical Monitor within 24 hours of awareness of the pregnancy. If the Investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the Investigator and the Medical Monitor/designee must occur.

~~All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).~~

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate ~~case report form (~~CRF~~)~~ page.

8.2 Study Follow Up

In this study, safety is a key endpoint of the study. ~~For participants who discontinue study treatment during the double-blind period of the study (prior to Week 52):~~

Study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study.

Participants who discontinue study treatment and remain in the study will be expected to complete scheduled safety and efficacy tests and assessments until the end of study or withdrawal of consent (see Table 2 and Table 3). Participants who discontinue study treatment and remain in the study should have all AEs collected up to 30 days after the last dose of study treatment. AE collection should continue until the end of study or withdrawal from the study.

At any point after discontinuing study treatment, if the participant makes the decision to withdraw from the study (Section 8.2), the following should be done:

- Early Discontinuation visit procedures (~~Table 2~~) should be completed.
- Participants and/or caregivers should receive a follow-up phone call approximately 30 days after ~~last dose~~ **discontinuation of study treatment** to collect relevant clinical information, including, but not limited to ~~safety data (i.e., AEs, SAEs) and vital status (e.g., ability to ambulate, cognitive disability, speech, dysphagia, dependence on wheelchair for mobility, placement in residential care, and death).~~
- ~~If possible, participants who discontinue study treatment should be encouraged to return to the clinic at Week 52 to complete Week 52 visit procedures. If the visit cannot be done in person by the participant, the site should attempt a phone call at approximately Week 52 to collect at a minimum vital status and SAE/AE information on the participant.~~

~~For participants who discontinue study treatment during the open-label extension period of the study (after Week 52):~~

- ~~Early Discontinuation visit procedures (Table 3) should be completed.~~
- ~~Participants and/or caregivers should receive a follow-up phone call approximately 30 days after last dose to collect relevant clinical information, including but not limited to~~, safety data (i.e., AEs, SAEs) and vital status (e.g., ability to ambulate, cognitive disability, speech, dysphagia, dependence on wheelchair for mobility, placement in residential care, and death**)**

~~Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 2 until death or the conclusion of the study.~~

8.3 Withdrawal From the Study

Participants who request to ~~discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up~~**withdraw from the study should complete the Early Discontinuation visit** procedures **(Table 2 and Table 3**).

Rationale: Clarified criteria for participants, to provide clear instructions on clinic visit participation, scheduled assessments, and monitoring of AEs as defined by whether the study participants discontinue from study treatment and either remain in the study or withdraw from the study.

This change also affects Section 2, Schedule of Activities (Table 2, Double-blind Period Procedural Outline, Notes; Table 3, Extension Period Procedural Outline, Notes), and Section 5.1.5, Discontinuation of Study Treatment and Withdrawal.

Section 15, Other Assessments

Change: Section 15.1 was added to include different PSP clinical phenotypes.

15.1 PSP phenotypes

Based on participant's medical history, Investigators will be asked to provide the participant's clinical phenotype as outlined in the Movement Disorder Society-PSP criteria [Höglinger 2017].

- **PSP with predominant Richardson-syndrome**
- **PSP with predominant ocular motor dysfunction**
- **PSP with predominant postural instability**
- **PSP with predominant Parkinsonism**
- **PSP with progressive gait freezing**
- **PSP with predominant frontal presentation**
- **PSP with predominant speech/language disorder**
- **PSP with predominant corticobasal syndrome**

Rationale: The text was added to outline PSP clinical phenotypes to aid the Investigator in selecting the PSP phenotype based on the participant's medical history.

SUMMARY OF CLARIFICATIONS TO THE PROTOCOL

In addition to the major changes described above, the following clarifications were made. These changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 2, Schedule of Activities (Table 2)

Change: The table was revised to clarify that CGI interview collected from Week 36 will be used to assign the Week 48 SEADL score.

Now reads:

Table 2: Double-Blind Procedural Outline

Procedure[a]	Week 0 (Day 1)	Weeks 4, 8, 16, 20, 28, 32, 40, 44[b] (±3 days)	Weeks 12, 24, 36 (±3 days)	Week 48 (±3 days)	Week 52 (±3 days)	Early Discontinuation[c,d]	Notes
Efficacy Assessments							
SEADL Phonemic Fluency, Letter-Number Sequencing, Color Trails Test, MoCA	X		X	X[f]			

[f] **CGI interviews collected from Week 36 will be used to review all areas of the functioning section (including complex daily activities and basic functions) and will be used to determine whether there have been any changes or additions to the functioning at the Week 48 visit, with both the caregiver and participant independently. This will be used to assign the Week 48 SEADL score.**

Rationale: Clarified that the Week 48 CGI interview with the participant and caregiver would not be collected and that the participants Week 48 SEADL score would be scored based on the Week 36 CGI interview. These changes are intended to facilitate the accurate completion of study efficacy assessments.

Section 2, Schedule of Activities (Table 3)

Change: The table was clarified to include the schedule for home visits. Scheduled visits were clarified to indicate the "week of visit" instead of "visit intervals."

Now reads:

Table 3: Extension Period Procedural Outline

Procedure	**Week 52**	**Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, and 192[a,b]** **(±7 days)** ~~4, 8, 16, 20 week intervals after Week 52[a,b]~~	**Weeks 64, 88, 112, 136, 160, 184[c]** **(±7 days)** ~~12 week intervals after Week 52[c]~~	**Weeks 76, 100, 124, 148, 172, 196[d]** **(±7 days)** ~~24 week intervals after Week 52[d]~~	Early Discontinuation[b]	Notes
Clinical Drug Supplies						
Dispense Study ~~Drug~~**Treatment**	**X**	X	X	X		Duration of infusion will be at least 1 hour.

[a] **Weeks 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, and 192 may qualify for home** visit**s if appropriate** ~~starting at Week 68.~~ See Section 5.1 for details.

[b] ~~Visit intervals of 4, 8, 16, and 20 after Week 52 (e.g., Weeks 56, 60, 68, 72, 80, 84, 92, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, and 192.~~

[c] ~~Visit intervals of 12 weeks after Week 52 (e.g., Weeks 64, 88, 112, 136, 160, and 184).~~

[d] ~~Visit intervals of 24 weeks after Week 52 (e.g., 76, 100, 124, 148, 172, and 196).~~

[b] **Participants who discontinue study treatment during the open-label extension period of the study (after Week 52) but remain enrolled in the study will be expected to complete scheduled safety and efficacy evaluations at Weeks 64, 76, 88, 100, 112, 124, 136, 148, 160, 172, 184, and 196.**

[c] Sample to be collected predose.

[d] **This 30-day assessment of AEs/SAEs may be done by phone if no visit occurs.**

Rationale: Clarified that the home visits started from Week 68 and not from Week 56 in the open label extension period. Visit intervals were updated to the week of visit to facilitate the accurate completion of study visits and improve conformity in the document.

This change also affects Section 5.1.4.

Section 4, Study Objectives and Endpoints

Change: The pons region of the brain was added in the list of baseline brain volume assessments as a secondary objective for the study.

Now reads:

Objective	**Endpoint**
Other Secondary	
To assess the efficacy of BIIB092, relative to placebo, as measured by absolute and percent change from baseline of brain volumes, as determined by magnetic resonance imaging (MRI), at Week 52 in the following regions: • Ventricles • Whole brain • Midbrain • **Pons** • Superior cerebellar peduncle • Third ventricle • Frontal lobe	The impact of BIIB092 on brain volumes, as determined by MRI in the following regions: • Ventricles • Whole brain • Midbrain • **Pons** • Superior cerebellar peduncle • Third ventricle • Frontal lobe will be evaluated relative to the absolute and percent changes from baseline at Week 52 ~~of~~ **in** the ~~drug~~**BIIB092**-treated participants **and compared** to that of the placebo-treated participants.

Rationale: Updated the comprehensive assessment of the impact of BIIB092 on brain volumes as determined by MRI, by including all areas of the brain assessed.

Section 11, Pharmacokinetic (Table 9)

Change: The table was simplified by presenting the Week 56 predose estimated sample collection time in place of the Week 52 postdose estimated sample collection time. Visit intervals were presented as corresponding weeks of visit.

Now reads:

Table 9: Pharmacokinetic Sampling Schedule

Study Week of Sample Collection	Event	Estimated Time (Relative to start of Infusion of BIIB092) Hour: Min	BIIB092 Blood Sample for Serum	BIIB092 CSF Sample[a]
Week 0 (Day 1)	Predose	00:00	X	X
Week 0 (Day 1)	EOI[b]	01:00	X	
Week 4	Predose	00:00	X	
Week 4	EOI[b]	01:00	X	
Week 12	Predose	00:00	X	
Week 24	Predose	00:00	X	
Week 24	EOI[b]	01:00	X	
Week 36	Predose	00:00	X	
Week 48	Predose	00:00	X	
Week 48	EOI[b]	01:00	X	
Week 52	Predose	00:00	X	**X**
~~Week 52~~ **Week 56**	~~Postdose~~[c] **Predose**	~~672:00~~ **00:00**	X	~~X~~
~~24 week intervals after Week 52~~ **Weeks 76, 100, 124, 148, 172, and 196**[d]	Predose	00:00	X	Week 100 only

CSF = cerebrospinal fluid; EOI = end of infusion.

[a] Collect at the time of LP ([redacted]).

[b] This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of **the** infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] **The** ~~Week 52 sampling at 672 hr after Week 52 dosing is the~~ scheduled predose sampling at Week 56 **is also the Week 52 postdose sampling (672 hours after Week 52 dosing).**

[d] **Visit intervals of 24 weeks after Week 52 (Weeks 76, 100, 124, 148, 172, and 196).**

Rationale: The Week 52 postdose sampling was the same sampling as that for Week 56 predose sampling and for clarity in presenting the sampling hours, Week 52 postdose was replaced by Week 56 predose in the table. CSF sample was collected at Week 52. Visit intervals were updated to the week of visit to facilitate the accurate completion of study visits and improve conformity in the document.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- Section 10.15, Safety (in Section 10: Adverse Events) was moved to Section 9.2: Safety Assessments (in Section 9: Study Assessments and Procedures)
- Section 5.3, Data Monitoring Committee and Other External Committees: updated information regarding reviewing unblinded data
- Section 5.7, Justification for Dose: deletion of dose and CSF eTau suppression data related to Study IPN-T3
- Section 7, Treatment: addition of information regarding rescue medication (epinephrine) that will be dispensed for home care for use in the event of an allergic reaction
- Section 6.2, Exclusion Criteria, and Section 7.7.1, Prohibited and/or Restricted Treatments: addition of hypnotics for sleep in the list of treatments allowed
- Section 14, Immunogenicity Assessments: clarification/revision from "discontinue" to "withdraw" in participants with ADA titers that are not stable
- Section 17.2, Populations for Analyses: clarification that additional analysis populations will be in the SAP and revision of mITT to ITT only (not modified intention-to-treat)
- Section 17.3, Handling of Missing Data: clarification that percentage of patients who withdrew (not discontinued) over time through Week 52 will be summarized.
- Section 17.4.1, Efficacy Analyses: clarification that efficacy analyses will be performed using the ITT population (not mITT) and revisions on the statistical analysis methods to be performed on the primary efficacy endpoints
- Section 17.4.1, Efficacy Analyses: clarification that in the MMRM model for the primary analysis of primary endpoint, the interaction between baseline value and visit is also added in to the MMRM model.
- Section 17.4.1, Efficacy Analyses: in the analysis summary table of the primary endpoint, the MMRM analysis for participants with complete data is removed.
- Section 17.4.1, Efficacy Analyses: the types and order of structures tested if analysis fails to converge was updated.
- Section 18, References: updates made re: new and deleted literature entries

- Appendix 1: updates on the list of abbreviations
- Appendix 2: updates on Subject Information and Consent
- The version number and date were revised throughout the protocol.
- The Table of Contents was updated.
- The term “subject/patient” was changed to “participant” pursuant to uniformity where applicable.
- The term “withdrawn from study” was used where applicable for participants who were no longer enrolled in the study.
- Reference to study “phase” was changed to “period” pursuant to uniformity where applicable.
- The term “study drug” was changed to “study treatment” pursuant to uniformity where applicable.
- The term “extracellular tau/eTau” was updated to “N-terminal tau” where applicable.
- The term free “N-terminal tau” was updated to unbound “N-terminal tau” where applicable.
- Minor editorial changes were made.
- Typographical and formatting errors were corrected.

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AMENDMENT SUMMARY

Biogen Protocol 251PP301

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Intravenously Administered BIIB092 in Participants with Progressive Supranuclear Palsy

Version 6

Date: 24 May 2018

EUDRA CT Number: 2016-002554-21

Version 6 of the protocol has been prepared for this amendment, which supersedes Version 5.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 251PP301was to correct an error.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 6.2, Exclusion Criteria

Change: The definition of 1 criterion (w/*i*) was revised.

Now reads:

w. Current hepatitis C or hepatitis B infection

i) Current hepatitis C infection (defined as positive HCV antibody and detectable HCV RNA). Participants with ~~negative~~ **positive** HCV antibody and undetectable HCV RNA are eligible to participate in the study (US Centers for Disease Control and Prevention).

ii) Current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or hepatitis B core antibody [anti-HBc]). Participants with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive anti-HBc, and positive hepatitis B surface antibody [anti-HBs]) or vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study (US Centers for Disease Control and Prevention).

Rationale: This change was necessary to correct an error in the decision criteria that would allow a participant who no longer has an active hepatitis C infection to enroll in the study.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

[redacted]

Now reads:

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Rationale: [redacted]

This change also affects Section 5.5.2 (Rationale for Inclusion of Key Biomarkers).

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

- The version number and date were revised throughout the protocol.
- The Table of Contents was updated.
- Typographical and formatting errors were corrected.

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AMENDMENT SUMMARY

Biogen Protocol 251PP301

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Intravenously Administered BIIB092 in Participants with Progressive Supranuclear Palsy

Version 5

Date: 16 May 2018

EUDRA CT Number: 2016-002554-21

Version 5 of the protocol has been prepared for this amendment, which supersedes Version 4.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 251PP301is an increase in the study sample size.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 17.1, Sample Size Determination

Now reads:

Approximately ~~396~~**459** participants will be randomly assigned, in a 2:1 ratio, to receive BIIB092 or placebo (~~264~~**306** participants in the BIIB092 treatment group and ~~132~~**153** in the placebo group). Anticipating a dropout rate of approximately 25% (based on previous clinical studies in participants with PSP), approximately ~~297~~**345** participants (~~198~~**230** participants in the BIIB092 treatment group and ~~99~~**115** participants in the placebo group) are expected to complete the study through Week 52.

Using a two-sided, two-sample t-test, with an alpha level set at 0.05, this sample size will provide ~~90~~**80**% power to detect a difference of ~~4.0~~**3.2** points in the change in PSPRS total score from baseline to Week 52 for BIIB092 relative to placebo, assuming a common standard deviation of 9.95 [Stamelou 2016] in the change in PSPRS total score from baseline to Week 52.

Rationale: Preliminary market research conducted with experts in the field indicates that a difference of 2.5 to 3.5 points in the primary efficacy endpoint (the Progressive Supranuclear Palsy Rating Score [PSPRS]) would represent a clinically meaningful treatment effect at 52 weeks. The sample size has been increased by approximately 15% to improve the estimated power of the study to detect a between-treatment difference in PSPRS of that magnitude.

This change also affects Section 5.1, Overall Design (including Figure 1); and Section 5.3, Number of Participants.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 1, Synopsis

The Synopsis was revised to reflect changes made throughout the protocol.

Section 4, Study Objectives and Endpoints

Change: Efficacy and safety objectives and endpoints for the open-label extension period were added.

Now reads:

Open-Label Extension Period	
To assess the long-term safety and tolerability of BIIB092 in participants with PSP.	**The tertiary endpoint will be incidence of AEs, SAEs, and SAEs accompanied by death.**
To assess the long-term efficacy of BIIB092 in participants with PSP.	**The tertiary endpoints will be change from baseline over the placebo-controlled period and long-term extension period for clinical and health-outcomes assessments.**

Rationale: The objectives and endpoints of the extension period were not previously stated.

Section 6.4.1, Retesting During Screening or Lead-In Period

Change: Improper reference to "re-enrollment" of participants who failed a previous screening was corrected, and the role of the Medical Monitor in determining testing requirements for re-screening was made clear.

Now reads:

Participant Re-~~enrollment~~**screening**: This study permits the re-~~enrollment~~**screening** of a participant ~~that~~ **who** ~~has discontinued the study as a pre-treatment failure~~ **screen-failed** up to 2 times (i.e., participant ~~h~~**w**as not ~~been~~ randomized ~~/ has not been~~ **or** treated). If re-~~enrolled~~**screened**, the participant must be re-consented. **The assessments to be conducted on re-screening will depend upon how much time passed since the previous Screening Visit. Please contact the Medical Monitor for guidance regarding the acceptability of any previous assessments completed.**

Rationale: Participants who failed screening previously are being re-screened, not re-enrolled. Consultation with the Medical Monitor will facilitate the determination of assessments that need to be repeated for effective re-screening and avoidance of unnecessary, intrusive testing.

[redacted]

Change: [redacted]

Now reads:

[redacted]

[redacted]

[redacted]

Rationale: The text was updated to reflect current policies and operational requirements.

Section 17.4.3, Interim Analysis

Change: An allowance was made for a possible interim analysis of study data during the double-blind treatment period.

Now reads:

An interim analysis for superiority may be performed before the last participant has had the opportunity to complete the Week 52 visit. An alpha spending function approach will be used for the analysis. In order to maintain the treatment blind in the event of this interim analysis, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim superiority analysis. The independent group will present the unblinded interim analysis to the DMC. The aim of this interim analysis is to allow the possibility to demonstrate treatment effect early. The analysis (including the details of the alpha spending approach) will be discussed in detail in the statistical analysis plan.

Rationale: Pursuant to responsible study management, an interim analysis may be justified to evaluate an apparent superiority of effect (or a safety concern) before 52 weeks of treatment have been completed.

SUMMARY OF CLARIFICATIONS TO THE PROTOCOL

In addition to the major changes described above, the following clarifications were made. These changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 2, Schedule of Activities (Table 1, Notes)

Change: The responsibility of the caregiver to accompany the participant to study visits was clarified in the Notes to the table.

Now reads:

Informed Consent for Caregiver	X	Caregiver is defined as th~~e~~**at** person ~~that~~**who** accompanies participant to ~~all/most~~ study visits and has frequent contact with participant of at least 3 hours per week at one time or at different times. **Only one caregiver can be designated for participant at a given time. At a minimum, caregiver should personally attend the following study visits: Screening, Baseline, Weeks 12, 24, 36, 48, 52, and Early Discontinuation. Although caregiver assessments cannot be conducted by telephone, caregiver should be available for telephone consultation regarding information on AEs and SAEs when not otherwise attending a scheduled visit.**

Rationale: This revision is intended to make certain that the caregiver is clearly advised of the importance of their commitment to proper conduct of the study.

This change also affects Table 3 (Extension Period Procedural Outline) and Section 6.1 (Inclusion Criteria, 1*d* and 2*g*).

Section 2, Schedule of Activities (Table 1, Footnote *a*)

Change: The timeframe during which Screening procedures may be conducted was clarified.

Now reads:

[a] **Screening procedures may be conducted ~~W~~w**ithin 42 days prior to first dose unless otherwise specified.

Rationale: This revision is intended to make certain that the Investigator is advised of flexibility regarding the completion of Screening procedures.

Section 2, Schedule of Activities (Table 2, Notes)

Change: The duration of BIIB092 infusion was clarified.

Now reads:

Dispense Study Drug	X	X	X	X	X		Duration of infusion will be ~~approximately~~ **at least** 1 hour.

Rationale: This revision is intended to make certain that the Investigator is advised that the infusion is not required to be completed within approximately 60 minutes.

This change also affects Section 2 (Schedule of Activities, Table 3, Notes) and Section 11 (Pharmacokinetic, Table 7, Pharmacokinetic Sampling Schedule).

Section 2, Schedule of Activities (Table 2, Footnotes *a & b*)

Change: The flexibility associated with the conduct of certain study visits was stated more explicitly.

Now reads:

[a] Efficacy assessments requiring ~~subject~~ **participant** ~~participation~~ **involvement** should be completed prior to dosing with study treatment unless otherwise specified in the notes~~.~~**; specific attention should be paid to conducting the Week 24 MRI within 7 days prior to the Week 24 dosing visit. The study visits at Weeks 0, 12, 24, 36, 48, 52, and Early Discontinuation, which involve the conduct of efficacy assessments, may be completed over a period of up to 3 consecutive days.**

[b] **Weeks 28, 32, 40, and 44 ~~M~~m**ay qualify for home visit if appropriate. See Section 5.1 for details.

Rationale: These changes are intended to facilitate the completion of certain study visits and improve procedural conformity regarding those visits involving efficacy assessments.

Section 5.5.2, Rationale for Inclusion of Key [redacted]

Change: The need for compliance with local regulatory and institutional requirements in the practice of [redacted] and pharmacogenetic analysis was explicitly recognized.

Now reads:

All participants will have blood collected for assessment of serum concentrations of [redacted] determined at baseline and at regular intervals during the study to confirm target engagement.

~~In addition~~**Where local regulations and institutional approvals allow**, a deoxyribonucleic acid (DNA) sample will be ~~collected~~**prepared** to support future studies examining the relationship between H1 and H2 haplotypes on tau protein levels.

Rationale: This change was made to formalize recognition of jurisdictional differences in the acceptability of collecting biological samples for exploratory research and the rights of participants who may choose to provide those samples.

Section 6.1, Inclusion Criteria

Change: Acceptability of consent provided by a legally authorized representative was recognized in 1 criterion (1*a*), and greater allowance was made for dose stabilization of select concomitant medications in 2 criteria (2*j* and *k*).

Now reads:

a. Participants**, or a legally authorized representative (where local regulations and institutional practices permit),** must have signed and dated an Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal ~~subject~~**participant** care.

j. If participant is receiving coenzyme Q10, levodopa/carbidopa, levodopa/benserazide, fava bean extract, a dopamine agonist, catechol-~~0~~**O**-methyltransferase inhibitor, amantadine, or other Parkinson's disease medications, the dose must have been stable for at least 60 days prior to ~~screening~~**baseline** and expected to remain stable for the double-blind period of the study.

k. Stable on other chronic medications for at least 30 days prior to ~~screening~~**baseline**.

Rationale: The intent of the change in criterion 1*a* is to allow for the involvement of those participants who can no longer consent freely due to progression of disease; the intent of the change in criteria 2*j* and 2*k* is to avoid unnecessary screening failures by allowing additional time to stabilize the dosing of chronic medications.

Section 6.2, Exclusion Criteria

Change: Under Subsection 1 (Medical Conditions), 4 criteria were revised (*a*, *e*, *l*, and *q*) and 1 criterion was added (*w*); under Subsection 2 (Prior/Concomitant Therapy), 2 criteria were revised (*a* and b); and, under Subsection 3 (Physical and Laboratory Test Findings), 1 criterion was deleted (*i*).

Now reads:

1. Medical Conditions

    a. Presence of other significant neurological or psychiatric disorders including (but not limited to) Alzheimer's disease, dementia with Lewy bodies; prion disease, Parkinson's disease (which has not subsequently been revised to a diagnosis of PSP); any psychotic disorder; severe bipolar or unipolar depression; ~~prior history of suicidal thoughts or behavior that are believed to represent a current safety risk;~~ seizure; brain tumor or other space-occupying lesion; history of **clinically significant** stroke **(e.g., stroke with neurological deficit)**; history of head injury with loss of consciousness for at least 15 minutes within the past 20 years.

e. History of or screening brain MRI scan indicative of significant abnormality, including, but not limited to, prior hemorrhage or infarct >1 cm^3, ≥3 lacunar infarcts, cerebral contusion, ~~encephalomalacia,~~ aneurysm, vascular malformation **>1cm^3**, subdural hematoma, hydrocephalus, space-occupying lesion (e.g., abscess or brain tumor ~~such as meningioma~~).

l. [redacted]

q. Any vaccination within 30 days prior to screening. **Vaccination may be allowed during the study according to guidance issued to study sites by the Sponsor; if necessary, please contact the Medical Monitor for that guidance.**

w. Current hepatitis C or hepatitis B infection

i) Current hepatitis C infection (defined as positive for HCV antibody and detectable HCV RNA). Participants with negative HCV antibody and undetectable HCV RNA are eligible to participate in the study (US Centers for Disease Control and Prevention).

ii) Current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or hepatitis B core antibody [anti-HBc]). Participants with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive anti-HBc, and positive hepatitis B surface antibody [anti-HBs]) or vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study (US Centers for Disease Control and Prevention).

2. Prior/Concomitant Therapy

a. Within 4 weeks of screening (first visit) or anticipated during the 52-week double blind period of the study, concurrent treatment with memantine; acetylcholinesterase inhibitors, antipsychotic agents or mood stabilizers (e.g., valproate, lithium); or benzodiazepines, with the following exceptions:

i) Low dose lorazepam or other short-acting medications may be used for sedation prior to MRI scans for those participants requiring sedation. At the discretion of the Investigator, 0.5 to 1 mg may be given orally prior to scan with a single repeat dose given if the first dose is ineffective. ~~No more than a total of 2 mg lorazepam may be used for any MRI scan.~~ Neuropsychological testing may not be performed on the same

day of lorazepam administration. Participants and caregiver must be informed of risks of lorazepam use prior to administration.

b. Receipt of systemic corticosteroids within 30 days prior to ~~screening~~**baseline**.

3. Physical and Laboratory Test Findings

~~i. Positive blood screen for hepatitis C antibody, hepatitis B surface antigen~~

Rationale: The changes in subsections 1 and 2 are intended to reduce inappropriate screening failures and provide greater flexibility in the clinical management of study participants; the deletion in subsection 3 was duplicative of the exclusion criterion under 1*w*.

Section 11, PHARMACOKINETIC (Table 7)

Change: The table was revised to include collection of the Week 52 predose sampling, and a footnote was added to clarify the nature of the Week 52 postdose sampling.

Now reads:

Table 7: Pharmacokinetic Sampling Schedule

Study Week of Sample Collection	Event	**Estimated** Time (Relative to start of infusion of BIIB092) Hour: Min	BIIB092 Blood Sample for Serum	BIIB092 CSF Sample[a]
Week 0 (Day 1)	Predose	00:00	X	X
Week 0 (Day 1)	EOI[b]	01:00	X	
Week 4	Predose	00:00	X	
Week 4	EOI[b]	01:00	X	
Week 12	Predose	00:00	X	
Week 24	Predose	00:00	X	
Week 24	EOI[b]	01:00	X	
Week 36	Predose	00:00	X	
Week 48	Predose	00:00	X	
Week 48	EOI[b]	01:00	X	
Week 52	**Predose**	**00:00**	**X**	
Week 52	Postdose[c]	672:00	X	X
24-week intervals after Week 52	Predose	00:00	X	Week 100 only

[a] Collect at the time of LP ([redacted]).

[b] EOI=End of Infusion~~,~~**;** ~~T~~**t**his this sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] **The Week 52 sampling at 672 hr after Week 52 dosing is the scheduled predose sampling at Week 56.**

Rationale: The original table failed to include the scheduled Week 52 predose sampling, and the nature of the Week 52 postdose sampling (as originally described) required clarification.

This change also affects Section 2 (Schedule of Activities; Table 3, PK Assessments).

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were revised throughout the protocol.
- The Table of Contents was updated.
- The term “subject” was changed to “participant” pursuant to uniformity.
- Reference to study “phase” was changed to “period pursuant to uniformity.
- Minor editorial changes were made.
- Typographical and formatting errors were corrected.

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AMENDMENT SUMMARY

Biogen Protocol 251PP301

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Intravenously Administered BIIB092 in Participants with Progressive Supranuclear Palsy

Version 4

Date: 14 November 2017

EUDRA CT Number: 2016-002554-21

Version 4 of the protocol has been prepared for this amendment, which supersedes Version 3.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 251PP301 is to add a missing safety assessment, 12-lead electrocardiogram (ECG), and to add instruction to the assess infusion site to the double-blind schedule of events.

Additionally, the following changes were made to Table 2: Double-Blind Procedural Outline:

- Pregnancy test was added at the Early Discontinuation visit.
- Footnote "a" language was updated.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 2, Schedule of Activities, Table 2: Double-Blind Procedural Outline

Now reads: Table 2: Double-Blind Procedural Outline

Procedure[a]	Week 0 (Day 1)	Weeks 4, 8, 16, 20, 28, 32, 40, 44[b] (±3 days)	Weeks 12, 24, 36 (±3 days)	Week 48 (±3 days)	Week 52 (±3 days)	Early Discontinuation[c]	Notes
Safety Assessments							
Vital Signs	X	X	X	X	X	X	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
12-Lead Electrocardiogram (ECG)	**X**		**See Notes**		**X**	**X**	**Week 24 only**
Assess Infusion Site	**X**	**X**	**X**	**X**	**X**	**X**	
Laboratory Tests	X	See Notes	X	X	X	X	Weeks 4 and 8 only.
Pregnancy Test	X	X	X	X	X	**X**	For WOCBP only (serum or urine - local/site) within 24 hours prior to dosing.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]

Abbreviations: AE = adverse event; CSF = cerebrospinal fluid; CGI = Clinical Global Impression; C-SSRSEOI = end of infusion; MDS-UPDRS = Movement Disorder Society (MDS)-sponsored revision of the Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; PK = pharmacokinetic; PSP = Progressive Supranuclear Palsy; PSPRS = Progressive Supranuclear Palsy Rating Scale; QoL = quality of life; RBANS = Repeatable Battery for the Assessment of Neuropsychological Disease Severity; [redacted]; SEADL = Schwab and England Activities of Daily Living scale; [redacted] WOCBP = women of childbearing potential.

[a] ~~All procedures/assessments should be done predose unless otherwise specified in the notes.~~ **Efficacy assessments requiring subject participation should be completed prior to dosing with study treatment unless otherwise specified in the notes.**

[b] May qualify for home visit if appropriate. See Section 5.1 for details.

c Early Discontinuation visit procedures should be completed for any participant who discontinues at any time prior to Week 52. If possible, participants who discontinue should be encouraged to return to the clinic at Week 52 to complete the Week 52 procedures. If the visit cannot be done in person by the participant, the site should attempt a phone call at approximately Week 52 to collect at a minimum vital status and SAE/AE information on the participant.

Rationale: These 2 assessments, 12-lead ECG and assessment of the infusion site, were added to the Version 4 protocol amendment as per the Version 1 protocol.

The pregnancy test assessment was added at the Early Discontinuation visit. This was an oversight in the BMS Version 1 of the protocol.

The footnote “a” was revised for clarity.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 3, Synopsis

The Synopsis was revised to reflect changes made throughout the protocol.

Section 2, Schedule of Activities, Table 1: Screening Procedural Outline

Change: Text regarding the [redacted] was revised.

Now reads:

Table 1: Screening Procedural Outline

Procedure	Screening Visit[a]	Notes
Lumbar Puncture (LP)	X	[redacted] ~~performed at selected sites ONLY~~ The baseline LP may be performed up to Day -1 to allow recovery before dosing. LP should be performed in the morning (between 08:00 and 12:00 hours) to minimize potential diurnal variation of cerebrospinal fluid (CSF) parameters. Any participant with an AE related to LP should not be dosed until the AE has resolved. Use of low dose acetylsalicylic acid (ASA) or other antiplatelet/anticoagulant medications may be associated with a higher risk of LP complications. At the discretion of the ~~i~~**I**nvestigator, if not contraindicated, low dose ASA or other antiplatelet/anticoagulant medications may be discontinued for a short period of time prior to performing the LP. Stop and start dates must be documented on the appropriate Concomitant Medication CRF. CSF may be assessed for BIIB092 concentrations, white and red blood cell counts, protein, glucose, levels of free eTau, total tau, phosphorylated tau, and neurofilament light chain (NfL). Participants should be observed for approximately 2 hours after the LP for AEs. LP can be done in either the decubitus or sitting position, however it is preferred that all LPs for each participant are performed in the same position. The position of the participant during the LP will be recorded. LP may be performed under fluoroscopy or with **computed tomography (**CT**)** guidance at the discretion of the ~~i~~**I**nvestigator.

Rationale: The statement was revised to clarify that the [redacted].

This section also affects Section, 2 Schedule of Activities, Table 2: Double-Blind Procedural Outline; Section, 2 Schedule of Activities, Table 3: On Treatment Procedural Outline for Long-Term Open-Label Phase; Section 5.1, Overall Design; and Section 11, Pharmacokinetic, Table 7: Pharmacokinetic Sampling Schedule.

Section 2, Schedule of Activities, Table 3: On Treatment Procedural Outline for Long-Term Open-Label Phase

Change:

The following changes were made:

- Physical measurement was added as a part of safety assessments.
- Pregnancy test assessment was added at the Early Discontinuation visit.
- Monitoring of serious adverse events (AEs) was revised.
- Efficacy assessments were revised.

Now reads:

Table 3: On Treatment Procedural Outline for Long-Term Open-Label Phase

Procedure	4, 8, 16, 20 week intervals after Week 52[ab] (±7 days)	12 week intervals after Week 52[c] (±7 days)	24 week intervals after Week 52[d] (±7 days)	Early Discontinuation	Notes
Safety Assessments					
Physical Examination		See Notes	X	X	At Week 64 only.
Targeted Physical Examination	X	X	X	X	Post-dose. Targeted, problem-focused physical examination performed at clinician's discretion (e.g., to evaluate any AEs).
Neurological Exam (NE)			See Notes		Week 100 only. Besides documenting signs of PSP, the NE should focus on any clinical evidence of increased intracranial pressure (e.g., history of headache, vomiting, or visual disturbances, and neurologic signs such as pupillary abnormalities and papilledema) that might contraindicate a lumbar puncture.
Physical Measurements		**X**	**X**	**X**	**Weight only.**
Vital Signs	X	X	X	X	
12-Lead Electrocardiogram (ECG)			X	X	
Assess Infusion site	X	X	X	X	
Laboratory Tests		See Notes	X	X	At Week 64 only.
Pregnancy Test	X	X	X	**X**	For WOCBP only (serum or urine - local/site).
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Adverse Event Reporting					

Procedure	4, 8, 16, 20 week intervals after Week 52[ab] (±7 days)	12 week intervals after Week 52[c] (±7 days)	24 week intervals after Week 52[d] (±7 days)	Early Discontinuation	Notes
Monitor for Non-Serious Adverse Events (NSAEs)	**Collection of NSAEs begins at initiation of study drug. Participants that discontinue early should receive a follow-up phone call 30 days after last dose.**				
Monitor for Serious Adverse Events (SAEs)	**See note in screening procedures.**				
Efficacy Assessments					
Progressive Supranuclear Palsy Rating Scale (PSPRS)		X	X	X	
MDS-UPDRS Part II, CGI, RBANS, PSP-QoL		See Notes	X	X	At Week 64 only.
SEADL, Phonemic Fluency, Letter-Number Sequencing, Color Trails Test, MoCA			X		
[redacted]			[redacted]		
[redacted]					
Magnetic Resonance Imaging (MRI)			See Notes		At Week 100 only.
Lumbar Puncture (LP)			See Notes		At Week 100 only. ([redacted]).

Rationale:

- Physical measurement assessment was added as a part of safety assessments to be consistent with the double-blind treatment phase.
- Pregnancy test assessment was added at Early Discontinuation visit, as it should be performed at every visit for a women of childbearing potential.
- Monitoring of serious AEs was revised to clarify that these events are monitored not only at 4-, 8-, 16-, and 20-week intervals after Week 52 but also at 12 and 24 weeks after Week 52 and at the Early Discontinuation visit.
- [redacted]

Section 6.2, Exclusion Criteria

Change: Exclusion criteria 2 (a) (i), 2 (a) (ii), 3 (c), 3 (e), 3 (g), and 3 (h) were updated.

Now reads:

- 2 (a) (i) Low dose lorazepam **or other short-acting medications** may be used for sedation prior to MRI scans for those participants requiring sedation. At the discretion of the **I**~~i~~nvestigator, 0.5 to 1 mg may be given orally prior to scan with a single repeat dose given if the first dose is ineffective. No more than a total of 2 mg lorazepam may be used for any MRI scan. Neuropsychological testing may not be performed on the same day of lorazepam administration. Participants and caregiver must be informed of risks of lorazepam use prior to administration.
- 2 (a) (ii) Participants who take short-acting benzodiazepines **(e.g., temazepam, zolpidem)** ~~(only temazepam or zolpidem are allowed)~~ for sleep may continue to do so if they have been on a stable dose for 30 days prior to screening.
- 3 (c) Total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 2 times the upper limit of normal (ULN), confirmed by repeat. **Elevated total bilirubin suspected to be due to Gilbert syndrome should be discussed with the Medical Monitor**.
- **3 (e)** Hematocrit less than 30%~~35% for males and less than 32% for females,~~ absolute neutrophil cell count of ≤1500/µL (with the exception of a documented history of a chronic benign neutropenia), or platelet cell count of <120,000/µL; INR >1.4 or

other coagulopathy, confirmed by repeat. (**Note: Participants with INR >1.4 due to antiplatelet/anticoagulant medications are eligible.)**

- [redacted]

- 3 (h) Hemoglobin A1C >~~7.5~~**8**%, confirmed by repeat.

Rationale:

- Text was added for clarity to determine the appropriate medication to be used for sedation prior to magnetic resonance imaging scans given a participant's medical history and clinical situation at the Investigator's discretion.

- Text was modified to give examples of short-acting benzodiazepines.

- Text was updated for clarity to allow subjects with Gilbert syndrome to be eligible for randomization in the study.

- Text was modified because hematocrit <35% for males and <32% in females is very prevalent in older subjects who are likely to participate in this study and because these hematocrit values are not commonly associated with AEs. Text was modified to allow participation of participants with INR >4 due to antiplatelet/anticoagulant medications.

- Text was updated to determine participant's eligibility based on Investigator's discussion with the Medical Monitor when participants' white blood cells (WBCs) >7 cells/mm^3 in the CSF. Depending on the circumstance, WBC >7 cells/mm^3may be allowed (e.g., traumatic spinal tap with WBC >7 cells/mm^3).

- Text was modified to allow participation of diabetic participants who are receiving medications.

This change also affects Section 7.7.1, Prohibited and/or Restricted Treatments.

Section 7.4, Dose Modification

Change: Text was updated.

Now reads:

Dosing visits **should generally** ~~are~~not **be** skipped, only delayed. **In the unusual circumstance where an extended delay occurs (e.g., 2 weeks or more), the Investigator should discuss this with the Medical Monitor.**

Rationale: Text was modified for clarity. Clarification was added to have the Investigator discuss with the Medical Monitor dosing modifications in cases of unusual circumstances. Depending on the situation, the dosing visit may need to be skipped.

Section 9.3, Other Assessments

Change: Text was updated.

Now reads:

[redacted]

Section, 10.5, Pregnancy

Change: Text was updated to reflect contraception requirements for women.

Now reads:

Subjects should not become pregnant or impregnate their partners **for the duration of treatment with study treatment(s) BIIB092 plus 5 half-lives of study treatment BIIB092 plus 30 days for females (duration of ovulatory cycle) or 90 days for males (duration of sperm turnover) for a total of 155 days or 215 days for females and males, respectively** ~~during the study and~~

~~for 5 times the half-life or 6 months, whichever is longer, after their last dose of study treatment~~. If a female subject becomes pregnant, study treatment must be discontinued immediately.

Rationale: The text was updated to be consistent with contraception requirements described in Section 6.1, Inclusion Criteria.

Appendix 4, Women of Childbearing Potential Definitions and Methods of Contraception

Change: The contraception requirements described in Appendix 4 of the protocol were updated to be consistent with contraception requirements described as part of eligibility requirements.

Now reads:

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

Any one of the approved methods of contraception listed below is required for the duration of this study and for ~~30~~**155** days after treatment has been discontinued.

Local laws and regulations may require use of alternative and/or additional contraception methods.

Contraceptive methods that are approved for use during and for ~~30~~**155** days after participation in this study are**:** *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 10.5 • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness.
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus) • Spermicide only • Lactation amenorrhea method (LAM)

Rationale: The contraception requirements for women were revised to be consistent with the study eligibility requirements described in Section 6.1, Inclusion Criteria.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- Typographical errors and formatting were corrected.
- In Section 3.2, minor edits were made to the text regarding monocloncal antibody for consistency.
- In Section 7, text was added to include cross-reference to Table 5.
- In Section 7.5, minor edits were made for clarity.
- In Section 8.1, Discontinuation From Study Treatment, and Section 8.1.1, Post-Study Treatment Follow-Up, reference to Section 5, Study Design, was updated to reflect Section 2, Schedule of Activities, in particular Table 2 or Table 3, as this section was more appropriate.
- In Section 9.2, Imaging Assessment for the Study, reference to the central core laboratory was updated to central imaging vendor for clarity.
- In Section 10.1, Time Period and Frequency for Collecting AE and SAE Information, the reference to the Investigator's Brochure section was updated to Section 6.6, Reference Safety Information, as per Biogen's Investigator Brochure.
- In Section 14, Immunogenicity Assessments, text was updated to match BMS protocol Version 1.
- In Appendix 1, List of Abbreviations, was updated.
- In Appendix 2, the text regarding legally authorized representative was deleted. This also affects section 10, Adverse Events.
- In Appendix 2, minor edits were made to subsection Clinical Study Report and Publications for clarity.
- In Appendix 3, Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting, text was updated to match the BMS protocol Version 1.

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AMENDMENT SUMMARY

Biogen Protocol 251PP301

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Intravenously Administered BIIB092 in Participants with Progressive Supranuclear Palsy

Version 3

Date: 13 September 2017

EUDRA CT NUMBER: 2016-002554-21

Version 3 of the protocol has been prepared for this amendment, which supersedes previous Version 1.0.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 251PP301 is to change the Sponsor name from BMS to Biogen. This includes replacing the BMS title page with the Biogen title page, inserting the Biogen Sponsor Signature Page and Biogen Sponsor Information section, changing the compound name from BMS-986168 to BIIB092 throughout the document, and changing the study name from CN002012 to 251PP301.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Cover Page, Sponsor Signature Page, Sponsor Information

Now reads:

Biogen MA Inc.
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Cambridge, MA 02142
United States

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United Kingdom

PROTOCOL NUMBER: **251PP301**

PHASE OF DEVELOPMENT: 2b

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Intravenously Administered BIIB092 in Participants with Progressive Supranuclear Palsy

EUDRA CT NUMBER: **2016-002554-21**

DATE: **13 September 2017**
Version 3
FINAL
Version 3 supersedes previous Version 1.0 dated 12 December 2016

SPONSOR SIGNATURE PAGE

Protocol 251PP301~~CN002012~~ was approved by:

_____ _____

[redacted], PhD **Date**

Biogen

SPONSOR INFORMATION

Biogen is responsible for the study.

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For urgent medical issues in which the study Medical Director should be contacted, please refer to the Study Reference Guide's Official Study Contact List for complete contact information.

Biogen may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

Rationale: Biogen is now the Sponsor of the study.

This change also affects the following sections and applicable subsections: Section 2, Schedule of Activities; Section 3, Introduction; Section 4, Objective and Endpoints; Section 5, Study Design; Section 5.1, Study Schematic (including Figure 5.1-1: Study Design Schematic); Section 6, Study Population; Section 7, Treatment; Section 8, Discontinuation from Study Treatment; Section 9, Study Assessments and Procedures; Section 10, Statistical Considerations; and Section 12, Appendices.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 1, Synopsis

The synopsis was revised to reflect changes made throughout the protocol.

Section 2, Schedule of Activities

Change: Table 1 was revised.

Now reads:

Efficacy Assessments		
Progressive Supranuclear Palsy Rating Scale (PSPRS)	X	
Repeatable Battery for the Assessment of Neuropsychological Disease Severity (RBANS)	X	
Montreal Cognitive Assessment (MoCA)	X	
Phonemic Fluency Test	X	
Letter-Number Sequencing Test (LNS)	X	
Color Trails Test (CTT)	X	Randomization will be stratified by **country and** screening CTT Part 2 score of either less than or equal to 170 seconds, or greater than 170 seconds.
Magnetic Resonance Imaging (MRI)	X	The MRI should be completed at least 14 days prior to first dose to allow for central assessment of image. A repeat MRI may be requested prior to randomization if protocol standards are not yet met. MRI image quality must be determined to be adequate and local interpretation performed to determine eligibility and also to rule out any contraindication to lumbar puncture for participants participating in the [redacted]

Rationale: The randomization scheme was amended to include country as an additional stratification factor. Country as a stratification factor was added to promote treatment balance within each country.
This change also affects Sections 5.3, Number of Participants and Section 7.2, Method of Treatment Assignment.

Change: Table 3 footnote was updated.

Now reads:

May qualify for home visit if appropriate starting at Week 68. See Section 5.1 for details.

[b] Visit intervals of 4, 8, 16, and 20 after Week 52 (e.g., Weeks 56, 60, 68, 72, 80, 84, ~~82~~**92**, 96, 104, 108, 116, 120, 128, 132, 140, 144, 152, 156, 164, 168, 176, 180, 188, and 192

[c] Visit intervals of 12 weeks after Week 52 (e.g., Weeks 64, 88, 112, 136, 160, and ~~182~~**184**).

[d] Visit intervals of 24 weeks after Week 52 (e.g., 76, 100, 124, 148, 172, and 196).

[e] Sample to be collected predose.

Rationale: The footnote was corrected since some of the weeks listed were incorrect. The current changes reflect the interval as stated.

Section 3.2 Background

Change: More current information on some of the studies was added.

Now reads:

BIIB092 was first introduced into clinical trials in the Phase 1 trial**s** conducted in the United States ~~(US)~~, Study CN002001 in healthy adult volunteers **and**~~. The Phase 1b PSP study (~~ **Study** CN002003~~)~~ **in subjects with PSP.**

~~and corresponding roll over study (CN002004) are ongoing in the US. Preliminary data available~~ **Results** from the first-in-human study, CN002001, indicate that administration of single doses of up to 4200 mg of BIIB092 in healthy subjects is safe and well tolerated. Mean suppression of the CSF eTau in that study ranged from 67% to 97% at doses ranging from 70 mg to 4200 mg.

Study CN002003 was a Phase 1b randomized, double-blind, placebo-controlled, MAD study to characterize the safety, tolerability, PK, PD and immunogenicity of BIIB092 doses of 150 mg, 700 mg and 2100 mg in subjects with PSP. All 3 doses were safe and well tolerated based on results from the dose escalation phase of the study. Treatment with monthly doses of BIIB092 decreased CSF free eTau by mean values of approximately 90%, 93% and 96% on Day 29 and 91%, 95% and 97% on Day 85 at doses of 150 mg, 700 mg and 2100 mg respectively.

Study 251PP201 is an ongoing open-label extension study to evaluate the long term safety and tolerability of multiple doses of BIIB092 in subjects with PSP who participated in CN002003.

~~Studies CN002003 and CN002004, Phase 1b study in participants with PSP and the associated roll over study, are currently ongoing to evaluate the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of multiple doses of BIIB092. Preliminary data indicate that multiple doses of 150 , 700 , and 2100 mg of BIIB092 are safe and well tolerated, with an apparent dose proportional increase in exposures, and a robust and persistent lowering of free eTau consistent with the observations in healthy participants.~~

Rationale: Updated status and general results on safety, tolerability and pharmacokinetics (PK) of completed clinical trials were available.

Section 3.3, Benefit/Risk Assessment

Change: Section 3.3 was updated.

Now reads:
The overall benefit/risk profile of BIIB092 in several nonclinical studies, the single dose study in normal healthy volunteers (CN002001), as well as the multiple dose study and associated ~~roll over study~~ **open label extension study** (Studies CN002003 and ~~CN002004 [~~Study 251PP201~~]~~) support further evaluation of the safety, tolerability, immunogenicity, PK, PD response, and clinical efficacy of BIIB092 in participants with PSP.

BIIB092 is an IgG4 isotype antibody that is considered to have a low potential for immunogenicity in humans based on nonclinical studies. There were no adverse effects noted at any dose tested in the pivotal toxicity studies in monkeys. Nonclinical findings were limited to decreases in CSF free eTau consistent with the intended pharmacology of BIIB092.

Studies evaluating the potential for reproductive and developmental toxicity have not been performed for BIIB092.

As of July 31, 2017, 114 subjects have been exposed to BIIB092 across all completed and ongoing clinical studies (Studies CN002001, CN002003, 251PP201 and 251PP301). Based on safety data from a completed Phase 1 studies in healthy volunteers (CN002001) and a completed Phase 1B study in subjects with PSP (Study CN002003), the majority of AEs reported to date have been mild to moderate in severity and transient in nature. There have been no deaths or discontinuations due to an AE reported in the program. There have been 4 SAEs reported in 3 subjects in the CN002003 study, all of which were considered not related to study drug by the Investigator.

~~Based on preliminary data from the CN002001 study and still ongoing studies CN002003 and CN002004, observed AEs to date have mostly been mild to moderate in severity and transient in nature. AEs considered related to the study drug by the investigator were belching, nausea, headache, and flushing. One AE of headache and one AE of diverticulitis were considered moderate; all other AEs were considered mild. Four (4) SAEs considered not related to study drug by the investigator have been reported to date in three (3) participants; one SAE was a urinary tract infection requiring hospitalization, one SAE was an aspiration pneumonia requiring hospitalization; the other two SAEs were aspiration pneumonia and a related metabolic encephalopathy in the same participant requiring hospitalization. Overall, there were no apparent BIIB092 treatment-related trends observed in the occurrences of AEs.~~

There is no information available about possible interaction of BIIB092 with other drugs, although no PK interactions are anticipated.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of BIIB092 may be found in the Investigator's Brochure. However, as BIIB092 is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur.

Rationale: Clinical experience text was updated to include results from Study CN002003 and align with the Investigator's Brochure.

Section 5.1 Overall Design

Change: The responsibility of approving in-home administration of the study treatment was changed.

Now reads: In the open-label portion of the study, visits occurring at 4, 8, 16 and 20 week intervals after Week 52, may qualify for a home visit starting with the Week 68 visit. However, in the event that the participant experienced a clinically significant infusion reaction during the first 24 weeks of the protocol, the participant should not be administered BIIB092 in the home unless previously approved by the study ~~Medical Monitor~~**Investigator**.

Rationale: The Investigator, and not the Medical Monitor, is the person who approves in-home administration of BIIB092.

Section 5.6 Justification for Dose

Change: Update for which dose data will be accrued.

Now reads: In the SAD study in normal healthy volunteers (CN002001), single doses of BIIB092 were safe and well tolerated at all doses tested (i.e., 21 mg to 4200 mg). A maximum tolerated dose was not identified. Robust suppression of free eTau in CSF (88% to 97%) was observed for at least 4 weeks after a single dose, compared to baseline, in the dose range of 210 mg to 4200 mg. The MAD study in participants with PSP (CN002003) assessed Q4W doses of BIIB092 of 150 mg, 700 mg and 2100 mg during the dose escalation phase of the study. All three doses were safe and well tolerated in participants with PSP, based on preliminary results from the dose escalation phase of the study. ~~Preliminary results also showed robust suppression of free eTau in CSF at the end of the first 4 week dosing interval, with 89%, 93%, and 97% suppression relative to baseline for 150 mg, 700 mg, and 2100 mg, respectively.~~ **Treatment with monthly doses of BIIB092 decreased CSF free eTau by mean values of approximately 90%, 93% and 96% on Day 29 and 91%, 95% and 97% on Day 85 at doses of 150 mg, 700 mg and 2100 mg respectively.** ~~Based on the near maximal suppression of eTau and the lack of any noteworthy findings on safety and tolerability of BIIB092, at the maximum dose of 2100 mg Q4W studied during the escalation phase of the study, the dose for the expansion panel in Study CN002003 was chosen to be continued at 2100 mg Q4W.~~ Additional data on safety, tolerability, PK, and PD of~~the 2100 mg~~ **all 3** dose **levels** are accruing with the ~~expansion panel~~**open label extension** of this study.

Rationale: Additional data on safety, tolerability, PK, and PD are accruing for all 3 doses of study treatment, not just in the 2100-mg dose group in the open-label extension panel.

Section 7, Treatment

Change: Table was revised to reflect updated study drug constituents and study drug information (based on the Investigator's Brochure) and language was added about how study drug will be labeled when provided to sites.

Now reads:

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) as listed:

Study Drug for Study 251PP301		
Medication	Potency	IP/Non-IP
BIIB092*	50 mg/mL	IP
Placebo** (0.9% Sodium Chloride)	N/A	IP

* **Drug supplies may be labeled as BIIB092 or BMS-986168. The two drug names refer to an identical drug substance.**

** 5% dextrose injection can be used if sodium chloride is not available.

Table 7.-1: Study treatments for 251PP301					
Product Description / Class and Dosage Form	**Potency**	**IP/Non-IMP**	**Blinded or Open-Label [a]**	**Packaging / Appearance**	**Storage Conditions (per label)**
BIIB092 Injection, 1000 mg/vial (50 mg/mL) The composition of the drug product is: 50 mg/mL, ~~010 mM Sodium Phosphate, 140 mM Sodium Chloride, 0.02% (w/v) Polysorbate 80, pH 6.1~~ **BIIB092, histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid, polysorbate 80, and sterile water for injection, pH 6.0**	50 mg/mL	IP	Open-label	**Clear to very opalescent, colorless to slightly yellow liquid, in which light (few) particulates may be present**	**Store Refrigerated 2°C to 8°C, protect from light. Do not freeze**
Placebo (0.9% Sodium Chloride or 5% Dextrose)[b]	0.9% NaCl Or 5% Dextrose	IP	N/A	Per Product Label	Per Product Label

[a] **BIIB092** is provided Open-label to the unblinded pharmacist. After study drug is prepared by the unblinded pharmacist all other study personnel will remain blinded to the identification of study drug (**BIIB092** vs. placebo) up to Week 52.

[b] Placebo is not provided by Biogen and obtained commercially by the site, storage should in accordance with the product label

Rationale: Until the end of 2017, study supplies will continue to be labeled BMS-986168. Early in 2018, drug labels will switch from the BMS compound name to the Biogen compound name. This text was added to address drug supply transition from BMS-labeled drug product to Biogen-labeled drug product and convey in the protocol that the two drug names are synonymous with one another.

Section 7.2, Method of Treatment Assignment

Change: Section 7.2 was updated to clarify when stratification by country will be implemented.

Now reads:

All participants will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log in information and directions on how to access the IRT. Randomization will be stratified by country and screening Color Trails Test Part 2 stratum of a score either less than or equal to 170 seconds or greater than 170 seconds. **Randomization will only be stratified by screening Color Trails Test Part 2 stratum under the IRT system for protocol Version 1. To promote treatment balance within each country, randomization will be stratified by both country and screening Color Trails Test Part 2 when the new IRT system for this protocol is in place.**

Rationale: The randomization scheme was amended to include country as an additional stratification factor. Text was added to clarify that stratification by country will not occur until the programming in IRT is updated to V1.3.

Section 8.3, Lost to Follow-Up

Change: Section 8.3 was revised to reflect alignment with processes at Biogen for patients lost to follow-up.

Now reads:

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- ~~If investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.~~
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

Rationale: The site Principal Investigator or designee will make every reasonable effort to contact any patient lost to follow up, a third party vendor will not be required to manage these activities. To date, the third party vendor services have not been required to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.

Section 10, Adverse Events

Change: Section 10 text was revised.

Now reads:

Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 5 times the half-life or 6 months, whichever is longer, after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued immediately.

The Investigator must report a pregnancy occurring in a female subject by faxing or emailing the appropriate form to Biogen within 24 hours of the site staff becoming aware of the pregnancy. Refer to the Study Contact List for complete contact information. The Investigator or site staff must report the outcome of the pregnancy to Biogen. A pregnancy is not considered an AE and should not be recorded on the AE CRF.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

~~If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to the Medical Monitor or their designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3~~

~~In most cases, the study treatment will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant safety). Please call the Medical Monitor within 24 hours of awareness of the pregnancy.~~

~~Protocol required procedures for study discontinuation and follow-up must be performed on the participant.~~

~~Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.~~

~~Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for~~

~~disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.~~

Potential Drug Induced Liver Injury (DILI)

Potential drug induced liver injury (DILI) is defined as:

AT (ALT or AST) elevation > 3 times upper limit of normal (ULN) AND

Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see **Section ~~9~~ 10** Appendix 3 for reporting details).

Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the Investigator's Brochure.

Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Appropriate personnel at Biogen will unblind SUSARs for the purpose of regulatory reporting. Biogen will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen will submit SUSARs to Investigators in a blinded fashion.

Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed or emailed to Biogen within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Biogen even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed or emailed to Biogen. All study treatment-related dosing information must be recorded on the dosing CRF.

Medical Emergency

In a medical emergency requiring immediate attention, site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or

designee) should contact the study's Medical Director. Refer to the Study Contact List for complete contact information.

Unblinding for Medical Emergency

In a medical emergency when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, or to personnel involved with the analysis and conduct of the study. The Investigator can contact Biogen to discuss such situations.

Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

Rationale: The changes to Section 10 were made to reflect compatibility and alignment with safety processes at Biogen.

Section 19, Signed Agreement of the Study Protocol
Change: This section was inserted into the protocol.

Now reads:
SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Intravenously Administered BIIB092 in Participants with Progressive Supranuclear Palsy," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature **Date**

_____

Investigator's Name (Print)

_____

Study Site (Print)

Rationale: The signature page was inserted in accordance with the process at Biogen

Appendix 2, Study Goverance Considerations, Informed Consent Process

Change: The text in Appendix 2 was revised.

Now reads:

Ethical Requirements

Biogen and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The investigator is responsible for endorsing all data on completed CRFs electronically, prior to any Interim lock or Database lock.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible f or supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Contract Research Organization will submit documents on behalf of the investigational sites worldwide in compliance with the local regulations.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen.

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

Biogen must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

At the completion or termination of the study, the study site must submit a close-out letter to the ethics committee and Biogen.

Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

The Investigator must reassess the patient's capacity to provide informed consent periodically over the course of the study. In the event the patient loses capacity to provide informed consent, the Investigator must obtain subject assent and consent by the legal representative (in accordance with local laws and regulations).

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and ethnicity will be collected during the study (unless the collection is not permitted by applicable law or not approved by the governing ethics committee) and the data will be used during analysis of study results.

A copy of the signed and dated ICF must be given to the subject or the subject's legally authorized representative. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the subject's medical record.

Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

During the study, subjects' race and ethnicity will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). These data will be used in the analysis of the safety and/or pharmacokinetic profile of the study treatment. It is unknown whether the effects of the study treatment are influenced by race or ethnicity.

Study reports will be used for research purposes only. The subject will not be identified by name in CRFs, study-related forms, study reports, or any related publications. Biogen, its partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen) with the subject before the subject makes a decision to participate in the study.

Registration of Study and Disclosure of Study Results

Biogen will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

~~REGULATORY AND ETHICAL CONSIDERATIONS GOOD CLINICAL PRACTICE~~

~~This study will be conducted in accordance with:~~

- ~~Good Clinical Practice (GCP),~~
- ~~as defined by the International Council on Harmonisation (ICH)~~
- ~~in accordance with the ethical principles underlying European Union Directive 2001/20/EC~~
- ~~United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)~~
- ~~applicable local requirements.~~

~~The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional~~

Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (e.g., advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

INFORMED CONSENT PROCESS

Investigators must ensure that subjects and their caregiver are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant and participant's caregiver, their legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the

~~informed consent discussion.~~

- ~~Obtain an informed consent signed and personally dated by the participant's caregiver and by the person who conducted the informed consent discussion.~~
- ~~Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.~~

~~If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.~~

~~Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.~~

~~The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.~~

~~The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.~~

~~The rights, safety, and well being of the study subjects are the most important considerations and should prevail over interests of science and society.~~

Rationale: Text regarding ethical considerations was updated to conform to Biogen template language. Additionally, text was added to outline course of action in the event of cognitive worsening of study participants over the study in the protocol. Also, clarification was needed to appropriately outline the responsibilities of the Investigator in situations where a study participant loses capacity to provide informed consent over the course of the study. This additional language is based on a Protocol Clarification Letter for Study 251PP301, dated 21 June 2017.

Appendix 3, Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting

Change: The text in Appendix 3 was revised.

Now reads:

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:

Related: An AE will be considered "related" to the use of the investigational product if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to a positive rechallenge, a reasonable temporal sequence between administration of the investigational product and the AE, a known response pattern of the suspected product, improvement following discontinuation or dose reduction, a biologically plausible relationship between the product and the AE, or a lack of an alternative explanation for the AE.

Not related: An AE will be considered "not related" to the use of the investigational product if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to the lack of reasonable temporal relationship between administration of the investigational product and the AE, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.

~~**Assessment of Causality**~~

~~The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:~~

~~Related: There is a reasonable causal relationship between study drug administration and the AE.~~

~~Not related: There is not a reasonable causal relationship between study drug administration and the AE.~~

~~The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.~~

REPORTING OF SAES TO SPONSOR

- SAEs, whether related or not related to study drug, and pregnancies must be reported to Biogen within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy **Notification and Outcome**~~Surveillance~~ Form (~~electronic or~~ paper forms).
- The preferred method for SAE data reporting collection is through the eCRF.
- The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning.
    - In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list. SAE

Facsimile Number: Refer to Contact Information list.

~~For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.~~

~~**SAE Telephone Contact** (required for SAE and pregnancy reporting): Refer to Contact Information list~~

Rationale: Appendix 3 was updated to reflect compatibility and alignment with safety processes at Biogen.

Appendix 4, Women of Childbearing Potential Definitions and Methods of Contraception

Change: Appendix 4 was revised.
Now reads:

Contraceptive methods that are approved for use during and for 30 days after participation in this study are: *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of

ovulation [b]
- Intrauterine device (IUD)[c]
- Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion

- Vasectomized partner

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 10.5.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

~~**Less Than Highly Effective Contraceptive Methods That Are User Dependent**~~

~~*Failure rate of >1% per year when used consistently and correctly.*~~

~~- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously~~
~~- Diaphragm with spermicide~~
~~- Cervical cap with spermicide~~
~~- Vaginal Sponge with spermicide~~
~~- Progestogen only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action~~

- **Unacceptable Methods of Contraception**

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)

- Withdrawal(coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

Rationale: Based on feedback from the Medicines and Healthcare products Regulatory Agency (MHRA), Appendix 4 was revised to align with the body of the protocol, which describes the need for highly effective contraceptive use.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- Table of Contents was updated.
- List of Abbreviations was updated.

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225 Binney Street
Cambridge, MA 02142
United States

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

AMENDMENT SUMMARY

Biogen Protocol 251PP301

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Intravenously Administered BIIB092 in Participants with Progressive Supranuclear Palsy

Version 2

Date: 25 August 2017

Version 2 of the protocol has been prepared for this amendment, which supersedes Version 1.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 251PP301 is to change the Sponsor name from BMS to Biogen. This includes replacing the BMS title page with the Biogen title page, inserting the Biogen Sponsor Signature Page and Biogen Sponsor Information section, changing the compound name from BMS-986168 to BIIB092 throughout the document, and changing the study name from CN002012 to 251PP301.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Cover Page, Sponsor Signature Page, Sponsor Information

Now reads:

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
United States

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

PROTOCOL NUMBER: 251PP301

PHASE OF DEVELOPMENT: 2/3

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Intravenously Administered BIIB092 in Participants with Progressive Supranuclear Palsy

EUDRA CT NUMBER: 2016-002554-21

DATE: 25 August 2017
Version 2
FINAL
Supersedes previous Version 1.0 dated 12 December 2016

SPONSOR SIGNATURE PAGE

Protocol 251PP301 was approved by:

_____ _____

[redacted], PhD **Date**

Biogen

SPONSOR INFORMATION

Biogen is responsible for the study.

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103-0027 Japan

Biogen Australia PTY Ltd.
Suite 1, Level 3
123 Epping Road
North Ryde, NSW 2113
Australia

For urgent medical issues in which the study Medical Director should be contacted, please refer to the Study Reference Guide's Official Study Contact List for complete contact information.

Biogen may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

Rationale: Biogen is now the Sponsor of the study.

This change also affects the following sections and applicable subsections: Section 2, Schedule of Activities; Section 3, Introduction; Section 4, Objective and Endpoints; Section 5, Study Design; Section 5.1, Study Schematic (including Figure 5.1-1: Study Design Schematic); Section 6, Study Population; Section 7, Treatment; Section 8, Discontinuation from Study Treatment; Section 9, Study Assessments and Procedures; Section 10, Statistical Considerations; and Section 12, Appendices.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 1, Synopsis

The synopsis was revised to reflect changes made throughout the protocol.

Section 3.3, Benefit/Risk Assessment

Change: Section 3.3 was updated.

Now reads:
The overall benefit/risk profile of BIIB092 in several nonclinical studies, the single dose study in normal healthy volunteers (CN002001), as well as the multiple dose study and associated roll over study (Studies CN002003 and CN002004 [Study 251PP201]) support further evaluation of the safety, tolerability, immunogenicity, PK, PD response, and clinical efficacy of BIIB092 in participants with PSP.

BIIB092 is an IgG4 isotype antibody that is considered to have a low potential for immunogenicity in humans based on nonclinical studies. There were no adverse effects noted at any dose tested in the pivotal toxicity studies in monkeys. Nonclinical findings were limited to decreases in CSF free eTau consistent with the intended pharmacology of BIIB092.

Studies evaluating the potential for reproductive and developmental toxicity have not been performed for BIIB092.

As of July 31, 2017, 114 subjects have been exposed to BIIB092 across all completed and ongoing clinical studies (Studies CN002001, CN002003, 251PP201 and 251PP301). Based on safety data from a completed Phase 1 studies in healthy volunteers (CN002001) and a completed Phase 1B study in subjects with PSP (Study CN002003), the majority of AEs reported to date have been mild to moderate in severity and transient in nature. There have been no deaths or discontinuations due to an AE reported in the program. There have been 4 SAEs reported in 3 subjects in the CN002003 study, all of which were considered not related to study drug by the Investigator.

~~Based on preliminary data from the CN002001 study and still ongoing studies CN002003 and CN002004, observed AEs to date have mostly been mild to moderate in severity and transient in nature. AEs considered related to the study drug by the investigator were belching, nausea, headache, and flushing. One AE of headache and one AE of diverticulitis were considered moderate; all other AEs were considered mild. Four (4) SAEs considered not related to study drug by the investigator have been reported to date in three (3) participants; one SAE was a urinary tract infection requiring hospitalization, one SAE was an aspiration pneumonia requiring~~

~~hospitalization; the other two SAEs were aspiration pneumonia and a related metabolic encephalopathy in the same participant requiring hospitalization. Overall, there were no apparent BIIB092 treatment-related trends observed in the occurrences of AEs.~~

There is no information available about possible interaction of BIIB092 with other drugs, although no PK interactions are anticipated.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of BIIB092 may be found in the Investigator's Brochure. However, as BIIB092 is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur.

Rationale: Clinical experience text was updated to include results from Study CN002003 and align with the Investigator's Brochure.

Section 2, Schedule of Activities

Change: Section 2 was revised.

Now reads:

Efficacy Assessments		
Progressive Supranuclear Palsy Rating Scale (PSPRS)	X	
Repeatable Batter for the Assessment of Neuropsychological Disease Severity (RBANS)	X	
Montreal Cognitive Assessment (MoCA)	X	
Phonemic Fluency Test	X	
Letter-Number Sequencing Test (LNS)	X	
Color Trails Test (CTT)	X	Randomization will be stratified by **country and** screening CTT Part 2 score of either less than or equal to 170 seconds, or greater than 170 seconds.
Magnetic Resonance Imaging (MRI)	X	The MRI should be completed at least 14 days prior to first dose to allow for central assessment of image. A repeat MRI may be requested prior to randomization if protocol standards are not yet met. MRI image quality must be determined to be adequate and local interpretation performed to determine eligibility and also to rule out any contraindication to lumbar puncture for participants participating in the [redacted]

Rationale: The randomization scheme was amended to include country as an additional stratification factor.

This change also affects Sections 5.3, Number of Participants and Section 7.2, Method of Treatment Assignment.

Section 7, Treatment

Change: Table was revised to reflect updated study drug information (based on the Investigator's Brochure) and language was added about how study drug will be labeled when provided to sites.

Now reads:

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) as listed:

Study Drug for 251PP301		
Medication	Potency	IP/Non-IP
BIIB092*	50 mg/mL	IP
Placebo** (0.9% Sodium Chloride)	N/A	IP

* **Drug supplies may be labeled as BIIB092 or BMS-986168. The two drug names refer to an identical drug substance.**

** 5% dextrose injection can be used if sodium chloride is not available.

Table 7.-1: Study treatments for 251PP301					
Product Description / Class and Dosage Form	**Potency**	**IP/Non-IMP**	**Blinded or Open-Label [a]**	**Packaging / Appearance**	**Storage Conditions (per label)**
BIIB092 Injection, 1000 mg/vial (50 mg/mL) The composition of the drug product is: 50 mg/mL, ~~010 mM Sodium Phosphate, 140 mM Sodium Chloride, 0.02% (w/v) Polysorbate 80, pH 6.1~~ **BIIB092, histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid, polysorbate 80, and sterile water for injection, pH 6.0**	50 mg/mL	IP	Open-label	**Clear to very opalescent, colorless to slightly yellow liquid, in which light (few) particulates may be present**	**Store Refrigerated 2°C to 8°C, protect from light. Do not freeze**
Placebo (0.9% Sodium Chloride or 5% Dextrose)[b]	0.9% NaCl Or 5% Dextrose	IP	N/A	Per Product Label	Per Product Label

[a] **BIIB092** is provided Open-label to the unblinded pharmacist. After study drug is prepared by the unblinded pharmacist all other study personnel will remain blinded to the identification of study drug (**BIIB092** vs. placebo) up to Week 52.

[b] Placebo is not provided by Biogen and obtained commercially by the site, storage should in accordance with the product label

Rationale: Until the end of 2017, study supplies will continue to be labeled BMS-986168. Early in 2018, drug labels will switch from the BMS compound name to the Biogen compound name. This text was added to address drug supply transition from BMS-labeled drug product to Biogen-labeled drug product and convey in the protocol that the two drug names are synonymous with one another.

Section 8.3, Lost to Follow-Up

Change: Section 8.3 was revised to reflect alignment with processes at Biogen for patients lost to follow-up.

Now reads:

1.1. Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.

- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.

- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.

- ~~If investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.~~

- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.

If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

Rationale: The site Principal Investigator or designee will make every reasonable effort to contact any patient lost to follow up, a third party vendor will not be required to manage these activities. To date, the third party vendor services have not been required to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.

Section 10, Adverse Events

Change: Section 10 was revised to reflect compatibility with safety processes at Biogen.

Now reads:

1.2. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 5 times the half-life or 6 months, whichever is longer, after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued immediately.

The Investigator must report a pregnancy occurring in a female subject by faxing or emailing the appropriate form to Biogen within 24 hours of the site staff becoming aware of the pregnancy. Refer to the Study Contact List for complete contact information. The Investigator or site staff must report the outcome of the pregnancy to Biogen. A pregnancy is not considered an AE and should not be recorded on the AE CRF.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

1.3. Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

1.4. Potential Drug Induced Liver Injury (DILI)

Potential drug induced liver injury (DILI) is defined as:

AT (ALT or AST) elevation > 3 times upper limit of normal (ULN) AND

Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 10 and Appendix 3 for reporting details).

1.5. Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

1.6. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the Investigator's Brochure.

1.7. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Appropriate personnel at Biogen will unblind SUSARs for the purpose of regulatory reporting. Biogen will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen will submit SUSARs to Investigators in a blinded fashion.

1.8. Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed or emailed to Biogen within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Biogen even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed or emailed to Biogen. All study treatment-related dosing information must be recorded on the dosing CRF.

1.9. Medical Emergency

In a medical emergency requiring immediate attention, site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should contact the study's Medical Director. Refer to the Study Contact List for complete contact information.

1.10. Unblinding for Medical Emergency

In a medical emergency when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator may access the subject's treatment

assignment by IRT. The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, or to personnel involved with the analysis and conduct of the study. The Investigator can contact Biogen to discuss such situations.

1.11. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

1.12. Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

Rationale: Section 6 was updated to reflect compatibility and alignment with safety processes at Biogen.

Appendix 2, Study Goverance Considerations, Informed Consent Process

Change: Appendix 2 was revised to reflect replacing BMS language regarding ethical considerations to Biogen template language. Additionally, text was added to outline course of action in the event of cognitive worsening of study participants over the study in the protocol.

Now reads:

Ethical Requirements

Biogen and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The investigator is responsible for endorsing all data on completed CRFs electronically, prior to any Interim lock or Database lock.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible f or supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. ICON plc will submit documents on behalf of the study sites in countries other than the US.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen.

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

Biogen must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

At the completion or termination of the study, the study site must submit a close-out letter to the ethics committee and Biogen.

Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

The Investigator must reassess the patient's capacity to provide informed consent periodically over the course of the study. In the event the patient loses capacity to provide informed consent, the Investigator must obtain subject assent and consent by the legal representative (in accordance with local laws and regulations).

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and ethnicity will be collected during the study (unless the collection is not permitted by applicable law or not approved by the governing ethics committee) and the data will be used during analysis of study results.

A copy of the signed and dated ICF must be given to the subject or the subject's legally authorized representative. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the subject's medical record.

Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

During the study, subjects' race and ethnicity will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). These data will be used in the analysis of the safety and/or pharmacokinetic profile of the study treatment. It is unknown whether the effects of the study treatment are influenced by race or ethnicity.

Study reports will be used for research purposes only. The subject will not be identified by name in CRFs, study-related forms, study reports, or any related publications. Biogen, its partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen) with the subject before the subject makes a decision to participate in the study.

Registration of Study and Disclosure of Study Results

Biogen will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

~~REGULATORY AND ETHICAL CONSIDERATIONS GOOD CLINICAL PRACTICE~~

~~This study will be conducted in accordance with:~~

- ~~Good Clinical Practice (GCP),~~
- ~~as defined by the International Council on Harmonisation (ICH)~~
- ~~in accordance with the ethical principles underlying European Union Directive 2001/20/EC~~
- ~~United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)~~
- ~~applicable local requirements.~~

~~The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.~~

~~All potential serious breaches must be reported to Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.~~

~~Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.~~

~~This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).~~

~~INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE~~

~~Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (e.g., advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.~~

~~The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.~~

Rationale: Text regarding ethical considerations was updated to conform to Biogen template language. Also, clarification was needed to appropriately outline the responsibilities of the Investigator in situations where a study participant loses capacity to provide informed consent over the course of the study. This additional language is based on a Protocol Clarification Letter for Study 251PP301, dated 21 June 2017.

Appendix 3, Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting

Change: Appendix 3 was revised to reflect compatibility with safety processes at Biogen.

Now reads:
The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:

> **Related: An AE will be considered "related" to the use of the investigational product if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to a positive rechallenge, a reasonable temporal sequence between administration of the investigational product and the AE, a known response pattern of the suspected product, improvement following discontinuation or dose reduction, a biologically plausible relationship between the product and the AE, or a lack of an alternative explanation for the AE.**
>
> **Not related: An AE will be considered "not related" to the use of the investigational product if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to the lack of reasonable temporal relationship between administration of the investigational product and the AE, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.**

Rationale: Appendix 3 was updated to reflect compatibility and alignment with safety processes at Biogen.

Appendix 4, Women of Childbearing Potential Definitions and Methods of Contraception

Change: Appendix 4 was revised to clarify contraceptive requirements.
Now reads:

Contraceptive methods that are approved for use during and for 30

days after participation in this study are: *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 10.5. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the

absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness
~~**Less Than Highly Effective Contraceptive Methods That Are User Dependent**~~ ~~*Failure rate of >1% per year when used consistently and correctly.*~~
~~• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously~~ ~~• Diaphragm with spermicide~~ ~~• Cervical cap with spermicide~~ ~~• Vaginal Sponge with spermicide~~ ~~• Progestogen only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action~~
• **Unacceptable Methods of Contraception**
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

Rationale: Based on feedback from the Medicines and Healthcare products Regulatory Agency (MHRA), Appendix 4 was revised to align with the body of the protocol, which describes the need for highly effective contraceptive use.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- Table of Contents was updated.
- List of Abbreviations was updated.