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PROTOCOL NUMBER: 228PD201 / NCT03318523

PHASE OF DEVELOPMENT: 2a

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study, with an Active-Treatment Dose-Blinded Period, to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of BIIB054 in Subjects with Parkinson's Disease

EUDRA CT NO: 2016-004610-95

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Version 8
FINAL

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SPONSOR SIGNATURE PAGE

Protocol 228PD201 was approved by:

[redacted]

13 AUGUST 2020

[redacted] PhD

Date (DD-Mon-YYYY)

[redacted]

Biogen

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

Biogen MA Inc. is the Sponsor of the study.

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For urgent medical issues in which the study's Medical Director should be contacted, please refer to the Study Reference Manual'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.

2. LIST OF ABBREVIATIONS

α-syn	alpha-synuclein
[redacted]	[redacted]
[redacted]	[redacted]
AE	adverse event
Anti-HBc	hepatitis B core antibody
Anti-HBs	hepatitis B surface antibody
APTT	activated partial thromboplastin time
AUC	area under the concentration-time curve
AUC_{tau}	area under the concentration-time curve within a dosing interval
CI	confidence interval
C_{max}	maximum observed concentration
COMT	catechol-*O*-methyltransferase
CRO	contract research organization
[redacted]	[redacted]
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DaT	dopamine transporter
DaTscan™	ioflupane I123 radioligand for imaging of dopamine transporter
DBP	diastolic blood pressure
DHA	Directions for Handling and Administration
[redacted]	[redacted]
eCRF	electronic case report form
EC_{50}	concentration at 50% of maximum observed biologic effect
EC_{90}	concentration at 90% of maximum observed biologic effect
ECG	electrocardiogram
[redacted]	[redacted]
E_{max}	maximum effect
[redacted]	[redacted]
[redacted]	[redacted]
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IgG	immunoglobulin G
INR	international normalized ratio
IRT	interactive response technology

ISF	interstitial fluid
ITT	intent-to-treat
IV	intravenous
LB	Lewy body
LN	Lewy neurite
LP	lumbar puncture
LSmeans	least-squares means
mAb	monoclonal antibody
MAO-B	monoamine oxidase type B
[redacted]	[redacted]
MCP-MOD	multiple comparison procedure-modelling
MDS-UPDRS	Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale
MMRM	mixed model for repeated measures
[redacted]	[redacted]
MRI	magnetic resonance imaging
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
[redacted]	[redacted]
PD	Parkinson's disease
[redacted]	[redacted]
PK	pharmacokinetic(s)
PT	prothrombin time
QALY	quality-adjusted life year
[redacted]	[redacted]
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SBR	striatal binding ratio
[redacted]	[redacted]
SD	standard deviation
SNCA	alpha-synuclein gene
SNRI	serotonin norepinephrine reuptake inhibitor
SPECT	single-photon emission computed tomography
SSRI	selective serotonin reuptake inhibitors
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
[redacted]	[redacted]

3. SYNOPSIS

Protocol Number:	228PD201
Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study, with an Active-Treatment Dose-Blinded Period, to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of BIIB054 in Subjects with Parkinson's Disease
Version Number	8
Name of Study Treatment:	BIIB054
Study Indication:	Parkinson's disease (PD)
Study Rationale	BIIB054 is a human monoclonal antibody that targets aggregated forms of alpha-synuclein (α-syn), and is being developed by Biogen for the treatment of PD. Neuropathological, genetic, and functional animal studies all point to a causative role of α-syn in the pathogenesis of PD. Alpha-synuclein is a primary structural component of Lewy bodies (LBs) and Lewy neurites, which are the pathological hallmarks of PD. Anatomical distribution, density, and severity of LB pathology are associated with clinical disease severity. Owing to the strong links between α-syn and PD pathogenesis, it has become an important target for potential disease-modifying treatments. BIIB054 binds with subnanomolar affinity to the N-terminal region (aa 4-10) of α-syn and does not bind to other homologous members of the synuclein family. The murine chimeric version of BIIB054 improved synuclein pathology in transgenic animal models that either overexpress α-syn or express mutated α-syn. This version of BIIB054 also improved motor performance in 2 different transgenic animal models that express mutated α-syn. Early stage PD patients were selected as the test population in this study, as binding of α-syn may be more effective in modifying the course of the disease when less neuronal damage is evident and the spread of disease pathology is more limited.

Phase of Development: 2a

Study Objectives and Endpoints:

Primary Objective	**Primary Endpoints**
To evaluate the clinical efficacy of BIIB054 via dose response using the change from baseline in Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Total Score	Change from baseline in MDS-UPDRS Total Score (Sum of Parts I, II, and III) at the primary timepoints of Week 52 and Week 72
Secondary Objectives	**Secondary Endpoints**
To evaluate the dose-related safety of BIIB054	Incidence of adverse events (AEs) and serious adverse events (SAEs)
To evaluate the clinical efficacy of BIIB054 via MDS-UPDRS Total Score	Change from baseline in MDS-UPDRS Total Score (Sum of Parts I, II, and III) at end of study
To assess the PK profile of BIIB054	Concentration of BIIB054 in the serum
To evaluate the clinical efficacy of BIIB054 based on MDS-UPDRS subparts	Change from baseline to Week 52, Week 72, and end of study in MDS-UPDRS of Subparts I, II, and III (each part separately)
To evaluate the pharmacodynamic effects of BIIB054 on the integrity of nigrostriatal dopaminergic nerve terminals	Change from baseline to Week 52 in striatal binding ratio (SBR) in the putamen, striatum, and caudate as measured by single-photon emission computed tomography (SPECT) imaging of the dopamine transporter (DaT) with ioflupane I123 (DaTscan™)
To evaluate the immunogenicity of BIIB054	Incidence and titer of anti-BIIB054 antibodies in the serum

Exploratory objectives and endpoints are listed in Section 6.

Study Design: Phase 2a, randomized, double-blind, parallel-group, placebo-controlled study (Year 1) with an active-treatment dose-blinded period (Years 2 through 4). The study will end when the last subject in the study has completed the Final Visit at the end of Year 2, 12 weeks after administration of

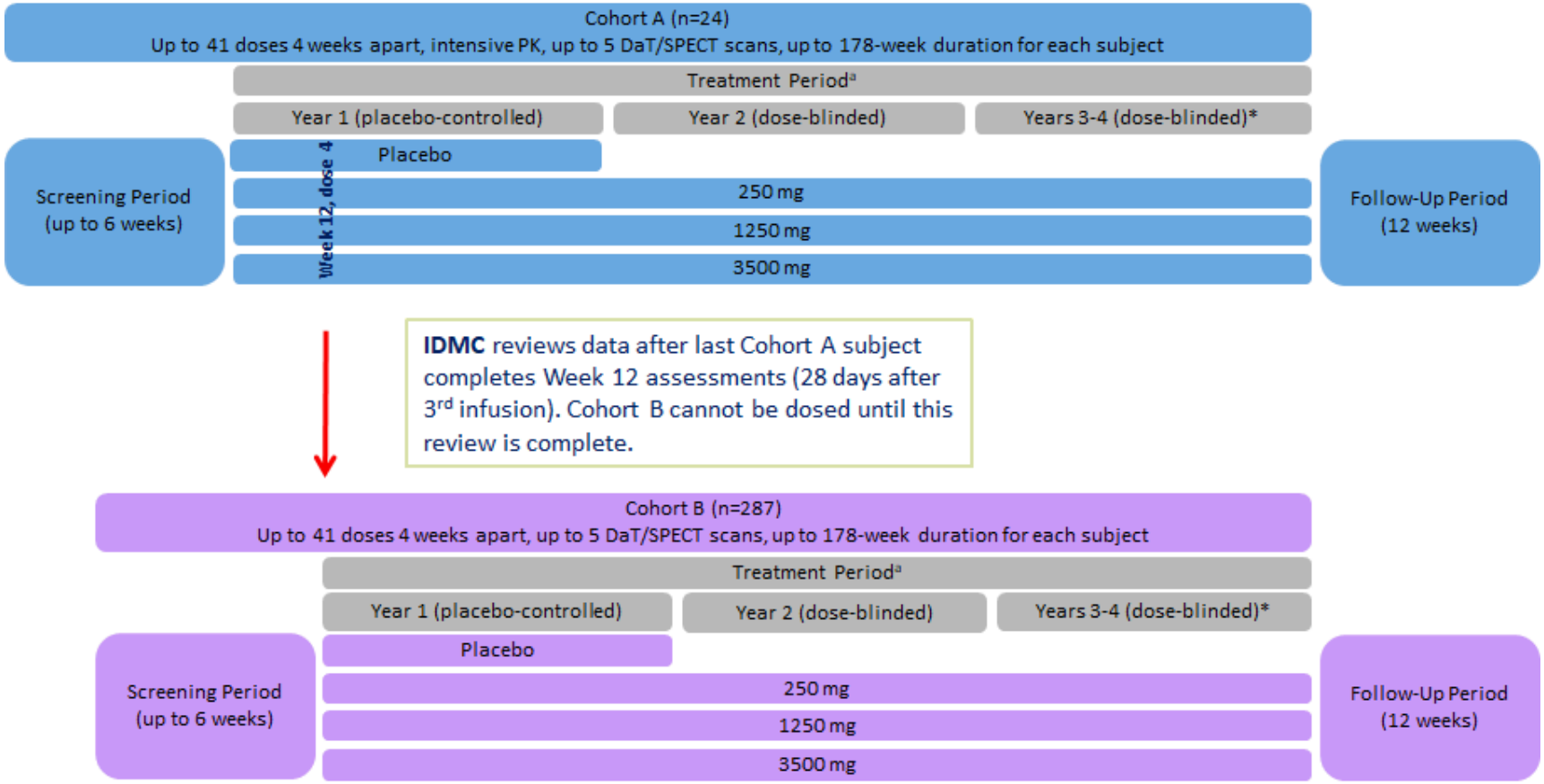
	the last dose at Week 96.
Study Location:	Approximately 85 sites are planned globally.
Number of Planned Subjects:	Approximately 311 subjects will be enrolled.
Study Population:	This study will be conducted in subjects aged 40 to 80 years at the time of informed consent, who have been diagnosed with clinically established PD within a maximum of 3 years prior to Screening, with no other known or suspected cause of Parkinsonism. Subjects must not receive any treatment for PD within 12 weeks prior to Day 1, and total duration of any previous PD treatment regimens should not exceed 30 days. Subjects should have a score of ≤ 2.5 on the Modified Hoehn and Yahr Scale, and should have screening DaT/SPECT results demonstrating activity consistent with neurodegenerative Parkinsonism. Detailed criteria are described in Section 8.
Treatment Groups:	In Year 1 (the placebo-controlled portion of the study), subjects will be randomized into the following 4 parallel dosing arms, to receive treatment every 4 weeks: • Arm 1: Placebo • Arm 2: BIIB054 250 mg • Arm 3: BIIB054 1250 mg • Arm 4: BIIB054 3500 mg Subjects will be enrolled in 2 cohorts. Cohort A will be randomized first and will include approximately 24 subjects. Cohort B will be randomized after all subjects in Cohort A complete Week 12 assessments and will include approximately 287 subjects. Dose levels, number of treatment arms, and number of subjects per arm in Cohort B may be adjusted based on the safety and PK data from Cohort A and on review by the independent data monitoring committee (IDMC). Any changes will be documented in a protocol amendment. Per this protocol amendment (Version 8), the actual enrollment is 357 subjects with 29 subjects randomized to Cohort A and 328 subjects randomized to Cohort B. After all subjects in Cohort A complete Week 12 assessments (28 days after their third infusion) and before

	dosing any subjects in Cohort B, all available safety and PK data will be reviewed by the IDMC. Only the IDMC will review unblinded data. The Sponsor, site staff, and subjects will remain blinded. No subjects in Cohort B may be dosed until the IDMC review is complete. During the review period, subjects in Cohort A will continue to be dosed every 4 weeks. Subjects will continue treatment in Year 2 (the active-treatment dose-blinded portion of the study). Subjects who received placebo in Year 1 will be randomized to 1 of the active-treatment arms to receive BIIB054 in Year 2. Subjects who received BIIB054 (250, 1250, or 3500 mg) in Year 1 will continue with the same dose regimen in Years 2 through 4.
Duration of Treatment and Follow-up:	The total duration of study participation for each subject will be at most 178 weeks, including a 6-week Screening period, a 48-week placebo-controlled treatment period, up to a 112-week active-treatment dose-blinded period, and a 12-week follow-up period. Not all subjects will have the opportunity for dosing past Year 2/Week 96.

4. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES FOR STUDY 228PD201

4.1. Study Schematic

Figure 1: Study Design

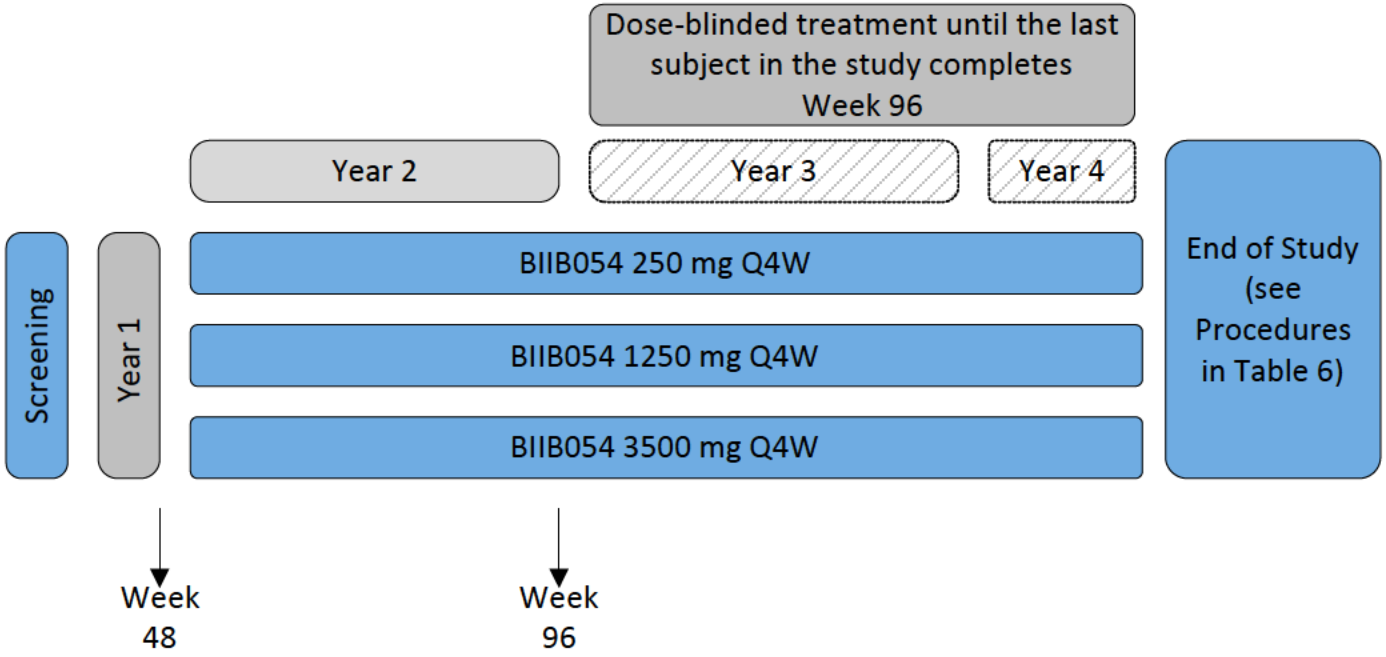


DaT = dopamine transporter; IDMC = independent data monitoring committee; PK = pharmacokinetic(s); SPECT = single-photon emission computed tomography

[a] Prior to Infusion 14 (first dose of Year 2), subjects who received placebo in Year 1 will be randomized to 1 of the active-treatment groups; these subjects will receive BIIB054 in Year 2. Subjects who received BIIB054 in Year 1 will continue with the same dose regimen in Years 2 through 4. Dosing will continue until the last subject in the study has had his or her Week 96 Visit. Not all subjects will have the opportunity for dosing past Year 2/Week 96.

Note: As of Protocol Version 8, actual enrollment was 357 subjects with 29 subjects randomized to Cohort A and 328 subjects randomized to Cohort B.

Figure 2: Overview of Study Dosing



Q4W = every 4 weeks.
Year 1 = Placebo-controlled period. Years 2 through 4 = Active-treatment dose-blinded period. Not all subjects will have the opportunity for dosing past Year 2/Week 96.

4.2. Schedule of Activities

Table 1: Cohort A: Infusions 1–3 (Year 1)

Tests and assessments	Screening ≤42 days before Day 1[1]	Infusions 1-3 Day 1/Baseline, Day 29 (±1 day), & Day 57 (±1 day)						Clinic Visits				Day 43 (Safety Telephone Call)
								Day 2, 30, 58	Day 4, 60	Day 8, 36, 64	Day 15, 71	
		Pre-infusion[2]	0m	Time after End of Last Infusion								
				≤10m	1h ±15m	2h ±15m	4h ±30m	24h ±2h	72h -2h/+1d	168h ±24h	336h ±24h	336h ±24h
Informed consent	X											
[redacted]												
Verification of eligibility		X[3]										
Medical history	X	X[3]										
Body weight	X	X										
Height	X											
Physical/neurological examination[4]	X	X[3]										
12-lead ECG[5]	X	X			X			X				
Vital signs[6]	X	X			X	X	X	X	X	X	X	
HbA_{1c}	X											
Urine pregnancy test[7]		X										
Serum pregnancy test[7]	X											
FSH test[8]	X											
Coagulation panel including platelet count	X											
Hematology, blood chemistry, urinalysis	X	X						X		X		
HBsAg, anti-HBc, anti-HBs, HCVAb, HIV	X											
Drug screen	X	X[3]										

Tests and assessments	Screening ≤42 days before Day 1[1]	Infusions 1-3 Day 1/Baseline, Day 29 (±1 day), & Day 57 (±1 day)						Clinic Visits				Day 43 (Safety Telephone Call)
								Day 2, 30, 58	Day 4, 60	Day 8, 36, 64	Day 15, 71	
		Pre-infusion[2]	0m	Time after End of Last Infusion								
				≤10m	1h ±15m	2h ±15m	4h ±30m	24h ±2h	72h -2h/+1d	168h ±24h	336h ±24h	336h ±24h
[redacted]												
Brain MRI[12]	X											
DaT/SPECT[12]	X											
Randomization		X[3]										
Study treatment infusion[13]			X									
BIIB054 serum PK sampling		X[14]		X	X[15]	X[15]	X[15]	X[16]	X	X[17]	X	
Serum for anti-BIIB054 antibodies		X									X[18]	
[redacted]												
MDS-UPDRS (full scale), includes Modified Hoehn and Yahr Scale[20]	X	X								X	X	
[redacted]												

Tests and assessments	Screening ≤42 days before Day 1[1]	Infusions 1-3 Day 1/Baseline, Day 29 (±1 day), & Day 57 (±1 day)						Clinic Visits				Day 43 (Safety Telephone Call)
								Day 2, 30, 58	Day 4, 60	Day 8, 36, 64	Day 15, 71	
		Pre-infusion[2]	0m	Time after End of Last Infusion								
				≤10m	1h ±15m	2h ±15m	4h ±30m	24h ±2h	72h -2h/+1d	168h ±24h	336h ±24h	336h ±24h
[redacted]												
C-SSRS[22]		X						X	X	X	X	
AE reporting[23]			ongoing									
Concomitant therapy and procedures reporting	ongoing											
SAE reporting	ongoing											

[redacted]; AE = adverse event; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; d = day(s); DaT = dopamine transporter; [redacted]; ECG = electrocardiogram; [redacted]; FSH = follicle stimulating hormone; h = hour(s); HbA_{1c} = glycated hemoglobin; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; HIV = human immunodeficiency virus; m = minute(s); MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; [redacted]; MRI = magnetic resonance imaging; [redacted]; PD = Parkinson's disease; [redacted]; PK = pharmacokinetic(s); [redacted]; [redacted]; SAE = serious adverse event; [redacted]; SPECT = single-photon emission computed tomography; [redacted].

[1] Screening assessments can be performed over ~2 days (need not be consecutive) to minimize subject burden. Subjects may be rescreened or screening tests repeated in certain circumstances (see Section 9.1).

[2] Assessments can occur on the day before dosing or predose on the day of dosing, at Investigator's discretion, except for the following: randomization, pregnancy test, vital signs, and ECG must be obtained predose on day of dosing. MDS-UPDRS results must be available before randomization. [redacted]

[3] Performed on Day 1 only.

[4] A full physical and neurological examination will be performed at the specified timepoints. At all other visits, a targeted physical and/or neurological examination will be performed if the Investigator determines it is warranted by adverse events.

[5] A 12-lead ECG will be obtained at each specified timepoint. Each must be performed after the subject has been resting in a supine position for at least 10 minutes. The ECGs will be read by the Investigator at collection. Predose readings **must be obtained predose on the day of dosing**.

[6] Vital signs will include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, body temperature, and respiratory rate and will be measured after the subject has been resting in a supine position for at least 10 minutes. Three separate SBP/DBP and pulse readings at least 15 minutes apart will be made at Screening to determine eligibility. Orthostatic vital sign measurements will also be obtained whenever blood pressure is read (see Section 14.1), but do not need to be repeated 3 times at Screening. Predose readings **must be obtained predose on the day of dosing**.

[7] Required for women of childbearing potential. Predose samples (urine test only) **must be collected predose on the day of dosing**.
[8] To confirm postmenopausal status in postmenopausal female subjects.
[redacted]
[10] Performed on Day 1 and Day 29 only.
[redacted]
[12] The MRI results will be read by the local radiologist at collection. Both MRI and DaT/SPECT results will be sent within 24 hours to a central reader for further evaluation and to confirm eligibility at Screening. Screening imaging assessments should be completed after all other eligibility criteria have been met, and before Day -7, to allow adequate time for evaluation of the results. Subjects will be contacted by telephone within 7 days following the DaT/SPECT procedure to monitor for AEs.
[13] Subjects will be under observation for at least 1 hour after the end of each infusion.
[14] Samples to be collected within 1 hour pre-infusion.
[15] Collected on Days 1 and 57 only.
[16] Collected on Days 2 and 58 only.
[17] Collected on Days 8 and 64 only.
[18] Collected on Day 15 only.
[redacted]
[22] The "Since Last Visit" version of the C-SSRS will be administered at all clinic visits following the Day 1/Baseline assessment. If the Investigator has any concern regarding the completed C-SSRS, the subject should be referred to psychiatric evaluation based on local standards of care.
[23] Nonserious AEs that occur during the Screening period and that are assessed by the Investigator as related to the ligand will be captured by the sites on the AE electronic case report form (eCRF). After the first dose of study treatment, all AEs are collected, both related and unrelated to the ligand (see Section 15.3.1).

Table 2: Cohort A: Infusions 4–13 (Year 1)

Tests and assessments	Infusions 4-13, Week (±3d)										PK Visits, Week (±3d)	Year 1 Week 52, (±3d)[2]
	12	16	20	24	28	32	36	40	44	48	22, 34, or 46[1]	
Physical/neurological examination[3,4]												X
Body weight[3]	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[3,5]	X			X			X			X		
Vital signs[3,6]	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[3,7]	X	X	X	X	X	X	X	X	X	X		
Coagulation panel including platelet count[8]			X							X		
Hematology, blood chemistry, urinalysis[3]	X	X	X	X	X	X	X	X	X	X		X
[redacted]												
Brain MRI[10]				X								X
DaT/SPECT[10]				X								X
Study treatment infusion[11]	X	X	X	X	X	X	X	X	X	X		
BIIB054 serum PK sampling	X[12]	X[12]		X[13]			X[12]				X	X[12]
Serum for anti-BIIB054 antibodies[3]				X			X					X
[redacted]												
MDS-UPDRS (full scale), includes Modified Hoehn and Yahr Scale[3,14]		X		X		X		X		X		X
[redacted]												

Tests and assessments	Infusions 4-13, Week (±3d)										PK Visits, Week (±3d)	Year 1 Week 52, (±3d)[2]
	12	16	20	24	28	32	36	40	44	48	22, 34, or 46[1]	
[redacted]												
C-SSRS[3,16]	X	X	X	X	X	X	X	X	X	X	X	X
AE/Concomitant therapy and procedures	ongoing											
SAE reporting	ongoing											

[redacted]; AE = adverse event; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; d = day(s); DaT = dopamine transporter; ECG = electrocardiogram; [redacted]; MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; MRI = magnetic resonance imaging; [redacted]; PD = Parkinson's disease; PK = pharmacokinetic(s); [redacted]; SAE = serious adverse event; [redacted]; SPECT = single-photon emission computed tomography; wk = week(s); [redacted].

[1] Subjects to complete only 1 of the 3 visits, at Week 22, 34, OR 46.

[2] Assessments shown for the Year 1 Week 52 Visit will be considered part of Year 1 of the study. Vital signs and pregnancy test will be obtained at the Year 2 Week 52 Visit (see Table 4). The Year 1 Week 52 and Year 2 Week 52 visits (first visit of Year 2) can be conducted as a single visit.

[3] Performed/collected pre-infusion on dosing days.

[4] A full physical and neurological examination will be performed at the specified timepoints. At all other visits, a targeted physical and/or neurological examination will be performed if the Investigator determines it is warranted by adverse events.

[5] A 12-lead ECG will be obtained at each specified timepoint. Each must be performed after the subject has been resting in a supine position for at least 10 minutes. The ECGs will be read by the Investigator at collection. Predose readings **must be obtained predose on the day of dosing**.

[6] Vital signs will include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, body temperature, and respiratory rate and will be measured after the subject has been resting in a supine position for at least 10 minutes. Predose readings **must be obtained predose on the day of dosing**. Orthostatic vital sign measurements will also be obtained whenever blood pressure is read, as described in Section 14.1.

[7] Required for women of childbearing potential. Predose samples **must be collected predose on the day of dosing**.

[8] [redacted] Results from the prior [redacted] samples and results of the most recent coagulation tests (within 42 days) including platelet count must be reviewed by the Investigator before each lumbar puncture can be performed.

[redacted]

[10] The MRI and DaT/SPECT assessment windows for all visits are ±7 days, except for week 52 MRI and DaT/SPECT which has -7 day window only to allow Year 2 dosing to be appropriately scheduled. The MRI results will be read by the local radiologist at collection. Both MRI and DaT/SPECT results will be sent within 24 hours to a central reader for further evaluation. Subjects will be contacted by telephone within 7 days following the DaT/SPECT procedure to monitor for AEs. See Section 7.2.2.3 for further details on subjects who start symptomatic Parkinson's disease (PD) medication during this study.

[11] Subjects will be under observation for at least 1 hour after the end of each infusion.

[12] Samples to be collected within 1 hour pre-infusion and within 1 hour following the end of infusion.

[13] Samples to be collected within 1 hour pre-infusion.

[14] Subjects who have started symptomatic PD medication during the study should refrain from taking the PD medication for approximately 12 hours prior to MDS-UPDRS [redacted] visits. MDS-UPDRS Part III [redacted] will be administered before the subjects take the PD medication [redacted]

[redacted]

The "Since Last Visit" version of the C-SSRS will be administered. If the Investigator has any concern regarding the completed C-SSRS, the subject should be referred to psychiatric evaluation based on local standards of care.

Table 3: Cohort B: Infusions 1–13 (Year 1)

Tests and assessments	Screening ≤42d Before Day 1[1]	Day 1[2] Baseline/ Infusion 1	Safety Telephone Calls 1d & 7d after Infusion 1[2]	Infusions 2-13, Week (±3d)													PK Visits, Week (±3d)	Year 1 Week 52, (±3d)[4]
				4[2]	Safety Telephone Calls 1d & 7d after Infusion 2[2]	8[2]	Safety Telephone Calls 1d & 7d after Infusion 3[2]	12	16	20	24	28	32	36	40	44	48	22, 34, or 46[3]	
Informed consent	X																		
[redacted]																			
Verification of eligibility		X[5]																	
Medical history	X	X[5]																	
Body weight[6]	X	X[5]		X		X		X	X	X	X	X	X	X	X	X	X	X	
Height	X																		
Physical/neurological examination[7]	X	X[5]																	X
12-lead ECG[6,8]	X	X[5]						X			X			X			X		
Vital signs[6,9]	X	X[5]		X		X		X	X	X	X	X	X	X	X	X	X	X	
HbA_{1c}	X																		
Urine pregnancy test[6,10]		X[5]		X		X		X	X	X	X	X	X	X	X	X	X		
Serum pregnancy test[10]	X																		
FSH test[11]	X																		
Coagulation panel including platelet count	X									X[12,13]							X[12,13]		
Hematology, blood chemistry, urinalysis[6]	X	X[5]						X			X			X			X		X
HBsAg, anti-HBc, anti-HBs, HCVAb, HIV	X																		
Drug screen	X	X[5]																	

Tests and assessments	Screening ≤42d Before Day 1[1]	Day 1[2] Baseline/ Infusion 1	Safety Telephone Calls 1d & 7d after Infusion 1[2]	Infusions 2-13, Week (±3d)														PK Visits, Week (±3d)	Year 1 Week 52, (±3d)[4]
				4[2]	Safety Telephone Calls 1d & 7d after Infusion 2[2]	8[2]	Safety Telephone Calls 1d & 7d after Infusion 3[2]	12	16	20	24	28	32	36	40	44	48	22, 34, or 46[3]	
[redacted]																			
Brain MRI[16]	X[17]										X								X
DaT/SPECT[16]	X[17]										X								X
Randomization		X[5]																	
Study treatment infusion[18]		X		X		X		X	X	X	X	X	X	X	X	X	X		
BIIB054 serum PK sampling[19]		X[5]		X		X		X	X		X			X				X	X
Serum for anti-BIIB054 antibodies[6]		X[5]		X							X			X					X
[redacted]																			
MDS-UPDRS (full scale), includes Modified Hoehn and Yahr Scale[6,23]	X	X[5]				X			X		X		X		X		X		X
[redacted]																			

Tests and assessments	Screening ≤42d Before Day 1[1]	Day 1[2] Baseline/ Infusion 1	Safety Telephone Calls 1d & 7d after Infusion 1[2]	Infusions 2-13, Week (±3d)														PK Visits, Week (±3d)	Year 1 Week 52, (±3d)[4]
				4[2]	Safety Telephone Calls 1d & 7d after Infusion 2[2]	8[2]	Safety Telephone Calls 1d & 7d after Infusion 3[2]	12	16	20	24	28	32	36	40	44	48	22, 34, or 46[3]	
[redacted]																			
C-SSRS[6,25]		X[5]		X		X		X	X	X	X	X	X	X	X	X	X	X	X
AE reporting[26]		ongoing																	
Concomitant therapy and procedures	ongoing																		
SAE reporting	ongoing																		

[redacted]; AE = adverse event; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; d = day(s); DaT = dopamine transporter; [redacted]; ECG = electrocardiogram; [redacted] FSH = follicle stimulating hormone; HbA_{1c} = glycated hemoglobin; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; HIV = human immunodeficiency virus; MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; [redacted]; MRI = magnetic resonance imaging; [redacted]; PD = Parkinson's disease; [redacted]; PK = pharmacokinetic(s); [redacted]; [redacted]; SAE = serious adverse event; [redacted]; SPECT = single-photon emission computed tomography; [redacted].

[1] Screening assessments can be performed over ~2 days (need not be consecutive) to minimize subject burden. Subjects may be rescreened or screening tests repeated in certain circumstances (see Section 9.1).

[2] Subjects will receive 6 Safety Telephone Calls to ask about AEs, SAEs, and concomitant medications approximately 1 day (24 hours) and 7 days (168 hours) after each of the first 3 infusions: Days 2 and 8 (follow-up after first infusion); Days 30 and 36 (follow-up after second infusion); and Days 58 and 64 (follow-up after third infusion).

[3] Subjects to complete only 1 of the 3 visits at Week 22, 34, OR 46.

[4] Assessments shown for the Year 1 Week 52 Visit will be considered part of Year 1 of the study. Vital signs and pregnancy test will be obtained at the Year 2 Week 52 Visit (see Table 4). The Year 1 Week 52 and Year 2 Week 52 visits (first visit of Year 2) can be conducted as a single visit.

[5] The specified baseline assessments should be performed on the day before dosing or predose on the day of dosing, at the Investigator's discretion, except for the following: randomization, pregnancy test, vital signs, and ECG must be obtained predose on the day of dosing. MDS-UPDRS results must be available before randomization.

[6] Performed/collected pre-infusion on dosing days.

[7] A full physical and neurological examination will be performed at the specified timepoints. At all other visits, a targeted physical and/or neurological examination will be performed if the Investigator determines it is warranted by adverse events.

[8] A 12-lead ECG will be obtained at each specified timepoint. Each must be performed after the subject has been resting in a supine position for at least 10 minutes. The ECGs will be read by the Investigator at collection. Predose readings **must be obtained predose on the day of dosing**.

[9] Vital signs will include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, body temperature, and respiratory rate and will be measured after the subject has been resting in a supine position for at least 10 minutes. Three separate SBP/DBP and pulse readings at least 15 minutes apart will be made at Screening to determine eligibility. Orthostatic vital sign measurements will also be obtained whenever blood pressure is read (see Section 14.1), but do not need to be repeated 3 times at Screening. Predose readings **must be obtained predose on the day of dosing**.

[10] Required for women of childbearing potential. Predose samples (urine test only) **must be collected predose on the day of dosing**.

[11] To confirm postmenopausal status in postmenopausal female subjects.

[13] Results from the prior samples and results of the most recent coagulation tests (within 42 days) including platelet count must be reviewed by the Investigator before each post-Day 1 lumbar puncture can be performed.

[14] Whole blood samples for , serum, urine, and other analyses (including PK) are required samples (under the main consent).

[16] The MRI and DaT/SPECT assessment windows for all visits are ±7 days, except for week 52 MRI and DaT/SPECT which has a -7 day window only to allow Year 2 dosing to be appropriately scheduled. The MRI results will be read by the local radiologist at collection. Both MRI and DaT/SPECT results will be sent within 24 hours to a central reader for further evaluation and to confirm eligibility at Screening. Subjects will be contacted by telephone within 7 days following the DaT/SPECT procedure to monitor for AEs. See Section 7.2.2.3 for further details for subjects who start symptomatic PD medication during this study.

[17] Screening imaging assessments should be completed after all other eligibility criteria have been met, and at least 8 business days before Day 1/randomization, to allow adequate time for evaluation of the results.

[18] Subjects will be under observation for at least 1 hour after the end of each infusion.

[19] Samples to be collected within 1 hour pre-infusion and within 1 hour following the end of infusion on dosing days.

[23] Subjects who have started symptomatic Parkinson's disease (PD) medication during this study (not applicable to the Screening or Day 1 Visit) should refrain from taking the PD medication for approximately 12 hours prior to MDS-UPDRS visits. MDS-UPDRS Part III will be administered before subjects take the PD medication .

[redacted]

The "Since Last Visit" version of the C-SSRS will be administered at all clinic visits following the Day 1/Baseline assessment. If the Investigator has any concern regarding the completed C-SSRS, the subject should be referred to psychiatric evaluation based on local standards of care.

[26] Nonserious AEs that occur during the Screening period and that are assessed by the Investigator as related to the ligand will be captured by the sites on the AE electronic case report form. After the first dose of study treatment, all AEs are collected, both related and unrelated to the ligand (see Section 15.3.1).

Table 4: Cohorts A and B: Infusions 14–25 (Year 2)

Tests and assessments	Year 2 Week 52 (±3d)[1] Infusion 14	Safety Telephone Calls 1d & 7d after Infusion 14[2]	Infusions 15-25[3] Week (±3d) 56	60	64	68	72	76	80	84	88	92	96[5]	Unsched Visit[3,4]
Body weight[6]	X			X			X			X			X	
Physical/neurological examination[7]			X	X										X
12-lead ECG[6,8]	X		X										X	
Vital signs[6,9]	X		X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test [6,10]	X		X	X	X	X	X	X	X	X	X	X	X	
Hematology, blood chemistry, urinalysis[6]				X									X	X
[redacted]														
Brain MRI[12]													X	
DaT/SPECT[12]													X	
Randomization[13]	X													
Study treatment infusion[14]	X		X	X	X	X	X	X	X	X	X	X	X	
BIIB054 serum PK sampling[15]	X			X						X			X	
Serum for anti-BIIB054 antibodies[6]				X						X			X	
[redacted]														
MDS-UPDRS (full scale), includes Modified Hoehn and Yahr Scale[6,17]				X			X			X			X	X
[redacted]														

Tests and assessments	Year 2 Week 52 (±3d)[1] Infusion 14	Safety Telephone Calls 1d & 7d after Infusion 14[2]	Infusions 15-25[3] Week (±3d) 56	60	64	68	72	76	80	84	88	92	96[5]	Unsched Visit[3,4]
[redacted]														
C-SSRS[6,19]			X	X	X	X	X	X	X	X	X	X	X	X
AE/Concomitant therapy and procedures	ongoing													
SAE reporting	ongoing													

[redacted]; AE = adverse event; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; d = day; DaT = dopamine transporter; ECG = electrocardiogram; [redacted]; ET = early termination; [redacted]; MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; [redacted]; MRI = magnetic resonance imaging; [redacted]; PD = Parkinson's disease; [redacted]; PK = pharmacokinetic(s); [redacted]; SAE = serious adverse event; [redacted]; SPECT = single-photon emission computed tomography; Unsched = unscheduled; [redacted].

[1] The Year 1 Week 52 and Year 2 Week 52 visits (first visit of Year 2) can be conducted as a single visit.

[2] Subjects will receive Safety Telephone Calls to ask about AEs, SAEs, and concomitant medications approximately 1 day (24 hours) and 7 days (168 hours) after Infusion 14 (follow-up after first infusion in Year 2).

[3] Remote Visits will be done in the event of a public health emergency that results in site closure, travel restrictions, or the study being deprioritized at the site such that visit(s) cannot occur. Use of a Remote Visit will not be done in place of an onsite visit simply due to subject preference. If a subject does not participate in a remote or clinic visit, a Safety Telephone Call must be conducted. Refer to Table 12, Table 13, and Table 14 for Remote Visit assessments.

[4] Unscheduled Visit can occur for safety-related issues at any time (as determined by the Investigator) or for administering the MDS-UPDRS prior to starting symptomatic PD medications outside of a scheduled visit. Additional tests may be performed at the Investigator's discretion.

[5] Consult Figure 4 to see if subject qualifies to continue dosing in Years 3 and 4 (if applicable).

[6] Performed/collected pre-infusion on dosing days.
[7] A full physical and neurological examination will be performed at the specified timepoints. At all other visits, a targeted physical and/or neurological examination will be performed if the Investigator determines it is warranted by adverse events.
[8] A 12-lead ECG will be obtained at each specified timepoint. Each must be performed after the subject has been resting in a supine position for at least 10 minutes. The ECGs will be read by the Investigator at collection. Predose readings **must be obtained predose on the day of dosing**.
[9] Vital signs will include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, body temperature, and respiratory rate and will be measured after the subject has been resting in a supine position for at least 10 minutes. Predose readings **must be obtained predose on the day of dosing**. Orthostatic vital sign measurements will also be obtained whenever blood pressure is read, as described in Section 14.1.
[10] Required for women of childbearing potential. Predose samples **must be collected predose on the day of dosing**.
[11] Whole blood samples for [redacted], serum, and urine samples [redacted] and other analyses are required samples (under the main consent).
[12] The MRI and DaT/SPECT assessment windows for all visits are ±7 days, except for week 52 MRI and DaT/SPECT which has a -7 day window only to allow Year 2 dosing to be appropriately scheduled. The MRI results will be read by the local radiologist at collection. Both MRI and DaT/SPECT results will be sent within 24 hours to a central reader for further evaluation. Subjects will be contacted by telephone within 7 days following the DaT/SPECT procedure to monitor for AEs. See Section 7.2.2.3 for further details for subjects who start symptomatic PD medication during this study.
[13] Prior to Infusion 14 (first dose of Year 2), subjects who received placebo in Year 1 will be randomized into 1 of the active-dosing arms to receive BIIB054 for Years 2 through 4. Subjects who received BIIB054 (250, 1250, or 3500 mg) in Year 1 of the study will continue with the same dose regimen in Years 2 through 4. No specific action related to randomization is required of the Investigators or study sites.
[14] Subjects will be under observation for at least 1 hour after the end of each infusion.
[15] Samples to be collected within 1 hour pre-infusion and within 1 hour following the end of infusion on dosing days.
[redacted]
[17] Subjects who have started symptomatic Parkinson's disease (PD) medication during this study should refrain from taking the PD medication for approximately 12 hours prior to MDS UPDRS [redacted] visits. MDS-UPDRS Part III [redacted] will be administered before subjects take the PD medication [redacted]
[redacted]
[19] The "Since Last Visit" version of the C-SSRS will be administered at all clinic visits. If the Investigator has any concern regarding the completed C-SSRS, the subject should be referred to psychiatric evaluation based on local standards of care.

Table 5: Cohorts A and B: Infusions 26–41 (Years 3 and 4)

	Year 3[2, 3] Infusions 26-38, Week (±3d) (13 monthly doses)													Year 4[2, 3] Infusions 39-41, Week (±3d) (3 monthly doses)			Unsched Visit[3, 4]
Tests and Assessments[1]	**100**	**104**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**	**160**	
Body weight[5]			X			X			X			X			X		
Physical/neurological examination[6]	X													X			X
12-lead ECG[5,7]	X													X			
Vital signs[5, 8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[5,9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology, blood chemistry, urinalysis[5]						X						X					X
[redacted]																	
Brain MRI[11]													X				
DaT/SPECT[11]													X				
Study treatment infusion[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
BIIB054 serum PK sampling[13]						X						X					
Serum for anti-BIIB054 antibodies[5]						X						X					
[redacted]																	
MDS-UPDRS (full scale), includes Modified Hoehn and Yahr Scale[5,15]			X			X			X			X			X		X
[redacted]																	

Tests and Assessments[1]	Year 3[2, 3] Infusions 26-38, Week (±3d) (13 monthly doses)												Year 4[2, 3] Infusions 39-41, Week (±3d) (3 monthly doses)			Unsched Visit[3, 4]
[redacted]																
C-SSRS[5, 17]		X		X		X		X		X		X		X		X	X
AE/Concomitant therapy and procedures	ongoing															
SAE reporting	ongoing															

[redacted]; AE = adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; d = day; DaT = dopamine transporter; ECG = electrocardiogram; [redacted]; MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; [redacted]; MRI = magnetic resonance imaging; PD = Parkinson's disease; [redacted]; PK = pharmacokinetic(s); [redacted]; SAE = serious adverse event; [redacted]; SPECT = single-photon emission computed tomography; Unsched = unscheduled; [redacted]

[1] For subjects whose Week 96 Visit is more than 1 month before the Last Subject Week 96 Visit (see Figure 4).

[2] During Years 3 and 4, subjects will receive infusions every 4 weeks. When the last subject has had the last dose in Year 2 (Week 96 Visit), no subjects will receive any further doses, and all remaining subjects will proceed to end of study procedures, as shown in Table 6.

[3] Remote Visits will be done in the event of a public health emergency that results in site closure, travel restrictions, or the study being deprioritized at the site such that visit(s) cannot occur. Use of a Remote Visit will not be done in place of an onsite visit simply due to subject preference. If a subject does not participate in a remote or clinic visit, a Safety Telephone Call must be conducted. Refer to Table 12, Table 13, and Table 14 for Remote Visit assessments.

[4] Unscheduled Visit can occur for safety related issues at any time (as determined by the Investigator) or for administering the MDS-UPDRS prior to starting symptomatic PD medications outside of a scheduled visit. Additional tests may be performed at the Investigator's discretion.

[5] Performed/collected pre-infusion on dosing days.

[6] A full physical and neurological examination will be performed at the specified timepoints. At all other visits, a targeted physical and/or neurological examination will be performed if the Investigator determines it is warranted by adverse events.

[7] A 12-lead ECG will be obtained at each specified timepoint. Each must be performed after the subject has been resting in a supine position for at least 10 minutes. The ECGs will be read by the Investigator at collection. Predose readings **must be obtained predose on the day of dosing**.

[8] Vital signs will include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, body temperature, and respiratory rate and will be measured after the subject has been resting in a supine position for at least 10 minutes. Predose readings **must be obtained predose on the day of dosing**. Orthostatic vital sign measurements will also be obtained whenever blood pressure is read, as described in Section 14.1.

[9] Required for women of childbearing potential. Predose samples **must be collected predose on the day of dosing**.

[10] Whole blood samples for [redacted], serum, and urine samples for [redacted] other analyses are required samples (under the main consent).

[11] The MRI and DaT/SPECT assessment windows for all visits are ±7 days, except for week 52 MRI and DaT/SPECT which has -7 day window only to allow Year 2 dosing to be appropriately scheduled. The MRI results will be read by the local radiologist at collection. Both MRI and DaT/SPECT results will be sent within 24 hours to a central reader for further evaluation. Subjects will be contacted by telephone within 7 days following the DaT/SPECT procedure to monitor for AEs. See Section 7.2.2.3 for further details for subjects who start symptomatic PD medication during this study.

[12] Subjects will be under observation for at least 1 hour after the end of each infusion.

[13] Samples to be collected within 1 hour pre-infusion and within 1 hour following the end of infusion on dosing days.

[redacted]

Subjects who have started symptomatic PD medication during this study should refrain from taking the PD medication for approximately 12 hours prior to MDS-UPDRS [redacted] visits. MDS-UPDRS Part III [redacted] will be administered before subjects take the PD medication [redacted]

[redacted]

[17] The "Since Last Visit" version of the C-SSRS will be administered approximately every 60 days. If the Investigator has any concern regarding the completed C-SSRS, the subject should be referred to psychiatric evaluation based on local standards of care.

Table 6: Cohorts A and B Early Termination and End of Study: 4 Weeks After Last Dose Through Final Visit

Tests and assessments	Last Dose +4 wk (±3d) /ET[1]	Safety Telephone Call (±2d) (Last Dose +8 wk)	Final Visit[1] (±3d) (Last Dose +12 wk)
Body weight	X		X
Physical/neurological examination[2]	X		X
Vital signs[3]	X		X
Serum pregnancy test[4]	X		X
Coagulation panel including platelet count			X
Hematology, blood chemistry, urinalysis	X		X
[redacted]			
Brain MRI[6]	X		
DaT/SPECT[6]	X		
BIIB054 serum PK sampling	X		X
Serum for anti-BIIB054 antibodies	X		X
[redacted]			
MDS-UPDRS (full scale), includes Modified Hoehn and Yahr Scale[7]	X		X
[redacted]			
C-SSRS[9]	X		X
AE/Concomitant therapy and procedures	ongoing		
SAE reporting	ongoing		

[redacted]; AE = adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; d = day; DaT = dopamine transporter; [redacted];

MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; [redacted]; MRI = magnetic resonance imaging; [redacted]; PD = Parkinson's disease; [redacted]; PK = pharmacokinetic(s); [redacted]; SAE = serious adverse event; [redacted]; SPECT = single-photon emission computed tomography; Unsched = unscheduled; wk = week; [redacted]

[1] Remote Visits will be done in the event of a public health emergency that results in site closure, travel restrictions, or the study being deprioritized at the site such that visit(s) cannot occur. Use of a Remote Visit will not be done in place of an onsite visit simply due to subject preference. If a subject does not participate in a remote or clinic visit, a Safety Telephone Call must be conducted. Refer to Table 12, Table 13, and Table 14 for Remote Visit assessments.

[2] A full physical and neurological examination will be performed at the specified timepoints. At all other visits, a targeted physical and/or neurological examination will be performed if the Investigator determines it is warranted by adverse events.

[3] Vital signs will include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, body temperature, and respiratory rate and will be measured after the subject has been resting in a supine position for at least 10 minutes. Orthostatic vital sign measurements will also be obtained whenever blood pressure is read, as described in Section 14.1.

[4] Required for women of childbearing potential.

[5] Whole blood samples for [redacted], serum, and urine samples [redacted] other analyses are required samples (under the main consent).

[6] Performed only for subjects who have not had the assessment at Week 96 (if withdrawing after Year 2) or Week 148 (if withdrawing after Year 3). Furthermore, DaT/SPECT is only to be performed if the time interval since the previous DaT/SPECT examination exceeds 23 weeks. This >23-week time interval restriction does not apply to MRI. The MRI and DaT/SPECT assessment windows for all visits are ±7 days, except for week 52 MRI and DaT/SPECT which has -7 day window only to allow Year 2 dosing to be appropriately scheduled. The MRI results will be read by the local radiologist at collection. Both MRI and DaT/SPECT results will be sent within 24 hours to a central reader for further evaluation. Subjects will be contacted by telephone within 7 days following the DaT/SPECT procedure to monitor for AEs.

[7] Subjects who have started symptomatic Parkinson's disease (PD) medication during this study should refrain from taking the PD medication for approximately 12 hours prior to MDS-UPDRS or [redacted]. MDS-UPDRS Part III [redacted] will be administered before subjects take the PD medication [redacted]

[redacted]

[9] The "Since Last Visit" version of the C-SSRS will be administered. If the Investigator has any concern regarding the completed C-SSRS, the subject should be referred to psychiatric evaluation based on local standards of care.

5. INTRODUCTION

BIIB054 is a human monoclonal antibody (mAb) that targets aggregated forms of alpha-synuclein (α-syn), and is being developed by Biogen for the treatment of Parkinson's disease (PD).

5.1. Overview of Parkinson's Disease

PD is the second most common neurodegenerative disease in the world [Bertram and Tanzi 2005]. In the United States, estimates of its prevalence vary, ranging from 430,000 to approximately 1 million affected persons [Beck 2016]. In Europe, available estimates of PD prevalence in recent generalizable studies of populous European Union countries [Hobson 2005; Morgante 2008; Totaro 2005; Wickremaratchi 2009] range from 0.11% in the United Kingdom [Hobson 2005] to 0.16% in central Italy [Totaro 2005]; these would correspond to a range of 600,000 to 800,000 persons living with PD in the European Union in 2016. In Israel, prevalence varies depending on the population studied, and is markedly higher among Israeli Jews (0.33%, or 28,000 cases in 2016) [Chillag-Talmor 2011] compared to the Israeli Arab population (0.04%, or 3400 cases) [Masalha 2010]. Across the world, the prevalent burden of PD is expected to double from 2005 to 2030, from approximately 4.5 million to 9 million cases [Dorsey 2007].

The incidence of PD increases with age; the disease is rare before age 50 years but affects up to 4% of the population in the oldest age groups [de Lau and Breteler 2006]. Men may be 1.5 times more likely to be affected than women, especially among patients older than 70 years of age, in western populations [Twelves 2003]. Severe disability or death may be expected in 35% of the patients within 5 years, in 65% of patients within 10 years, and in 80% of patients within 15 years of onset [Poewe 2006; Schrag and Banks 2006; Schrag 2000; Shulman 2006]**.** The economic burden of PD in the United States was approximately $15 billion in 2010 [Kowal 2013].

PD is clinically diagnosed by the constellation of rest tremor, bradykinesia, and rigidity. Other frequent symptoms include stooped posture, hypomimia, hypophonia, micrographia, and loss of postural stability. Although diagnosis of PD by clinicians is reasonably accurate [Jellinger 2016], pathologic hallmarks seen postmortem are required to make a definitive diagnosis. These include the loss of dopaminergic neurons in the pars compacta in the substantia nigra, and the presence of Lewy bodies (LBs) and Lewy neurites (LNs), which are α-syn-containing inclusions [Gelb 1999]. Cross-sectional and longitudinal studies show a relationship between the anatomical distribution of LB pathology and the presence or absence of key motor, psychiatric, autonomic, and cognitive symptoms. Similarly, the density and severity of LB pathology are associated with the severity of motor and cognitive impairment [Beach 2009] and the number of late-stage PD complications (falls, residential care, cognitive impairment, and psychosis) [Kempster 2010].

The motor syndrome of PD is related to the degeneration of dopaminergic neurons, although catecholaminergic and serotonergic brain stem neurons may also degenerate. The discovery of

genes related to PD has helped elucidate the molecular mechanism involved in the pathogenesis of PD. Genetic studies have identified point mutations, as well as duplications and triplications of the α-syn gene (*SNCA*) that are associated with familial, early onset, and aggressive PD [Nuytemans 2010]. There is a link between seemingly sporadic PD and α-syn gene expression in that polymorphisms in the promoter region and reduced epigenetic silencing are associated with an increased risk of PD [Jowaed 2010]. Taken together, these genetic studies suggest a dose-response relationship and argue for a gain of function in PD [Martin 2011]. The current view of the molecular mechanism suggests that aggregation of α-syn is influenced by both genetic and environmental factors. The main pathological finding associated with PD is formation of protein aggregates in the brain, which are composed mostly of fibrillar α-syn. Further, it is believed that synuclein abnormalities in the brain trigger or are otherwise related to a series of dysfunctions at the cellular level, including abnormalities of vesicular trafficking, mitochondrial function, autophagy, and consequent inflammation [Olanow and Kordower 2009].

5.2. Current Therapies for Parkinson's Disease

Current treatment for PD is directed at providing relief from motor symptoms associated with the disease. There is no neuroprotective therapy that halts or delays disease progression [Connolly and Lang 2014]. Motor impairment is most closely linked to reductions in dopamine in the basal ganglia of the brain. Most treatments that are specifically approved for PD increase dopaminergic transmission within the brain. The primary treatments for PD include administration of levodopa, often in conjunction with inhibitors of dopamine metabolism, including monoamine oxidase type B (MAO-B) and catechol-*O*-methyltransferase (COMT) inhibitors, or dopamine agonists. Levodopa is the mainstay of treatment in PD and is the most effective treatment for motor symptoms. It is typically given in combination with a dopamine decarboxylase inhibitor (benserazide or carbidopa). Dopamine agonists (pramipexole, ropinirole, and rotigotine) are frequently used as first-line agents, especially in younger patients. Other first-line therapies include MAO-B inhibitors (selegiline and rasagiline) and amantadine. Other agents are used in an off-label fashion to treat particular symptoms, e.g., anticholinergics such as trihexyphenidyl and benztropine for tremors. All these agents offer varying levels of success in treating motor symptoms, but none of them seem to change the rate of PD progression and all of them have adverse effects that limit their use.

In later stages of PD, motor fluctuation and dyskinesia may limit the effectiveness of medical treatment despite combining the first-line agents plus COMT inhibitors to try and increase dopamine levels through various pathways. Apomorphine, a fast-acting dopamine agonist, can be used as rescue therapy during off periods. Dopaminergic therapies are also administered via routes other than oral administration to tackle the issue of motor fluctuations by continuous delivery (e.g., levodopa-carbidopa intestinal gel given through gastrojejunostomy and subcutaneous apomorphine pump). Surgical treatment using different techniques (generally deep brain stimulation) targeting various locations in the brain (thalamus, globus pallidus, and subthalamic nucleus) can alleviate adverse motor symptoms and has become more common, but it also poses unique challenges and has limitations. Treatment options for presumptively nondopaminergic symptoms, such as loss of balance and freezing of gait, remain scarce. Rivastigmine has been approved for treatment of cognitive symptoms in PD. Droxidopa was

recently approved for the treatment of orthostatic hypotension. However, there is currently no approved disease-modifying therapy used to halt or delay disease progression of PD. All existing treatments for PD provide only partial relief of motor symptoms and may worsen other symptoms. Thus, there remains a high unmet medical need for neuroprotective agents that can slow or halt the progression of disease-related pathology in patients with PD.

5.3. Profile of Previous Experience with BIIB054

5.3.1. Nonclinical Experience

Nonclinical pharmacology, pharmacokinetic (PK), and toxicology studies have been performed to support clinical development of BIIB054. In vitro and in vivo studies were conducted using BIIB054, a human mAb consisting of 2 immunoglobulin G (IgG) 1 heavy and 2 lambda (λ) light chains connected by inter-chain disulfide bonds, or a chimeric mouse IgG2a/λ analog (ch12F4). Mouse, rat, and cynomolgus monkey were chosen as pharmacologically relevant species because BIIB054 binds similarly to α-syn from the human, mouse, rat, and monkey.

The binding of BIIB054 to α-syn was evaluated using purified recombinant proteins and human brain tissue extracts. These studies established that BIIB054 binds to both soluble monomeric and aggregated forms of α-syn, with preferential binding to aggregated α-syn in diseased brain tissue, and is highly specific for α-syn (concentration at 50% of maximum observed biologic effect [EC_{50}] of ~0.25 nM for fibrillar and EC_{50} of ~39 nM for soluble monomeric α-syn) relative to the closely related β- and γ-synucleins (no detectable binding). Immunohistochemistry showed BIIB054 staining of LB pathology in brain tissue from patients with PD and dementia with LB.

In vivo pharmacology studies demonstrated significant treatment effects on brain α-syn burden and/or motor performance with BIIB054 and ch12F4. These studies were performed in transgenic mouse models, which overexpress either wild-type or mutant human α-syn under central nervous system-specific promoters, and, with aging, accumulate α-syn in the brain and develop motor function deficits. ch12F4 also reduced α-syn pathology and restored motor performance in mouse models of α-syn spreading induced by intracerebrally inoculated α-syn fibrils. These models recapitulate important aspects of α-syn pathology in the brain, and these animals exhibit motor deficits that may be directly linked to reduced dopamine. Penetration of BIIB054 into the brain, binding to pathology, and a short-term rise in plasma α-syn were demonstrated following systemic administration.

The PK profile of BIIB054 was determined in single-dose studies in mice, rats, and cynomolgus monkeys. The toxicokinetic characteristics of BIIB054 were evaluated in 4-week, repeat-dose toxicology studies in monkeys and rats, and a 26-week, repeat-dose toxicology study in rats.

The following Good Laboratory Practice studies were conducted to assess the nonclinical safety of BIIB054: an in vitro evaluation in human blood, two 4-week repeat-dose general toxicology studies in rats and monkeys, and one 26-week, repeat-dose chronic toxicology study in rats. Safety pharmacology assessments were conducted as part of the repeat-dose studies.

The treatment duration of the chronic toxicology study was 26 weeks, with an additional 12-week recovery period. There were no clinical observations and no drug-related animal deaths. There were no clinical signs or changes in body weight, food consumption, or clinical pathology (serum chemistry, hematology, coagulation, or urinalysis) at the end of the 26-week treatment or 12-week recovery periods. There were no gross lesions, organ weight changes, or microscopic observations. BIIB054 was not immunogenic in rats; no anti-drug antibody response was noted under the conditions of the study. At 13 weeks and 26 weeks, higher mean total protein levels and globulin levels, as well as lower mean albumin/globulin ratios, were present in males and females in the 150 and 450 mg/kg groups. These findings were attributed to the increased levels of BIIB054 (a protein and immunoglobulin) and not considered a toxicological effect. There were no BIIB054-related changes in blood chemistry after the 12-week recovery period. No adverse effect level for this chronic toxicology study was detected at the highest dose, 450 mg/kg (maximum feasible dose level based on drug concentration and dosing volume).

See the Investigator's Brochure for detailed information on nonclinical studies.

5.3.2. Clinical Experience

A Phase 1, first-in-human study (228HV101) to evaluate single-ascending doses in healthy volunteers and subjects with PD was completed. This was a randomized, placebo-controlled study designed to evaluate the safety, tolerability, and PK of single doses of BIIB054.

Healthy volunteers were assigned to 1 of 6 cohorts and randomized to receive a single intravenous (IV) dose of BIIB054 (1, 5, 15, 45, 90, or 135 mg/kg) or placebo. Cohort 7 included subjects with PD, who received a single dose of BIIB054 (15 or 45 mg/kg) or placebo.

As of 19 May 2019, 48 healthy volunteers had received BIIB054 (up to a single dose of 135 mg/kg) or placebo, and 18 subjects with PD had received BIIB054 (up to 45 mg/kg) or placebo.

Study 228HV101 is complete and indicated that BIIB054 was well tolerated at single doses, including dose levels similar to and higher than those in Study 228PD201. See the Investigator's Brochure for the most up-to-date information.

5.4. Study Rationale

BIIB054 is a novel, human-derived mAb that targets primarily aggregated forms of α-syn and is being developed by Biogen for the treatment of PD.

Neuropathological, genetic, and functional animal studies all point to a causative role of α-syn in the pathogenesis of PD; α-syn is a primary structural component of LBs and LNs, which are the pathological hallmarks of PD. The distribution of this pathology is associated with clinical disease severity. Mutations and multiplications of the α-syn gene are associated with early onset and aggressive PD [Nuytemans 2010], and changes in expression can increase the risk for sporadic PD [Jowaed 2010]. Transgenic mouse models expressing mutated α-syn or exogenous

wild-type α-syn recapitulate aspects of PD [Luk 2012a; Luk 2012b; Masliah 2000]. Based on the link between α-syn and risk for and progression of PD, interventions that reduce α-syn pathology may slow the clinical progression of disease; therefore, α-syn has become an important target for potential disease-modifying treatments.

BIIB054 binds with subnanomolar affinity to the N-terminal region (aa 4-10) of α-syn and does not bind to other highly homologous members of the synuclein family. The murine chimeric version of BIIB054 improved synuclein pathology in transgenic animal models that either overexpress α-syn or express mutated α-syn. This version of BIIB054 also improved motor performance in 2 different transgenic animal models that express mutated α-syn. The ability of BIIB054 to bind preferentially to aggregated forms of α-syn and reduce pathology in nonclinical studies suggests that BIIB054 may have the potential to slow the progression of PD, and perhaps delay the onset of severe disability. BIIB054 has the potential to be the first-in-class disease-modifying therapy in PD that would fulfill a high unmet need.

This study will be conducted in subjects with PD to enable characterization of the efficacy, safety and PK profile of BIIB054, as well as the effect of BIIB054 on pharmacodynamic markers in the presence of the biological target, α-syn.

Early stage PD patients were selected as the test population in this study and will likely be the target population in subsequent studies. Binding of α-syn may be more effective in modifying the course of the disease and, thus, is more likely to delay disease progression when less neuronal damage is evident and the spread of disease pathology is more limited [Braak 2002].

5.5. Rationale for Dosing Regimen

In this study, subjects will receive an IV infusion of study treatment (placebo [Year 1 only] or BIIB054 250 mg, 1250 mg, or 3500 mg) once every 4 weeks. Subjects will receive a total of up to 41 doses: 13 doses in Year 1 (placebo-controlled portion of the study) and up to 28 doses in Years 2 through 4 (active-treatment dose-blinded portion of the study). The dose levels of BIIB054 were selected based on in vitro data on the affinity of BIIB054 to aggregated α-syn, nonclinical toxicology data, and BIIB054 safety, tolerability, and PK data from healthy volunteers in the Phase 1 human study.

In vitro studies established that BIIB054 binds to both soluble and aggregated forms of α-syn, with a higher apparent binding affinity for aggregates. The EC_{50} of BIIB054 for aggregated α-syn was estimated at approximately 0.25 nM, and the EC_{90} was estimated at approximately 2.1 nM (0.0375 and 0.315 µg/mL, respectively). These EC_{50} and EC_{90} concentrations were used as target values for dose selection. See the BIIB054 Investigator's Brochure for further details.

In the Phase 1, first-in-human study (228HV101), serum and cerebrospinal fluid (CSF) concentrations in healthy volunteers were described using a population PK model. Subsequently, estimated PK parameters as well as between subject variability and residual variability estimates from healthy volunteers were used to simulate 1000 serum and CSF steady-state profiles. Emerging data from the PD cohort suggests that PK is similar between healthy volunteer and PD subjects. To account for weight differences between healthy

volunteers and the target Phase 2a population of PD subjects, the Parkinson's Progression Markers Initiative study database was used as a source of weight distribution data in PD patients.

Simulations of CSF profiles in PD subjects were conducted for several dose levels to enable dose selection. CSF and brain interstitial fluid (ISF) concentrations of BIIB054 were assumed to be equal. Given the favorable safety profile of BIIB054 in the previous study 228HV101 and based on PK modeling from that study, a fixed-dose approach is to be implemented in this study.

Simulations based on preliminary serum and CSF data from the first-in-human study 228HV101 indicate that for the 250 mg dose, the BIIB054 concentration in CSF and ISF at steady state is projected to be above EC_{50} for the majority of subjects (Figure 3). The highest dose (3500 mg) was selected to maintain these levels above EC_{90}, to increase the likelihood of demonstrating efficacy for BIIB054. An intermediate dose of 1250 mg is expected to maintain a CSF and ISF level at or above EC_{90}, as well as provide adequate separation between doses to elucidate the exposure-response relationship.

Nonclinical pharmacology data also suggest that the dose of 250 mg is expected to provide minimal efficacy based on studies in the D-Line synuclein transgenic mouse (see the BIIB054 Investigator's Brochure for further details). The estimated efficacious exposure in the mouse was approximately 1317 day*µg/mL. Clearance of BIIB054 in healthy volunteers is on average 0.1248 L/day. Thus, using Dose = Clearance × area under the concentration-time curve (AUC), the projected mean minimum pharmacologically efficacious dose is approximately 164 mg.

Overall, all 3 doses are expected to be safe and well tolerated in humans. The highest planned dose (3500 mg) is expected to yield median steady-state area under the concentration-time curve within a dosing interval (AUC_{tau}) and maximum observed concentration (C_{max}) values approximately 8- to 9-fold lower than those observed at the no observed adverse effect level in the 26-week toxicology study in rats (Table 7).

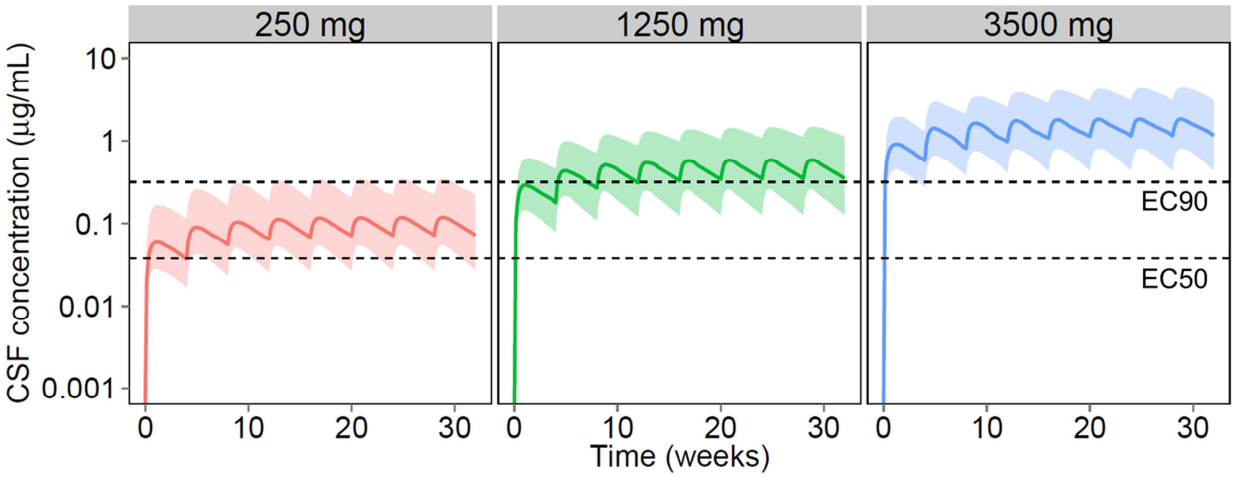
Table 7: Projected Median Steady-State Serum AUC_{tau}, Steady-State C_{max} and Safety Margins for Proposed Phase 2a Doses, Based on Simulations of 1000 PD Subjects

Dose (mg)	Projected parameters		Safety margins[a]	
	AUC_{tau} (h*µg/mL)	C_{max} (µg/mL)	AUC_{tau}	C_{max}
250	42700	175	131	114
1250	214000	882	26	23
3500	612000	2480	9	8

AUC_{tau} = area under the concentration-time curve within a dosing interval; C_{max} = maximum observed concentration; NOAEL = no observed adverse effect level.

[a] Calculated based on mean $AUC_{0\text{-}168h}$ and C_{max} after the last dose of BIIB054 in the 26-week rat toxicology study. AUC_{tau} at NOAEL = $AUC_{0\text{-}168h}$*4 = 5,580,000 h*µg/mL.

Figure 3: Simulated Cerebrospinal Fluid Concentration – Time Profiles for Proposed Doses in the Phase 2a Study



CSF = cerebrospinal fluid; EC_{50} = half-maximal effective concentration

Solid line = population median; shaded area = 5th-95th percentile

5.5.1. Rationale for Comparator/Reference Product or Placebo

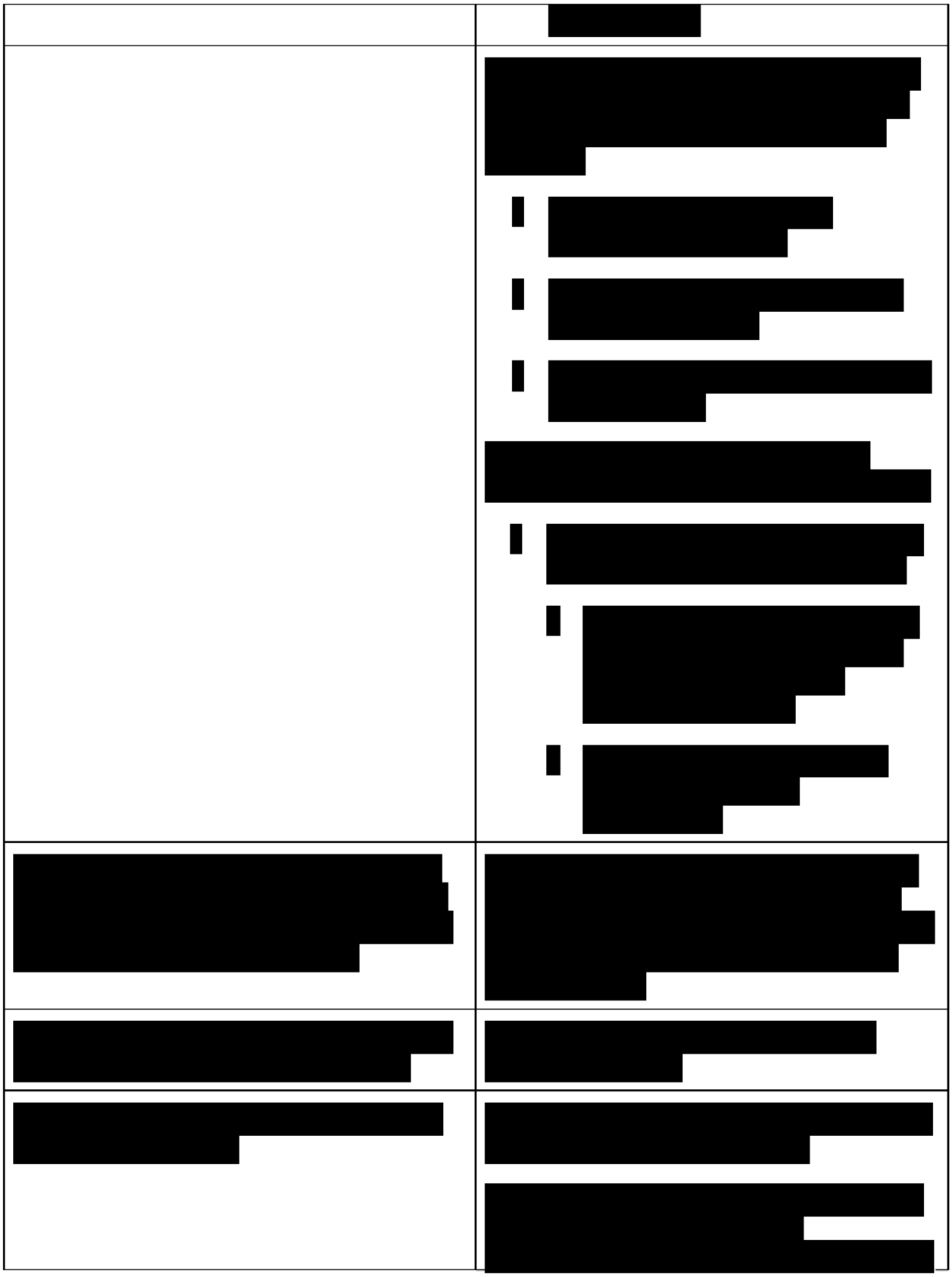
As no disease-modifying therapy for PD is currently available, placebo is deemed to be an appropriate comparator.

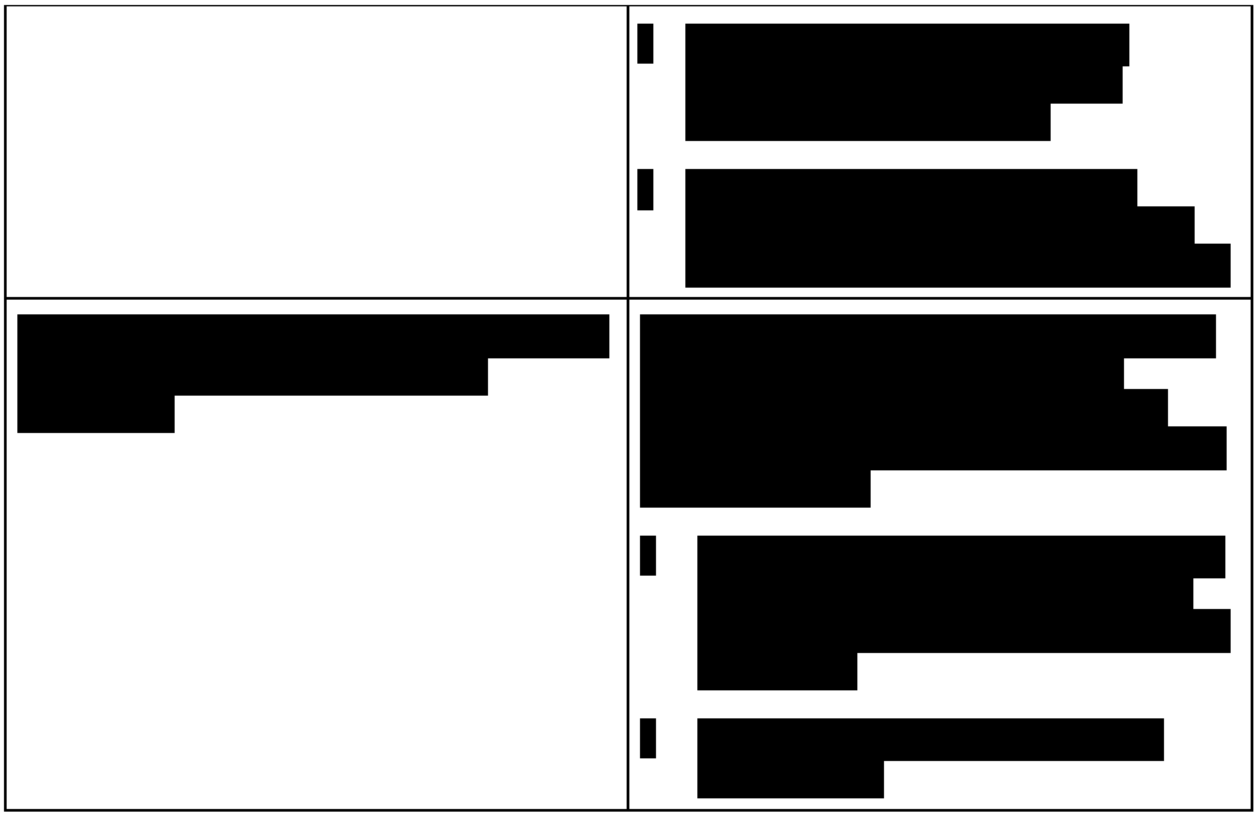
The use of placebo does not increase the risk to subjects, since subjects are being selected for this study on the basis of the presence of PD symptoms of insufficient impact to demand institution of medical treatment at the initiation of the study. Subjects will be allowed to start treatment for PD should symptom severity warrant treatment during the study.

6. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoints
To evaluate the clinical efficacy of BIIB054 via dose response using the change from baseline in Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Total Score	Change from baseline in MDS-UPDRS Total Score (Sum of Parts I, II, and III) at the primary timepoints of Week 52 and Week 72
Secondary Objectives	**Secondary Endpoints**
To evaluate the dose-related safety of BIIB054	Incidence of adverse events (AEs) and serious adverse events (SAEs)
To evaluate the clinical efficacy of BIIB054 via MDS-UPDRS Total Score	Change from baseline in MDS-UPDRS Total Score (Sum of Parts I, II, and III) at end of study
To assess the PK profile of BIIB054	Concentration of BIIB054 in the serum
To evaluate the clinical efficacy of BIIB054 based on MDS-UPDRS subparts	Change from baseline to Week 52, Week 72, and end of study in MDS-UPDRS of Subparts I, II, and III (each part separately)
To evaluate the pharmacodynamic effects of BIIB054 on the integrity of nigrostriatal dopaminergic nerve terminals	Change from baseline to Week 52 in striatal binding ratio (SBR) in the putamen, striatum, and caudate as measured by single-photon emission computed tomography (SPECT) imaging of the dopamine transporter (DaT) with ioflupane I123 (DaTscan™)
To evaluate the immunogenicity of BIIB054	Incidence and titer of anti-BIIB054 antibodies in the serum
Exploratory Objectives	**Exploratory Endpoints**
[redacted]	[redacted]

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





7. STUDY DESIGN

7.1. Study Overview

This Phase 2a, randomized, double-blind, parallel-group, placebo-controlled study (Year 1) with an active-treatment dose-blinded period (Years 2 through 4) will examine the efficacy, safety, PK, and pharmacodynamics of BIIB054, administered every 4 weeks via IV infusion to adult subjects with PD. Approximately 311 subjects will be enrolled at about 85 sites globally.

7.1.1. Year 1 (Placebo-Controlled Portion of the Study)

Prior to the first dose in Year 1, all subjects in the study will be randomized into 4 arms, to receive 13 doses of BIIB054 (250, 1250, or 3500 mg) or placebo.

Subjects will be enrolled into 2 cohorts. Cohort A will be randomized first and will include approximately 24 subjects. Cohort B will be randomized after all subjects in Cohort A complete Week 12 assessments and will include approximately 287 subjects. Dose levels, number of treatment arms, and number of subjects per arm in Cohort B may be adjusted based on the results from Cohort A and a review by the independent data monitoring committee (IDMC). Per this protocol amendment (Version 8), the actual enrollment is 357 subjects with 29 subjects randomized to Cohort A and 328 subjects randomized to Cohort B.

After all subjects in Cohort A complete Week 12 assessments (28 days after their third infusion), and before dosing any subjects in Cohort B, all available safety and PK data will be reviewed by the IDMC. No subjects in Cohort B may be dosed until the IDMC review is complete. The study schematic is presented in Figure 1. After IDMC review is complete, subjects in Cohort B will be randomized, and dosing may begin. During the review period, subjects in Cohort A will continue to be dosed on a schedule of once every 4 weeks.

The first IDMC meeting will occur after the last subject in Cohort A completes Week 12 assessments, or approximately 6 months after the first subject has been enrolled in Cohort A, whichever comes first. Regular IDMC meetings will occur approximately every 3 months after the first meeting. Additional information on the IDMC meetings is included in the IDMC charter.

[redacted]

Any changes will be documented in a protocol amendment.

7.1.2. Years 2 through 4 (Active-Treatment Dose-Blinded Portion of the Study)

The Year 1 Week 52 and Year 2 Week 52 visits (first visit of Year 2) can be conducted as a single visit. Prior to Infusion 14 (the first dose of Year 2; Year 2 Week 52 visit), subjects who

received placebo in Year 1 will be randomized into 1 of the active-dosing arms for Year 2; these subjects will receive BIIB054 in Year 2. Subjects who received BIIB054 (1250 mg or 3500 mg) in Year 1 of the study will continue with the same dose regimen in Year 2. Subjects receiving the 250-mg dose in Year 1 may be randomized to 1 of the 2 highest doses of BIIB054 in Year 2 based on IDMC review of data. No specific action related to randomization is required of investigators or study sites at Year 2 Week 52.

Subjects will receive 12 additional doses of BIIB054 (250, 1250, or 3500 mg) in Year 2 and up to 16 additional doses in Years 3 and 4. Up until the last subject in the study has had his or her last dose in Year 2 of the study (Week 96 Visit), eligible subjects will be able to continue treatment once every 4 weeks.

Subjects who complete dosing through Week 96 and the Final Visit 12 weeks after the last visit will be considered Year 2 completers in the eCRF.

See Figure 2 for a depiction of the duration of dosing in Years 3 and 4 for subjects continuing dosing past Week 96.

Figure 4 presents a flowchart for dosing and procedures from Week 96 through end of study, including how to determine which subjects are eligible to continue dosing past Week 96.

7.2. Overall Study Duration and Follow-Up

The total duration of study participation for each subject will be up to approximately 178 weeks, including a 6-week Screening period before the first study treatment infusion, a 48-week placebo-controlled treatment period, up to a 112-week active-treatment dose-blinded period, and a 12-week follow-up period.

Note: In the event of a public health emergency that results in site closure, travel restrictions, or the study being deprioritized at the site such that clinic visit(s) cannot occur, Remote Visits will be done. Use of a Remote Visit will not be done in place of an onsite visit simply due to subject preference. If a subject does not participate in a remote or clinic visit, a Safety Telephone Call must be conducted. Refer to Table 12, Table 13, and Table 14 for Remote Visit assessments.

7.2.1. Screening

Subject eligibility for the study will be determined within 42 days prior to study randomization on Day 1.

The Screening Visit assessments (excluding imaging) may be performed over 1 to 2 days, which need not be consecutive, to minimize subject burden. The imaging assessments (DaT/SPECT and brain MRI) should be done after all other eligibility criteria have been met and before Day -7 for Cohort A and at least 8 business days before Day 1/randomization for Cohort B, to allow adequate time for evaluation of the results.

7.2.2. Study Treatment

Eligible subjects will report to the study site to receive study treatment administered by IV infusion every 4 weeks. The infusion duration will be 1 hour (± 10 minutes). Subjects will be under observation for at least 1 hour after the end of each infusion. The Investigator or designee must contact the study's Medical Monitor in advance if they would like to adjust the infusion duration or administration conditions based on the subject's ability to tolerate infusion.

7.2.2.1. Year 1

In Year 1 (placebo-controlled portion) of the study, subjects will receive study treatment for 48 weeks, for a total of 13 dosing visits, beginning on Day 1.

Specified assessments on Day 1, Week 24, and Week 48 in both cohorts (and on Day 29 and Day 57 in Cohort A only) may be completed on the day before dosing or the day of dosing (e.g., Day -1 or Day 1 for the Day 1 Baseline Visit), at the discretion of the Investigator, except as noted in the Schedule of Assessments (e.g., randomization, pregnancy test, vital signs, and electrocardiogram [ECG]) must be obtained pre-infusion on the day of dosing).

7.2.2.2. Years 2 through 4

In Years 2 through 4 (active-treatment dose-blinded portion) of the study, subjects will receive BIIB054 every 4 weeks until the last subject in the study receives the Week 96 dose (up to 112 weeks [28 doses]).

7.2.2.3. Treatment with Parkinson's Disease Medications

Medications used to treat the symptoms of PD (hereafter referred to as symptomatic PD medications) will be listed in the Study Reference Manual. Subjects should refrain from using symptomatic PD medications **for as long as possible**, and in particular for at least 6 months following Day 1.

The entire MDS-UPDRS assessment (Parts I to IV) should be performed as close as possible before subjects receive their first dose of symptomatic PD medication, either at a scheduled visit or included in an unscheduled visit.

It is recommended that subjects who plan to start symptomatic PD medication either outside of a visit window or outside of the DaT/SPECT window wait, if possible, until after the next DaT/SPECT to start the medication, provided that a DaT/SPECT visit is planned within 1 month. (As an alternative, if the subject cannot wait to start symptomatic PD medication, the DaT/SPECT window of ±7 days, except for Week 52 MRI and DaT/SPECT which has a -7 day window only to allow Year 2 dosing to be appropriately scheduled, may be expanded so that it extends from -28 days to +7 days.) If the subject is not due for DaT/SPECT at the next scheduled visit per the Schedule of Activities, it is not necessary to have this scan performed prior to starting symptomatic PD medications.

Once they have started symptomatic PD medication, subjects should refrain from taking the PD medication for approximately 12 hours prior to study visits at which MDS-UPDRS [redacted] assessments will be conducted (see Section 4.2). At those visits, subjects taking PD medication should come to the clinic prior to taking their morning dose, and should refrain from taking their PD medication until after completion of the MDS-UPDRS Part III assessment [redacted].

See Section 13.1 for a description of the timing of clinical function assessments relative to administration of the symptomatic PD medication.

During Year 1 of the study (up to and including the Year 1 Week 52 Visit), subjects taking levodopa (preferred symptomatic PD medication) or other symptomatic PD medications should be encouraged to manage their symptoms with a single medication (e.g., levodopa/carbidopa or levodopa/benserazide). Once subjects enter Year 2 (active-treatment dose-blinded portion of the study), there will be no restrictions on the number or classes of symptomatic PD medications to be introduced, although use of PD medications that may affect interpretation of DaT/SPECT is to be discouraged until the final DaT/SPECT assessment (Week 96/148 Visit). See Section 11.3.1.1 for further description of the recommended PD medications.

7.2.3. Follow-Up Visits and Final Visit

Follow-up visits are described in the following subsections.

Subjects who withdraw prematurely from the study will be asked to return to complete an Early Termination Visit within 4 weeks (±3 days) of their last study treatment and a Final Visit 12 weeks (±3 days) after their last study treatment.

7.2.3.1. Cohort A, Year 1

During Year 1, in addition to dosing day visits, subjects in Cohort A will return to the study site for 12 follow-up clinic visits on Days 2, 30, and 58 (24 hours after infusions 1-3); Days 4 and 60 (72 hours after infusions 1 and 3); Days 8, 36, and 64 (168 hours after infusions 1-3); Days 15 and 71 (336 hours after infusions 1 and 3); **1 visit only** at Week 22, 34, or 46; and at the Week 52 Visit.

A subject will return to the clinic for only 1 of the 3 visits at Week 22, 34, or 46 for PK sampling; the timing of the visit will be randomly assigned at the time of treatment assignment. However, should any subject have a scheduling conflict on the assigned date, the Investigator may reschedule to 1 of the other 2 timeslots.

During Year 1, subjects in Cohort A will have 1 Safety Telephone Call, on Day 43 (336 hours after the second infusion).

7.2.3.2. Cohort B, Year 1

During Year 1, in addition to dosing day visits, subjects in Cohort B will have 2 follow-up clinic visits: **1 visit only** at Week 22, 34, or 46; and the Week 52 Visit.

A subject will return to the clinic for only 1 of the 3 visits at Week 22, 34, or 46 for PK sampling; the timing for the visit will be randomly assigned at the time of treatment assignment. However, should any subject have a scheduling conflict on the assigned date, the Investigator may reschedule to 1 of the other 2 timeslots.

During Year 1, subjects in Cohort B will have 6 Safety Telephone Calls, on Days 2, 8, 30, 36, 58, and 64 (24 hours and 168 hours after each of the first 3 doses).

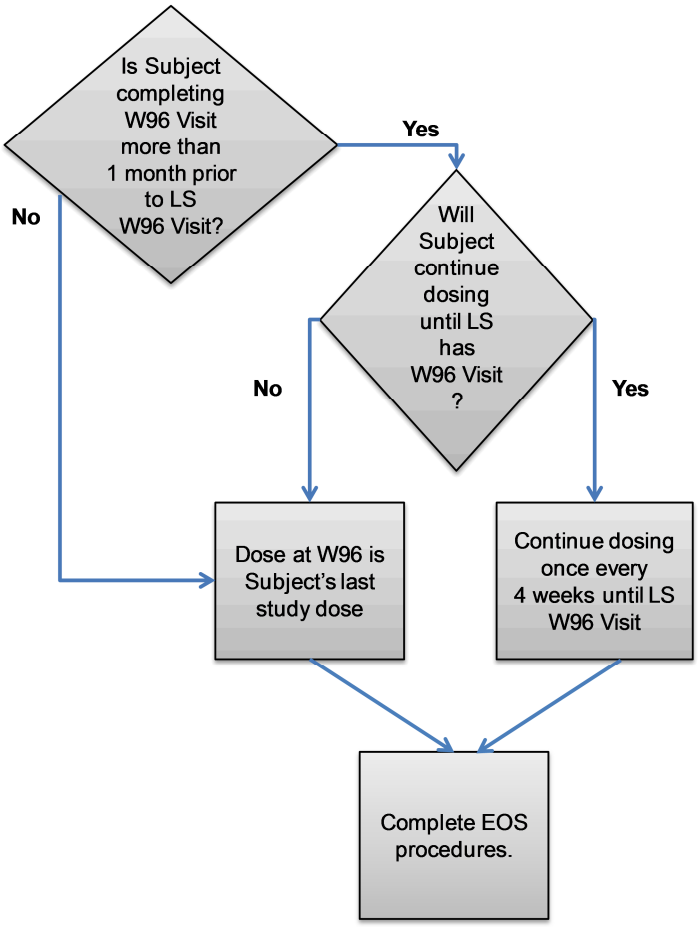
7.2.3.3. Cohorts A and B, Years 2 through 4

At the beginning of Year 2, in addition to the dosing visits, subjects will have 2 Safety Telephone Calls, 1 day and 7 days after Infusion 14 (the first infusion in Year 2).

For the purposes of this section, Last Subject will be defined as the final subject in the study to complete a Week 96 Visit. The date of the Last Subject's Week 96 Visit will be communicated to all sites. As shown in Figure 4, subjects whose Week 96 Visit is more than 1 month before the Last Subject's Week 96 Visit should continue dosing every 4 weeks; all other subjects should receive their last study dose at the Week 96 Visit.

Following the final dose of study treatment at any time during the study, all subjects will follow end of study procedures as shown in Table 6: an additional visit/Early Termination Visit 4 weeks after the last dose, a Safety Telephone Call 8 weeks after the last dose, and the Final Visit 12 weeks after the last dose. Final Visit procedures should be performed at the subject's last study visit, even in the case of scheduling difficulties.

Figure 4: Flowchart for Week 96 to End of Study for Subjects Eligible to be Treated in Years 3 and 4



EOS = end of study; LS = last subject; W = week.

7.2.4. Unscheduled Visits

Unscheduled clinic visits may occur at any time, at the discretion of the Investigator, for safety-related issues. They may also occur to administer the MDS-UPDRS prior to the first dose of symptomatic PD medication, for subjects who start their medication outside of a scheduled visit. Assessments specified in Table 4 (Year 2) and Table 5 (Years 3 and 4) should be performed at every unscheduled visit; additional assessments may be performed at the Investigator's discretion.

7.2.5. Early Termination

For subjects terminating (i.e., discontinuing both study treatment and study assessments) early, it is recommended that the assessments of the Early Termination Visit be performed within 4 weeks after the last dose of study treatment. The Safety Telephone Call should be performed

approximately 8 weeks after the last dose, and the assessments of the Final Visit should be performed approximately 12 weeks after the last dose. Final Visit procedures should be performed at the subject's last study visit, even in the case of scheduling difficulties. For Early Termination and end of study procedures, see Table 6.

7.2.6. Study Stopping Rules

Biogen may terminate this study at any time, after informing Investigators. Biogen will notify Investigators if the study is to be placed on hold, completed, or terminated.

For Cohort A until initiation of dosing in Cohort B:

After evaluation of the safety, tolerability, and PK data by the IDMC, further dosing may be terminated if any of the following is observed:

- Two similar SAEs or clinically significant AEs, unless clearly unrelated to BIIB054, are reported for subjects on active study treatment.
- Three or more similar AEs are reported for subjects on active study treatment (unless these events are clearly unrelated to BIIB054) that are not tolerable, as reported by the subject (e.g., severe dizziness) and/or deemed a medically unacceptable risk by the IDMC and/or Sponsor.
- Sponsor requests that dosing be terminated.

For both cohorts after initiation of dosing in Cohort B:

Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

7.3. End of Study

The end of study is last subject, last visit.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening, or at the timepoint specified in the individual eligibility criterion listed:

1. Able to understand the purpose and risks of the study and to provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.

2. Diagnosed with PD within a maximum of 3 years (based on month and year of diagnosis) prior to Screening. Subjects must have:
    a. An asymmetric or bilateral presentation of one of the following:
        – resting tremor and bradykinesia
        – bradykinesia and rigidity
        – rigidity and resting tremor

        OR

        – either asymmetric resting tremor or asymmetric bradykinesia.
    b. No known or suspected cause of Parkinsonism other than neurodegenerative PD. Subjects with drug-induced Parkinsonism (e.g., metoclopramide and flunarizine), metabolic identified neurogenetic disorders (e.g., Wilson's disease), encephalitis, or Parkinson Plus syndromes, other forms of atypical Parkinsonian syndromes (e.g., progressive supranuclear palsy and multiple system atrophy), or Lewy body dementia are not allowed in the study.
3. Has not received any medication for the treatment of the motor symptoms of PD (including, but not limited to, levodopa and levodopa-containing products, dopamine agonists, monoamine oxidase inhibitors, centrally-acting anticholinergics, amantadine, zonisamide; see list of PD medications in the Study Reference Manual) for at least 12 weeks prior to Day 1 and, in the opinion of the Investigator, is not expected to require PD treatment for at least 6 months following Day 1. Maximum total duration of prior PD regimens should not exceed 30 days. Stable (at least 8 weeks) dosages of medications that are used to treat conditions other than PD tremor (e.g., beta-blockers, benzodiazepines, and barbiturates) are allowed. Further guidance will be provided by the study's Medical Monitor on a case by case basis.

4. Aged 40 to 80 years, inclusive, at the time of the main informed consent.

5. Body mass index from 19 kg/m^2 to 35 kg/m^2.

6. For Cohort A only, nonsmoker during the 6 months prior to Day 1 and willing to abstain from smoking throughout the study period.

7. Score of ≤2.5 on the Modified Hoehn and Yahr Scale.

8. Screening DaT/SPECT results demonstrating activity in the striatum is either asymmetric, absent in the putamen and/or one or both caudate nuclei, consistent with neurodegenerative Parkinsonism, as assessed with qualitative, visual assessment. DaT/SPECT images will be reviewed by a central reader to confirm eligibility.

9. All women of childbearing potential and all men must practice highly effective contraception during the study and for 6 months after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening, or at the timepoint specified in the individual criterion listed:

Medical History

1. History of or positive test result at Screening for human immunodeficiency virus (HIV). The requirement for testing at Screening may be omitted if it is not permitted by local regulations.

2. History of, or positive test result at Screening for, hepatitis C virus antibody (HCVAb).

3. Current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or total hepatitis B core antibody [anti-HBc]). Subjects 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.

4. Presence of freezing of gait.

5. MoCA score <23 or other significant cognitive impairment or clinical dementia that, in the opinion of the Investigator, would interfere with study evaluation.

6. Unstable psychiatric illness, including psychosis, suicidal ideation, or untreated major depression within 90 days before Screening, as determined by the Investigator.

7. History or Screening MRI results showing evidence of structural abnormalities that could contribute to the subject's clinical state, or any finding that might pose a risk to the subject, or might prevent a satisfactory MRI assessment for safety monitoring. MRI results will be reviewed by a central reader to confirm eligibility at Screening.

8. History of drug or alcohol abuse within the past 5 years (as defined by the Investigator), a positive urine drug test, or an unwillingness to abstain from these substances during clinic visit days. Subjects who test positive for cannabinoids due to occasional marijuana use, as determined by the Investigator, and who agree to refrain from using marijuana for the duration of the study may be enrolled at Investigator's discretion, after a consultation with the Sponsor. The use of cannabinoids other than marijuana (e.g., cannabinoid cream or gel) is acceptable, unless the use is considered to be drug abuse by the Principal Investigator, which is exclusionary.

9. History of severe allergic or anaphylactic reactions, or history of hypersensitivity to BIIB054 or any of the inactive ingredients in the drug product (refer to the Investigator's Brochure for information on the clinical formulation) or to radioligands or iodine used in the study.

10. Transient ischemic attack or stroke, or any unexplained loss of consciousness within 1 year before Screening.

11. History of unstable angina, myocardial infarction, chronic heart failure (New York Heart Association Class III or IV), or clinically significant conduction abnormalities (e.g., unstable atrial fibrillation) within 1 year before Screening.

12. History of malignancy or carcinoma. The following exceptions may be made after discussion with the Sponsor:

    - Subjects with cancers in remission for more than 5 years prior to Screening

    - Subjects with a history of basal cell or squamous cell carcinomas of the skin that have been completely excised and are considered cured.

13. History of any clinically significant endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, renal, ischemic or cardiovascular, or other major diseases, as determined by the Investigator.

14. History of any brain surgery for PD (e.g., pallidotomy, deep brain stimulation, or fetal tissue transplant).

15. Surgery within 12 weeks before Day 1 (other than minor cosmetic surgery and minor dental surgery, as determined by the Investigator).

16. Clinically significant abnormal laboratory test values at Screening, as determined by the Investigator.

17. Chronic, uncontrolled hypertension (average of 3 systolic blood pressure [SBP] readings at Screening >165 mmHg or average diastolic blood pressure [DBP] ≥100 mmHg, or any documented SBP reading >180 mmHg or DBP ≥100 mmHg within the 3 months before Day 1), or orthostatic hypotension that is clinically significant as determined by the Investigator.

18. Clinically significant (as determined by the Investigator) 12-lead ECG abnormalities, including but not limited to confirmed demonstration of corrected QT interval using the Fridericia correction method of >460 msec [men] and >470 msec [women] before study treatment administration, if considered clinically significant by the Investigator.

19. Poorly controlled diabetes mellitus, as defined by having dosage adjustment of diabetic medication within 3 months before dosing (Day 1) or glycated hemoglobin value ≥8% at Screening.

20. Screening value for hemoglobin <12 g/dL for men or <11 g/dL for women.

21. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., values of aspartate aminotransferase, or alanine aminotransferase, or total bilirubin ≥2 times the upper limit of normal).

22. Indication of impaired renal function at Screening (estimated glomerular filtration rate <60 mL/min).

23. Screening values of coagulation parameters including platelet count, international normalized ratio (INR), prothrombin time (PT), and activated partial thromboplastin time (APTT) that are not generally within normal ranges. Subjects with nonclinically significant and stable out-of-range values may be allowed in the study at the discretion of the Investigator, and only after a consultation with the Medical Monitor.

24. Currently active infection or serious infection (e.g., pneumonia, septicemia) within 8 weeks before Day 1, as determined by the Investigator.

25. Presence of risk for increased or uncontrolled bleeding and/or risk of bleeding that is not managed optimally and could place a subject at an increased risk for bleeding. These could include, but are not limited to, known underlying disorders of the coagulation cascade, platelet function, or platelet count (e.g., hemophilia, Von Willebrand's disease, liver disease).

26. **For subjects enrolling at sites where LPs will be performed:** Subjects with the following characteristics will be excluded from participation in LP procedures:

    - Any history of lumbar surgery for any reason (e.g., herniated disc) that in the opinion of the Investigator would interfere with or pose risks to the LP procedure

    - Other contraindications to having a LP (at Screening and prior to subsequent LPs), including but not limited to:

        – Low platelet count (below 50,000 cells/μL), or Screening values of INR, PT, or APTT that indicate that a LP cannot be performed safely in the opinion of the Investigator

- Taking any antiplatelet medication (e.g., aspirin >100 mg daily, clopidogrel, or nonsteroidal anti-inflammatory drugs [NSAIDs]) within 7 days prior to the planned LP or anticipated need for antiplatelet medication within 48 hours after an LP

- Taking anticoagulant medication (warfarin, heparinoids, and direct coagulation factor inhibitors, e.g., apixaban, dabigatran, rivaroxaban) within 7 days prior to the planned LP or anticipated need for antiplatelet medication with 48 hours after an LP

- X-ray, MRI, or myelographic evidence of significant lumbar spine abnormalities or other anatomical factors at or near the LP site that might interfere with performance of LP

Treatment History

27. Participation in any passive immunotherapy study targeting α-syn, other than the BIIB054 Phase 1 study 228HV101. Subjects who participated in Study 228HV101 must meet all entry criteria for the present study, and cannot have received BIIB054 within 24 weeks before Day 1 of Study 228PD201.

28. Participation in any active immunotherapy study targeting α-syn.

29. Use of any of the following medications within 180 days before Day 1: typical or atypical antipsychotics (including, but not limited to, clozapine, olanzapine, flunarizine, and aripiprazole), metoclopramide, or alpha methyldopa.

30. Use of any of the following medications within 90 days before Day 1: methylphenidate, cinnarizine, tetrabenazine, reserpine, amphetamine, memantine, cholinesterase inhibitors (rivastigmine, donepezil, galantamine, and tacrine), or monoamine oxidase type A inhibitors (pargyline, phenelzine, and tranylcypromine).

31. Use of medicines that strongly bind to the dopamine transporter and may interfere with DaT/SPECT including amphetamine, benztropine, bupropion, cocaine, mazindol, methylphenidate, phentermine, and sertraline within 30 days before the Screening DaT/SPECT.

32. Use of any glucagon-like peptide-1 (GLP-1) agonists (e.g., exenatide, liraglutide, lixisenatide, albiglutide, and dulaglutide) within 90 days before Day 1.

33. Use of nilotinib within 90 days before Day 1.

34. Use of allowed medications not previously specified at doses that have not been stable for at least 8 weeks before Day 1, and/or that are not expected to remain stable for the duration of the study.

35. Use of selective serotonin reuptake inhibitors (SSRIs) (with the exception of sertraline, which is prohibited) or serotonin norepinephrine reuptake inhibitors (SNRIs) at doses that have not been stable for at least 3 months before Day 1 and/or that are not expected to remain stable for the duration of the study.

36. Vitamins, supplements, herbal/alternative health preparations, and other over-the-counter medications at doses that are not expected to remain stable from Screening through Day 1.

37. Participation or planned enrollment in any other clinical study or treatment with any investigational drug or investigational use of an approved therapy within 30 days (or 5 half-lives, whichever is longer) before Screening.

Other

38. Contraindication for MRI (pacemaker, ferromagnetic objects in the body, claustrophobia, etc.).

39. Presence of a ventriculoperitoneal shunt.

40. Female subjects who are pregnant, currently breastfeeding, or attempting to conceive during the study.

41. Blood donation (1 unit or more) within 8 weeks before Day 1 (must also refrain from donating blood for the duration of the study).

42. Unwillingness or inability to comply with study requirements, including the presence of any condition (physical, mental, or social) that prevents the subject from participating in visits as scheduled.

43. Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the subject unsuitable for enrollment.

44. Previous registration in this study. Subjects previously enrolled in Study 228HV101 are eligible provided they meet the criteria of Study 228PD201 and were not administered BIIB054 within 24 weeks before Day 1.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

Subjects must provide informed consent before any screening tests are performed (see Section 17.3). When a subject signs the main informed consent form (ICF), that subject is considered to be enrolled in the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study.

Individuals who do not meet the criteria for participation in this study (i.e., a screen failure) may not be rescreened, except in the following circumstances:

Subjects with urinary tract infection detected on screening urinalysis may be rescreened once after the infection has been treated and resolved.

Rescreening for other reasons may be allowed after consultation with the Sponsor. In addition, eligible subjects who are not able to complete the Day 1 Visit within 42 days of starting their screening assessments may be rescreened at the discretion of the Sponsor. All screening assessments will be repeated except for the main ICF, [redacted], confirmation of PD diagnosis, height measurement, blood sampling for ribonucleic acid (RNA), MRI, and DaT/SPECT unless determined otherwise by the sponsor. For female subjects, if initial follicle-stimulating hormone (FSH) level confirmed postmenopausal state, it does not need to be repeated.

Coagulation, blood chemistry, and hematology tests may be repeated once if, in the opinion of the Investigator, values of the initial tests are only slightly out of range. For central laboratory normal ranges, please refer to the Study Reference Manual. Subjects who have other nonclinically significant out-of-range laboratory results may be retested 1 time only after discussion with the Medical Monitor.

The rescreen and repeat parameters apply to any subject that was screened under any version of this protocol.

9.2. Randomization and Registration of Subjects

Subjects will be registered and randomized at Day 1, after all baseline assessments have been completed. In particular, prior to randomization at Day 1, the Investigator must verify that the subjects are eligible according to criteria in Section 8.1 and Section 8.2 (including confirmation of DaT deficit by central reader) and that the MDS-UPDRS results from Day 1 are available. No subject may begin treatment prior to assignment of a unique identification number (registration) and randomization. The identification number will be used on study-related documents pertaining to the subject. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

Subjects will be randomized at Day 1 into 1 of 4 parallel dosing arms to receive placebo or BIIB054 (250 mg, 1250 mg, and 3500 mg). Cohort A (approximately 24 subjects) will be enrolled and randomized first in a 1:1:1:1 ratio. Randomization and dosing for Cohort B (approximately 287 subjects) will start after all subjects in Cohort A complete Week 12 assessments, and all available safety and PK data are reviewed by the IDMC. Randomization of subjects in Cohort B will be stratified by baseline (Day 1) MDS-UPDRS Part I + II + III total scores (≤35 and >35) and striatum SBR (≤1.2 and >1.2), and subjects will be randomized at Day 1 into 1 of 4 parallel dosing arms to receive placebo (n=82) or BIIB054 (250 mg [n=41], 1250 mg [n=82], or 3500 mg [n=82]) in each stratum.

All subjects who were randomized to receive placebo in Year 1 will be randomized, in equal ratio, to 1 of the active BIIB054 treatments for Year 2. For subjects receiving placebo in Cohort A, this randomization will occur prior to Infusion 14; for subjects receiving placebo in Cohort B, this randomization will occur at the time of the baseline Day 1 randomization (Year 1). Subjects who received BIIB054 (1250 mg or 3500 mg) in Year 1 will continue with the same dose regimen in Year 2. In addition, the decision of whether to randomize subjects who receive the 250-mg dose in Year 1 to 1 of the 2 highest doses of BIIB054 in Year 2 will be made after the IDMC review of Cohort A Week 12 data.

Per this protocol amendment (Version 8), the actual enrollment is 357 subjects based on the same randomization ratio as described above for Cohort A (n=29) and Cohort B (n=328).

Refer to the Study Reference Manual for details on registration and randomization.

9.3. Blinding Procedures

This is a 2-part randomized, double-blinded study. Year 1 is the placebo-controlled portion of the study; Years 2 through 4 are the active-treatment dose-blinded portion of the study.

All study staff (Sponsor and study site staff) will be blinded to the subject treatment assignments. During Year 1, subjects will be administered either placebo or 1 of 3 dose levels of BIIB054. In Years 2 through 4, all subjects will receive BIIB054, but subjects, Investigators, and study staff will remain blinded as to the dose level assignment. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the study team, either at the study site or at Biogen, except the unblinded Pharmacist (or designee) and the unblinded Pharmacy Monitor. At the end of the study (i.e., after the clinical study report is finalized), if unblinding will not jeopardize the results of ongoing related studies, Biogen will provide the randomization codes to Investigators, who then can inform their subjects about the treatment received.

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue BIIB054 for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences an AE that necessitates permanent discontinuation of study treatment.
- The subject experiences a medical emergency that necessitates unblinding of the subject's treatment assignment.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.

The primary reason for discontinuation of study treatment must be recorded in the subject's electronic case report form (eCRF).

Subjects who discontinue study treatment will be encouraged to remain in the study and complete all appropriate protocol-specified tests and assessments. At a minimum, the following assessments should be performed at the timepoints shown on the schedule of assessments tables in Table 1 through Table 6: MDS-UPDRS, [redacted].

For subjects terminating early (i.e., discontinuing both study treatment and study assessments before Week 96), it is recommended that the assessments of the Early Termination Visit be performed within 4 weeks after the last dose of study treatment. The Safety Telephone Call should be performed approximately 8 weeks after the last dose, and the assessments of the Final Visit should be performed approximately 12 weeks after the last dose. Final Visit procedures should be performed at the subject's last study visit, even in the case of scheduling difficulties. For Early Termination/Follow-up and end of study procedures, see Table 6.

10.2. Withdrawal of Subjects From Study

Subjects must be withdrawn from the study for any one of the following reasons:

- The subject withdraws consent.

- The subject enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.

- The subject is unwilling or unable to comply with the protocol.

The primary reason for the subject's withdrawal from the study must be recorded in the subject's eCRF.

For subjects terminating early (i.e., discontinuing both study treatment and study assessments), it is recommended that the assessments of the Early Termination Visit be performed within 4 weeks after the last dose of study treatment. The Safety Telephone Call should be performed approximately 8 weeks after the last dose, and the assessments of the Final Visit should be performed approximately 12 weeks after the last dose. Final Visit procedures should be performed at the subject's last study visit, even in the case of scheduling difficulties. For Early Termination and end of study procedures, see Table 6.

Subjects in Cohort A only who withdraw from the study prior to completing the Final Visit may be replaced at the discretion of the Sponsor. A replacement subject will receive the same study treatment and dosage as the subject who discontinued treatment.

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the Directions for Handling and Administration (DHA).

Study treatment will be administered by the study site staff via IV infusion once every 4 weeks. If there is a deviation from this schedule, there should be at least 7 days between infusions. The duration of the infusion will be approximately 1 hour. The Investigator or designee must contact the study's Medical Monitor in advance if they would like to adjust the infusion duration or administration conditions based on the subject's ability to tolerate infusion.

11.1.1. Year 1 (Placebo-Controlled Portion of the Study)

Prior to the first dose of Year 1, subjects will be randomized into 4 parallel dosing arms as follows:

- Arm 1: placebo
- Arm 2: BIIB054 250 mg
- Arm 3: BIIB054 1250 mg
- Arm 4: BIIB054 3500 mg

11.1.2. Years 2 through 4 (Active-Treatment Dose-Blinded Portion of the Study)

Prior to Infusion 14 (first dose of Year 2), subjects who received placebo in Year 1 will be randomized to 1 of the active-treatment arms for Year 2; these subjects will receive BIIB054 in Years 2 through 4. Subjects who received BIIB054 (250, 1250, or 3500 mg) in Year 1 will continue to receive the same dose regimen of BIIB054 in Years 2 through 4.

11.2. Modification of Dose and/or Treatment Schedule

Dose levels, number of treatment arms, and number of subjects per arm for Cohort B may be modified based on emerging Cohort A safety and PK data, and review by the IDMC.

Any changes will be documented in a protocol amendment.

11.3. Concomitant Therapy and Procedures

11.3.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the time a subject is screened for the study and the Final Visit.

11.3.1.1. Allowed Concomitant Therapy

- Symptomatic PD treatment may be initiated during a subject's participation in the study at the discretion of the Investigator, although subjects should refrain from taking symptomatic PD medications **for as long as possible** (in particular, for at least 6 months following Day 1). For subjects who do require PD treatment, it is recommended that treatment start with immediate-release levodopa/carbidopa at a dose of 25/100 mg 3 times a day (or equivalent dosage of levodopa/benserazide in locations where levodopa/carbidopa is not available). The dose of levodopa/carbidopa may be titrated until satisfactory symptomatic relief is achieved. Subjects receiving levodopa/carbidopa should remain on their initially established dose as long as possible. Adjunctive use of COMT inhibitors, sustained-release levodopa/carbidopa preparations, dopamine agonists, MAO-B inhibitors, and zonisamide is discouraged, and use of amantadine and anticholinergic medications is prohibited in Year 1 of the study. For subjects who do require PD treatment, it is recommended that treatment start with immediate-release levodopa/carbidopa at a dose of 25/100 mg 3 times a day (or equivalent dosage of levodopa/benserazide in locations where levodopa/carbidopa is not available). The dose of levodopa/carbidopa may be titrated until satisfactory symptomatic relief is achieved. Subjects receiving levodopa/carbidopa should remain on their initially established dose as long as possible. Adjunctive use of COMT inhibitors, sustained-release levodopa/carbidopa preparations, dopamine agonists, MAO-B inhibitors, and zonisamide is discouraged, and use of amantadine and anticholinergic medications is prohibited in Year 1 of the study. Prior to initiating treatment with symptomatic PD medication, the Investigator should provide the [redacted] Medical Monitor with a description of the Parkinsonian manifestations that require treatment and a rationale for the choice of medication.

  During Year 1 of the study (up to and including the Year 1 Week 52 Visit), subjects taking levodopa (preferred symptomatic PD medication) or other symptomatic PD medications should be encouraged to manage their symptoms with a single medication (e.g., levodopa/carbidopa or levodopa/benserazide). Once subjects enter Year 2 (active-treatment dose-blinded portion of the study), there will be no restrictions on the number or classes of symptomatic PD medications to be introduced, although use of PD medications that may affect interpretation of DaT/SPECT is to be discouraged until the final DaT/SPECT assessment (Week 96/148 Visit).

  Further guidance on allowed and disallowed concomitant medications will be provided by the study's Medical Monitor on a case by case basis. See Section 7.2.2.3 for a description of timing of the start of symptomatic PD medications relative to scheduled study visits. See Section 13.1 for a description of the timing of clinical function assessments relative to administration of PD medication.

- SSRIs (with the exception of sertraline, which is prohibited) and SNRIs are allowed provided that the subject is on a stable dose for at least 3 months prior to Day 1 and the dose is expected to remain stable for the duration of the study.

- Medications for chronic conditions are allowed provided that the subject is on a stable dose for at least 8 weeks prior to Day 1 and the dose is expected to remain stable for the duration of the study.

- Aspirin ≤100 mg daily.

- Acetaminophen and NSAIDs are allowed if used according to the local label guidelines. NSAIDs and clopidogrel must be avoided before and after LP procedures, as described in Section 11.3.1.2.

- Vaccinations with live or attenuated vaccines are allowed during the study; however, administration of any vaccination/booster should not be given within 10 days before a dosing visit and for 10 days after a dosing visit.

- Routine vitamin therapy is allowed. Subjects should not change administration of vitamins, supplements, herbal/alternative health preparations, or over-the-counter medications unless required for symptom management (e.g., pain) during the study; such medications and preparations must be recorded on the appropriate eCRF page.

11.3.1.2. Disallowed Concomitant Therapy

- Typical or atypical antipsychotics (including clozapine, olanzapine, flunarizine, and aripiprazole), metoclopramide, and alpha methyldopa.

- Tricyclic antidepressants.

- Amantadine or anticholinergic medications for PD in Year 1 of the study.

- Amphetamine, benztropine, bupropion, cocaine, mazindol, methylphenidate, phentermine, sertraline, cinnarizine, tetrabenazine, reserpine, memantine, cholinesterase inhibitors (rivastigmine, donepezil, galantamine, and tacrine) or monoamine oxidase type A inhibitors (pargyline, phenelzine, and tranylcypromine).

- GLP-1 agonists, e.g., exenatide, liraglutide, lixisenatide, albiglutide, and dulaglutide.

- Nilotinib.

- Immunosuppressive drugs (including systemic corticosteroids). Short-term corticosteroids for the treatment of reversible conditions and local corticosteroids may be permitted, following a consultation with the Sponsor.

- Parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis.

- Any investigational drug.

- For subjects who are participating in LPs: Any antiplatelet medication (e.g., aspirin >100 mg daily, clopidogrel, or NSAIDs) or any anticoagulant medication (warfarin, heparinoids, and direct coagulation factor inhibitors, e.g., apixaban, dabigatran, rivaroxaban) is prohibited from 7 days before to 48 hours after each LP procedure.

Subjects should be instructed to continue the medications that they were receiving at enrollment (see Section 11.3.1.1 for allowed concomitant therapy) and to avoid starting any new medications or herbal preparations during the study period, since they may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Subjects should inform the Investigator of any changes in medication.

11.3.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the subject is screened for the study and the Final Visit.

Subjects should be encouraged to continue their prior physical activity regimen without interruption or change throughout the study.

Transcranial magnetic stimulation and brain surgery for PD are disallowed concomitant procedures.

11.4. Continuation of Treatment

Subjects who complete this study and do not discontinue study treatment may be offered the option to enter an extension study (under a separate protocol), provided they meet all eligibility criteria for that study.

11.5. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff.

Subjects who complete dosing through Week 96 and the Final Visit 12 weeks after the last visit will be considered Year 2 completers in the eCRF.

12. STUDY TREATMENT MANAGEMENT

Study site staff will administer study treatment and should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatments are for one-time use only; do not use any study treatment remaining in the vial for another subject.

12.1. BIIB054

BIIB054 is supplied as a liquid drug product in 5-mL vials containing 250 mg BIIB054 per vial. The drug product is formulated using sodium citrate dihydrate, citric acid monohydrate, L-arginine hydrochloride, and polysorbate 80. BIIB054 is manufactured, handled, and stored in accordance with applicable Good Manufacturing Practices.

The contents of the BIIB054 label will be in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, study treatment identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. The expiry or use-by date is stored in the interactive response technology (IRT) system, and printable assignment reports are available to site personnel. BIIB054 should not be used after the expiration, expiry, or use-by date.

12.1.1. BIIB054 Preparation

The individual preparing BIIB054 should carefully review the instructions provided in the DHA.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials or study treatment, do not use the study treatment. The vial in question should be saved at the study site and the problem immediately reported to Biogen.

12.1.2. BIIB054 Storage

Study treatment must be stored in a secure location.

BIIB054 is to be stored at 2°C to 8°C (36°F to 46°F), in a monitored, locked refrigerator with limited access. For the most up-to-date storage requirements, follow the instructions provided in the DHA. BIIB054 is to be protected from light, protected from freezing, and should not be shaken.

12.1.3. BIIB054 Handling and Disposal

The Investigator must return all used and unused vials of BIIB054 as instructed by Biogen unless approved for onsite destruction.

If any BIIB054 supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from Biogen, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. BIIB054 Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed or lost.

Unless otherwise notified, all vials both used and unused must be saved for study treatment accountability. At the end of the study, reconciliation must be made between the amount of BIIB054 supplied, dispensed, and subsequently destroyed, lost, or returned to Biogen. A written explanation must be provided for any discrepancies.

12.2. Placebo

Commercially available saline, provided by the site, will be used as placebo. The manufacturer's directions for material storage and handling are to be followed, as are standard clinical practices for ensuring sterility of the material.

13. CLINICAL FUNCTION, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

See Section 4 for the timing of all assessments; further detail regarding the order of the assessments will be provided in the Study Reference Manual.

See Section 7.2.2.3 for further information on the timing of the start of symptomatic PD medications relative to scheduled study visits. See Section 11.3.1.1 for further information on the recommended PD medications.

Remote Visits will be done in the event of a public health emergency that results in site closure, travel restrictions, or the study being deprioritized at the site such that visit(s) cannot occur. Use of a Remote Visit will not be done in place of an onsite visit simply due to subject preference. Refer to Table 12, Table 13, for Table 14 for clinical function assessments to be conducted during the Remote Visit.

13.1. Clinical Function Assessments

Clinical function assessments are performed by qualified raters, preferably those who are not involved in other aspects of subject clinical care and management, including clinical safety assessments. The same rater should perform a given assessment across all visits.

The following assessments will be performed to evaluate effects of BIIB054 on clinical function:

13.1.1. Motor Function and Related Activities of Daily Living

13.1.1.1. Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale (Including Modified Hoehn and Yahr Scale)

MDS-UPDRS is a multimodal scale assessing impairment and disability. It is separated into 4 subscales:

- Part I assesses nonmotor experiences of daily living.
- Part II assesses motor experiences of daily living that reflect the patients' subjective perception of their own condition.
- Part III assesses the motor signs of PD and is administered by the Investigator.
- Part IV assesses motor complications, dyskinesias, and motor fluctuations using historical and objective information.

Hoehn and Yahr Scale is included within the MDS-UPDRS, and is a commonly used system for describing PD manifestation, severity, and progression. The scale allocates stages from 0 to 5 to indicate the relative level of disability.

For subjects taking levodopa or other symptomatic PD medications, the entire MDS-UPDRS assessment (Parts I to IV) should be performed before subjects receive their first dose of this medication. Once they have started symptomatic PD medication, subjects should refrain from taking their PD medications for approximately 12 hours prior to study visits at which MDS-UPDRS [redacted] assessments will be conducted. Part III of the MDS-UPDRS [redacted] should be performed as soon as possible after the subject arrives in the clinic (see Section 13.1.1.3). Parts I, II, and IV of the MDS-UPDRS may be performed at a later point during the study visit, as described in the Study Reference Manual.

[redacted]

[redacted]

[redacted]

[redacted]

13.2. Pharmacokinetic Assessments

For subjects in Cohort A, the following parameters will be calculated by non-compartmental analysis to assess the serum PK of BIIB054 after the first dose (Day 1) and the third dose (Day 57):

- C_{max}
- Observed concentration at the end of the dosing interval (C_{trough})
- Time to reach maximum concentration (T_{max})
- AUC_{tau}
- Accumulation ratio

The serum PK of BIIB054 for subjects in Cohorts A and B will also be characterized by a nonlinear mixed effect approach. [redacted]

13.3. Pharmacodynamic Assessments

The following tests will be performed to assess the pharmacodynamic properties of BIIB054.

13.3.1. Imaging Assessments

13.3.1.1. Single-Photon Emission Computed Tomography Scan of the Dopamine Transporter

Biological effects of BIIB054 on brain dopamine neurons and nerve terminals will be assessed using DaT/SPECT imaging. Subjects will undergo DaT/SPECT imaging at Baseline and at specified timepoints. The DaT/SPECT imaging procedure will be performed using DaTscan, administered IV. Before the DaTscan injection, subjects will be pretreated with stable iodine (10 drops of a saturated solution of potassium iodide) to reduce the uptake of DaTscan by the thyroid. Subjects will be injected with 3 to 5 mCi of DaTscan. Within a 4-hour (±30 minutes) window following the injection, subjects will undergo SPECT imaging on the camera. Subjects will be monitored by study site staff for AEs on the day that a DaT/SPECT scan is obtained. Subjects will also be contacted by telephone within 7 days following the injection/scan.

[redacted]

[redacted]

[redacted]

14. SAFETY ASSESSMENTS

Refer to Section 4 for the timing of all safety assessments; further details regarding the order of the assessments will be provided in the Study Reference Manual.

Remote Visits will be done in the event of a public health emergency that results in site closure, travel restrictions, or the study being deprioritized at the site such that visit(s) cannot occur. Use of a Remote Visit will not be done in place of an onsite visit simply due to subject preference. If a subject does not participate in a remote or clinic visit, a Safety Telephone Call must be conducted to collect AEs, SAEs, concomitant medications and any procedures. Refer to Table 12, Table 13, and Table 14 for Remote Visit assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of BIIB054:

- AE and SAE recording.
- Physical and neurological examinations performed by the Investigator, Subinvestigator, or qualified designated personnel.
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Vital sign measurements: temperature, pulse rate, SBP, DBP, and respiratory rate will be measured after the subject has been resting in a supine position for at least 10 minutes. Orthostatic vital sign measurements will be obtained whenever blood pressure is read, in the following manner: after supine blood pressure and pulse rate are measured, the subject should stand, and blood pressure and pulse rate should be measured after standing 1 minute and 3 minutes.

  To determine eligibility at the Screening Visit, after a 10-minute rest period, the supine SBP/DBP and pulse reading should be performed 3 separate times, at least 15 minutes apart, with the last supine measurement followed by 1 orthostatic SBP/DBP and pulse measurement each at 1 minute and 3 minutes after standing. At subsequent visits, supine vital signs need to be measured only once, followed by orthostatic vital sign measurements at 1 and 3 minutes after standing.
- Weight measurements.
- 12-lead ECGs must be performed after the subject has been resting in a supine position for at least 10 minutes. The ECGs will be read by the Investigator at collection. Copies of all raw ECG data must be made available to Biogen.
- Concomitant therapy and procedure recording.

- Brain MRI safety findings (may include T1, fluid-attenuated inversion recovery, and gradient echo) or other modalities and sequences (to be detailed in the Imaging/MRI Manual). MRI results will be read by the local radiologist at collection and then sent within 24 hours to a central reader for further evaluation and to confirm eligibility at Screening.

[redacted]

14.2. Laboratory Safety Assessments

The following laboratory assessments will be performed to evaluate the safety profile of BIIB054:

- Hematology: Complete blood count with differential and platelet count, INR, PT, and APTT
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium
- Urinalysis: dipstick for blood, protein, and glucose (microscopic examination may also be performed)

[redacted]

[redacted]

14.3. Immunogenicity Assessments

The following assessments will be performed to determine the safety of BIIB054:

- Collection and analysis of serum samples for the presence and titer of anti-BIIB054 antibodies

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the main ICF, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

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

Determination of whether an abnormal laboratory value, vital sign result, MRI result, physical/neurological examination finding, and/or ECG result meet the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless 1 or more of the following criteria are met:

- The result meets the criteria for an SAE.
- The result requires the subject to receive specific corrective therapy.
- The result is considered by the Investigator to be clinically significant.

15.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Results in a congenital anomaly/birth defect
- Is a medically important event

A medically important event is an AE that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

15.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized. The study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
  - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2.
- The relationship of the event to study treatment, to the LP procedure, and to the DaTscan (ioflupane I123 Injection) radioligand (hereafter referred to as the radioligand), as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment, to the Lumbar Puncture Procedure, and to the Radioligand

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment, to the LP procedure, and to the radioligand.

Relationship of Event to Study Treatment	
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.
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.
Relationship of Event to LP	
Not related	An AE will be considered "not related" to the LP procedure if there is not a reasonable possibility that the event has been caused by the LP procedure. Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between the LP procedure and the AE, the presence of a biologically implausible relationship between the LP procedure and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the LP procedure if there is a reasonable possibility that the event may have been caused by the LP procedure. Factors that point toward this assessment include but are not limited to: a reasonable temporal sequence between the LP procedure and the AE, a known response pattern of the LP procedure (e.g., bleeding from the puncture site), a biologically plausible relationship between the LP procedure and the AE, or a lack of an alternative explanation for the AE.
Relationship of Event to Radioligand	
Not related	An AE will be considered "not related" to the use of the radioligand if there is not a reasonable possibility that the event has been caused by the radioligand. Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between administration of the radioligand and the AE, the presence of a biologically implausible relationship between the radioligand and the AE, or the presence of a more likely alternative explanation for the AE.

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

15.2.3. Severity of Events

The severity of AEs and SAEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Any AE not listed in the CTCAE will be graded as follows:

Severity of Event	
Grade	Definition
1	Mild AE (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)
2	Moderate AE (minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADLs)
3	Severe or medically significant AE (not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADLs)
4	Life-threatening AE (urgent intervention indicated)
5	Death related to AE

15.2.4. Expectedness of Events

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

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE (including SAEs) experienced by the subject between the time of first dose of study treatment and the Final Visit is to be recorded on the eCRF, regardless of the severity of the event, its relationship to study treatment, its relationship to the LP procedure, or its relationship to the radioligand. Nonserious AEs that occur during the Screening period and that are assessed by the Investigator as related to the ligand will be captured by the sites on the AE eCRF. At each study visit, the Investigator will assess the subject for AEs and will record any new AEs or updates to previously reported AEs on the eCRF.

AEs that are ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status. AE outcome will be recorded on the eCRF, as applicable.

15.3.2. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the main ICF and the Final Visit is to be recorded on an SAE form, regardless of the severity of the event, its relationship to study treatment, its relationship to the LP procedure, or its relationship to the radioligand. SAEs must be reported to Biogen within 24 hours as described in Section 15.3.3.

Follow-up information regarding an SAE also must be reported within 24 hours. Subjects will be followed for all SAEs until the Final Visit. Thereafter, an SAE should be reported to Biogen only if the Investigator considers it to be related to study treatment.

Any SAE that is ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

15.3.3. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify Biogen within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject has signed the main ICF and the Final Visit must be reported to Biogen within 24 hours of the study site staff becoming aware of the event. After the Final Visit, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** to Biogen regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event
- The relationship of the event to study treatment, to the LP procedure, or to the radioligand

To report initial or follow-up information on an SAE, fax a completed SAE form; refer to the Study Reference Manual for complete contact information.

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate eCRF. 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.

15.3.4. 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.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 6 months 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 from first dose of study treatment up to 6 months after the last dose, by faxing the appropriate form to Biogen within 24 hours of the study site staff becoming aware of the pregnancy; refer to the Study Reference Manual for complete contact information. The Investigator or study 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 eCRF.

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.

15.4.2. 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 eCRF; however, all overdoses must be recorded on an Overdose form and faxed 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 to Biogen. All study treatment-related dosing information must be recorded on the dosing eCRF.

15.4.3. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should inform the study's Medical Monitor of the event as soon as it is feasible to do so. Refer to the Study Reference Manual's Official Study Contact List for complete contact information.

15.4.3.1. 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 or designee may access the subject's treatment assignment by IRT. When possible, the Investigator or designee should attempt to contact the study's Medical Monitor to discuss the emergency. 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, nor to personnel involved with the analysis and conduct of the study. The Investigator can contact Biogen to discuss such situations.

15.5. Contraception Requirements

All women of childbearing potential and all men must practice highly effective contraception during the study and for 6 months after their last dose of study treatment. In addition, male subjects should not donate sperm for the duration of the study and for at least 6 months after their last dose of study treatment.

For the purposes of this study, women who do not meet one of the following criteria listed below are considered to be physiologically capable of becoming pregnant and are, therefore, defined as women of childbearing potential:

- Postmenopausal
  - 12 continuous months of natural (spontaneous) amenorrhea without an alternative medical cause and a serum follicle stimulating hormone level >40 mIU/mL
  - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation)

For the purposes of the study, highly effective contraception is defined as use of 1 of the following:

For female subjects:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal methods of contraception associated with the inhibition of ovulation.
- Established use of oral, injected, or implanted progestogen-only hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine hormone-releasing system.

- Bilateral tubal occlusion.

- Sex with a male partner who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

For male subjects:

- A vasectomy with subsequent negative semen analysis.

- Sex with a woman who uses the methods described for female subjects if she is of childbearing potential.

True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, on the eCRF regardless of the severity, relationship to study treatment, relationship to the LP procedure, or relationship to the radioligand.

- Determine the seriousness, relationship to study treatment, relationship to the LP procedure, relationship to the radioligand, and severity of each event.

- Determine the onset and resolution dates of each event.

- Monitor and record all pregnancies in female subjects and follow up on the outcome of all pregnancies.

- Complete an SAE form for each SAE and fax it to Biogen within 24 hours of the study site staff becoming aware of the event.

- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Biogen within 24 hours of the study site staff becoming aware of new information.

- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.

- Pursue AE follow-up information, if possible, until the event has resolved or become stable. Record AE follow-up information, including resolution, on the eCRF, as applicable.

- Report SAEs to local ethics committees, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.

- Biogen is to notify all appropriate regulatory authorities, central ethics committees, central institutional review boards and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Safety

16.1.1. Analysis Population

The safety population is defined as all subjects who received at least 1 dose of study treatment (BIIB054 or placebo). The same definition applies to Years 1 through 4.

16.1.2. Methods of Analysis

AEs will be coded using the Medical Dictionary for Regulatory Activities. In general, safety endpoints will be summarized using descriptive statistics.

Safety analyses will be done separately, as follows:

- Year 1 (placebo-controlled portion of the study): All data will be summarized by treatment group (e.g., placebo; 250 mg, 1250 mg, and 3500 mg of BIIB054; and total BIIB054).

- Years 2 through 4 (active-treatment dose-blinded portion of the study) and overall experience: Data from Years 2 through 4 and combined data from Years 1 through 4 (active-treatment dose-blinded portion of the study as well as overall experience on BIIB054 from the combined placebo-controlled portion and active-treatment dose-blinded portion of the study) will be summarized by treatment group.

The primary evaluation of safety will cover Year 1 of the study (placebo-controlled period, from baseline to Week 52).

Any safety data collected from in-clinic or remote visits will be included in the statistical analysis.

16.1.2.1. Adverse Events

All analyses of AEs will be based on the principle of treatment emergence. An AE is considered to be treatment emergent if it has an onset date on or after the date of first dosing, or if it was present prior to the first dose and subsequently worsened. Incidences of all AEs will be presented by system organ class and preferred term by treatment group and overall active group. In addition, incidence of all AEs by severity, by relationship to study treatment, and by relationship to LP procedure will be presented. Data after subjects started symptomatic PD medications will be analyzed both ways (included and excluded).

16.1.2.2. Clinical Laboratory Results

Clinical laboratory evaluations include hematology, blood chemistry, and urinalysis. Analyses of clinically significant abnormalities, shifts from baseline to post-baseline relative to the normal range, as well as change from baseline by visit will be presented by treatment group and overall active group.

16.1.2.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities, which will be defined in more detail in the statistical analysis plan (SAP). Incidence of clinically relevant abnormalities in vital signs will be summarized by treatment group and overall active group.

16.1.2.4. Electrocardiogram

The analysis of ECGs will focus on clinically relevant abnormalities, which will be defined in more detail in the SAP. ECG changes from baseline will be summarized using descriptive statistics and presented by treatment group, overall active group, and timepoint.

16.1.2.5. Physical and Neurological Examinations

Abnormal findings during physical and neurological examinations will be recorded as AEs and will be reflected in the summary of AEs.

16.1.2.6. Columbia Suicide Severity Rating Scale

C-SSRS data will be summarized using descriptive statistics and presented by treatment group and overall active group.

16.1.2.7. Magnetic Resonance Imaging

Subjects' brain MRIs will be categorized by normal and abnormal. Shift tables for MRI results will be presented by visit for each treatment group and overall active group.

16.2. Pharmacodynamics – Imaging Analyses

16.2.1. Analysis Population

The pharmacodynamic population is defined as a subset of the intent-to-treat (ITT) population with at least 1 post-baseline pharmacodynamic measurement. The ITT population is defined in Section 16.5.2.1.

16.2.2. Methods of Analysis

Year 1 (placebo-controlled portion of the study):

The pharmacodynamic effects of BIIB054 on the integrity of nigrostriatal dopaminergic nerve terminals will be evaluated via DaT/SPECT imaging. The main DaT/SPECT outcome of interest are the change from baseline to Week 52 in the putamen ipsilateral to the clinically affected side SBR, putamen SBR, striatum SBR, and caudate SBR. The change in SBR will be analyzed using the mixed model for repeated measures (MMRM). The model may include the fixed effect of the treatment group, baseline DaT/SPECT values, baseline MDS-UPDRS I + II + III total score value, and visit. The model may include interaction terms between baseline MDS-UPDRS total score and visit, between baseline DaT/SPECT values and visit. Correlation among repeated measures within subject will be considered in the model. The multiple comparison procedure-modelling (MCP-MOD) method may be used to assess and model dose-response.

Years 2 through 4 (active-treatment dose-blinded portion of the study):

Descriptive statistics will be used to summarize the change from study baseline in DaT/SPECT imaging SBR to Week 96/148 by treatment group. Exploratory statistical comparisons may be made to evaluate the impact of immediate versus delayed initiation of BIIB054, with applicable statistical methods.

Missing data due to the impact of the COVID-19 public health emergency will be considered missing at random in the statistical analyses. [redacted]

16.3. Pharmacokinetics

16.3.1. Analysis Population

The population for PK analysis is defined as all subjects in the ITT population who have at least 1 measurable BIIB054 concentration in serum [redacted]. The ITT population is defined in Section 16.5.1.

16.3.2. Methods of Analysis

Samples for measuring serum [redacted] concentration of BIIB054 will be collected as specified in Section 4.2. Serum PK parameters will be calculated by non-compartmental and/or compartmental methods. [redacted] For Cohort A, PK parameters calculated by a non-compartmental method will also be summarized using descriptive statistics.

Mean serum concentrations of BIIB054 versus time will be plotted by treatment group on both a linear and a logarithmic scale for Cohort A (doses 1 and 3 only). Dose proportionality will be assessed for AUC_{tau} and C_{max}.

Atypical serum drug concentrations (such as very low or very high) will be excluded from the analysis if no apparent explanation exists. Concentration observations will also be removed from the data set if corresponding dosing or sampling times are missing or cannot be reconstructed. Concentration data with below limit of quantification value will be removed from analysis. All deletions of data points will be appropriately documented.

Population PK analysis may be conducted to estimate BIIB054 population PK parameters and to identify potential covariates (e.g., demographics, body weight, and anti-BIIB054 mAb) on the variability of BIIB054 PK. Results will be presented in a separate report.

16.4. Immunogenicity Data

16.4.1. Analysis Population

Immunogenicity analysis will be performed for all subjects in the safety population.

16.4.2. Methods of Analysis

The incidence of anti-BIIB054 antibody will be summarized by visit and by treatment group.

16.5. Clinical Function

16.5.1. Analysis Population

The ITT population is defined as all randomized subjects who receive at least 1 dose of study treatment. Data from corresponding dose levels in Cohort A and Cohort B will be pooled for all analyses.

The per protocol population, mainly for the purpose of Year 1 analyses, is defined as a subset of the ITT population who receives at least 70% (10 doses) of study treatment during Year 1 and has not missed consecutive doses.

16.5.2. Methods of Analysis

In general, analyses for clinical function will be done in 2 ways: (1) Year 1 (placebo-controlled portion of the study) and (2) Years 2 through 4 (active-treatment dose-blinded portion of the study) and overall experience (combined data from Years 1 through 4).

In general, all data collected from in-clinic or remote visits will be included in the statistical analyses. The impact of remote assessments on the statistical analyses may be assessed.

Missing data due to the impact of the COVID-19 public health emergency will be considered missing at random in the statistical analyses. Analysis to evaluate the impact of the current COVID-19 emergency and any future public health emergency will be described in the SAP.

16.5.2.1. Year 1 (Placebo-Controlled Portion of the Study)

The changes in clinical function, including motor [redacted] (MDS-UPDRS, [redacted] outcome measures will be included in the analyses in Year 1 (Week 52).

Analyses of these endpoints will be performed in the ITT population, with select endpoints (e.g., MDS-UPDRS) also analyzed using the per protocol population.

Changes from baseline in the primary endpoint MDS-UPDRS Part I + II + III total scores at Week 52 will be analyzed using the MMRM. The model may include fixed effect of treatment group, baseline MDS-UPDRS I + II + III total score values, region, PD subtype, baseline DaT/SPECT striatum SBR values, visit, and the interaction terms between treatment and visit, between baseline MDS-UPDRS I + II+ III total score by visit, and between baseline DaT/SPECT striatum SBR values and visit. The correlation between repeated measures of the outcomes will be taken into consideration in the model. Dose-response relationship will be tested based on the MCP-MOD method (potential candidate models will include linear, linear-log, quadratic, maximum effect (E_{max}), and logistic models, as specified in Section 16.9). A multiple comparison adjustment method will be applied to control the overall type I error at 0.05 in the study, due to the primary endpoint of MDS-UPDRS total score being analyzed at Week 52 and Week 72, and superiority against placebo is considered reached in study if statistically significant result is achieved at either timepoint. The details of the multiple comparison adjustment method will be pre-specified in the SAP. Pairwise comparison of each active group versus placebo will also be conducted, however, no additional multiplicity adjustment will be made, and nominal p-values will be reported.

Secondary endpoints, e.g., change from baseline in the MDS-UPDRS subscores (e.g., Part I, II, or III score, Part II and III total score) will be analyzed in a similar model, but no additional multiplicity adjustment will be made or for other secondary endpoints. Additional details will be provided in the SAP.

[redacted]

[redacted] Cox's

proportional hazard model will be used to analyze the data, where appropriate. The model may adjust for baseline MDS-UPDRS values, region, PD subtype, baseline Modified Hoehn and Yahr stage, prior usage status of symptomatic PD medication, and baseline DaT/SPECT striatum SBR values. If the proportionality assumption does not hold, the log rank test will be used. More details will be described in the SAP.

16.5.2.2. Years 2 through 4 (Active-Treatment Dose-Blinded Portion of the Study) and Overall Experience

At Week 72, the primary endpoint of changes from baseline in MDS-UPDRS Part I + II + III total scores will be analyzed using the MMRM, similar to the Year 1 analyses with similar covariates in the model. The treatment groups included in the model will be the delayed start/initiation group (placebo to BIIB054), and the immediate start/initiation groups (the original 250 mg, 1250 mg and 3500 mg BIIB054 groups). Dose response relationship will be tested based on the MCP-MOD method (potential candidate models will include linear, linear-log, quadratic, E_{max}, and logistic models, as specified in Section 16.9). A multiple comparison adjustment method will be applied to control the overall type I error at 0.05 in the study, due to the MDS-UPDRS Part I + II + III total score being analyzed at Week 52 and Week 72 and success of efficacy is considered at either timepoint. The details of the method will be pre-specified in the SAP. The results of the analysis will be considered statistically significant after applying the multiple comparison adjustment method. Pairwise comparison of each immediate start group versus the delayed start group will also be conducted; however, no additional multiplicity adjustment will be made, and nominal p-values will be reported.

Secondary endpoints, e.g. change from baseline in the MDS-UPDRS subparts (e.g., Part I, II, or III, IV score, Part II and III total score) or change in MDS-UPDRS I + II + III total score at end of study, will be analyzed in a similar model, but no additional multiplicity adjustment will be made for secondary endpoints.

[redacted]

[redacted] Cox's proportional hazard model will be used to analyze the data where appropriate. The model may adjust for baseline MDS-UPDRS values, region, PD subtype, baseline Modified Hoehn and Yahr stage, prior usage status of symptomatic PD medication, and baseline DaT/SPECT striatum SBR values as appropriate. If the proportionality assumption does not hold, the log rank test will be used. More details will be described in the SAP.

These outcome measures will be summarized by treatment group. [redacted]

[redacted]

16.8. Interim Analyses

Safety and PK data only will be reviewed by the IDMC after subjects in Cohort A have completed Week 12 Visit assessments, and before dosing any subjects in Cohort B.

After subjects in Cohort A complete the Week 24 Visit, [redacted], all available serum PK, [redacted] from Cohort A will be analyzed by a statistical/PK team independent of the study. The grouped level summary statistics will be reviewed only by a limited number of individuals at Biogen who are not involved in the management of the subjects or subject-level data for the study. No changes to the study design are expected based on this review.

For the purpose of planning for future studies, an administrative interim analysis may be performed when approximately 60% of the subjects have completed the Week 52 Visit. A small unblinded team from Biogen, separate from the study management team, will have access to the unblinded interim analysis results.

A full analysis of the 1-year data will be performed after all subjects have completed the Week 52 Visit. A small unblinded team from Biogen, separate from the study management team, will have access to the unblinded 1-year analysis results.

An interim analysis when all subjects have completed the Week 72 Visit is planned to be conducted. A small unblinded team from Biogen, separate from the study management team, will have access to the unblinded interim analysis results.

A multiple comparison adjustment method will be applied to control the overall type I error at 0.05 in the study, due to the primary endpoint of change from baseline in MDS-UPDRS total score being analyzed at Week 52 and Week 72, and superiority against placebo is considered reached in the study if statistically significant result is achieved at either timepoint at the respective adjusted alpha-level. The details of the multiple comparison adjustment method will be pre-specified in the SAP. No additional multiplicity adjustments will be made for secondary or exploratory endpoint analyses.

A blinded sample size re-estimation may be conducted when approximately 10% of subjects have completed the Week 52 Visit or approximately 1 month before enrollment is projected to be completed, whichever is earlier. The study sample size may be increased based on this blinded data review. There may be small adjustments to the percentage depending on actual enrollment rate. Details will be provided in the SAP.

16.9. Sample Size Considerations

The sample size calculation is based on changes in MDS-UPDRS Part I + II + III total score at Week 52 and at Week 72 of treatment. Based on data from the Parkinson's Progression Markers Initiative study, the placebo subject's mean and standard deviation (SD) at Week 52 and Week 72 are assumed to be 8.0 (10.64) and 9.6 (13.7) respectively. Assuming a maximum of 55% reduction in the change from baseline in the active group with maximum response relative to placebo group, the mean (SD) for this active group will be 3.2 (10.64) and 3.84 (13.7) respectively at Week 52 and Week 72, and the responses for other active groups are assumed to be somewhere between 0 and the maximum response. The primary analysis will be based on the MCP-MOD method to detect a dose-response trend while controlling for multiplicity. Optimal contrasts will be constructed to detect potential dose-response trend under common dose-response curves (e.g., E_{max}, exponential, logistic, linear in log dose, and quadratic model, which are illustrated with parameters shown in Figure 5 which will be used for both Week 52 and Week 72). The planned enrollment is 311 subjects total (24 subjects in Cohort A and 287 subjects in Cohort B, Table 8). Actual enrollment is 357 subjects. In Cohort A, 29 subjects were randomized in a 1:1:1:1 ratio to each of the treatment groups, while in Cohort B 328 subjects were randomized in 2:1:2:2 ratio to the placebo, 250 mg, 1250 mg, and 3500 mg groups. Based on the actual enrollment, the estimated number of subjects by cohort and treatment groups are given in Table 9 below. After accounting for dropout rate of 10% and 15% at Week 52 and Week 72, respectively, the estimated sample sizes are given in Table 10 and Table 11. With the updated sample size, the study will provide an average power of approximately 80% to detect the dose-response trend over 1 year of treatment, based on a 2-sided type I error of 0.05 and approximately 73% of power at the Week 72 analyses, based on a 2-sided type I error of 0.05. Overall, the sample size in the study will provide approximately 89% power. If there are any modifications to the candidate dose-response curves/models or parameters, the final candidate models for the MCP-MOD will be prespecified and described in the SAP.

With an estimated sample size of 100 subjects dosed per arm in the 1250 mg and 3500 mg arms, the study has 80% probability of detecting AEs with a rate of 1.2% or greater in these 2 arms, and a 90% probability of detecting AEs occurring with a rate of 2.1% or greater.

Figure 5: Candidate Models for Dose-Response

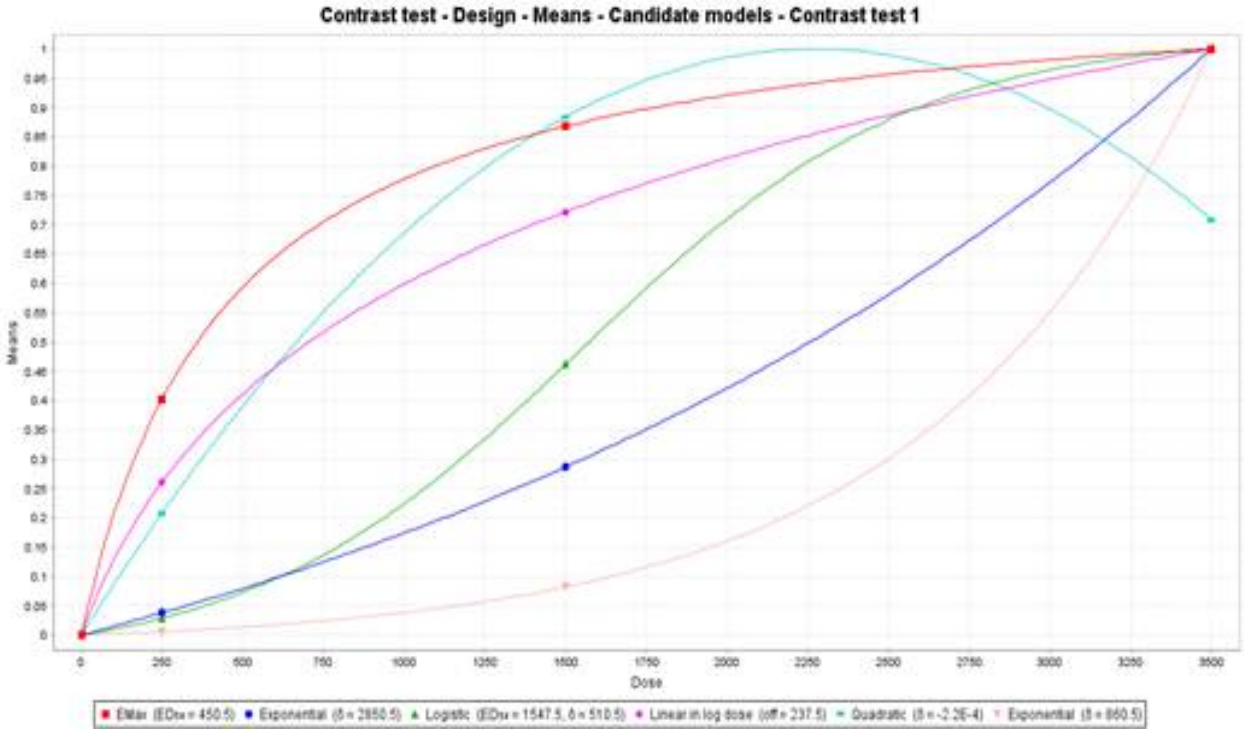


Table 8: Estimated Sample Size Per Group (Planned)

	Treatment Group				
Cohort	**Placebo**	**BIIB054 250 mg**	**BIIB054 1250 mg**	**BIIB054 3500 mg**	**Total**
Cohort A	6	6	6	6	24
Cohort B	82	41	82	82	287
Total	88	47	88	88	311

Table 9: Estimated Sample Size Per Group Based on Actual Enrollment (Before Drop-Outs)

	Treatment Group				
Cohort	**Placebo**	**BIIB054 250 mg**	**BIIB054 1250 mg**	**BIIB054 3500 mg**	**Total**
Cohort A	8	7	7	7	29
Cohort B	93	47	94	94	328
Total	101	54	101	101	357

Table 10: Estimated Sample Size Per Group Based on Actual Enrollment (After Adjusting for 10% Drop-Out At Week 52

	Treatment Group				
Cohort	**Placebo**	**BIIB054 250 mg**	**BIIB054 1250 mg**	**BIIB054 3500 mg**	**Total**
Cohort A	7	6	6	6	25
Cohort B	84	42	84	84	294
Total	91	48	90	90	319

Table 11: Estimated Sample Size Per Group Based on Actual Enrollment (After Adjusting for 15% Drop-Out At Week 72

	Treatment Group				
Cohort	**Placebo**	**BIIB054 250 mg**	**BIIB054 1250 mg**	**BIIB054 3500 mg**	**Total**
Cohort A	7	6	6	6	25
Cohort B	79	40	80	80	279
Total	86	46	86	86	304

17. ETHICAL REQUIREMENTS

Biogen, [redacted] 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 eCRFs via signature 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.

17.1. Declaration of Helsinki

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

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICFs, and other required study documents prior to starting the study. [redacted] will submit documents on behalf of the investigational sites with central institutional review boards. Investigational sites with local institutional review boards will submit documents themselves, and [redacted] will provide the necessary documentation.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the ethics committee or institutional review board. 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 or institutional review board, 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 or institutional review board 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 or institutional review board at required intervals and not less than annually.

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

17.3. 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 main ICF must be obtained from the subject or subject's legally authorized representative (e.g., legal guardian), as applicable, in accordance with local practice 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; see Section 17.4.

[redacted]

A copy of the signed and dated ICF(s) must be given to the subject or the subject's legally authorized representative. The original signed and dated ICFs 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.

17.4. 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 PK profile of the study treatment. It is unknown whether the effects of the study treatment are influenced by race or ethnicity. There could be inter-racial and ethnic differences that may impact the reaction or response to the study treatment, leading to a different benefit/risk balance in the various racial or ethnic subgroups. Therefore, information on race and ethnicity can provide relevant and valuable information for a

more thorough evaluation of the safety profile, the pharmacokinetics/ pharmacodynamics, [redacted], and benefit of the study treatment in the target population.

Study reports will be used for research purposes only. The subject will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Biogen, its partners and designees, ethics committees, institutional review boards, 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.

17.5. Compensation for Injury

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

17.6. 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.

17.7. 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.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Control and Quality Assurance

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the sites for clarification and resolution, as appropriate. The Investigator is responsible for endorsing all eCRF data prior to any interim or final database lock.

During and/or after completion of the study, quality assurance officers named by Biogen or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be explained if necessary (e.g., with an audit trail). The Investigator should maintain a record of the location(s) of essential documents.

The Clinical Monitor will visit the Investigator at regular intervals during the study and after the study has completed, as appropriate. A clinical site monitoring plan will detail who performs the monitoring, how often, and the extent of review. It also will provide the monitoring strategy, with emphasis on subject safety, data integrity, and critical data and processes.

During these visits, eCRFs, supporting documentation, and essential documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of subject rights and well-being, protocol adherence, quality of data (accurate, complete, and verifiable), study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, Investigator, and Biogen.

18.5. Publications

Details are included in the clinical trial agreement for this study.

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. Contract Research Organization

[redacted] will be responsible for administrative aspects of the study including but not limited to study initiation, monitoring, management of SAE reports, and data management. Before subjects are screened at each study site, the contract research organization (CRO) will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or enrolled, the IRT vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

19.1.3. Electronic or Remote Data Capture

Subject information will be captured and managed by study sites on eCRFs by a Web-based electronic data capture tool that will be configured and supported by [redacted]

Electronic clinical outcome assessments will be entered by site staff on a handheld device, developed and supported by Medavante. Site staff will monitor data via a secure web portal developed and supported by Medavante.

19.1.4. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by Biogen to store samples collected from subjects in this study for [redacted] hemoglobin, drug concentrations, and anti-BIIB054 antibodies in whole blood, plasma, serum, urine, [redacted]; these samples may be analyzed by a central laboratory or a third-party laboratory, as applicable. A central laboratory will also perform the safety laboratory tests noted in the Schedule of Activities tables (Table 1 through Table 6): blood chemistry, hematology, urinalysis, glycated hemoglobin, serum pregnancy testing, FSH, drug screening, HBsAg, anti-HBc, anti-HBs, HCVAb, HIV, and coagulation panels. In addition, if repeat coagulation or hematology tests are required, the samples may be collected in the clinic and sent to the local laboratory for analysis.

[redacted]

All other laboratory-based assessments will be performed by Biogen or designee.

Duplicate laboratory samples may be collected as a backup in case the original sample is lost or not evaluable.

19.1.5. Central Facility for Other Assessments

Central imaging vendors will be selected by Biogen to read and interpret all MRI and DaT/SPECT scans.

[redacted]

19.1.6. Clinical Assessments

Biogen selected a rater management group to establish rater qualification, study specific training, and oversight. The study raters are required to complete qualifications steps and required training prior to administering study clinical assessments. The rater management group will oversee the clinical assessments per project-specific plans.

19.2. Study Committees

19.2.1. Advisory Committee

Advisory committees will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The advisory committees will meet to monitor subject accrual and to monitor compliance with the protocol at individual study sites as described in the committee charter. The advisory committees will be blinded to subject treatment assignments. The advisory committees will determine whether the study should be stopped or amended for reasons other than safety.

Members of the advisory committees will include, but not be limited to, the Medical Director, Clinical Operations Lead, and Project Statistician from Biogen, and participating Investigators. Biogen will designate the chairperson of the advisory committees.

19.2.2. Independent Data Monitoring Committee

An IDMC will review safety and PK data after subjects in Cohort A have completed Week 12 Visit assessments, and before dosing any subjects in Cohort B. The first IDMC meeting will occur after the last subject in Cohort A completes Week 12 assessments or approximately 6 months after the first subject has been enrolled in Cohort A, whichever comes first. Regular IDMC meetings will occur approximately every 3 months after the first meeting. Additional information on the IDMC meetings is included in the IDMC charter.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and/or institutional review board and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be

approved by the ethics committee and/or institutional review board before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICFs may require similar modifications (see Section 17).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory authorities and ethics committees and/or institutional review board must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local, regional, or national laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen will designate one of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors, including but not limited to, the Investigator's experience and reputation in the studied indication; the Investigator's contribution to the study in terms of design, management, and/or subject enrollment; or by other factors determined to be relevant by Biogen.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study, with an Active-Treatment Dose-Blinded Period, to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of BIIB054 in Subjects with Parkinson's Disease," 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)

APPENDIX 1. REMOTE VISITS – SCHEDULE OF ACTIVITIES

Table 12: Cohorts A and B: Remote Visits in Year 2

	Week (±3d)											Unsched Visit[1]
Tests and Assessments	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96[2]**	
MDS-UPDRS (full scale), include Modified Hoehn and Yahr Scale[3]		X			X			X			X	X
[redacted]												
C-SSRS[5]	X	X	X	X	X	X	X	X	X	X	X	X
AE/Concomitant therapy and procedures	Ongoing											
SAE reporting	Ongoing											

[redacted]; AE = adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; d = day; [redacted]; MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; [redacted]; PD = Parkinson's disease; [redacted]; SAE = serious adverse event; [redacted]; Unsched = unscheduled; [redacted].

[1] Unscheduled Visit can occur for safety-related issues at any time (as determined by the Investigator) or for administering the MDS-UPDRS prior to starting symptomatic PD medications outside of a scheduled visit. Additional tests may be performed at the Investigator's discretion.
[2] Consult Figure 4 to see if subject qualifies to continue dosing in Years 3 and 4 (if applicable).
[3] Subjects who have started symptomatic PD medication during this study should refrain from taking the PD medication for approximately 12 hours prior to MDS-UPDRS visits. MDS-UPDRS Part III will be administered before subjects take the PD medication, [redacted]

[redacted]

[5] The "Since Last Visit" version of the C-SSRS will be administered at all Remote Visits. If the Investigator has any concern regarding the completed C-SSRS, the subject should be referred to psychiatric evaluation based on local standards of care.

Table 13: Cohorts A and B: Remote Visits in Years 3 and 4

Tests and Assessments	Year 3 Week (±3d)													Year 4 Week (±3d)			Unsched Visit[1]
	100	104	108	112	116	120	124	128	132	136	140	144	148	152	156	160	
MDS-UPDRS (full scale), includes Modified Hoehn and Yahr Scale[2]			X			X			X			X			X		X
[redacted]																	
C-SSRS[4]		X		X		X		X		X		X		X		X	X
AE/Concomitant therapy and procedures	Ongoing																
SAE reporting	Ongoing																

[redacted]; AE = adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; d = day; [redacted]; MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; [redacted]; PD = Parkinson's disease; [redacted]; SAE = serious adverse event; [redacted]; Unsched = unscheduled; [redacted].

[1] Unscheduled Visit can occur for safety-related issues at any time (as determined by the Investigator) or for administering the MDS-UPDRS prior to starting symptomatic PD medications outside of a scheduled visit. Additional tests may be performed at the Investigator's discretion.

[2] Subjects who have started symptomatic PD medication during this study should refrain from taking the PD medication for approximately 12 hours prior to MDS-UPDRS visits. MDS-UPDRS Part III will be administered before subjects take the PD medication, [redacted]

[redacted]

[4] The "Since Last Visit" version of the C-SSRS will be administered approximately every 60 days. If the Investigator has any concern regarding the completed C-SSRS, the subject should be referred to psychiatric evaluation based on local standards of care.

Table 14: Cohorts A and B Remote Early Termination and End of Study: 4 Weeks After Last Dose Through Final Visit

Tests and assessments	Last Dose +4 wk (±3d)/ET	Safety Telephone Call (±2d) (Last Dose +8 wk)	Final Visit (±3 d) (Last Dose + 12 wk)
MDS-UPDRS (full scale), includes Modified Hoehn and Yahr Scale[1]	X		X
[redacted]			
C-SSRS[3]	X		X
AE/Concomitant therapy and procedures	Ongoing		
SAE reporting	Ongoing		

[redacted]; AE = adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; d = day; [redacted] MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; [redacted]; PD = Parkinson's disease; [redacted]; SAE = serious adverse event; [redacted]; Unsched = unscheduled; wk = week; [redacted].

[1] Subjects who have started symptomatic PD medication during this study should refrain from taking the PD medication for approximately 12 hours prior to MDS UPDRS visits. MDS-UPDRS Part III will be administered before subjects take the PD medication, [redacted]

[3] The "Since Last Visit" version of the C-SSRS will be administered. If the Investigator has any concern regarding the completed C-SSRS, the subject should be referred to psychiatric evaluation based on local standards of care.

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AMENDMENT SUMMARY

Biogen Protocol 228PD201

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study, with an Active-Treatment Dose-Blinded Period, to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of BIIB054 in Subjects with Parkinson's Disease

Version 7

Date: 03 February 2020

EUDRA CT Number: 2016-004610-95

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 228PD201 is to specify the timing of DaT/SPECT scans for certain participants, as requested by the German Radiology Authority.

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

Section 4.2, Schedule of Activities, Table 6, footnote 5

Now reads:

Performed only for subjects who have not had the assessment at Week 96 (if withdrawing after Year 2) or Week 148 (if withdrawing after Year 3). **Further, DaT/SPECT is only to be performed if the time interval since the previous DaT/SPECT examination exceeds 23 weeks. This >23-week time interval restriction does not apply to MRI.** The MRI and DaT/SPECT assessment windows **for all visits** are ±7 days. The MRI results will be read by the local radiologist at collection. Both MRI and DaT/SPECT results will be sent within 24 hours to a central reader for further evaluation. Subjects will be contacted by telephone within 7 days following the DaT/SPECT procedure to monitor for AEs.

Rationale: This text was added in order to specify the minimum time interval required between SPECT visits to ensure that participant radiation exposures are kept at a safe limit, at the request of the German Radiology Authority.

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 4.2, Schedule of Activities, Table 1

Change: AE reporting and concomitant medications/procedures reporting were split into separate rows and the timing of these activities was updated. Footnote 23 was updated accordingly.**Now reads:**

	Screening ≤42 days before Day 1[1]	Infusions 1-3 Day 1/Baseline, Day 29 (±1 day), & Day 57 (±1 day)					Clinic Visits				Day 43 (Safety Telephone Call)
							Day 2, 30, 58	Day 4, 60	Day 8, 36, 64	Day 15, 71	
		Pre-infusion[2]	0m	Time after End of Last Infusion							
Tests and assessments				≤10m	1h ±15m	2h ±15m	4h ±30m	24h ±2h	72h -2h/+1d	168h ±24h	336h ±24h	336h ±24h
AE reporting[23]			**ongoing**									
Concomitant therapy and procedures reporting	**ongoing**											

Footnote 23 now reads:

[23]Nonserious AEs that occur during the Screening period and that are assessed by the Investigator as related to the ligand will be captured by the sites on the AE electronic case report form (eCRF). **After the first dose of study treatment, all AEs are collected, both related and unrelated to the ligand (see Section 15.3.1).**

Rationale: This change clarifies that reporting of concomitant therapy and procedures should begin during screening, while reporting of AEs not related to the radioligand should not start until study treatment has been administered.

This change also affects Section 4.2, Schedule of Activities, Table 3 and footnote 26.

Section 4.2, Schedule of Activities, Table 4

Change: An X was added in the BIIB054 serum PK sampling row under Year 2 Week 52. Footnote 1 was added to the Year 2 Week 52 column heading, and subsequent footnote numbering was updated accordingly. **Now reads:**

Tests and assessments	Year 2 Week 52 (±3d)[1] Infusion 14	Safety Telephone Calls 1d & 7d after Infusion 14[2]	Infusions 15-25, Week (±3d) 56	60	64	68	72	76	80	84	88	92	96[4]	Unsched Visit[3]
Body weight[5]	X			X			X			X			X	
Physical/neurological examination[6]			X	X										X
12-lead ECG[5,7]	X		X										X	
Vital signs[5,8]	X		X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test [5,9]	X		X	X	X	X	X	X	X	X	X	X	X	
Hematology, blood chemistry, urinalysis[5]				X									X	X
Whole blood for RNA[5,10]				X									X	
Brain MRI[11]													X	
DaT/SPECT[11]													X	
Randomization[12]	X													
Study treatment infusion[13]	X		X	X	X	X	X	X	X	X	X	X	X	
BIIB054 serum PK sampling[14]	**X**			X						X			X	

Rationale: Because the BIB054 serum PK sampling box for Year 2 Week 2 was not marked in this Schedule of Activities, sites were not consistently obtaining the required Week 52 post-dose PK sample. This change was made to help prevent future protocol deviations and ensure adequate PK sample collection. The table now matches Table 3.

Section 7.1.2, Years 2 through 4 (Active-Treatment Dose-Blinded Portion of the Study)

Change: Language was added to clarify that both clinic visits scheduled for Week 52 can be conducted as a single visit.

Now reads: The Year 1 Week 52 and Year 2 Week 52 visits (first visit of Year 2) can be conducted as a single visit. Prior to Infusion 14 (the first dose of Year 2**; Year 2 Week 52 visit**), subjects who received placebo in Year 1 will be randomized into 1 of the active-dosing arms for Year 2; these subjects will receive BIIB054 in Year 2.

Rationale: Allowing these temporally proximal visits to be combined reduces the burden on participants without sacrificing data collection and provides clarity for study sites.

This change also affects Section 4.2, Schedule of Activities, Table 2, footnote 2; Table 3, footnote 4; and Table 4, footnote 1.

Section 7.2.2.3, Treatment with Parkinson's Disease Medications

Change: Language was added to clarify that the Week 52 MRI and DaT/SPECT scans have a window of only -7 days (rather than ±7).

Now reads: It is recommended that subjects who plan to start symptomatic PD medication either outside of a visit window or outside of the DaT/SPECT window wait, if possible, until after the next DaT/SPECT to start the medication, provided that a DaT/SPECT visit is planned within 1 month. (As an alternative, if the subject cannot wait to start symptomatic PD medication, the DaT/SPECT window of ±7 days**, except for Week 52 MRI and DaT/SPECT which has a -7 day window only to allow Year 2 dosing to be appropriately scheduled,** may be expanded so that it extends from -28 days to +7 days.) If the subject is not due for DaT/SPECT at the next scheduled visit per the Schedule of Activities, it is not necessary to have this scan performed prior to starting symptomatic PD medications.

Rationale: This change was made to prevent disruption of a timely start to Year 2 dosing that could result from waiting to conduct the Week 52 MRI and DaT/SPECT scans up to 7 days after the Week 52 visit.

This change also affects Section 4.2, Schedule of Activities, Table 2, footnote 10; Table 3, footnote 16; Table 4, footnote 11; Table 5, footnote 10; and Table 6, footnote 5.

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.
- In Section 7.2.3, Follow-Up Visits and Final Visit, the window for the Early Termination and Final Visits was corrected to ± 3 days to be consistent with the Schedule of Activities.
- Figure 1, Study Design, was updated with the correct maximum numbers of doses (41) and study weeks (178).
- Table 4 footnotes were renumbered to accommodate the addition of a footnote.
- The PK sampling collection window for the Year 1 Week 52 visit by participants in Cohort A was clarified by adding footnote 12 to that box in Table 2.
- In Section 7.1.2, Years 2 through 4 (Active-Treatment Dose-Blinded Portion of the Study), language was added from Table 4, footnote 12 to remind sites that randomization of participants who received BIIB054 in Year 1 is unnecessary at the start of Year 2.

LIST OF ABBREVIATIONS

AE	adverse event
DaT/SPECT	dopamine transporter/single-photon emission computed tomography
MRI	magnetic resonance imaging
PK	pharmacokinetic(s)

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AMENDMENT SUMMARY

Biogen Protocol 228PD201

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study, with an Active-Treatment Dose-Blinded Period, to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of BIIB054 in Subjects with Parkinson's Disease

Version 6

Date: 11 July 2019

EUDRA CT Number: 2016-004610-95

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 228PD201 is to extend the active treatment dose-blinded period from Year 2 into Years 3 and 4. Dosing will end when the last subject has received the last dose in Year 2 (at Week 96), and the study will end when the last subject has had the Final Visit in Year 2 (12 weeks after the last dose [Week 108 visit]).

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

Section 7.1, Study Overview

Now reads:

This Phase 2a, randomized, double-blind, parallel-group, placebo-controlled study (Year 1) with an active-treatment dose-blinded period (Year**s** 2 **through 4**) will examine the safety, PK, and pharmacodynamics of BIIB054, administered every 4 weeks via IV infusion to adult subjects with PD. Approximately 311 subjects will be enrolled at about 85 sites globally.

Rationale: The active-treatment dose-blinded period was extended to collect additional data.

This change also affects Section 4.1, Study Schematic (Figure 1 and Figure 2 [new figure]); Section 4.2, Schedule of Activities (Table 4, Table 5 [new table], and Table 6 [new table]); Section 5.5, Rationale for Dosing Regimen; Section 6.3.2, Years 2 through 4 (Active-Treatment Dose-Blinded Portion of the Study); Section 7.1.2, Years 2 through 4 (Active-Treatment Dose-Blinded Portion of the Study); Section 7.2, Overall Study Duration and Follow-up; Section 7.2.2.2, Years 2 through 4; Section 7.2.3.3, Cohorts A and B, Years 2 through 4 (including addition of Figure 4); Section 7.2.4, Unscheduled Visits; Section 7.2.5, Early Termination; Section 9.3, Blinding Procedures; Section 10.2, Withdrawal of Subjects from Study; Section 11.1.2, Years 2 through 4 (Active-Treatment Dose-Blinded Portion of the Study); Section 11.5, Compliance; Section 16.1.1, Analysis Population; Section 16.1.2, Methods of Analysis; Section 16.2.2, Methods of Analysis; Section 16.5.2, Methods of Analysis; Section 16.5.2.2, Years 2 through 4 (Active-Treatment Dose-Blinded Portion of the Study) and Overall Experience; Section 19.1.4, Central Laboratories for Laboratory Assessments.

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 10.1, Discontinuation of Study Treatment

Change: Procedures for subjects discontinuing study treatment but remaining in the study were clarified.

Now reads:

[…]

Subjects who discontinue study treatment will be encouraged to remain in the study and complete all appropriate protocol-specified tests and assessments. **At a minimum, the following assessments should be performed at the timepoints shown on the schedule of assessments in Table 1 through Table 6: MDS-UPDRS, [redacted], DaTScan, [redacted], and [redacted].**

For ~~It is recommended that~~ subjects **terminating**~~who terminate~~ early (i.e., **discontinuing**~~discontinue~~ both study treatment and study assessments **before Week 96), it is recommended that** ~~) perform~~ the assessments of the Early Termination Visit **be performed** within 4 weeks after the last dose of study treatment. The Safety Telephone Call should be performed approximately 8 weeks after the last dose, and the assessments of the Final Visit should be performed approximately 12 weeks after the last dose. **Final Visit procedures should be performed at the subject's last study visit, even in the case of scheduling difficulties. For Early Termination/Follow-up and end of study procedures, see Table 6.**

Rationale: The changes provide additional clarity to study sites for study conduct.

Section 11.1, Regimen

Change: Guidance was added for subjects whose dose of study treatment is substantially delayed or missed.

Now reads:

Study treatment will be administered by the study site staff via IV infusion once every 4 weeks. **If there is a deviation from this schedule there should be at least 7 days between infusions.** The duration of the infusion will be approximately 1 hour. The Investigator or designee must

contact the study's Medical Monitor in advance if they would like to adjust the infusion duration or administration conditions based on the subject's ability to tolerate infusion.

Rationale: The change protects subject safety and provides clarity to study sites.

Section 11.3.1.1, Allowed Concomitant Therapy

Change: Dosing of subjects requiring symptomatic treatment with levodopa preparations was clarified.

Now reads:

Symptomatic PD treatment may be initiated during a subject's participation in the study at the discretion of the Investigator, although subjects should refrain from taking symptomatic PD medications **for as long as possible** (in particular, for at least 6 months following Day 1). For subjects who do require PD treatment, it is recommended that treatment start with immediate-release levodopa/carbidopa at a dose of 25/100 mg 3 times a day (or equivalent dosage of levodopa/benserazide in locations where levodopa/carbidopa is not available). The dose of levodopa/carbidopa may be titrated until satisfactory symptomatic relief is achieved. Subjects receiving levodopa/carbidopa should remain on their initially established dose as long as possible. Adjunctive use of COMT inhibitors, sustained-release levodopa/carbidopa preparations, dopamine agonists, MAO-B inhibitors, and zonisamide is discouraged, and use of amantadine and anticholinergic medications is prohibited in Year 1 of the study. **For subjects who do require PD treatment, it is recommended that treatment start with immediate-release levodopa/carbidopa at a dose of 25/100 mg 3 times a day (or equivalent dosage of levodopa/benserazide in locations where levodopa/carbidopa is not available). The dose of levodopa/carbidopa may be titrated until satisfactory symptomatic relief is achieved. Subjects receiving levodopa/carbidopa should remain on their initially established dose as long as possible. Adjunctive use of COMT inhibitors, sustained-release levodopa/carbidopa preparations, dopamine agonists, MAO-B inhibitors, and zonisamide is discouraged, and use of amantadine and anticholinergic medications is prohibited in Year 1 of the study. Prior to initiating treatment with symptomatic PD medication the Investigator should provide the [redacted] Medical Monitor with a description of the Parkinsonian manifestations that require treatment and a rationale for the choice of medication.**

[…]

Rationale: The change protects subject safety and provides clarity to study sites.

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.
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Minor changes were made to Schedule of Activities Tables 1, 2, and 3, primarily in the footnotes, to add clarity for some assessments and to align with recent protocol template updates.
- In Schedule of Activities Tables 1 through 6, urine and serum pregnancy tests were separated into unique line item entries for clarity and to align with recent protocol template updates.
- Section 5.3.2, Clinical Experience, text on Study 228HV101 was updated for consistency with Investigator's Brochure V6.0.
- Section 7.2.2.3, Treatment with Parkinson's Disease Medications, clarifications were added regarding the timing of MDS-UPDRS and DaT/SPECT to assist study sites.
- Section 7.2.3, Follow-Up Visits and Final Visit, a statement was added to provide clarity for study sites.
- Section 8.1, Inclusion Criteria, Criterion #2 was clarified.
- Section 8.2, Exclusion Criteria, Criteria #8, #18, and #26 were clarified.

- Section 11.3.1.2, Disallowed Concomitant Therapy, subjects participating in lumbar punctures were clarified.

- Section 11.4, Continuation of Treatment, potential future study was clarified.

- Section 15.2.3, Severity of Events, the version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) was updated to reflect the most recent version.

- Typographical errors and formatting were corrected.

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AMENDMENT SUMMARY

Biogen Protocol 228PD201

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study, with an Active-Treatment Dose-Blinded Period, to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of BIIB054 in Subjects with Parkinson's Disease

Version 5

Date: 12 February 2019

EUDRA CT Number: 2016-004610-95

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 228PD201is to extend the screening period by 1 week (7 days).

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

Section 7.2, Overall Study Duration and Follow-Up

Now reads:

The total duration of study participation for each subject will be up to approximately ~~113~~ **114** weeks, including a ~~5~~ **6**-week Screening period before the first study treatment infusion, a 48-week placebo-controlled treatment period, a 48-week active-treatment dose-blinded period, and a 12-week follow-up period.

Rationale: The screening window was increased by 1 week in order to ease the burden of screening procedures on subjects and to allow the sites a sufficient amount of time to complete the screening assessments.

This change also affects Section 4.1, Study Schematic; Section 4.2, Schedule of Activities (Tables 1 and 3); Section 7.2.1, Screening; and Section 9.1, Screening and Enrollment.

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 4.2, Schedule of Activities

Change: In Table 2 and Table 3, coagulation panel assessment edited to take place at Week 48 instead of Week 44 [redacted].

Now reads:

Table 2: Cohort A: Infusions 4–13 (Year 1)

	Infusions 4-13, Week (±3 d)										PK Visits, Week (±3 d)	Year 1 Week 52, (±3 d)[2]
Tests and assessments	12	16	20	24	28	32	36	40	44	48	22, 34, or 46[1]	
Coagulation panel including platelet count[8]			X						~~X~~	**X**		

[redacted]

Table 3 Cohort B: Infusions 1–13 (Year 1)

				Infusions 2-13, Week (±3 d)														PK Visits, Week (±3 d)	
Tests and assessments	Screening ≤~~35~~ **42** d Before Day 1[1]	Day 1[2] Baseline/ Infusion 1	Safety Telephone Calls 1d & 7d after Infusion 1[2]	4[2]	Safety Telephone Calls 1d & 7d after Infusion 2[2]	8[2]	Safety Telephone Calls 1d & 7d after Infusion 3[2]	12	16	20	24	28	32	36	40	44	48	22, 34, or 46[3]	Year 1 Week 52, (±3 d)[4]
Coagulation panel including platelet count	X									X[12,13]						~~X~~[12,13]	**X**[12,13]		

[redacted]

[redacted]

This change also affects Section 14.2, Laboratory Safety Assessments.

Section 15.3.1, Adverse Events

Change: Text was added to clarify that any nonserious adverse events that occur during the Screening period and are related to the ligand will be captured on the electronic case report form (eCRF).

Now reads:

Any AE (including SAEs) experienced by the subject between the time of first dose of study treatment and the Final Visit is to be recorded on the **e**CRF, regardless of the severity of the event, its relationship to study treatment, its relationship to the LP procedure, or its relationship to the radioligand. **Nonserious AEs that occur during the Screening period and that are assessed by the Investigator as related to the ligand will be captured by the sites on the AE eCRF.** At each study visit, the Investigator will assess the subject for AEs and will record any new AEs or updates to previously reported AEs on the **e**CRF.

Rationale: This text was added to fulfill the terms of the safety data exchange with the company that provides the ligand.

This change also affects Section 4.2, Schedule of Activities (Table 1, footnote 23 and Table 3, footnote 26).

Section 16.8, Interim Analyses

Change: A second interim analysis was added for when all subjects complete their Week 72 Visits.

Now reads:

…

For the purpose of planning for future studies, ~~A~~an administrative interim analysis may be performed ~~for the purpose of planning future studies after~~ **when** approximately 60% of the subjects have completed the Week 52 Visit**, and a second interim analysis when all subjects have completed the Week 72 Visit**.

…

Rationale: This data cut is being added to assess primary endpoint readout after subjects have received BIIB054 for approximately 6 months since the previous interim analysis.

Change: Blinded sample size re-estimation was decreased from 25% to 10% of subject completion at Week 52 or 1 month prior to the completion of enrollment, whichever is first.

Now reads:

…

A blinded sample size re-estimation may be conducted when approximately ~~25~~ **10**% of subjects have completed the Week 52 Visit **or approximately 1 month before enrollment is projected to be completed, whichever is earlier**.

…

Rationale: The timing of the sample size re-estimation is being changed as the study is enrolling faster than anticipated and the data need to be analyzed prior to closing enrollment out for the study in case sample size changes are warranted.

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.
- Text was clarified throughout the protocol to specify the use of electronic case report forms.
- Section 4.2, Schedule of Activities, Table 1 (footnote 20), Table 2 (footnote 14), Table 3 (footnote 23) and Table 4 (footnote 17); Section 7.2.2.3, Treatment with Parkinson's Disease Medications; Section 13.1.1.1, Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale (Including Modified Hoehn and Yahr Scale); and [redacted], text was added to ease restrictions on time frame for subjects to take Parkinson's disease medication prior to study visits at which Movement Disorder Society Sponsored Revision of the United Parkinson's Disease Rating Scale or quantitative movement assessment will be conducted.
- Section 5.3.2, Clinical Experience, text was updated with current subject dosing information for Study 228HV101.
- Section 7.1.1, Year 1 (Placebo-Controlled Portion of the Study), and Section 11.2, Modification of Dose and/or Treatment Schedule, text was added to clarify that any changes to these sections will be documented in a protocol amendment.
- Section 8.2, Exclusion Criteria (criterion 26), text was added to allow the Investigator discretion as to when a LP can be safely performed based on laboratory values.
- Section 8.2, Exclusion Criteria (criterion 26); Section 11.3.1.1, Allowed Concomitant Therapy; and Section 11.3.1.2, Disallowed Concomitant Therapy, the minimum dose of aspirin use allowed by subjects was increased from 81 to 100 mg.
- Section 9.1, Screening and Enrollment, text was added to clarify that rescreen and repeat parameters apply to any subject under any version of the protocol.
- Section 11.3.1.1, Allowed Concomitant Therapy, zonisamide was added as a drug whose adjunctive use is discouraged.
- Section 11.3.1.2, Disallowed Concomitant Therapy, benztropine, bupropion, cocaine, mazindol, phentermine, and sertraline were added as disallowed concomitant medications.
- Typographical errors and formatting were corrected.

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AMENDMENT SUMMARY

Biogen Protocol 228PD201

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study, with an Active-Treatment Dose-Blinded Period, to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of BIIB054 in Subjects with Parkinson's Disease

Version 4

Date: 15 August 2018

EUDRA CT Number: 2016-004610-95

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

PRIMARY REASON FOR AMENDMENT

The primary reason the sponsor has initiated this amendment to Protocol 228PD201 is to add retesting and rescreening flexibility for subjects with nonclinically significant out-of-range laboratory results as well as those who cannot complete the Day 1 visit within the designated screening period.

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

Section 9.1, Screening and Enrollment

Now reads:

Rescreening for other reasons may be allowed after consultation with the Sponsor. In addition, eligible subjects who are not able to complete the Day 1 Visit within 35 days of starting their screening assessments may be rescreened at the discretion of the Sponsor. All screening assessments will be repeated except for the main ICF, [redacted], confirmation of PD diagnosis, height measurement, blood sampling for ribonucleic acid (RNA), MRI, and DaT/SPECT unless determined otherwise by the sponsor. For female subjects, if initial follicle-stimulating hormone (FSH) level confirmed postmenopausal state, it does not need to be repeated.

Coagulation, **blood chemistry, and hematology** tests may be repeated once if, in the opinion of the Investigator, values of the initial tests are only slightly out of range. For **central laboratory** normal ranges, please refer to the Study Reference Manual. **Subjects who have other nonclinically significant out-of-range laboratory results may be retested 1 time only after discussion with the Medical Monitor.**

Rationale: This language was added to support study enrollment. It allows for more flexibility for rescreening and lessens the probability that subjects will be unnecessarily excluded from the study for nonclinically significant laboratory results. It also, gives subjects who are taking study prohibited medications the opportunity to stop these treatments and rescreen after an appropriate washout period. Additionally, this new text makes all sections of the protocol consistent with regards to retesting of samples.

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 4.2, Schedule of Activities

Change: Testing of hepatitis B surface antibodies (anti-HBs) was added to the list of viral screens in Table 1.

Now reads:

Tests and assessments	Screening ≤35 days before Day 1[1]	Infusions 1-3 Day 1/Baseline, Day 29 (±1 day), & Day 57 (±1 day)						Clinic Visits				Day 43 (Safety Telephone Call)
								Day 2, 30, 58	Day 4, 60	Day 8, 36, 64	Day 15, 71	
		Pre-infusion[2]	0m	Time after End of Last Infusion								
				≤10m	1h ±15m	2h ±15m	4h ±30m	24h ±2h	72h -2h/+1d	168h ±24h	336h ±24h	336h ±24h
HBsAg, anti-HBc, **anti-HBs**, HCVAb, HIV	X											

Rationale: anti-HBs are a diagnostic marker of hepatitis B infection, the presence of which is an exclusion criterion for the study.

This change also affects Section 4.2, Schedule of Activities, Table 3.

Section 4.2, Schedule of Activities

Change: Reference to a 7-day follow-up phone call following DaT/SPECT was add to Table 1, Footnote 12.

Now reads:

[12] The MRI results will be read by the local radiologist at collection. Both MRI and DaT/SPECT results will be sent within 24 hours to a central reader for further evaluation and to confirm eligibility at Screening. Screening imaging assessments should be completed after all other eligibility criteria have been met, and before Day -7, to allow adequate time for evaluation of the results. **Subjects will be contacted by telephone within 7 days following the DaT/SPECT procedure to monitor for AEs.**

Rationale: This text was added for clarity and consistency. Section 13.3.1.1 indicates that subjects will receive a post-DaT/SPECT safety phone call; this information should be referenced in the Schedule of Activities.

This change also affects Section 4.2, Schedule of Activities, Table 2, Footnote 10; Table 3, Footnote 16; and Table 4, Footnote 11.

Section 4.2, Schedule of Activities

Change: Table 2, Footnote 15 was removed.

Now reads:

~~[15] Performed/collected pre-infusion for dosing visits,~~ [redacted]

Rationale: The footnote was determined to be unnecessary. It is stated in Section 13.1 and elsewhere in the Schedule of Activities table at which point (pre- or post-infusion) that assessments should be performed.

This change also affects Section 4.2, Table 3, Footnote 24; and Table 4, Footnote 18.

Section 4.2, Schedule of Activities

Change: Table 3, Footnote 5 was removed from the "Study treatment infusion" Day 1 visit.

Now reads:

Tests and assessments	Screening ≤35 d Before Day 1[1]	Day 1[2] Baseline/ Infusion 1
Study treatment infusion[18]		X[5]

Rationale: This footnote refers to assessments and is therefore not applicable to this activity. Its original placement was in error.

Section 4.2, Schedule of Activities

Change: Footnote 17 in Table 3 was updated to allow at least 8 business days for evaluation of imaging results before subject randomization.

Now reads:

[17] Screening imaging assessments should be completed after all other eligibility criteria have been met, and ~~before Day 7~~ **at least 8 business days before Day 1/randomization**, to allow adequate time for evaluation of the results.

Rationale: For Cohort B, it was determined that 7 days did not provide enough time to complete the evaluation of imaging results, which are required for enrollment in the study. An extension of this period to at least 8 business days will provide adequate turnaround time for this to be completed before randomization.

This change also affects Section 7.2.1, Screening.

Section 4.2, Schedule of Activities

Change: Changed text in Table 4 Footnote 1 to indicate that Year 2 randomization will be performed prior to Year 2 Week 52 Visit.

Now reads:

[1] **Randomization for Year 2 will be performed prior to the Year 2 Week 52 Visit.** Study treatment infusion and the assessments shown will be considered part of Year 2 of the study and will be performed after all assessments for the Year 1 Week 52 Visit are completed (see Table 2 and Table 3)~~., with the exception that randomization for Year 2 may be performed prior to the Year 2 Week 52 Visit.~~ The Year 2 Week 52 assessments may be performed on the same day as the Year 1 Week 52 Visit or on the next day; however, pregnancy test, vital signs, and ECG must be obtained predose on the same day as dosing for Infusion 14, and randomization for Year 2 must be performed prior to Infusion 14.

Rationale: The wording of this footnote was adjusted slightly for clarity. Section 9.2 was changed to specify that Year 2 randomization will be performed prior to Infusion 14 for Cohort A and on Day 1 for Cohort B. Therefore, it is now more accurate to definitively state that randomization will occur prior to Year 2.

Section 6.1, Primary Objective and Endpoint

Change: The incidence of abnormalities or changes in a variety of assessments and measures was removed as a safety endpoint.

Now reads:

- ~~Incidence of abnormalities or change from baseline in clinical laboratory test data, vital sign measurements, neurological and physical examination findings, electrocardiograms (ECGs), and brain magnetic resonance imaging (MRI) safety findings (may include T1, fluid attenuated inversion recovery, and gradient echo)~~

Rationale:

The language has been modified to enable Biogen to better comply with clinical trial transparency reporting requirements. Because these assessments were individually listed as a separate endpoint, clinical trial registries required reporting of any and all abnormalities, regardless of their clinical significance, at all timepoints where they were observed. This was found to be complicated and unnecessary, as in most cases, only clinically significant abnormalities would be considered important. Further, any such clinically significant abnormalities would also get documented as AEs or SAEs making their reporting duplicative.

No changes will be made to the actual safety assessments that are performed or how these safety assessments are monitored in this study.

Section 6.3.1, Year 1 (Placebo-Controlled Portion of the Study)

[redacted]

Section 7.2.2, Study Treatment

Change: Specific time parameters were added around the intravenous infusion procedure.

Now reads:

The infusion duration will be ~~approximately~~ 1 hour **(± 10 minutes)**.

Rationale: Text was added to standardize the infusion procedure and allow for less ambiguity around the determination of deviations.

Section 8.1, Inclusion Criteria

Change: In inclusion criterion 3, the list of prohibited Parkinson's Disease (PD)-specific medications was revised and language was added to allow for stable doses of medications being taken for non-PD-related conditions.

Now reads:

1. Has not received **any medication for the treatment of the motor symptoms of PD (including, but not limited to,** levodopa **and levodopa-containing products,** ~~or any other treatment for PD (~~dopamine agonists**, monoamine oxidase inhibitors,** ~~amantadine,~~ **centrally-acting** anticholinergics, **amantadine,** ~~MAO-B inhibitors, or safinamide~~**zonisamide**; see list of PD medications in the Study Reference Manual) for at least 12 weeks prior to Day 1 and, in the opinion of the Investigator, is not expected to require PD treatment for at least 6 months following Day 1. Maximum total duration of

prior PD regimens should not exceed 30 days. **Stable (at least 8 weeks) dosages of medications that are used to treat conditions other than PD tremor (e.g., beta-blockers, benzodiazepines, and barbiturates) are allowed. Further guidance will be provided by the study's Medical Monitor on a case by case basis.**

Rationale: In order to properly evaluate the effect of BIIB054 on clinical study endpoints it is critical that the medications being utilized by study subjects do not have substantial effects on the motor symptoms of PD.

This change also affects Section 11.3.1.1, Allowed concomitant Therapy

Section 8.2, Exclusion Criteria

Change: In exclusion criterion 3, the language and abbreviations defining hepatitis B virus infection were revised.

Now reads:

3. Current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or total hepatitis B core antibody [~~HBcAb~~ **anti-HBc**]). Subjects with immunity to hepatitis B from previous natural infection ~~(defined as negative HBsAg, positive hepatitis B surface antibody immunoglobulin G, and positive HBcAb) or vaccination (defined as positive anti-HBs)~~ **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.

Rationale: The language was updated to conform to new language and abbreviations used by the United States Centers for Disease Control and Prevention.

This change also affects Section 2, List of Abbreviations; Section 4.2, Schedule of Activities, Tables 1 and 3; and Section 19.1.4, Central Laboratories for Laboratory Assessments.

Section 8.2, Exclusion Criteria

Change: Exclusion criterion 18 was updated with new language on electrocardiogram (ECG) abnormalities.

Now reads:

18. Clinically significant (as determined by the Investigator) 12-lead ECG abnormalities, including ~~prolongation of~~ **confirmed demonstration of** corrected QT interval ~~(e.g., repeated demonstration of a corrected QT interval~~ using the Fridericia **correction method of** >460 msec [men] and >470 msec [women] before study treatment administration~~)~~.

Rationale: Criteria for assessing ECG abnormalities were updated to harmonize with that of other studies.

Section 8.2, Exclusion Criteria

Change: Exclusion criterion 26 and 34, pertaining to anticoagulant medication, was changed.

Now reads:

26. For subjects enrolling at sites where LPs will be performed: Subjects with the following characteristics will be excluded from participation in LP procedures:

- Any history of lumbar surgery for any reason (e.g., herniated disc) that in the opinion of the Investigator would interfere with or pose risks to the LP procedure
- Other contraindications to having a LP, including but not limited to:
  - Low platelet count (below 50,000 cells/μL), or Screening values of INR, PT, or APTT that are not within normal ranges
  - Taking any antiplatelet medication (e.g., aspirin >81 mg daily, clopidogrel, or nonsteroidal anti-inflammatory drugs [NSAIDs]) within 7 days prior to the planned LP or anticipated need for antiplatelet medication within 48 hours after an LP
  - Taking anticoagulant medication (warfarin, heparinoids, and direct coagulation factor inhibitors, e.g., apixaban, dabigatran, rivaroxaban) **within 7 days prior to the planned LP or anticipated need for antiplatelet medication with 48 hours after an LP.**
  - X-ray, MRI, or myelographic evidence of significant lumbar spine abnormalities or other anatomical factors at or near the LP site that might interfere with performance of LP

~~34. Use of anticoagulant medications within 90 days before Day 1 (warfarin, heparinoids, and direct coagulation factor inhibitors e.g., apixaban, dabigatran, rivaroxaban).~~

Rationale: The exclusion of anticoagulant medications for all subject throughout the study was determined to be too restrictive. The use of anticoagulants is primarily a safety concern for those who are undergoing a lumbar puncture (LP) procedure. Because LPs will only be performed on a subset of subjects at particular timepoints, the restriction on these medications was limited to the time immediately before and after a scheduled LP procedure.

This change also affects Section 11.3.1.2, Disallowed Concomitant Therapy

Section 8.2, Exclusion Criteria

Change: Exclusion criterion 36 was updated to include serotonin norepinephrine reuptake inhibitors (SNRIs) and specifically exclude the selective serotonin reuptake inhibitor (SSRI), sertraline.

Now reads:

36. Use of selective serotonin reuptake inhibitors (SSRIs), **(with the exception of sertraline, which is prohibited) or serotonin norepinephrine reuptake inhibitors (SNRIs)** at doses that have not been stable for at least 3 months before Day 1 and/or that are not expected to remain stable for the duration of the study.

Rationale: There is published evidence to suggest that like SSRIs, SNRIs may also have a small effect on DaT/SPECT results. For this reason, it would be necessary for subjects to maintain stable doses during the study to allow for accurate assessment of BIIB054 treatment-induced changes. Additionally, even though sertraline is an SSRI, it is specifically excluded in exclusion criterion 31 due to its ability to interfere with DaT/SPECT.

This change also affects Section 11.3.1.1, Allowed Concomitant Therapy

Section 9.2, Randomization and Registration of Subjects

Change: Part numbers were added to the description of the Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) assessment score.

Now reads:

Randomization of subjects in Cohort B will be stratified by baseline (Day 1) MDS-UPDRS **Part I, II, and III total** scores (≤35 and >35) and striatum SBR (≤1.2 and >1.2), and subjects will be randomized at Day 1 into 1 of 4 parallel dosing arms to receive placebo (n=82) or BIIB054 (250 mg [n=41], 1250 mg [n=82], or 3500 mg [n=82]) in each strata.

Rationale: The text was updated to clarify that the MDS-UPDRS scores for each subject will be derived from Parts I, II, and III of that assessment.

This change also affects Section 16.9, Sample Size Considerations.

Section 9.2, Randomization and Registration of Subjects

Change: The DaT/SPECT striatal binding ratio (SPR) value was updated.

Now reads:

Randomization of subjects in Cohort B will be stratified by baseline (Day 1) MDS-UPDRS Part I, II, and III total scores (≤35 and >35) and striatum SBR (≤~~1.1~~**1.2** and >~~1.1~~**1.2**), and subjects will be randomized at Day 1 into 1 of 4 parallel dosing arms to receive placebo (n=82) or BIIB054 (250 mg [n=41], 1250 mg [n=82], or 3500 mg [n=82]) in each strata.

Rationale: Striatal SBR values will be used to improve randomization across treatment arms in Cohort B. The striatal SBR value in the original protocol (1.1) was determined using an evaluation of a large data set of publicly available baseline DaT/SPECT scans of PD patients (n=~300; Parkinson's Progression Markers Initiative [PPMI]). Direct comparison of the PPMI and SPARK reconstruction/processing pipelines revealed a small, albeit significant, increase in SBR values with application of our standardized and scalable SPARK DaT/SPECT pipeline, resulting in a rightward shift in the overall distribution across the population. To account for this, the SBR cutoff value will be amended to 1.2 so as to allow a more equal separation of subjects based on DaT/SPECT values.

Section 9.2, Randomization and Registration of Subjects

Change: Language was added to allow flexibility to randomize the lowest (250 mg) BIIB054 dosing cohort to a higher dosing cohort in Year 2 of the study. It also clarifies the timing of the Year 2 randomization.

Now reads:

~~Prior to receiving Infusion 14, which will be the first infusion of Year 2 (active treatment dose blinded portion of the study), subjects who received placebo in Year 1 will be randomized to 1 of the active arms to receive BIIB054 in Year 2. Subjects who received BIIB054 in Year 1 will continue with the same dose regimen in Year 2.~~ **All subjects who were randomized to receive placebo in Year 1 will be randomized, in equal ratio, to one of the active BIIB054 treatments for Year 2**. **For subjects receiving placebo in Cohort A, the randomization will occur prior to Infusion 14. For subjects receiving placebo in Cohort B, this randomization will at the time of the baseline Day 1 randomization (Year 1). Subjects who received BIIB054 (1250 mg or 3500 mg) in Year 1 will continue with the same dose regimen in Year 2. In addition, the decision of whether or not to randomize subjects who receive the 250-mg dose in Year 1 to 1 of the 2 highest doses of BIIB054 in Year 2 will be made after the IDMC review of Cohort A Week 12 data.**

Rationale: Language was added to allow for greater flexibility in establishing Year 2 dosing assignments. Previous language in the protocol only allowed for placebo subjects from Year 1 to be randomized to active BIIB054 treatment arms in Year 2. Because the 250-mg dose of BIIB054 may be too low to achieve clinical effect, language was added to allow flexibility to also randomize the 250-mg dosing cohort subjects to a higher dosing cohort in Year 2 of the study. This new language also clarifies the timing of the subject's randomization to their Year 2 treatment assignment.

This change also affects Section 4.1, Study Schematic; Section 4.2, Schedule of Activities, Table 4 (Footnote 13); Section 7.1.2, Year 2 (Active-Treatment Dose-Blinded Portion of the Study); Section 11.1.2,Year 2 (Active-Treatment Dose-Blinded Portion of the Study).

Section 11.2, Modification of Dose and/or Treatment Schedule

Change: Removed language requiring changes to be documented in a protocol amendment and restricting dose level changes after randomization.

Now reads:

Dose levels, number of treatment arms, and number of subjects per arm for Cohort B may be modified based on emerging Cohort A safety and PK data, and review by the IDMC. ~~Any changes will be documented in a protocol amendment. No changes in dose level are permitted for an individual subject once randomized.~~

Rationale: Section 9.2 of the protocol was updated to allow for potential rerandomization of subjects to higher dose levels in Year 2 of the study. Consequently, dose changes should not be strictly prohibited in the protocol. Further, the need for a protocol amendment for such study changes should be evaluated on a case-by-case basis.

This change also affects Section 7.1.1, Year 1 (Placebo-Controlled Portion of the Study); and Section 7.2.2, Study Treatment.

Section 11.5, Compliance

Change: A section pertaining to compliance with treatment was added.

Now reads:

11.5. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff.

Rationale: Compliance with dosing is necessary to allow for accurate assessment of the effects of BIIB054 treatment. The original template under which this protocol was written did not include such language. Therefore, this section was added to clarify site staff's role in ensuring and documenting treatment compliance.

Section 13.1, Clinical Function Assessments

Change: Language was added to specify Biogen's preferred procedures regarding the rating of the clinical function assessments.

Now reads:

Clinical function assessments are performed by qualified raters, preferably those who are not involved in other aspects of subject clinical care and management, including clinical safety assessments. The same rater should perform a given assessment across all visits.

Rationale: Biogen is recommending these rating procedures to better maintain study blinding, reduce the chance of bias, and improve the constancy of data collection.

Section 13.3.1.1, Single-Photon Emission Computed Tomography Scan of the Dopamine Transporter

Change: The sentence pertaining to additional imaging at phenoconversion in previously asymptomatic subjects was deleted.

Now reads:

Biological effects of BIIB054 on brain dopamine neurons and nerve terminals will be assessed using DaT/SPECT imaging. Subjects will undergo DaT/SPECT imaging at Baseline and at specified timepoints. ~~Subjects may also undergo an additional imaging at the time of phenoconversion to motor PD in previously asymptomatic subjects.~~ The DaT/SPECT imaging procedure will be performed using DaTscan, administered IV. Before the DaTscan injection, subjects will be pretreated with stable iodine (10 drops of a saturated solution of potassium iodide) to reduce the uptake of DaTscan by the thyroid. Subjects will be injected with 3 to 5 mCi of DaTscan. Within a 4-hour (±30 minutes) window following the injection, subjects will undergo SPECT imaging on the camera. Subjects will be monitored by study site staff for AEs

on the day that a DaT/SPECT scan is obtained. Subjects will also be contacted by telephone within 7 days following the injection/scan.

Rationale: The deleted sentence is not necessary as this study is only open to subjects who already have a PD diagnosis. Asymptomatic subjects would not have been eligible to participate. This statement was originally included in error.

Section 14.2, Laboratory Safety Assessments

Change: The language regarding coagulation testing was changed to allow for the use of samples collected at non-study visits

Now reads:

- Coagulation panel, including platelet count, INR, PT, and APTT will be measured no more than 35 days before performing an LP. Before an LP can be performed, results of the most recent ~~(i.e., performed at previous visit within 35 days)~~ coagulation tests, including platelet count, must be reviewed by the Investigator and must indicate that an LP can be performed safely. ~~If repeat tests are clinically indicated in the opinion of the Investigator, then these tests may be performed locally~~ **The most recent tests may be those completed by the central laboratory from a previous study visit within 35 days (i.e., Screening) or may be performed by a local laboratory if needed** to facilitate timely review.~~, and. r~~Results must be reviewed before an LP can be performed.

Rationale: This change was made to clarify to sites that it is allowable for coagulation samples to be collected at non-study visits (as an unscheduled sample) and tested at local laboratories on occasions when the subject's latest study visit was beyond the acceptable time range.

This change also affects Section 4.2, Schedule of Activities, Table 2, Footnote 8; and Table 3, Footnote 13.

Section 15.1.1, Adverse Event

Change: Magnetic resonance imaging (MRI) and physical/neurological examination were added to the list of abnormal results that could constitute an adverse event.

Now reads:

Determination of whether an abnormal laboratory value, vital sign result, **MRI result, physical/neurological examination finding,** and/or ECG result meet the definition of an AE will be made by the Investigator.

Rationale: This was added to provide a more complete listing of results that could be reported as an adverse event.

Section 16.8, Interim Analysis

[redacted]

Section 16.8, Interim Analysis

Change: Language regarding the percentage of subjects needed to consider a sample size re-estimation was adjusted and expanded.

Now reads:

A blinded sample size re-estimation may be conducted when approximately ~~30%~~ **25%** of subjects have completed the Week 52 Visit. The study sample size may be increased based on this blinded data review. **There may be small adjustments to the percentage depending on actual enrollment rate.** Details will be provided in the SAP.

Rationale: The percentage of subjects completing the Week 52 Visit needed to consider sample size re-estimation was lowered slightly based on current enrollment numbers. Flexible language was also added to allow for further adjustments if necessary.

Section 19.1.6, Neurocognitive Assessments

Change: Heading and language within Section 19.1.6 was changed to specify "clinical" assessments.

Now reads:

19.1.6. ~~Neurocognitive~~ **Clinical** Assessments

Biogen selected a rater management group to establish rater qualification, study specific training, and oversight. The study raters are required to complete qualifications steps and required training prior to administering study **clinical** assessments. The rater management group will oversee the **clinical** assessments per project-specific plans.

Rationale: The language was broadened to recognize that the raters perform more than just the "neurocognitive" 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 updated throughout the protocol.
- Section 2, List of Abbreviations, was updated, and some abbreviations throughout document were changed.
- The Table of Contents, List of Tables, and List of Figures were updated to reflect changes throughout the text.
- Minor grammatical corrections were made to Section 4.1, Study Schematic Figure 1 and Section 4.2, Schedule of Activities Table 3
- The name of the contract research organization was changed from [redacted] to [redacted]
- Typographical errors and formatting were corrected.

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AMENDMENT SUMMARY

Biogen Protocol 228PD201

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study, with an Active-Treatment Dose-Blinded Period, to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of BIIB054 in Subjects with Parkinson's Disease

Version 3

Date: 22 October 2017

EUDRA CT Number: 2016-004610-95

Version 3 of the protocol has been prepared for this amendment, which supersedes Version 2.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 228PD201 is to add a 1-year active-treatment dose-blinded period, extending the total study treatment period to 2 years.

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

Section 7.2, Overall Study Duration and Follow-Up

Now reads:

The total duration of study participation for each subject will be **up to** approximately ~~65~~ **113** weeks, including a 5-week Screening period before the first study treatment infusion, a 48-week **placebo-controlled** treatment period, **a 48-week active-treatment dose-blinded period,** and a 12-week follow–up period.

Rationale: The changes were made to provide additional long-term safety data. [redacted] This change will also enhance recruitment and retention by assuring subjects that they will receive active study treatment at some point during the study (and if they receive active study treatment in Year 1, they would receive it for a longer period of time with the addition of Year 2).

The overall change in study design and study duration also affects the study title; Section 4.1, Study Schematic; and Section 7.1, Study Overview.

To coordinate with this change, there has been a corresponding modification of study procedures, including dosing procedures and number of doses. In particular, a new Schedule of Activities table (Table 4) has been added for Year 2 (the active-treatment dose-blinded period), and the Early Termination, Safety Telephone Call, Unscheduled Visit, and Final Visit procedures of Tables 2 and 3 have been moved to Table 4. These changes are described in Section 4.2, Schedule of Activities of the protocol; for detailed revisions to the tables, see the track changes version of each table in Appendix A of this document. The change to study procedures also affects Section 5.5, Rationale for Dosing Regimen; Section 7.1.2, Year 2 (Active-Treatment Dose-Blinded Portion of the Study); Section 7.2.2., Study Treatment; Section 7.2.3, Follow-Up Visits and Final Visit; and Section 11.3.1, Concomitant Therapy.

Corresponding modifications have been made to the study objectives and endpoints. These modifications include changes to clarify timing of existing objectives and endpoints with respect to Year 1, and the addition of new objectives and endpoints for Year 2; these changes are described in Section 6.1, Primary Objective and Endpoint; Section 6.2, Secondary Objectives and Endpoints; and Section 6.3, Additional Objectives and Endpoints. Modifications have also been made to the statistical analyses (Section 16, Statistical Methods and Determination of Sample Size), including a new interim analysis at the end of Year 1 and new analyses for Year 2.

There has also been a corresponding change to subject randomization and treatment assignments: prior to Infusion 14 (first dose of Year 2), subjects who had received placebo in Year 1 are randomized to 1 of the active-treatment arms to receive BIIB054 in Year 2, as described in

Section 11.1, Regimen. The change to subject randomization and treatment assignments also affects Section 7.1.2, Year 2 (Active-Treatment Dose-Blinded Portion of the Study); Section 9.2, Randomization and Registration of Subjects; and Section 9.3, Blinding Procedures.

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 6.3.1, Year 1 (Placebo-Controlled Portion of the Study)

Section 6.3.1, Year 1 (Placebo-Controlled Portion of the Study)

[redacted]

Section 6.3.1, Year 1 (Placebo-Controlled Portion of the Study)

[redacted]

Section 7.2.6, Study Stopping Rules

Change: The timing was modified for the study stopping rules.

Now reads:

Biogen may terminate this study at any time, after informing Investigators. Biogen will notify Investigators if the study is to be placed on hold, completed, or terminated.

For Cohort A **until initiation of dosing in Cohort B**:

After evaluation of the safety, tolerability, and PK data by the IDMC, further dosing may be terminated if any of the following is observed:

- Two similar SAEs or ~~2~~ clinically significant AEs, unless clearly unrelated to BIIB054, are reported for subjects on active study treatment.
- Three or more similar AEs are reported for subjects on active study treatment (unless these events are clearly unrelated to BIIB054) that are not tolerable, as reported by the subject (e.g., severe dizziness) and/or deemed a medically unacceptable risk by the IDMC and/or Sponsor.
- Sponsor requests that dosing be terminated.

For **both cohorts after initiation of dosing in** Cohort B:

~~e~~**C**onditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

Rationale: The more comprehensive stopping criteria for Cohort A are only necessary until dosing has begun in Cohort B.

Section 8.2, Exclusion Criteria

Change: The reference to uncorrected QT interval was removed from Exclusion Criterion 18 for ECG abnormalities.

Now reads:

18. Clinically significant (as determined by the Investigator) 12-lead ECG abnormalities, including prolongation of corrected QT interval (e.g., repeated demonstration of a ~~QT or~~ corrected QT interval using the Fridericia formula >460 msec [men] and >470 msec [women] before study treatment administration).

Rationale: This change was made for accuracy. Only the corrected QT interval applies here.

Section 8.2, Exclusion Criteria

Change: Nilotinib was explicitly excluded at study entry in the newly added Exclusion Criterion 33, and also disallowed during the study.

Now reads:

~~32.~~33. Use of nilotinib within 90 days before Day 1.

Rationale: This change was made to prohibit use of nilotinib at study entry and as a concomitant medication during this study, because the drug has considerable side effects in its safety profile.

This change also affects Section 11.3.1.2, Disallowed Concomitant Therapy.

[redacted]

Section 13.2, Pharmacokinetic Assessments

Change: The text describing the pharmacokinetic (PK) parameters has been modified to refer specifically to the first and third doses for subjects in Cohort A. The list of PK parameters and the text describing PK analyses has been updated.

Now reads:

For subjects in Cohort A, ~~T~~the following parameters will be calculated **by non-compartmental analysis** to assess the serum PK of BIIB054**~~,~~ after the first dose (Day 1) and the third dose (Day 57)**~~when feasible~~:

- C_{max}
- ~~Minimum o~~**O**bserved concentration **at the end of the dosing interval (C_{trough})**
- Time to reach maximum ~~observed~~ concentration **(T_{max})**
- ~~Elimination half-life~~
- ~~Volume of distribution at steady state~~
- ~~Clearance~~

- AUC_{tau}
- **Accumulation ratio**

The serum PK of BIIB054 for subjects in Cohorts A and B will also be characterized by a nonlinear mixed effect approach. [redacted].

Rationale: These changes were made for accuracy and clarity. Due to the study design, elimination half-life and clearance cannot be calculated by non-compartmental methods. Volume of distribution at steady state was previously estimated in the Phase 1 study 228HV101. The accumulation ratio was added because it is a standard parameter for a multiple-dose study.

Section 16.1.2.5, Physical and Neurological Examinations

Change: The text describing the statistical analysis of physical and neurological examinations has been modified to remove clinically relevant abnormalities other than adverse events (AEs).

Now reads:

~~The analysis of physical and neurological examinations will focus on clinically relevant abnormalities, which will be defined in more detail in the SAP. Changes from baseline in physical and neurological examinations will be summarized using descriptive statistics and presented by treatment group, overall active group, and timepoint.~~

Abnormal findings during physical and neurological examinations will be recorded as AEs and will be reflected in the summary of AEs. ~~In addition, abnormalities on neurological examination may be summarized separately using descriptive statistics.~~

Rationale: These changes were made to correct an error. Abnormalities detected during physical and neurological examinations will only be recorded as AEs.

Section 16.3, Pharmacokinetics

[redacted]

[redacted]

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The protocol name, version number, and date were updated throughout the protocol.
- A statement was added to the footnotes for baseline assessments in Section 4.2, Schedule of Activities, Table 1 and Table 3, and to the text in Section 9.2, Randomization and Registration of Subjects, to clarify that MDS-UPDRS results must be available before randomization at Day 1. The MDS-UPDRS results are required for stratification.
- The footnotes for vital signs in Section 4.2, Schedule of Activities, Table 1 and Table 3, and the text in Section 14.1, Clinical Safety Assessments, were modified to clarify the procedures for orthostatic vital signs measurements at Screening.
- The name for the Visits at Week 22, 34, or 46 in Section 4.2, Schedule of Activities, Table 2 and Table 3 was modified from "Clinic Visit" to "PK Visit", and it was clarified that this visit is for routine PK sampling rather than for population PK. This change also affected the text in Section 7.2.3.1, Cohort A, Year 1, and similar text was added to Section 7.2.3.2, Cohort B, Year 1.
- The reference to the baseline assessments footnote in Section 4.2, Schedule of Activities, Table 3, was moved from the column header for the Day 1 Visit to appropriate cells below that, in order to avoid duplication with a similar footnote for the clinical function assessments.
- The Safety Telephone Call in Section 4.2, Schedule of Activities, Table 3, was re-formatted from a row to a column for clarity and consistency with the other Schedule of Activities tables.

- The text regarding changes in dose level in Section 7.2.2, Study Treatment, and Section 11.2, Modification of Dose and/or Treatment Schedule, was clarified to indicate that it applies to an individual subject once randomized.
- The text in Section 7.2.2.3, Treatment with Parkinson's Disease Medications, and Section 11.3.1.1, Allowed Concomitant Therapy, was modified to emphasize that subjects should refrain from symptomatic PD medications for as long as possible, particularly for the first 6 months of treatment. The text in Section 7.2.2.3 was also modified to clarify the window for DaT/SPECT.
- The Unscheduled Visit description in Section 7.2.3 (formerly Unscheduled Visits and Follow-Up) was modified to clarify that an unscheduled visit could also be prompted

by the need to administer the MDS-UPDRS prior to starting symptomatic PD medications outside of a scheduled visit, and to clarify the tests to be performed. In addition, this text for unscheduled visits was moved to a new Section 7.2.4, Unscheduled Visits. The title for the remaining text in Section 7.2.3 was modified to Follow-Up Visits and Final Visit, and the sentence regarding the timing of the final follow-up visit was moved to Section 7.2.3.3, Cohorts A and B, Year 2, for clarity.

- The title of Section 7.2.5 was modified from "Early Termination Visit and Final Visit" to "Early Termination" to coordinate with the text in that section, which includes the Early Termination Visit, a Safety Telephone Call, and the Final Visit.
- The text for the first study stopping rule in Section 7.2.6, Study Stopping Rules, was modified to clarify that it applies to 2 events, either serious adverse events (SAEs) or clinically significant AEs.
- The text in Section 8.2, Exclusion Criteria, for the exclusion criterion for participation in another clinical study or treatment with an investigational drug or therapy, was modified for clarity.
- Guidance on potential modifications to infusion duration and guidance on the requirement to maintain dose levels in Section 7.2.2, Study Treatment, have been repeated in Section 11.1, Regimen, and Section 11.2, Modification of Dose and/or Treatment Schedule, respectively, for clarity and completeness.
- The text in Section 11.4, Continuation of Treatment, has been modified to indicate that further treatment may be offered in an open-label extension study under a separate protocol.
- The description of coordination of symptomatic Parkinson's Disease medications with clinical function assessments has been modified in Section 13.1.1.1, Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale, Including Modified Hoehn and Yahr Scale, and [redacted] for clarity and consistency with Section 7.2.2.3, Treatment with Parkinson's Disease Medications.

APPENDIX A. SCHEDULE OF ACTIVITIES TABLES

The following tables show the changes in the Schedule of Activities tables from Protocol V2 to V3.

For ease of readability, changes to the tables are shown using images of tracked changes from the amended protocol rather than with bolding and strikethrough.

Table 1: Cohort A: Infusions 1–3 (Year 1)

Table 1: Cohort A: Infusions 1–3 (Year 1)

Tests and assessments	Screening ≤35 days before Day 1[1]	Infusions 1-3 Day 1/Baseline, Day 29 (±1 day), & Day 57 (±1 day)		Clinic Visits								Day 43 (Safety Telephone Call)
								Day 2, 30, 58	Day 4, 60	Day 8, 36, 64	Day 15, 71	
		Pre-infusion[2]	0m	Time after End of Last Infusion								
				≤10m	1h ±15m	2h ±15m	4h ±30m	24h ±2h	72h -2h/+1d	168h ±24h	336h ±24h	336h ±24h
Informed consent	X											
[redacted]												
Verification of eligibility		X[3]										
Medical history	X	X[3]										
Body weight	X	X										
Height	X											
Physical/neurological examination[4]	X	X[3]										
12-lead ECG[5]	X	X			X			X				
Vital signs[6]	X	X			X	X	X	X	X	X	X	
HbA_{1c}	X											
Pregnancy test[7]	Serum	X										
FSH test[8]	X											
Coagulation panel including platelet count	X											
Hematology, blood chemistry, urinalysis	X	X						X		X		
HBsAg, HBcAb, HCVAb, HIV	X											
Drug screen	X	X[3]										

Tests and assessments	Screening ≤35 days before Day 1[1]	Infusions 1-3 Day 1/Baseline, Day 29 (±1 day), & Day 57 (±1 day)						Clinic Visits				Day 43 (Safety Telephone Call)
								Day 2, 30, 58	Day 4, 60	Day 8, 36, 64	Day 15, 71	
		Pre-infusion[2]	0m	Time after End of Last Infusion								
				≤10m	1h ±15m	2h ±15m	4h ±30m	24h ±2h	72h -2h/+1d	168h ±24h	336h ±24h	336h ±24h
[redacted]												
Brain MRI[12]	X											
DaT/SPECT[12]	X											
Randomization		X[3]										
Study treatment infusion[13]			X									
BIIB054 PK sampling		X[14]		X	X[15]	X[15]	X[15]	X[16]	X	X[17]	X	
Serum for anti-BIIB054 antibodies		X									X[18]	
[redacted]												
MDS-UPDRS (full scale), includes Modified Hoehn and Yahr Scale[20]	X	X								X	X	
[redacted]												

Tests and assessments	Screening ≤35 days before Day 1[1]	Infusions 1-3 Day 1/Baseline, Day 29 (±1 day), & Day 57 (±1 day)						Clinic Visits				Day 43 (Safety Telephone Call)
		Pre-infusion[2]	0m	Time after End of Last Infusion				Day 2, 30, 58	Day 4, 60	Day 8, 36, 64	Day 15, 71	
				≤10m	1h ±15m	2h ±15m	4h ±30m	24h ±2h	72h -2h/+1d	168h ±24h	336h ±24h	336h ±24h
[redacted]												
C-SSRS[22]		X						X	X	X	X	
AE/Concomitant therapy and procedures reporting		ongoing										
SAE reporting	ongoing											

[redacted] AE = adverse event; [redacted] C-SSRS = Columbia Suicide Severity Rating Scale; d = day(s); DaT = dopamine transporter; [redacted] ECG = electrocardiogram; [redacted] FSH = follicle stimulating hormone; h = hour(s); HbA_{1c} = glycated hemoglobin; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; HIV = human immunodeficiency virus; m = minute(s); MDS-UPDRS = Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale; [redacted] MRI = magnetic resonance imaging; [redacted] PK = pharmacokinetic(s); [redacted] SAE = serious adverse event; [redacted] SPECT = single-photon emission computed tomography.

1 Screening assessments can be performed over ~2 days (need not be consecutive) to minimize subject burden. Subjects may be rescreened or screening tests repeated in certain circumstances (see Section 9.1).

2 Assessments can occur on the day before dosing or predose on the day of dosing, at Investigator's discretion, except for the following: randomization, pregnancy test, vital signs, and ECG must be obtained predose on day of dosing. MDS-UPDRS results must be available before randomization. [redacted]

3 Performed on Day 1 only.

4 A full physical and neurological examination will be performed at the specified timepoints. At all other visits, a targeted physical and/or neurological examination will be performed if the Investigator determines it is warranted by adverse events.

5 A 12-lead ECG will be obtained at each specified timepoint. Each must be performed after the subject has been resting in a supine position for at least 10 minutes. The ECGs will be read by the Investigator at collection. Predose readings **must be obtained predose on the day of dosing**.

6 Vital signs will include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, body temperature, and respiratory rate and will be measured after the subject has been resting in a supine position for at least 10 minutes. Three separate SBP/DBP and pulse readings at least 15 minutes apart will be made at Screening to determine eligibility. ~~Predose readings must be obtained predose on the day of dosing.~~ Orthostatic vital sign measurements will also be obtained whenever blood pressure is read~~, as described in~~ (see Section 14.1), but do not need to be repeated 3 times at Screening. Predose readings **must be obtained predose on the day of dosing**.

7 Required for women of childbearing potential. Predose samples **must be collected predose on the day of dosing**. Serum will be collected at Screening; urine will be collected at all other visits.

8 To confirm postmenopausal status in postmenopausal female subjects.

9 Whole blood samples for [redacted] serum, urine, [redacted] other analyses are required samples (under the main consent).

10 Performed on Day 1 and Day 29 only. [redacted]

[12] The MRI results will be read by the local radiologist at collection. Both MRI and DaT/SPECT results will be sent within 24 hours to a central reader for further evaluation and to confirm eligibility at Screening. Screening imaging assessments should be completed after all other eligibility criteria have been met, and before Day -7, to allow adequate time for evaluation of the results.

[13] Subjects will be under observation for at least 1 hour after the end of each infusion.

[14] Samples to be collected within 1 hour pre-infusion.

[15] Collected on Days 1 and 57 only.

[16] Collected on Days 2 and 58 only.

[17] Collected on Days 8 and 64 only.

[18] Collected on Day 15 only.

[redacted]

[20] Subjects who have started symptomatic Parkinson's disease (PD) medication during the study (not applicable to the Screening or Day 1 Visit), should refrain from taking the PD medication for 12 hours prior to MDS-UPDRS visits. MDS-UPDRS Part III will be administered before subjects take the PD medication.

[redacted]

[22] The "Since Last Visit" version of the C-SSRS will be administered at all clinic visits following the Day 1/Baseline assessment. If the Investigator has any concern regarding the completed C-SSRS, the subject should be referred to psychiatric evaluation based on local standards of care.

Table 2: Cohort A: Infusions 4–13 (Year 1)

Table 2: Cohort A: Infusions 4–13 ~~and Follow Up~~ (Year 1)

Tests and assessments	Infusions 4-13, Week (±3 d)										~~PK~~Clinic Visits, Week (±3 d)	Year 1
	12	16	20	24	28	32	36	40	44	48	22, 34, or 46[1] ~~(for PopPK)~~	Week 52 ~~/ET (Last Dose +4 wk)~~[2], (±3 d)[2]
Physical/neurological examination[43, ~~54~~]												X
Body weight[43]	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[43, ~~65~~]	X			X			X			X		
Vital signs[43, ~~76~~]	X	X	X	X	X	X	X	X	X	X	X	~~X~~
Pregnancy test[43, ~~87~~]	X	X	X	X	X	X	X	X	X	X		~~X~~
Coagulation panel including platelet count[~~98~~]			X						X			
Hematology, blood chemistry, urinalysis[43]	X	X	X	X	X	X	X	X	X	X		X
[redacted]												
Brain MRI[~~11~~10]				X								X
DaT/SPECT[~~11~~10]				X								X
Study treatment infusion[~~13~~11]	X	X	X	X	X	X	X	X	X	X		
BIIB054 PK sampling	X[~~14~~12]	X[~~14~~12]		X[~~15~~13]			X[~~14~~12]				X	X
Serum for anti-BIIB054 antibodies[43]				X			X					X
[redacted]												
MDS-UPDRS (full scale), includes Modified Hoehn and Yahr Scale[43, ~~16~~14]		X		X[~~17~~15]		X		X		X[~~17~~15]		X
[redacted]												

Tests and assessments	Infusions 4-13, Week (±3 d)										PK~~Clinic~~ Visits, Week (±3 d)	Year 1 Week 52~~/ET (Last Dose +4 wk)~~[2], (±3 d)[2]
	12	16	20	24	28	32	36	40	44	48	22, 34, or 46[1] ~~(for PopPK)~~	
[redacted]												
C-SSRS~~[3],[10]~~[7]	X	X	X	X	X	X	X	X	X	X	X	X
AE/Concomitant therapy and procedures	ongoing											
SAE reporting	ongoing											

[redacted] AE = adverse event; [redacted] C-SSRS = Columbia Suicide Severity Rating Scale; d = day(s); DaT = dopamine transporter; ECG = electrocardiogram; ~~ET = early termination;~~ MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; [redacted] MRI = magnetic resonance imaging; [redacted] PK = pharmacokinetic; ~~PopPK = population PK;~~ [redacted] SAE = serious adverse event; [redacted] SPECT = single-photon emission computed tomography; wk = week(s).

1 Subjects to complete only 1 of the 3 visits, at Week 22, 34, OR 46.

2 Assessments shown for the Year 1 Week 52 Visit will be considered part of Year 1 of the study. Vital signs and pregnancy test will be obtained at the Year 2 Week 52 Visit (see Table 4).

~~3 For subjects terminating early, it is recommended that the assessments of the Early Termination Visit be performed within 4 weeks after the last dose of study treatment, a Safety Telephone Call be performed approximately 8 weeks after the last dose, and the Final Visit be performed approximately 12 weeks after the last dose.~~

~~3 Unscheduled Visit can occur at any time, as determined by the Investigator, for safety-related issues. Additional tests may be performed at the Investigator's discretion.~~

~~3~~[3] Performed/collected pre-infusion on dosing days.

~~4~~[4] A full physical and neurological examination will be performed at the specified timepoints. At all other visits, a targeted physical and/or neurological examination will be performed if the Investigator determines it is warranted by adverse events.

~~5~~[5] A 12-lead ECG will be obtained at each specified timepoint. Each must be performed after the subject has been resting in a supine position for at least 10 minutes. The ECGs will be read by the Investigator at collection. Predose readings **must be obtained predose on the day of dosing**.

[redacted]

[6] Vital signs will include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, body temperature, and respiratory rate and will be measured after the subject has been resting in a supine position for at least 10 minutes. Predose readings **must be obtained predose on the day of dosing**. Orthostatic vital sign measurements will also be obtained whenever blood pressure is read, as described in Section 14.1.

[7] Required for women of childbearing potential. Predose samples **must be collected predose on the day of dosing**. Serum will be collected at the Final Visit. Urine will be collected at all other visits.

[8] Lumbar puncture should be performed consistently at the same time of day (±3 hours) to avoid diurnal fluctuation and should be performed pre-infusion on dosing days. The lumbar puncture assessment window is -2 weeks. Results from the prior CSF samples and results of the most recent coagulation tests (from a study visit within 35 days) including platelet count must be reviewed by the Investigator before each lumbar puncture can be performed.

[9] Whole blood samples for [redacted] serum, urine, [redacted] ther analyses are required samples (under the main consent).

[10] The MRI and DaT/SPECT assessment windows are ±7 days. The MRI results will be read by the local radiologist at collection. Both MRI and DaT/SPECT results will be sent within 24 hours to a central reader for further evaluation. See Section 7.2.2.3 ~~7.2.2.1~~ for further details on subjects who start symptomatic PD medication during this study.

[12] ~~Performed only if the last assessment occurred >12 weeks before the Final Visit.~~

[11] Subjects will be under observation for at least 1 hour after the end of each infusion.

[12] Samples to be collected within 1 hour pre-infusion and within 1 hour following the end of infusion.

[13] Samples to be collected within 1 hour pre-infusion.

[14] Subjects who have started symptomatic PD medication during the study should refrain from taking the PD medication for 12 hours prior to MDS-UPDRS [redacted] visits. MDS-UPDRS Part III [redacted] will be administered before the subjects take the PD medication [redacted]

[15] Performed/collected pre-infusion for dosing visits, [redacted] At the Investigator's discretion, these assessments may be administered in the clinic on the day prior to dosing.

[redacted]

[17] The "Since Last Visit" version of the C-SSRS will be administered. If the Investigator has any concern regarding the completed C-SSRS, the subject should be referred to psychiatric evaluation based on local standards of care.

Table 3: Cohort B: Infusions 1-13 (Year 1)

Table 3: Cohort B: ~~Schedule of Assessments~~ Infusions 1-13 (Year 1)

Tests and assessments	Screening ≤35 d Before Day 1[1]	Day 1[2,~~3~~] Baseline/ Infusion 1	Safety Telephone Calls 1d & 7d after Infusion 1[2]	Infusions 2-13, Week (±3 d)														PK~~Clinic~~ Visits, Week (±3 d)	Year 1 Week 52,~~/ ET (Last Dose + 4 wk)~~[5] (±3 d)[4]
				4[2]	Safety Telephone Calls 1d & 7d after Infusion 2[2]	8[2]	Safety Telephone Calls 1d & 7d after Infusion 3[2]	12	16	20	24	28	32	36	40	44	48	22, 34, or 46[43] ~~(for PopPK~~	
Informed consent	X																		
[redacted]																			
Verification of eligibility		X[5]																	
Medical history	X	X[5]																	
Body weight[~~7~~6]	X	X[5]		X		X		X	X	X	X	X	X	X	X	X	X	X	
Height	X																		
Physical/neurological examination[~~8~~7]	X	X[5]																	X
12-lead ECG[~~7~~6,~~9~~8]	X	X[5]						X			X			X			X		
Vital signs[~~7~~6,~~10~~9]	X	X[5]		X		X		X	X	X	X	X	X	X	X	X	X	X	~~X~~
HbA_{1c}	X																		
Pregnancy test[~~7~~6,~~11~~10]	Serum	X[5]		X		X		X	X	X	X	X	X	X	X	X	X		~~X~~
FSH test[~~12~~11]	X																		
Coagulation panel including platelet count	X									X[~~13~~12,~~14~~13]						X[~~13~~12,~~14~~13]			
Hematology, blood chemistry, urinalysis[~~7~~6]	X	X[5]						X			X			X			X		X
HBsAg, HBcAb, HCVAb, HIV	X																		
Drug screen	X	X[5]																	
[redacted]																			

Tests and assessments	Screening ≤35 d Before Day 1[1]	Day 1[2,3] Baseline/ Infusion 1	Safety Telephone Calls 1d & 7d after Infusion 1[2]	Infusions 2-13, Week (±3 d)														PK~~Clinic~~ Visits, Week (±3 d)	Year 1 Week 52,~~/ ET (Last Dose + 4 wk)~~[5] (±3 d)[4]
				4[2]	Safety Telephone Calls 1d & 7d after Infusion 2[2]	8[2]	Safety Telephone Calls 1d & 7d after Infusion 3[2]	12	16	20	24	28	32	36	40	44	48	22, 34, or 46[4,2] ~~(for PopPK~~	
[redacted]																			
Brain MRI[17~~,16~~]	X[18~~,17~~]										X								X
DaT/SPECT[17~~,16~~]	X[18~~,17~~]										X								X
Randomization		X[3]																	
Study treatment infusion[20~~,18~~]		X[3]		X		X		X	X	X	X	X	X	X	X	X	X		
~~Safety Telephone Call 1 d and 7 d after infusion[3]~~		~~X~~		~~X~~		~~X~~													
BIIB054 PK sampling[21~~,19~~]		X[3]		X		X		X	X		X			X				X	X
Serum for anti-BIIB054 antibodies[~~7~~6]		X[3]		X							X			X					X
[redacted]																			
MDS-UPDRS (full scale), includes Modified Hoehn and Yahr Scale[~~7~~6,~~25~~23]	X	X[5,~~26~~24]				X			X		X~~62~~4		X		X		X~~62~~4		X
[redacted]																			

Tests and assessments	Screening ≤35 d Before Day 1[1]	Day 1[2,3] Baseline/ Infusion 1	Safety Telephone Calls 1d & 7d after Infusion 1[2]	Infusions 2-13, Week (±3 d)													PK~~Clinic~~ Visits, Week (±3 d)	Year 1 Week 52,[4] ~~ET (Last Dose + 4 wk)[5]~~ (±3 d)[4]
				4[2]	Safety Telephone Calls 1d & 7d after Infusion 2[2]	8[2]	Safety Telephone Calls 1d & 7d after Infusion 3[2]	12	16	20	24	28	32	36	40	44	48	22, 34, or 46[3] ~~(for PopPK~~	
[redacted]																		
C-SSRS[~~2~~6,~~2~~6]		X[5]		X		X		X	X	X	X	X	X	X	X	X	X	X	X
AE/ Concomitant therapy and procedures		ongoing																
SAE reporting		ongoing																

[redacted] AE = adverse event; [redacted] C-SSRS = Columbia Suicide Severity Rating Scale; d = day(s); DaT = dopamine transporter; [redacted] ECG = electrocardiogram; [redacted] ~~ET = early termination;~~ FSH = follicle stimulating hormone; HbA_{1c} = glycated hemoglobin; HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; HCVAb = Hepatitis C virus antibody; HIV = human immunodeficiency virus; MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; [redacted] MRI = magnetic resonance imaging; [redacted] PK = pharmacokinetic; ~~PopPK = population PK;~~ [redacted] SAE = serious adverse event; [redacted] SPECT = single-photon emission computed tomography; ~~Unsch = unscheduled~~.

1 Screening assessments can be performed over ~2 days (need not be consecutive) to minimize subject burden. Subjects may be rescreened or screening tests repeated in certain circumstances (see Section 9.1).

2 Subjects will receive 6 Safety Telephone Calls to ask about AEs, SAEs, and concomitant medications approximately 1 day (24 hours) and 7 days (168 hours) after each of the first 3 infusions: Days 2 and 8 (follow-up after first infusion); Days 30 and 36 (follow-up after second infusion); and Days 58 and 64 (follow-up after third infusion).

3 Subjects to complete only 1 of the 3 visits at Week 22, 34, OR 46.

4 Assessments shown for the Year 1 Week 52 Visit will be considered part of Year 1 of the study. Vital signs and pregnancy test will be obtained at the Year 2 Week 52 Visit (see Table 4).

[3][5] ~~All~~ The specified baseline assessments should be performed ~~on~~ the day before dosing or predose on the day of dosing, at the Investigator's discretion, except for the following: randomization, pregnancy test, vital signs, and ECG must be obtained predose on the day of dosing. MDS-UPDRS results must be available before randomization.

~~[4] Subjects to complete only 1 of the 3 visits at Week 22, 34, OR 46.~~

~~[5] For subjects terminating early, it is recommended that the assessments of the Early Termination Visit be performed within 4 weeks after the last dose of study treatment, a Safety Telephone Call be performed approximately 8 weeks after the last dose, and the Final Visit be performed approximately 12 weeks after the last dose.~~

~~[6] Unscheduled Visit can occur at any time, as determined by the Investigator, for safety-related issues. Additional tests may be performed at the Investigator's discretion.~~

[7][6] Performed/collected pre-infusion on dosing days.

[8][7] A full physical and neurological examination will be performed at the specified timepoints. At all other visits, a targeted physical and/or neurological examination will be performed if the Investigator determines it is warranted by adverse events.

[9][8] A 12-lead ECG will be obtained at each specified timepoint. Each must be performed after the subject has been resting in a supine position for at least 10 minutes. The ECGs will be read by the Investigator at collection. Predose readings **must be obtained predose on the day of dosing**.

[10][9] Vital signs will include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, body temperature, and respiratory rate and will be measured after the subject has been resting in a supine position for at least 10 minutes. Three separate SBP/DBP and pulse readings at least 15 minutes apart will be made at Screening to determine eligibility. ~~Predose readings must be obtained predose on the day of dosing.~~ Orthostatic vital sign measurements will also be obtained whenever blood pressure is read~~, as described in~~ (see Section 14.1), but do not need to be repeated 3 times at Screening. Predose readings **must be obtained predose on the day of dosing**.

[11][10] Required for women of childbearing potential. Predose samples **must be collected predose on the day of dosing**. Serum will be collected at the Screening and Final Visits. Urine will be collected at all other visits.

[12][11] To confirm postmenopausal status in postmenopausal female subjects.

[13][12] Required only for subjects at sites administering lumbar punctures.

[14][13] [redacted] Results from the prior [redacted] samples and results of the most recent coagulation tests (from a study visit within 35 days) including platelet count must be reviewed by the Investigator before each post-Day 1 lumbar puncture can be performed.

[15][14] Whole blood samples for [redacted] serum, urine, [redacted] other analyses are required samples (under the main consent).

[redacted]

[17][16] The MRI and DaT/SPECT assessment windows are ±7 days. The MRI results will be read by the local radiologist at collection. Both MRI and DaT/SPECT results will be sent within 24 hours to a central reader for further evaluation and to confirm eligibility at Screening. See Section 7.2.2.3 ~~7.2.2.1~~ for further details for subjects who start symptomatic PD medication during this study.

[18][17] Screening imaging assessments should be completed after all other eligibility criteria have been met, and before Day -7, to allow adequate time for evaluation of the results.

~~[19] Performed only if the last assessment occurred >12 weeks before the Final Visit.~~

[20][18] Subjects will be under observation for at least 1 hour after the end of each infusion.

[21][19] Samples to be collected within 1 hour pre-infusion and within 1 hour following the end of infusion on dosing days.

[22][20] Samples to be collected within 1 hour pre-infusion on dosing days.

[redacted]

[23][23] Subjects who have started symptomatic Parkinson's disease (PD) medication during this study (not applicable to the Screening or Day 1 Visit) should refrain from taking the PD medication for 12 hours prior to MDS-UPDRS [redacted] visits. MDS-UPDRS Part III [redacted] will be administered before subjects take the PD medication [redacted]

[24][24] Performed/collected on the day before dosing or pre-infusion on the day of dosing, at the Investigator's discretion, [redacted]

[redacted]

[26][25] The "Since Last Visit" version of the C-SSRS will be administered at all clinic visits following the Day 1/Baseline assessment. If the Investigator has any concern regarding the completed C-SSRS, the subject should be referred to psychiatric evaluation based on local standards of care.

Table 4: Cohorts A and B: Infusions 14–25 (Year 2) and Follow-Up

Table 4: Cohorts A and B: Infusions 14–25 (Year 2) and Follow-Up

Tests and assessments	Year 2 Week 52 (±3 d)[1] Infusion 14	Safety Telephone Calls 1d & 7d after Infusion 14[2]	Infusions 15-25, Week (±3 d) 56	60	64	68	72	76	80	84	88	92	96	Week 100 (±3 d)/ET (Last Dose +4 wk)[3]	Safety Telephone Call Week 104 (±2 d)/ Last Dose +8 wk[3]	Unsched Visit[4]	Final Visit Week 108 (±3 d)/ Last Dose +12 wk[3]
Body weight[5]	X			X			X			X			X	X			X
Physical/neurological examination[6]			X	X										X		X	X
12-lead ECG[5,7]	X		X										X				
Vital signs[5,8]	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
Pregnancy test[5,9]	X		X	X	X	X	X	X	X	X	X	X	X	X			Serum
Coagulation panel including platelet count																	X
Hematology, blood chemistry, urinalysis[5]				X									X	X		X	X
[redacted]																	
Brain MRI[11]													X	X[12]			
DaT/SPECT[11]													X	X[12]			
Randomization[13]	X																
Study treatment infusion[14]	X		X	X	X	X	X	X	X	X	X	X	X				
BIIB054 PK sampling[15]				X						X			X	X			X
Serum for anti-BIIB054 antibodies[5]				X						X			X	X			X
[redacted]																	
MDS-UPDRS (full scale), includes Modified Hoehn and Yahr Scale[5,17]				X			X[18]			X			X[18]	X		X	X
[redacted]																	

Tests and assessments	Year 2 Week 52 (±3 d)[1] Infusion 14	Safety Telephone Calls 1d & 7d after Infusion 14[2]	Infusions 15-25, Week (±3 d) 56	60	64	68	72	76	80	84	88	92	96	Week 100 (±3 d)/ET (Last Dose +4 wk)[3]	Safety Telephone Call Week 104 (±2 d)/ Last Dose +8 wk[3]	Unsched Visit[4]	Final Visit Week 108 (±3 d)/ Last Dose +12 wk[3]
[redacted]																	
C-SSRS[5,20]			X	X	X	X	X	X	X	X	X	X	X	X		X	X
AE/ Concomitant therapy and procedures	ongoing																
SAE reporting	ongoing																

[redacted] AE = adverse event; [redacted] C-SSRS = Columbia Suicide Severity Rating Scale; DaT = dopamine transporter; ECG = electrocardiogram; ET = early termination; MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; MRI = magnetic resonance imaging; [redacted] PK = pharmacokinetic; [redacted] SAE = serious adverse event; [redacted] SPECT = single-photon emission computed tomography; Unsched = unscheduled.

1 Study treatment infusion and the assessments shown will be considered part of Year 2 of the study and will be performed after all assessments for the Year 1 Week 52 Visit are completed (see Table 2 and Table 3), with the exception that randomization for Year 2 may be performed prior to the Year 2 Week 52 Visit. The Year 2 Week 52 assessments may be performed on the same day as the Year 1 Week 52 Visit or on the day after; however, pregnancy test, vital signs, and ECG must be obtained predose on the same day as dosing for Infusion 14, and randomization for Year 2 must be performed prior to Infusion 14.

2 Subjects will receive Safety Telephone Calls to ask about AEs, SAEs, and concomitant medications approximately 1 day (24 hours) and 7 days (168 hours) after Infusion 14 (follow-up after first infusion in Year 2).

3 For subjects terminating early, it is recommended that the assessments of the Early Termination Visit be performed within 4 weeks after the last dose of study treatment, a Safety Telephone Call be performed approximately 8 weeks after the last dose, and the Final Visit be performed approximately 12 weeks after the last dose.

4 Unscheduled Visit can occur for safety-related issues at any time (as determined by the Investigator), or for administering the MDS-UPDRS prior to starting symptomatic PD medications outside of a scheduled visit. Additional tests may be performed at the Investigator's discretion.

5 Performed/collected pre-infusion on dosing days.

6 A full physical and neurological examination will be performed at the specified timepoints. At all other visits, a targeted physical and/or neurological examination will be performed if the Investigator determines it is warranted by adverse events.

7 A 12-lead ECG will be obtained at each specified timepoint. Each must be performed after the subject has been resting in a supine position for at least 10 minutes. The ECGs will be read by the Investigator at collection. Predose readings **must be obtained predose on the day of dosing**.

[8] Vital signs will include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, body temperature, and respiratory rate and will be measured after the subject has been resting in a supine position for at least 10 minutes. Predose readings **must be obtained predose on the day of dosing**. Orthostatic vital sign measurements will also be obtained whenever blood pressure is read, as described in Section 14.1.

[9] Required for women of childbearing potential. Predose samples **must be collected predose on the day of dosing**. Serum will be collected at the Final Visit. Urine will be collected at all other visits.

[10] Whole blood samples for [redacted] serum, and urine samples [redacted] other analyses are required samples (under the main consent).

[11] The MRI and DaT/SPECT assessment windows are ±7 days. The MRI results will be read by the local radiologist at collection. Both MRI and DaT/SPECT results will be sent within 24 hours to a central reader for further evaluation. See Section 7.2.2.3 for further details for subjects who start symptomatic PD medication during this study.

[12] Performed only for subjects who have not had the assessment at Week 96.

[13] Prior to Infusion 14 (first dose of Year 2), subjects who received placebo in Year 1 will be randomized into 1 of the active dosing arms to receive BIIB054 for Year 2. Subjects who received BIIB054 in Year 1 of the study will continue with the same dose regimen in Year 2.

[14] Subjects will be under observation for at least 1 hour after the end of each infusion.

[15] Samples to be collected within 1 hour pre-infusion and within 1 hour following the end of infusion on dosing days.

[16] Samples to be collected within 1 hour pre-infusion on dosing days.

[17] Subjects who have started symptomatic Parkinson's disease (PD) medication during this study should refrain from taking the PD medication for 12 hours prior to MDS-UPDRS or [redacted] MDS-UPDRS Part III [redacted] will be administered before subjects take the PD medication [redacted]

[18] Performed/collected on the day before dosing or pre-infusion on the day of dosing, at the Investigator's discretion. [redacted]

[20] The "Since Last Visit" version of the C-SSRS will be administered at all clinic visits. If the Investigator has any concern regarding the completed C-SSRS, the subject should be referred to psychiatric evaluation based on local standards of care.

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AMENDMENT SUMMARY

Biogen Protocol 228PD201

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Pharmacokinetics, and Pharmacodynamics of BIIB054 in Subjects with Parkinson's Disease

Version 2

Date: 09 August 2017

EUDRA CT Number: 2016-004610-95

Version 2 of the protocol has been prepared for this amendment, which supersedes Version 1.

PRIMARY REASON FOR AMENDMENT

The primary reasons for this amendment to Protocol 228PD201 are as follows:

- The length of the treatment period and total duration of subject participation in the study have been reduced.
- The number of subjects in the study has been increased and the sample size considerations supporting that change have been updated.
- Key inclusion criteria were modified as follows:
  - Inclusion criterion 2 was modified to reduce the time from past diagnosis with PD, to clarify clinical presentation details, and to indicate that subjects with Lewy body dementia would not be included in the study.
  - Inclusion criterion 3 was modified to lengthen the washout duration for levodopa treatment before entry into the study from 4 weeks to 12 weeks, to describe PD medications excluded, and to shorten the maximum duration of allowed prior PD treatment regimens from 3 months to 30 days.
- The dose levels were changed from 3 mg/kg, 15 mg/kg, and 45 mg/kg (dosing based on body weight) to 250 mg, 1250 mg, and 3500 mg (fixed dosing) for both cohorts.

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

Section 7.2, Overall Study Duration and Follow-Up

Now reads:

The **total** duration of study participation for each subject will be approximately ~~89 weeks~~ **65 weeks**, including a 5-week Screening period ~~-~~before the first study treatment infusion, a ~~72-week~~ **48-week** treatment period, and a 12-week follow–up period ~~-n~~.

Rationale: The shorter treatment duration will allow earlier data collection and acceleration to a future Phase 3 study.

This change also affects Section 4.1, Study Schematic; Section 4.2, Schedule of Activities; and Section 7.2.2, Study Treatment.

To coordinate with this change, there has been a corresponding decrease in the number of study treatment doses (from 19 to 13 doses). The change in number of doses affects Section 4.1, Study Schematic; Section 4.2, Schedule of Activities; Section 7.1, Study Overview; Section 7.2.2, Study Treatment; and Section 16.5.1, Clinical Function (under Analysis Population).

There has also been a corresponding change in the number and naming of study visits during the treatment period. The change in visit descriptions affects Section 4.2, Schedule of Activities; Section 7.2.4, Unscheduled Visits and Follow-Up; Section 16.2.2, Pharmacodynamic – Imaging Analyses (under Methods of Analysis); and Section 16.5.2, Clinical Function (under Methods of Analysis).

Section 16.9, Sample Size Considerations

Now reads:

The sample size calculation is based on **changes in SBR observed using** ~~pharmacologic parameters, i.e.,~~ **DaT**/SPECT ~~with DaTscan~~. Based on re-analysis of data from the Parkinson**'s** Progression Marker**s** Initiative study, putamen ipsilateral to the clinically more severely affected side was selected as the region of interest for the purpose of sample size calculation, as it shows one of the highest mean to standard deviation (SD) ratios ~~and most rapid rates of change over time~~. Based on mean changes from baseline to 12-month ~~and 24 month~~ SBR from the Parkinson's Progression Marker**s** Initiative study, it is assumed~~, by linear extrapolation,~~ that the mean change (SD) from baseline **to** Week ~~76~~ **52** for the placebo group will be ~~0.18 (0.167)~~ **0.138 (0.156)**. Assuming a maximum 40% reduction in the change from baseline of the active group with maximum response relative to placebo group, the mean (SD) for this active group will be ~~0.108 (0.167)~~ **0.083 (0.156)** and the responses for other active groups are assumed to be somewhere between placebo and the maximum response. The primary analysis will be based on **the** MCP-MOD method to detect a dose-response trend while controlling for multiplicity. Optimal contrasts will be constructed to detect potential dose-response trend under common dose-response curves (e.g., E_{max}, exponential, logistic, linear in log dose, and quadratic model, which are illustrated with parameters shown in **Figure 3** ~~Figure 2~~). It has also been determined that in Cohort A, 24 subjects will be randomized in a 1:1:1:1 ratio to each of the treatment groups, while in Cohort B, subjects will be randomized in 2:1:2:2 ratio to the placebo, ~~3 mg/kg~~ **250 mg**, ~~15 mg/kg~~ **1250 mg**, and ~~45 mg/kg~~ **3500 mg** groups. A sample size of ~~52:26:52:52~~ **82:41:82:82** in the respective treatment groups in Cohort B, together with the sample size in Cohort A, will provide an average power of approximately 80% to detect the dose-response trend, based on a 2-sided type I error of 0.2. If the 2-sided type I error is 0.1, the power is approximately ~~68%~~ **70%**. The sample size will be ~~58:32:58:58~~ **88:47:88:88** placebo:~~3 mg/kg~~**250 mg**:~~15 mg/kg~~**1250 mg**:~~45 mg/kg~~**3500 mg**, with a total of ~~206~~ **311** subjects **to be enrolled** for the study (**Table 5 and Table 6**). A 15% dropout rate has been ~~adjusted~~ **assumed** for ~~in~~ this calculation. **If there are any modifications to the candidate dose-response curves/models or parameters, the final candidate models for the MCP-MOD will be prespecified and described in the SAP.**

With a sample size of 88 subjects per arm in the 1250 mg and 3500 mg arms, the study has approximately 70% power to detect a 40% reduction in the active group relative to placebo in the change from baseline to Week 52 MDS-UPDRS total score, assuming the placebo mean change (SD) is 8.0 (10.64), based on the Parkinson's Progression Markers Initiative study data and a 2-sided alpha of 0.2.

With a sample size of 88 subjects per arm in the 1250 mg and 3500 mg arms, the study has 80% probability of detecting AEs with a rate of 1.8% or greater in these 2 arms, and a 90% probability of detecting AEs occurring with a rate of 2.6% or greater.

Figure ~~32~~: Response Shapes

[original figure replaced with the one below]

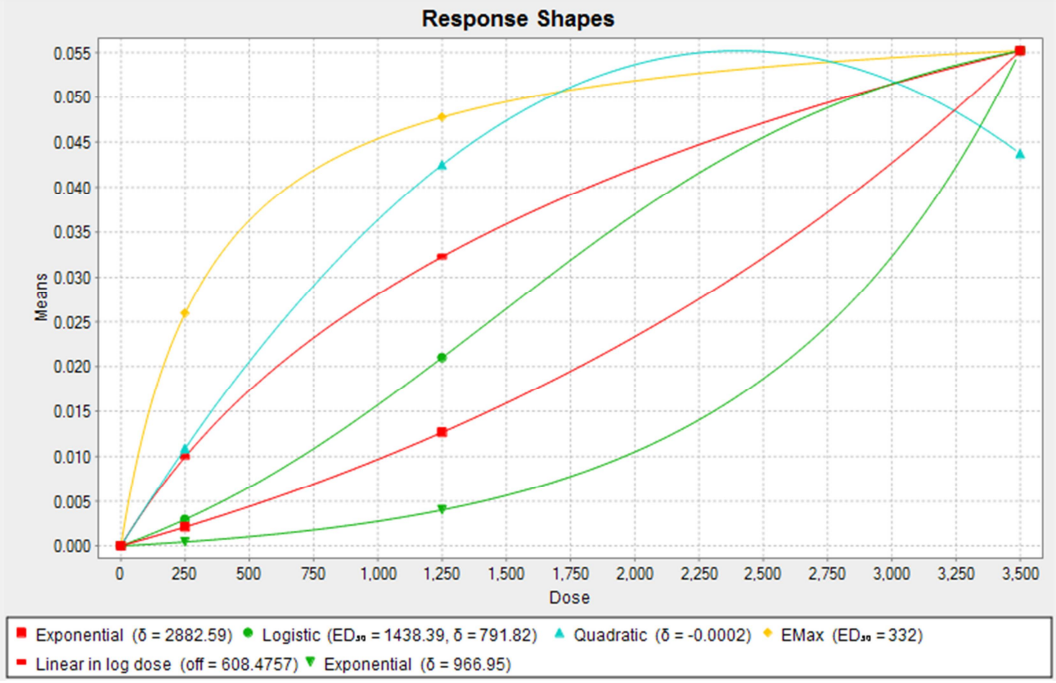


Table 5: Sample Size Before Adjusting for 15% Dropout Rate

Cohort	Treatment Group				
	Placebo	**BIIB054 250 mg**	**BIIB054 1250 mg**	**BIIB054 3500 mg**	**Total**
Cohort A	**5**	**5**	**5**	**5**	**20**
Cohort B	**69**	**34**	**69**	**69**	**241**
Total	**74**	**39**	**74**	**74**	**261**

~~Table 4~~ Table 6: Sample Size **After Adjusting for 15% Dropout Rate**

~~Dose~~ Cohort	Treatment Group				
	Placebo	BIIB054 ~~3 mg/kg~~**250 mg**	BIIB054 ~~15 mg/kg~~**1250 mg**	BIIB054 ~~45 mg/kg~~**3500 mg**	Total
Cohort A	6	6	6	6	24
Cohort B	~~52~~**82**	~~26~~**41**	~~52~~**82**	~~52~~**82**	~~182~~**287**
Total	~~58~~**88**	~~32~~**47**	~~58~~**88**	~~58~~**88**	~~206~~**311**

Rationale: The number of subjects in the study was increased in order to allow enough power for statistical analyses based on DaT/SPECT with a shorter treatment duration. The updated response shape diagram (now Figure 3) and tables support the sample size calculations. Power to detect changes in MDS-UPDRS score and AE incidence has also been provided.

This change also affects Section 4.1, Study Schematic; Section 7.1, Study Overview; Section 9.2, Randomization and Registration of Subjects; and Section 11.1, Regimen.

To coordinate with this change, there was a corresponding increase in the number of study sites. The change in the number of study sites affects Section 7.1, Study Overview.

Section 8.1, Inclusion Criteria

Inclusion criterion 2:

Now reads:

2. Diagnosed with ~~idiopathic~~ PD **with**in ~~the last~~ **a maximum of** ~~5~~ **3** years ~~without motor fluctuations or dyskinesia~~ **prior to Screening**. Subjects must have:
    a. **An asymmetric or bilateral presentation of** ~~O~~**o**ne of the following:
        – resting tremor and bradykinesia
        – bradykinesia and rigidity
        – rigidity and resting tremor

          OR

        – either asymmetric resting tremor or asymmetric bradykinesia.
    b. No known or suspected cause of Parkinsonism other than ~~idiopathic~~ **neurodegenerative** PD**.** ~~: i.e., no presence of~~ **Subjects with** drug-induced Parkinsonism (e.g., metoclopramide and flunarizine), metabolic identified neurogenetic disorders (e.g., Wilson's disease), encephalitis, or Parkinson Plus syndromes, ~~or~~ other forms of atypical Parkinsonian syndromes (e.g., progressive supranuclear palsy and multiple system atrophy)**, or Lewy body dementia are not allowed in the study**.

Rationale: The change to inclusion criterion 2 was made because subjects with a longer time from diagnosis would likely have static disease or even be starting to decline, and BIIB054 is unlikely to be effective for them. The shorter time from diagnosis is also consistent with that in the majority of other studies of disease-modifying therapies for PD. Clinical presentation of symptoms has been modified for accuracy and clarity.

The changes to inclusion criterion 2b clarify that Lewy body dementia would rule out neurodegenerative PD and is not included in the intended subject population.

Inclusion criterion 3:

Now reads:

3. Has not received levodopa ~~for at least 4 weeks,~~ or any other treatment for PD ~~symptoms~~ **(dopamine agonists, amantadine, anticholinergics, MAO-B inhibitors, or safinamide)** for at least 12 weeks ~~before Screening~~ **prior to Day 1** and, in the opinion of the Investigator, is not expected to require ~~symptomatic therapy~~ **PD treatment** for at least 6 months following Day 1. Maximum **total** duration of ~~previous levodopa treatment~~ **prior PD regimens** should not exceed ~~3 months~~ **30 days**.

Rationale: The longer washout of prior levodopa and the shorter maximum duration of prior PD regimens are intended to avoid inclusion of subjects with slowly progressing disease, as well as those with atypical Parkinsonian syndromes, who could dilute the outcomes signal in the study. In addition, the washout period was defined relative to Day 1 in order to provide a fixed reference point and for consistency with other inclusion and exclusion criteria.

Section 7.1, Study Overview

Now reads:

…All subjects in the study will be randomized into 4 arms, to receive ~~19~~ **13** doses of BIIB054 (~~3, 15, or 45 mg/kg~~ **250, 1250, or 3500 mg**) or placebo.

Rationale: Given the favorable safety profile of BIIB054 in the first-in-human Study 228HV101 and based on PK modeling from that study, a fixed-dose approach was chosen for this study. Fixed doses will result in greater compliance and reduced potential for medication errors. Projected safety margins for both approaches are similar and on average are estimated to be 9 (AUC_{tau}) and 8 (C_{max}) for the 3500 mg fixed dose, and 7 (AUC_{tau}) and 14 (C_{max}) for a 45 mg/kg dose.

This change also affects Section 4.1, Study Schematic; Section 5.5, Rationale for Dosing Regimen; Section 9.2, Randomization and Registration of Subjects; Section 11.1, Regimen; and Section 16.8, Sample Size Considerations.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented in the order that they appear in the protocol. 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.

For detailed revisions to the tables in Section 4.2 (Schedule of Activities), see the track changes version of each table in Appendix A of this document, as follows:

- Table 1 (Cohort A: Infusions 1-3): Appendix A, Table 1
- Table 2 (Cohort A: Infusions 4-13 and Follow-Up): Appendix A, Table 2
- Table 3 (Cohort B: Schedule of Assessments): Appendix A, Table 3

Section 4.2, Schedule of Activities

[redacted]

Rationale: These changes were made to clarify the requirements for informed consents, [redacted]. All the applicable informed consents should be signed at Screening, before the relevant sample collections.

Section 4.2, Schedule of Activities

Change: The timing of the physical and neurological examination assessments was modified.

In Table 1 (Cohort A: Infusions 1-3), a physical/neurological examination has been added to the Pre-infusion visit at Day 1/Baseline and removed from the Day 2/30/58, Day 4/60, Day 8/36/64, and Day 15/71 Visits. In Table 2 (Cohort A: Infusions 4-13 and Follow-Up), the physical/neurological examination has been removed from the Week 12 through Week 48 Visits and from the Week 22, 34, or 46 clinic visit. In Table 3 (Cohort B: Schedule of Assessments), the physical/neurological examination has been removed from the Week 4 through Week 48 Visits and from the Week 22, 34, or 46 clinic visit. A footnote has been added to all 3 tables to indicate that targeted examinations will be performed as needed at other visits.

Now reads for Table 1 (same text for Table 2, footnote 5 and Table 3, footnote 8)**:**

[4] **A full physical and neurological examination will be performed at the specified timepoints. At all other visits, a targeted physical and/or neurological examination will be performed if the Investigator determines it is warranted by adverse events.**

Rationale: Physical and neurological examinations are needed for the first infusion visit in Cohort A for safety monitoring. However, the remaining assessments for physical/neurological examination in both cohorts have been reduced in favor of targeted physical and neurological examinations, which can be performed if the Investigator determines that they are warranted by adverse events.

Section 4.2, Schedule of Activities

Change: Triplicate electrocardiogram (ECG) assessments will no longer be conducted, and paper ECGs are no longer specified.

Now reads for Table 1 (same text for Table 2, footnote 6 and Table 3, footnote 9):

[45] ~~Triplicate~~ **A** 12-lead ~~(paper)~~ ECG~~s~~ will be obtained at each specified timepoint. Each must be performed after the subject has been resting in a supine position for at least 10 minutes. The ECGs will be read by the Investigator at collection. Predose readings must be obtained **predose** on the day of dosing.

Rationale: Since no clinically significant ECG abnormalities have been noted in the Phase 1 Study 228HV101 to date, triplicate ECGs are not necessary for this study. ECGs will be obtained in an appropriate format (to be specified in the Study Reference Manual).

Section 4.2, Schedule of Activities

Change: [redacted]

Now reads for Table 1 (same text as footnote 9 is used for Table 2, footnote 10 and similar text is used for Table 3, footnote 15; same text as footnote 11 is used for in Table 3, footnote 16):

[redacted]

[10] **Performed on Day 1 and Day 29 only.**

[redacted]

Rationale: [redacted]

[redacted]

Section 4.2, Schedule of Activities

Change: The brain MRI was removed from the Day 1, Day 29, Day 57, and Week 12 Visits for Cohort A and from Week 12 for Cohort B. The brain MRI and DaT/SPECT at Week 48 were removed for both cohorts due to the shortened study duration. The footnotes to the brain MRI and DaT/SPECT rows of the Schedule of Activities tables have been modified to clarify which results need to be read at collection. In addition, the following changes were made:

- The DaTscan assessment was renamed as DaT/SPECT throughout the protocol.
- In Table 1, the footnote for MRI and DaT/SPECT has been merged with the footnote for screening imaging assessments.

Now reads for Table 1:

[9][12] The ~~DaTscan and~~ MRI results will be read by the ~~Investigator~~ **local radiologist** at collection. **Both MRI and DaT/SPECT results will be** ~~and then~~ sent within 24 hours to a central reader for further evaluation and to confirm eligibility at Screening. Screening imaging assessments should be completed after all other eligibility criteria have been met, and before Day -7, to allow adequate time for evaluation of the results.

Now reads for Table 2 (similar text for Table 3, footnote 17, which also incorporates text from the former footnote 15)**:**

[9][11] The MRI~~/~~ **and DaT/SPECT**~~scan~~ assessment windows ~~is~~ **are** ±7 days. **The MRI results will be read by the local radiologist at collection. Both MRI and DaT/SPECT results will be sent within 24 hours to a central reader for further evaluation. See Section 7.2.2.1 for further details on subjects who start symptomatic PD medication during this study.**

Rationale: The brain MRI at Screening is sufficient for the early visits for Cohort A, and brain MRI and DaT/SPECT approximately every 6 months are sufficient for the later timepoints.

Only the MRI results need to be read at collection, and the footnote changes clarify that the local radiologist rather than the Investigator will read the results at collection. Both MRI and DaT/SPECT results continue to be sent to a central reader within 24 hours for evaluation and to confirm eligibility at Screening.

The name of the assessment has been corrected from DaTscan (the radioligand) to DaT/SPECT (the imaging procedure) throughout the protocol.

This change also affects Section 14.1, Clinical Safety Assessments.

Section 4.2, Schedule of Activities

Change: Footnotes were added to Table 1 (Cohort A: Infusions 1-3), Table 2 (Cohort A: Infusions 4-13 and Follow-Up), and Table 3 (Cohort B: Schedule of Assessments) to specify the duration of subject observation after each infusion of study treatment.

Now reads for Table 1 (same text for Table 2, footnote 13 and Table 3, footnote 20):

[13] **Subjects will be under observation for at least 1 hour after the end of each infusion.**

Rationale: The additional monitoring allows further assessment of subject safety following the infusion, as appropriate given that this is the first multiple-dose clinical study.

This change also affects Section 7.2.2, Study Treatment.

Section 4.2, Schedule of Activities

[redacted]

Section 4.2, Schedule of Activities

Change: Footnotes have been modified for the clinical function assessments in Table 1 (Cohort A: Infusions 1-3), Table 2 (Cohort A: Infusions 4-13 and Follow-Up), and Table 3 (Cohort B: Schedule of Assessments).

- The footnote to the MDS-UPDRS assessment in all 3 tables giving the timing of administration of the full scale has been removed. Full-scale MDS-UPDRS, including the Modified Hoehn and Yahr Scale, will be administered at all timepoints; this information is now reflected in the row for this assessment.

[redacted]

- Footnotes have been added or modified to describe timing of the MDS-UPDRS, [redacted] assessments relative to BIIB054 dosing and relative to administration of medication to treat PD symptoms for subjects who start symptomatic PD medication during the study.

[redacted]

Now reads for Table 1:

~~[18] Includes Modified Hoehn and Yahr Scale. Full scale to be administered at Screening and Day 1; Parts II and III only to be administered at all other visits.~~

[20] **Subjects who have started symptomatic Parkinson's disease (PD) medication during the study (not applicable to the Screening or Day 1 Visit), should refrain from taking the PD medication for 12 hours prior to MDS-UPDRS visits. MDS-UPDRS Part III and [redacted] will be administered before subjects take the PD medication.**

Now reads for Table 2 (similar text for Table 3, former footnote 22 and current footnotes 25 and 26)**:**

~~[14] Includes Modified Hoehn and Yahr Scale. Full scale to be administered at Week 24, Week 48, and Week 76; Parts II and III only to be administered at all other visits.~~

~~[15]~~[16] ~~If the s~~Subjects ~~is receiving~~**who have started symptomatic PD** medication ~~to treat PD symptoms~~**during the ~~,~~study** ~~subject~~ should **refrain from taking the PD medication for 12 hours prior to MDS-UPDRS visits.** MDS-UPDRS **Part III and** [redacted] will be administered ~~in the off condition (~~before the subjects take~~s~~ the **PD** medication~~) AND in the on condition (at least 1 hour after the subject takes the medication);~~ [redacted].

[redacted]

Rationale: MDS-UPDRS assessments have been modified to collection of the full scale at all timepoints. Frequent assessment using the full-scale MDS-UPDRS will allow complete assessment of disease and motor activity and will help reduce variability in this measure. The statistical analysis will continue to include MDS-UPDRS subscores, in order to gain a better understanding of BIIB054 impact on various clinical functions (e.g., motor and nonmotor activities of daily living, motor function).

[redacted]

The new or modified footnotes provide guidance regarding the timing of the clinical function assessments relative to BIIB054 dosing. The extra flexibility relative to BIIB054 dosing will reduce subject burden for visits with extensive assessments.

For subjects who start symptomatic PD medication during the study, guidance is provided regarding the timing of the clinical function assessments relative to the start of PD medication. The 12-hour washout of PD medication prior to visits with an MDS-UPDRS assessment minimizes the contribution of the PD medication to the MDS-UPDRS and [redacted] assessments. At MDS-UPDRS assessment visits, there is no longer a requirement to administer the MDS-UPDRS assessment after the subject receives their PD medication for that day. [redacted]

This change also affects Section 7.2.2, Treatment; and Section 13.1, Clinical Function Assessments.

[redacted]

[redacted]

Section 4.2, Schedule of Activities

Change: The footnotes for the Day 1 column in Table 1 (Cohort A: Infusions 1-3) and Table 3 (Cohort B: Schedule of Assessments) have been modified to clarify the timing of assessments relative to dosing.

Now reads for Table 1:

[2] Assessments can occur on the day before dosing or **predose on** the day of dosing, at Investigator's discretion, except ~~as noted~~ **for the following: ~~(e.g.,~~ randomization,** pregnancy test, vital signs, and ECG~~s~~ must be obtained predose on day of dosing~~)~~. [redacted]

Now reads for Table 3:

[3] All baseline assessments should be performed ~~prior to infusion.~~ **on the day before dosing or predose on the day of dosing, at the Investigator's discretion, except for the following: randomization, pregnancy test, vital signs, and ECG must be obtained predose on the day of dosing.**

[26] **Performed/collected on the day before dosing or pre-infusion on the day of dosing, at the Investigator's discretion,** [redacted]**.**

In addition, footnotes for the pregnancy test, vital signs, and ECGs in Table 1, Table 2, and Table 3 have been modified to state that these assessments must be performed predose on the day of dosing.

Rationale: These changes were made for clarity and to add flexibility for assessment on the day prior to dosing where possible at visits with extensive assessments. Randomization was added as an exception to assessment on the day prior to dosing; randomization must be performed predose on the day of dosing in order to allow key eligibility assessments to be performed on Day 1. Footnote text regarding the pregnancy test, vital signs, and ECGs has been modified to clarify that they must be performed predose on the day of dosing. [redacted].

This change also affects Section 7.2.2, Treatment.

Section 4.2, Schedule of Activities

Change: The title for Table 2 (Cohort A: Infusions 4-13 and Follow-Up) has been revised, and study visits for Table 2 and Table 3 (Cohort B: Schedule of Assessments) have been adjusted, to

reflect the shorter treatment duration. Clarifications have been made for the follow-up clinic visits and visits for subjects terminating early. Table 2 (Cohort A) now applies to Infusions 4-13 (rather than Infusions 4-19). In addition, the following changes have been made to Table 2 (Cohort A) and Table 3 (Cohort B):

- Columns for the previous Week 52, 56, 60, 64, 68, and 72 Visits have been removed (this change is not apparent in track changes).
- The number of Week 48 assessments has been reduced and this visit has been modeled after the Week 40 Visit. For that reason, certain assessments (brain MRI, DaT/SPECT, BIIB54 PK sampling, serum for anti-BIIB054 antibodies, [redacted] have been either removed or moved to the Week 52/ET Visit if not already assessed at that visit.
- The follow-up visits at Week 22, 34, or 46 are now labeled as clinic visits for population PK. Week 58 has been removed from these visit options, and the window for the clinic visits has been expanded from ±2 days to ±3 days.
- The Week 76 Visit is now labeled Week 52/ET. The Safety Telephone Call will occur at Week 56 (rather than Week 80), or 8 weeks after the last dose for subjects who terminate early. The Final/ET Visit has been renamed as the Final Visit and will occur at Week 60 (rather than Week 84), or 12 weeks after the last dose for subjects who terminate early.

Rationale: These changes were made to coordinate with the shorter treatment duration. The changes for the clinic visits were made for completeness, and the visit window changed for consistency with that of the other visits. The changes for the Week 52 Visit, Safety Telephone Call, and Final Visit were made to clarify procedures for subjects who terminate early.

These changes coordinate with changes in Section 7.2, Overall Study Duration and Follow-Up; and Section 7.2.4, Early Termination Visit and Final Visit.

Section 4.2, Schedule of Activities

Change: The text for the footnote regarding the clinic visits at Week 22, 34, or 46 has been modified for Table 2 (Cohort A: Infusions 4-13 and Follow-Up) and Table 3 (Cohort B: Schedule of Assessments).

Now reads for Table 2 (same text for Table 3, footnote 4)**:**

[1] Subjects to complete only 1 ~~out~~ of the ~~4~~ **3** visits**,** at Week 22, 34, **OR** 46~~, OR 58~~. ~~Timing will be assigned via interactive response technology; however, should any subjects have a scheduling conflict on the assigned date, the Investigator may reschedule to 1 of the other 3 timeslots.~~

Rationale: This change was made for consistency with modifications to the study visits. Information on how the visit is assigned is provided in the protocol.

This change also affects Section 7.2.3, Unscheduled Visits and Follow-Up.

Section 4.2, Schedule of Activities

Change: A new footnote was added to the Week 52/ET Visit, the Safety Telephone Call (Week 56), and the Final Visit (Week 60) columns of Table 2 (Cohort A: Infusions 4-13 and Follow-Up) and Table 3 (Cohort B: Schedule of Assessments) to indicate the recommended timing of assessments for subjects who terminate early.

Now reads for Table 2 (same text for Table 3, footnote 5):

[2] **For subjects terminating early, it is recommended that the assessments of the Early Termination Visit be performed within 4 weeks after the last dose of study treatment, a Safety Telephone Call be performed approximately 8 weeks after the last dose, and the Final Visit be performed approximately 12 weeks after the last dose.**

Rationale: This change was made to provide the recommended timing of the Early Termination Visit, Safety Telephone Call, and Final Visit assessments for subjects who terminate early.

This change coordinates with changes in the new Section 7.2.4 (Early Termination Visit and Final Visit), and corresponding changes in Section 10.1 (Discontinuation of Study Treatment) and Section 10.2 (Withdrawal of Subjects from the Study).

Section 4.2, Schedule of Activities

Change: An MDS-UPDRS assessment has been added to the Unscheduled Visit in Table 2 (Cohort A: Infusions 4-13 and Follow-Up) and Table 3 (Cohort B: Schedule of Assessments). The footnote for the Unscheduled Visit has been modified to indicate that additional tests may be performed at the Investigator's discretion.

Now reads for Table 2 (same text for Table 3, footnote 6):

[~~2~~**3**] Unscheduled Visit can occur at any time, as determined by the Investigator, for safety-related issues. **Additional tests may be performed at the Investigator's discretion.**

Rationale: The MDS-UPDRS assessment provides valuable data on clinical function for subjects who are seen at the clinic between scheduled visits. The footnote change allows for flexibility in the additional tests to monitor subject safety depending on the subject's condition.

Section 4.2, Schedule of Activities

Change: Body weight has been added as an assessment at the Week 22, 34, or 46 clinic visit in Table 2 (Cohort A: Infusions 4-13 and Follow-Up) and Table 3 (Cohort B: Schedule of Assessments).

Rationale: Body weight has been added at this visit for safety monitoring and to support PK analyses.

Section 4.2, Schedule of Activities

Change: The header for the AE/Concomitant therapy and procedures row in Table 2 (Cohort A: Infusions 4-13 and Follow-Up) and Table 3 (Cohort B: Schedule of Assessments) has been modified to remove physical activity reporting.

Now reads:

AE/Concomitant therapy and procedures~~/ Physical activity reporting~~

[redacted]

Section 4.2, Schedule of Activities

Change: A row has been added to Table 3 (Cohort B: Schedule of Assessments) for a Safety Telephone Call 1 day and 7 days after infusion, with telephone calls after the first 3 infusions.

Rationale: This change is to clarify that Safety Telephone Calls should be performed at the specified timepoints, to emphasize information provided in footnote 2.

Section 4.2, Schedule of Activities

Change: The frequency of hematology, blood chemistry, and urinalysis assessments has been reduced to approximately every 12 weeks for Cohort B (Week 4, 8, 16, 20, 28, 32, 40, and 44 assessments have been removed).

Rationale: Quarterly assessments are sufficient in Cohort B, given the more extensive monitoring in Cohort A.

Section 5.5, Rationale for Dosing Regimen

Change: The rationale for dosing has been updated to reflect the data supporting fixed dosing.

Now reads:

In this study, ~~S~~subjects will receive an IV infusion of study treatment **(BIIB054 250 mg, 1250 mg, or 3500 mg ~~BIIB054~~, or placebo)** once every 4 weeks, for a total of ~~19~~ **13** doses. The dose levels of BIIB054 ~~selected for this study (3, 15, and 45 mg/kg)~~ were ~~calculated~~ **selected** based on **in vitro data on the affinity of BIIB054 to aggregated α-syn,** nonclinical toxicology data**,** and **BIIB054** safety, tolerability, and PK data from **healthy volunteers in** the Phase 1 ~~SAD~~ human study.

~~The highest planned dose (45 mg/kg) is expected to yield mean steady state area under the concentration-time curve (AUC) from time zero to the time of next dosing (AUC_{tau}) and maximum observed concentration (C_{max}) values approximately 7- to 8-fold lower than those observed at the no-observed-adverse-effect level in the 26-week toxicology study in rats. Based on nonclinical efficacy data and in vitro binding affinity of BIIB054 to aggregated α-syn, 3 mg/kg IV infusion once every 4 weeks was selected as the minimally efficacious dose. Based on~~

~~preliminary serum and cerebrospinal fluid (CSF) data from the first-in-human SAD study, at the 3 mg/kg dose, BIIB054 concentration in CSF and brain interstitial fluid (ISF) at steady state is projected to be above EC_{50} for the majority of subjects. An intermediate dose of 15 mg/kg is expected to maintain a CSF and ISF target at or above EC_{90}, as well as provide adequate separation between doses to elucidate the exposure-response relationship.~~

In vitro studies established that BIIB054 binds to both soluble and aggregated forms of α-syn, with a higher apparent binding affinity for aggregates. The half-maximal effective concentration (EC_{50}) of BIIB054 for aggregated α-syn was estimated at approximately 0.25 nM, and the EC_{90} estimated at approximately 2.1 nM (0.0375 and 0.315 µg/mL, respectively). These EC_{50} and EC_{90} concentrations were used as target values for dose selection. See the BIIB054 Investigator's Brochure for further details.

In the Phase 1, first-in-human study (228HV101), serum and cerebrospinal fluid (CSF) concentrations in healthy volunteers were described using a population PK model. Subsequently, estimated PK parameters as well as between subject variability and residual variability estimates from healthy volunteers were used to simulate 1000 serum and CSF steady-state profiles. Emerging data from the PD cohort suggests that PK is similar between healthy volunteer and PD subjects. To account for weight differences between healthy volunteers and the target Phase 2 population of PD subjects, the Parkinson's Progression Markers Initiative study database was used as a source of weight distribution data in PD patients.

Simulations of CSF profiles in PD subjects were conducted for several dose levels to enable dose selection. CSF and brain interstitial fluid (ISF) concentrations of BIIB054 were assumed to be equal. Given the favorable safety profile of BIIB054 in the previous study 228HV101 and based on PK modeling from that study, a fixed-dose approach is to be implemented in this study.

Simulations based on preliminary serum and CSF data from the first-in-human study 228HV101 indicate that for the 250 mg dose, the BIIB054 concentration in CSF and ISF at steady state is projected to be above EC_{50} for the majority of subjects (Figure 2). The highest dose (3500 mg) was selected to maintain these levels above EC_{90}, to increase the likelihood of demonstrating efficacy for BIIB054. An intermediate dose of 1250 mg is expected to maintain a CSF and ISF level at or above EC_{90}, as well as provide adequate separation between doses to elucidate the exposure-response relationship.

Nonclinical pharmacology data also suggest that the dose of 250 mg is expected to provide minimal efficacy based on studies in the D-Line synuclein transgenic mouse (see the BIIB054 Investigator's Brochure for further details). The estimated efficacious exposure in the mouse was approximately 1317 day*µg/mL. Clearance of BIIB054 in healthy volunteers is on average 0.1248 L/day. Thus, using Dose = Clearance × area under the concentration-time curve (AUC), the projected mean minimum pharmacologically efficacious dose is approximately 164 mg.

Overall, all 3 doses are expected to be safe and well tolerated in humans. The highest planned dose (3500 mg) is expected to yield median steady-state area under the concentration-time curve within a dosing interval (AUC_{tau}) and maximum observed

concentration (C_{max}) values approximately 8- to 9-fold lower than those observed at the no observed adverse effect level in the 26-week toxicology study in rats (Table 4).

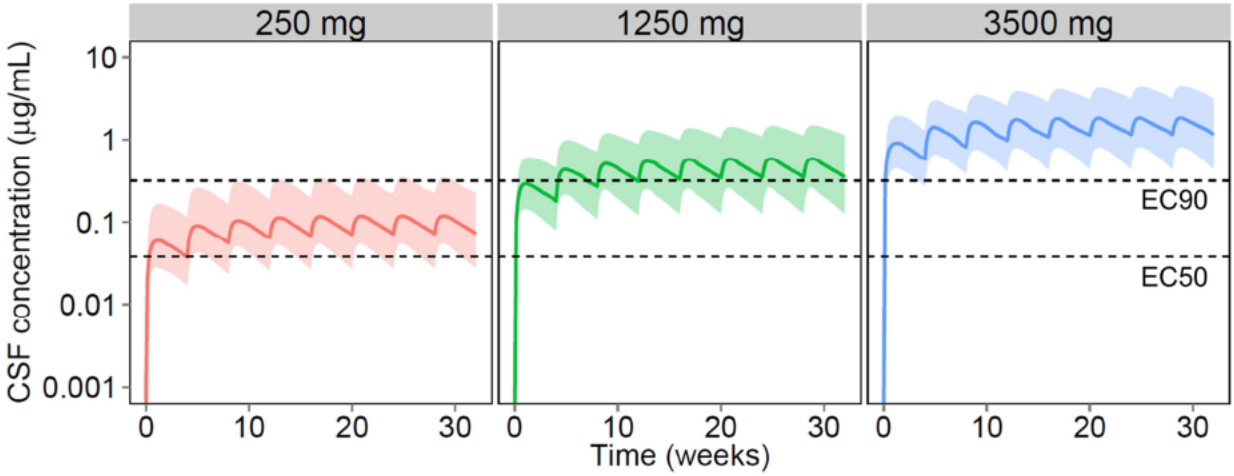
Table 4: Projected Median Steady-State Serum AUC_{tau}, Steady-State C_{max} and Safety Margins for Proposed Phase 2 Doses, Based on Simulations of 1000 PD Subjects

Dose (mg)	Projected parameters		Safety margins[a]	
	AUC_{tau} (h*µg/mL)	C_{max} (µg/mL)	AUC_{tau}	C_{max}
250	42700	175	131	114
1250	214000	882	26	23
3500	612000	2480	9	8

AUC_{tau} = area under the concentration-time curve within a dosing interval; C_{max} = maximum observed concentration

[a] Calculated based on mean $AUC_{0\text{-}168h}$ and C_{max} after the last dose of BIIB054 in the 26-week rat toxicology study. AUC_{tau} at NOAEL = $AUC_{0\text{-}168h}$*4 = 5,580,000 h*µg/mL.

Figure 1: Simulated Cerebrospinal Fluid Concentration – Time Profiles for Proposed Doses in the Phase 2 Study



CSF = cerebrospinal fluid; EC_{50} = half-maximal effective concentration

Solid line = population median; shaded area = 5th-95th percentile

Rationale: The added text describes the data supporting the fixed-dose regimen for study treatment.

[redacted]

[redacted]

[redacted]

Section 7.1, Study Overview

Change: Text was added regarding adjustment of the number of treatment arms, as well as the dose levels and number of subjects per arm, in Cohort B.

Now reads:

Dose level**s, number of treatment arms,** and number of subjects per arm in Cohort B may be adjusted based on the results from Cohort A **and a review by the independent data monitoring committee (IDMC)**. Any changes will be documented in a protocol amendment.

Rationale: The number of treatment arms, the dose levels, and the number of subjects per arm may be adjusted in Cohort B based on IDMC review of data from Cohort A, thereby allowing additional flexibility in the study design for Cohort B.

This change also affects Section 11.2, Modification of Dose and/or Treatment Schedule.

Section 7.1, Study Overview

Change: The text regarding timing of the IDMC meetings was modified.

Now reads:

~~In addition to~~ **The first IDMC** meeting **will occur** after the last subject in Cohort A completes Week 12 assessments, ~~the IDMC will meet regularly, starting~~ **or approximately** 6 months after the first subject has been enrolled **in Cohort A, whichever comes first.**~~and~~ **Regular IDMC meetings will occur approximately** every 3 months ~~there~~after **the first meeting**. Additional information on the IDMC meetings is included in the IDMC charter.

Rationale: This change was made to clarify that the first IDMC meeting could occur at either of 2 timepoints, depending on the enrollment rate.

This change also affects Section 19.2.2, Independent Data Monitoring Committee.

Section 7.2.2, Study Treatment

Change: An observation period of 1 hour has been added after each infusion. The text regarding infusion duration has been modified and text has been added regarding adjustments to infusion duration or administration conditions.

Now reads:

Eligible subjects will report to the study site to receive study treatment~~,~~ administered **by** IV **infusion~~,~~** every 4 ~~-~~weeks for ~~72 weeks~~ **48 weeks,** for a total of ~~19~~ **13** dosing visits, beginning on Day 1. The infusion duration will be **approximately** 1 hour ~~±5 minutes~~. **Subjects will be under observation for at least 1 hour after the end of each infusion. The Investigator or designee must contact the study's Medical Monitor in advance if they would like to adjust the infusion duration or administration conditions based on the subject's ability to tolerate infusion. No changes in dose level are permitted.**

Rationale: The additional monitoring allows further assessment of subject safety following the infusion, as appropriate, given that this is the first multiple-dose clinical study. The infusion duration has been modified for additional flexibility at the study site. Changes in dose level are not allowed, but guidance is provided for adjustment to the infusion duration or other administration conditions.

This change also affects Section 4.2, Schedule of Activities, and Section 11.1, Regimen.

Section 7.2.2.1, Treatment with Parkinson's Disease Medications

Change: A new section has been added to describe timing recommendations for treatment with PD medications.

Now reads:

Medications used to treat the symptoms of PD (hereafter referred to as symptomatic PD medications) will be listed in the Study Reference Manual. Subjects should refrain from using symptomatic PD medications for as long as possible, at least 6 months following Day 1. For subjects who do require PD treatment, see Section 11.3.1.1 for a description of the recommended medications.

The entire MDS-UPDRS assessment (Parts I to IV) should be performed before subjects receive their first dose of symptomatic PD medication, either at a scheduled visit or included in an unscheduled visit.

It is recommended that subjects who plan to start symptomatic PD medication either outside of a visit window or outside of the DaT/SPECT window wait, if possible, until after the next DaT/SPECT to start the medication, provided that a DaT/SPECT visit is planned within 1 month. (As an alternative, if the subject cannot wait to start symptomatic PD medication, the DaT/SPECT window may be expanded so that it extends from -28 days to +7 days.)

Once they have started symptomatic PD medication, subjects should refrain from taking the PD medication for 12 hours prior to study visits at which MDS-UPDRS assessments

will be conducted (see Section 4.2). At those visits, subjects taking PD medication should come to the clinic prior to taking their morning dose, and should refrain from taking their PD medication until after completion of the MDS-UPDRS Part III assessment and [redacted].

See Section 13.1 for a description of the timing of clinical function assessments relative to administration of the symptomatic PD medication.

Rationale: The new text was added to explicitly state the timing recommendations and to describe coordination of the PD medication with key clinical function assessments (DaT/SPECT and MDS-UPDRS).

This change also affects Section 4.2, Schedule of Activities.

Section 7.2.4, Early Termination Visit and Final Visit

Change: A new section was added to indicate the recommended timing of the assessments at this visit for subjects who terminate early. In addition, the former Final/ET Visit was divided into 2 separate visits, an Early Termination Visit and a Final Visit.

Now reads:

7.2.4. Early Termination Visit and Final Visit

For subjects terminating early (i.e., discontinuing both study treatment and study assessments), it is recommended that the assessments of the Early Termination Visit be performed within 4 weeks after the last dose of study treatment. The Safety Telephone Call should be performed approximately 8 weeks after the last dose, and the assessments of the Final Visit should be performed approximately 12 weeks after the last dose.

Rationale: This change was made to allow appropriate monitoring of subjects who terminate early and to clarify the procedures and timing of the assessments for those subjects.

This change also affects Section 7.2.3, Unscheduled Visits and Follow-Up; Section 10.1, Discontinuation of Study Treatment; and Section 10.2, Withdrawal of Subjects From the Study. This change coordinates with changes to Section 4.2, Schedule of Activities, Table 2 (footnote 3) and Table 3 (footnote 6).

Section 7.2.5, Study Stopping Rules

Change: Specific AE criteria for terminating dosing have been added for Cohort A.

Now reads:

Biogen may terminate this study at any time, after informing Investigators. Biogen will notify Investigators if the study is to be placed on hold, completed, or terminated.

For Cohort A:

After evaluation of the safety, tolerability, and PK data by the IDMC, further dosing may be terminated if any of the following is observed:

- **Two similar SAEs or 2 clinically significant AEs, unless clearly unrelated to BIIB054, are reported for subjects on active study treatment.**
- **Three or more similar AEs are reported for subjects on active study treatment (unless these events are clearly unrelated to BIIB054) that are not tolerable, as reported by the subject (e.g., severe dizziness) and/or deemed a medically unacceptable risk by the IDMC and/or Sponsor.**
- **Sponsor requests that dosing be terminated.**

For Cohort B:

~~C~~**c**onditions that may warrant termination of the study include, but are not limited to, the following:

…

Rationale: The new text was added to provide more detailed guidance on terminating dosing for Cohort A, since this is the first group of subjects to receive multiple doses of BIIB054.

Section 8.1, Inclusion Criteria

Change: Inclusion criterion 8 was modified to clarify the criteria for inclusion based on DaT/SPECT results.

Now reads:

8. Screening **DaT/**SPECT ~~with DaTscan~~ results **demonstrating activity in the striatum is either asymmetric, absent in the putamen and/or one or both caudate nuclei,** consistent with ~~dopamine transporter deficit based on high probability of~~ **neurodegenerative** ~~p~~**P**arkinsonism**, as assessed** with qualitative, visual assessment. **DaT/**SPECT ~~results~~ **images** will be ~~sent to~~ **reviewed by** a central reader to confirm eligibility.

Rationale: This criterion was modified for consistency with the approved DaTscan label.

Section 8.2, Exclusion Criteria

Change: Exclusion criterion 1 regarding history of or positive test results for human immunodeficiency virus was modified to provide an exception for local regulations.

Now reads:

1. History of or positive test result at Screening for human immunodeficiency virus **(HIV)**. **The requirement for testing at Screening may be omitted if it is not permitted by local regulations.**

Rationale: This change was made to allow flexibility depending on local regulations and for consistency with updates to the Sponsor's protocol template.

Section 8.2, Exclusion Criteria

Change: Exclusion criterion 2 regarding history of or positive hepatitis B or C results was divided into 2 exclusion criteria and modified for hepatitis B to refer to current hepatitis B infection and immunity to hepatitis B.

Now reads:

2. History of**,** or positive test result at Screening for**,** hepatitis C virus antibody (HCVAb).
3. ~~or hepatitis B virus (defined as positive for hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb]).~~**Current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or hepatitis B core antibody [HBcAb]). Subjects with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive hepatitis B surface antibody immunoglobulin G, and positive HBcAb) or vaccination (defined as positive anti-HBs) are eligible to participate in the study.**

Rationale: This change was made for accuracy and for consistency with updates to the Sponsor's protocol template.

Section 8.2, Exclusion Criteria

Change: Exclusion criterion 9 regarding allergic reaction or hypersensitivity has been modified to focus on study treatments and reagents used during the study.

Now reads:

~~8.~~**9. History of** ~~Clinically significant~~ **severe** allergi~~es~~**c or anaphylactic reactions**, ~~as determined by the Investigator, including~~ **or history of** hypersensitivity to **BIIB054 or any of the inactive ingredients in the drug product (refer to the Investigator's Brochure for information on the clinical formulation) or to** radioligands ~~to be~~ **or iodine** used in the study~~, a broad range of anesthetics, or iodine~~.

Rationale: These changes were made to clarify that the types of allergic or hypersensitivity reactions of concern are those associated with agents administered during the study, including BIIB054 and inactive ingredients in the drug product, as well as the radioligand and iodine. This approach is consistent with that of other Sponsor studies.

Section 8.2, Exclusion Criteria

Change: Exclusion criterion 17 was modified to clarify the criteria for excluding hypertension and orthostatic hypotension.

Now reads:

17. Chronic, uncontrolled hypertension (average of 3 systolic blood pressure [SBP]~~/diastolic blood pressure [DBP]~~ readings at Screening >165 **mmHg~~/~~ or average diastolic blood pressure [DBP]** ≥100 mmHg, **or** any documented SBP~~/DBP~~ reading >180 **mmHg~~/~~ or DBP** ≥100 mmHg within the 3 months before Day 1), or ~~severe~~ orthostatic hypotension **that is clinically significant as determined by the Investigator**.

Rationale: This change was made to specify that the exclusion criterion for hypertension applies to either elevated SBP or elevated DBP, and to clarify the exclusion criterion for orthostatic hypotension.

Section 8.2, Exclusion Criteria

Change: In exclusion criterion 19, the glycated hemoglobin cutoff value for poorly controlled diabetes mellitus has been increased.

Now reads:

19. Poorly controlled diabetes mellitus, as defined by having dosage adjustment of diabetic medication within 3 months before dosing (Day 1) or glycated hemoglobin value ≥~~7~~**8**% at Screening.

Rationale: This change was made to allow greater flexibility in enrolling subjects without affecting overall safety.

Section 8.2, Exclusion Criteria

Change: In exclusion criterion 20, the units for hemoglobin values were changed from mg/dL to g/dL.

Now reads:

20. Screening value for hemoglobin <12 ~~m~~g/dL for men or <11 ~~m~~g/dL for women.

Rationale: This change was made to correct an error in the units for the hemoglobin exclusion criterion.

Section 8.2, Exclusion Criteria

Change: The criteria for excluded liver function test values were clarified in exclusion criterion 21, and the exclusion criterion for impaired renal function was clarified and made into a separate exclusion criterion.

Now reads:

21. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., values of aspartate aminotransferase**,** ~~and~~ **or** alanine aminotransferase**, or total bilirubin** ≥2 times the upper limit of normal)**.**

~~20.~~**22.** ~~and/or I~~indication of impaired renal function at Screening (~~e.g.,~~ estimated glomerular filtration rate ~~[calculated according to the Modification of Diet in Renal Disease equation]~~ <60 mL/min) ~~and corroborating history and physical examination~~.

Rationale: The exclusion for elevated liver function tests was modified to clarify that it would apply to either aspartate aminotransferase or alanine aminotransferase, and to add a criterion for exclusion of elevated total bilirubin levels. The exclusion for impaired renal function was clarified to remove the requirement for a specific calculation and the requirement for corroborating history and physical examination.

Section 8.2, Exclusion Criteria

Change: Additional guidance was added for coagulation parameters in exclusion criterion 23.

Now reads:

~~21.~~**23.** Screening values of coagulation parameters including platelet count, international normalized ratio (INR), prothrombin time (PT), and activated partial thromboplastin time (APTT) that are not **generally** within normal ranges. **Subjects with nonclinically significant and stable out-of-range values may be allowed in the study at the discretion of the Investigator, and only after a consultation with the Medical Monitor.**

Rationale: This change was made to allow greater flexibility in enrolling subjects with nonclinically significant abnormal values for coagulation parameters.

Section 8.2, Exclusion Criteria

Change: The criteria for exclusion of risk factors for bleeding were clarified in exclusion criterion 25.

Now reads:

~~23.~~**25.** Presence of risk for increased or uncontrolled bleeding and/or risk of bleeding that is not managed optimally and could place a subject at an increased risk for ~~intraoperative or postoperative~~ bleeding. These could include, but are not limited to, ~~anatomical factors at or near the LP site (e.g., vascular abnormalities, neoplasms, or other abnormalities) and~~ known underlying disorders of the coagulation cascade, platelet function, or platelet count (e.g., hemophilia, Von Willebrand's disease, liver disease).

Rationale: The criterion was modified to broadly refer to bleeding rather than operative bleeding, since only some subjects will get an LP. A shortened version of the text regarding anatomical factors at or near the LP site was moved to exclusion criterion 26 for subjects enrolled at sites where LPs will be performed, in order to group the LP items together.

Section 8.2, Exclusion Criteria

Change: Text for exclusion criterion 26 for lumbar surgery has been modified to exclude only lumbar surgery that would interfere with or pose a risk to the LP procedure, and to clarify contraindications to having an LP.

Now reads:

~~24.~~**26.** For subjects enrolling at sites where LPs will be performed: **Subjects with the following characteristics will be excluded from participation in LP procedures:**

- **Any** ~~H~~**h**istory of lumbar surgery for any reason (e.g., herniated disc) **that in the opinion of the Investigator would interfere with or pose risks to the LP procedure** ~~or~~
- ~~o~~**O**ther contraindications to having a LP, including but not limited to~~,~~**:**
  - **Low platelet count (below 50,000 cells/µL), or Screening values of INR, PT, or APTT that are not within normal ranges**
  - **Taking any antiplatelet medication (e.g., aspirin >81 mg daily, clopidogrel, or nonsteroidal anti-inflammatory drugs [NSAIDs]) within 7 days prior to the planned LP or anticipated need for antiplatelet medication within 48 hours after an LP**
  - **Taking anticoagulant medication (warfarin, heparinoids, and direct coagulation factor inhibitors, e.g., apixaban, dabigatran, rivaroxaban)**
  - ~~chronic back pain sufficient to interfere with ADL on a regular basis; prominent scoliosis;~~ X-ray, MRI, or myelographic evidence of significant lumbar spine abnormalities **or other anatomical factors at or near the LP site** that might interfere with performance of LP~~; history of chronic tension or migraine headaches; or a refractory or prolonged headache or other complication after a prior LP, including that performed at the Screening Visit that did not resolve with conservative treatment. Note: all clinically significant (in the opinion of the Investigator) post-LP symptoms must have resolved prior to dosing on Day 1.~~

…

~~32. For subjects enrolling at sites where LPs will be performed: Anticipated need, in the opinion of the Investigator, for administration of any antiplatelet or anticoagulant medication (e.g., clopidogrel, aspirin >81 mg daily) for 7 days before or 48 hours after an LP. Aspirin ≤81 mg daily is permitted.~~

Rationale: This change was made because, given the high frequency of degenerative disease of the spine in the elderly population, previous lumbar surgery is common and will not necessarily interfere with the LP.

Exclusion based on low platelet count and current administration of antiplatelet medication allows integration of this exclusion criterion with former exclusion criterion 32; the description

of the washout period for these medications has also been clarified. The exclusion of abnormal coagulation test results at Screening allows coordination with the modifications to exclusion criterion 23 for coagulation test results.

Wording has been added to clarify that subjects taking anticoagulant medications should not receive an LP procedure due to the risk to these subjects when they suspend those medications.

Exclusion due to chronic back pain has been removed due to the likelihood of nonspecific reasons for chronic back pain. Other anatomical factors at or near the LP site were added to the exclusion criterion for X-ray, MRI, or myelographic evidence of significant lumbar spine abnormalities in order to group similar items together (this text was moved from the former exclusion criterion 23). Prominent scoliosis was removed as an explicit item in the list because it would be covered by this more general exclusion criterion for lumbar spine abnormalities or anatomical factors that might interfere with an LP.

History of chronic tension or migraine headaches and refractory or prolonged post-LP headache were removed as exclusion criteria to avoid unnecessary exclusion of subjects with other causes for these events.

This change also affects Section 11.3.1.1, Allowed Concomitant Therapy; and Section 11.3.1.2, Disallowed Concomitant Therapy.

Section 8.2, Exclusion Criteria

Change: The former exclusion criterion 25 regarding PD symptom response to levodopa was removed.

Now reads:

~~25. PD symptoms (except tremor) did not respond to levodopa, if previously treated.~~

Rationale: Because the duration of prior levodopa treatment has been reduced, this exclusion criterion is no longer relevant.

Section 8.2, Exclusion Criteria

Change: The former Exclusion criterion 26 regarding vaccination was removed.

Now reads:

~~26. Administration of any vaccination/booster within 10 days before a dosing visit and for 10 days after a dosing visit.~~

Rationale: This criterion was removed because the corresponding text in Section 11.3.1.1, Allowed Concomitant Therapy, sufficiently describes the restrictions for vaccination.

Section 8.2, Exclusion Criteria

Change: Two new exclusion criteria were added for immunotherapy that targets α-syn.

Now reads:

27. **Participation in any passive immunotherapy study targeting α-syn, other than the BIIB054 Phase 1 study 228HV101. Subjects who participated in Study 228HV101 must meet all entry criteria for the present study, and cannot have received BIIB054 within 24 weeks before Day 1 of Study 228PD201.**
28. **Participation in any active immunotherapy study targeting α-syn.**

Rationale: This change was made because immunotherapy that targets α-syn other than BIIB054 may confound the results of the study.

Section 8.2, Exclusion Criteria

Change: A new exclusion criterion was added for medicines that strongly bind to the dopamine transporter and may interfere with DaT/SPECT.

Now reads:

31. **Use of medicines that strongly bind to the dopamine transporter and may interfere with DaT/SPECT including amphetamine, benztropine, bupropion, cocaine, mazindol, methylphenidate, phentermine, and sertraline within 30 days before the Screening DaT/SPECT.**

Rationale: This change was made because the use of medicines that interfere with DaT/SPECT may confound data contributing to the secondary endpoint of change in striatal binding ratio.

Section 8.2, Exclusion Criteria

Change: A new exclusion criterion was added for use of glucagon-like peptide-1 agonists.

Now reads:

32. **Use of any glucagon-like peptide-1 (GLP-1) agonists (e.g., exenatide, liraglutide, lixisenatide, albiglutide, and dulaglutide) within 90 days before Day 1.**

Rationale: This change was made because these agonists may confound the effects of study treatment on measures of PD progression.

This change also affects Section 11.3.1.2, Disallowed Concomitant Therapy.

Section 8.2, Exclusion Criteria

Change: A new exclusion criterion was added for use of anticoagulant medications.

Now reads:

33. **Use of anticoagulant medications within 90 days before Day 1 (warfarin, heparinoids, and direct coagulation factor inhibitors e.g., apixaban, dabigatran, rivaroxaban).**

Rationale: Anticoagulant medications are disallowed at study entry and during the study (previous text in the prior exclusion criterion 32 allowed these medications with a washout period, but these medications should be avoided completely) in order to prevent risk of bleeding due to multiple blood draws and, as applicable, for LP.

Section 8.2, Exclusion Criteria

Change: The time period required for stable doses of selective serotonin reuptake inhibitors (SSRIs) in exclusion criterion 35 has been shortened from 6 months to 3 months.

Now reads:

~~29.~~**35.** Use of selective serotonin reuptake inhibitors (SSRIs) at doses that have not been stable for at least ~~6~~ **3** months before Day 1 and/or that are not expected to remain stable for the duration of the study.

Rationale: This change was made because stable SSRI doses for 3 months are now considered sufficient for and allow greater flexibility in enrolling subjects.

This change also affects Section 11.3.1.1, Allowed Concomitant Therapy.

Section 8.2, Exclusion Criteria

Change: The exclusion criterion regarding over-the-counter medications, including vitamins and herbal/alternative health preparations, has been clarified.

Now reads:

~~30.~~**36.** ~~Subjects who have used over-the-counter medication, including megadose (intake of 20 to 600 times the recommended daily dose) vitamin therapy within 7 days before Day 1, or herbal/alternative health preparations or procedures within 14 days before Day 1, unless agreed as not clinically relevant by the Investigator and Sponsor. Routine vitamin therapy is allowed.~~ **Vitamins, supplements, herbal/alternative health preparations, and other over-the-counter medications at doses that are not expected to remain stable from Screening through Day 1.**

Rationale: This change was made because vitamins, supplements, herbal/alternative health preparations, and other over-the-counter medications are allowed for this study provided the dose is stable prior to entry and during the study. Routine safety monitoring will detect adverse events associated with these medications.

This change also affects Section 11.3.1.1, Allowed Concomitant Therapy; and Section 11.3.1.2, Disallowed Concomitant Therapy.

Section 9.1, Screening and Enrollment

Change: Text was added to define screen failures and to state what information should be recorded for screen failures.

Now reads:

Subjects must provide informed consent before any screening tests are performed (see Section 17.3). When a subject signs the **main** informed consent form (ICF), that subject is considered to be enrolled in the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. ~~If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log.~~

Individuals who do not meet the criteria for participation in this study (i.e., a screen failure) may not be rescreened, except in the following circumstances:

Subjects with urinary tract infection detected on screening urinalysis may be rescreened once after the infection has been treated and resolved.

Coagulation tests may be repeated once if, in the opinion of the Investigator, values of the initial tests are only slightly out of range. For normal ranges please refer to the Study Reference ~~Guide~~ **Manual**.

Rationale: This change was made to clarify the definition of a screen failure and the procedures for recording information on screen failure subjects.

This change also affects Section 4.2, Schedule of Activities, Table 1, footnote 1 and Table 3, footnote 1.

Section 11.3.1.1, Allowed Concomitant Therapy

Change: Text was added or modified regarding the allowed use of symptomatic PD medications, aspirin, acetaminophen, and NSAIDs, as well as the use of vitamins, supplements, herbal/alternative health preparations, and over-the-counter medications.

Now reads:

- Symptomatic PD treatment ~~(e.g., MAO-B inhibitors, levodopa, and dopaminergic agonists)~~ may be initiated during a subject's participation in the study at the discretion of the Investigator, although subjects should ~~be encouraged to~~ refrain from **taking** symptomatic PD medications for as long as possible~~;~~ **(at least 6 months following Day 1)**. **For subjects who do require PD treatment, it is recommended that treatment start with immediate-release levodopa/carbidopa at a dose of 25/100 mg 3 times a day (or equivalent dosage of levodopa/benserazide in locations where levodopa/carbidopa is not available). The dose of levodopa/carbidopa may be titrated until satisfactory symptomatic relief is achieved. Subjects receiving levodopa/carbidopa should remain on their initially established dose as long as possible. Adjunctive use of catechol-O-methyltransferase (COMT) inhibitors, sustained-release levodopa/carbidopa preparations, dopamine agonists, and MAO-B inhibitors is discouraged, and use of amantadine and anticholinergic medications is prohibited.**

See Section 7.2.2.1 for a description of timing of the start of symptomatic PD medications relative to scheduled study visits. See Section 13.1 for a description of the timing of clinical function assessments relative to administration of PD medication.

- SSRIs are allowed provided that the subject is on a stable dose for at least ~~6~~ **3** months prior to Day 1 and the dose is expected to remain stable for the duration of the study.
- Medications for chronic conditions are allowed provided that the subject is on a stable dose for at least 8 weeks prior to Day 1 and the dose is expected to remain stable for the duration of the study.
- Aspirin ≤81 mg daily ~~(will need a 7-14 day washout before LP)~~.
- ~~Routine vitamin therapy is allowed.~~
- Acetaminophen and ~~nonsteroidal anti-inflammatory drugs~~ **NSAIDs** are allowed if used according to the local label guidelines. **NSAIDs and clopidogrel must be avoided before and after LP procedures, as described in Section 11.3.1.2.**
- Vaccinations with live or attenuated vaccines are allowed during the study; however, administration of any vaccination/booster should not be given within 10 days before a dosing visit and for 10 days after a dosing visit.
- **Routine vitamin therapy is allowed. Subjects should not change administration of vitamins, supplements, herbal/alternative health preparations, or over-the-counter medications unless required for symptom management (e.g., pain) during the study; such medications and preparations must be recorded on the appropriate CRF page.**

Rationale: Text was added to clarify and expand guidance regarding the types and doses for permitted symptomatic PD medications. Low-dose aspirin does not require a washout before LP. Conditions for use of NSAIDs and clopidogrel were clarified by referring to excluded uses in the Disallowed Concomitant Therapy section. Vitamin, supplements, herbal/alternative health preparations, and over-the-counter medications should stay on a stable dose unless changes are needed to manage symptoms.

Section 11.3.1.2, Disallowed Concomitant Therapy

Change: Text was added regarding conditions for use of short-term corticosteroids, anticoagulant medications, and NSAIDs during the study. GLP-1 agonists were added as disallowed medications. Megadose vitamins were removed as disallowed medications. Additional guidance has been provided for subjects continuing prior medications or starting new medications during the study.

Now reads:

~~Subjects should be instructed to contact their Investigators before taking any new medications, including nonprescription drugs and herbal preparations.~~

- Typical or atypical antipsychotics (including clozapine, olanzapine, flunarizine, and aripiprazole), metoclopramide, and alpha methyldopa.
- Tricyclic antidepressants.
- Amantadine or anticholinergic medications for ~~Parkinson's disease~~**PD**.
- Methylphenidate, cinnarizine, tetrabenazine, reserpine, amphetamine, memantine, cholestinerase inhibitors (rivastigmine, donepezil, galantamine, and tacrine) or monoamine oxidase type A inhibitors (pargyline, phenelzine, and tranylcypromine).
- **GLP-1 agonists, e.g., exenatide, liraglutide, lixisenatide, albiglutide, and dulaglutide.**
- Immunosuppressive drugs (including systemic corticosteroids). **Short-term corticosteroids for the treatment of reversible conditions and** ~~**L**~~**l**ocal corticosteroids may be permitted**,** ~~at~~ **following a consultation with the** Sponsor ~~discretion~~.
- Parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis.
- Any investigational drug.
- ~~Megadose (intake of 20 to 600 times the recommended daily dose) vitamin therapy.~~
- For subjects enrolling at sites performing LPs: Any antiplatelet~~ or anticoagulant~~ medication (e.g., aspirin >81 mg daily, clopidogrel, or NSAIDs~~warfarin, and Factor IX and X antagonists~~) is prohibited from 7 days before to 48 hours after each LP procedure.
- **Anticoagulant medications (warfarin, heparinoids, and direct coagulation factor inhibitors, e.g., apixaban, dabigatran, rivaroxaban).**

Subjects should be instructed to continue the medications that they were receiving at enrollment (see Section 11.3.1.1 for allowed concomitant therapy) and to avoid starting any new medications or herbal preparations during the study period, since they may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Subjects should inform the Investigator of any changes in medication.

Rationale: These changes were made for clarity. Use of short-term corticosteroids is permitted for the treatment of reversible conditions at the Sponsor's discretion. No long-term immunosuppression is expected from this type of corticosteroid usage.

Use of NSAIDs is allowed if suspended prior to and after an LP procedure. Use of anticoagulants is prohibited under all conditions, to prevent possible bleeding that could result from blood sample collection or LPs. Use of GLP-1 agonists is not allowed during the study, since they may confound effects of study treatment on measures of PD progression.

Use of megadose vitamins is not specifically disallowed during the study, since there is no anticipated drug-drug interaction with these medications and there should be no significant safety impact for subjects who are already tolerating them at stable doses.

Section 11.3.2, Concomitant Procedures

Change: Text was added indicating that subjects should continue their physical activity regimen without change during the study. Brain surgery for PD was added to the list of disallowed concomitant procedures.

Now reads:

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the subject is screened for the study and the Final ~~Follow-up/Early Termination~~ Visit.

Subjects should be encouraged to continue their prior physical activity regimen without interruption or change throughout the study.

Transcranial magnetic stimulation **and brain surgery for PD** ~~is a~~ **are** disallowed concomitant procedures.

Rationale: These changes were made to provide guidance regarding physical activity and to clarify that the exclusion of brain surgery for PD continues to apply during the study.

Section 11.4, Continuation of Treatment

Change: A new section was added to describe provisions for further access to study treatment.

Now reads:

11.4. Continuation of Treatment

Subjects who complete the Week 48 Visit and do not discontinue study drug treatment may be offered the option to enter an extension study, provided they meet all eligibility criteria for that study.

Rationale: The new text was added because subjects may have access to continued treatment in a long-term extension study.

Section 13.1, Clinical Function Assessments

Change: Text has been added to describe the following clinical function assessments, which will be performed during the study: Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), [redacted]

[redacted]

Section 13.3, Pharmacodynamic Assessments

Change: This section was reorganized to separate imaging and [redacted]. New text was added to describe the imaging assessments and existing text for the imaging assessments was revised. [redacted]

Now reads:

The following tests will be performed to assess the pharmacodynamic properties of BIIB054~~:~~**.**

13.3.1. Imaging Assessments

13.3.1.1. Single-Photon Emission Computed Tomography Scan of the Dopamine Transporter

Biological effects of BIIB054 on brain dopamine neurons and nerve terminals will be assessed ~~via~~ **using DaT**/SPECT imaging ~~using DaTscan~~. **Subjects will undergo DaT/SPECT imaging at Baseline and at specified timepoints. Subjects may also undergo an additional imaging at the time of phenoconversion to motor PD in previously asymptomatic subjects. The DaT/SPECT imaging procedure will be performed using DaTscan, administered IV. Before the DaTscan injection, subjects will be pretreated with stable iodine (10 drops of a saturated solution of potassium iodide) to reduce the uptake of DaTscan by the thyroid. Subjects will be injected with 3 to 5 mCi of DaTscan. Within a 4-hour (±30 minutes) window following the injection, subjects will undergo SPECT imaging on the camera. Subjects will be monitored by study site staff for AEs on the day that a DaT/SPECT scan is obtained. Subjects will also be contacted by telephone within 7 days following the injection/scan.**

[redacted]

[redacted]

Section 14.1, Clinical Safety Assessments

Change: Further detail has been added for the brain MRI assessment.

Now reads:

- Brain MRI safety findings (may include T1, fluid-attenuated inversion recovery, and gradient echo)~~,~~ or other modalities and sequences (to be detailed in the Imaging/MRI Manual). **MRI results will be read by the local radiologist at collection and then sent within 24 hours to a central reader for further evaluation and to confirm eligibility at Screening.**

  Screening MRI results must be reviewed by the local radiologist before the Day 1 LP can be performed. For subsequent LPs, MRI must be performed, but review of the MRI results is not required before these LPs are performed. It is recommended that the MRI be performed prior to the LP for subject comfort.

Rationale: This text was added to describe reading of the brain MRI results and coordination between the brain MRI and the LP procedure. The review of the Screening MRI by the local radiologist is required before the Day 1 LP to ensure that subjects do not have structural lesions or conditions that mimic PD, and to prevent unnecessary LPs.

Section 14.2, Laboratory Safety Assessments

Change: Absolute neutrophil count was removed from the list of hematology assessments. [redacted].

Now reads:

The following laboratory assessments will be performed to evaluate the safety profile of BIIB054:

- Hematology: Complete blood count with differential and platelet count, ~~absolute neutrophil count,~~ INR, PT, and APTT
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium
- Urinalysis: dipstick for blood, protein, and glucose (microscopic examination may also be performed)
- [redacted]

[redacted]

Rationale: Absolute neutrophil count was removed because complete blood count with differential will include derivation of absolute counts for all cell types, thus eliminating the need to explicitly mention absolute neutrophil count.

[redacted]

Section 15.2, Safety Classifications

Change: Where applicable, text regarding collection of data for relationship of adverse events to study treatment has been expanded to include relationship to the LP procedure and relationship to the DaTscan radioligand.

Now reads:

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2.
- The relationship of the event to study treatment**, to the LP procedure, and to the DaTscan (ioflupane I123 Injection) radioligand (hereafter referred to as the radioligand),** as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

Rationale: This change was made because the data recorded for an adverse event (AE) and the analyses performed will include the event's relationship to the LP procedure and relationship to the radioligand, as well as the relationship to the study treatment. The AE relationship to the LP procedure and relationship to the radioligand are both recorded in the CRF (and if applicable in the SAE forms).

Summaries of both the AE relationship to study treatment and relationship to the LP procedure will be presented in the study results and included in the safety analyses for the study. The AE relationship to the radioligand will be reported to the radioligand manufacturer but will not be included in the presentation of the study results or the safety analyses.

This change also affects Section 15.2.2, Relationship of Events to Study Treatment, to the Lumbar Puncture Procedure, and to the Radioligand; Section 15.3.1, Adverse Events; Section 15.3.2, Serious Adverse Events; Section 15.3.3, Immediate Reporting of Serious Adverse Events; Section 15.6.1, The Investigator; and Section 16.1.2.1, Adverse Events.

Section 15.5, Contraception Requirements

Change: Two items were added and additional modifications were made to the list of possible definitions of highly effective contraception for females.

Now reads:

For female~~s~~ **subjects**:

- **Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal methods of contraception associated with the inhibition of ovulation.**
- Established use of oral, injected, or implanted **progestogen-only** hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine **hormone-releasing** system.
- **Bilateral tubal occlusion.**
- Sex with a male partner who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

Rationale: The changes clarify the definition of highly effective contraception for female subjects, consistent with the Sponsor's protocol template.

Section 15.5, Contraception Requirements

Change: A new item was added to the definition of highly effective contraception for males.

Now reads:

For male~~s~~ **subjects**:

- A vasectomy with **subsequent** negative semen analysis ~~at follow up~~.

- **Sex with a woman who uses the methods described for female subjects if she is of childbearing potential.**

Rationale: This change allows for inclusion of male subjects whose partner uses acceptable methods of highly effective contraception, as an alternative to vasectomy.

[redacted]

[redacted]

Section 16.8, Interim Analyses

Change: The timing of the interim analysis has been revised and a statement has been added regarding blinded sample size re-estimation.

Now reads:

An **administrative** interim analysis ~~will~~ **may** be performed for the purpose of planning future studies after ~~all~~ **approximately 60% of the** subjects have completed the Week ~~48~~ **52** ~~r~~**Visit**. No changes will be made for this study based on the interim analysis results. No type I error adjustment will be made. A small unblinded team from Biogen, separate from the study management team, will have access to the unblinded interim analysis results.

A blinded sample size re-estimation may be conducted when approximately 30% of subjects have completed the Week 52 Visit. The study sample size may be increased based on this blinded data review. Details will be provided in the SAP.

Rationale: These changes were made because the blinded sample size re-estimation may allow for an increase in the sample size based on variability in the DaT/SPECT or MDS-UPDRS data, in order to ensure sufficient data for a clear conclusion for these measures.

Section 17.3, Subject Information and Consent

Change: Text has been modified regarding collection of race and ethnicity data, and text has been added to describe the consents [redacted]

Now reads:

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; see Section 17.4.

[redacted]

Rationale: The text about collection of race and ethnicity data was added to accommodate local regulations and ethics committee input, and is consistent with updates to the Sponsor's protocol template. [redacted]

Section 17.4, Subject Data Protection

Change: Details were added to the text justifying collection of subjects' race and ethnicity data.

Now reads:

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 ~~may~~ **will** be used in the analysis of the safety and/or PK profile of the study treatment. **It is unknown whether the effects of the study treatment are influenced by race or ethnicity.** ~~While currently unknown, there may be factors related to race or ethnicity that could influence response to study treatment.~~ **There could be inter-racial and ethnic differences that may impact the reaction or response to the study treatment, leading to a different benefit/risk balance in the various racial or ethnic subgroups. Therefore, information on race and ethnicity can provide relevant and valuable information for a more thorough evaluation of the safety profile, the pharmacokinetics/pharmacodynamics, [redacted], and benefit of the study treatment in the target population.**

Rationale: These changes were made to provide further justification for the collection of race and ethnicity data (where permitted), and are consistent with updates to the Sponsor's protocol template.

This change also affects Section 17.3, Subject Information and Consent.

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.
- Minor typographical errors were corrected throughout the protocol.
- In Section 4.2 (Schedule of Activities), the following changes were made to correct errors, maintain consistency, or emphasize information already provided in the body of the protocol:
  - A cross-reference to Section 14.1 (Clinical Safety Assessments) was added to the vital signs footnotes for Table 1 (Cohort A: Infusions 1-3), footnote 6; Table 2 (Cohort A: Infusions 4-13 and Follow-Up), footnote 7; and Table 3 (Cohort B: Schedule of Assessments), footnote 10, for additional detail about the orthostatic vital sign measurements.
  - Text was added to the C-SSRS footnotes for Table 1 (Cohort A: Infusions 1-3) stating that subjects should be referred for psychiatric evaluation if the Investigator has any concern regarding the C-SSRS results, for consistency with text already present for the C-SSRS footnote in Table 2 (Cohort A: Infusions 4-13 and Follow-Up) and Table 3 (Cohort B: Schedule of Assessments).
  - Footnotes in Table 1 (Cohort A: Infusions 1-3), starting with the former footnote 19, were renumbered to correct an error in use of footnote numbers.
  - In Table 3 (Cohort B: Schedule of Assessments), an incorrect footnote (the former footnote 5) for alternate visit timing was removed from the drug screen assessment at Day 1 Baseline/Infusion 1.
- Minor clarifications were made throughout the protocol, including the following:
  - In Section 5.1 (Overview of Parkinson's Disease), the prevalence data for PD was updated to reflect the global population.
  - In Section 5.3.2 (Clinical Experience), the summary of the first-in-human Phase 1 Study 228HV101 has been updated, including an update to reflect current enrollment data.
  - In Section 6.1 (Primary Objective and Endpoint), the brain MRI endpoint was moved to the list of clinical laboratory items.
  - In Section 6.3 (Additional Objectives and Endpoints), the endpoint for time to start of medications for PD symptoms was moved to clarify that it is not a change in health-related quality of life or a mental health endpoint.

- In Section 7.2.3 (Unscheduled Visits and Follow-Up), text was modified to clarify that unscheduled clinic visits may occur at any time, consistent with Section 4.2, Schedule of Activities (Table 2, footnote 3 and Table 3, footnote 6).
- Text was modified in Section 7.2.3.1 (Cohort A) and Section 7.2.3.2 (Cohort B) to clarify that subjects from each cohort will be randomly assigned to 1 of the 3 visits at Week 22, 34, or 46 at the time of treatment assignment.
- Minor modifications were made for clarity in Section 8.1, inclusion criterion 4 (for age) and inclusion criterion 6 (for nonsmoking status), and in Section 8.2, exclusion criterion 7 (for Screening MRI), exclusion criterion 38 (for MRI contraindications), and exclusion criterion 44 (for previous registration in this study).
- In Section 11.1 (Regimen) and Section 12 (Study Treatment Management), a phrase was added to clarify that study treatment is administered by study site staff.
- [redacted]
- In Section 14.1 (Clinical Safety Assessments), modifications were made to clarify the time window between repeated vital sign assessments and the time window for resting in a supine position for the ECG assessments, for consistency with Schedule of Activities Tables 1, 2, and 3 in Section 4.2.
- In Section 15.4.3 (Medical Emergency), text regarding notification of a medical emergency has been modified to indicate that the Investigator or designee should inform the Medical Monitor of the event as soon as feasible.
- In Section 15.5 (Contraception Requirements), references to "effective contraception" were modified to "highly effective contraception" for consistency with inclusion criterion 9.
- Section 16 (Statistical Methods and Determination of Sample Size) was reorganized so that the order of the analyses follows the order of the objectives and endpoints in Section 6 (Study Objectives and Endpoints).
- In Section 16.1.2.1 (Adverse Events), the definition of treatment-emergent AEs was modified to clarify that this category includes AEs that were present prior to the first dose and subsequently worsen.
- In Section 16.5.1 (Analysis Population) and Section 16.5.2 (Methods of Analysis), the clinical function population was renamed as the per protocol population, for consistency with other Sponsor studies.
- In Section 17.3 (Subject Information and Consent), parents were removed from the list of legally authorized representatives, since the subjects are adults

>40 years old. In addition, since either the subject or their legally authorized representative can give consent, the text was clarified to allow for a copy of the consent forms to be given to the subject or the subject's legally authorized representative.

- In Section 19.1.4 (Central Laboratories for Laboratory Assessments), changes were made to clarify which test samples are collected or analyzed by the central laboratory and which tests are analyzed by the local laboratory.
- In Section 19.5 (Retention of Study Data), changes were made to clarify that regional and national laws and regulations will be followed in addition to local laws and regulations.

- Updates were made throughout the protocol for consistency with updates to the Sponsor's protocol template, as follows:
  - Section 9.2 (Randomization and Registration of Subjects): A statement was added to clarify that the subject identification number will be used on study-related documents.
  - Section 9.3 (Blinding Procedures): Information was added to describe conditions under which the randomization code would be provided to Investigators after completion of the study.
  - Section 10 (Discontinuation of Study Treatment and/or Withdrawal of Subjects from the Study): A modification was made to clarify that the primary reason for discontinuation or withdrawal must be recorded in the case report form (CRF).
  - Section 12.1 (BIIB054): Modifications were made to the text to clarify that drug handling and storage are also in accordance with Good Manufacturing Practice, and to clarify the label content.
  - [redacted]
  - Section 15 (Safety Definitions, Recording, Reporting, and Responsibilities): References to [redacted] Lifecycle Safety or designee have been replaced with Biogen.
  - Section 15.1.1 (Adverse Event): The definition of AEs for abnormal laboratory values was clarified and expanded to include abnormal vital sign and ECG results.
  - Section 15.1.2 (Serious Adverse Event): The definition of medically important events was clarified.
  - Section 15.2.3 (Severity of Events): The definitions of mild, moderate, severe, and life-threatening AEs were added.
  - Section 15.3.1 (Adverse Events): A sentence was added to explicitly specify that the Investigator will assess the subject for AEs at each visit, and record any new or updated AE data on the CRF. Text was also added to indicate that ongoing

AEs will be monitored until the event resolves, stabilizes, or returns to baseline status, and that the outcome will be recorded on the CRF.

- Section 15.4.1 (Pregnancy): The text regarding recording of a pregnancy was clarified.
- Section 15.6.1 (The Investigator): The text was modified to clarify and explicitly state the Investigator's responsibilities for recording AE and AE follow-up information.
- Section 17 (Ethical Requirements): The text was modified to clarify and explicitly state that the Investigator is responsible for endorsing data on completed CRFs prior to any interim or database lock. The Investigator is also responsible for supervising delegates and implementing procedures to ensure integrity of study conduct and data.
- Section 18.2 (Quality Control and Quality Assurance) and Section 18.3 (Monitoring of the Study): These sections have been updated to clarify the relevant responsibilities and processes for these tasks.

APPENDIX A. SCHEDULE OF ACTIVITIES TABLES

The following tables show the changes in the Schedule of Activities tables from Protocol V1 to V2.

For ease of readability, changes to the tables are shown using images of tracked changes from the amended protocol rather than with bolding and strikethrough.

Table 1: Cohort A: Infusions 1–3

Tests and assessments	Screening ≤35 days before Day 1[1]	Infusions 1-3 Day 1/Baseline, Day 29 (±1 day), & Day 57 (±1 day)						Clinic Visits				Day 43 (Safety Telephone Call)
								Day 2, 30, 58	Day 4, 60	Day 8, 36, 64	Day 15, 71	
		Pre-infusion[2]	0m	Time ~~(minutes [m], hours [h], or days [d])~~ after End of Last Infusion								
				≤10m	1h ±15m	2h ±15m	4h ±30m	24h ±2h	72h -2h/+1d	168h ±24h	336h ±24h	336h ±24h
Informed consent	X											
[redacted]												
Verification of eligibility		X[3]										
Medical history	X	X[3]										
Body weight	X	X										
Height	X											
Physical/neurological examination[4]	X	X[3]						~~X~~	~~X~~	~~X~~	~~X~~	
12-lead ~~paper~~ ECG[4,5]	X	X			X			X				
Vital signs[5,6]	X	X			X	X	X	X	X	X	X	
HbA_{1c}	X											
Pregnancy test[6,7]	Serum	X										
FSH test[7,8]	X											
Coagulation panel including platelet count	X											
Hematology, blood chemistry, urinalysis	X	X						X		X		
HBsAg, HBcAb, HCVAb, HIV	X											
Drug screen	X	X[3]										

Tests and assessments	Screening ≤35 days before Day 1[1]	Infusions 1-3 Day 1/Baseline, Day 29 (±1 day), & Day 57 (±1 day)						Clinic Visits				Day 43 (Safety Telephone Call)
								Day 2, 30, 58	Day 4, 60	Day 8, 36, 64	Day 15, 71	
		Pre-infusion[2]	0m	Time ~~(minutes [m], hours [h], or days [d])~~ after End of Last Infusion								
				≤10m	1h ±15m	2h ±15m	4h ±30m	24h ±2h	72h -2h/+1d	168h ±24h	336h ±24h	336h ±24h
[redacted]												
Brain MRI[9,12]	X[10]	~~X~~[11]										
DaT SPECT ~~with DaTscan~~[9,12]	X[10]											
Randomization		X[3]										
Study treatment infusion[13]			X									
BIIB054 PK sampling		X[13,14]		X	X[13,15]	X[13,15]	X[13,15]	X[14,16]	X	X[15,17]	X	
Serum for anti-BIIB054 antibodies		X									X[14,18]	
[redacted]												
MDS-UPDRS (full scale), includes Modified Hoehn and Yahr Scale[19,20]	X	X								X	X	
[redacted]												

Tests and assessments	Screening ≤35 days before Day 1[1]	Infusions 1-3 Day 1/Baseline, Day 29 (±1 day), & Day 57 (±1 day)						Clinic Visits				Day 43 (Safety Telephone Call)
		Pre-infusion[2]	0m	Time ~~(minutes [m], hours [h], or days [d])~~ after End of Last Infusion				Day 2, 30, 58	Day 4, 60	Day 8, 36, 64	Day 15, 71	
				≤10m	1h ±15m	2h ±15m	4h ±30m	24h ±2h	72h -2h/+1d	168h ±24h	336h ±24h	336h ±24h
[redacted]												
C-SSRS~~[21][22]~~		X						X	X	X	X	
AE/Concomitant therapy and procedures reporting		ongoing										
SAE reporting	ongoing											

[redacted] AE = adverse event; [redacted] C-SSRS = Columbia Suicide Severity Rating Scale; d = day(s); DaT = dopamine transporter; [redacted] ECG = electrocardiogram; [redacted] FSH = follicle stimulating hormone; h = hour(s); HbA_{1c} = glycated hemoglobin; HBcAb = ~~H~~hepatitis B core antibody; HBsAg = ~~H~~hepatitis B surface antigen; HCVAb = ~~H~~hepatitis C virus antibody; HIV = human immunodeficiency virus; m = minute(s); MDS-UPDRS = Movement Disorder Society -Sponsored Revision of the Unified Parkinson's Disease Rating Scale; [redacted] MRI = magnetic resonance imaging; [redacted] PK = pharmacokinetic(s); [redacted] SAE = serious adverse event; [redacted] SPECT = single-photon emission computed tomography.

1 Screening assessments can be performed over ~2 days (need not be consecutive) to minimize subject burden. Subjects may be rescreened or screening tests repeated in certain circumstances (see Section 9.1).

2 Assessments can occur on the day before dosing or predose on the day of dosing, at Investigator's discretion, except ~~as noted~~ for the following: (e.g., randomization, pregnancy test, vital signs, and ECG~~s~~ must be obtained predose on day of dosing). [redacted]

3 Performed on Day 1 only.

4 A full physical and neurological examination will be performed at the specified timepoints. At all other visits, a targeted physical and/or neurological examination will be performed if the Investigator determines it is warranted by adverse events.

~~4~~5 ~~Triplicate~~ A 12-lead ~~(paper)~~ ECG~~s~~ will be obtained at each specified timepoint. Each must be performed after the subject has been resting in a supine position for at least 10 minutes. The ECGs will be read by the Investigator at collection. Predose readings **must be obtained predose on the day of dosing**.

~~5~~6 Vital signs will include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, body temperature, and respiratory rate and will be measured after the subject has been resting in a supine position for at least 10 minutes. Three separate SBP/DBP readings at least 15 minutes apart will be made at Screening to determine eligibility. Predose readings **must be obtained predose on the day of dosing**. Orthostatic vital sign measurements will also be obtained whenever blood pressure is read, as described in Section 14.1.

~~6~~7 Required for women of childbearing potential. Predose samples **must be collected predose on the day of dosing**. Serum will be collected at Screening; urine will be collected at all other visits.

~~7~~8 To confirm postmenopausal status in postmenopausal female subjects.

9 Whole blood samples for [redacted] serum, urine, [redacted] and other analyses are required samples (under the main consent).

10 Performed on Day 1 and Day 29 only.

[redacted]

[9][12] The ~~DaTscan and~~ MRI results will be read by the ~~Investigator~~ local radiologist at collection. Both MRI and DaT/SPECT results will be ~~and then~~ sent within 24 hours to a central reader for further evaluation and to confirm eligibility at Screening.

~~[10] Screening imaging assessments should be completed after all other eligibility criteria have been met, and before Day -7, to allow adequate time for evaluation of the results.~~

~~[11] Performed on Days 29 and 57 (±2 days) only.~~[13] Subjects will be under observation for at least 1 hour after the end of each infusion.

[~~12~~][14] Samples to be collected within 1 hour pre-infusion.

[~~13~~][15] Collected on Days 1 and 57 only.

[~~14~~][16] Collected on Days 2 and 58 only.

[~~15~~][17] Collected on Days 8 and 64 only.

[~~16~~][18] Collected on Day 15 only.

[redacted]

[20] Subjects who have started symptomatic Parkinson's disease (PD) medication during the study (not applicable to the Screening or Day 1 Visit), should refrain from taking the PD medication for 12 hours prior to MDS-UPDRS visits. MDS-UPDRS Part III [redacted] will be administered before subjects take the PD medication.

[redacted]

[~~17~~][21] The "Since Last Visit" version of the C-SSRS will be administered at all clinic visits following the Day 1/~~b~~Baseline assessment. If the Investigator has any concern regarding the completed C-SSRS, the subject should be referred to psychiatric evaluation based on local standards of care.

Table 2: Cohort A: Infusions 4–13 and Follow-Up

Tests and assessments	Infusions 4-~~19~~13, Week (±3 d)										~~Follow-up~~ Clinic Visits, Week (±~~2~~3 d)		~~80~~ (Safety Telephone Call) Week 56 (±2 d)/ Last Dose +8 wk[33]	Unscheduled Visit[23]	Final/ ~~ET~~ Visit Week 60~~Week 84~~ / (±3 d)/ Last Dose +12 wk[32]
	12	16	20	24	28	32	36	40	44	48	22, 34, or 46~~, or 58~~[1] (for PopPK)	~~76~~52/ET (Last Dose +~~4~~ wk)[2]			
Physical/neurological examination[24, 5]	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X		X	X
Body weight[24]	X	X	X	X	X	X	X	X	X	X	X				X
12-lead ~~paper~~ ECG[24,42]	X			X			X			X					
Vital signs[24,57]	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Pregnancy test[24,68]	X	X	X	X	X	X	X	X	X	X		X			Serum
Coagulation panel including platelet count[29]			X						X						
Hematology, blood chemistry, urinalysis[24]	X	X	X	X	X	X	X	X	X	X		X		X	X
[redacted]															
Brain MRI[11]	~~X~~[9]			X[9]						~~X~~[9]		X[9]			X[10~~12~~]
~~DaT~~ SPECT ~~with DaTscan~~[11]				X[9]						~~X~~[9]		X[9]			X[10~~12~~]
Study treatment infusion[13]	X	X	X	X	X	X	X	X	X	X					
BIIB054 PK sampling	X[~~11~~15]	X[~~11~~14]		X[~~11~~13]			X[~~11~~15]			~~X~~[11]	X	X			X
Serum for anti-BIIB054 antibodies[24]				X			X			~~X~~		X			X
[redacted]															
MDS-UPDRS (full scale), includes Modified Hoehn and Yahr Scale[3,44, 16]		X		X[~~11~~17]		X		X		X[~~11~~17]		X[~~11~~18]		X	X[18]
[redacted]															

Tests and assessments	Infusions 4-~~19~~13, Week (±3 d)										~~Follow-up~~ Clinic Visits, Week (±~~2~~3 d)		~~80~~ (Safety Telephone Call) Week 56 (±2 d)/ Last Dose +8 wk[33]	Unscheduled Visit[23]	Final~~/ ET~~ Visit Week 60~~Week 84~~ / (±3 d)/ Last Dose +12 wk[32]
	12	16	20	24	28	32	36	40	44	48	22, 34, or 46~~, or 58~~[1] (for PopPK)	~~76~~52/ET (Last Dose +~~4~~ wk)[2]			
[redacted]															
C-SSRS[34,~~14~~19]	X	X	X	X	X	X	X	X	X	X	X	X		X	X
AE/~~-~~Concomitant therapy and procedures~~/ Physical activity reporting~~	ongoing														
SAE reporting	ongoing														

[redacted] AE = adverse event; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; d = day(s); DaT = dopamine transporter; ECG = electrocardiogram; [redacted] ET = early termination; MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; [redacted] MRI = magnetic resonance imaging; [redacted] PK = pharmacokinetic; PopPK = population PK; [redacted] SAE = serious adverse event; [redacted] SPECT = single-photon emission computed tomography; wk = week(s).

1 Subjects to complete only 1 ~~out~~ of the ~~4~~ 3 visits, at Week 22, 34, OR 46~~, OR 58~~. ~~Timing will be assigned via interactive response technology; however, should any subjects have a scheduling conflict on the assigned date, the Investigator may reschedule to 1 of the other 3 timeslots.~~

2 For subjects terminating early, it is recommended that the assessments of the Early Termination Visit be performed within 4 weeks after the last dose of study treatment, a Safety Telephone Call be performed approximately 8 weeks after the last dose, and the Final Visit be performed approximately 12 weeks after the last dose.

~~2~~3 Unscheduled Visit can occur at any time, as determined by the Investigator, for safety-related issues. Additional tests may be performed at the Investigator's discretion.

~~3~~4 Performed/collected pre-infusion on dosing days.

5 A full physical and neurological examination will be performed at the specified timepoints. At all other visits, a targeted physical and/or neurological examination will be performed if the Investigator determines it is warranted by adverse events.

~~4~~6 ~~Triplicate~~ A 12-lead ~~(paper)~~ ECG~~s~~ will be obtained at each specified timepoint. Each must be performed after the subject has been resting in a supine position for at least 10 minutes. The ECGs will be read by the Investigator at collection. Predose readings **must be obtained predose on the day of dosing.**

~~5~~7 Vital signs will include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, body temperature, and respiratory rate and will be measured after the subject has been resting in a supine position for at least 10 minutes. Predose readings **must be obtained predose on the day of dosing.** Orthostatic vital sign measurements will also be obtained whenever blood pressure is read, as described in Section 14.1.

[redacted]

[8] Required for women of childbearing potential. Predose samples must be collected predose on the day of dosing. Serum will be collected at the Final ~~Early Termination~~ Visit. Urine will be collected at all other visits.

[redacted]

[9] [redacted] Results from the prior [redacted] samples and results of the most recent coagulation tests (from a study visit within 35 days) including platelet count must be reviewed by the Investigator before each lumbar puncture can be performed.

[10] [redacted] Whole blood samples for [redacted] serum, urine, [redacted] and other analyses are required samples (under the main consent).

[11] The MRI and DaT/SPECT ~~scan~~ assessment windows ~~is~~ are ±7 days. The MRI results will be read by the local radiologist at collection. Both MRI and DaT/SPECT results will be sent within 24 hours to a central reader for further evaluation. See Section 7.2.2.1 for further details on subjects who start symptomatic PD medication during this study.

[10][12] Performed only if the last assessment occurred >12 weeks before the Final ~~Follow-up/Early Termination~~ Visit.

[13] Subjects will be under observation for at least 1 hour after the end of each infusion.

[11][14] Samples to be collected within 1 hour pre-infusion and within 1 hour following the end of infusion.

[12][15] Samples to be collected within 1 hour pre-infusion.

[redacted]

~~[14] Includes Modified Hoehn and Yahr Scale. Full scale to be administered at Week 24, Week 48, and Week 76; Parts II and III only to be administered at all other visits.~~

[15][16] ~~If the s~~Subjects ~~is receiving~~who have started symptomatic PD medication ~~to treat PD symptoms,~~ during the study should refrain from taking the PD medication for 12 hours prior to MDS-UPDRS visits. MDS-UPDRS Part III [redacted] will be administered ~~in the off condition (~~before the subjects takes the PD medication~~). AND in the on condition (at least 1 hour after the subject takes the medication);~~ [redacted]

[17] Performed/collected pre-infusion for dosing visits. [redacted] At the Investigator's discretion, these assessments may be administered in the clinic on the day prior to dosing.

[redacted]

[16][18] The "Since Last Visit" version of the C-SSRS will be administered. If the Investigator has any concern regarding the completed C-SSRS~~s~~, the subject should be referred to psychiatric evaluation based on local standards of care.

Table 3: Cohort B: Schedule of Assessments

Tests and assessments	Screening ≤35 d ~~b~~Before Day 1[1]	Day 1[2,3] Baseline/ Infusion 1	Infusions 2-~~19~~13, ~~at~~ Week (±3 d)												Clinic Visits, Week (±~~2~~3 d)		Safety Telephone Call Week 56 ~~Week 80~~ (±2 d)~~/~~ Last Dose +8 wk[5]	Unsched Visit[25]	Final~~/ ET~~ Visit Week 60 ~~Week 84~~ (±3 d)/Last Dose +12 wk[5]
			4[2]	8[2]	12	16	20	24	28	32	36	40	44	48	22, 34, or 46, ~~or 58~~[4] (for PopPK)	~~76~~ 52/ ET (Last Dose + 4- wk)[5]			
Informed consent	X																		
[redacted]																			
Verification of eligibility		X																	
Medical history	X	X																	
Body weight[6,7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Height	X																		
Physical/neurological examination[6,8]	X	X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X		X	X
12-lead ~~paper~~ ECG[6,7,~~9~~]	X	X			X			X			X			X					
Vital signs[6,7,~~8~~10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
HbA_{1c}	X																		
Pregnancy test[6,~~8~~11]	Serum	X	X	X	X	X	X	X	X	X	X	X	X	X		X			Serum
FSH test[~~10~~12]	X																		
Coagulation panel including platelet count	X						X[13,14]						X[~~11~~13, 14]						

Tests and assessments	Screening ≤35 d ~~b~~Before Day 1[1]	Day 1[2,3] Baseline/ Infusion 1	Infusions 2-~~19~~13, ~~at~~ Week (±3 d)												Clinic Visits, Week (±~~2~~3 d)		Safety Telephone Call Week 56 ~~Week 80~~ (±2 d)~~/~~ Last Dose +8 wk[5]	Unsched Visit[52]	Final~~/ ET~~ Visit Week 60 ~~Week 84~~ (±3 d)/Last Dose +12 wk[5]
			4[2]	8[2]	12	16	20	24	28	32	36	40	44	48	22, 34, or 46, ~~or 58~~[4] (for PopPK)	~~76~~ 52/ ET (Last Dose + 4 wk)[5]			
Hematology, blood chemistry, urinalysis[6,7]	X	X	~~X~~	~~X~~	X	~~X~~	~~X~~	X	~~X~~	~~X~~	X	~~X~~	~~X~~	X		X		X	X
HBsAg, HBcAb, HCVAb, HIV	X																		
Drug screen	X	X[5]																	
[redacted]																			
Brain MRI[13,17]	X[14,18]				~~X~~[15]			X[15]						~~X~~[15]		X[15]			X[14,19]
DaT/SPECT ~~with DaTscan~~[13,17]	X[14,18]							X[15]						~~X~~[15]		X[15]			X[14,19]
Randomization		X[6]																	
Study treatment infusion[20]		X	X	X	X	X	X	X	X	X	X	X	X	X					
Safety Telephone Call 1 d and 7 d after infusion[2]		X	X	X															
BIIB054 PK sampling[17,21]		X	X	X	X	X		X			X			~~X~~	X	X			X
Serum for anti-BIIB054 antibodies[6,7]		X	X					X			X			~~X~~		X			X
[redacted]																			

Tests and assessments	Screening ≤35 d ~~b~~Before Day 1[1]	Day 1[2,3] Baseline/ Infusion 1	Infusions 2-~~19~~13, ~~at~~ Week (±3 d)											Clinic Visits, Week (±~~2~~3 d)		Safety Telephone Call Week 56 ~~Week 80~~ (±2 d)-/ Last Dose +8 wk[5]	Unsched Visit[25]	Final/ ~~ET~~ Visit Week 60 ~~Week 84~~ (±3 d)/Last Dose +12 wk[5]
			4[2]	8[2]	12	16	20	24	28	32	36	40	44	48	22, 34, or 46, ~~or 58~~[4] (for PopPK)	~~76~~ 52/ ET (Last Dose + 4 wk)[5]			
MDS-UPDRS (full scale), includes Modified Hoehn and Yahr Scale[6,22,7, 25]	X	X[26]		X		X		X[23,26]		X		X		X[23,26]		X[23]		X	X
[redacted]																			
C-SSRS[67,24,28]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
AE/ Concomitant therapy and procedures~~/ Physical activity reporting~~		ongoing																	
SAE reporting		ongoing																	

[redacted] AE = adverse event; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; d = day(s); DaT = dopamine transporter; [redacted] ECG = electrocardiogram; [redacted]

[redacted] ET = early termination; FSH = follicle stimulating hormone; HbA_{1c} = glycated hemoglobin; HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; HCVAb = Hepatitis C virus antibody; HIV = human immunodeficiency virus; MDS-UPDRS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; [redacted] MRI = magnetic resonance imaging; [redacted] PK = pharmacokinetic; PopPK = population PK; [redacted] SAE = serious adverse event; [redacted] SPECT = single-photon emission computed tomography; Unsch = unscheduled.

1 Screening assessments can be performed over ~2 days (need not be consecutive) to minimize subject burden. Subjects may be rescreened or screening tests repeated in certain circumstances (see Section 9.1).

2 Subjects will receive 6 ~~s~~Safety ~~follow-up t~~Telephone ~~c~~Calls to ask about AEs, SAEs, and concomitant medications~~,~~ approximately 1 day (24 hours) and 7 days (168 hours) after each of the first 3 infusions: Days 2 and 8 (follow-up after ~~1st~~ first infusion); Days 30 and 36 (follow-up after ~~2nd~~ second infusion); and Days 58 and 64 (follow-up after ~~3rd~~ third infusion).

3 All baseline assessments should be performed ~~prior to infusion.~~ on the day before dosing or predose on the day of dosing, at the Investigator's discretion, except for the following: randomization, pregnancy test, vital signs, and ECG must be obtained predose on the day of dosing.

4 Subjects to complete only 1 ~~out~~ of the ~~4~~ 3 visits at Week 22, 34, OR 46~~, OR 58~~. ~~Timing will be assigned via interactive response technology; however, should any subjects have a scheduling conflict on the assigned date, the Investigator may reschedule to 1 of the other 3 timeslots.~~

5 For subjects terminating early, it is recommended that the assessments of the Early Termination Visit be performed within 4 weeks after the last dose of study treatment, a Safety Telephone Call be performed approximately 8 weeks after the last dose, and the Final Visit be performed approximately 12 weeks after the last dose.

~~5~~6 Unscheduled Visit can occur at any time, as determined by the Investigator, for safety-related issues. Additional tests may be performed at the Investigator's discretion.

~~6~~7 Performed/collected pre-infusion on dosing days.

8 A full physical and neurological examination will be performed at the specified timepoints. At all other visits, a targeted physical and/or neurological examination will be performed if the Investigator determines it is warranted by adverse events.

~~7~~9 ~~Triplicate~~ A 12-lead ~~(paper)~~ ECG~~s~~ will be obtained at each specified timepoint. Each must be performed after the subject has been resting in a supine position for at least 10 minutes. The ECGs will be read by the Investigator at collection. Predose readings **must be obtained predose on the day of dosing.**

~~8~~10 Vital signs will include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, body temperature, and respiratory rate and will be measured after the subject has been resting in a supine position for at least 10 minutes. Three separate SBP/DBP readings at least 15 minutes apart will be made at Screening to determine eligibility. Predose readings **must be obtained predose on the day of dosing.** Orthostatic vital sign measurements will also be obtained whenever blood pressure is read, as described in Section 14.1.

~~9~~11 Required for women of childbearing potential. Predose samples **must be collected predose on the day of dosing.** Serum will be collected at the Screening and Final ~~Early Termination~~ Visits. Urine will be collected at all other visits.

~~10~~12 To confirm postmenopausal status in postmenopausal female subjects.

[redacted]

~~11~~14 [redacted] Results from the prior [redacted] samples and results of the most recent coagulation tests (from a study visit within 35 days) including platelet count must be reviewed by the Investigator before each post-Day 1 lumbar puncture can be performed.

~~12~~15 Whole blood samples for RNA analysis and plasma, serum, urine, [redacted] and other analyses are required samples (under the main consent).

~~13~~16 [redacted] The [redacted] whole blood sample [redacted] (under the main consent) and may be obtained at any **one** timepoint during the study, after all eligibility criteria have been met ~~and subjects have signed the Genetic Informed Consent form~~.

~~13~~17 The MRI and DaT/SPECT assessment windows are ±7 days. The ~~DaTscan and~~ MRI results will be read by the ~~Investigator~~ local radiologist at collection. Both MRI and DaT/SPECT results will be ~~and then~~ sent within 24 hours to a central reader for further evaluation and to confirm eligibility at Screening. See Section 7.2.2.1 for further details for subjects who start symptomatic PD medication during this study.

~~14~~18 Screening imaging assessments should be completed after all other eligibility criteria have been met, and before Day -7, to allow adequate time for evaluation of the results.

~~15~~ ~~The MRI/DaTscan assessment window is ±7 days.~~

~~16~~[18] Performed only if the last assessment occurred >12 weeks before the Final ~~Early Termination~~ Visit.
[20] Subjects will be under observation for at least 1 hour after the end of each infusion.

~~17~~[21] Samples to be collected within 1 hour pre-infusion and within 1 hour following the end of infusion on dosing days.
~~18~~[22] Samples to be collected within 1 hour pre-infusion on dosing days.

[redacted]

~~19~~ Includes Modified Hoehn and Yahr Scale. Full scale to be administered at Screening, Baseline, Week 24, Week 48, and Week 76; Parts II and III only to be administered at all other visits.

~~20~~[23] ~~If the s~~Subjects ~~is receiving~~who have started symptomatic Parkinson's disease (PD) medication ~~to treat PD symptoms~~during this study (not applicable to the Screening or Day 1 Visit), ~~,~~ should refrain from taking the PD medication for 12 hours prior to MDS-UPDRS visits. MDS-UPDRS Part III [redacted] will be administered ~~in the off condition (~~before ~~the~~ subjects take~~s~~ the PD medication) ~~AND in the on condition (at least 1 hour after the subject takes the medication);~~ [redacted]

[26] Performed/collected on the day before dosing or pre-infusion on the day of dosing, at the Investigator's discretion. [redacted]

~~21~~[28] The "Since Last Visit" version of the C-SSRS will be administered at all clinic visits following the Day 1 ~~b~~Baseline assessment. If the Investigator has any concern regarding the completed C-SSR~~S~~s, the subject should be referred to psychiatric evaluation based on local standards of care.