COVER PAGE

Official Title:	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of BIIB122/DNL151 in Participants with Parkinson's Disease and Pathogenic LRRK2 Variants
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PROTOCOL NUMBER: 283PD302

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of BIIB122/DNL151 in Participants with Parkinson's Disease and Pathogenic LRRK2 Variants

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SPONSOR INFORMATION

This study is a collaboration between Biogen and Denali. Biogen is responsible for the study.

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

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

SPONSOR SIGNATURE PAGE

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Date (DD-MMM-YYYY)

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1. KEY STUDY ELEMENTS

1.1. Synopsis

Protocol Title:	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of BIIB122/DNL151 in Participants with Parkinson's Disease and Pathogenic LRRK2 Variants	
Protocol Number:	283PD302	
Version Number:	2.0	
Name of Study Treatment:	Research Name:	BIIB122 (also known as DNL151)
	Generic Name:	Not applicable
	Trade Names:	Not applicable
Study Phase:	3	
Study Indication:	Parkinson's Disease	
Study Rationale:	BIIB122 is a selective, orally bioavailable, central nervous system-penetrant, reversible inhibitor of LRRK2 that is being codeveloped by Biogen, Inc., and Denali Therapeutics Inc. as a potential treatment for patients with PD. Inhibition of LRRK2 kinase, a genetically validated target, is expected to improve lysosomal function in patients with PD who do (LRRK2-PD) and do not have pathogenic LRRK2 variants. This Phase 3, multicenter, randomized, double-blind, placebo-controlled study is designed to determine the efficacy and safety of BIIB122 in participants with LRRK2-PD (participants with a clinical diagnosis of PD who carry a pathogenic LRRK2 variant) who are in the early stage of the disease.	
Rationale for Dose and Schedule Selection:	A BIIB122 dose of 225 mg or placebo administered orally QD in a 1:1 randomization ratio is proposed for this study. [redacted] A 225 mg QD dose is hypothesized to be a	

safe and well tolerated dose to restore lysosomal function and modify clinical progression of PD.

Study Objectives and Endpoints

Primary Objective	Primary Endpoint
To evaluate the efficacy of BIIB122 225 mg compared with placebo, based on the time to confirmed worsening in MDS UPDRS Parts II and III combined score	Time to confirmed worsening in MDS UPDRS Parts II and III over the treatment period (minimum 96 weeks and maximum 180 weeks)
Secondary Objectives	**Secondary Endpoints**
To evaluate the safety and tolerability of BIIB122 225 mg compared with placebo when administered for 96 to 180 weeks in participants with LRRK2-PD	Incidence of AEs and SAEs
To evaluate the efficacy of BIIB122 225 mg compared with placebo, based on the time to confirmed worsening in MDS UPDRS Part II score	Time to confirmed worsening in MDS UPDRS Part II score over the treatment period
To evaluate the efficacy of BIIB122 225 mg compared with placebo, based on change in the MDS-UPDRS Parts II and III combined score, when administered for 96 weeks in participants with LRRK2-PD	Change in MDS-UPDRS Parts II and III combined score from Baseline to Week 96
To evaluate the efficacy of BIIB122 225 mg compared with placebo, based on change in mSE-ADL score	Time to confirmed worsening in mSE-ADL score over the treatment period
To evaluate the efficacy of BIIB122 225 mg compared with placebo, based on change in MDS-UPDRS Parts I, II, and III combined score	Change in MDS-UPDRS Parts I, II, and III combined score from Baseline to Week 96

[redacted]

Study Design: This Phase 3, multicenter, randomized, double-blind, placebo-controlled study is designed to determine the efficacy and safety of BIIB122 in participants with LRRK2-PD who are in the early stage of the disease. The study population is defined as participants with a clinical diagnosis of early-stage PD who

	carry a pathogenic variant in the LRRK2 gene (e.g., *G2019S*, *N1437H*, *R1441G*, *R1441C*, *R1441H*, *Y1699C*, or *I2020T*). The overall study design is shown in Figure 1.
Study Location:	Approximately 55 sites globally are planned.
Study Population:	This study will be conducted in participants who meet the following criteria: • aged 30 to 80, inclusive, at the time of informed consent • diagnosed with PD, meeting the Movement Disorder Society Clinical Diagnostic Criteria, within 5 years of Screening Visit • mHY scale Stages 1 to 2.5 (in OFF state), inclusive, at Screening • MDS-UPDRS Parts II and III (in OFF state) combined score ≤ 40 at Screening • screening genetic test results verifying the presence of a pathogenic LRRK2 variant (e.g., *G2019S, N1437H, R1441G, R1441C, R1441H, Y1699C,* or *I2020T*). Confirmation of this eligibility requirement may come from an accredited genetic test. Detailed criteria are described in Section 6.
Number of Planned Participants:	Approximately 400 participants will be randomized.
Treatment Groups:	Eligible participants will be randomly assigned in a 1:1 ratio to receive BIIB122 225 mg or matching placebo tablets orally QD during the double-blind, placebo-controlled treatment period.
Sample Size Determination:	A minimum of approximately [redacted] events would be required to detect a [redacted] relative treatment effect for BIIB122 [redacted] for the primary endpoint with [redacted] power, at the 2-sided significance level of [redacted]. Up to 2 potential interim efficacy analyses, pending regulatory feedback, may be conducted in which case approximately [redacted] events would be needed to achieve approximately [redacted] power for the study. With a sample size of approximately [redacted] participants per treatment group, followed for a minimum of [redacted] weeks ([redacted] weeks of treatment followed by [redacted] weeks of SFU) and a maximum of

[redacted] weeks ([redacted] weeks of treatment followed by [redacted] weeks of SFU), a total number of up to [redacted] events is expected to have been reached when all participants complete the planned treatment period and provides the study with approximately [redacted] power with 2 potential IAs. These estimates assume a median time to confirmed worsening of [redacted] weeks (approximately [redacted] months) in the placebo group, and a [redacted] annual exponential dropout/censoring rate.

Visit Schedule:

[redacted]

Study assessments conducted at each visit are listed in the Schedule of Activities (Table 1).

Duration of Study Participation:

The total study duration for each participant (including the Screening period) will be a minimum of approximately 103 weeks and a maximum of approximately 187 weeks as follows:

- 5-week Screening period [redacted]
- 96-week minimum to 180-week maximum (when the total number of events for the primary endpoint reaches approximately 200 events) double-blind, placebo-controlled treatment period
- [redacted]

Benefit-Risk Analysis:

There is a significant need for an effective disease modifying therapy that delays PD progression, which is not addressed by current therapies. Lysosomal dysfunction contributes to disease risk in PD patients, suggesting that therapeutics that reduce LRRK2 kinase activity may provide benefit for patients with PD.

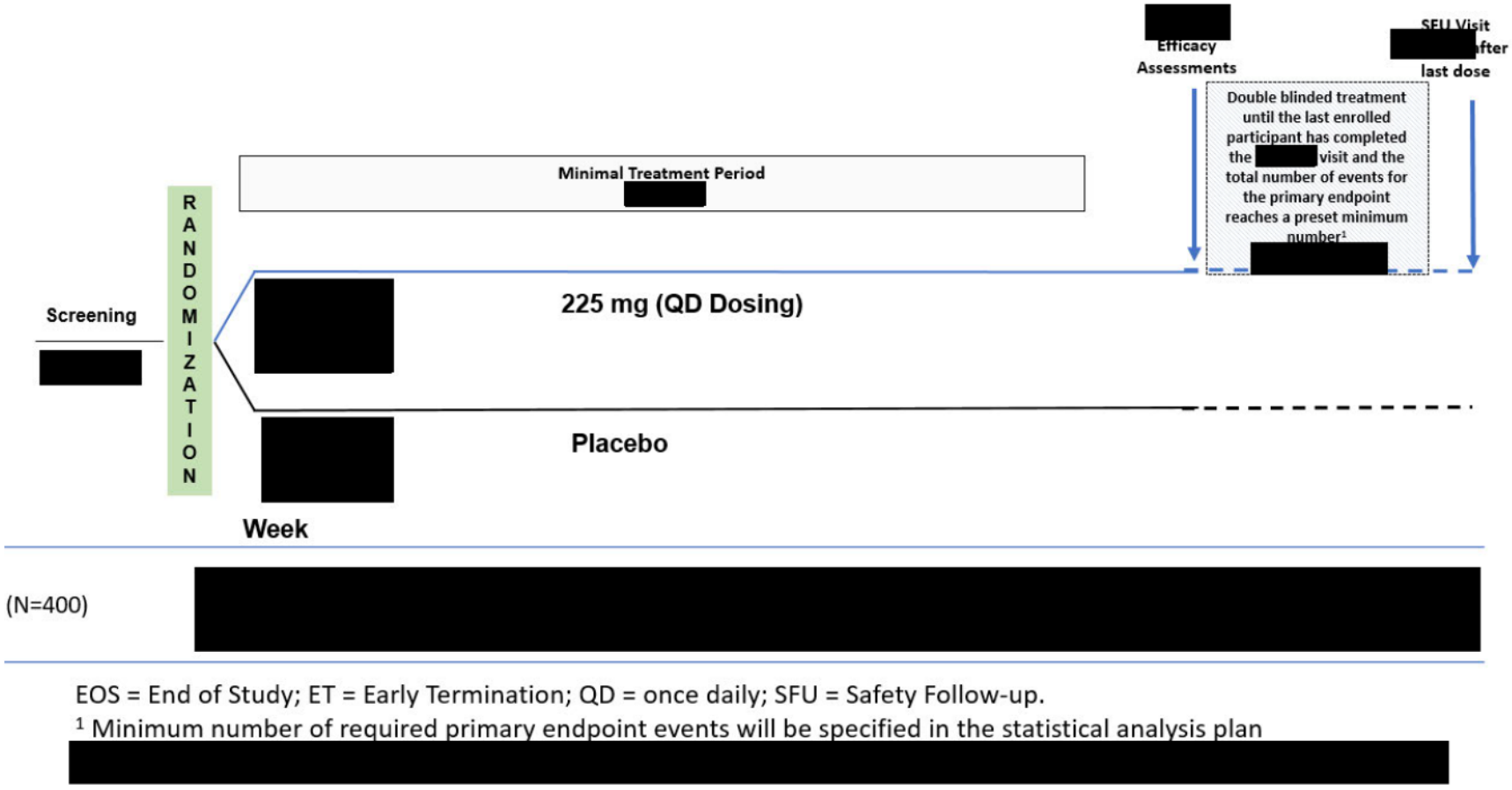
The data from previous clinical studies with doses of up to 300 mg QD in participants with PD (28 days exposure), and up to 400 mg BID in healthy volunteers (14 days exposure)

demonstrate that BIIB122 is generally safe and well tolerated. Furthermore, these doses (and their associated AUC) exceed the BIIB122 225 mg QD dose proposed for this current study. The safety of BIIB122 was also supported in the [redacted]-week and [redacted]-week chronic toxicology studies in rats and monkeys, respectively. The safety margins were established at [redacted]× (rats) and [redacted] × (monkeys) of human total drug plasma exposure at 225 mg QD. Therefore, the benefit-risk assessment is positive and supports the development of BIIB122 for the treatment of PD.

See Section 3.3 for a more detailed description.

1.2. Study Design Schematic

Figure 1: Sample Study Design



EOS = End of Study; ET = Early Termination; QD = once daily; SFU = Safety Follow-up.

[1] Minimum number of required primary endpoint events will be specified in the statistical analysis plan

[redacted]

1.3. Schedule of Activities

Table 1: Schedule of Activities

		Placebo Controlled, Double-Blind Treatment Period																						
Visit	**Screening[2]**	**Baseline[3]**																				**EOT/ ET[4]**	**SFU**	**UV[1]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		**23**	
[redacted]																								
Main ICF	X																							
[redacted]																								
General Procedures																								
Inclusion/ Exclusion Criteria	X	X																						

		Placebo Controlled, Double-Blind Treatment Period																						
Visit	**Screening[2]**	**Baseline[3]**																				**EOT/ ET[4]**	**SFU**	**UV[1]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		**23**	
[redacted]																								
Drug Screen	X	X																						
Medical History	X																							
Demographics	X																							
Height	X																							
Viral Serology	X																							
FSH[7]	X																							
Serum Pregnancy Test[8]	X										X				X							X	X	X	
Urine Pregnancy Test[8]		X	X	X	X		X		X			X	X	X		X	X	X	X	X	X				
Genetic Testing[9]	X																							
Randomization		X																						
Study Drug Dispensation		X	X	X	X		X		X		X	X	X	X	X	X	X	X							X

		Placebo Controlled, Double-Blind Treatment Period																						
Visit	**Screening[2]**	**Baseline[3]**																				**EOT/ ET[4]**	**SFU**	**UV[1]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		**23**	
[redacted]																								
Study Drug Administration		X[10]																						X
Efficacy Assessments[11]																								
MDS-UPDRS (Parts I to IV)[12]	X[13]	X			X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
[redacted]																								
mSE-ADL		X			X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
[redacted]																								

		Placebo Controlled, Double-Blind Treatment Period																						
Visit	**Screening[2]**	**Baseline[3]**																				**EOT/ ET[4]**	**SFU**	**UV[1]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		**23**
[redacted]																								

		Placebo Controlled, Double-Blind Treatment Period																						
Visit	**Screening[2]**	**Baseline[3]**																				**EOT/ ET[4]**	**SFU**	**UV[1]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		**23**
[redacted]																								

		Placebo Controlled, Double-Blind Treatment Period																						
Visit	**Screening[2]**	**Baseline[3]**																				**EOT/ ET[4]**	**SFU**	**UV[1]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		**23**	
[redacted]																									
Safety Assessments[26]																									
Physical Examination Including Weight	X	X	X	X	X		X		X		X		X		X		X		X		X	X	X	X	
Neurological Examination	X	X	X	X	X		X		X		X		X		X		X		X		X	X	X	X	
Vital Signs (Temperature, BP, HR, Respiratory Rate)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Orthostatic HR and BP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PFTs[27]	X	X		X	X		X		X		X		X		X		X		X		X	X	X	X	
Pulse Oximetry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

		Placebo Controlled, Double-Blind Treatment Period																						
Visit	**Screening[2]**	**Baseline[3]**																				**EOT/ ET[4]**	**SFU**	**UV[1]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**		**23**	
[redacted]																									
Safety Laboratory Tests[28]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[29]	X	X	X	X	X		X		X		X		X		X		X		X		X	X	X	X	
C-SSRS[30]		X	X	X	X		X		X		X		X		X		X		X		X	X	X	X	
Adverse Event Reporting and Concomitant Therapy and Procedures Recording[31]		----------X----------																							
[redacted]																									
Serious Adverse Event Reporting	----------X----------																								

		Placebo Controlled, Double-Blind Treatment Period																						
Visit	**Screening[2]**	**Baseline[3]**																				**EOT/ ET[4]**	**SFU**	**UV[1]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	
[redacted]																								

[1]Refer to Section 5.4 for details of UV visits occurring for changes in PD medication and other reasons. If study drug is due to be administered the day of the visit, it will be administered at the visit.

[2]Screening assessments can be performed over approximately 2 days (need not be consecutive) to minimize participant burden. The overall screening window will be increased by 7 days to a maximum of 42 days for participants in the [redacted] to allow enough time to complete assessments.

[3]Baseline visit may be split over 2 consecutive days when deemed necessary by Investigator. Dosing and timed assessments must be performed on the second baseline visit day.

[4]The EOT Visit is scheduled to align with a participant's last dose. If a participant discontinues study treatment but remains in the study, the EOT Visit will occur at the next scheduled visit. Participants who permanently discontinue study treatment early will be encouraged to continue study participation, maintaining the same schedule of study assessments as participants continuing in the double-blind treatment period. The ET Visit will occur if a participant withdraws from the study.

[redacted]

[7]Where applicable, postmenopausal status must be confirmed as follows: for women ≤ 55 years of age, 52 continuous weeks of natural (spontaneous) amenorrhea without an alternative medical cause and a serum FSH level ≥ 40 mIU/mL; for women > 55 years of age, 52 continuous weeks of natural (spontaneous)

amenorrhea without an alternative medical cause and a serum FSH level ≥ 40 mIU/mL, or at least 5 continuous years of natural (spontaneous) amenorrhea without an alternative medical cause.

[8]For women of childbearing potential, a serum pregnancy test will be performed at Screening, [redacted], EOT/ET Visit, and the SFU Visit; a urine pregnancy test will be performed at other study visits as indicated.

[9]The single genetic testing sample collected at Screening will be sent to the central genetics laboratory for all participants and will be used for both eligibility and exploratory genomics (See Section 9.5).

[10]The treatment period will begin at randomization (Day 1) and end with the participant's last dose of study treatment. At Baseline, participants will be provided with adequate instructions and guidance for correct use of study treatment digital blister wallets and digital adherence monitoring at home. For all in-clinic visits, study treatment will be administered by study site staff. The number of tablets taken and the dates of administration will be documented through digital adherence monitoring using the digital blister wallet with the corresponding mobile application and transferred to the database electronically. Manual adherence monitoring, e.g., pill counting, may be implemented in conjunction with or as an alternative to the digital blister wallet where necessary.

[11]All efficacy assessments must be performed before BIIB122 dosing at the baseline visit.

[12]Participants taking PD therapy (e.g., levodopa, dopamine agonists, MAO-B inhibitors, anticholinergics, amantadine) [redacted]

[26]All safety assessments must be performed before BIIB122 dosing at the baseline visit.

[27]Perform PFTs (FVC, FEV1, FEV1-to-FVC ratio, and hemoglobin-adjusted DL_{CO}) as described in the PFT manual (e.g., additional PFTs may be performed for participants with pulmonary symptoms of unknown etiology). Every effort should be made to perform the PFTs at a similar time of day (± 4 hours) of the in-clinic visits and to have the same respiratory therapist or qualified staff member conduct all PFTs for a given participant. Unscheduled PFTs may also be performed for participants who develop respiratory symptoms during participation in the study (Appendix B).

[28]Includes serum chemistry (including renal function tests and LFTs), hematology, urinalysis, and coagulation.

[29]Perform 12-lead ECGs predose and 4 hours (± 1.5 hours) postdose [redacted] visits. In addition, perform 12-lead ECGs at [redacted], at any time during the visit, irrespective of study treatment administration.

[30]At Baseline, use the Baseline/Screening version of the C-SSRS and assess for lifetime and preceding 6 months suicidal ideation and behavior. At all other visits, use the Since Last Visit version of the C-SSRS.

[31]Nonserious AEs that occur during the Screening period and that are assessed by the Investigator as related to [redacted] will be captured by the sites on the AE eCRF. After the first dose of study treatment, all AEs are collected, both related and unrelated to the ligand.

2. LIST OF ABBREVIATIONS

[redacted]	[redacted]
ACR	albumin-to-creatinine ratio
ADE	adverse device effect
ADL	activities of daily living
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
aPTT	activated partial thromboplastin time
AR	accumulation ratio
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BID	twice daily
BIO	biomarkers
[redacted]	[redacted]
BP	blood pressure
BUN	blood urea nitrogen
[redacted]	[redacted]
[redacted]	[redacted]
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CNS	central nervous system
COMT	catechol O-methyl transferase
COVID-19	coronavirus disease
CRO	clinical research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CT	computed tomography

CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome
[redacted]	[redacted]
DDI	drug-drug interaction
DHA	Directions for Handling and Administration
DL_{CO}	diffusing capacity of lungs for carbon monoxide
[redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
EDA	electrodermal activity
EOS	end of study
EOT	end of treatment
[redacted]	[redacted]
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in the first second
[redacted]	[redacted]
FIH	first in human
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide 1
GX	genomics
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCP	health care professional
HIV	human immunodeficiency virus
HR	heart rate
IA	interim analysis
ICF	informed consent form

ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous(ly)
LFT	liver function test
LP	lumbar puncture
LRRK2	leucine-rich repeat kinase 2
MAD	multiple ascending dose
MAO-B	monoamine oxidase B
MCP	multiplicity control procedure
[redacted]	[redacted]
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MDZ	Midazolam
[redacted]	[redacted]
MMRM	mixed model for repeated measures
[redacted]	[redacted]
[redacted]	[redacted]
mSE-ADL	modified Schwab and England Activities of Daily Living Scale
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drugs
[redacted]	[redacted]
PD	Parkinson's disease
[redacted]	[redacted]
[redacted]	[redacted]
PFT	pulmonary function test
[redacted]	[redacted]
[redacted]	[redacted]
PI	Principal Investigator

PK	pharmacokinetic(s)
PPMI	Parkinson's Progression Markers Initiative
pRab10	phosphorylated Rab10
PT	prothrombin time
QALY	quality-adjusted life-year
QD	once daily
Rab10	Rab GTPase involved in vesicular trafficking
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SFU	safety follow-up
SUSAR	suspected unexpected serious adverse reaction
UADE	unanticipated adverse device effect
ULN	upper limit of normal
US	United States
UV	unscheduled visit

3. INTRODUCTION

3.1. Study Rationale

BIIB122 is a selective, orally bioavailable, central nervous system-penetrant, reversible inhibitor of LRRK2 that is being codeveloped by Biogen, Inc., and Denali Therapeutics Inc. as a potential treatment for patients with PD. Inhibition of LRRK2 kinase, a genetically validated target, is expected to improve lysosomal function in patients with PD who do (LRRK2-PD) and do not have pathogenic LRRK2 variants. LRRK2 variants are an established cause of PD, accounting for approximately 4% to 5% of familial PD [Chai and Lim 2013; Healy 2008]. Familial LRRK2 variants are transmitted in an autosomal dominant pattern of inheritance with incomplete penetrance [Marder 2015]. In addition, low frequency pathogenic variants within the LRRK2 gene are a genetic risk factor and account for 1% to 2% of 'sporadic' PD cases [Chai and Lim 2013; Cookson 2015; Healy 2008; Hernandez 2016] and common noncoding PD genetic risk factor variants in and around LRRK2 have also been identified [Lill 2012; Nalls 2019]. The majority of identified pathogenic variants in LRRK2 are located within its catalytic domains, including the most common variant associated with LRRK2-PD, *G2019S*. These variants are hypothesized to increase LRRK2 kinase activity, either through direct mechanisms within the kinase domain, or through indirect mechanisms [Sheng 2012; West 2007]. While the exact pathogenic mechanisms remain unknown, LRRK2 is believed to play a role in intracellular trafficking in the endolysosomal system [Cookson 2016; Henry 2015]. BIIB122 may intervene in an important disease pathway in PD and prevent or curb the accumulation of motor and nonmotor disabilities that define the progression of PD.

This Phase 3, multicenter, randomized, double-blind, placebo-controlled study is designed to determine the efficacy and safety of BIIB122 in participants with a clinical diagnosis of PD who carry a pathogenic LRRK2 variant and are in the early stage of the disease. Use of placebo is justified as no disease modifying therapies are approved for PD at this time.

3.1.1. Rationale for Study Population

This study will enroll participants with a clinical diagnosis of PD who are in the early stages of the disease and carry a pathogenic variant in the LRRK2 gene (e.g., *G2019S*, *N1437H*, *R1441G*, *R1441C*, *R1441H*, *Y1699C*, or *I2020T*). Because LRRK2 genetic status may influence patient response to BIIB122 treatment, only patients with LRRK2 pathogenic genetic variation will enroll in this study.

Participants with early-stage PD were selected because BIIB122 is hypothesized to have greater effect on PD symptoms and progression when administered earlier in the disease. In early-stage disease, when there is less neurodegeneration in the dopaminergic neurons, the potential exists to restore or preserve lysosomal function in a higher percentage of neurons than in later-stage disease. Pathological studies have shown that, 4 years after a clinical diagnosis of PD, there is already a substantial reduction in staining for dopamine terminals in the dorsal striatum [Kordower 2013]. Therefore, treatments administered in later PD stages may be less effective in restoring function of dopaminergic neurons and reducing further neurodegeneration.

All participants must provide written informed consent before any study procedures are performed. The Screening Visit will occur within 5 weeks (35 days), [redacted]

3.1.2. Rationale for Dosing Regimen

A BIIB122 dose of 225 mg or placebo administered orally QD in a 1:1 randomization ratio is proposed for this study. Dose selection is based on the [redacted] Clinical efficacy is hypothesized to require a dose level that [redacted] Confirmation of CNS LRRK2 pathway modulation is also desired since the primary Parkinson's disease pathology is in the CNS. The selected 225 mg QD dose is the lowest dose that satisfies the following requirements:

1. [redacted]
2. [redacted]
3. [redacted]

A [redacted]% reduction in pS935 LRRK2 was selected for the level of target engagement, since this magnitude of kinase inhibition is believed to be required to normalize the [redacted] in kinase activity demonstrated in LRRK2 *G2019S* variant carriers [Melachroinou 2020; Steger 2016; Wang 2021].

In Phase 1 healthy volunteers, there was a reduction in pS935 LRRK2 of ≥ [redacted]% at doses ≥ [redacted] mg daily and ≥ [redacted]% reduction at doses ≥ [redacted] mg QD daily. At doses ≥ [redacted] mg QD, there was also a ≥ [redacted]% reduction in pRab10 in PBMC, a direct substrate of LRRK2 kinase. In addition, a dose-dependent reduction in urinary [redacted] was observed at doses ≥ [redacted] mg and median reduction in total LRRK2 protein in CSF was observed at doses ≥ [redacted] mg QD. Similar biomarker results were demonstrated in the Phase 1b PD study where BIIB122 achieved pS935 LRKK2 kinase inhibition by ≥ [redacted]% in whole blood and reduction of pRab10 in PBMC [redacted], as well as a reduction in urine [redacted] at the [redacted] mg dose. Based on the currently available data, [redacted]

The placebo-controlled, double-blind treatment period in this study allows enough disease progression in the placebo group to detect an effect size of ≥ 35% reduction in time to confirmed

worsening in MDS-UPDRS Parts II and III combined score with the current sample size. The minimum 96-week treatment period expands the safety exposure data for BIIB122.

3.2. Background

3.2.1. Overview of Parkinson's Disease

Refer to Section 3.1 in the Investigator's Brochure for detailed information.

3.2.2. Current Therapies for Parkinson's Disease

Currently approved treatments improve motor symptoms but do not address the underlying cause of PD. Over time, these symptomatic therapies lose effectiveness and are associated with increasing frequency and severity of adverse effects, such as dyskinesias and hallucinations. In addition, nonmotor symptoms, including depression, anxiety, sleep disorders, cognitive impairment, and dementia, are disabling and common features of PD but are poorly addressed by current therapies [Aarsland 1996; Khoo 2013; Lyons and Pahwa 2011; Seppi 2019; Truong 2008].

As such, PD patients inevitably experience mounting disabilities over the years to decades that they live with the disease [Hely 2005]. Thus, there is a significant need for an effective disease-modifying therapy to prevent the progressive motor and nonmotor disabilities.

3.2.3. Profile of Previous Experience With BIIB122

The safety, tolerability, and PK of orally administered BIIB122 has been evaluated in multiple Phase 1 clinical studies. See the Investigator's Brochure for detailed information on relevant nonclinical and clinical studies, both completed and ongoing.

As of 12 November 2022, a total of 340 participants have received at least 1 dose of BIIB122 (26 participants with Parkinson's disease and 314 healthy volunteers).

Variability following repeated dosing of BIIB122 was low-to-moderate across all doses from [redacted] mg to [redacted] mg QD (≤ [redacted]%) and [redacted] to [redacted] mg BID (≤ 35%). The mean CSF-to-unbound plasma concentration ratio ranged from approximately [redacted] to [redacted] across a dose range from [redacted] to [redacted] mg QD and from [redacted] to [redacted] for doses of [redacted] to [redacted] mg BID in healthy participants. This ratio was approximately [redacted] for doses from [redacted] to [redacted] mg QD in participants with Parkinson's disease. Taken together, these data suggest [redacted].

Following single or multiple oral doses from 15 to 300 mg QD, BIIB122 was rapidly absorbed, with T_{max} ranging from 1.0 to 1.5 hours postdose. The $t_{½}$ of BIIB122 varied from approximately 47 (± 11) hours at 45 mg to 93 (± 102) hours at 300 mg, after 10 daily doses. Following 10 oral daily doses from 45 mg to 300 mg, BIIB122 showed accumulation in C_{max} [redacted] and AUC [redacted]. After multiple oral daily administration of BIIB122 [redacted] mg, plasma C_{max} and AUC were [redacted] on Day 10 (healthy participants) and Day 28 (PD patients), suggesting that steady state is reached by Day 10.

Data from 2 DDI studies (Studies DNLI-C-0002 and DNLI-C-0005) established BIIB122 as [redacted] to coadministration with [redacted], with approximately [redacted]-fold increase in AUC, approximately [redacted] increase in C_{max}, and [redacted] from [redacted]-fold to [redacted]-fold when coadministered with either diltiazem XL (moderate 3A4 inhibitor) or itraconazole (strong 3A4 inhibitor) at steady-state. In Study DNLI-C-0008, the impact of BIIB122 on the PK of a single oral dose of MDZ, a model victim CYP3A substrate, was assessed. The study results characterized BIIB122 as a [redacted], as demonstrated by the observed [redacted]% [redacted] in MDZ AUC_{inf}, which falls within the FDA definition of [redacted] of greater than [redacted]% and less than [redacted]% [FDA 2020].

Based on safety data from Parts 1 through 3 of the Phase 1b study (DNLI-C-0003), BIIB122 was generally well tolerated at 80-, 130-, or 300-mg QD for 28 days in participants with Parkinson's disease. No deaths, other SAEs, or AESIs were reported. Two participants had a TEAE leading to study drug discontinuation: 1 participant in the BIIB122 130-mg QD group (hypotension) and 1 participant in the BIIB122 300-mg QD group (hypotension). The TEAEs reported for ≥ 2 participants that were more frequent for BIIB122 than placebo across all doses tested were headache, back pain, nasopharyngitis, procedural pain, nausea, dizziness, hypotension, orthostatic hypotension, and fatigue. The majority of TEAEs were mild. Two participants (5.6%) experienced a severe TEAE (asymptomatic hypotension [80 mg/130 mg/placebo cohort] and headache [300-mg/placebo cohort]).

No other clinically significant changes in safety laboratory tests, vital signs, ECG, PFTs, C-SSRS, or neurological examination results were observed.

Administration of BIIB122 80-, 130-, and 300-mg doses QD for 28 days in participants with Parkinson's disease resulted in [redacted] inhibition of LRRK2 activity, as measured by median percent reductions from baseline in whole-blood pS935 LRRK2 and PBMC pT73 Rab10 levels [redacted].

3.3. Benefit-Risk Assessment

While the safety and efficacy of BIIB122 will be confirmed in this study, it is hypothesized that reducing LRRK2 kinase activity may provide benefit for patients with PD independent of LRRK2 genetic status. The proposed population for this study will consist of participants with early-stage PD with pathogenic LRRK2 variants. Currently approved treatments improve motor symptoms but do not address the underlying cause of the disease. Thus, there is a significant need for an effective disease-modifying therapy that delays progression, which is not addressed by current therapies. The pharmacodynamic response profile of BIIB122 [redacted] mg QD is supportive of a potential efficacy as detailed in Section 3.1.2.

Nonclinical safety pharmacology studies were performed to determine the effects of BIIB122 on the cardiovascular, respiratory, and neurological systems. [redacted] was observed in rats and monkeys only at [redacted] QD. Similarly, [redacted] were observed in monkeys at BIIB122 exposure [redacted] QD and included [redacted] were observed in a

[redacted]-finding study. These findings were reversed following a [redacted]-hour treatment-free period. [redacted]. The nonclinical toxicology studies for the duration of up to [redacted]-weeks in rats and [redacted]-weeks in monkeys indicated that the [redacted] are [redacted] The NOAELs were [redacted] mg/kg (rat) and [redacted] mg/kg (monkey), with corresponding AUCs as presented in Table 2. Histological evaluations showed the multifocal vacuolation of Type II pneumocytes in monkeys. This finding was fully reversible and considered nonadverse. It has been reported that multiple and structurally distinct LRRK2 inhibitors cause pharmacologically driven lung findings consisting of lamellar body changes in type II pneumocytes [Baptista 2020; Fuji 2015]. Renal findings in monkeys were limited to a nonadverse and partially reversable minimal to slight tubular cell pigment. Renal findings were morphologically consistent with the early manifestations of findings reported in LRRK2 knockout mice related to pharmacological inhibition of the LRRK2 [Baptista 2013; Herzig 2011; Ness 2013]. Detailed information can be found in the Investigator's Brochure. Overall, the results of the nonclinical safety studies in rats and monkeys support continued development of BIIB122 and the inclusion of women of childbearing potential and men.

Table 2: Safety Margins

Study	Dose	Total AUC µM*h	AUC Safety Margin to NOAEL in Rats	AUC Safety Margin to NOAEL in Monkeys
Chronic toxicology in rats ([redacted]-week)	[redacted] mg/kg[1]	[redacted]	NA	NA
Chronic toxicology in monkeys ([redacted]-week)	[redacted] mg/kg[1]	[redacted]	NA	NA
Phase 1[2] ([redacted] and [redacted] days)	[redacted] mg QD	[redacted]	[redacted]	[redacted]
	[redacted] mg QD	[redacted]	[redacted]	[redacted]
	[redacted] mg QD	[redacted]	[redacted]	[redacted]
Phase 1 ([redacted] days)	[redacted] mg BID	[redacted]	[redacted]	[redacted]
	[redacted] mg BID	[redacted]	[redacted]	[redacted]
Phase 1 (DNLI-C-0008) ([redacted] days)	[redacted] mg QD	[redacted]	[redacted]	[redacted]

[1] NOAEL

[2] Results from [redacted]-day study DNLI-C-0001 are shown. The AUC in [redacted]-day study at [redacted] mg QD was [redacted] µM*hr

Results from previous clinical studies with doses of up to 300 mg QD in participants with PD (28 days exposure), and up to 400 mg BID in healthy volunteers (14 days exposure) demonstrate that BIIB122 is generally safe and well tolerated. Detailed safety information can be found in the Investigator's Brochure.

The dose selected for Study 283PD302 is 225 mg QD, which corresponds to safety margins of [redacted]- and [redacted]-fold for AUC at the NOAEL in monkeys and rats, respectively, based on the largest AUC exposure reported in study DNLI-C-0008 (Table 2).

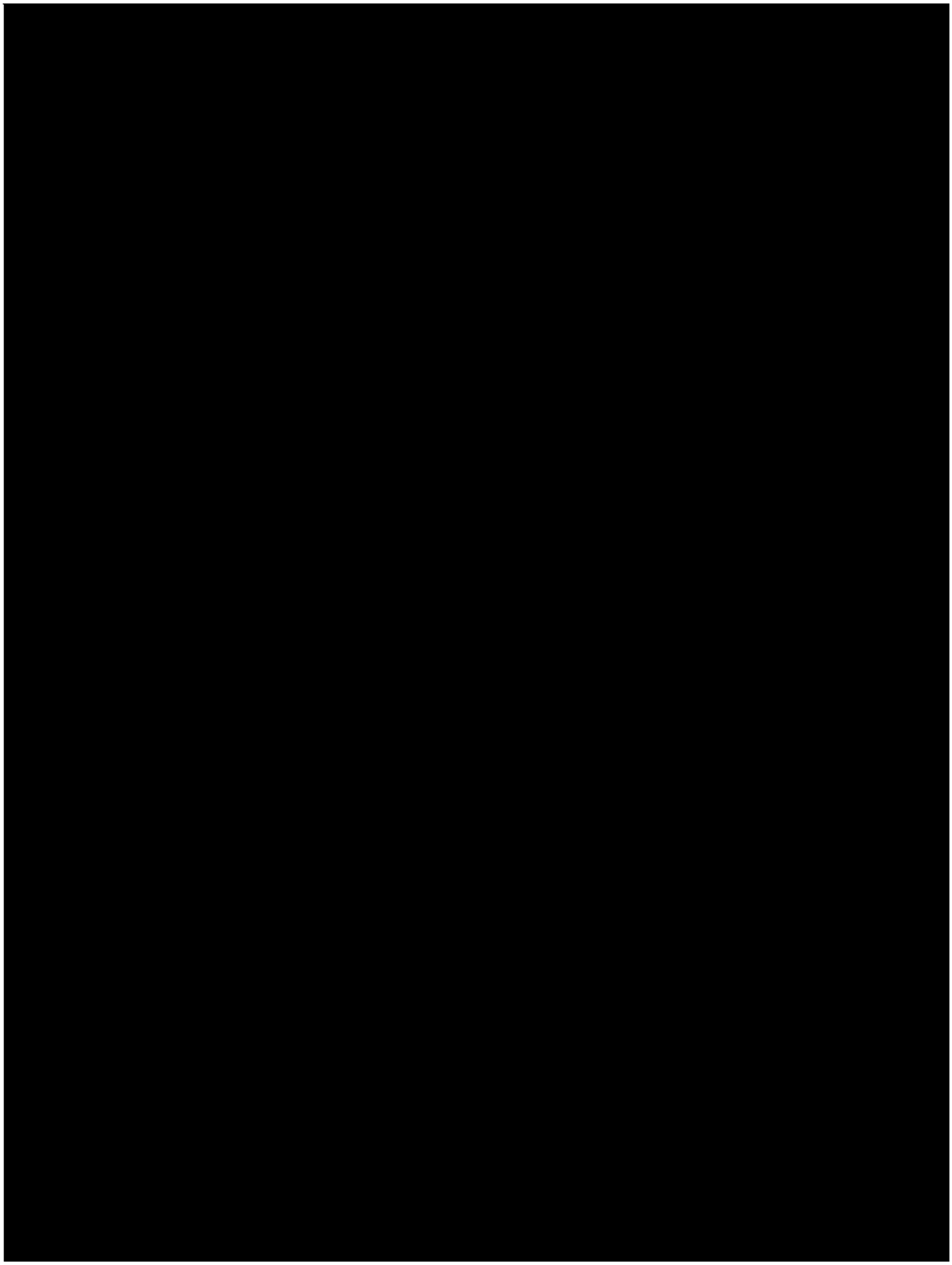
In addition, higher drug plasma exposures were achieved in previous clinical trials of BIIB122 in healthy volunteers and PD participants. The AUC at the dose of [redacted] mg BID was [redacted] µM*h after 14 days of BIIB122 administration (Table 2).

This study will include a Safety Cohort, and safety measures will include specific eligibility criteria to reduce risk to participants, monitoring of safety laboratory values at baseline and during study, real-time monitoring of SAEs, real-time monitoring of protocol-defined AESIs, safety monitoring by an IDMC, and predefined dose stopping criteria with regard to [redacted]. Further details on the Safety Cohort and the Safety Monitoring Plan can be found in Section 5.1 and Appendix B, respectively. [redacted] [Whiffin 2019].

In conclusion, the risks identified from nonclinical and clinical safety studies are manageable. Given the unmet need for a therapeutic treatment that may slow the progression of PD, BIIB122 has an overall favorable benefit-risk profile supporting further continued development of BIIB122 in PD patients.

4. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoint
To evaluate the efficacy of BIIB122 225 mg compared with placebo, based on the time to confirmed worsening in MDS-UPDRS Parts II and III combined score	Time to confirmed worsening in MDS-UPDRS Parts II and III over the treatment period (minimum 96 weeks and maximum 180 weeks)
Secondary Objectives	**Secondary Endpoints**
To evaluate the safety and tolerability of BIIB122 225 mg compared with placebo when administered for 96 to 180 weeks	Incidence of AEs and SAEs
To evaluate the efficacy of BIIB122 225 mg compared with placebo, based on the time to confirmed worsening in MDS-UPDRS Part II score	Time to confirmed worsening in MDS-UPDRS Part II score over the treatment period
To evaluate the efficacy of BIIB122 225 mg compared with placebo, based on change in the MDS-UPDRS Parts II and III combined score, when administered for 96 weeks	Change in MDS-UPDRS Parts II and III combined score from Baseline to Week 96
To evaluate the efficacy of BIIB122 225 mg compared with placebo, based on change in mSE-ADL score	Time to confirmed worsening in mSE-ADL score over the treatment period
To evaluate the efficacy of BIIB122 225 mg compared with placebo, based on change in MDS-UPDRS Parts I, II, and III combined score	Change in MDS-UPDRS Parts I, II, and III combined score from Baseline to Week 96



5. STUDY DESIGN

5.1. Study Overview

This Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study is designed to evaluate the efficacy and safety of BIIB122 in approximately 400 participants with LRRK2-PD who are in the early stage of the disease. The study will be conducted at approximately 55 study sites globally. The study population is defined as participants with a clinical diagnosis of PD within 5 years of the Screening Visit, a mHY 1-2.5 (in OFF state), who carry a pathogenic variant in the LRRK2 gene (e.g., *G2019S, N1437H, R1441G, R1441C, R1441H, Y1699C,* or *I2020T*).

Randomization will be performed using IRT. Participants will be randomly assigned to receive BIIB122 225 mg or placebo orally QD in a 1:1 ratio. [redacted]

The double-blind placebo-controlled treatment period is a minimum of [redacted] weeks and could be as long as [redacted] weeks for each participant. The study duration depends on when the last enrolled participant has completed the [redacted] Visit and number of events for the primary endpoint reaches a minimum number to provide approximately [redacted] power for the study, which will be specified in the SAP, since the minimum number depends on the number, timing, and nature of planned interim analyses. Each participant will have a SFU Visit 2 weeks after the last dose. The majority of in-clinic visits occur at [redacted]-week intervals.

The safety of BIIB122 will be evaluated as follows:

Safety Cohort

[redacted]

[redacted]

[redacted] (see Figure 1).

[redacted]

See Appendix A for details on procedures to follow in the event of a public health emergency.

5.2. Study Duration for Participants

The total study duration for each participant (including the Screening period) will be a minimum of approximately 103 weeks and a maximum of approximately 187 weeks as follows:

- [redacted] Screening period [redacted]
- [redacted] minimum to [redacted] maximum (when the total number of events for the primary endpoint reaches approximately [redacted] events) double-blind, placebo-controlled treatment period
- [redacted] SFU period

[redacted]

The study duration for each participant depends on the time point at which he or she enters the study and will be after both the last participant completes SFU (Week [redacted] + [redacted] weeks or [redacted] weeks after the last dose in case of early termination) and the minimum target number of primary endpoint events has been reached. Based on timing of last participant in and rate of primary endpoint events, sites will be contacted to schedule EOT and SFU for enrolled participants.

The EOT/ET Visit is a visit where assessments are performed for participants who either discontinue study treatment early or withdraw from the study. The EOT Visit is scheduled to align with a participant's last dose. If a participant discontinues study treatment but remains in the study, the EOT Visit will occur at the next scheduled visit. Participants who permanently discontinue study treatment early will be encouraged to continue study participation, maintaining the same schedule of study assessments as participants continuing in the double-blind treatment period. The ET Visit will occur if a participant withdraws from the study.

The end of study date for a participant may be the last study visit, last follow-up telephone conversation, or last protocol-specified assessment, or if the participant has ongoing AEs that are being followed, the date may be the date of AE resolution.

See Figure 1 for a schematic of the study design.

5.3. Study Stopping Rules

The Sponsor may terminate this study at any time, after informing Investigators. The Sponsor will notify Investigators and its partner when the study is to be placed on hold, completed, or terminated. Study drug administration may be terminated by the Sponsor at the recommendation of the IDMC based exclusively on safety and tolerability data, or at the discretion of the Sponsor.

5.4. Unscheduled Visits

For participants requiring an initiation of or a change in PD medication that is planned to occur between regularly scheduled visits, an UV should be conducted prior to PD medication initiation or change and at least 2 weeks from the closest scheduled visit. At the UV due to initiation or change in PD medication, efficacy assessments as detailed in the Schedule of Activities (see Table 1) and additional safety assessments that are deemed medically appropriate and necessary by the Investigator will be performed.

For UVs performed for any other reason, the safety assessments that are deemed medically appropriate and necessary by the Investigator will be performed. These UVs can occur at any time, independent of scheduled in-clinic visits (see Table 1).

Data collected during UVs should be recorded on eCRFs.

5.5. End of Study

The end of study is last participant, last visit. This is expected to occur approximately 98 weeks after the last participant is enrolled. The end of study date for a participant may be the last study visit, last follow-up telephone conversation, or last protocol-specified assessment. If the participant has ongoing AEs that are being followed, the date may be the date of AE resolution. Study completion is defined as either the date when last participant, last visit occurs or the date at which the last data point required for statistical analysis or SFU is received from the last participant, whichever occurs later.

[redacted]

6. STUDY POPULATION

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

6.1. Inclusion Criteria

1. Ability of the participant and/or his/her legally authorized representative (e.g., parent, spouse, or legal guardian), as appropriate and applicable, to understand the purpose and risks of the study, to provide informed consent, and to authorize the use of confidential health information in accordance with national and local privacy regulations.

2. Ability of the participant to communicate with the Investigator and study staff.

3. Male and female participants aged 30 to 80 years, inclusive, at the time of informed consent.

4. Clinical diagnosis of PD meeting the Movement Disorder Society Clinical Diagnostic Criteria [Postuma 2015] within 5 years of the Screening Visit, inclusive, and at least 30 years of age at the time of diagnosis.

5. mHY scale, Stages 1 to 2.5 (in OFF state), inclusive, at Screening.

6. MDS-UPDRS Parts II and III (in OFF state) combined score $\leq$ 40 at Screening.

7. [redacted]

8. Screening genetic test results verifying the presence of a pathogenic LRRK2 variant (e.g., *G2019S*, *N1437H*, *R1441G*, *R1441C*, *R1441H*, *Y1699C*, or *I2020T*). Participants with additional LRRK2 variants may be included if data emerge to convincingly support an association of the variants with LRRK2-PD pathogenicity. Confirmation of this eligibility requirement may come from an accredited genetic test (see Section 9.5).

9. Only when available, historical 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. Additional details are provided in Section 6.3.4.

10. All women of childbearing potential must practice effective contraception during the study and for 3 months after their last dose of study treatment as described in Section 11.6. In addition, participants should not donate eggs during the study and for at least 3 months after their last dose of study treatment.

6.2. Exclusion Criteria

Medical History and Current Health Status

1. Clinically significant neurologic disorder other than PD, including, but not limited to, stroke, dementia, or seizure within 5 years of Screening Visit, in the opinion of the Investigator.

2. Clinical evidence of atypical parkinsonism (e.g., multiple-system atrophy or progressive supranuclear palsy) or evidence of drug-induced parkinsonism.

3. Previous or current participation in a gene therapy trial for PD.

4. History of brain surgical intervention for PD (e.g., deep-brain stimulation, pallidotomy).

5. Any physical condition that may confound the motor assessment (MDS-UPDRS) over time (e.g., severe arthritis, severe dyskinesias, traumatic injuries with permanent physical disability).

[redacted]

7. Clinically significant abnormal laboratory test values, as determined by the Investigator, during Screening. Details regarding retesting are provided in Section 6.3.2. Details regarding rescreening are provided in Section 6.3.3.

8. Hospitalization for any reason during the 4 weeks before Screening.

9. Any of the following vital sign abnormalities at the Screening or Baseline Visit (if vital sign values are out of range, testing may be repeated once):

   - [redacted]

- Orthostatic BP: Decrease in SBP > [redacted] mmHg upon standing for [redacted] minutes with or without symptoms
- Orthostatic HR: Increase in HR > [redacted] bpm upon standing for [redacted] minutes with or without symptoms
- Supine or sitting SBP: < [redacted] or > [redacted] mmHg
- Supine or sitting HR: < [redacted] or > [redacted] bpm

HR assessed by vital signs, rather than 12-lead ECG, will be used.

10. Abnormal PFT results at the Screening Visit, defined as any of the following: (the best value among the acceptable triplicate measures of FVC and FEV_1 and duplicate measures of hemoglobin-adjusted DL_{CO})
    - FVC: < [redacted] % predicted
    - DL_{CO} (hemoglobin-adjusted): < [redacted] % predicted
    - Resting O_2 saturation:< [redacted] % based on pulse oximetry

[redacted]

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

14. Current hepatitis B infection (defined as positive for HBsAg and/or total anti-HBc). Participants with immunity to hepatitis B from previous natural infection (defined as negative HbsAg, positive anti-HBc, and positive hepatitis B surface antibody [anti-HBs]) or vaccination (defined as negative HbsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study.

15. Evidence of acute viral, autoimmune, alcoholic, or other types of hepatitis or clinically significant hepatic impairment or hepatobiliary disease at the Screening Visit, including

ALT, AST, or total bilirubin > 1.5 × ULN (unless due to Gilbert's syndrome based on bilirubin fractionation) within 6 months of the Screening Visit.

16. History or positive test result at Screening for human immunodeficiency virus.

17. History of or ongoing malignant disease, including solid tumors and hematologic malignancies (with the exception of basal cell carcinomas and squamous cell carcinomas of the skin that have been completely excised and considered cured ≥ 1 year prior to Baseline). Participants with cancers in remission for > 5 years prior to Baseline may be included after discussion with the Sponsor.

18. Current or history of clinically significant cardiovascular disease or abnormal assessments, including any of the following:

    - Myocardial infarction or unstable angina within 6 months prior to Screening.
    - Ventricular tachycardia, family or personal history of long QT syndrome, atrial fibrillation or flutter, or other significant arrythmias.
    - New York Heart Association Class III or IV congestive heart failure.
    - History of cardiac syncope, or syncope/near syncope of unknown etiology in the past 6 years or any syncope/near syncope in the last 3 years.
    - Clinically significant (as determined by the Investigator) 12-lead ECG abnormalities.
    - Confirmed demonstration of corrected QT interval, using Fridericia's correction method, of > 450 ms for male participants and > 460 ms for female participants. If out of range, the ECG may be repeated once at Screening and once prior to dosing. A participant must not be randomized/dosed if the repeat value is still out of range.

19. Participants with uncontrolled hypertension. Participants with a history of stable hypertension treated with allowed antihypertensive agents may be included, provided the doses of concomitant antihypertensive agents are stable for > 3 months prior to Baseline and no more than three antihypertensive agents are required.

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

21. History of drug or alcohol abuse within the past 5 years (as defined by the Investigator), a positive urine drug test at Screening (**exception**: participants who test positive for benzodiazepines may be included in the study, at the discretion of the Investigator), or an unwillingness to abstain from these substances during in-clinic visit days. Participants 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 Investigator, which is exclusionary.

22. Participants who are pregnant or currently breastfeeding, and those intending to become pregnant during the study.

23. Any condition affecting study drug absorption (e.g., gastrectomy).

Medications

24. Use of the following medication classes within 30 days or 5 half-lives (whichever is longer) of the first dose administration, or anticipated need for any of the following, for the entire duration of study participation:

    a. [redacted]

    b. [redacted]

    Refer to [redacted] for a partial list of [redacted]

25. Use of [redacted]

26. Use of an herbal treatment that affects [redacted], such as [redacted], within 30 days or 5 half-lives (whichever is longer) of the first dose administration or planned use during the study period.

27. History of systemic hypersensitivity reaction to BIIB122, the excipients contained in the formulation, and if appropriate, any diagnostic agents to be administered during the study.

28. Use of *Mucuna pruriens*, GLP-1 agonists, typical or atypical antipsychotics, cinnarizine, metoclopramide, tetrabenazine, reserpine or alpha methyldopa within 90 days from Screening or planned use during the study period.

Other

29. Inability to comply with study requirements.

30. Have withdrawn or discontinued from this or any clinical study evaluating BIIB122.

31. Participation in a clinical study involving administration of an investigational drug (new chemical entity), device, or surgery within 90 days or 5 half-lives of the Screening, whichever is longer. Participants may be rescreened after an appropriate interval, rather than being excluded.

32. [redacted]

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

[redacted]

6.3. Screening, Retesting, and Screen Failures

6.3.1. Screening

Once informed consent is obtained, screening assessments can occur. At this time, a unique identification number is assigned that will be used on study-related documents pertaining to the participant. Any identification numbers that are assigned will not be reused even if the participant does not receive treatment or continue in the study. Study sites are required to document all screened participants initially considered for inclusion in the study. Patients with prior genetic testing from accredited sources may be exempt from genetic testing at Screening.

6.3.2. Retesting

During screening, participants who have an out-of-range result that is not clinically significant in the opinion of the Investigator can be retested once at the discretion of the Sponsor.

Participants who have clinically significant abnormal laboratory test values for an acute medical condition (e.g., leukocytosis for urinary tract infection or other minor infection) that resolves with or without treatment during the Screening period may be retested.

Participants who have clinically significant abnormal laboratory test values for what appears to be a chronic medical condition (e.g., renal insufficiency) should not be retested.

Participants who have PFT values out of range may have the testing repeated once during the Screening period (≥ 5 days prior to Baseline).

6.3.3. Screen Failures

Screen failures are defined as participants who sign the ICF but are not subsequently randomized/dosed. If a participant is considered a screen failure, the reasons for exclusion must be documented in the participant's source documents and on the screening log. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Participants who fail screening criteria can be rescreened once after review by the Medical Monitor, at the discretion of the Sponsor.

Screen-failed participants will be reconsented if they are to be rescreened and will receive a new screening number. All screening assessments will be repeated except for confirmation of PD diagnosis, height measurement, and blood sampling for DNA, unless determined otherwise by the Sponsor. For female participants, if the initial FSH level confirmed postmenopausal state, it does not need to be repeated.

[redacted]

[redacted]

7. STUDY TREATMENT

7.1. Regimen

Participants will receive either BIIB122 225 mg or placebo QD orally for up to 180 weeks. Participants should take study treatment with fluid.

Participants may take their missed dose as soon as they remember to take it in the same day. If the participant remembers the day after the dose was missed, only the next dose should be taken. Only 1 dose is to be taken per day.

7.2. Study Treatment Interruption

Study treatment dosing will be interrupted for any participant who meets predefined safety thresholds (see Appendix B for details). [redacted]

7.3. Study Treatment Management

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

Site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA aligns with all other references, including the protocol.

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to participants enrolled in this study. Once study treatment is prepared for a participant, it can be administered only to that participant. Study treatment is for one time use only; do not use any study treatment tablets remaining in the [redacted] for another participant. [redacted] are utilized to ensure fidelity to the dosing regimen specified in the study protocol.

7.3.1. BIIB122

BIIB122 is supplied as an oral tablet in child-resistant [redacted] containing [redacted] mg per tablet.

The contents of the BIIB122 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, kit number, expiry or use-by date, and other pertinent information in accordance with local law. Study treatment should not be used after the expiry or use-by date.

7.3.1.1. Study Treatment Instructions for Participants

At Baseline, participants will be provided with adequate instructions and guidance for correct use of study treatment digital blister wallets and digital adherence monitoring at home.

7.3.1.2. Preparation

The individual preparing BIIB122 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 [redacted] or study treatment, do not use the study treatment. The [redacted] in question should be saved at the study site and the problem immediately reported to the Sponsor. Contact information for reporting a problem is provided in the Study Reference Guide (or comparable study document).

7.3.1.3. Storage

Study treatment must be stored in a secure location.

BIIB122 is to be stored at controlled room temperature in a monitored, locked storage container, with limited access. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

7.3.1.4. Handling and Disposal

The Investigator must return all used and unused [redacted] of BIIB122 as instructed by the Sponsor unless approved for onsite destruction.

If any BIIB122 supplies are to be destroyed at the study site, the institution or appropriate site staff must obtain prior approval from the Sponsor, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, the Sponsor 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.

7.3.1.5. 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, amount returned by the participant, and accounts of any study treatment accidentally or deliberately destroyed or lost.

Unless otherwise notified, all [redacted] both used and unused must be saved for study treatment accountability. By the end of the study, reconciliation must be made between the amount of BIIB122 supplied, dispensed, and subsequently destroyed, lost, or returned to the Sponsor. A written explanation must be provided for any discrepancies.

7.3.2. Placebo and/or Comparator or Reference Product

The same packaging, storage temperature, and excipient material applies to the placebo as for BIIB122.

7.4. Blinding Procedures

The Investigator, Sponsor, study staff, and participants will remain blinded to the treatment assignments. To maintain the study blind, it is imperative that treatment assignments are not shared with the participants, their families, or any member of the blinded study team, at the site, Sponsor, and CRO.

At the end of the study (i.e., once the clinical study report is finalized), if unblinding will not jeopardize the results of ongoing related studies, the Sponsor will provide the randomization codes to Investigators, who then can inform their participants about the treatment received.

In the event of a medical emergency that requires unblinding of a participant's treatment assignment, refer to Section 11.4.3.

7.5. Precautions

Not applicable

7.6. Compliance

The number of tablets taken and dates of administration will be documented through digital adherence monitoring using digital blister wallets and the corresponding mobile application and transferred to the database electronically. Compliance with treatment dosing is to be monitored and recorded by site staff. Manual adherence monitoring, e.g., pill counting, may be implemented in conjunction with or as an alternative to the digital blister wallet where necessary.

7.7. Concomitant Therapy and Procedures

7.7.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered from the time of screening through SFU, as well as UVs.

Participants must be instructed to contact their Investigators before taking any new medications, including nonprescription drugs, vitamins, and herbal preparations. Participants enrolling in the

study should not be expected to start or change PD medications from Screening through the first [redacted] weeks after enrollment (as judged by the Investigator).

7.7.1.1. Initiation of or Change in PD Medication

Investigators should make every attempt to conduct an in-clinic visit (scheduled or unscheduled) to assess safety and efficacy measures prior to initiating or changing PD medications (e.g., levodopa, dopamine agonists, MAO-B inhibitors, anticholinergics, adenosine receptor antagonists, COMT inhibitors). See Section 5.4 for additional details.

7.7.1.2. Allowed Concomitant Therapy

Participants should be instructed to continue the medications that they were receiving at enrollment and to avoid starting any new medications or herbal preparations during the study period, since they may confound the results of the study. The following concomitant therapies are allowed during study participation:

- PD medications that have been stable for at least [redacted] days prior to Screening. PD medications should not be expected to change from Screening through at least [redacted] weeks after enrollment as judged by the Investigator.

- Standard of care medications for PD (i.e., levodopa, dopamine agonists, MAO-B inhibitors, anticholinergics, adenosine receptor antagonists, COMT inhibitors) may be initiated during a participant's participation in the study at the discretion of the Investigator to manage PD symptoms. The Sponsor recommends minimizing changes to PD medications during the trial, as medically appropriate in the opinion of Investigator.

- Medications for antihypertensive agents (no more than 3 agents used) and other chronic conditions are allowed provided that the participant is on a stable dose for > 3 months prior to baseline and the dose 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 7.7.1.3.

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

- Routine vitamin therapy is allowed. Participants 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.

Participants must inform the Investigator of any changes in medication. Investigators should make every attempt to conduct an in-clinic visit prior to initiating or changing PD medications.

See Section 17.5 for potential mitigations including modification to permissible concomitant medications.

7.7.1.3. Disallowed Concomitant Therapy

The use of disallowed concomitant therapies will lead to study treatment discontinuation as described in Section 8, at the discretion of the Investigator and/or Medical Monitor. Prior to the initiation of [redacted] the Medical Monitor and/or Sponsor should be consulted. Participants must refrain from the following disallowed concomitant therapies during study participation:

- Use of some compounds that may affect metabolism of BIIB122 (see Section 3.2.3 for a description of the important potential DDI effects), including but not limited to:

[redacted]

- Use of *Mucuna pruriens*, GLP-1 agonists, typical or atypical antipsychotics, cinnarizine, metoclopramide, tetrabenazine, reserpine and alpha methyldopa.

- For participants who are receiving 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 [redacted].

- Any investigational drug.

Medically indicated medication or treatment should not be withheld.

Further guidance on allowed and disallowed concomitant medications will be provided by the study's Medical Monitor on a case-by-case basis.

7.7.2. Cautionary Concomitant Substances

- Caution should be exercised for study participants who take [redacted] substrate drugs. Participants should be monitored for changes in tolerability or efficacy of this drug class. Participants are recommended to stagger [redacted] drugs and study treatment by at least 8 hours.

  A partial list of [redacted] can be found in [redacted]

- Caution should be exercised for study participants who take sensitive [redacted] drugs with a narrow therapeutic index. Participants should be monitored for changes in tolerability or efficacy of this drug class.

  A partial list of drugs in this class can be found in [redacted]

- Participants should refrain from excessive use of alcohol during the study; no more than 2 units of alcohol at a given time, or > 14 units per week for males and > 7 units per week for females. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL) wine.

7.7.3. 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 from the time of participant screening to the SFU and any UVs.

7.8. Continuation of Treatment after Study Completion

No further provisions are made for access to the study treatment after the study. If study treatment is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

8. DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL OF PARTICIPANTS FROM THE STUDY

8.1. Discontinuation of Study Treatment

Study treatment interruption is discussed in Section 7.2.

The use of disallowed concomitant therapies, described in Section 7.7.1.3, will lead to study treatment discontinuation, at the discretion of the Investigator and/or Medical Monitor.

A participant *must* permanently discontinue study treatment for any of the following reasons:

- The participant becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 11.4.1.
- The participant withdraws consent to continue study treatment.
- The participant experiences an AE that necessitates permanent discontinuation of study treatment.
- The participant experiences a medical emergency that necessitates unblinding of the participant's treatment assignment.
- The participant requires use of [redacted] or requires prolonged (≥ 1 month) use of [redacted]
- At the discretion of the Investigator for medical reasons.

The primary reason for discontinuation of study treatment must be recorded in the participant's eCRF.

The ET Visit will occur if a participant withdraws from the study.

If a participant discontinues study treatment but remains in the study, the EOT Visit will occur at the next scheduled visit. Participants who permanently discontinue study treatment early will be encouraged to continue study participation, maintaining the same schedule of study assessments as participants continuing in the double-blind treatment period.

8.2. Lost to Follow-Up

Participants will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, that participant will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.3. Withdrawal of Participants From the Study

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

- The participant withdraws consent for participation in the study.

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

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

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

Participants who withdraw from the study should undergo an ET Visit unless withdrawal is due to death or withdrawal of consent. Final follow-up visit assessments will be performed at the ET Visit. If an ET Visit cannot be performed, every effort must be made by the study site to contact the participant (e.g., by phone) to collect safety follow-up assessments remotely and the reason for discontinuation. The measures taken to follow-up must be documented.

Participants who withdraw from the study, for reasons other than a safety or tolerability event, may be replaced at discretion of the Sponsor.

9. EFFICACY, [redacted] ASSESSMENTS

See Section 1.3 for the timing of all assessments.

Refer to the Study Reference Guide for additional information.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, participants will be asked to return to the study site to have the evaluations repeated.

[redacted]

9.1. Clinical Efficacy Assessments

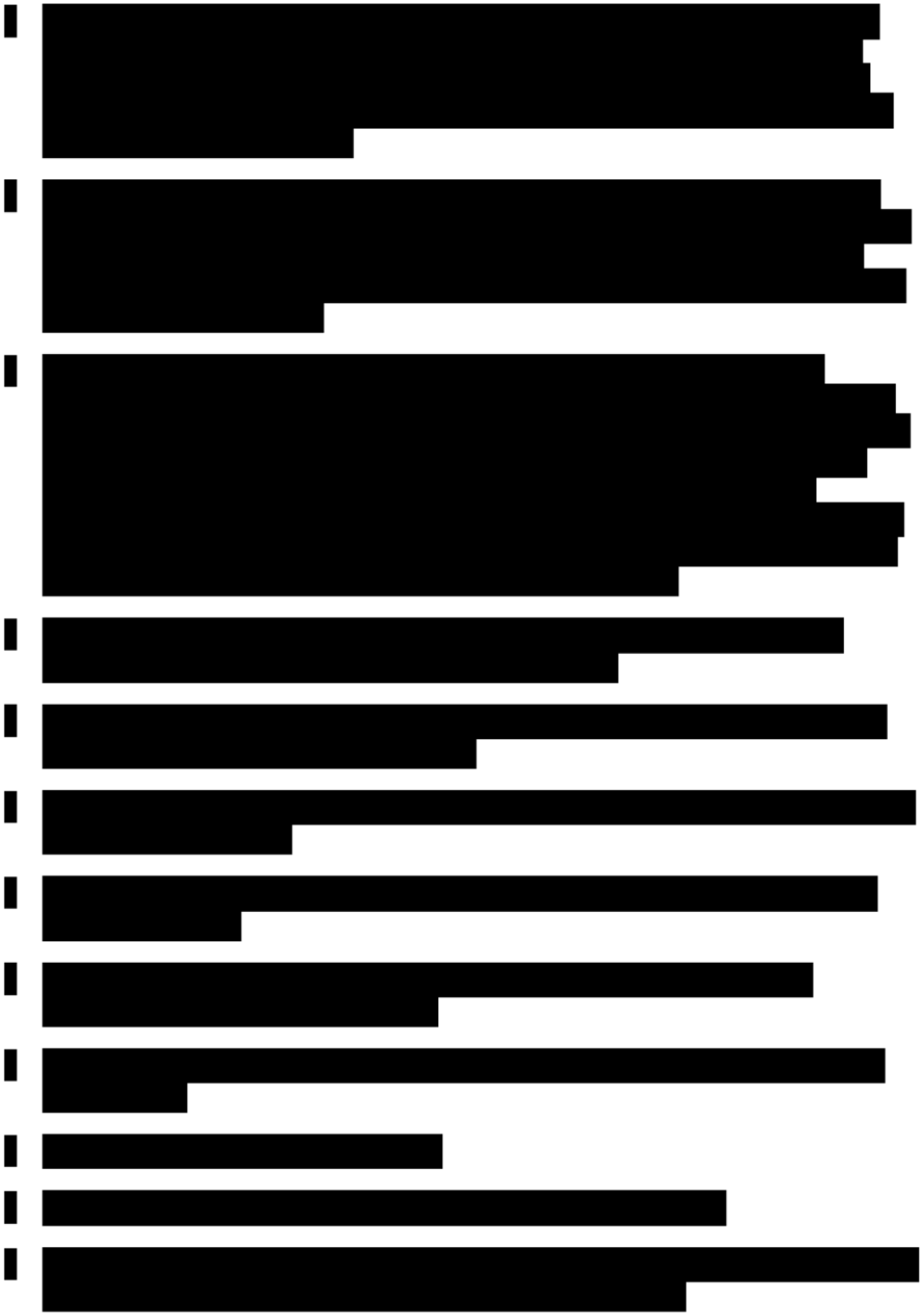
Participants taking PD medications (e.g., levodopa, dopamine agonists, MAO-B inhibitors, anticholinergics, amantadine) during the study should perform the MDS-UPDRS Part III and [redacted] in the OFF state (PD medication held for ≥ 8 hours before the time of assessment) at in-clinic visits. [redacted]

The following clinical assessments will be performed to evaluate the efficacy of BIIB122. At the baseline visit, all efficacy assessments will be performed before BIIB122 dosing.

- MDS-UPDRS is a multimodal scale assessing impairment and disability, includes Parts I to IV.
  - Part I assesses nonmotor experiences of daily living, administered by the participant.
  - Part II assesses motor experiences of daily living that reflect the participant's subjective perception of their own condition, administered by the participant.
  - Part III assesses the motor signs of PD, administered by the rater/certified individual.
  - Part IV assesses motor complications of PD, administered by the participant.

[redacted]

- The mSE-ADL scale reflects the speed, ease, and independence with which an individual performs daily activities or personal chores.



[redacted]

9.2. Laboratory Efficacy Assessments

Not applicable.

[redacted]

[redacted]

10. SAFETY ASSESSMENTS

See Section 1.3 for the timing of all safety assessments.

10.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of BIIB122. At the baseline visit, all safety assessments must be performed before BIIB122 dosing.

- AE and SAE recording
- Physical (including weight) and neurological examinations
- Vital sign measurements (temperature, HR, BP, and respiratory rate). Blood pressure will be measured after the participant has been resting in a seated position for at least 5 minutes. Orthostatic vital sign measurements will be obtained whenever blood pressure is read, in the following manner: after supine blood pressure and heart rate are measured, the participant should stand, and blood pressure and heart rate should be measured after standing 1 minute and again after 3 total minutes.
- 12-Lead ECGs
- C-SSRS
- Concomitant therapy and procedure recording
- PFTs
- Pulse oximetry

10.2. Laboratory Safety Assessments

Samples will be analyzed using Good Laboratory Practice-validated assays.

The following laboratory assessments will be performed to evaluate the safety profile of BIIB122. At the baseline visit, all safety assessments must be performed before BIIB122 dosing.

- Hematology: Complete blood count with differential and platelet count
- Serum chemistry: Electrolytes, total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, calcium, and phosphorus
- Coagulation: INR, PT, and APTT
- Urinalysis: Dipstick for blood, protein, and glucose (microscopic examination may also be performed) and urine ACR

- Serum and/or urine pregnancy tests

10.3. Product-Specific Safety Assessments

Not applicable.

11. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs, device AEs, ADEs, and device deficiencies. If an AE, device AE, ADE, or device deficiency occurs, the first concern should be for the safety of the participant. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each participant and/or his/her legally authorized representative, in accordance with local practice and regulations, must be given the names and telephone numbers of site staff for reporting SAEs, device SAEs, UADEs, reportable device deficiencies, pregnancies, overdoses, and medical emergencies. Throughout the protocol, the Sponsor is named, but reporting may be done through a CRO.

For the classification of [redacted], refer to the [redacted] Investigator's Brochure. Safety monitoring, recording, and reporting are described in the sections below.

11.1. Definitions

11.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation participant 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 assessment such as an abnormal laboratory value), 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 assessment (e.g., laboratory value, vital sign, and electrocardiogram) result meets the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless one or more of the following criteria are met:

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

11.1.2. 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 participant 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 participant 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.)

11.1.3. 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 participant is hospitalized. The study site must document all 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 participant's consent to be 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 participant's consent to be 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 participant 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 11.1.2 is met.

11.2. Safety Classifications

11.2.1. 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 11.1.2.

- [redacted]
- The severity of the event as defined in Section 11.2.3.

11.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs, to the study treatment, [redacted]

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.
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]

11.2.3. Severity of Events

The severity of AEs and SAEs will be graded using 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 activities of daily living)
3	Severe or medically significant AE (not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living)
4	Life-threatening AE (urgent intervention indicated)
5	Death related to AE

11.2.4. Expectedness of Events

Expectedness of all SAEs will be determined by the Sponsor according to the BIIB122 Investigator's Brochure.

11.3. Monitoring and Recording Events

11.3.1. Adverse Events

Any AE experienced by the participant between the time of first dose of study treatment and safety follow up is to be recorded on the eCRF, regardless of the severity of the event or its relationship to study treatment, [redacted] 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 participant for AEs and will record any new AEs or updates to previously reported AEs on the eCRF.

AEs that are ongoing when the participant 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 not be recorded on the eCRF.

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

11.3.3. Serious Adverse Events

Any SAE experienced by the participant between the time of the signing of the ICF and the safety follow up is to be recorded on an SAE form, regardless of the severity of the event, its relationship to study treatment, [redacted] Thereafter, the event should be reported to the Sponsor only if the Investigator considers the SAE to be related to study treatment.

SAEs must be reported to the Sponsor within 24 hours (as described in Section 11.3.4 or according to national law). Follow-up information regarding an SAE also must be reported within 24 hours.

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

11.3.4. Immediate Reporting of Serious Adverse Events and AESIs

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

Reporting Information for SAEs and AESI

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

- Whether or not the participant has undergone study-related procedures
- Whether or not the participant has received study treatment
- The severity of the event
- The relationship of the event to study treatment, [redacted]

To report initial or follow-up information on an SAE and/or AESIs, fax a completed appropriate form; refer to the Study Reference Guide's Official Study Contact List for complete contact information.

11.3.4.1. 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 or according to national law. The Investigator should make every effort to obtain and send death certificates and autopsy reports to the Sponsor. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

11.3.5. Suspected Unexpected Serious Adverse Reactions

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

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

11.4. Procedures for Handling Special Situations

11.4.1. Pregnancy

Participants should not become pregnant during and for 3 months after their last dose of study treatment. If a female participant becomes pregnant, study treatment must be discontinued immediately.

The Investigator must report a pregnancy occurring in a female participant from first dose of study drug to 3 months after their last dose by faxing or emailing the appropriate form to the Sponsor within 24 hours of the site staff becoming aware of the pregnancy. Refer to the Study Reference Guide's Official Study Contact List for complete contact information. The Investigator or site staff must report the outcome of the pregnancy to the Sponsor. 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 participants should be reported as an SAE if conception occurred during the study treatment period or within 3 months from their last dose of study treatment, whichever is longer.

11.4.2. Overdose

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

11.4.3. Medical Emergency

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

11.4.3.1. Unblinding for Medical Emergency

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

11.5. Device Safety Definitions and Reporting Requirements

Follow this section for reporting events during the use of [redacted].

11.5.1. Device Deficiency

Device deficiency is defined as any inadequacy in the identity, quality, durability, reliability, safety, or performance of an investigational device, including malfunction, use errors, or inadequacy in information supplied by the manufacturer.

Any case of a device deficiency that might have led to an SAE if an appropriate action had not been taken, an intervention had not occurred, or circumstances had been less fortunate and that occurred after the first use of the device by participant and before study completion or premature study withdrawal is to additionally be recorded on a Clinical Trial Device Reporting Form. The site must formally notify the Sponsor within 24 hours of becoming aware of the device deficiency. Follow-up information regarding such device deficiency also must be reported within 24 hours.

11.5.2. Device Adverse Event and Adverse Device Effect

A device AE is any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs, including an abnormal laboratory finding, in participants, users, or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

An ADE is defined as any AE related to the use of an investigational medical device.

Any device AE or ADE experienced by a participant after the first use of the device by participant and before study completion or premature study withdrawal is to be recorded on the AE eCRF.

11.5.3. Device Serious Adverse Event and Unanticipated Adverse Device Effect

A device SAE means any AE that led to any of the following:

- Death
- Serious deterioration in the health of the participants that resulted in any of the following:
    - Life-threatening illness or injury
    - Permanent impairment of a body structure or a body function
    - Hospitalization or prolongation of patient hospitalization
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
    - Chronic disease
- Fetal distress, fetal death, or a congenital physical or mental impairment or birth defect

A UADE is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or

application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

The criteria for seriousness include the following:

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Causes disability or permanent damage
- Results in persistent or significant disability/incapacity
- Requires intervention to prevent permanent impairment/damage
- Results in congenital anomaly/birth defect
- Is any other medically important event that, in the opinion of the Investigator, may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above

Any device SAE or UADE experienced by a participant after the first use of the device by participant and before study completion or premature study withdrawal is to be recorded on the AE eCRF and on a Clinical Trial Device Reporting Form within 24 hours of awareness of the event. Additionally, in the US, the study site must formally notify the IRB of UADEs within 10 working days of site awareness of the event.

Participants will be followed for these events until study completion or premature study withdrawal. Any event that is ongoing when the participant completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

11.5.4. Relationship of Events and Effects to Study Devices

The following should be considered when evaluating if an effect or device deficiency is caused by or associated with [redacted]:

- An event has a temporal relationship with investigational device use/application or procedures
- An event involves a body site or organ that:
    - The investigational device or procedures are applied to
    - The investigational device or procedures have an effect on
- A serious event follows a known response pattern to the medical device (if the response pattern is previously known)
- Discontinuation of medical device application (or a reduction in the level of activation/exposure) and reintroduction of its use (or an increase in the level of activation/exposure) and impact on the serious event (when clinically feasible)
- Other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment) have been adequately ruled out
- Harm to the participant is due to error in use

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious effect.

11.5.5. Severity of Device Events and Effects

The following definitions should be considered when evaluating the severity of UADEs, device AEs and device SAEs:

Severity of Event	
Mild	Symptoms barely noticeable to participant or do not make participant uncomfortable; do not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms.
Moderate	Symptoms of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptoms may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with study treatment; treatment for symptoms may be given and/or participant hospitalized.

[redacted]

11.6. Contraception Requirements

All women of childbearing potential must ensure that effective contraception is used during the study and for 3 months after their last dose of study treatment. In addition, participants should not donate eggs for the duration of the study and for at least 3 months after their last dose of study treatment.

For the purposes of this study, women of childbearing potential are defined as all women physiologically capable of becoming pregnant, UNLESS they meet one of the following conditions:

- Postmenopausal
    - 52 continuous weeks of natural (spontaneous) amenorrhea without an alternative medical cause and a serum FSH level > 40 mIU/mL
    - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation, where applicable according to local guidelines.

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

For females:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal methods of contraception.
- Established use of oral, injected, or implanted progestogen-only hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine hormone-releasing system.
- Barrier methods of contraception.
- Bilateral tubal occlusion.
- Sex with a male who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

*Women of childbearing potential who are using hormonal contraceptives as a primary method of birth control will require an additional nonhormonal method of contraception to ensure effective contraception during the study and for at least 3 months after their last dose of study treatment. Women of childbearing potential who are not taking hormonal contraceptives as the primary method of birth control only require 1 form of effective contraception.

True abstinence, when this is consistent with the preferred and usual lifestyle of the participant, 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 study. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 11.4.1.

11.7. Safety Responsibilities

11.7.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, SAEs, UADEs, and device deficiencies, on the eCRF regardless of the severity or relationship to study treatment [redacted]

- Determine the seriousness, relationship to study treatment, [redacted], relationship to study device, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies in female participants and follow up on the outcome of all pregnancies.
- Complete the appropriate form for each SAE, reportable device deficiency, device SAE, and UADE and fax or email it to the Sponsor within 24 hours of the site staff becoming aware of the event or according to national law.
- Pursue follow-up information actively and persistently for reported events. Follow-up information must be reported to the Sponsor within 24 hours of the site staff becoming aware of new information or according to national law.
- Ensure all AE, SAE, UADE, and reportable device deficiency reports are supported by documentation in the participants' 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.
- In the US, formally notify the IRB within 10 working days of the site staff becoming aware of a UADE.

11.7.2. The Sponsor

The Sponsor's responsibilities include the following:

- Before a site can enroll any participants, the Clinical Monitor is responsible for reviewing with site staff the definitions of AE, SAE, ADE, UADE, and device deficiency, as well as the instructions for monitoring, recording, and reporting AEs, SAEs, device AEs, device SAEs, ADEs, UADEs, and device deficiencies.
- The Sponsor is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, UADEs, and reportable device deficiencies as required by local law, within required time frames.

12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 4.

12.1. General Considerations

The study is conducted to evaluate the efficacy and safety of BIIB122 in participants with early-stage PD who carry a pathogenic LRRK2 variant. Detailed methodology for summary and statistical analyses of the data collected in this study are outlined here and further detailed in a SAP, which will be maintained by the sponsor. If there are discrepancies between the description of the statistical methods between the protocol and the SAP, the SAP will override the protocol.

12.2. Analysis Sets

FAS: all randomized participants who receive at least 1 dose of study treatment.

Safety analysis set: all randomized participants who receive at least 1 dose of study treatment.

[redacted]

12.3. Methods of Analysis for Efficacy Endpoints

12.3.1. Analysis of the Primary Endpoints

The primary efficacy endpoint is time to confirmed worsening in MDS-UPDRS Parts II and III combined score over the treatment period. Confirmed worsening is defined as [redacted]

[redacted]

[redacted]

12.3.2. Analysis of Secondary Endpoints

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.7. Methods of Analysis for Safety Endpoints

12.7.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. Any safety data collected from in-clinic or remote visits will be included in the statistical analysis.

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 by visit. In addition, incidences of all AEs by severity, by relationship to study treatment [redacted] will be presented. Data after participants started symptomatic PD medications will be analyzed both ways (included and excluded).

12.7.2. Clinical Laboratory Results

Clinical laboratory evaluations include hematology, blood chemistry, urinalysis, coagulation, and LFTs. 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.

12.7.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities, which will be defined in more detail in the SAP. Incidence of clinically relevant abnormalities in vital signs will be summarized by treatment group and visit.

12.7.4. C-SSRS

C-SSRS data will be summarized using descriptive statistics (number of participants, mean, standard deviation, median, minimum, and maximum) for continuous variables, using frequency and percentage for discrete variables, and will be presented by treatment group and visit.

12.7.5. ECG

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, visit, and timepoint.

12.7.6. PFT

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

12.7.7. Physical and Neurological Examinations

Abnormal findings deemed medically significant by the Investigator and reported as an AE will be reflected in the summary of AEs.

12.8. Methods of Analysis for Immunogenicity Data

Not applicable.

12.9. Interim Analyses

Up to 2 IAs, one earlier and one later in the study, pending regulatory feedback, may be performed for efficacy over the course of the study. A Lan-Demets alpha-spending function will be used to approximate the O'Brien Fleming for the interim and final analysis, to control the overall type I error alpha level at 0.05 two-sided. Additional details will be described in the SAP.

12.10. Sample Size Considerations

A minimum of approximately [redacted] events would be required to detect a ≥[redacted]% relative treatment effect for BIIB122 (hazard ratio = [redacted]) for the primary endpoint with ≥[redacted]% power, at the

2-sided significance level of [redacted]%. Up to [redacted] potential interim efficacy analyses, described in Section 12.9, may be conducted in which case approximately [redacted] events would be needed to achieve approximately ≥[redacted]% power for the study. With a sample size of approximately [redacted] participants per treatment group, followed for a minimum of [redacted] weeks ([redacted] weeks of treatment followed by [redacted] weeks of SFU) and a maximum of [redacted] weeks ([redacted] weeks of treatment followed by [redacted] weeks of SFU), a total number of up to [redacted] events is expected to have been reached when all participants complete the planned treatment period and provides the study with approximately ≥[redacted]% power with [redacted] potential IAs. These estimates assume a median time to confirmed worsening of [redacted] weeks (approximately [redacted] months) in the placebo group, and a [redacted]% annual exponential dropout/censoring rate. Placebo group progression rate assumptions are from [redacted], and the assumed treatment effect size is based on survey results of physicians.

13. ETHICAL AND REGULATORY REQUIREMENTS

The Sponsor, any contracted third party, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable ICH and GCP guidelines and conduct the study according to local regulations.

The Investigators are responsible for demonstrating timely oversight of all clinical trial data from their site, including data external to the electronic data capture system, such as laboratory, imaging, and electronic clinical outcomes assessment data. Investigators must approve all their data on completed eCRFs by signing electronically, at the participant, visit, or casebook level, at any time prior to an interim lock or database lock, as well as before any subsequent re-lock. The electronic data capture system does not prohibit Investigator approval or signing in any way.

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

13.1. Declaration of Helsinki

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

13.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. [redacted] will submit documents on behalf of the study sites in countries other than the United States. 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, the Sponsor must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to the Sponsor. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and the Sponsor.

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

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

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

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

13.3. Changes to Final Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect participant safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee 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, the Sponsor may, at any time, amend this protocol to eliminate an apparent immediate hazard to a participant. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Section 13.4).

13.4. Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, informed consent with the approved ICF must be obtained.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the participant must be explained to the participant and/or the participant's legally authorized representative (e.g., legal guardian), as applicable, in accordance with local practice and regulations. The participant and/or the participant's legally authorized representative as applicable, in accordance with local practice and regulations must be given sufficient time to consider whether to participate in the study.

Separate informed consent to participate in the substudies must be given by the participant and/or the participant's legally authorized representative, as applicable, in accordance with local practice and regulations.

In addition, participants who have the capacity should provide their assent to participate in the study. The level of information provided to participants should match their level of understanding as determined by the Investigator and in accordance with applicable regulations and guidelines.

A copy of the signed and dated ICF and assent must be given to the participant and/or the participant's legally authorized representative, as applicable, in accordance with local practice and regulations. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original and copies of the signed and dated ICFs.

Confirmation of informed consent and assent must also be documented in the participant's medical record.

When additional information that may affect participants' willingness to continue in the study becomes available, the Investigators will be notified in a timely manner, according to all local and applicable law. An updated ICF may be required.

13.5. Participant Data Protection

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

During the study, participants' 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 [redacted] 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 [redacted], and benefit of the study treatment in the target population.

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

13.6. Compensation for Injury

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

13.7. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in the Sponsor or its partnering company) with the participant before the participant makes a decision to participate in the study.

13.8. Study Report Signatory

The Sponsor will designate one or more of the participating 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 participant enrollment; or by other factors determined to be relevant by the Sponsor.

The Sponsor will follow all applicable local regulations pertaining to study report signatories.

13.9. Registration of Study and Disclosure of Study Results

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

The Sponsor also will notify, when required, the regulatory authorities and ethics committees about the completion or termination of this study and send a copy of the study synopsis in accordance with necessary timelines.

13.10. 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, national, or regional laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization from the Sponsor to destroy study records. In addition, the Investigator must notify the Sponsor 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.

14. KEY ROLES AND STUDY GOVERNANCE COMMITTEES

14.1. Site Staff

Each study site will have a minimum of 2 separate HCPs: a *treating* HCP and a *rating* HCP.

1. A *treating* HCP is responsible for the following. The PI or Sub-Investigator can serve as a treating HCP.

   - Administration of clinical efficacy assessments, with the exception of Part III of the MDS-UPDRS and [redacted]. The *treating* HCP may delegate certain assessments to be performed by appropriately qualified and trained site staff.
   - Management of routine neurological care of the subject.
   - Assessment (including assignment of causality) and treatment of AEs.
   - Review of selected hematology and blood chemistry results from the central laboratory to assess if the subject's study treatment should be temporarily withheld or permanently discontinued according to the criteria detailed in Appendix B.

2. A *rating* HCP is responsible for administering Part III of the MDS-UPDRS and [redacted]. The *rating* HCP is designated by the PI at each study site.

The *rating* HCP must not be involved with any other aspect of participant care and management and must remain blinded to AEs, concomitant therapy, laboratory data, imaging data, or any other data that have the potential of revealing the treatment assignment. PIs cannot serve as *rating* HCPs. *Treating* HCPs must not discuss AEs with the rating HCP.

To ensure consistency across sites, the *treating* and *rating* HCPs must complete the standardized study-specific qualification process on clinical efficacy assessment scoring prior to administration of the specific assessment at their site. All sites must attempt to have the *treating* and *rating* HCPs for specific efficacy assessments remain consistent throughout the study.

Each participant should have the same HCP perform the participants' specific efficacy assessments throughout the study. A qualified back-up HCP should only conduct efficacy assessments in place of the primary HCP if extenuating circumstances result in the primary HCP being unavailable (e.g., due to illness, vacation, or travel) and with permission from the Sponsor. Refer to the Study Reference Guide for additional information. If a *treating* or *rating* HCP must be replaced, the new HCP must undergo the study-specific qualification process prior to administration of the assessment.

The roles of the *rating* HCP and *treating* HCP are NOT interchangeable at the participant level. If the *rating* HCP has administered Part III of the MDS-UPDRS and [redacted] to a participant, they may not administer other assessments to that participant at any point during the study.

14.2. Vendors

Biogen will ensure oversight of any study-related duties and functions carried out on its behalf and will specify in writing all duties and functions that are transferred.

14.2.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including but not limited to study initiation, management of SAE reports, monitoring, and data management.

14.2.2. Interactive Response Technology

IRT will be used in this study. Before participants 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.

14.2.3. Electronic or Remote Data Capture

Participant information will be captured and managed by study sites on eCRFs by a Web-based electronic data capture tool configured by Biogen and hosted by the electronic/remote data capture vendor.

Electronic Clinical Outcome Assessment will be entered by participant, rater, and site staff on a Web-based tool. Site staff will monitor data via a secure Web portal.

The number of tablets taken and the dates of administration will be documented through digital adherence monitoring using digital blister wallets with the corresponding mobile application and transferred to the database electronically.

[redacted]

14.2.5. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by the Sponsor to store samples collected from participants in this study for [redacted], hematology, and drug concentrations in whole blood, plasma, serum, urine, and CSF. 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 (Table 1): serum chemistry (including renal function tests and LFTs), hematology, urinalysis, serum pregnancy testing, FSH, drug screening, HBsAg, anti-HBc, anti-HBs, HCV antibody, 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. A local laboratory may also be used by the study site to analyze urine pregnancy tests and LFTs, if needed.

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.

14.2.6. Central Facility for Other Assessments

A central facility has been selected by the Sponsor for rater assessments, PFTs, and ECGs. [redacted]

14.2.7. Rater Management

The Sponsor has selected a rater management group to establish rater qualifications, provide study-specific training about the rater process, and provide 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 according to project-specific plans.

14.3. Study Committees

14.3.1. Advisory Committee

An advisory committee will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The advisory committee will meet at least annually to monitor participant accrual and to monitor compliance with the protocol at individual study sites. The advisory committee will be blinded to participant treatment assignments.

Members of the advisory committee will include the Medical Director, Clinical Operations Lead, Clinical Trial Lead, and Project Statistician from the Sponsor, and participating key opinion leaders. The Sponsor will designate one of the participating key opinion leaders to be the chairperson of the advisory committee.

14.3.2. Independent Data Monitoring Committee

An IDMC will monitor accumulating participant safety data during the study ([redacted]). A dedicated safety data review for the Safety Cohort will be conducted by the IDMC approximately [redacted] weeks after the [redacted] participant is randomized and dosed, to evaluate the appropriateness of the protocol safety monitoring procedures. The role and responsibilities of the IDMC and further details will be included in the IDMC Charter.

15. ADMINISTRATIVE PROCEDURES

15.1. Study Site Initiation

The Investigator must not screen any participants prior to the Sponsor completing a study initiation visit. This initiation visit with the Investigator and other site staff, as appropriate, will include a detailed review of the protocol, study procedures, and study responsibilities.

15.2. 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 the Sponsor 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.

15.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the participants' 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 study site 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 participant 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. Documentation of results will be provided to the Sponsor in a timely fashion to allow follow-up and verification of compliance with the monitoring plan. Remote evaluation of data (centralized monitoring) may also be conducted and reported as defined in the monitoring plan.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of participant 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.

15.4. 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.

15.5. Publications

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

APPENDIX A. CONTINGENCY MEASURES TO ENABLE STUDY CONDUCT IN EXCEPTIONAL CIRCUMSTANCES

This appendix is intended for countries and/or sites in geographical areas where a health emergency (e.g., COVID-19 pandemic) or natural disaster has affected a study site's ability to conduct the study because travel restrictions have been imposed or there is a risk to participants/study staff with attendance at study sites for study visits. The following sections provide potential study adaptations that can be introduced if participants are unable to attend study visits. These contingency measures are designed to provide flexibility and minimize disruptions in the conduct of the study.

The Sponsor will determine appropriate commencement and end date for each contingency measure where the duration of the mitigations described in this appendix may begin at the onset of site restrictions for a specific site and/or country and may end once those restrictions are lifted and in accordance with local laws and regulations. The adaptations to the visits and procedures described in this appendix are alternations or deviations to the main protocol procedures.

The contingency measures described in this appendix will be implemented only in exceptional cases and after the site has received written notification from the Sponsor. The Sponsor may not need to employ all measures described below (Section 17) in the event of such circumstances, but only those necessary to prevent disruptions in the progress of the study. The Sponsor will have the final authority to decide which mitigations can be implemented, in accordance with local laws and regulations.

16. COMMUNICATION OF MITIGATION IMPLEMENTATION

16.1. Investigator and Institutional Review Board Notification

Study modifications that affect participant safety, are a health authority request, or are substantial changes in study design, endpoints, and/or procedures will require a protocol amendment. Study sites will be responsible for notifying any required boards or committees.

16.2. Participant Notification/Informed Consent Form Updates

Sites will ensure that participants sign an ICF that includes all potential risk mitigation options noted in this appendix prior to implementation. The Investigator will be responsible for notifying participants if/when any contingency measures will be implemented.

17. POTENTIAL MITIGATIONS

17.1. Virtual Visits

The Sponsor may determine that applicable study visits and relevant study procedures can be conducted as televisits.

17.2. Changes to Treatment Administration

17.2.1. Study Treatment Administration via Alternative Study Site and/or Personnel

Not applicable.

17.2.2. Home Delivery of Study Treatment

If a participant is unable to come in for an in-clinic visit to obtain study treatment, the study treatment may be shipped from the study site to the participant via a courier service, if allowed per country and site regulations and approved by the Sponsor, making sure to document appropriately as required (e.g., potentially in the Pharmacy Manual or Protocol Deviation Log).

17.3. Use of Alternative Medical Facilities

With Sponsor approval, study visits may be performed at alternative medical facilities if travel to the study site is not feasible. Alternative medical facilities may include but are not limited to the participant's primary care physician, a local clinic or hospital, or a mobile medical service that meets the participant outside of the study site. Details on which visits and procedures are eligible to be performed at alternative medical facilities will be provided by the Sponsor in writing. All procedures performed at alternative medical facilities will need to be performed as described in this protocol, and medical staff will need to be trained accordingly.

17.4. Remote Monitoring

The Clinical Monitor may perform monitoring activities remotely, and in accordance with Sponsor guidelines, if on-site monitoring is not allowed per local/regional restrictions. Monitoring details are documented in the Clinical Site Monitoring Plan.

17.5. Modification to Permissible Concomitant Medications

The Global Safety Officer may perform a risk-benefit assessment for allowing participants to receive critical medical treatments (e.g., COVID-19 vaccines) during the study if such treatments would typically not be permitted by the exclusion criteria or as concomitant therapies. If the Global Safety Officer identifies the need (i.e., possible effect of the study drug on the critical medical treatment), a formal risk management process may be initiated. With Sponsor approval, applicable study procedures may be modified to accommodate critical medical treatments.

17.6. Other Unforeseen Mitigations

Additional adaptions to the study that are not described above may be required. The Sponsor will have the right to amend the measures, as necessary, with approval from the applicable governing body. Decisions will be communicated as noted in this appendix.

APPENDIX B. SAFETY MONITORING PLAN

[redacted] **Serious Adverse Events**

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

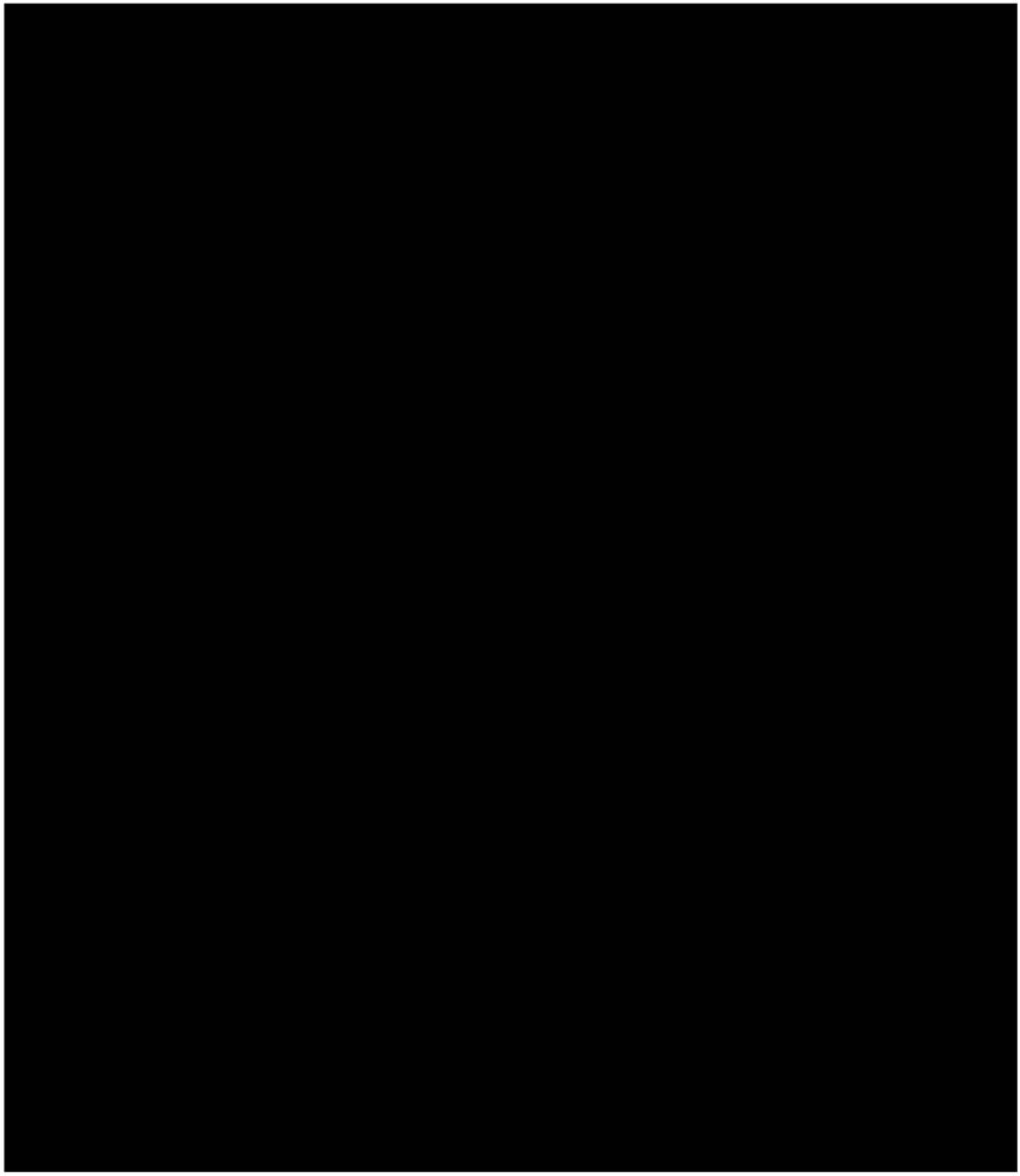
[redacted]

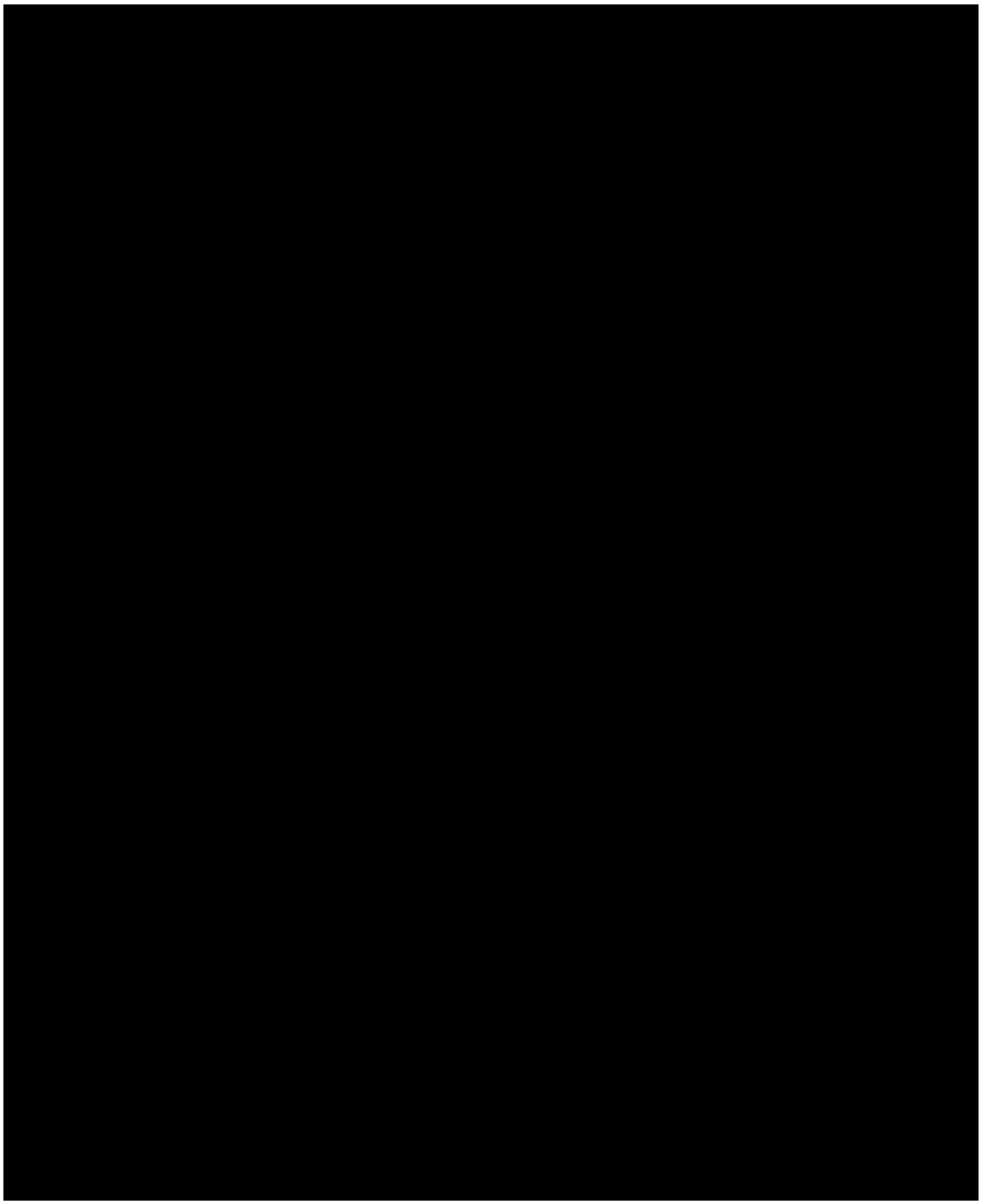
[redacted]

- [redacted]

[redacted]

[redacted]





[redacted]

[redacted]

[redacted]

Independent Data Monitoring Committee

An IDMC will monitor accumulating participant safety data during the course of the study as described in Section 14.3.2 of the protocol.

[redacted]

[redacted]

[redacted]

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19. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of BIIB122/DNL151 in Participants with Parkinson's Disease and Pathogenic LRRK2 Variants" 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)

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AMENDMENT SUMMARY

Biogen Protocol 283PD302

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of BIIB122/DNL151 in Participants with Parkinson's Disease and Pathogenic LRRK2 Variants

Version 2.0

Date: 09 April 2023

EUDRA CT Number: 2022-000747-77

Version 2.0 of the protocol has been prepared for this amendment, which supersedes Version 1.0 dated 21 April 2022.

PRIMARY REASON FOR AMENDMENT

The primary reasons for this amendment to Protocol 283PD302 include:

- Addition of a category of medications to be used with caution and corresponding updates to exclusionary medications and disallowed concomitant medications
- Addition of 3 new efficacy assessments [redacted]
- Reclassification of the [redacted] as an investigational medical device

Section 7.7.2, Cautionary Concomitant Substances

Now reads:

- **Caution should be exercised for study participants who take [redacted] drugs. Participants should be monitored for changes in tolerability or efficacy of this drug class. Participants are recommended to stagger [redacted] drugs and study treatment by at least 8 hours.**

  [redacted]
- **Caution should be exercised for study participants who take [redacted] drugs with a narrow therapeutic index. Participants should be monitored for changes in tolerability or efficacy of this drug class.**

  [redacted]
- **Participants should refrain from excessive use of alcohol during the study; no more than 2 units of alcohol at a given time, or > 14 units per week for males and > 7 units per week for females. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL) wine.**

Rationale:

- [redacted] were added as cautionary to align with results from in vitro and PBPK modelling studies which indicate that there could be a [redacted] on concomitant administration of BIIB122 with [redacted] drugs as BIIB122 could [redacted].
- The use of [redacted] has been changed from exclusionary and disallowed concomitant therapy in V1 of the protocol to cautionary to align with results from a recent Phase 1 study showing BIIB122 to be a [redacted] of [redacted].
- Excessive use of alcohol was added as cautionary based on health authority feedback.

The change associated with [redacted] also affects Section 6.2, Exclusion Criteria (#25); Section 7.7.1.3, Disallowed Concomitant Therapy.

Section 4, Study Objectives and Endpoints

Now reads:

[redacted]	[redacted]

[redacted]	[redacted]

Rationale: [redacted]

These changes also affect Section 1.3 (Table 1), Schedule of activities; Section 9.1 (Clinical Efficacy Assessments).

Section 11.5, Device Safety Definitions and Reporting Requirements

Change: A new section associated with device safety definitions and reporting requirements was added to the protocol.

Now reads:

11.5 Device Safety Definitions and Reporting Requirements

Follow this section for reporting events during the use of [redacted].

Section 11.5.1, Device Deficiency

Device deficiency is defined as any inadequacy in the identity, quality, durability, reliability, safety, or performance of an investigational device, including malfunction, use errors, or inadequacy in information supplied by the manufacturer.

Any case of a device deficiency that might have led to an SAE if an appropriate action had not been taken, an intervention had not occurred, or circumstances had been less fortunate and that occurred after the first use of the device by participant and before study completion or premature study withdrawal is to additionally be recorded on a Clinical Trial Device Reporting Form. The site must formally notify the Sponsor within 24 hours of becoming aware of the device deficiency. Follow-up information regarding such device deficiency also must be reported within 24 hours.

Section 11.5.2, Device Adverse Event and Adverse Device Effect

A device AE is any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs, including an abnormal laboratory finding, in participants, users, or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

An ADE is defined as any AE related to the use of an investigational medical device.

Any device AE or ADE experienced by a participant after the first use of the device by participant and before study completion or premature study withdrawal is to be recorded on the AE eCRF.

Section 11.5.3, Device Serious Adverse Event and Unanticipated Adverse Device Effect

A device SAE means any AE that led to any of the following:

- **Death**
- **Serious deterioration in the health of the participants that resulted in any of the following:**
    - **Life-threatening illness or injury**
    - **Permanent impairment of a body structure or a body function**
    - **Hospitalization or prolongation of patient hospitalization**
    - **Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function**
    - **Chronic disease**
- **Fetal distress, fetal death, or a congenital physical or mental impairment or birth defect**

A UADE is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

The criteria for seriousness include the following:

- **Requires inpatient hospitalization or prolongation of existing hospitalization**
- **Causes disability or permanent damage**
- **Results in persistent or significant disability/incapacity**
- **Requires intervention to prevent permanent impairment/damage**
- **Results in congenital anomaly/birth defect**

- **Is any other medically important event that, in the opinion of the Investigator, may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above**

Any device SAE or UADE experienced by a participant after the first use of the device by participant and before study completion or premature study withdrawal is to be recorded on the AE eCRF and on a Clinical Trial Device Reporting Form within 24 hours of awareness of the event. Additionally, in the US, the study site must formally notify the IRB of UADEs within 10 working days of site awareness of the event.

Participants will be followed for these events until study completion or premature study withdrawal. Any event that is ongoing when the participant completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

Section11.5.4, Relationship of Events and Effects to Study Devices

The following should be considered when evaluating if an effect or device deficiency is caused by or associated with [redacted]

- **An event has a temporal relationship with investigational device use/application or procedures**
- **An event involves a body site or organ that:**
  - **The investigational device or procedures are applied to**
  - **The investigational device or procedures have an effect on**
- **A serious event follows a known response pattern to the medical device (if the response pattern is previously known)**
- **Discontinuation of medical device application (or a reduction in the level of activation/exposure) and reintroduction of its use (or an increase in the level of activation/exposure) and impact on the serious event (when clinically feasible)**
- **Other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment) have been adequately ruled out**
- **Harm to the participant is due to error in use**

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious effect.

Section 11.5.5, Severity of Device Events and Effects

The following definitions should be considered when evaluating the severity of UADEs, device AEs, and device SAEs:

Severity of Event	
Mild	**Symptoms barely noticeable to participant or do not make participant uncomfortable; do not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms.**
Moderate	**Symptoms of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptoms may be needed.**
Severe	**Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with study treatment; treatment for symptoms may be given and/or participant hospitalized.**

Section 11.5.6, Expectedness of Device Events and Effects

Refer to the [redacted] Investigator's Brochure for information on any expected/anticipated device AEs or ADEs associated with the use of [redacted].

Rationale: The classification of the [redacted] application in V2 of the protocol was changed to investigational medical device. This classification required addition of safety reporting specific to devices.

This change also affects Section 1.3 (Table 1), Schedule of Activities; Section 11, Safety Definitions, Recording, Reporting, and Responsibilities; Section 11.7.1, The Investigator; and Section 11.7.2, The Sponsor.

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~~.

Section1.1, Synopsis

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

Section 1.3, Schedule of activities

Change:

- Study drug dispensation was added to Table 1.
- Footnotes for Table 1 were updated.

Now reads:

		Placebo Controlled, Double-Blind Treatment Period																						
Visit	**Screening[2]**	**Baseline[3]**																				**EOT/ ET[4]**	**SFU**	**UV[1]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	
[redacted]																								
Study Drug Dispensation		X	X	X	X		X		X		X	X	X	X	X	X	X	X						X

Rationale: Study drug dispensation was added to clarify when sites are to access IRT to dispense new IP kits and to show when IP is not to be dispensed at safety cohort visits.

Now reads:

[3]Baseline visit may be split over 2 consecutive days when deemed necessary by Investigator. Dosing and timed assessments must be performed on the second baseline visit day.

Rationale: A footnote was added to allow for the baseline visit to be split over 2 consecutive days when deemed necessary by the Investigator.

[redacted]

---

[11]All efficacy assessments must be performed before BIIB122 dosing at the baseline visit.

Rationale: A footnote was added to clarify the timing of efficacy assessments in relation to dosing at baseline.

This change also affects Section 9.1, Clinical Efficacy Assessments.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

---

[26]All safety assessments must be performed before BIIB122 dosing at the baseline visit.

Rationale: A footnote was added to clarify the timing of safety assessments in relation to dosing at baseline.

This change also affects Section 10.1, Clinical Safety Assessments and Section 10.2, Laboratory Safety Assessments.

[redacted]

Section 3.3, Benefit-Risk Assessment

Change: This section was updated with data from the DNLI-C-0008 study. Modifications were made to Table 2 headers and an extra footnote was added to the table.

Now reads:

Table 2 Safety Margins

Study	Dose	Total AUC µM*hr ~~(SD)~~	**AUC** Safety Margin to NOAEL in Rats	**AUC** Safety Margin to NOAEL in Monkeys
Chronic toxicology in rats (26-week)	[redacted] mg/kg[1]	[redacted]	~~1~~**NA**	NA
Chronic toxicology in monkeys (39-week)	[redacted] mg/kg[1]	[redacted]	NA	~~1~~**NA**
Phase 1[2] (10 and 28 days)	[redacted] mg QD	[redacted]	[redacted]	[redacted]
	[redacted] mg QD	[redacted]	[redacted]	[redacted]
	[redacted] mg QD	[redacted]	[redacted]	[redacted]
Phase 1 (14 days)	[redacted] mg BID	[redacted]	[redacted]	[redacted]
	[redacted] mg BID	[redacted]	[redacted]	[redacted]
Phase 1 (DNLI-C-0008) (11 days)	[redacted] **mg QD**	[redacted]	[redacted]	[redacted]

[1]NOAEL

[2]Results from 10-day study DNLI-C-0001 are shown. The AUC in 28-day study at [redacted] mg QD was [redacted] µM hr.

The dose selected for Study 283PD302 is 225 mg QD, which corresponds to safety margins of [redacted] and [redacted] fold for AUC at the NOAEL in monkeys and rats, respectively, based on the largest AUC exposure reported in study DNLI-C-0008 ~~which corresponds to~~ [redacted] ~~monkeys and the 26-week study in rats, respectively~~ (Table 2).

In addition, higher drug plasma exposures were achieved in previous clinical trials of BIIB122 in healthy volunteers and PD participants. ~~(Table 2).~~ [redacted] ~~, whereas t~~**T**he AUC at the [redacted] dose of [redacted] mg BID was [redacted] µM*h after 14 days of BIIB122 administration **(Table 2).**

Rationale: This section was updated to include the safety margin based on the total plasma exposure at the dose of 225 mg QD in the Phase 1 DNLI-C-0008 study. Updates were also made for clarity and to align with the information in the Phase 2 protocol 283PD201.

Section 5.1, Study Design

Change: A minor revision was made to the text describing the timing of the safety data review conducted by the IDMC for the Safety Cohort.

Now reads:

Approximately [redacted] ~~twelve~~ weeks after the [redacted] participant is randomized and dosed, a dedicated safety data review for this cohort will be conducted by the IDMC to evaluate the appropriateness of the protocol safety monitoring procedures.

Rationale: To clarify the timing of the safety data review.

Section 6.2, Exclusion Criteria

Change:

- PFT repeated testing has been removed (EC #10).
- A benzodiazepine-positive drug test will not be exclusionary to study participation (EC #21).
- The list of [redacted] was modified (EC #24).
- Exclusionary medications were updated to align with the Disallowed Medications (EC #28).

Now reads:

10. Abnormal PFT results at the Screening Visit, defined as any of the following (the best value among the acceptable triplicate measures of FVC and FEV1 and duplicate measures of hemoglobin-adjusted DL_{CO}); ~~if PFT values are out of range, testing may be repeated once during the Screening period ≥ 5 days prior to Baseline):~~

Rationale: The deleted text was added to Section 6.3.2 so that all retesting information is in the same section of the protocol.

This change also affects Section 6.3.2, Retesting.

---

21. History of drug or alcohol abuse within the past 5 years (as defined by the Investigator), a positive urine drug test at Screening ~~or Study Day 1~~ (**exception**: **participants who test positive for benzodiazepines may be included in the study, at the discretion of the Investigator)**, or an unwillingness to abstain from these substances during in-clinic visit days. Participants 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 Investigator, which is exclusionary.

Rationale: An update was made to group eligibility lab assessments to the Screening visit. A change was also made to clarify that participants who test positive for benzodiazepines at Screening may be eligible for the study at the discretion of the Investigator.

---

24. Use of the following medication classes within 30 days or 5 half-lives (whichever is longer) of the first dose administration, or anticipated need for any of the following, for the entire duration of study participation:

[redacted]

Refer to [redacted]

25. Use of [redacted] or any [redacted]

Rationale:

[redacted]

---

27. History of systemic hypersensitivity reaction to BIIB122, the excipients contained in the formulation, and if appropriate, any diagnostic agents to be administered during the study.

Rationale:

This criterion was renumbered from EC#24 to EC#27 for consistency across protocols.

---

28. Use of *Mucuna pruriens*, **GLP-1 agonists, typical or atypical antipsychotics, cinnarizine, metoclopramide, tetrabenazine, reserpine or alpha methyldopa** within 90 days from Screening or planned use during the study period.

Rationale: Medications that may influence PD symptoms and were previously included only in the Disallowed Concomitant Medication Section 7.7.1.3 are now added to exclusion criteria for clarity.

Section 7.7.1.3, Disallowed Concomitant Therapy

Change:

- [redacted] was modified.
- Disallowed concomitant medications specific to [redacted] which is not required for eligibility assessments was deleted.
- Medications that may influence PD symptoms were consolidated.

Now reads:

The use of disallowed concomitant therapies will lead to study treatment discontinuation as described in Section 8.1, at the discretion of the Investigator and/or Medical Monitor. Prior to the initiation of [redacted] and [redacted] the Medical Monitor and/or Sponsor should be consulted. Participants must refrain from the following disallowed concomitant therapies during study participation:

- [redacted]
- Use of *Mucuna pruriens*, **GLP-1 agonists, typical or atypical antipsychotics, cinnarizine, metoclopramide, tetrabenazine, reserpine and alpha methyldopa**.
- For participants who are receiving 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.
- ~~Typical or atypical antipsychotics (including clozapine, olanzapine, flunarizine, and aripiprazole), metoclopramide, and alpha methyldopa.~~
- ~~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.~~
- Any investigational drug.

Medically indicated medication or treatment should not be withheld.

Further guidance on allowed and disallowed concomitant medications will be provided by the study's Medical Monitor on a case-by-case basis.

Rationale:

- Changes were made to align with the information in the Phase 2 protocol 283PD201.
- [redacted]
- Disallowed medications specific for participants undergoing [redacted] analysis outside the study SOA were deleted. Instructions on the use of these medications when [redacted] is performed for reasons outlined in [redacted] are included in that section.
- Medications that may influence PD symptoms were consolidated to align with Section 6.2, Exclusion Criteria (#27).

The modifications in [redacted] also affect Section 8.1, Discontinuation of Study Treatment.

The changes associated with [redacted] also affect [redacted]

Section 9.1, Clinical Efficacy Assessments

Change: [redacted] was changed to [redacted].

Now reads:

- The [redacted] L scale reflects the speed, ease, and independence with which an individual performs daily activities or personal chores.

Rationale: The change from [redacted] to [redacted] will allow the use of a 5.0 threshold, rather than a 10.0 threshold for confirmed worsening for the [redacted] endpoint, and it will increase the sensitivity and power of this endpoint to detect progression.

This change also affects Section 4, Objectives and Endpoints; Section 1.3, Schedule of Activities; Section 12.3.1, Analysis of the Primary Endpoint.

[redacted]

- [redacted]
- [redacted]

[redacted]

This change also affects

Section 11.3.4, Immediate Reporting of Serious Adverse Events **and AESIs**

Change: This section was updated to include AESIs.

Now reads:

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

Reporting Information for SAEs **and AESIs**
A report *must be submitted* to the Sponsor regardless of the following: • Whether or not the participant has undergone study-related procedures • Whether or not the participant has received study treatment • The severity of the event • The relationship of the event to study treatment, or

To report initial or follow-up information on an SAE **and/or AESIs**, fax a completed ~~SAE~~ **appropriate** form; refer to the Study Reference Guide's Official Study Contact List for complete contact information.

Rationale: The section was updated to clarify the reporting information for immediate reporting of AESIs.

Section 12.10, Sample Size Considerations

Change: A statement was added that effect size will be based on survey results of physicians.

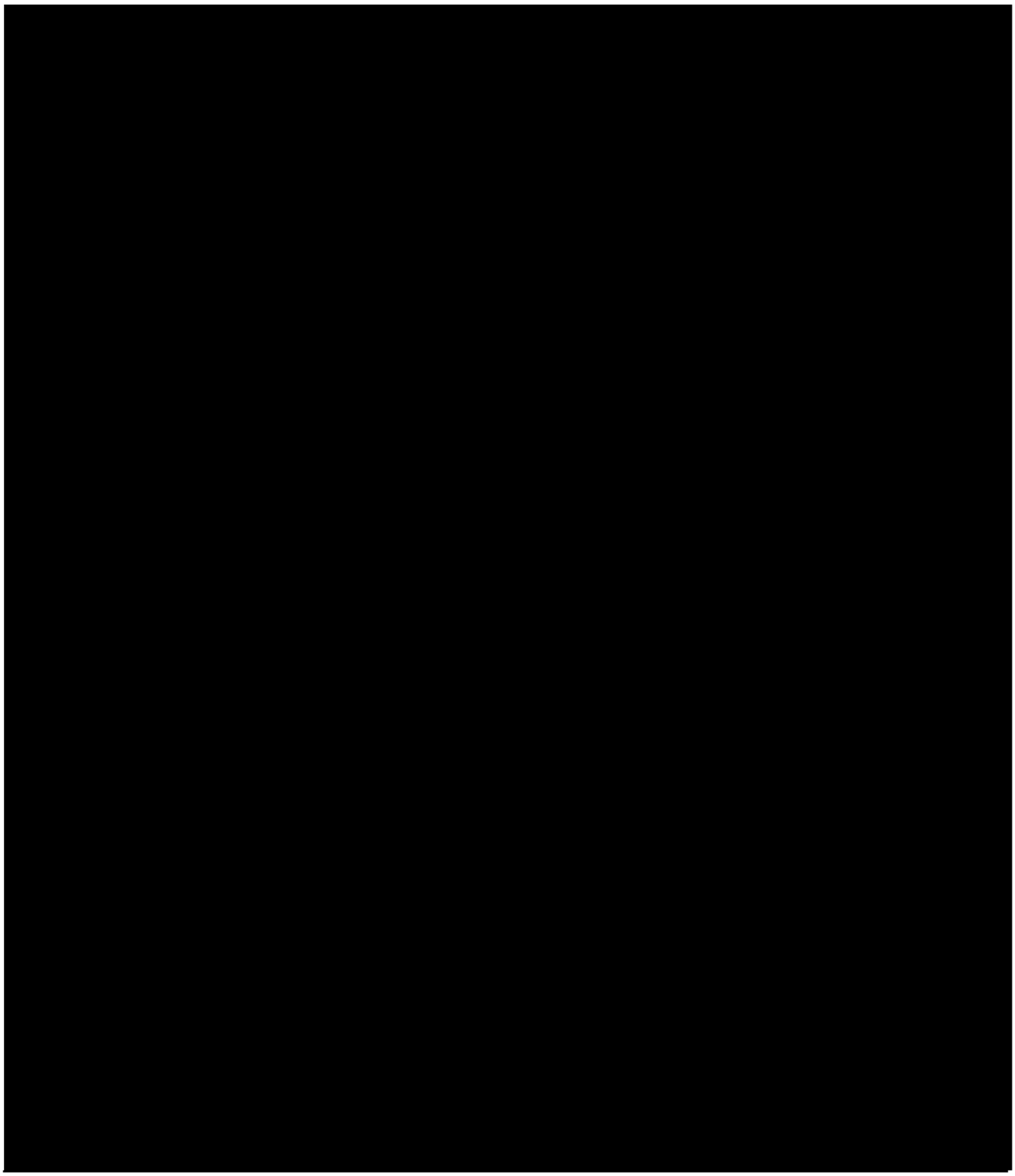
Now reads:

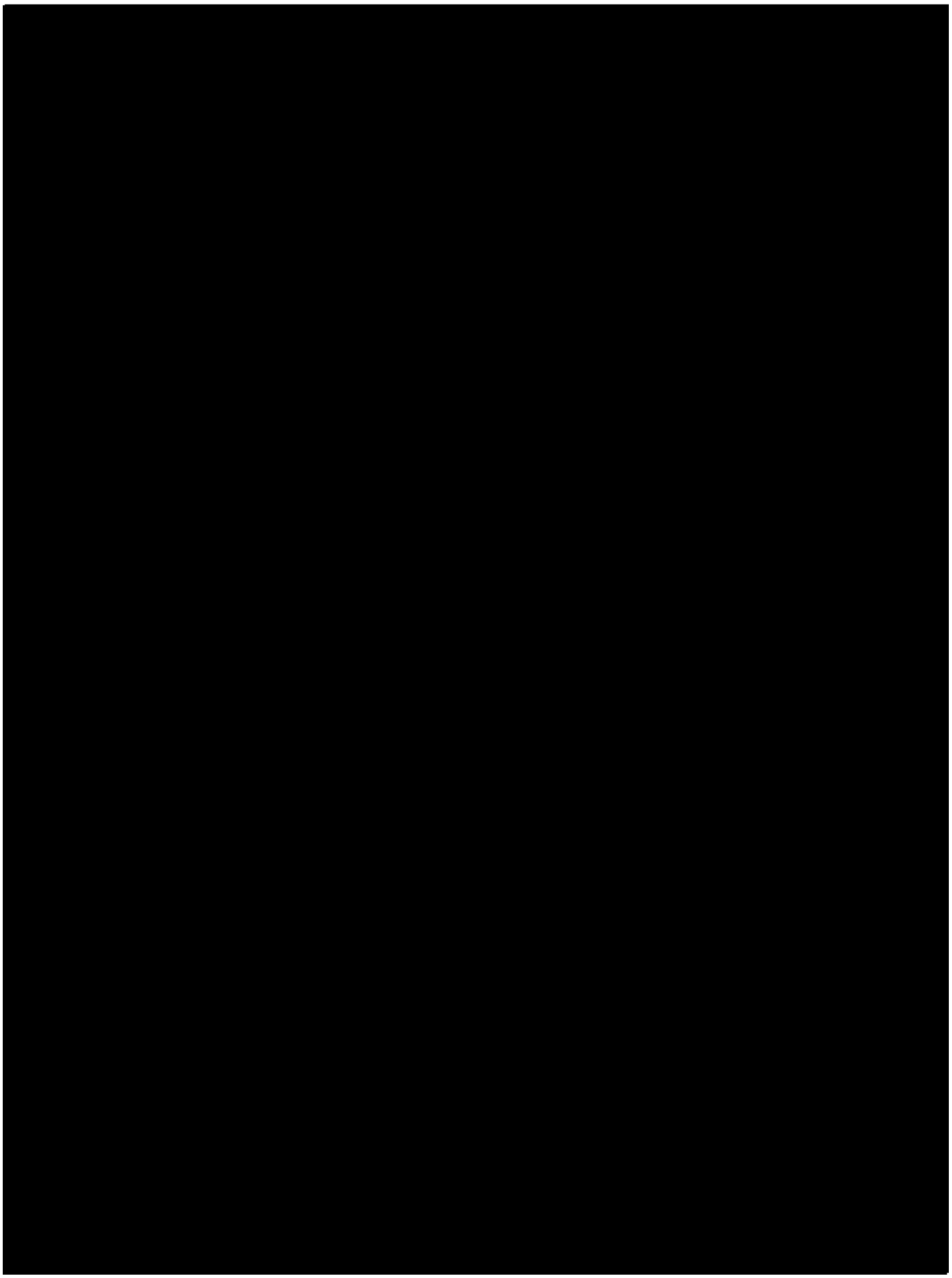
A minimum of approximately [redacted] events would be required to detect a ≥[redacted]% relative treatment effect for BIIB122 (hazard ratio = [redacted]) for the primary endpoint with ≥[redacted]% power, at the 2-sided significance level of [redacted]%. Up to [redacted] potential interim efficacy analyses, described in Section 12.9, may be conducted in which case approximately 200 events would be needed to achieve approximately ≥[redacted]% power for the study. With a sample size of approximately [redacted] participants per treatment group, followed for a minimum of [redacted] weeks ([redacted] weeks of treatment followed by [redacted] weeks of SFU) and a maximum of [redacted] weeks ([redacted] weeks of treatment followed by [redacted] weeks of SFU), a total number of up to [redacted] events is expected to have been reached when all participants complete the planned treatment period and provides the study with approximately ≥[redacted]% power with [redacted] potential IAs. These estimates assume a median time to confirmed worsening of [redacted] weeks (approximately [redacted] months) in the placebo group, and a [redacted]% annual exponential dropout/censoring rate. **Placebo group progression rate assumptions are from [redacted], and the assumed treatment effect size is based on survey results of physicians.**

Rationale: This statement was added to provide support for the effect size used in study design calculations.

[redacted]

[redacted]





[redacted]

Rationale: The updates were made for clarification and to align with FDA guidance on drug-induced liver injury.

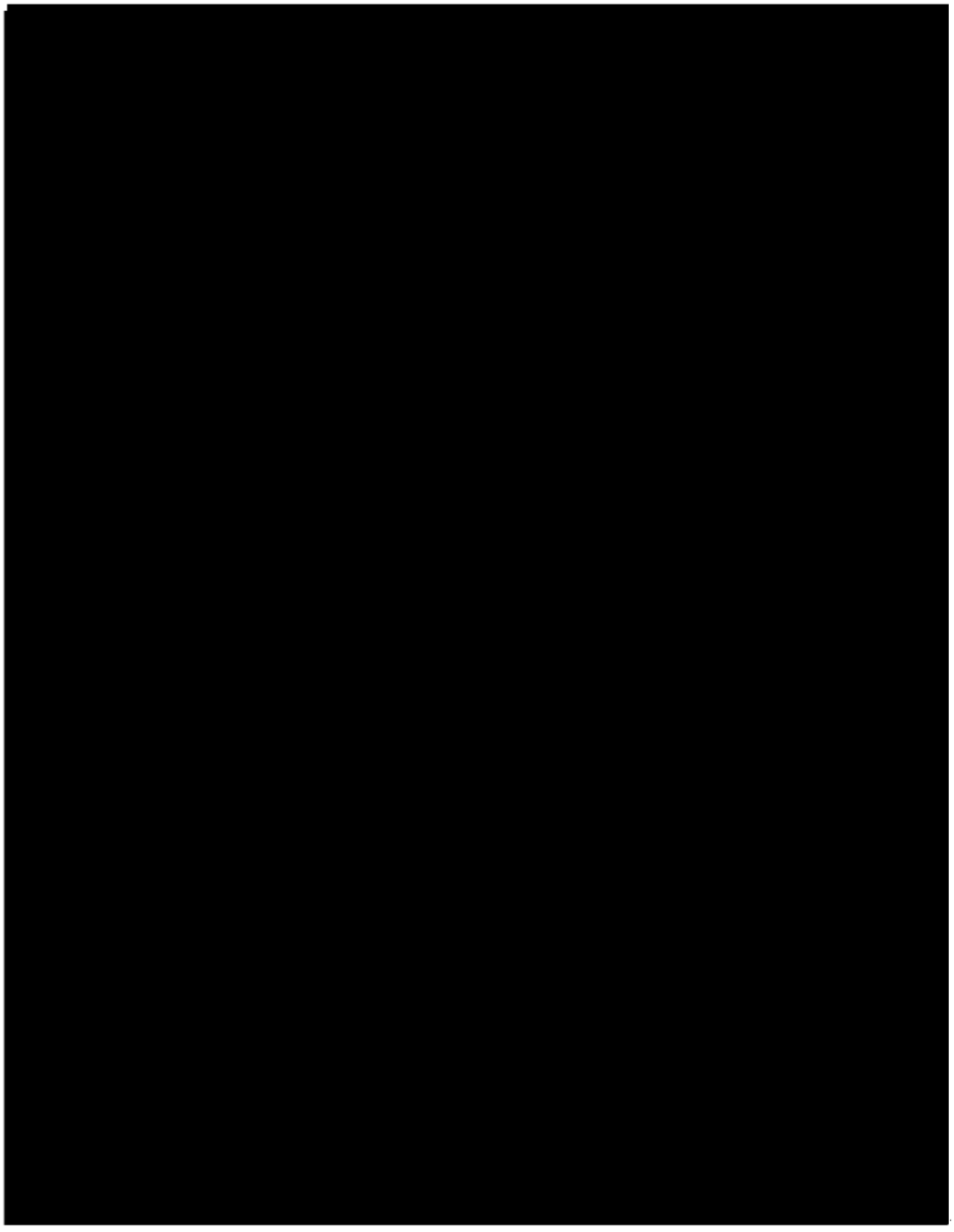
[redacted]

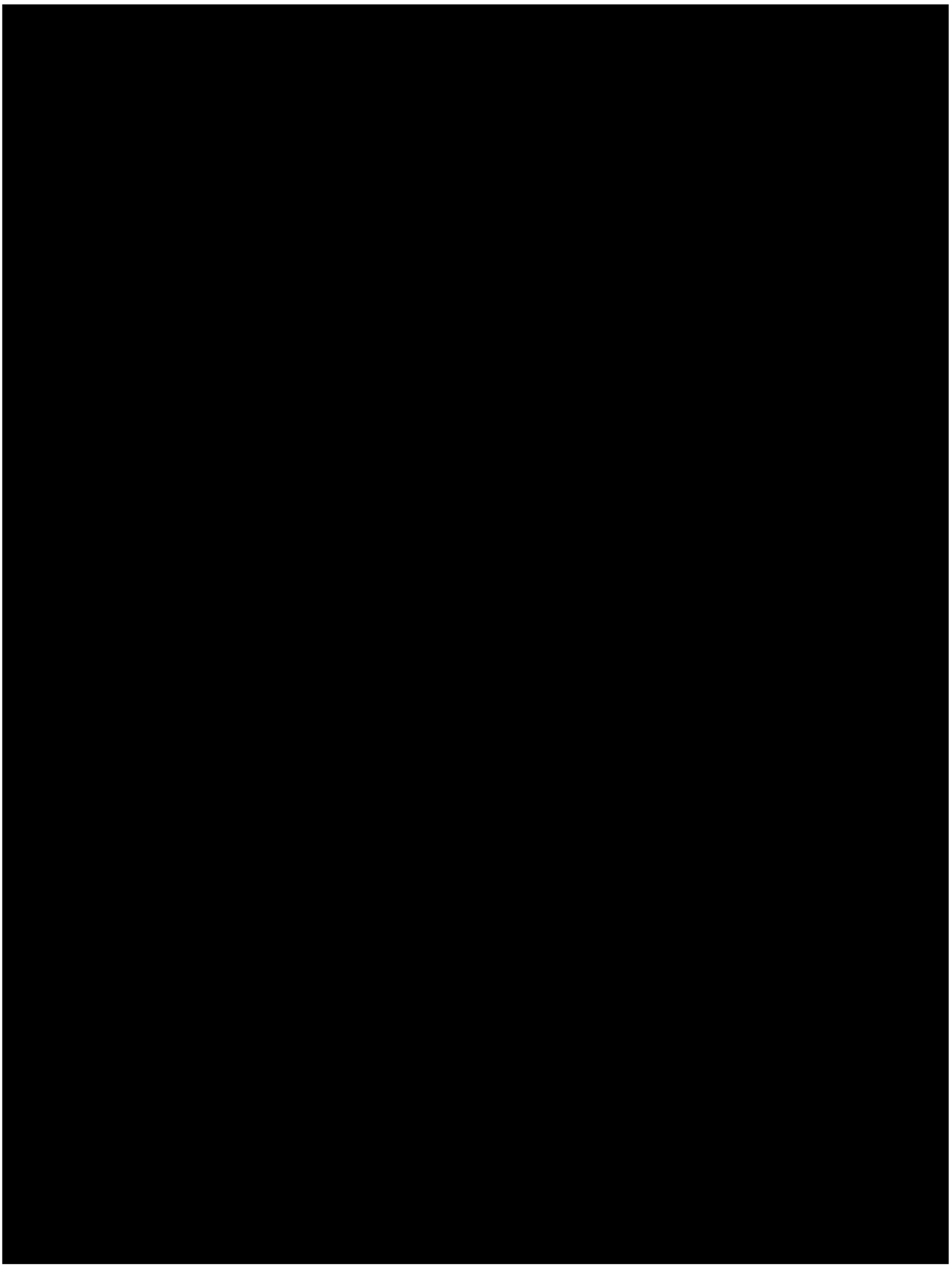
Change:

[redacted] was modified.

Now reads:

(The 2 tables below have been deleted and replaced with Table 6 and Table 7.)





[redacted]

Change: A new appendix was added.

Now reads:

[redacted]

Rationale: [redacted] was added to provide partial lists of concomitant medications that should be used with caution with BIIB122, including [redacted] and [redacted] with a narrow therapeutic index.

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.
- In Section 1.3, Table 1 (Schedule of Activities) rescreening information was deleted from footnote 2 as there is a detailed description available in Section 6.3.3 (Screen Failures) and minor rewording was applied to footnote 13.
- Clarifying text was added in [redacted]
- Typographical errors and formatting were corrected.

LIST OF ABBREVIATIONS

[redacted]	[redacted]
ADE	adverse device effect
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BID	twice daily
[redacted]	[redacted]
CSF	cerebrospinal fluid
CT	computed tomography
CYP	cytochrome P450
CYP3A4	cytochrome P450 Family 3 Subfamily A Member 4
[redacted]	[redacted]
DDI	drug-drug interaction
DLco	diffusing capacity of lungs for carbon monoxide (hemoglobin adjusted)
[redacted]	[redacted]
EC	exclusion criteria
eCRF	electronic case report form
[redacted]	[redacted]
ET	early termination
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in the first second
[redacted]	[redacted]
FVC	forced vital capacity
GLP-1	glucagon-like peptide 1
HPLC	high performance liquid chromatography
IgG	immunoglobulin G
INR	international normalized ratio
IP	Investigation product
IRB	Institutional Review Broad
IRT	interactive response technology
LP	lumbar puncture
LRRK2	leucine-rich repeat kinase 2
[redacted]	[redacted]
MDZ	Midazolam
[redacted]	[redacted]
mSE-ADL	modified Schwab and England Activities of Daily Living Scale

NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drugs
O_2	oxygen
PD	Parkinson's disease
[redacted]	[redacted]
PFT	pulmonary function test
[redacted]	[redacted]
PK	pharmacokinetic
PPMI	Parkinson's Progression Markers Initiative
QD	once daily
SAE	serious adverse event
SE-ADL	Schwab and England Activities of Daily Living Scale
SFU	safety follow-up
SOA	schedule of activities
UADE	unanticipated adverse device effect
ULN	upper limit of normal
UV	unscheduled visit