SPARK

228PD201

Statistical Analysis Plan

Placebo-Controlled Period (Year 1)

STATISTICAL ANALYSIS PLAN
Placebo-Controlled Period

Product Studied: BIIB054
Protocol Number: 228PD201

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

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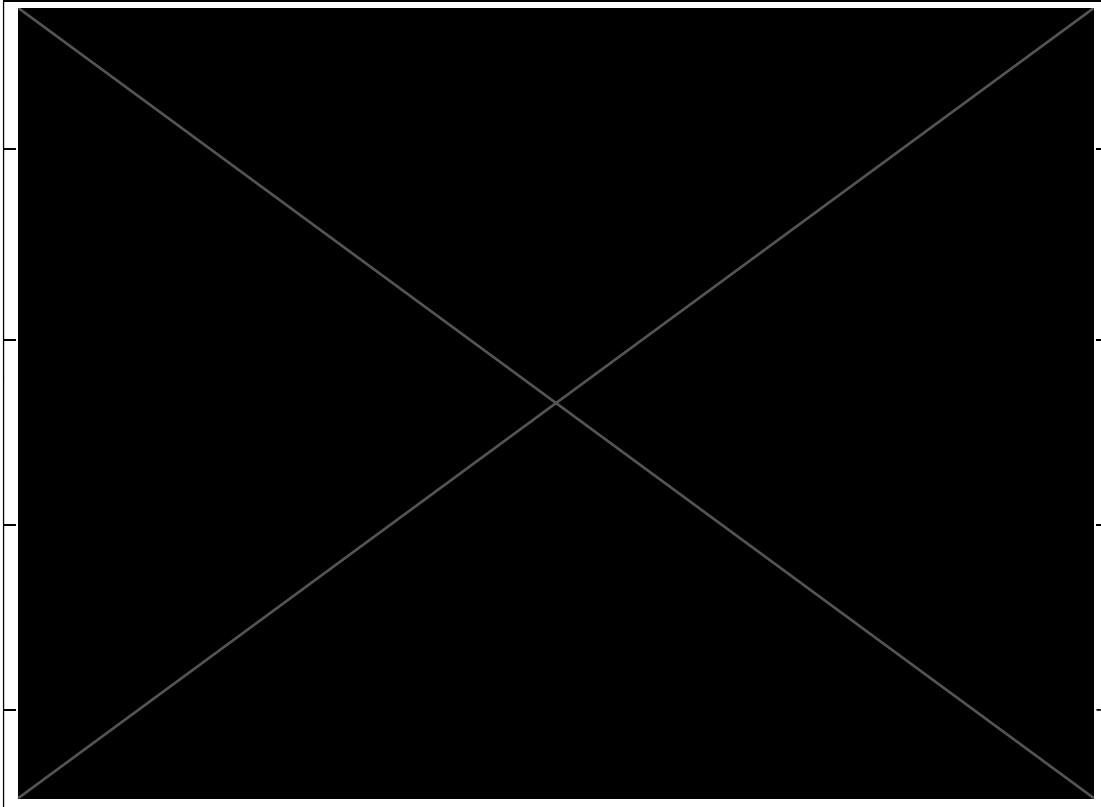

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List of Abbreviations

α-syn	Alpha-synuclein
ABC-16	The Activities-Specific Balance Confidence Scale
ADA	anti-drug antibodies
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
BL	baseline
BLQ	below the limit of quantification
BMI	body mass index
BPM	beats per minute
BRP-AUC	body region progression AUC
C_{max}	observed maximum serum aducanumab concentration
C_{min}	observed minimum serum aducanumab concentration
CI	confidence interval
CPP	Clinical Pharmacology and Pharmacometrics
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAT	Common Toxicity Criteria for Adverse Events
CV	coefficient of variation
DaT	dopamine transporter
DaTscan™	Ioflupane I123 radioligand for imaging of dopamine transporter
DBE	dose blinded extension
DBP	diastolic blood pressure
EC_{50}	Concentration at 50% of maximum observed biologic effect
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
EP-RPS	Early Parkinson's Region Progression Score
EQ-5D	EuroQol health status measure
ER	exposure-response
ESS	Epworth Sleepiness Scale
FFQ	Freezing/Falls Questionnaire
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
INR	International normalized ratio
ITT	intent-to-treat

IXRS	Interactive Voice/Web Response System
LE	Lower Extremity
LOCF	last observation carried forward
LP	lumbar puncture
LSmeans	least-square means
IV	intravenous
mAb	monoclonal antibody
MAO-B	monoamine oxidase type B
MCID	minimal clinically important difference
MCP-MOD	multiple comparison procedure – modeling
MDS-UPDRS	Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
PASE	Physical Activity Scale of the Elderly
PCS	potentially clinically significant
PD	Parkinson's disease
PDQ-39	39-point Parkinson's Disease Questionnaire
PIGD	Postural Instability Gait Difficulty
PK	pharmacokinetic(s)
PT	preferred term
PP	per-protocol
QMA	quantitative movement assessment
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SBR	striatal binding ratio
SCOPA-AUT	Scales for Outcomes in Parkinson's Disease – Autonomic
SD	standard deviation
SE	standard error
SE-ADL	Schwab & England Activities of Daily Living
SOC	system organ class
SPECT	single-photon emission computed tomography
TEAE	treatment-emergent adverse event
TD	Tremor Dominant
TUG	Timed Up and Go test
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization
WOQ	Wearing Off Questionnaire

1 SCOPE OF WORK IN THE STATISTICAL ANAYSIS PLAN

This statistical analysis plan (SAP) only covers the analyses for the placebo-controlled portion of the study (Year 1). Hereafter, the placebo-controlled portion of the study will be referred to as "the study" in the rest of this SAP (e.g., completion of the study means completion of the placebo-controlled portion). A separate SAP will be prepared for the analyses of the dose-blinded extension period and integrated analyses across both portions of the study.

2 DESCRIPTION OF OBJECTIVES AND ENDPOINTS

The objectives and endpoints of the study are listed below.

The secondary efficacy endpoints have been ranked based on the order of clinical importance.

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

To evaluate the immunogenicity of BIIB054	Incidence and titer of anti-BIIB054 antibodies in the serum
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the effect of BIIB054 on measures of clinical function and quality of life	Changes from baseline to Week 52, Week 72, and end of study in motor function and related activities of daily living (ADL) as measured by the following: • Modified Schwab and England ADL scale • MDS-UPDRS total score (including Part IV) and subpart combinations • Early Parkinson's Regional Progression Score (EP-RPS) based on MDS-UPDRS • Time to start of medications for PD symptoms, or an increase of MDS-UPDRS Part III total score ≥ MCID, whichever comes first • Quantitative movement assessment (QMA) evaluated via wearable sensors (APDM Opal sensor system with Mobility Lab software): – Measures of gait impairment and postural instability, assessed during a 2-minute walking task, Timed Up and Go (TUG) test, and postural sway test – Measures of hand dexterity and leg agility assessed during tasks conducted with upper and lower body extremities – Measures of resting tremor assessed during an arm rest task • Physical Activity Scale for the Elderly (PASE)
	Change from baseline to Week 52, Week 72, and end of study in gait impairment, postural instability, and falls as measured by the MDS-UPDRS, the Freezing/Falls

	Questionnaire (FFQ), and the incidence of relevant AEs
	Change from baseline to Week 52, Week 72, and end of study in cognitive function as measured by the Montreal Cognitive Assessment (MoCA)
	Change from baseline to Week 52, Week 72, and end of study in non-motor somatic aspects of PD as measured by the following: • Epworth Sleepiness Scale (ESS) • Scale for Outcomes in Parkinson's Disease for Autonomic Symptoms (SCOPA-AUT)
	Change from baseline to Week 52, Week 72, and end of study in health-related quality of life and mental health as measured by the following: • 39-point Parkinson's Disease Questionnaire (PDQ-39) • EuroQol 5 dimensions questionnaire (5-level) [EQ-5D-5L] • Activities-Specific Balance Confidence Scale (ABC-16) For subjects who start levodopa as their symptomatic PD medication during the study: • Emergence of wearing-off of levodopa effect, as measured by the following: – Change from baseline to Week 52, Week 72, and end of study in the Wearing-off Questionnaire (19 items) [WOQ-19] – Change from baseline to end of study in Part IV of the MDS-UPDRS

To explore the utility of QMA techniques in the assessment of early manifestations of PD and its ability to track motor dysfunction into intermediate stages of PD disability	The utility of the APDM Opal sensor system with Mobility Lab software by comparison with other functional outcome measures in the study from baseline to Week 52, Week 72, and end of study
For the subset of subjects who receive an LP, to assess CSF concentrations of BIIB054	Concentrations of BIIB054 in CSF from baseline to Week 52
To evaluate the effects of BIIB054 on levels of potential biomarkers	Changes from baseline to Week 52 and end of study in total α-syn concentration Change from baseline to Week 52 and end of study in levels of α-syn:BIIB054 antigen:antibody complexes in the plasma and to Week 52 (for the LP subset only) in CSF Changes from baseline to Week 52 in biogenic amine neurotransmitters and their metabolites in CSF (LP subset only) Changes from baseline to Week 52 of additional markers of neurodegeneration in CSF, which may include, but are not limited to tau, phosphorylated tau, neurofilament light chain, and YKL-40 (LP subset only)
To explore the effects of BIIB054 over time on possible imaging biomarkers	Change from baseline to Week 52, Week 96 and end of study in biomarkers of neurodegeneration via structural, neuromelanin-sensitive, and susceptibility-weighted magnetic resonance imaging (MRI) sequences (to be detailed in the Imaging/MRI Manual) Change from baseline to Week 96 and end of study in DaT/SPECT SBR
To collect data on the emergence of milestones associated with disease progression	• Time to start of medication for PD symptoms and need for additional symptomatic PD medication • Neuropsychiatric complications, as measured by Parts I and IV of the MDS-UPDRS and the incidence of relevant AEs

To explore the impact of immediate versus delayed initiation of BIIB054 within each treatment group on the clinical course of PD and related biomarkers during Years 2 through 4	Incidence and/or time to onset of disease milestones for the following parameters: • Cognitive impairment as measured by MoCA • Gait impairment, postural instability and falls as measured by MSD-UPDRS, the FFQ, and the incidence of relevant AEs • Levodopa treatment-related complications (wearing-off, dyskinesia), as measured by the WOQ-19 and Part IV of the MDS-UPDRS • Time to start of medication for PD symptoms and need for additional symptomatic PD medication • Neuropsychiatric complications, as measured by Parts I and IV of the MDS UPDRS and the incidence of relevant AEs
To explore the treatment effect of BIIB054 on disease progression rates and time to progression.	Disease progression is defined as confirmed increase in Hoehn and Yahr Scale or confirmed minimal clinically meaningful difference (MCID) [worsening] of any part of the MDS-UPDRS • Disease Control Rate is the proportion of subjects who did not progress (met the criteria above) at Week 52, Week 72, and end of study • Time to disease progression (per the criteria above) • Time to disease progression based on confirmed MCID worsening in MDS-UPDRS Part III

3 STUDY DESIGN

3.1 Study Overview

This Phase 2a, randomized, double-blind, parallel-group, placebo-controlled study (Year 1) with an active-treatment dose-blinded period (Years 2 through 4) will examine the efficacy, safety, PK, and pharmacodynamics of BIIB054, administered every 4 weeks via IV infusion

to adult subjects with PD. Approximately 311 subjects will be enrolled at about 85 sites globally.

3.1.1 Year 1 (Placebo-Controlled Portion of the Study)

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

Subjects will be enrolled into 2 cohorts. Cohort A will be randomized first, in a 1:1:1:1 ratio into each of th e4 treatment arm and will include approximately 24 subjects. Randomization and dosing for Cohort B (approximately 287 planned subjects) will start after all subjects in Cohort A complete Week 12 assessments, and all available safety and PK data are reviewed by the IDMC. Randomization of subjects in Cohort B will be stratified by baseline (Day 1) MDS-UPDRS Part I + II + III total scores (≤35 and >35) and striatum SBR (≤1.2 and >1.2), and subjects will be randomized at Day 1 into 1 of 4 parallel dosing arms in each stratum.

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

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

At a subset of sites (including all Cohort A sites), LP will be performed for collection of CSF samples from approximately 100 subjects; further details will be provided in section 14.2 in the protocol and the Study Reference Manual.

THe Week 48 infusion is the last infusion of the placebo-controlled period, and Week 52 is the first dosing of the Dose-blinded portion of the study.

3.1.2 Years 2 Through 4 (Active-Treatment Dose-Blinded Portion of the Study)

Prior to Infusion 14 (the first dose of Year 2) at Week 52, subjects who received placebo in Year 1 will be randomized into 1 of the active-dosing arms for Year 2; these subjects will receive BIIB054 in Year 2. Subjects who received BIIB054 (1250 mg or 3500 mg) in Year 1 of the study will continue with the same dose regimen in Year 2. Subjects receiving the 250-mg dose in Year 1 continued on their original dose assignement.

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

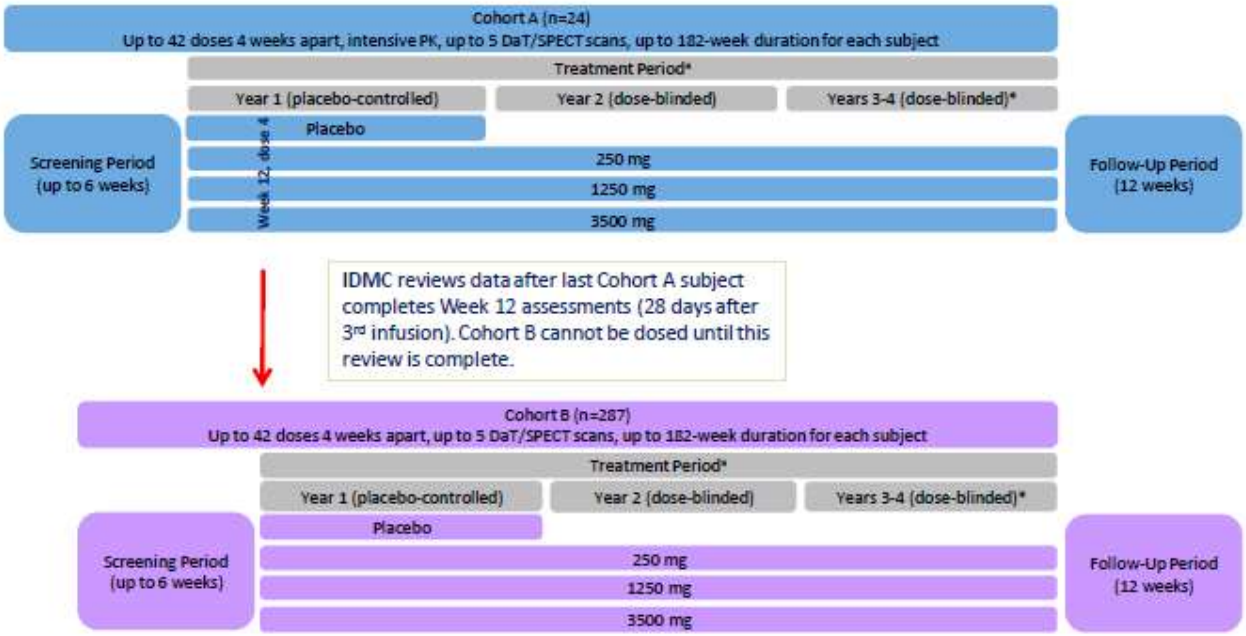
Subjects who complete dosing through Week 96 and the Final Visit 12 weeks after the last visit will be considered Year 2 completers in the eCRF.

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

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

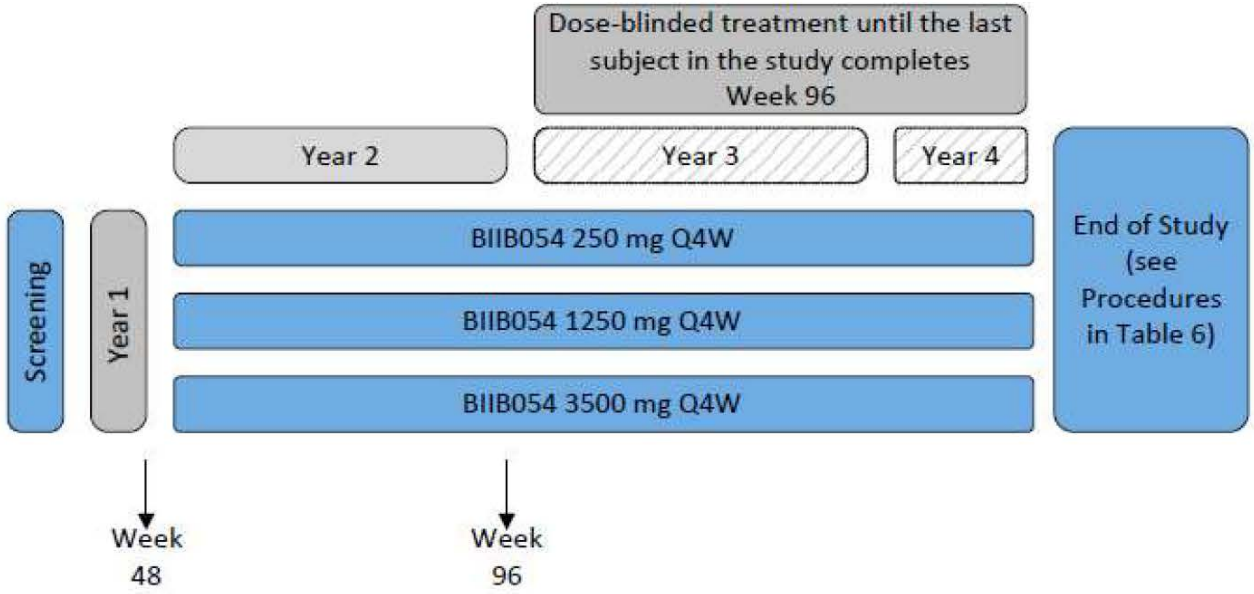
3.2 Study Schematic

Figure 1: Study Design



DaT = dopamine transporter; IDMC = independent data monitoring committee; PK = pharmacokinetic(s); SPECT = single-photon emi
tomography
[a] Prior to Infusion 14 (first dose of Year 2), subjects who received placebo in Year 1 will be randomized to 1 of the active-treatment gr
receive BIIB054 in Year 2. Subjects who received BIIB054 in Year 1 will continue with the same dose regimen in Years 2 through 4.
the last subject in the study has had his or her Week 96 Visit. Not all subjects will have the opportunity for dosing past Year 2/Week 9

Figure 2: Overview of Study Dosing:



Q4W = every 4 weeks.

Year 1 = Placebo-controlled period. Years 2 through 4 = Active-treatment dose-blinded period. Not all subjects will have the opportunity for dosing

3.3 Schedule of Events

See Protocol Section 4.2.

4 SAMPLE SIZE JUSTIFICATION

The sample size calculation is based on changes in MDS-UPDRS Part I + II + III total score at Week 52 and at Week 72 of treatment. Based on data from the Parkinson's Progression Markers Initiative study, the placebo subject's mean and standard deviation (SD) at Week 52 and Week 72 are assumed to be 8.0 (10.64) and 9.6 (13.7) respectively. Assuming a maximum of 55% reduction in the change from baseline in the active group with maximum response relative to placebo group, the mean (SD) for this active group will be 3.2 (10.64) and 3.84 (13.7) respectively at Week 52 and Week 72, and the responses for other active groups are assumed to be somewhere between 0 and the maximum response. The primary analysis will be based on the MCP-MOD method to detect a dose-response trend while controlling for multiplicity. Optimal contrasts will be constructed to detect potential dose-response trend under common dose-response curves (e.g., E_{max}, exponential, logistic, linear in log dose, and quadratic model, which are illustrated with parameters shown in Figure 4.1 which will be used for both Week 52 and Week 72). The planned enrollment is 311 subjects total (24 subjects in Cohort A and 287 subjects in Cohort B, 4.1). Actual enrollment is 357 subjects. In Cohort A, 29 subjects were randomized in a 1:1:1:1 ratio to each of the treatment groups, while in Cohort B 328 subjects were randomized in 2:1:2:2 ratio to the placebo, 250 mg, 1250 mg, and 3500 mg groups. Based on the actual enrollment, the estimated number of subjects by cohort and treatment groups are given in Table 4.4.2 below. After accounting for dropout rate of 10% and 15% at Week 52 and Week 72, respectively, the estimated sample sizes are given in Table and Table 1. With the updated sample size, the study will provide an average power of approximately 80% to detect the dose-response trend over 1 year of treatment, based on a 2-sided type I error of 0.05 and approximately 73% of power at the Week 72 analyses, based on a 2-sided type I error of 0.05. Overall, the sample size in the study will provide approximately 89% power, taking into consideration success at either Week 52 or Week 72. The final candidate models for the MCP-MOD are prespecified and described below.

With an estimated sample size of 100 subjects dosed per arm in the 1250 mg and 3500 mg arms, the study has 80% probability of detecting AEs with a rate of 1.6% or greater in these 2 arms, and a 90% probability of detecting AEs occurring with a rate of 2.3% or greater.

Table 4.1: Estimated Sample Size Per Group (Planned)

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

Table 4.2: Estimated Sample Size Per Group Based on Actual Enrollment (Before Drop-Outs)

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

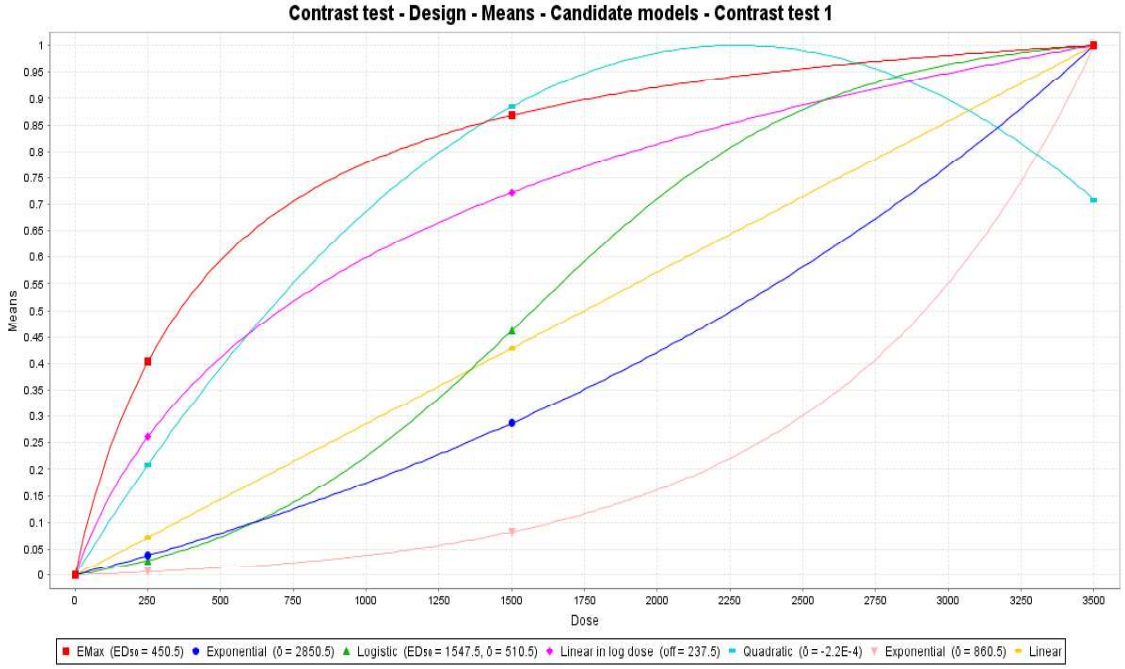
Table 4.3: Estimated Sample Size Per Group Based on Actual Enrollment (After Adjusting for 10% Drop-Out At Week 52

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

Table 1: Estimated Sample Size Per Group Based on Actual Enrollment (After Adjusting for 15% Drop-Out At Week 72

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

Figure 4.1: Candidate Models for Dose-Response



5 STATISTICAL ANALYSIS METHODS

5.1 General Considerations

Summary tables will be presented using descriptive summary statistics. For continuous variables, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, and range (minimum and maximum). For categorical variables, this will generally include: number of subjects randomized or dosed, number with data, and the percent of those with data in each category.

Unless otherwise specified, baseline value is defined as the most recent non-missing measurement collected prior to the first dose. Change from baseline will be defined as post-baseline value minus baseline value.

Statistical testing will be performed to assess efficacy endpoints by conducting pairwise comparison between each BIIB054 group and placebo, and no multiplicity will be adjusted. Unless stated otherwise, all the statistical tests will be 2-sided with a statistical significance level of 0.05 .

The statistical software, SAS® will be used for all summaries and analyses.

5.1.1 End of Study (EOS) and End of Treatment (EOT)

For subjects who complete the placebo-controlled period of the study, EOS visit is defined as Week 52 visit; for subjects who are early terminated, EOS visit is defined as the scheduled

follow-up visit after EOT visit. For subjects who complete the treatment, EOT visit is defined as Week 48.

5.1.2 Analysis Population

- Intent-to-treat (ITT) population:
  The intent-to-treat population is defined as all randomized subjects who received at least one dose of study treatment (BIIB054 or placebo).

- Per-protocol (PP) population:
  The per-protocol population is defined as a subset of the ITT population who received at least 70% (10 doses) of study treatment (BIIB054 or placebo).

- Safety population:
  The safety population is defined as all subjects who received at least one dose of study treatment (BIIB054 or placebo).

- PK population:
  The PK population is defined as all subjects in the ITT population who had at least one measurable BIIB054 concentration in serum or CSF.

- Pharmacodynamic population:
  The pharmacodynamic population is defined as all subjects in the ITT population who had at least one post-baseline pharmacodynamic measurement.

- Immunogenicity population:
  The analysis population for immunogenicity is defined as all subjects in the safety population.

- Biomarker population:
  The biomarker population is defined as a subset of the ITT population with at least one post-baseline biomarker measurement.

5.2 Background Characteristics

The summaries in this section will be based on the ITT population. Unless otherwise specified, all the summary tables and listings will be presented by treatment group.

5.2.1 Accounting of Subjects

The summary of subject disposition will include number (%) of subjects randomized, number (%) subjects randomized but not dosed, number (%) of subjects who completed the treatment/study, and number (%) of subjects who discontinued treatment and/or withdrew from study. For subjects who discontinued treatment and/or withdrew from study, the reasons for discontinuation and/or withdrawal, and days on treatment and days on study will be summarized and listed. The pattern (time and rate) of treatment discontinuation and study

withdrawal will be displayed by Kaplan-Meier plot. The number of subjects in each analysis population will be summarized.

In addition, number of subjects dosed and number of subjects who completed the treatment/study will be summarized by country (region) and site.

The categorization of region is based not only on consideration of geography but also on type of health care system and access to health care in each country. The categories for regions will be:

- Region 1: United States (US);
- Region 2: European countries (including Austria, France, Germany, Israel, Italy, Poland, Spain and United Kingdom) and Canada.

5.2.2 Demographics and Baseline Characteristics

Demographic data, including age (in years), age category (40-50, 51-60, 61-70, 71-80 years), gender, race, ethnicity, height, weight, body mass index (BMI), country (region) and year of education at baseline will be summarized by treatment groups and overall.

Baseline PD history will be summarized by treatment groups and overall, using descriptive statistics. Time since onset of PD symptoms (in years), time since PD diagnosis (in years), subtype of PD (PIGD, TD or indeterminate), side predominately affected at disease onset, symptoms presented at PD diagnosis and immediate family with a history of Parkinson's Disease will be summarized. MDS-UPDRS total and subtotal scores, PIGD, TD, and LE subscore, Hoehn and Yahr stage, modified Schwab and England-ADL (SE-ADL), PASE, QMA, MoCA, ESS, SCOPA-AUT, PDQ-39, EQ-5D-5L, ABC-16, WOQ-19 and FFQ will be summarized. DaT/SPECT imaging outcomes, structural MRI imaging and neuromelanin MRI imaging outcomes will also be summarized. Baseline MDS-UPDRS score is defined as the Day 1 visit, if Day 1 visit score is not available, screening visit will be used. Baseline PD history data will be listed.

Number (%) of subjects with any PD treatment history will be summarized by treatment groups and overall. Total duration of previous therapies and reason for stopping therapies will be summarized. Number (%) of subjects who had taken MAO-B inhibitors, Dopamine Agonist, Levodopa and other PD medications will be displayed by treatment groups and overall. A listing of PD treatment history will be generated.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number (%) of subjects with history (including both ongoing and not ongoing medical conditions) will be summarized by system organ class and preferred term, and by preferred term only. A listing of medical history will be generated.

5.2.3 Concomitant Medications and Non-drug Therapies

All concomitant medications will be coded using the World Health Organization (WHO) medication dictionary. All concomitant non-drug therapies will be coded using the MedDRA dictionary. A concomitant medication/therapy will be defined as any therapy that was taken

on or after the day of the first dose of study drug. This include therapies that start prior to the initiation of the first dose if their use continues on or after the date of first dose. To determine whether medications and/or non-drug therapies with missing start or stop dates are concomitant with study treatment, the following additional criteria will be used:

- If both the start and stop dates of a therapy are missing, then the therapy will be considered concomitant;
- If the start date is missing and the stop date of the therapy falls on/after the first dose date, then the therapy will be considered concomitant;
- If the start date is missing and the stop date of the therapy falls before the first dose date, then the therapy will be considered non-concomitant;
- If the start date of a therapy is prior to the date of the first dose and the stop date of the therapy is missing and the therapy is listed as ongoing, that therapy will be considered concomitant;
- If the start date of a therapy is prior to the date of first dose and the stop date of that therapy is missing and the therapy is not listed as ongoing, that therapy will be considered non-concomitant.
- If the start date of a therapy is on/after the date of first dose but in the treatment period (last dosing date+28 days) and the stop date of that therapy is missing, then that therapy will be considered concomitant.
- If the start date of a therapy is on/after the treatment period (last dosing date+28 days) and the stop date of that therapy is missing, then that therapy will be considered non-concomitant.

For a record with a partial start/end date, the year/month of the partial date will be compared to that of the date of first dose to determine whether it is concomitant.

The number and percent of subjects taking concomitant medication and non-drug treatments will be summarized by treatment group and overall. Concomitant PD medication will be summarized separately from the other concomitant medication.

5.2.4 Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a Protocol Deviation log and categorized as major or minor deviations. The major protocol deviations will be summarized and listed. The minor protocol deviations will also be listed. Number (%) of subjects with at least one major deviation will be summarized by category. The protocol deviation related to COVID-19 will be listed.

5.2.5 Study Drug Exposure and Study Drug Compliance

The number of infusions administered will be summarized as both continuous and category variables (categories as integers from 1 to 13, and 1-3, 4-6, 7-9, 10-13). The number of weeks on study drug, calculated as (date of last dose – date of first dose +1)/7, will be summarized

as a categorical variable (every 8 weeks from 0 to ≥48 Weeks) as well as a continuous variable. Overall compliance, which is the percentage of drug infusions actually received over 13 planned doses, will be summarized regardless of study completion for all subjects. Percentage of study treatment taken up to the last dose, calculated as (the actual number of infusions / the number of infusions a subject is expected to take until the date of last infusion), will be summarized as a continuous variable. This table will be presented by treatment group. For subjects who completed study, the number of expected infusions is 13. For subjects who withdrew from study early, the number of expected infusions is the planned number of infusions before the time of withdrawal.

A listing of study drug administration records, including infusion start date and time, infusion stop date and time, total volume prepared, total volume administered, location of infusion, initial infusion rate, dose interruption or rate change or not, time of interruption or rate change, infusion rate after interruption or rate of change, reason for interruption or rate change will be provided.

5.3 Efficacy Endpoints

5.3.1 General Consideration

Clinical efficacy (clinical function) Assessments include Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), quantitative movement assessment (QMA), modified Schwab & England Activities of Daily Living (SE-ADL), Physical Activity Scale of the Elderly (PASE), Montreal Cognitive Assessment (MoCA), Epworth Sleepiness Scale (ESS), Scales for Outcomes in Parkinson's Disease - Autonomic (SCOPA-AUT), 39-point Parkinson's Disease Questionnaire (PDQ-39), EQ-5D-5L, Activities-Specific Balance Confidence Scale (ABC-16), Wearing Off Questionnaire (WOQ-19) and Freezing/Falls Questionnaire (FFQ). The questionnaire as well as the scoring algorithm for all these clinical assessments are described in Appendix I.

Unless otherwise noted, the analysis will be performed based on all the subjects in both Cohort A and B and the common visits. For numerical outcomes, the actual value and the change from baseline will be presented by treatment group and visit. For categorical outcome, the count and frequency will be summarized by treatment group and visit.

Analysis population

All clinical function endpoints will be evaluated in the ITT population as defined in Section 5.1.2. MDS-UPDRS and QMA may also be analyzed in the per protocol population as defined in Section 5.1.2.

Baseline value

MDS-UPDRS, modified SE-ADL and PASE are assessed at both screening visit and Day 1 visit. QMA, ESS, SCOPA-AUT, PDQ-39, EQ-5D-5L, ABC-16, WOQ-19 and FFQ are assessed at Day 1 visit but not the screening visit. MoCA and ESS are assessed at the

screening visit but not Day 1 visit. For all of them, the baseline values are defined as the latest data collected prior to or on the first dose date.

Visit windows for mapping clinical function endpoint

Assessments from all scheduled visits, EOT visit and EOS visit, and unscheduled visits will be mapped to an appropriate analysis visit using a windowing scheme (Appendix II).

Handling missingness of itemed question score

For MDS-UPDRS, the maximum number of missing item allowable to provide a valid standard score for each part are: 2 for Part I, 2 for Part II, 9 for Part III, and 0 for Part IV. For each part, if no item is missing, the total score is the sum of all the item scores in the part. If some items are missing, the total score is the sum of all available item scores multiplied by the total number of items in the part and then divided by the number of items with available scores. MDS-UPDRS Part I+II+III (II+III) total score is the sum of all relevant part scores. As subjects were not guided to enter 0 to the Part IV questionnaire before they start symptomatic PD medication, some subjects left blank to the Part IV items at applicable visits. Therefore, we will impute the missing item in Part IV as 0. The total score is missing if and only if any relevant part score is missing (Stebbins et. al. 2015). For all other clinical endpoints, if more than half of the items are missing, then the total score is set to be missing. Otherwise, the missing item score will be imputed and used to derive the total score. In particular, if an item score is missing at a post baseline visit, it will be imputed by last observation carried forward method. And if an item score is missing at baseline, it will be imputed by the median of the item score among all the subjects of the same PD subtype (PIGD-dominant, Tremor-dominant, Indeterminate) in the study who have a baseline score in the item.

5.3.2 MDS-UPDRS

5.3.2.1 Primary efficacy endpoint

Estimand:

The estimand of the primary analysis is the mean difference of the change from baseline in MDS-UPDRS I+II+III total score at Week 52 between treatment groups in the ITT population in a hypothetical setting where subjects do not start PD medication. MDS-UPDRS data collected after the intercurrent events, i.e., subjects start PD medication will be excluded in the primary analysis. Specifically, the estimand takes the following into consideration:

A. Population: ITT population as defined in Section 5.1.2
B. Variable: change from baseline to Week 52 in MDS-UPDRS score
C. Intercurrent events: had PD medication not been made available to subjects prior to Week 52
D. Population-level summary: difference in variable means between treatment conditions.

MMRM will be used as the primary analysis to analyze the change from baseline in MDS-UPDRS score. The model includes the fixed effects of treatment group, time (categorical), baseline PD subtype (categorical; PIGD vs TD vs indeterminate), prior use of PD medication (categorical), treatment group-by-time interaction, region (categorical), baseline MDS-UPDRS I+II+III total (continuous), baseline MDS-UPDRS I+II+III total by time interaction and baseline striatum SBR values (continuous), and baseline striatum SBR by time interaction. A random intercept and slope will be included in the model to model the random effects within subjects. If small sample size in subgroups of PD types causes lack of model convergence, the indeterminate group will be combined with the TD group. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Least square means (LSmeans) of each treatment group as well as treatment difference between BIIB054 groups and placebo will be displayed with 95% CI and p-value at Week 52. If the distribution of the outcome is highly skewed, p-value will be generated from the MMRM model based on ranked data. In the primary analysis, missing data are assumed to be missing at random (Rubin 1976), and MDS-UPDRS I+II+III score is impacted by PD medication.

The multiple comparison procedure-modelling (MCP-MOD) method will be used to assess the dose-response relationship while controlling for multiplicity (Pinheiro 2013). The dose-response parameter of interest for MCP-MOD are the least-squares means (LSmeans) at Week 52 for each treatment group from the MMRM model. The underlying models to be tested are specified in Figure 4.1. P-value of dose response will be presented. Details of MCP-MOD procedure are specified in Appendix III.

A multiple comparison adjustment method will be applied to control the overall type I error at 0.05 in the study, due to the primary endpoint of change from baseline in MDS-UPDRS total score being analyzed at Week 52 and Week 72, and superiority against placebo is considered reached in the study if statistically significant result is achieved at either timepoint at the respective adjusted alpha-level. This will be applied to the p-value from the MCP-MOD model. Please refer to Section 6 “Interim Analyses” for more detail.

Nominal p-values for pair-wise comparison of each active group vs placebo will be reported, no additional multiple comparison adjustment will be applied.

Item 1.6 of features of dopamine dysregulation syndrome will be excluded to calculate all the scores.

5.3.2.2 Secondary endpoints and additional exploratory MDS-UPDRS based endpoints

The analysis approach and the MMRM model as described for the primary endpoint will be performed for additional MDS-UPDRS based endpoints as listed below, except that, 1) the baseline MDS-UPDRS I+II+III total score term in the model will be replaced by the corresponding baseline value of MDS-UPDRS total or sub-part score being analyzed, 2) MCP-MOD dose-response may be performed, 3) no additional multiple comparison adjustment will be applied for secondary efficacy and exploratory efficacy endpoints

- MDS-UPDRS Parts I, II, III (**Secondary Efficacy Endpoints**),
- MDS-UPDRS Parts II+III, Ib+II+III

- Postural Instability -Gait Difficulty (PIGD) score (mean score of MDS-UPDRS items 2.12+2.13+3.10+3.11+3.12),
- Lower Extremity (LE) score (mean score of MDS-UPDRS items 3.10+3.11+3.12+3.13+3.3d+3.3e+3.7a+3.7b +3.8a+3.8b+3.17c+3.17d+2.12+2.13), and Tremor score (mean score of MDS-UPDRS items 2.10+3.15a+3.15b+3.16a+3.16b+3.17a+3.17b+3.17c+3.17d+3.17e+3.18).

5.3.2.3 Sensitivity analysis

A sensitivity analysis will be conducted for MDS-UPDRS based endpoints, by including the data after PD medication assessed in the "OFF" status, that is, the assessment was made at least 12 hours since the last time the subject took the medication, or assessed in the "off" status by the rater, or if subject reported not taking PD medication at that visit.

The analyses will be performed based on the same MMRM model as described for the primary endpoint, except the following:

- An unstructured covariance matrix will be used to model the within-subject variance-covariance errors (instead of random intercept and slope). If the unstructured covariance structure matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be used.

The table below summarizes the detailed information.

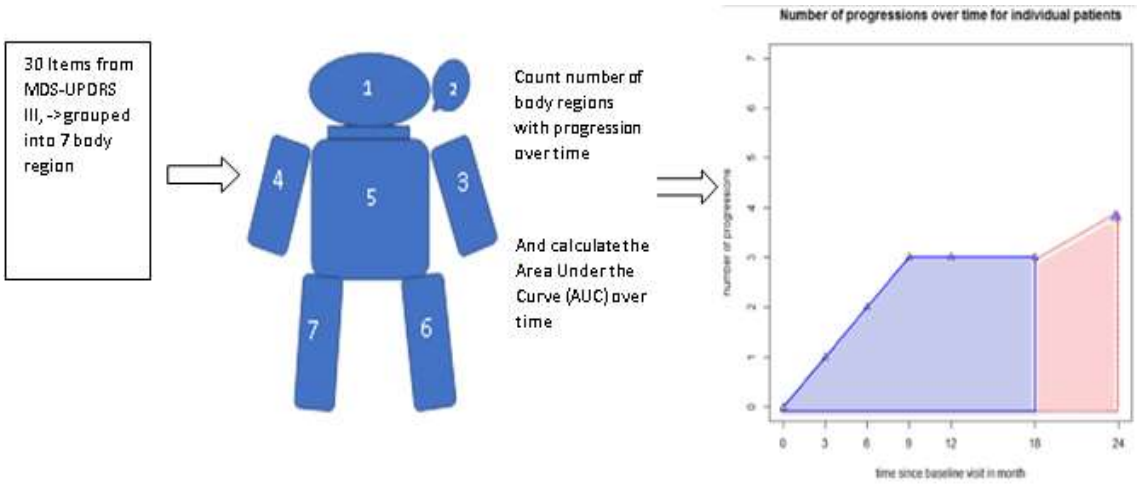
		Primary analyses		Sensivity analyses	
MDS-UPDRS endpoints	Type	MMRM model covariance structure	Data after PD medications included (Y/N)	MMRM model covariance structure	Data after PD medications included (Y/N)
I+II+III	Primary	Based on random slope and intercept	N	Based on pre-specified covariance structure (UN if no convergency issue occurs)	Y
I	Secondary		N		Y
II	Secondary		N		Y
III	Secondary		N		Y
II+III	Exploratory		N		Y
Ib+II+III	Exploratory		N		Y
I+II+III	Exploratory		N		Y

PIGD	Exploratory		N		Y
Tremor	Exploratory		N		Y
LE	Exploratory		N		Y

5.3.2.4 Early Parkinson's Regional Progression Score (EP-RPS) measure

The Early Parkinson's Regional Progression Score (EP-RPS) measure is a novel method of assessing disease progression based on a modified scoring algorithm for the MDS-UPDRS Part III items that is potentially more reliable and sensitive to progression in early stages of PD, as compared with change in MDS-UPDRS Part III total score. The new concept has been developed to capture the spread of the progression of disease symptoms across body regions as a reflection of the underlying topographic spread of pathology. Figure 5.1 shows a general diagram of the concept of EP-RPS and the detailed definition are provided in Appendix IV.

Figure 5.1: Diagram of the concept of EP-RPS measure



EP-RPS will be summarized and analyzed by using ANCOVA model. The model will include the endpoint as the outcome, fixed effect of treatment group (categorical) and adjust for region (categorical), baseline PD subtype (categorical), baseline MDS-UPDRS Part III total score (continuous) and baseline striatum SBR values (continuous). Least square means (LSmeans) of each treatment group as well as treatment difference between BIIB054 groups and placebo will be displayed with 95% CI and p-value at Week 52. MDS-UPDRS Data after the PD medication will be included and excluded in two separate analyses, since this endpoint is unknown, though expected to be minimally impacted by PD medications and including the data will reduce the amount of missing data.

Spearman's correlation of this endpoint with change from baseline at Week 52 in MDS-UPDRS Part III will be calculated.

5.3.2.5 Time to start of PD medication, or an increase of MDS-UPDRS Part III total ≥ MCID (4.63), whichever comes earlier

Time to start of PD medication, or an increase of MDS-UPDRS Part III total score ≥4.63, the minimal clinically important difference (MCID) [Horvach 2017], whichever comes earlier, will be estimated using the Kaplan-Meier method. Cox's proportional hazard model will be used to analyze the data. The model will adjust for baseline MDS-UPDRS III score (continuous), region (categorical), prior use of PD medication (categorical), baseline PD subtype (categorical), and baseline striatum SBR values (continuous). Hazard ratio of each BIIB054 group vs. placebo group with 95% CI will be displayed. P-value of the test on whether hazard ratio is 1 will also be presented. Proportionality assumption will be tested, and if the assumption does not hold, the log rank test will be used to test the treatment differences.

5.3.2.6 Time to start of PD medication

Time to start of PD medication will be analyzed in the same fashion as the analysis of time to start of PD medication, or an increase of MDS-UPDRS Part III total ≥MCID (4.63), whichever comes earlier. However, the proportional harzard model will not be performed, as the proportionality assumption is not valid due to the study design where subjects who need a PD medication will wait till month 6 before starting to take the medication.

Additionally, time to start of PD medication due to worsening of PD symptoms will be analyzed in the same fashion. In this outcome, start of PD medication due to other reasons but not due to worsening of PD symptoms is not considered as an event.

5.3.2.7 Time to disease progression and DCR (Disease Control Rate)

Disease progression is defined as confirmed increase in Hoehn and Yahr > 0 or a confirmed MCID worsening in MDS-UPDRS part I or II or III [Horvach et. al. 2015; Horvach 2017]. If the disease progression criteria is not met, then the disease is considered as within control (i.e. Disease control rate is 1-disease progression rate). .

Summary table will be presented for the disease progression and disease control rates. The difference between active and placebo group groups will be tested based on a logistic model. The model will adjust for baseline MDS-UPDRS I+II+III score (continuous), region (categorical), baseline Hoehn and Yahr (categorical: <2 vs >=2), prior use of PD medication (categorical), baseline PD subtype (categorical), and baseline striatum SBR values (continuous). Time to disease progression will be further analyzed using the Cox's proportional hazard model. The model will adjust for baseline MDS-UPDRS I+II+III score (continuous), region (categorical), baseline Hoehn and Yahr (categorical: <2 vs >=2), prior use of PD medication (categorical), baseline PD subtype (categorical), and baseline striatum SBR values (continuous). Proportionality assumption will be tested, and if the assumption does not hold, the log rank test will be used to test the treatment differences. MDS-UPDRS and Hoehn and Yahr data after PD medications will be included and excluded in the analysis respectively, due to the impact of the score change by PD medications.

Time to disease progression based on confirmed MCID worsening in MDS-UPDRS Part III will be analyzed based on the similar approach as above, except replacing baseline MDS-UPDRS I+II+III score with baseline Part III score and removing the baseline Hoehn and Yahr as a covariate.

5.3.2.8 Subgroup analysis

Subgroup analyses will be performed for the outcomes of MDS-UPDRS part III and I+II+III respectively in the subgroups of the following baseline covariates. The MMRM model is the same as the one in the primary analyses. If the MMRM model of a specific subgroup does not converge, no results will be displayed for that subgroup. A forest plot will be generated to present the results of all subgroups together.

- Age (above v.s. below median)
- Gender (male v.s. female)
- region, (US v.s. Other)
- prior use of PD medication (Yes v.s. No)
- time since onset of PD symptoms (above v.s. below median)
- baseline type of PD (tremor-dominant v.s PIGD-dominant v.s. Indeterminate)
- baseline MDS-UPDRS III (above v.s. below median)
- baseline MDS-UPDRS I+II+III (above v.s. below median),
- baseline modified H&Y stage (<=1.5 v.s. >=2)
- baseline MoCA (above v.s. below median)
- baseline total striatum SBR measure, occipital reference (<=mean-sd v.s >mean-sd to <=mean+sd v.s. >mean+sd)
- baseline contralateral putamen SBR measure, occipital reference (<=mean-sd v.s >mean-sd to <=mean+sd v.s. >mean+sd)
- baseline ipsilateral putamen SBR measure, occipital reference (<=mean-sd v.s >mean-sd to <=mean+sd v.s. >mean+sd)
- baseline GRE total substantia nigra neuromelanin ROI normalized (region 4) neuromelanin signal (above v.s. below median),
- baseline GRE total substantia nigra neuromelanin ROI volume in cm3 (above v.s. below median),
- baseline total striatum volume (above v.s. below median),
- baseline lateral ventricle volume (above v.s. below median),
- baseline CSF aggregated alpha synuclein (postive v.s. negative),
- baseline CSF neurofilament concentration (above v.s. below median),
- baseline stride time variability (above v.s. below median),

Subgroup analysis will be performed respectively by including and excluding data after PD medication. The forest plot will be generated respectively as well. Besides, subgroup analysis of time to start of PD medication will be performed for the subgroup of regions (US v.s. Italy v.s Other)

5.3.2.9 Per-protocol analysis

The per-protocol analysis will be performed in the same fashion as the primary analysis for MDS-UPDRS I+II+III, but by applying in the per-protocol population as defined in Section 4.1. If the per-protocol population is largely the same as the ITT population, i.e., ≥90% of subjects included in the ITT population are also included in the per-protocol population, then the per-protocol analysis will not be performed.

5.3.3 Other clinical efficacy endpoints

Other clinical efficacy (function) and quality of life assessments are listed as below. The questionnaire as well as the scoring algorithm for these clinical assessments are described in Appendix I.

- Modified Schwab & England Activities of Daily Living (SE-ADL) (longitudinal)*,
- Physical Activity Scale of the Elderly (PASE) (longitudinal)*,
- Montreal Cognitive Assessment (MoCA) (longitudinal),
- Epworth Sleepiness Scale (ESS) (longitudinal),
- Scales for Outcomes in Parkinson's Disease - Autonomic (SCOPA-AUT) (longitudinal),
- 39-point Parkinson's Disease Questionnaire (PDQ-39) (longitudinal),*
- EQ-5D-5L(longitudinal)*,
- Activities-Specific Balance Confidence Scale (ABC-16) (longitudinal)*,
- Wearing Off Questionnaire (WOQ-19) (binary),
- Freezing/Falls Questionnaire (FFQ) (binary),
- Clinical Global Impressions Improvement (CGI-I) Scale (collected at Week 52 in the US sites only)*,
- Patient Global Impression of Change (PGI-C) (collected at Week 52 in the US sites only)*.

Data after PD medication will be included in the analysis for all the outcomes except modified SE-ADL.

For each clinical assessments that are collected longitudinally, an MMRM model will be used to analyze the change from baseline in the continuous clinical outcome, with addition of adjustment for the corresponding baseline outcome value and its interaction with time. i.e. the model will include fixed effects of treatment group (categorical), time (categorical), region (categorical), treatment group-by-time interaction, baseline value of the corresponding outcome (continuous), baseline value of the outcome by time interaction, baseline MDS-UPDRS I+II+III total score (continuous), baseline MDS-UPDRS I+II+III total score-by-time interaction, baseline striatum SBR values (continuous), and baseline striatum SBR by time interaction. The endpoints listed with a "*" next to them, will additionally include the baseline PD subtype (categorical) as a covariate. An unstructured covariance matrix will be used to model the within-subject variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will

be used. Least square means (LSmeans) of each treatment group as well as treatment difference between BIIB054 groups and placebo will be displayed with 95% CI and p-value at Week 52.

For CGI-I and PGI-C that are only collected at Week 52, an ANCOVA model will be used to analyze the data and adjust for the covariates of baseline MDS-UPDRS I+II+III (continuous) and baseline straiatum SBR values (continuous), and baseline PD subtype (categorical).

The Spearman's correlation of change from baseline at Week 52 in each clinical outcome with that of the MDS-UPDRS I+II+III, EP-RPS and the key QMA measures will be computed by including and excluding data after PD medication respectively

5.3.4 QMA

The initial QMA metrics chosen for the SAP were determined by combining three sources of information: 1) in-depth literature search for well-designed research studies that used in-clinic digital measurements to track PD severity or progression; 2) three data sources available internally that measured severity of PD with digital measurements and internal research performed by scientists from the Digital and Quantitative Medicine group; and 3) physician intuition and input as to the best metrics that will track changes in PD signs over time.

All three sources of information were integrated and compared to make an initial determination of which QMA metrics should be included in the SAP. The selected metrics can be found in Table below. As the study progresses, additional analyses will be conducted to determine if these are the best metrics to track disease progression, or to combine these metrics. Adjustments/changes may be made to the selected metrics based on the data collected during the course of the study that will assess how successfully each metric tracks disease progression.

Actual value and the changes from baseline in each metrics will be summarized by treatment group and by visit using descriptive statistics. The primary analyses will exclude data after the start of PD medications. Correlation between each metrics with the MDS-UPDRS scores will be computed. MMRM model will be performed to analyze the change from baseline on key metrics. The model is similar to that used for the primary endpoint, except it will adjust for the baseline QMA values and its interaction with time. i.e. the model will include fixed effects of treatment group (categorical), region (categorical), prior use of PD medication (categorical), baseline PD subtype (categorical), time (categorical), treatment group-by-time interaction, corresponding baseline QMA outcome (continuous), corresponding baseline QMA outcome by time interaction, baseline MDS-UPDRS I+II+III total score, baseline MDS-UPDRS I+II+III total score-by-time interaction, baseline striatum SBR value (continuous), baseline striatum SBR by time interaction. The same methods as in the MDS-UPDRS primary analysis will be considered for the covariance structure and the degrees of freedom. Least square means (LSmeans) of each treatment group as well as treatment difference between BIIB054 groups and placebo will be displayed with 95% CI and p-values. To reduce the undue influence of extreme outliers on the statistical analyses, outliers with

changes from baseline that are greater or smaller than mean+/- 5 xSD (5 times of SD) may be excluded from the primary analyses.

Sensitivity analyses of QMA data including data after PD medication, may be performed, based on the same MMRM model above, except that AVISIT will be treated as a continuous variable.

Analyses of additional QMA metrics not specified in the table below may also be performed, using similar MMRM model as described above. Exploratory analysis of QMA metrics as a biomarker of tracking disease progression may be performed.

List of prioritized/pre-specified QMA metrics included in the Week 52 analyses.

Metric	Interpretation
Turn velocity (deg/s)	QMA turn velocity ranges from 0 to positive infinity. A higher score implies a better outcome.
Contralateral foot strike angle (deg)	QMA foot strike angle ranges from -60 to 90 degrees. Contralateral refers to the side of the body contralateral to the clinically affected side. A higher score implies a better outcome.
Ipsilateral foot strike angle (deg)	QMA foot strike angle ranges from -60 to 90 degrees. Ipsilateral refers to the side of the body ipsilateral to the clinically affected side. A higher score implies a better outcome.
Contralateral arm swing velocity (deg/s)	QMA arm swing velocity ranges from 0 to positive infinity. Contralateral refers to the side of the body contralateral to the clinically affected side. A higher score implies a better outcome.
Ipsilateral arm swing velocity (deg/s)	QMA arm swing velocity ranges from 0 to positive infinity. Ipsilateral refers to the side of the body ipsilateral to the clinically affected side. A higher score implies a better outcome.
Stride length (m)	QMA stride length ranges from 0 to positive infinity. Ipsilateral refers to the side of the body ipsilateral to the clinically affected side. A higher score implies a better outcome.
Gait cycle duration SD (stride time variability)	QMA gait cycle duration SD (stride time variability) ranges from 0 to positive infinity. A higher score implies a worse outcome.
QMA composite z score	Composite z-score combining 36 individual metrics from repetitive tasks of wrist rotation, leg lifts and toe taps, and resting tremor (wrists and foots) assessments, excluding gait. Examples of the 36 individual metrics includes displacement, velocity, coefficient of variation of amplitude and velocity, and spectral entropy measure for resting tremor. Seven z-score is calculated from metrics from each

	limb/task and the overall composite z-score is a sum of these 7 z-score. Refer to Appendix V for more detail. QMA composite score ranges from negative infinity to positive infinity. A higher score implies a worse outcome.

5.3.5 Assessment of the Impact of Covid-19 on the clinical outcome analyses

As this study is on-going when the Covid-19 public health emergency (PHE) occurred, subject visits and data collection were impacted, including missing visits, missed assessments, delayed visits and/or some visits were performed via remote assessments, e.g. telephone/video visits. Every effort was made to document these impacted study activities systematically on the eCRF and othe electronic source data.

A complete listing of all visits impacted (e.g. missed visits, delayed or assessment done via remote visits) will be listed in the clinical study report.

In addition, subgroup analyses of the selected key clinical outcome MDS-UPDRS will be performed on a subset of subjects who did not have >=3 consecutive missing doses throughout the study to further evaluate the impact of Covid-19 on the study. The same MMRM model for the primary analyses will be used for the subgroup analyses.

In addition, due to Covid-19, some visits were delayed. A few subjects will have their Week 52 imaging done at later visits up to Week 72 and these will still be considered as Week 52 visit data in the analyses for Week 52. These data were not included in the Week 52 database lock in time, but will be included in the Week 72 database, and the related Week 52 imaging analyses will be updated at the time of the Week 72 interim analyses.

5.4 Safety Analysis

5.4.1 General Considerations

Analysis population

All safety endpoints will be evaluated in the safety population (all subjects dosed) as defined in Section 5.1.2.

Methods of analysis

All adverse events (AEs) and serious adverse events (SAEs), clinical laboratory abnormalities, vital sign measurements, physical and neurological examination findings, 12-lead ECG readings, disease activity by brain MRI metrics, body weight and Columbia Suicide Severity Rating Scale (C-SSRS) will be evaluated for safety. Safety data collected by EOS defined in Section 5.1.1 will be used for the safety analyses. The main safety analysis will include data after PD medication. Additional analyses may be performed by excluding

data after PD medication. Unless mentioned otherwise, all safety data will be summarized by treatment group and overall active group.

Although treatment assignment error is not expected, if some subjects received different study treatment than the randomization allocation, the safety analyses will be based on the actual treatment allocation. Specifically, if a subject who was assigned placebo received BIIB054 at any visit at the same dose level by mistake, this subject will be included in the BIIB054 group of that dose in the safety statistical analyses; if a subject was assigned placebo or BIIB054 of certain dose level, but received BIIB054 at multiple dose level by mistake, this subject will be included in the BIIB054 group of the dose level that were taken the most frequently in the safety statistical analyses; on the other hand, if a subject who was assigned BIIB054 does receive placebo by mistake, this subject will be included under placebo group in the safety statistical analyses only when this subject received placebo at all study visits.

For the clinical laboratory assessments, vital sign measurements and 12-lead ECG readings, subjects in Cohort A have additional post-baseline visits between Day 1 and Week 12, comparing to Cohort B. The summary of numerical changes over time, i.e., the quantitative analysis will be based on the pooled data of both Cohort A and Cohort B and the common visits. All the qualitative analyses including the shift analysis, grade analysis and so on will be based on all the data of Cohort A and Cohort B of all visits. All the listings will be based on all the data of Cohort A and Cohort B of all visits.

Visit windows for mapping safety endpoint

For safety data that are summarized by visit, assessment from all scheduled visits, EOT visit, EOS visit and unscheduled visits will be mapped to an appropriate analysis visit using a windowing scheme (Appendix II).

5.4.2 Clinical Adverse Events

For this study, any AE experienced by a subject between the time of first dose of study treatment (Day 1/Baseline) and the end of study visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. Any SAE experienced by the subject between the time the subject has signed the ICF and the end of study visit is to be recorded, regardless of the severity of the event or its relationship to study treatment.

All AEs will be coded using the MedDRA and will be analyzed based on the principle of treatment emergence. An AE will be regarded as treatment-emergent if it was present prior to the first dose and subsequently worsened in severity or was not present prior to first dose but subsequently appeared.

In order to define treatment emergence for AE with missing start or stop dates, the following additional criteria will be used:

- If both the start and stop dates for a particular event are missing, then that event is considered treatment-emergent;
- If the start date for a particular event is missing and the stop date/time falls after the first dose date/time, then that event is considered treatment-emergent;

- If the start date is the same as the first dose date, and the start time is missing, then that event is considered treatment-emergent.

For events with a partial start date, the year/month of the event date will be compared to that of the first dosing date to determine whether the event is treatment emergent.

Only TEAEs and TESAEs will be summarized in the tables, unless otherwise specified. All SAEs (including pre-dosing SAEs) will be included in the listing of SAEs, with an indicator of pre-dosing or treatment-emergent. Only TEAEs will be included in other AE listings, if not otherwise specified.

The overall summary table of AEs will present the number of subjects with the following events for each treatment group, BIIB054 total and overall. A subject is counted only once in each category.

- Any AE;
- AE by severity as measured in CTCAE grade of version 5.0: 1 (mild), 2 (moderate), 3 (severe or medically significant), 4 (life-threatening), 5 (death)
- Study drug-related AE;
- Lumbar puncture procedure-related AE;
- Radioligand related AE;
- Any SAE;
- Study drug-related SAE;
- Lumbar puncture procedure-related SAE;
- Radioligand related SAE;
- AE leading to discontinuation of study treatment; and
- AEs leading to withdrawal from study
- Death

The incidence of AEs will be summarized using the primary system organ class (SOC) or preferred term (PT) or both, sorted by decreasing frequency and alphabetical order, respectively. Additionally, AEs at least 5% higher in incidence for any active group compared to placebo group will be summarized by SOC and PT.

The incidence of AEs will also be summarized by severity as measured in CTCAE grade of version 5.0 using system organ class and preferred term. Within each system organ class or/and preferred term, the same subject will be counted only once. Under the same system organ class or/and preferred term, the occurrence of the adverse event with the greatest severity will be used in the calculation of incidence by severity.

The study drug related AEs, lumbar puncture related AEs and radioligand related AEs will be summarized by SOC, PT and treatment group as well.

The incidence of SAEs will be summarized by primary system organ class, preferred term and treatment group. Study drug related SAEs, lumbar puncture related SAE and radioligand related SAEs will be summarized in the same fashion as well.

Tables of AEs that led to study drug discontinuation and AEs that led to study withdrawal by SOC, PT and treatment group will be presented.

Listings of all AEs, SAEs, AEs that led to study drug discontinuation, and AEs that led to study withdrawal will be presented. Listing of death will be provided if applicable.

In some AE/SAE listings, complete AE start and end dates are needed to calculate the relative study days of AE start and end. Therefore, any partial date will be imputed for these listings. Specifically, the partial AE start date will be imputed as the earliest possible date on or after the first dose based on the partial information, and the partial AE end date will be imputed as the latest possible date on or before the EOS.

AEs around the time of infusion

The incidence of AEs within 2 hours from infusion start will be summarized by preferred term and visit for each treatment group. At each visit, the same subject will be counted only once within each preferred term. Preferred terms will be ordered by decreasing frequency of AEs in the BIIB054 total column. Listings of such AEs within 2 hours from infusion start will be provided by treatment group.

5.4.3 Clinical Laboratory Data

The following clinical laboratory parameters are assessed in the protocol:

- Hematology: Complete blood count with differential and platelet count, INR, prothrombin time, and APTT
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium
- Urinalysis: dipstick for blood, protein, and glucose (microscopic examination may also be performed)
- For sites performing LPs (Year 1): Lumbar puncture will be performed in all subjects in Cohort A and at a subset of sites in Cohort B, for approximately 100 subjects across Cohorts A and B. The LP procedure will collect CSF samples for PK, pharmacodynamic, and biomarker analysis. For each subject, LP should be performed consistently at the same time of day (±3 hours) to avoid diurnal fluctuation and should be performed pre-infusion on dosing days.
    - Coagulation panel, including platelet count, INR, prothrombin time, and APTT will be measured no more than 35 days before performing an LP. Before an LP can be performed, results of the most recent (i.e., performed at previous visit within 35 days) coagulation tests, including platelet count, must be reviewed by the Investigator and must indicate that an LP can be performed safely. If repeat tests are clinically indicated in the opinion of the Investigator, then these tests may be performed locally to facilitate timely review, and results must be reviewed before an LP can be performed.
    - CSF samples will be analyzed by a local laboratory for red blood cell count, white blood cell count, protein, and glucose. For the post-Day 1 LPs, results

of the most recent CSF sample analysis must be reviewed by the Investigator before each subsequent LP is performed.

All the laboratory tables and listings, unless otherwise specified, will be presented by treatment group.

5.4.3.1 Quantitative laboratory analyses

For numeric laboratory parameters, actual values, change and percent change from baseline will be summarized by visit. Number of evaluable subjects, mean, standard deviation, median, min and max values will be presented at each visit.

Plots of mean values (with standard deviation) for key numeric laboratory parameters by visit will be provided.

Visit windows for by visit summaries

For laboratory by visit summaries, the analysis visit should be defined using visit windows in Appendix II. If there is more than 1 value in the same analysis visit window (>1 value for the same analysis visit) for a certain parameter for a subject, then the closest record to the target visit day will be used for the by visit analysis. If there are 2 values in the same analysis visit window with the same distance from the target visit day for a certain parameter for a subject, then the record with the later date will be used for the by visit analysis. If there are 2 values on the same day for a certain parameter for a subject, then the record with the later time will be used for the by visit analysis. If there are 2 records on the same date and time, then use the average value for quantitative parameters and the worse value for qualitative parameters.

5.4.3.2 Qualitative laboratory analyses

For all qualitative analyses, all values will be included (not just the "analyzed record" within each visit window in the quantitative analyses).

Shift analyses

Laboratory data will be summarized using shift tables where appropriate. Each subject's hematology, blood chemistry and urinalysis numeric values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory or as "unknown" if no result is available. Each subject's urinalysis categorical values will be flagged as "positive", "negative", or "unknown" if no value is available. Shifts from baseline to high/low status will be presented for hematology, blood chemistry and urinalysis numeric parameters, and shifts from baseline to abnormal (positive) will be presented for urinalysis categorical parameters.

In the hematology, blood chemistry and urinalysis numeric values shift summary tables, entries are numbers of subjects shift to low (or high) divided by number of subjects at risk

followed by corresponding percentages. Number at risk for shifting to low (or high) is the number of subjects whose baseline value was not low (or high) and who had at least one post-baseline evaluation. Shift to low includes normal to low, high to low, and unknown to low. Shift to high includes normal to high, low to high, and unknown to high.

In the urinalysis categorical values shift summary table, entries are numbers of subjects shift to abnormal (positive) divided by number of subjects at risk followed by corresponding percentages. Number at risk for shift to abnormal (positive) is the number of subjects whose baseline value was not abnormal (positive) and who had at least one post-baseline evaluation. Shift to abnormal (positive) includes normal or negative to positive and unknown to positive.

Potentially Clinically Significant (PCS) laboratory abnormalities analyses

For hematology, blood chemistry and urinalysis, the number of subjects with potentially clinically significant laboratory abnormalities post-baseline will be summarized for the parameters provided in Table 5.1. Subjects need to have at least one post-baseline evaluation in order to be included in the analysis.

Listings will also be presented for all subjects with any PCS laboratory abnormalities. In these listings, each subject's complete history from screening to last study visit for that specific laboratory test meeting the PCS criteria will be listed; any abnormal values based on the normal ranges of the central laboratory and abnormal values based on PCS criteria will be separately flagged in the same listing.

Table 5.1. Criteria to Determine Potentially Clinically Significant (PCS) Laboratory Abnormalities

Clinical Laboratory Outlier Criteria			
Parameter name	**PCS Low**	**PCS High**	**STANDARD UNIT in the SDTM dataset**
HEMATOLOGY			
Basophils Absolute	N/A	>1.6 x 10^9/L	10^9/L
Eosinophils	N/A	>1.6 x 10^9/L	10^9/L
Erythrocytes (RBC)	≤3.5 x 10^{12}/L	≥6.4 x 10^{12}/L	10^{12}/L
Hematocrit - Females	≤0.32	≥0.54	L/L
Hematocrit - Males	≤0.37	≥0.60	L/L
Hemoglobin - Females	≤95 g/L	≥175 g/L	g/L
Hemoglobin - Males	≤115 g/L	≥190 g/L	g/L
Leukocytes (WBC)	<3.0 x 10^9/L	>16 x 10^9/L	10^9/L
Lymphocytes	<0.8 x 10^9/L	>12 x 10^9/L	10^9/L
Monocytes	N/A	>2.5 x 10^9/L	10^9/L
Neutrophils	<1.5 x 10^9/L	>13.5 x 10^9/L	10^9/L
Platelet count	≤75 x 10^9/L	≥700 x 10^9/L	10^9/L
BLOOD CHEMISTRY			
Albumin	≤25 g/L	≥625 g/L	g/L
Alkaline phosphatase (ALP)	N/A	>3 x ULN	IU/L
Alanine aminotransferase (ALT)	N/A	>3 x ULN	U/L
Aspartate aminotransferase (AST)	N/A	>3 x ULN	IU/L
Bicarbonate	≤16 mmol/L	≥35 mmol/L	mmol/L

Clinical Laboratory Outlier Criteria			
Parameter name	**PCS Low**	**PCS High**	**STANDARD UNIT in the SDTM dataset**
Bilirubin	N/A	>1.5 x ULN	umol/L
Calcium	≤2 mmol/L	≥3 mmol/L	Mmol/L
Chloride	≤90 mmol/L	≥118 mmol/L	Mmol/L
Creatinine	N/A	≥176.8 umol/L	Umol/L
Gamma-Glutamyl Transferase	N/A	>3 x ULN	U/L
Glucose	≤2.2 mmol/L	≥9.7 mmol/L	Mmol/L
Potassium	≤3 mmol/L	≥6 mmol/L	Mmol/L
Phosphate	≤0.6 mmol/L	≥1.7 mmol/L	Mmol/L
Protein	≤45 g/L	≥100 g/L	g/L
Sodium	≤126 mmol/L	≥156 mmol/L	Mmol/L
Urate	N/A	>475.88 umol/L (female); >594.85 umol/L (male)	umol/L
Urea Nitrogen	N/A	≥10.7 mmol/L	Mmol/L
URINALYSIS			
Glucose	N/A	Trace or ≥ ++++	
Protein	N/A	Trace or ≥ ++	
Occult Blood	N/A	Trace or ≥+	
ULN = upper limit of normal			

Potential serious hepatotoxicity

Potential serious hepatotoxicity is defined as ALT or AST > 3x ULN and total bilirubin > 2x ULN at any time post-baseline, not necessarily concurrent. A scatterplot of the maximum post-baseline ALT or AST value relative to ULN and maximum post-baseline total bilirubin value relative to ULN (not necessarily concurrent) will be provided. In addition, a line plot of ALT, AST, ALP and total bilirubin values over time for each subject with potential serious hepatotoxicity will be provided. .

A listing of subjects with potential serious hepatotoxicity will be provided with the concurrent records labeled. Concurrent is defined as on the same day. Subjects with ALT > 1x ULN, > 3x ULN, > 5x ULN, > 10x ULN or > 20x ULN, subjects with AST > 1x ULN, > 3x ULN, > 5x ULN, > 10x ULN or > 20x ULN, subjects with total bilirubin > 1x ULN, >1.5x ULN or > 2x ULN, subjects with ALP >1x ULN or >1.5x ULN, and subjects with AST or ALT > 3x ULN post-baseline accompanied by concurrently elevated total bilirubin > 1.5x ULN or > 2x ULN will be labeled.

5.4.4 Vital Sign Data

Vital sign parameters include diastolic blood pressure, systolic blood pressure, body temperature, pulse rate and respiration rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes. The analysis of vital signs will focus on the incidence of clinically relevant abnormalities based on the following criteria in Table 5.2.

Table 5.2. Criteria Used to Clinically Relevant Abnormalities in Vital Signs

Variable	Low	High
Body temperature	<36 degrees C	>38 degrees C
Pulse Rate	<60 bpm	>100 bpm
Systolic Blood Pressure (Supine)	<90 mm Hg or a decrease from baseline of >30 mm Hg	>140 mm Hg or an increase from baseline of >40 mm Hg
Orthostatic Systolic Blood Pressure	> 20 mm Hg decrease from supine to 3-minute standing measure	
Diastolic Blood Pressure	< 50 mm Hg or a decrease from baseline of > 20 mm Hg	≥90 mm Hg or an increase from basleine of >30 mm Hg
Orthostatic Diastolic Blood Pressure	>10 mm Hg decrease from supine to 3-minute standing measure	
Respiration Rate	< 12 breaths per minute	>20 breaths per minute
Weight	≥7% decrease from BL	≥7 % increase from BL
BL= baseline; bpm = beats per minute		

Note: the clinically relevant abnormality criteria will be evaluated based on the supine measure unless otherwise mentioned.

A summary table for subjects with any clinically relevant post-baseline abnormalities will be provided. In the summary table, entries are numbers of subjects with an abnormality divided by number of subjects evaluated followed by corresponding percentages. Number evaluated is the number of subjects who had a baseline assessment and at least one post-baseline assessment for that vital sign.

The descriptive statistics for actual values and change from baseline will be summarized over time for each treatment group and overall active group. The line of mean vital sign over time by treatment group will be graphed.

A subject listing will be presented for subjects with any post-baseline clinically relevant abnormalities in vital signs. In this listing, each subject's complete vital sign values from screening to last study visit will be listed with abnormalities labeled.

Visit windows for by visit summaries

For vital sign visit summaries, the analysis visit will be defined by visit window in Appendix II. For the same parameter for a subject, if there is more than 1 record in the same analysis visit window), then select the record closest to the target visit day. If there are 2 records in the same analysis visit window with the same distance from the target visit day, then select the record with the later date. If there are 2 records on the same date, then use the average value for quantitative parameters and the worse value for qualitative parameters.

5.4.5 ECG Data

Actual value and change from Baseline in ECG will be summarized using descriptive statistics and presented by treatment group, overall active group and visit.

The ECG result is classified as normal or abnormal. The post baseline abnormal ECG result is further classified as abnormal AE or Abnormal but not AE. Shift table from normal or

unknown ECG at baseline to abnormal post-baseline ECG will be summarized. The worst post-baseline record of each subject is selected. Subjects with abnormal post-baseline ECG status will be listed.

In addition, the number of subjects with potential QTcF interval outlier post-baseline will be summarized by treatment group. The criteria of defining QTcF interval outliers is specified in Table 5.3.

Table 5.3. Criteria used for QTcF interval outlier

Variable	Low	High
QTcF interval (msec.)	NA	>450; >480; >500
Increase in QTcF interval (msec.)	NA	>30; >60

Visit windows for by visit summaries

For ECG visit summaries, the analysis visit will be defined by visit window in Appendix II. For the same subject, if there is more than 1 record in the same analysis visit window, then the record closest to the target visit day is selected. If there are 2 records in the same analysis visit window with the same distance from the target visit day, then the record with the later date is selected. If there are 2 records on the same date, then the worse record is selected.

5.4.6 Physical and Neurological Examination

Abnormal findings during physical and neurological examinations are captured as adverse events and will be reflected in the summary of AEs.

5.4.7 C-SSRS Data

The Columbia Suicide Severity Rating Scale (C-SSRS) is an assessment that evaluates suicidal ideation and behavior. C-SSRS measurements are collected with respect to "Lifetime: time he/she felt most suicidal" and "P3M: time he/she felt most suicidal during the past 3 month" at baseline, and with respect to "Since last visit" at post-baseline visit.

There are 11 common "Yes/No" questions at baseline and post-baseline visits. Five questions on *suicidal ideation* and five questions on *suicidal behavior* are re-ordered and follow increasing severity order respectively as shown in Table 5.4; another question on *self-injurious behavior without suicidal intent* is listed separately. In particular, only subjects who answered "Yes" to question 2 will proceed to question 3, 4 and 5, and the questions in the section of intensity of ideation. Thus, for any subjects who answered "No" to question 2, an answer "No" will also be assumed to question 3, 4, and 5. An additional "Yes/No" question is used to record if subject had committed suicide in post-baseline visits.

Table 5.4: C-SSRS re-ordered questions

Suicidal Ideation	
Question 1	Wish to be dead
Question 2	Non-specific active suicidal thoughts

Question 3	Active suicidal ideation with any methods (not plan) without intent to act
Question 4	Active suicidal ideation with some intent to act, without specific plan
Question 5	Active suicidal ideation with specific plan and intent
Suicidal Behavior	
Question 6	Preparatory acts or behavior
Question 7	Aborted attempt
Question 8	Interrupted attempt
Question 9	Actual attempt
Question 10	Suicidal behavior
Question 11 (post-baseline visits only)	Suicide
Self-Injurious Behavior without Suicidal Intent	
Question 12	Self-injurious behavior without suicidal intent

A subject is considered to have *suicidal ideation* at the period of interest if a "Yes" is answered to any of the five suicidal ideation questions (Question 1-5). A subject is considered to have *suicidal behavior* at the period of interest if a "Yes" is answered to any of the five suicidal behavior questions (Question 6-10) at baseline or a "Yes" is answered to any of the six suicidal behavior questions (Question 6-11) at post-baseline visit.

A subject's *Suicidal Ideation Score* is defined as the maximal suicidal ideation question number (maximal of 1-5) with an answer "Yes" per visit. The score is defined as 0 if the subject answered "No" to all 5 Suicidal Ideation questions at that visit.

The following analyses on C-SSRS measurements will be conducted:

- Descriptive summary of subjects who answered "Yes" to any question 1-12 as well as subjects who had suicidal ideation or suicidal behavior at baseline and at any post-baseline visit. the denominator for summary is the number of subjects who were dosed and had a baseline assessment and at least one post-baseline assessment for each question.

Listing of subjects having a post-baseline suicidal ideation will be provided. The listing will display both baseline and post-baseline suicidal ideation scores for each subject.

5.4.8 MRI Safety Data

Brain MRI safety finding (may include T1, fluid-attenuated inversion recovery, gradient echo) or other modalities and sequences (to be detailed in Imaging/MRI manual) are assessed at Screening visit, Week 24 and 52 visits.

The MRI safety result is classified as normal or abnormal. Shift table from normal or unknown MRI at baseline to abnormal post-baseline MRI will be summarized. The worst post-baseline record of each subject is selected. A listing of details for abnormal brain MRI findings will also be presented.

5.5 Pharmacodynamic -Imaging Analysis

5.5.1 Type of imaging techniques and imaging outcomes

There are three types of imaging techniques used in the study:

(1) DaT/SPECT imaging,

(2) neuromelanin-sensitive and susceptibility-weighted MRI imaging (to be detailed in the Imaging/MRI Manual)

(3) structural MRI imaging (to be detailed in the Imaging/MRI Manual)

DaT/SPECT imaging assesses the biological effects of BIIB054 on brain dopamine neurons and nerve terminals. DaT-associated outcome measures include the estimates of anterior and posterior putamen, caudate, as well as total striatum striatal binding ratio (SBR), a measure that compares signal intensity in the region of interest to that in the occipital cortex, a region relatively devoid of dopamine nerve terminals. Measurements are obtained both ipsilateral and contralateral to the side of worst motor symptoms, anterior, posterior as well as combining both sides.

Neuromelanin MRI imaging is an exploratory imaging biomarker that estimates changes in the brain region that contains dopamine nerve cell bodies and includes 33 volume and intensity measures.

Structural MRI imaging is another exploratory imaging biomarker; 13 volume measurements will be explored. All the metrics are specified in Appendix VI.

5.5.2 Analysis population

All pharmacodynamic imaging endpoints will be evaluated based on the Pharmacodynamics population as defined in Section 5.1.2.

5.5.3 Baseline value

Baseline value is defined as the latest data collected at any time prior to the first dose, or if collected only after dosing the earliest data on the first dose date, given the data is collected within 1 week after first dose date.

5.5.4 Outlier of percent change from baseline

If the percent change from baseline in a post-baseline value of a DaT/SPECT SBR measure is greater than 50% or less than -50%, the post-baseline value of the DaT/SPECT measures is considered as physiologically implausible, and therefore will be excluded in the analysis.

5.5.5 Analysis methods

The estimand of the primary analysis for imaging outcome measure is the mean difference of the change from baseline in the imaging measure at Week 52 between treatment groups in the

pharmacodynamics population regardless of whether start of PD medication had occurred or not. Specifically, the estimand takes the following into consideration:

A. Population: pharmacodynamics population as defined in Section 5.1.2;
B. Variable: change from baseline to Week 52 in the imaging measure;
C. Intercurrent events: regardless of whether start of PD medication had occurred or not;
D. Population-level summary: difference in variable means between each active treatment and placebo group

A set of DaT/SPECT measures and neuromelanin MRI and structural MRI have been selected for the statistical anlayses based on literature review and clinical inputs before the DBL. Please see Appendix VI for the listed measures.

Data collected after subjects who have begun taking PD medication will be included in the primary analysis. Change and percent change from baseline will be summarized by visit and treatment groups using descriptive statistics. Change or percent change from baseline in the imaging measures will be analyzed using the mixed model for repeated measures (MMRM), which includes the fixed effect of the treatment group (categorical), time (categorical), interaction between treatment group and time, region (categorical), baseline imaging values (continuous), baseline imaging values by time interaction, baseline MDS-UPDRS I+II+III total score (continuous) and baseline MDS-UPDRS I+II+III total score by time interaction. An unstructured covariance matrix will be used to model the within-subject variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Least square means (LSmeans) of each treatment group as well as treatment difference between each BIIB054 groups and placebo will be displayed with 95% CI and p-value at Week 52. If the distribution of the outcome is highly skewed, p-value will be generated from the MMRM model based on the rank data. In the primary analysis, missing data are assumed to be missing at random (Rubin 1976), and the PD medication is assumed to have minimal impact on the imaging measures.

The same MCP-MOD method as used in the primary analyses of MDS-UPDRS I+II+III may be used to assess and model dose-response relationship of the imaging outcomes.

5.5.6 Sensitivity analysis

A sensitivity analysis will be performed using the same MMRM model in the primary analysis, but by excluding DaT/SPECT values that are collected after subjects starting PD medications.

The sensitivity analysis will be performed only for the key DaT/SPECT measures as specified in the Appendix VI.

5.5.7 Correlation analysis

Spearman's correlation of change from baseline to Week 52 will be computed for the following imaging and MDS-UPDRS parameters. For the pairs with MDS-UPDRS III, I+II+III and EP-RPS correlation will be computed respectively by including and excluding data after PD medication. For the other pairs, correlation will be computed by including the data after PD medication only.

- DaT-SPECT Striatum total SBR (25. STR_SBR) x MDS-UPDRS III
- DaT-SPECT Striatum total SBR (25. STR_SBR) x MDS-UPDRS I+II+III
- DaT-SPECT Striatum total SBR (25. STR_SBR) x Early Parkinson's Regional Progression Score (EP-RPS)
- DaT-SPECT Striatum total SBR (25. STR_SBR) x structural MRI Striatum total volume (13. STR_VOL)
- DaT-SPECT Striatum total SBR (25. STR_SBR) x SNc total volume via GRE (23. GRE_NM_VOL)
- DaT-SPECT Striatum total SBR (25. STR_SBR) x SNc total intensity ref 4 via GRE (98. GRE_NM_NMSIG_R4)
- NM-MRI SNc total volume via GRE (23. GRE_NM_VOL) x NM-MRI SNc total volume via TSE (9. TSE_NM_VOL)
- NM-MRI SNc total intensity ref 4 via GRE (98. GRE_NM_NMSIG_R4) x NM-MRI SNc total intensity ref 4 via TSE (37. TSE_NM_NMSIG_R4)

5.6 Pharmacodynamic -Biomarker Analysis

5.6.1 Analysis population

All pharmacodynamic biomarker endpoints will be evaluated based on the biomarker population as defined in Section 5.1.2.

5.6.2 Baseline value

Baseline value is defined as the latest data collected prior to or on the first dose date. If there is no data collected prior to or on the first dose date, i.e., data is collected only after the first dose date, then baseline value is the earliest data, given the data is collected within 1 week after first dose date.

5.6.3 Method of analysis

Plasma, serum, urine, and CSF samples may be assayed for biomarkers that may include, but will not be limited to, total α-syn, biogenic amine neurotransmitters and their metabolites, modified species of α-syn, levels of α-syn:BIIB054 antigen:antibody complexes, and markers of neurodegeneration. CSF samples will be collected only in the subset of subjects who receive an LP.

Data for these exploratory potential biomarker candidates related to BIIB054 biological activity or PD will be summarized by treatment group and by visit using descriptive statistics

for plasma and CSF total α-syn and time to 50% maximum fluorescence protein misfolding cyclic amplification of alpha-synuclein (PMCA). Change from baseline of PMCA in CSF using mixed model repeated measures will be provided. Data listings, line plots, boxplots and bar plots will be provided as well. Additionally, Area under the curve of the concentration or change by time may be calculated. Dose-response may be assessed, in an ANCOVA model with the change or percent change as the response outcome and adjustments for baseline values of the biomarkers. Appropriate transformation of the outcome may be performed (e.g., logarithmic) where deemed fitting to the data.

For total alpha-synuclein concentrations above the upper limit of quantification(ULOQ or ALQ), the analysis values will be imputed by LOQ, e.g. >400,000 pg/mL. For concentrations recorded as larger than certain values, such as >50,000 pg/mL due run out of kits to further dilute, the analysis value will be imputed by maximum concentration recorded, such as 50,000 pg/mL in this example.

For total alpha-synuclein in CSF, the value of below the lower limit of quantification (BLQ) will be imputed by half of the lower limit of quantitation (LLOQ). For total alpha-synuclein in plasma, serum or urine, the value of BLQ will be imputed by 0. Data with values of not done (ND) or quantity not sufficient (QNS) will be set to missing. BLQ or ALQ values are not expected for PMCA.

Details related to additional analyses for future exploratory biomarkers not related to BIIB054 or PD, where applicable and where assessed, will be documented separately.

5.6.4 RNA Biomarker Analyses

Results from any RNA biomarker research (for use related to BIIB054 or PD and also, where applicable and where performed, for future exploratory use not related to BIIB054 or PD) will be documented separately.

5.7 Pharmacokinetics Analysis

The PK analysis population as defined in Section 5.1.2 will be used for the description of the concentration-time profiles and for the estimation of PK parameters.

A serum drug concentration that is deemed inconsistent with dosing (very low or very high) will be excluded from the analysis if no apparent explanation exists. Concentration observations may also be removed from the data set if corresponding dosing or sampling times are missing or cannot be imputed. Concentration data with below limit of quantification value will be excluded. All exclusions of data points or subjects from the analysis will be appropriately documented.

In addition, a detailed listing of sampling time (actual and nominal) and corresponding concentration at each time point for all subjects in the PK population will be provided. Presence of anti-BIIB054 antibody will also be listed and summarized. Additional listings may be generated as deemed necessary.

5.7.1 PK Concentration Profile

Descriptive statistics (N, arithmetic mean, standard deviation, geometric mean, CV, median, minimum, maximum, 25th and 75th percentiles) will be used to summarize concentration of BIIB054 in serum and CSF by visit and treatment groups. The ratios of CSF to serum BIIB054 concentration will be computed at the timepoints when both are available.

Mean serum concentrations of BIIB054 versus time will be plotted by treatment group on both a linear and a logarithmic scale for Cohort A (doses 1 and 3 only). Dose proportionality will be assessed for Cohort A (doses 1 and 3 only) as deemed appropriate.

Additional listings or plots may be generated as deemed necessary.

5.7.2 Serum PK Parameters

All listed PK parameters below will be computed by non-compartmental methods, as data permits, from serum concentration-time data for cohort A. For cohort B, only C_{trough} will be reported, due to sparse PK collection.

Parameter	Definition/Calculation
C_{max}	Observed maximum concentration
C_{trough}	Observed concentration at the end of the dosing interval
T_{max}	Time to reach maximum concentration
AUC_{tau}	area under the concentration-time curve within a dosing interval tau
Accumulation ratio	Using C_{max}, $C_{trough,\ and}$ AUC_{tau}

Individual subject PK parameter data will be listed. Descriptive statistics (N, mean, standard deviation, geometric mean, CV, median, minimum, maximum, 25th and 75th percentiles) will be used to summarize the PK parameters.

Population PK analysis will be conducted to estimate BIIB054 population PK parameters and to identify potential covariates (e.g., demographics, body weight, anti-BIIB054 mAb etc.) on the variability of BIIB054 PK. In addition, an exposure-response (ER) analysis will be conducted to detect any ER relationship trend and potential covariate using any primary or secondary endpoint and BIIB054 exposure metrics as deemed appropriate. Other tables and figures based on the population PK and ER analyses will be generated by Clinical Pharmacology and Pharmacometrics (CPP) team and will be included in a separate report from CPP.

5.8 Immunogenicity Analysis

5.8.1 Analysis Methods for Immunogenicity Data

Immunogenicity population as defined in Section 5.1.2 will be used to analyze immunogenicity data.

For immunogenicity, baseline value is defined as the latest data collected at any time prior to the first dose, or if collected only after dosing the earliest data on the first dose date. More specifically, if samples are only available prior to the first dose, or samples are available both prior to first dose date and on the first dose date, baseline is the latest sample prior to the first dose date. However, if samples are only available on the first dose date but not prior to the first date, baseline is the earliest sample on the first dose date.

A study subject will be given "antibody positive" status if they have at least one confirmed positive sample result at any time during the treatment or post-treatment evaluation periods. A study subject will be given "antibody negative" status if all evaluated antibody sample results are antibody negative.

Anti-BIIB054 antibody responses in antibody-positive subjects are defined as treatment emergent if a subject is:

- ADA-negative at baseline and ADA-positive post-baseline, or
- ADA-positive at baseline and had a greater than 2-fold increase in antibody titer post-baseline.

Summary table of the number and percentage of treatment-emergent anti- BIIB054-positive and -negative antibody events by visit will be displayed for each active treatment groups. A listing of all anti- BIIB054 antibody results will also be provided.

6 INTERIM ANALYSIS

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

After subjects in Cohort A complete the Week 24 Visit, the CSF PK, all available serum PK, and biomarker data (specifically the α-syn levels and complex formation data, if available) from Cohort A will be analyzed by a statistical/PK team independent of the study. The grouped level summary statistics will be reviewed only by a limited number of individuals at Biogen who are not involved in the management of the subjects or subject-level data for the study. No changes to the study design are expected based on this review.

For the purpose of planning for future studies, an administrative interim analysis may be performed when approximately 60% of the subjects have completed the Week 52 Visit. A small unblinded team from Biogen, separate from the study management team, will have access to the unblinded interim analysis results. As of the finalization of protocol Version 8 and all subjects have completed Week 52 visits, this analyses was not conducted

A full analysis of the 1-year data will be performed after all subjects have completed the Week 52 Visit. A small unblinded team from Biogen, separate from the study management team, will have access to the unblinded 1-year analysis results. All efficacy endpoints will be analyzed at the Week 52 analyses. All available safety data will also be summarized.

An interim analysis when all subjects have completed the Week 72 Visit is planned to be conducted. A small unblinded team from Biogen, separate from the study management team, will have access to the unblinded interim analysis results. All efficacy endpoints and available biomarkers will be analyzed at the Week 72 analyses. Selected key safety data (e.g. summary of AE and SAE, summary of MRI safety findings and incidence of anti-drug

antibodies) will be summarized, as this is only a snapshort of the safety profile at the time of the Week 72 interim analysis, and the comprehensive safety profile will be presented at the End of Study

A multiple comparison adjustment method will be applied to control the overall type I error at 0.05 in the study, due to the primary endpoint of change from baseline in MDS-UPDRS total score being analyzed at Week 52 and Week 72, and superiority against placebo is considered reached in the study if statistically significant result is achieved at either timepoint at the respective adjusted alpha-level.

An improved fall-back procedure will be used to control the overall type I error at 0.05 level due to multiple-testing. An alpha of 0.04 will be allocated to the Week 52 primary endpoint analyses and an alpha of 0.01 will be allocated to the Week 72 primary endpoint analysis.

- If the Week 52 analysis is statistically significant at the 0.04 level (i.e. p-value ≤0.04), the alpha of 0.04 will be transferred (recycled) to the Week 72 analysis, and Week 72 will have alpha=0.05.
- If the Week 52 analysis is not statistically significant at the 0.04 level, alpha of 0.01 will be used for the Week 72 analysis. Statistically significance is considered achieved if the p-value is ≤0.01 at Week 72.
- If statistically significance is achieved at the Week 72, in either scenarios above, then the alpha of 0.01 will be transferred (recycled) back to Week 52, and the Week 52 primary analysis will be re-evaluated for statistically signifance at the 0.05 level. This will only change the conclusion of the Week 52 results if the initial p-value is greater than 0.04 and ≤0.05.

No additional multiplicity adjustments will be made for secondary or exploratory endpoint analyses.

A blinded sample size re-estimation may be conducted when approximately 10% of subjects have completed the Week 52 Visit or approximately 1 month before enrollment is projected to be completed, whichever is earlier (description of method is below). The study sample size may be increased based on this blinded data review. There may be small adjustments to the percentage depending on actual enrollment rate. As of the finaliation of protocol Version 8 (Aug 2020), all subjects have completed Week 52 visits, this analyses was not conducted.

Blind sample size re-estimation

The sample size for this study may be reassessed in a blinded manner in a cutoff date of February 2020, by which time approximately 78/311 (25%) of subjects will complete the Week 52 visit.

The standard deviation (SD) of the change from baseline to Week 52 in the putamen ipsilateral side SBR will be estimated based on the blinded data using a modified version of Gould-Shih simple adjustment on sample variance (Zucker et al. 1999):

$$s_{adj}^2 = s_{os}^2 - \frac{2N}{9(N-1)}\delta^2,$$

where N denotes the number of subjects included in the analysis for blinded sample size re-estimation (subjects with both baseline and Week 52 data of the putamen ipsilateral side SBR available at the time of sample size re-estimation), δ is the assumed true treatment effect (same treatment effect assumed for high, medium and low dose group in this analysis), and s_{os}^2 is the unadjusted one sample variance of the estimate of the change from baseline to Week 52 in the putamen ipsilateral side SBR from the pooled blinded data.

The recommendation of sample size increase depends on the comparison of s_{adj}^2 with 0.156, the assumed value of SD for the current sample size (see Section 4). If s_{adj}^2 is less than or equal to 0.156, the value used for sample size calculation when planning the study, the study will continue with the original planned sample size 311. If s_{adj}^2 is greater than 0.156, the study will continue with an increased sample size. The increased sample size will be calculated by using the same MCP-MOD method as specified in Protocol 16.9, subject to a maximum of 413, which is a 30% increase on the original sample size.

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8 Appendix

8.1 Appendix I: Questionnaires

Please refer to the separate Appendix document for the details of the questionnaire as well as the corresponding scoring algorithm.

8.2 Appendix II: Visit Window Mapping

Please refer to the separate Appendix document for the details of the visit window mapping rule for all the study endpoints.

8.3 Appendix III: Description of MCP-MOD method

MCP-MOD method works in the following steps.

Step 1: Set of candidate models

Candidate models include Emax (ED50=450.5), Exponential (δ=2850.5), logistic (ED50=1547.5, δ=510.5), linear-log (off=237.5), quadratic (δ=-0.0002), Exponential (δ=860.5) and Linear. The response shapes are displayed in Figure 4.1 in the SAP.

Step 2: Optimal model contrast

The LSmeans at Week 52 and the covariance matrix of the LSmeans will be estimated from the MMRM model and used to determine the optimal contrasts. The coefficients of the contrasts are pre-specified during the design stage once the candidate models are selected in Step 1.

Step 3: Testing for dose response signal

A multiple contrast test will be used to test the overall dose response signal and to identify all contrasts that have adjusted p-values less than or equal to the pre-specified alpha controlling for multiplicity at Week 52 and Week 72. As a result, the significance of the dose response signal will be established.

Step 4: Model selection

Value of AIC will be presented together with the p-values for the dose response models in Step 3.

8.4 Appendix IV: Definition of the Early Parkinson's Regional Progression Score (EP-RPS)

EP-RPS is derived in the following steps based on MDS-UPDRS Part III motor assessments.

Step 1: group the 30 MDS-UPDRS Part III items into 7 body regions as below (item 3.11 of freezing of gait, item of 3.13 of posture and item 3.18 of constancy of rest are excluded.)

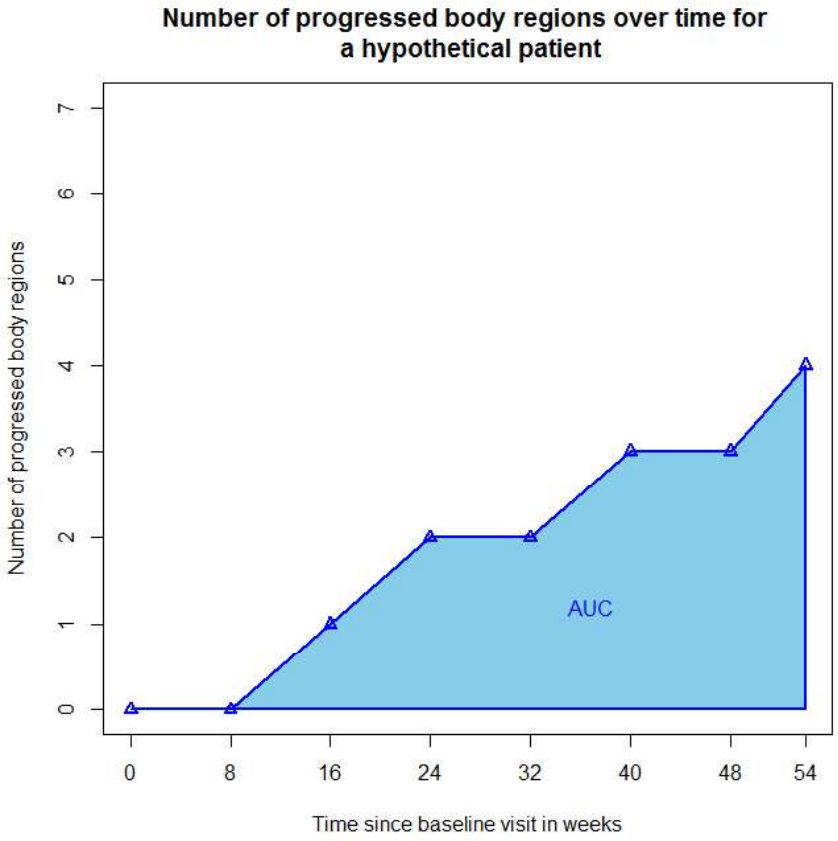
Body region	Question items in UPDRS Part III questionnaire	Variable names in SAS data set
Right hand	3.3b Rigidity-RUE 3.4a Finger Tapping-Right hand 3.5a Hand movements-Right hand 3.6a Pronation-supination movements-Right hand 3.15a Postural tremor-Right hand 3.16a Kinetic tremor-Right hand 3.17a Rest tremor amplitude-RUE	3.3b NP3RIGRU 3.4a NP3FTAPR 3.5a NP3HMOVR 3.6a NP3PRSPR 3.15a NP3PTRMR 3.16a NP3KTRMR 3.17a NP3RTARU
Left hand	3.3c Rigidity-LUE 3.4b Finger Tapping-Left hand 3.5b Hand movements-Left hand 3.6b Pronation-supination movements-Left hand 3.15b Postural tremor-Left hand 3.16b Kinetic tremor-Left hand 3.17b Rest tremor amplitude-LUE	3.3c NP3RIGLU 3.4b NP3FTAPL 3.5b NP3HMOVL 3.6b NP3PRSPL 3.15b NP3PTRML 3.16b NP3KTRML 3.17b NP3RTALU
Right leg	3.3d Rigidity-RLE 3.7a Toe tapping-Right foot 3.8a Leg agility-Right leg 3.17c Rest tremor amplitude-RLE	3.3d PN3RIGRL 3.7a NP3TTAPR 3.8a NP3LGAGR 3.17c NP3RTARL
Left leg	3.3e Rigidity-LLE 3.7b Toe tapping-Left foot 3.8b Leg agility-Left leg 3.17d Rest tremor amplitude-LLE	3.3e NP3RIGLL 3.7b NP3TTAPL 3.8b NP3LGAGL 3.17d NP3RTALL
Trunk	3.3a Rigidity-Neck 3.9 Arising from chair 3.10 Gait 3.12 Postural Stability 3.13 Posture	3.3a NP3RIGN 3.9 NP3RISNG 3.10 NP3GAIT 3.12 NP3PSTBL 3.13 NP3POSTR
Speech	3.1 Speech	3.1 NP3SPCH
Face	3.2 Facial expression 3.17e Rest tremor amplitude-Lip/jaw	3.2 NP3FACXP 3.17e NP3RTALJ

Step 2: For each body region, derive the region score as the maximum score of all the items included in the region. As a result, a score will be derived per subject per visit per body region.

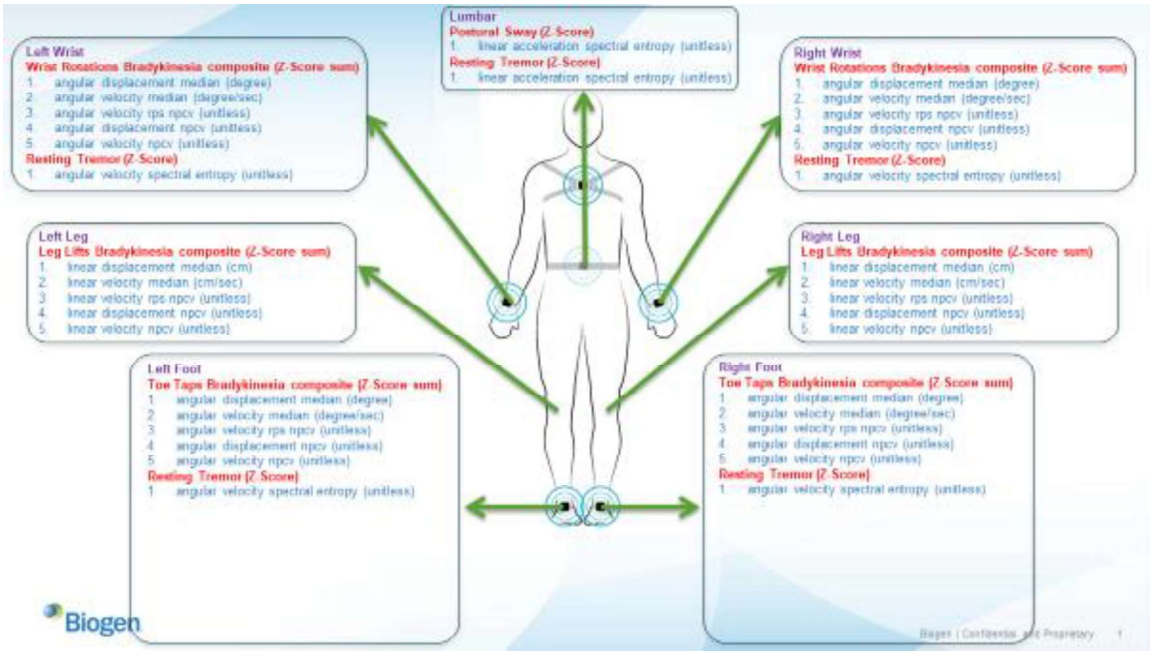
Step 3: For each subject at each visit, count the total number of progressed body region. A body region is progressed at visit t if and only if the change from baseline in the body region score is greater than or equal to 1 at visit t, and the change is confirmed by the next visit after visit t. A body region is progressed by visit s, if and only if the body region is progressed prior to or at visit s.

Step 4: For each subject at each visit, derive the body region progression AUC as the weighted average of the number of progressed body regions of all the visits before the current visit. The weight of each visit is proportional to the time elapsed from the previous visit to the current visit. Alternatively, the body region progression AUC at visit t can be computed as the area from baseline to visit t under the trajectory curve of the number of progressed body regions by time, divided by the total number of years elapsed from baseline to visit t. Missing data will be imputed by linear interpolation for the intermediate missing visits and by linear extrapolation for the trailing missing visits.

For illustration purpose, suppose a subject had 0, 1, 2, 2, 3, 3 and 4 body regions with progression at Week 8, 16, 24, 32, 40, 48 and 54 visits respectively, then the subject's progression AUC value is as shown in the following plot.



8.5 Appendix V QMA Z-score composite compositions:



8.6 Appendix VI: Imaging biomarker measure

Please refer to the appendix document for all the parameters generated for all the imaging scans. Table 8.1, 8.2 and 8.3 below show the parameters that are selected for statistical analyses.

Table 8.1. DaT/SPECT measures used in statistical analyses

	Primary analyses		Sensitivity analysis	
Measure	Change from baseline	Percent change from baseline	Change from baseline	Percent change from baseline
Total Striatum SBR	**Y**	**Y**	**Y**	**Y**
Total Putamen SBR	**Y**	**Y**	**Y**	**Y**
Total Caudate SBR	**Y**	N	N	N

Ipsilateral Striatum SBR	**Y**	**Y**	**Y**	**Y**
Contralateral Striatum SBR	**Y**	**Y**	**Y**	**Y**
Ipsilateral Putamen SBR	**Y**	**Y**	**Y**	**Y**
Contralateral Putamen SBR	**Y**	**Y**	**Y**	**Y**
Ipsilateral Caudate SBR	**Y**	N	N	N
Contralateral Caudate SBR	**Y**	N	N	N
Ipsilateral Statistical ROI SBR	**Y**	N	N	N
Contralateral Statistical ROI SBR	**Y**	N	N	N
Anterior half (based on volume) of the Ipsilateral Putamen SBR	**Y**	N	N	N
Posterior half (based on volume) of the Ipsilateral Putamen SBR	**Y**	N	N	N

Note 1: "Y" implies that a MMRM analyses will be conducted for the change or percent change from baseline in the imaging measure. "N" implies that the MMRM analyses will not be conducted.

Table 8.2. neuromelanin-sensitive and susceptibility-weighted MRI measures used in statistical analyses

	Primary analyses		Sensitivity analysis	
Measure	Change from baseline	Percent change from baseline	Change from baseline	Percent change from baseline
GRE Total Neuromelanin ROI Volume	**Y**	N	N	N
GRE Total Neuromelanin ROI Normalized Region 2 Neuromelanin Signal	**Y**	N	N	N
GRE Total Neuromelanin ROI Normalized Region 4 Neuromelanin Signal	**Y**	N	N	N

GRE Total Lateral Neuromelanin ROI Normalized Region 2 Neuromelanin Signal	**Y**	N	N	N
GRE Total Lateral Neuromelanin ROI Normalized Region 4 Neuromelanin Signal	**Y**	N	N	N
TSE Total Neuromelanin ROI volume	**Y**	N	N	N
TSE Total Neuromelanin ROI Normalized Region 2 Neuromelanin Signal	**Y**	N	N	N
TSE Total Neuromelanin ROI Normalized Region 4 Neuromelanin Signal	**Y**	N	N	N
TSE Total Lateral Neuromelanin ROI Normalized Region 2 Neuromelanin Signal	**Y**	N	N	N
TSE Total Lateral Neuromelanin ROI Normalized Region 4 Neuromelanin Signal	**Y**	N	N	N

Note 1: "Y" implies that a MMRM analyses will be conducted for the change or percent change from baseline in the imaging measure. "N" implies that the MMRM analyses will not be conducted.

Table 8.3. structural MRI measures used in statistical analyses

	Primary analyses		Sensitivity analysis	
Measure	Change from baseline	Percent change from baseline	Change from baseline	Percent change from baseline
Total Striatum Volume	**Y**	N	N	N
Total Putamen Volume	**Y**	N	N	N
Total Caudate Volume	**Y**	N	N	N
Total Nucleus Basalis Volume	**Y**	N	N	N

Note 1: "Y" implies that a MMRM analyses will be conducted for the change or percent change from baseline in the imaging measure. "N" implies that the MMRM analyses will not be conducted.

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