Statistical Analysis Plan

– Open label extension period

Version No.: 1.0

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

Name of Study Treatment: BIIB092

Protocol No.: 251PP301 / NCT03068468

Study Phase: Phase 2b

APPROVAL

This document has been reviewed and approved by:

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ABBREVIATIONS

Term	Definition
ADA	Anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CGI-C	Clinical Global Impression Change
CGI-S	Clinical Global Impression Severity
Cinf	end-of-infusion serum concentration

Term	Definition
CSF	cerebrospinal fluid
[redacted]	[redacted]
CTCAE	Common Toxicity Criteria for Adverse Events
Ctrough	trough serum concentration
CTT	Color Trails Test
ECG	electrocardiogram
eTau	extracellular tau
EuroQol	European Quality of Life
ICH	International Conference on Harmonisation
INR	international normalized ratio
IP	investigational product
ITT	intent-to-treat
IV	intravenous
LLOQ	lower limit of quantification
LNS	Letter number sequence
LP	lumbar puncture
MDS-UPDRS	Movement Disorder Society-sponsored revision of the Unified
MMRM	mixed model repeated measures
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
NfL	neurofilament light chain
OLE	open-label extension
PCS	potentially clinically significant
PD	pharmacodynamic(s)
PE	physical examination
PK	pharmacokinetic(s)
[redacted]	[redacted]
PSP	progressive supranuclear palsy
PSP-QoL	Progressive Supranuclear Palsy Quality of life scale
PSPRS	Progressive Supranuclear Palsy Rating Scale
Q4W	every 4 weeks
QMA	quantitative movement assessments

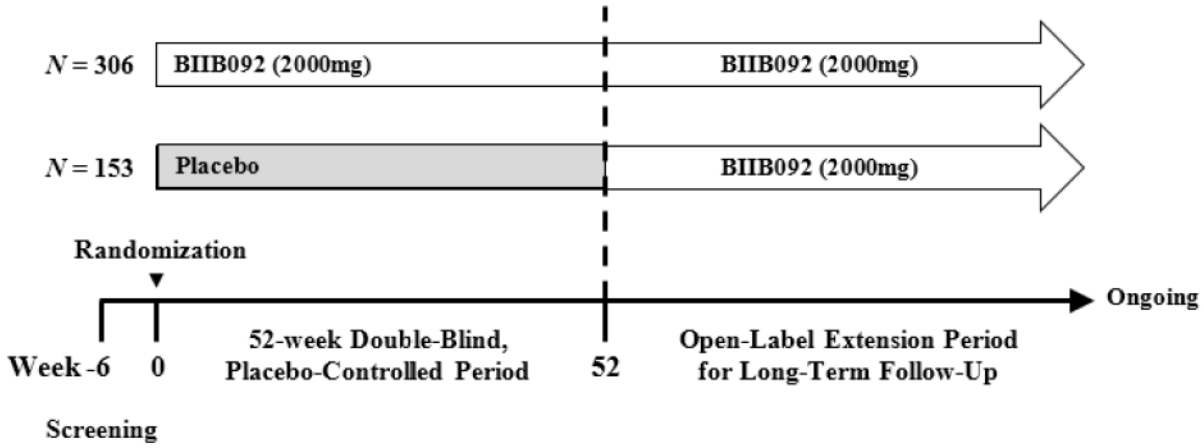
Term	Definition
RBANS	Repeatable Battery for the Assessment of Neuropsychological Disease Severity
[redacted]	[redacted]
SAE	serious adverse event
SEADL	Schwab and England Activities of Daily Living
[redacted]	[redacted]
ULN	upper limit of normal
US	United States
WOCBP	women of childbearing potential

1 OVERVIEW OF THE STUDY

1.1 Study Design

The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



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

Overall study design: The study design schematic is presented in Figure 1. The study will consist of a 52-week double-blind treatment period, which will be followed by a long-term open label extension period for follow up. Participants will be randomized to receive BIIB092 or placebo. Approximately 459 participants in total will be randomized in a 2:1 ratio to receive BIIB092 or placebo (306 participants active or 153 placebo). In the double-blind treatment period of the study, participants will be dosed approximately once every 4 weeks (Q4W) for approximately 48 weeks (up to a total of 13 times). At Week 52, participants completing the double-blind treatment period may choose to continue into the open-label extension period of this study, in which, all participants will receive BIIB092. Participants will be dosed approximately once- every 4 weeks throughout the duration of the open-label extension period. The duration of the open-label extension will vary depending on the date of enrollment of the participant in the study. The study is expected to continue until BIIB092 is commercially available, the development program is terminated, or the study is terminated at the discretion of the sponsor, whichever comes first.

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

Study assessments:

- Participants will be closely monitored for safety throughout the study. Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations, including assessments for anti-drug antibody (ADA) will be performed. AEs will be closely monitored. [redacted]
- PSP related signs, symptoms and quality of life will be assessed using clinical assessments: PSP Rating Scale (PSPRS), Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS Part II), Schwab and England Activities of Daily Living (SEADL) scale, Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Change (CGI-C), Montreal Cognitive Assessment (MoCA), [redacted] and PSP Quality of Life scale (PSP-QoL) and neuropsychological testing (RBANS, phonemic fluency, letter-number sequencing, and color trails test).
- Caregiver burden will also be assessed [redacted].
- Blood will be collected for ADA (as part of the assessment for immunogenicity) PK, PD, and exploratory biomarker analysis from each participant during this study in the double-blind period and in the open-label extension period.
- Structural changes in brain regions associated with PSP disease progression will be assessed using MRI. It is anticipated that each participant will have total of 4 MRIs over the course of the study, including an MRI during the screening period (up to Day -14) and at Weeks 24, 52, and 100.
- [redacted]
- Participants in the QMA substudy will undergo quantitative assessments of core motor features of PSP using wearable sensors to measure gait, postural instability, motor function, and falls.

Home visits: After Week 24, except for those visits when clinical scales, LPs, or MRI assessments are performed, visits and procedures may be performed in the home as long as appropriate services are available to perform the required study procedures and adequately monitor for potential safety events. In the double-blind period of the study, Weeks 28, 32, 40, and 44 may qualify for home visits.

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

Discontinuation of Study treatment and/or Study Withdrawal: Participants who discontinue study treatment may belong to 1 of the following groups:

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

Participants who discontinue study treatment during the double-blind period of the study (prior to Week 52) and remain enrolled in the study will be expected to complete the scheduled safety and efficacy evaluations until the end of the study or until the decision is made to withdraw from the study (see **Error! Reference source not found.** for schedule of evaluations in the Protocol). AEs/SAE collection will be up to 30 days after the last dose of study treatment and will continue for as long as the participant remains enrolled in the study.

Early discontinuation visit procedures should be completed for any participant who discontinues study treatment and also withdraws from the study at any time prior to end of study. All SAEs that occur until 30 days after last dose of study treatment should be monitored and/or recorded. In the double-blind period, participants who withdraw from the study should be encouraged to return to the clinic at Week 52 to complete the Week 52 procedures. Further details on the schedule of assessment is contained in Section 2 of the protocol.

1.2 Number of Participants

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

1.3 Start of Study and End of Study Definitions

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

1.4 Treatment

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

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
BIIB092	2000 mg	Once every 4 weeks (Q4W)	IV
Placebo	Matching dose volume 0.9% NaCl or 5% Dextrose	Once every 4 weeks (Q4W)	IV

All participants are centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, each user receives log in information and directions on how to access the IRT. Randomization is stratified by country and screening CTT Part 2 completion time of either ≤ 170 or > 170 seconds.

2 DESCRIPTION OF OBJECTIVES AND ENDPOINTS

The objectives and endpoints from the protocol Section 4 are described below.

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

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

• Frontal lobe • Pons	will be evaluated relative to the absolute and percent changes from baseline at Week 52 in the BIIB092-treated participants and compared to that of the placebo-treated participants.
Tertiary/Exploratory	
[redacted]	[redacted]

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

3 GENERAL CONSIDERATIONS

3.1 General Methods

This statistical analysis plan (SAP) is for the purpose of the interim analysis which will use data collected in the placebo-controlled (PC) and open label extension (OLE) periods once all subjects have completed the PC period. It covers the analyses for the OLE portion of the study and analyses across both the PC and the OLE periods. The analysis for the PC period is documented in a separate 251PP301 placebo-controlled SAP. The analyses of selected exploratory endpoints may be documented separately. Since the objectives and endpoints given in Section 2 are taken directly from the protocol which covers both PC and OLE periods, only analyses relevant to the OLE

period which will have sufficient data at the time of the interim analysis will be presented in this SAP.

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, 25% percentile, 75% percentile, 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, change from baseline will be defined as post-baseline value minus baseline value. See Section 3.3 for the definition of baseline.

Unless stated otherwise, all statistical tests will be 2-sided with statistical significance level of 0.05.

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

The health care region used in the analysis (referred as region in this SAP) is defined as:

- US: United States
- Non-US: Australia, Austria, Canada, France, Germany, Greece, Italy, Russian, Spain, United Kingdom, Japan and Korea

The term "subject" is the equivalent to "participant" used in the protocol.

This OLE period analysis plan does not include listings since they are provided in the placebo-controlled period analysis (please refer to the 251PP301 placebo-controlled SAP). These listings will include all data in the placebo-controlled and OLE periods (all data in the study), with an indicator of the study period (screening, placebo-controlled, or OLE) for each record to indicate when the event occurred.

3.2 Population

- Dosed subjects: enrolled subjects who received at least one dose of study therapy, i.e., blinded therapy (BIIB092 or placebo) or open-label BIIB092. This is the same as the "Treated participants" in Section 17.2 of the protocol.

- Intent-to-treat (ITT) population:
  The intent-to-treat population is defined as all randomized subjects who received at least one dose of blinded study treatment (BIIB092 or placebo).

- Safety population: all randomized subjects who received at least one dose of study treatment (BIIB092 or placebo).

- Efficacy MRI population: the subset of the ITT population who had a least one measurable brain volumetric measurement.

- Safety MRI population: the subset of the safety population who had a least one post-baseline safety MRI.

- Serum PK analysis population: the subset of the safety population who had at least one measurable post-baseline BIIB092 concentration in serum.

- CSF PK analysis population: the subset of the safety population who had at least one measurable post-baseline BIIB092 concentration in CSF.

- CSF PD analysis population: the subset of the safety population who had both baseline and at least one measurable post-baseline N -terminal tau CSF sample.

- Anti-drug antibody (ADA) analysis population: the subset of the safety population who had at least one post-dose sample evaluable for ADA.

OLE treatment groups for analyses

Analyses for efficacy data will be displayed by the following treatment groups according to randomization assignment at the start of the placebo-controlled period:

- BIIB092 early start: subjects who are assigned to (1) receive BIIB092 in the placebo-controlled period and (2) continue receiving BIIB092 in the OLE period
- BIIB092 late start: subjects who are assigned to (1) receive placebo in the placebo-controlled period and (2) switch to BIIB092 in the OLE period

Unless otherwise specified, analyses for safety, PK, and ADA data will be displayed by the following treatment groups according to dose received:

- BIIB092 early start: subjects who receive BIIB092 in the placebo-controlled period (regardless of randomization assignment)
- BIIB092 late start: subjects who receive only placebo in the placebo-controlled period (regardless of randomization assignment) and switch to receive BIIB092 in the OLE period
- BIIB092 total: subjects in either BIIB092 early or late start treatment groups

If all subjects received study treatment according to their randomization assignments during the placebo-controlled period (i.e. no subject assigned to placebo received BIIB092, and no subject assigned to BIIB092 received only placebo) then the assignment of subjects to treatment groups will be the same as those for efficacy.

3.2 Analysis Period

Depending on the purpose, different analyses will be conducted on the following study periods:

1. **OLE period**. Only data in the OLE period will be included in these analyses. This OLE analysis period will be applied to all the AE analyses, and the analyses will include all subjects who were dosed in the OLE period.

2. **Placebo-controlled and OLE period**. All the data in the placebo-controlled and OLE periods will be included in these analyses. This analysis period will be applied to all efficacy analyses. The analyses will include all subjects who were dosed in the study including those who did not enroll into the OLE period.

3. **Active treatment (placebo-controlled and OLE) period**. The active treatment period is defined as the study period(s) in which a subject received BIIB092. For early start subjects, all data from placebo-controlled and OLE periods will be included. For late start subjects,

only data in the OLE period will be included. This analysis period will be applied to all safety analyses, and the analyses will include all subjects who were dosed in the study except for subjects who received only placebo in the placebo-controlled period and did not get dosed in the OLE period.

For a given output, both the analysis population and the analysis period will determine which subjects will be included. For example, the incidence table of adverse events in the OLE period will include subjects in the safety population for the OLE period, i.e., all randomized subjects who received at least one dose of study treatment in the OLE period. The incidence rate table of adverse events in the active treatment (placebo-controlled and OLE) period will include subjects in the safety population for the active treatment period, i.e., all randomized subjects who received at least one dose of treatment in the active treatment period. In this SAP we do not separately define the analysis population in each analysis period.

3.3 Baseline

Placebo-controlled and OLE period: Unless otherwise specified, baseline for the Placebo-controlled and OLE period refers to the baseline value for the PC dosing period and is defined as the most recent non-missing measurement collected prior to the first dose of study drug.

Active treatment period baseline is defined as the last non-missing measurement collected prior to the first dose of study drug received in the dosing period (PC or OLE) in which a subject first receives BIIB092. Active treatment period baseline will be used for the Active treatment (placebo-controlled and OLE) period and OLE period analyses, unless otherwise specified.

The summaries in this section will be based on the ITT population. Analysis period will be specified for each table or figure. Unless otherwise specified, summary tables will be presented by OLE treatment group.

4 STUDY SUBJECTS

4.1 Accounting of subjects

Number of subjects who completed the PC period, and number of subjects who enrolled in the OLE period will be summarized. Disposition in the OLE period will be summarized for subjects enrolled in OLE. The summary data will include number (%) of subjects dosed in the OLE period, number (%) of subjects ongoing in the OLE, number (%) of subjects who completed the treatment/study in OLE, and number (%) of subjects who discontinued treatment and/or withdrew from study in OLE. Disposition in the entire study period (PC and OLE period) will also be summarized. The summary will include number (%) of subjects randomized, number (%) of subjects dosed in each period, and number (%) of subjects who discontinued treatment and/or withdrew from study in either PC or OLE period.

4.2 Demographic and Baseline Disease Characteristics

Demographics, baseline characteristics, and medical history will be summarized for subjects enrolled in the OLE period and for subjects not enrolled in the OLE period, respectively.

4.3 Study Drug Exposure and Study Drug Compliance

A summary table of study drug exposure and compliance in the OLE period will be provided. Number of doses (BIIB092) received will be summarized as a categorical variable (categories of 1-5, 6-10, 11-15, 16-20, 21-26, 27-39, 40-52 and 53-65) as well as a continuous variable. The number of doses (BIIB092) received via home infusion will be summarized. Number of weeks on study treatment (BIIB092), calculated as (date of last dose – date of first dose +28)/7, will be summarized as a categorical variable (every 6 months for the first 2 years of OLE, and then every year) as well as a continuous variable. Percentage of study treatment taken up to the last dose, calculated as (the actual number of doses divided by the number of doses a subject is expected to take until the date of last dose)*100, will be summarized as a continuous variable. This table will be presented by OLE treatment group. A similar table will also be provided on the active treatment (PC and OLE) period in order to summarize the exposure data while subjects are on BIIB092.

4.4 Medications and Non-drug therapies

The number (%) of subjects taking concomitant medication and non-drug therapies (defined as diagnostic procedures or medical treatment procedures) in the OLE period will be summarized. In addition, number of subjects in the ITT population that have taken any concomitant medications and non-drug therapies in the active treatment (placebo-controlled and OLE) period will be summarized.

Parkinson's disease medications taken concomitantly at baseline of the placebo-controlled period are defined as Parkinson's disease medications that were being taken at the time of the first dose, i.e., started prior to the first dose and continued until after the first dose. For subjects enrolled in the OLE period, the number (%) of subjects taking Parkinson's disease medications concomitantly at the baseline of the placebo-controlled period will be summarized. A similar summary will be provided for subjects taking Parkinson's disease medication concomitantly at the baseline of the OLE period. In addition, number of subjects using Parkinson's disease medications concomitantly at baseline of the OLE period will be summarized by individual medication. Subjects who have any change in Parkinson's disease medications during the OLE period will be summarized overall and by the timing of change, i.e., the number of subjects changing between Week 52 and Week 64, the number of subjects changing between Week 64 and Week 76, etc.

4.5 Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a Protocol Deviation log and categorized as key or non-key deviations based on Protocol Deviation Classification (see Appendix of the placebo-controlled SAP). Key protocol deviations that occurred in the OLE period will be summarized for subjects enrolled in the OLE. Key protocol deviations for all ITT subjects in the combined placebo-controlled and OLE periods will also be summarized.

5 EFFICACY DATA

5.1 General Considerations

The analysis population for efficacy analysis is the ITT population and data from both the placebo-controlled and OLE periods will be included. All efficacy analyses will be presented by BIIB092 late start and BIIB092 early start groups, and along with the by-visit comparison between the two groups.

There will be no multiple comparison adjustments.

5.2 Visit windows for mapping efficacy endpoint

For efficacy data that are summarized or analyzed by visit, data collected on all scheduled visits and all unscheduled visits will be mapped to an appropriate analysis visit using the windowing scheme shown in Table 1. If there are 2 or more assessments available in the same analysis window for a subject, the assessment that is closest to the target visit day will be used for analysis. If there are 2 or more assessments in the same analysis window with the same distance from the target visit day, the later assessment will be used.

Table 1 Visit Windows for Primary Endpoint: PSPRS

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing value on or prior to the first dose date
Week 12	85	[43, 126]
Week 24	169	[127,210]
Week 36	253	[211, 294]
Week 48	337	[295, 350]
Week 52	365	[351, 378]
Week 64	449	[407, 490]
Week 76	533	[491, 574]
Week 88	617	[575, 658]
Week 100	701	[659, 742]
Week 112	785	[743, 826]
Week 124	869	[827, 910]
Week 136	953	[911, 994]
Week 148	1037	[995, 1078]
Week 160	1121	[1079, 1162]
Week 172	1205	[1163, 1246]
Week 184	1289	[1247, 1330]
Week 196	1373	>=1331

Table 2 (a) Visit Windows for Key Secondary Efficacy Endpoints (MDS-UPDRS, CGI, PSP cognitive composite battery and PSP-QoL) and RBANS

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing value on or prior to the first dose date
Week 12	85	[43, 126]
Week 24	169	[127,210]
Week 36	253	[211, 308]
Week 52	365	[309, 378]
Week 64	449	[407, 490]
Week 76	533	[491, 616]
Week 100	701	[617, 784]
Week 124	869	[785, 952]
Week 148	1037	[953, 1120]
Week 172	1205	[1121, 1288]
Week 196	1373	>=1289

Table 3 (b) Visit Windows for Key Secondary Efficacy Endpoint PSP cognitive composite battery (13 individual subtests)

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing value on or prior to the first dose date
Week 12	85	[43, 126]
Week 24	169	[127,210]
Week 36	253	[211, 308]
Week 52	365	[309, 378]
Week 76	533	[449, 616]
Week 100	701	[617, 784]
Week 124	869	[785, 952]
Week 148	1037	[953, 1120]
Week 172	1205	[1121, 1288]
Week 196	1373	>=1289

Table 4 **Visit Windows for Other Secondary Efficacy Endpoints: SEADL, Phonemic Fluency Test, WAIS-IV Letter Number Sequencing Task, Color Trails test, and MoCA**

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing value on or prior to the first dose date
Week 12	85	[43, 126]
Week 24	169	[127,210]
Week 36	253	[211, 294]
Week 48	337	[295, 434]
Week 76	533	[435, 616]
Week 100	701	[617, 784]
Week 124	869	[785, 952]
Week 148	1037	[953, 1120]
Week 172	1205	[1121, 1288]
Week 196	1373	>=1289

[redacted]

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

Table 5 Visit Windows for Volumetric MRI

Analysis visit	Target visit day	Analysis visit window
Baseline	1	<=84
Week 24	169	[85, 252]
Week 52	365	[281, 448]
Week 100	701	[617, 784]

Table 6: Visit Windows for CSF PD analysis data

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 52	365	[274, 532]
Week 100	701	>=533

Handling of missing items for scales

Please refer to the placebo-controlled SAP for the imputation method. The same method will be applied to efficacy endpoints collected in the OLE period.

5.3 Considerations for interim analysis

For the interim analysis, the efficacy analysis in the OLE period will only focus on the primary and key secondary efficacy endpoints:

- 28-item PSPRS total score and 15-item PSPRS total score,
- MDS-UPDRS Part II, CGI-C, PSP cognitive composite battery, and PSP-QoL.

For the primary endpoint PSPRS, the following analyses will also be conducted:

- By-visit shift from baseline analysis and the by-visit categorical summary for each individual item in the 28-item PSPRS will be presented. The same analyses will be performed for each item of the 15-item PSPRS.
- The change from baseline in each of the 6 subscales of 28-item PSPRS will be summarized by visit, analyzed by MMRM and plotted over time. The same analysis will be applied to the 3 subscales of 15-item PSPRS (gait/limb, ocular motor, and bulbar).

Because too few patients will have reached Week 100 at the time of interim analysis database lock, the CSF PD analysis and the efficacy MRI analysis will not be conducted.

5.4 By Visit Summary and Mixed Model Repeated Measures (MMRM) Model

Change from baseline analyses will be performed using summary statistics and MMRM. Visits with too few data may be excluded from the MMRM analysis. Line plots for adjusted mean change from baseline over time will be provided.

Considerations for base MMRM model for change from baseline analyses

The baseline and change from baseline for a parameter of interest will be summarized by OLE treatment group at each post-baseline visit. A MMRM model will be used as the primary analysis to analyze change from baseline using fixed effects of OLE treatment group, time (categorical), OLE treatment group-by-time interaction, baseline for the parameter of interest, (baseline for the parameter of interest) by time interaction, baseline Color Trails 2 test (≤ 170 or > 170 seconds) and region. An unstructured covariance matrix will be used to model the within-patient 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.

6 SAFETY DATA

6.1 General Considerations

6.1.1 Analysis population

Safety population will be used for safety analyses of AEs, clinical laboratory data, [redacted] data, ECG data, and vital signs data. The safety MRI population will be used for the analysis of safety MRI data.

6.1.2 Analysis period and analysis displays

The analysis period will be specified for each output. Analysis periods in this SAP are:

- OLE period – for AE analyses
- active treatment (placebo-controlled and OLE) period - for all safety analyses

Safety data will be summarized by OLE treatment group (BIIB092 early start, BIIB092 late start, and in addition BIIB092 total).

6.1.3 Visit windows

Visit windows will be mutually exclusive, contain no gaps, and end at the midpoint between scheduled post-baseline visits, with the midpoint itself assigned to the subsequent visit window. If two or more evaluations occur in the same visit window, the evaluation closest to the target visit day will be selected for inclusion in the analysis. If multiple evaluations on different days are equally close to the target visit day, then the latest evaluation will be selected for inclusion in the analysis. If multiple evaluations occur on the same day, the earliest value will be chosen for analysis if time of collection is available; a scheduled value will be chosen before an unscheduled or early discontinuation record.

6.1.4 Incidence, incidence proportion and incidence rate

- Incidence and incidence proportion will be provided in incidence proportion tables. Incidence is defined as the number of subjects who experienced an event. Incidence proportion is defined as the number of subjects who experienced an event divided by total number of subjects in the analysis population, i.e., percentage. Each subject will be counted only once within each category.

- Incidence and incidence rate will be provided in incidence rate tables. Two different kinds of incidence rate tables will be provided as appropriate for different analyses. Definitions are provided below.

    - Follow-up adjusted incidence rate (FAIR) – defined as the number of subjects with an event divided by the total follow-up time among the subjects in the analysis population (e.g., incidence rate per 100 subject-years). The total follow-up time (subject-years) is the sum of all subjects' follow-up time, where a subject's follow-up time is calculated as the number of days (inclusive) from first dose of treatment until the last day on study divided by 365.25. For active treatment period analyses, the first dose of treatment is considered the first dose received in the study period (PC or OLE) in which a subject first receives BIIB092. Each subject will be counted only once within each category.

    - Exposure-adjusted incidence rate (EAIR) – defined as the number of subjects with an event divided by the total exposure adjusted follow-up time (i.e. total time at risk for the event) among the subjects in the analysis population (e.g., incidence rate per 100 subject-years). The exposure adjusted follow-up time (time at risk for the event) for a subject is the time from the first dose of study drug in the first BIIB092 dosing period (PC or OLE) to the initial occurrence of the event for subjects who experienced the event, and is the time from first dose of study drug in the first BIIB092 dosing period to the end of follow-up (the last day on study) for subjects who did not experience the event. The total time at risk is the sum of all subjects' time at risk. Each subject will be counted only once within each category.

6.2 Clinical Adverse Events

6.2.1 Treatment-emergent AEs (TEAEs)

All AEs will be analyzed based on the principle of treatment emergence. A treatment-emergent AE is defined as an AE that started or worsened after the start of first dose of study treatment.

To define treatment emergence for AEs with missing start or stop date or time the following additional criteria will be used:

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

For AEs 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.

In addition, SAEs that occurred since a subject was screened in the study and prior to the first dose of study treatment, which by definition are not treatment-emergent, will be included in relevant listings but will not be summarized.

Only TEAEs will be included in the AE tables, unless otherwise specified.

6.2.2 Summary and incidence analysis

Overall summary of AE table will be done for the OLE period, as well as for the active treatment (placebo-controlled and OLE) period presented by OLE treatment group. The following information will be summarized: the number of subjects with any AE, with any AE by maximum severity (as assessed by the investigator), the number of subjects with any related AE (related to study drug as assessed by investigator), the number of subjects with SAE, the number of subjects with related SAE, the number of subjects with AE leading to study drug discontinuation, the number of subjects with an AE that led to withdrawal from the study and the number of subjects with a fatal event.

The sorting order for AE incidence tables, unless otherwise specified, will be by decreasing frequency order of "BIIB092 total" column within each category in the tables presented by OLE treatment group. A subject is counted only once within each category in each table. For example, for the table of AEs by system organ class and preferred terms sorted by decreasing frequency presented by treatment group, system organ class will be presented in decreasing frequency order of BIIB092 total column, and within each system organ class, preferred terms will be presented in decreasing frequency order of BIIB092 total column. A subject is counted only once within each system organ class and preferred term.

The following AE incidence proportion tables will be provided for the OLE period (presented by the OLE treatment group unless otherwise specified):

1. AEs by system organ class and preferred term sorted by decreasing frequency
2. AEs by system organ class and preferred term sorted by alphabetical order
3. AEs by system organ class, high level group term and preferred term
4. AEs by system organ class
5. AEs by preferred term
6. AEs with an incidence of 2% or more in any treatment group by preferred term
7. AEs with an incidence of 5% or more in any treatment group by preferred term
8. Severe or very severe AEs by system organ class and preferred term
9. Severe or very severe AEs by preferred term
10. AEs by maximum severity by system organ class and preferred term. (System organ class will be presented alphabetically. Preferred terms will be presented in decreasing frequency order. Maximum severity will be presented within each preferred term in the order of mild, moderate, severe, very severe, unknown and total. A subject will be counted only once at the maximum severity within each system organ class and preferred term.)
11. AEs by maximum severity by preferred term. (Preferred terms will be presented in decreasing frequency order. Maximum severity will be presented within each preferred term in the order of mild, moderate, severe, very severe, unknown and total. A subject will be counted only once at the maximum severity within each preferred term.)
12. Related AEs by system organ class and preferred term
13. SAEs by system organ class and preferred term
14. SAEs by preferred term

15. Related SAEs by system organ class and preferred term
16. AEs that led to discontinuation of study treatment by system organ class and preferred term
17. AEs that led to withdrawal from study by system organ class and preferred term
18. SAEs with fatal outcome by system organ class and preferred term
19. AEs by 12-week intervals by system organ class and preferred term
20. SAEs by 12-week intervals by system organ class and preferred term

In addition to listings provided as part of the analysis described in the placebo-controlled SAP, a listing of AEs that led to withdrawal from study will be provided.

6.2.3 Incidence rate analysis

Due to the different length of active treatment (placebo-controlled and OLE) period in early start versus late start subjects, FAIR (defined in Section 6.1) tables will be used for following AE analyses for the active treatment (placebo-controlled and OLE) period (presented by OLE treatment group):

1. AEs by system organ class and preferred term sorted by decreasing frequency
2. AEs by system organ class, high level group term and preferred term
3. AEs by preferred term
4. Severe or very severe AEs by system organ class and preferred term
5. Severe or very severe AEs by preferred term
6. Related AEs by system organ class and preferred term
7. SAEs by system organ class and preferred term
8. SAEs by preferred term
9. Related SAEs by system organ class and preferred term

6.2.4 Adverse event of special interest

Immunogenicity is an AESI in the BIIB092 clinical development program. Adverse events representing potential immune/hypersensitivity reactions will be identified using customized MedDRA search criteria: Anaphylactic reaction, Angioedema, and Severe cutaneous adverse reactions via SMQ (narrow and broad) search; Eosinophilia, and Miscellaneous terms. Further details are given in Appendix 11.1.

An incidence proportion table for potential immune/hypersensitivity reactions organized by SMQ/Miscellaneous categories and by PT (for both AEs and SAEs), and similarly for potential immune/hypersensitivity reactions for subjects with and without treatment emergent positive anti-drug antibody (ADA) results will be presented for both AEs and SAEs for the OLE Period. Positive treatment emergent ADA will be based on the definition in Section 8 using the integrated placebo-controlled and open label extension data.

An exposure adjusted incident rate table will be provided for the active treatment (placebo-controlled and OLE) period.

The following analyses (incidence proportion only) will be performed for the OLE period to explore the relationship between ADAs and the safety of BIIB092:

- AEs for subjects with and without positive treatment emergent ADAs
- SAEs for subjects with and without positive treatment emergent ADAs

6.2.5 Infusion reactions

Infusion reactions will be identified through 1) temporal association, defined as those events which occur on the day of an infusion or the subsequent two calendar days after an infusion; and 2) through a custom MedDRA search of preferred terms. The list of custom MedDRA search terms can be found in Appendix 11.2. A serious infusion reaction is a serious adverse event which is identified by one or both methods.

For the OLE period, an overall summary of infusion reactions will be provided with the number of subjects (n, %) with any infusion reaction; with any infusion reaction identified by temporal association only; with any infusion reaction identified through the custom search only; and any infusion reaction identified through both methods. Additionally, the following incidence proportion tables will be provided for the OLE period:

1. Infusion reactions (temporal association or custom search) by SOC and PT
2. Serious infusion reactions (temporal association or custom search) by SOC and PT
3. Infusion reactions (temporal association or custom search) for subjects with and without positive treatment emergent ADAs by PT
4. Serious infusion reactions (temporal association or custom search) for subjects with and without positive treatment emergent ADAs by PT
5. Infusion reactions that occurred in temporal association to an infusion by physical location of infusion (in-clinic vs. home) by SOC and PT
6. Serious infusion reactions that occurred in temporal association to an infusion by physical location of infusion (in-clinic vs. home) by SOC and PT
7. Infusion reactions identified through custom search criteria by PT
8. Infusion reactions (temporal association or custom search) by 12-week intervals by PT

Positive treatment emergent ADA will be based on the definition in Section 8 using the integrated placebo-controlled and open label extension data.

An exposure adjusted incident rate table for infusion reactions will be provided for the active treatment (placebo-controlled and OLE) period.

Additionally, the following incidence proportion tables will be provided for the active treatment (placebo-controlled and OLE) period:

1. Infusion reactions that occurred in temporal association to an infusion by physical location of infusion (in-clinic vs. home) by SOC and PT
2. Serious infusion reactions that occurred in temporal association to an infusion by physical location of infusion (in-clinic vs. home) by SOC and PT

6.3 Clinical Laboratory Data

The following scheduled clinical laboratory parameters are to be assessed:

Hematology	
Red blood cell count	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Serum Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) Uric acid Glucose	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase Thyroid stimulating hormone (TSH)- screening only
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein or leukocyte esterase are positive on the dipstick	
Serology	
Serum for hepatitis C antibody, hepatitis B surface antigen (screening only)	
Other Analyses	
INR	
Prothrombin Time (PT)	

Hemoglobin A1C (HbA1C)- screening only
Pregnancy test (WOCBP only: screening, predose, discharge).
Follicle stimulating hormone (FSH) (screening only for women)
[redacted]

Summaries of clinical laboratory data will be performed for scheduled laboratory parameters, excluding CSF parameters. Listings of individual laboratory measurements by subjects for all the parameters, both scheduled and unscheduled, will be provided as per the placebo-controlled SAP.

Analysis period and analysis displays

The analysis period and analysis displays are defined in Section 6.1.2.

6.3.1 Quantitative analyses

Actual values, change from baseline and percent change from baseline will be summarized by visit for hematology, blood chemistry, coagulation (INR and prothrombin time), and the urinalysis parameters specific gravity and pH (actual values over time only), for all the visits in the active treatment (placebo-controlled and OLE) period. Number of evaluable subjects, mean, standard deviation, 25% and 75% quartiles, min and max values will be presented at each visit.

Plots of mean values (with standard error) for numeric laboratory parameters at each visit for all the visits in the active treatment (placebo-controlled and OLE) period will be provided. Mean values at timepoints where n< 20 will not be plotted.

Visit windows for by visit summaries

For laboratory by visit summaries, the analysis visit should be defined using visit windows (see Tables 7 and 8 below).

Table 7 Visit Windows for Laboratory by Visit Summaries for BIIB092 Early Start Subjects

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing value prior to the first dose of study drug in the PC dosing period
Week 4	29	[1 (post-dose only), 42]
Week 8	57	[43, 70]
Week 12	85	[71, 126]
Week 24	169	[127, 210]
Week 36	253	[211, 294]

Analysis visit	Target visit day	Analysis visit window
Week 48	337	[295, 350]
Week 52	365	[351, 406]
Week 64	449	[407, 490]
Week 76	533	[491, 616]
Week 100	701	[617, 784]
Week 124	869	[785,952]
Week 148	1037	[953,1120]
Week 172	1205	[1121,1288]
Week 196	1373	>=1289
Analysis Visit, Target visit day and Analysis visit window are calculated relative to the day of first dose of study drug (BIIB092 or placebo) in the PC dosing period.		

Table 8 Visit Windows for Laboratory by Visit Summaries for BIIB092 Late Start Subjects

Analysis visit	Target visit day	Analysis visit window
OLE Baseline	1	Most recent non-missing value prior to the first dose of study drug in the OLE dosing period
Week 12	85	[1 (post-dose only), 126]
Week 24	169	[127 252]
Week 48	337	[253, 420]
Week 72	505	[421, 588]
Week 96	673	[589, 756]
Week 120	841	[757, 924]
Week 144	1009	>=925
Analysis Visit, Target visit day and Analysis visit window are calculated relative to the day of first dose of study drug in the OLE dosing period..		

6.3.2 Qualitative 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 for the active treatment (placebo-controlled and OLE) period. Each subject's hematology, blood chemistry, coagulation and urinalysis (excluding microscopic examination) 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 (parameters of protein, glucose, blood, and leukocyte esterase) will be flagged as "abnormal" if positive, "normal" if negative, or "unknown" if no value is available.

For each parameter, the analysis will be based on subjects with at least one post-baseline value. Shifts from baseline to high/low status will be presented for hematology, blood chemistry and urinalysis (specific gravity and pH) numeric parameters, and shifts from baseline to abnormal (positive) will be presented for urinalysis categorical parameters (protein, glucose, blood, and leukocyte esterase). 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. Subjects need to have at least one post-baseline evaluation and a baseline value either unknown or not low/high/abnormal (including missing) in order to be included in the analysis.

For early start subjects, the placebo-controlled baseline will be used and shifts that occurred in either placebo-controlled or OLE period will be included. For late start subjects, the active treatment period baseline will be used and shifts that occurred in the OLE period based on the active treatment period baseline will be included.

Potentially Clinically Significant laboratory abnormalities analyses

For hematology, blood chemistry and urinalysis, the number of subjects with potentially clinically significant (PCS) laboratory abnormalities post-baseline will be summarized for the parameters provided in Table 9 for the active treatment (placebo-controlled and OLE) period.

Subjects need to have at least one post-baseline evaluation in the active treatment period and a baseline value not potentially clinically significant (including missing) in order to be included in the analysis.

Same as the shift analysis, for early start subjects, the placebo-controlled baseline will be used and abnormalities that occurred in either placebo-controlled or OLE period will be included. For late start subjects, the active treatment period baseline will be used and the PCS abnormalities that occurred in the OLE period based on the active treatment period baseline will be included.

Table 9: Criteria to Determine Potentially Clinically Significant (PCS) Laboratory Abnormalities

Clinical Laboratory Outlier Criteria		
Parameter name	**PCS Low**	**PCS High**
HEMATOLOGY		
White blood cells	$<3.0 \times 10^9$/L	$>16 \times 10^9$/L
Lymphocytes	$<0.8 \times 10^9$/L	$>12 \times 10^9$/L
Neutrophils	$<1.5 \times 10^9$/L	$>13.5 \times 10^9$/L
Monocytes	N/A	$>2.5 \times 10^9$/L
Eosinophils	N/A	$>1.6 \times 10^9$/L
Basophils	N/A	$>1.6 \times 10^9$/L
Red blood cells	$\leq 3.5 \times 10^{12}$/L	$\geq 6.4 \times 10^{12}$/L
Hemoglobin - Females	≤95 g/L	≥175 g/L
Hemoglobin - Males	≤115 g/L	≥190 g/L
Hematocrit - Females	≤0.32 L/L	≥0.54 L/L
Hematocrit - Males	≤0.37 L/L	≥0.60 L/L

Clinical Laboratory Outlier Criteria		
Parameter name	**PCS Low**	**PCS High**
Platelet count	≤75 x 10^9/L	≥700 x 10^9/L
BLOOD CHEMISTRY		
Alanine aminotransferase (ALT)	N/A	>3 x ULN
Aspartate aminotransferase (AST)	N/A	>3 x ULN
Alkaline phosphatase (ALP)	N/A	>3 x ULN
Total bilirubin	N/A	>1.5 x ULN
Blood urea nitrogen (BUN)	N/A	≥10.7 mmol/L
Creatinine	N/A	≥176.8 umol/L
Sodium	≤126 mmol/L	≥156 mmol/L
Potassium	≤3 mmol/L	≥6 mmol/L
Chloride	≤90 mmol/L	≥118 mmol/L
Glucose	≤2.2 mmol/L	≥9.7 mmol/L
Calcium	≤2 mmol/L	≥3 mmol/L
Phosphorus	≤0.6 mmol/L	≥1.7 mmol/L
Albumin	≤25 g/L	≥625 g/L
Total protein	≤45 g/L	≥100 g/L
URINALYSIS		
Glucose	N/A	≥1000 mg/dL
Protein	N/A	≥ 100 mg/dL
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 in the active treatment (placebo-controlled and OLE) period, 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) for each subject will be provided. A line plot of ALT, AST, ALP and total bilirubin values over time for subjects with potential serious hepatotoxicity will be provided. In addition, 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 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 presented. Concurrent is defined as on the same day. A listing of subjects with potential serious hepatotoxicity will be provided as part of the analysis specified by the placebo-controlled SAP.

6.4 ECGs

For analyses of the active treatment (placebo-controlled and OLE) period, active treatment period baseline will be used.

All of the available ECG parameter values from each subject will be included in the ECG data set. Although all recorded ECG parameter values will be included in the data listings (as part of the analysis specified by the placebo-controlled SAP), only values recorded at or near scheduled time points will be included in the summary statistics (see Table 8). The summary of ECGs at scheduled visits will be presented by the OLE treatment group through the combined active treatment (placebo-controlled and OLE) period. The ECG windowing should follow the requirements specified in the final protocol. All individual values for QT interval, QT interval corrected for heart

rate by Bazett's formula (QTcB), and QT interval corrected for heart rate by Fridericia's formula (QTcF) will be presented in the data listings (as part of the analysis specified by the placebo-controlled SAP). QT, QTcB, and QTcF will also be included in the summary statistics, but only QTcF will be analyzed and discussed in the report.

All available non-missing values of ECG parameters should be used in the summaries, and analyses for the double-blind and open-label treatment period. However, if QTcF is missing and RR interval in seconds is available, then QTcF will be calculated as

$$QTcF = \frac{QT}{RR^{1/3}}$$

If both QTcF and RR in seconds are missing, then QTcF will be calculated as

$$QTcF = \frac{QT}{(60/HEART\ RATE)^{1/3}}$$

Table 10 Visit Windows for ECG Visit Summaries for BIIB092 Early Start subjects

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing value prior to the first dose of study drug in the PC dosing period
Week 24	169	[1 (post-dose only), 266]
Week 52	365	[267, 448]
Week 76	533	[449, 616]
Week 100	701	[617, 784]
Week 124	869	[785,952]
Week 148	1037	[953,1120]
Week 172	1205	[1121,1288]
Week 196	1373	>=1289
Target visit day and Analysis visit window are calculated relative to the day of first dose of study drug (BIIB092 or placebo) in the PC dosing period.		

Table 11 Visit Windows for ECG by Visit Summaries for BIIB092 Late Start subjects

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing value prior to the first dose of study drug in the OLE dosing period
Week 24	169	[1 (post-dose only), 252]
Week 48	337	[253, 420]

Analysis visit	Target visit day	Analysis visit window
Week 72	505	[421, 588]
Week 96	673	[589, 756]
Week 120	841	[757, 924]
Week 144	1009	>=925
Analysis Visit, Target visit day and Analysis visit window are calculated relative to the day of first dose of study drug in the OLE dosing period.		

6.4.1 Analysis of Central Tendency

Summary statistics (n, mean, SD, median, minimum, and maximum) will be presented for each ECG parameter and the corresponding changes from baseline by the OLE treatment group through the combined placebo-controlled and OLE period. Frequency distribution of maximum postdose ECG intervals tables will also be generated.

6.4.2 Categorical Analysis

The frequency distribution of subjects maximum recorded post-dose QTcF, PR, QRS, and ΔQTcF will be tabulated by treatment and summarized within the CSR for the following ranges:

- For QTcF: QTcF ≤ 450 msec, 450 msec < QTcF ≤ 480 msec, 480 msec < QTcF ≤ 500 msec, QTcF > 500 msec
- For PR: PR ≤ 200 msec, PR > 200 msec
- For QRS: QRS ≤ 120 msec, QRS > 120 msec
- For ΔQTcF: ΔQTcF ≤ 30 msec, 30 msec < ΔQTcF ≤ 60 msec, ΔQTcF > 60 msec

Individual QTcF, PR, QRS, or ΔQTcF values meeting these criteria will be flagged in the data listing as part of the analysis specified in the placebo-controlled SAP.

6.5 Vital Signs

Active treatment period baseline will be used for the vital sign summaries.

Vital sign parameters include body temperature, systolic blood pressure, diastolic blood pressure, heart rate, respiration rate and weight. The descriptive statistics for actual values will be summarized by all the visits in the combined active treatment (placebo-controlled and OLE) period. The number of subjects, mean, standard deviation, median, minimum and maximum will be presented at each visit. Line plots of mean vital sign over time by OLE treatment group will be provided for the combined placebo-controlled and OLE period.

Summary of change from baseline including number of subjects, mean, standard deviation, median, minimum and maximum values will be summarized in the active treatment (placebo-controlled and OLE) period. Placebo-controlled baseline will be used for early start subjects and active treatment period baseline will be used for late start subjects.

The analysis of vital signs will also focus on the incidence of clinically relevant outliers based on the following criteria. The incidence and percentage of clinically relevant outliers determined by each criterion will be summarized in the active treatment (placebo-controlled and OLE) period by treatment group. A listing of subjects with clinically relevant vital signs will be provided as part of the analysis specified in the placebo-controlled SAP.

Table 12: Criteria Used to Assess Potential Clinically Relevant Outliers in Vital Signs

Variable	Low	High
Systolic Blood Pressure	<90 mm Hg or ≥20 mm Hg decrease from Baseline (BL)	>180 mm Hg or ≥20 mm Hg increase from BL
Diastolic Blood Pressure	< 50 mm Hg or ≥15 mm Hg decrease from BL	>105 mg Hg or ≥15 mm Hg increase from BL
Heart Rate	<50 bpm or ≥ 15 bpm decrease from BL	>120 bpm or ≥ 15 bpm increase from BL
Temperature	>2 degree C decrease from BL	>38.5 C or >2 degrees C increase from BL
Respiration Rate	< 10 breaths per minute or ≥ 50% decrease from BL	>25 breaths per minute or ≥50% increase from BL
Weight	≥7% decrease from BL	≥7 % increase from BL
BL= baseline; bpm = beats per minute		

Visit windows for by visit summaries

For vital sign by visit summaries, the analysis visit should be defined using windows (see Tables 13 and 14 below). If there is more than 1 value in the same analysis visit window 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.

Table 13: Visit Windows for Vital Sign by Visit Summaries for BIIB092 Early Start Subjects

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing value prior to the first dose of study drug in the PC dosing period
Week 4	29	[1 (post-dose only), 42]
Week 8	57	[43, 70]
Week 12	85	[71, 98]
Week 16	113	[99, 126]
Week 20	141	[127, 154]
Week 24	169	[155, 182]
Week 28	197	[183, 210]
Week 32	225	[211, 238]
Week 36	253	[239, 266]
Week 40	281	[267, 294]

Analysis visit	Target visit day	Analysis visit window
Week 44	309	[295, 322]
Week 48	337	[323, 350]
Week 52	365	[351, 378]
Week 56	393	[379, 406]
Week 60	421	[407, 434]
Week 64	449	[435, 462]
Week 68	477	[463, 490]
Week 72	505	[491, 518]
Week 76	533	[519, 546]
Week 80	561	[547, 574]
Week 84	589	[575, 602]
Week 88	617	[603, 630]
Week 92	645	[631, 658]
Week 96	673	[659, 686]
Week 100	701	[687, 714]
Week 104	729	[715, 742]
Week 108	757	[743, 770]
Week 112	785	[771, 798]
Week 116	813	[799, 826]
Week 120	841	[827, 854]
Week 124	869	[855, 882]
Week 128	897	[883, 910]
Week 132	925	[911, 938]
Week 136	953	[939, 966]
Week 140	981	[967, 994]
Week 144	1009	[995, 1022]
Week 148	1037	[1023, 1050]
Week 152	1065	[1051, 1078]
Week 156	1093	[1079, 1106]
Week 160	1121	[1107, 1134]
Week 164	1149	[1135, 1162]
Week 168	1177	[1163, 1190]
Week 172	1205	[1191, 1218]
Week 176	1233	[1219, 1246]
Week 180	1261	[1247, 1274]
Week 184	1289	[1275, 1302]
Week 188	1317	[1303, 1330]
Week 192	1345	[1331, 1358]
Week 196	1373	>=1359

Target visit day and Analysis visit window are calculated relative to the day of first dose of study drug (BIIB092 or placebo) in the PC dosing period.

Table 14: Visit Windows for Vital Sign by Visit Summaries for BIIB092 Late Start subjects

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing value prior to the first dose of study drug in the OLE dosing period
Week 4	29	[1 (post-dose only), 42]
Week 8	57	[43, 70]
Week 12	85	[71, 98]
Week 16	113	[99, 126]
Week 20	141	[127, 154]
Week 24	169	[155, 182]
Week 28	197	[183, 210]
Week 32	225	[211, 238]
Week 36	253	[239, 266]
Week 40	281	[267, 294]
Week 44	309	[295, 322]
Week 48	337	[323, 350]
Week 52	365	[351, 378]
Week 56	393	[379, 406]
Week 60	421	[407, 434]
Week 64	449	[435, 462]
Week 68	477	[463, 490]
Week 72	505	[491, 518]
Week 76	533	[519, 546]
Week 80	561	[547, 574]
Week 84	589	[575, 602]
Week 88	617	[603, 630]
Week 92	645	[631, 658]
Week 96	673	[659, 686]
Week 100	701	[687, 714]
Week 104	729	[715, 742]
Week 108	757	[743, 770]
Week 112	785	[771, 798]
Week 116	813	[799, 826]
Week 120	841	[827, 854]
Week 124	869	[855, 882]
Week 128	897	[883, 910]
Week 132	925	[911, 938]
Week 136	953	[939, 966]
Week 140	981	[967, 994]
Week 144	1009	>=995
Analysis Visit, Target visit day and Analysis visit window are calculated relative to the day of first dose of study drug in the OLE dosing period..		

6.6 Physical Examination

Physical examination data will be listed.

6.7 Neurological Examination

Neurological examination data will be listed.

[redacted]

6.9 MRI Results

New post-baseline MRI findings will be summarized for (1) microhemorrhages, (2) macrohemorrhages, (3) superficial siderosis and (4) vasogenic edema. New findings are defined as findings that were not present in the previous scan, or that have increased in size compared to the previous scan.

A by-subject listing of MRI results is provided for enrolled subjects with new safety findings (i.e., those with a "Yes" response to the new safety findings question at any time during the study) as part of the analysis specified in the placebo-controlled SAP.

7 PHARMACOKINETIC DATA

Serum samples will be collected at protocol designated times for BIIB092 pharmacokinetic assessments from subjects in the serum PK analysis population. CSF samples will be collected at protocol designated times for BIIB092 CSF pharmacokinetic assessments from subjects in the CSF PK analysis population.

7.10 CSF Concentration Data

The CSF PK analysis population will be used for the analysis of CSF concentration data.

CSF concentrations from 251PP301 will be listed and summarized by treatment group and visit. Summary statistics of CSF N-terminal tau at Weeks 0, 52 and 100 will be summarized by treatment in the active treatment (placebo-controlled and OLE) period. The relationship between CSF BIIB092 concentrations and CSF N-terminal tau changes at Weeks 0, 52 and 100 will be explored graphically.

CSF concentrations along with the scheduled (nominal) and actual sampling times (i.e., time from dosing) will be listed (when applicable) for each subject, group, and day. Differences between scheduled and actual sampling times will also be listed for all subjects. Percentage differences between actual administered dose and nominal dose will also be listed.

CSF concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for CSF concentrations, all BLQ values will be set to half the LLOQ value. Mean CSF concentrations that are BLQ will be presented as BLQ, and the SD and %CV will be reported as not applicable. Summary statistics of the CSF concentrations will be tabulated by day and scheduled time point. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling days or times, or large deviations between actual dose and nominal dose.

Because too few patients will have reached Week 100 at the time of interim analysis database lock, the CSF PK analysis will not be conducted for the purposes of this interim analysis.

7.11 Serum Pharmacokinetics

The PK Population will be used for all listings, summaries, and statistical analyses. Analysis will include all valid data in the PK dataset for BIIB092 in the active treatment (placebo-controlled and OLE) period.

In this study, additional samples for serum PK, referred to as "event driven" samples, may be collected for subjects with hypersensitivity events. Data from these samples will be considered part of a subject's overall serum PK assessment.

Subject serum BIIB092 concentrations will be listed and summarized by treatment group and visit.

The individual serum PK parameter C_{trough} will be listed for BIIB092 including any exclusions and reasons for exclusions. Summary statistics will be tabulated by treatment group and visit. Plots of individual C_{trough} over time may be provided. Overlays of individual C_{trough} over time may be provided by treatment. Plots of mean (+ SE) C_{trough} versus time will be presented by treatment group. Geometric means and coefficients of variation will also be presented for C_{trough}.

[redacted]

geometric %CV, median, minimum, and maximum) for serum concentrations, BLQ value pre day 1 of study treatment will be set to 0, all post first dose of study treatment BLQ values will be set to half the LLOQ value. Mean serum concentrations that are BLQ will be presented as BLQ, and the SD and %CV will be reported as not applicable. Summary statistics of the serum concentrations will be tabulated by group, day, and scheduled time point. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

Mean (± SE) serum concentration vs. time (scheduled) profiles for the treatment group will be presented graphically on linear and semilogarithmic scales. Serum concentration vs. time (actual) profiles from Day 1 to Week 100, for each subject, may be provided. Samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

8 ANTI-DRUG ANTIBODY DATA

Analyses for anti-drug antibodies (ADAs) will be based on subjects in the ADA population, defined as subjects in the safety population who had at least one post-dose evaluation for ADAs.

Active treatment period baseline will be used for ADA. If baseline is missing then it will be imputed as negative.

The following definitions will be used in the analysis of ADA data:

- Treatment emergent positive:
  - A post-baseline subject sample that is positive when the baseline sample is negative; or
  - A post- baseline subject sample that has a titer greater than or equal to 4 times the baseline sample titer when the baseline sample is positive. If the titer value is not available for a positive baseline result, then the baseline titer value will be imputed as the minimum required dilution (MRD); or
  - A positive post-baseline result where no titer is available, regardless of baseline value
- Persistently positive: Two or more treatment emergent positive ADA results, where the time between the first and last positive results is 16 weeks or more; or if there are no further samples available 16 weeks or more following a treatment emergent positive result (including the OLE period).
- Transiently positive: more than one treatment-emergent positive evaluation, less than 16 weeks apart, or a single treatment emergent positive (not including pretreatment) when there are samples available 16 weeks or more following the positive result.

The number and percentage of subjects with any sample that tested positive in the ADA assay (including at baseline), and the number and percentage of subjects without any positive post-treatment result (regardless of baseline) will be presented. The number of subjects with treatment emergent positive at each visit and at any time post-baseline will be presented; the number and percentage of subjects with persistently positive response and subjects with transiently positive responses will be presented similarly.

In this study, additional samples for ADA, referred to as "event driven" samples, may be collected for subjects with hypersensitivity events. Data from these samples will be considered part of a subject's overall ADA assessment.

Associations of ADA with PK and/or select AEs may be explored.

9 SAMPLE SIZE CONSIDERATIONS

All subjects who participated in the placebo-controlled period and met the criteria for OLE period will be eligible to enter into the OLE period.

10 References

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11 Appendix

11.1 Adverse event of special interest search

The following search will be performed using MedDRA 22.0.

- Anaphylactic reaction SMQ narrow and broad
- Angioedema SMQ narrow and broad
- Severe cutaneous adverse reactions SMQ narrow and broad
- Eosinophilia (PT terms: Eosinophilia; Eosinophil count increased; Allergic eosinophilia; Pulmonary eosinophilia)
- Miscellaneous terms
    - Cytokine release syndrome PT
    - Infusion related reaction PT
    - Infusion site reaction PT
    - Allergic conditions NEC HLT
    - Drug hypersensitivity PT
    - Documented hypersensitivity to administered product PT
    - Vasculitis PT
    - Systemic Lupus erythematosus PT
    - Rheumatoid arthritis PT
    - Antibody test positive PT
    - Antibody test abnormal PT
    - Antibody test PT
    - Drug specific antibody present PT
    - Neutralising antibodies PT
    - Neutralising antibodies positive PT
    - Non-neutralising antibodies positive PT

11.2 Infusion reactions custom search

The following preferred terms are considered as part of the custom MedDRA search (version 22.0) for infusion reactions:

- Infusion site reaction
- Infusion site rash
- Infusion site dermatitis
- Infusion site hypersensitivity
- Infusion site photosensitivity reaction
- Infusion site urticaria
- Infusion site eczema
- Infusion site vasculitis
- Infusion site recall reaction
- Infusion related reaction
- Administration site rash
- Administration site dermatitis
- Administration site eczema
- Administration site hypersensitivity
- Administration site urticaria
- Administration site photosensitivity reaction
- Administration site recall reaction
- Administration site vasculitis
- Administration related reaction
- Injection site dermatitis
- Injection site hypersensitivity
- Injection site rash
- Injection site urticaria
- Injection site photosensitivity reaction
- Injection site eczema
- Injection site recall reaction
- Injection site vasculitis
- Injection related reaction
- Immediate post-injection reaction
- allergic reaction to excipient
- reaction to excipient
- cytokine storm
- cytokine release syndrome
- immune-mediated adverse reaction

Statistical Analysis Plan-

Placebo-Controlled Period

Version No.: 2.0

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

Name of Study Treatment: BIIB092

Protocol No.: 251PP301

Study Phase: Phase 2b

APPROVAL

This document has been reviewed and approved by:

[redacted] Safety Statistician	Signature	Date
[redacted] SMT Statistician	Signature	Date
[redacted] Safety Statistician	[redacted] Signature	13 SEP 2019 Date
[redacted]	Signature	Date
[redacted]	Signature	Date
[redacted]	[redacted] Signature	12 SEP 2019 Date

APPROVAL

This document has been reviewed and approved by:

[redacted] Safety Statistician	[redacted] Signature	13 Sept 2019 Date
[redacted] SMT Statistician	[redacted] Signature	13 Sep 2019 Date
[redacted] Safety Statistician	[redacted] Signature	Date
[redacted]	[redacted] ture	13 SEP 2019 Date
[redacted]	[redacted] Signature	13 SEP 2019 Date
[redacted]	Signature	Date

TABLE OF CONTENTS

ABBREVIATIONS

Term	Definition
AD	Alzheimer's disease
AE	adverse event
AESI	Adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CGI-C	Clinical Global Impression Change
CGI-S	Clinical Global Impression Severity
Cinf	end-of-infusion serum concentration
CIR	copy increment from reference
CRF	case report form, paper or electronic
CSF	cerebrospinal fluid
[redacted]	[redacted]
CTA	clinical trial agreement
CTCAE	Common Toxicity Criteria for Adverse Events
Ctrough	Trough serum concentration
CTT	Color Trails Test
ECG	electrocardiogram
eCRF	electronic case report form
eTau	extracellular tau
EuroQol	European Quality of Life
[redacted]	[redacted]
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board

Term	Definition
IRT	Interactive Response Technology
ITT	intent-to-treat
IV	intravenous
J2R	Jump to reference
LNS	Letter number sequence
LP	lumbar puncture
MedDRA	Medical Dictionary for Regulatory Activities
MAPT	microtubule-associated protein tau
MCS	mental component summary
MCMC	Markov chain Monte Carlo
MDS-UPDRS	Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale
MMRM	mixed model repeated measures
MMSE	Mini-Mental State Exam
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
NfL	neurofilament light
OLE	open label extension
[redacted]	[redacted]
PCS	potentially clinically significant, physical component summary
PD	pharmacodynamic(s)
PE	physical examination
PK	pharmacokinetic(s)
PMM	pattern mixture model
[redacted]	[redacted]
PSP	progressive supranuclear palsy
PSPRS	Progressive Supranuclear Palsy Rating Scale
PSP-QoL	Progressive Supranuclear Palsy Quality of Life scale
PT	Preferred Term
Q4W	every 4 weeks
QMA	quantitative movement assessments
[redacted]	[redacted]

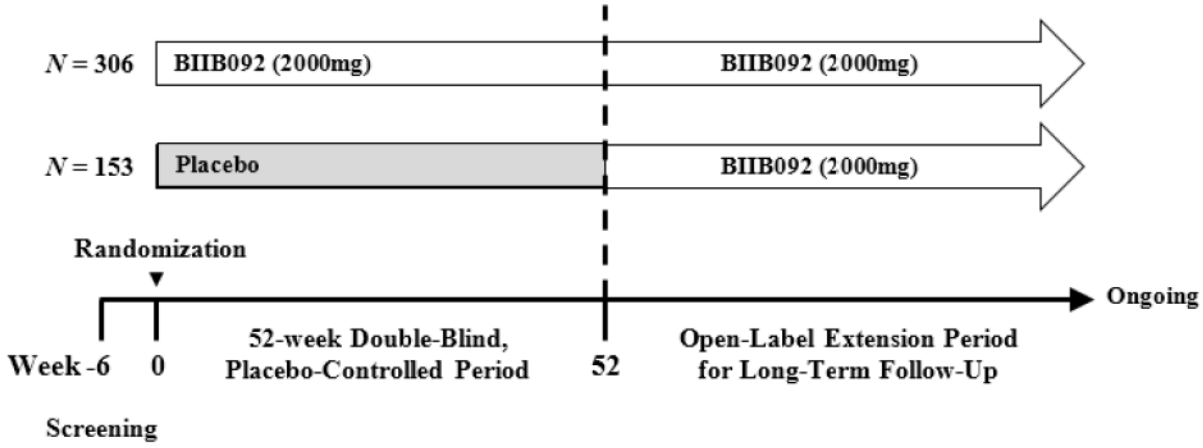
Term	Definition
RBANS	Repeatable Battery for the Assessment of Neuropsychological Disease Severity
SAE	serious adverse event
SAP	statistical analysis plan
SEADL	Schwab and England Activities of Daily Living
[redacted]	[redacted]
SOC	System Organ Class
ULN	upper limit of normal
US	United States
WAIS-IV	Wechsler Adult Intelligence Scale - IV
WHODrug	World Health Organization Drug
WOCBP	women of childbearing potential

1 OVERVIEW OF THE STUDY

1.1 Study Design

The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



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

Overall study design: The study design schematic is presented in Figure 1. The study will consist of a 52-week double-blind treatment period, which will be followed by a long-term open label extension period for follow up. Participants will be randomized to receive BIIB092 or placebo. Approximately 459 participants in total will be randomized in a 2:1 ratio to receive BIIB092 or placebo (306 participants active or 153 placebo). In the double-blind treatment period of the study, participants will be dosed approximately once every 4 weeks (Q4W) for approximately 48 weeks (up to a total of 13 times). At Week 52, participants completing the double-blind treatment period may choose to continue into the open-label extension period of this study, in which, all participants will receive BIIB092. Participants will be dosed approximately once- every 4 weeks throughout the duration of the open-label extension period. The duration of the open-label extension will vary depending on the date of enrollment of the participant in the study. The study is expected to continue until BIIB092 is commercially available, the development program is terminated, or the study is terminated at the discretion of the sponsor, whichever comes first.

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

Study assessments:

- Participants will be closely monitored for safety throughout the study. Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory

evaluations, including assessments for immunogenicity will be performed. AEs will be closely monitored. [redacted]

- PSP related signs, symptoms and quality of life will be assessed using clinical assessments: PSP Rating Scale (PSPRS), Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS Part II), Schwab and England Activities of Daily Living (SEADL) scale, Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Change (CGI-C), Montreal Cognitive Assessment (MoCA), [redacted] and PSP Quality of Life scale (PSP-QoL) and neuropsychological testing (RBANS, phonemic fluency, letter-number sequencing, and color trails test).
- Caregiver burden will also be assessed [redacted].
- Blood will be collected for immunogenicity, PK, PD, and exploratory biomarker analysis from each participant during this study in the double-blind period and in the open-label extension period.
- Structural changes in brain regions associated with PSP disease progression will be assessed using MRI. It is anticipated that each participant will have total of 4 MRIs over the course of the study, including an MRI during the screening period (up to Day -14) and at Weeks 24, 52, and 100.
- [redacted]
- Participants in the QMA substudy will undergo quantitative assessments of core motor features of PSP using wearable sensors to measure gait, postural instability, motor function, and falls.

Home visits: After Week 24, except for those visits when clinical scales, LPs, or MRI assessments are performed, visits and procedures may be performed in the home as long as appropriate services are available to perform the required study procedures and adequately monitor for potential safety events. In the double-blind period of the study, Weeks 28, 32, 40, and 44 may qualify for home visits.

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

Discontinuation of Study treatment and/or Study Withdrawal: Participants who discontinue study treatment may belong to 1 of the following groups:

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

- Participants who discontinue study treatment and immediately withdraw from the study

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

Early discontinuation visit procedures should be completed for any participant who discontinues study treatment and also withdraws from the study at any time prior to end of study. All SAEs that occur until 30 days after last dose of study treatment should be monitored and/or recorded. In the double-blind period, participants who withdraw from the study should be encouraged to return to the clinic at Week 52 to complete the Week 52 procedures. Further details on the schedule of assessment is contained in Section 2 of the protocol.

1.2 Number of Participants

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

1.3 Start of Study and End of Study Definitions

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

1.4 Treatment

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

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
BIIB092	2000 mg	Once every 4 weeks (Q4W)	IV
Placebo	Matching dose volume at 0.9% NaCl or 5% Dextrose	Once every 4 weeks (Q4W)	IV

All participants are centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, each user receives log in information and directions on how to access the IRT. Randomization is stratified by country and screening CTT Part 2 completion time of either ≤ 170 or > 170 seconds.

2 DESCRIPTION OF OBJECTIVES AND ENDPOINTS

The objectives and endpoints from the protocol Section 4 are described below.

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

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

[redacted]

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

3 GENERAL CONSIDERATIONS

3.1 General Methods

This statistical analysis plan (SAP) only covers the analyses for the double-blind placebo-controlled portion of the study. Hereafter, the double-blind, 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 open label extension (OLE) period and integrated analyses across both portions of the study. The analyses of selected exploratory endpoints may be documented separately. The term "subject" used in this SAP and in the analyses is equivalent to the term "participant" used in the Protocol.

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, 25% percentile, 75% percentile, 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.

In general, listings will include all data in the placebo-controlled and OLE periods (all data in the study), with an indicator of the study period (screening, placebo-controlled, or OLE) for each record to indicate when the event occurred.

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.

Unless stated otherwise, all statistical tests will be 2-sided with statistical significance level of 0.05.

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

The health care region used in the analysis (referred as region in this SAP) is defined as:

- US: United States
- Non-US: Australia, Austria, Canada, France, Germany, Greece, Italy, Russian, Spain, United Kingdom, Japan and Korea

3.2 Populations

- Enrolled subjects: all subjects who signed informed consent and were assigned a subject identification number.

- Randomized subjects: enrolled subjects who received a randomization treatment assignment from the Interactive Response Technology (BIIB092 or placebo).

- Dosed subjects: enrolled subjects who received at least one dose of study therapy, i.e., blinded therapy (BIIB092 or placebo) or open-label BIIB092. This is the same as the "Treated participants" in Section 17.2 of the protocol.

- Intent-to-treat (ITT) population: all randomized subjects who received at least one dose of blinded study treatment (BIIB092 or placebo).

- Per-protocol population: all subjects in the ITT population who also
    - had no violations of the following inclusion criteria:
        - Probable or possible PSP as defined in Section 6.1.2 of the protocol;
            a. Based on the following
                - A progressive history of postural instability during the first 3 years that symptoms are present
                  OR
                - A progressive history of falls during the first 3 years that symptoms are present
            b. Based on the following
                - Vertical supranuclear gaze palsy defined as clear limitation of the range of voluntary gaze in the vertical more than in the

horizontal plane, more than expected with age, which is overcome by activation with the vestibulo-ocular reflex (at later stages, the vestibulo-ocular reflex may be lost, or the maneuver prevented by nuchal rigidity).

OR

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

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

d. An akinetic-rigid syndrome

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

- Able to ambulate independently or with assistance defined as the ability to take at least 10 steps with a walker (guarding is allowed provided there is no contact) or the ability to take at least 10 steps without a walker or cane with the assistance of another person who can only have contact with one upper extremity.

- had at least 10 infusions.

- Efficacy MRI population: the subset of the ITT population who had a least one measurable brain volumetric measurement.

- Safety population: all randomized subjects who received at least one dose of study treatment (BIIB092 or placebo).

- Safety MRI population: the subset of the safety population who had at least one post-baseline safety MRI.

- Serum PK analysis population: the subset of the safety population who had at least one measurable post-baseline BIIB092 concentration in serum.

- CSF PK analysis population: the subset of the safety population who had at least one measurable post-baseline BIIB092 concentration in CSF.

- Anti-drug antibody (ADA) analysis population: the subset of the safety population who had at least one post-dose sample evaluable for anti-drug antibody.

3.3 Treatment groups for analysis

Analyses using the ITT population, Per Protocol population, and Efficacy MRI population will be performed according to the treatment groups to which subjects were randomized unless otherwise specified.

For the safety population and populations defined above which are based on the safety population, safety treatment groups will be used for analysis unless otherwise specified. If a subject received one or more doses of BIIB092 then he/she will be included in the BIIB092 safety treatment group. If a subject only received doses of placebo, he/she will be included in the placebo safety treatment group.

A listing of subjects whose safety treatment group is different from their randomized treatment group will be provided.

For serum PK and CSF PK populations, a subject may be excluded from analysis due to key protocol deviations.

4 STUDY SUBJECTS

Analyses in the section will be based on ITT population unless otherwise indicated.

4.1 Accounting of subjects

Disposition will be summarized for the randomized subjects population by treatment group and the summary data will include number (%) of subjects randomized and dosed, number (%) of subjects who completed the treatment/study, and number (%) of subjects who discontinued treatment and/or withdrew from study. The number of subjects discontinued from study treatment/withdrew from study will also be summarized by treatment group and by baseline 28-item and 15-item PSPRS total score ($\leq$ median, $>$ median). 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 number of subjects discontinuing treatment will be summarized in time intervals, i.e., 0 to < 12 weeks, >=12 to <24 weeks, >=24 to <36 weeks, >=36 to <48 weeks, and >= 48 weeks. A similar summary will be done for subjects who withdrew from study. Number of subjects excluded from the per-protocol population will also be summarized. Time to treatment discontinuation and time to study withdrawal will be displayed by Kaplan-Meier plot by treatment group.

The number of subjects in each analysis population will be summarized. The number of subjects dosed will be summarized by region as defined in Section 3.1, country and site. In addition, the number of subjects who completed the treatment/study will be summarized by region, country and site.

A randomization listing including country, CTT 2, randomization number, randomization date, and the protocol version, as well as a listing of randomized subjects excluded from the ITT

population, and a listing of dosed subjects excluded from the PP population will be provided. Subjects with a mismatch between randomization CTT 2 categorization and actual CTT 2 categorization will be listed.

4.2 Demographic and Baseline Disease Characteristics

The demographic data including age, sex, ethnicity, race, height, weight, and body mass index (BMI) will be summarized. Race and ethnicity will be presented as Unknown for subjects where collection of these data is not permitted per local regulations. Age will also be presented using the following groupings: <41, 41-50, 51-60, 61-70, 71-80, 81-86, >86 years; ⩽64, 65-74 and ≥75; and ≤median, >median where median is the median age based on the overall ITT population.

Summary of the baseline characteristics of PSP will include the following baseline clinical assessments:

- 28-item PSPRS total score* and 28-item PSPRS (≤median, >median) where median is based on the overall ITT population;
- 15-item PSPRS total score* and 15-item PSPRS (≤median, >median) where median is based on the overall ITT population;
- MDS-UPDRS Part II*;
- PSP cognitive composite battery*;
- CGI-S*;
- [redacted]
- CTT 2* and two categorizations: ≤170 and >170 secs*, and <240 and ≥240 secs;
- Mini-Mental State Exam (MMSE) and MMSE (<20 and ≥20);
- number of years since first PSP signs and symptoms*;
- number of years since diagnosis of PSP*;
- tau haplotype (H1/H1, H1/H2, or H2/H2)*;
- Parkinson's Disease medication use at baseline (yes or no; see Section 4.4 for definition of Parkinson's Disease medication use at baseline)*;
- SEADL;
- Phonemic Fluency Test;
- Letter Number Sequencing Test total score and longest letter number sequence score;
- CTT 1;
- MoCA;
- RBANS;
- Possible or probable PSP;

- 28-item PSPRS Gait item 26 at baseline (<3, >=3).

A separate table which summarizes key baseline characteristics of PSP (those marked with * above) will be provided. Subject listings will be generated for demographics and baseline characteristics of PSP.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 22.0 or higher). The number (%) of subjects with history (including both ongoing and not ongoing) medical conditions will be summarized by SOC and PT. A listing of medical history will be generated.

The number (%) of subjects for each PSP phenotype retrospectively reported at symptom onset will be summarized. Shift from baseline to Week 52 of PSP phenotype will also be tabulated.

4.3 Study Drug Exposure and Study Drug Compliance

The analysis in this section will be based on safety population. Number of doses (i.e. infusions of BIIB092 or placebo) received will be summarized as a categorical variable (as integers from 1 to 13; as ≥10; and as 1-5, 6-9, 10-13, ≥14) as well as a continuous variable. Due to the once monthly dosing schedule, one dose of study drug is considered 28 days of study treatment exposure. The number of weeks on study treatment (BIIB092 or placebo), calculated as (date of last dose – date of first dose +28)/7, will be summarized as a categorical variable (>0-4, >4-14, >14-22, >22-30, >30-38, >38-46, and >46 weeks) as well as a continuous variable. Percentage of study drug taken up to the last dose, calculated as (the actual number of doses divided by the number of doses a subject is expected to take up to and including the date of the last doses)*100, will be summarized as a continuous variable. The number of years on study treatment (BIIB092 or placebo), calculated as (date of last dose – date of first dose +28)/365.25, will be summarized as a continuous variable. Duration of Follow-up (years), calculated as [(date of last day of placebo-controlled period) - (date of first dose of placebo or BIIB092) + 1]/365.25 will be summarized as a continuous variable, including the sum across subjects presented as total duration of follow-up (years).

The time on study after treatment discontinuation will be calculated as follows:

- Positive time on study after treatment discontinuation: For subjects whose date of last day on study is more than 28 days after the last dose, time on study after treatment discontinuation (in weeks) will be calculated as ((Date of last day on study) – (Date of last dose of placebo or BIIB092 +28))/7;
- No time on study after treatment discontinuation: For subjects whose date of last day on study is less than or equal to 28 days after the date of last dose (placebo or BIIB092), time on study (weeks) after treatment discontinuation is considered 0.

For this analysis, subjects are considered to have discontinued treatment if they either discontinued treatment early in the PC period or if they completed treatment in the PC period and are not dosed in the OLE. The number (%) of subjects with no time on study after treatment discontinuation and with positive time on study after treatment discontinuation will be summarized. Time on study (weeks) after treatment discontinuation will be summarized as a continuous variable, including the sum across subjects presented as total time on study (weeks) after treatment discontinuation.

A listing of study drug administration records, including total volume prepared and total volume infused at each infusion, and cumulative number of doses will be provided.

A listing of drug supply information (e.g. lot number) will also be provided.

A listing with information on infusion interruptions and infusion rate reductions will be provided.

4.4 Medications and Non-drug therapies

4.4.1 Concomitant medication

The previous and concomitant medication eCRF contains medications administered up to 4 weeks prior to study drug administration. The focus of the analyses will be on concomitant medications/therapies.

All medications will be coded using the World Health Organization Drug (WHODrug March 2019 or higher) dictionary. All non-drug therapies (defined as diagnostic procedures or medical treatment procedures) will be coded using the MedDRA dictionary version 22.0 or higher. A concomitant medication (therapy) will be defined as any that was taken on or after the day of the first dose of study drug. This includes therapies that start prior to the initiation of the first dose if their use continues on or after the date of first dose. To define concomitant use for therapies with missing start or stop dates, the following additional criteria will be used:

- if both the start and stop dates of a therapy are missing, that therapy will be considered concomitant.
- if the start date of a therapy is missing and the stop date of that therapy fall on or after the date of the first dose, that therapy will be considered concomitant.
- if the start date of a therapy is prior to the date of the first dose and the stop date of that therapy is missing and the therapy is listed as continuing, that therapy will be considered concomitant, or
- if the start date of a therapy is prior to the date of the first dose and the stop date of that therapy is missing and the therapy is not listed as continuing, that therapy will be considered concomitant.

For a therapy with a partial start date, the year/month of the therapy date will be compared to that of the first dosing date to determine whether the therapy is concomitant.

The number (%) of subjects taking concomitant medication and non-drug therapies will be summarized. Medications and non-drug therapies will be listed, including medications that were stopped during the 4 weeks prior to the date of first dose.

Parkinson's disease medications taken concomitantly at baseline are defined as Parkinson's disease medications that were being taken at the time of the first dose, i.e., started prior to the first dose and continued until after the first dose. The number (%) of subjects taking Parkinson's disease medications concomitantly at baseline will be summarized. In addition, number of subjects using Parkinson's disease medications concomitantly at baseline will be summarized by individual medication. Subjects who have any change in Parkinson's disease medications after the initiation of study treatment will be summarized overall and by the timing of change every 3 months, i.e., the number of subjects changing in 0- 12 weeks, the number of subjects changing between 12 - 24

weeks, etc. Subjects who have changes in multiple intervals will be counted in each interval. A listing of subjects with any change in Parkinson's disease medications in the study will be provided.

4.4.2 Disallowed therapies

Per Section 7.7.1 of the Protocol, prohibited and/or restricted medications taken prior to study treatment administration and during the study are described below. Medications taken within 4 weeks prior to study treatment administration and during study treatment must be recorded on the case report form (CRF).

1. Prior exposure to BIIB092.
2. Within 4 weeks of screening or anticipated during the 52-week double-blind portion of the study, concurrent treatment with memantine; acetylcholinesterase inhibitors; antipsychotic agents or mood stabilizers (e.g., valproate, lithium); or benzodiazepines are disallowed, with the following exceptions:

   a. Low dose lorazepam or other short-acting medications may be used for sedation prior to MRI scans for those participants requiring sedation. At the discretion of the Investigator, 0.5 to 1 mg may be given orally prior to scan with a single repeat dose given if the first dose is ineffective. Neuropsychological testing may not be performed on the same day of lorazepam administration. Participants and caregiver must be informed of risks of lorazepam use prior to administration.

   b. Participants who take short-acting benzodiazepines or other hypnotics (e.g., temazepam, zolpidem) for sleep may continue to do so if they have been on a stable dose for 30 days prior to screening.

   c. Clonazepam may be used for treatment of restless legs syndrome, dystonia, or painful rigidity associated with PSP if the dose has been stable for 60 days prior to screening.

   d. Quetiapine or clozapine may be permitted if at a stable dose for at least 60 days prior to screening.

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

The incidence of disallowed medications will be summarized. A listing of subjects who took any disallowed medications will be provided.

4.5 Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a Protocol Deviation log and categorized as key or non-key deviations based on Protocol Deviation Classification Form. The key protocol deviations will be summarized by treatment group. Listings will be generated for the key or non-key protocol deviations, respectively.

5 EFFICACY DATA

5.1 General Considerations

All efficacy analyses will be performed on the ITT population. In addition, the primary and the key secondary endpoints will also be performed on the PP population.

The primary, sensitivity and supplementary analyses for the primary and key secondary endpoints are listed in the below table.

Table 1 Analysis for Primary and Key Secondary Endpoints

Endpoint	Analysis	Analysis Population	SAP Section
28-item PSPRS total score, 15-item PSPRS total score	Primary: Analysis of change from baseline at Week 52 (MMRM)	ITT	5.2.3
	Sensitivity: Copy increment from reference method (MMRM)	ITT	5.2.4.1
	Sensitivity: Jump to reference method (MMRM)	ITT	5.2.4.2
	Sensitivity: Imputation by natural disease progression (ANCOVA)	ITT	5.2.4.3
	Sensitivity: Tipping point analysis (ANCOVA)	ITT	5.2.4.4
	Sensitivity: Pattern mixture model (MMRM)	ITT	5.2.4.5
	Supplementary: PSPRS subscale analysis (MMRM)	ITT	5.2.5.1
	Supplementary: Time to clinical outcome analysis (Kaplan Meier analysis and Cox proportional hazard model)	ITT	5.2.5.2
	Supplementary: Censoring after intercurrent events (MMRM)*	ITT	5.2.5.3
	Supplementary: Per-protocol analysis (MMRM)	Per-protocol	5.2.5.4
	Supplementary: Responder analysis (Logistic regression)	ITT	5.2.5.5

	Supplementary: Slope analysis (MMRM)	ITT	5.2.5.6
	Supplementary: Divergence effect analysis (MMRM)	ITT	5.2.5.7
MDS-UPDRS Part II, PSP cognitive composite battery, PSP-QoL	Primary: Analysis of change from baseline at Week 52 (MMRM)	ITT	5.3.1.1 5.3.1.3 5.3.1.4
	Sensitivity: Pattern mixture model (MMRM)	ITT	5.3.1.5
	Supplementary: Censoring after intercurrent events (MMRM)*	ITT	5.3.1.5
	Supplementary: Per-protocol analysis (MMRM)	Per-protocol	5.3.1.5
	Supplementary: Slope analysis (MMRM)	ITT	5.3.1.5
	Supplementary: Divergence effect analysis (MMRM)	ITT	5.3.1.5
	Supplementary: Subscale analysis for PSP cognitive composite battery (MMRM)	ITT	5.3.1.5
CGI-C	Primary: Analysis at Week 52 (MMRM)	ITT	5.3.1.2
	Sensitivity: Pattern mixture model (MMRM)	ITT	5.3.1.5
	Supplementary: Censoring after intercurrent events (MMRM)*	ITT	5.3.1.5
	Supplementary: Per-protocol analysis (MMRM)	Per-protocol	5.3.1.5
	Supplementary: Slope analysis (MMRM)	ITT	5.3.1.5
	Supplementary: Divergence effect analysis (MMRM)	ITT	5.3.1.5

* Analysis excludes data collected after the intercurrent event of premature discontinuation of the study treatment. All other analyses will include data collected after intercurrent events [ICH E9 (R1) Addendum 2017].

5.1.1 Visit windows for mapping efficacy endpoint

For efficacy data that are summarized or analyzed by visit, data collected on all scheduled visits and all unscheduled visits will be mapped to an appropriate analysis visit using the windowing scheme shown in Tables 2-6. If there are 2 or more assessments available in the same analysis window for a subject, the assessment that is closest to the target visit day will be used for analysis. If there are 2 or more assessments in the same analysis window with the same distance from the target visit day, the later assessment will be used.

Table 2 Visit Windows for Primary Endpoint: PSPRS

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing value on or prior to the first dose date
Week 12	85	[43, 126]
Week 24	169	[127, 210]
Week 36	253	[211, 294]
Week 48	337	[295, 350]
Week 52	365	[351, 378]

Table 3 Visit Windows for Key Secondary Efficacy Endpoints (MDS-UPDRS, CGI, PSP cognitive composite battery, and PSP-QoL) and RBANS

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing value on or prior to the first dose date
Week 12	85	[43, 126]
Week 24	169	[127, 210]
Week 36	253	[211, 308]
Week 52	365	[309, 378]

Table 4 Visit Windows for Other Secondary Efficacy Endpoints: SEADL, Phonemic Fluency Test, WAIS-IV Letter Number Sequencing Task, Color Trails test, and MoCA

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing value on or prior to the first dose date
Week 12	85	[43, 126]
Week 24	169	[127, 210]
Week 36	253	[211, 294]
Week 48	337	[295, 434]

Table 5 **Visit Windows for Tertiary/Exploratory endpoints: [redacted] and [redacted]**

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing value on or prior to the first dose date, except for [redacted]
Week 24	169	[85, 252]
Week 48	337	[253, 434]

Table 6 **Visit Windows for volumetric MRI**

Analysis visit	Target visit day	Analysis visit window
Baseline	1	<=84
Week 24	169	[85, 252]
Week 52	365	[281, 448]

5.1.2 Handling of missing items for scales

If any of the individual items for the MDS-UPDRS Part II and MoCA is missing, the total score of the corresponding endpoint will be imputed by prorating the observed scores [van Ginkel 2010].

- For MDS-UPDRS Part II, if 3 or fewer of 13 items (<25%) are missing, the total score will be imputed by the prorating algorithm. If more than 3 items are missing, the total score of MDS-UPDRS Part II at that visit will be considered missing.
- For MoCA, if 1 domain (<25%) of the 7 domains is missing, the total score will be imputed using the same prorating algorithm; if more than 1 domains are missing, the total score at that visit will be considered as missing.

For CTT 1 and 2, if any test scores are missing due to participant too impaired, participant refused, refusal (subject or informant), physical reason, or too impaired (cognitively or psychiatrically), the missing values will be imputed to 240 seconds. If subjects failed the CTT pretest (hence no CTT was assessed), or did not complete CTT within the time limit of 240 seconds, the missing values will be imputed to 240 seconds as well.

For Letter number sequence test, if partial item scores are missing due to participant too impaired, participant refused, refusal (subject or informant), physical reason or too impaired (cognitively or psychiatrically), the missing LNS total raw score will be imputed with the sum of completed item scores, and the longest LNS total raw score will be imputed with the count of longest sequence (string) numbers and letters correctly reproduced by participant.

For each of the individual component tests in the PSP cognitive composite battery, if partial item scores within a test are missing due to participant too impaired, participant refused, refusal (subject or informant), physical reason, or too impaired (cognitively or psychiatrically), the missing test score will be imputed using the sum of completed item scores.

5.1.3 Considerations for multiple comparison adjustments

Key secondary endpoints have been rank prioritized, in the order shown in Section 2. In order to control for a Type I error for the key secondary endpoints, a sequential closed testing procedure will be used. If statistical significance is not achieved for a key secondary endpoint, all key secondary endpoint(s) of a lower rank will not be considered statistically significant.

There will be no multiple comparison adjustments for the sensitivity or supplementary analyses for the primary and key secondary efficacy endpoints, the non-key secondary endpoints, the tertiary efficacy endpoints, the subgroup analyses or the additional analyses.

5.1.4 Considerations for base MMRM model for change from baseline analyses

The observed value and change from baseline for a parameter of interest will be summarized by treatment group at each post-baseline visit. A mixed model repeated measures (MMRM) model will be used as the primary analysis to analyze change from baseline using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for the parameter of interest, (baseline for the parameter of interest) by time interaction, baseline Color Trails 2 test (≤ 170 or > 170 seconds) and region (see healthcare region definitions in Section 3.1). 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. If the unstructured variance-covariance structure does not converge in the MMRM model and a structured model is used, the sandwich estimator will be used to get the variance of the treatment effect estimator. The adjusted mean of each treatment group, as well as the treatment group differences will be displayed with 95% CI and p-value. In the primary analysis of each endpoint, missing data are assumed to be missing at random [Rubin 1976].

5.2 Primary Efficacy Endpoint

Two primary endpoints meeting evidentiary requirements of the US, and Europe/Japan, respectively were selected: change from baseline in 15-item PSPRS at Week 52 (US); and change from baseline in 28-item PSPRS at Week 52 (Europe and Japan). For each region, only the endpoint which met evidentiary requirements of the region is considered primary and the other is considered a non-key secondary endpoint.

The original PSPRS comprises 28 items in 6 areas. Six items (1, 2, 20-23) are rated on a 3-point scale (0-2) and 22 remaining items are rated on 5-point scale (0-4). Six subscale scores are auto-calculated as follows:

- History: sum of 7 item scores with total maximum score of 24 points: item 1 withdrawal, item 2 irritability, item 3 dysphagia for solids, item 4 knife and fork, item 5 falls, item 6 urinary incontinence, item 7 sleep difficulty;
- Mentation: sum of 4 item scores with total maximum score of 16 points: item 8 disorientation, item 9 bradyphrenia, item 10 emotional incontinence, item 11 grasping;
- Bulbar: sum of 2 item scores with total maximum score of 8 points: item 12 dysarthria and item 13 dysphagia for liquids;
- Ocular: sum of 4 item scores with total maximum score of 16 points: item 14 upward eye movement, item 15 downward eye movement, item 16 left-right eye movement, item 17 eyelid dysfunction;
- Limb: sum of 6 item scores with total maximum score of 16 points: item 18 limb rigidity, item 19 limb dystonia. item 20 finger tapping, item 21 toe tapping, item 22 apraxia of hand movement, item 23 tremor;
- Gait: sum of 5 item scores with total maximum score of 20 points: item 24 neck rigidity, item 25 arising from chair, item 26 gait, item 27 postural stability, item 28 sitting down.

5.2.1 Primary endpoint for United States (US)

Fifteen items were selected from the original 28-item PSPRS to form a 15-item PSPRS: items 3, 4, 5, 12, 13, 14, 15, 16, 17, 19, 24, 25, 26, 27, and 28. Among these 15 items, response options of 13 items will be collapsed and rescored (details are provided in Section 11.1) [redacted]

Based on factor analysis of pooled historical data, three domains were identified: gait/limb function (8 items, including items 4, 5, 19, 24-28), ocular motor (4 items, including average of items 14-16 and item 17), and bulbar (3 items, including items 3, 12, 13). The change from baseline at Week 52 in this 15-item PSPRS total score is used as the primary endpoint for US. The terms "15-item PSPRS" and "15-item PSPRS total score" will be used interchangeably. The 28-item PSPRS will be included in the dossier as supportive information for the US.

5.2.2 Primary endpoint for Europe and Japan

The original 28-PSPRS total score is auto-calculated as the sum of all 28 item scores, and ranges from 0 (normal) to 100 points. The change from baseline at Week 52 in this 28-item PSPRS is the primary endpoint for Europe and Japan. The terms "28-item PSPRS" and "28-item PSPRS total score" will be used interchangeably. The 15-item PSPRS will be included in the dossier as supportive information for Europe and Japan.

5.2.3 Primary analysis

The primary analysis of the primary endpoints, change from baseline in 15-item and 28-item PSPRS at Week 52, is the treatment policy approach [ICH E9 (R1) Addendum 2014, 2017]. The estimand of the primary analysis is defined as:

- Population: all subjects in the ITT population
- Variable: change from baseline in PSPRS at Week 52
- Handling of intercurrent events: regardless of intercurrent events (example, treatment discontinuation)
- Summary statistics: difference in variable means between treatment groups

The primary analysis will be based on the MMRM model described in Section 5.1. A line plot of adjusted mean change from baseline over time and a bar plot of results at Week 52 will also be provided.

In addition to this primary analysis, some sensitivity analyses (Section 5.2.4) and supplementary analyses (Section 5.2.5) will be performed. Forest plots of adjusted mean change from baseline versus placebo at Week 52 from primary, sensitivity and supplementary analyses will be provided. A listing of primary endpoints will be provided.

5.2.4 Sensitivity analysis

The following sensitivity analyses will be performed to assess the robustness of the primary analysis to deviation from the missing-at-random assumption. All the sensitivity analyses will be conducted for the ITT population for both 15-item and 28-item PSPRS.

5.2.4.1 Copy increment from reference (CIR) method

The CIR method (which is the same as the copy difference from control method described in the study protocol) will be applied to impute the post-withdrawal data for any subject assigned to BIIB092 treatment who withdraws from study early based on data from the placebo group rather than the subject's own randomized treatment group [Carpenter et al. 2013]. Specifically, for a subject assigned to BIIB092 treatment who withdraws early, his or her mean trajectory after early withdrawal is assumed to be parallel to the mean trajectory of the placebo group, and the difference between the two means is the same as the difference at the time of withdrawal. This method assumes that any benefit gained from previous treatment will be retained, but subjects progress as if they were on placebo after withdrawal from study. For any subject on placebo who withdraws early, his or her post-withdrawal profile will be imputed following the missing-at-random principle. Implementation details can be found in Section 11.2.1.

After all missing data have been imputed, MMRM model described in Section 5.1 will be applied for analysis.

5.2.4.2 Jump to reference method (J2R)

The J2R method will be applied to impute the post-withdrawal data for any subject assigned to BIIB092 treatment who withdraws from study early based on data from the placebo group rather than the subject's own randomized treatment group [Carpenter et al. 2013]. Specifically, for a subject assigned to BIIB092 treatment who withdraws early, his or her mean trajectory after early

withdrawal is assumed to be the same mean trajectory as the placebo group. This method assumes that any benefit gained from previous treatment will be immediately lost. For any subject on placebo who withdraws early, his or her post-withdrawal profile will be imputed following the missing-at-random principle. Implementation details can be found in Section 11.2.2.

After all missing data have been imputed, MMRM model described in Section 5.1 will be applied for analysis.

5.2.4.3 **Imputed by natural disease progression**

After early withdrawal from the study, subjects are assumed to exhibit an evolution of the disease similar as the natural disease progression (for all treatment groups) in this imputation method. The missing data at Week 52 for this study will be imputed using the linear extrapolation approach. Missing data are imputed by assuming historical placebo progression (11.39 points/year)) in the 28-item PSPRS total score from the visit of the last observation prior to Week 52. For example, if a participant discontinues at Week 24 with 28-item PSPRS total score of 41 points, then the Week 52 value is imputed with 41 + 11.39*(1-(24/52)). The natural disease progression, 11.39 points/year in 28-item PSPRS and 9.34 points/year in 15-item PSPRS, were determined based on an analysis of subjects with PSP disease onset < 5 years from the Davunetide study. After all missing data have been imputed, an ANCOVA model adjusting for treatment group, baseline PSPRS, baseline Color Trails 2 test (≤ 170 or > 170 seconds) and region will be applied to analyze the change from baseline in PSPRS total score at Week 52.

5.2.4.4 **Tipping point analysis**

The tipping-point analysis is a progressive stress-testing to assess how severe departures from missing-at-random must be in order to overturn the conclusion of the primary analysis [Yan et al. 2009]. For our study, subjects are assumed to have worse scores after early withdrawal from study compared to subjects who remain on study.

The missing data are first imputed by the standard multiple imputation (assuming missing at random). To reflect the worse performance after early withdrawal, pre-specified shift parameters δ_c and δ_t (e.g., the difference between δ_c and δ_t is the observed treatment effect rounded up to the next integer) are added to the imputed values for subjects on placebo and BIIB092, respectively. The adjusted multiple imputed datasets will then be analyzed by an ANCOVA model and the results will be combined using the Rubin's rule for inference.

A range of shift parameters δ_c and δ_t will be applied and p-value will be presented for each combination of δ_c and δ_t. The tipping region is defined as the combinations of δ_c and δ_t such that the treatment effect is no longer significant (p-value greater than the significance level). Plot of tipping region for change from baseline in PSPRS at Week 52 will be presented.

The scientific plausibility of the tipping region will be evaluated. If implausible departures from the missing-at-random assumption (large δ) are needed in order to change the results from statistically significant to insignificant, the results of the primary analysis are considered to be robust to departure from the missing-at-random assumption.

5.2.4.5 Pattern mixture model

The pattern mixture model (PMM) represents a general and flexible framework to model the predictive distribution of missing data conditional on the observed data [Little 1993, 1994]. It allows formulating assumptions regarding missing data in a transparent and clinically interpretable manner.

In the PMM framework, subjects are grouped into missing patterns so that subjects in the same pattern share similar missingness characteristics. In this analysis, missing patterns will be defined according to the reasons for early withdrawal from study as reported on the electronic case report form (eCRF). The following two patterns will be considered:

- Subjects who withdraw due to reasons that may be related to efficacy, including lack of efficacy, subject request to discontinue study treatment, subject withdrew consent, poor/non-compliance, death and withdrawal by caregiver;
- Subjects who withdraw due to reasons that are unlikely related to efficacy, including adverse event, lost to follow-up, pregnancy, subject no longer meets study criteria, administrative reason by sponsor, and other.

Subjects who withdraw due to reasons that may be related to efficacy will be penalized and their missing data will be imputed using the copy increment from reference (CIR) method [Carpenter et al. 2013] (see Section 5.2.4.1 for description of the CIR method). Subjects who withdraw due to reasons that are unlikely related to efficacy will be handled using the missing-at-random assumption and their missing data will be imputed using the standard multiple imputation method [Rubin 1987]. Subjects with missing data due to reasons other than early withdrawal (such as item missing, out of window, etc.) will be handled using the missing-at-random assumption. For both imputation methods, the following covariates will be included in the imputation model: treatment group, baseline PSPRS, baseline Color Trails 2 test (≤ 170 or > 170 seconds), region and observed post baseline PSPRS total score (data from each visit as a covariate). Implementation details can be found in Section 11.2.3.

The imputed datasets will be analyzed by MMRM model described in Section 5.1. The analyzed results from the imputed datasets will be combined based on Rubin's rules [Rubin 1987] assuming that the statistics estimated from each imputed dataset are normally distributed.

If intermediate missing values are encountered (such as data missing at Week 12 but are available at subsequent visits), a Markov chain Monte Carlo (MCMC) method that assumes multivariate normality will be used to impute the intermediate missing values and produce a monotone missing pattern (data with only terminal missing and no intermediate missing) [Li 1988; Schafer 1997].

5.2.5 Supplementary analysis

5.2.5.1 PSPRS subscales and item level scores

The 28-item PSPRS is comprised of 6 subscales: History, Mentation, Bulbar, Ocular, Limb, and Gait. 28-item PSPRS is the sum of the scores for these 6 subscales. For each of the 6 subscales, the baseline value and the change from baseline at each post-baseline visit will be summarized by treatment group. The same MMRM model as the primary analysis will also be applied to the 6

subscales. A forest plot of adjusted mean change from baseline verse placebo at Week 52 from of each subscale will be provided. A categorical summary of each of the 28 items will be performed.

The same summary and MMRM analyses will be applied to the 3 subscales of 15-item PSPRS, gait/limb function, ocular motor and bulbar. A categorical summary of each of the 15 items will also be performed.

5.2.5.2 **PSPRS time to clinical outcome and shift analysis**

Time to clinical outcome analysis will include the following clinical outcome definitions based on selected items in the 28-item PSPRS:

- Loss of independent walking: change from 0, 1, 2 or 3 at baseline to 4 at any post-baseline visits up to Week 52 in Item 26 Gait;
- Unintelligible speech: change from 0, 1, 2, or 3 at baseline to 4 at any post-baseline visits up to Week 52 in Item 12 Dysarthria;
- Unable to do activities of daily Living: change from 0, 1, 2 or 3 at baseline to 4 at any post-baseline visits up to Week 52 in Item 4 Using knife & fork, buttoning clothes, washing;
- Require use of feeding tube: change from 0, 1, 2 or 3 at baseline to 4 at any post-baseline visits up to Week 52 in Item 3 dysphagia solids or Item 13 dysphagia liquids;
- Any clinical outcome: meet any of the above four clinical outcomes.

Time to clinical outcome is defined as the time from the first dose to the first clinical outcome in the placebo-controlled period. Subjects who don't reach the clinical outcomes will be censored and the censoring date is the last date in the placebo-controlled period. Time to clinical outcome will be displayed by Kaplan-Meier plot by treatment group and also be analyzed using a Cox proportional hazards model adjusting for treatment group, baseline Color Trails 2 test (≤ 170 or > 170 seconds) and region.

With the recognition that death can often be directly related to the progression of PSP and the development of the clinical outcome under consideration, we will reanalyze the data using the time to clinical outcome or death as a composite outcome for each clinical outcome defined above.

Shifts from baseline to each score value at post baseline visits for individual item for all the 28 items in PSPRS will be presented. The same shift from baseline analysis will be applied to each item in the 15-item PSPRS.

5.2.5.3 **Censoring after intercurrent events**

The primary analysis (Section 5.2.3) will be repeated with the data censored after the intercurrent event of premature discontinuation of the study treatment. The estimate of this analysis reflects the treatment effect of BIIB092 if the drug is taken as directed.

5.2.5.4 **Per-protocol analysis**

The per-protocol analysis will be done using the same model as the primary analysis (Section 5.1) and applied in the per-protocol population (Section 3.2).

5.2.5.5 **Responder analysis**

To further assess whether subjects on BIIB092 progress differently from those on placebo, responder analysis will be conducted. The responders will be determined by a threshold of the primary endpoint, i.e., subjects whose change from baseline PSPRS at Week 52 is smaller than or equal to the threshold will be classified as responders (not worsening) and otherwise will be classified as non-responders (worsening). All subjects with missing data at Week 52 will be classified as non-responders.

The responder analysis will be conducted for two threshold values i.e., subjects whose change from baseline in 28-item PSPRS at Week 52 are less than or equal to the threshold values. The number of responders and the response rate will be summarized by treatment group. The dichotomized response, responder vs. non-responder, will be modeled using a logistic regression adjusting for the following variables: treatment group, baseline PSPRS, baseline Color Trails 2 test (≤ 170 or > 170 seconds) and region. In addition to the two selected threshold values, the continuous responder curve that displays the percentage of responders under a wide range of threshold values will be presented by treatment group. The same analyses will be applied to 15-item PSPRS total score using two other threshold values. The threshold values determined using anchor- and distributed-based methods on Davunetide study data are: 6 points and 11 points for 28-item PSPRS change score; 4 points and 9 points for 15-item PSPRS change score.

Since all missing data will be considered as non-response, which is a special form of missing-not-at-random, this analysis can provide additional insights for the robustness of the primary analysis results.

5.2.5.6 **Slope analysis**

Slope analysis will be conducted to assess the difference between the BIIB092 treatment group and placebo group in the slope of change from baseline in PSPRS up to Week 52. A reduction in the slope of the BIIB092 treatment group compared with placebo group would indicate a slower rate of disease progression, thus reflecting a disease modifying effect of BIIB092. A MMRM model will be used, with dependent variable as the change from baseline score in PSPRS at each visit and with fixed effects of treatment group, time (continuous), treatment group-by-time interaction, baseline PSPRS score, (baseline PSPRS score) by time interaction, baseline Color Trails 2 test (≤ 170 or > 170 seconds) and region. The continuous time variable is calculated as number of years since the 1st infusion, so the slope estimate reflects the annual rate of change. The same methods as in the primary analysis of each endpoint will be considered for the covariance structure and the degrees of freedom.

5.2.5.7 **Divergence effect analysis**

A divergence effect analysis will be performed to assess whether the treatment difference between the BIIB092 treated subjects and the placebo subjects increases over time [Li 2017]. A linear trend test will be conducted on treatment difference at Week 12, 24, 36, 48 and 52 estimated from the MMRM model of Section 5.2.3, to assess if the slope of the treatment difference is positive or not.

Let the estimate of treatment difference be δ_i at time point t_i, where $t_i = 12, 24, 36, 48,$ and 52 (week). The least-square estimate of the slope is

$$\beta_{DIF} = \frac{\sum(t_i - \bar{t})\delta_i}{\sum(t_i - \bar{t})^2},$$

where $\bar{t}$ is the mean of t_i's. The hypothesis to be tested is

$$H_0: \beta_{DIF} \leq 0 \quad \text{versus} \quad H_a: \beta_{DIF} > 0.$$

Given β_{DIF} is a linear combination of the treatment difference δ_i, this analysis can be implemented by the "estimate" statement in the SAS proc mixed procedure.

5.3 Secondary Efficacy Endpoints

5.3.1 Key Secondary Efficacy Endpoints

The key secondary endpoints include MDS-UPDRS Part II, CGI-C, PSP cognitive composite battery and PSP-QoL. The sequential test described in Section 5.1 will be used to test the key secondary endpoints in the following order: MDS-UPDRS Part II, CGI-C, PSP cognitive composite battery, PSP-QoL physical scale, PSP-QoL mental scale and PSP-QoL VAS. An overall summary of all key secondary endpoints will be provided. A line plot of adjusted mean change from baseline over time and a bar plot of adjusted mean change from baseline at Week 52 will be provided for all key secondary endpoints with the exception for CGI-C where only adjusted mean will be used. Listings will be provided for all secondary efficacy endpoints.

5.3.1.1 Primary analysis of MDS-UPDRS Part II

The MDS-UPDRS Part II includes 13 items assessing motor aspects of experiences of daily living. These include speech, saliva and drooling, chewing and swallowing, handwriting, doing hobbies and other activities, eating tasks, tremor, dressing, hygiene, turning in bed, getting out of bed, walking and balance, and freezing. Each individual item has a 5-point scale, ranging from 0 to 4: 0 for "Normal"; 1 for "Slight"; 2 for "Mild"; 3 for "Moderate"; and 4 for "Severe". The total score is calculated by adding all required item scores, and ranges from 0 to 52.

The primary analysis of change from baseline MDS-UPDRS Part II scores will be based on the base MMRM model described in Section 5.1. A line plot of adjusted mean change from baseline over time and a bar plot of adjusted mean change from baseline at Week 52 will be provided.

5.3.1.2 Primary analysis of CGI-C

The CGI-C form is the second part of a two-part structure CGI interview. It is intended to determine the change in the participant's current clinical status, relative to the baseline visit, where CGI-S is used. The CGI-S measures the overall clinical global impression of disease severity using a 7-point scale. The CGI-C scale measures the change in the participant's change in clinical status from the baseline visit at a specific time point using a 7-point scale: 1 for "Marked Improvement"; 2 for "Moderate Improvement"; 3 for "Minimal Improvement"; 4 for "No Change"; 5 for "Minimal Worsening"; 6 for "Moderate Worsening"; 7 for "Marked Worsening". Only one answer can be chosen.

The CGI-C scores will be summarized by treatment group at each post-baseline visit. An MMRM model will be used as the primary analysis to analyze CGI-C using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline CGI-S, baseline CGI-S by time

interaction, baseline Color Trails 2 test (≤ 170 or > 170 seconds) and region. The same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom. A line plot of adjusted mean over time will be provided.

5.3.1.3 Primary analysis of PSP cognitive composite battery

The PSP cognitive composite battery will be used to identify and characterize abnormal cognitive decline in PSP subjects. The PSP cognitive composite battery includes 13 sub-tests in total: 11 tests from the RBANS (only the picture naming is excluded), letter number sequencing test, and phonemic fluency test. The factor analysis suggested three domains:

- Memory and learning: List Learning, Story Memory, List Recall, List Recognition and Story Recall
- Visual-Motor function: Figure Copy, Coding and Figure recall
- Working memory and Executive: Semantic Fluency, Digit Span, Line Orientation, Letter Number Sequencing test and Phonemic Fluency test

For each of the 13 sub-tests, a z-score will be calculated based on scores from baseline data of PASSPORT study. [redacted]

[redacted]

The z-score for each domain is calculated as the sum of z-scores of the completed tests divided by the number of tests completed. A final total composite z-score of the PSP cognitive composite battery is calculated as the average of three domain z-scores. If there are any missing values for domain z-scores, then no final composite z-score will be calculated.

The RBANS is collected at Weeks 0, 12, 24, 36, and 52, while the letter number sequence test and phonemic fluence test are collected at Weeks 0, 12, 24, 36, and 48. The windowing rule of RBANS (Section 5.1.1 Table 3) will be applied to all sub-tests.

The composite z-score will be used for the primary analysis of the PSP cognitive composite battery using the base MMRM model described in Section 5.1. A line plot of adjusted mean change from baseline over time will also be provided.

5.3.1.4 **Primary analysis of PSP-QoL**

The PSP-QoL is a participant-reported outcome measure developed specifically for assessing the health-related quality of life in people living with PSP. It is a validated 45-item questionnaire and visual analog scale that is comprised of two subscales: physical health state (22 items), which covers mobility, dysarthria, dysphagia, visual disturbances, self-care, and activities of daily living, and mental health state (23 items), which covers emotional, cognitive and social functioning. Items are given a 6-reponse option format (No Problem, Slight Problem, Moderate Problem, Marked Problem, Extreme Problem and Not Applicable). The subscale results are calculated from summing the respective items for that subscale and transforming the scores into a range of 0 to 100, with higher scores indicating a greater impact of the disease on the aspect measured. The transformation algorithm for physical and mental scales is 100*(observed score -minimal possible score)/(max possible score - minimal possible score) where the minimal possible score is 0.

The PSP-QoL also comprises of a Life Satisfaction rating gauge, which is a visual analog scale with a range of 0 (worst) to 100 (best).

The primary analysis of change from baseline PSP-QoL physical scale, mental scale and life satisfaction rating scale scores will be based on the base MMRM model described in Section 5.1. A line plot of adjusted mean change from baseline over time will be provided.

5.3.1.5 **Sensitivity and Supplementary analysis**

The following sensitivity and supplementary analyses that are planned for the primary efficacy endpoint will also be conducted for the key secondary efficacy endpoints:

- Pattern mixture model
- Censoring after intercurrent events
- Per-protocol analysis
- Slope analysis
- Divergence effect analysis

For the 3 domain z-scores of the PSP cognitive composite battery, the baseline value and the change from baseline at each post-baseline visit will be summarized by treatment group. The same

MMRM model as the primary analysis will also be applied to the domain z-scores. A forest plot of adjusted mean change from baseline versus placebo at Week 52 from each domain will be provided.

For the total score of the 11 RBANS tests, the baseline value and the change from baseline at each post-baseline visit will be summarized by treatment group. The same MMRM model as the primary analysis will also be applied to this total score of 11 RBANS tests.

For CGI-C, the categorical summary of the proportions (1) in each score category (1-7) and (2) improvement, no change and worsening will be performed.

5.3.2 Non-Key Secondary Efficacy Endpoints

Non-key secondary endpoints are tested at an uncontrolled alpha level of 0.05 per endpoint. The P values resulting from these analyses are considered as nominal and descriptive in nature.

Sections 5.3.2.1 through 5.3.2.6 provide additional details about the efficacy assessments.

5.3.2.1 **SEADL Scale**

The SEADL scale is a means of assessing a person's ability to perform daily activities in terms of speed and independence through a percentage figure. The rating is determined by a qualified staff member according to the participant's self-reported functional ability of specific criteria, with 100% indicating total independence (healthy), falling to 0% (bedridden), which indicates a state of complete dependence. The SEADL comprises of one question to be rated by selecting a value ranging from 100% to 0%, in 11 answer options: 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, and 0%. Each answer option has specific clinical descriptors and only one answer can be chosen.

The primary analysis of change from baseline SEADL will be based on the base MMRM model described in Section 5.1.

Categorical summary of the proportions in each score category (0%-100%) will also be performed.

5.3.2.2 **CGI-S**

The CGI-S measures the overall global clinical impression of disease severity using a 7-point scale. The CGI-S asks the clinician one question: "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" which is rated on the following 7-point scale: 1 for "Normal, not at all ill"; 2 for "Borderline mentally ill; 3 for "Mildly ill; 4 for "Moderately ill; 5 for "Markedly ill; 6 for "Severely ill; 7 for "Among the most extremely ill subjects". Only one answer can be chosen.

The primary analysis of change from baseline CGI-S scores will be based on the base MMRM model described in Section 5.1.

Categorical summary of the proportions in each score category (1-7) will also be performed.

5.3.2.3 **Phonemic Fluency Test**

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

The score for each trial is auto-calculated as follows:

- Trial 1: Total number of correct responses for the first letter (range 1 to 40);
- Trial 2: Total number of correct responses for the second letter (range 1 to 40).

The total score from the two trials will be used for analysis.

The visit assignment for each form with associated letters is shown below.

Form	Letters	Visits
A	F, L	Screening, Week 24
B	T, S	Visit 1, Week 48
C	R, M	Week 12, Week 36

The primary analysis of change from baseline phonemic fluency test scores will be based on the base MMRM model described in Section 5.1.

5.3.2.4 **WAIS-IV Letter Number Sequencing Task**

The WAIS-IV (Wechsler Adult Intelligence Scale--IV) LNS Task contains 10 items. Each item has 3 trials, and all 3 trials need to be rated as Incorrect (0) or Correct (1) before the rater is allowed to move to the following item.
The LNS total raw score (0 to 30 range) is auto-calculated by summing the 10 individual item scores (range 0 to 3 for each item).

The longest LNS total raw score (2 to 8 range) is auto-calculated from the count of the longest sequence (string) of numbers and letters correctly reproduced by participant.

The primary analysis of change from baseline LNS total raw scores and change from baseline longest LNS total raw score will be based on the base MMRM model described in Section 5.1.

5.3.2.5 **Color Trails Test**

The CTT is a language-free version of the Trail Making Test and was developed to allow for broader cross-cultural assessment. The form consists of two parts, CTT 1 and CTT 2.

For CTT 1, the participant simply has to connect the numbered circles, in order, from 1 to 25, by drawing a continuous line from circle to circle.

For CTT 2, the test demand is the same, except the participant must alternate between colors while connecting the circles.

The score for each part of the test is the total time required for completion in seconds. The maximum time allowed for each test trial is 240 seconds.

The primary analysis of change from baseline CTT 1 will be based on the base MMRM model described in Section 5.1.

The primary analysis of change from baseline CTT 2 will be based on the base MMRM model described in Section 5.1 along with removing the CTT 2 factor in the model.

5.3.2.6 **MoCA**

The MoCA is a one-page 30-point test designed as a rapid screening instrument for mild cognitive dysfunction. Scores for 8 cognitive domains are calculated: visuospatial/executive (maximum of 5 points); naming (maximum of 3 points); memory (total number of words remembered correctly across 2 trials; no points); attention (sum of scores for 3 questions; maximum of 6 points); language (sum of scores for 2 questions; maximum of 3 points); abstraction (maximum of 2 points); delayed recall (maximum of 5 points); orientation (maximum of 6 points). The total score is calculated by summing all domain scores (excluding memory) and adding a point for participant's education level $\leq$ 12 years. The maximum total score is 30 points; a score of 26 or above is considered normal.

The primary analysis of change from baseline MoCA total scores will be based on the base MMRM model described in Section 5.1.

5.3.2.7 **RBANS**

The RBANS was developed for the dual purposes of identifying and characterizing abnormal cognitive decline in the older adult. The full battery is composed of 12 subtests: List Learning; Story Memory; Figure Copy; Line Orientation; Picture Naming; Semantic Fluency; Digit Span; Coding; List Recall; List Recognition; Story Recall; and Figure Recall. Five Sum of Index Scores are calculated from the 12 subtests:

- List Learning and Story Memory
- Figure Copy and Line Orientation
- Picture Naming and Semantic Fluency
- Digit Span and Coding
- List Recall, List Recognition, Story Recall and Figure Recall

The total scale score is calculated from the 5 Index Scores which will be used for the primary analysis of RBANS. The primary analysis of change from baseline RBANS scores will be based on the base MMRM model described in Section 5.1. A line plot of adjusted mean change from baseline over time will be provided. A listing will also be generated.

For the 5 RBANS index scores, the baseline value and the change from baseline at each post-baseline visit will be summarized by treatment group. The same MMRM model as the primary analysis will also be applied to the 5 sum of index scores.

5.3.2.8 **Volumetric MRI Analysis**

Brain volumetric measurements will be carried out to estimate brain volumes of 7 primary brain regions of particular relevance in PSP: ventricles, whole brain, midbrain, pons, superior cerebellar peduncle, third ventricle and frontal lobes. In addition, volumes of secondary brain structures (e.g., brainstem, cerebral cortex, cerebrum, lateral ventricles, left caudate nucleus, right caudate nucleus, medulla oblongata, total gray matter and total white matter) and other brain structures (e.g. cerebellum, fourth ventricles, left/right hippocampus, left/right inferior ventricles, left/right occipital lobe, left/right parietal lobe, left/right temporal lobe) will be measured.

The change from baseline in absolute volumes which pass endpoint QC and are measured on the same MRI scanner as used at screening will be the primary MRI efficacy endpoint for analysis. The efficacy MRI analysis population will be used for the analysis of volumetric MRI data. The absolute values, change and percent change from baseline in volumes of all brain regions will be summarized by treatment group and by visit. The change from baseline in volumes of the primary regions and the secondary regions will be analyzed using the MMRM model described in Section 5.1. For the primary brain regions, the adjusted mean change from baseline in volumes will be presented graphically by line plot. A forest plot for adjusted mean % change from baseline at Week 52 for the primary brain regions will also be provided. A listing of the primary brain region volumetric MRI data will be provided.

5.4 Tertiary Efficacy Endpoints

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5.5 Subgroup Analysis

Subgroup analyses will be performed for the primary and the key secondary endpoints. The following pre-defined subgroups will be considered:

Demographics:

- Sex (female, male)
- Age (≤ median, >median);
- Race (White, Non-White);
- Region (US, Non-US);

Baseline characteristics:

- Baseline color trails 2 test categorization (≤ 170 or > 170 seconds);
- Time since first onset of PSP symptom (≤ median, >median)
- Baseline 28-item PSPRS total score (≤ median, > median)
- Baseline 15-item PSPRS total score (≤ median, > median)
- Baseline use of Parkinson's disease medication (yes, no; see Section 4.4 for definition of Parkinson's Disease medication use at baseline);
- Possible or probable PSP
- 28-item PSPRS Gait item 26 at baseline (<3, >=3)
- tau haplotype (H1/H1, H1/H2, or H2/H2)

Subjects in each subgroup category will be analyzed separately using the same MMRM analysis of the primary and key secondary endpoints. Forest plots of adjusted mean change from baseline versus placebo at Week 52 from all subgroup analyses will also be provided. Subgroup analyses will not be performed if one of the subgroups is below 10% of the total number of subjects analyzed. Subgroup analyses will not be performed if the analysis model cannot converge.

[redacted]

[redacted]

6 SAFETY DATA

6.1 General Considerations

6.1.1 Analysis population

The safety population will be used for safety analyses of AEs, SAEs, clinical laboratory data, [redacted] data, ECG data and vital sign data. The safety MRI population will be used for the analysis of safety MRI data.

6.1.2 Visit windows

Visit windows will be mutually exclusive, contain no gaps, and end at the midpoint between scheduled post-baseline visits, with the midpoint itself assigned to the subsequent visit window. If two or more evaluations occur in the same visit window, the evaluation closest to the target visit day will be selected for inclusion in the analysis. If multiple evaluations on different days are equally close to the target visit day, then the latest evaluation will be selected for inclusion in the analysis. If multiple evaluations occur on the same day, the earliest value will be chosen for analysis if time of collection is available; a scheduled value will be chosen before an unscheduled or early discontinuation record.

6.1.3 Incidence, incidence proportion, and incidence rate

- Incidence and incidence proportion will be provided in incidence proportion tables. Incidence is defined as the number of subjects who experienced an event. Incidence proportion is defined as the number of subjects who experienced an event divided by total number of subjects in the analysis population, i.e., percentage. Each subject will be counted only once within each category.

- Incidence and incidence rate will be provided in incidence rate tables. Follow-up adjusted incidence rate will be used and is defined as the number of subjects with an event divided by the total follow-up time among the subjects in the analysis population (e.g., incidence rate per 100 subject-years). The total follow-up time (subject-years) is the sum of all subjects' follow-up time, where a subject's follow-up time is calculated as the number of days (inclusive) from first dose of study drug until the last day on study, divided by 365.25. For analyses of events after treatment discontinuation, time after treatment discontinuation will be used to compute total follow-up time. Each subject will be counted only once within each category.

6.2 Clinical Adverse Events

6.2.1 Treatment-emergent AEs (TEAEs)

All AEs will be analyzed based on the principle of treatment emergence. A treatment-emergent AE was defined as an AE that started or worsened after the start of first dose of study drug.

To define treatment emergence for AEs with missing start or stop date or time the following additional criteria will be used:

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

For AEs 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.

In addition, SAEs that occurred since a subject was screened in the study and prior to the first infusion of study drug, which by definition are not treatment-emergent, will be included in relevant listings but will not be summarized.

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

6.2.2 Summary and incidence analysis

Overall summary of AE table will summarize the number of subjects with any AE, with any AE by maximum severity (as assessed by the investigator), the number of subjects with any related AE (related to study drug as assessed by investigator), the number of subjects with SAE, the number of subjects with related SAE, the number of subjects with AE leading to study drug discontinuation, and the number of fatal AEs.

The sorting order for AE incidence tables, unless otherwise specified, will be by decreasing frequency order of "BIIB092" column. A subject is counted only once within each category in each table. For example, for the table of AEs by SOC and PTs sorted by decreasing frequency presented by treatment group, SOC will be presented in decreasing frequency order of BIIB092 column, and within each SOC, PTs will be presented in decreasing frequency order of BIIB092 column. A subject is counted only once within each SOC and PT.

The following AE incidence tables will be provided:

1. AEs by SOC and PT
2. AEs by SOC and PT sorted by alphabetical order
3. AEs by SOC, high level group term and PT

4. AEs by SOC
5. AEs by PT
6. AEs with at least 2% higher incidence for BIIB092 compared to placebo by SOC and PT
7. AEs with at least 2% higher incidence for BIIB092 compared to placebo by 12-week intervals by SOC and PT
8. AEs with an incidence of 2% or more in any treatment group by 12-week intervals by PT
9. AEs with an incidence of 2% or more in any treatment group by PT
10. AEs with an incidence of 5% or more in any treatment group by PT
11. Severe or very severe AEs by SOC and PT
12. Severe or very severe AEs by PT
13. AEs by maximum severity by SOC and PT. (SOC will be presented alphabetically. PTs will be presented in decreasing frequency order. Maximum severity will be presented within each PT in the order of mild, moderate, severe, very severe, unknown and total. A subject will be counted only once at the maximum severity within each SOC and PT.)
14. AEs by maximum severity by PT. (PTs will be presented in decreasing frequency order. Maximum severity will be presented within each PT in the order of mild, moderate, severe, very severe, unknown and total. A subject will be counted only once at the maximum severity within each PT.)
15. Related AEs by SOC and PT
16. SAEs by SOC and PT
17. SAEs by PT
18. Related SAEs by SOC and PT
19. AEs that led to discontinuation of study treatment by SOC and PT
20. SAEs with fatal outcome by SOC and PT
21. AEs by 12-week intervals by SOC and PT
22. SAEs by 12-week intervals by SOC and PT

The following listings will be provided.

1. Listing of AEs
2. Listing of SAEs (including pre-dosing SAEs)
3. Listing of AEs that led to discontinuation of study treatment
4. Listing of SAEs with fatal outcome

6.2.3 Adverse event of special interest

Immunogenicity is an AESI in the BIIB092 clinical development program. Adverse events representing potential immune/hypersensitivity reactions will be identified using customized MedDRA search criteria: Anaphylactic reaction, Angioedema, and Severe cutaneous adverse reactions via SMQ (narrow and broad) search; Eosinophilia, and Miscellaneous terms. Further details are given in Appendix 11.3.

An incidence proportion table for potential immune/hypersensitivity reactions organized by SMQ/Miscellaneous categories and by PT (for both AEs and SAEs), and similarly for potential immune/hypersensitivity reactions for subjects with and without treatment emergent positive anti-drug antibody (ADA) results (as defined in Section 8) will be presented for both AEs and SAEs. A listing of potential immune/hypersensitivity reactions will be provided.

The following analyses (incidence proportion only) will be performed to explore the relationship between ADAs and the safety of BIIB092:

- AEs for subjects with and without treatment emergent positive ADAs
- SAEs for subjects with and without treatment emergent positive ADAs

In this study, additional samples for ADA, referred to as "event driven" samples, may be collected for subjects with hypersensitivity events. A listing of AEs for subjects with any event driven ADA samples will be provided.

6.2.4 Infusion reactions

Infusion reactions will be identified through 1) temporal association, defined as those adverse events which occur on the day of an infusion or the subsequent two calendar days after an infusion; and 2) through a custom MedDRA search of preferred terms (Appendix 11.4). A serious infusion reaction is a serious adverse event which is identified by one or both methods. An overall summary of infusion reactions will be provided with the number of subjects (n, %) with any infusion reaction; with any infusion reaction identified by temporal association only; with any infusion reaction identified through the custom search only; and any infusion reaction identified through both methods. A listing of infusion reactions will be provided. Additionally, the following incidence proportion tables will be provided:

1. Infusion reactions that occurred in temporal association to an infusion by SOC and PT
2. Serious infusion reactions that occurred in temporal association to an infusion by SOC and PT
3. Infusion reactions identified through custom search criteria by PT
4. Serious infusion reactions identified through custom search criteria by PT
5. Infusion reactions (temporal association or custom search) by 12-week intervals by PT

6.2.5 Incidence rate analysis

Follow-up adjusted incidence rate for the placebo-controlled period will be summarized by SOC and PT.

6.3 Clinical Laboratory Data

The following scheduled clinical laboratory parameters are to be assessed:

Hematology	
Red blood cell count	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Serum Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) Uric acid Glucose	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase Thyroid stimulating hormone (TSH)- screening only
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein or leukocyte esterase are positive on the dipstick	
Serology	
Serum for hepatitis C antibody, hepatitis B surface antigen (screening only)	
Other Analyses	

INR
Prothrombin Time
Hemoglobin A1C (HbA1C)- screening only
Pregnancy test (WOCBP only: screening, predose, discharge).
Follicle stimulating hormone (FSH) (screening only for women only)

Summaries of clinical laboratory data will be performed for scheduled laboratory parameters only. Listings of individual laboratory measurements by subjects for all the parameters, both scheduled and unscheduled, will be provided.

6.3.1 Quantitative analyses

Actual values, change from baseline and percent change from baseline will be summarized by visit for hematology, blood chemistry, coagulation (INR and prothrombin time), and the urinalysis parameters specific gravity and pH (actual values over time only). Number of evaluable subjects, mean, standard deviation, median, 25% and 75% quartiles, minimum and maximum values will be presented at each visit. Plots of mean values (with standard error) for actual values at each visit will be provided; mean values at timepoints where n< 20 will not be plotted.

Visit windows for by visit summaries

For laboratory by visit summaries, the analysis visit should be defined using visit windows (see Table 8).

Table 8 Visit Windows for Laboratory by Visit Summaries

Analysis visit	**Target visit day**	**Analysis visit window**
Baseline	1	Most recent non-missing pre-dose value
Week 4	29	[1 (post-dose only), 42]
Week 8	57	[43, 70]
Week 12	85	[71, 126]
Week 24	169	[127, 210]
Week 36	253	[211, 294]
Week 48	337	[295, 350]
Week 52	365	[351, the end day of the placebo-controlled period *]
* The end day of the placebo-controlled period is the last day before the first dose in OLE for subjects who enter OLE, and is the last day in study for subjects who do not enter OLE.		

6.3.2 Qualitative 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, coagulation and urinalysis (excluding microscopic examination) 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 values for protein, glucose, blood, and leukocyte esterase will be flagged as "abnormal" if positive, "normal" if negative, or "unknown" if no value is available.

For each parameter, the analysis will be based on subjects with at least one post-baseline value. Shifts from baseline to high/low status will be presented for hematology, blood chemistry, coagulation and urinalysis (specific gravity and pH), and shifts from baseline to abnormal (or unknown to abnormal) will be presented for urinalysis parameters (protein, glucose, blood, and leukocyte esterase). 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. Subjects need to have at least one post-baseline evaluation and a baseline value either unknown or not low/high/abnormal in order to be included in the analysis.

Grade analyses

Each scheduled laboratory parameter will be summarized both by worst post-baseline grade and by worst cumulative post-baseline grade; this analysis includes the primary endpoints of Grade 3 and 4 laboratory abnormalities. Subjects need to have at least one post-baseline evaluation in order to be included in the analysis. Common Terminology Criteria for Adverse Events v4.0.3 (CTCAE) published on 14 June 2010 will be used for grade determination. Grade determination is based solely on laboratory values and does not take other clinical information into account; therefore, a lower grade may be assigned to a laboratory parameter result since clinical information does not contribute to the grading assessment. Thus, the incidence of higher grades may be underestimated.

For calcium (mmol/L), the laboratory result will be corrected by the concurrent albumin (g/L) result for CTCAE grade determination. The derivation of the corrected calcium (mmol/L) will be derived as follows:

Corrected calcium (mmol/L) = ¼ * [calcium(mmol/L) - 0.8*(0.1 *albumin(g/L) -4)]

Potentially Clinically Significant laboratory abnormalities analyses

For hematology, blood chemistry and urinalysis, the number of subjects with potentially clinically significant (PCS) laboratory abnormalities post-baseline will be summarized for the parameters provided in Table 9, which also shows the thresholds used to determine PCS results. Subjects need

to have at least one post-baseline evaluation and a baseline value not PCS (including missing) in order to be included in the analysis. A listing will be provided for subjects with any PCS result post-baseline.

Table 9 Criteria to Determine Potentially Clinically Significant (PCS) Laboratory Abnormalities

Clinical Laboratory Outlier Criteria		
Parameter name	**PCS Low**	**PCS High**
HEMATOLOGY		
White blood cells	<3.0 x 10^9/L	>16 x 10^9/L
Lymphocytes	<0.8 x 10^9/L	>12 x 10^9/L
Neutrophils	<1.5 x 10^9/L	>13.5 x 10^9/L
Monocytes	N/A	>2.5 x 10^9/L
Eosinophils	N/A	>1.6 x 10^9/L
Basophils	N/A	>1.6 x 10^9/L
Red blood cells	⩽3.5 x 10^{12}/L	⩾6.4 x 10^{12}/L
Hemoglobin - Females	⩽95 g/L	⩾175 g/L
Hemoglobin - Males	⩽115 g/L	⩾190 g/L
Hematocrit - Females	⩽0.32 L/L	⩾0.54 L/L
Hematocrit - Males	⩽0.37 L/L	⩾0.60 L/L
Platelet count	⩽75 x 10^9/L	⩾700 x 10^9/L
BLOOD CHEMISTRY		
Alanine aminotransferase (ALT)	N/A	>3 x ULN
Aspartate aminotransferase (AST)	N/A	>3 x ULN
Alkaline phosphatase (ALP)	N/A	>3 x ULN
Total bilirubin	N/A	>1.5 x ULN
Blood urea nitrogen (BUN)	N/A	⩾10.7 mmol/L
Creatinine	N/A	⩾176.8 umol/L
Sodium	⩽126 mmol/L	⩾156 mmol/L
Potassium	⩽3 mmol/L	⩾6 mmol/L
Chloride	⩽90 mmol/L	⩾118 mmol/L
Glucose	⩽2.2 mmol/L	⩾9.7 mmol/L
Calcium	⩽2 mmol/L	⩾3 mmol/L
Phosphorus	⩽0.6 mmol/L	⩾1.7 mmol/L
Albumin	⩽25 g/L	⩾625 g/L
Total protein	⩽45 g/L	⩾100 g/L
URINALYSIS		
Glucose	N/A	⩾ 1000 mg/dL
Protein	N/A	⩾ 100 mg/dL
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) for each subject will be provided. A line plot of ALT, AST, ALP and total bilirubin values over time for subjects with potential serious hepatotoxicity will be provided. In addition, 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 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 presented. Concurrent is defined as on the same day. A listing of subjects with potential serious hepatotoxicity will be provided.

6.4 ECGs

All individual values for QT interval, QT interval corrected for heart rate by Bazett's formula (QTcB), and QT interval corrected for heart rate by Fridericia's formula (QTcF) will be presented in the data listings. QT, QTcB, and QTcF will also be included in the summary statistics.

All available non-missing values of ECG parameters should be used in the listings, summaries, and analyses for the double-blind and open-label treatment periods. However, if QTcF is missing and RR interval in seconds is available, then QTcF will be calculated as

$$QTcF = \frac{QT}{RR^{1/3}}$$

If both QTcF and RR in seconds are missing, then QTcF will be calculated as

$$QTcF = \frac{QT}{(60/HEART\ RATE)^{1/3}}$$

Although all recorded ECG parameter values, including abnormal ECG findings, will be included in the data listings, only quantitative values recorded at or near scheduled time points will be included in the summary statistics (see Table 10).

Table 10 Visit Windows for ECG

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 24	169	[1 (post-dose only), 266]
Week 52	365	[267, the end day of the placebo-controlled period *]
* The end day of the placebo-controlled period is the last day before the first dose in OLE for subjects who enter OLE, and is the last day in study for subjects who do not enter OLE.		

6.4.1 Analysis of Central Tendency

Summary statistics (n, mean, SD, median, minimum, and maximum) will be presented for each ECG parameter and the corresponding changes from baseline by treatment and time point. Frequency distribution of maximum postdose ECG intervals tables will also be generated.

6.4.2 Categorical Analysis

The frequency distribution of subjects maximum recorded post-dose QTcF, PR, QRS, and ΔQTcF (change from baseline in QTcF) will be tabulated by treatment and summarized within the CSR for the following ranges:

- For QTcF: QTcF ≤ 450 msec, 450 msec < QTcF ≤ 480 msec, 480 msec < QTcF ≤ 500 msec, QTcF > 500 msec
- For PR: PR ≤ 200 msec, PR > 200 msec
- For QRS: QRS ≤ 120 msec, QRS > 120 msec
- For ΔQTcF: ΔQTcF ≤ 30 msec, 30 msec < ΔQTcF ≤ 60 msec, ΔQTcF > 60 msec

Individual QTcF, PR, QRS, or ΔQTcF values meeting these criteria will be flagged in the data listing.

6.5 Vital Signs

Vital sign parameters include body temperature, systolic blood pressure, diastolic blood pressure, heart rate, respiration rate and weight. The descriptive statistics for actual values and change from baseline will be summarized at each visit. Plot of mean vital sign values at each visit will be provided.

The analysis of vital signs will also focus on the incidence of clinically relevant outliers based on the following criteria. The incidence and percentage of clinically relevant outliers determined by each criterion will be summarized. A listing of subjects with clinically relevant vital signs will be provided.

Table 11 Criteria Used to Assess Potential Clinically Relevant Outliers in Vital Signs

Variable	Low	High
Systolic Blood Pressure	<90 mm Hg or ≥20 mm Hg decrease from Baseline (BL)	>180 mm Hg or ≥20 mm Hg increase from BL
Diastolic Blood Pressure	< 50 mm Hg or ≥15 mm Hg decrease from BL	>105 mg Hg or ≥15 mm Hg increase from BL
Heart Rate	<50 bpm or ≥ 15 bpm decrease from BL	>120 bpm or ≥ 15 bpm increase from BL
Temperature	>2 degree C decrease from BL	>38.5 C or >2 degrees C increase from BL

Respiration Rate	< 10 breaths per minute or ≥ 50% decrease from BL	>25 breaths per minute or ≥50% increase from BL
Weight	≥7% decrease from BL	≥7 % increase from BL
BL= baseline; bpm = beats per minute		

Visit windows for by visit summaries

For vital sign by visit summaries, the analysis visit should be defined using windows (see Table below).

Table 12 Visit Windows for Vital Sign by Visit Summaries

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 4	29	[1 (post-dose only), 42]
Week 8	57	[43, 70]
Week 12	85	[71, 98]
Week 16	113	[99, 126]
Week 20	141	[127, 154]
Week 24	169	[155, 182]
Week 28	197	[183, 210]
Week 32	225	[211, 238]
Week 36	253	[239, 266]
Week 40	281	[267, 294]
Week 44	309	[295, 322]
Week 48	337	[323, 350]
Week 52	365	[351, the end day of the placebo-controlled period*]
* The end day of the placebo-controlled period is the last day before the first dose in OLE for subjects who enter OLE, and is the last day in study for subjects who do not enter OLE.		

6.6 Physical Examination

Physical examination data will be listed.

6.7 Neurological Examination

Neurological examination data will be listed.

[redacted]

[redacted]

[redacted]

6.9 MRI Results

New post-baseline MRI findings will be summarized for (1) microhemorrhages, (2) macrohemorrhages, (3) superficial siderosis and (4) vasogenic edema.

A by-subject listing of MRI results is provided for enrolled subjects with new safety findings (i.e., those with a "Yes" response to the new safety findings question at any time during the study).

7 PHARMACOKINETIC DATA

CSF samples will be collected at protocol designated times for BIIB092 pharmacokinetic assessments from subjects [redacted]. Serum samples will be collected at protocol designated times for BIIB092 pharmacokinetic assessments from subjects.

7.1 CSF Concentration Data

The CSF PK analysis population will be used for the analysis of CSF concentration data.

CSF concentrations along with the scheduled (nominal) and actual sampling times (i.e., time from dosing) will be listed (when applicable) for each subject, group, and day. Differences between scheduled and actual sampling times will also be listed for all subjects. Percentage differences between actual administered dose and nominal dose will also be listed.

CSF concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for CSF concentrations, all BLQ values will be set to half the LLOQ value. Mean CSF concentrations that are BLQ will be presented as BLQ, and the SD and %CV will be reported as not applicable. Summary statistics of the CSF concentrations will be tabulated by day and scheduled time point. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling days or times, or large deviations between actual dose and nominal dose.

7.2 Serum Pharmacokinetics

The PK analysis population will be used for all listings, summaries, and statistical analyses. Analysis will include all valid data in the PK dataset for BIIB092. The listings will also include data from the OLE period.

Subject serum BIIB092 concentrations will be listed only.

Individual serum PK parameters C_{trough} and C_{inf} will be listed for BIIB092 including any exclusions. Summary statistics (including geometric means and coefficients of variation) will be tabulated for each PK parameter by visit. Plots of individual C_{trough} and C_{inf} over time will be provided.

Serum concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for plasma concentrations, BLQ value pre day 1 of study treatment will be set to 0, all post first dose of study treatment BLQ values will be set to half the LLOQ value. Mean serum concentrations that are BLQ will be presented as BLQ, and the SD and %CV will be reported as not applicable. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

Serum concentration vs. time (actual) profiles from Day 1 to Week 48, for each subject, as well as the mean (± SE) serum concentration vs. time (scheduled) profiles for the treatment group, will be presented graphically on linear and semilogarithmic scales. Samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

8 ANTI-DRUG ANTIBODY DATA

The anti-drug antibody (ADA) population will be used for the analysis of ADA data. All available ADA data will be listed. ADA data will be listed for subjects with any positive ADA result. Associations of ADA measures with PK and/or select AEs may be explored as needed.

The baseline value is defined as the last available value prior to first dose of placebo or BIIB092. For subjects with missing baseline assessment, the most conservative approach will be taken, and they will be considered negative for ADA at baseline.

The following definitions will be used in the analysis of ADA data:

- Treatment emergent positive:
  - A post-baseline subject sample that is positive when the baseline sample is negative; or
  - A post- baseline subject sample that has a titer greater than or equal to 4 times the baseline sample titer when the baseline sample is positive. If the titer value is not available for a positive baseline result, then the baseline titer value will be imputed as the minimum required dilution (MRD); or
  - A positive post-baseline result where no titer is available, regardless of baseline value
- Persistently positive: Two or more treatment emergent positive ADA results, where the time between the first and last positive results is 16 weeks or more; or if there are no further samples available 16 weeks or more following a treatment emergent positive result (including the OLE period).
- Transiently positive: more than one treatment-emergent positive evaluation, less than 16 weeks apart; or a single treatment emergent positive (not including pretreatment) when there are samples available 16 weeks or more following the positive result.

The following will be tabulated by treatment group: the number and percentage of subjects with any baseline sample that tested positive in the ADA assay; the number and percentage of subjects with any sample that tested positive in the ADA assay (including at baseline); the number and percentage of subjects with treatment emergent positive at each visit and at any time post-baseline; the number and percentage of subjects with persistently positive samples and similarly for transiently positive samples; the number and percentage of subjects with no treatment emergent positive ADA sample.

In this study, additional samples for ADA, referred to as "event driven" samples, may be collected for subjects with hypersensitivity events. ADA data will be listed for subjects with any event driven sample. Data from these samples will be considered part of a subject's overall ADA assessment.

The analysis windows are defined based on the scheduled post-baseline visits for ADA in Table 13. The same visit windowing approach described in Section 6.1.2 will be used.

Table 13 Visit Windows for Anti-drug Antibody

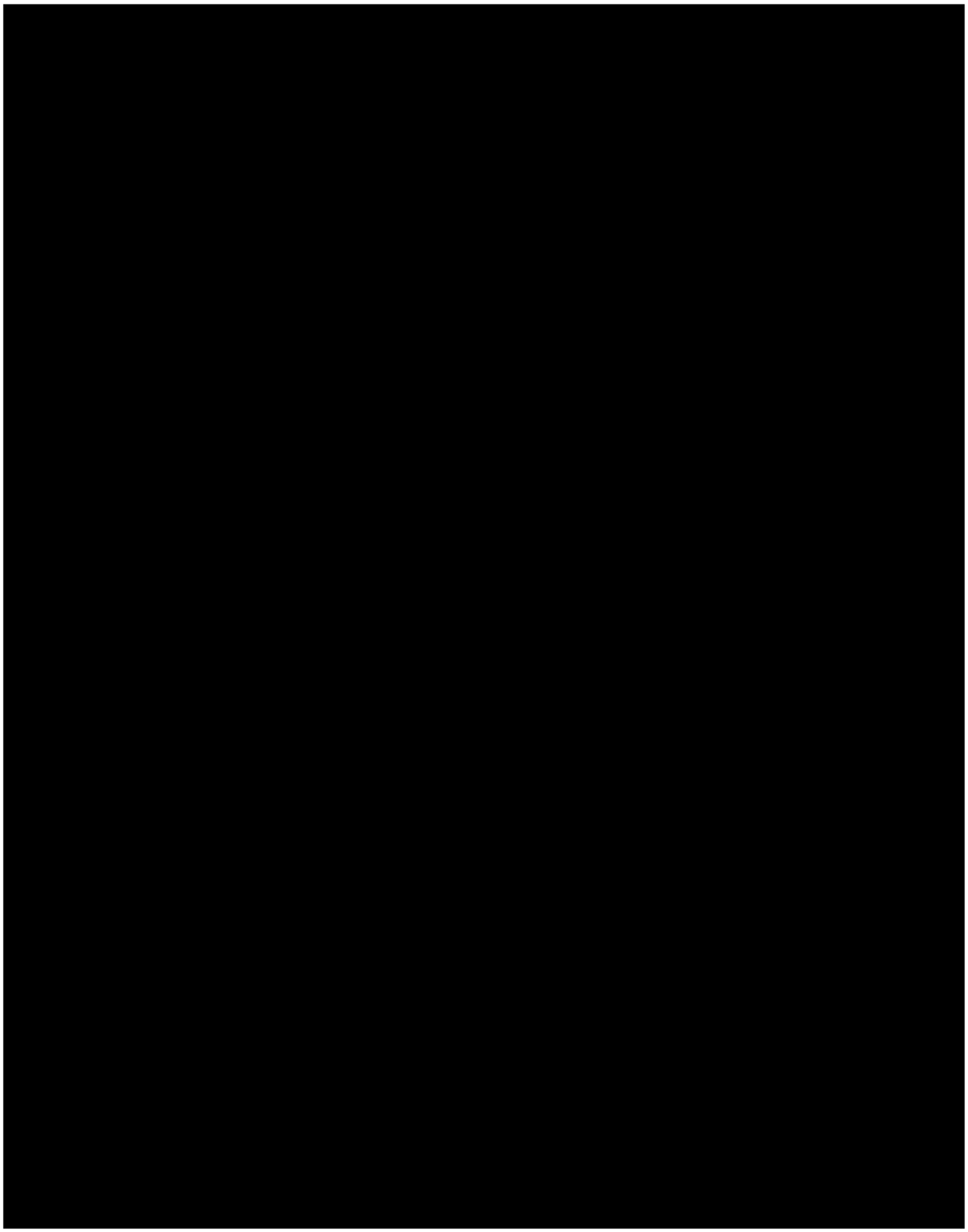
Analysis visit	Target visit day	Analysis visit window
Baseline	1	Last available value prior to the first dose of study drug
Week 4	29	[1 (post-dose only), 42]
Week 8	57	[43, 70]

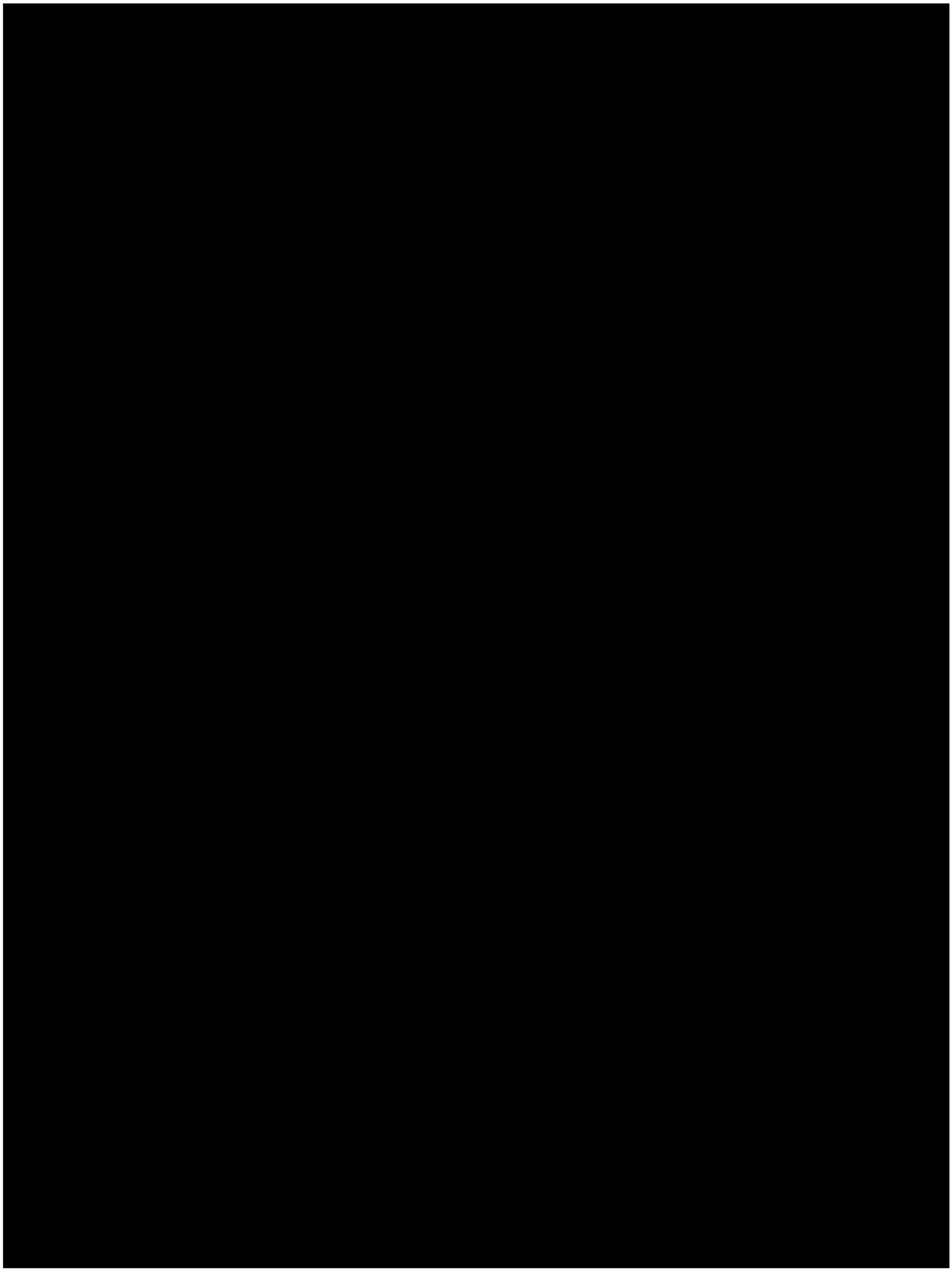
Week 12	85	[71, 126]
Week 24	169	[127, 210]
Week 36	253	[211, 294]
Week 48	337	[295, the end day of the placebo-controlled period*]
* The end day of the placebo-controlled period is the last day before the first dose in OLE for subjects who enter OLE, and is the last day in study for subjects who do not enter OLE.		

9 SAMPLE SIZE CONSIDERATIONS

Approximately 459 male and female participants will be enrolled in this study. Approximately 459 participants will be randomly assigned, in 2:1 ratio, to receive 2000 mg of BIIB092 or placebo (306 participants active and 153 placebo) administered by IV approximately once Q4W. Randomization will be stratified by country and screening Color Trails Test Part 2 score of either ≤ to 170 seconds, or ≥ 170 seconds. Anticipating a dropout rate of approximately 25%, approximately 345 participants (230 participants in the BIIB092 treatment group and 115 participants in the placebo group) are expected to complete the study through Week 52.

11 APPENDIX





[redacted]

11.2 Implementation of the Copy Increment from Reference, Jump to Reference and Pattern Mixture Model

11.2.1 Copy Increment from Reference (CIR)

The dataset will first be imputed to monotone missing using PROC MI with the MCMC and impute=monotone option. Imputation will be carried out 1000 times and any internal missing observations, including missing baseline covariates and intermediate missing in the response variable will be replaced with the average across all imputations.

For the resulted data with monotone missing, the following steps will be used to create imputed datasets:

(1) Data from all subjects will be used to fit a multivariate normal distribution with unstructured mean and unstructured variance using a Bayesian approach with a noninformative prior for the mean and a conjugate prior for the variance covariance matrix.
(2) Draw a pseudo-independent sample for the linear predictor parameters and the covariance parameters from the joint posterior distribution obtained in step (1). Both steps (1) and (2) will be done using PROC MCMC in SAS.
(3) Use the linear predictor parameters and the covariance parameters obtained in step (2) to construct new mean vectors separately for each treatment group (placebo and BIIB092). Specifically, the newly constructed mean vector for someone on treatment group T whose last observed visit was visit k is calculated as

$$\mu_T^{(k)} = \begin{cases} \mu_{i,T}, & if\ i \le k \\ \mu_{k,T} - \mu_{k,P} + \mu_{i,P}, & if\ i > k \end{cases}$$

Here P represents the placebo group. For subjects with no post-baseline records, or subjects on the placebo group, the newly constructed mean vector is the same as the placebo mean.
(4) Using $\mu_T^{(k)}$ from step (3) and covariance parameters from step (2), find the conditional normal distribution of the visit with missing data, and use this conditional distribution to impute the missing data.

11.2.2 Jump to Reference (J2R)

The dataset will first be imputed to monotone missing using PROC MI with the MCMC and impute=monotone option. Imputation will be carried out 1000 times and any internal missing observations, including missing baseline covariates and intermediate missing in the response variable will be replaced with the average across all imputations.

For the resulted data with monotone missing, the following steps will be used to create imputed datasets:

(1) Data from all subjects will be used to fit a multivariate normal distribution with unstructured mean and unstructured variance using a Bayesian approach with a noninformative prior for the mean and a conjugate prior for the variance covariance matrix.

(2) Draw a pseudo-independent sample for the linear predictor parameters and the covariance parameters from the joint posterior distribution obtained in step (1). Both steps (1) and (2) will be done using PROC MCMC in SAS.
(3) Use the linear predictor parameters and the covariance parameters obtained in step (2) to construct new mean vectors separately for each treatment group (placebo and BIIB092). Specifically, the newly constructed mean vector for someone on treatment group T whose last observed visit was visit k is calculated as

$$\mu_T^{(k)} = \begin{cases} \mu_{i,T}, & if\ i \le k \\ \mu_{i,P}, & if\ i > k \end{cases}$$

Here P represents the placebo group. For subjects with no post-baseline records, or subjects on the placebo group, the newly constructed mean vector is the same as the placebo mean. Using $\mu_T^{(k)}$ from step (3) and covariance parameters from step (2), find the conditional normal distribution of the visit with missing data, and use this conditional distribution to impute the missing data.

11.2.3 Pattern Mixture Model

Subjects will be assigned one of the following three patterns:

1. Completer: subjects with no missing data at Week 12, 24, 26, 48 and 52 for primary endpoints and at Week 12, 24, 36 and 52 for key secondary endpoints;
2. Subjects who withdrew due to reasons that may be related to efficacy, including lack of efficacy, subject request to discontinue study treatment, subject withdrew consent, poor/non-compliance, death, and withdrawal by caregiver;
3. All the other subjects with missing data.

The dataset will first be imputed to monotone missing using PROC MI with the MCMC and impute=monotone option. Imputation will be carried out 1000 times and any internal missing observations, including missing baseline covariates and intermediate missing in the response variable will be replaced with the average across all imputations.

For the resulted data with monotone missing, the following steps will be used to create imputed datasets:

(1) Subset subjects in pattern 1 and pattern 2, and impute the missing data using the copy increment from reference method described in Section 10.2.1.
(2) Subset subjects in pattern 1 and pattern 3, and impute the missing data using PROC MI with the MONOTONE REG option.
(3) Combined datasets obtained in steps (1) and (2).

11.3 Adverse event of special interest custom search criteria

Immunogenicity is an AESI in the BIIB092 clinical development program. Adverse events representing potential immune/hypersensitivity reactions will be identified using the following customized MedDRA search criteria:

- Anaphylactic reaction SMQ narrow and broad
- Angioedema SMQ narrow and broad

- Severe cutaneous adverse reactions SMQ narrow and broad
- Eosinophilia (PT terms: Eosinophilia; Eosinophil count increased; Allergic eosinophilia; Pulmonary eosinophilia)
- Miscellaneous terms

    - Cytokine release syndrome PT
    - Infusion related reaction PT
    - Infusion site reaction PT
    - Allergic conditions NEC HLT
    - Drug hypersensitivity PT
    - Documented hypersensitivity to administered product PT
    - Vasculitis PT
    - Systemic Lupus erythematosus PT
    - Rheumatoid arthritis PT
    - Antibody test positive PT
    - Antibody test abnormal PT
    - Antibody test PT
    - Drug specific antibody present PT
    - Neutralising antibodies PT
    - Neutralising antibodies positive PT
    - Non-neutralising antibodies positive PT
    - Respiratory dyskinesia PT

11.4 Infusion reactions custom search

- Infusion site reaction
- Infusion site rash
- Infusion site dermatitis
- Infusion site hypersensitivity
- Infusion site photosensitivity reaction
- Infusion site urticaria
- Infusion site eczema
- Infusion site vasculitis
- Infusion site recall reaction
- Infusion related reaction
- Administration site rash
- Administration site dermatitis
- Administration site eczema
- Administration site hypersensitivity
- Administration site urticaria
- Administration site photosensitivity reaction
- Administration site recall reaction
- Administration site vasculitis
- Administration related reaction

- Injection site dermatitis
- Injection site hypersensitivity
- Injection site rash
- Injection site urticaria
- Injection site photosensitivity reaction
- Injection site eczema
- Injection site recall reaction
- Injection site vasculitis
- Injection related reaction
- Immediate post-injection reaction
- allergic reaction to excipient
- reaction to excipient
- cytokine storm
- cytokine release syndrome
- immune-mediated adverse reaction

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