TANGO

251AD201/NCT03352557

Statistical Analysis Plan

Long-Term Extension Period

STATISTICAL ANALYSIS PLAN
Long-Term Extension Period

Product Studied: Gosuranemab
Protocol Number: 251AD201

Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Tolerability, and Efficacy of BIIB092 in Subjects with Mild Cognitive Impairment due to Alzheimer's Disease or with Mild Alzheimer's Disease

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List of Abbreviations

AD	Alzheimer's disease
ADA	Anti-drug Antibody
ADAS-Cog 13	Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items)
ADCOMS	AD Composite Score
ADCS-ADL	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory
ADCS-iADL	ADCS-ADL Instrumental Total Score
ADCS-bADL	ADCS-ADL Basic Total Score
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	Activated Partial Thromboplastin Tim
AST	aspartate aminotransferase
BLQ	below the limit of quantification
BMI	body mass index
bpm	beats per minute
BUN	blood urea nitrogen
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CI	confidence interval
C_{trough}	Observed trough serum BIIB092 concentration collected at end of dosing interval (before next infusion starts)
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variation
DKEFS	Delis-Kaplan Executive Function System
DSST	Digit Symbol Substitution Test
ECG	electrocardiogram
EMACC	Early AD/ MCI Alzheimer's Cognitive Composite
Emax	Maximum response
EOS	End of study
EOT	End of treatment
ET	Early termination
FAQ	Functional Activities Questionnaire
FAS	Full Analysis Set
eCOG	Everyday Cognition
ICH	International Conference on Harmonisation
INR	Prothrombin Intl. Normalized Ratio
IRT	interactive response technology
iADRS	The Integrated Alzheimer's Disease Rating Scale
LS	Lease Square Mean
ISLR	International Shopping List Test Delayed Recall
ISLT	International Shopping List Test Immediate Recall
LLOQ	lower limit of quantification
LTE	long-term extension
LP	Lumbar puncture
MA	macrohemorrhages
MCI	mild cognitive impairment

MedDRA	Medical Dictionary for Regulatory Activities
mH	microhemorrhages
MMRM	mixed-model repeated measures
MMSE	Mini-Mental State Examination3
MRI	magnetic resonance imaging
NPI-10	Neuropsychiatric Inventory-10
PC	Placebo control
PCP	Placebo control period
PCS	potentially clinically significant
PD	Pharmacodynamics(s)
PET	positron emission tomography
PLS	Partial least squares
PK	pharmacokinetic(s)
PT	Preferred term
PT	Prothrombin Time
Qol-AD	Quality of Life for Alzheimer's Desease
QTcF	Corrected QT interval by Fredericia
ROI	region of interest
RUD-Lite	Resource Utilization in Dementia – Lite Version
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System organ class
SS	superficial siderosis
SUVR	standard uptake value ratio
TEAE	treatment-emergent adverse event
TIV	Total Intracranial Volume
Trails A	Trail Making Test, Part A
ULN	upper limit of normal
VE	vasogenic edema
WHO	World Health Organization
ZBI	Zarit Burden Interview

1 Introduction

This statistical analysis plan (SAP) covers the analyses of the LTE period and the analyses across both the placebo-controlled period and the LTE period of the study, 251AD201. A separate SAP has been prepared for the analyses of the placebo-controlled period.

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.

2 DESCRIPTION OF LONG-TERM EXTENSION (LTE) OBJECTIVES AND ENDPOINTS

2.1 Primary LTE Objective and Endpoint

The primary objective for the long-term extension (LTE) period is to evaluate the long-term safety and tolerability of BIIB092 in participants with MCI due to AD or with mild AD.

The primary safety endpoint that relates to this objective is the incidence of AEs and SAEs over the placebo-controlled period and LTE period of the study.

2.2 Exploratory LTE Objectives and Endpoints

- To further evaluate the immunogenicity of BIIB092 after multiple doses in participants with MCI due to AD or with mild AD as measured by the incidence of anti-BIIB092 antibodies in serum over time up to Week 238.
- To further assess the effect of BIIB092 on disease progression as measured by fluid and radiological biomarkers, as well as additional clinical and health outcomes as measured by the following:
  - Changes over the placebo-controlled period and LTE period on the CDR-SB, MMSE, ISLT, Category Fluency and Letter Fluency tests from the DKEFS, DSST, Trails A, eCog, ADCS-ADL, FAQ, ADAS-Cog-13 (13-item), and NPI-10
  - Changes over the placebo-controlled period and LTE period on the ZBI, QoL-AD, and RUD-Lite
  - Changes over the placebo-controlled period and LTE period in CSF and blood biomarkers (for those who consent to participate in the optional CSF sampling substudy)
  - Changes over the placebo-controlled period and LTE period on 18F-MK6240 PET and MRI brain morphometric measures (for those who consent to participate in the optional PET substudy)
- To assess BIIB092 PK in serum (trough serum BIIB092 concentrations) and in CSF (for those who consent to participate in the optional CSF sampling substudy) from the samples collected at the visits indicated in the Schedule of Activities in participants with MCI due to AD or with mild AD.

2.3 Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group study consisting of a double-blind, placebo-controlled period and an LTE period.

The study includes 2 substudies to address exploratory study objectives: a tau PET substudy and a CSF sampling substudy. The tau PET substudy is mandatory at study sites that have access to the ^{18}F-MK6240 PET radioligand and have the capability to perform ^{18}F-MK6240 PET scans. During the placebo-controlled period, the CSF sampling substudy is mandatory at all study sites that do not have access to the 18F-MK6240 PET radioligand. Participants will provide consent during Screening to participate in at least 1 of these substudies during the placebo-controlled period. Participants enrolled in the LTE period and who are participating in the tau PET substudy are required to continue participation in the tau PET substudy. Participation in the CSF sampling substudy during the LTE will be optional for all study participants, although participation is encouraged.

This study will be conducted in participants aged 50 to 80 years, inclusive, with MCI due to AD or mild AD according to National Institute on Aging-Alzheimer's Association criteria. Participants must have amyloid beta positivity confirmed at Screening by either CSF sampling or an amyloid PET scan. Participants must also perform at least 1 standard deviation below the age-adjusted normative mean on either the ISLT or the International Shopping List Test Delayed Recall and have a CDR global score of 0.5 for MCI due to AD or 0.5 or 1 for mild AD, an MMSE score of 22 to 30 (inclusive), and a CDR Memory Box score of $\geqslant$0.5.

During the dose-blinded LTE period, participants will receive BIIB092 by IV once every 4 weeks beginning at Week 80. Participants who were randomized to receive BIIB092 during the placebo-controlled period will continue to receive BIIB092 at the dose they were randomly assigned. Participants randomized to receive placebo during the placebo-controlled period will receive BIIB092 at the high dose (2000 mg) once every 4 weeks during the LTE period.

The total duration for participants who complete the placebo-controlled period and do not enter the LTE period will be approximately 99 weeks. For participants who complete both the placebo-controlled period and the LTE period, the total study duration will be approximately 247 weeks.

Participants who meet the LTE inclusion and exclusion criteria will be eligible to enter the dose-blinded LTE period, which includes the LTE Screening Period of approximately 4 weeks starting at Week 76, the 144-week Treatment Period starting at Week 80, the EOS Visit at Week 226, and the Follow-up Visit at Week 238.

Participants will have approximately 39 outpatient clinic visits during the LTE period:

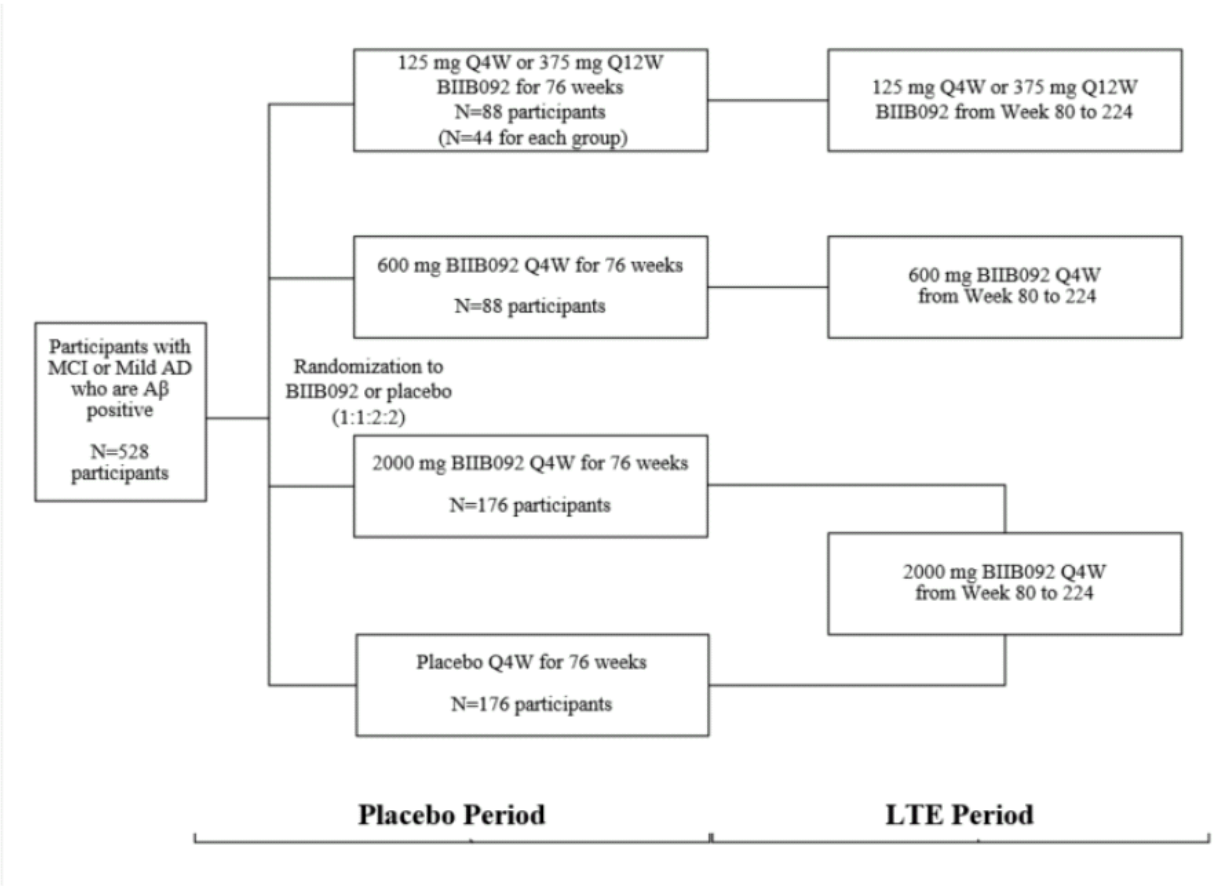
- Participant eligibility will be determined at Week 76 or Week 78 of the placebo-controlled period and confirmed at Week 80 of the LTE period.
- At the Week 80 Visit, eligible participants will have scheduled assessments per the Schedule of Activities and receive the first infusion of BIIB092 during the LTE period. All participants receiving placebo in the placebo-controlled period will receive BIIB092 at the high dose (2000 mg) once every 4 weeks during the LTE period.
- Participants will return to the clinic at 4-week intervals during the Treatment Period for infusions of study treatment and study assessments.

- The last dose of study treatment will be administered at Week 224 (End-of-Treatment Visit). The EOS Visit will occur at Week 226 and the Follow-up Visit at Week 238.
  - Participants who discontinue study treatment prematurely will be asked to remain in the study and continue all protocol-specified visits and procedures. These participants should be encouraged to attend at least the Week 104, 128, 152, 176, 200, and 226 Visits, depending on when treatment was discontinued, and undergo all the scheduled procedures. At a minimum, these visits should include assessment of AEs/SAEs and concomitant medications and key clinical assessments, including at least the CDR, MMSE, ISLT, ADAS-Cog 13, ADCS-ADL, and FAQ. Participants who discontinue study treatment prematurely will also be asked to return to the study site for a Follow-up Safety Visit 14 weeks after receiving the last dose of study treatment.
  - Participants who withdraw from the study prematurely are to return to the study site for an Early Termination Visit and assessments and for the Follow-up Safety Visit 14 weeks after receiving the last dose of study treatment.

Certain visits during the study may be conducted as home visits as specified in the Schedule of Activities, if the Investigator is in agreement and appropriate services are available to perform the required study procedures and adequately monitor for potential safety events.

2.4 Study Schematic

Figure 1: Study Design



Aβ = amyloid beta; AD = Alzheimer's disease; EOS = End of Study; LTE = long-term extension; MCI = mild cognitive impairment; N = number of participants; Q4W = once every 4 weeks; Q12W = once every 12 weeks

Note: Overall, participants will have a 2:1 chance of being randomized to BIIB092 versus placebo during the placebo-controlled period, and all participants will receive BIIB092 during the dose-blinded LTE period.

Note: The study comprises a double-blind, placebo-controlled period and an LTE period. The total duration for participants who complete the placebo-controlled period and do not enter the LTE period will be approximately 99 weeks. The total study duration for participants who complete both the placebo-controlled period and the LTE period will be approximately 247 weeks. The double-blind placebo-controlled period comprises a Screening Period of approximately 9 weeks (65 days), a Treatment Period of 76 weeks, and for participants not entering the LTE period, an EOS Visit at Week 78 and a Follow-up Safety Visit at Week 90, or approximately 14 weeks after the last dose of study treatment. The LTE period comprises an LTE Screening Period of approximately 4 weeks starting at Week 76, a 144-week Treatment Period starting at Week 80, an

EOS Visit at Week 226, and a Follow-up Safety Visit at Week 238, or approximately 14 weeks after the last dose of study treatment.

3 Definitions

3.1 Analysis Sets

- Full Analysis Set (FAS):
  The FAS includes all randomized subjects who received at least one dose of study treatment (BIIB092 or placebo). In analyses performed on the FAS, subjects will be analyzed, based on the intention-to-treat principle, according to their randomized treatment assignment regardless of treatment received.

- Safety Analysis Set:

  The safety Analysis Set includes all randomized subjects who received at least one dose of study treatment (BIIB092 or placebo), essentially the same set of participants included in the FAS. In analyses performed on the Safety Analysis Set, subjects will be analyzed according to their actual treatment received.

- Safety MRI Evaluable Set:
  The Safety MRI Evaluable Set is defined as subjects in the FAS who had at least one post-baseline safety MRI scan.

- Serum PK Evaluable Set:
  The serum PK evaluable set is defined as subjects in the FAS who had at least one measurable post-baseline BIIB092 concentration in serum before the End of Study of LTE.

- CSF PK Evaluable Set:
  The CSF PK evaluable set is defined as subjects in the FAS who had at least one measurable post-baseline BIIB092 concentration in CSF.

- CSF PD Evaluable Set:
  The CSF PD evaluable set is defined as subjects in the FAS who had lumbar puncture (LP), which will be used in analyses, such as subject accounting and summary of AE related to LP. The CSF PD Modified Evaluable Set is defined as subjects in the FAS who have baseline and at least one post baseline assessment of the specific parameter being analyzed in CSF.

- Tau PET Evaluable Set
  The tau PET evaluable set is defined as subjects in the FAS who had tau PET, which will be used in analyses, such as subject accounting and summary of AE related to tau PET. The tau PET Modified Evaluable Set is defined as subjects in the FAS who had a valid baseline and a post-baseline tau PET SUVR measure using the 18F-MK6240 tracer.

- Anti-drug antibody (ADA) Evaluable Set:
  The evaluable set for anti-drug antibody is defined as subjects in the FAS who have an evaluable post-baseline ADA sample.

3.2 Analyses Period

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

1. LTE period. Only data in the LTE period will be included in these analyses. This LTE analysis period will be applied to all the AE analyses, and the analyses will include all subjects who were dosed in the LTE period.
2. Placebo-controlled and LTE period. All the data in the placebo-controlled and LTE periods will be included in these analyses. This analysis period will be applied to analyses including, but not limited to all efficacy analyses and listings. The analyses will include all subjects who were dosed in the study including those who did not enroll into the LTE period. For example, line plot of CDR sum of box mean change from baseline over time. in the placebo-controlled and LTE period.
3. Placebo-controlled and LTE active treatment period. Active treatment period is defined as the study period(s) that a subject received BIIB092. For early start subjects – subjects who received BIIB092 in both placebo-controlled and LTE period, all the data (placebo-controlled and LTE periods) will be included in the analyses. For late start subjects – subjects who received placebo in the Placebo-controlled period and BIIB092 in the LTE period, only data in the LTE period will be included. This analysis period will be applied to majority of safety tables, 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 LTE period. An example is the incidence rate of adverse events in the placebo-controlled and LTE active treatment period.

Subjects to be included in a certain output is determined by both the analysis set and the analysis period. For example, the incidence table of adverse events in the LTE period will include subjects in the safety population for the LTE period, i.e., all randomized subjects who received at least one dose of study treatment in the LTE period. The incidence rate table of adverse events in the placebo-controlled and LTE active treatment 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 study treatment in the active treatment period. In this SAP we do not separately define the analysis set in each analysis period.

3.3 Study Treatment

For efficacy and health outcome analyses, the following LTE treatment groups of BIIB092 (per randomization) will be evaluated:

- low-dose (BIIB092 -125mg once every 4weeks or 375mg once every 12weeks)

- medium-dose (BIIB092 - 600mg once every 4 weeks)
- early start high-dose (BIIB092 - 2000mg once every 4 weeks)
- late start high-dose (BIIB092 - 2000mg once every 4 weeks)

For other analyses, such as safety, PK, PD, biomarker, and anti-drug antibody analyses, low dose group will be split out for different frequencies. The following LTE treatment groups of BIIB092 will be evaluated:

- low-dose 125mg once every 4weeks
- low-dose 375mg once every 12weeks
- medium-dose (BIIB092 - 600mg once every 4 weeks)
- early start high-dose (BIIB092 - 2000mg once every 4 weeks)
- late start high-dose (BIIB092 - 2000mg once every 4 weeks)

Since subjects in low-dose group and medium-dose group are taking the same treatment from the start of placebo-controlled period to the end of LTE period, so the subjects in these treatment groups are all considered as early start subjects. Late start subjects refer to subjects who were on placebo during placebo-controlled period then switched to high-dose (BIIB092 - 2000mg once every 4 weeks). Throughout this SAP, these study treatment schemes will be referred as LTE treatment.

3.4 Dates and Points of Reference

The study day and baseline are defined for each analyses period respectively

1. LTE period
   - Study Day 1: the date of the first dose of study treatment in the LTE period
   - Study Day
     - For a date on or after Study Day 1

       Study Day = (Date of Interest) – (Study Day 1) + 1
     - For a date before Study Day 1

       Study Day = (Date of Interest) – (Study Day 1)
   - LTE baseline: the baseline value for the LTE period is defined as the most recent non-missing measurement collected prior to the first dose in the LTE period.
   - Change from baseline will be defined as post-baseline value minus baseline value
2. Placebo-controlled and LTE period
   - Study Day 1: the date of the first dose of study treatment in the PC period

- Study Day
    - For a date on or after Study Day 1

      Study Day = (Date of Interest) – (Study Day 1) + 1
    - For a date before Study Day 1

      Study Day = (Date of Interest) – (Study Day 1)
- PC and LTE baseline: the baseline value for the Placebo-controlled and LTE period is defined as the most recent non-missing measurement collected prior to the first dose in the PC period.
- Change from baseline will be defined as post-baseline value minus baseline value

3. Placebo-controlled and LTE active treatment period

- Study Day 1: the date of the first dose of BIIB092. For low-dose, medium-dose and early start high-dose subjects, this will be the date of first dose of BIIB092 in the placebo-controlled (PC) period; for late start high-dose subjects, this will be the date of first dose of BIIB092 in the LTE period.
- Study Day
    - For a date on or after Study Day 1

      Study Day = (Date of Interest) – (Study Day 1) + 1
    - For a date before Study Day 1

      Study Day = (Date of Interest) – (Study Day 1)
- Active treatment baseline: the baseline value for the active treatment period and is defined as the most recent non-missing measurement collected prior to study day 1.
- Change from baseline will be defined as post-baseline value minus baseline value

  For data that are summarized by visit, assessment from all scheduled visits, EOS visit and unscheduled visits will be mapped to an appropriate analysis visit using a windowing scheme as describe in Appendix I

3.5 Key Derived Variables

- Handling of missing items for scales
    - If any of the individual items for the primary efficacy endpoint and exploratory efficacy endpoints is missing, the total score of the corresponding endpoint will be imputed by prorating the observed scores [van Ginkel 2010].
    - For ADAS-Cog13, if 3 or fewer of 13 items (<25%) are missing, the total score will be imputed by the following algorithm: Total score = total score from the completed items * [maximum total score (=85) / maximum total score for the

completed items]. The imputed number will be rounded up to the nearest integer. If more than 3 items are missing, the total score of ADAS-Cog 13 at that visit will be considered missing.

- For ADCS-ADL, if 8 or fewer of 32 items (<25%) are missing, the total score will be imputed by a similar algorithm as that for ADAS-Cog 13. The imputed number will be rounded down to the nearest integer. If more than 8 items are missing, the total score for ADCS-ADL at that visit will be considered missing.
- The same imputation algorithm will be applied to CDR-SB and MMSE, if only 1 box (of 6) of CDR is missing or if only 2 or fewer items (out of 11) are missing for MMSE. The imputed CDR-SB will be rounded up to the nearest half integer, and the imputed MMSE will be rounded down to the nearest integer. If the score from more than 1 box of CDR or more than 2 items of MMSE is not available, the CDR-SB or MMSE at that visit will be considered missing.
- The total score of the tertiary endpoint NPI-10 and FAQ will be imputed using the same prorating principle and round up to the nearest integer if only 1 item (out of 10) is missing.

- iADRS derivation

The iADRS is a composite score based on ADAS-Cog and ADCS-iADL (instrumental ADCS-ADL) [Wessels et al. 2015, Wessels et al. 2018]. The iADRS is calculated as a linear combination of total scores of the two individual components, the ADAS-Cog13 (score range 0 to 85) and the ADCS-iADL (score range 0 to 59). Because higher score on the ADAS-Cog13 reflect worse performance, whereas higher scores on the ADCS-iADL reflect better performance, the ADAS-Cog score is multiplied by (-1) in the calculation of the integrated scale. To anchor the ADAS-Cog at 0, a constant (85) is added. The iADRS score is then computed as the sum of the transformed ADAS-Cog13 and the ADCS-ADL, as shown in the formula below:

$$\text{iADRS score} = [\,(-1)\,(\text{ADAS-Cog13}) + 85] + \text{ADCS-iADL}$$

The iADRS score ranges from 0 to 144 with lower scores indicating worse performance. If either ADAS-Cog13 or ADCS-iADL is missing, the iADRS score will be considered missing.

- EMACC derivation

The EMACC is a new and sensitive composite of well-known and validated neuropsychological tests that is suitable for examining the effect of disease modifying compounds on cognitive decline in the early Alzheimer Disease or MCI stage of Alzheimer's disease [Jaeger et al. 2018].

Cognitive variables (ISLT, DKEFS Category Fluency total correct score, DKEFS Letter Fluency, DSST, Trails A total time to complete) will be z-score transformed using the

baseline score's mean and SD. The EMACC will be computed by taking the average of the z-scores across the five tests. If Trails A is missing, EMACC will be computed by taking the average of the z-scores across the remaining four tests. For the rest 4 component scores, if any of them is missing then the composite score will be missing.

- ADCOMS derivation

ADCOMS is a novel instrument developed to improve the sensitivity of currently available cognitive and functional measures for subjects in the prodromal stage of AD and mild AD dementia. It consists of 4 Alzheimer's Disease Assessment Scale–cognitive subscale items, 2 Mini-Mental State Examination items, and all 6 Clinical Dementia Rating—Sum of Boxes items (Table 1). The composite score is a weighted linear combination of the individual scales items using the corresponding partial least squares (PLS) coefficients as weighting factors as listed in Table 1 [Wang et al. 2016]. If any of the individual item is missing, then the composite score will be missing. The range of ADCOMS is between 0 and 1.97.

Table 1. Items included in ADCOMS and their corresponding PLS coefficients

Scale	Item name	PLS coefficients
ADAS-cog	Delayed word recall	0.008
	Orientation	0.017
	Word recognition	0.004
	Word finding difficulty	0.016
MMSE	Orientation time	0.042
	Drawing	0.038
CDR-SB	Personal care	0.054
	Community affairs	0.109
	Home and hobbies	0.089
	Judgement and problem solving	0.069
	Memory	0.059
	Orientation	0.078

ADAS-cog, Alzheimer's Disease Assessment Scale–cognitive subscale; CDR-SB, Clinical Dementia Rating, sum of boxes; MMSE, Mini-Mental State Exam; PLS, partial least squares.

3.6 Stratification Factors and Subgroup Variables

Stratification factors are:

- Tau PET/CSF sampling substudy enrollment (If subjects enrolled in both substudies, subjects will be counted as tau PET substudy)
- Region (US, Australia, Japan, EU < EU countries include France, Germany, Italy, Spain, and Sweden >, Poland)
- Baseline disease stage (MCI or mild AD)
- Baseline AD symptomatic medication use (Yes/No)

All stratification factors are based on subjects' status at PC baseline. A comprehensive list of baseline AD symptomatic medication can be found in PC SAP.

No subgroup analyses will be conducted.

4 List of Planned Study Analyses

There are two milestone LTE analyses planned for this study: LTE analysis at PC period database lock and the final analysis. The final analysis, which is also known as End of LTE analysis, will only be performed when the LTE study is completed.

4.1 LTE interim analyses at PC period database lock

The LTE interim analyses (IA) will be performed at the PC period database lock after the last patient out in the PC period. All the efficacy analyses described in Section 5.3 will be performed with available efficacy data up to week 104 at the PC period database lock. Given the timeline of scheduled data collection, only a few subjects will have tau PET, CSF biomarker and health outcomes data collected in LTE visits. No LTE analyses of tau PET, biomarker or health outcomes will be included at LTE IA at PC period database lock.

4.2 Final analysis

The LTE analyses will be performed at the end of the LTE period database lock after the last patient out in the LTE period. All the analyses described in Section 5 will be performed with complete data of in the study.

5 Statistical Methods for Planned Analyses

5.1 General Considerations

Summary tables will be presented using descriptive summary statistics. For continuous variables, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, 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.

5.2 Study Subjects

The summaries in this section will be based on the FAS. Analysis period will be specified for each table or figure. Unless otherwise specified, summary tables will be presented by LTE treatment group. If not otherwise specified in later text in this SAP, listings will include all data in the placebo-controlled and LTE periods (all data in the study), with an indicator of the study period (pre-dosing, placebo-controlled, or LTE) for each record to indicate when the event occurred. Listings will be presented by LTE treatment group.

5.2.1 Accounting of Subject

Disposition in the LTE period will be summarized for subjects enrolled in LTE. The summary data will include number (%) of subjects randomized and dosed, number (%) of subjects who completed the treatment/study in LTE, and number (%) of subjects who discontinued treatment and/or withdrew from study in LTE. For subjects who discontinued treatment and/or withdrew from study, the reasons for discontinuation and/or withdrawal, days on treatment and days on study in LTE period will be summarized and listed.

Number (%) of subjects who completed the placebo-controlled period but did not enter the LTE period, number (%) of subjects enrolled in LTE (who signed the LTE informed consent) and number (%) of subjects dosed in LTE period will be summarized by LTE treatment group.

5.2.2 Demographics and Baseline Characteristics

Demographics, baseline characteristics, medical history and AD treatment history at PC period baseline will be summarized for subjects enrolled in the LTE period. Please refer to the SAP for the placebo-controlled period.

5.2.2.1 Concomitant Medications and Non-drug Therapies

The number (%) of subjects taking concomitant medication and non-drug therapies in the LTE period will be summarized. In addition, number of subjects in the FAS that have taken any concomitant medications in the placebo-controlled and LTE active treatment period will be summarized.–Concomitant medications and non-drug therapies will be listed for placebo-controlled and LTE period.

For subjects enrolled in the LTE period, the number (%) of subjects taking AD symptomatic medications concomitantly during the LTE period will be summarized. Please refer to the placebo-controlled SAP for definitions of concomitant therapies and AD symptomatic medication use at baseline.

Disallowed Therapies

Per Section 11.4.1.2 of the Protocol, prohibited and/or restricted medications taken prior to study treatment administration and during the study will be monitored. Disallowed therapies will be reported as Protocol Deviations.

5.2.3 Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a Protocol Deviation log and categorized as major or minor deviations based on Protocol Deviation Classification. The major protocol deviations occurred in the LTE period will be summarized for subjects enrolled in LTE. The major protocol deviations for all FAS subjects in the combined placebo-controlled and LTE periods will also be summarized. Major and minor protocol deviations for all FAS subjects will be listed, respectively, across the placebo-controlled period and the LTE period. Subjects who had incorrect dose assigned by interactive response technology (IRT) in LTE will be summarized and listed. This data will be provided by the unblinded monitors. All summaries for protocol deviations will be presented only by LTE treatment group.

5.2.4 Study Drug Exposure and Study Drug Compliance

A summary table of study drug exposure and compliance in the placebo-controlled and LTE active treatment period will be provided. Number of infusions (BIIB092) received will be summarized as a categorical variable (categories as integers from 1 to 20, and 1-5, 6-10, 11-15, 15-20, 21-26) as well as a continuous variable. Number of weeks on study treatment (BIIB092), calculated as (date of last dose – date of first dose +1)/7, will be summarized as a categorical variable (every 8 weeks from 0 to >= 96 weeks) as well as a continuous variable. Percentage of study treatment taken up to the last dose, calculated as (the actual number of infusions / by the number of infusions a subject is expected to take until the date of last infusion) *100, will be summarized as a continuous variable. This table will be presented only by LTE treatment group. Similar outputs will also be generated for LTE period.

A listing of study drug administration records will be provided for the combined placebo-controlled and LTE period.

5.2.5 COVID-19 Related Analysis

5.2.5.1 Accounting of subjects who discontinued due to COVID-19

The disposition table due to COVID-19 will be generated for LTE period. The listing of subjects who discontinued treatment and/or withdrew from study due to COVID-19 will be generated for PC and LTE period. Please refer to the placebo-controlled SAP for more details.

5.2.5.2 Concomitant Non-Drug Treatment for COVID-19

The summary table for the number of subjects using concomitant Non-Drug Treatment for COVID-19 will be summarized for both LTE period and PC and LTE active treatment period. Please refer to the placebo-controlled SAP for more details.

5.2.5.3 COVID-19 Effect on Drug Compliance

Effect of COVID-19 on drug compliance may be assessed for LTE period. Please refer to the placebo-controlled SAP for more details.

5.2.5.4 COVID-19 Protocol Deviation

The table of protocol deviations due to COVID-19 and the summary of impact and reason for major protocol deviations due to COVID-19 will be generated for LTE period. Please refer to the placebo-controlled SAP for more details.

5.2.5.5 Protocol Alternation Due to COVID-19cx

Protocol alternation due to COVID-19 will be listed for PC and LTE period. Please refer to the placebo-controlled SAP for more details.

5.3 Efficacy Analysis

5.3.1 General Considerations

The analysis population for efficacy analysis is the same as the FAS and data from both the placebo-controlled and LTE periods will be include. All efficacy analyses will be presented by study treatment groups as defined in Section 3.3. The early start high-dose subjects are the subjects who were randomized to high-dose BIIB092 group in the PC period, and the late start high-dose subjects are the subjects who were randomized to Placebo in the PC period, regardless of enrollment of the LTE period or not.

The following comparison will be evaluated for the long-term efficacy of BIIB092:

- The early start high dose compared with the late start high dose.

The comparisons between low-dose and late start high dose, and middle-dose and late start high dose might be conducted. There will be no multiple comparison adjustments.

Visit windows for mapping efficacy endpoint

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

5.3.2 Method of Analysis

5.3.2.1 Considerations for base MMRM model for change from baseline analyses

A mixed model with repeated measures (MMRM) will be used to analyze changes from baseline in a parameter of interest using fixed effects of LTE treatment group, visit (categorical), LTE treatment group-by-visit interaction, baseline of the parameter of interest, baseline of the parameter of interest-by-visit interaction, region (Japan and Australia will be combined), baseline MMSE, baseline disease stage, and baseline AD symptomatic medication use. The correlation between repeated measures of the outcomes will be taken into consideration. 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 first-order autoregressive covariance structure followed by the heterogeneous Toeplitz covariance structure will be used. The least-squares (LS) means, the differences in LS means between each LTE treatment group versus placebo at each visit, 95% confidence intervals (CIs), and p-values will be presented. In the primary analysis of each endpoint, missing data are assumed to be missing at random [Rubin 1976].

For the LTE interim analysis at PC DBL, only records up to week 104 will be included in the MMRM model.

5.3.3 Primary Efficacy Endpoint

Estimand 1 (treatment policy strategy): The difference in change from baseline CDR-SB scores in subjects assigned to BIIB092 group in the PC period, comparing to late start BIIB092 group, regardless what actual treatment is received acknowledging a participant may miss more than four infusions, consecutively, change AD symptomatic medication and/or discontinue treatment early

- Analysis set: all subjects in the FAS
- Variable: The change from baseline CDR-SB scores at the week of interest regardless of intercurrent events (ICEs)
- Analysis set level summary: Least square (LS) mean difference from MMRM model in change from baseline between BIIB092 and placebo
- ICEs and Strategies for Addressing ICEs:

  ICEs include

  - AD symptomatic medication change (treatment policy strategy)
  - Treatment discontinuation (treatment policy strategy)
  - Missing more than or equal to four infusions consecutively (treatment policy strategy)

Since a treatment policy strategy will be used for all ICEs in this estimand, all observed data will be included regardless of miss more than or equal to four infusions consecutively, treatment discontinuation or AD symptomatic medication change. At LTE interim analysis, the primary

analysis is the mean difference of the change from baseline CDR-SB scores at Week 104 between treatment groups in the FAS who have a baseline and at least one post-baseline CDR-SB score [ICH E9 (R1) Addendum 2014, 2017]. At final analysis, the primary analysis is the mean difference of the change from baseline CDR-SB scores at the week of interest between treatment groups in the FAS who have a baseline and at least one post-baseline CDR-SB score. All observed data will be included in the primary analysis, including data collected after intercurrent events [ICH E9 (R1) Addendum 2017], i.e., treatment discontinuation or a change in concomitant use of AD symptomatic medication

The baseline and change from baseline CDR-SB scores at each post-baseline visit will be summarized by LTE treatment group. A mixed model with repeated measures (MMRM) will be used to analyze changes from Baseline in CDR-SB as described in Section 5.3.2.1.A line plot of adjusted mean change from baseline over time will be provided.

5.3.4 Exploratory Efficacy Endpoints

The clinical endpoints assessing AD progression from Baseline include the results of the MMSE, ADAS-Cog13, ADCS-ADL, ISLT, eCog, FAQ, NPI-10, EMACC (composite score of ISLT, DKEFS, DSST, and Trails A), ADCOMS (composite score of selected items from CDR, MMSE, and ADAS-Cog 13) and iADRS.

The by visit summary and MMRM analysis will be performed for MMSE, ISLT, eCog, ADCS-ADL, FAQ, ADAS-Cog-13 (13-item), NPI-10, EMACC, ADCOMS, and iADRS as described in Section 5.3.2.1. For LTE interim analysis at PC DBL, all available records up to week 104 will be analyzed in MMRM table. The baseline and change from baseline scores at each post-baseline visit will be summarized by LTE treatment group at final analysis.

5.4 Safety Analyses

5.4.1 General Considerations

5.4.1.1 Analysis Population

The safety analysis set will be used for safety analyses of AEs, SAEs, clinical laboratory data, Columbia Suicide Severity Rating Scale (C-SSRS) data, ECG data and vital sign data. The safety MRI evaluable set will be used for the analysis of safety MRI data.

5.4.1.2 LTE Safety Treatment Groups

Since all the subjects are supposed to receive active treatment in LTE, the LTE safety treatment groups which are the same as the LTE treatment groups will be used for all the safety analyses.

5.4.1.3 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. Incidence rate of an event based on the entire follow-up time – defined as the number of subjects who experienced an event divided by the total of entire follow-up time among the subjects in the analysis set (e.g., incidence rate per 100 subject-years). The entire follow-up time for a subject (subject-years) is defined as 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. Each subject will be counted only once within each category.

5.4.2 Clinical Adverse Events

Treatment-emergent AEs (TEAE)

A treatment-emergent AE is defined as AE that started or worsened after the start of first infusion of study treatment in LTE period.

First dose for below definitions is the first dose in LTE period

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 and stop time is after the first dose or missing, then that event is considered treatment emergent.

For AEs with a partial start date, the following imputation method will be used to determine if the event is treatment emergent:

- When only the day is missing, and the year/month is equal to the year/month of first dose date, and the AE stop date is missing or on/after the first dose date, then use the first dose date as AE start date. Otherwise impute the AE start date as the first day (1) of the AE start month
- When the AE start month is missing, and the year equals to the year of first dose date, and the AE stop date is missing or on/after the first dose date, then use the first dose date as AE start date. Otherwise impute the AE start date as the first day (01January) of the AE start year

For AEs with a partial end date, the following imputation method will be used:

- When only the day is missing, and the year/month equal to the year/month of the last date on study, then use the last date on study as AE stop date. Otherwise impute the AE stop date as the last day of the AE stop month
- When the AE stop month is missing, and the year equals to the year of last date on study, then use the last date on study as AE stop date. Otherwise impute the AE stop date as the last day (31December) of the AE stop year

Only TEAEs will be included in the tables, unless otherwise specified. All SAEs (including pre-dosing SAEs) will be included in the listing of SAEs, with an indicator of pre-dosing or treatment-emergent. Only TEAEs will be included in other AE listings, if not otherwise specified. A listing of AE will be provided for the combined placebo-controlled and LTE period.

Pre-treatment AE: AE starting before LTE first dose are considered pre-treatment AE for LTE period if it does not qualify for above TEAE definition i.e., no worsening.

Analysis period and analysis displays

Analysis period will be specified for each output. However, for either analysis period in this SAP (LTE period or placebo-controlled and LTE active treatment period), AE data will be summarized by LTE treatment group (5 LTE treatment groups as low-dose BIIB092 125mg/4weeks, low-dose BIIB092 375mg/12weeks, medium-dose, early start high-dose, late start high-dose, and BIIB092 total). Listings will include all data in placebo-controlled and LTE period (all data in the study), with an indicator of the study period (pre-dosing, placebo-controlled, or LTE) for each record when the event occurred.

5.4.2.1 Summary and Incidence Analysis

Overall summary of AE table will be done for the LTE period and placebo-controlled and LTE active treatment period, presented by LTE treatment group. The following information will be summarized: the number of subjects with any AE, with any AE by maximum severity, 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 drug withdrawal, the number of subjects with AE leading to study withdrawal, and the number of subjects with a fatal event.

The sorting order of AE incidence tables, unless otherwise specified, will be by decreasing frequency order of "BIIB092 total" column within each category in the tables presented by LTE 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 LTE 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 tables will be provided for the LTE period. Selected tables (marked with *) will be presented for incidence rate of AEs for the placebo-controlled and LTE active treatment period:

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 *
4. AEs at least 2% higher in incidence by system organ class and preferred term for early start BIIB092 2000 mg/4wk compared to late start BIIB092 2000 mg/4wk presented only for LTE period
5. AEs by preferred term *
6. AEs by preferred term with an incidence of 5% or more
7. AEs by maximum severity by system organ class and preferred term by decreasing frequency (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, unknown and total. A subject will be counted only once at the maximum severity within each system organ class and preferred term.)
8. AEs by maximum severity by preferred term
9. Severe AEs by system organ class and preferred term by decreasing frequency *
10. Severed AEs by preferred term *
11. Related AEs by system organ class and preferred term by decreasing frequency *
12. AEs related to tau PET ligand by system organ class and preferred term by decreasing frequency (using tau PET population)
13. SAEs by system organ class and preferred term by decreasing frequency *
14. SAEs by preferred term *
15. Related SAEs by system organ class and preferred term by decreasing frequency *
16. SAEs with fatal outcome by system organ class and preferred term by decreasing frequency
17. AEs that led to drug interrupted by system organ class and preferred term by decreasing frequency
18. AEs that led to discontinuation of study treatment by system organ class and preferred term by decreasing frequency
19. AEs that led to withdrawal from study by system organ class and preferred term by decreasing frequency
20. AEs related to lumbar puncture (LP) by system organ class and preferred term (using CSF population)

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 infusion interruption
4. Listing of AEs that led to discontinuation of study drug
5. Listing of AEs that led to withdrawal from study
6. Listing of AEs related to tau PET ligands
7. Listing of SAEs with fatal outcome
8. Listing of AEs related to lumbar puncture (LP)
9. Listing of death
10. Listing of pre-treatment AEs

5.4.2.2 Incidence Rate Analysis

Incidence rate of AEs based on the entire follow-up time for subjects with at least 1 AE in LTE period may be summarized by system organ class and preferred terms. The incidence rate tables will be presented by LTE treatment group. The entire follow-up time for LTE period is from the first dose in LTE period until the last day on study.

Follow-up adjusted incidence rate of AEs may also be summarized for placebo-controlled and LTE active treatment period, ue to the different length of placebo-controlled and LTE active treatment period in early start versus late start high-dose BIIB002 subjects. The entire follow-up time is from the first dose in active treatment period (placebo-controlled period first dose of BIIB092 for early start subjects and LTE period first dose of BIIB092 for late start subjects) until the last day in the study.

5.4.2.3 Infusion Reactions

Please refer to the placebo-controlled period SAP for infusion reaction definitions. The same infusion reaction tables as described in placebo-controlled period SAP will be summarized for LTE period by LTE treatment groups.

5.4.2.4 AE of Special Interest

Please refer to the placebo-controlled period SAP for AEs of special interest. The same tables as described in placebo-controlled period SAP will be summarized for LTE by LTE treatment groups.

5.4.3 Clinical Laboratory Data

The following clinical laboratory parameters are assessed in the protocol:

- Hematology: red blood cell count, platelet count, hemoglobin level, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and total white blood cell count with absolute counts and percentages of neutrophils, monocytes, lymphocytes, eosinophils, and basophils
- Blood chemistry: total protein, albumin, creatinine, BUN, uric acid, bilirubin (total and direct), alkaline phosphatase, ALT, AST, lactate dehydrogenase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium
- Urinalysis: color, specific gravity, pH, protein, glucose, leukocyte esterase, blood, and ketones (and microscopic examination, if abnormal)
- Coagulation: Activated Partial Thromboplastin Time (APTT), Prothrombin Intl. Normalized Ratio (INR), Prothrombin Time (PT)

Analysis period will be specified for each table or figure. Unless otherwise specified, all the laboratory tables will be summarized by LTE treatment group. Listings will include all data in the study, with an indicator of the study period (pre-dosing, placebo-controlled, or LTE) for each record when the assessment occurred. Listings will be presented by PC treatment group.

Study day and analysis visit window for analyses using LTE baseline will be derived based on the first day of study drug in LTE. Details are specified in Appendix I.

5.4.3.1 Quantitative analyses

For numeric laboratory parameters, actual values will be summarized by visit for all the visits in the placebo-controlled and LTE active treatment 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 actual values (with standard error) at each visit for all the visits in the placebo-controlled and LTE active treatment period will be provided.

Summary of change from baseline and percent change from baseline for numeric laboratory parameters will be done on the placebo-controlled and LTE active treatment period. LTE baseline will be used for late start high-dose group subjects, while placebo-controlled baseline will be used for the rest of the subjects (low-dose BIIB092 125mg/4weeks, low-dose BIIB092 375mg/12weeks, medium-dose, early start high-dose). Number of evaluable subjects, mean, standard deviation, 25% and 75% quartiles, min and max values will be presented at each visit.

Listings of individual laboratory measurements by patients for all the parameters will be provided.

Visit windows for by visit summaries

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

5.4.3.2 Qualitative analyses

For 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 placebo-controlled and LTE active treatment period. Each subject's hematology, blood chemistry and urinalysis 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.

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, serology, and urinalysis. 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 not low or high (including missing) in order to be included in the analysis for corresponding categories in the analyses.

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

Potentially Clinically Significant laboratory abnormalities analyses

Please refer to the placebo-controlled SAP for the parameters and criteria for potentially clinically significant laboratory abnormalities analyses.

The number of subjects with potentially clinically significant laboratory abnormalities post-baseline will be summarized for the placebo-controlled and LTE active treatment 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 LTE period will be included. For late start subjects, the LTE baseline will be used and PCS abnormalities that occurred in the LTE period based on LTE baseline will be included.

Potential serious hepatotoxicity

In this SAP, we define potential serious hepatotoxicity as ALT or AST > 3x ULN and total bilirubin > 2x ULN at any time post-baseline in the placebo-controlled and LTE active treatment 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 in the active treatment period 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 in the active treatment period will be presented. A listing of subjects with potential serious hepatotoxicity will be provided with the concurrent records labeled. Concurrent is defined as on the same day.

5.4.4 C-SSRS Data

Suicidal ideation events include 11 categories: (1) Wish To Be Dead, (2) Non-Specific Active Thoughts, (3) Active Thoughts Without Intent To Act, (4) Active Thoughts With Some Intent—No Plan, (5) Active Thoughts with Plan and Intent. Suicidal behavior events include: (6) Preparatory acts or behavior, (7) Aborted Attempt, (8) Interrupted Attempt, (9) Actual Attempt, (10) Suicidal behavior, (11) Completed Suicide. Another "Yes/No" question of whether the subject has engaged in non-suicidal self-injurious behavior is also collected.

The analysis will be based on the safety population. Number of subjects in each ideation category at any post-baseline visit, number of subjects in each suicidal behavior category at any post-baseline visit, number of subjects with at least one suicidal ideation or behavior event at any post-baseline visit, and subjects who have engaged in non-suicidal self-injurious behavior at any post-baseline visit will be summarized in the placebo-controlled and LTE active treatment period. A listing of C-SSRS data by subjects will be provided.

5.4.5 ECG Data

5.4.5.1 ECG analyses

Actual values of numeric ECG parameters will be summarized by visit. number of evaluable subjects, mean, standard deviation, 25% and 75% quartiles, min and max values will be presented at each visit for placebo-controlled and LTE period active treatment period. Similarly change from baseline values will be summarized in the same fashion for placebo-controlled and LTE active treatment period.

Summary of ECGs (number of normal, <abnormal, not adverse event>, or <abnormal, adverse event>) at scheduled visits will be presented by the LTE treatment group through the placebo-controlled and LTE active treatment period.

Shift table from normal or unknown ECG at baseline to ever abnormal ((<abnormal, not adverse event>, or <abnormal, adverse event>) post-baseline ECG will be summarized for the placebo-controlled and LTE active treatment group. The worst post-baseline record of each subject is selected.

For the above mentioned ECG analyses, for early start subjects, the placebo-controlled baseline will be used while for late start subjects, the LTE baseline will be used.

In addition, PR and QTcF values will be summarized. Please see the detail in the SAP for placebo-controlled period.

Visit windows for by visit summaries

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

5.4.6 Vital Sign Data

5.4.6.1 Vital Sign Data Analyses

Vital sign parameters include temperature, diastolic blood pressure, systolic blood pressure, heart rate, and respiration rate. The descriptive statistics for actual values will be summarized by all the visits in the combined placebo-controlled and LTE active treatment period. The lines of mean vital sign over time by LTE treatment group will be graphed in the combined placebo-controlled and LTE active treatment period.

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

A by-patient listing for all vital sign parameters in the combined placebo-controlled and LTE period will also be presented.

The analysis of vital signs will also focus on the incidence of clinically relevant outliers.

For details of criteria to assess potential clinically relevant outliers in vital sign, refer to section 5.4.6 in the SAP for the placebo-controlled period. The number of clinically relevant outliers determined by each criterion will be summarized across combined placebo-controlled and LTE active treatment period by treatment group.

Visit windows for by visit summaries

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

5.4.7 Physical Examination

Clinically significant findings during physical examinations will be recorded as AEs. Abnormal findings from physical examination will be included in AE listing..

5.4.8 Neurological Examination

Clinically significant findings during neurological examinations will be recorded as AEs. Abnormal findings from neurological examination will be included in AE listing..

5.4.9 Safety MRI Data

The following MRI data will be summarized by LTE treatment group using safety MRI population for placebo-controlled and LTE active treatment period:

- Number of subjects with new or worsening of vasogenic edema (VE) at post-baseline
  - New VE or questionable VE is considered as subjects who has a VE which is worsening as post-baseline or for the following:
    - The subject has answered "Not-Applicable" at any post-baseline visit for question: VE on this MRI as compared to previous MRI
    - The subject has answered "VE present and increased in size" at any post-baseline visit for question: VE on this MRI as compared to previous MRI
  - Worsening of VE from baseline is defined as any severity increase compared to baseline. The following sequence indicates the increase of the severity:

    No VE present < Questionable presence of VE (Mild Severity) < Questionable presence of VE (Moderate Severity) < Questionable presence of VE (Severe Severity) < VE present (Mild Severity) < VE present (Moderate Severity) < VE present (Severe Severity)

- Number of subjects with new microhemorrhages (mH) findings at post-baseline
  - New mH is define as subjects who has mH increased in number and/or size at any post-baseline comparing to the baseline. If a subject has no mHs at baseline, then new mH is defined as any initial identification at any post-baseline visit.
- Number of subjects with macrohemorrhages (MA) (>1cm) at post-baseline
- Number of subjects with new superficial siderosis (SS) (>1cm^3) at post-baseline
- Number of subjects with new SS (≤1cm^3) at post-baseline

5.4.10 COVID-19 Related Safety Analysis

All AE tables due to COVID-19 will be summarized for LTE period and PC and LTE active treatment period. Please refer to the placebo-controlled SAP for more details.

5.5 Pharmacokinetics Analysis

The Serum PK evaluable set as defined in Section 3.1, will be used for the description of the serum concentration data, and for the estimation of serum PK parameters. The CSF PK evaluable set as defined in Section 3.1, will be used for the description of CSF concentration data. PK analysis will be conducted with serum and CSF concentrations of BIIB092 by visit and dose group. Subjects who receive BIIB092 125mg once every 4 weeks will be analyzed separately from those who receive 375mg once every 12 weeks. The summaries and listing will be done using the combined placebo-controlled and LTE active treatment period.

Atypical drug concentrations (e.g., very low or very high) will be excluded from the analysis, if no apparent explanation exists. Concentration observations will also be removed from the data set if

i) corresponding dosing or sampling times are missing or cannot be reconstructed

ii) large deviations between actual administered dose and nominal dose exists

iii) large deviations between scheduled and actual sampling days or times exists

iv) large deviations between actual and nominal dose administration time exists.

All deletions of data points will be appropriately documented.

5.5.1 Serum and CSF PK Concentration Profile

Individual serum and CSF concentrations will be listed for BIIB092. Concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". Differences between scheduled and actual sampling times will be listed for these subjects, along with the percentage differences between nominal and actual dose amount. Additional listings may be generated as deemed necessary.

Descriptive statistics (N, arithmetic mean, standard deviation, geometric mean, CV, median, minimum, and maximum), will also be used to summarize serum PK and CSF concentrations of BIIB092 by visit/scheduled time points and dose group. For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for serum PK, BLQ value on pre-day 1 of study treatment will be set to 0, and all post first dose of study treatment BLQ values will be set to half the LLOQ value. In linear and semi- plots, all BLQ values will be treated as LLOQ/2. Mean CSF concentrations that are BLQ will be presented as BLQ, and the SD and %CV will be reported as not applicable. When summarizing concentrations or PK parameters in serum and CSF, a minimum of 2 values are required to show the arithmetic mean and geometric mean, and at least 3 values are required to show the standard deviation and coefficient of variation (CV).

Serum and CSF concentrations of BIIB092 will be plotted versus time by dose group on both a linear and a logarithmic scale. Additional plots may be included as deemed necessary.

CSF to serum concentration ratio will be computed using pre-infusion concentrations at week 12, 48, 76, 128, 176, and 224. Individual ratios along with descriptive statistics (N, arithmetic mean, standard deviation, geometric mean, CV, median, minimum, and maximum) at 12, 48, 76, 128,

176, and 224 weeks, by dose will be listed. Any BLQ value will be excluded from CSF to serum ratio calculation, and exclusions will be appropriately documented. Individual CSF vs. serum concentrations above LLOQ (for both serum and CSF) will be plotted (scatter plot) by week, color coded by dose.

5.5.1 Serum PK Parameters

The following PK parameters will be listed per visit, as data permits, from serum concentration data:

Parameter	Definition/Calculation	Units
C_{trough}	Observed trough serum BIIB092 concentration collected at end of dosing interval (before next infusion starts)	ug/mL

Individual PK parameter data will be listed. Descriptive statistics (N, mean, standard deviation, CV, median, minimum, and maximum) will be used to summarize the PK parameters by visit and dose. Geometric means (by visit and dose) will also be presented. Box plots and plots of individual C_{trough} over time will be provided.

5.6 Biomarker

The CSF PD evaluable set or CSF PD modified evaluable set as defined in Section 3.1, will be used for the statistical modeling of CSF PD data.

5.6.1 Pharmacodynamics Analysis

The actual, change from baseline, and percentage change from baseline of CSF N-terminal tau will be summarized to evaluate pharmacodynamics effect after multiple IV infusions of BIIB092. For descriptive statistics, BLQ is imputed as LLOQ/2. For individual subject listings, BLQs are listed as BLQ. Summary statistics will be generated showing N, mean, median, standard deviation, Q1, Q3, minimum and maximum results over time by treatment group for CSF N-terminal tau for placebo-control and LTE period.

Mean (± standard error) plots of change from baseline of CSF N-terminal over time by treatment group and mean (± standard error) % change of CSF N-terminal tau over time by treatment group may be presented.

5.6.2 Structural MRI Analysis

No subjects reached week 226, the primary analysis timepoint for structural MRI. Therefore, structural MRI is not reported or statistically analyzed for the LTE period.

5.6.3 Tau PET Analysis

All tau PET analysis will be using tau PET evaluable set defined in Section 3.1

5.6.3.1 By visit summary

The baseline, change and percent change from baseline tau PET SUVR scores will be summarized by LTE treatment groups by visit for placebo-controlled and LTE period for each primary (Braak 1&2, Braak 3&4, and Braak 5&6) and secondary (Posterior composite, Temporal composite, Amyloid composite, Frontal cortex, Parietal cortex, Occipital cortex, Anterior cingulate cortex, Posterior cingulate cortex, Lateral temporal cortex, Inferior temporal cortex, Medial temporal lobe, Lateral temporal lobe) target region and primary reference region (Cerebellum (superior section eroded)). Visit window is defined in Appendix I.

5.7 Anti-Drug Antibody Analysis

5.7.1 Analysis Methods for Anti-Drug Antibody Data

Anti-Drug Antibody (ADA) population will be used to analyze ADA data.

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

For the definitions of treatment emergent positive, persistently positive, and transiently positive, please refer to the placebo-controlled SAP.

Summary table listing the number and percentage of all anti-BIIB092-positive and -negative antibody events by LTE treatment group and visits throughout the placebo-controlled and LTE active treatment period will be displayed.

In addition, a summary table of patients with treatment-emergent, persistent, and transient responses will be presented by LTE treatment group during the placebo-controlled and LTE active treatment period. A listing of anti-BIIB092 antibody results will also be provided.

Visit windows for by visit summaries

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

5.8 Additional Exploratory Endpoints

5.8.1 Health Outcomes

The FAS will be used for the analysis of health outcomes data for LTE period. The result will be listed by LTE treatment group for placebo-controlled and LTE period.

6 Appendix I: Visit Window Mapping

For data that are summarized by visit and longitudinal analysis, assessment from all scheduled visits including EOT visit and EOS visit, and all unscheduled visits will be mapped to an appropriate analysis visit using a windowing scheme. Analysis visit windows are defined in [Table 1 - Table 12] for different endpoints.

If there are 2 or more assessments from visits other than EOT or EOS visits mapped to the same analysis visit 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 from visits other than EOT or EOS visits mapped to the same analysis visit with the same distance from the target visit day, then select the later one(s) for the analysis. If there are 2 or more assessments from visits other than EOT or EOS visits mapped to the same analysis visit and on the same day, use the average value for quantitative parameters and the worst value for qualitative parameters for analysis.

Table 1. Visit Windows for Efficacy Endpoints

Efficacy Endpoint	Analysis visit	Target visit day	Analysis visit window
CDR, NPI-10, ADAS-Cog13, FAQ, and ADCS-ADL	Baseline	1	Most recent non-missing pre-dose value
	Week 24	169	[2, 267]
	Week 52	365	[268, 456]
	Week 78	547	[457, the end day of the placebo-controlled period [1]]
	Week 104	729	[one day after the start day of the LTE period[2] , 813]
	Week 128	897	[814, 981]
	Week 152	1065	[982, 1149]
	Week 176	1233	[1150, 1317]
	Week 200	1401	[1318, 1492]
	Week 226	1582	≥1493
ISLT, DKEFS, DSST, Trails A,	Baseline800-	1	Most recent non-missing pre-dose value
	Week 12	85	[2, 141]
	Week 28	197	[142, 239]
	Week 40	281	[240, 337]
	Week 56	393	[338, 435]
	Week 68	477	[436, 512]
	Week 78	547	[513, the end day of the placebo-controlled period [1]]
	Week 108	757	[one day after the start day of the LTE period[2], 841]

Efficacy Endpoint	Analysis visit	Target visit day	Analysis visit window
	Week 132	925	[842, 1009]
	Week 156	1093	[1010, 1261]
	Week 204	1429	[1262, 1506]
	Week 226	1582	≥1507
eCog	Baseline	1	Most recent non-missing pre-dose value
	Week 28	197	[2, 295]
	Week 56	393	[296, 470]
	Week 78	547	[471, the end day of the placebo-controlled period [1]]
	Week 108	757	[one day after the start day of the LTE period[2], 841]
	Week 132	925	[842, 1009]
	Week 156	1093	[1010, 1261]
	Week 204	1429	[1262, 1506]
	Week 226	1582	≥1507
MMSE	Baseline	1	Most recent non-missing pre-dose value
	Week 12	85	[2, 127]
	Week 24	169	[128, 225]
	Week 40	281	[226, 323]
	Week 52	365	[324, 421]
	Week 68	477	[422, 512]
	Week 78	547	[513, the end day of the placebo-controlled period[1]]
	Week 104	729	[one day after the start day of the LTE period[2], 813]
	Week 128	897	[814, 981]
	Week 152	1065	[982, 1149]
	Week 176	1233	[1150, 1317]
	Week 200	1401	[1318, 1492]
	Week 226	1582	≥1493
	1 The end day of the placebo-controlled period is the last day on or before the first infusion in LTE for subjects who enter LTE and is the last day in study for subjects who do not enter LTE. 2 The start day of the LTE period is the day of the first infusion in the LTE period.		

Table 2. Visit Windows for Laboratory by Visit Summaries using Placebo-Controlled Baseline

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 12	85	[2, 127]
Week 24	169	[128, 253]
Week 48	337	[254, 421]
Week 72	505	[422, 526]
Week 78	547	[527, 630* or the end day of the placebo-controlled period[1]]
Week 90*	631	[631, the last day in the study]
Week 100	701	[the start day of the LTE period[2], 785]
Week 124	869	[786, 953]
Week 148	1037	[954, 1121]
Week 172	1205	[1122, 1289]
Week 196	1373	[1290, 1457]
Week 220	1541	[1458, 1562]
Week 226	1582	[1563, 1625]
Week 238	1667	≥1626
* Applicable only for the subjects who do not go to LTE. They are expected to have week 90 follow-up assessment. 1 The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE and is the last day in study for subjects who do not enter LTE. 2 The start day of the LTE period is the day of the first infusion in the LTE period.		

Table 3. Visit Windows for Laboratory by Visit Summaries using LTE Baseline

Analysis visit	Target visit day	Analysis visit window	Protocol visit
Baseline	1	Most recent non-missing value prior to the first infusion in LTE	
Week 24	169	[2, 253]	Week 100
Week 48	337	[254, 421]	Week 124
Week 72	505	[422, 526]	Week 148
Week 100	701	[527, 785]	Week 172
Week 124	869	[786, 953]	Week 196
Week 148	1037	[954, 1121]	Week 220 and Week 226
Week 172	1205	≥1122	Week 238
Note: Study day and analysis visit window are derived based on the first day of study drug in LTE.			

Table 4. Visit Window for Coagulation Panel by Visit Summaries using Placebo-Controlled Baseline

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 8	57	[2,183]
Week 44	309	[184, 407]
Week 72	505	[408, the end day of the placebo-controlled period[1]]
Week 124	869	[the start day of the LTE period[2], 1037]
Week 172	1205	[1038, 1373]
Week 220	1541	> 1373

1 The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE and is the last day in study for subjects who do not enter LTE.
2 The start day of the LTE period is the day of the first infusion in the LTE period.

Table 5. Visit Window for Coagulation Panel by Visit Summaries using LTE Baseline

Analysis visit	Target visit day	Analysis visit window	Protocol visit
Baseline	Most recent non-missing value	Most recent non-missing value prior to the first infusion in LTE	Week 72
Week 44	309	[2, 477]	Week 124
Week 72	645	[478, 813]	Week 172
Week 124	981	> 813	Week 220

Table 6. Visit Windows for ECG by Visit Summaries for Placebo-Controlled and LTE Period using Placebo-Controlled Baseline

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
D1 Post dose	1	Day1: 15 min post dose or 1 hour post dose
Week 12	85	[2, 127]
Week 24	169	[128, 253]
Week 48	337	[254, 421]
Week 72	505	[422, 526]
Week 78	547	[527, 630* or the end day of the placebo-controlled period[1]]
Week 90*	631	[631, the last day in the study]
Week 104	729	[the start day of the LTE period[2], 813]
Week 128	897	[814, 981]
Week 152	1065	[982, 1149]
Week 176	1233	[1150, 1317]
Week 200	1401	[1318, 1492]
Week 226	1582	[1493, 1625]
Week 238	1667	[1626, the end day of the LTE period]

* Applicable only for the subjects who do not go to LTE. They are expected to have week 90 follow-up assessment.
1 The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE and is the last day in study for subjects who do not enter LTE.
2 The start day of the LTE period is the day of the first infusion in the LTE period.

Table 7. Visit Windows for ECG by Visit Summaries using LTE Baseline

Analysis visit	Target visit day	Analysis visit window	Protocol visit
Baseline	Most recent non-missing value prior to the first infusion in LTE	Most recent non-missing value prior to the first infusion in LTE	Week 78

Analysis visit	Target visit day	Analysis visit window	Protocol visit
Week 24	169	[the start day of the LTE period, 253]	Week 104
Week 48	337	[254, 421]	Week 128
Week 72	505	[422, 589]	Week 152
Week 104	673	[590, 757]	Week 176
Week 128	841	[758, 932]	Week 200
Week 152	1023	[933, 1065]	Week 226
Week 176	1107	>1065	Week 238
Day 1 is the first infusion day in LTE period			

Table 8. Visit Windows for Vital Sign by Visit Summaries using Placebo-Controlled Baseline

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
D1 Post dose	1	Day 1 post dose infusion (if more than one Day 1 post dose results available, the average of the available results will be used)
Week 4– Pre dose	29	[2, 43] (Pre-dose assessment)
Week 4- Post dose	29	[2, 43] (Post dose assessment)
Week 8– Pre dose	57	[44, 71] (Pre-dose assessment)
Week 8- Post dose	57	[44, 71] (Post dose assessment)
Week 12– Pre dose	85	[72, 99] (Pre-dose assessment)
Week 12- Post dose	85	[72, 99] (Post dose assessment)
Week 16	113	[100, 127]
Week 20	141	[128, 155]
Week 24	169	[156, 183]
Week 28	197	[184, 211]
Week 32	225	[212, 239]
Week 36	253	[240, 267]
Week 40	281	[268, 295]
Week 44	309	[296, 323]
Week 48	337	[324, 351]
Week 52	365	[352, 379]
Week 56	393	[380, 407]
Week 60	421	[408, 435]
Week 64	449	[436, 463]
Week 68	477	[464, 491]
Week 72	505	[492, 519]
Week 76	533	[520, 540]
Week 78	547	[541, 589* or the end day of the placebo-controlled period[1]]
Week 90*	631	[590, the last day in the study]
Week 80	561	[the start day of the LTE period[2], 575]
Week 84	589	[576, 603]
Week 88	617	[604, 631]
Week 92	645	[632, 659]
Week 96	673	[660, 687]

Analysis visit	Target visit day	Analysis visit window
Week 100	701	[688, 715]
Week 104	729	[716, 743]
Week 108	757	[744, 771]
Week 112	785	[772, 799]
Week 116	813	[800, 827]
Week 120	841	[828, 855]
Week 124	869	[856, 883]
Week 128	897	[884, 911]
Week 132	925	[912, 939]
Week 136	953	[940, 967]
Week 140	981	[968, 995]
Week 144	1009	[996, 1023]
Week 148	1037	[1024, 1051]
Week 152	1065	[1052, 1079]
Week 156	1093	[1080, 1107]
Week 160	1121	[1108, 1135]
Week 164	1149	[1136, 1163]
Week 168	1177	[1164, 1191]
Week 172	1205	[1192, 1219]
Week 176	1233	[1220, 1247]
Week 180	1261	[1248, 1275]
Week 184	1289	[1276, 1303]
Week 188	1317	[1304, 1331]
Week 192	1345	[1332, 1359]
Week 196	1373	[1360, 1387]
Week 200	1401	[1388, 1415]
Week 204	1429	[1416, 1443]
Week 208	1457	[1444, 1471]
Week 212	1485	[1472, 1499]
Week 216	1513	[1500, 1527]
Week 220	1541	[1528, 1555]
Week 224	1569	[1556, 1576]
Week 226	1582	[1577, 1625]
Week 238	1667	[1626, the end of the LTE period]

* Applicable only for the subjects who do not go to LTE. They are expected to have week 90 follow-up assessment.
1 The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, and is the last day in study for subjects who do not enter LTE.
2 The start day of the LTE period is the day of the first infusion in the LTE period.

Table 9. Visit Windows for Vital Sign by Visit Summaries using LTE baseline

Analysis visit	Target visit day	Analysis visit window	Protocol visit
LTE Baseline	1	Most recent non-missing value prior to the first infusion in LTE	Week 80 pre dose
D1 Post dose	1	Day 1 post dose infusion (if more than one Day 1 post dose results available, the average of the available results will be used)	Week 80 post dose
Week 4– Pre dose	29	[2, 43] (Pre-dose assessment)	Week 84 (Pre-dose assessment)
Week 4-- Post dose	29	[2, 43] (Post dose assessment)	Week 84 (Post dose assessment)
Week 8– Pre dose	57	[44, 71] (Pre-dose assessment)	Week 88 (Pre-dose assessment)
Week 8- Post dose	57	[44, 71] (Post dose assessment)	Week 88 (Post dose assessment)
Week 12– Pre dose	85	[72, 99] (Pre-dose assessment)	Week 92 (Pre-dose assessment)
Week 12- Post dose	85	[72, 99] (Post dose assessment)	Week 92 (Post dose assessment)
Week 16	113	[100, 127]	Week 96
Week 20	141	[128, 155]	Week 100
Week 24	169	[156, 183]	Week 104
Week 28	197	[184, 211]	Week 108
Week 32	225	[212, 239]	Week 112
Week 36	253	[240, 267]	Week 116
Week 40	281	[268, 295]	Week 120
Week 44	309	[296, 323]	Week 124
Week 48	337	[324, 351]	Week 128
Week 52	365	[352, 379]	Week 132
Week 56	393	[380, 407]	Week 136
Week 60	421	[408, 435]	Week 140
Week 64	449	[436, 463]	Week 144
Week 68	477	[464, 491]	Week 148
Week 72	505	[492, 519]	Week 152
Week 76	533	[520, 547]	Week 156
Week 80	561	[548, 575]	Week 160
Week 84	589	[576, 603]	Week 164
Week 88	617	[604, 631]	Week 168
Week 92	645	[632, 659]	Week 172
Week 96	673	[660, 687]	Week 176
Week 100	701	[688, 715]	Week 180
Week 104	729	[716, 743]	Week 184
Week 108	757	[744, 771]	Week 188
Week 112	785	[772, 799]	Week 192
Week 116	813	[800, 827]	Week 196
Week 120	841	[828, 855]	Week 200
Week 124	869	[856, 883]	Week 204
Week 128	897	[884, 911]	Week 208
Week 132	925	[912, 939]	Week 212
Week 136	953	[940, 967]	Week 216
Week 140	981	[968, 995]	Week 220
Week 144	1009	[996, 1023]	Week 224
Week 148	1037	[1024, 1051]	Week 226
Week 152	1065	[1052, the end day of the LTE period]	Week 238

Table 10. Visit Windows for ADA data using Placebo controlled baseline

Analysis visit	Target visit day	Analysis visit window
Baseline	1	See baseline definition in Section 3.7.1
Week 4	29	[2, 99]
Week 24	169	[100, 253]
Week 48	337	[254, 435]
Week 76	533	[436, the end day of the placebo-controlled period[1]]
Week 80	561	[the start day of the LTE period[2], 645]
Week 104	729	[646, 771]
Week 116	813	[772, 953]
Week 156	1093	[954, 1163]
Week 176	1233	[1164, 1303]
Week 196	1373	[1304, 1471]
Week 224	1569	[1472, 1618]
Week 238	1667	≥1619

1 The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, and is the last day in study for subjects who do not enter LTE.
2 The start day of the LTE period is the day of the first infusion in the LTE period.

Table 11. Visit Windows for ADA data using LTE Baseline

Analysis visit	Target visit day	Analysis visit window	Protocol visit
Baseline	Most recent non-missing value prior to the first infusion in LTE	Most recent non-missing value prior to the first infusion in LTE	Week 80
Week 24	169	[2, 253]	Week 104
Week 48	337	[254, 435]	Week 116
Week 76	533	[436, 631]	Week 156
Week 104	729	[632, 771]	Week 176
Week 116	813	[772, 953]	Week 196
Week 156	1093	[954, 1163]	Week 224
Week 176	1233	>1163	Week 238

Day 1 is the first infusion day in LTE period

Table 12. Visit Windows for tau PET data

Analysis visit *	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 52	364	[120, 456]
Week 78	547	[457, 727*]
Week 152	1065	[728, 1324]
Week 226	1583	>1325

* 180 days after Week 78 target date.

Table 13. Visit Windows for C-SSRS data using Placebo controlled baseline

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 24	169	[2, 267]
Week 52	365	[268, 456]
Week 78	547	[457, the last day of the PC period[1]]]
Week 104	729	[the start day of the LTE period[2], 813]
Week 128	897	[814, 981]
Week 152	1065	[982, 1149]
Week 176	1233	[1150, 1317]
Week 200	1401	[1318, 1492]
Week 226	1583	>1492
1. The end day of the placebo-controlled period is the last day before the first infusion in LTE, and is the last day in study for subjects who do not enter LTE. 2. The start day of the LTE period is the day of first infusion in LTE period.		

Table 14. Visit Windows for C-SSRS by Visit Summaries using LTE Baseline

Analysis visit	Target visit day	Analysis visit window	Protocol visit
Baseline	Most recent non-missing value prior to the first infusion in LTE	Most recent non-missing value prior to the first infusion in LTE	Week 78
Week 24	169	[the start day of the LTE period, 253]	Week 104
Week 52	337	[254, 421]	Week 128
Week 78	505	[422, 589]	Week 152
Week 104	673	[590, 757]	Week 176
Week 128	841	[758, 932]	Week 200
Week 152	1023	> 932	Week 226
Day 1 is the first infusion day in LTE period			

Table 15. Visit Windows for safety MRI data with placebo-controlled baseline

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 28	197	[90, 281]
Week 52	365	[282, 456]
Week 78	547	[457, the last day of the PC period[1]]
Week 104	729	[the start day of LTE period[2], 911]
Week 156	1093	[912, 1338]
Week 226	1583	≥ 1339
1. The end day of the placebo-controlled period is the last day before the first infusion in LTE,and is the last day in study for subjects who do not enter LTE. 2. The start day of the LTE period is the day of first infusion in LTE period.		

Table 16. Visit Windows for safety MRI data with LTE baseline

Analysis visit	Target visit day	Analysis visit window	Protocol specified visit
Baseline	1	Most recent non-missing pre-dose value	Week 78
Week 28	169	[2, 351]	Week 104
Week 52	533	[352, 778]	Week 156
Week 78	1023	>778	Week 226

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