Tango

251AD201/NCT03352557

Statistical Analysis Plan

Placebo-Controlled Period

STATISTICAL ANALYSIS PLAN
Placebo-Controlled Period

Product Studied: BIIB092
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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Table of Contents

LIST OF ABBREVIATIONS **6**

1 INTRODUCTION **8**

2 STUDY OVERVIEW **8**

2.1 PRIMARY OBJECTIVE AND ENDPOINT 8
2.2 SECONDARY OBJECTIVES AND ENDPOINTS 8
2.3 EXPLORATORY OBJECTIVES AND ENDPOINTS 8
2.4 STUDY DESIGN 9
2.5 STUDY SCHEMATIC 12
2.6 SAMPLE SIZE JUSTIFICATION 13

3 DEFINITIONS **14**

3.1 DATES AND POINTS OF REFERENCE 14
3.2 STUDY TREATMENT 15
3.3 KEY DERIVED VARIABLES 15
3.4 STRATIFICATION FACTORS AND SUBGROUP VARIABLES 19
3.5 ANALYSIS SETS 20

4 LIST OF PLANNED STUDY ANALYSES **22**

4.1 INTERIM ANALYSIS 22
4.2 FINAL ANALYSIS 22

5 STATISTICAL ANALYSIS METHODS **22**

5.1 GENERAL CONSIDERATIONS 22
5.2 STUDY SUBJECTS 22
5.2.1 Accounting of Subjects *22*
5.2.2 Demographics and Baseline Characteristics *23*
5.2.3 Concomitant Medications and Non-drug Therapies *24*
5.2.4 Protocol Deviations *25*
5.2.5 Study Drug Exposure and Study Drug Compliance *25*
5.2.6 COVID-19 Related Analysis *25*
5.2.6.1 Accounting of subjects who discontinued due to Covid-19 25
5.2.6.2 Concomitant Non-Drug Treatment for Covid-19 26
5.2.6.3 Covid-19 Effect on Drug Compliance 26
5.2.6.4 Covid-19 Protocol Deviation 26
5.2.6.5 Protocol Alternation Due to Covid-19 26
5.3 EFFICACY ANALYSIS 26
5.3.1 General Considerations *26*
5.3.1.1 Covid-19 consideration 27
5.3.2 Considerations for base MMRM model for change from baseline analyses *28*
5.3.3 Primary Efficacy Endpoint *28*
5.3.3.1 Primary analysis 28
5.3.3.2 Sensitivity analysis 29
5.3.3.3 Per-protocol analysis 31
5.3.4 Exploratory Efficacy Endpoints *32*
5.3.5 Subgroup Analysis *32*
5.3.6 Additional Analysis *32*
5.3.6.1 CDR Subscores, CDR Global Score, ADCS-bADL, ADCS-iADL and individual scores for CDR, ADCS-ADL and ADAS-Cog 13 32
5.3.6.2 Slope analysis 33
5.3.6.3 Summary of CDR-SB, ADAS-Cog 13 total score, and MMSE by tau PET reduction at Week 78 33
5.3.6.4 Responder analysis of CDR-SB 34
5.4 SAFETY ANALYSIS 34
5.4.1 General Considerations *34*
5.4.1.1 Analysis Set 34
5.4.1.2 Safety treatment groups 34
5.4.1.3 Incidence, incidence proportion and incidence rate 35

5.4.2 Clinical Adverse Events *35*
5.4.2.1 Treatment-emergent AEs (TEAEs) 35
5.4.2.2 Summary and incidence analysis 36
5.4.2.3 Incidence rate analysis 37
5.4.2.4 Infusion reactions 38
5.4.2.5 Adverse event of special interest 38
5.4.3 Clinical Laboratory Data *38*
5.4.3.1 Quantitative analyses 39
5.4.3.2 Qualitative analyses 39
5.4.4 C-SSRS Data *41*
5.4.5 ECG Data *41*
5.4.6 Vital Sign Data *42*
5.4.7 Physical Examination *43*
5.4.8 Neurological Examination *43*
5.4.9 Safety MRI Data *43*
5.4.10 COVID-19 Related Safety analysis *44*
5.5 PHARMACOKINETICS ANALYSIS 44
5.5.1 Serum and CSF PK Concentration Data *45*
5.5.2 Serum PK Parameters *45*
5.6 BIOMARKER 46
5.6.1 Pharmacodynamics Analysis *46*
5.6.2 Structural MRI Analysis *47*
5.6.2.1 By visit summary and MMRM model 47
5.6.2.2 Pearson and Spearman correlation 47
5.6.3 Tau PET Analysis *47*
5.6.3.1 Tau PET substudy 47
5.6.3.2 Tau PET target and reference regions 48
5.6.3.3 Tau PET primary analysis 48
5.6.3.4 Correlation between Tau PET vs. Cognitive results and other assessments 49
5.6.3.5 Subgroup analysis 50
5.7 ANTI-DRUG ANTIBODY ANALYSIS 50
5.7.1 Analysis Methods for Anti-drug antibody Data *50*
5.8 HEALTH OUTCOMES 51
5.8.1 QoL-AD and ZBI *51*
5.8.2 RUD-Lite *51*

6 CHANGES FROM PROTOCOL-SPECIFIED ANALYSES 53

6.1 MMRM MODEL 54
6.2 MCP-MOD MODEL 54

7 APPENDIX I: VISIT WINDOW MAPPING 55

8 APPENDIX II: DESCRIPTION OF MCP-MOD METHOD 59

9 APPENDIX III: QUESTIONNAIRE 60

9.1 CLINICAL DEMENTIA RATING SCALE (CDR) 60
9.2 MINI-MENTAL STATE EXAMINATION (MMSE) 60
9.3 INTERNATIONAL SHOPPING LIST TEST IMMEDIATE RECALL (ISLT) 60
9.4 DELIS-KAPLAN EXECUTIVE FUNCTION SYSTEM (DKEFS) 61
9.5 DIGIT SYMBOL SUBSTITUTION TEST (DSST) 61
9.6 TRAIL MAKING TEST, PART A (TRAIL A) 62
9.7 EVERYDAY COGNITION (ECOG) 62
9.8 ALZHEIMER'S DISEASE COOPERATIVE STUDY – ACTIVITIES OF DAILY LIVING (ADCS-ADL) 63
9.9 FUNCTIONAL ACTIVITIES QUESTIONNAIRE (FAQ) 63
9.10 ALZHEIMER'S DISEASE ASSESSMENT SCALE –COGNITIVE (13 ITEM) (ADAS-COG 13) 63
9.11 NEUROPSYCHIATRIC INVENTORY – 10 (NPI-10) 63
9.12 ZARIT BURDEN INTERVIEW (ZBI) 64
9.13 QUALITY OF LIFE FOR ALZHEIMER'S DISEASE (QOL-AD) 64
9.14 RESOURCE UTILIZATION IN DEMENTIA-LITE VERSION (RUD-LITE) 64

10 APPENDIX IV: ADVERSE EVENT OF SPECIAL INTEREST CUSTOM SEARCH CRITERIA 66

11 APPENDIX V: INFUSION REACTIONS CUSTOM SEARCH 67

12 REFERENCES 68

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
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ApoE	Apolipoprotein E
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
CIR	Copy Increment from Reference
C_{max}	Observed Maximum Serum BIIB092 Concentration
C_{min}	Observed Minimum Serum BIIB092 Concentration
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
eCRF	Electronic Case Report Form
ICE	Intercurrent Event
ICH	International Conference on Harmonisation
INR	Prothrombin Intl. Normalized Ratio
IRT	Interactive Response Technology
LS	Lease Square Mean

iADRS	The Integrated Alzheimer's Disease Rating Scale
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	Macrohemorrhage
MCI	Mild Cognitive Impairment
MCMC	Markov Chain Monte Carlo
MCP-MOD	Multiple Comparison Procedure - Modelling
MedDRA	Medical Dictionary for Regulatory Activities
mH	Microhemorrhages
MMRM	Mixed-Model Repeated Measures
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NIA-AA	National Institute on Aging-Alzheimer's Association
NPI-10	Neuropsychiatric Inventory-10
PCS	Potentially Clinically Significant
PD	Pharmacodynamics(S)
PET	Positron Emission Tomography
pH	Potential of Hydrogen
PLS	Partial Least Squares
PMM	Pattern Mixture Model
PK	Pharmacokinetic(S)
PPS	Per-Protocol Analysis Set
PT	Preferred Term
PT	Prothrombin Time
Qol-AD	Quality of Life for Alzheimer's Disease
QTcF	Corrected QT Interval by Fredericia
RC_{min}	Accumulation Ratio Using C_{min}
RC_{max}	Accumulation Ratio Using C_{max}
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) only covers the analyses for the primary, secondary and exploratory objectives for the placebo-controlled period of 251AD201. Hereafter, the placebo-controlled period 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 LTE period and integrated analyses across both portions of the study.

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 Study Overview

2.1 Primary Objective and Endpoint

The primary objective of the study for the placebo-controlled period is to evaluate the safety and tolerability of BIIB092 in participants with MCI due to AD or with mild AD.

The primary safety endpoints that relate to this objective are the incidence of adverse events (AEs) and serious AEs (SAEs) during the placebo-controlled period.

2.2 Secondary Objectives and Endpoints

- To evaluate the efficacy of multiple doses of BIIB092 in slowing cognitive and functional impairment in participants with MCI due to AD or with mild AD as measured by the change from Baseline over time at Week 78 on the Clinical Dementia Rating Scale (CDR) -Sum of Boxes (CDR-SB). This is the primary efficacy objective, with the primary efficacy endpoint.
- To 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 90.

2.3 Exploratory objectives and endpoints

- To assess the effect of BIIB092 on the clinical progression of AD as measured by changes from Baseline over time up to Week78 on the Mini-Mental State Examination (MMSE), International Shopping List Test Immediate Recall (ISLT), Category Fluency and Letter Fluency tests from the Delis-Kaplan Executive Function System (DKEFS), Digit Symbol Substitution Test (DSST), Trail Making Test Part A(Trails A), Everyday Cognition(eCog), Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), Functional Activities Questionnaire (FAQ), Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog13 [13item]), and Neuropsychiatric Inventory-10 (NPI-10).

- To assess the effect of BIIB092 on changes in caregiver burden and participant quality of life as measured by changes from Baseline over time up to Week 68 on the Zarit Burden Interview (ZBI) and Quality of Life for Alzheimer's Disease (QoL-AD).
- To assess the effect of BIIB092 on resource utilization as measured by the Resource Utilization in Dementia-Lite (RUD-Lite) Version results over time up to Week 68.
- To assess BIIB092 pharmacokinetics (PK) in serum (trough serum BIIB092 concentrations and end-of-infusion serum BIIB092 concentrations) from the samples collected at the visits indicated in the Schedule of Activities in participants with MCI due to AD or with mild AD.
- To assess BIIB092 PK in CSF from the samples collected at the visits indicated in the Schedule of Activities in participants with MCI due to AD or with mild AD who consent to participate in the CSF sampling substudy.
- To assess the effect of BIIB092 on tau protein concentrations in CSF (in subjects consenting to participate in the CSF sampling substudy) as measured by changes from Baseline over time up to Week 76 in CSF N-terminal eTau concentration.
- To assess the effect of BIIB092 on biomarkers in blood as measured by changes from Baseline over time up to Week76 on blood levels of disease-related biomarkers, including but not limited to, tau and other markers of neurodegenerative disease.
- To assess the effect of BIIB092 on disease-related biomarkers in CSF (only for participants who consent to participate in the CSF sampling substudy) as measured by changes from Baseline over time up to Week76 in disease-related CSF biomarkers, including but not limited to, phosphor-tau, neurogranin, and neurofilament (neurofilament light and phospho-neurofilament heavy).
- To assess the effect of BIIB092 on cerebral tau changes (in participants consenting to participate in the tau positron emission tomography [PET] substudy) as measured by changes from Baseline over time up to Week 78 on ^{18}F-MK6240 PET binding signal in certain brain regions.
- To assess the effect of BIIB092 on brain structure as measured by changes from Baseline over time up to Week 78 on magnetic resonance imaging (MRI) morphometric measures, including volume of certain brain areas.

2.4 Study Design

Study 251AD201 (TANGO) is a Phase 2, randomized, double-blind, placebo-controlled study of BIIB092 in subjects aged 50 to 80 years inclusive, with MCI due to AD or mild AD according to National Institute on Aging-Alzheimer's Association criteria (NIA-AA). Subjects must have Aβ positivity confirmed at Screening by either CSF sampling or an amyloid PET scan. Subjects must also perform at 1 standard deviation (SD) below the age-adjusted normative mean on either the ISLT or the International Shopping List Test Delayed Recall (ISLR) and have a Clinical 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 ≥0.5.

The study is conducted in a parallel-group design, with 3 BIIB092 dose groups (including 4 BIIB092 doses) and a placebo group. Approximately 528 subjects was planned to be randomized across approximately 90 study sites globally. Subjects were stratified by tau PET/CSF sampling substudy enrollment (see substudy description below), region, baseline disease stage (MCI or mild AD), and baseline AD symptomatic medication use. Subjects who enroll in both substudies will be considered as enrolled in the tau PET substudy for randomization purposes.

The study consists of a double-blind, placebo-controlled period and a dose-blinded 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. The 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 End-of-Study (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. However, the Screening Period for the placebo-controlled period may be extended up to 90 days in consultation with the Medical Monitor in advance and provided that written documentation is received from the Sponsor or delegate (e.g., for logistical issues such as PET radioligands). At the end of the placebo-controlled period, participants who meet the LTE entry criteria may enter the dose-blinded LTE period. The LTE period comprises an LTE Screening Period of approximately 4 weeks starting at Week 76, a 144-week Treatment Period, 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.

Randomized participants will receive 1 of the following study treatments by IV infusion, starting on Study Day 1 during the placebo-controlled period:

- low-dose BIIB092 -125mg once every 4 weeks or 375mg once every 12 weeks and placebo at the other 4-week dosing visits to maintain the treatment blind (88 subjects in total, 44 per regimen)
- medium-dose BIIB092 -600mg once every 4 weeks (88 subjects)
- high-dose BIIB092 -2000mg once every 4 weeks (176 subjects)
- placebo (176 subjects)

Overall, participants will have a 2:1 chance of being randomized to BIIB092 or to placebo during the placebo-controlled period.

During the LTE period, 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 receiving placebo during the placebo-controlled period will receive BIIB092 at the high dose (2000 mg) once every 4 weeks during the LTE period. The BIIB092 dose concentration (i.e. low, medium, or high) to which participants are assigned to receive during LTE period may be changed based on emerging data from the BIIB092 clinical development program.

Throughout the study, all participants should be observed and monitored by study staff for a minimum of 1 hour after the end of an infusion. Participants who experience an AE or SAE related to BIIB092 infusion should remain at the site or be sent to an inpatient monitoring

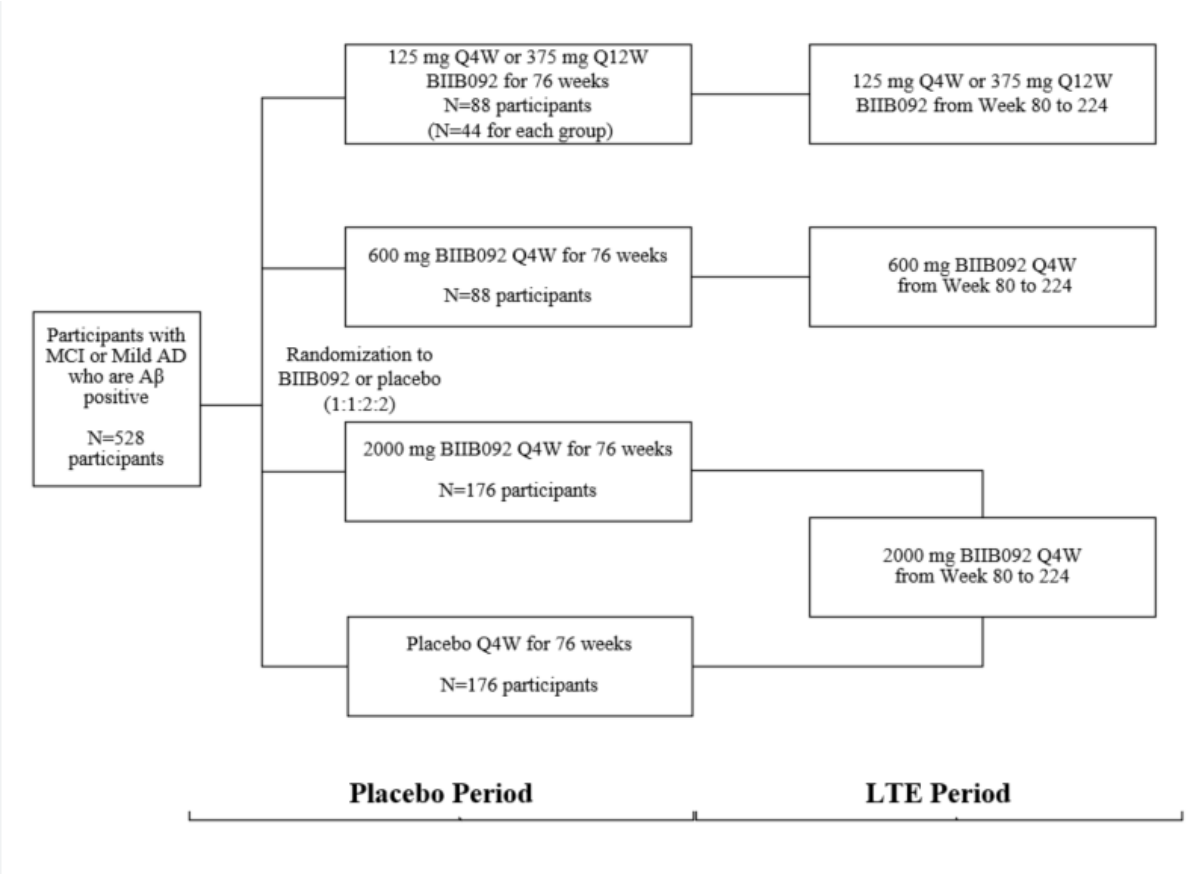
facility until the Investigator has determined that the event(s) has resolved or do not require further monitoring at the site or in an inpatient setting.

Investigators, study staff (except for a designated Pharmacist/Technician), and study subjects and their families, caregivers, legal representatives will be blinded to the subjects' randomized treatment assignments.

This 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 ^{18}F-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 will be encouraged. Participants may withdraw consent to participate in the substudies at any time.

2.5 Study Schematic

Figure 1. Study Design with Planned Sample Size



Aβ = amyloid beta; AD = Alzheimer's disease; EOS = End of Study; LTE = long-term extension; MCI = mild cognitive impairment; N = planned 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.

2.6 Sample Size Justification

There was no formal sample size calculation for the primary endpoint of safety.

The planned sample size is 528 subjects, randomized in a 1:1:2:2 ratio, with 88 subjects assigned to the BIIB092 low-dose group (44 assigned to 125mg once every 4weeks and 44 assigned to 375mg once every 12 weeks), 88 subjects assigned to the medium-dose group (600mg once every 4weeks), 176 subjects assigned to the high-dose group (2000mg once every 4 weeks), and 176 subjects assigned to the placebo group. This sample size provides approximately 80% power to detect a dose-response relationship in the change from baseline in CDR-SB (primary efficacy endpoint) at 18 months (Week 78), assuming a mean change of 1.99 from baseline in CDR-SB at 18 months in the placebo group and a common SD of 2.38, a maximal 40% reduction for the highest BIIB092 dose group compared with the placebo group, and an estimated 20% dropout rate at 18 months (Week 78) in this study. Six different dose-response relationships will be tested at the 2-sided 5% significance level, using the MCP-MOD method to control for multiplicity. Optimal contrasts will be constructed to detect potential dose-response trends under common dose-response curves (e.g., Emax, exponential, logistic, linear in log dose, and quadratic model) which are illustrated with the parameters shown in Figure2.

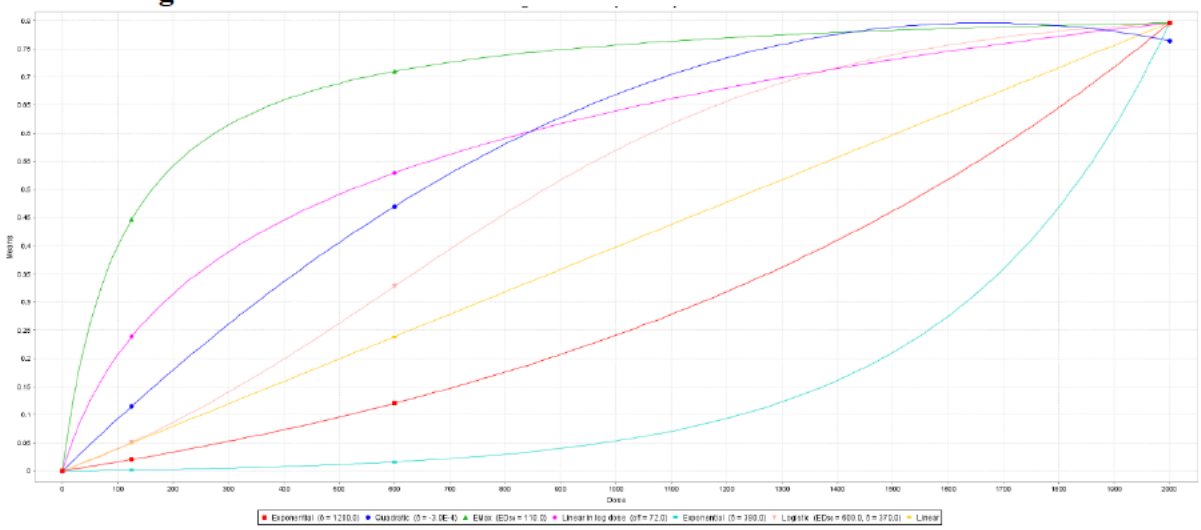
The mean and SD of the change from baseline in CDR-SB at 18 months for the placebo group is based on available Alzheimer's Disease Neuroimaging Initiative (ADNI) data from ADNI1, ADNI2, and ADNI GO (amyloid positive from amyloid PET or CSF, MMSE ≥22, CDR global score of 0.5 for late MCI and 0.5 or 1 for mild AD).

Based on mean changes in tau PET from Baseline to 9 months and 18 months in the Longitudinal Flortaucipir A05 study, it is assumed, by linear extrapolation, that the mean (SD) change from Baseline to 12 months (Week 52) for the placebo group in this study is assumed to be 0.034(0.033). Following the same MCP-MOD method under the same dose-response curves and parameters, the planned sample size for the tau PET substudy is 330 subjects, in a 1:1:2:2 randomization ratio, with 55 subjects assigned to the BIIB092 low-dose group (27 assigned to 125mg once every 4weeks and 28 assigned to the 375 mg once every 12weeks), 55 subjects assigned to the medium-dose group (600 mg once every 4weeks), 110 subjects assigned to the high-dose group (2000 mg once every 4weeks), and 110 subjects assigned to the placebo group to provide approximately 80% power to detect a maximal 40% reduction (mean change of 0.0136) and a common SD (0.033) for the highest BIIB092 dose group compared with the placebo group, with an estimated 15% dropout rate at 12 months (Week 52). Similarly, 6 different dose-response relationships will be tested at the 2-sided 5% significance level using the MCP-MOD method to control for multiplicity.

There was no formal sample size calculation for the CSF sampling substudy.

Sample size re-estimation was not done. However, blinded power was re-evaluated based on final randomized number of subjects after enrollment completed. Detailed information was documented in Note to File (251ad201 NTF_power re-estimation in CMF).

Figure 2 Dose-Response Shapes based on Clinical Dementia Rating Scale – Sum of Boxes Mean Change from Baseline at Week 78



ED_{50} = median effective dose; Emax = maximum response
Note: This figure was generated using ADDPLAN® DF Version 3.1.8, by Aptiv solutions.

3 Definitions

3.1 Dates and Points of Reference

- Study Day 1: the date of the first dose of study treatment
- 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)

- Baseline value is defined as the most recent non-missing measurement collected prior to the first dose, unless otherwise specified
- Change from baseline will be defined as post-baseline value minus baseline value
- Percent change from baseline will be defined as post-baseline value minus baseline value then divided by baseline value
- Visit windows for analysis:

  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

3.2 Study Treatment

For efficacy, health outcome, statistical modeling of fluid PD and imaging biomarker analyses, the following treatment groups of BIIB092 (per randomization) will be evaluated and compared with placebo:

- Placebo
- low-dose BIIB092 -125mg once every 4weeks or 375mg once every 12weeks
- medium-dose BIIB092 - 600mg once every 4 weeks
- high-dose BIIB092 - 2000mg once every 4 weeks

The following treatment groups of BIIB092 will be evaluated for other analyses, such as study subject accounting, safety, fluid PD biomarkers and PK analyses, low dose group will be split out for different frequencies. If determined necessary, statistical modeling of fluid PD biomarkers may be conducted using the following treatment groups, as well.

- Placebo
- low-dose BIIB092 -125mg once every 4weeks
- low-dose BIIB092 - 375mg once every 12weeks
- medium-dose BIIB092 - 600mg once every 4 weeks
- high-dose BIIB092 - 2000mg once every 4 weeks

3.3 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. Following the similar idea, for ADCS-iADL, if 6 or fewer out of 26 items are missing, the score will be imputed. For ADCS-bADL, if only 1 out of 6 items is missing, the total score will be imputed.
  - 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 exploratory 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 56). Because higher score on the ADAS-Cog13 reflect worse performance, whereas higher scores on the iADCS-ADL 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 141 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 total correct score, DSST total score, Trails A total time to complete) will be z-score transformed using the baseline score's mean and SD. For Trails A total time to complete, negative one (-1) will be multiplied when calculate the z-score. The EMACC score will be computed by taking the average of the z-scores across the five tests. Since the direction of Trails A total time to complete will be reversed, the higher EMACC score means cognitive improvement. 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 scale's items using the corresponding PLS coefficients as weighting factors as listed in Table 1 [Wang et al. 2016]. The lower ADCOMS score shows clinical improvement. 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.

The formula for ADCOMS composite score is as below:

ADCOMS = ADCDRL * 0.008 + ADCOR * 0.017 + ADCRG * 0.004 + ADCDIF * 0.016 + (5 – MMS101) * 0.042 + (1 – MMS111) *0.038 + CDR0106 * 0.054 + CDR0104 * 0.109 + CDR0105 * 0.089 + CDR0103 * 0.069 + CDR0101 * 0.059 + CDR0102 * 0.078

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

Scale	Item ID	Item name	PLS coefficients
ADAS-cog	ADCDRL	Delayed word recall	0.008
	ADCOR	Orientation	0.017
	ADCRG	Word recognition	0.004
	ADCDIF	Word finding difficulty	0.016
MMSE	MMS101	Orientation time	0.042
	MMS111	Drawing	0.038
CDR-SB	CDR0106	Personal care	0.054
	CDR0104	Community affairs	0.109
	CDR0105	Home and hobbies	0.089
	CDR0103	Judgement and problem solving	0.069
	CDR0101	Memory	0.059
	CDR0102	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.

- Adjusted structural MRI volume (% of TIV)

The adjusted structural MRI volume is defined as the percentage of ROI volume to the total intracranial volume (TIV). For example, the adjusted lateral ventricles volume at week 78 = (lateral ventricles volume at week 78/TIV) * 100%. The TIV (total intracranial volume) is measured at baseline and kept the same for all post-baseline visit.

3.4 Stratification Factors and Subgroup Variables

Stratification factors are:

- Tau PET/CSF 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), and Poland]
- Baseline disease stage (MCI or mild AD)
- Baseline AD symptomatic medication use (Yes or No)

Subgroup variables for the subgroup analysis in efficacy (Section 5.3.5)

- Baseline clinical stage (MCI due to AD or mild AD) per the Investigator's assessment based on the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria
- Tau level at baseline measuring by tau PET (e.g. SUVR in primary target regions with primary reference region), CSF p-tau, or blood p-tau
- TIV adjusted hippocampal volume at baseline (quartiles of total hippocampal volume expressed as a % of TIV)
- Laboratory ApoE ε4 status (carrier/non-carrier)
- Use of AD symptomatic medication at baseline (yes or no)
- Age category (e.g. < 65, 65-<70, 70-<75, >=75)
- Gender (female or male)
- MMSE at baseline (e.g. ≥ median MMSE score at baseline vs. < median MMSE score at baseline)
- CDR global score at baseline (0.5 vs 1)
- Health Care Regions (US vs. other countries):
  - US
  - Non-US (Australia, Japan, France, Germany, Italy, Spain, Sweden, and Poland)

  * may analyze a country or countries separately if their data is not consistent comparing to other countries within the same category

Additional subgroup variables for subgroup analysis in efficacy:

- Magnitude of change on tau PET measures for the primary targets and reference regions at Week 78:
  - Change from baseline less than (mean - one standard deviation) of the placebo group at Week 78 vs.
  - Change from baseline greater than or equal (mean - one standard deviation) of the placebo group at Week 78

Subgroup variables for the subgroup analysis in Tau PET (Section 5.6.3.5) for primary target regions [Braak 1 and 2, Braak 3 and 4, Braak 5 and 6] with primary reference region (Cerebellum [superior section eroded]). Other target regions and reference regions may be explored.

- Baseline clinical stage (MCI due to AD and mild)
- Tau PET level at baseline (e.g. quartiles),

- Baseline amyloid PET level (where available), for Amyloid Composite ROI SUVR measure as the target region with Cerebellum as the reference region using florbetapir tracer only [e.g. quartiles] (subjects who provided baseline amyloid level)
- Use of AD symptomatic medication at baseline (yes or no)
- Age category (e.g. < 65, 65-<70, 70-<75, >=75)
- Gender (female or male)
- MMSE at baseline (e.g. > median MMSE score at baseline vs. < median MMSE score at baseline)

In addition, the following subgroup analysis may be explored for analysis:

- AD symptomatic concomitant medication change during the study duration (Yes vs. No)
- Subjects who received >=10 infusions vs subjects who received <10 infusions
- Baseline ISLT score
- Time since AD diagnosis
- Time since AD symptom onset

3.5 Analysis Sets

- 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).

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

- Per-Protocol Analysis Set:
  The Per-Protocol Analysis Set is defined as all subjects in the FAS and
  - had no violations of the following inclusion criteria:
    - Must have evidence of cerebral Aβ accumulation, as determined by an amyloid PET scan or by CSF testing
    - Must have the following at baseline:
      - CDR global score of 0.5 or 1
      - MMSE score of 22 to 30 (inclusive)
      - CDR Memory Box score of ≥0.5
  - had at least 14 infusions

  - did not miss ≥4 infusions consecutively
  - did not make any change to concomitant AD symptomatic medications during the study

- 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.

- 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 PCP.

- 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.

- Blood PD Evaluable Set:
  The blood PD Evaluable Set is defined as subjects in the FAS who had baseline and at least one post baseline assessment of the specific parameter being analyzed in blood before the End of Study of PCP.

- 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.

- Structural MRI Evaluable Set:
  The Structural MRI Evaluable Set is defined as subjects in the FAS who have an evaluable baseline and a post-baseline structural MRI scan.

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

4 List of Planned Study Analyses

4.1 Interim Analysis

The protocol of 251AD201 covers PC and LTE periods. Therefore, end of PC period analysis will be considered as an interim analysis for this protocol. All planned analyses in this SAP will be finalized.

At the time of PC database lock, an interim analysis of LTE period will be conducted. A separate SAP will be prepared for the analyses of the LTE period and integrated analyses across both portions of the study.

4.2 Final analysis

At the end of the long-term extension after which the study will be finally locked and analyzed.

5 Statistical Analysis Methods

5.1 General Considerations

Summary tables will be presented using descriptive summary statistics. For continuous variables, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, 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. Unless otherwise specified, summary tables will be presented by treatment group: placebo, BIIB092 125 mg/4wk, BIIB092 375 mg/12wk, BIIB092 600 mg/4wk, BIIB092 2000 mg/4wk, and total. All of the listings will be presented by treatment group, unless otherwise specified.

5.2.1 Accounting of Subjects

Disposition of subjects will be summarized and the summary data will include number (%) of subjects randomized and dosed, number (%) of subjects in each analysis set, number (%) of subjects who completed the treatment/study, number (%) of subjects who are active in the treatment period, number (%) of subjects who discontinued treatment and/or withdrew from study, and number (%) of subjects who discontinued treatment yet completed the placebo-controlled period. For subjects who discontinued treatment and/or withdrew from study, the reasons for discontinuation and/or withdrawal will be summarized and listed. Subjects excluded from the per-protocol analysis set will also be listed.

In addition, the following will be summarized for country, substudies (CSF and Tau PET), and baseline clinical stage (MCI and Mild):

- Number of subjects dosed
- Number of subjects who completed treatment
- Number of subjects who completed the study

5.2.2 Demographics and Baseline Characteristics

The demographic data including age, gender, ethnicity, race, height, weight, body mass index (BMI), years of formal education, substudy enrollment, and region will be summarized. Age will also be categorized and presented using the following grouping: < 65, 65-<70, 70-<75, >=75. In addition, Asian group will also be summarized for the following subclassification: Chinese, Indian, Japanese, Korean, and other.

Summary of the baseline characteristics of AD includes baseline clinical stage (MCI due to AD or mild AD), years since first AD symptom(s), years since diagnosis of AD, laboratory ApoE status (carrier, non-carrier, and undetermined), baseline AD symptomatic medication use (yes or no; see Section 4.2.3 for definition of AD symptomatic medication use at baseline), ISLT raw score, ISLT z-score, ISLR raw score, ISLR z-score, CDR global score, CDR memory box score, CDR sum of boxes score, CDR cognitive subscore, CDR functional subscore, MMSE, ADAS-Cog 13, ADCS-ADL, ADCS-iADL, ADCS-bADL, EMACC, ADCOMS and iADRS. ApoE carrier will be further classified as homozygote and heterozygote. MMSE will also be categorized by the following subgroups: <22, 22-24, 25-27, and 28-30. Baseline Amyloid PET level will be summarized for Amyloid Composite ROI SUVR measure as the target region with Cerebellum as the reference region, using florbetapir tracer only.

Subject listings will be generated for demographics and baseline characteristics.

The same summary will be also conducted for MCI subjects, Mild subjects, tau PET evaluable set (including subjects enrolled in both tau PET and CSF substudies) and CSF PD evaluable set.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 23.1). The number (%) of subjects with history (including both ongoing and not ongoing medical conditions) will be summarized by system organ class and preferred term. A listing of medical history will be generated.

Previous treatment of AD stopped prior to the date of first infusion, duration of previous therapies and reason for stopping treatment will be summarized by treatment group. Listing of previous AD treatment will also be generated.

Note that ApoE status is defined as below:

- ApoE carrier: E2/E4, E3/E4, E4/E4
    - Heterozygote: E2/E4, E3/E4
    - Homozygote: E4/E4
- ApoE non-carrier: E2/E2, E2/E3, E3/E3

5.2.3 Concomitant Medications and Non-drug Therapies

All concomitant medications will be coded using the World Health Organization (WHO) medication dictionary (version: WHODrug Globa B3 MAR20). All concomitant non-drug therapies will be coded using the MedDRA dictionary. A concomitant medication/therapy will be defined as any therapy that was taken on or after the day of the first dose of study drug. This 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 non-concomitant.

For a therapy with a partial start and/or stop date, the following imputation method will be used to determine if the event is concomitant:

- If the start day is missing, then impute the first day of the month (01) as the day
- If the start day and month are missing then impute the first day of the year (01January) as the start day
- If the stop day is missing then impute the last day of the month as the day
- If the stop day and month are missing then impute the last day (31December) of the year as the stop day

The number (%) of subjects taking concomitant medication and non-drug therapies will be summarized by treatment group. Listings of concomitant medications and non-drug therapies will be presented.

AD symptomatic medications taken concomitantly at baseline are defined as AD symptomatic 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 AD symptomatic medications concomitantly at baseline will be summarized. Subjects who have any new or change in AD symptomatic medications after the initiation of study treatment will be summarized by the timing of change, i.e., the number of subjects first changing between Day 1 and Week 24, the number of subjects changing between Week 24 and Week 52, etc., subjects who have changes in multiple intervals may be counted in each interval. The start and stop date/time of AD symptomatic medication will be listed for these subjects.

AD symptomatic medications including the following terms will be considered:

Anticholinesterases, Donepezil, Donepezil hydrochloride, Galantamine, Galantamine hydrobromide, Huperzine A, Mimopezil, Nivabex, Rivastigmine, Rivastigmine tartrate, Robinulneostigmine, Tacrine, Tacrine hydrochloride, Mortha, Energix, Memantine, Memantine hydrochloride, Donamem, and Gemcitabine Hydrochloride.

5.2.4 Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a Protocol Deviation log and categorized as major or minor deviations based on Protocol Deviation Classification. The major protocol deviations will be summarized and listed. The minor protocol deviations will also be listed. Subjects who had incorrect dose assigned by interactive response technology (IRT) will be summarized and listed. This data will be provided by the unblinded monitors after database lock.

5.2.5 Study Drug Exposure and Study Drug Compliance

Number of infusions (BIIB092 or placebo) received will be summarized as a categorical variable (categories as integers from 1 to 20, and 1-5, 6-10, 11-15, and 15-20) as well as a continuous variable. Number of consecutively missed infusions will be summarized as a categorical variable (categories as consecutively missed 2, 3, 4, >=5). Number of weeks on study treatment (BIIB092 or placebo), 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 >= 72 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 by treatment group.

A listing of study drug administration records, including dose level at each infusion, cumulative number of infusions and cumulative dose will be provided.

A listing of study drug administration records for placebo subjects who received any doses of active treatment will be provided.

5.2.6 COVID-19 Related Analysis

5.2.6.1 Accounting of subjects who discontinued due to Covid-19

Disposition of subjects will be summarized for subjects who discontinued due to Covid-19. The summary data will include number (%) of subjects who died due to Covid-19, AE due to Covid-19 and all the other reasons which led to discontinue treatment and/or study because of Covid-19.
For subjects who discontinued treatment and/or withdrew from study due to covid-19, the reasons for discontinuation and/or withdrawal will be listed with days on treatment and days on study.

5.2.6.2 Concomitant Non-Drug Treatment for Covid-19

The number (%) of subjects using concomitant Non-Drug Treatment for Covid-19 will be summarized by treatment group.
Date imputation will be done as per Section 5.2.3

5.2.6.3 Covid-19 Effect on Drug Compliance

Effect of Covid-19 on Drug compliance may be assessed by a summary table. Total number of expected infusions, Number of Missed doses due to covid-19, Average missed dose per subject with its SD, Number of infusions delayed, Average delay in dosing per subject with its SD, and Number of alternate methods of infusion due to covid-19, Average alternate dosing per subject with its SD may be presented.

5.2.6.4 Covid-19 Protocol Deviation

Covid-19 protocol deviation will be summarized. Number of subjects with any protocol deviation, list of Major protocol deviation including Non-Data protocol deviation, Not done, Out of window, Performed at alternate location, Performed by caregiver, Performed remotely, Self-administered, Rater change and Other will be presented.
PD due to covid-19 will be listed including all major and minor deviations by treatment group and subject. Type of PD, PD category, PD text and deviation day will be presented in the listing.

5.2.6.5 Protocol Alternation Due to Covid-19

Protocol alternation due to covid-19 will be listed by treatment group and subject. Type of protocol alternation, Protocol alternation category, Protocol alternation text and Alternation day will be presented in the listing.

5.3 Efficacy Analysis

5.3.1 General Considerations

The efficacy analysis will be presented by treatment group (per randomization). The change from baseline scores of primary efficacy and exploratory efficacy endpoints will be summarized by treatment group at each post-baseline visit for FAS.

The primary, sensitivity, supplementary and additional analyses for the primary efficacy and exploratory efficacy secondary endpoints are listed in Table 2.

Table 2. Analysis for Primary efficacy and exploratory efficacy Endpoints

Endpoint	Analysis	Analysis Set
CDR-SB	Primary: Analysis of change from baseline at Week 78 (MMRM)	FAS

	Primary: Dose-response (MCP-MOD)	FAS
	Sensitivity: Censoring after intercurrent events (MMRM), Pattern mixture model; copy increment from reference (CIR) method	FAS
	Per-protocol analysis (MMRM)	Per-Protocol
	Additional: Responder analysis (Logistic regression)	FAS
	Subgroup analysis	FAS
	Slope analysis	FAS
MMSE, ADAS-Cog13, ADCS-ADL, ISLT, eCog, FAQ	Primary: Analysis of change from baseline at Week 78 (MMRM)	FAS
	Primary: Dose-response (MCP-MOD) [(1)]	FAS
	Subgroup analysis [(2)]	FAS
	Slope analysis	FAS
EMACC, ADCOMS, iADRS	Primary: Analysis of change from baseline at Week 78 (MMRM)	FAS
	Subgroup analysis	FAS
CDR individual domain score, CDR Cognitive score, CDR functional score, ADCS-ADL individual item score, ADCS-bADL, ADCS-iADL, ADAS-Cog 13 individual item score, NPI-10, ISLT, DKERS, DSST and Trails A	Analysis of change from baseline at Week 78 (MMRM)	FAS

[(1)] MCP-MOD may be conducted for eCog, FAQ, and other endpoints as exploratory analysis.
[(2)] Subgroup analysis will only be conducted for MMSE, ADAS-Cog13, ADCS-ADL.

5.3.1.1 Covid-19 consideration

If a participant and his/her study partner is unable to attend a scheduled study visit, selected prioritized clinical assessments (e.g. CDR, ADCS-ADL, ISLT, DKEFS CFT and LFT, CSSRS) may be able to be performed via telephone. These assessments will be included in efficacy analysis.

5.3.2 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 treatment, time, treatment-by-time interaction, baseline of the parameter of interest, baseline of the parameter of interest-by-time interaction, baseline MMSE, region (Japan and Australia will be combined), disease stage (MCI versus mild AD), 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 treatment group versus placebo at post-baseline visits, 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].

5.3.3 Primary Efficacy Endpoint

5.3.3.1 Primary analysis

Estimand 1: The difference in change from baseline CDR-SB scores at Week 78 in subjects assigned to BIIB92, comparing to placebo group, regardless of what actual treatment is received, acknowledging a participant may miss ≥4 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 Week 78 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 ≥ 4 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. The primary analysis is the mean difference of the change from baseline CDR-SB scores at Week 78 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]. 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.

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. A line plot of adjusted mean change from baseline over time will be provided.

The multiple comparison procedure modelling (MCP-MOD) method (Appendix II) will be used to assess and model dose-response relationships (potential candidate models will include linear, linear-log, quadratic, maximum response [Emax], and logistic models as specified in protocol Section 16.10) while controlling for multiplicity. The dose-response parameter of interest for MCP-MOD will be the LS means at Week 78 for each dose group from the mixed-effects model. Pairwise comparisons of each BIIB092 dose group versus placebo will also be conducted. A line plot of final dose-response relationship may be provided.

If model assumption for MMRM does not hold, nonparametric analysis will be conducted.

5.3.3.2 Sensitivity analysis

The following sensitivity analyses may 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 FAS.

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:
  - withdrawal by subject - desire for change in treatment (unrelated to safety)
  - withdrawal by subject – other
  - withdrawal by caregiver - desire for change in treatment (unrelated to safety)
  - withdrawal by caregiver - unable to continue to enable participation due to illness/hospitalization/death
  - withdrawal by caregiver - other
  - physician decision - unrelated to safety
  - death
  - non-compliance with study drug treatment
  - disease progression
  - other
- Subjects who withdraw due to reasons that are unlikely related to efficacy, including:
  - adverse event
  - randomized by mistake
  - lost to follow-up

- pregnancy
- withdrawal by subject - planning for pregnancy
- withdrawal by subject - study visit burden/scheduling conflicts
- withdrawal by subject - concern about study procedures/perceived risks
- withdrawal by subject - relocation (moving or has moved)
- withdrawal by caregiver - study visit burden/scheduling conflicts
- withdrawal by caregiver - concern about study procedures/perceived risks
- withdrawal by caregiver -relocation (moving or has moved)
- protocol deviation
- site terminated by sponsor
- study terminated by sponsor
- technical problems

The pattern (time and rate) of study withdrawal will be displayed by Kaplan-Meier plot for each missing pattern within each treatment group. 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]. 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 that do not have change from baseline CDR-SB at Week 78 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, baseline of the parameter of interest, baseline MMSE, region, disease stage (MCI versus mild AD), and baseline AD symptomatic medication use.

The imputed datasets will be analyzed by an analysis of covariance (ANCOVA) model adjusting fixed effects of treatment, baseline of the parameter of interest, region, disease stage (MCI versus mild AD), baseline MMSE, and baseline AD symptomatic medication use. 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 26 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].

Copy increment from reference method

The copy increment from reference (CIR) method may be applied to impute the post-withdrawal data for any BIIB92 treated subject 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 on BIIB92 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. After all missing data have been imputed, an ANCOVA model adjusting treatment group, baseline of the parameter of interest, baseline MMSE, region, disease stage (MCI versus mild AD), and baseline AD symptomatic medication use will be applied to analyze the change from baseline of CDR-SB.

Censoring after intercurrent events

Estimand 2: The treatment effects of BIIB92 had all participants never missed ≥4 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 Week 78 with data after ICEs are set to missing
- Analysis set level summary: Least square (LS) mean difference from MMRM model in change from baseline between BIIB92 and placebo
- ICEs and Strategies for Addressing ICEs:

  ICEs include

  - AD symptomatic medication change (hypothetical strategy)
  - Treatment discontinuation (hypothetical strategy)
  - Missing more ≥ 4 infusions consecutively (hypothetical strategy)

The estimand of this analysis reflects the treatment effect of BIIB092 if the drug is taken as directed. The primary analysis for Estimand 1 will be repeated with the data censored after any of the following intercurrent events (if multiple events occur to the same subject, data after the earliest event will be censored):

- premature discontinuation of the study treatment
- any change to concomitant AD symptomatic medications after the initiation of study treatment
- missing more than or equal to four infusions consecutively

5.3.3.3 Per-protocol analysis

Estimand 3: The treatment effect of BIIB92 in subjects included in PPS regardless if subjects discontinue treatment early

- Analysis set: all subjects in the PPS
- Variable: The change from baseline CDR-SB scores at Week 78 regardless of intercurrent events (ICEs)
- Analysis set level summary: Least square (LS) mean difference from MMRM model in change from baseline between BIIB92 and placebo
- ICEs and Strategies for Addressing ICEs:

  ICEs include

- Treatment discontinuation (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 treatment discontinuation early.

The per-protocol analysis will be done using the same model as the primary analysis (Section 4.3.2.1) and applying in the Per-Protocol Analysis Set (Section 3.5).

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, DKEFS Category Fluency, DKEFS Letter Fluency, DSST, Trails A, eCog, FAQ, NPI-10, iADRS, EMACC and ADCOMS.

A mixed model with repeated measures (MMRM) may be used to analyze changes from Baseline as described in Section 5.3.2. A line plot of adjusted mean change from baseline over time will be provided.

For MMSE, ADAS-Cog13, ADCS-ADL, ISLT, eCog, FAQ, and other exploratory efficacy endpoints multiple comparison procedure modelling (MCP-MOD) method (Appendix II) may be used to assess and model dose-response relationships (potential candidate models will include linear, linear-log, quadratic, maximum response [Emax], and logistic models as specified in Section16.10) while controlling for multiplicity. The dose-response parameter of interest for MCP-MOD will be the LS means at Week78 for each dose group from the mixed-effects model. Pairwise comparisons of each BIIB092 dose group versus placebo will also be conducted. A line plot of final dose-response relationship will be provided.

5.3.5 Subgroup Analysis

Subgroup analyses will be performed for the primary endpoint (CDR-SB) and exploratory endpoints (e.g. MMSE, ADAS-Cog13, ADCS-ADL, iADRS, EMACC, and ADCOMS). The subgroups to be considered are in Section 3.4.

Subjects in each subgroup category will be analyzed separately using the same mixed model with repeated measures (MMRM) used to analyze changes from Baseline as described in Section 5.3.2. A forest plots of adjusted mean change from baseline at Week 78 will be provided.

5.3.6 Additional Analysis

5.3.6.1 CDR Subscores, CDR Global Score, ADCS-bADL, ADCS-iADL and individual scores for CDR, ADCS-ADL and ADAS-Cog 13

The CDR is comprised of 6 domains: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. CDR-SB is the sum of the scores for these 6 domains. In addition, two CDR subscores have been proposed [Tractenberg 2005]: a “cognitive” subscore equaling the sum of the Memory, Orientation, and Judgment and Problem Solving box scores, and a “functional” subscore equaling the sum of Community Affairs, Home and Hobbies and Personal Care box scores. For each of the 6 domains, and the

CDR cognitive subscore and CDR functional subscore, the actual value and the change from baseline at each visit will be summarized by treatment group. The same MMRM model as the primary analysis will also be applied to the CDR individual domains, cognitive subscore and CDR functional subscore.

The CDR global score is a composite score obtained by combining the 6 sub-domain scores using a scoring algorithm that weights memory as the primary domain and all other domains as secondary [Morris 1993]. The actual and change from baseline in CDR global score will be summarized (as a categorical variable) by treatment group at each visit. In addition, subjects with $\geq$ 0.5 worsening in CDR global score may be summarized by treatment group at each post-baseline visit.

ADCS-ADL basic total score (ADCS-bADL) and ADSL-ADL instrumental total score (ADCS-iADL) will also be calculated in addition of ADCS-ADL total score. ADCS-bADL, which contains 6 out of 23 ADCS-ADL items, is measuring the basic self-care tasks which are generally recognizable in all cultures such as feeding, mobility, toileting, bathing, grooming and dressing. The measure and conceptualization of ADCS-iADL, which contains 17 out of 23 ADCS-ADL items, is more complex due to the influence of cultural norms and gender roles that may impact which tasks are even attempted by a patient. As such, scales that measure iADLs tend to include a broad range of activities. The same MMRM model as the primary analysis will also be applied for ADCS-ADL, ADCS-ADL individual items, ADCS-bADL and ADCS-iADL.

Similarly, the same MMRM model used for ADAS-Cog 13, will be applied for ADAS-Cog 13 individual items.

5.3.6.2 Slope analysis

Slope analysis will be conducted to assess the difference between each BIIB092 treatment group and placebo in the slope of clinical measures from baseline up to Week 78. A reduction in the slope of clinical worsening in the BIIB092 treatment group compared with placebo would indicate a slower rate of disease progression, thus reflecting a disease modifying effect of BIIB092. This analysis will be conducted for the CDR-SB, MMSE, ISLT, eCog, ADCS-ADL, FAQ, ADAS-Cog 13, NPI-10, and may be conducted for other exploratory endpoints. A linear mixed model will be used, with change from baseline as dependent variable at each visit and with fixed effects of treatment, time (as a continuous variable), treatment-by-time interaction, baseline of the parameter of interest, baseline of the parameter of interest-by-time interaction, baseline MMSE, region, disease stage (MCI versus mild AD), and baseline AD symptomatic medication use. Random intercept and slope will also be included in the model to characterize subject-specific progression. In addition, a quadratic linear mixed model may also be fitted to address potential non-linearity associated with natural disease progression and/or non-constant treatment effect over the treatment course.

5.3.6.3 Summary of CDR-SB, ADAS-Cog 13 total score, and MMSE by tau PET reduction at Week 78

Subjects may be separated into 2 subgroups based on the magnitude of change on tau PET measures for the primary target and reference regions at Week 78: (1) change from baseline

less than (mean - one standard deviation) of the placebo group at Week 78; (2) change from baseline greater than or equal (mean - one standard deviation) of the placebo group at Week 78. MMRM model or by visit summaries for CDR-SB, ADAS-Cog 13 total score, and MMSE may be conducted on these 2 subgroups by treatment groups.

5.3.6.4 Responder analysis of CDR-SB

To further assess whether subjects on BIIB092 progress differently from those on placebo, responder analysis may be conducted. The responders will be determined by a threshold of the primary endpoint, i.e., subjects whose change from baseline CDR-SB at Week 78 is smaller than the threshold will be classified as responders and otherwise will be classified as non-responders. All subjects with missing data at Week 78 will be classified as non-responders.

The continuous responder curve that displays the percentage of responders under a wide range of threshold values will be presented by treatment group. The responder analysis may be conducted for threshold value 0.5 or 1.5, i.e., subjects whose change from baseline CDR-SB at Week 78 $\leq$ 0.5 may be classified as responders. The number of responders and the response rate may be summarized by treatment group. In addition, the dichotomized response, responder vs. non-responder, may be modeled using a logistic regression with the covariates: fixed effects of treatment, baseline of CDR-SB, baseline of MMSE, region, disease stage (MCI versus mild AD), and baseline AD symptomatic medication use (Y/N). 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.

5.4 Safety Analysis

5.4.1 General Considerations

For subjects who enrolled in LTE period, AEs and SAEs started after Week 78 will be entered and reported in LTE period.

5.4.1.1 Analysis Set

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 Safety treatment groups

Different from the randomization treatment groups, if a subject who was randomized to placebo group accidentally received one or more doses of the active treatment during the study, he/she will be classified as either low (BIIB092 125 mg/4wk or BIIB092 375 mg/12wk), medium or high dose group according to the majority of active treatment dose he/she received, for all the safety analyses (Section 3.5). If a subject randomized to BIIB092 treatment groups but received all placebo throughout the study, this subject will be counted in placebo group. A listing of such subjects will be provided, as described in Section 5.2.5. Safety treatment groups will be

the same as the randomization treatment groups for other subjects (subjects randomized to active treatment groups, and subjects randomized to placebo without any accidental active dose).

5.4.1.3 Incidence, incidence proportion and incidence rate

- Incidence and incidence proportion will be provided in incidence 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 set, 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

5.4.2.1 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 infusion 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 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) and AEs (including pre-dosing AEs related to tau PET) will be included in the listing, with an indicator of pre-dosing or treatment emergent.

5.4.2.2 Summary and incidence analysis

Overall summary of AE table will summarize the number of subjects with any AE, with any AE by maximum severity, 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 of subjects with a fatal event. This table will be done by treatment group.

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 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 tables will be provided (presented by 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
4. AEs at least 2% higher in incidence by system organ class and preferred term for BIIB092 2000 mg/4wk compared to placebo
5. AEs by preferred term
6. Adverse events with an incidence of 5% or more in any treatment group by preferred term
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. Severe 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 (Subjects in tau PET evaluable set)
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 (Subjects in CSF PD evaluable set)

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

5.4.2.3 Incidence rate analysis

Follow-up adjusted incidence rate of AEs for the placebo-controlled period may be summarized by SOC and PT as below

- 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 population. The entire follow-up time for a subject

is defined as the time from the first dose until the last day on study. Each subject will be counted only once within each category.

5.4.2.4 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. 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 (Appendix V) 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

5.4.2.5 Adverse event of special interest

Anti-drug antibody is an AESI in the BIIB092 clinical development program. Adverse events representing potential immune/hypersensitivity reactions will be identified using customized MedDRA search criteria, including: Anaphylactic reaction SMQ narrow, Allergic conditions NEC HLT, and miscellaneous PTs. Further details are given in (Appendix IV)10

An incidence proportion table for potential immune/hypersensitivity reactions by PT, and similarly for potential immune/hypersensitivity reactions for subjects with and without treatment emergent positive anti-drug antibody (ADA) results (as defined in Section 5.7) by PT may be presented. A listing of potential immune/hypersensitivity reactions will be provided.

The following analyses (incidence proportion only) may be performed 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

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)

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

5.4.3.1 Quantitative analyses

For numeric laboratory parameters, actual values, change from baseline and percent change from baseline 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 coagulation, only actual value summaries will be presented.

Plots of actual values and change from baseline for numeric laboratory parameters at each visit will be provided.

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

Shift analyses

Laboratory data will be summarized using shift tables where appropriate. Each subject's hematology, blood chemistry and urinalysis 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.

Potentially Clinically Significant laboratory abnormalities analyses

For hematology, blood chemistry and urinalysis, the number of subjects with potentially clinically significant laboratory abnormalities post-baseline will be summarized for the parameters provided in Table 3. Subjects need to have at least one post-baseline evaluation and a baseline value not potentially clinically significant (including missing) in order to be included in the analysis.

Table 3. 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	≤32%	≥54%
Hematocrit - Males	≤37%	≥60%
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
Bicarbonate	≤16 mmol/L	≥35 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	⩾ ++++
Ketones	N/A	⩾ ++++
Protein	N/A	⩾ ++

Clinical Laboratory Outlier Criteria		
Parameter name	**PCS Low**	**PCS High**
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, a summary of 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. 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

Suicide-related events based on the Columbia Suicide Severity Rating Scale (CSSRS) at post-baseline visits will be summarized by treatment group. Suicidal ideation events include: (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 Analysis Set.

Number of subjects in each ideation category at any post-baseline visit, number of subjects in each suicidal ideation and 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. A listing of subjects with suicide-related events will be provided.

5.4.5 ECG Data

Actual and change from baseline 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.

Summary of ECGs (number of normal, <abnormal, not adverse event>, or <abnormal, adverse event>) at scheduled visits will be presented by treatment group.

Shift table from normal or unknown ECG at baseline to abnormal post-baseline ECG (<abnormal, not adverse event>, or <abnormal, adverse event>) will be summarized. Denominator will be number of subjects who have a baseline value not abnormal (including unknown) and at least one post-baseline value.

In addition, PR and QTcF values will be summarized for below categories:

- QTcF interval (msec) at post-baseline in below categories:
  - >450
  - >480
  - >500
- QTcF increase from baseline (msec) in below categories:
  - >30
  - >60
- PR interval (msec) at post-baseline in below categories:
  - ≤ 200
  - > 200

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

Vital sign parameters include temperature, diastolic blood pressure, systolic blood pressure, heart rate, and respiration rate. The descriptive statistics for actual values and change from baseline will be summarized over time for each treatment group. Plot of mean vital sign values at each visit will be provided. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes. A by-patient listing will also be presented.

The analysis of vital signs will also focus on the incidence of clinically relevant outliers based on the following criteria (Table 4 – study specific and Table 5 – required by STAN V2). The number of clinically relevant outliers determined by each criterion will be summarized by treatment group.

Table 4. Criteria Used to Assess Potential Clinically Relevant Outliers in Vital Signs

Variable	Low	High
Systolic Blood Pressure	<90 mm Hg post-BL or ⩾20 mm Hg decrease from Baseline (BL)	>180 mm Hg post-BL or ⩾20 mm Hg increase from BL
Diastolic Blood Pressure	<50 mm Hg post-BL or ≥15 mm Hg decrease from BL	>105 mg Hg post-BL or ⩾15 mm Hg increase from BL
Heart Rate	<50 bpm post-BL or ⩾ 15 bpm decrease from BL	>120 bpm post-BL or ≥15 bpm increase from BL
Temperature	>2 degree C decrease from BL	>38 .5℃ or >2℃ increase from BL
Respiration Rate	< 10 breaths per minute or ≥ 50% decrease from BL	>25 breaths per minute or ≥50% increase from BL

BL= baseline; bpm = beats per minute

Table 5. Criteria for post-baseline vital sign abnormalities

Variable	Criteria
Temperature	<36 degrees C >38 degrees C
Heart rate	<60bpm >100bpm
Systolic blood pressure	<90 mmHg >140 mmHg >160 mmHg
Diastolic blood pressure	<50 mmHg >90 mmHg >100 mmHg
Weight	7% or more increase from BL 7% or more decrease from BL
Respiratory rate	<12 breaths/min >20 breaths/min
BL= baseline; bpm = beats per minute	

The number of subjects evaluated and the number and percentage of subjects with clinically relevant outliers will be presented 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

Since clinically significant findings during physical examinations will be recorded as AEs, a listing of physical examination data will be presented.

5.4.8 Neurological Examination

Since clinically significant findings during neurological examinations will be recorded as AEs, a listing of neurological examination data will be presented.

5.4.9 Safety MRI Data

The following MRI data will be summarized by treatment group using safety MRI evaluable set:

- 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 VEVE present < Questionable presence of VE (VE (Mild Severity) < Questionable presence of VE (Moderate Severity) < Questionable presence of VE (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 superficial siderosis (SS) (>1cm^3) at post-baseline
- Number of subjects with SS (≤1cm^3) at post-baseline

5.4.10 COVID-19 Related Safety analysis

Overall summary of COVID-19 adverse events will be presented. Number of subjects with Covid-19 AE, severity, related events, serious events, related serious events, events leading to drug withdrawal, events leading to study discontinuation and AE with Fatal outcomes may be included in the summary.

AEs by system organ class and preferred term sorted by decreasing frequency will also be presented.

5.5 Pharmacokinetics Analysis

The Serum PK evaluable set as defined in Section 3.5, 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 3.5, 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. For subjects whose serum and CSF sample collected after LTE first infusion will be excluded.

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.

Population PK analysis may be conducted to estimate BIIB092 population PK parameters and to identify potential covariates (e.g., demographics, body weight, and anti-BIIB092 antibodies) on the variability of BIIB092 PK. Results will be presented in a separate report.

In addition, an exposure-response (E-R) analysis will be conducted by Pharmacometrics group to detect any E-R relationship trend and potential covariate using any primary or secondary endpoint and BIIB092 exposure metrics as deemed appropriate. Other tables and figures based on the population PK and E-R analyses will be generated by Clinical Pharmacology and Pharmacometrics (CPP) team and will be included in a separate report from CPP. This analysis may not be included in the CSR.

5.5.1 Serum and CSF PK Concentration Data

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 may 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-logarithmic 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, and 76. Individual ratios along with descriptive statistics (N, arithmetic mean, standard deviation, geometric mean, CV, median, minimum, and maximum) at 12, 48, and 76 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.

5.5.2 Serum PK Parameters

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

Parameter	Definition/Calculation	Units
C_{max}	Observed maximum serum BIIB092 concentration collected at end of infusion	ug/mL
C_{trough}	Observed troughtrough 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_{max} and C_{trough} over time will be provided.

5.6 Biomarker

5.6.1 Pharmacodynamics Analysis

The CSF PD evaluable set or CSF PD modified evaluable set as defined in Section 3.5, will be used for the statistical modeling of CSF PD data.

The actual, change from baseline, and percentage change from baseline of CSF N-terminal tau and CSF p-tau, and possibly CSF markers of synaptic change or neurofilament 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. For CSF to serum ratio calculation, BLQ are excluded, as a ratio using the imputed values will lead to unreasonable estimates. 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.

Pearson and Spearman correlations between PD parameters (CSF n-terminal tau, CSF p-tau and possibly CSF synaptic or neurofilament marker change from baseline values) and CDR-SB, ADAS-Cog-13 total score, ADCS-ADL total score and MMSE scores change from baseline values may be evaluated using Pearson and Spearman correlation at Week 52 and Week 78, respectively. Pearson and Spearman partial correlations adjusting for age, corresponding baseline PD parameters and baseline clinical assessment may also be explored.

For subjects who had both CSF and tau PET assessments. Their data may be used to evaluate the correlation between CSF PD parameters and key tau PET parameters at Baseline, 1 year (Week 48 for CSF and Week 52 for tau PET) and 18 months (Week 76 for CSF and Week 78 for tau PET). Pearson and Spearman correlations and partial correlations adjusting for age and corresponding baseline values may be evaluated.

In addition, MMRM model specified in Section 5.3.2 without region as one of the covariates will be done for p-tau. Age may be considered as one of the covariates. In addition, these analyses might be considered for total tau, N-terminal tau and other fluid biomarkers. For PD biomarker by visit summaries and MMRM models, the analysis visit should be defined using visit windows (Table 16 in Appendix I). Week 12 data will not be used in the MMRM due to small sample size.

Adjusted mean (± standard error) plots of change from baseline of CSF N-terminal tau and p-tau over time by treatment group and mean % change of CSF N-terminal tau and p-tau over time by treatment group may be presented. The exposure response relationships may be explored graphically as appropriate.

Other Fluid Biomarker Analysis

Other PD parameters analyzed may include, but not limited to, other measures of phospho-tau, biomarkers of synaptic change and neurofilament in CSF and in some cases blood if available.

Data for these exploratory potential biomarker candidates related to BIIB092 biological activity or disease progression may be summarized using descriptive statistics and will be presented by treatment group.

5.6.2 Structural MRI Analysis

Structural magnetic resonance imaging (MRI) results analyzed may include, but will not be limited to, volume measures of hippocampus, whole brain, whole cortex and lateral ventricles. The analyses will be based on Structural MRI evaluable set as defined in Section 3.5.

Structural MRI is performed on all randomized subjects at screening visit, Week 28, Week 52, Week 78 and early termination visits. Structural MRI readings with QC failure or major scanner upgrade will not be included in the analysis.

5.6.2.1 By visit summary and MMRM model

The actual values and change from baseline values will be summarized by treatment groups (placebo, low dose, medium dose and high dose) and by visit for each of the ROI measurements up to Week 78 for Structural MRI evaluable set.

In addition, some of the parameters measuring volumetric MRI ROIs will be analyzed as a percentage of total intracranial volume at baseline (i.e. "% of TIV"). The selected ROIs (e.g., lateral ventricles) volumes (% of TIV) will also by summarized by treatment for each visit for Structural MRI evaluable set.

A mixed model with repeated measures (MMRM) will be used to analyze changes from baseline as described in Section 5.3.2, including age as covariate. The MMRM analyses will be performed on both the raw volume (all ROIs) and the adjusted volume (% of TIV, for selected ROIs only, e.g. lateral ventricles).

5.6.2.2 Pearson and Spearman correlation

Pearson and Spearman correlations between change from baseline volume MRI at Week 78 and change from baseline CDR-SB at Week 78 will be conducted by treatment groups. Pearson and Spearman partial correlation adjusting for age, corresponding baseline volume MRI measure, baseline TIV and baseline CDR-SB will also be conducted by treatment groups at Week 78. The estimated correlation coefficients, p-values and the 95% confidence intervals will be provided. Given that reductions in volume MRI may precede clinical effects (e.g., slowing of clinical decline), Pearson and Spearman correlations and partial correlations between change from baseline volume MRI at Week 52 and change from baseline CDR-SB at Week 78 might also be conducted. Similar models may be conducted for MMSE, ADAS-Cog-13 total score, and ADCS-ADL total score.

5.6.3 Tau PET Analysis

5.6.3.1 Tau PET substudy

The tau PET substudy (using ^{18}F-MK6240 tracer only) will include a subset of subjects in USA and Australia. Subjects enrolled into the tau PET substudy will receive serial ^{18}F-MK6240 Tau

PET scans at Screening, Week 52 and Week 78/Early Termination to investigate the effect of BIIB092 on cerebral tau pathology. The analyses for Tau PET will be based on Tau PET evaluable set or Tau PET modified evaluable set as defined in Section 3.5.

5.6.3.2 Tau PET target and reference regions

Tau PET standardized uptake value ratio (SUVR) is a quantitative measure of cerebral tau level. The SUVR was calculated as the ratio of tracer binding in target brain region (brain regions expected to harbor tau pathology) to reference region (brain region devoid of tau pathology).

For the SUVR measures the following target and reference regions may be analyzed.

- The primary target regions include: Braak 1 and 2, Braak 3 and 4, and Braak 5 and 6.
- Secondary target regions may include: 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.
- The primary reference region is Cerebellum (superior section eroded).
- Other exploratory reference regions may include: cortex (superior section eroded) and Cerebellum (superior and inferior section eroded).

In addition to SUVR measures, Tau PET extent measures may also be analyzed. The extent measure is an exploratory approach of quantifying the spatial extent of tau pathology in brain regions of interest. The Tau PET extent measures for Braak 1 and 2, Braak 3 and 4, Braak 5 and 6, Whole cortex using Cerebellum (superior section eroded) as reference region may be analyzed.

SUVR and extent measures derived from additional target and reference region combinations may be explored.

5.6.3.3 Tau PET primary analysis

The actual and change from baseline tau PET measures will be summarized by treatment groups and by visit for each target region and the primary reference region.

For tau PET by visit summaries and MMRM models, the analysis visit should be defined using visit windows (see 0 in Appendix I). The rationale is to use consistent analysis visit windows as for the efficacy endpoints for Week 52 and Week 78. If there is more than 1 value in the same analysis visit window (>1 value for the same analysis visit) for a certain parameter for a subject, then select the closest record to the target visit day for the by visit analysis. If they are with the same distance from the target visit day, then select the later one for the by visit analysis.

MMRM model

A mixed model with repeated measures (MMRM) will be used to analyze changes from Baseline in tau PET measures as described in Section 5.3.2 without geographic region as one of the covariates for all tau PET primary target regions and primary reference regionregion. Age is adjusted in the model as a continuous covariate. A line plot of adjusted mean change

from baseline over time will be provided. A supplementary MMRM analysis may also be performed using the primary target regions and primary reference region on the Tau PET population excluding subjects with change in smoking status during the study duration.

A forest plot of adjusted mean change from baseline at Week 78 may be provided for other secondary target regions (using primary reference region) and the primary target regions (using other exploratory reference regions).

MCP-MOD model

The multiple comparison procedure modelling (MCP-MOD) method (Appendix II) will be used to assess and model dose-response relationships (potential candidate models will include linear, linear-log, quadratic, maximum response [Emax], and logistic models as specified in Section16.10) while controlling for multiplicity for the primary regions (Braak 1 and 2, Braak 3 and 4, Braak 5 and 6) using the primary reference region (Cerebellum, superior section eroded).) The dose-response parameter of interest for MCP-MOD will be the LS means at Week78 for each dose group from the mixed-effects model. Pairwise comparisons of each BIIB092 dose group versus placebo will also be conducted. A line plot of final dose-response relationship will be provided.

5.6.3.4 Correlation between Tau PET vs. Cognitive results and other assessments

Pearson and Spearman correlation

Pearson and Spearman correlations between change from baseline tau PET primary summary measures at Week 78 and change from baseline CDR-SB at Week 78 may be conducted by treatment groups in subjects participating in tau PET substudy. Pearson and Spearman partial correlation adjusting for age, corresponding baseline tau PET measure and baseline CDR-SB will also be conducted by treatment groups at Week 78. The estimated correlation coefficients, p-values and the 95% confidence intervals will be provided. Same analyses will be used to analyze the correlations between change from baseline of tau PET at Week 52 and change from baseline of CDR-SB at Week 52. Given that reductions in tau burden may precede clinical effects (e.g., slowing of clinical decline), Pearson and Spearman correlations and partial correlations between change from baseline tau PET composite ROI at Week 52 and change from baseline CDR-SB at Week 78 will also be conducted. Similar models maybe conducted for MMSE, ADAS-Cog-13 total score, and ADCS-ADL total score.

ANCOVA model

An Analysis of Covariance (ANCOVA) approach might be used to explore the treatment effect with respect to change from baseline of tau PET at week 78 and change from baseline of CDR-SB at week 78. If a significant treatment benefit on CDR-SB is detected at week 78, three ANCOVA models will be included: Model 1 for change from baseline of tau PET at week 78, with factors of treatment, corresponding tau PET baseline value, age, baseline disease stage (MCI vs. mild AD), and baseline AD symptomatic medication use; Model 2 for change from baseline of CDR-SB at week 78, with factors of treatment, baseline CDR-SB, baseline tau PET value, age, baseline disease stage (MCI vs. mild AD), and baseline AD symptomatic medication use; Model 3 for change from baseline of CDR-SB at week 78, with factors in model 2, plus change from baseline of tau PET at week 78. The estimated treatment

effect, the associated 95% CI and p-value of the coefficient will be presented to show how much of the treatment effect with respect to CDR-SB can be explained by the treatment effect with respect to tau PET.

The same analyses might be explored for other clinical assessments: ADAS-Cog 13 total score, MMSE score and ADCS-ADL score. The same ANCOVA model might be used to analyze the treatment effect with respect to clinical endpoint and tau PET at different timepoint (both at week 52, or change from baseline of tau PET at week 52 with change from baseline of clinical assessment at week 78).

Correlation between tau PET and structural MRI

Pearson and Spearman correlations between change from baseline tau PET primary summary measures at Week 78 and change from baseline structural MRI at Week 78 may be conducted by treatment groups for key tau PET and structural MRI parameters. Pearson and Spearman partial correlation adjusting for age, corresponding baseline tau PET measure and baseline structural MRI measures may also be conducted by treatment groups at Week 78.

5.6.3.5 Subgroup analysis

Subgroup analysis may be conducted using the same MMRM model for the subgroup defined Section 3.4. Categorical covariates will be moved out of the model if they are used as a subgroup factor; for example, AD stage at baseline and AD symptomatic medication use at baseline.

5.7 Anti-drug Antibody Analysis

5.7.1 Analysis Methods for Anti-drug antibody Data

Anti-drug antibody (ADA) evaluable set will be used to analyze ADA data. For ADA endpoints, the following treatment groups will be presented in both tables and listings: placebo, BIIB092 125 mg/4wk, BIIB092 375 mg/12wk, BIIB092 600 mg/4wk, BIIB092 2000 mg/4wk, and BIIB092 total. 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.

Treatment emergent positive: Anti-BIIB092 antibody responses in antibody-positive subjects are defined as treatment emergent if a patient is:

- ADA-negative at baseline and ADA-positive post-baseline, or
- ADA-positive at baseline and had a greater than or equal to 4-fold increase in antibody titer post-baseline. 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: Anti-BIIB092 antibody responses in antibody-positive subjects are defined as persistent, if more than one positive evaluation occurs ≥16 weeks apart, regardless of the number of negative results between positive results, or if a positive evaluation occurs at the last time point with no further samples available.

Transiently positive: Anti-BIIB092 antibody responses in antibody-positive subjects are defined as transient, if a subject is treatment emergent positive at a single timepoint not including the last sampling timepoint, or treatment emergent with multiple positive anti-BIIB092 results <16 weeks apart, with the final timepoint being ADA negative.

Summary table with the number and percentage of all anti-BIIB092 positive antibody events by treatment group and visit will be displayed. In addition, a summary table of patients with treatment-emergent, persistent, and transient responses will be presented by treatment group. 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 Health Outcomes

The FAS will be used for the analysis of health outcomes data.

5.8.1 QoL-AD and ZBI

The actual and changes from baseline scores for health outcome measures in the ZBI total score, QoL-AD total score up to Week 68, will be summarized by treatment group.

A mixed model with repeated measures (MMRM) will be used to analyze changes from Baseline in ZBI and QoL-AD measures as described in Section 4.3.2 for ZBI and QOL-AD.

5.8.2 RUD-Lite

RUD-Lite is a brief measure of resource utilization developed for use in clinical trials for Alzheimer's disease. The RUD-Lite is completed by the caregiver and allows for cost calculation of caregiver burden. Components of the RUD-Lite include informal caregiver time, living accommodations and long-term care, use of respite, home nursing, and day care. Outpatient, hospital, and social services visits, as well as formal and informal caregiver time, are also captured. There are two different forms of the RUD-Lite: one for use at baseline and one for use at subsequent visits.

RUD-Lite consists of continuous and categorical items (see Table 5).

Table 6. RUD-Lite Items

Item	Parameter (Units)	Type
Caregiver Items in Last 30 Days		
1	Time per day or night spent asleep (hours)	Continuous

Item	Parameter (Units)	Type
2A	Time spent per day assisting subject with tasks (toilet visit, eating, etc.) (hours)	Continuous
2B	Days spent assisting subject with tasks (toilet visit, eating, etc.) (days)	Continuous
3A	Time spent per day assisting subject with tasks (shopping, food preparation, etc.) (hours)	Continuous
3B	Days spent assisting subject with tasks (shopping, food preparation, etc.) (days)	Continuous
4A	Time spent per day supervising subject (hours)	Continuous
4B	Days spent supervising subject (days)	Continuous
Caregiver Work Status in Last 30 Days		
2A	Missed any whole days of work	Continuous
2B	Missed any part of days of work	Continuous
Patient Current Living Accommodation		
1	Any permanent changes since last visit	Categorical (yes, no), post-baseline only
1[a], 2	Current living accommodation	Categorical (own home, ..., other)
2[a]	With whom subject lives	Categorical (alone, ..., not applicable)
3[a], 4	Temporary living accommodation	Categorical (own home, ..., other)
Patient Health Care Resource Utilization in Last 30 Days (Baseline) or Since Last Visit (Post-Baseline)		
1	How many times admitted to hospital	Continuous
2	Ward type, if admitted to hospital	Categorical (geriatric, ..., other)
3	How many times received care in hospital emergency room	Continuous
4	Visited health care professional (doctor, physiotherapist, etc.)	Categorical (yes, no)
4	Type of care, if visited health care professional	Categorical (general practitioner, ..., other)
5	Received nursing service	Categorical (yes, no)
5	Type of care, if received nursing service	Categorical (district nurse, ..., other)

[a] Baseline

For Caregiver Items in Last 30 Days, Items 1, 2A, 3A, and 4A, the total time spent (hours) in the last 30 days will be calculated as time per day (or night) x 30 days. The actual score for all the items in this section will be summarized by visit.

For caregiver work status, the percentage of caregivers working for pay will be summarized by treatment group at each time point. In addition, among those caregivers working for pay, the following summary will be provided by treatment group at each time point:

- The number of entire work days missed
- The percentage of caregivers of those who are working, who missed at least 1 entire day of work
- The number of partial work days missed
- The percentage of caregivers of those are working, who missed at least part of a day of work

For subject current living accommodation, the proportion of subjects who have a change in permanent living accommodation will be summarized by treatment group at each time point. Number of nights spent in the temporary living accommodation for subjects with a temporary change will also be summarized.

For subject health care resource utilization, the following summary will be provided by treatment group at each time point.

- Percentage of subjects admitted to hospital; number of times and nights admitted to hospital for subjects admitted to hospital
- Percentage of subjects received care in hospital emergency room; number of times of emergency room care for subjects received care in hospital emergency room
- Percentage of subjects visited health care professional (doctor, physiotherapist, etc.); number of times visited for subjects visited health care professional

Percentage of subjects received nursing care; number of visits and hours of nursing care for subjects received nursing care.

6 Changes from Protocol-Specified Analyses

In order to follow Biogen standard, the below population names have been changed. However, the definition remains the same.

Protocol specified name	SAP name
Intent-to-treat population	Full Analysis Set
Per-protocol population	Per-Protocol Analysis Set
Safety population	Safety Analysis Set
Safety MRI population	Safety MRI Evaluable Set
Serum PK analysis population	Serum PK Evaluable Set
CSF PK analysis population	CSF PK Evaluable Set
Serum PD population	Serum PD Evaluable Set
CSF PD population	CSF PD Evaluable Set
Tau PET population	Tau PET Evaluable Set

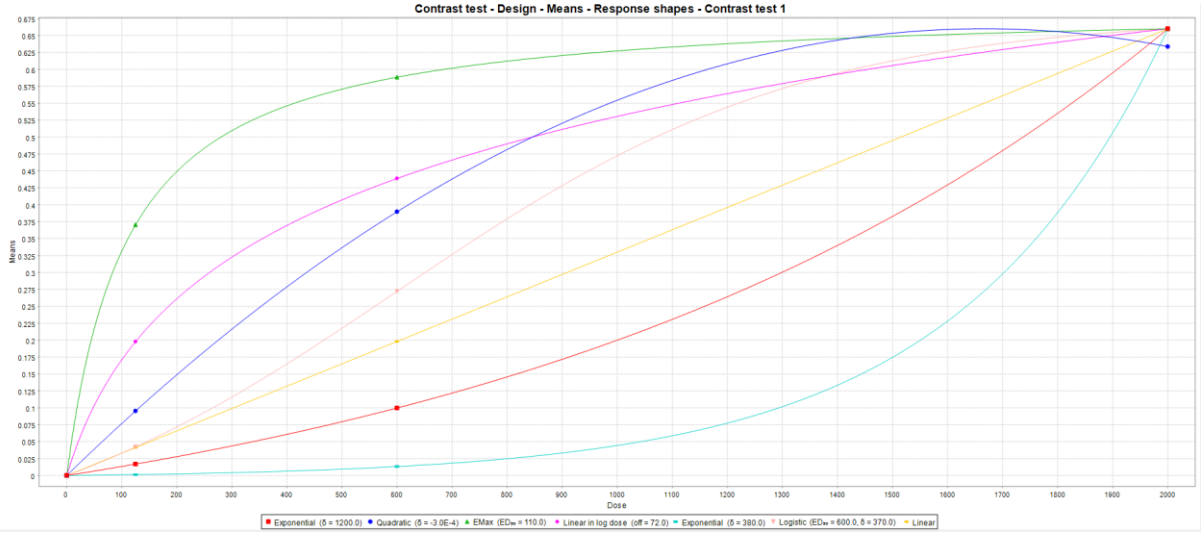
Structural MRI population	Structural MRI Evaluable Set
Anti-drug antibody population	Anti-Drug Antibody Evaluable Set

6.1 MMRM model

The MMRM model specified in SAP section includes “baseline MMSE” as one more fixed effect than protocol section 16.4.2.1 and 16.4.2.2.

6.2 MCP-MOD model

Besides six planed dose-response relationships as illustrated in Figure2, linear dose-response relationship was added for both models to detect the change from baseline in CDR-SB and tau PET. The approximately power remains at 80%.



7 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 7 - Table 15] for different endpoints. To define analysis visit window, the target visit day is calculated as (week number*7+1). The lower bound of visit window is calculated as target day−(target day−target day of previous visit)/2+1, except for the first post-baseline visit window whose lower bound is set as Day 2; the upper bound of visit window is calculated as target day+(target day of next visit−target day)/2.

If there are 2 or more assessments from visits, including EOT and 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, including EOT and 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, including EOT and 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 7. 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, *]
ISLT, DKEFS, DSST, Trails A,	Baseline	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, *]
eCog	Baseline	1	Most recent non-missing pre-dose value
	Week 28	197	[2, 295]
	Week 56	393	[296, 470]
	Week 78	547	[471, *]
MMSE	Baseline	1	Most recent non-missing pre-dose value
	Week 12	85	[2, 127]

Efficacy Endpoint	Analysis visit	Target visit day	Analysis visit window
	Week 24	169	[128, 225]
	Week 40	281	[226, 323]
	Week 52	365	[324, 421]
	Week 68	477	[422, 512]
	Week 78	547	[513, *]
	* Up to the end day of the placebo-controlled period.		

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 12	85	[2, 127]
Week 24	169	[128, 253]
Week 48	337	[254, 421]
Week 72	505	[422, 526]
Week 78	547	[527, 589] If subjects who enter LTE, visit window is: [527, the end day of the placebo-controlled period]
Week 90	631	[590, the end day of the placebo-controlled period]

Table 9. Visit Windows for ECG by Visit Summaries

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
D1 Post dose	1	Any day 1 post dose infusion
Week 12	85	[2, 127]
Week 24	169	[128, 253]
Week 48	337	[254, 421]
Week 72	505	[422, 526]
Week 78	547	[527, 589] If subjects who enter LTE, visit window is: [527, the end day of the placebo-controlled period]
Week 90	631	[590, the end day of the placebo-controlled period]

Table 10. 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
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)

Analysis visit	Target visit day	Analysis visit window
Week 4 – Pre dose	29	[2, 43] (Pre-dose assessment)
Week 4 – Post dose	29	[2, 43] (Post dose infusion)
Week 8 – Pre dose	57	[44, 71] (Pre-dose assessment)
Week 8 – Post dose	57	[44, 71] (Post dose infusion)
Week 12 – Pre dose	85	[72, 99] (Pre-dose assessment)
Week12 – Post dose	85	[72, 99] (Post dose infusion)
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] If subjects who enter LTE, visit window is: [541, the end day of the placebo-controlled period]
Week 90	631	[590, the end day of the placebo-controlled period]

Table 11. Visit Windows for ADA by Visit Summarized

Analysis visit	Target visit day	Analysis visit window
Baseline	1	See baseline definition in Section 5.7
Week 4	29	[2, 99]
Week 24	169	[100, 253]
Week 48	337	[254, 435]
Week 76	533	[436, 582] If subjects who enter LTE, visit window is: [436, the end day of the placebo-controlled period]
Week 90	631	[583, the end day of the placebo-controlled 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	365	[120, 456]
Week 78	547	[457, *]
* The upper bound of Week 78, for subjects not enrolled into LTE, is the last day in study for PC period; for subjects enrolled into LTE, their Week 78 upper bound is less than the day of third infusion in LTE (Due to Covid-19, subjects could complete Week 78 tau PET after week 78 but before third infusion in LTE.)		

Table 13. Visit Windows for structural MRI data

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 end day of the placebo-controlled period]

Table 14. Visit Windows for C-SSRS data

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 end day of the placebo-controlled period]

Table 15. Visit Windows for Health Outcome (RUD-Lite, ZBI, and Qol-AD) data

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 20	141	[2, 239]
Week 48	337	[240, 407]
Week 68	477	[408, the end day of the placebo-controlled period]

Table 16. Visit Windows for CSF PD biomarker data

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 12	85	[2, 211]
Week 48	337	[212, 456]
Week 76	533	[457, the end day of the placebo-controlled period]

Table 17. Visit Windows for Serum PD biomarker data

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value

Analysis visit	Target visit day	Analysis visit window
Week 16	113	[2, 225]
Week 48	337	[226, 379]
Week 60	421	[380, 477]
Week 76	533	[478, the end day of the placebo-controlled period]

8 Appendix II: Description of MCP-MOD method

MCP-MOD method works in the following steps.

Step 1: Set of candidate models

Candidate models include linear, exponential (δ = 1200), quadratic (δ=-0.0003), Emax (ED50=110), linear in log dose (off = 72), exponential (δ=380) and logistic (ED50 = 600, δ=370). The response shapes are displayed in 0.

Step 2: Optimal model contrast

The LS means at Week 78 and the covariance matrix of the LS means will be estimated from the mixed model and used to determine the optimal contrasts. The coefficients of the contrasts are pre-specified during the design stage once the candidate models are selected in Step 1.

Step 3: Testing for dose response signal

A multiple contrast test will be used to test the overall dose response signal and to identify all contrasts that have adjusted p-values<0.1 for one sided. As a result, the significance of the dose response signal was established and all models with a significant contrast will be considered in the next step.

Step 4: Model selection

AIC criterion will be used to select the best model for Step 5.

Step 5: Dose estimation

The model selected in Step 4 will be used to fit the data. The fitted model and corresponding confidence interval will be displayed graphically. The minimum effective dose giving the 40% reduction or the clinically relevant improvement 25% reduction over placebo will be estimated along with the 90% and 95% confidence interval. This step may be explored if there is a significant dose response.

9 Appendix III: Questionnaire

9.1 Clinical Dementia Rating Scale (CDR)

The CDR is derived from a semi-structured interview with the patient and an appropriate informant and rates impairment in each of six cognitive categories (Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care) on a five-point scale in which none = 0, questionable = 0.5, mild = 1, moderate = 2, and severe = 3. (Note: Personal Care has no questionable impairment level.) From the six individual category ratings, or "box scores", the global CDR is established by clinical scoring rules where CDR 0 = no dementia and CDR 0.5, 1, 2, or 3 indicates questionable, mild, moderate, or severe dementia. The usefulness of the CDR may result from several factors: (1) it is clinically based (i.e., independent of psychometric test scores); (2) the six categories used for rating dementia severity are directly linked to validated clinical diagnostic criteria for AD; (3) it has high inter-rater reliability for physicians and non-physicians; and (4) and expanded and more quantitative version of the scale can be achieved by summing the ratings in each of the six categories to provide the Sum of Bases. [Morris 1993]

9.2 Mini-Mental State Examination (MMSE)

The Mini-Mental State Examination (MMSE) includes eleven questions, requires only 5-10 min to administer. It is "mini" because it concentrates only on the cognitive aspects of mental functions, and excluded questions concerning mood, abnormal mental experiences and the form of thinking. But within the cognitive realm it is thorough.

The MMS is divided into two sections, the first of which requires vocal responses only and covers orientation, memory, and attention; the maximum score is 21. The second part tests ability to name, follow verbal and written commands, write a sentence spontaneously, and copy a complex polygon similar to a Bender-Gestalt Figure; the maximum score is nine. Because of the reading and writing involved in Part II, patients with severely impaired vision may have some extra difficulty that can usually be eased by large writing and allowed for in the scoring. Maximum total score is 30. [Folstein MF 1975]

9.3 International Shopping List Test Immediate Recall (ISLT)

The International Shopping List Test (ISLT) is a 12-word, 3-trial word learning test with established construct and criterion validity, and high reliability for the detection of memory impairment in AD

The design of the ISLT allows it to be used for the assessment of memory in individuals from different languages, cultures or geographic regions without the necessity of the complex translations or cultural adaptions that must be applied to other verbal memory tests, such as the Free and Cued Selective Reminding Test (FCSRT) or Wechsler Memory Scale Logical Memory Test (LM), which were developed and validated in well-educated and middle-class settings

The ISLT has been used extensively to measure the magnitude and nature of memory impairment in experimental and clinical studies; however, there is less information about the

utility of the ISLT to screen individuals' memory for entry into clinical trials in prodromal AD [Paul Maruff 2017].

9.4 Delis-Kaplan Executive Function System (DKEFS)

The Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) provides a standardized assessment of higher-level cognitive functions, called executive functions, in children, adolescents, and adults between the ages of 8 and 89. The D-KEFS is composed of the following nine stand-alone tests that can be individually or group administered: Trail Making Test; Verbal Fluency Test; Design Fluency Test; Color-Word Interference Test; Sorting Test; Twenty Questions Test; Word Context Test; Tower Test; and Proverb Test. Most of these D-KEFS tests use a game-like format without employing right/wrong feedback procedures; this is intended to reduce unproductive discouragements and frustrations caused by repeated negative feedback during testing.

The D-KEFS Verbal Fluency Test (VF) is comprised of three testing conditions: Letter Fluency, Category Fluency, and Category Switching. The VF measures multiple aspects of verbal behavioral productivity and cognitive flexibility. It evaluates effectiveness of novel and semantic search strategies and assesses flexibility in the implementation of semantic search strategies. The process approach enables further evaluation of self-monitoring of information search, as well as difficulties related to initiation and sustaining effort. There are three conditions in the VF in which the examinee must say as many words as they can by letter, category, and category switching prompts.

1. Letter Fluency: The examinee says words beginning with a specified letter as quickly as possible;

2. Category Fluency: The examinee is asked to say words belonging to a designated semantic category; and

3. Category Switching: The examinee must alternate between saying words from two different; semantic categories.

In this study, only Letter Fluency and Category Fluency tests are used, but NOT Category Switching. The Letter Fluency test measures the examinee's ability to generate words fluently in an effortful, phonemic format. The Category Fluency test measures the examinee's ability to generate words fluently from overlearned concepts.

9.5 Digit Symbol Substitution Test (DSST)

The Digit Symbol Substitution Test (DSST) was initially developed as an experimental tool over a century ago by researchers seeking to understand human associative learning. The DSST is a paper-and-pencil cognitive test presented on a single sheet of paper that requires a subject to match symbols to numbers according to a key located on the top of the page. The subject copies the symbol into spaces below a row of numbers. The number of correct symbols within the allowed time, usually 90 to 120 seconds, constitutes the score.

This study is using the most recent version of Wechsler Adult Intelligence Scale (WAIS), the fourth edition (WAIS IV). The duration of DSST in this version is 120 seconds. The DSST measures a range of cognitive operations. Good performance on the DSST requires intact motor speed, attention, and visuo perceptual functions, including scanning and the ability to write or

draw (ie, basic manual dexterity). That the DSST is sensitive to age effects is well known. The DSST has been a useful tool to demonstrate age differences in the effects of drugs on cognition, for example, owing to reduced clearance resulting in higher plasma concentrations in older than in younger subjects. [Judith Jaeger, 2018]

9.6 Trail Making Test, Part A (Trail A)

Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order, and the participants were asked to connect the numbers in order as quickly as possible. The total completion time will be evaluated as final result. The maximal allowed time is <5mins in our study. Longitudinal studies have shown that the Trail Making Test is capable of forecasting clinical and functional changes in patients with Alzheimer's disease (Chen et al., 2001). Moreover, in older adults, Trail Making Test performance has been related to physical decline and higher risk of mortality [Vazzana et al., 2010, Jordi Llinàs-Reglà, 2017].

9.7 Everyday Cognition (eCog)

The Everyday Cognition (eCog) scales were developed in response to some of the limitations of existing instruments. One goal in developing the eCog was to measure relatively mild functional changes that may predate loss of independence in major activities of daily living. A second aim in developing the eCog was to assess functional abilities that are clearly linked to specific cognitive abilities, in other words, the everyday correlates of specific neuropsychological impairments.

The original version of the eCog is an informant-based measure of cognitively-relevant everyday abilities comprised of 39 items, covering six cognitively-relevant domains: Everyday Memory, Everyday Language, Everyday Visuospatial Abilities, and Everyday Planning, Everyday Organization, and Everyday Divided Attention. For each item, informants compare the participant's current level of everyday functioning with how he or she functioned 10 years earlier. In this way, individuals serve as their own control. Ratings are made on a four-point scale: 1 = better or no change compared to 10 years earlier, 2 = questionable/occasionally worse, 3 = consistently a little worse, 4 = consistently much worse. The original eCog was developed through a rigorous process that included initial pilot testing of a larger potential pool of items. A goal of that initial pilot testing was to identify and discard items with obvious poor psychometric properties. For example, items were not retained if they were associated with a high percentage of "I don't know" responses – indicating the item did not readily apply to many individuals or was not frequently observed by an informant. However, few functional abilities will universally apply to all individuals so an 'I don't know' response option was retained. The original version has been shown to have excellent psychometric properties including good test-retest reliability ($r = 0.82$, $p<.001$) as well as evidence of various aspects of validity including content, construction, convergent and divergent, and external validity [Sarah Tomaszewski Farias, 2011].

9.8 Alzheimer's disease Cooperative Study – Activities of Daily Living (ADCS-ADL)

The ADCS-ADL was designed to assess patients' ability to complete activities relevant to elderly individuals. It is a subjective assessment, with the patient rated by an informant, based on their performance over the previous 4 weeks.

The ADCS-ADL has 23-item which focuses on complex items, such as reading, pastime activities, and household chores, and is appropriate for the assessment of mild to moderate AD. Each item has descriptions of performance levels and corresponding scores; the informant is asked to choose the most accurate description of the patient's performance during the past 4 weeks. The ADCS-ADL23 Total score ranges from 0 (worst) to 78 (best). [Galasko et al. 1997; Robert et al. 2010]. ADCS-ADL basic (ADCS-bADL) total score includes questions 1 (eating), 2 (walking), 3 (bowel and bladder function at the toilet), 4 (bathing), 5 (grooming), and 6b (getting dressed). ADCS-ADL instrumental (ADCS-iADL) total score includes 6a (selecting his/her first set of clothes), and the remaining questions from 7 -23 in ADCS-ADL.

9.9 Functional Activities Questionnaire (FAQ)

The Functional Activities Questionnaire (FAQ) is not self-administered but is completed by a lay informant such as the spouse, a relative, or a close friend. There are 10 questions included. For each activity, four levels ranging from dependence (scored 3) to independence (scored 0) are specified. For activities not normally undertaken by the person, the informant must specify whether the person would be unable to undertake the task if required (scored 1) or could do so if required (0). The total score is the sum of individual item scores; higher scores reflect greater dependency. [Robert I. Pfeffer, 1982]

9.10 Alzheimer's disease Assessment Scale –Cognitive (13 item) (ADAS-Cog 13)

The modified ADAS-Cog 13-item scale (Mohs et al. 1997) includes all original ADAS-Cog items with the addition of a number cancellation task and a delayed free recall task, for a total of 85 points. As in the parent instrument, higher scores indicated greater severity. According to Mohs and colleagues, the purpose of these additional items was to increase the number of cognitive domains and range of symptom severity without a substantial increase in the time required for administration. [Jeannine Skinner, 2012]

9.11 Neuropsychiatric Inventory – 10 (NPI-10)

The Neuropsychiatric Inventory (NPI) was developed by Cummings et al. (1994) to assess dementia-related behavioral symptoms which they felt other measures did not sufficiently address. The NPI originally examined 10 sub-domains of behavioral functioning: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor activity. The NPI is administrated to caregivers of dementia patients. A screening question is asked about each sub-domain. If the responses to these questions indicate that the patient has problems with a particular sub-domain of behavior, the caregiver is only then asked all the questions about that domain, rating the frequency of the symptoms on a 4-point scale, their severity on a 3-point scale, and the distress the symptom

causes them on a 5-point scale. The score of each item is then calculated by multiplying severity by frequency, thus obtaining a score ranging between 0 and 12. The total NPI score is finally obtained by adding all the single item scores (thus, ranging from 0 to 120). Higher scores indicate greater psychopathology.

9.12 Zarit Burden Interview (ZBI)

The Zarit Burden Interview (ZBI), which provides a comprehensive assessment of both objective and subjective burden, is one of the most commonly used burden measures and has been validated in many culturally or ethnically different populations.

The Zarit Burden Interview (ZBI) is a 22-item instrument for measuring the caregiver's perceived burden of providing family care. The 22 items are assessed on a 5-point Likert scale, ranging from 0 = 'never' to 4 = 'nearly always'. Item scores are added up to give a total score ranging from 0 to 88, with higher scores indicating greater burden. The questions focus on major areas such as caregiver's health, psychological well-being, finances, social life and the relationship between the caregiver and the patient [Boon Kheng Seng, 2010].

9.13 Quality of Life for Alzheimer's disease (Qol-AD)

QOL is an important consideration in AD because of the devastating impact of this currently incurable disease on patients and caregivers. From the patient's perspective, QOL measures may assist understanding of the magnitude of the impact of treatment intervention, whereas, from a payer perspective, QOL measures can provide a common metric of comparison across disease states. The QOL-AD has been shown to have excellent internal consistency reliability for both patient and caregiver reports (a 5 0.84 and 0.86, respectively) at all levels of cognitive functioning and good validity as indicated by correlations with measures of depression, day-to-day functioning, and pleasant events frequency. Thorgrimsen and colleagues [2003] reported the QOL-AD to have good content validity, construct validity, interrater reliability (all Cohen's kappa values .0.70), test-retest reliability, and internal consistency (Cronbach a coefficient of 0.82). QOL is measured using the 13-item QOL-AD scale (total score range 13–52; higher scores indicate better QOL). The QOL-AD scale uses a scale of 1–4 (poor, fair, good, or excellent) to rate a variety of life domains, including the patient's physical health, mood, relationships, activities, and ability to complete tasks [Kristin Kahle-Wrobleski, 2017].

9.14 Resource Utilization in Dementia-Lite Version (RUD-Lite)

The RUD was designed for use in clinical trials to assess the level of resource usage among patients with dementia. As the full RUD tool is extensive, a shortened version was created – the RUD Lite.

The RUD Lite consists of two sections: one about the caregiver (including questions about the caregiver him- or herself, and time spent caring for the patient), and one about the patient (including questions about the patient's living arrangements and their healthcare resource usage).

The RUD Lite is a questionnaire rather than an assessment scale, and, as such, it is not 'scored'. Instead, individual questions of the patient component provide resource use information, such as the number of hospitalizations, and the number of nights spent in hospital.

Regarding the caregiver component, the number of hours per day that the caregiver cares for the patient is recorded, based on a typical care day during the past month. This is broken down into time spent assisting with personal ADLs (such as bathing and dressing), time spent assisting with instrumental ADLs (more complex activities such as shopping and housekeeping), and time spent supervising the patient. [Wimo & Winblad. Brain Aging 2003;3(1):48–59]

10 Appendix IV: Adverse event of special interest custom search criteria

Anti-drug antibody is an AESI in the BIIB092 clinical development program. Adverse events representing potential immune/hypersensitivity reactions will be identified using the following customized MedDRA (23.1) 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 (23.1) 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)
- HLT Allergic conditions NEC
- Miscellaneous terms
    - Antibody test
    - Antibody test abnormal
    - Antibody test positive
    - Cytokine release syndrome
    - Documented hypersensitivity to administered product
    - Drug specific antibody present
    - Infusion related reaction
    - Infusion site reaction
    - Neutralising antibodies
    - Neutralising antibodies positive
    - Non-neutralising antibodies positive
    - Respiratory dyskinesia
    - Rheumatoid arthritis
    - Systemic lupus erythematosus
    - Vasculitis

11 Appendix V: 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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Judith Jaeger, PhD, MPA: Digit Symbol Substitution Test the Case for Sensitivity Over Specificity in Neuropsychological Testing

Caterina Rosano: Digit Symbol Substitution test and future clinical and subclinical disorders of cognition, mobility and mood in older adult

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In Person Signer Events	Signature	Timestamp

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Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
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Signing Complete	Security Checked	31 March 2021 | 17:11
Completed	Security Checked	31 March 2021 | 17:11

Payment Events	Status	Timestamps