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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number	761269
Link to EDR	\\CDSESUB1\evsprod\BLA761269\0002
Submission Date	12/14/2021
Submission Type	351(a), priority review
Brand Name	LEQEMBI™
Generic Name	Lecanemab-irmb
Dosage Form and Strength	100 mg/mL solution in a single-dose vial • 500 mg/5 mL • 200 mg/2 mL
Route of Administration	Intravenous infusion
Proposed Indication	Treatment of Alzheimer's Disease
Proposed Dose/Regimen	10 mg/kg administered as an intravenous infusion over approximately one hour, once every two weeks
Applicant	Eisai Inc.
Associated IND	IND 105081
OCP Review Team	Yifei Zhang, Ph.D., Vishnu Sharma, Ph.D., Mohsen Rajabiabhari, Ph.D., Xiulian Du, Ph.D., Atul Bhattaram, Ph.D., Yow-Ming, Wang, Ph.D., Bilal AbuAsal, Ph.D., Sreedharan Sabarinath, Ph.D., Hao Zhu, Ph.D., Ramana Uppoor, Ph.D.
OCP Final Signatory	Mehul Mehta, Ph.D.

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1. EXECUTIVE SUMMARY

In this original Biologics License Application (BLA), Eisai Inc. is seeking approval for lecanemab (LEQEMBI™) under the accelerated approval pathway for the treatment of Alzheimer's Disease (AD). Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. Lecanemab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. The recommended starting and maintenance dose is 10 mg/kg administered as an intravenous infusion over approximately one hour, once every two weeks.

The clinical development program for the lecanemab BLA submission consists of 5 ongoing or completed clinical studies. Study BAN2401-G000-201 is a Phase 2 registrational study that evaluated the safety and efficacy of lecanemab in patients with early AD, which is defined as mild cognitive impairment (MCI) or mild dementia stage of AD. Study BAN2401-A001-101 and BAN2401-J081-104 are completed Phase 1 studies that evaluated single or multiple doses of lecanemab (0.1 to 15 mg/kg) administered to subjects with mild to moderate AD (Study 101) and MCI due to AD and mild AD (Study 104). Additionally, data from two ongoing Phase 3 studies in early AD (Study BAN2401-G000-301) and preclinical AD (Study BAN2401-G000-303) patients also contributed to the evaluation of safety.

Reduction in brain amyloid has been established as a biomarker reasonably likely to predict clinical benefit in subjects with AD. The applicant is seeking accelerated approval of LEQEMBI based on reduction in amyloid beta plaques observed in Study 201. Study 201 is a multicenter, double-blind, placebo-controlled Phase 2 study which includes a completed Core phase that provides the primary dataset for the evaluation of safety and efficacy, an ongoing open-label extension (OLE) phase, and a Gap period between the two phases. The lecanemab dose levels tested in the Core phase include 2.5 mg/kg biweekly, 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg monthly, and 10 mg/kg biweekly. At the recommended dosing regimen of 10 mg/kg once every two weeks, the amyloid reduction from baseline as measured by PET Standard Uptake Value Ratio (SUVR) was statistically significant ($P<0.001$ at Week 53 and Week 79) versus placebo. The effectiveness of lecanemab for the treatment of AD is also supported by the dose/time-dependent effect on clinical endpoints including Alzheimer's Disease Composite Score (ADCOMS), Clinical Dementia Rating – Sum of Boxes (CDR-SB), and Alzheimer's Disease Assessment Scale – Cognitive subscale with 14 tasks (ADAS-Cog14). Further, the change in plasma biomarkers (i.e., plasma p-tau181 and plasma Aβ42/40 ratio) provided additional mechanistic support for the treatment effect of lecanemab.

The lecanemab clinical pharmacology program was designed to describe the pharmacokinetics (PK) of lecanemab, evaluate the effects of intrinsic factors, and assess the relationships between lecanemab PK exposure and response outcomes, including pharmacodynamics (PD), efficacy, and safety. The primary objectives of this review are: (1) to evaluate the acceptability of general dosing recommendations and the need for dose adjustment based on intrinsic factors; (2) to evaluate the changes in biomarker levels and their correlations with clinical outcomes during treatment with lecanemab; and (3) to evaluate the effect of immunogenicity on PK, PD, and safety.

1.1 Recommendations

The Office of Clinical Pharmacology reviewed this BLA and recommends accelerated approval from a clinical pharmacology perspective. The focus of this review and specific recommendations and comments are summarized below.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Primary evidence of effectiveness is based on reported reduction in brain amyloid from the adequate and well-controlled Phase 2 study (Study 201) in early AD patients. The effectiveness of lecanemab is also supported by the exposure-response relationships from Study 201 on primary and secondary clinical endpoints and plasma biomarkers.
General dosing instructions	• The recommended starting and maintenance dose is 10 mg/kg administered as an intravenous infusion over approximately one hour, once every two weeks. • Dilution in 250 mL of 0.9% Sodium Chloride Injection, USP, is required prior to administration. • Administer as an intravenous infusion via a terminal low-protein binding 0.2 micron in-line filter.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustment is needed based on intrinsic or extrinsic factors. There was no significant effect of age, race, liver enzymes, creatinine clearance, and APOE4 carrier status on lecanemab clearance. Sex, body weight, and albumin were found to impact exposure to lecanemab. However, none of these covariates were found to be clinically significant to warrant dose adjustment.
Labeling	The proposed labeling concepts are generally acceptable. However, the review team recommends the following edits to Sections 12.2 and 12.6: • Revise the labeling claims in Section 12.2 (b) (4) • Revise the labeling claims in Section 12.6 to reflect the limitations in anti-drug antibody (ADA) and neutralizing antibody (NAb) assays and its potential impact on the incidence and clinical relevance of antibody formation.
Bridge between the to-be-marketed and clinical trial formulations	Formulations with different manufacturing processes (b) (4) of lecanemab were used in clinical studies and are different with the to-be-marketed formulation (process (b) (4)). Lecanemab exposure following intravenous administration of the 2 formulations (Process (b) (4) and Process (b) (4)) used in the clinical studies summarized in this submission were comparable, with an estimated relative bioavailability (b) (4) of 99.8%.

	In accordance with ICH Q5E guidelines, the applicant conducted comparability studies to demonstrate analytical similarity between different formulations. Please refer to OBP review about the analytical comparability between the processes used in clinical studies (Processes (b) (4) and (b) (4)) and the to-be-marketed product (Process (b) (4)).

1.2 Post-Marketing Requirements and Commitments

To obtain meaningful immunogenicity results, a PMR is recommended by the clinical pharmacology review team. To fulfill the PMR, the applicant needs to use improved and validated assays of ADA and NAb to evaluate their impacts on the pharmacokinetics, pharmacodynamics, safety, and efficacy of lecanemab in patients enrolled in the confirmatory study. Please refer to OBP review for another PMR to develop and validate ADA and NAb assays with improved sensitivity.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

Lecanemab is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. The accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of Alzheimer's disease. Lecanemab reduces amyloid beta plaques as evaluated in Study 201.

Distribution

The mean value for central volume of distribution at steady-state is 3.22 L (95% confidence interval is 3.15-3.28).

Elimination

Lecanemab is expected to be degraded by proteolytic enzymes into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs. The mean clearance of lecanemab is 0.434 (0.420-0.451) L/day, and the mean terminal half-life is 5 to 7 days.

Lecanemab clearance was not affected by age, race, liver enzymes, creatinine clearance, and APOE4 carrier status. The covariates effects of body weight, albumin, and sex were small and not clinically meaningful. Therefore, no dose adjustment is recommended for lecanemab based on these covariates.

Specific Populations

No dedicated clinical studies were performed in subjects with renal or hepatic impairment. Generally, the IgG monoclonal antibodies undergo elimination via intracellular catabolism, and the impact of renal/hepatic impairment on the pharmacokinetics of lecanemab is unlikely to be clinically relevant. Therefore, no dose adjustment is recommended for patients with hepatic/renal impairment.

Immunogenicity

During the 18-month treatment period in Study 1, 63/154 (40.9%) of patients treated with LEQEMBI (10 mg/kg biweekly) developed anti-lecanemab-irmb antibodies. Of these patients neutralizing anti-lecanemab-irmb antibodies were detected in 16/63 (25.4%) patients. However, the assays used to measure anti-lecanemab-irmb antibodies and neutralizing antibodies are subject to interference by serum lecanemab concentrations, possibly resulting in an underestimation of the incidence of antibody formation. Therefore, there is insufficient information to characterize the effects of anti-lecanemab-irmb antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of LEQEMBI.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended starting and maintenance dose of lecanemab is 10 mg/kg and the dosing frequency is once every 2 weeks. Lecanemab is administered as an intravenous infusion over approximately one hour. The dosing regimen was tested in the pivotal Phase 2 Study in patients with early AD.

2.2.2 Therapeutic individualization

No therapeutic individualization is recommended based on intrinsic/extrinsic factors. As a monoclonal antibody administered by intravenous route, food-drug interactions are not anticipated for lecanemab, and the drug-drug interaction liability is considered low. In addition, renal/hepatic impairment is not expected to impact the pharmacokinetics of lecanemab.

2.3 Outstanding Issues

The ADA and NAb assays have drug tolerance levels that are lower than most of the pre-dose lecanemab concentrations in Study 201 Core at the dose of 10 mg Q2W, which affects the data interpretability regarding the incidence and clinical impact of antibody formation. Improved assays of ADA and NAb need to be developed with drug tolerance levels that allow data interpretation for most of the study participants. The applicant needs to use improved and validated assays to determine the incidence of ADA and NAb in the confirmatory study, and to evaluate the potential impact of ADA and NAb on the pharmacokinetics, pharmacodynamics, safety, and efficacy of lecanemab.

2.4 Summary of Labeling Recommendations

The proposed labeling concepts are generally acceptable. However, the review team has the following recommendations for Labeling Sections 12.2 and 12.6:

Labeling Section 12.2 Pharmacodynamics

- Plasma p-tau181 and plasma Aβ42/40 ratio: The bioanalytical method validation has a few scientific gaps, including insufficient coverage of long-term stability and inadequate matrix effect evaluation. The reported changes in these biomarkers following treatment with lecanemab compared to placebo are unlikely to be a random occurrence and cannot be fully attributed to the inadequacy of method validation (please refer to Appendix 4.3 for additional details). Therefore, the review team recommends including qualitative statements in labeling Section 12.2 to reflect the changes in plasma p-tau181 and Aβ42/40 ratio following 10 mg/kg biweekly dosing compared to placebo observed in Study 201 Core. Further, the review team recommends including a statement to highlight the uncertainties in bioanalysis if inclusion of any quantitative description of plasma biomarkers is considered clinically necessary in other sections of the label.
- (b) (4)
- Exposure-Response Relationships: Higher exposures to lecanemab were associated with greater reduction in amyloid beta plaque (SUVR) and clinical decline. Higher exposures to lecanemab were also associated with greater increase in plasma Aβ42/40 ratio and greater reduction in plasma p-tau181. In addition, reduction in amyloid beta plaque (SUVR) was associated with slowing of clinical decline.

Labeling Section 12.6 Immunogenicity

The review team noted that most of the pre-dose lecanemab concentrations were above the drug tolerance level for the ADA and NAb assays. This limitation in ADA assay resulted in ADA negative inconclusive status for a majority of study samples, which created challenges to evaluate the clinical impact of ADA on PK, PD, efficacy, and safety. Thus, the review team recommends to state in the label that:

- The ADA and NAb assays are subject to interference by serum lecanemab concentrations, possibly resulting in an underestimation of the incidence of antibody formation.
- Therefore, there is insufficient information to characterize the effects of anti-lecanemab-irmb antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of LEQEMBI.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Lecanemab, also known as BAN2401, is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) directed against aggregated soluble and insoluble forms of amyloid beta. It selectively targets large soluble protofibrils relative to monomers, with preferential activity over insoluble fibrils.

Lecanemab is being developed as a treatment for Alzheimer's disease (AD), and this submission is seeking accelerated approval of lecanemab for the treatment of mild cognitive impairment or mild dementia stage of AD. Lecanemab has been supplied in clinical studies as a liquid drug product in vials, which is diluted with saline prior to intravenous infusion.

Current therapeutic agents for patients with mild, moderate, and severe AD dementia consist of symptomatic therapies that include acetylcholinesterase inhibitors (AChEIs), such as donepezil, and the N-methyl-D-aspartate receptor antagonist, memantine. These agents provide symptomatic benefit and do not prevent progression of the disease process. In June 2021, aducanumab (Aduhelm®) was approved in the US under the accelerated approval pathway for the treatment of AD based on a reduction in amyloid beta plaques.

The clinical development program for the lecanemab BLA submission consists of 5 ongoing or completed clinical studies. Study BAN2401-G000-201 is the registrational trial to evaluate safety, tolerability, and efficacy of lecanemab, and it was a multicenter, double-blind, placebo-controlled, parallel-group Phase 2 study with a completed Core phase and an ongoing OLE Phase. Study BAN2401-A001-101 and BAN2401-J081-104 are completed Phase 1 studies that evaluated single or multiple doses of lecanemab (0.1 to 15 mg/kg) administered to subjects with mild to moderate AD (Study 101) and MCI due to AD and mild AD (Study 104). Additionally, two ongoing phase 3 studies in early AD (Study BAN2401-G000-301) and preclinical AD (Study BAN2401-G000-303) patients also contributed to the evaluation of safety. Please refer to Clinical Review for details of safety evaluation.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Lecanemab is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. The accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of Alzheimer's disease. Lecanemab reduces amyloid beta plaques.
QT Prolongation	No formal QT evaluation has been conducted for lecanemab. As a large molecule, lecanemab has a low likelihood to directly interact with ion channels.
General Information	
Bioanalysis	The applicant used LC-MS/MS and ELISA methods to determine the concentration of lecanemab in human serum. In addition, Aβ[1-42] protein

	in human CSF samples was determined by ELISA assay. The Aβ42 and Aβ40 in human plasma were determined by LC-MS/MS. Commercial assay kits were used to quantify p-tau181 in CSF and plasma. Refer to Section 4.1 for details on the validation and performance of bioanalytical methods.
Dose Proportionality	The peak concentration (C_{max}) and AUC_{0-24h} of lecanemab increased dose proportionally in the dose range of 0.3 to 15 mg/kg after a single dose.
Accumulation	Steady state concentrations of lecanemab were reached after 6 weeks of 10 mg/kg biweekly treatment and systemic accumulation was 1.4-fold.
Immunogenicity	In Study 201 Core, 63/154 (40.9%) of LEQEMBI-treated patients (10 mg/kg biweekly) developed anti-lecanemab-irmb antibodies. Of these patients neutralizing anti-lecanemab-irmb antibodies were detected in 16/63 (25.4%) patients. However, the assays used to measure anti-lecanemab-irmb antibodies and neutralizing antibodies are subject to interference by serum lecanemab concentrations, possibly resulting in an underestimation of the incidence of antibody formation. Therefore, there is insufficient information to characterize the effects of anti-lecanemab-irmb antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of LEQEMBI.
Absorption	
C_{max} and AUC	At steady-state, the mean (CV%) C_{max} of lecanemab is 307 (21.5%) µg/mL, and mean (CV%) AUC_{0-tau} is 37700 (25.5%) µg·h/mL
T_{max}	Approximately 2 hours at the dose of 10 mg/kg
Distribution	
Volume of Distribution	The mean value (95% CI) for central volume of distribution at steady-state is 3.22 L (3.15-3.28).
Elimination	
Terminal Elimination half-life	Lecanemab clearance (95% CI) is 0.434 (0.420-0.451) L/day. The terminal half-life is 5 to 7 days.
Metabolism/Excretion	As a humanized IgG1 monoclonal antibody, lecanemab is expected to be degraded by proteolytic enzymes into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs.

3.3 Clinical Pharmacology Review Questions

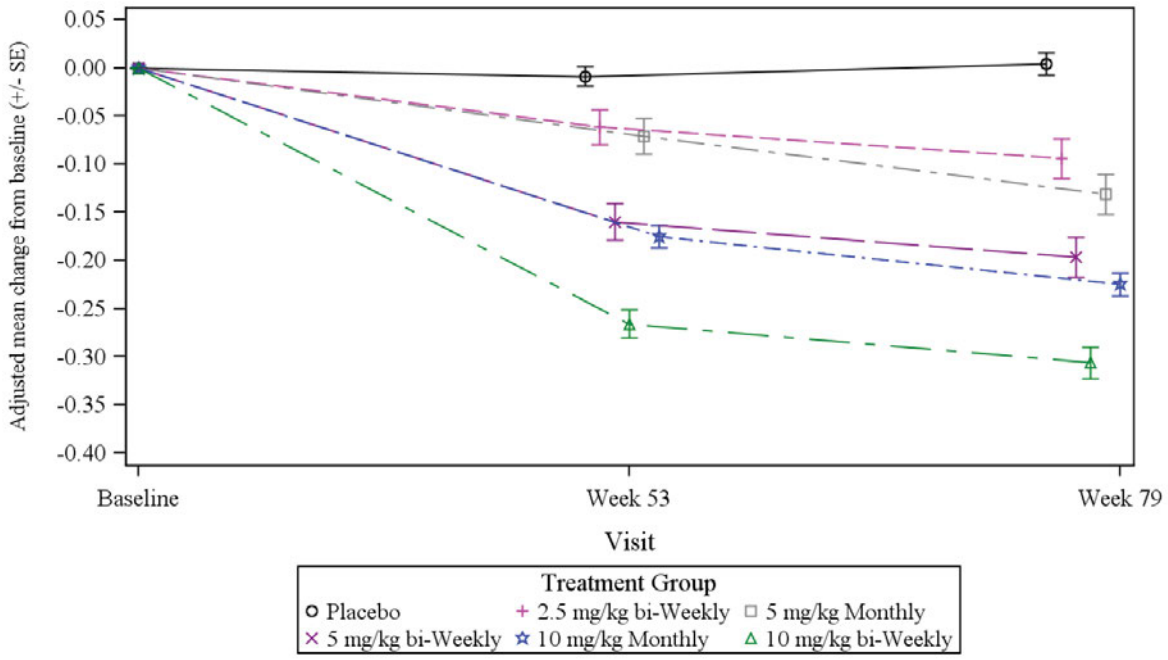
3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The primary evidence of effectiveness for the treatment of AD is based on the effect of lecanemab on brain amyloid, a biomarker reasonably likely to predict clinical benefit, as observed in the adequate and well-controlled Phase 2 Study BAN2401-G000-201 (Study 201). Study 201 included Core, Gap, and OLE phases. The Study 201 Core had an 18-month double-blind treatment period and a 3-months Follow-up period, which provides the primary dataset for the evaluation of safety and efficacy. The dosing regimens evaluated in Study 201 Core included lecanemab 2.5 mg/kg biweekly, 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg monthly, and 10 mg/kg biweekly. The primary endpoint was change from Baseline in ADCOMS at 12 months of treatment compared to placebo, while all subjects were required

to complete 18 months of study irrespective of results of the 12-months interim analysis. It was followed with a Gap period between the end of Core and the start of OLE Phase where subjects were off lecanemab (i.e., untreated) for 9 to 59 months (mean 24 months). The OLE phase is currently ongoing, in which all the subjects receive lecanemab 10 mg/kg biweekly.

A dose and time-dependent effect on the reduction of brain amyloid was demonstrated in Study 201 Core (**Figure 1**). At the proposed therapeutic dose of lecanemab 10 mg/kg biweekly, the amyloid change from baseline (CFB) as measured by PET SUVR was statistically significant (P<0.001 at Week 53 and Week 79) versus placebo. A least-square (LS) mean reduction in PET SUVR of 0.306 was observed after 18 months of lecanemab treatment compared to an LS mean increase of 0.004 for placebo. The mean amyloid PET SUVR following lecanemab 10 mg/kg biweekly treatment for 18 months was below the SUVR threshold for amyloid positivity of 1.17. Approximately 65% and 81% of subjects were converted from amyloid positive to negative by visual read at 12 and 18 months, respectively, compared to 12 % and 22 % for the subjects in the placebo group. Overall, these results of conversion to amyloid negativity indicate that lecanemab treatment significantly clears amyloid from the brain.

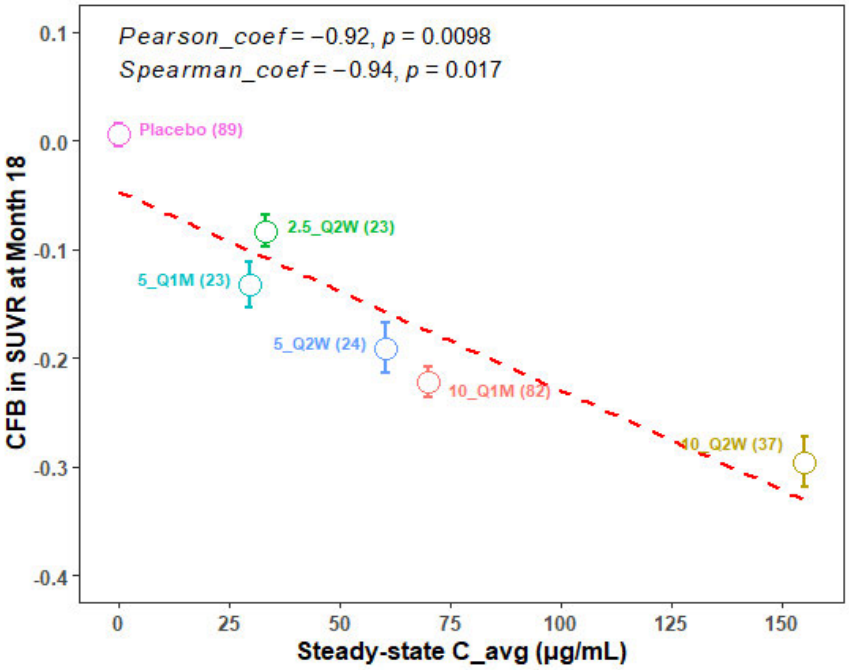
Figure 1 Least Square Mean (± SE) Change from Baseline in Brain Amyloid Levels as Measured by Amyloid PET SUVR Normalized to Whole Cerebellum Mask by Visit – Study 201 Core



Source: Applicant's Study 201 Core Clinical Study Report Figure 14.2.2.3.4e.

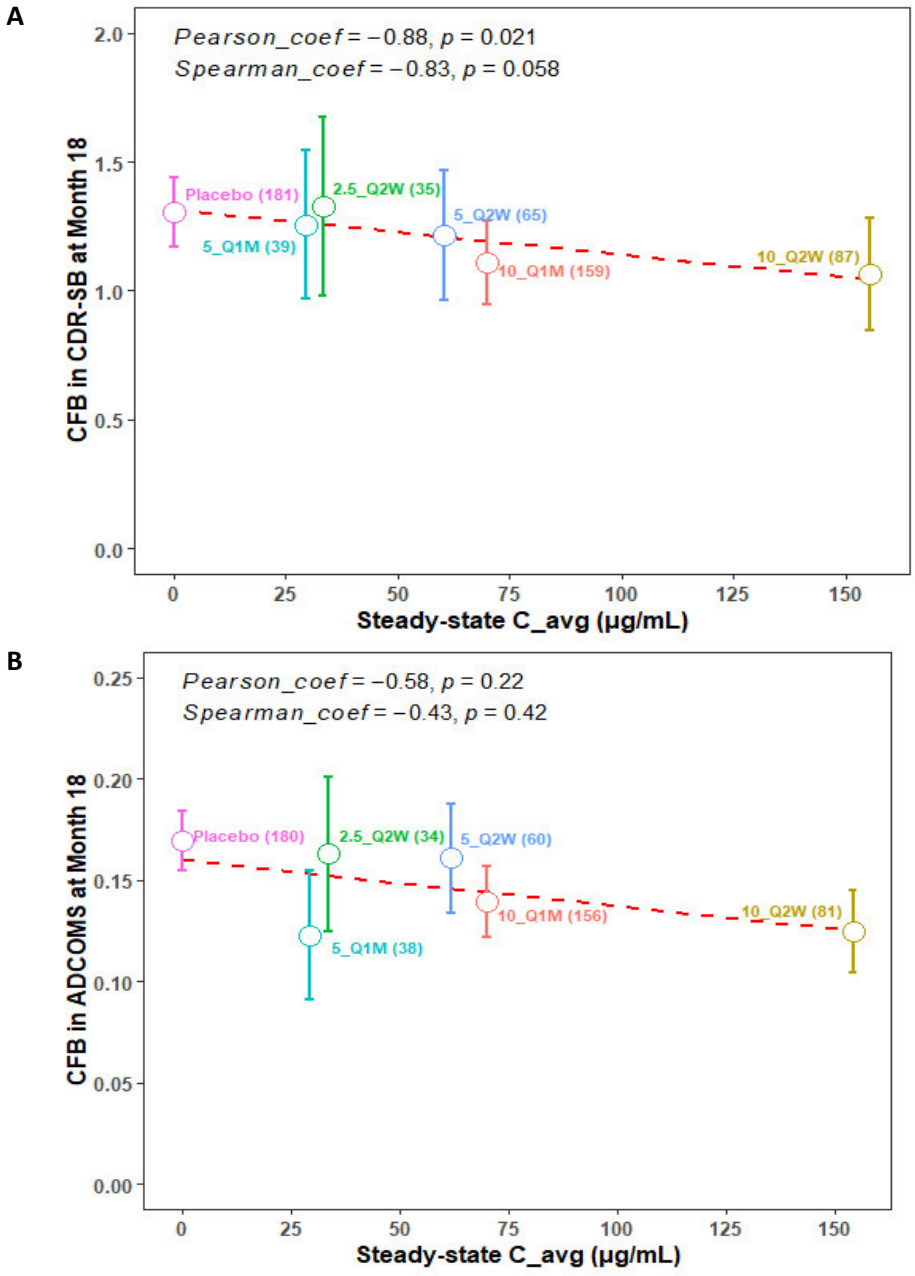
The effectiveness of lecanemab as a treatment for AD is also supported by the exposure-response relationships for amyloid PET and clinical efficacy endpoints in Study 201 Core. At 18 month after the initiation of treatment, higher lecanemab average plasma concentration at steady state ($C_{ss,avg}$) was associated with greater reduction in amyloid PET SUVR (**Figure 2**). In addition, an association was observed between higher lecanemab PK exposures ($C_{ss,avg}$) and greater reduction in clinical decline. As shown in **Figure 3A**, higher $C_{ss,avg}$ of lecanemab was associated with less increase from baseline in Clinical Dementia Rating – Sum of Boxes (CDR-SB) at month 18. Similar trends were observed with other clinical efficacy endpoints including Alzheimer's Disease Composite Score (ADCOMS) and Alzheimer's Disease Assessment Scale – Cognitive subscale with 14 tasks (ADAS-Cog14), as shown in **Figure 3B and Figure 3C**. In addition to the correlation using observed data in Figure 3, model-based exposure-response analyses demonstrated that higher exposures to lecanemab were associated with greater reduction in decline in CDR-SB, ADCOMS, and ADAS-Cog14 over time (refer to Appendix 4.4.1.2, **Figure 13**).

Figure 2 Relationship Between Lecanemab Exposure ($C_{ss,avg}$) and the Change from Baseline in Amyloid PET SUVR at Month 18



Source: Reviewer's analysis.
Circles and error bars represent mean and ± standard errors respectively.

Figure 3 Relationships Between Lecanemab Exposure ($C_{ss,avg}$) and the Change from Baseline in Clinical Endpoints Including CDR-SB (A), ADCOMS (B) and ADAS-Cog14 (C) at Month 18



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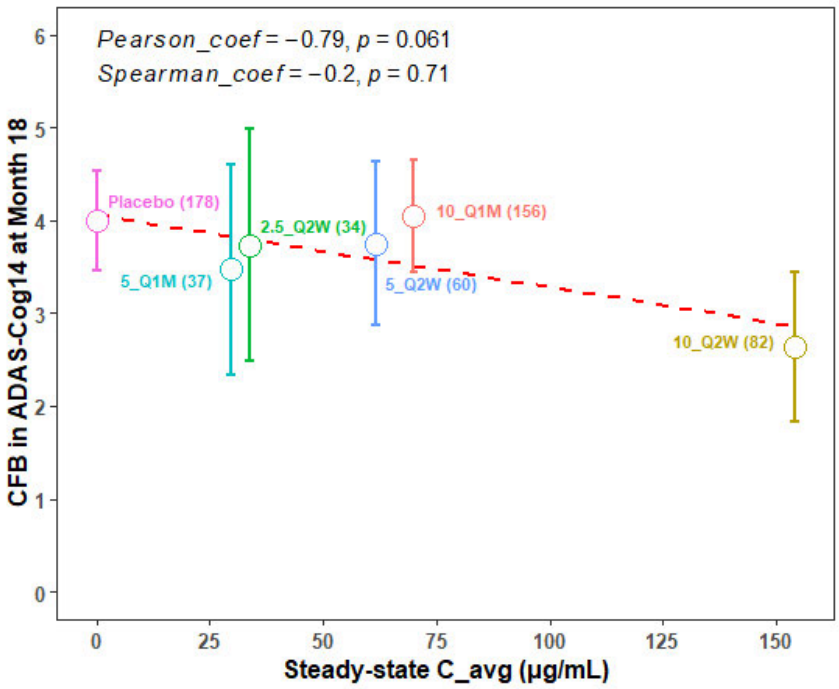
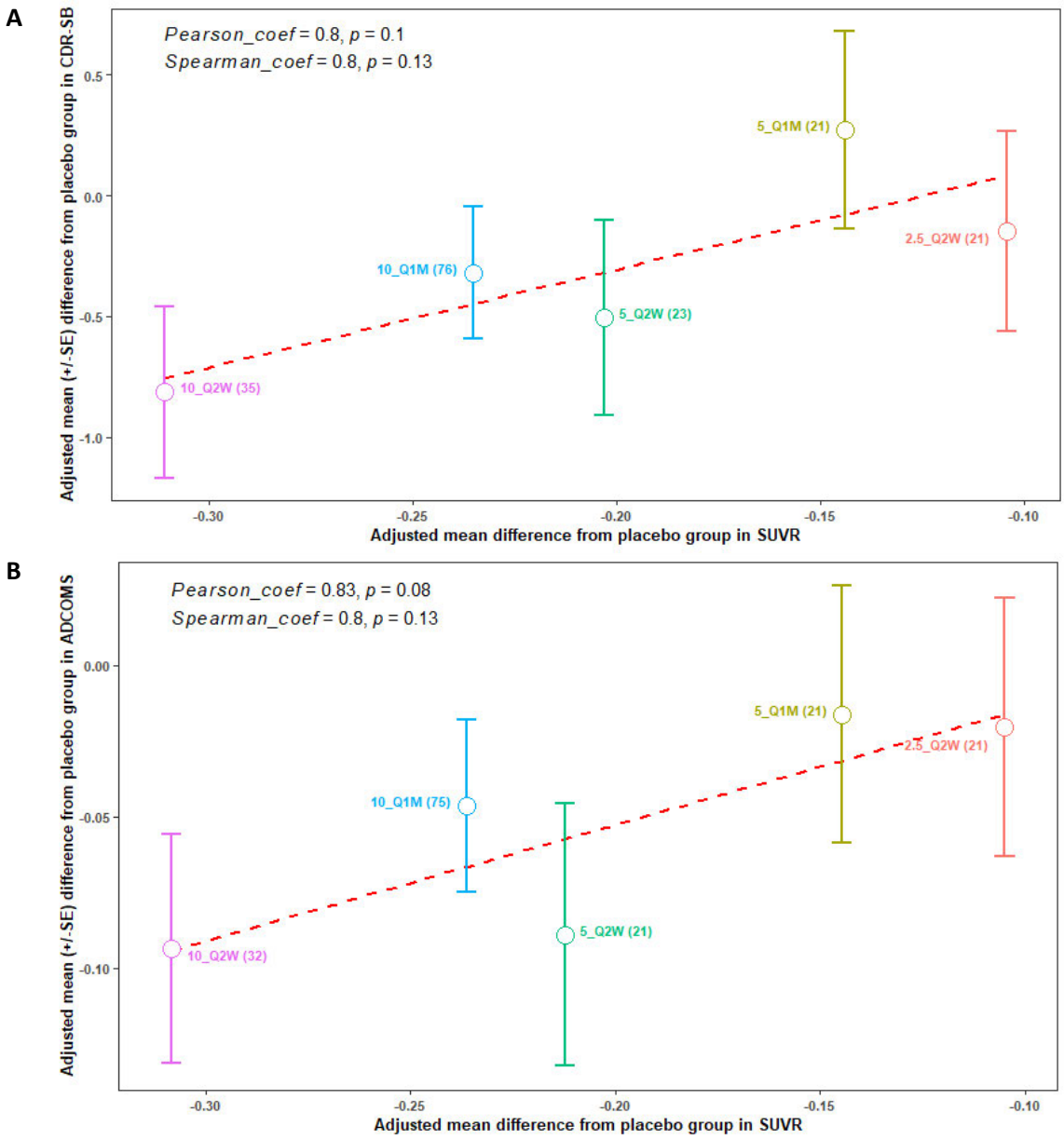


Source: Reviewer's analysis.
Circles and error bars represent mean and ± standard errors respectively.

The associations between amyloid PET-SUVR and clinical endpoints (CDR-SB, ADCOMS and ADAS-Cog14) from Study 201 Core are shown in **Figure 4**. The data suggest that reduction in amyloid PET-SUVR were associated with reduction in clinical decline on CDR-SB, ADCOMS, and ADAS-Cog14. Additionally, the SUVR-Efficacy models predicted SUVR change-dependent slowing of disease progression over time (refer to Appendix 4.4.1.3, **Figure 16**).

Figure 4 Relationship Between Adjusted Mean (+/-SE) Difference from Placebo Group in Clinical Endpoints and Adjusted Mean Difference from Placebo in Amyloid PET-SUVR at Month 18



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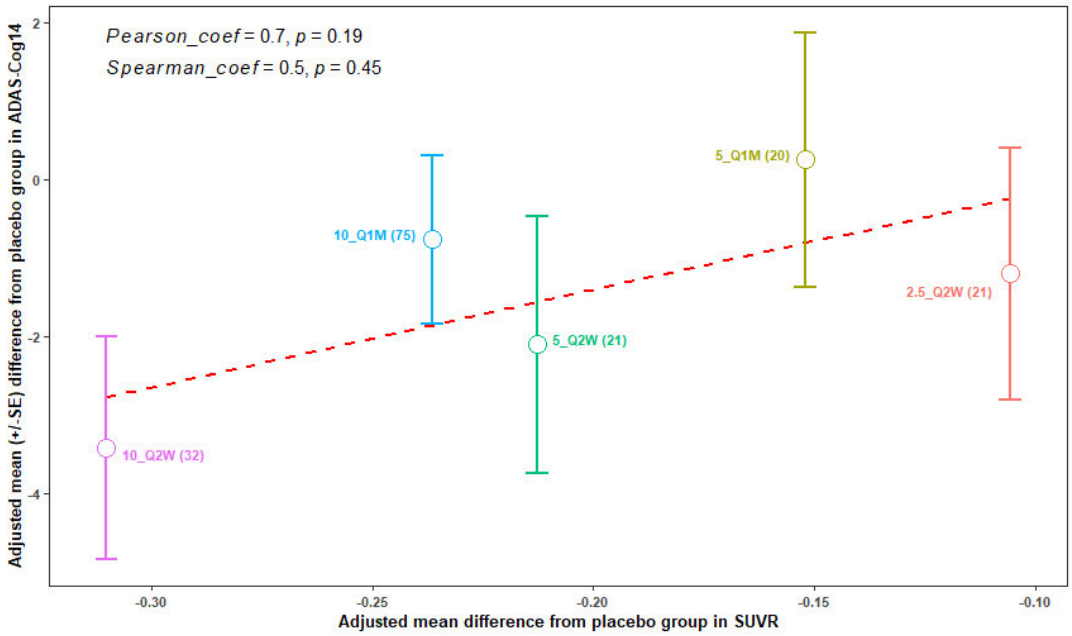


Note: PD analysis set 2 dataset was used for the analysis which included subjects who had sufficient amyloid PET data to derive at least 1 amyloid parameter. Clinical endpoints and amyloid PET SUVR data at Month 12 and Month 18 were included in the MMRM analysis to compute adjusted mean difference.
CDR-SB: Clinical Dementia Rating – Sum of Boxes; ADCOMS: Alzheimer's Disease Composite Score; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; MMRM: mixed-effect models with repeated measures; PET: positron emission tomography, SUVR: standard uptake value ratio
Source: Reviewer's analysis.

In addition to the data listed above, the applicant submitted plasma and CSF biomarker data to supplement the evaluation of the treatment effect and support mechanistic activity of lecanemab and drug-related effect on downstream AD pathophysiology. These biomarkers included plasma Aβ42/40 ratio, CSF Aβ[1–42], and the human tau protein phosphorylated at threonine in position 181 (p-tau181) in plasma and CSF. Literature reports suggest that the soluble biomarkers such as p-tau181 and Aβ42/40 were altered in AD dementia and have potential value for diagnostic/prognostic purposes or as a pharmacodynamic biomarker to support benefit for the treatment of early AD[1,2,3,4,5]. The review team note that the bioanalytical method validations for CSF Aβ[1–42] and CSF p-tau181 have major limitations (b) (4) For plasma p-tau181 and Aβ42/40 ratio, although

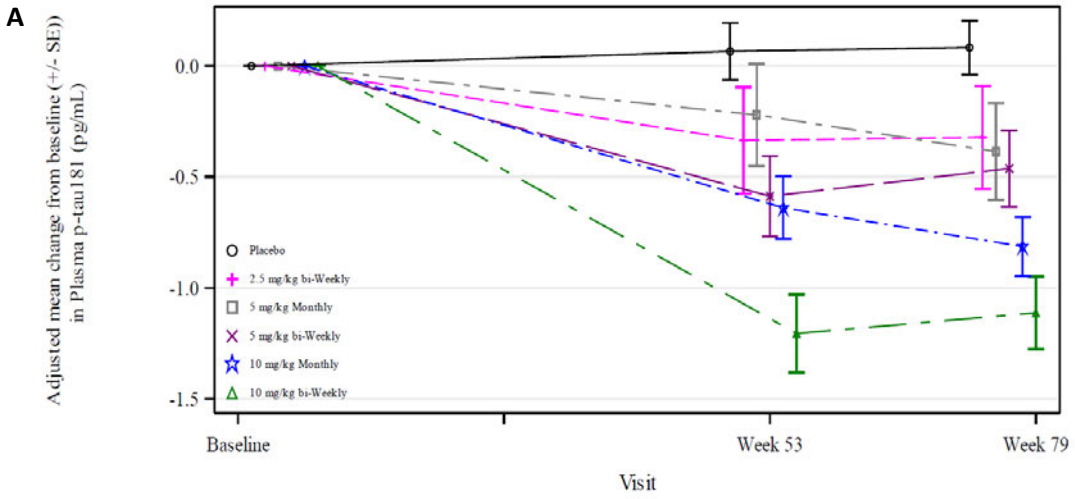
[1] Simrén, J. et al. The diagnostic and prognostic capabilities of plasma biomarkers in Alzheimer's disease. Alzheimers Dement. 17(7):1145-1156 (2021).
[2] Cummings, J. and Kinney J. Biomarkers for Alzheimer's Disease: Context of Use, Qualification, and Roadmap for Clinical Implementation. Medicina (Kaunas). 58(7):952 (2022).
[3] Therriault, J. et al. Association of plasma P-tau181 with memory decline in non-demented adults. Brain Commun. 3(3): fcab136 (2021).
[4] Chatterjee, P. et al. Diagnostic and prognostic plasma biomarkers for preclinical Alzheimer's disease. Alzheimers Dement. 18(6): 1141–1154 (2022).
[5] Karikari, T. K. et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. Lancet Neurol. 19(5), 422–433 (2020).

the bioanalytical method validations were also not fully established, the observed relative change across treatment arms cannot be accounted for by the uncertainties in bioanalysis. Hence, the review team recommends using qualitative descriptions for the plasma biomarker results, and all the quantitative analyses of the plasma biomarker data presented in this review should be interpreted with caution. Please refer to Appendix 4.3 for more details.

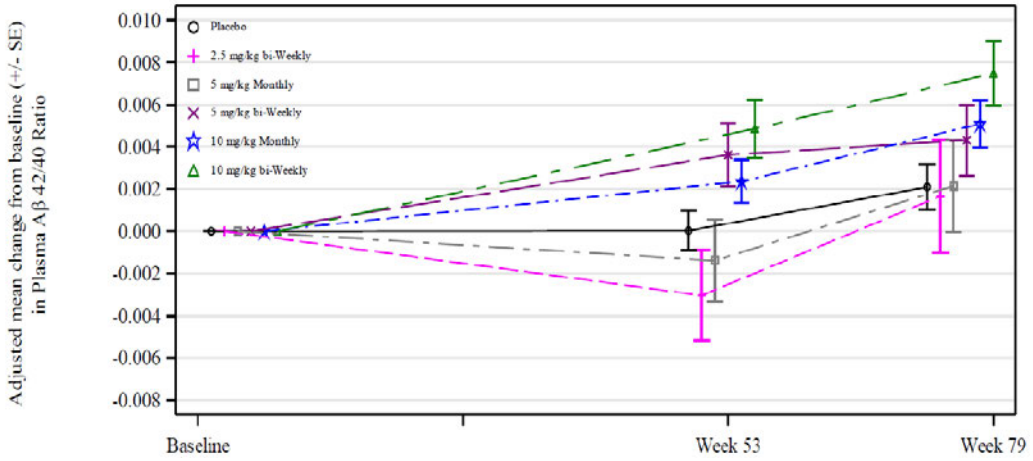
In Study 201 Core, a dose dependent reduction in plasma p-tau181 was observed with lecanemab treatment (**Figure 5A**). In addition, an increase in plasma Aβ42/40 ratio was observed following treatment with lecanemab at 5 mg/kg biweekly, 10 mg/kg monthly, and 10 mg/kg biweekly dosing compared to placebo (**Figure 5B**). Higher lecanemab exposures were observed to be associated with greater increase in plasma Aβ42/40 ratio and greater reduction in plasma p-tau181 (Appendix 4.3.1 **Figure 6** and **Figure 8**). However, the CSF Aβ[1–42] and CSF p-tau181 bioanalytical method validation had major limitations identified in multiple aspects, and no conclusion is warranted based on CSF biomarker data.

Besides Study 201 Core, the applicant also submitted biomarker data including plasma Aβ42/40 ratio and plasma p-tau181 during the Gap period and OLE period after resuming the treatment. Please refer to **Appendix 4.3** for further details in data assessments of the plasma and CSF biomarkers, and refer to **Appendices 4.1.2 and 4.1.3** for bioanalytical method validation and performance for these biomarkers.

Figure 5 Least Square Mean (± SE) Change from Baseline in Plasma p-tau181 (A) and Plasma Aβ42/40 Ratio (B) Over Time in Study 201 Core



B



Source: Applicant's Integrated Summary of Efficacy. (A) Page 67, Figure 8. (B) Page 66, Figure 7

The applicant has conducted PK/PD modeling for amyloid PET-SUVR, clinical efficacy endpoints, plasma and CSF biomarkers, and ARIA-E incidence. The results for amyloid PET-SUVR and clinical efficacy endpoints are consistent with the observed data in Study 201 Core as mentioned above (**Figure 2, Figure 3, and Figure 4**). The review team note that these analyses are informative, however, quantitative conclusions cannot be made from the PK/PD modeling of Aβ42/40 ratio and p-tau181 in plasma due to the limitations in bioanalytical validation. Please refer to Appendix 4.4 Pharmacometrics Analysis for the details on the applicant's population PK/PD analysis, and refer to the clinical and OBP reviews for more information on efficacy and safety assessments and SUVR assay.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The applicant is seeking approval for the lecanemab dose of 10 mg/kg administered every two weeks (Q2W) by intravenous infusion over approximately one hour. The proposed dosing regimen was the highest dose evaluated in the pivotal Phase 2 study. Based on the observed effect of lecanemab on amyloid PET-SUVR, clinical endpoints, safety, and the exposure-response relationships, this regimen was shown to be effective and well-tolerated.

The recommended dosing regimen 10 mg/kg biweekly has demonstrated the largest effect among the tested doses on amyloid PET-SUVR and clinical efficacy endpoints. As shown in **Figure 1**, the 10 mg/kg biweekly dosing regimen resulted in a larger and faster decrease in brain amyloid levels as measured by PET SUVR compared to 10 mg/kg monthly dosing. After 18 months of treatment with lecanemab, the least square mean CFB in amyloid PET SUVR was 0.306 for 10 mg/kg biweekly dosing, versus 0.225 for the 10 mg/kg monthly dosing. In addition, with 10 mg/kg biweekly dosing regimen, the conversion of amyloid status from positive to negative was observed in 65% and 81% of subjects at 12 months and 18 months, respectively, which was higher than the percentage values with 10 mg/kg monthly dosing (42% and 77%, respectively). These results suggest that the 10 mg/kg biweekly dosing was more effective to clear the amyloid from the brain compared to 10 mg/kg monthly dosing of lecanemab. In addition, greatest reduction in cognitive decline as assessed by CDR-SB, ADCOMS and ADAS-Cog14 were also achieved with the 10 mg/kg biweekly dosing. Please refer to the clinical review for the details on the effect of each dosing regimens on the clinical endpoints.

Lecanemab 10 mg/kg biweekly dosing was generally well-tolerated. The most common treatment-emergent adverse events (TEAEs) were infusion reactions and amyloid-related imaging abnormalities-edema/effusion (ARIA-E). In Study 201 Core, treatment-emergent ARIA-E was reported in approximately 10% of the subjects for each of the highest lecanemab dose groups (25/253 for 10 mg/kg biweekly dosing, and 16/161 for 10 mg/kg monthly dosing). In the subgroup of patients receiving 10 mg/kg lecanemab biweekly, the ARIA-E incidence was higher in APOE4 carriers (14.3%) than in APOE4 noncarriers (8.0%). Given the lower rate of ARIA-E compared to other anti-amyloid mAbs, dose titration is not needed for lecanemab. The applicant also explored the relationship between incidence of ARIA-E and lecanemab PK exposures using logistic regression. As shown in **Figure 20A** in Appendix 4.4.1.4, model-predicted proportion of subjects with ARIA-E increases with $C_{ss,max}$, and the proportion was higher for APOE4 carriers. Please refer to Appendix 4.4.1.4 for more details.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. Dose adjustment is not necessary based on intrinsic factors such as age, race, sex, body weight, renal or hepatic impairment. No dedicated renal or hepatic impairment studies were conducted.

Population pharmacokinetic analysis was conducted on data from 725 subjects to evaluate the impact of intrinsic factors. Lecanemab clearance was not affected by age, race, liver enzymes, creatinine clearance, and APOE4 carrier status. Covariate effects included in the final PK model were body weight, albumin, sex, and ADA positive status as time-variant covariate on clearance, body weight and sex on central volume of distribution, and Japanese race on peripheral volume of distribution. The effect of covariates on the population PK parameters were small and not considered as clinically meaningful.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No. Lecanemab is administered by intravenous infusion, and the food-drug interaction is not anticipated. Lecanemab exposure is not expected to influence or be influenced by the cytochrome P450-mediated metabolic pathways associated with co-administered drugs. Lecanemab does not appear to be a cytokine or immunomodulator. Lecanemab elimination is expected to occur through normal degradative pathways for immunoglobulins and the systemic clearance should not be affected by small-molecule concomitant medications.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support approval of the to-be-marketed formulation?

Various formulations with different manufacturing processes (b) (4) of lecanemab were used in clinical studies and are different with the to-be-marketed formulation (process (b) (4)).

Process (b) (4) (producing formulation A) was used in studies 101, 104, 201 Core and OLE Phase. Process (b) (4) producing formulation B) was introduced to (b) (4) and it was used in Study 201 OLE Phase. Pop-PK analysis showed that lecanemab exposure following intravenous administration of the two formulations (Process (b) (4) and Process (b) (4)) used in the Studies 101, 104 and 201 Core and OLE were comparable. The process (b) (4)

(producing formulation [redacted] No bioequivalence study was conducted to compare the formulations.

In accordance with ICH Q5E guidelines, the applicant conducted comparability studies to demonstrate analytical similarity between different formulations. Based on internal discussion with OBP and clinical review teams, it was concluded that the bridging is adequate between the clinical and commercial formulations. Please refer to the review by OBP team for the details in analytical similarity.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 Bioanalysis for Lecanemab in human serum

4.1.1.1 ELISA for Lecanemab in serum

An enzyme-linked immunosorbent assay (ELISA) method was initially developed and validated by [redacted] to measure lecanemab in some human serum samples from Study 101. [redacted] The validated assay quantitation range for lecanemab in human serum was 6.00 to 75.0 µg/mL.

The serum samples analyzed by ELISA method were from Study 101 single ascending dose cohorts (SAD)1, SAD2, SAD3, SAD4 (except Days 10 and 21), SAD5 (except Day 21 and Day 28), and multiple ascending dose (MAD)1 (Days 1, 2, 21, 28, 49 and 56) cohorts. The remaining samples in Study 101 and all serum samples from Studies 104 and 201 (Core and OLE Phase) were analyzed by [redacted] using a more sensitive LC-MS/MS method as described in Section 4.1.1.2.

4.1.1.2 Hybrid LC-MS/MS for Lecanemab in serum

The applicant used a hybrid assay consisting of an immunopurification step followed by a tryptic digestion step and liquid chromatography and tandem mass spectrometry (LC-MS/MS) to determine the concentration of lecanemab in human serum [redacted] was monitored as a surrogate for lecanemab. [redacted] was used as the internal standard (IS), and [redacted] was monitored as a surrogate. This assay was determined to have a higher sensitivity and a wider linear range (0.5 - 150 µg/mL) for lecanemab in human serum, as compared with the ELISA method. [redacted], the acceptance criteria for the LC-MS/MS method was expanded to 20/25% as is typical in the quantitation of large molecules with an ELISA method.

The method BTM-1425-R0 was initially developed and validated for use in studies BAN2401-A001-101, BAN2401-J081-104, and BAN2401-G000-201 Core. An updated version of the method (BTM-1425-R3, using 96-well plate formats and automation equipment) was subsequently developed and partial-validated, and used in Study BAN2401-G000-201 OLE.

It should be noted that approximately 2% of human serum samples were out of established stability (371 days in human serum at -70°C). The maximum time of serum samples in storage was 1636 days at -70°C in Study 201 Core and 948 days at -70°C in Study 201 OLE. In response to Information Request received on March 11, 2022 (Sequence No. 0024), the applicant noted that additional long-term stability assessment is ongoing, and reports will be submitted to the Agency.

Cross-method validation of the LC-MS/MS assay with the ELISA assay was demonstrated using serum-spiked, blinded quality control (QC) samples and 32 incurred samples from Study 101. The cross-validation results met acceptance criteria.

Overall, the method was validated in compliance with the standards set forth in the FDA Bioanalytical Method Validation guidance, except for the long-term stability. The human serum samples out of established stability are a small fraction, and therefore not expected to impact the interpretability of population PK and exposure-response analyses. Summary of the validation parameters for both the methods are presented in **Tables 1**.

Table 1 Bioanalytical Validation for Determination of Lecanemab in Human Serum by LC-MS/MS

Method No.	BTM-1425-R0	BTM-1425-R3
Validation Report	EIS-R1696 (full validation)	E1S-R1696A2 (partial validation)
QC concentrations	1.5 µg/mL, 12 µg/mL, and 112.5 µg/mL	0.500 µg/mL, 1.50 µg/mL, 12.0 µg/mL, 60.0 µg/mL, 113 µg/mL
Standard Curve Concentrations and linearity R^2	0.5, 1, 3, 6, 20, 40, 120, 150 µg/mL, $R^2 \geq 0.9791$	0.500 - 150 µg/mL, $R^2 \geq 0.9867$
Lower limit of quantitation (LLOQ)	0.5 µg/mL	0.5 µg/mL
QC Intra-run precision (%CV)	Run 1: 5.8, 7.0, 4.9 Run 2: 5.2, 7.2, 4.5 Run 3: 12.9, 7.6, 3.8	Run 1: 5.8, 2.4, 2.9, 1.4, 19.6 Run 2: 10.0, 8.3, 3.2, 6.1, 11.5 Run 3: 8.0, 8.7, 1.8, 6.1, 3.1
QC Intra-run accuracy (%Bias)	Run 1: -3.0, 3.2, 1.1 Run 2: -4.1, 2.6, 5.4 Run 3: -8.2, -9.6, -12.8	Run 1: 9.2, 3.3, -2.5, -0.8, 0.9 Run 2: -0.2, -9.3, -14.2, -14.0, -15.0 Run 3: 7.8, 0.7, -3.3, -2.7, -1.8
QC Inter-run precision (%CV)	8.4, 9.1, 9.2	8.5, 8.6, 6.4, 7.8, 14.8
QC Inter-run accuracy (%Bias)	-5.1, -1.3, -2.1	5.6, -2.0, -6.7, -5.8, -5.3
Average recovery of the Analyte (%)	25.9	42.7
Average recovery of the IS (%)	12.3	N/A
Dilution integrity	450 µg/mL diluted 20-fold	450 µg/mL diluted 4-fold
QC sample bench-top stability	19 hours at room temperature	6 hours at room temperature
QC sample freeze/thaw stability	3 freeze (-70 °C)/thaw cycles	5 cycles for -70 °C

Processed sample stability	73.5 hours at room temperature	175.0 hours at 4 °C
QC sample long-term storage stability	34 days at -70 °C	371 days at -70 °C
IS-normalized Matrix factor	1.35 ± 0.13 (%CV= 9.6%) at 1.5 µg/mL	1.34 (%CV = 11.3%) at 1.50 µg/mL 1.31 (%CV = 4.6%) at 113 µg/mL
Selectivity	No interfering peaks detected	
Carryover	Not significant	

4.1.2 Bioanalysis of amyloid beta in human CSF and plasma

4.1.2.1 Determination of amyloid beta (Aβ) (1-42) protein in human CSF samples for ELISA studies BAN2401-J081-104 and BAN2401-G000-201

The applicant used a partially validated ELISA assay to determine Aβ (1-42) protein in human CSF samples. The ELISA assay used a commercial kit manufactured by Innogenetics and Fujirebio to determine the concentration of β-Amyloid (1-42) in CSF matrix. The amyloid peptide in CSF samples is captured by a monoclonal antibody, 21F12 (IgG2a) and then incubated with a biotinylated antibody, 3D6 (IgG2b) and detected by a peroxidase-labeled streptavidin after adding substrate. The color intensity correlates with human β-amyloid(l-42) protein concentration in the sample.

The applicant used method MOS-CMF-103.v1 to analyze samples from study BAN2401-J081-104 and method MOS-CMF-103.v2 to analyze samples from study BAN2401-G000-201. **Table 2** is a summary of performance characteristics of these two methods. Briefly, the two methods have different calibration range and used different test kits from the same manufacturer. The applicant stated that the cross-validation between the two versions of test kits was conducted by the manufacturer. The β-amyloid (1-42) concentrations between the two kits were significantly correlated (r = 0.971) and fell within the normal lot-to-lot variability. The test kit contains ready-to-use calibration standards at 6 different concentrations and Quality Control samples (QCs) at 2 different concentrations.

In the validation for method version 1, intra-run precision was evaluated by measuring 17 replicates of one pooled CSF sample. Inter-run precision was evaluated by measuring one pooled CSF samples from 30 different runs. The validation report did not describe the sources for these pooled CSF samples. The assay precision was ≤15% for intra-run and ≤20% for inter-run. The applicant did not perform the accuracy, selectivity, and matrix effect for the assay during the validation. In the validation for method version 2, intra-run precision was evaluated by measuring 16 replicates of average and low-level CSF pool. Inter-run precision was evaluated by measuring two pooled CSF samples (low and high) from 20 different runs. The assay precision was ≤15%.

Below is the list of the deficiencies related to validation parameter.

Inadequate data to support the use of buffer matrix for calibration standards:

(b) (4)

(b) (4)

Insufficient precision data:

(b) (4)

(b) (4)

However, the data was not provided. Proper demonstration of inter-run precision at the claimed analytical measurement range should be performed according to the recommendations in the FDA's BMV guidance.

Table 2 Bioanalytical Validation for Determination of β -Amyloid (1-42) in Human CSF by ELISA

Method No.	mos-cmf-103.v1	mos-cmf-103.v2
Validation Report	(b) (4)	
Internal QC concentrations (pooled CSF samples used in sample analysis runs)		
QC concentration (pooled CSF samples used in validation study)		
Standard calibrator concentration		
Standard Curve range		
Lower limit of quantitation (LLOQ)		
QC Intra-run precision (%CV)		
QC Intra-run relative accuracy (%Nominal)		
QC Inter-run precision (%CV)		
QC Inter-run relative accuracy (%Nominal)		
Average recovery of the Analyte (%)		
Dilution integrity		
Parallelism		
QC sample bench-top stability		
QC sample freeze/thaw (Applicant report)		

QC sample freeze/thaw (FDA review)	(b) (4)
Processed sample stability	
QC sample long-term storage stability	
Selectivity	

No relative accuracy data:

(b) (4) . Therefore, the assay accuracy at the claimed analytical measuring range cannot be assessed. (b) (4)

Discrepancy in Freeze- Thaw (F/T) stability report:

(b) (4) . Therefore, the reliability of the F/T data (b) (4) cannot be assured.

Insufficient short-term stability:

(b) (4) The validation did not assess the short-term stability, therefore the integrity of the analyte during the sample processing cannot be assured.

Insufficient Long-term stability:

(b) (4) Therefore, the stability of the analyte for the duration of the study cannot be assured.

In summary, the method validation has multiple deficiencies that potentially impact the analytical results. Of note, the sample storage duration exceeded the established stability period (b) (4) therefore, the integrity of analyte during study conduct cannot be assured. As such, the reliability of amyloid β (1-42) protein concentrations data in the CSF samples from studies concentration data from Studies BAN2401-J081-104 and BAN2401-G000-201 is uncertain.

(b) (4)

However, limited data provided in the literature and manufacturer does not provide adequate stability demonstration.

4.1.2.2 Determination of amyloid beta (Aβ) peptide isoforms (Aβ42 and Aβ40) in human plasma using liquid chromatography tandem mass spectrometry (LC-MS/MS) CLIA assay.

The applicant used a validated method to measure amyloid beta (Aβ) peptide isoforms (Aβ42 and Aβ40) in human plasma by LC-MS/MS. (b) (4)

. The method validation parameters are presented in **Tables 3**.

Table 3 Bioanalytical Validation for Determination of Aβ 40 and Aβ 42 in Human Plasma by LC-MS/MS

Method validation report number	135087.2. C2N Diagnostics Plasma Aβ CLIA Validation
Standard curve range	(b) (4)
Standard curve concentration	
Minimum required dilutions	
Regressing model and weighting	
QCs accuracy and precision runs	
Selectivity & matrix effect	
Interference & specificity	
Hemolysis effect	

Lipemic effect	(b) (4)
Dilution linearity	
Bench-top/process stability	
Freeze-Thaw stability	
Long-term storage	
Parallelism	
Carry over	

In summary, the method validation has multiple deficiencies that potentially impact the analytical results. Of note, the matrix effect was not assessed and the storage duration for study samples exceeded the established stability period (b) (4). The applicant provided a summary report which contained information about the stability studies, including freezer stability, refrigerated stability, room temperature stability, Freeze/Thaw stability, and Long-term stability to support the Study BAN2401-G000-201. However, the report does not contain stability data generated from the experiments to verify the information in the report. (b) (4)

Therefore, the stability data does not cover the duration of samples storage and integrity of the analyte during the study conduct cannot be assured. As such, the reliability of Aβ peptides concentrations data in the plasma samples from Study BAN2401-G000-201 is uncertain. (b) (4)

Following the mid-cycle meeting, the applicant submitted literature and additional long-term stability assessment protocol included in DMF (b) (4) in support of long-term stability of amyloid beta (Aβ) peptide isoforms (Aβ42 and Aβ40) in human plasma matrix. However, limited data provided in the literature and DMF does not provide adequate stability demonstration. Please refer to Appendix 4.3 for the impact of this issue on data interpretation for plasma Aβ42/40 ratio.

4.1.3 Bioanalysis of p-tau181 in human CSF and plasma

4.1.3.1 Bioanalysis of p-tau181 in CSF (sample analysis report: MSE6QBAR86 and BAR79/E97)

The applicant used a commercialized diagnostic kit to quantify the p-tau181 in CSF with an ELISA method. (b) (4)

The original validation was performed in 2010. This original method was used to analyze 46 sample from study: BAN2401-J081-104 (report# Bar79/E97) and 501 samples from study BAN2401-G000-201 (report# Bar86/E6Q). Even though two kits, each with different ranges, were adopted in studies BAN2401-J081-104 and BAN2401-G000-201, no further validation had been performed prior to sample analysis.

The applicant preformed limited method validation; see a summary of the method validation performance shown in **Table 4**. (b) (4) FDA has recommended performing full validation when adopting the diagnostic kit to applicant's application. The applicant did not perform the full validation per FDA guidance. This resulted in an incomplete validation with following deficiencies:

- No established calibration range for the determination of the unknown sample concentration was available prior to the sample analysis of study BAN2401-J081-104 and BAN2401-G000-201. The calibration range should be established based on accuracy and precision meeting pre-defined acceptance criteria according to the FDA's BMV guidance.
- No matrix effect study data are available to support sample analysis that used un-diluted sample.
- No accuracy and precision were assessed with the five levels of appropriate QCs to ensure the method performance robustness.
- No raw data are available to verify the sample stability at bench top, and during storage in the refrigerator (2-8°C) and freezer (-70°C); thus, no sufficient stability data to support the sample handling and storage, which includes the storage durations of 12-month for study BAN2401-J081-104 and approximately 2-year for study BAN2401-G000-201 as stated in 1113-efficacy-information-amendment.pdf.
- No cross-validation data to ensure the consistency of sample measurement from two kits while the two versions of kits with different ranges were used in two studies (BAN2401-J081-104 and BAN2401-G000-201).

Table 4 Method Performance in Validation*

(*Copy of Table 5 of 1113-efficacy-information-amendment.pdf)

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of phospho-tau(181P), B-Amyloid (1-42) and hTauAg ELISA method with (b) (4)
Method Description	
Materials used for standard calibration curve and concentration	
Validated assay range	
Materials used for quality controls (QCs) and concentration	
Minimum required dilutions (MRDs)	
Source and lot of reagents	
Regressing model and weighting	
Validation parameters	
Standard calibration curve performance during accuracy and precision runs	
Performance of QCs during accuracy and precision runs	
Selectivity & matrix effect	
Interference & specificity	
Hemolysis effect	
Lipemic effect	
Dilution linearity & hook effect	
Bench-top/process stability	
Freeze-Thaw stability	
Long-term storage	
Parallelism	

(b) (4)

The impacts on sample results are not clear and the reliability of the reported concentration cannot be verified.

Table 5 Calibration curve performance -study BAR86/E6Q

(Refer to study BAR86/E6Q, Table 9 of 1113-efficacy-information-amendment.pdf)

(b) (4)

Table 6 Calibration curve performance -study BAR97/E79

(Refer to study BAR97/E79, Table 9 of 1113-efficacy-information-amendment.pdf)

Table 9 Calibration Curve Data for PTau Protein, contd.

(b) (4)

[redacted]

In summary, although the applicant claimed the kit performed well as indicated in the package for the originator kit, no data are available to confirm the assay performance in the applicant's test environment for their sample analysis. The precision data with a few CSF samples are not sufficient to ensure the whole list of assay performance characteristics including storage stability. Therefore, the method validation is not sufficient to support the quantification of p-tau181 in CSF. The data reported for study BAN2401-G000-201 (reports BAR86/E6Q) and study BAN2401-J081-104 (report BAR79/E97) should be interpreted with caution.

4.1.3.2 Bioanalysis of p-tau181 in plasma (sample analysis report: 110-r12068, study BAN2401-G000-201)

The applicant used a commercial Simoa p-tau181 Advantage V2 Assay Kit to determine the concentration of p-tau181 in plasma. (b) (4)

[redacted]

The method was validated for use in analyzing samples collected from study BAN2401-G000-201.

(b) (4)

.

Reviewer's comments:

- **Matrix effect for samples with concentrations below LQC** (b) (4)

- **Insufficient QC samples** (b) (4)

- **Insufficient data to support no interference from hemolysis and drug** (b) (4)

- **Insufficient long-term stability data** (b) (4)

[redacted] (b) (4) Please refer to Appendix 4.3 for the impact of this issue on plasma p-tau181 data interpretation.

Summary

Overall, the method was validated as shown in **Table 7**. [redacted] (b) (4) However, as stated in reviewer's comments, the validation lacks data to

- validate the range bracketed with the appropriate QC samples,
- clarify the matrix effect to support the appropriateness of using the buffer as a surrogate matrix (a buffer) different from that of study samples (plasma),
- assess interference from hemolysis, and
- demonstrate long-term stability sufficient to cover the sample storage duration.

Thus, the reliability of the concentration data for study BAN2401-G000-201 remains to be demonstrated.

Table 7 Summary of method validation parameters

(Source: Validation Report #110-r11817-r1, 110-r11817-a1)

Bioanalytical Method Validation Report	Report Title: Validation Report for Method BTM-3467: Quantitation of p-tau181 in Human Plasma (K2EDTA) [redacted] (b) (4) . Report Number: 110-r11817-r1 and 110-r11817-a1
Standard Calibration Curve Range	[redacted] (b) (4)
Low Limit of Quantitation	
Inter-assay Precision (%CV)	
Inter-assay Accuracy (%RE)	
Intra-assay Precision (%CV)	
Intra-assay Accuracy (%RE)	
Refrigerator	
Bench-top Stability	
Freeze-thaw Stability	
Long-term Stability	
Interference	

4.2 Clinical PK Assessments

Study BAN2401-A001-101

In the SAD part, 48 eligible adult subjects with mild to moderate AD were randomized (3:1) to receive lecanemab or placebo administered as a single 60- to 75-minute intravenous infusion. Treatment consisted of single ascending doses in 6 cohorts (0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, 10.0 mg/kg, and 15.0 mg/kg). In the MAD part, 24 subjects received sequential multiple ascending doses. Lecanemab was administered monthly for up to 4 doses at the dose levels of 0.3 mg/kg, 1 mg/kg, and 3 mg/kg (MAD1 to MAD3) and biweekly for up to 7 doses at the dose level of 10 mg/kg (MAD4). Blood PK samples were collected at predose, immediately at the end of the infusion, and 0.5, 1, 2, 4, 8 and 24 hours after the end of the infusion, and a single sample on Day 10, Day 21, Day 28, Day 90, Day 180. The PK parameters were calculated with noncompartmental methods from SAD and MAD parts and summarized in **Table 8** and **Table 9** below.

Table 8 Pharmacokinetic Parameters of Lecanemab after Single IV Dose Administration in Study 101

Cohort	Dose (mg/kg)	C_{max} (µg/mL)		t_{max} (hours)	$AUC_{(0\text{-}24h)}$ (µg*h/mL)		$AUC_{(0\text{-}t)}$ (µg*h/mL)		$AUC_{(0\text{-}inf)}$ (µg*h/mL)		$t_{1/2}$ (hours)
		Mean (SD)	CV%	Median (min, max)	Mean (SD)	CV%	Mean (SD)	CV%	Mean (SD)	CV%	Mean (SD)
SAD2	0.3	8.50 (2.42)	25.3	2.20 (1.50, 5.00)	136	NC	43.8 (21.1)	60.3	NC	NC	NC
SAD3	1	24.7 (3.62)	14.7	1.78 (1.28, 5.00)	432 (99.6)	22.2	1090 (959)	67.8	NC	NC	103 (-)
SAD4	3	74.2 (11.1)	14.8	1.83 (1.22, 5.20)	1390 (140)	9.75	7170 (1320)	20.6	7430 (1210)	17.7	83.5 (13.7)
SAD5	10	264 (32.4)	12.4	2.00 (1.23, 5.13)	5010 (550)	11.0	35700 (6070)	19.2	38000 (7340)	22.0	165 (45.5)
SAD6	15	418 (54.5)	13.1	2.00 (2.00, 3.00)	7630 (593)	8.06	62000 (14700)	26.2	66900 (17600)	29.8	174 (36.1)

Source: Applicant's Summary of Clinical Pharmacology, Page 27, Table 2.7.2-5

Table 9 Lecanemab PK Parameters after the First and Last Infusions in Study 101

Cohort (Dose Level, mg/kg)	Dose Day	In-fusion No.	C_{max} (µg/mL)		t_{max} (hours)	$AUC_{(0\text{-}24h)}$ (µg·h/mL)		$AUC_{(0\text{-}\tau)}$ (µg·h/mL)		$t_{½}$ (hours)
			Mean (SD)	CV%	Median (min, max)	Mean (SD)	CV%	Mean (SD)	CV%	Mean (SD)
MAD1 (0.3) Monthly	1	1	7.62 (0.63)	8.44	1.75 (1.00, 2.02)	156 (12.1)	7.73	NA	NA	NC
	84	4	7.26 (1.53)	20.7	2.32 (1.03, 5.42)	133 (23.4)	17.0	NA	NA	NC
MAD2 (1.0) Monthly	1	1	30.9 (3.54)	12.0	2.00 (1.00, 3.22)	548 (68.9)	12.7	NA	NA	133 (20.6)
	84	4	30.6 (4.59)	15.6	1.61 (1.17, 5.07)	470 (110)	25.1	NA	NA	NC
MAD3 (3.0) Monthly	1	1	81.4 (16.2)	20.1	2.08 (1.00, 5.53)	1380 (339)	25.1	NA	NA	133 (27.4)
	84	4	68.8 (8.98)	13.9	2.10 (1.67, 2.42)	1220 (132)	11.3	NA	NA	NC
MAD4 (10) Biweekly	1	1	267 (61.8)	21.1	1.67 (1.27, 3.08)	4750 (1210)	23.9	27200 (8820)	30.5	105 (22.1)
	84	7	307 (70.2)	21.5	1.88 (1.13, 3.10)	5720 (1230)	19.6	37700 (9110)	25.5	127 (29.9)

Source: Applicant's Summary of Clinical Pharmacology, Page 29, Table 2.7.2-6

The mean C_{max} and $AUC_{(0\text{-}24h)}$ values of lecanemab increased approximately proportionally with lecanemab dose increases. This proportionality was observed across the range of 0.3 to 15 mg/kg for SAD cohorts (**Table 8**) and also observed across the range of 0.3 to 10 mg/kg for MAD cohorts after the 1st and last (4th or 7th) infusions (**Table 9**). T_{max} occurred at an average of 2 hours from the start of infusion. The mean half-life of lecanemab was 5 to 7 days when administered at doses of 1 mg/kg or higher. With 10 mg/kg biweekly dosing in the MAD study, the steady state concentrations of lecanemab were reached after 6 weeks of treatment, with accumulation ratio of approximately 1.4 based on AUC (**Table 9**).

Study BAN2401-J081-104

Study 104 was a multiple ascending dose study in a total of 24 Japanese subjects (8 subjects per cohort: 6 for lecanemab and 2 for placebo) with MCI due to AD and mild AD. Cohorts 1, 2, and 3 received doses of 2.5, 5, and 10 mg/kg of lecanemab, respectively. In the treatment period, lecanemab or placebo was administered as an intravenous infusion followed by a 6-week washout period after the first dose. Then, lecanemab or placebo was administered once every 2 weeks over 60 minutes for a total of 5 infusions (8 weeks) to evaluate the safety, tolerability, and PK of lecanemab. The PK parameters after single dose (**Table 10**) and multiple doses (**Table 11**) are listed below.

Table 10 Summary of Pharmacokinetic Parameters of Lecanemab After Single Intravenous Administration in Study 104

PK Parameter	BAN2401		
	2.5 mg/kg (n=6)	5 mg/kg (n=6)	10 mg/kg (n=7)
C_{max} (µg/mL)	64.2 (13.6)	133 (9.14)	235 (34.1)
t_{max} (h)	2.140 (1.07, 4.90)	2.055 (1.95, 3.12)	2.080 (1.07, 2.87)
$AUC_{(0\text{-}t)}$ (µg•h/mL)	7070 (1180)	17800 (6640)	32600 (9780)
$AUC_{(0\text{-}24h)}$ (µg•h/mL)	1140 (243)	2420 (428)	4550 (639)
$AUC_{(0\text{-}336h)}$ (µg•h/mL)	6220 (1170)	14900 (4410)	26800 (6430)
$AUC_{(0\text{-}inf)}$ (µg•h/mL)	7320 (1120)	18200 (6970)	33000 (9800)
$t_{1/2}$ (h)	153 (30.0)	149 (52.0)	159 (16.0)
CL (L/h/kg)	0.000349 (0.0000531)	0.000310 (0.000117)	0.000325 (0.0000934)
V_{ss} (L/kg)	0.0620 (0.0155)	0.0531 (0.0137)	0.0619 (0.0122)

Source: Applicant's CSR of Study 104, Page 94 Table 12

Table 11 Lecanemab PK Parameters after Multiple Dose Administration Once Every 2 Weeks for a Total of 5 Infusions – Study 104

PK Parameter	BAN2401		
	2.5 mg/kg (n=6)	5 mg/kg (n=5)	10 mg/kg (n=6)
$C_{ss,max}$ (µg/mL)	72.8 (19.4)	154 (26.3)	299 (45.7)
$t_{ss,max}$ (h)	1.150 (1.03, 2.15)	1.920 (0.95, 2.83)	2.010 (1.00, 4.90)
$AUC_{(0-24h)}$ (µg•h/mL)	1380 (268)	3050 (486)	5830 (887)
$AUC_{(0-\tau)}$ (µg•h/mL)	8980 (1690)	22700 (7790)	39500 (7330)
$R_{ac}(C_{max})$	1.12 (0.0757)	1.17 (0.189)	1.31 (0.143)
$R_{ac}(AUC)$	1.45 (0.136)	1.51 (0.348)	1.59 (0.220)

Source: Applicant's CSR of Study 104, Page 100 Table 14

4.3 Assessments of Biomarker Results

4.3.1 Effect of Lecanemab on Biomarkers in Plasma and CSF

The applicant submitted plasma and CSF biomarker data to supplement the evaluation of the treatment effect of lecanemab. The review team noted that the bioanalytical method validations for CSF p-tau181 and CSF Aβ[1–42] have major limitations [redacted] (b) (4) For plasma p-tau181 and Aβ42/40 ratio, although the bioanalytical method validations were also not fully established, the observed relative change across treatment arms cannot be falsified by the uncertainties in bioanalysis. Hence, the review team recommends using qualitative descriptions for the plasma biomarker results, and all the quantitative analyses of the plasma biomarker data presented in this review should be interpreted with caution.

The observed data on biomarkers from Study 201 Core including plasma p-tau181, plasma Aβ42/40 ratio, CSF p-tau181, and CSF Aβ[1–42] are described below. Besides Study 201 Core, the applicant also submitted biomarker data including plasma Aβ42/40 ratio and plasma p-tau181 during the Gap period and OLE period after resuming the treatment. [redacted] (b) (4)

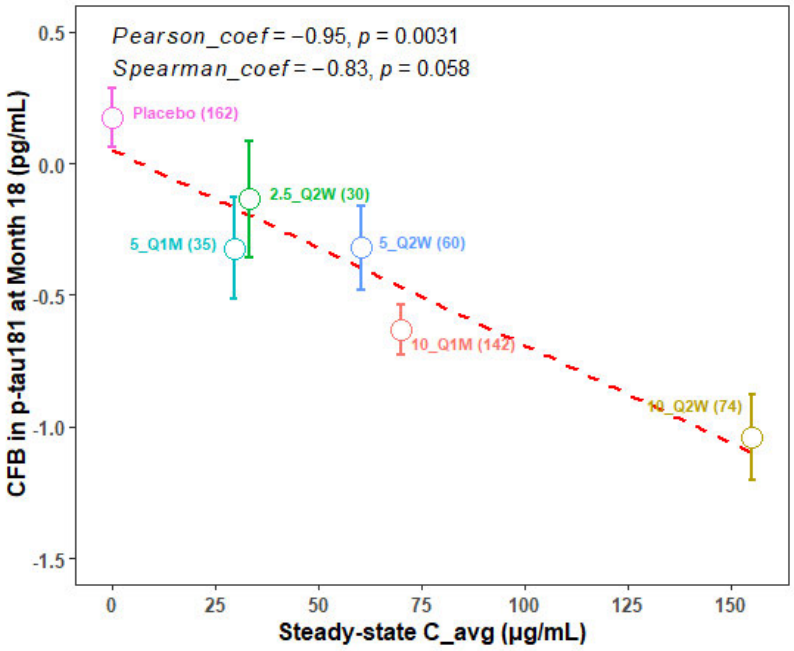
Plasma p-tau181

A dose-dependent reduction in plasma p-tau181 was observed in Study 201 Core (Section 3.3.1, **Figure 5A)**. An association was also observed between higher lecanemab exposure and greater reduction in plasma p-tau181 (**Figure 6**).

The bioanalytical method for plasma p-tau181 was not fully validated, such as insufficient coverage for long-term stability (refer to Appendix 4.1.3). To examine the potential impact of stability issue on the analysis result, the review team examined the plasma p-tau181 data in relation to the duration of

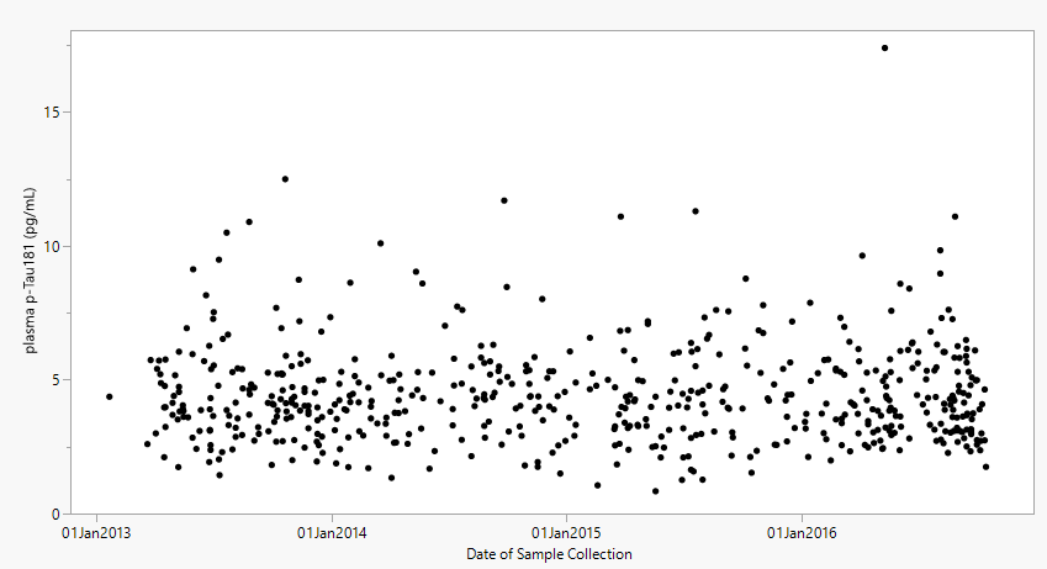
sample storage. **Figure 7** shows that no correlation was observed between the plasma p-tau181 concentration at baseline and sample storage duration. The team noted that the analysis does not inform the stability of the samples within the first four years of storage.

Figure 6 Relationship between Lecanemab Average Concentrations and Plasma p-tau181 Changes from Baseline at Month 18



Source: Reviewer's analysis. Circle and Error bars represents mean ± standard errors respectively.

Figure 7 Plasma p-tau181 Concentration at Baseline in Study 201 Core



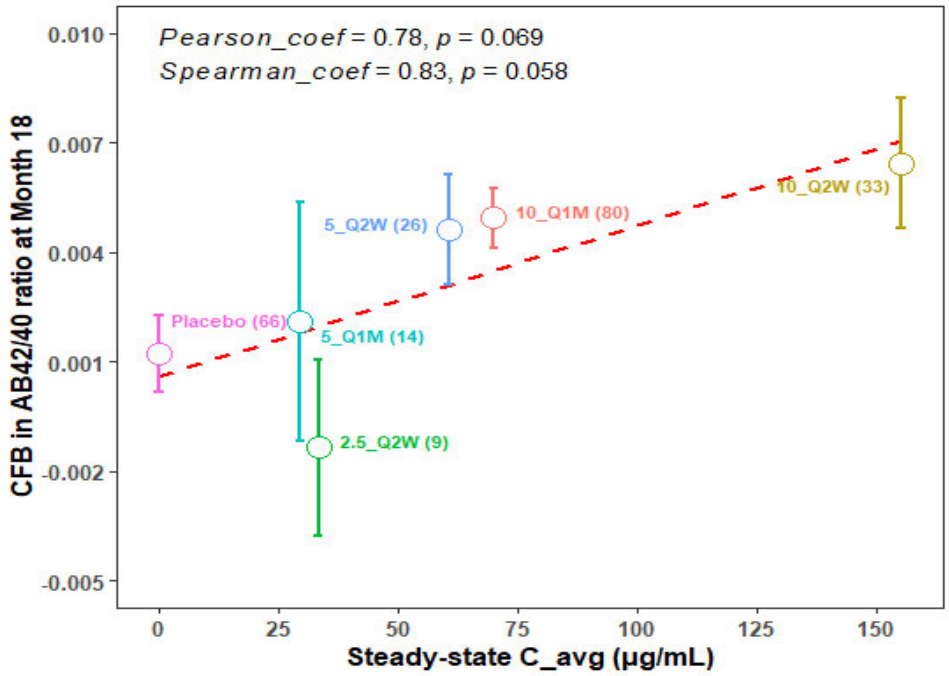
Source: Reviewer's Analysis. The analysis of all the plasma samples for p-tau181 were conducted within two weeks (Aug 19, 2021 to Sep 03, 2021, refer to applicant's sample analysis report 110-R12068). The sample collection date was therefore used to reflect the duration of sample storage (approximately 4-8 years).

Considering the dose- and exposure- dependent reduction in plasma p-tau181 following treatment with lecanemab, the review team believes that the effect of lecanemab on plasma p-tau181 observed in Study 201 Core is unlikely a random occurrence and cannot be fully attributed to the inadequacy of method validation. Hence, the review team recommends to include a qualitative description in the labeling Section 12.2 to reflect the reduction in plasma p-tau181 observed with LEQEMBI 10 mg/kg biweekly dosing compared to placebo. Further, the review team recommends including a disclaimer statement to highlight the uncertainties in bioanalysis if including quantitative data on plasma p-tau181 is considered clinically necessary in other sections of the label.

Plasma Aβ42/40 Ratio

Study 201 Core suggested a trend of increase in plasma Aβ42/40 ratio compared to placebo following lecanemab treatment of 5 mg/kg biweekly, 10 mg/kg monthly, and 10 mg/kg biweekly dosing (**Figure 5B**). An association was also observed between higher lecanemab exposure and greater increase in plasma Aβ42/40 ratio (**Figure 8**).

Figure 8 Relationship between Lecanemab Average Concentrations and Plasma Aβ42/40 ratio Changes from Baseline at Month 18



Source: Reviewer's analysis. Circle and Error bars represents mean ± standard errors respectively.

The bioanalytical method for plasma amyloid was not fully validated, such as insufficient coverage for the long-term stability (refer to Appendix Section 4.1.2.2). The review team evaluated potential impact of the uncertainties in bioanalytical method on the observed results, along with literature reports

supporting the long-term stability of Aβ1-40 and Aβ1-42[6,7]. Based on the data available, the review team agreed that the increase in Aβ42/40 ratio observed in Study 201 Core with 10 mg/kg biweekly dosing compared to placebo is unlikely a random occurrence. Hence, the review team recommends to include a qualitative description in the labeling Section 12.2 to reflect the increase in plasma Aβ42/40 ratio observed with LEQEMBI 10 mg/kg biweekly dosing compared to placebo. Further, the review team recommends including a disclaimer statement to highlight the uncertainties in bioanalysis if including quantitative data on plasma Aβ42/40 ratio is considered clinically necessary in other sections of the label.

CSF Aβ[1–42] and CSF p-tau181

In addition to insufficient evidence on long-term stability and matrix effect, the review team identified major limitations in biomarker assay validation for both CSF Aβ[1–42] and CSF p-tau181 (e.g., precision and accuracy, refer to Sections 4.1.2 and 4.1.3), (b) (4)

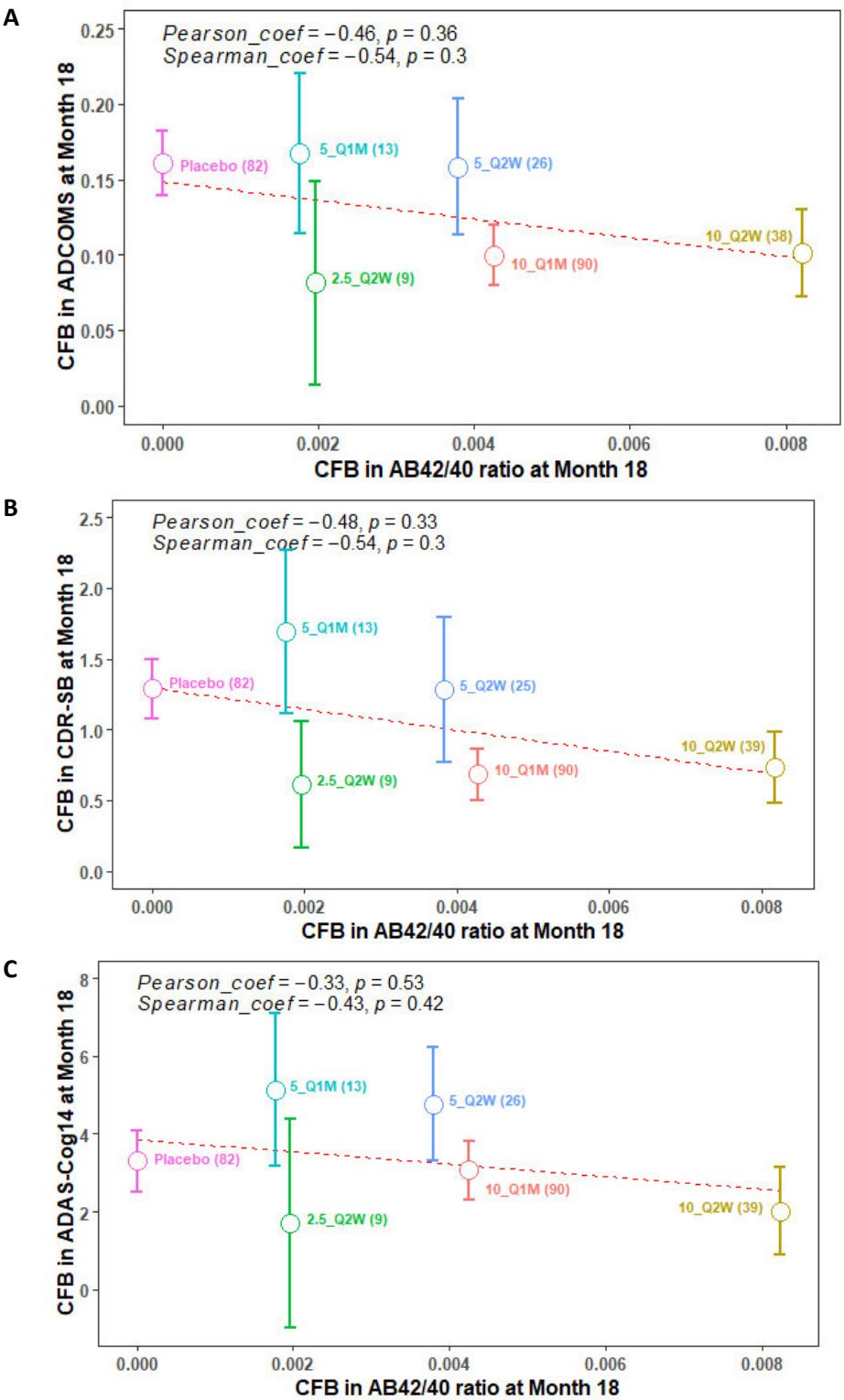
4.3.2 Relationships Between Plasma Biomarkers and Clinical Endpoints

The review team evaluated the relationships between plasma biomarkers (Aβ42/40 and p-tau181) and clinical endpoints (ADCOMS, CDR-SB, and ADAS-Cog14) using observed data from Study 201 Core (**Figure 9** and **Figure 10**). The results suggested a trend that the increases in plasma Aβ42/40 and decreases in plasma p-tau181 were associated with reduction in clinical decline on ADCOMS, CDR-SB, and ADAS-Cog14. This trend was also consistent with applicant's PK/PD modeling (refer to Appendix 4.4.1.3). However, considering potential limitation of the data quality (refer to Appendix 4.1.2 and 4.1.3), the review team did not make a definite conclusion in the USPI regarding the associations based on these data.

[6] Chiu M. et al, Long-Term Storage Effects on Stability of Aβ1-40, Aβ1-42, and Total Tau Proteins in Human Plasma Samples Measured with Immunomagnetic Reduction Assays. Dement Geriatr Cogn Dis Extra . 2019 Feb 12;9(1):77-86.

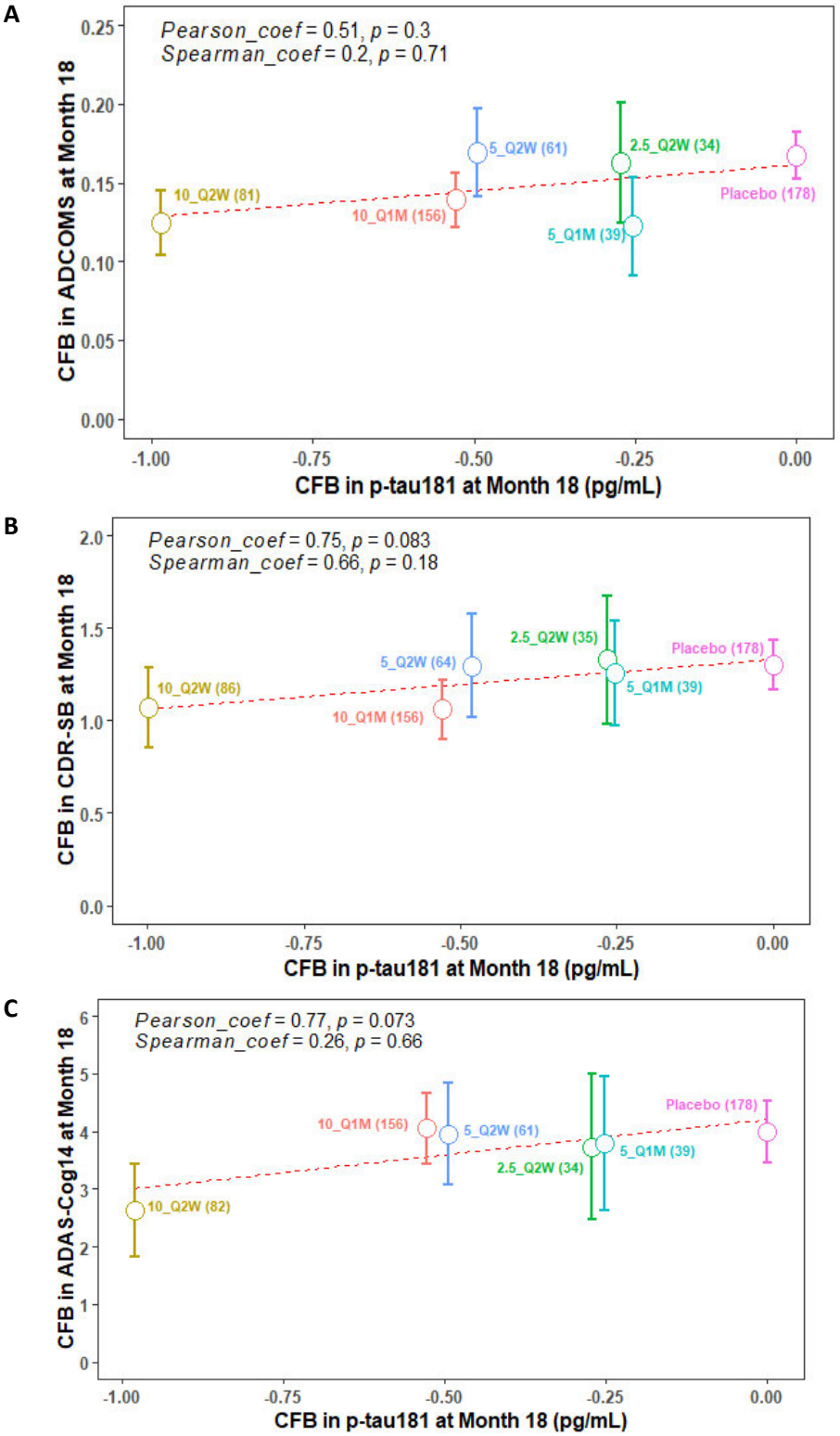
[7] Schubert C. et al, Effect of Long-Term Storage on the Reliability of Blood Biomarkers for Alzheimer's Disease and Neurodegeneration. J Alzheimers Dis. 2022;85(3):1021-1029

Figure 9 Relationship between Plasma Aβ42/40 at Month 18 and Efficacy Endpoints (ADCOMS, CDR-SB, and ADAS-Cog14) Changes from Baseline at Month 18



Circles and error bars represent mean and ± standard errors respectively.
Source: Reviewer's analysis

Figure 10 Relationship between Plasma p-tau181 at Month 18 and Efficacy Endpoints (ADCOMS, CDR-SB, and ADAS-Cog14) Changes from Baseline at Month 18



Circles and error bars represent mean and ± standard errors respectively.
Source: Reviewer's analysis

4.4 Pharmacometrics Analyses

This document is a review of the applicant's population pharmacokinetic (PK) and PK-pharmacodynamic (PD) analysis of lecanemab.

4.4.1 Applicant's Analysis

4.4.1.1 Population PK analysis

Objectives: To describe serum PK of lecanemab in patients with Alzheimer's Disease (AD) and to assess the impact of covariates on the PK of lecanemab.

Data: Pharmacokinetic data of 9027 samples from 725 subjects enrolled in 3 studies (Studies 101, 104 and 201 Core and OLE) were used to develop Pop PK models for lecanemab. The baseline characteristics of subjects is provided in the **Table 12**.

Method: Nonlinear mixed effect modeling was used for PK model development using NONMEM v7.4.3. The previously developed PopPK model (two-compartment model with linear first-order elimination) was updated following pooling additional data from Study 201 OLE. The relationship of continuous covariates and PK parameter was described with power models; and categorical covariate-PK parameter relationship was described using a power structure with the most common level of the covariate being the reference. Impact of covariates on lecanemab exposures (AUC and C_{max}) was evaluated using a forest plot analysis.

Results: The PK of lecanemab was described by two-compartment model with zero-order input and first-order elimination. Covariates such as weight, albumin, sex and ADA were added on clearance; weight and sex were added on the central volume of distribution; and Japanese race were added on peripheral volume of distribution. The parameter estimates of the final population PK model for lecanemab are shown in **Table 13**. The population PK model for lecanemab was assessed with diagnostics plots including goodness-of-fit and visual predictive checks (VPC) (**Figure 11**). The effect of the covariates on the steady-state C_{max} and AUC of lecanemab is shown in **Figure 12**, which suggested none of the significant covariates have any clinically meaningful effect on PK exposure (C_{max} and AUC) of lecanemab to warrant any dose adjustment, as the confidence intervals of all covariates overlapped the reference 80-125% interval.

Table 12 Summary of Baseline Characteristics in the PK Analysis of Lecanemab

Covariate (unit)	Mean (SD)	Median	Range (Min-Max)
Age (years)	71.0 (8.2)	71.0	50.0 – 93.0
Weight (kg)	73.7 (14.7)	73.4	41.2 – 124.7
Albumin (g/L)	42.9 (2.9)	43.0	35.0 – 53.0
ADA titer	70.2 (486)	5	1-15625
Dose	0.3 mg/kg single dose=6; 0.3 mg/kg monthly=6, 1 mg/kg single dose=6, 1 mg/kg monthly=6, 2.5 mg/kg bi-weekly=58, 3 mg/kg single dose=6, 3 mg/kg monthly=6, 5 mg/kg bi-weekly=98, 5 mg/kg monthly=51, 10 mg/kg single dose=6, 10 mg/kg bi-weekly=219, 10 mg/kg monthly=251 15 mg/kg single dose=6		
Sex	Females = 340; Males = 385		
Race	White = 626, Black/African American = 26 Asian/Other Asian (excluding Chinese and Japanese) = 15 Japanese = 50, American Indian/Alaskan/Other/Missing=8		
Number of observations for ADA	Study 101: ADA negative = 629; ADA positive = 25, missing = 7 Study 101: ADA negative = 281; ADA positive = 90 Study 201 (Core): ADA negative inconclusive = 226; ADA negative conclusive = 3975; ADA positive = 906; missing = 561 Study 201 (OLE): ADA negative = 2097; ADA positive = 226; missing = 4		
Number of observations for manufacturing process	Process (b) (4) = 8568; Process (b) (4) = 459		

Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD1-v1, Nov 19, 2021, Page 35, Table 1

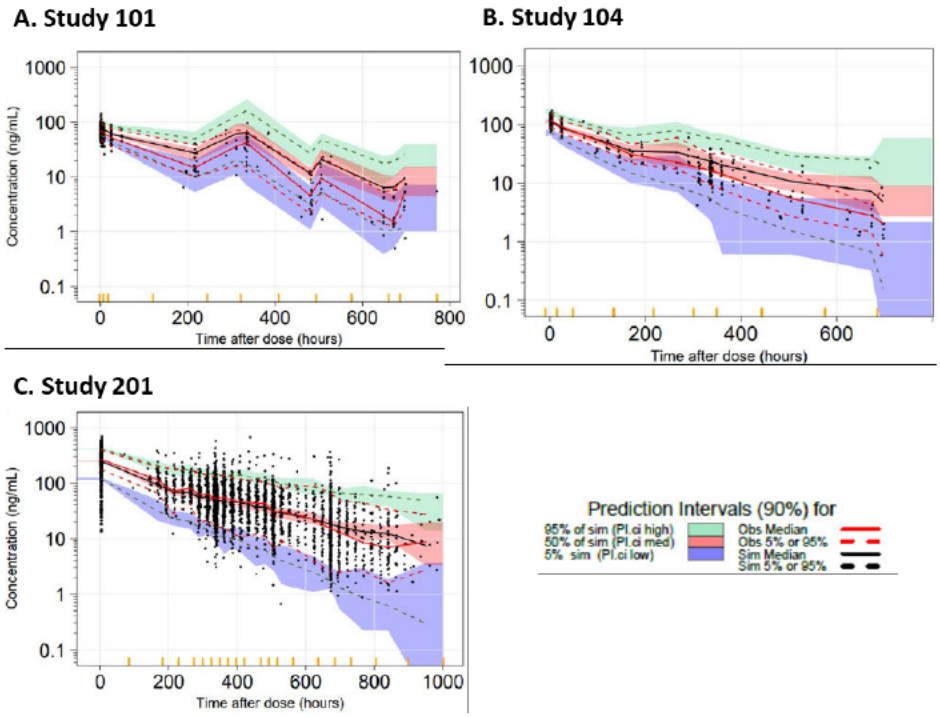
Table 13 Parameter Estimates of the Final Population PK Model for Lecanemab

Parameter	Point Estimate	%RSE	95% CI
Clearance: CL			
Basal CL (L/h)	0.0181	2.55	0.0172 – 0.0190
Effect of body weight on CL (exponent)	0.403	9.73	0.326 – 0.480
Effect of albumin on CL (exponent)	-0.243	17.2	-0.325 – -0.161
Effect of sex on CL (ratio)	0.792	3.43	0.739 – 0.845
Effect of ADA positive on CL (ratio)	1.09	0.586	1.08 – 1.10
Relative Bioavailability (F1) for Manufacturing Process (b) (4)			
F1	0.998	4.07	0.918 – 1.08
Central volume of distribution: V1			
Basal V1 (L)	3.22	1.18	3.15 – 3.29
Effect of body weight on V1 (exponent)	0.606	7.52	0.517 – 0.695
Effect of sex on V1 (ratio)	0.893	1.75	0.862 – 0.924
Inter-compartment Clearance: Q			
Basal Q (L/h)	0.0349	8.02	0.0294 – 0.0404
Peripheral volume of distribution: V2			
Basal V2 (L)	2.19	7.21	1.88 – 2.50
Effect of Japanese race on V2 (ratio)			
Inter-individual variability (%CV)			
CL	38.9	6.69	-
V1	14.0	8.38	-
V2	99.5	7.91	-
F1	34.2	17.7	
Residual variability (%CV)			
Proportional Study 101	14.0	3.49	-
Proportional Study 104	19.7	4.66	-
Proportional Study 201	30.3	0.803	-

%RSE=percent relative standard error of the estimate = SE/parameter estimate * 100;
CL=clearance; V1=central volume of distribution; Q=inter-compartment clearance; V2= peripheral volume of distribution; L = liter; h = hour; CI = confidence interval; %CV = Square root of variance *100.

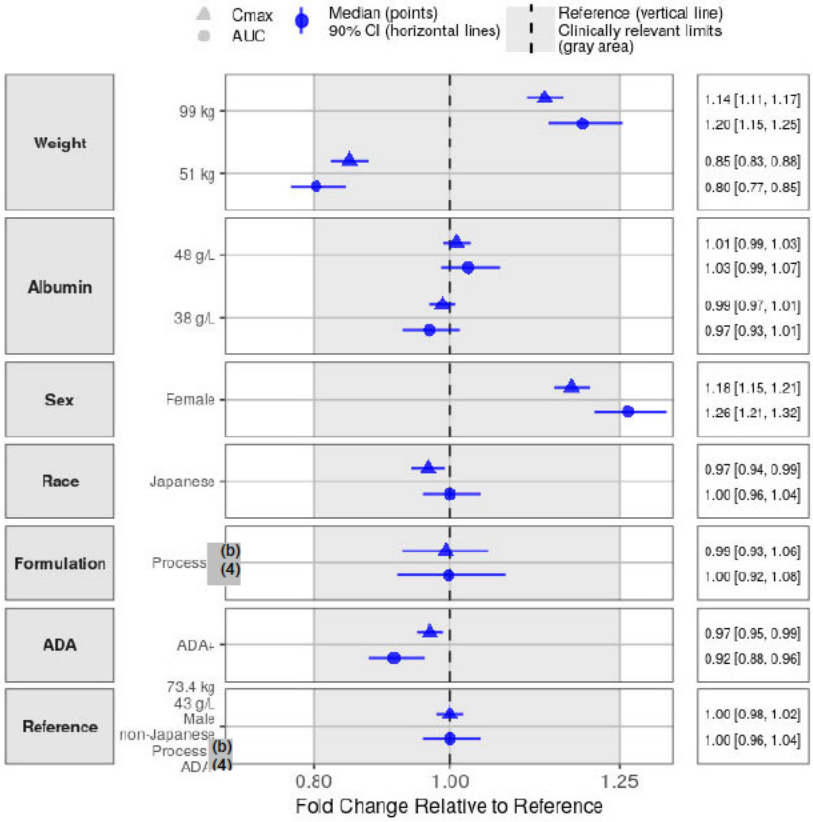
Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD1-v1, Nov 19, 2021, Page 45, Table 9

Figure 11 Prediction Corrected Visual Predictive Checks for The Final PK Model by Study



Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD1-v1, Nov 19, 2021, Page 49, Figure 12

Figure 12 Forest Plot of Covariate Effect in Final PK Model on PK of Lecanemab



Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD1-v1, Nov 19, 2021, Page 47, Figure 9

4.4.1.2 Population PK-PD model of Efficacy

Objectives: To describe the relationship between model-predicted serum lecanemab exposure to efficacy variables (Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog14), Alzheimer's Disease Composite Score (ADCOMS), Clinical Dementia Rating Sum of Boxes (CDR-SB))

Data: The data from Study 201 Core was used to develop Pop PK-PD models of efficacy. The baseline covariate characteristics of subjects is provided in the **Table 14**.

Method: Model development of longitudinal PK/PD models for efficacy endpoints (ADCOMS, CDRSB, and ADAS-Cog14) consisted of two steps: (i) development of disease progression model using placebo-treated subject data; and (ii) Adding drug on disease progression using data in all subjects. In terms of PK exposure, the PK model-derived $C_{ss,max}$ or $C_{ss,avg}$ were explored. Absolute score was used as the all-efficacy endpoints.

Results: The linear disease progression model was adequate to describe the disease progression for all clinical endpoints (ADCOMS, CDR-SB, and ADAS-Cog14) over time. The exposure effect on disease progression was introduced in the model as a linear function. For all endpoints, $C_{ss,avg}$ was selected as lecanemab exposure parameter because model stability (i.e., initial estimate independency) was better with $C_{ss,avg}$ than with $C_{ss,max}$.

The following covariates included in the final PK/PD model of efficacy: (i) concomitant AD treatment and diagnosis on intercept for ADCOMS; (ii) concomitant AD treatment on slope; diagnosis on intercept for CDR-SB; (iii) age, concomitant AD treatment and diagnosis on slope; concomitant AD treatment and diagnosis on intercept for ADAS-Cog14. The final parameter estimates for PK/PD models for efficacy endpoints (ADCOMS, CDR-SB and ADAS-Cog14) are shown in **Table 15**. Of note, 95% CI of the drug effect (DESLOPE: effect of lecanemab exposure on disease progression) did not contain zero, and thus was statistically significant ($p<0.05$). The PK/PD model-predicted a dose dependent reduction in decline in CDR-SB, ADCOMS, and ADAS-Cog14 over time (**Figure 13**). The population PK-PD model was assessed with diagnostics plots including goodness-of-fit and VPC (**Figure 14**).

Table 14 Summary of Baseline Characteristics in the PK-PD Analysis of Efficacy

Covariate (unit)	ADCOMS (N = 751)	CDR-SB (N = 751)	ADAS-Cog (N = 750)	MMSE (N = 752)
Age (years)	72 (50 - 90)			
Weight (kg)	72.5 (29.2 - 124.7)			
Dose	Placebo = 236 ; 2.5 mg/kg bi-weekly = 48; 5 mg/kg monthly = 47; 5 mg/kg bi-weekly = 84; 10 mg/kg monthly = 211; 10 mg/kg bi-weekly = 125	Placebo = 236 ; 2.5 mg/kg bi-weekly = 48; 5 mg/kg monthly = 47; 5 mg/kg bi-weekly = 84; 10 mg/kg monthly = 211; 10 mg/kg bi-weekly = 125	Placebo = 235 ; 2.5 mg/kg bi-weekly = 48; 5 mg/kg monthly = 47; 5 mg/kg bi-weekly = 84; 10 mg/kg monthly = 211; 10 mg/kg bi-weekly = 125	Placebo = 236 ; 2.5 mg/kg bi-weekly = 48; 5 mg/kg monthly = 47; 5 mg/kg bi-weekly = 84; 10 mg/kg monthly = 211; 10 mg/kg bi-weekly = 126
Gender	Females = 381 Males = 370	Females = 381 Males = 370	Females = 381 Males = 369	Females = 382 Males = 370
Race	White=678 Others=73	White=678 Others=73	White=677 Others=73	White=679 Others=73
APOE4 carrier status	Negative= 221 Positive = 530	Negative= 221 Positive = 530	Negative = 221 Positive = 529	Negative = 222 Positive = 530
Diagnosis	MCI = 483 Mild AD = 268	MCI = 483 Mild AD = 268	MCI = 483 Mild AD = 267	MCI = 483 Mild AD = 269
Concomitant medication[a]	YES = 421 NO = 330	YES = 421 NO = 330	YES = 420 NO = 330	YES = 422 NO = 330

Min = minimum value; Max = maximum value; MCI = Mild cognitive impairment; AD = Alzheimer's Disease.
[a]with acetylcholinesterase inhibitors (AChEIs) and/or memantine.

Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-v1.1, April 15, 2019, Page 61, Table 8

Table 15 Parameter *Estimates of the Final Population* PK-*PD Model for Efficacy of Lecanemab*

***A.* ADCOMS**

Parameter [Units]	Point Estimate	%RSE	95% CI
EFF = Θ_{INT} * Θ^{DIAG} * Θ^{CMD} + SLP *(1- DESLOPE*$C_{ss,av}$)*Time			
INT for MCI and without concomitant AD treatment [Θ_{INT}]	0.274	2.10	0.263 – 0.285
Ratio of INT for Mild AD [Θ^{DIAG}]	1.60	3.21	1.50 – 1.70
Ratio of INT for concomitant AD treatment [Θ^{CMD}]	1.13	2.30	1.08 – 1.18
SLP (/day)	0.000272	6.76	0.000236 – 0.000308
DESLOPE (per $C_{ss,av}$ unit [µg/mL])	0.00251	24.5	0.00130 – 0.00372
Inter-individual variability			
INT (%CV)	36.3%	6.14	
SLP (SD)	0.000309	10.1	
DESLOPE (SD)	0.00430	31.7	
Residual variability			
Proportional error (%CV)	14.4	4.36	
Additive error (SD)	0.0439	6.53	

B. **CDR-SB**

Parameter [Units]	**Point Estimate**	**%RSE**	**95% CI**
EFF =Θ_{INT}* Θ^{DIAG} + SLP* Θ^{CMD} *(1- DESLOPE*Css,av)*Time			
INT for MCI [Θ_{INT}]	2.19	2.01	2.10 – 2.28
Ratio of INT for Mild AD [Θ^{DIAG}]	1.70	3.39	1.59 – 1.81
SLP without concomitant AD treatment (/day)	0.00139	14.1	0.00101 – 0.00177
Ratio of SLP for concomitant AD treatment [Θ^{CMD}]	1.86	13.5	1.37 – 2.35
DESLOPE (per $C_{ss,av}$ unit [µg/mL])	0.00291	24.2	0.00153 – 0.00429
Inter-individual variability			
INT (%CV)	39.9%	6.18	
SLP (SD)	0.00263	10.1	
DESLOPE (SD)	0.00549	27.7	
Residual variability			
Proportional error (%CV)	17.3	3.08	
Additive error (SD)	0.321	6.59	

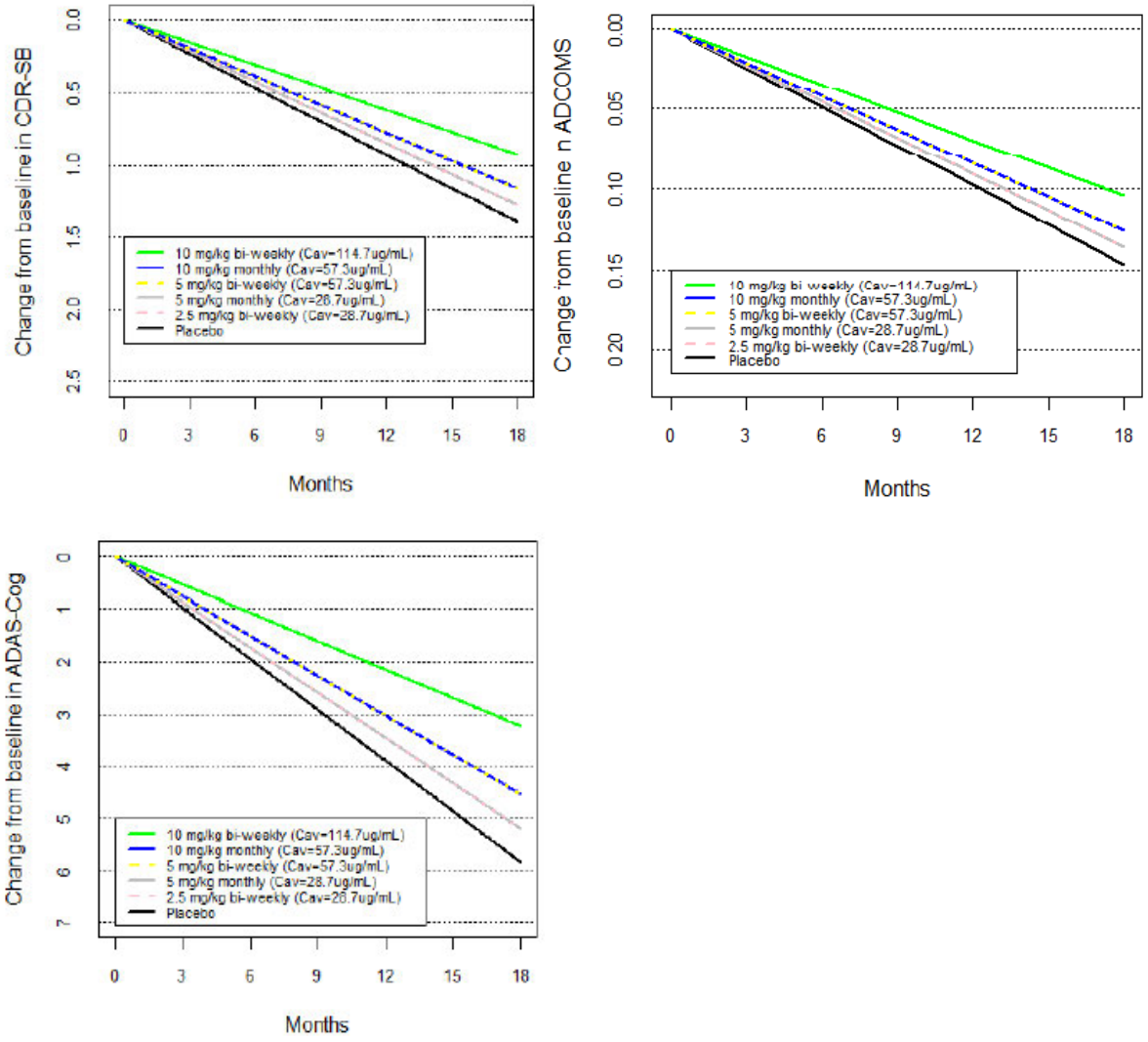
C. **ADAS-Cog14**

Parameter [Units]	**Point Estimate**	**%RSE**	**95% CI**
EFF =Θ_{INT}* Θ^{DIAG1} * Θ^{CMD1} + SLP*(Age/72) $^{\Theta AGE}$* Θ^{DIAG2} * Θ^{CMD2} *(1- DESLOPE*$C_{ss,av}$)*Time			
INT for MCI and without concomitant AD treatment [Θ_{INT}]	18.3	1.89	17.6 – 19.0
Ratio of INT for Mild AD [Θ^{DIAG1}]	1.28	2.89	1.21 – 1.35
Ratio of INT for concomitant AD treatment [Θ^{CMD1}]	1.08	2.20	1.03 – 1.13
SLP for MCI and without concomitant AD treatment (/day)	0.00381	17.9	0.00247 – 0.00515
Age effect on SLP [Θ^{AGE}]	-2.47	18.7	-3.38 – -1.56
Ratio of SLP for Mild AD [Θ^{DIAG2}]	1.58	13.0	1.18 – 1.98
Ratio of SLP for concomitant AD treatment [Θ^{CMD2}]	1.80	16.7	1.21 – 2.39
DESLOPE (per $C_{ss,av}$ unit [µg/mL])	0.00392	17.9	0.00254 – 0.00530
Inter-individual variability			
INT (%CV)	32.1%	5.35	
SLP (SD)	0.0106	9.73	
DESLOPE (SD)	0.00612	26.0	
Residual variability			
Proportional error (%CV)	8.37	6.97	
Additive error (SD)	2.18	5.46	

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100, CI = confidence interval, INT: baseline clinical score, SLP: disease progression rate, DESLOPE: effect of BAN2401 exposure on disease progression.

Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-v1.1, April 15, 2019, Page 87, Table 45-47

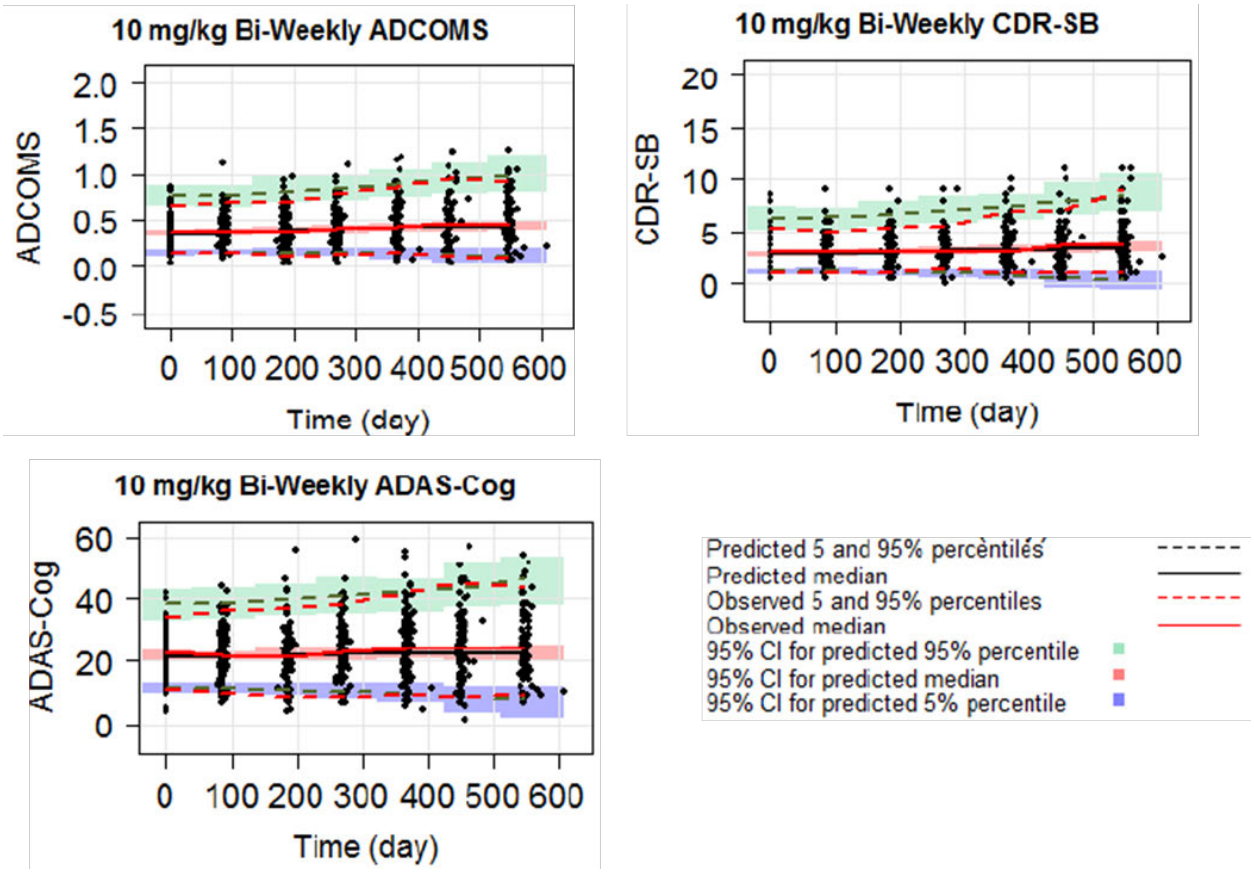
Figure 13 Time Course of Predicted Change from Baseline in Clinical Endpoints (ADCOMS, CDR-SB, and ADAS-Cog14) at Various Dosing Regimens



Time course of CDR-SB is shown for subject with concomitant AD treatment; Time course of ADAS-Cog14 is shown for mild AD subject with concomitant AD treatment

Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-v1.1, April 15, 2019, Page 89-91, Figure 12-14

Figure 14 Visual Predictive Checks for the Final PK-PD Model of Efficacy for 10 mg/kg Q2W



Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-v1.1, April 15, 2019, Page 95, Figure 16-18

4.4.1.3 Population PK-PD model of biomarkers and its relationship with efficacy endpoints

PK/PD analysis for amyloid standard uptake value ratio (SUVR)

Objectives: To describe the relationship between model-predicted serum lecanemab exposure and brain amyloid as measured by PET SUVR calculated from reference region whole cerebellum mask

Data: The PK-PD data of 1213 samples from 374 subjects enrolled in Study 201 Core and OLE were used to develop Pop PK-PD models for SUVR. The baseline covariate characteristics of subjects is provided in the **Table 16**.

Method: Previously developed PK/PD models for SUVR (an indirect response model with serum lecanemab concentration in the central compartment inducing the reduction of amyloid plaque) was updated following pooling additional data from Study 201 OLE. Covariate analysis was performed for the effect of age, weight, APOE4 carrier status, sex, AD diagnosis (MCI or mild AD), ADA and NAb status at subject level.

Results: The relationship between serum lecanemab concentration and the amyloid SUVR reduction time course was best described by an indirect response model with serum lecanemab concentration in the central compartment inducing the reduction of amyloid plaque. Covariates such as age were added on Emax; and APOE4 carrier were added on baseline. The parameter estimates of the final population PK-PD model for lecanemab are shown in **Table 17**. The population PK-PD model was assessed with diagnostics plots including goodness-of-fit and VPC (**Figure 15**).

Table 16 Summary of Baseline Characteristics in the PK-PD Analysis for Amyloid SUVR

Covariate (unit)	Mean (SD)	Median	Range (Min-Max)
Age (years)	71.5 (8.1)	72.0	50.0 – 89.0
Weight (kg)	74.3 (15.1)	73.7	29.2 – 118.7
Baseline SUVr[1)]	1.38 (0.17)	1.40	0.76 – 1.84
Dose in Core	Placebo= 115, 2.5 mg/kg bi-weekly=30, 5 mg/kg monthly=30, 5 mg/kg bi-weekly=36, 10 mg/kg monthly=105, 10 mg/kg bi-weekly=58		
Sex	Females = 179; Males = 195		
APOE4 carrier status	Negative = 113; Positive = 261		
Diagnosis	MCI = 262; Mild AD = 112		
ADA at subject level	Negative = 213; Positive = 161		
Neutralizing ADA at subject level	ADA(+)/NAb(+) = 30; ADA(+)/NAb(−) = 131		

ADA(+) = ADA positive; ADA(−) = ADA negative; NAb(+) = neutralizing ADA positive; NAb(−) = neutralizing ADA negative
1) Missing in 1 subject

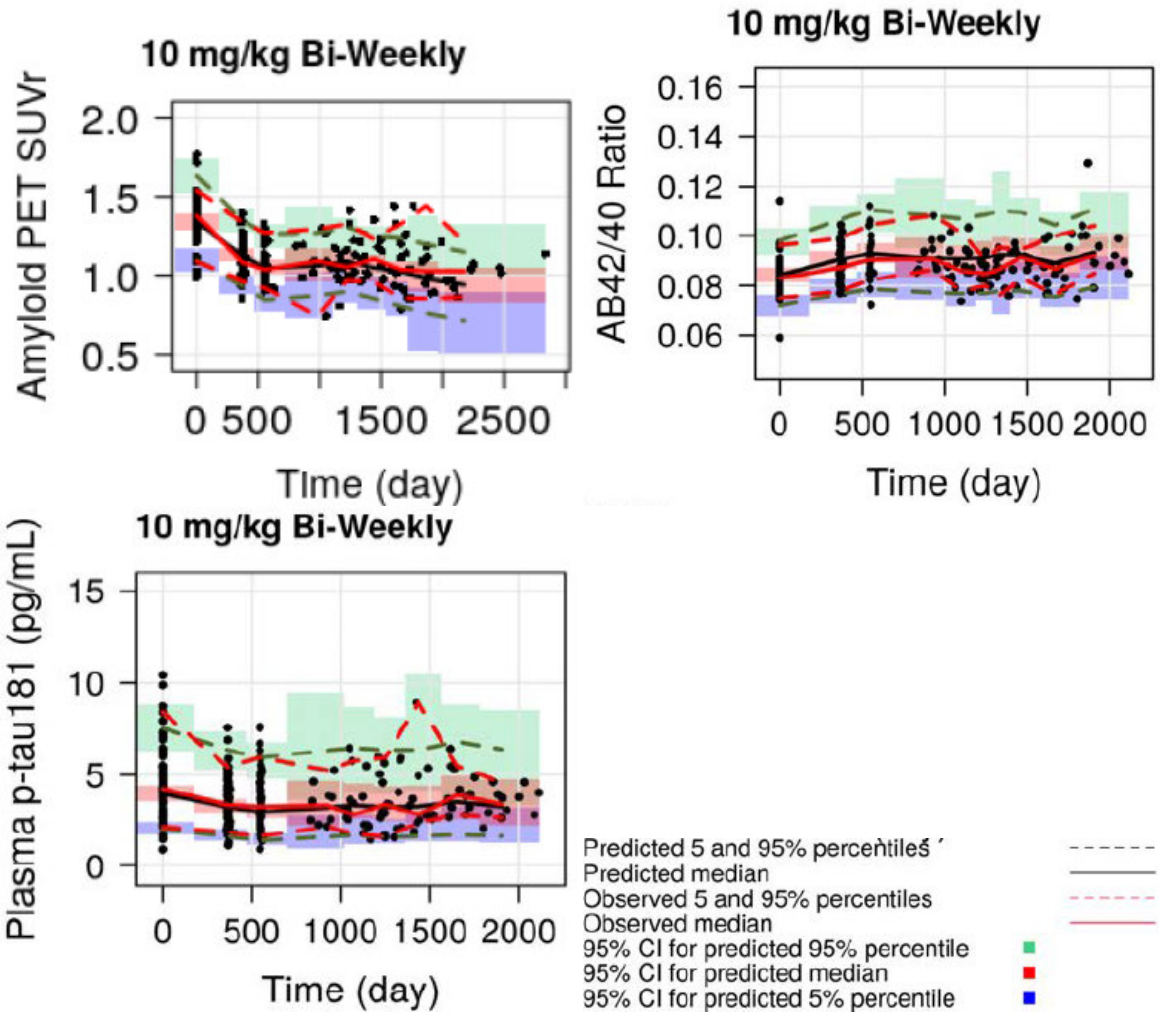
Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD1-v1, Nov 19, 2021, Page 12

Table 17 Parameter Estimates of the Final Population PK-PD Model for Amyloid SUVR

	NONMEM	
Parameter	**Point Estimate**	**%RSE**
Baseline		
Basal baseline	1.34	0.873
Effect of *APOE*4 carrier on baseline (vs. noncarrier)	1.04	1.04
K_{in}		
Basal K_{in} (1/year)	0.232	11.1
E_{max}		
Basal E_{max}	1.54	11.8
effect of age on E_{max} (exponent)	1.58	20.9
EC_{50}		
Basal EC_{50} (μg/mL)	75.0	19.6
Inter-individual variability (SD)		
Baseline	10.9	8.12
Correlation Baseline_E_{max} (R)	0.669	11.5
E_{max}	50.3	12.0
Residual variability		
Proportional (%CV)	5.01	2.75

Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD1-v1, Nov 19, 2021, Page 55, Table 15

Figure 15 Visual Predictive Checks for the Final PK-PD Model of biomarker for lecanemab 10 mg/kg Q2W



Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD1-v1, Nov 19, 2021, Page 59, Figure 17; Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD2-v1, Nov 19, 2021, Page 43; Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD3-v1, Nov 22, 2021, Page 36

Relationship between amyloid SUVR and Efficacy endpoints

Objectives: To describe the relationship between model-predicted serum amyloid PET SUVR change to efficacy variables (ADAS-Cog14, ADCOMS, CDR-SB)

Data: The data from Study 201 Core was used to explore relationship between SUVR and efficacy. The baseline covariate characteristics of subjects is provided in the **Table 18**.

Method: Linear disease progression model was used to describe SUVR-efficacy-time relationship, in which model-predicted change in SUVR was used as a predictor for efficacy endpoints. Absolute score was used for all efficacy endpoints.

Results: The biomarker effect on disease progression was introduced in the model as a linear function and was a significant predictor of efficacy endpoints. The following covariates included in the final SUVR-efficacy model: (i) mild dementia on ADCOMS baseline and slope for ADCOMS; (ii) mild dementia on CDR-SB baseline for CDR-SB; and (iii) mild dementia and body weight on ADAS-Cog14 baseline; and mild dementia and age on slope for ADAS-Cog14. The parameter estimates of the final SUVR-efficacy models are shown in **Table 19**. Overall, 95% CIs for the drug effect by change of SUVR (KSUVR) did not include zero, indicating significance correlation in the relationship between SUVR and clinical endpoints. The SUVR-Efficacy model predicted SUVR change dependent reduction in disease progression over time (**Figure 16**). The SUVR-efficacy models were assessed with diagnostics plots including goodness-of-fit and VPC (**Figure 17**).

Table 18 Summary of Baseline Characteristics in the SUVR-Efficacy

Covariate (unit or subject number)	Mean (SD)	Median	Range (Min-Max)
Age (years)	71.0 (8.2)	72.0	50.0 – 90.0
Weight (kg)	73.0 (14.7)	72.7	29.2 – 124.7
Baseline CDR-SB (N=829)	2.94 (1.39)	3.00	0.50 – 9.00
Baseline ADCOMS (N=827)	0.376 (0.160)	0.365	0.0378 – 0.942
Baseline ADAS-Cog (N=825)	22.3 (7.47)	22.0	3.67 – 48.3
Dose	Placebo= 238 2.5 mg/kg bi-weekly= 52 5 mg/kg monthly=50 5 mg/kg bi-weekly=90 10 mg/kg monthly=247 10 mg/kg bi-weekly=152		
Sex	Females = 411; Males = 418		
Race	White = 751 Black/African American = 20 Asian/Other Asian (excluding Chinese and Japanese) = 20 Japanese = 34 American Indian/Alaskan/Other/Missing=4		
APOE4 carrier status	Negative = 236; Positive = 593		
Diagnosis	MCI = 532; Mild AD = 297		
ADA at subject level	Negative = 477; Positive = 352		
Neutralizing ADA at subject level	ADA(+)/NAb(+) = 69; ADA(+)/NAb(−) = 283		

ADA(+) = ADA positive; ADA(−) = ADA negative; NAb(+) = neutralizing ADA positive; NAb(−) = neutralizing ADA negative

Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD1-v1, Nov 19, 2021, Page 13

Table 19 Parameter *Estimates of the Final Population SUVR-Efficacy model of Lecanemab*

A. **ADCOMS**

	NONMEM		Bootstrap	
Parameter	**Point Estimate**	**95% CI**	**Median**	**95% CI**
Baseline ADCOMS [BADC]	0.291	0.280-0.302	0.291	0.284 – 0.298
effect mild AD dementia ADCOMS baseline	1.62	1.54-1.70		
Progression rate [SLP] (1/day)	0.000249	0.000215 - 0.000283	0.000247	0.000196 – 0.000273
Rate constant for SUVr [KSUVR]	1.19	0.661 - 1.72	1.16	0.584 – 1.55
effect mild dementia due to AD on SLP	1.44	1.15 – 1.73	1.45	1.21 – 1.72
Inter-individual variability				
Baseline CDR-SB (CV%)	36.7	34.2 – 39.1	36.8	34.8 – 39.4
Progression rate (SD, 1/day)	0.0000135	0.0000117 – 0.0000150	0.0000134	0.0000107 – 0.0000147
Rate constant for SUVr (SD)	1.77	0.652 – 2.41	1.92	1.17 – 2.32
Residual variability				
Proportional (CV%)	14.2	12.8 – 15.6	14.2	13.0 – 15.8
Additive (SD)	0.0445	0.0384 – 0.0506	0.0444	0.0389 – 0.0486

CI = confidence interval; SD = standard deviation

B. **CDR-SB**

	NONMEM		Bootstrap	
Parameter	**Point Estimate**	**95% CI**	**Median**	**95% CI**
Baseline CDR-SB [BCDR]	2.17	2.08 – 2.26	2.17	2.09 - 2.25
effect mild AD dementia on CDR-SB baseline	1.71	1.61 – 1.81	1.71	1.60 – 1.82
Progression rate [SLP] (1/day)	0.00212	0.00182 – 0.00242	0.00213	0.00177 – 0.00251
Rate constant for SUVr [KSUVR]	1.37	0.892 – 1.85	1.34	0.814 – 1.80
Inter-individual variability				
Baseline CDR-SB (CV%)	39.7	37.2 – 42.2	39.7	37.4 – 42.2
Progression rate (SD, 1/day)	0.000116	0.0000999 - 0.000130	0.000117	0.000101 – 0.000133
rate constant for SUVr [KSUVR] (SD)	2.51	1.75 – 3.10	2.50	1.61 – 3.19
Residual variability				
Proportional (CV%)	17.3	15.8 – 18.8	17.3	15.7 – 18.8
Additive (SD)	0.320	0.270 – 0.370	0.321	0.259 – 0.367

CI = confidence interval; SD = standard deviation

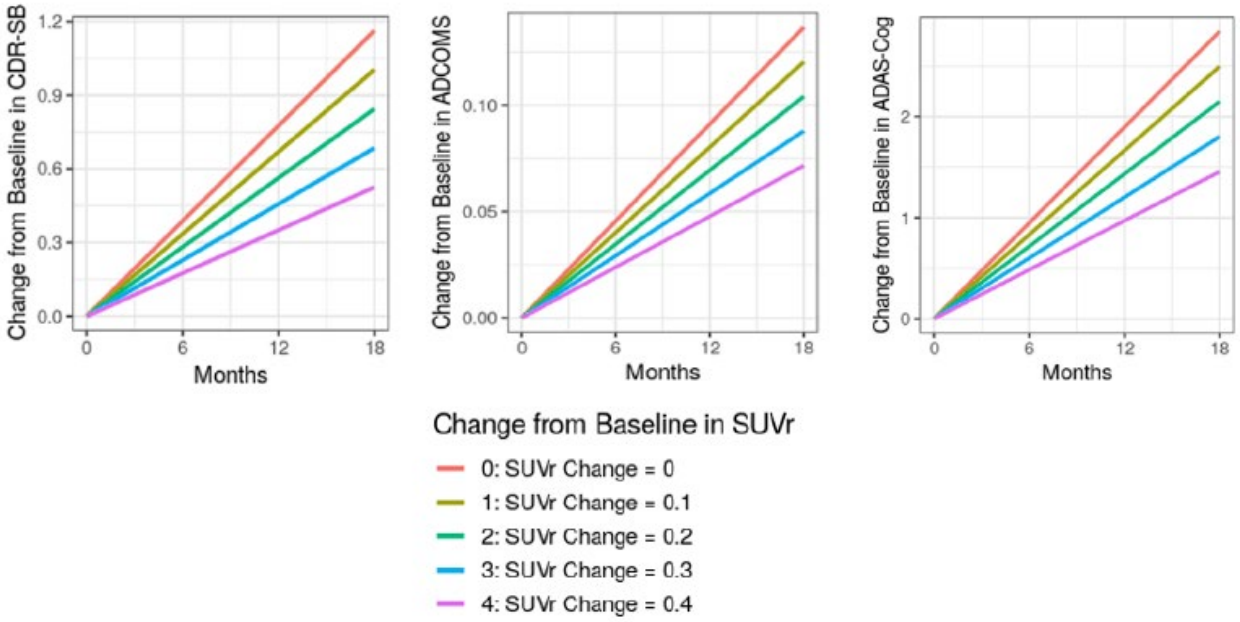
C. **ADAS-Cog14**

	NONMEM		Bootstrap	
Parameter	**Point Estimate**	**95% CI**	**Median**	**95% CI**
Baseline ADAS-Cog [BADAS]	18.8	18.3 – 19.4	18.9	18.3 – 19.4
effect of mild AD dementia on ADAS-Cog baseline	1.31	1.25 – 1.36	1.30	1.24 – 1.37
effect of body weight [exponent] on ADAS-Cog baseline	-0.248	-0.356 - -0.141	-0.249	-0.335 - -0.155
Progression rate [SLP] (1/day)	0.00518	0.00408 - 0.00628	0.00509	0.00407 – 0.00637
effect of mild AD dementia on SLP	1.83	1.31 – 2.35	1.85	1.35 – 2.45
effect of age [exponent]on SLP	-2.12	-3.25 – -0.980	-2.17	-3.32 - -0.804
Rate constant for SUVr [KSUVR]	1.22	0.892 - 1.55	1.19	0.620 – 1.73
Inter-individual variability				
Baseline ADAS-Cog (CV%)	31.9	29.8 – 33.8	31.8	29.8 – 33.6
Progression rate (SD, 1/day)	0.000487	0.000411 – 0.000552	0.000478	0.000410 – 0.000557
Rate constant for SUVr (SD)	2.04	0.852 – 2.75	2.02	0.842 – 3.08
Residual variability				
Proportional (CV%)	8.29	7.35 – 9.22	8.27	7.36 – 9.10
Additive (SD)	2.18	2.01 – 2.35	2.19	2.02 – 2.35

CI = confidence interval; SD = standard deviation

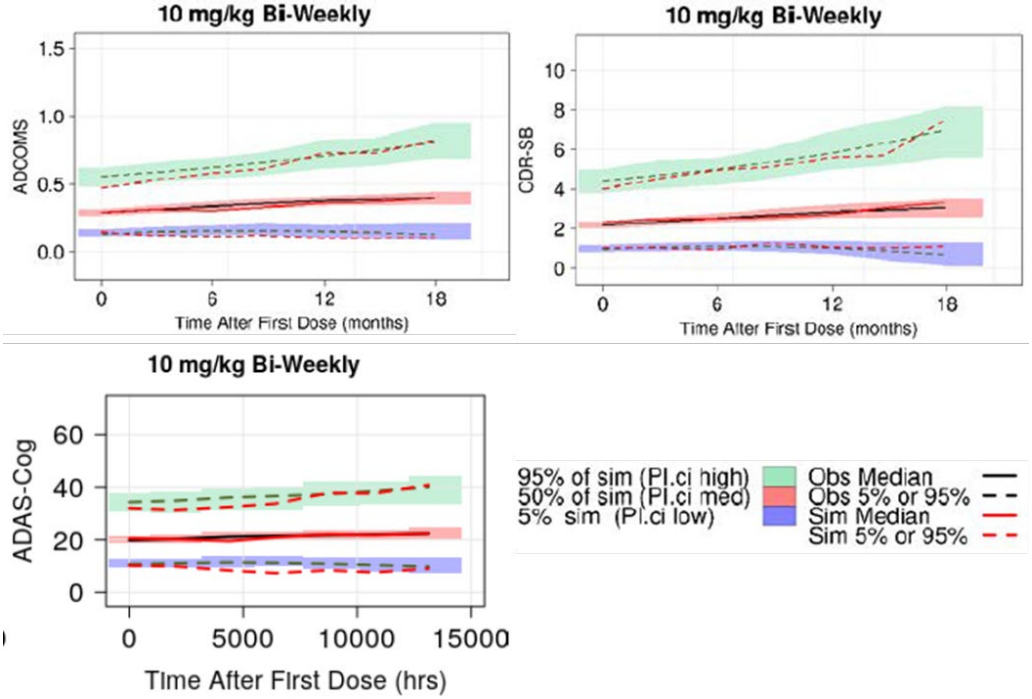
Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD1-v1, Nov 19, 2021, Page 76, 82, 88, Table 28, 33, 38

Figure 16 Time Course of Predicted Change from Baseline in Clinical Endpoints (ADCOMS, CDR-SB, and ADAS-Cog14) by SUVR change



Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD1-v1, Nov 19, 2021, Page 77, 83 and 89, Figure 26, 28 and 30

Figure 17 Visual Predictive Checks for the Final SUVR-Efficacy model for lecanemab 10 mg/kg Q2W



Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD1-v1, Nov 19, 2021, Page 78, 84, 90, Figure 27,29, 31

PK/PD analysis for plasma Aβ42/40 ratio

Objectives: To describe the relationship between model-predicted serum lecanemab exposure and plasma Aβ42/40 ratio.

Data: The PK-PD data of 1254 samples from 284 subjects enrolled in Study 01 Core and OLE were used to develop Pop PK-PD models for plasma Aβ42/40 ratio. The baseline covariate characteristics of subjects is provided in the **Table 20**.

Method: The PK exposure-plasma Aβ42/40 ratio was explored with an indirect response model with the lecanemab concentration increasing the plasma Aβ42/40 ratio using Study 201 Core and OLE data. Covariate analysis was performed for the effect of age, weight, APOE4 carrier status, sex, AD diagnosis, ADA and neutralizing ADA.

Results: The relationship between the lecanemab concentration and the Aβ42/40 ratio change time course was described by an indirect response model with the lecanemab concentration increasing the plasma Aβ42/40 ratio as a linear function. No covariate effects were added in the model. The parameter estimates of the final population PK-PD model for plasma Aβ42/40 ratio are shown in **Table 21**. The population PK-PD model was assessed with diagnostics plots including goodness-of-fit and VPC (**Figure 15**).

Table 20 Summary of Baseline Characteristics in the PK-PD Analysis for plasma Aβ42/40 ratio

Covariate (unit)	Mean (SD)	Median	Range (Min-Max)
Age (years)	71.1 (8.2)	72.0	50.0 – 88.0
Weight (kg)	70.9 (14.5)	70.7	35.9 – 111.8
Baseline plasma Aβ42/40 ratio	0.0845 (0.0082)	0.0836	0.0591 – 0.145
Baseline CDR-SB	2.87 (1.36)	3.00	0.50 – 7.00
Baseline ADCOMS	0.363 (0.156)	0.359	0.0378 – 0.873
Baseline ADAS-Cog	21.7 (7.49)	21.3	3.67 – 48.3
Dose in Core	Placebo= 88, 2.5 mg/kg bi-weekly=13, 5 mg/kg monthly=16, 5 mg/kg bi-weekly=29, 10 mg/kg monthly=95, 10 mg/kg bi-weekly=43		
Sex	Females = 146; Males = 138		
APOE4 carrier status	Negative = 82; Positive = 202		
Diagnosis	MCI = 189; Mild AD = 95		
ADA at subject level	Negative = 168; Positive = 116		
Neutralizing ADA at subject level	ADA(+)/NAb(+) = 26; ADA(+)/NAb(−) = 90		

ADA(+) = ADA positive; ADA(−) = ADA negative; NAb(+) = neutralizing ADA positive; NAb(−) = neutralizing ADA negative

Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD2-v1, Nov 19, 2021, Page 8

Table 21 Parameter Estimates of the Final Population PK-PD Model for plasma Aβ42/40 ratio

	NONMEM		Bootstrap	
Parameter	**Point Estimate**	**%RSE**	**Median**	**95% CI**
Baseline				
Baseline plsama Aβ42/40 ratio	0.08423	4.275	0.08429	0.08344 - 0.08519
K_{out}				
K_{out} (1/year)	0.3673	1.966	0.3678	0.2554 - 0.5212
Exposure Effect Slope				
Slope (1/ug/mL)	0.001554	9.317	0.001553	0.001104 - 0.002126
Inter-individual variability (CV%)				
Baseline	6.776	16.11	6.733	4.577 – 8.761
Slope	44.10	11.10	44.33	21.36 – 58.90
Residual variability				
Proportional (CV%)	6.405	2.820	6.421	6.032 – 6.819

%RSE=percent relative standard error of the estimate = SE/parameter estimate * 100;
K_{out} = rate constant of degradation; CI = confidence interval

Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD2-v1, Nov 19, 2021, Page 29, Table 4

Relationship between plasma Aβ42/40 ratio and Efficacy endpoints

Objectives: To describe the relationship between plasma Aβ42/40 ratio and efficacy endpoints (ADAS-Cog14, ADCOMS, CDR-SB).

Data: The data from Study 201 Core was used to explore relationship between plasma Aβ42/40 ratio and efficacy. The baseline covariate characteristics of subjects is provided in the **Table 20**.

Method: Linear disease progression model was used to describe plasma Aβ42/40 -efficacy-time relationship, in which model-predicted change in plasma Aβ42/40 ratio was used as a predictor for efficacy endpoints. Absolute clinical efficacy endpoint scores were used in the analysis.

Results: The biomarker effect on disease progression was introduced in the model as a linear function and was a significant predictor for efficacy endpoints (CDR-SB and ADCOMS). The following covariates included in the final plasma Aβ42/40 -efficacy models: (i) mild dementia on ADCOMS baseline for ADCOMS; and (ii) mild dementia on CDR-SB baseline for CDR-SB. The parameter estimates of the final plasma Aβ42/40 ratio - efficacy models are shown in **Table 22**. Overall, 95% CIs for the drug effect by change of plasma Aβ42/40 (KABETA) did not include zero for ADCOMS and CDR-SB, indicating significant correlation in the relationship between plasma Aβ42/40 and these two clinical endpoints. The plasma Aβ42/40 - efficacy model showed that an increase in plasma Aβ42/40 was associated with reduction in clinical decline on ADCOMS, and CDR-SB. In plasma Aβ42/40 - ADAS-Cog14 analysis, plasma Aβ42/40 ratio was not a significant predictor of ADAS-Cog14, but the estimated KABETA was 17.2 (95% CI: -23.3 - 57.7) suggested directionally plasma Aβ42/40 ratio increases from baseline were related to reduction in clinical decline on ADAS-Cog14. The plasma Aβ42/40 ratio-efficacy models were assessed with diagnostics plots including goodness-of-fit and VPC (**Figure 18**).

Table 22 Parameter *Estimates of the Final Population Plasma Aβ42/40 Ratio -Efficacy model of Lecanemab*

A. ADCOMS

	NONMEM		Bootstrap	
Parameter	**Point Estimate**	**%RSE**	**Median**	**95% CI**
Baseline ADCOMS [BADCOMS]	0.2819	3.417	0.2831	0.2649 – 0.3039
Effect of mild AD on ADCOMS baseline	1.642	4.716	1.637	1.483 – 1.788
Progression rate [SLP] (1/day)	0.0002349	9.568	0.0002316	0.0001930 – 0.0002791
Rate constant for the effect of change of plasma Aβ42/40 ratio [KABETA]	29.87	35.19	30.64	3.175 – 48.23
Inter-individual variability				
Baseline ADCOMS (CV%)	38.87	5.863	38.56	33.44 – 43.19
Progression rate (SD, 1/day)	0.00001329	7.223	0.00001325	0.00001131 – 0.00001495
Residual variability				
Proportional (CV%)	13.75	7.878	13.76	11.42 – 15.79
Additive (SD)	0.04570	9.939	0.04561	0.03657 – 0.05418

%RSE=percent relative standard error of the estimate = SE/parameter estimate * 100;
CI = confidence interval; SD = standard deviation

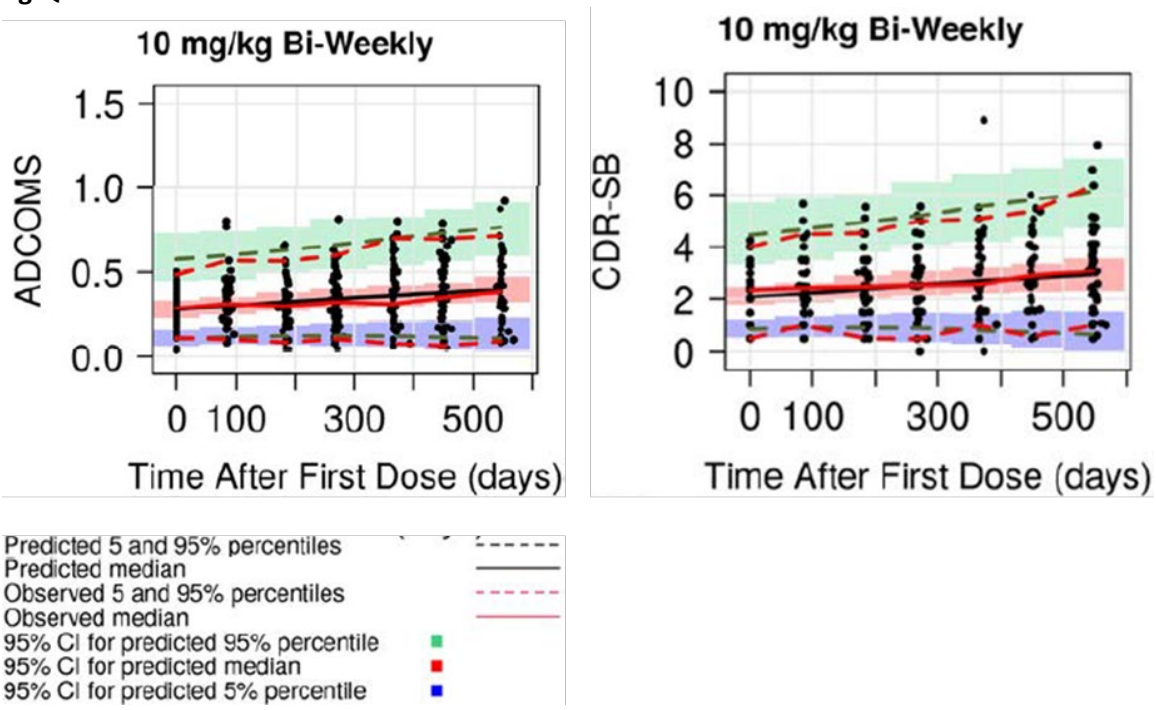
B. CDR-SB

	NONMEM		Bootstrap	
Parameter	**Point Estimate**	**%RSE**	**Median**	**95% CI**
Baseline CDR-SB [BCDR]	2.109	3.639	2.105	1.942 – 2.260
Effect of mild AD on CDR-SB baseline	1.691	5.289	1.685	1.505 – 1.887
Progression rate [SLP] (1/day)	0.001829	11.59	0.001806	0.001449 – 0.002303
Rate constant for the effect of change of plasma Aβ42/40 ratio [KABETA]	33.81	37.95	37.01	5.15 – 53.36
Inter-individual variability				
Baseline CDR-SB (CV%)	42.19	5.250	42.00	37.66 – 46.51
Progression rate (SD, 1/day)	0.0001235	7.561	0.0001233	0.0001051 – 0.0001401
Residual variability				
Proportional (CV%)	17.13	6.165	17.01	14.89 – 19.23
Additive (SD)	0.3248	10.12	0.3231	0.2493 – 0.3973

%RSE=percent relative standard error of the estimate = SE/parameter estimate * 100;
CI = confidence interval; SD = standard deviation

Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD2-v1, Nov 19, 2021, Page 41, Table 13

Figure 18 Visual Predictive Checks for the Final Plasma Aβ42/40 Ratio-Efficacy model for lecanemab 10 mg/kg Q2W



Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD2-v1, Nov 19, 2021, Page 43,48, Figure 12,14

PK/PD analysis for plasma p-tau181

Objectives: To describe the relationship between model-predicted serum lecanemab exposure and plasma p-tau181.

Data: The PK-PD data of 2021 samples from 562 subjects enrolled in Study 201 Core and OLE were used to develop Pop PK-PD models for plasma p-tau181. The baseline covariate characteristics of subjects is provided in the **Table 23**.

Method: The PK exposure-plasma p-tau181 was explored with an indirect response model with the lecanemab concentration as a linear function decreasing the plasma p-tau181 formation rate. Covariate analysis was performed for the effect of APOE4 carrier status, sex, AD diagnosis (MCI or mild AD), ADA, neutralizing ADA, age, body weight, and baseline p-tau181.

Results: Body weight was added on baseline plasma p-tau181. The parameter estimates of the final population PK-PD model for plasma p-tau181 are shown in **Table 24**. The population PK-PD model was assessed with diagnostics plots including goodness-of-fit and VPC (**Figure 15**).

Table 23 Summary of Baseline Characteristics in the PK-PD Analysis for Plasma p-tau181

Covariate (unit)	Mean (SD)	Median	Range (Min-Max)
Age (years)	71.0 (8.3)	72.0	50 -- 89
Weight (kg)	72.5 (14.6)	72.2	29.2 – 118.7
Baseline plasma p-tau181	4.43 (1.85)	4.15	0.84 – 17.4
Dose in Core	Placebo = 179 2.5 mg/kg bi-weekly = 36 5 mg/kg bi-weekly = 70 5 mg/kg monthly = 38 10 mg/kg bi-weekly = 84 10 mg/kg monthly = 155		
Sex	Females = 286; Males = 276		
Race	White = 500 Black/African American = 12 Asian/Other Asian (excluding Chinese and Japanese) = 15 Japanese = 32 Chinese = 1 Other = 3		
APOE4 carrier status	Negative = 169; Positive = 393		
Diagnosis	MCI = 374; Mild AD = 188		
ADA at subject level	Negative = 327; Positive = 235		
Neutralizing ADA at subject level	ADA(+)/NAb(+) = 37; ADA(+)/NAb(−) = 198		

ADA(+) = ADA positive; ADA(−) = ADA negative; NAb(+) = neutralizing ADA positive; NAb(−) = neutralizing ADA negative

Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD3-v1, Nov 22, 2021, Page 9

Table 24 Parameter Estimates of the Final Population PK-PD Model for Plasma p-tau181

	NONMEM		Bootstrap	
Parameter	**Point Estimate**	**%RSE**	**Median**	**95% CI**
Baseline				
Baseline plasma p-tau181	4.06	1.61	4.06	3.97 – 4.14
Effect of body weight on baseline (exponent)	-0.300	24.2	-0.304	-0.439 – -0.211
K_{out}				
K_{out} (1/year)	0.468	20.7	0.502	0.183 – 0.934
Exposure Effect Slope				
Slope (1/ug/mL)	0.00313	15.6	0.00328	0.00178 – 0.00596
Inter-individual variability				
Baseline (%CV)	35.1	5.63	35.1	33.0 – 37.4
Slope (SD)	0.00151	50.2	0.00162	0.000662 – 0.00280
Residual variability				
Proportional (CV%)	19.4	2.39	19.4	18.3 – 20.6

%RSE=percent relative standard error of the estimate = SE/parameter estimate * 100;
K_{out} = rate constant of degradation; CI = confidence interval

Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD3-v1, Nov 22, 2021, Page 35, Table 8

Relationship between plasma p-tau181 and Efficacy endpoints

Objectives: To describe the relationship between plasma p-tau181 and efficacy endpoints (ADAS-Cog14, ADCOMS, CDR-SB).

Data: The data from Study 201 Core was used to explore relationship between plasma p-tau181 and efficacy. The baseline covariate characteristics of subjects is provided in the **Table 25**.

Method: Linear disease progression model was used to describe plasma p-tau181 -efficacy-time relationship, in which model-predicted change in plasma p-tau181 was used as a predictor for efficacy endpoints. Absolute clinical efficacy endpoint scores were used in the analysis.

Results: The biomarker effect on disease progression was introduced in the model as a linear function and was a significant predictor for efficacy endpoints. The following covariates included in the final plasma p-tau181 -efficacy models: (i) mild dementia on ADCOMS baseline; and concomitant AChEI on both baseline and slope for ADCOMS; (ii) mild dementia on CDR-SB baseline; and concomitant AChEI on slope for CDR-SB; and (iii) mild dementia and concomitant AChEI on both ADAS-Cog14 baseline and slope; and age on slope for ADAS-Cog14. The parameter estimates of the final plasma p-tau181 - efficacy models are shown in **Table 26**. Overall, 95% CIs for the drug effect by change of plasma p-tau181 did not include zero, indicating significant association between plasma p-tau181 and clinical endpoints. The plasma p-tau181- efficacy model showed that a decrease in plasma p-tau181 was associated with reduction in clinical decline on ADCOMS, CDR-SB, and ADAS-Cog14. The plasma p-tau181- efficacy models were assessed with diagnostics plots including goodness-of-fit and visual predictive checks (VPC) (**Figure 19**).

Table 25 Summary of Baseline Characteristics in the Plasma p-tau181- Efficacy Analysis

Covariate (unit or subject number)	Mean (SD)	Median	Range (Min-Max)
Age (years)	71.0 (8.2)	72.0	50.0 – 90.0
Weight (kg)	73.0 (14.7)	72.7	29.2 – 124.7
Baseline CDR-SB (N=829)	2.94 (1.39)	3.00	0.50 – 9.00
Baseline ADCOMS (N=827)	0.376 (0.160)	0.365	0.0378 – 0.942
Baseline ADAS-Cog (N=825)	22.3 (7.47)	22.0	3.67 – 48.3
Dose in Core	Placebo= 238 2.5 mg/kg bi-weekly= 52 5 mg/kg bi-weekly=90 5 mg/kg monthly=50 10 mg/kg bi-weekly=152 10 mg/kg monthly=247		
Sex	Females = 411; Males = 418		
Race	White = 751 Black/African American = 20 Asian/Other Asian (excluding Chinese and Japanese) = 20 Japanese = 34 Other=4		
APOE4 carrier status	Negative = 236; Positive = 593		
Diagnosis	MCI = 532; Mild AD = 297		
Concomitant AChE inhibitor	No = 380; Yes = 449		
Concomitant memantine	No = 706; Yes = 123		
ADA at subject level	Negative = 477; Positive = 352		
Neutralizing ADA at subject level	ADA(+)/NAb(+) = 69; ADA(+)/NAb(−) = 283		

ADA(+) = ADA positive; ADA(−) = ADA negative; NAb(+) = neutralizing ADA positive; NAb(−) = neutralizing ADA negative

Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD3-v1, Nov 22, 2021, Page 10

Table 26 Parameter Estimates of the Final Population Plasma p-tau181 -Efficacy model of Lecanemab

A. ADCOMS

	NONMEM		Bootstrap	
Parameter	**Point Estimate**	**%RSE**	**Median**	**95% CI**
Baseline ADCOMS [BADC]	0.277	2.25	0.276	0.264 – 0.289
Effect of mild AD on ADCOMS baseline	1.58	2.68	1.58	1.50 – 1.67
Effect of concomitant AChEI on ADCOMS baseline	1.12	2.61	1.12	1.06 – 1.17
Progression rate [SLP] (1/day)	0.000237	6.67	0.000238	0.000196 – 0.000271
Effect of concomitant AChEI on SLP	1.41	10.5	1.42	1.14 – 1.68
Rate constant for the effect of change of plasma p-tau181 [KPTAU]	0.232	24.4	0.227	0.0973 –0.356
Inter-individual variability				
Baseline ADCOMS (CV%)	35.9	6.81	36.0	33.5 – 38.2
Progression rate (SD, 1/day)	0.0000130	10.9	0.0000130	0.0000114 – 0.0000145
Rate constant for the effect of change of plasma p-tau181 (SD)	0.434	52.5	0.440	0.00447 – 0.642
Residual variability				
Proportional (CV%)	14.3	4.90	14.3	12.6 – 15.8
Additive (SD)	0.0440	7.05	0.0441	0.0373 – 0.0498

%RSE=percent relative standard error of the estimate = SE/parameter estimate * 100;
CI = confidence interval; SD = standard deviation; AChEI = Acetylcholine esterase inhibitors.

B. CDR-SB

	NONMEM		Bootstrap	
Parameter	**Point Estimate**	**%RSE**	**Median**	**95% CI**
Baseline CDR-SB [BCDR]	2.18	2.00	2.18	2.08 – 2.26
Effect of mild AD on CDR-SB baseline	1.70	3.02	1.71	1.59 – 1.82
Progression rate [SLP] (1/day)	0.00149	12.6	0.00149	0.00114 – 0.00187
Effect of concomitant AChEI on SLP	1.67	12.9	1.70	1.33 – 2.19
Rate constant for the effect of change of plasma p-tau181 [KPTAU]	0.309	29.1	0.307	0.151 – 0.445
Inter-individual variability				
Baseline CDR-SB (CV%)	39.6	6.50	39.7	37.3 – 42.2
Progression rate (SD, 1/day)	0.000109	12.6	0.000109	0.0000958 – 0.000123
Rate constant for the effect of change of plasma p-tau181 (SD)	0.764	45.2	0.767	0.465 – 1.05
Residual variability				
Proportional (CV%)	17.4	4.24	17.4	15.7 – 18.8
Additive (SD)	0.321	7.98	0.321	0.257 – 0.369

%RSE=percent relative standard error of the estimate = SE/parameter estimate * 100;
CI = confidence interval; SD = standard deviation; AChEI = Acetylcholine esterase inhibitors.

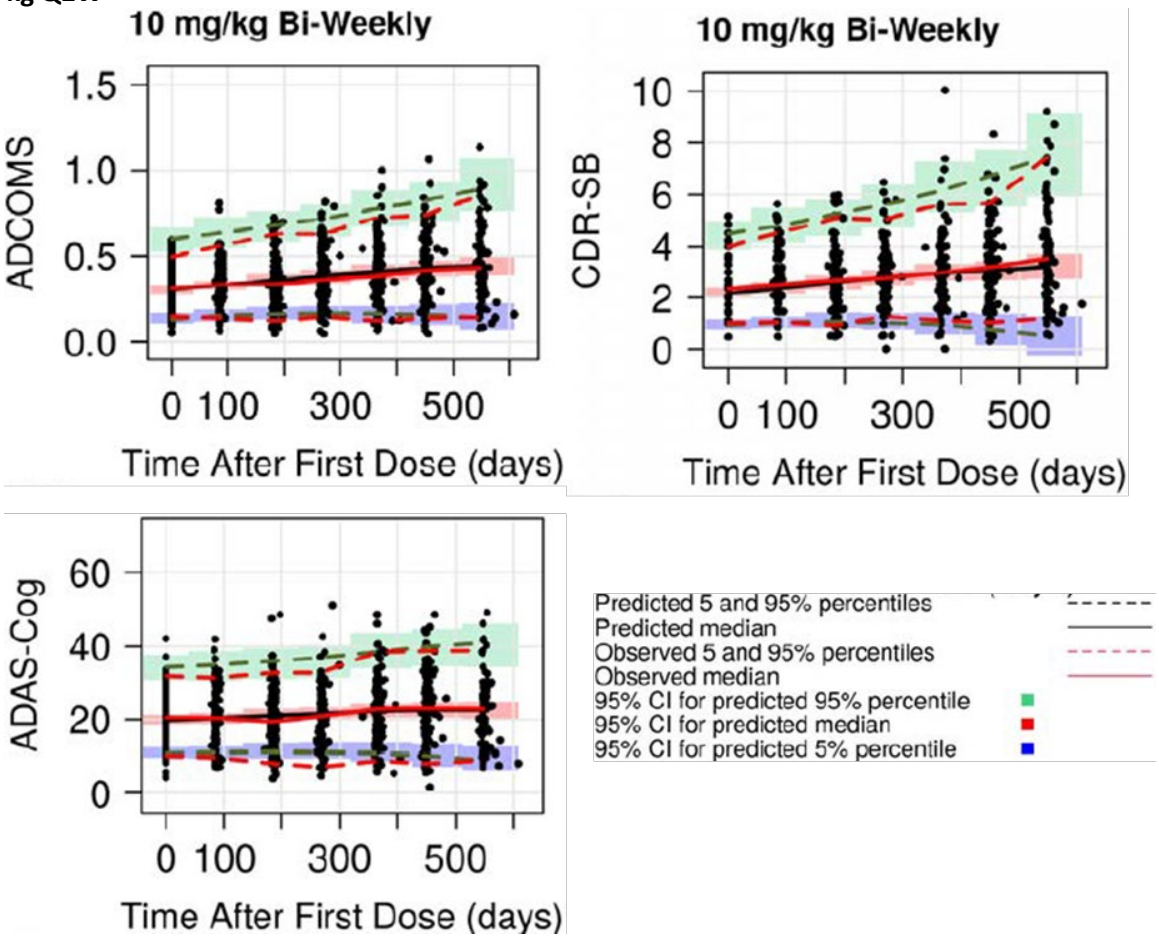
C. ADAS-Cog14

	NONMEM		Bootstrap	
Parameter	**Point Estimate**	**%RSE**	**Median**	**95% CI**
Baseline ADAS-Cog [BADAS]	18.9	1.48	18.9	18.3 – 19.4
Effect of mild AD on ADAS-Cog baseline	1.30	2.31	1.30	1.25 – 1.36
Effect of body weight on ADAS-Cog baseline	-0.248	22.1	-0.251	-0.357 – -0.139
Progression rate [SLP] (1/day)	0.00288	22.6	0.00286	0.00168 – 0.00415
Effect of mild AD on SLP	1.53	14.4	1.57	1.21 – 2.05
Effect of concomitant AChEI on SLP	2.36	21.7	2.44	1.61 – 3.77
Effect of age on SLP	-2.41	22.8	-2.40	-3.74 – -1.36
Rate constant for the effect of change of plasma p-tau181 [KPTAU]	0.313	28.1	0.304	0.128 – 0.484
Inter-individual variability				
Baseline ADAS-Cog (CV%)	31.8	6.44	31.7	29.6 – 33.6
Progression rate (SD, 1/day)	0.000453	13.6	0.000449	0.000385 – 0.000506
Rate constant for the effect of change of plasma p-tau181 (SD)	0.668	40.4	0.691	0.344 – 0.997
Residual variability				
Proportional (CV%)	8.35	5.77	8.35	7.32 – 9.12
Additive (SD)	2.17	4.07	2.17	2.00 – 2.34

%RSE=percent relative standard error of the estimate = SE/parameter estimate * 100;
CI = confidence interval; SD = standard deviation; AChEI = Acetylcholine esterase inhibitors.

Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD3-v1, Nov 22, 2021, Page 47,54,59, Table 17,22, 27

Figure 19 Visual Predictive Checks for the Final Plasma p-tau181 - Efficacy model for lecanemab 10 mg/kg Q2W



Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-ADD3-v1, Nov 22, 2021, Page 49,55,61, Figure 11,13,15

4.4.1.4 Population PK-PD model of Safety

Objectives: To describe the relationship between model-predicted serum lecanemab exposure to amyloid related imaging abnormality edema (ARIA-E).

Data: The data from Study 201 Core was used to develop Pop PK-PD models of safety. The baseline covariate characteristics of subjects is provided in the **Table 27**.

Method: Logistic regression was explored to examine the relationship between incidence of ARIA-E and lecanemab exposure. Log-hazard model including lecanemab exposure effect and attenuation factor of exposure effects was considered for the analysis of time to the first event of ARIA-E. In terms of PK exposure, the PK model-derived $C_{ss,max}$ or $C_{ss,avg}$ before/at the safety assessment were explored.

Results: For ARIA-E incidence, final logistic regression model included an intercept, a linear term with respect to lecanemab $C_{ss,max}$ and an effect of APOE4 carrier. APOE4 carrier status (p = 0.040) did not meet the covariate selection criteria of P < 0.01, however the effect of APOE4 carrier status was included in the model from the perspective of clinical interest. The final parameter estimates for PK/PD models for ARIA-E incidences are shown in **Table 28A**. As shown in **Figure 20A**, model-predicted proportion of subjects with ARIA-E increases with higher $C_{ss,max}$, and the proportion was higher for APOE4 carriers.

For time- first event of ARIA-E, final log-hazard model included an intercept, a linear term with respect to lecanemab $C_{ss,max}$ with attenuation factor and an effect of APOE4 carrier. APOE4 carrier status (p = 0.022) did not meet the covariate selection criteria of P < 0.01, however the effect of APOE4 carrier status was included in the model from the perspective of clinical interest. The final parameter estimates for Log-Hazard Model for Time to First ARIA-E are shown in **Table 28B**. The predictive performance of the final model was assessed using VPC (**Figure 20B)**, which showed good agreement of simulated and observed data for lecanemab 10 mg/kg Q2W.

Table 27 Summary of Baseline Characteristics in the PK-PD Analysis of ARIA-E

Covariate (unit)	Mean (SD)	Median	Range (Min-Max)
Age (years)	71.3 (8.2)	72	50 - 90
Weight (kg)	72.9 (14.7)	72.6	29.2 – 124.7
Dose	Placebo = 245 ; 2.5 mg/kg bi-weekly = 52; 5 mg/kg monthly = 51; 5 mg/kg bi-weekly = 92; 10 mg/kg monthly = 251; 10 mg/kg bi-weekly = 161		
Gender	Females = 422, Males = 430		
Race	White=772, Others=80		
APOE4 carrier status	Negative = 243 ; Positive = 609		
Diagnosis	MCI = 546 ; Mild AD = 306		
Concomitant medication[a]	YES = 458, NO = 394		

a: with acetylcholinesterase inhibitors (AChEIs) and/or memantine.

SD = standard deviation, Min = minimum value; Max = maximum value; MCI = Mild cognitive impairment; AD = Alzheimer's Disease.

Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-v1.1, April 15, 2019, Page 8

Table 28 Parameter Estimates of the Final Population PK-PD Model for safety of Lecanemab

A. **Logistic regression model for ARIA-E incidences**

Parameter	Point estimate	%RSE	Bootstrap median (95% CI)
Logit = INT + SLP*$C_{ss,max}$ + APOE4			
INT: Intercept	-4.87	9.67	-4.98 (-6.15 – -4.15)
SLP: Slope of BAN2401 $C_{ss,max}$ effect (per $C_{ss,max}$ unit [µg/mL])	0.00714	17.2	0.00734 (0.00488 – 0.0101)
APOE4: Effect of APOE4 carrier	0.735	49.9	0.769 (0.117 – 1.726)

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CI: confidence interval

B. Log-Hazard Model Parameter Estimates for Time to First ARIA-E

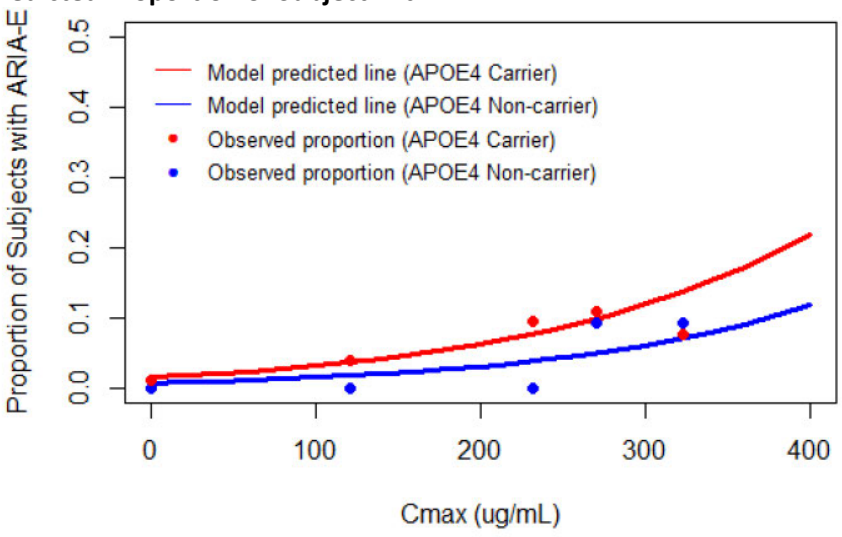
Parameter	Point estimate	%RSE	Bootstrap median (95% CI)
Log h(t) = B+SLOPE* $C_{ss,max}$*exp(-Ktol*t)			
B: baseline risk ; *APOE4 carrier*	-10.2	3.55	-10.2 (-11.0 – -9.69)
; *APOE4 non-carrier*	-10.5	6.22	-10.6 (-12.2 – -9.59)
SLOPE: Slope of BAN2401 $C_{ss,max}$ effect (per $C_{ss,max}$ unit [µg/mL]) ; *APOE4 carrier*	0.0131	11.2	0.0132 (0.0105 – 0.0163)
; *APOE4 non-carrier*	0.0103	25.3	0.0104 (0.0055 – 0.0155)
Ktol: attenuation rate constant(/day)	0.00479	31.9	0.00477 (0.00256 – 0.00779)

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CI: confidence interval.

Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-v1.1, April 15, 2019, Page 141, 143, Table 90,92

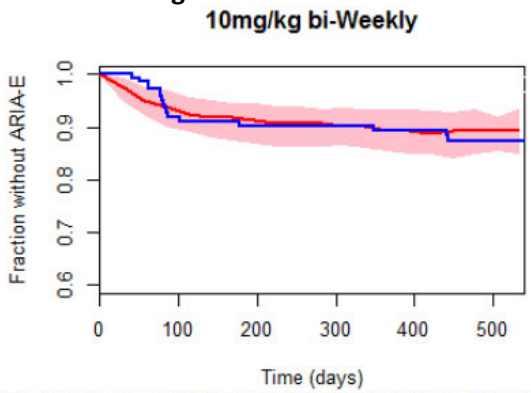
Figure 20 Model Evaluation for PK/PD Model for ARIA-E incidences and time-to-first event of ARIA-E

A. Model Predicted Proportion of Subject with ARIA-E



Filled circles represent the observed proportion of subject with ARIA-E for each $C_{ss,max}$ quartile (1Q-4Q), plotted at the median $C_{ss,max}$ of each group. Solid line represents the model predicted line.

B. Visual Predictive Check of ARIA-E Log-Hazard Model



Red lines and pink areas are predicted medians and 90% prediction intervals from 500 simulated replicates; blue lines are Kaplan-Meier curves based on observed data

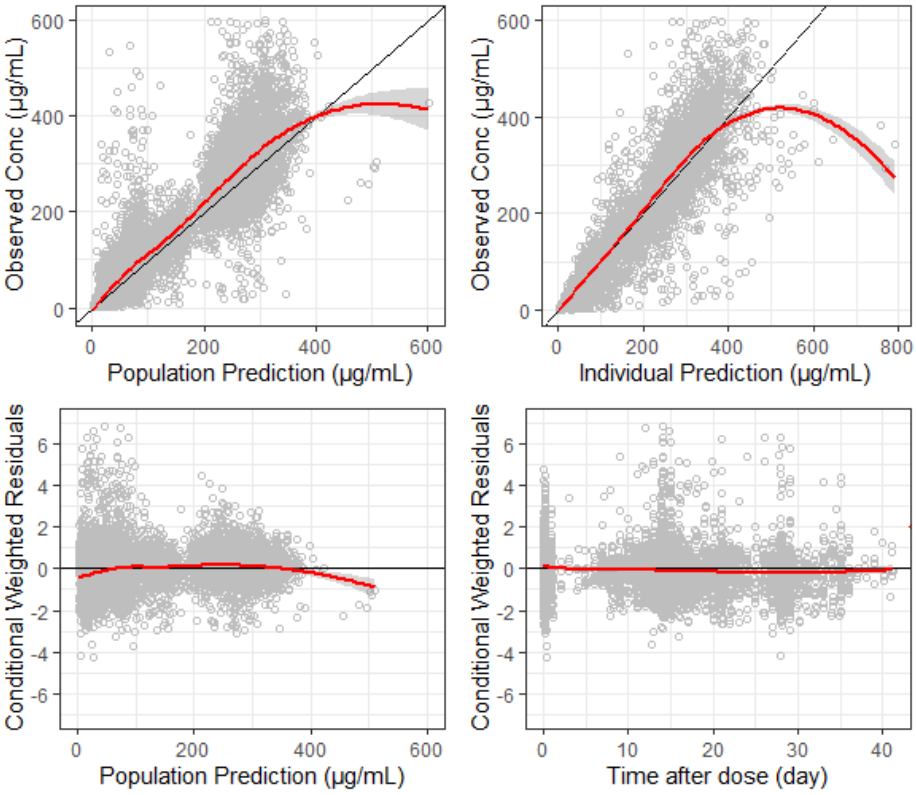
Source: Applicant pop PK-PD report # CPMS-BAN2401-002R-v1.1, April 15, 2019, Page 142,144, Figure 44-45

4.4.2 Reviewer's Analysis

4.4.2.1 Applicant's Pop PK model evaluation

The reviewer was able to run the applicant's final PK model and obtained similar results as reported by the applicant. Model diagnostics for lecanemab are shown in **Figure 21**.

Figure 21 Goodness-Of-Fit Plots of the Final Population PK Model for Lecanemab



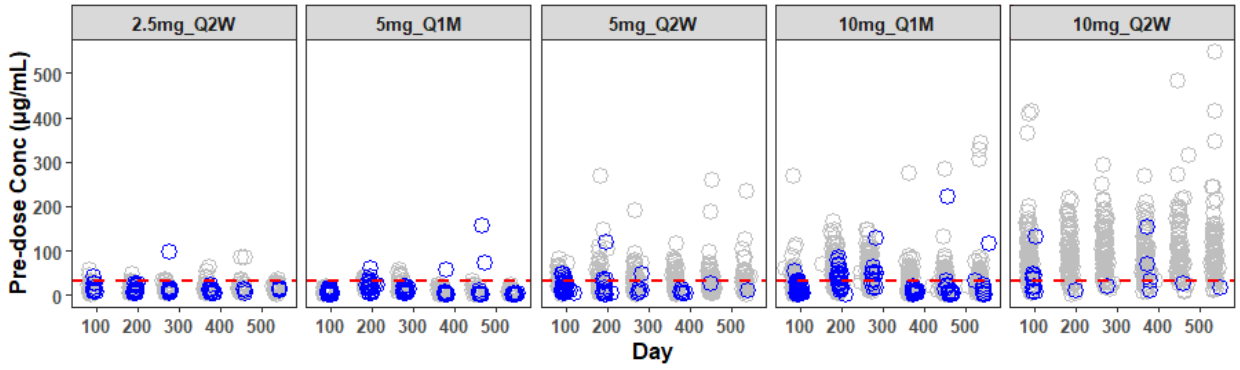
Source: Reviewer's analysis

The applicant's pop-PK model was used to inform following statements of the proposed label Section 12.3:

- [redacted]
- *The mean value (95% CI) for central volume of distribution at steady-state is 3.22 L (3.15-3.28).*
- [redacted] *The terminal half-life is 5 to 7 days.*
- *Sex, body weight, albumin* [redacted] *were found to impact exposure to* [redacted] *However, none of these covariates were found to be clinically significant.*

Reviewer agrees with all above-mentioned statements proposed by the applicant [redacted] For ADA effect on lecanemab PK, the applicant's population PK analysis showed that the subjects with positive ADA status will have [redacted] lower AUC and [redacted] lower C_{max}, which suggested no clinically meaningful effect on the PK of lecanemab (**Figure 12**). However, the ADA assay used to determine ADA incidences have drug tolerance level of 31.3 µg/mL. At dose of 10 mg Q2W, majority of PK samples were higher than drug tolerance level (**Figure 22**), which makes the ADA results for this dose group unreliable. Therefore, population PK analysis was not suitable to evaluate the impact of ADA on the PK of lecanemab 10 mg/kg Q2W.

Figure 22 Observed Pre-dose concentrations Stratified by Dose Group and Colored by ADA status in Study 201



Blue circle: ADA positive; Grey Circle: ADA negative; Red line: drug tolerance level of 31.3 ug/mL
Source: Reviewer's analysis

4.4.2.2 Applicant's Pop PK/PD model for biomarkers and efficacy evaluation

Applicant evaluated the relationship between lecanemab PK exposures, biomarkers, and clinical endpoints as summarized in the Appendix 4.4.1. The reviewer was able to run all the applicant's final PK-PD models and obtained similar results as reported by the applicant. Reviewer has also independently evaluated the relationship between lecanemab PK exposures, biomarkers, and clinical endpoints using

observed data from Study 201 Core. The focus of the analysis was to evaluate the statements of the proposed label Section 12.2-Exposure-Response Relationships.

Reviewer agrees with the following relationships between PK exposures, PET SUVR, and clinical endpoints as summarized in applicant's proposed Labeling Section 12.2 based on the population PK and PK-PD analysis of lecanemab.

For CSF and plasma biomarkers, please refer to Appendix 4.3.

References:

1. Population PK-PD report # CPMS-BAN2401-002R-v1.1: Population Pharmacokinetic & Pharmacokinetic/Pharmacodynamic Analyses of BAN2401 in Patients with Early Alzheimer's Disease, 15 April 2019.
2. Population PK-PD report # CPMS-BAN2401-002R-ADD1-v1: Population Pharmacokinetic & Pharmacokinetic/Pharmacodynamic Analyses of Lecanemab in Patients with Early Alzheimer's Disease Addendum 1 (PK, Amyloid PET, Amyloid PET-Efficacy, Safety), 19 November 2021.
3. Population PK-PD report # CPMS-BAN2401-002R-ADD2-v1: Population Pharmacokinetic/ Pharmacodynamic Analyses of Lecanemab in Patients with Early Alzheimer's Disease Addendum 2 (Plasma Aβ42/40 ratio, Amyloid PET SUVr, Efficacy), 19 November 2021.
4. Population PK-PD report # CPMS-BAN2401-002R-ADD3-v1: Population Pharmacokinetic/ Pharmacodynamic Analyses of Lecanemab in Patients with Early Alzheimer's Disease Addendum 3 (Plasma p-tau181, Amyloid PET SUVr, Efficacy), 22 November 2021.

4.5 Immunogenicity

4.5.1 Classification of Subjects as ADA/NAb Positive vs. Negative

Applicant's Analysis

During the 18-month treatment period in Study 201 Core, treatment emergent anti-lecanemab antibodies (ADA) were tested positive in at least one serum sample in 40.9% (63/154) of patients treated with lecanemab 10 mg/kg biweekly and were generally characterized by low titers. Of these patients, treatment emergent anti-lecanemab neutralizing antibodies (NAb) were tested positive in at least one serum sample in 25.4% (16/63) of patients treated with lecanemab 10 mg/kg biweekly and were generally characterized by low titers.

Reviewer's Comments

The review team noted that the drug tolerance levels for the ADA and NAb assays were 31.3 µg/mL for the 50 ng/mL and 5000 ng/mL of positive control respectively in Study 201 Core. However, most of the pre-dose drug concentrations in this study were above 31.3 µg/mL at the dose of 10 mg Q2W (refer to **Figure 22** in Appendix 4.4.2.1), which makes the ADA results unreliable. The negative result of an ADA sample is considered "inconclusive" if the drug concentration exceeded the drug tolerance level, because the presence of lecanemab in the sample interfered with the ADA assay. An Information Request was sent to the Sponsor to clarify on the adequacy of ADA/NAb assays regarding drug tolerance, and the impact of this issue on the data interpretability.

The IR response dated June 14, 2022 stated that the majority (84%) of the lecanemab 10 mg/kg biweekly subjects could be classified as either ADA positive or ADA negative conclusive. However, the review team identified a different number of "ADA negative conclusive" subjects as compared to the subject number in Sponsor's analysis in the IR response. A follow-up IR was thus sent to the Sponsor to request for a detailed list of lecanemab concentration and ADA status of each sample and subject. The IR response submitted on August 8, 2022 suggested the discrepancy was due to Sponsor's incorrect definition of ADA negative conclusive. In short, the review team does not accept the Sponsor's approach of classifying the screening negative samples as "negative conclusive" when the drug concentrations in the samples exceed the drug tolerance level.

The OCP review team concluded that the observed incidence of ADA and NAb positivity may be underestimated, since the subjects classified as "negative inconclusive" could be potentially ADA positive. Although the immunogenicity assays were not adequate to provide an accurate estimation of ADA/NAb incidence, the review team proposed to include applicant's estimated incidences into the labeling as this might be informative on potential clinical significance of immunogenicity effect.

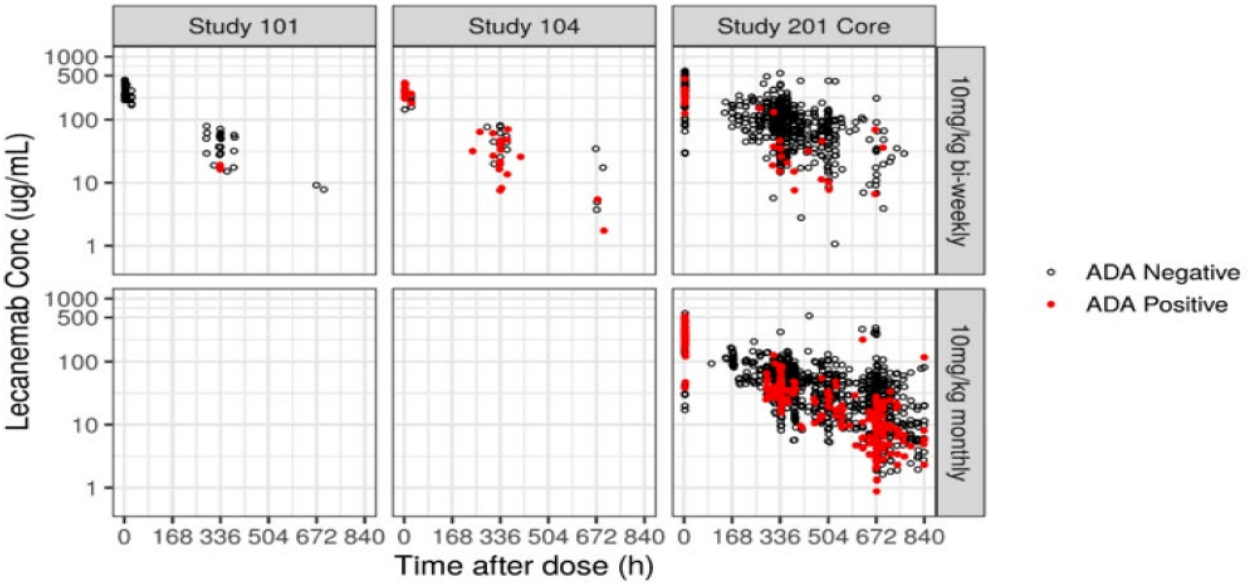
The review team recommends to include the following language in labeling to describe the limitation of ADA assay and the impact on estimation of ADA incidence: "the assays used to measure anti-lecanemab-irmb antibodies and neutralizing antibodies are subject to interference by serum lecanemab concentrations, possibly resulting in an underestimation of the incidence of antibody formation." Please refer to the review by OBP for bioanalytical method validation and performance of ADA and NAb.

4.5.2 Effect of Immunogenicity on PK and PD

Applicant's Initial Analysis

No clinically meaningful effect was observed for ADA impact on PK or PD based on sponsor's pop-PK/PD analysis. For the effect of ADA on PK, slight decrease in AUC and C_{max} was observed in subjects with positive ADA status as shown in observed data (**Figure 23**) and stated in applicant's population PK analysis (Appendix 4.4.1.1, **Figure 12**). The difference in PK exposure was not considered clinically meaningful based on the comparison of PD effect. According to Sponsor's analysis (**Figure 24**), both ADA positive subjects and ADA negative conclusive subjects achieved an amyloid negative level (PET SUVR = 1.17) by Week 53.

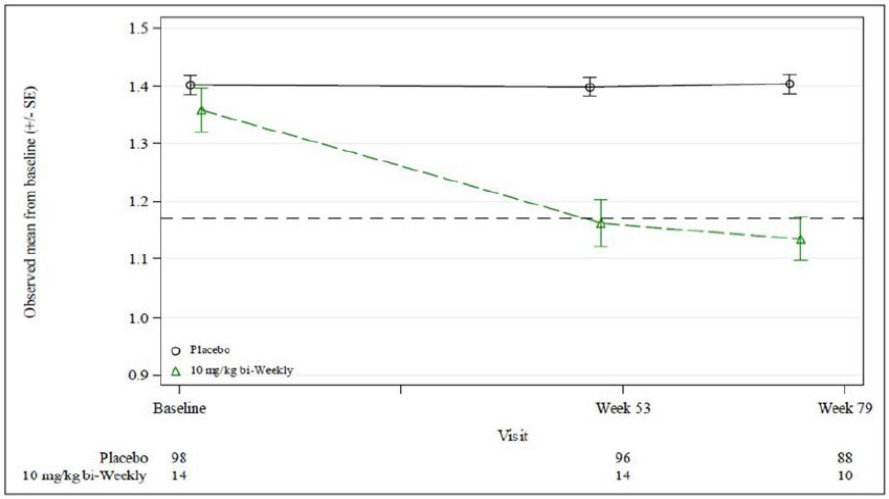
Figure 23 Observed Lecanemab Serum Concentrations Stratified by ADA Status



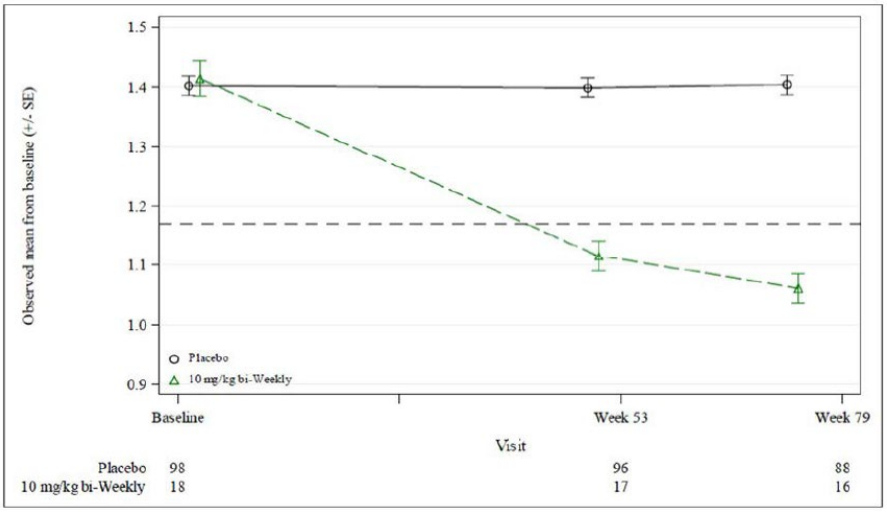
Source: Applicant's summary of clinical pharmacology, Section 2.7.2.3.2, page 41, Figure 2.7.2-5

Figure 24 Mean (+/- SE) Change from Baseline in Brain Amyloid Levels as Measured by Amyloid PET by Visit and ADA Status in Study 201 Core, ADA positive (A) and ADA negative conclusive (B)

A



B



Source: Applicant's Integrated Summary of Immunogenicity, Figure 14, page 44-45

Reviewer's Comments on Applicant's Initial Analysis

Assessment of impact of immunogenicity on PK and PD requires accurate classification of subjects into categories including "ADA positive", "ADA negative conclusive" and others (as appropriate), which was not achieved in the Sponsor's initial analysis. To explore the potential to characterize the impact of immunogenicity despite the inadequacy of ADA assay, the review team requested further analysis from the Sponsor. The Sponsor submitted the IR response on September 13, 2022, with updated analysis to evaluate the impact of ADA on PK and PD (**Figure 25**). In this exploratory analysis, the modified classification criteria were used for ADA negative conclusive, as listed below:

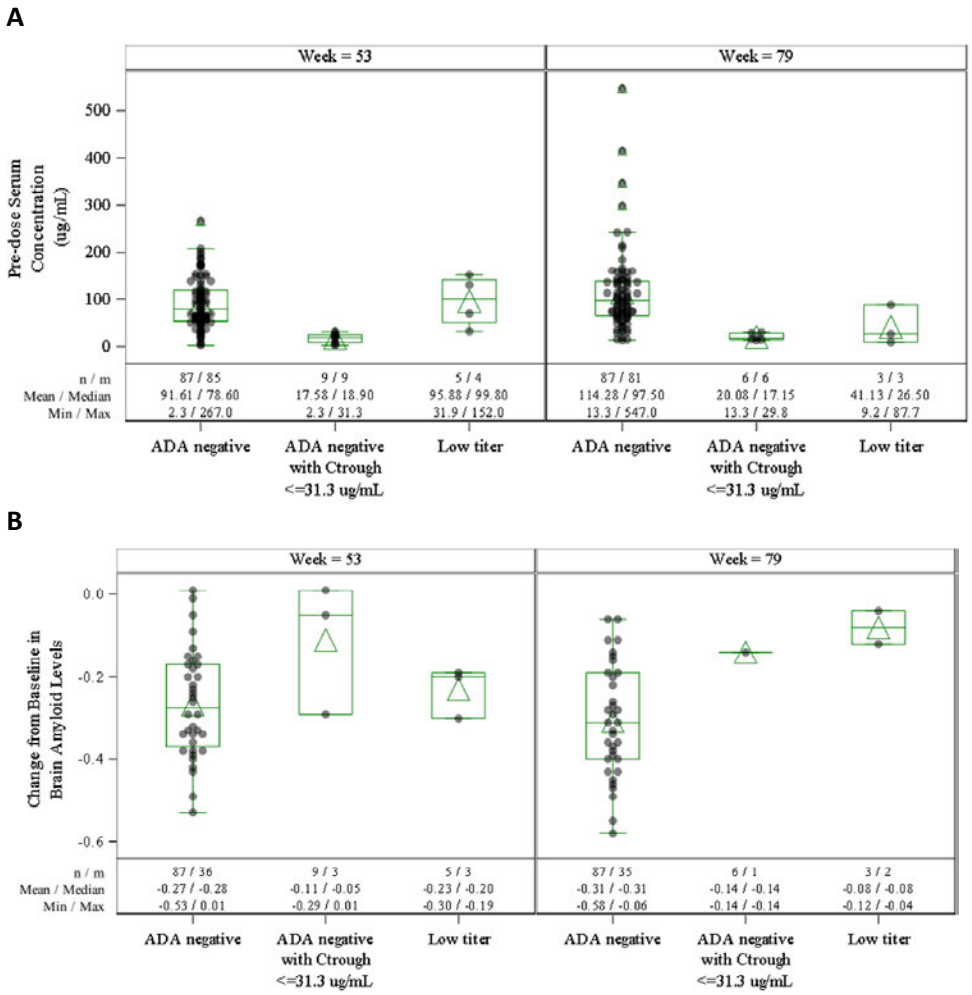
- Subjects with evaluable ADA (at least one baseline and one post-baseline ADA sample).

- Final ADA negative status (ADA subject-level status of negative conclusive [NC] or negative inconclusive [NI]).
- At least one post-baseline negative ADA sample (screening negative [SN], NC, NI) with C_{trough} ≤ drug tolerance level (31.3 µg/mL for Study 201).

Applicant's Updated Analysis

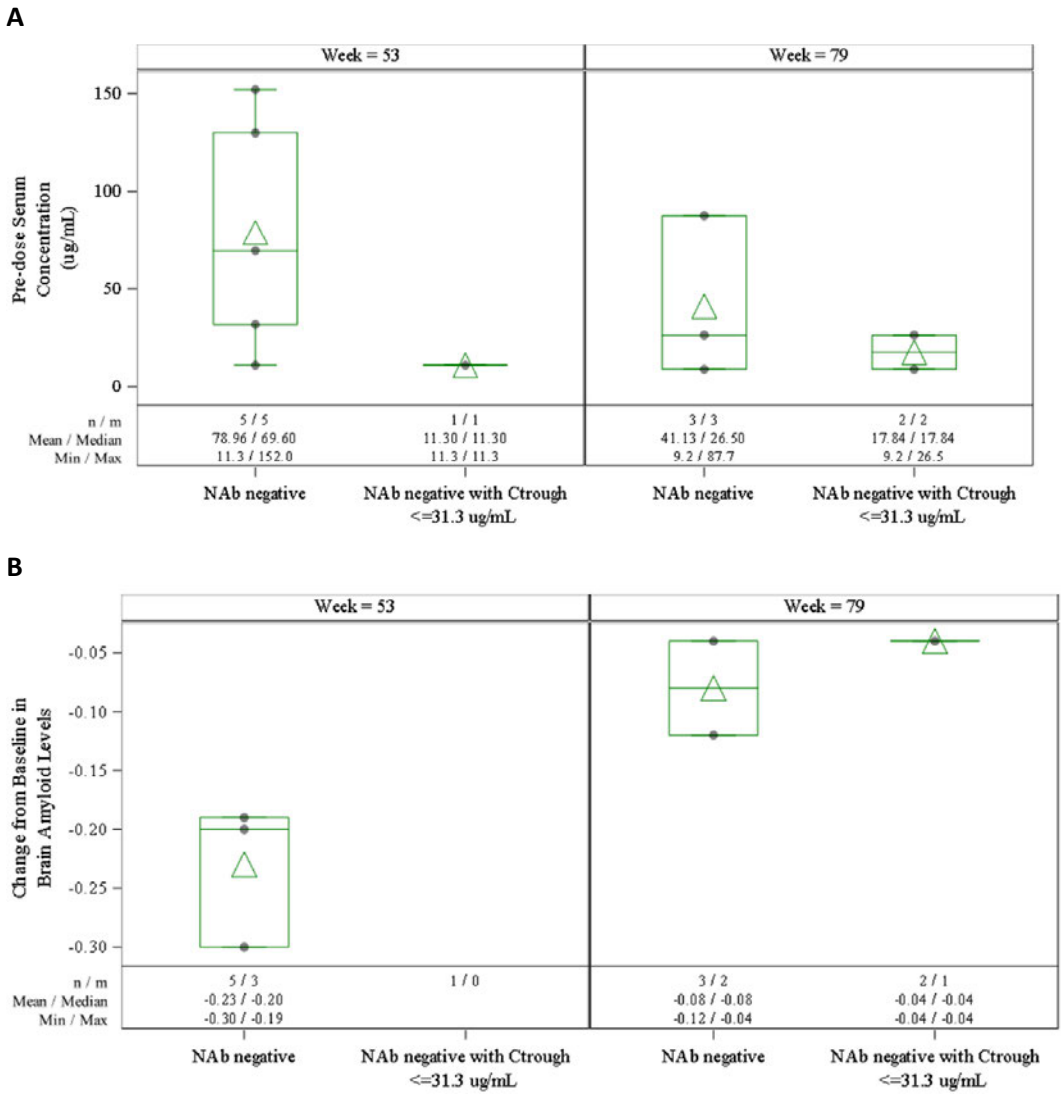
Each boxplot presents the following groups at the sample-level at Week 53 and Week 79: ADA negative (SN, NC, or NI); ADA negative with C_{trough} ≤ 31.3 µg/mL; and ADA positive with low titer (titer ≤ 5). No ADA positive sample had a titer higher than 5. Similar analysis was conducted for NAb (**Figure 26**), and no samples were NAb positive at Week 53 or Week 79.

Figure 25 Applicant's analysis regarding impact of ADA on PK and PD using modified criteria. (A) Pre-dose Lecanemab Serum Concentration (µg/mL) and (B) Change from Baseline in Brain Amyloid Levels as Measured by Amyloid PET SUVR for 10 mg/kg Biweekly by ADA Titer and Visit in Study 201 Core



Source: Sponsor's IR response submitted on September 13, 2022, page 4-5, Figure 1 and Figure 2. n/m: number of samples in each group, and number of samples with pre-dose lecanemab serum concentration measurement in each group.

Figure 26 Applicant's analysis regarding impact of NAb on PK and PD using modified criteria. (A) Pre-dose Lecanemab Serum Concentration (µg/mL) and (B) Change from Baseline in Brain Amyloid Levels as Measured by Amyloid PET SUVR for 10 mg/kg Biweekly by NAb Titer and Visit in Study 201 Core



Source: Sponsor's IR response submitted on September 13, 2022, page 6-7, Figure 3 and Figure 4. n/m: number of samples in each group, and number of samples with pre-dose lecanemab serum concentration measurement in each group.

Reviewer's Comment on Applicant's Updated Analysis

The review team noted multiple limitations with the analysis. Firstly, the ADA assay is limited by the drug tolerance issue and is therefore not reliable for accurate classification of ADA positive vs. negative status. Secondly, there were limited number of samples with observed ADA positive status in the updated analysis, which does not allow comparison of effect on PK or PD between samples with different ADA titers. Thirdly, with a large portion of ADA negative inconclusive samples, it is unclear how

many of them were in fact ADA positive, and how they might impact the assessment. Hence, the review team recommends to state the following in labeling: there is insufficient information to characterize the effects of anti-lecanemab-irmb antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of LEQEMBI.

To ensure obtaining meaningful immunogenicity results, a PMR is recommended by the clinical pharmacology review team. To fulfill the PMR, the applicant needs to use improved and validated assays to determine the incidence of ADA and NAb in the confirmatory study, and to evaluate the impact of ADA and NAb on the pharmacokinetics, pharmacodynamics, safety, and efficacy of lecanemab. Please refer to OBP review for another PMR to develop and validate ADA and NAb assays with improved sensitivity.

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