# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761248Orig1s000

# CLINICAL PHARMACOLOGY REVIEW(S)

# Office of Clinical Pharmacology (OCP) Review

| | |
|---|---|
| Applicant | Eli Lilly and Company |
| Product (Generic Name) | Donanemab (LY3002813) |
| Product (Trade Name) | KISUNLA® |
| Link to EDR | \\CDSESUB1\evsprod\BLA761248\0104 |
| BLA Submission | 761248 (Sequence 0104) |
| Dosage Form (Strength) | 350 mg/20 mL (17.5 mg/mL) in a single-dose vial |
| Route of Administration | Intravenous Infusion |
| Proposed Dosing regimen | 700 mg administered as an intravenous infusion over approximately 30 minutes every four weeks for the first three doses, followed by 1400 mg every four weeks. |
| Proposed Indication | Treatment of Alzheimer's disease. Treatment with KISUNLA should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in the clinical trials. |
| Submission Date | 12 June 2023 |
| OCP Review Team | Anantha Ram Nookala*, Ph.D., Michael Bewernitz*, Ph.D., Mohsen Rajabiabhari*, Ph.D., Xiulian Du*, Ph.D., Hobart Rogers*, Pharm.D., Ph.D., Jeffrey Kraft#, Ph.D., Yow-Ming Wang#, Ph.D., Atul Bhattaram#, 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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| OND Division | Division of Neurology I (DN1) |

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# Contents

# 1. Executive Summary

Donanemab (Tradename: KISUNLA®) is a recombinant humanized immunoglobulin G1 monoclonal antibody (mAb) designed to target the N-terminal, third amino acid, pyroglutamate formation (N3pG) amyloid beta epitope found in cerebral amyloid plaques. Previously, its Biologics License Application (BLA) 761248 received a complete response letter for the treatment of Alzheimer's disease (AD) via an accelerated approval pathway on January 18, 2023, due to its insufficient long-term safety experience. Please refer to OCP review in DARRTS dated 01/17/2023 for details. In this BLA 761248 resubmission, Eli Lilly and Company, the applicant, is seeking traditional approval of donanemab for the treatment of AD. The proposed dosing regimen for donanemab involves administering 700 mg given as an intravenous (IV) infusion over approximately 30 minutes every four weeks for the first three doses. Subsequent infusions consist of 1400 mg IV infusions over approximately 30 minutes, also administered every four weeks. The sponsor proposes to consider stopping donanemab treatment once amyloid plaque is cleared.

In this resubmission, the applicant has provided the results from a Phase 3 registrational trial (AACI). The AACI trial included 1736 subjects and was a multicenter, randomized, double-blind, phase 3 study followed by an open-label extension phase (Study AACI-LTE). The registration trial assessed the safety, efficacy, and tolerability of donanemab compared to a placebo group in individuals with early symptomatic AD. This evaluation was carried out using the proposed dosing regimen.

The results from the AACI trial demonstrated a statistically significant reduction in AD clinical decline in both the low/medium tau population and the combined population as measured using the iADRS (primary endpoint) and CDR-SB, ADAS-Cog13, and ADCS-iADL (key secondary endpoints). The evidence of effectiveness is also supported by 1) findings from the phase 2 Study AACG, 2) amyloid PET imaging data from AACI and AACG, 3) plasma biomarker data supporting downsteam AD pathophysiology, and 4) exposure-response analysis evaluating the relationship between donanemab treatment and reduction in clinical decline (iADRS and CDR-SB) from studies AACG and AACI.

In Study AACI, a time-dependent decrease in the amyloid PET was observed with donanemab treatment compared to the placebo. The mean amyloid PET reduction observed in Study AACI was comparable to that observed in Phase 2 Study AACG. Two phase 1 studies demonstrated a dose- and time-dependent decrease in amyloid PET. Please refer to OCP review in DARRTS dated 01/17/2023 for details on amyloid PET reduction from phase 1 and 2 studies. Changes in plasma biomarkers [tau phosphorylated at threonine 217 (p-tau217), tau phosphorylated at threonine 181 (p-tau181), and glial fibrillary acidic protein (GFAP)] further support for the effects of donanemab on downstream AD pathophysiology. Exposure-response analysis supported

the reduction in clinical decline measured on iADRS and CDR-SB with donanemab treatment.

The primary focus of this review is to (1) assess the acceptability of general dosing recommendations, including stopping treatment upon amyloid clearance, and explore the need for dose optimization based on extrinsic and intrinsic factors, (2) evaluate changes in biomarkers and exposure-response data to substantiate evidence of effectiveness, and (3) assess the impact of immunogenicity on PK, PD, and efficacy.

## 1.1 Recommendations

The Office of Clinical Pharmacology team reviewed the information submitted under this BLA 761248 and recommends approval of KISUNLA® indicated for the treatment of Alzheimer's Disease from a clinical pharmacology perspective.

Key review issues with specific recommendations and comments are summarized below:

| Review Issues | Recommendations and Comments |
|---|---|
| Pivotal evidence of effectiveness | The evidence of effectiveness for donanemab for the treatment of AD is from a pivotal Phase 3 study (AACI). The evidence of effectiveness was based on reduction in clinical decline measured using iADRS (primary endpoint), CDR-SB, ADCS-iADL, and ADAS-Cog13 (key secondary endpoints).<br><br>Additional support of effectiveness is provided by amyloid PET reduction, treatment-response relationships, and mechanistic support for downstream AD pathophysiology from plasma biomarker (p-tau217, p-tau181, and GFAP) data. |
| General dosing instructions | Administer 700 mg by IV infusion every 4 weeks over approximately 30 minutes for the first three doses. Subsequent doses are 1400 mg IV infusions over approximately 30 minutes every 4 weeks. All doses are administered intravenously after dilution (b) (4) 0.9% Sodium Chloride Injection, USP.<br><br>The sponsor proposed to consider stopping treatment after amyloid clearance based on clinical efficacy and biomarker changes. However, limitations include reliance on a 12-month off-treatment period for calculating amyloid PET reaccumulation rate, data from a small subset of subjects |

| | |
|---|---|
| | for calculating amyloid PET reaccumulation rate beyond 76 weeks, lack of evaluation for long-term efficacy beyond 76 weeks and exclusion of participants continuing on donanemab despite meeting dose cessation criteria. Therefore, the proposed dosing regimen, except for stopping donanemab treatment after amyloid plaque clearance, is acceptable from OCP review team. |
| Dosing in patient groups (intrinsic and extrinsic factors) | No dosage adjustments are recommended based on intrinsic and extrinsic factors such as age, race, sex, APOE4 genotype, baseline tau levels, renal or hepatic impairment. Body weight and ADA titer were identified as covariates to impact donanemab exposures. However, the change in the exposures was not found to have a clinically meaningful effect on slowing of clinical decline and therefore, no dose adjustments are warranted. Neither APOE4 genotype nor baseline tau level affected donanemab PK.<br><br>The efficacy of donanemab in patients with different APOE4 genotype was evaluated; APOE4 non-carriers and heterozygotes showed nominally higher treatment benefit and lower ARIA risk compared to homozygotes. Changes in in amyloid PET and plasma biomarkers (p-tau217, p-tau181, and GFAP) reflected changes in clinical efficacy. However, given the positive trends in treatment benefit and biomarkers for all subgroups, the review team recommends dosing in all APOE4 genotypes.<br><br>Metabolic/transporter mediated interactions or impact of food does not apply for donanemab. |
| Bridge between the “to-be-marketed” and clinical trial formulations | No differences were noted between the pivotal clinical trial and to-be-marketed (solution) donanemab formulations. |

## 1.2 Post marketing requirements and commitments

None.

# 2. Summary of Clinical Pharmacology Assessment

## 2.1 Pharmacology and Clinical Pharmacokinetics

For information of mechanism of action, ADME characteristics, therapeutic individualization, please refer to the clinical pharmacology review in DARRTS dated 01/17/2023.

**Immunogenicity:**

Postbaseline, 793 participants in the donanemab group were evaluable for treatment-emergent ADAs (TE-ADAs) during the treatment period from Study AACI. Of these subjects, TE-ADAs were detected in 693 subjects; these subjects are therefore deemed ADA+ and the ADA incidence is 693/793 (87.4%). Neutralizing antibodies (NAbs) were detected in all the ADA+ subjects (693/693; 100%). The presence of TE-ADAs affected various PK measures, such as $C_{min,ss}$ and $AUC_{ss}$. Also, the presence of TE-ADAs affected amyloid plaque reduction; subjects with higher maximum ADA titer had less amyloid PET reduction compared to subjects with lower maximum ADA titer. However, the changes in amyloid PET associated with high ADA titer did not translate into changes in efficacy measured on iADRS and CDR-SB up to week 76. (Please refer to Section 4.2.2 and 4.2.3 for more information).

## 2.2 Dosing and Therapeutic Individualization

### *2.2.1 General Dosing*

The general dosing regimen is 700 mg diluted in 0.9% sodium chloride to a final concentration of 4 mg/mL to 10 mg/mL and administered as IV infusion over 30 minutes every four weeks for the first three doses. Subsequent infusions are 1400 mg IV infusions over 30 minutes administered every 4 weeks. The sponsor proposed to consider stopping treatment after amyloid is cleared. However, due to limitations as discussed in section 3.3.2, OCP review team considers the proposed dosing regimen acceptable except for the proposal to consider stopping donanemab treatment after amyloid plaque is cleared.

### *2.2.2 Therapeutic individualization*

No therapeutic individualization is necessary based on intrinsic and extrinsic factors such as age, race, sex, APOE4 genotype, baseline tau levels renal impairment, hepatic impairment or ADA status. Donanemab is administered by IV route, and therefore, food-drug interactions are not anticipated. In addition, its CYP enzyme/transporter-based drug-drug interaction liability is considered low.

## 2.3 Outstanding Issues

None.

## 2.4 Summary of Labeling Recommendations

The proposed labeling concepts in Section 12.2 and 12.3 are generally acceptable. The Office of Clinical Pharmacology recommends the following labeling edits:

Section 12.2:

- The Applicant proposed to use plasma p-tau217 data from Study AACI. While the quantitative data can be presented, the review team recommends including the following statement in the table; “Results should be interpreted with caution due to uncertainties in bioanalysis.”

Section 12.6:

- The Applicant proposed to use ADA/NAb incidence based on data from Study AACI (b) (4), the review team recommends including the data from Study AACI (Phase 3 study).

# 3. Comprehensive Clinical Pharmacology Review

## 3.1 Overview of the Product and Regulatory Background

Donanemab is a humanized IgG1 mAb that is composed of 2 identical Ig kappa light chains and 2 identical Ig gamma heavy chains. Donanemab is anticipated to selectively target the N-terminal, third amino acid, pyroglutamate formation (N3pG) amyloid beta epitope present in cerebral amyloid plaques to exert its therapeutic effects in AD. Donanemab is supplied at a concentration of 17.5 mg/mL (350 mg/20 mL) in a single-use glass vial for dilution in 0.9% sodium chloride prior to intravenous infusion.

Donanemab was granted fast track designation in July 2018 and breakthrough therapy designation in June 2021. The agency issued a complete response letter on 01/18/2023 denying accelerated approval of donanemab due to insufficient long-term safety experience. In the current submission, the applicant is seeking traditional approval of donanemab. This is based on safety and efficacy data obtained from the Phase 3 Study AACI, along with integrated safety data from Studies AACI and AACG. Furthermore, the clinical pharmacology properties of donanemab were assessed in two phase 1 studies (Study AACC and AACD). These studies involved the evaluation of both single doses (ranging from 0.1 to 40 mg/kg) and multiple doses (ranging from 0.1 to 20 mg/kg) of donanemab in patients with mild cognitive impairment due to AD or mild-to-moderate AD. Additionally, safety information on donanemab was derived from ongoing studies, including the AACI safety addendum, AACI long-term extension, Study AACH, and Study AACN in subjects with early symptomatic AD. Please refer to Clinical Review for details of safety evaluation.

## 3.2 General Pharmacology and Pharmacokinetic Properties

In single doses ranging from 10 to 40 mg/kg (approximately 2 times the proposed recommended dosage of 1400 mg for a 70 kg body weight), exposures (Cmax and AUC) of donanemab exhibited a proportional increase. Upon repeated dosing with 10 mg/kg or 20 mg/kg every 4 weeks, the AUC ratio from Day 141 to Day 1 was 1.06 and 1.26, respectively, indicating minimal accumulation.

The central volume of distribution is measured at 3.36 L. Donanemab undergoes degradation by proteolytic enzymes and is not expected to undergo renal elimination or metabolism by hepatic enzymes. The mean terminal half-life of donanemab is approximately 12.1 days, and its clearance is 0.0255 L/h. Age, sex, or race did not demonstrate a significant impact on the pharmacokinetics of donanemab. Although body weight and maximum ADA titer were found to influence donanemab pharmacokinetics, the resulting changes did not affect clinical efficacy.

For additional details, please refer to the OCP review in DARRTS dated 01/17/2023.

## 3.3 Clinical Pharmacology Questions

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

The pivotal evidence supporting the effectiveness of donanemab treatment is from Study AACI and is based on a statistically significant reduction in the clinical decline of AD as measured by the iADRS score at 76 weeks, compared to a placebo, in two predefined primary analysis populations: the low/medium tau population and the combined population. Additionally, donanemab treatment demonstrated a significant reduction in AD clinical progression across all secondary endpoints, which assessed cognitive and functional decline, including the CDR-SB, ADAS-Cog13, and ADCS-iADL scales, at 76 weeks compared to the placebo. The efficacy of donanemab was further supported by its effects on brain amyloid PET levels, downstream plasma biomarkers, and exposure-response relationships, as observed in Studies AACI and AACG.

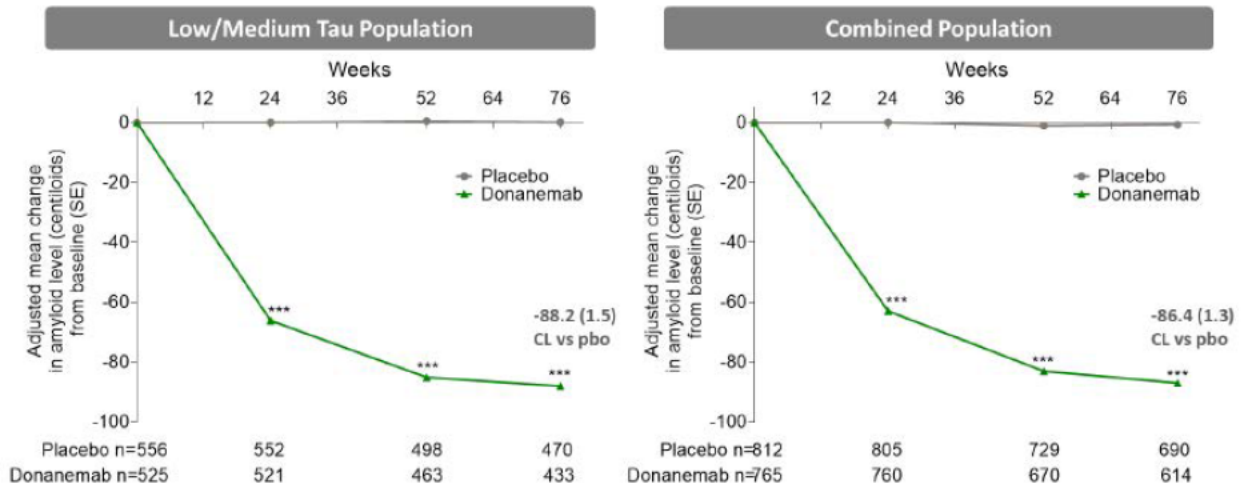
Study AACI was a randomized, multicenter, double-blind, placebo-controlled, Phase 3 study designed to evaluate the efficacy and safety of donanemab in subjects with early symptomatic AD. The study enrolled participants aged 59 to 86 years who had experienced a gradual and progressive decline in memory functions for at least six months, with a MMSE score between 20 to 28 and evidence of pathologic tau deposition on a flortaucipir PET scan. Participants were categorized into those with low/medium ($1.10 \leq SUVr \leq 1.46$) and high ($SUVr > 1.46$) levels of tau pathology at baseline. These eligible participants were randomly assigned in a 1:1 ratio to receive either donanemab or a placebo for a duration of 76 weeks during the double-blind period, followed by an open-label extension phase.

The results from the Study AACI met the primary and key secondary endpoints, showing a statistically significant difference between donanemab and placebo in terms of the change from baseline in iADRS at 76 weeks. Donanemab treatment resulted in a reduction of clinical decline measured on iADRS, with an adjusted mean treatment difference of 3.3 (35% less decline compared to placebo) in the low/medium tau population and 2.9 (22% less decline compared to placebo) in the combined (low/medium and high tau) population. Donanemab treatment also resulted in a reduction of clinical decline measured on CDR-SB, with an adjusted mean treatment difference of 0.68 (37% less decline compared to placebo) in the low/medium tau population and 0.67 (29% less decline compared to placebo) in the combined population. Please refer to clinical review and statistical review for additional details on efficacy assessment.

The evidence of efficacy is supported by data from amyloid PET, plasma biomarkers, and exposure-response relationships from phase 2 and phase 3 studies. In Study AACI, donanemab-treated participants across study populations showed a time-dependent reduction in amyloid plaque levels compared to those receiving the placebo. This

reduction was assessed through amyloid PET measurements at Weeks 24, 52, and 76 (**Figure 1**). In the low/medium tau population and the combined population, the mean (standard error, SE; p-value) change at week 76 was -88.2 centiloids (1.5; p<0.001) and -86.4 centiloids (1.3; p<0.001), respectively compared to placebo. The mean amyloid PET reduction observed in Study AACI was comparable to that observed in Phase 2 Study AACG (-85.1 centiloids at week 76 (p<0.001) compared to the placebo group).

***Figure 1: Change in Amyloid PET from Baseline to Week 76 in Study AACI***




Abbreviations: CL = Centiloid; n = number of participants; Pbo = placebo; SE = standard error. *** p<.0001.

Source: Applicant's summary of clinical overview; Figure 2.5.4.3; Pg-38

Participants who achieved amyloid plaque reduction (<11 centiloid at one scan or between 11 to 24.1 centiloid in successive scans) based on amyloid PET scans at Week 24 or Week 52 were switched to receive a placebo for the remainder of the double-blind period (**Table 1**). Approximately 74% (321/437) of the low/medium tau population and 69% (429/620) of the combined population met the criteria for placebo reduction at week 76, based on amyloid PET levels.

***Table 1: Percentage of Donanemab Treated Participants Who Met the Reduction Criteria to Switch to Placebo***

| | **Week 24** | **Week 52** | **Week 76** |
|---|---|---|---|
| Low/Medium Tau Population, % (n/N) | 20.3 (106/521[a]) | 51.9 (241/464[a]) | 73.5 (321/437[a]) |
| Combined Population, % (n/N) | 17.1 (130/761[a]) | 46.6 (313/672[a]) | 69.2 (429/620[a]) |

Abbreviations: n = number of participants in the specified category; N = number of participants in the population.

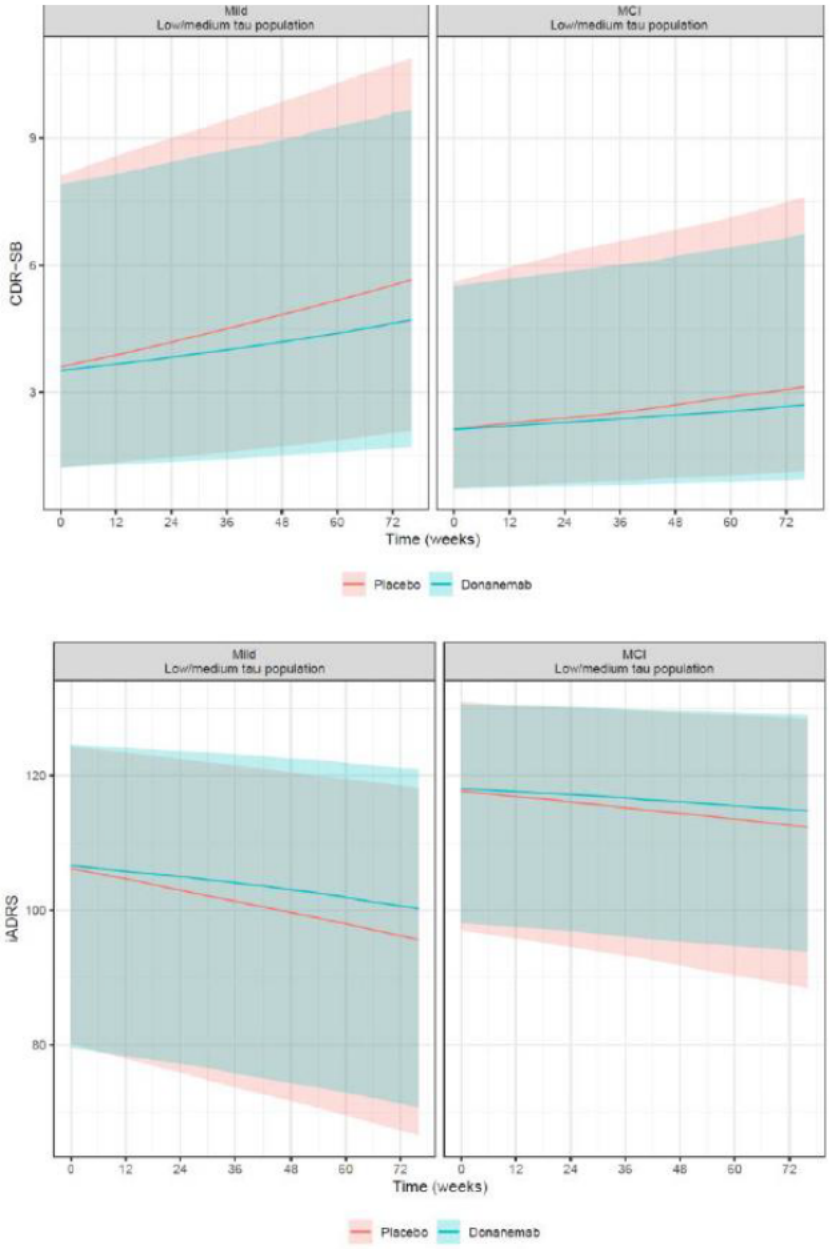
a - Included participants from unscheduled visits at each time point.

Source: Applicant's summary of clinical efficacy; Table 2.7.3.5; Pg-43

The proportion of subjects achieving amyloid PET reduction to <24.1 centiloids (CL) (equates to a negative visual read on an amyloid PET scan according to the sponsor) increased with an increase in the treatment duration. Among participants receiving donanemab, 34% (178/521), 71% (330/463), and 80% (347/433) achieved amyloid PET values <24.1 CL at weeks 24, 52, and 76, respectively, in the low/medium tau population. In the combined population, 30% (226/761), 66% (443/670), and 76% (469/614) of participants achieved amyloid PET values <24.1 CL at weeks 24, 52, and 76, respectively. Four placebo-treated participants achieved amyloid PET values <24.1 CL at any time point during the double-blind period. Additional support for donanemab treatment mediated dose- and time-dependent reduction in amyloid PET is obtained from studies AACC, AACD, and AACG. Please refer to the OCP review in DARRTS dated 01/17/2023 for more information. The evidence of effectiveness is also supported by exposure-response analysis evaluating the relationship of donanemab treatment to amyloid PET and reduction in clinical decline.

Donanemab treatment reduced disease progression rate estimated using exposure-amyloid plaque-scores model on iADRS by 33.2%, while donanemab treatment reduced progression rate as measured by CDR-SB by 36.3% in the low/medium tau population (**Figure 2**).

***Figure 2: Simulated CDR-SB (top panel) and iADRS (bottom panel) score for participants with MCI and participants with mild dementia due to AD in the low/medium tau population For 72 Weeks***

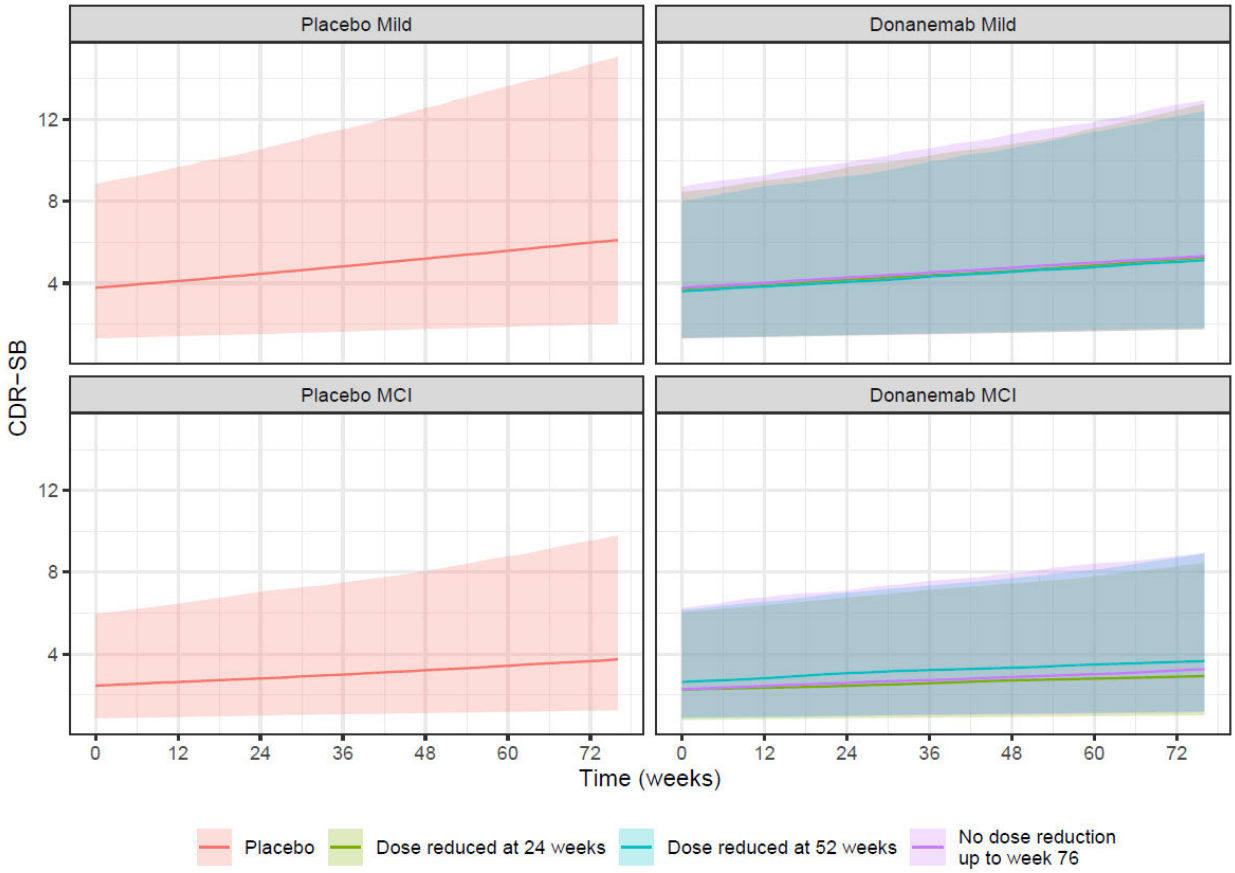



*AD = Alzheimer's disease; CDR-SB = clinical dementia rating-sum of boxes; iADRS = integrated Alzheimer's disease rating scale; MCI = mild cognitive impairment; Mild = mild dementia due to Alzheimer's disease. Patients were simulated to follow dosing treatment regimen, including the potential for down-titration based on Centiloids at Weeks 24 and 52. Median (90% prediction interval) is shown by solid line and shaded areas.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 95 of 245*

In the combined population, disease progression rate on iADRS score was reduced by 29.3%, while progression rate as measured by CDR-SB was reduced by 31.7% (**Figure 3**). Please refer to pharmacometrics analyses section 4.4.5 Disease Progression for further details on the modeling analysis.

***Figure 3: Simulated CDR-SB for participants with MCI and participants with mild dementia due to AD in the Combined Population By Treatment Druation over 72 Weeks***




*CDR-SB = clinical dementia rating-sum of boxes; MCI = mild cognitive impairment; Mild = mild dementia due to Alzheimer's disease. Patients were simulated to follow dosing treatment regimen, including the potential for down-titration based on Centiloids at Weeks 24 and 52. Median (90% prediction interval) is shown by solid line and shaded areas.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 97 of 245*

The applicant also submitted data on tau PET biomarker, tau phosphorylated at threonine 217 (p-tau217), tau phosphorylated at threonine 181 (p-tau181), glial fibrillary acidic protein (GFAP), and Neurofilament Light Chain (NfL) in plasma, to evaluate donanemab -related effects on potential markers of downstream AD pathophysiology. The results are discussed below.

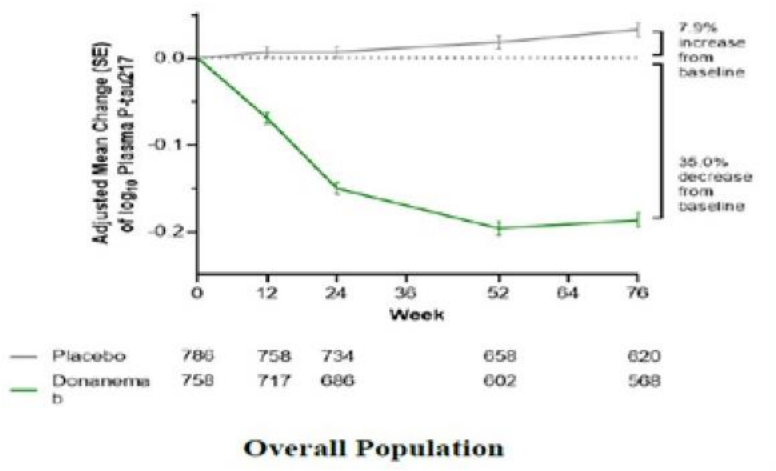
*Tau PET*

The applicant has evaluated the changes in brain tau PET deposition measured using flortaucipir F18 upon treatment with donanemab. There were no significant differences between donanemab and placebo groups in either the low/medium tau population or the combined population when comparing the changes in frontal lobe tau and AD-signature-weighted-SUVr. Please see the clinical review for details on Tau PET results.

*Plasma p-tau217*

Both the low/medium tau population and the high tau population exhibited a time-dependent reduction in plasma p-tau217 levels. At week 76, donanemab treatment resulted in a reduction of approximately 35% from baseline while placebo increased by about 8% from baseline in the combined population (**Figure 4**). Similar results were observed for the low/medium tau population.

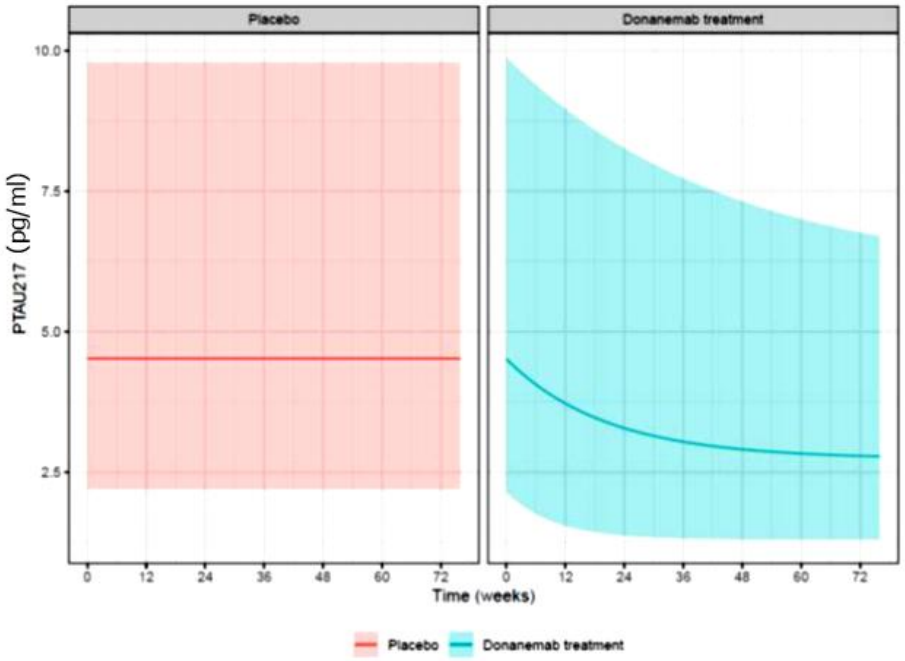
***Figure 4: Change in Plasma p-tau217 from Baseline by Treatment in Study AACI***




Source: Applicant's AACI CSR; Figure AACI.5.14; Pg-161

The exposure-response analysis evaluating the relationship between p-tau217 and donanemab suggested that donanemab treatment reduced the formation rate of plasma p-tau217 (**Figure 5**). Please refer to section 4.4.3 P-tau217 of the appendix for further details on the modeling analysis.

***Figure 5: Simulation from final plasma P-tau217 model for placebo and with donanemab treatment***



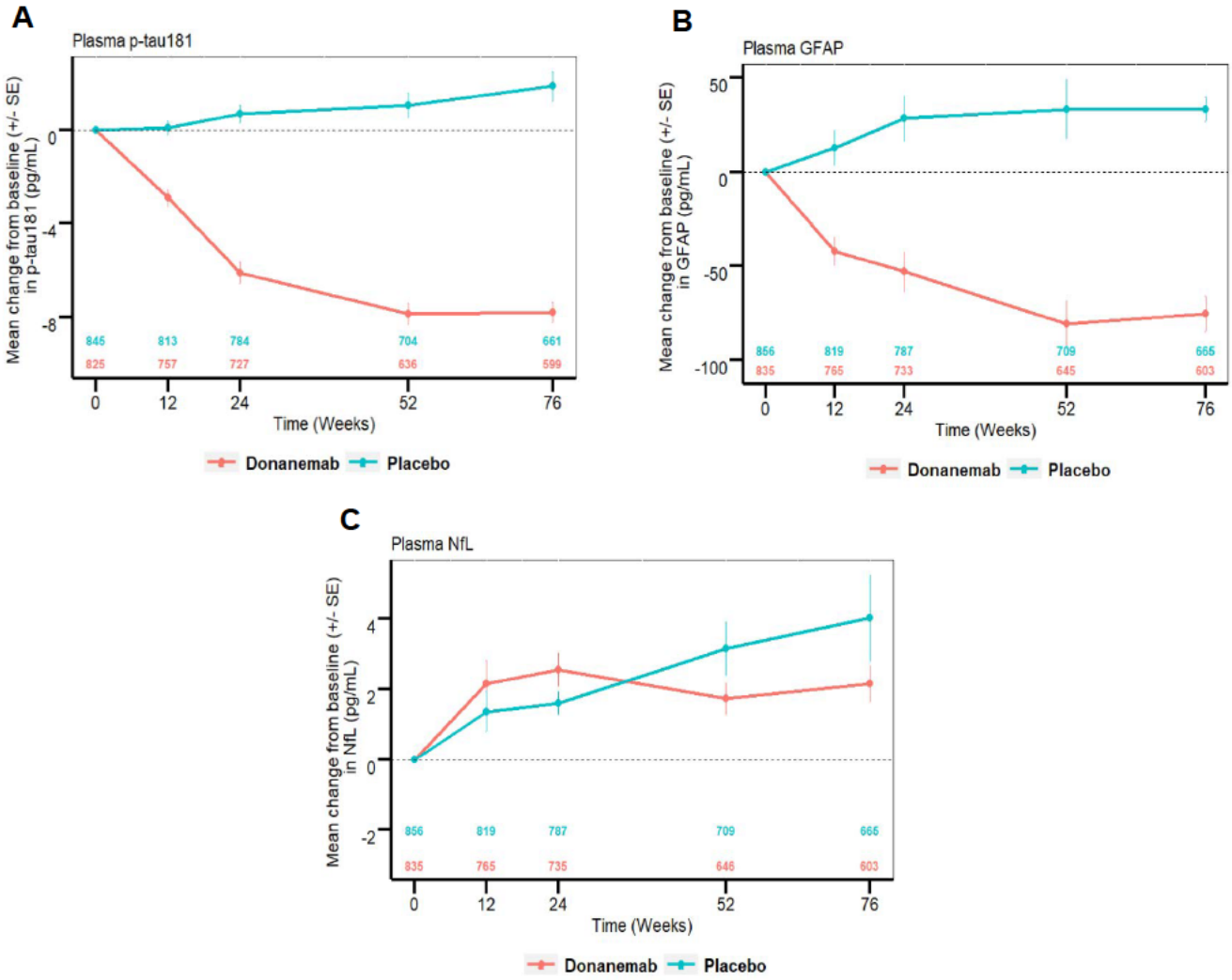

*P-tau217 = tau phosphorylated at threonine 217;. The shaded areas represent a 90% prediction interval. The lines represent the median prediction. Patients were simulated to follow dosing treatment regimen as applied in Study AACI. Actual participants' titer time courses, weight, age, and baseline PD values sampled from the NONMEM dataset.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 92 of 245*

*Plasma p-tau181, GFAP and NfL*

A time-dependent decrease in the plasma p-tau181 and GFAP, but not plasma NfL were observed upon donanemab treatment compared to placebo in both low/medium tau population and combined population (**Figure 6**).

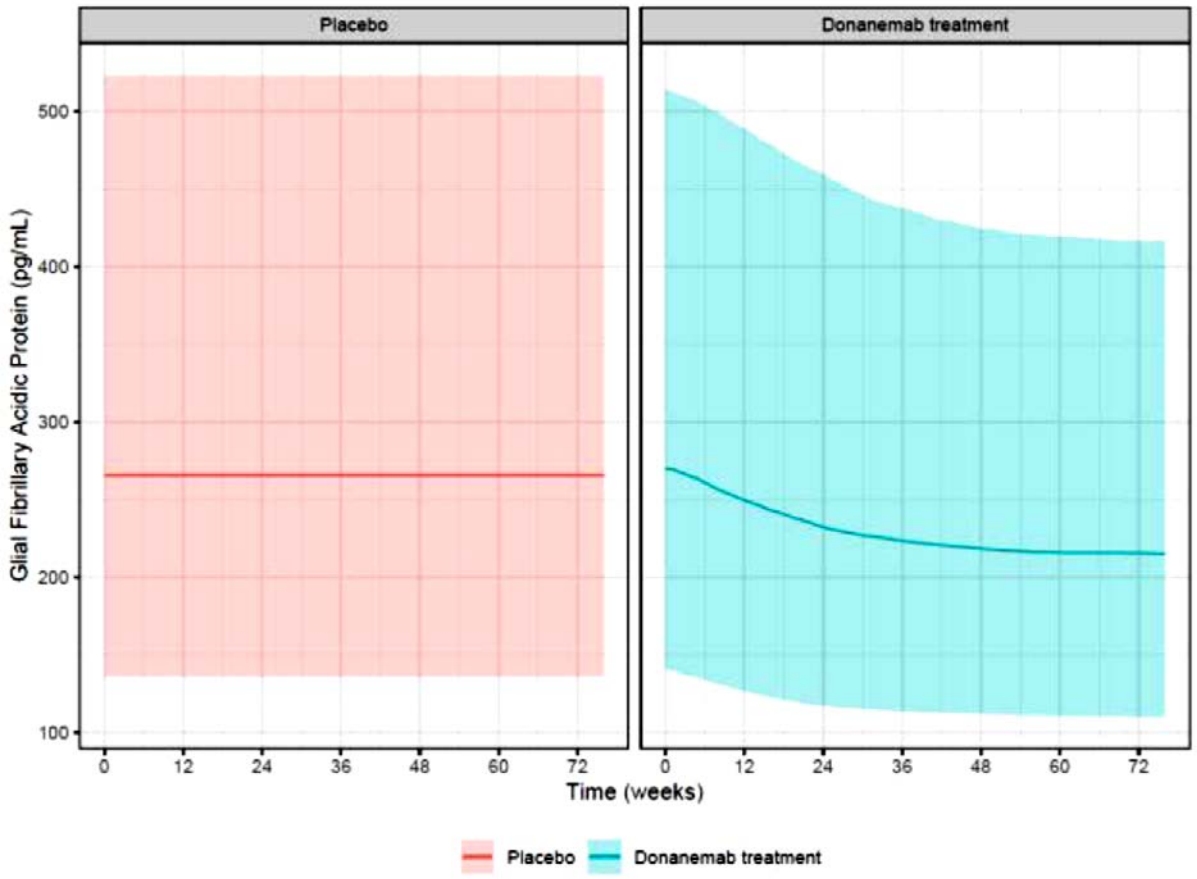
***Figure 6: Change from Baseline in Plasma Biomarkers Over Time in Study AACI***




Source: Reviewer's Analysis

The exposure-response analysis evaluating the relationship between amyloid plaque, GFAP and donanemab suggested that the decrease in amyloid plaque load following donanemab treatment led to reduction in plasma GFAP (**Figure 7**). Please refer to the appendix section 4.4.4 GFAP for further details on the modeling analysis.

***Figure 7: Simulation from final GFAP model for placebo and with donanemab treatment***




*GFAP = glial fibrillary acidic protein. The shaded areas represent a 90% prediction interval. The lines represent the median prediction. Patients were simulated to follow dosing treatment regimen as applied in Study AACI. Actual participants' titer time courses, weight, age, and baseline PD values sampled from the NONMEM dataset.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 92 of 245*

For all the plasma biomarkers, it should be noted that the long-term stability along with other bioanalytical method validation aspects were not adequately established (refer to Appendix 4.1). Therefore, while qualitative descriptions are appropriate, the interpretation of any quantitative analysis results should be approached with caution.

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

Yes, the proposed donanemab dosing regimen as indicated in section 1.1 except for the proposal to consider stopping treatment after amyoid plaque is cleared is acceptable from clinical pharmacology standpoint.

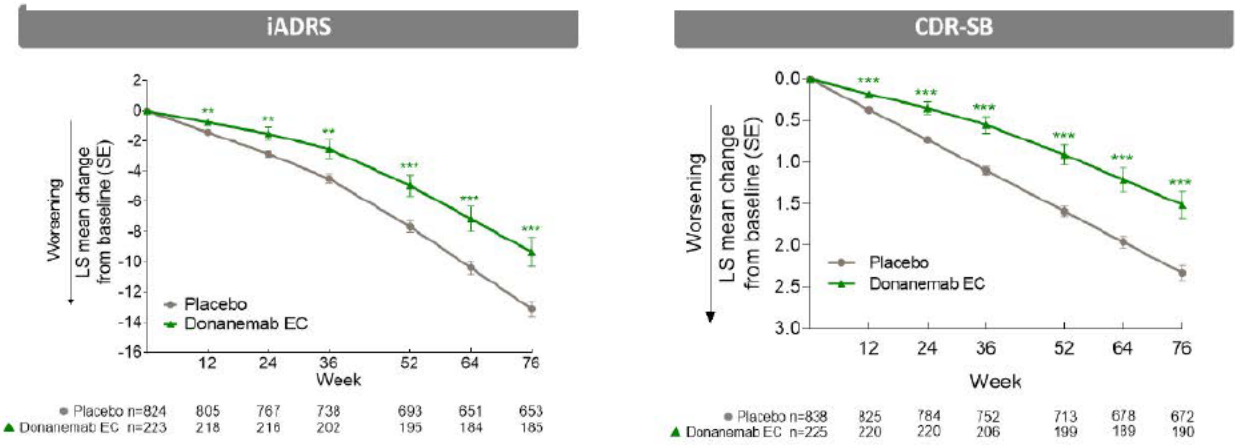
The applicant is seeking approval of the donanemab dosing regimen which includes 700 mg dose administered as IV infusions for the first three doses followed by 1400 mg IV infusions every 4 weeks. Applicant is also proposing to consider stopping donanemab trearment once the brain amyloid plaque is cleared. This dosing regimen with a minor difference was evaluated in Study AACI where donanemab treatment was stopped if sufficient reduction amyloid PET was achieved (<11 centiloid at one scan or between 11 to 24.1 centiloid in successive scans). In Study AACI, nearly 70% of participants in the combined population at 18 months met the eligibility criteria for dose cessation. Based on the observed effect of donanemab on clinical endpoints, amyloid PET reduction, reduction in plasma biomarkers, and biomarker exposure-response relationships, this regimen is considered reasonable in terms of safety and efficacy.

The review team evaluated the adequacy of the sponsor's proposal to consider stopping donanemab treatment based on amyloid PET imaging criteria. The rationale was based on the following.

A. Efficacy data in subjects who met the criteria for early amyloid clearance (<24.1 CL) at Week 24
B. Biomarker data in subjects who received donanemab for 24 weeks
C. Amyloid PET re-accumulation rate in subjects who received donanemab for 24 weeks

A. **Efficacy data in subjects who met the criteria for early amyloid clearance (<24.1 CL) at Week 24:** A statistically significant reduction in clinical decline on both iADRS and CDR-SB at Week 76 was observed in a subset of patients who met the criteria for early amyloid clearance (<24.1 CL) at Week 24 (**Figure 8**). The magnitude of donanemab treatment effect in this subset at week 76 was comparable to the overall population. However, this subset of patients also included participants who continued to receive donanemab treatment atleast until week 52.

***Figure 8: iADRS and CDR-SB Change from Baseline by Treatment in Participants with Amyloid PET <24.1 CL in the Combined Population***

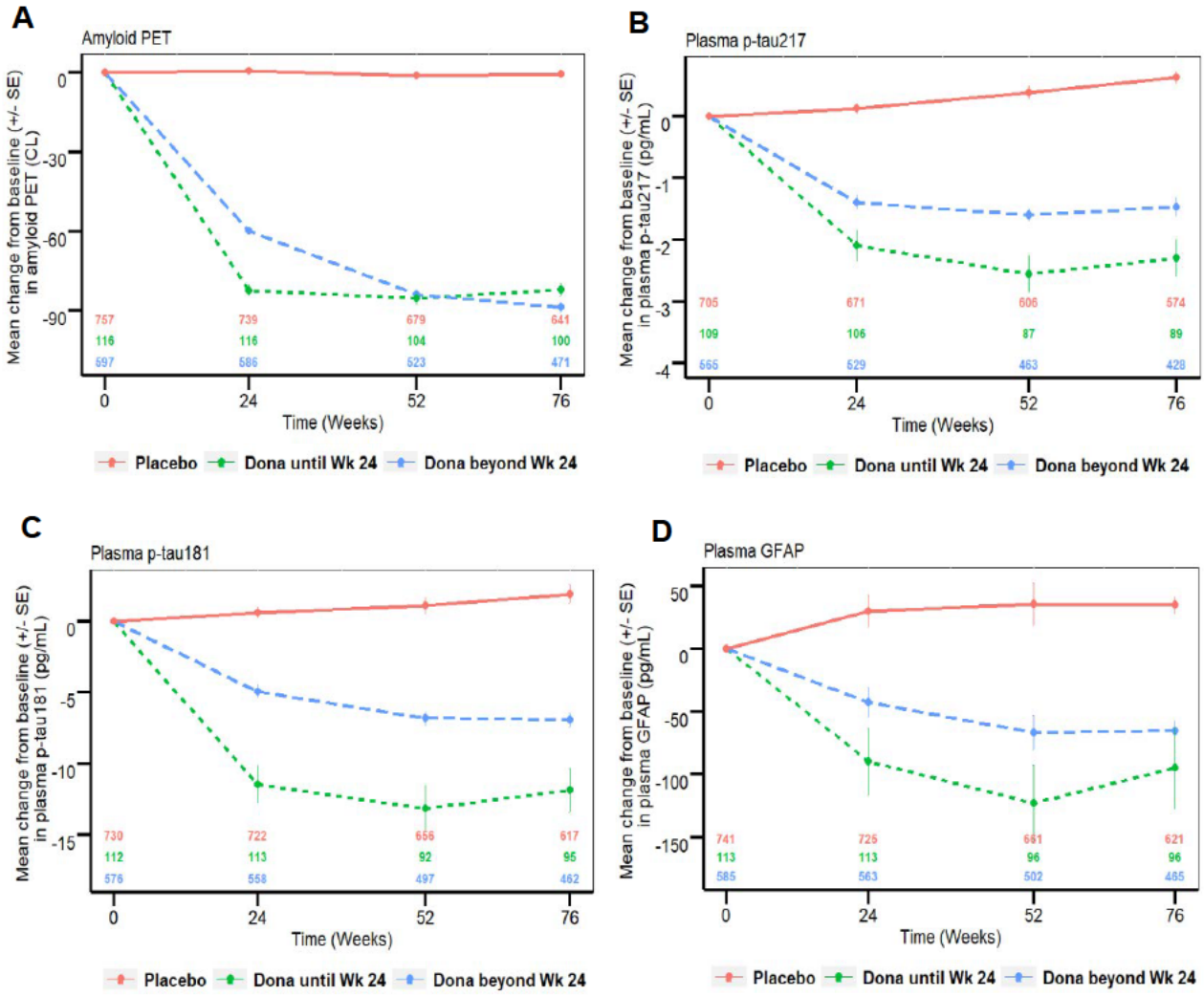



Abbreviations: CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; EC = early clearance (donanemab treated participants who had amyloid PET <24.1 CL by 24 weeks); iADRS = integrated Alzheimer's Disease Rating Scale, LS mean = least squares mean; n = number of participants; SE = standard error. ***p <.001, **p <.01.

Source: Applicant's summary of clinical efficacy; Figure 2.7.3.6; Pg-54

B. **Biomarker changes in subjects who received donanemab for 24 weeks:** Among participants who switched from donanemab to placebo at Week 24, significant amyloid PET reduction was observed at week 24 which sustained until week 76 (**Figure 9**). The mean change from baseline ± SE at Weeks 24, 52, and 76 were -82.4 ± 2.24, -85.5 ± 2.46, and -82.0 ± 2.43, respectively. No significant differences in the amyloid PET were observed at week 76 when compared with subjects who received donanemab beyond 24 weeks (52 or 76 weeks). Similarly, for plasma biomarkers, the reductions observed at week 24 were sustained until week 76. By week 76, the reductions in the mean plasma biomarkers in subjects who received donanemab for 24 weeks were larger compared with subjects who received donanemab beyond 24 weeks (52 or 76 weeks). The observed differences may be attributed to the different baseline characteristics between the two groups.

***Figure 9: Change in Biomarkers in Subjects who Received Donanemab for 24 weeks or more than 24 weeks in Study AACI***

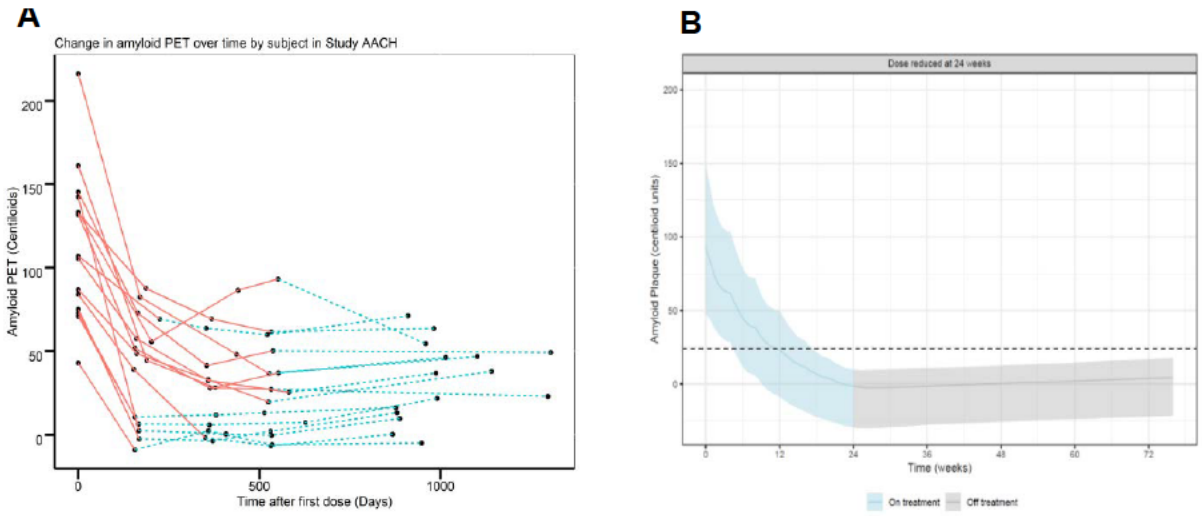


Abbreviations: Dona until Wk 24 = Donanemab treated subjects who received treatment for 24 weeks; Dona beyond Wk 24 = Donanemab treated subjects who received treatment for 52 or 76 weeks

Source: Reviewer's Analysis

C. **Amyloid PET re-accumulation rate in subjects who received donanemab for 24 weeks:** Sustained reductions in amyloid PET until week 76 were observed among participants who switched from donanemab to placebo at Week 24 (N=130). These results indicated that no significant amyloid PET re-accumulation was observed in these participants by week 76. Further, a small group of subjects (N=15) enrolled in study AACH were evaluated for amyloid PET re-accumulation for approximately 2 years (range from 13 to 27 months; mean of 22 months),) after the last dose. This group included subjects who have stopped treatment by week 52 (n=7) and week 76 (n=8) with mean baseline amyloid PET values of 85 and 140 CL, respectively. In these subjects, the amyloid PET values began to increase with a median rate of 2.86 centiloids/year (**Figure 10A**). Additionally, the amyloid PET re-accumulation rate estimated from modeling and simulation from studies AACI and AACG supported the observed data, with an estimated rate of 2.80 centiloids/year based on the 3-year time frame for which obserations are provided (**Figure 10B**; Refer to section 4.4.1 for additional details on modeling analysis).

***Figure 10: Amyoid PET re-accumulation Rate***




Source: Reviewer's Analysis (Figure 6A); Applicant's Population PK/PD Report, Page 89 (Figure 6B).

Abbreviations: On treatment = Time subjects remained on donanemab treatment; Off treatment = Time subjects remained off donanemab treatment

Notes: For Figure 6B, model was developed using data from Studies AACD, AACG, AACH, and AACI. Reference line shows 24.1 Centiloids. Median (90% prediction intervals) are represented by solid line and shaded area.

However, the following limitations exist which do not support the inclusion of sponsor's proposal to consider stopping donanemab treatment (b) (4).

- Majority of the amyloid PET reaccumulation rate data is based on the subjects who stopped donanemab treatment at week 24. The off-treatment period of 12 months may not be sufficient, especially considering that the last dose of donanemab administered to patients who have stopped dosing at Week 24 may continue to exert a pharmacodynamic effect for some time after dose cessation as shown with single dose of donanemab.
- Amyloid PET reaccumulation rate beyond 76 weeks was calculated from a small subset of participants (n=15) which may not be a reflective of general population with diverse baseline characteristics.
- The applicant has not evaluated the long-term efficacy beyond 76 weeks in subjects who have stopped donanemab treatment by week 24. It is not known if the efficacy of donanemab will be observed beyond 76 weeks after stopping the donanemab treatment at Week 24.
- Study AACI did not include participants who have continued to receive donanemab despite meeting the dose cessation criteria based on the amyloid PET. This would have helped to understand if efficacy observed with donanemab would have improved or not.

The most commonly reported AEs include Amyloid Related Imaging Abnormality (ARIA) – microhemorrhages and superficial siderosis (ARIA-H), Edema/Effusions (ARIA-E), headache, infusion related reactions, and nausea. In studies AACI and AACG, higher incidences of ARIA-E and ARIA-H were observed; ARIA-E was observed in 24% of participants treated with donanemab compared to 2% on placebo and ARIA-H was observed in 25% of patients treated with donanemab, compared to 11% on placebo. Please refer the clinical review for more details.

Therefore, based on the available data, the proposed dosing regimen except for the proposal to consider stopping donanemab treatment after amyloid plaque is cleared is acceptable from clinical pharmacology standpoint.

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

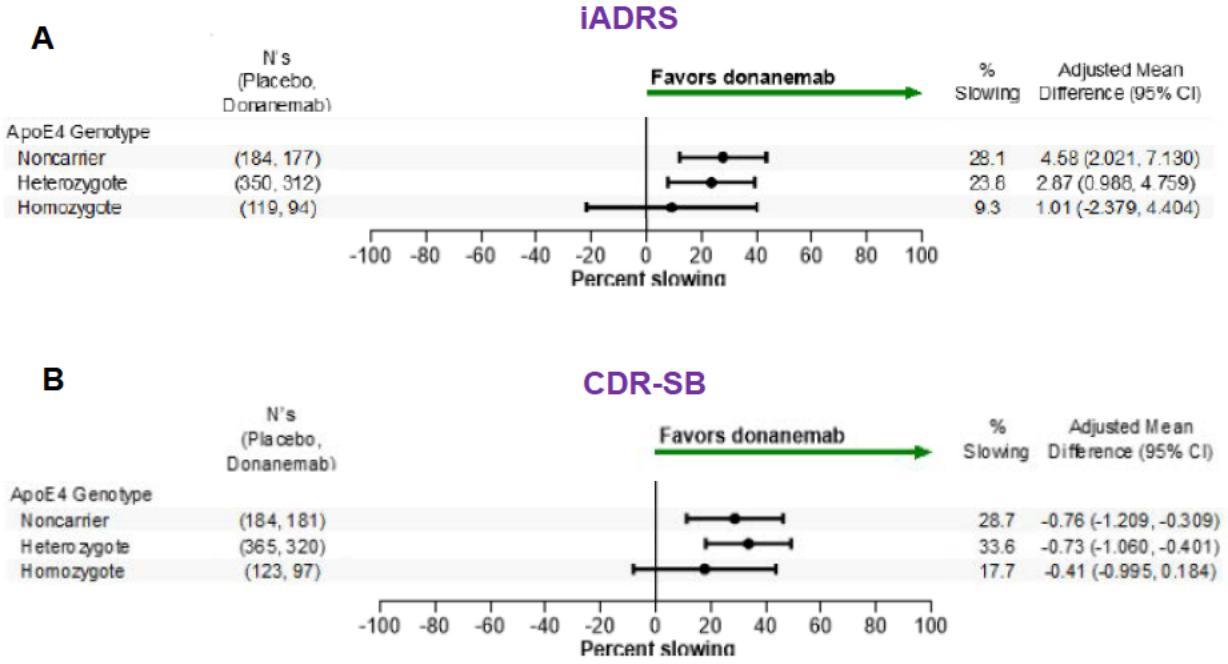
No. There is no need for alternative donanemab dose or dosing regimen for subpopulation based on the intrinsic factors such as body weight, age, race, sex, BMI, APOE4 carrier status, renal or hepatic impairment and extrinsic factor such as ADA status. No dedicated renal and hepatic impairment studies were conducted. Population pharmacokinetic analysis was conducted on data from 2131 participants (46 participants from Study AACD, 131 participants from Study AACG, 54 participants from Study AACH, Part B, and 1900 participants from AACI [PC and Safety Addendum]) to evaluate the impact of intrinsic and extrinsic factors. Body weight and ADA were identified to affect

donanemab pharmacokinetics, but however were not found to affect the clinical efficacy and therefore no dosage adjustments were warranted. For additional details, please refer to the Appendix 4.2 and OCP review dated 01/17/2023 in DARRTS.

### *3.3.4 What clinical pharmacology information is available to inform the assessment of benefit and risk in subgroups with different APOE4 genotypes?*

In the pivotal phase 3 Study AACI, the distribution of APOE ε4 (APOE4) genotypes was as follows: 16.7% (289/1736) were APOE4 homozygotes, 53.8% (930/1736) were APOE4 heterozygotes, and 29.5% (510/1736) were APOE4 non-carriers. The sponsor conducted an exploratory subgroup analysis for iADRS and CDR-SB based on the APOE4 genotype to assess the consistency of treatment effects (**Figure 11**). For both clinical endpoints (iADRS and CDR-SB), APOE4 non-carriers and heterozygotes showed comparable treatment benefits, while homozygotes exhibited a trend towards a lower treatment benefit. It is important to note that the treatment effects on both clinical end points favored donanemab in all APOE4 genotypes. Further, these analyses are considered exploratory, and the study was not powered to detect the differences between APOE4 genotypes. To inform the benefit-risk assessment of donanemab treatment for patients with different APOE4 genotypes, the review team evaluated the impact of APOE4 genotype on amyloid PET, plasma biomarkers, PK, and exposure-response analysis as summarized below.

***Figure 11: Subgroup Analysis of Clinical End Points by APOE4 genotype in Study AACI***




Source: Adapted from Applicant's AACI Study Report; Figure AACI.5.16. (page-177) and AACI.5.18. (Pg-179).

Abbreviations: CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; iADRS = integrated Alzheimer's Disease Rating Scale

Consistent with efficacy results, APOE4 heterozygotes and non-carriers demonstrated a higher reduction in amyloid PET compared to APOE4 homozygotes (refer to **Figure 12**). At Week 76, the median change in amyloid PET from baseline was -64.2, -86.5, and -90.5 centiloids for homozygotes, heterozygotes, and non-carriers, respectively. The percentage of subjects who achieved amyloid plaque levels of <11 centiloids and <24.1 centiloids across different APOE4 genotype subgroups are presented in **Table 2**. These results indicate that a lower percentage of APOE4 homozygotes achieved amyloid PET reduction to <24.1 or <11 centiloids by week 76 across compared to APOE4 heterozygotes and non-carriers. Further, the median reduction in plasma p-tau217, p-tau181, and GFAP levels due to donanemab treatment was more pronounced in heterozygotes and non-carriers at Week 76 compared to homozygotes (**Figure 12**). Notably, baseline amyloid PET levels were similar across all APOE4 subgroups, but differences were observed in baseline plasma biomarkers (p-tau217, p-tau181, and GFAP). While homozygotes showed a lower change in biomarkers compared to heterozygotes and non-carriers, it is important to note that the differences still favored donanemab treatment compared to placebo.

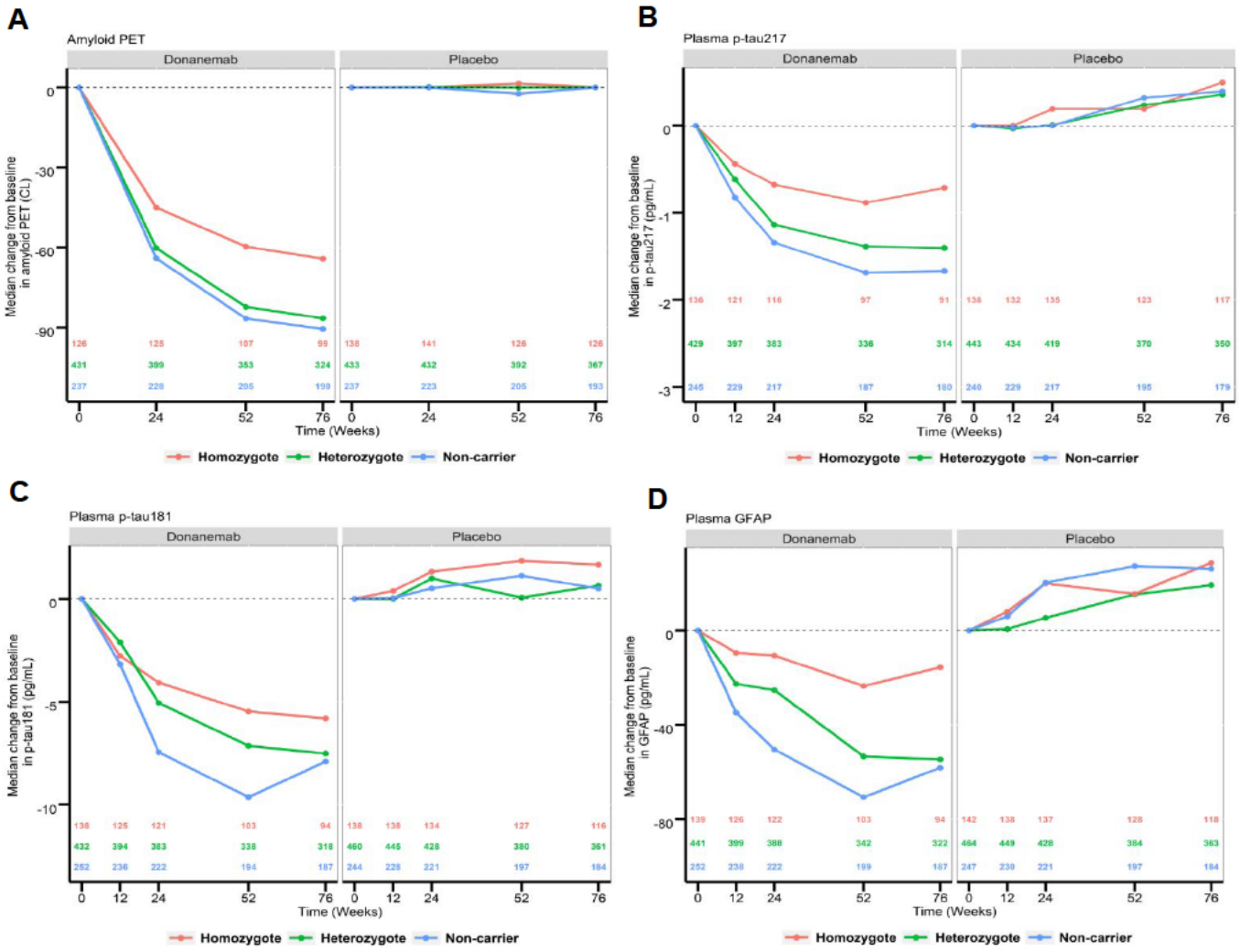
***Table 2: Percentage of Donanemab Treated Participants by APOE4 genotype with Amyloid PET levels <24.1 or 11 centiloids at Week 76***

| APOE ε4 subgroup | **<24.1 Centiloid** | **<11 Centiloid** |
|---|---|---|
| Homozygotes, % (n/N) | 55.6 (55/99) | 23.2 (23/99) |
| Heterozygotes, % (n/N) | 74.1 (247/324) | 53.1 (172/324) |
| Non-carriers, % (n/N) | 86.8 (165/190) | 64.7 (123/190) |

Abbreviations: n = number of subjects who met the criteria; N = Total number of subjects in the subgroup.

Source: Reviewer's Analysis

***Figure 12: Changes in Biomarkers Over Time by APOE4 status in Study AACI***




Source: Reviewers Analysis

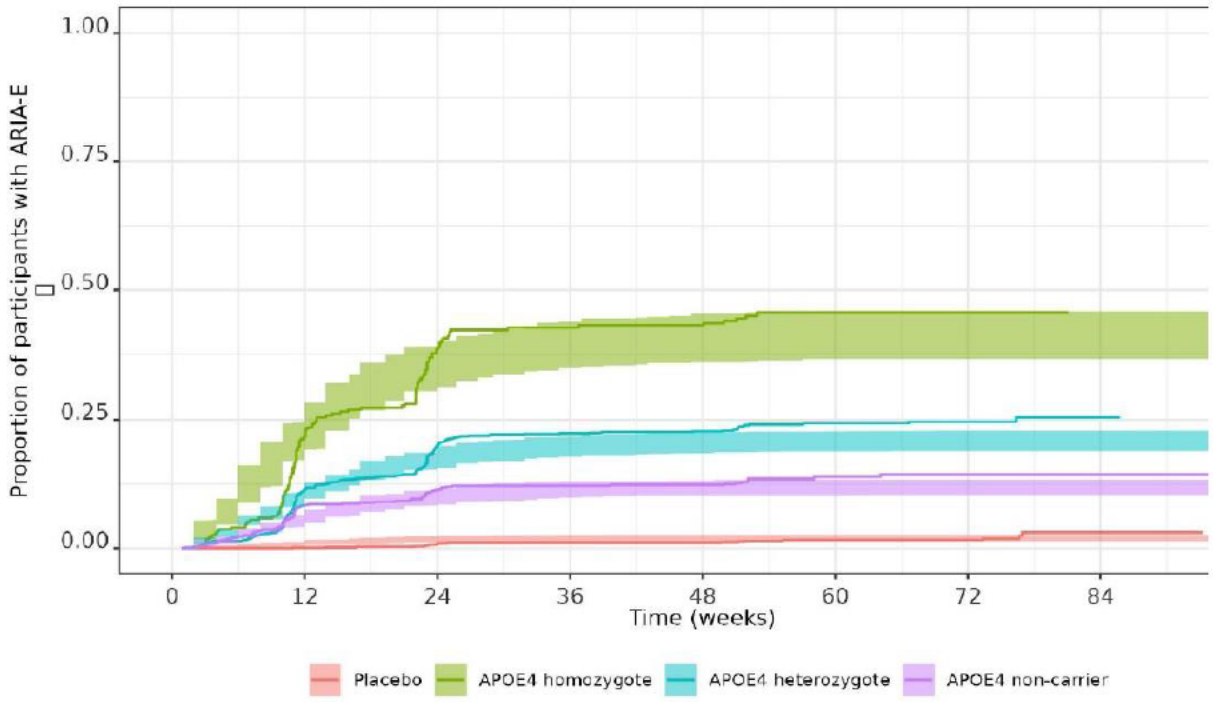
We explored changes in PK to explain the differences in clinical endpoints and biomarkers among different APOE4 genotypes. For subjects in studies AACI and AACG, receiving donanemab at a dose of 700 mg q4w for the first three doses followed by 1400 mg q4w, the predicted average steady-state concentrations in non-carriers, heterozygotes, and homozygotes for APOE4 were 67.4, 68.5, and 65.1 ug/mL, respectively. These results indicate that PK was similar across different APOE4 genotypes and may not explain the observed differences in clinical end points and biomarkers.

The applicant also conducted modeling analysis to assess the potential impact of APOE4 carrier status on amyloid PET and clinical end points. The results indicated that APOE4 carrier status was not identified as a significant predictor influencing amyloid PET reduction. However, APOE4 status was identified as a predictor of rate of disease

progression for CDR-SB and iADRS. For additional details, please refer to Sections 4.4.1 and 4.4.5 for the applicant's modeling analysis.

Within the donanemab group, a higher incidence of ARIA-E, ARIA-H, ARIA-H microhemorrhage, and ARIA-H superficial siderosis was observed in APOE4 homozygotes, followed by heterozygotes and non-carriers. Modeling was also conducted to characterize the exposure-response relationship of donanemab concentration and dosing regimen regarding first incidence of overall ARIA-E. The results indicated that the ARIA-E baseline hazard differed by APOE 4 genotype, with 1.8 times higher hazard in APOE4 heterozygotes and 3.9 times higher in APOE4 homozygotes compared with noncarriers by Week 24 (**Figure 13**). Although the model identified participants with higher Cav,ss (233 µg/mL) to have an increased risk of ARIA-E compared to those with median Cav,ss (52.1 µg/mL), the number of subjects with a high Cav,ss was limited.

***Figure 13: Observed and Model Predicted ARIA-E Incidence by APOE4 Carrier Status***




Source: Applicant's population pk-pd report; page-59

Abbreviations: APOE4 = apolipoprotein E4; ARIA-E = amyloid-related imaging abnormalities-edema/effusions.

Notes: The solid lines are the Kaplan-Meier plot of the observed data, and the shaded areas are the 95% confidence intervals for the simulated data.

In summary, the efficacy endpoints and biomarkers showed positive trends across all APOE4 genotypes. While the review team acknowledges variations in the magnitude of

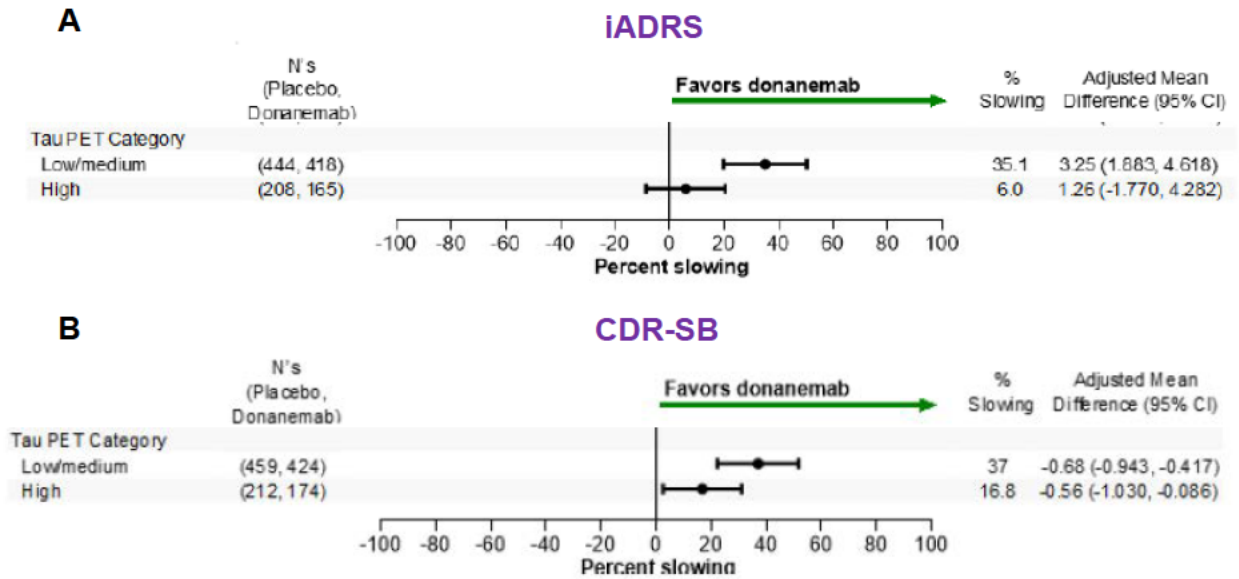
treatment effect among APOE4 genotypes, given the exploratory nature of the analyses and the lack of a comprehensive understanding, we defer to the clinical team regarding the inclusion of a benefit/risk assessment description based on APOE4 genotypes in labeling. For further details on the impact of the APOE4 genotype on the benefit and risk assessment of donanemab, please refer to Appendix 4.5 Pharmacogenomics Review and the Clinical Review.

### *3.3.5 What clinical pharmacology information is available to inform the assessment of benefit and risk in subgroups with different baseline tau?*

In the pivotal phase 3 Study AACI, 31.8% (552/1736) were categorized as having high tau (SUVr at baseline >1.46) and 68.2% (1182/1736) were categorized as having low/medium tau (SUVr at baseline: ≥1.10 to ≤1.46). According to the sponsor, subjects with baseline tau SUVr <1.10 (categorized as very low or no tau) were excluded from Study AACI due to their anticipated slow clinical progression, making it challenging to observe significant treatment effects in an 18-month study. The sponsor conducted an exploratory subgroup analysis for iADRS and CDR-SB in participants enrolled in the AACI DB period based on the tau status (low/medium versus high) to assess the consistency of treatment effects (refer to **Figure 14**). While the treatment benefit with donanemab appeared to trend positively for both clinical end points (iADRS and CDR-SB) in low/medium tau and high tau groups, subjects with low/medium tau appeared to have a higher treatment benefit compared to subjects with high tau. These analyses are considered exploratory, and the study was not powered to detect the differences between baseline tau subgroups. The sponsor proposes allowing donanemab treatment to subjects irrespective of their baseline tau status. To inform the benefit assessment of donanemab treatment for patients with different baseline tau levels, the review team evaluated the impact of baseline tau on amyloid PET, plasma biomarkers, and PK as summarized below.

A cohort of subjects with no or very low tau status were enrolled in the open-label addendum to Study AACI (AACI Safety Addendum) as they did not meet the tau PET scan eligibility criteria for the Study AACI placebo-controlled Main Study. Clinical efficacy data were not collected while amyloid PET and plasma biomarker (p-tau217 and GFAP) were collected from these subjects for 76 weeks. The subjects with no/very low tau exhibited lower baseline values for amyloid PET and plasma biomarkers compared to subjects with low/moderate or high tau, possibly indicating an earlier disease state (**Figure 15**).

***Figure 14: Subgroup Analysis of Clinical End Points by Baseline Tau Status in Study AACI***




Source: Adapted from Applicant's AACI Study Report; Figure AACI.5.16. (page-177) and AACI.5.18. (Pg-179

Abbreviations: CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; iADRS = integrated Alzheimer's Disease Rating Scale

Consistent with results from subjects with low/medium tau and high tau, following donanemab treatment, a time-dependent reduction in amyloid PET was observed in subjects with no/very low tau compared to baseline. The median amyloid PET remaining at 76 weeks after donanemab treatment was comparable across different baseline tau subgroups (**Figure 15**). The percentage of subjects who achieved amyloid plaque levels of <11 centiloids and <24.1 centiloids across different baseline tau subgroups are presented in **Table 3**. These results indicate that comparable number percentage of subjects achieved amyloid PET reduction to <24.1 or 11 centiloids by week 76 across different baseline tau subgroups. Similarly, a time dependent decrease in plasma p-tau217 and plasma GFAP levels was observed with donanemab treatment across different baseline tau subgroups compared to placebo (**Figure 15**). Overall, these results indicate that significant reductions were observed in amyloid PET and plasma biomarkers regardless of baseline tau levels with donanemab treatment.

***Table 3: Percentage of Donanemab Treated Participants by Tau Subgroup with Amyloid PET levels <24.1 or 11 centiloids at Week 76***

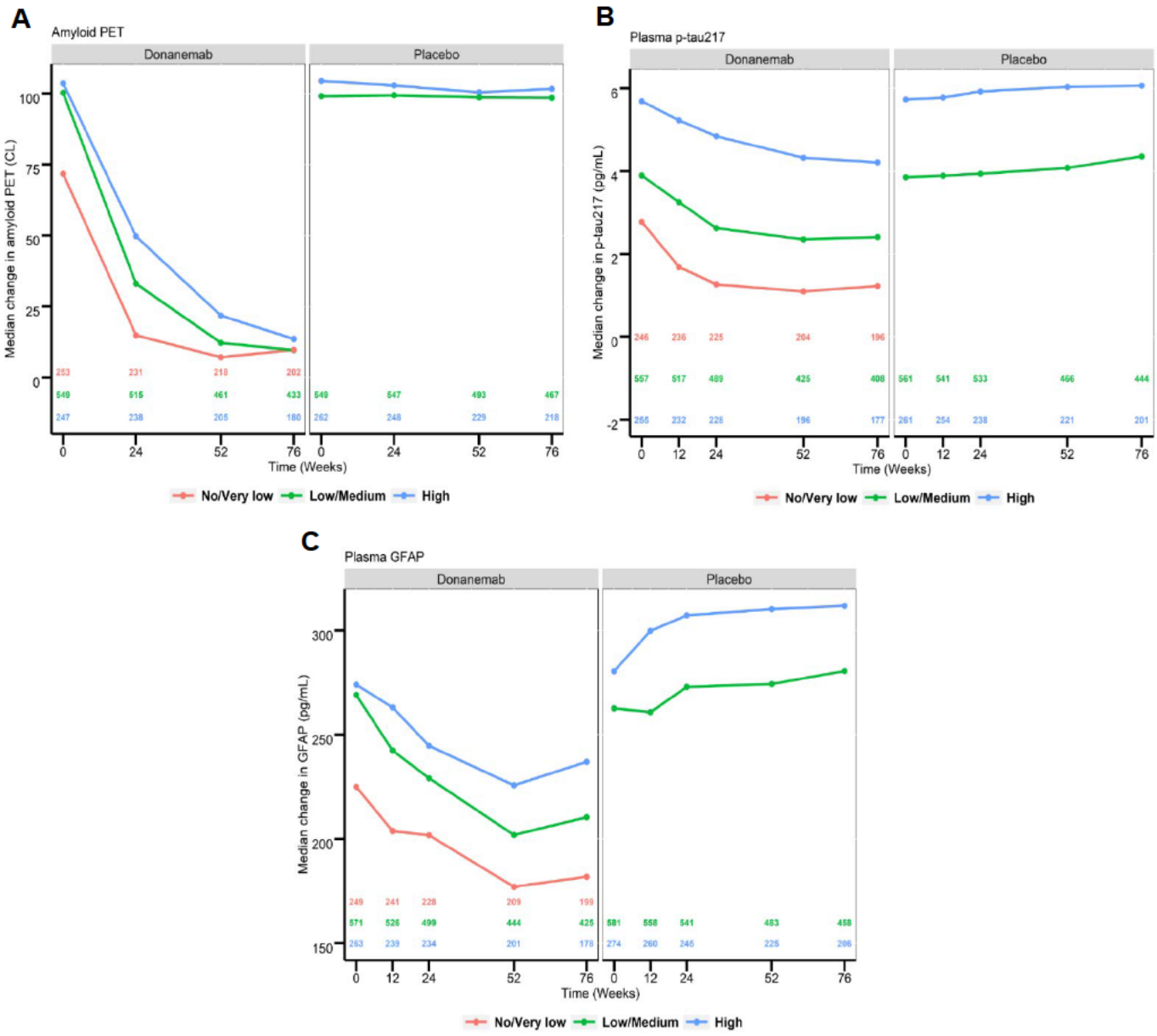
| | **<24.1 Centiloid** | **<11 Centiloid** |
|---|---|---|
| No/Very Low Tau Population, % (n/N) | 83.7 (169/202) | 53.5 (108/202) |
| Low/Medium (Intermediate) Tau Population, % (n/N) | 79.4 (344/433) | 54.3 (235/433) |

| | | |
|---|---|---|
| High Tau Population, % (n/N) | 68.3 (123/180) | 46.1 (83/180) |

Abbreviations: n = number of subjects who met the criteria; N = Total number of subjects in the subgroup.

Source: Reviewer's Analysis

***Figure 15: Change in Biomarkers over Time by Baseline Tau Status in Study AACI***




Source: Reviewer's Analysis

We explored changes in PK to explain the differences in clinical endpoints among baseline tau subgroups. For subjects in studies AACI and AACG receiving donanemab at a dose of 700 mg q4w for first three doses followed by 1400 mg q4w, the predicted average steady-state concentration in subjects with no tau (baseline tau SUVR < 1.10),

low tau (1.10 ≤ baseline tau SUVR < 1.23), medium tau (1.23 ≤ baseline tau SUVR < 1.46), and high tau (baseline tau SUVR ≥ 1.46) is 65.2, 67.3, 68.2, and 68.7 ug/mL, respectively. These results indicate that PK was similar among baseline tau subgroups and may not explain the observed differences in clinical end points.

In summary, as significant reductions were observed in amyloid PET and plasma biomarkers in subjects with very low/no baseline tau, the review team recommends the use of donanemab in this population. Further, the observed differences in clinical efficacy between low/medium tau and high tau subgroups could not be attributed to differences in PK. Given the comparable reductions in amyloid PET and plasma biomarkers across all subgroups, the review team does not propose alternate dosing recommendations based on baseline tau levels.

### *3.3.6 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?*

Yes. Donanemab solution formulation is supplied as a 17.5-mg/mL solution drug product in a 20-mL glass vial and is the proposed to-be-marketed formulation. The applicant used the same solution formulation of donanemab drug product in the pivotal Study AACI.

# 4. Appendix

## 4.1. Summary of Bioanalytical Method Validation

### *4.1.1 Bioanalysis of donanemab in human serum*

For the determination of serum donanemab concentrations from Study AACI, the applicant used an Enzyme-Linked Immunosorbent Assay (ELISA) method (Report 8352-531). This report along with two other validation reports (Reports 8248-152 and 8338-154) were reviewed previously. Please refer to the OCP review in DARRTS dated 01/17/2023 for more information. The ELISA method was validated in compliance with the standards set forth in the 2018 FDA Bioanalytical Method Validation guidance. Accuracy and precision of QC samples were ≤20% (and ≤25% at LLOQ and ULOQ), and calibration curves for the ELISA bioanalytical assay were within acceptable limits. Further, based on the recoveries and passing rates of spiked controls and incurred serum sample pools, the cross validation was considered acceptable.

### *4.1.2 Bioanalysis of p-tau217 in human plasma*

For the determination of plasma p-tau217 concentrations, the applicant used an Immunoaffinity (IA)-LC-MS/MS method. (b) (4) Summary of the validation parameters submitted by the applicant are presented in **Table 4**.

***Table 4: Summary of Bioanalytical Method Performance in Plasma – Phospho-Tau 217 (p-tau217) Assay***

| Validation Parameters | Results |
|---|---|
| Analytical Measuring Range (Linearity) | (b) (4) |
| Precision | |
| Trueness/Accuracy | |
| Carryover | |
| Sensitivity | |
| Clinical Measurement Range | |
| Specificity/Interference | |

*Source: Applicant Validation Report for the p-tau217 Method*

*Abbreviations: nptau217 = non-phosphorylated tau217; ptau217 = phosphorylated tau217*

*Notes: Only assay for ptau217 was reviewed in the submission*

However, deficiencies were identified in the validation plan which are described below.

a. **Inadequate long term stability duration:** (b) (4)

b. **Inadequate data to support the use of different matrices for calibrators and actual samples:** (b) (4)

c. **No parallelism data:** (b) (4)

d. **Insufficient number of calibrator levels:** (b) (4)

### *4.1.3 Bioanalysis of p-tau181 in human plasma*

The applicant used Simoa® pTau-181 Advantage V2.1 Kit to determine the concentrations of p-tau181 in human plasma samples from Study AACI. (b) (4)

(b) (4)

Summary of the validation parameters submitted by the applicant are presented in **Table 5**.

***Table 5: Summary of Bioanalytical Method Performance in Plasma – Phospho-Tau 181 (p-tau181) Assay***

| Test | Claim |
|---|---|
| LOD | (b) (4) |
| Analytical LLOQ | |
| Functional LLOQ | |
| 4PL Curve CV Profiling LLOQ | |
| Calibrator B/A AEB | |
| Calibrator A AEB | |
| Calibrator G AEB | |
| Precision | |
| Admixture Linearity | |
| Curve Storage | |
| Drift | |
| Normal Samples | |

*Source: Applicant Validation Report for the P-tau181b Method*

However, deficiencies were identified in the validation plan which are described below.

a. **Inadequate long term stability duration:** (b) (4)

b. **Insufficient number of EQC samples:** (b) (4)

### *4.1.4 Bioanalysis of GFAP in human plasma*

The applicant used Simoa® Neurology 2-Plex B Advantage Kit to determine the concentrations of GFAP in human plasma samples from Study AACI. (b) (4)

Summary of the validation parameters submitted by the applicant are presented in **Table 6**.

***Table 6: Summary of Bioanalytical Method Performance in Plasma GFAP Assay***

| Test | Claim |
|---|---|
| LOD | (b) (4) |
| Analytical LLOQ | |
| Functional LLOQ | |
| Calibrator B/A | |
| Calibrator A | |
| Calibrator H | |
| Reproducibility Precision | |
| Spike and Recovery* | |
| Dilution Linearity* | |
| Normal Samples | |
| Kit Stability* | |

*Source: Applicant Validation Report for the Plasma GFAP Method*

Several deficiencies were identified in the GFAP validation plan. Firstly, the long-term stability of GFAP (b) (4) does not adequately support the stability of samples from Study AACI, (b) (4) . Extrapolating stability data (b) (4) is deemed inappropriate. Secondly, the validation plan (b) (4) . However, this approach is insufficient (b) (4) . Thirdly, spike recovery experiments revealed (b) (4)

A reduction in plasma GFAP was observed with donanemab treatment compared to placebo in Study AACI. However, (b) (4)

(b) (4)

## 4.2. Impact of Immunogenicity

For the determination of ADAs, the applicant used an affinity capture and elution bridge immunogenicity assay. The assay was developed at Lilly Research Laboratories (Eli Lilly and Company, Indianapolis, Indiana, USA) and validated at (b) (4) . Various method validation parameters for assessing immunogenicity were considered adequate. Please refer to the immunogenicity assay review by OBP for additional details.

### *4.2.1 Impact of immunogenicity on PK*

To evaluate the impact of immunogenicity on PK, we compared the observed concentrations in ADA+ and ADA- subjects with time-matched PK and ADA data. The average donanemab concentrations (ADA+ and ADA- groups) were calculated at each timepoint and are presented in **Table 7** and **Figure 16**. The results show that the mean concentrations in ADA+ subjects were lower than ADA- subjects at all the time points. The geometric mean ratio (GMR) of concentrations between ADA+ and ADA- groups by time point and the related 90% CI are presented in **Table 7** and **Figure 17**. Subjects in the ADA+ group had lower pre-dose concentrations at all the evaluated time points with lower concentrations in ADA+ group starting from week 4, i.e., at the end of the first dosing interval.

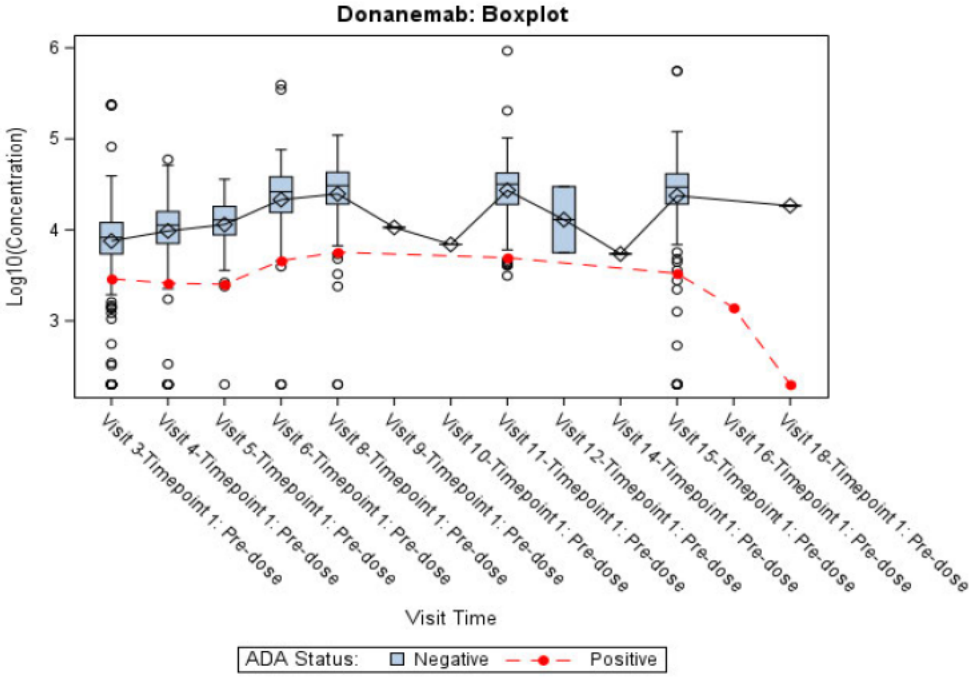
**Table 7: Study AACI - Summary of average concentration by ADA status**

| Visit # | Timepoint | Total N | Donanemab Concentration (µg/mL), geometric mean | | | | GMR (90%CI) **ADA+/ADA-** |
|---|---|---|---|---|---|---|---|
| | | | ADA+ group | N | ADA- group | N | |
| 3 | Week 4 | 827 | 2.96 | 284 | 7.53 | 543 | 0.39 (0.3,0.4) |
| 4 | Week 8 | 788 | 2.59 | 596 | 9.72 | 192 | 0.27 (0.2,0.3) |
| 5 | Week 12 | 733 | 2.52 | 664 | 11.44 | 69 | 0.22 (0.2, 0.3) |
| 6 | Week 16 | 759 | 4.59 | 672 | 21.48 | 87 | 0.2 (0.2,0.3) |
| 8 | Week 24 | 724 | 5.68 | 624 | 24.82 | 100 | 0.2 (0.2,0.3) |
| 11 | Week 36 | 689 | 4.95 | 551 | 27.23 | 138 | 0.18 (0.1,0.2) |
| 15 | Week 52 | 643 | 3.33 | 438 | 23.74 | 205 | 0.14 (0.1,0.2) |

Abbreviations: N: number of subjects; GMR: geometric mean ratio; CI: confidence interval; BLQ: below limit of quantification; ADA status represents the ADA reported for study samples at each study visit

*Source: Reviewer's analysis*

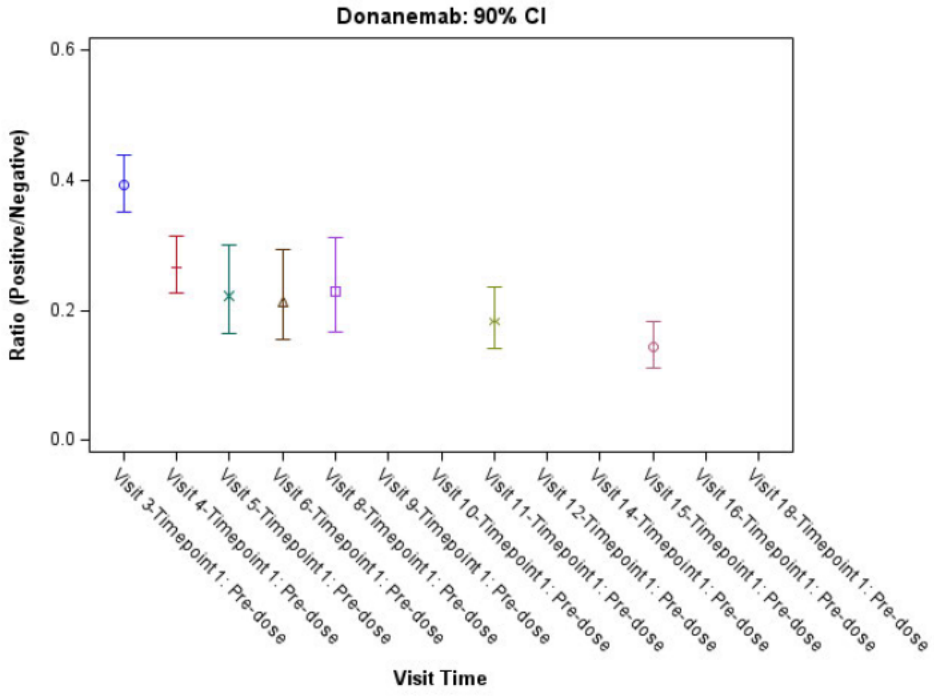
### *Figure 16: Donanemab concentrations from ADA positive and ADA negative subjects during the treatment period*




*Source: Reviewer's analysis*

*Notes: The donanemab concentrations at each visit in the ADA negative group are presented in a blue box and the ADA positive group are presented as a line plot. Open rhombus and solid red circle represents the mean donanemab concentrations at each time point.*

***Figure 17: Donanemab Geometric Mean Ratios in ADA Positive Subjects Compared to ADA Negative Subjects at Various Time Points in Study AACI***

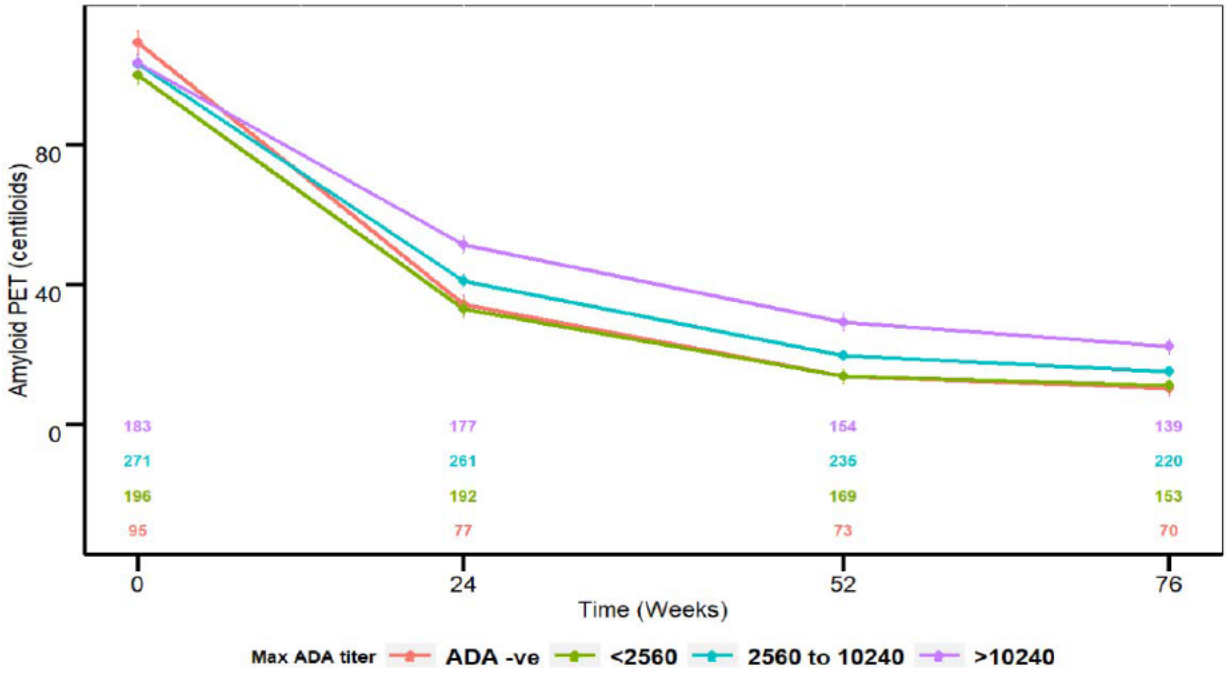



*Source: Reviewer's analysis*

### *4.2.2 Impact of immunogenicity on amyloid PET reduction*

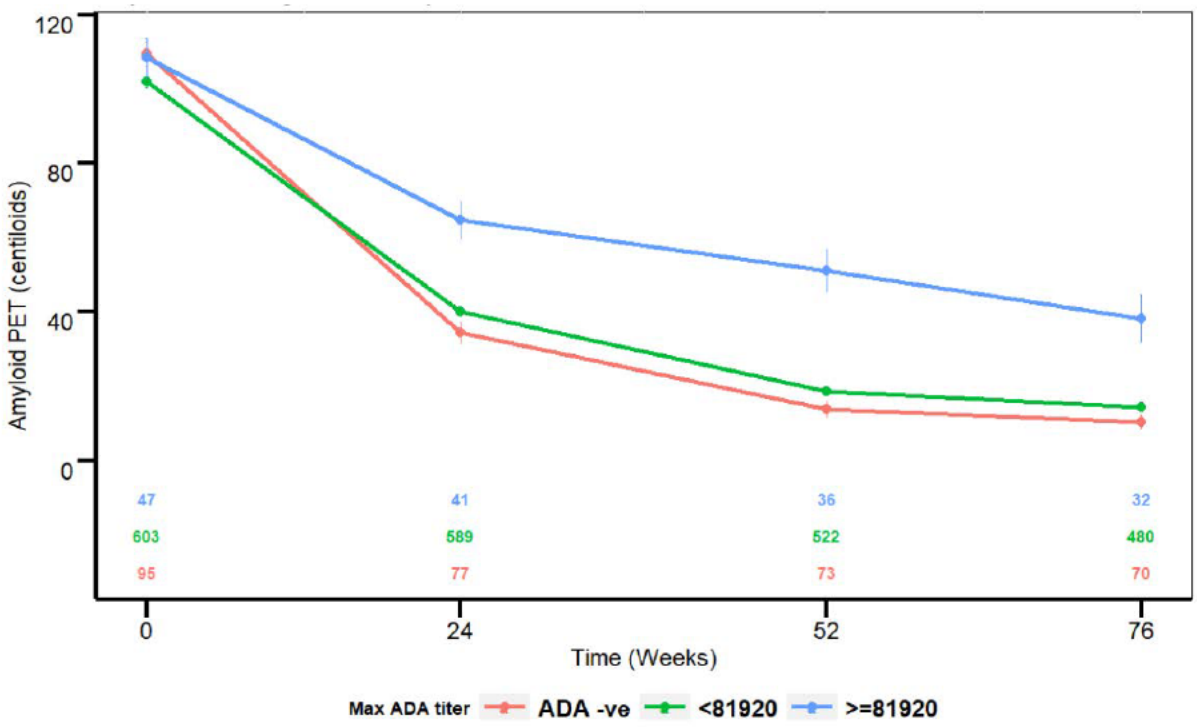
To evaluate if the ADA titer mediated changes in donanemab exposures were translated to a reduced PD effect (amyloid PET reduction), the subjects were divided into ADA+ and ADA- groups and the change in amyloid PET over time was evaluated. The results indicated that ADA- subjects had slightly higher amyloid PET reduction by week 76 compared to ADA positive subjects (figure not presented). To further evaluate the effect of maximum ADA titer on amyloid PET reduction, the ADA+ subjects were divided into three different quantiles (**Figure 18**). The results indicated that the reduction in amyloid PET was observed irrespective of the observed maximum titer. However, subjects with higher maximum ADA titer, appeared to have less amyloid PET reduction compared to ADA negative subjects or less ADA titer. The mean change in amyloid PET from baseline in subjects with maximum ADA titer >10240 was 81.2 CL compared to ~99 CL in amyloid negative subjects. As subjects with higher maximum ADA titer had lower amyloid PET reduction from baseline, additional analysis was conducted to evaluate the changes in amyloid PET reduction in subjects with maximum ADA titer ≥81920 (**Figure 19**). The mean change in amyloid PET from baseline in subjects with maximum ADA titer ≥81920 was 70.2 CL compared to 87.5 CL in subjects maximum ADA titer <81920. The overall findings suggest that as the maximum ADA titer increased, there was less reduction observed in amyloid PET.

***Figure 18: Change in Amyloid PET by Maximum ADA Titer***




*Source: Reviewer's analysis*

***Figure 19: Change in Amyloid PET over Time by High vs Low maximum ADA Titer***

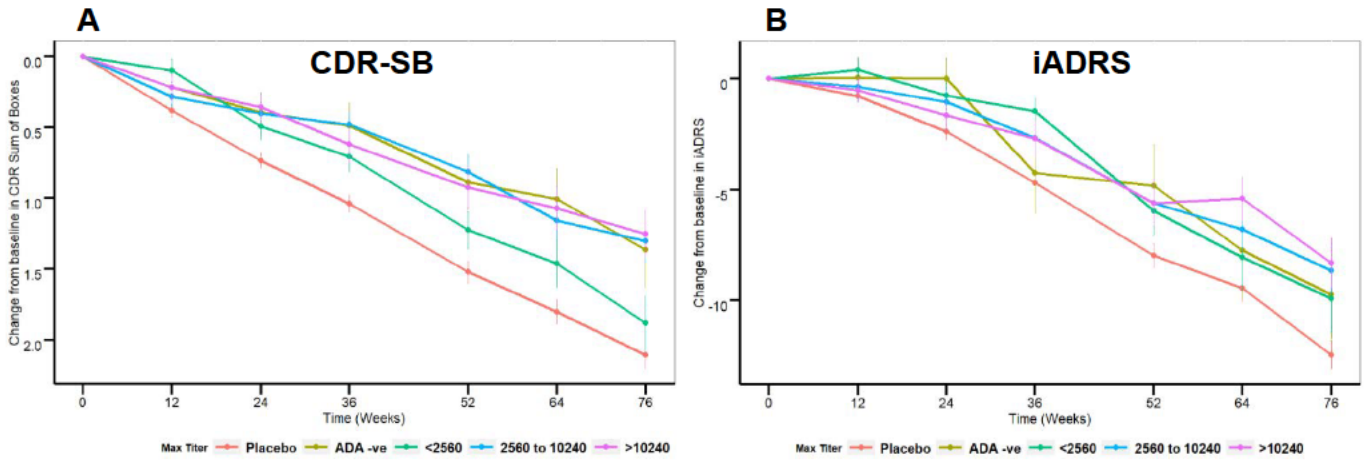



*Source: Reviewer's analysis*

### *4.2.3 Impact of immunogenicity on Efficacy*

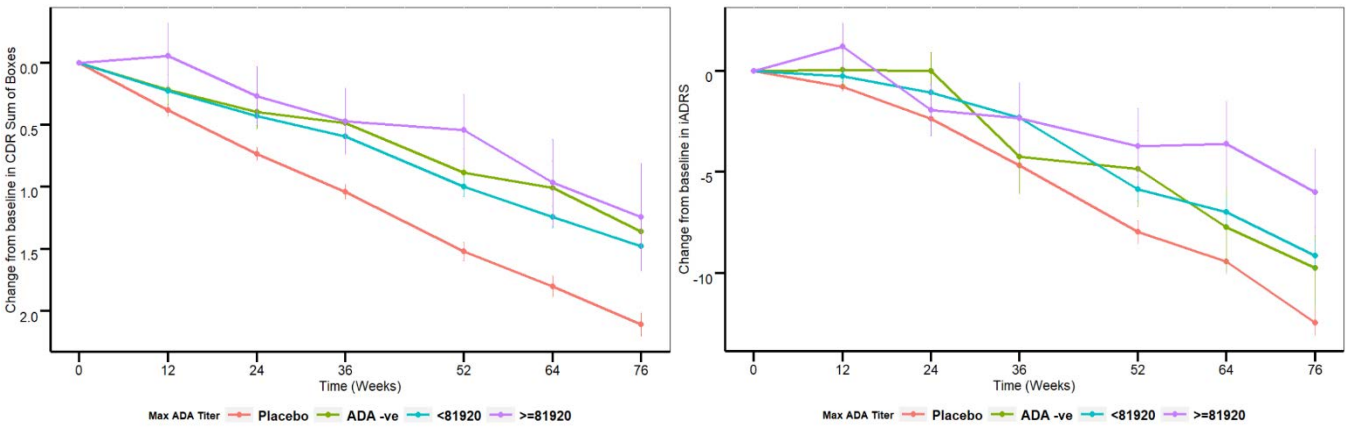
The results from the impact of immunogenicity on amyloid PET indicated that the mean change in amyloid PET from baseline was reduced as the maximum ADA titer increased. To evaluate if the changes in amyloid PET reduction associated with maximum ADA titer translated to changes in clinical efficacy scales measured on iADRS and CDR-SB. Similar to analysis of impact of immunogenicity on amyloid PET, the subjects were divided into three different quantiles and changes in iADRS and CDR-SB from baseline were evaluated. The results indicated that comparable efficacy measured on iADRS and CDR-SB was maintained irrespective of the high maximum ADA titer (**Figure 20**). Additional analysis was conducted to evaluate if the changes in amyloid PET reduction observed in subjects with maximum ADA titer ≥81920 translated to changes in clinical efficacy (**Figure 21**). The results indicated that subjects with maximum ADA titer ≥81920 had comparable efficacy compared to subjects with maximum ADA titer <81920. Efficacy measured on CDR-SB and iADRS was maintained with donanemab treatment despite the presence of neutralizing bodies. Overall, these results indicated that the changes in amyloid PET associated with high ADA titer did not translate into changes in efficacy.

***Figure 20: Change from Baseline in CDR-SB and iADRS by Maximum ADA Titer***




*Source: Reviewer's analysis*

***Figure 21: Change from Baseline in CDR-SB and iADRS by Low vs High Maximum ADA Titer***




*Source: Reviewer's analysis*

## 4.3 Population PK Review

### *4.3.1 Population PK Model*

The population PK model used to describe the pharmacokinetics (PK) of donanemab and characterize the relationship between donanemab PK with demographics and other covariates was reviewed previously and was considered acceptable (Refer to OCP review in DARRTS dated 01/17/2023).

In the current submission, the applicant updated the model by including the data from Study AACI. The PK dataset contained 22,288 observations from 2131 participants (46 participants from Study AACD, 131 participants from Study AACG, 54 participants from Study AACH, Part B, and 1900 participants from AACI [PC and Safety Addendum]). The selected final model has 2 compartments following IV infusion, with interparticipant variability on CL, as well as central and peripheral volumes of distribution. Additionally, clearance and distributional clearance were scaled allometrically by weight, and central and peripheral volumes of distribution were also scaled allometrically with weight, using exponents of 0.8 for clearance terms and 1 for volume terms. Following stepwise covariate modeling, the final model identified effect of titer change over time on clearance as a significant covariate.

***Table 8: Pharmacokinetic and Covariate Parameters in Population***

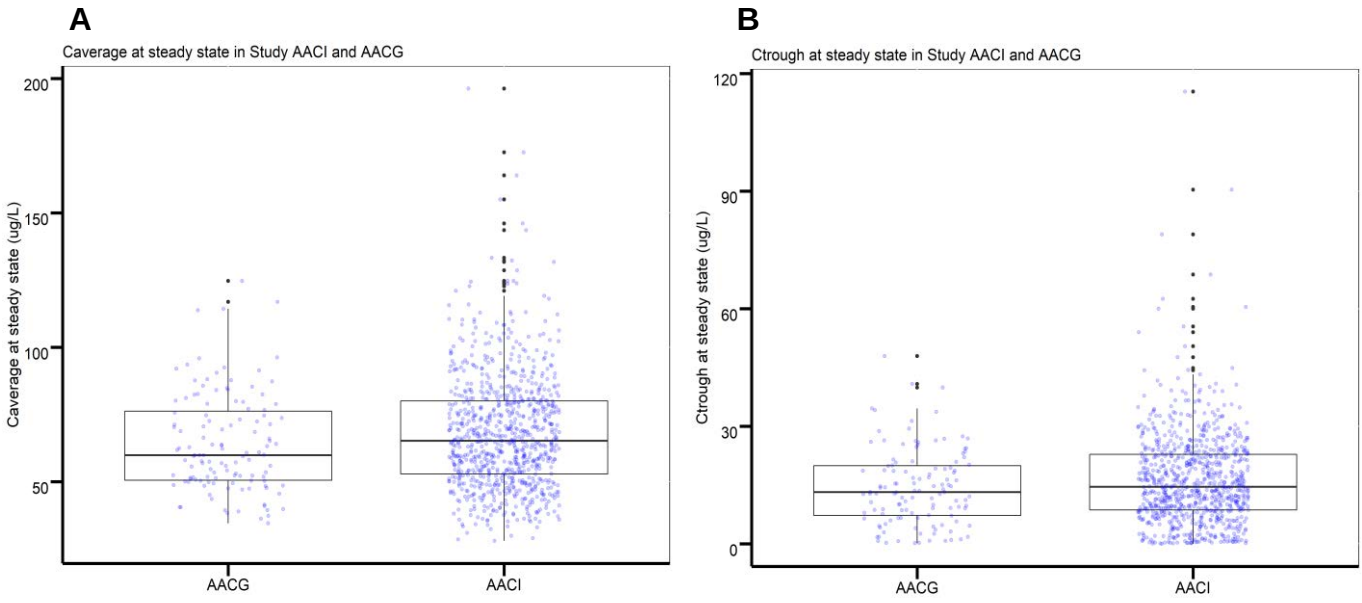
| Parameter | Base Model Population Mean (95% CI)[a] | Final Model Population Mean (95% CI)[a] |
|---|---|---|
| CL (L/h)[b] | 0.0300 (0.0288, 0.0320) | 0.0255 (0.0243, 0.0271) |
| V1 (L)[c] | 3.40 (3.35, 3.44) | 3.36 (3.31, 3.40) |
| V2 (L)[d] | 4.48 (3.94, 5.25) | 4.83 (4.26, 5.73) |
| Q (L/h)[e] | 0.0196 (0.0166, 0.0247) | 0.0200 (0.0163, 0.0248) |
| **Covariate effects** | | |
| *Covariate effect on Clf* | | |
| Effect of titer | NA | 0.0487 (0.0436, 0.0552) |
| **Between-participant variability CV% (95% CI)[a, g]** | | |
| CL | 28.6% (26.6, 30.4) | 24.9% (23.1, 26.8) |
| V1 | 18.7% (14.6, 23.1) | 18.7% (14.7, 22.7) |
| V2 | 74.6% (67.2, 81.5) | 93.9% (81.8, 109) |
| **Residual unexplained variability** | | |
| Proportional (%) | 46.9% (45.5, 48.2) | 44.4% (43.3, 45.4) |
| Additive (ng/mL) | 94.0 (79.4, 109) | 91.5 (79.5, 106) |

Source: *ly3002813-population-pk-pd-report_us_sub2-donan, page 52*

Abbreviations: CI = confidence interval; CL = clearance; CV = coefficient of variation; NA = not applicable; V1 = volume of distribution, central compartment; V2 = volume of distribution, peripheral compartment; Q = intercompartment clearance; WT = weight at baseline.

Similar PK exposures were observed in Study AACI compared to Study AACG which may explain the comparable reductions observed in amyloid PET between these studies (**Figure 22**).

***Figure 22: Steady State Concentrations of Average and Trough in Studies AACI and AACG***




Source: Reviewer's Analysis

*<u>Reviewer's Comments:</u> Even after the inclusion of PK data from Study AACI, the same PK model was able to adequately explain donanemab pharmacokinetics.*

## 4.4 Exposure-Response Analyses

Report ly3002813-population-pk-pd-report_us_sub2-donan.pdf, titled "*Population Pharmacokinetic and Pharmacodynamic Analyses of Studies I5T-MC-AACD, I5T-MC-AACG, I5T-MCAACH (Parts B and C), and I5T-MC-AACI (PC and Safety Addendum)*" was submitted to module 5335 in sequence 0104. The exposure-response analyses described in this report assess the relationship of donanemab exposure with amyloid plaque reduction, ARIA-E, P-tau217, plasma GFAP, iADRS, and CDR-SB. The amyloid data were measured in study AACD, AACG, AACH (parts B and C), and AACI (placebo-controlled phase and safety addendum phase). The ARIA-E, iADRS, and CDR-SB data were obtained from study AACG and ACCI. The PK values applied in these analyses were obtained from individual PK paramter estimates from the population PK analyses (see section 4.3.1 Population PK Model for details) using individual dosing history for each subject. The analyes were performed using NONMEM version 7.5.0 software.

[*Reviewer comment: Exposure-response analyses for these endpoints were previously submitted in sequence 0002 and reviewed by OCP. Please refer to the clinical pharmacology review of NDA 761248 archived on 2023/01/17 for details. The current submission includes updates to each E-R model with a larger data base of PD observations.*

*The Applicant used the name run001 to refer to the final model for PPK, ARIA-E TTE, and P-tau217.*]

### *4.4.1 Amyloid-Plaque Reduction*

#### *4.4.1.1 Modeling*

The dataset used for these analyses contains 12128 amyloid plaque measurements from n=2023 subjects from studies AACD, AACG, AACH, and AACI. The median observation time is 12 months. The maximum observation time is 25.1 months.

The applicant applied a turnover model (also known as an indirect response model) to describe the amyloid plaque data. The treatment effect was implemented as stimulating the plaque degradation term when PK is over a threshold concentration. This model is parameterized in terms of a plaque elimination half-life and baseline plaque level. The Applicant applied a Box-Cox transformation to the between subject variability term for the baseline amyloid value. Covariates tested on the half-life and baseline amyloid plaque parameters included age, weight, ADA titer, TE ADA status, time from diagnosis, and baseline tau PET SUVR as continuous relationships, and low/medium (PET SUVR ≤1.46) and high (tau PET SUVR >1.46) and APOE4 status as categorical relationships. The final model (run077) did not include any covariates. Parameter estimates for the final model are presented in **Table 9**.

**Table 9: Parameter Estimates for the Final Amyloid Plaque Reduction Model (run077)**

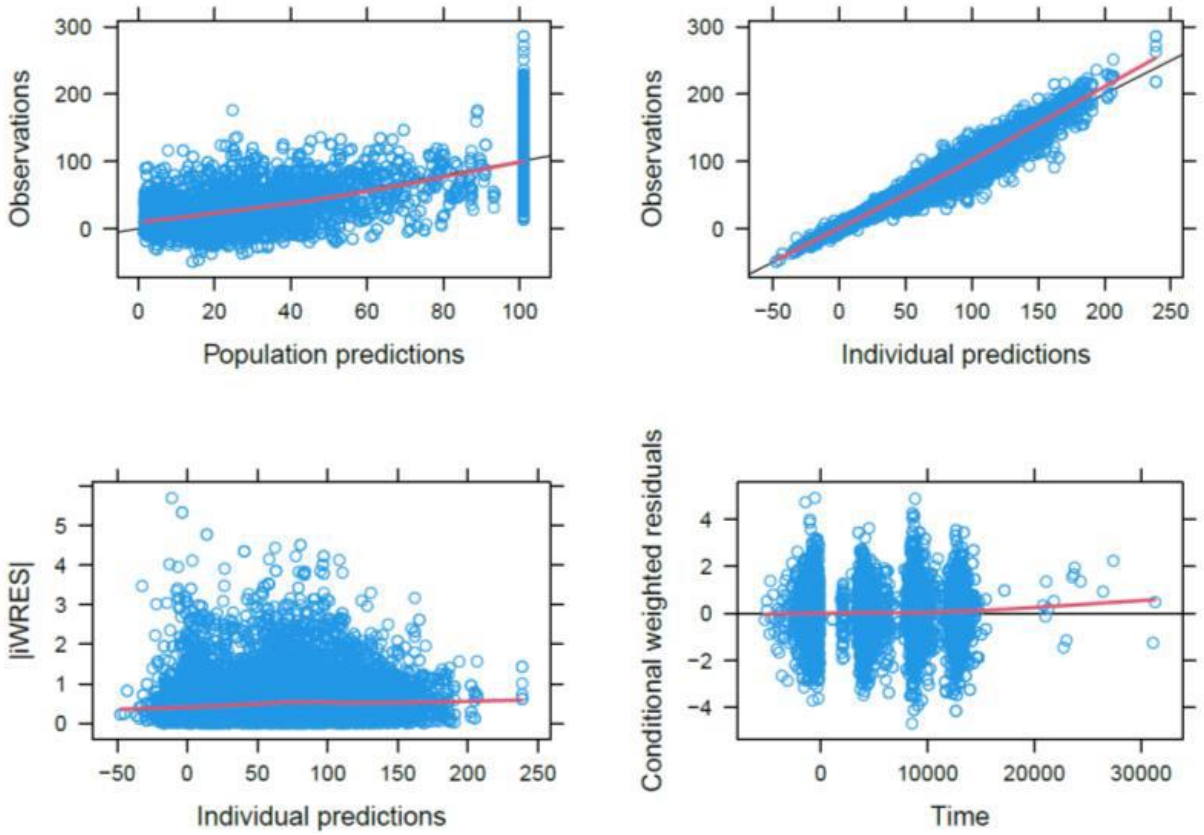
| Parameter | Final Model (95% CI)[a] |
|---|---|
| Treatment effect | 90.3 (45.0, 112) |
| Plaque removal half-life (hr) | 151,000 (93,100; 184,000) |
| Baseline amyloid plaque (Centiloids) | 101 (99.4, 103) |
| Baseline amyloid plaque box-cox transformation shape parameter | -0.576 (-0.737, -0.425) |
| Threshold concentration associated with treatment effect (µg/mL) | 15.2 (8.54, 18.0) |
| **Between-participant variability CV% (95% CI)** | |
| Plaque removal half-life | 74.6% (61.0, 83.4) |
| Baseline amyloid plaque | 32.3% (30.7, 33.4) |
| Plaque scaler (SD in Centiloid) | 23.0 (21.1, 26.2) |
| **Residual unexplained variability** | |
| Additive (Centiloid) | 2.82 (2.33, 3.21) |
| Proportional (%) | 13.8% (13.1, 14.4) |

*CI = confidence interval; CV = coefficient of variation; SD = standard deviation. a 95% CI from bootstrap.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 55 of 245*

Key diagnostic plots are presented in **Figure 23** and **Figure 24**.

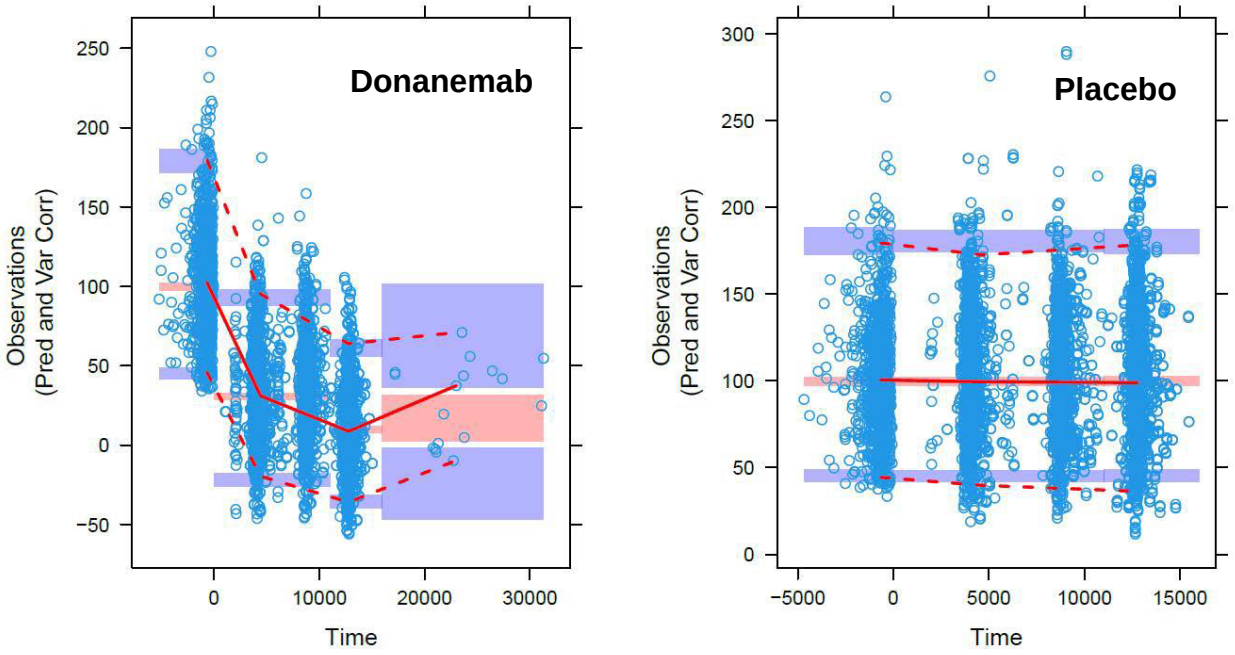
***Figure 23: Diagnostic plots for the amyloid-plaque reduction PKPD model***




*PET = positron emission tomography.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 168 of 245*

***Figure 24: Visual predictive check for the final PKPD model for Amyloid Plaque Reduction***




*Solid red line: median of ob served concentrations; dashed red lines: 5th and 95th percentiles of observed concentrations; red shaded area: 95% confidence interval for the median of simulated data; blue shaded areas: 95% confidence intervals for the 5th and 95th percentiles of simulated data; blue full circles: individual observed amyloid plaque data. Data and predictions are stratified by placebo (right panel, TRT0 = 2) and donanemab treatment (left panel, TRT0 = 1). X-axis depicts hours and y-axis depicts Centiloids.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 56 of 245*

The Applicant concludes the following:

- An exposure-response analysis described the relationship with amyloid reduction as measured using amyloid PET. Treatment effect was associated with maintaining serum donanemab concentrations above a median (95% CI) threshold concentration of 15.2 (8.54, 18.0) µg/mL. No covariate effects, including APOE ε 4 and baseline tau burden, influencing amyloid removal were identified.
- Although serum clearance of donanemab increased with increasing ADA titer, leading to clearance increasing by approximately 39% at the highest titer in studies included in the meta PK/PD analysis (Studies AACD, AACG, AACH Parts B and C, and AACI [PC and Safety Addendum]), there was a significant overlap in concentrations across different titers, even between extreme ADA titers (<1:5120 and >1:20480). The majority (more than 80%) of participants maintained average concentrations above the threshold efficacy concentration.

- The impact of completing active treatment on plaque reaccumulation was investigated by simulations using treatment exposure-response (amyloid plaque) model using previously published methods (Shcherbinin et al. 2022; Gueorguieva et al. 2023). The amyloid reaccumulation rate (median, 95% CI) is estimated at 2.80 (2.16, 3.11) Centiloids/year. These findings are supported by natural accumulation modeling studies (Jagust et al. 2021) showing approximately 3.3 Centiloids/year as the estimated rate of the natural amyloid accumulation model.

[*Reviewer comment: The eta shrinkage is 12.4%, 5, and 13.8% for half-life, baseline amyloid, and the scaler parameters, respectively. Epsilon shrinkage is 12.4%. The between subject variability was highest for the treatment effect (90.3%).*

*The diagnostic plots (Figure 23) do not indicate the presence of systemic bias with respect to time nor prediction magnitude. The visual predictive check (VPC; Figure 24) indicates that the model is able to represent the overall distribution of amyloid measurements in the pooled treatment arm as well as in the pooled placebo arm reasonably well.*

*The condition number is 36 which does not suggest overparameterization. Correlation among parameters is low. The Applicant's PKPD model for amyloid plaque reduction is acceptable.*]

#### *4.4.1.2 Simulation*

The Applicant used the exposure-response model for amyloid reduction to simulate effect of donanemab concentration, baseline amyloid pet, effect of completion active treatment, and effect of APOE ε4 on amyloid levels.

**Donanemab Concentration Effect on Amyloid Reduction**

The Applicant's final amyloid reduction model included treatment effect was associated with maintaining a median (95% CI) threshold concentration of 15.2 (8.54, 18.0) µg/mL.

To assess the effect titer impact, PK parameters were calculated for ADA- and each titer category using simulations with 3000 virtual participants. Applicant estimated median, 5th, 20th, 80th, and 95th percentiles for trough concentrations, AUC, average drug concentration (Cav) and Cmax at steady state for different titer cutoff as well as ADA-negative status. The results are presented in Table 10.

***Table 10: Simulated Steady-State PK By ADA Status and Titer.***

| | Median (90% CI): 50th (5th-95th Percentiles) | | | |
|---|---|---|---|---|
| **ADA status/titer category** | **AUCτ,ss** | **Caverage,ss** | **Cmax,ss** | **Ctrough,ss** |
| **units** | [µg*h/mL] | [µg/mL] | [µg/mL] | [µg/mL] |
| **ADA negative** | 53500 (34900, 91500) | 79.6 (52.0, 136) | 381 (255, 559) | 22.2 (5.63, 55.3) |
| **<1:5120** | 43700 (26200, 76100) | 65 (38.9, 113) | 358 (232, 558) | 13.6 (3.04, 37.6) |
| **1:5120-1:20480** | 37800 (23500, 63000) | 56.3 (35, 93.7) | 350 (231, 561) | 10.0 (1.87, 25.6) |
| **>1:20480** | 36300 (22300, 69200) | 54 (33.1, 103) | 350 (224, 565) | 9.33 (1.47, 28.3) |
| | **Median (60% CI): 50th (20th-80th Percentiles)** | | | |
| **ADA negative** | 53500 (42600, 68500) | 79.6 (63.3, 102) | 381 (307, 454) | 22.2 (11.6, 33.6) |
| **<1:5120** | 43700 (33600, 58500) | 65 (50.0, 87.1) | 358 (286, 449) | 13.6 (7.05, 23.9) |
| **1:5120-1:20480** | 37800 (29600, 48800) | 56.3 (44.1, 72.6) | 350 (279, 440) | 10.0 (5.11,17.0) |
| **>1:20480** | 36300 (28500, 50100) | 54 (42.4, 74.6) | 350 (274, 437) | 9.33 (4.58, 16.4) |

*ADA = antidrug antibody; AUC□,ss = area under the concentration versus time curve during 1 dosing interval at steady state; Caverage,ss = average drug concentration under steady-state conditions during multiple dosing; CI = confidence interval; Cmax,ss = maximum observed drug concentration during a dosing interval at steady state; Ctrough,ss = minimum observed drug concentration during a dosing interval at steady state; TE ADA = treatment-emergent antidrug antibody.*

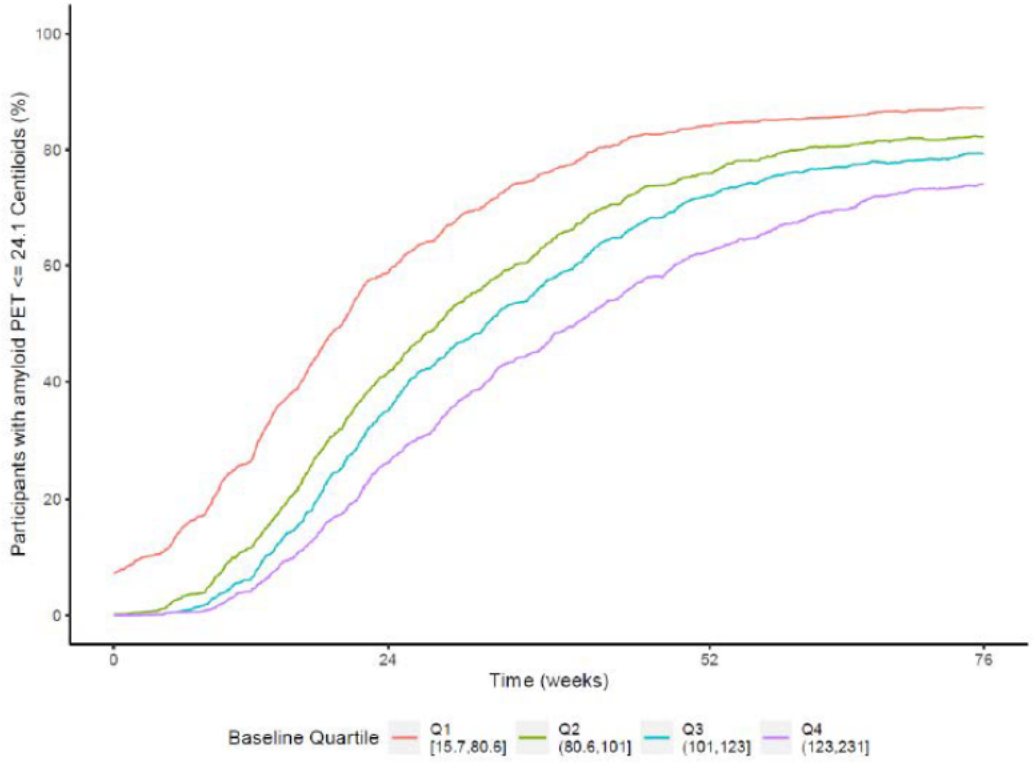
*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 84 of 245*

Applicant reports that the simulated median average and trough concentrations for the majority (80%) of participants were close to the median (15.2 µg/mL) and the 97.5th percentile (18.0 µg/mL) of the CI for the estimated threshold concentration required for plaque removal.

### Effect of Baseline Amyloid on Time to < 24.1 Centiloids

The Applicant simulated 2000 subjects' amyloid plaque levels using the dosing algorithm from studies AACG and AACI. The proportion of subjects achieving levels < 24.1 Centiloids, is presented in **Figure 25**.

***Figure 25: Percentage of participants achieving amyloid plaque clearance (<24.1 Centiloids) by duration on treatment and by quartiles of baseline amyloid PET assessed using treatment exposure response model***



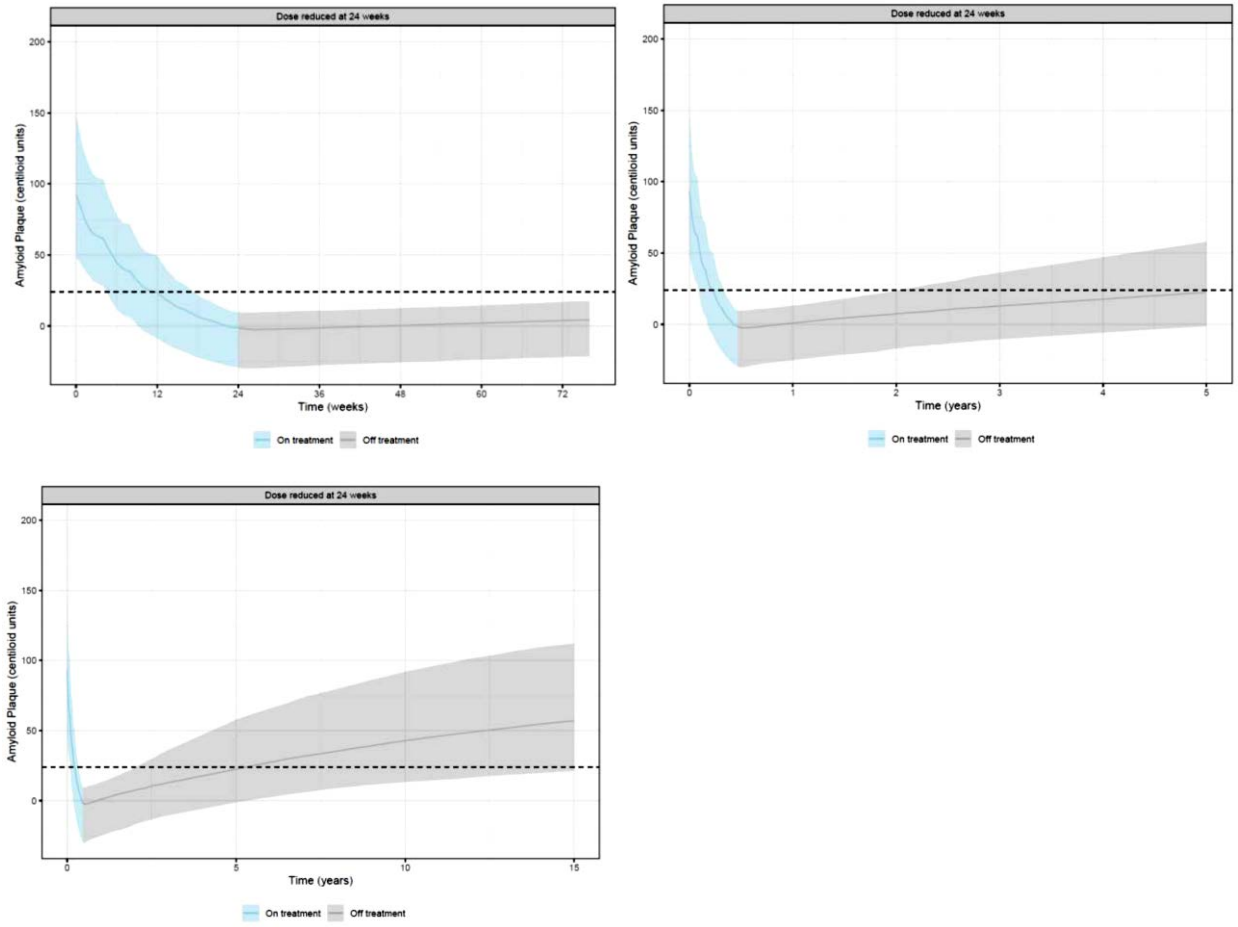

Abbreviations: PET = positron emission tomography; Q = quartiles.

[*Reviewer comment: The analyses indicate that higher baseline amyloid pet levels require more time on treatment to reach a target level such as 24.1 Centiloids. This finding is plausible.* ]

### Effect of Completing Active Treatment on Plaque Reaccumulation

The Applicant applied the amyloid plaque reduction model to simulate the re-accumulation of amyloid plaque upon cessation of donanemab treatment. This simulation exercise involved subjects who achieved < 11 Centiloids amyloid plaque by 6 months (form studies AACG and AACI), completed donanemab treatment, and were followed for 1.5 years (studies AACG and AACI) and further to ~3 years (from observation of a subgroup of the same participants who were followed in Study AACH, Part C). These analyses assumed a linear rate of amyloid reaccumulation rate over time beyond the maximum observed period of 3 years. (b) (4) The results of simulated plaque reaccumulation are presented in **Figure 26**.

***Figure 26: Simulated Amyloid Plaque Profile For Subjects That Achieved < 11 Centiloids and Stopped Treatment by Week 24***




*Abbreviations: AACD = Study I5T-MC-AACD; AACG = Study I5T-MC-AACG; AACH = Study I5T-MC-AACH; AACI = Study I5T-MC-AACI. Top two panels: Participants (n = 10,000) were simulated to follow dosing treatment regimen as described in the Methods section. Model developed using data from Studies AACD, AACG, AACH, and AACI. Reference line shows 24.1 Centiloids. Median (90% prediction intervals) are represented by solid line and shaded area.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 89 of 245*

The Applicant concludes the following:

- The amyloid reaccumulation rate (median, 95% CI) is estimated at 2.80 (2.16, 3.11) Centiloids/year.
- These findings are supported by natural accumulation modeling studies[1] showing approximately 3.3 Centiloids/year (where it took 6.4 years for amyloid to increase from 4 Centiloids to 25 Centiloids; (25-4)/6.4 = 3.28) as the estimated rate of the natural amyloid accumulation model.

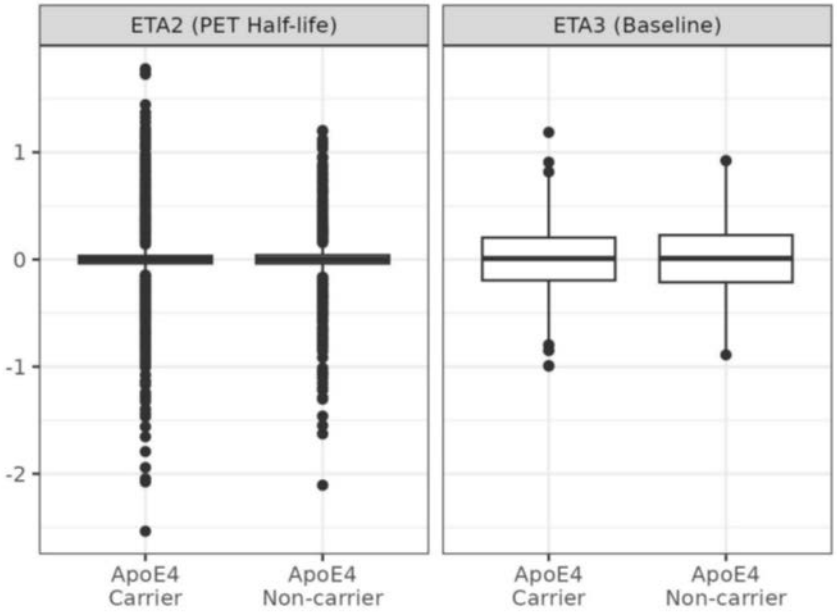
[*Reviewer comment: The Applicant's simulated re-accumulation rate appears reasonable to estimate the amyloid re-accumulation rate within the 3-year time frame within which there are observed amyloid measurements. It is not clear that the amyloid reaccumulation rate can be reliably generalized outside of the 3-year time frame for which observations are provided.*]

**Effect of APOE4 Status on Baseline Amyloid and Amyloid Removal Half-Life**

The Applicant states that none of the investigated covariates (age, weight, baseline tau, ADA titer, time from diagnosis, and APOE e4 carrier status) were identified as covariates in the amyloid PET model. A plot of eta values for baseline amyloid and eta values for amyloid half-life by APOE status are presented in **Figure 27**.

[1] Jagust WJ, Landau SM, Alzheimer's Disease Neuroimaging Initiative. Temporal dynamics of Beta-amyloid accumulation in aging and Alzheimer's disease. Neurol. 2021;96(9):e1347-e1357. https://doi.org/10.1212/WNL.0000000000011524

***Figure 27: Between Subject Variability of Amyloid Half-Life and Baseline Amyloid For the Final Amyloid Plaque Model***




*ApoE4 = apolipoprotein subtype E allele 4; PET = positron emission tomography; participants with unknown carrier status (N = 0.4) were grouped with carriers. Lower and upper hinges correspond to 25th and 75th percentiles; the upper whisker extends from the hinge to the largest value no further than 1.5 × inter-quartile range.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 91 of 245*

The Applicant concludes that the individual predictions of amyloid PET baseline and PET half-life were similar between APOE e4 carriers and non-carriers.

[*Reviewer comment: The distribution of eta values in Figure 27 support the decision to not include APOE4 status as a covariate on baseline or half-life.*]

### *4.4.2 ARIA-E*

The analysis of time-to-first ARIA-E data included 2974 subjects where 462 subjects had at least 1 ARIA-E event. In subjects with multiple events, only the first event was used. The subjects in the dataset came from studies AACG and AACI. The Applicant assessed exponential, Weibull, and Gompertz hazard models. The probability density function was estimated for individuals that experience ARIA-E at time=t and the probably of not having ARIA-E at time=t was estimated for subjects who did not have an ARIA-E event during the observation period (or were censored). Drug concentrations were estimated for subjects using individual PK parameters with the observed dosing history.

The covariates tested with the three hazard models include APOE ε4, age of the study participant, time since onset of symptoms of Alzheimer's disease, time since diagnosis of Alzheimer's disease, baseline C-reactive protein, antidrug antibodies, initial rate of plaque removal and sex. A stepwise forward inclusion, backward elimination (stepwise covariate modeling) was implemented. Linear, power, and exponential covariate relationships were evaluated. OFV reduction, clinical relevance, magnitude of effect, and precision of the estimates were taken into consideration for covariate selection. The parameter estimates for the final TTE model (run001) are presented in Table 11.

***Table 11: Parameter Estimates for the Final ARIA-E Time-to-Event Model (run001)***

| Parameter | Base Model Mean Estimate (95% CI)[a] | Final Model Mean Estimate (95% CI)[a] |
|---|---|---|
| Baseline hazard | -14.2 (-16.9, -12.9) | -15.2 (-17.81, -13.29) |
| Weibull Shape | 0.715 (0.506, 1.16) | 0.819 (0.52, 1.23) |
| Gompertz Shape | -0.000728 (-0.000967, -0.000571) | -0.000767 (-0.00096, -0.00059) |
| APOE ε4 homozygotes on the baseline hazard | -0.0961 (-0.116, -0.0744) | -0.0943 (-0.116, -0.076) |
| APOE ε4 heterozygotes on the baseline hazard | -0.0426 (-0.0598, -0.0246) | -0.0423 (-0.057, -0.028) |
| Placebo treatment on the baseline hazard | 0.204 (0.158, 0.236) | 0.133 (0.102, 0.172) |
| Number of microhemorrhages on baseline hazard | NA | -0.0189 (-0.026, -0.011) |
| $C_{av,ss}$ on baseline hazard | NA | -0.000905 (-0.0011, -0.00066) |

For Base Model:

$$dHaz/dt = HAZ = e^{(-14.2*(1+\theta_{1placebo})*(1+\theta_{2APOE\,44})*(1+\theta_{2APOE\,24/34}))} * e^{(-0.000728*t)} * e^{(0.715*Log(t))}$$

where HAZ denotes the instantaneous hazard for an ARIA-E event, and $\theta_{1placebo}$ *is* 0.204 *for Placebo* , $\theta_{2APOE\,44}$ *is* $-0.0961$ *for APOE homozygotes on drug treatment;* $\theta_{2APOE24,34}$ *is* $-0.0426$ *for APOE heterozygotes on drug treatment.*

For Final Model:

$$dHaz/dt = HAZ = e^{(-15.2*(1+\theta_{1placebo})*(1+\theta_{2APOE\,44})*(1+\theta_{2APOEHetero})*[(1+\theta_{3BASEMM})*(BASEMM-0)]*[(1+\theta_{4CAV})*(CAV-52.01))} * e^{(-0.000767*t)} * e^{(0.819*Log(t))}$$

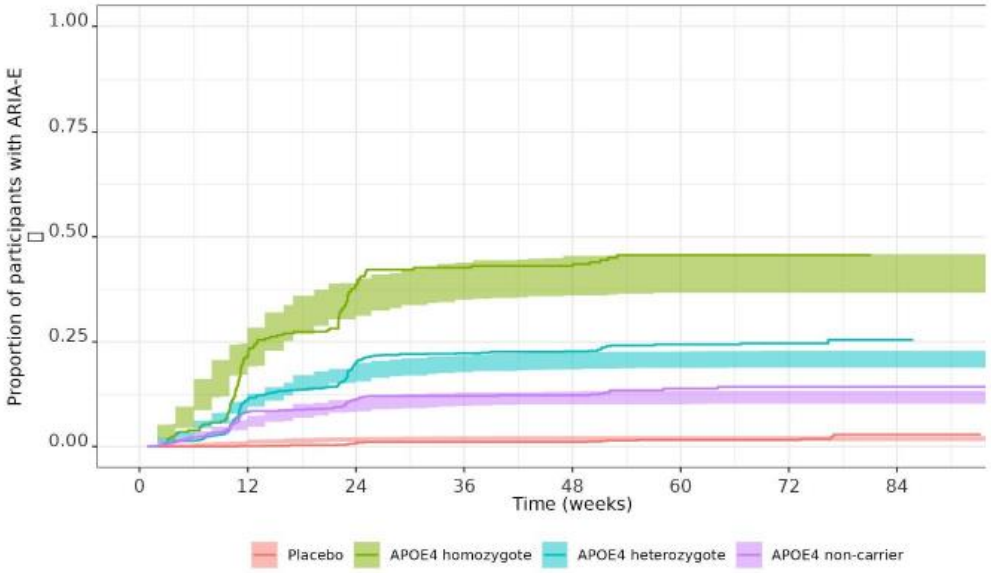
where HAZ denotes the instantaneous hazard for an ARIA-E event, and $\theta_{1placebo}$ *is* 0.133 *for Placebo* , $\theta_{2APOE\,44}$ *is* $-0.0943$ *for APOE homozygotes on drug treatment;* $\theta_{2APOE24,34}$ *is* $-0.0423$ *for APOE heterozygotes on drug treatment;* $\theta_{3BASEMM}$ *is* $-0.0189$ *and* $\theta_{4CAV}$ *is* $-0.000905$.

*APOE ε4 = apolipoprotein E4; ARIA-E = amyloid-related imaging abnormalities-edema/effusions; CI = confidence interval; Cav,ss = average serum concentration at steady state; NA = not applicable.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 58 of 245*

A visual predictive check is presented in **Figure 28**.

***Figure 28: Visual predictive check for the final ARIA-E TTE Model (run001)***




*APOE4 = apolipoprotein E4; ARIA-E = amyloid-related imaging abnormalities-edema/effusions. Note: The solid lines are the Kaplan-Meier plot of the observed data, and the shaded areas are the 95% confidence intervals for the simulated data.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 59 of 245*

The Applicant concludes the following:

- There is a clear donanemab treatment effect for ARIA-E. ARIA-E hazard (that is, instantaneous risk) is driven by the baseline hazard, donanemab treatment, APOE e4 genotype, average concentration at steady state, number of baseline microhemorrhages, and time components.
- ARIA-E baseline hazard differed by APOE ε4 genotype, and by Week 24, it was 1.8 times higher in heterozygote APOE ε4 compared with noncarriers, 3.9 times higher in homozygote APOE ε4 compared with noncarriers, and 2.1 times higher in homozygotes APOE ε4 compared with heterozygotes APOE ε4.
- The baseline hazard for ARIA-E increased with the increase of number of microhemorrhages (evaluated for up to and including 4 baseline microhemorrhages).
- Participants with higher Cav,ss have an increased risk of ARIA-E compared with those with median Cav,ss. The baseline hazard for ARIA-E was 1.2 times higher in participants with the highest observed Cav,ss (233 µg/mL, n = 1; 0.05% of the PK evaluable population) compared with those with median Cav,ss (52.1 µg/mL, n = 2131; 50% of the PK evaluable population).
- The risk of ARIA-E was similar regardless of age, time since onset of symptoms of AD, time since diagnosis of AD, baseline MMSE, antithrombotic medication during study period, white matter disease, sex, baseline C-reactive protein, ADA titer,

baseline amyloid plaque, initial rate of plaque removal, superficial siderosis present at baseline, baseline tau burden, AUCss, Cmax,ss, and Ctrough,ss. The analysis used data from Studies AACG and AACI, both of which examined a single dosage regimen.

- Although immunogenicity had an impact on PK, there was no statistically significant impact of immunogenicity on risk of ARIA-E based on these analyses.

[*Reviewer comment: The VPC presented in Figure 28 demonstrates overlap between the 90% prediction intervals with the Kaplan-Meier plot of the observed data across the treatment groups and by APOE status.*

*The ARIA-E model in the original submission did not include PK as a covariate in the final model. However, the ARIA-E model in the current submission includes PK as a covariate such that subjects with higher Cav,ss have increased ARIA-E risk. One possible explanation for this change in the ARIA-E TTE model may be that the PK effect could not be detected with the smaller dataset available in the original submission (37 ARIA-E events from n=254 subjects) but is detectable in larger dataset in the current submission (462 ARIA-E events from n=2974 subjects).*]

### *4.4.3 P-tau217*

The Applicant utilized a turnover model (also known as an indirect response model) to describe the time course of plasma p-tau217 (P-tau217). In this modeling approach, donanemab was assessed as inhibiting the formation of P-tau217. The final dataset includes 7195 observations from n=1675 subjects. Individual post-hoc participant parameters from the final population PK and the amyloid plaque models were added to the P-tau217 dataset to obtain predicted drug concentrations and amyloid plaque levels for individual patients. The Applicant assessed age at entry, APOE ε4 carrier status, gender, race, weight at entry, presence of TE ADA, time since onset of symptoms of AD, time since diagnosis of AD, and baseline tau PET SUVR as potential covariates on baseline P-tau217. The parameter estimates for the final P-tau217 model (run001) are presented in Table 12.

***Table 12: Parameter Estimates for the Final P-tau217 Model (run001)***

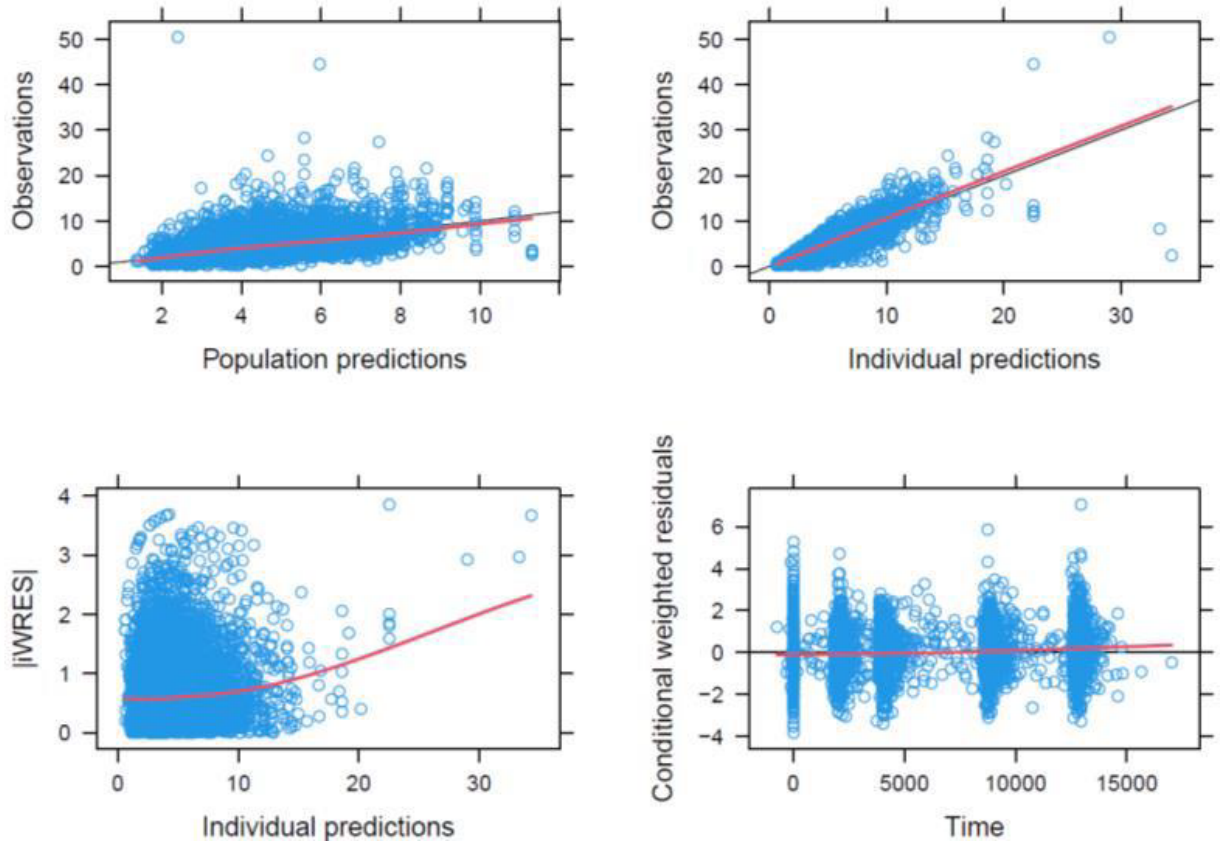
| Parameter | Base Model Population Mean (95% CI)[a] | Final Model Population Mean (95% CI)[a] |
|---|---|---|
| Kin (pg/mL/h) | 0.00131 (0.00113, 0.00156) | 0.00132 (0.00112, 0.00159) |
| Baseline P-tau217 concentration (pg/mL) | 4.53 (4.41, 4.62) | 4.40 (4.31, 4.49) |
| Treatment effect | 1.54 (1.40, 1.69) | 1.54 (1.41, 1.65) |
| **Covariate effects** | | |
| *Covariate effect on Baseline P-tau217 Concentration* | | |
| Effect of baseline tau PET SUVR[b] | NA | 1.27 (1.17, 1.36) |
| **Between-participant variability CV% (95% CI)[c]** | | |
| Baseline P-tau217 concentration (pg/mL) | 48.6% (46.2%, 50.7%) | 38.5% (36.5, 40.5) |
| **Residual unexplained variability** | | |
| Proportional (%)<br><br>Additive (pg/mL) | 25.3% (24.4%, 26.2%)<br>0.14 (0.057, 0.218) | 25.3% 24.4, 26.2<br>0.135 (0.036, 0.209) |

*BTAUSUVR = Baseline Tau PET SUVR; CI = confidence interval; CV = coefficient of variation; Kin = formation rate; NA = not applicable; P-tau217 = tau phosphorylated at threonine 217; PET = positron emission tomography; SUVR = standardized uptake value ratio.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 60 of 245*

Key diagnostic plots are presented in **Figure 29** and **Figure 30**.

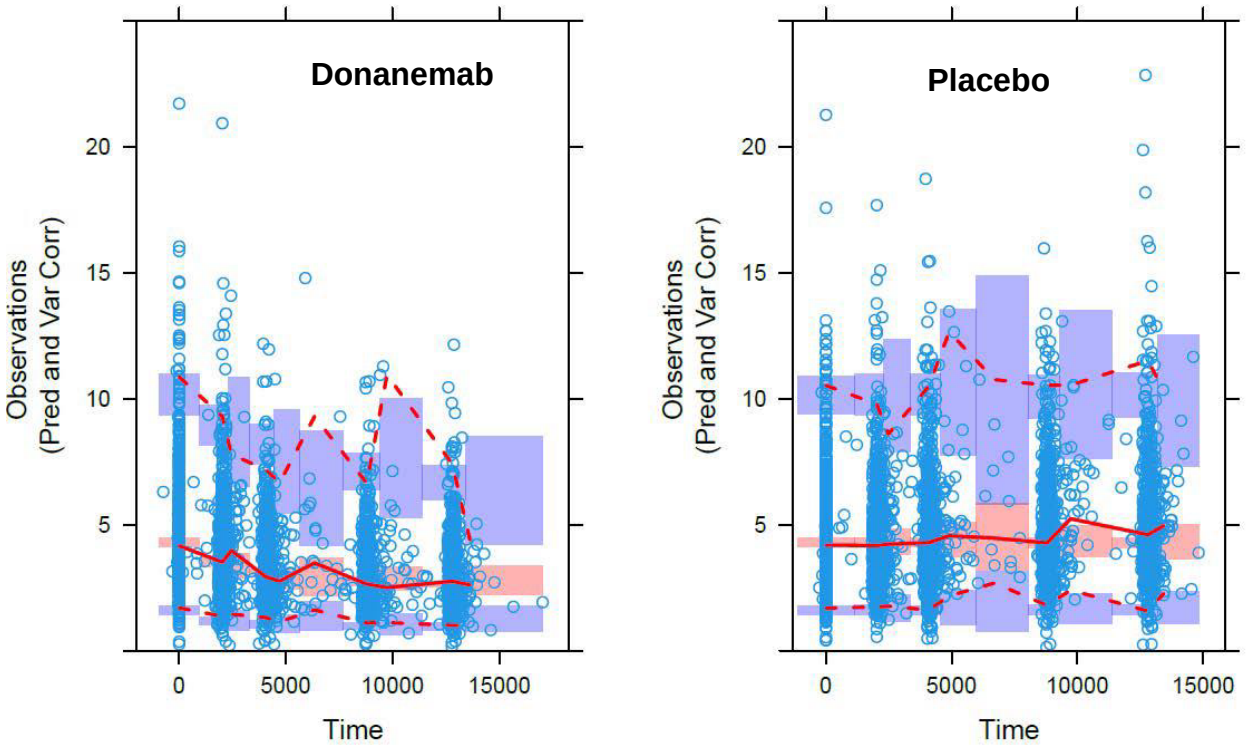
***Figure 29: Diagnostic plots for the final P-tau217 Model (run001)***




*iWRES = individual weighted residuals; P-tau217 = tau phosphorylated at threonine 217.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 234 of 245*

***Figure 30: Visual Predictive Check for the final P-tau217 Model (run001)***




*P-tau217 = tau phosphorylated at threonine 217. The points are the observed P-tau217 concentration in pg/mL plotted across time from first dose in hours. The lines are the 5th, 50th, and 95th percentiles of the observed data. The shaded areas are the model-predicted 95% confidence interval of the corresponding percentiles. The left panel is donanemab treatment and right panel is placebo.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 61 of 245*

The Applicant applied the model to simulate the P-tau217 concentration time profile in treatment versus placebo subjects (see **Figure 5** in section "3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?").

The Applicant concludes:

- Donanemab treatment reduced the formation rate of plasma P-tau217.
- A statistically significant relationship was identified between baseline P-tau217 and baseline tau PET SUVR, with higher P-tau217 concentrations associated with higher values of tau SUVR.

[*Reviewer comment: The modeling results indicate an effect of donanemab on the lowering of P-tau21. These analyses suggest between baseline tau PET SUVR and baseline P-tau217, such that increases in P-tau217 are associated with higher baseline tau PET SUVR values.*]

### *4.4.4 GFAP*

A turnover model was applied to describe the time course of plasma glial fibrillary acidic protein (GFAP). The effect of donanemab treatment on GFAP was addressed via two approaches: 1) treatment inhibits the GFAP formation process, and 2) reduction in amyloid load inhibits the GFAP formation process. The Applicant states that both approaches describe the data well. The Applicant selected the model using amyloid as a predictor of GFAP in part due to a published article describing a positive correlation observed between amyloid load and plasma GFAP[2]. Age at entry, sex, weight at entry, eGFR, baseline MMSE, baseline tau PET SUVR, and baseline P-tau217 were assessed as covariates on baseline GFAP concentration. None of these variables were selected for inclusion as covariates in the final model. The parameter estimates for the final model (run216) are presented in Table *13*.

Table 13: Parameter Estimates for the Final GFAP Model (run216)

| Parameter | Final Model Population Mean (95% CI)[a] |
|---|---|
| Kin (pg/mL/h) | 0.381 (0.260, 0.628) |
| Baseline GFAP concentration (pg/mL) | 269 (264, 274) |
| Effect of amyloid reduction on Kin | 0.237 (0.222, -0.257) |
| **Between-participant variability CV% (95% CI)[b]** | |
| Baseline GFAP concentration (pg/mL) | 41.9% (40.3, 43.4) |
| **Residual unexplained variability** | |
| Proportional (%) | 18.6% (18.1, 19.1) |

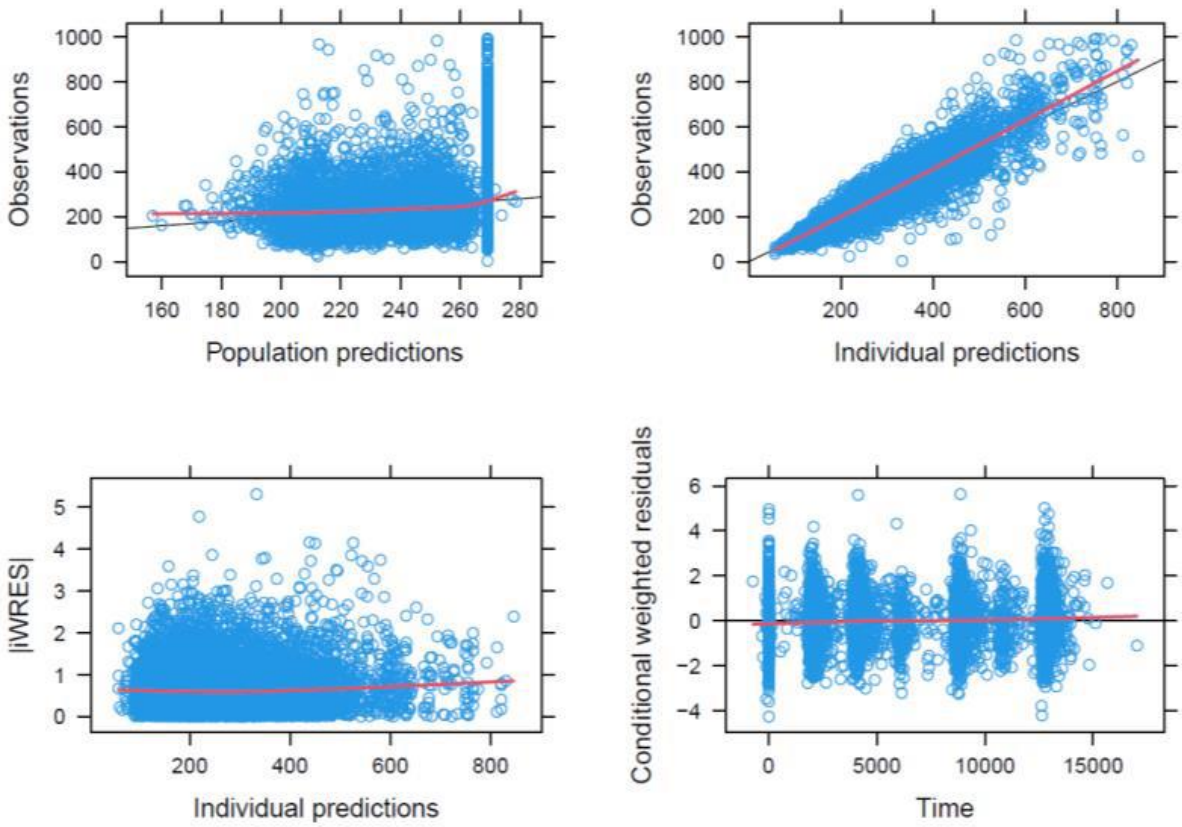
*CI = confidence interval; CV = coefficient of variation; GFAP = glial fibrillary acidic protein; Kin = formation rate.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 62 of 245*

Key diagnostic plots are presented in **Figure 31** and **Figure 32**.

[2] Pereira JB, Janelidze S, Smith R, et al. Plasma GFAP is an early marker of amyloid-β but not tau pathology in Alzheimer's disease. Brain. 2021;144(11),3505-3516.

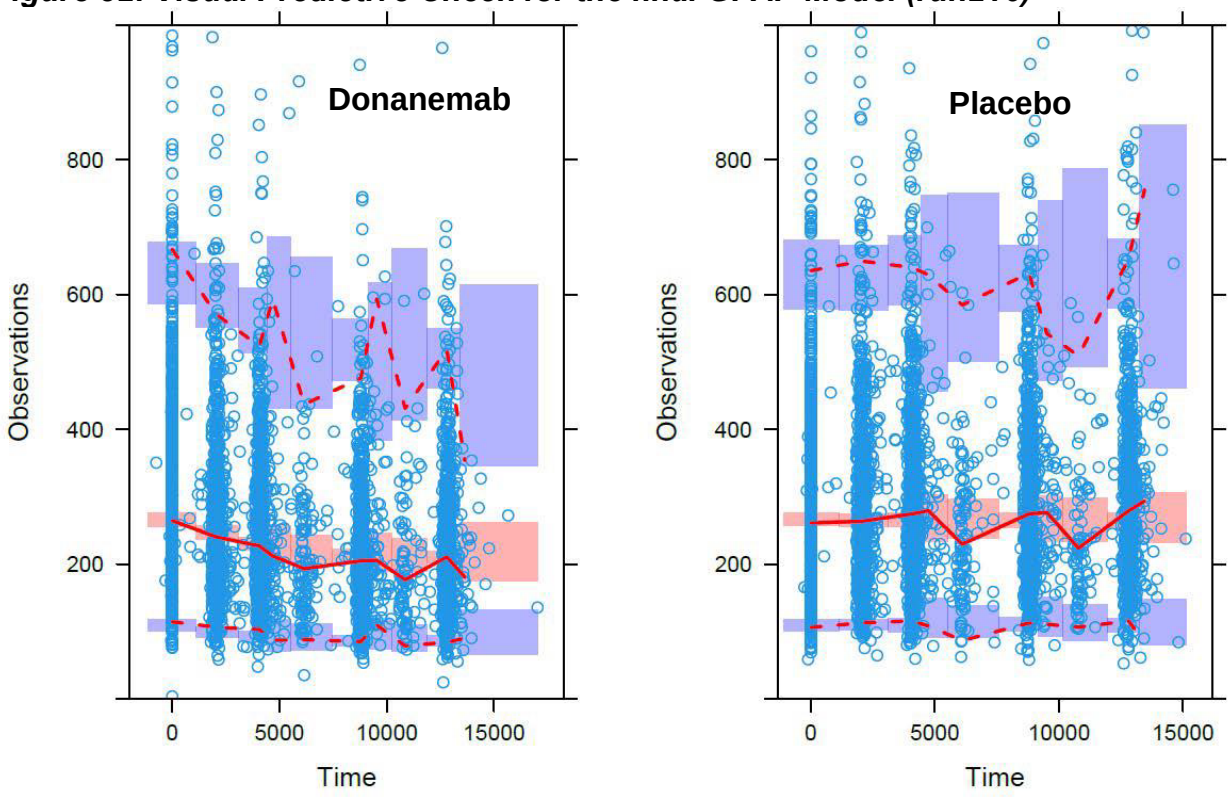
***Figure 31: Diagnostic plots for the final GFAP Model (run216)***




*GFAP = glial fibrillary acidic protein; iWRES = individual weighted residuals.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 245 of 245*

***Figure 32: Visual Predictive Check for the final GFAP Model (run216)***




*GFAP = glial fibrillary acidic protein. The points are the observed plasma glial fibrillary acidic protein concentration in pg/mL plotted across time from the first dose in hours. The lines are the 5th, 50th, and 95th percentiles of the observed data. The shaded areas are the model-predicted 95% confidence interval of the corresponding percentiles. The left panel is donanemab treatment and the right panel is placebo.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 63 of 245*

Applicant applied the model to simulate the GFAP concentration time profile in treatment versus placebo subjects (see **Figure 7** in section "3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?").

The Applicant concludes the following:

- Donanemab treatment was found to reduce the rate of formation of plasma GFAP.
- Reduction in amyloid load (a relative change from baseline) was associated with decrease in the rate of GFAP formation.

[*Reviewer comment: The approach to use amyloid as the predictor for GFAP is reasonable. The model adequately describes the GFAP data. The modeling results indicate an effect of donanemab on reducing GFAP.*]

### *4.4.5 Disease Progression*

Separate disease progression models for iADRS as well as CDR-SB. The approach was identical for both models. The CDR-SB model was coded to constraining predictions within the 0 to 18 range and within 0 to 144 for iADRS. Richard's logistic regression was selected for the disease progression model to ensure constrained predictions within the acceptable range as well as accounting for possible non-linear disease progression and heteroscedasity of the residual error. Beta regression was used to account for decreasing variance in residual error as data approach the boundary values.

The Applicant assessed drug exposure using maximum effect models as well as threshold models as a single dose level was studied. The effect of amyloid PET values (express as absolute change from baseline or relative change from baseline) was assessed as a predictor of disease progression rate.

Covariate effects were assessed on baseline measure value, disease progression rate, and drug effect. Variables screen as covariate were APOE ε4 genotype, baseline tau PET SUVR, baseline amyloid PET, age of the study participant, time since onset of symptoms of AD, time since diagnosis of AD, baseline MMSE, TE ADA, ADA titer, sex, and body weight. The Applicant assessed linear, power, and expontial forms of covariate relationships. Covariate selection was based on OFV reduction, clinical relevance, magnitude of effect, and precision of the estimates.

For both the iADRS and CDR-SB models, the treatment effect is active at any time when the concentration in the central compartment is greater than an estimated threshold concentration. Otherwise, the treatment effect is inactive when concentrations are below the threshold. PK values were obtained using the individual estimates from the population PK model and observed dosing history for each subject. The parameter estimates for the final disease progression models for CDR-SB as well as iADRS are presented in Table 14.

[*Reviewer comment: The Applicant states that a concentration effect-relationship could not be identified for either iADRS or CDR-SB models as only one dose regimen was assessed in studies AACG and AACI. For this reason, the Applicant implemented the concentration threshold approach.*]

***Table 14: Parameter Estimates for the Final Disease Progression Models for iADRS (run102) and CDR-SB (run101) – Treatment Effect***

| | iADRS | | CDR-SB | |
|---|---|---|---|---|
| **Parameter** | **Estimate (%SEE)** | **Bootstrap (95% CI)** | **Estimate (%SEE)** | **Bootstrap (95% CI)** |
| Baseline score [a] | -1.06[b] (1.85) | (-1.09, -1.02) | -1.39[b] (1.87) | (-1.43, -1.34) |
| Disease progression rate ($week^{-1}$) [c] | -5.20 (0.396) | (-5.33, -5.07) | -4.71 (0.465) | (-4.85, -4.58) |
| Shape factor | 1 (Fixed) | — | 1 (Fixed) | — |
| Residual error[d] | 111 (0.796) | (105, 119) | 43.0 (0.558) | (38.3, 47.2) |
| Reduction in disease progression (%) | 45.9 (6.73) | (0.310, 0.588) | 44.9 (5.77) | (0.349, 0.549) |
| Effect of baseline ADDIG on baseline score | 0.0456[a] (12.9) | (0.0325, 0.0590) | 0.0705[b] (13.6) | (0.0537, 0.0879) |
| Effect of age on baseline score | 0.0190[a] (10.4) | (0.0147, 0.0222) | 0.0217[b] (14.1) | (0.0164, 0.0270) |
| Effect of categorical baseline MMSE on baseline score | -0.453[a] (7.86) | (-0.502, -0.406) | -0.559[b] (8.19) | (-0.657, -0.456) |
| Effect of gender on baseline score | 0.0933 (23.2) | (0.0451, 0.137) | — | — |
| Effect of very low tau group on baseline score | -0.183[a] (20.0) | (-0.245, -0.132) | -0.261[b] (18.9) | (-0.365, -0.153) |
| Effect of high tau group on baseline score | 0.240[a] (12.9) | (0.182, 0.293) | 0.306[b] (16.6) | (0.230, 0.374) |
| Effect of very low tau group on treatment effect[e] | — | — | -0.283 (73.9) | (-0.910, 0.503) |
| Effect of high tau group on treatment effect[e] | -0.702 (6.54) | (-0.939, -0.370) | -0.597 (9.35) | (-0.935, -0.192) |
| Effect of age on disease progression[f] | 0.0157 (8.54) | (0.00797, 0.0251) | 0.0101 (16.1) | (0.00126, 0.0212) |
| APOE ε4 effect on disease progression[f] | -0.131 (10.7) | (-0.231, -0.00935) | -0.114 (14.0) | (-0.236, 0.0226) |
| Effect of categorical baseline MMSE on disease progression[f] | -0.341 (9.62) | (-0.471, -0.215) | -0.243 (14.2) | (-0.376, -0.101) |
| Effect of very low tau group on disease progression[f] | -0.300 (13.7) | (-0.464, -0.117) | -0.245 (18.2) | (-0.398, -0.0695) |
| Effect of high tau group on disease progression[f] | 0.877 (4.71) | (0.659, 1.12) | 0.596 (6.59) | (0.384, 0.953) |
| Threshold concentration | 3540 (69.2) | (324, 13300) | 200[g] (Fixed) | — |
| Population variability in the baseline score (%CV) | 46.2 (3.14) | (44.7, 47.6) | 69.4 (2.52) | (65.9, 73.5) |

*AADIAG = time from diagnosis of Alzheimer's disease; CI = confidence interval; CV = coefficient of variance; MCI = mild cognitive impairment; SEE = standard error of the estimate; Tau groups defined as: <1.10 (low tau, 'no tau' in specifications); ≤1.10 to <1.46 (groups low and medium tau from specifications); ≥1.46 (high tau, 'high tau' in specifications).*

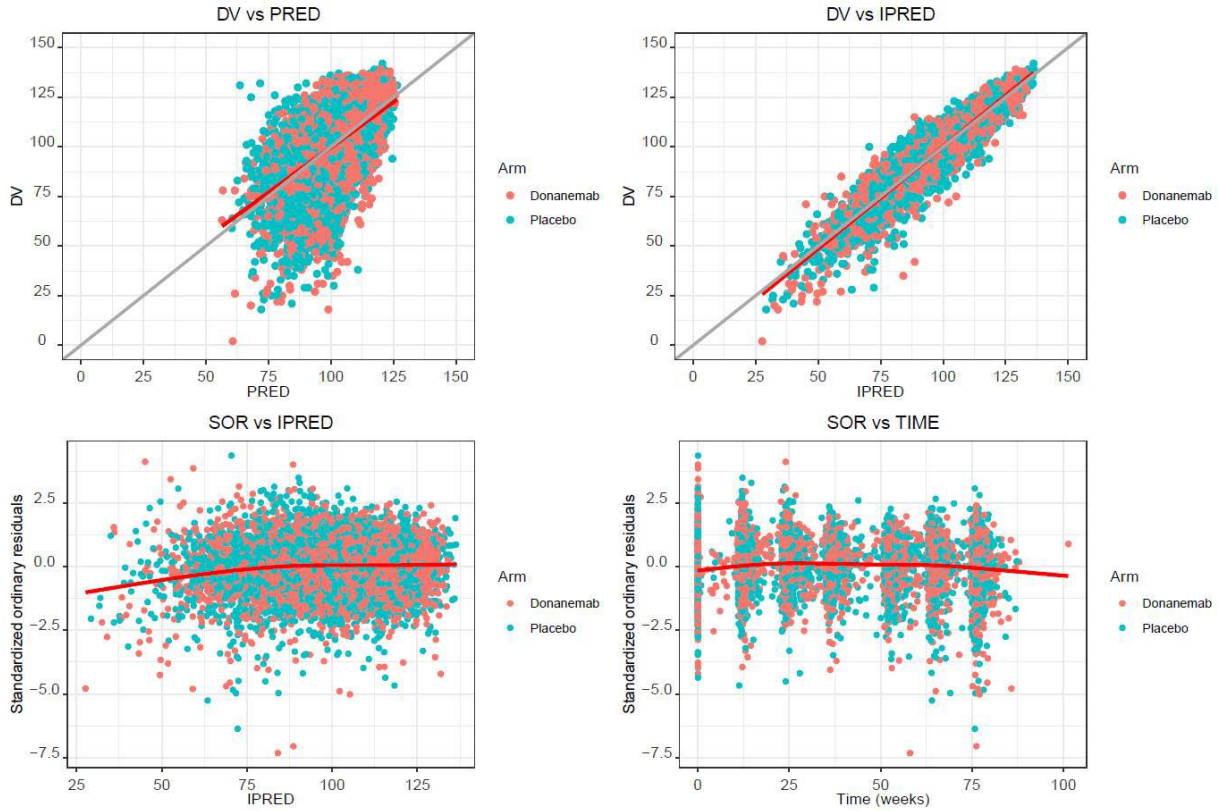
*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 66-67 of 245*

The diagnostic plots and modeling conclusions for each model can be found in the next sections.

### *4.4.5.1 iADRS Modeling*

The Key diagnostic plots for iADRS disease progression model are shown in Figure 33 and **Figure 34**.

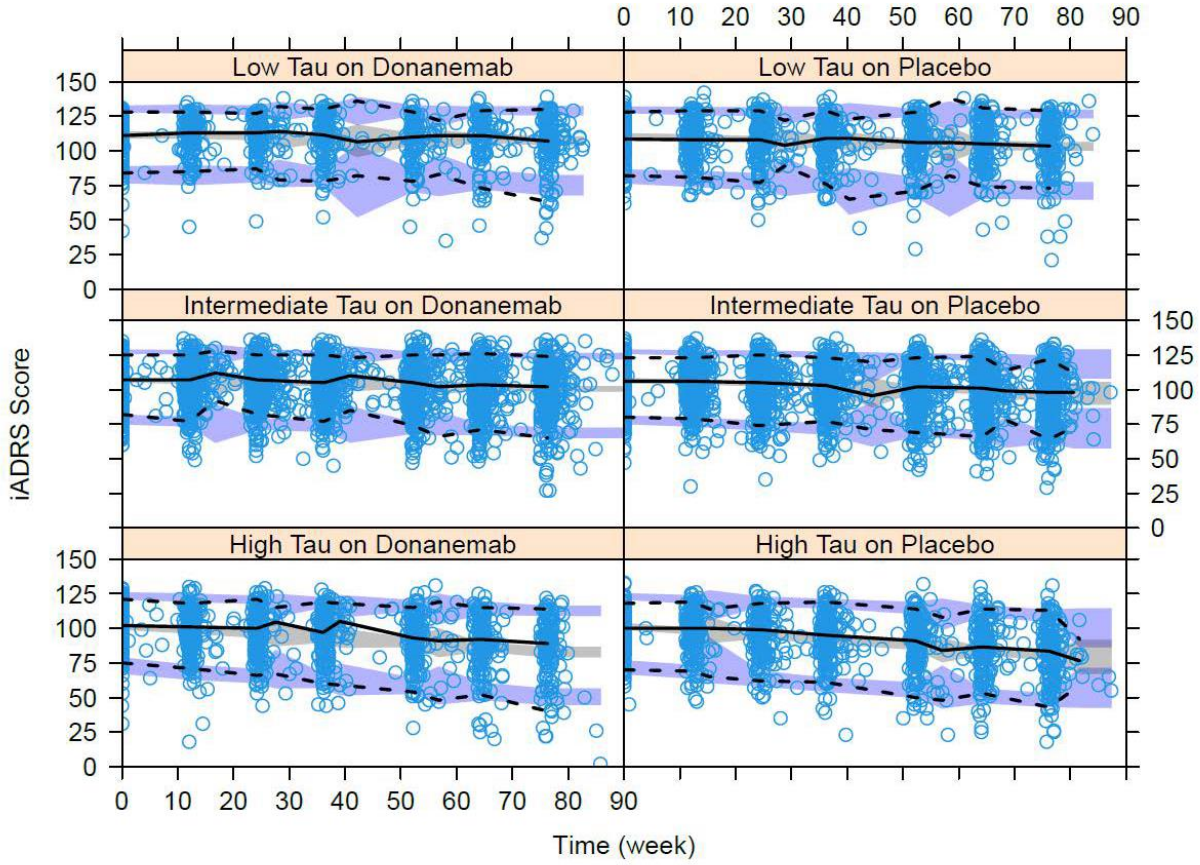
*Figure 33: Diagnostic plots for the final iADRS Model (run102) – Treatment Effect*




*DV = dependent variable; iADRS = integrated Alzheimer's disease rating scale; IPRED = individually predicted value; LOWESS = locally weighted scatterplot smoothing; PRED = population predicted values; SOR = standardized ordinary residuals. LOWESS fit, a smoothed value given by a weighted linear least-squares regression over the span of observations, for data are presented (black line) in addition to a line of identity (gray line on top panel).*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 68 of 245*

***Figure 34: Visual Predictive Check for the final iADRS Model (run102) – Treatment Effect***




*AD = Alzheimer's disease; iADRS = integrated Alzheimer's disease rating scale; SUVR = standardized uptake value ratio. Very Low Tau: <1.10 SUVR Intermediate label = low/medium Tau: SUVR <1.10, with a topographic deposition pattern consistent with advanced AD (AD++), or ≤1.10 SUVR ≤1.46, with a topographic deposition pattern consistent with moderate AD (AD+). High Tau: SUVR >1.46, with a topographic deposition pattern consistent with either moderate (AD+) or advanced AD (AD++). The points are the observed data. The lines are the 5th, 50th, and 95th percentiles of the observed data. The shaded areas are the model-predicted 95% confidence interval of the corresponding percentiles.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 69 of 245*

In addition to the treatment effect model, the Applciant developed an alternate disease progression model where amyloid beta was used as a predictor of iADRS disease progression. The alternate model is discussed in detail in section 4.4.5.4 Use of Biomarkers as Predictors of Disease Progression. Conclusions can be found in section 4.4.5.5 Conclusions.

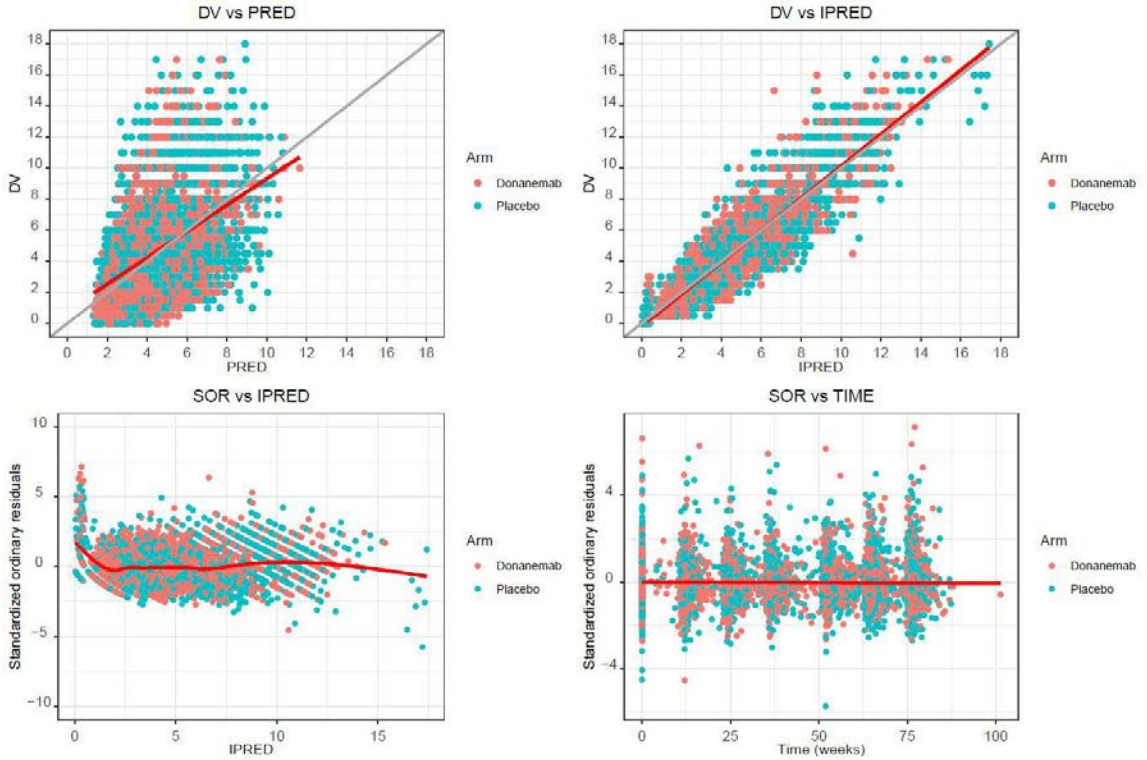
[*Reviewer comment: The eta shrinkage for between subject variability in baseline iADRS is 2.5%. Epsilon shrinkage is not applicable as this model does not include residual variability.*

*The diagnostic plots (Figure 33) do not suggest the presence of systemtic bias with respect to time or magntidue of prediction. The visual predictive check (Figure 34) suggests that the model describes the data well for treatment and placebo at low, intermediate, and high tau levels. Overall, the Applicant's disease progression model for iADRS using a treatment effect is acceptable.*]

#### *4.4.5.2 CDR-SB Modeling*

The Key diagnostic plots for CDR-SB disease progression model are shown in **Figure 35** and **Figure 36**.

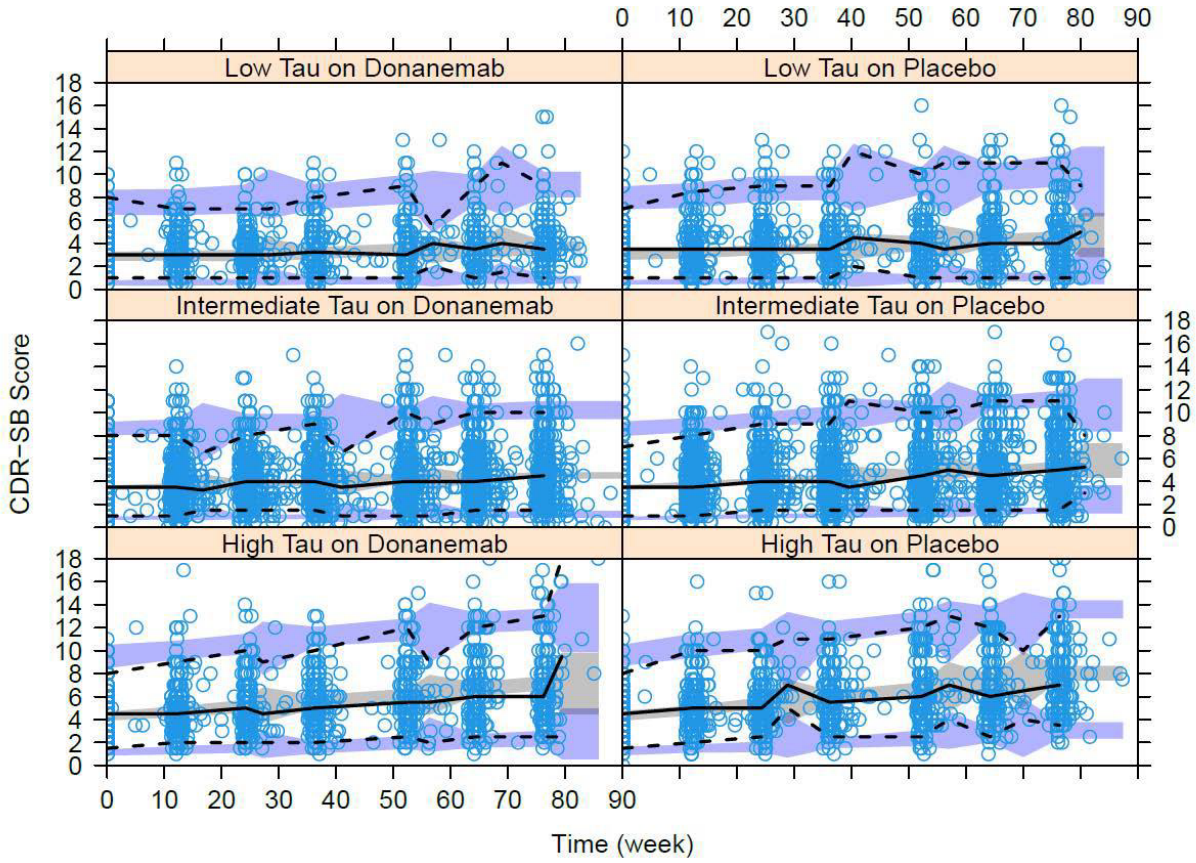
***Figure 35: Diagnostic plots for the final CDR-SB Model (run101) – Treatment Effect***




*CDR-SB = clinical dementia rating-sum of boxes; DV = dependent variable; IPRED = individually predicted value; LOWESS = locally weighted scatterplot smoothing; PRED = population predicted values; SOR = standardized ordinary residuals. LOWESS fit, a smoothed value given by a weighted linear least-squares regression over the span of observations, for data are presented (black line) in addition to a line of identity (gray line on top panel). Four participants with inconsistent observations were removed from these plots. For completeness, their observations are included in appendix plots.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 70 of 245*

***Figure 36: Visual Predictive Check for the final CDR-SB Model (run101) – Treatment Effect***




*AD = Alzheimer's disease; CDR-SB = clinical dementia rating-sum of boxes; SUVR = standardized uptake value ratio. Very Low Tau: <1.10 SUVR Intermediate = low/medium Tau: SUVR <1.10, with a topographic deposition pattern consistent with advanced AD (AD++), or ≤1.10 SUVR ≤1.46, with a topographic deposition pattern consistent with moderate AD (AD+). High Tau: SUVR >1.46, with a topographic deposition pattern consistent with either moderate (AD+) or advanced AD (AD++). The points are the observed data. The lines are the 5th, 50th, and 95th percentiles of the observed data. The shaded areas are the model-predicted 95% confidence interval of the corresponding percentiles.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 71 of 245*

In addition to the treatment effect model, the Applicant developed an alternate disease progression model where amyloid beta was used as a predictor of CDR-SB disease progression rate. The alternate model is discussed in detail in section "4.4.5.4 Use of Biomarkers as Predictors of Disease Progression". Conclusions can be found in section 4.4.5.5 Conclusions.

.

[*Reviewer comment: The eta shrinkage for between subject variability in baseline CDR-SB is 3.1%. Epsilon shrinkage is not applicable as this model does not include residual variability.*

*The goodness of fit plots (Figure 35) do not show any signs of bias with respect to time nor measurement magnitude. The visual predictive check (Figure 36) indicates that the model describes the CDR-SB data well for treatment and placebo groups at low, intermediate, and high tau levels.*

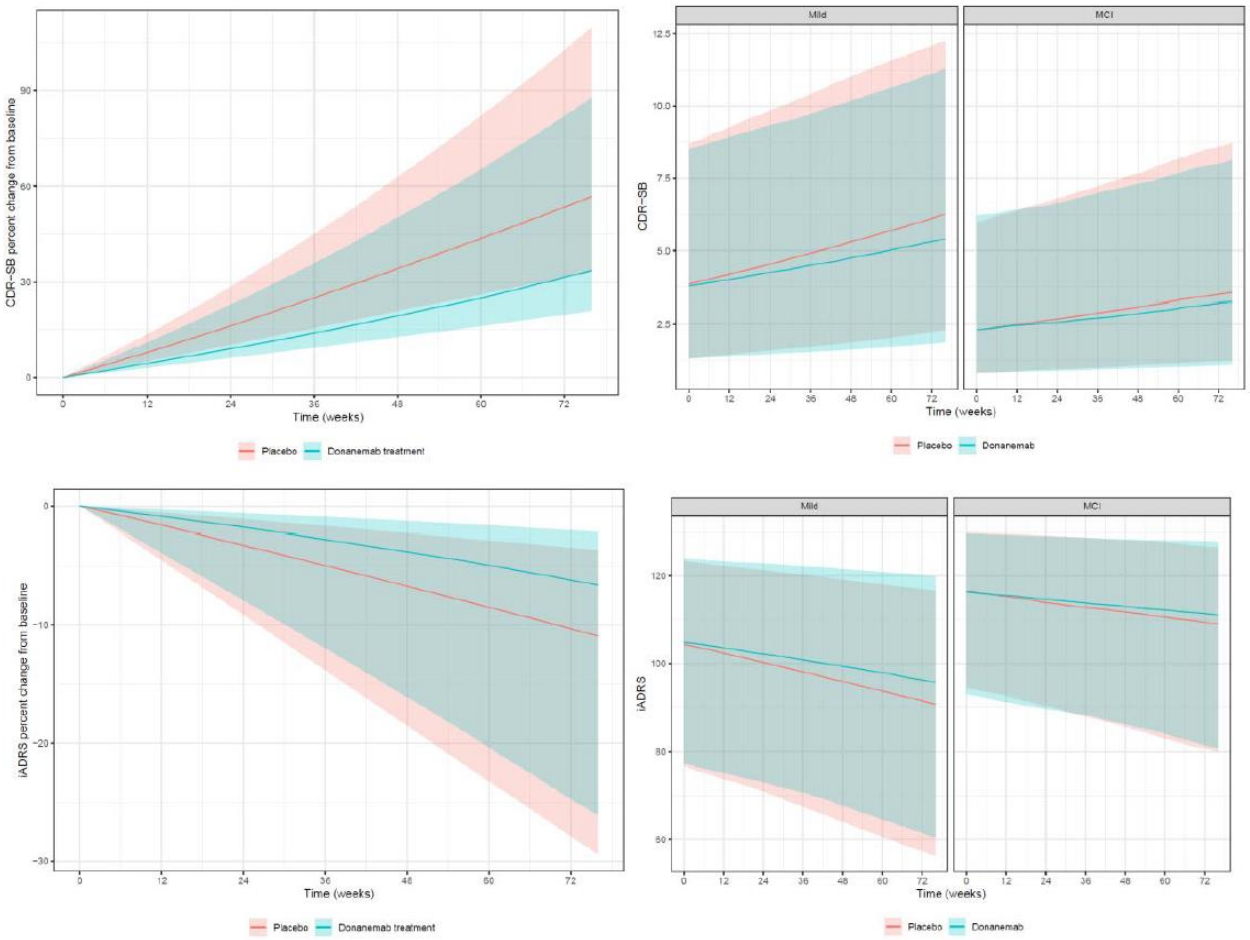
*Overall, the treatment effect disease progression model for CDR-SB is acceptable.*]

#### *4.4.5.3 Simulations*

The Applicant conducted 6000 simulations of the available population using the disease progression model. Simulations assessed the effect of baseline disease state (mild cognitive impairment [a.k.a. MCI] versus mild dementia due to Alzheimer's disease [a.k.a. mild]), tau (low/medium tau versus combined population), and the effect of ceasing donanemab treatment when amyloid plaque levels decrease below 24.1 Centiloids. The Combined Population is subjects with low/medium tau combined with subjects with high tau. The simulations for iADRS and CDR-SB are presented side-by-side.

**Figure 37** shows the predicted donamemab treatment effect in subjects with mild dementia due to Alzheimer's disease versus mild cognitive impairment in the combined population.

***Figure 37: Simulated CDR-SB (top panel) and iADRS (bottom panel) score for participants with MCI and participants with mild dementia due to AD in the combined population For 72 Weeks***



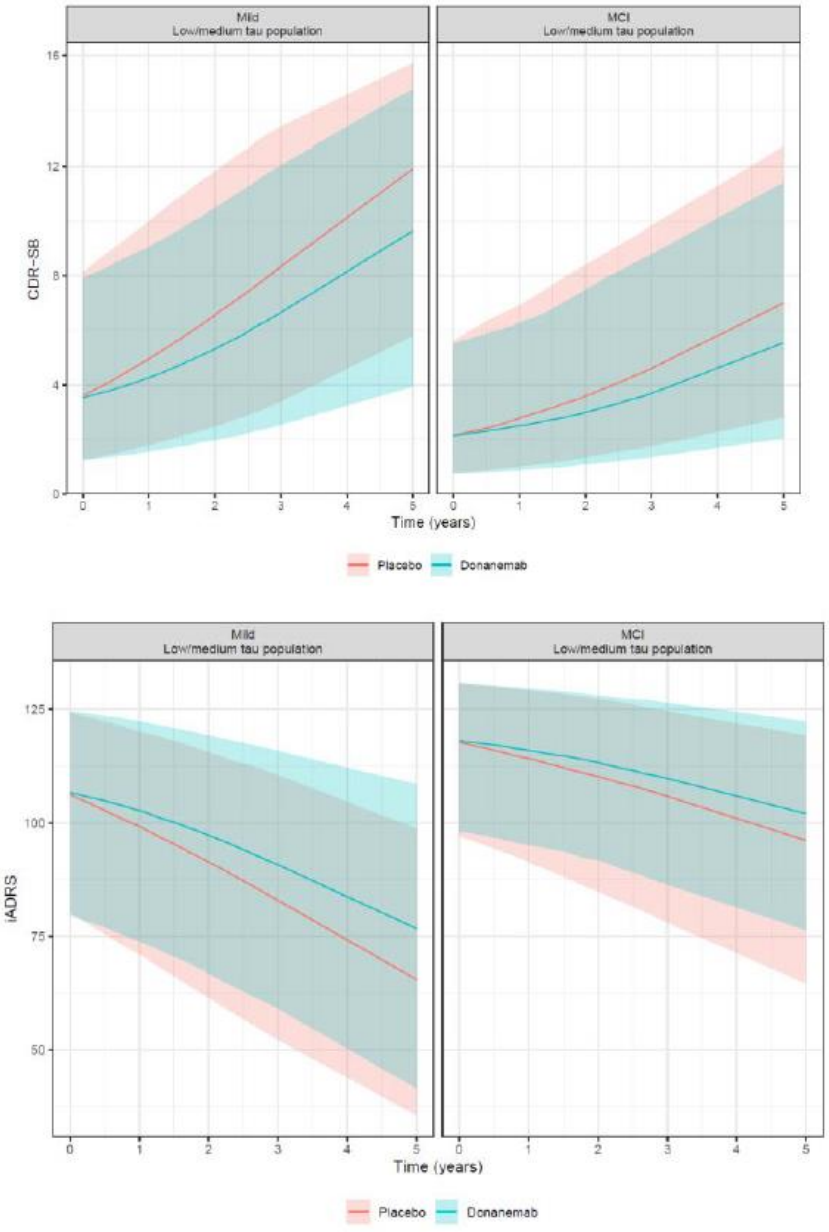

*AD = Alzheimer's disease; CDR-SB = clinical dementia rating-sum of boxes; iADRS = integrated Alzheimer's disease rating scale; MCI = mild cognitive impairment; Mild = mild dementia due to Alzheimer's disease; Patients were simulated to follow dosing treatment regimen, including the potential for down-titration based on Centiloids at Weeks 24 and 52. Median (95% prediction interval) is shown by solid line and shaded areas.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 94 of 245*

**Figure 2** in section “3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?” shows the predicted donamemab treatment effect in subjects with mild dementia due to Alzheimer’s disease versus mild cognitive impairment for the low/medium tau population over a 72 week duration.

**Figure 38** shows the predicted donamemab treatment effect in subjects with mild dementia due to Alzheimer’s disease versus mild cognitive impairment for the low/medium tau population over a 5-year duration.

***Figure 38: Simulated CDR-SB (top panel) and iADRS (bottom panel) score for participants with MCI and participants with mild dementia due to AD in the <u>low/medium tau</u> population For <u>5 Years</u>***




*AD = Alzheimer's disease; CDR-SB = clinical dementia rating-sum of boxes; iADRS = integrated Alzheimer's disease rating scale; MCI = mild cognitive impairment; Mild = mild dementia due to Alzheimer's disease; Simulation extended to 5 years to demonstrate that the effect of relative disease slowing following donanemab treatment, increases over time. Patients were simulated to follow dosing treatment regimen, including the potential for down-titration based on Centiloids at Weeks 24 and 52. Median (90% prediction interval) is shown by solid line and shaded areas.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 96 of 245*

**Figure 3** in section “3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?” shows simulated CDR-SB by treatment duration for participants with MCI and participants with mild dementia due to AD in the combined population over 72 weeks.

[*Reviewer comment: The simulations in **Figure 3** do not suggest a clear relationship between timing of dose reduction (reduction at 24 weeks, reduction at 52 weeks, or no dose reduction up to week 76) and CDR-SB through 76 weeks of treatment.* ]

Conclusions can be found in section 4.4.5.5 Conclusions.

#### *4.4.5.4 Use of Biomarkers as Predictors of Disease Progression*

Alternate forms of the disease progression models for iADRS and CDR-SB were developed. The alternate form used amyloid beta values as the predictor instead of a treatment effect. The amyloid value was assessed as an absolute change from baseline as well as a relative change from baseline. Similar to the threshold concentration estimated in the treatment effect model, this alternate model employed an estimate of a threshold amyloid plaque reduction for activation of a reduction in disease progression rate. The amyloid levels used in this model were predicted using the amyloid plaque reduction model (see section 4.4.1 Amyloid-Plaque Reduction for details). A comparison of the model parameterized with a treatment effect versus the model parameterized with amyloid as a predictor is provided in ***Table 15***.

***Table 15: Changes in Objective Function When Using Treatment Effect versus Amyloid To Predict Disease Progression for iADRS or CDR-SB***

| | ΔOFV for Treatment Effect | ΔOFV for Amyloid as Predictor |
|---|---|---|
| iADRS[a] | -115 | -74.7 |
| CDR-SB[b] | -126 | -108 |

*CDR-SB = clinical dementia rating-sum of boxes; iADRS = integrated Alzheimer's disease rating scale; OFV = objective function value. A) Three degrees of freedom relative to the final model; treatment/amyloid effect and any related covariate effect were removed. B) Four degrees of freedom relative to the final model; treatment/amyloid effect and any related covariate effect were removed.*

*Source: sequence 0104, module 5335, ly3002813-population-pk-pd-report_us_sub2-donan.pdf, page 64 of 245*

The Applicant concludes that the greater reduction in objective function value using the treatment effect versus amyloid as a predictor suggests that the treatment effect has a better correlation with iADRS and CDR-SB than amyloid PET alone in the current dataset.

[*Reviewer comment: These findings are consistent with a positive relationship between amyloid plaque reduction and improvement in iADRS or improvement in CDR-SB.*]

#### *4.4.5.5 Conclusions*

The Applicant provides the following conclusions regarding disease progression modeling for iADRS and CDR-SB:

- There was an observed effect in both low/medium (intermediate) tau and combined (low/medium tau and high tau) populations.
- Disease progression rate estimated using exposure-amyloid plaque-scores model on iADRS was reduced by 33.2%, while progression as measured by CDR-SB was reduced by 36.3% in the low/medium tau population. In the combined population, disease progression rate on iADRS score was reduced by 29.3% (p<.001), while progression as measured by CDR-SB was reduced by 31.7% (p<.001).
- TE ADA and ADA titer was tested on the treatment effect term of the model and was not found to be statistically significant for iADRS or CDR-SB.
- Limitations of disease progression analysis were that the model was built only on data that explored a single dosing regimen with a relatively narrow range of exposures.

[*Reviewer comment: The Applicant's exposure-response analyses support a treatment effect of donanemab on reducing disease progression rate in terms of iADRS as well as CDR-SB. Benefit is shown in the low/tau group as well as the combined tau group.*]

## 4.5 DTPM Review

**OFFICE OF CLINICAL PHARMACOLOGY**

**DIVISION OF TRANSLATIONAL AND PRECISION MEDICINE REVIEW**

| | |
|---|---|
| **NDA/BLA Number** | 761248 |
| **Submission Date** | 6/12/2023 |
| **Applicant Name** | Eli Lilly Inc |
| **Generic Name** | Donanemab |
| **Proposed Indication** | Treatment of Alzheimer's Disease |
| **Primary Reviewer** | Hobart Rogers, Pharm.D., Ph.D. |
| **Secondary Reviewer** | Jeff Kraft, Ph.D. |

### Executive summary

Donanemab is an intravenously-infused monoclonal antibody directed against insoluble N-truncated pyroglutamate amyloid beta in the brain. The applicant has submitted the BLA for approval, primarily relying on a 76-week, placebo-controlled study in 1727 patients with early Alzheimer's disease treated with either donanemab or placebo. Overall, donanemab met the primary endpoint of change in iADRs from baseline at week 76 in the low/medium tau population compared to placebo ($p < 0.001$). Treatment with donanemab resulted in increases in both ARIA-E, and ARIA-H. There was an increased risk of ARIA-E and ARIA-H based on the number of APOE ε4 alleles, with the risk being highest in the homozygous group.

The purpose of this review is to evaluate the Applicant's submission to determine if *APOE ε4* genotype is associated with the safety or efficacy of donanemab. The findings of this review indicate that *APOE ε4* genotype is associated with both the safety and efficacy of donanemab. Specifically, the *APOE4 ε4* allele increased the risk of both ARIA-E and ARIA-H in an allele-dose dependent manner. Moreover, data from the confirmatory study (AACI) indicates that there is diminished pharmacodynamic response, and a slight trend toward lower responses on clinical endpoints following treatment with donanemab in *APOE* ε4 homozygous patients. In summary, our findings support that there are

differences in both the safety and efficacy of donanemab for *APOE ε4* homozygous patients.

## 1 Background

The Applicant (Eli Lilly Inc.) submitted a BLA for donanemab in the treatment of Alzheimer's Disease. Donanemab is a novel monoclonal antibody designed to bind to and remove insoluble N-truncated pyroglutamate amyloid beta. Study AACI serves as the confirmatory trial to verify the clinical benefit of donanemab.

The confirmatory study (AACI) met the primary endpoint of integrated Alzheimer's Disease Rating Scale (iADRS) at week 76 ($p<0.001$). In addition, it met the secondary endpoints of Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), Alzheimer's Disease Assessment Scale – Cognitive subscale with 13 tasks (ADAS-$Cog_{13}$), and Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living (ADCS-iADL), and Clinical Dementia Rating Scale – Global Score (CDR-G).

Donanemab was relatively well tolerated, however serious adverse events were noted in both amyloid related imagining abnormalities- edema/effusion (ARIA-E) and ARIA-hemorrhage (ARIA-H). Approximately 70% of the AACI participants were APOE ε4 carriers. APOE ε4 carrier status influenced the frequency of any ARIA. The incidence of both ARIA-E and ARIA-H was higher in the homozygous APOE ε4 population. The frequency of ARIA-E was highest in homozygous carriers (41.1%), followed by heterozygote carriers (23.8%), and noncarriers (14.8%). Similar results were observed for ARIA-H, with the highest frequency in homozygous carriers (53.6%), followed by heterozygote carriers (30.8%), and noncarriers (18.9%).

The proposed dosage of donanemab is 700 mg administered as an intravenous infusion over approximately 30 minutes every four weeks for the first three doses, followed by 1400 mg every four weeks for additional doses.

In the US, there is one other product (lecanemab) under full approval and one product (aducanumab) approved under the accelerated approval pathway for the treatment of AD based on a reduction in amyloid beta plaques.

The purpose of this review is to evaluate the association between *APOE ε4* genotype and the safety and efficacy of donanemab.

## 2 Submission Contents Related to Genomics

APOE genotyping was a mandatory part of the clinical program. Investigators were blinded to the results and the sample was assayed by a Lilly-designated laboratory. In trial AACI, the APOE genotype sample was able to be collected at an alternative visit if

not collected at baseline. A whole blood sample was also collected for pharmacogenetic analysis, as specified in the Schedule of Assessments where local regulations allowed.

Trial AACI enrolled 1736 trial participants, of which 289 subjects were identified as homozygous *APOE ε4* carriers, 930 subjects were heterozygous *APOE ε4* carriers, and 510 subjects were *APOE ε4* noncarriers.

Primary and secondary efficacy endpoints as well as safety outcomse were evaluated in *APOE* genotype subgroups.

The Applicant proposed the following language related to *APOE* genotype in their draft labeling:



## 3 Key Question and Summary of Findings

### 3.1 Does efficacy and safety of donanemab differ based on *APOE ε4* genotype?

Yes, *APOE ε4* genotype does appear to impact both the safety and efficacy of donanemab. *APOE* ε4 carriers have a higher risk for both ARIA-E and H, with the risk being highest in *APOE ε4* homozygotes. In addition, *APOE ε4* homozygotes appear to have a diminished response to donanemab compared to *APOE ε4* carriers and noncarriers, which is supported by diminished pharmacodynamic responses (biomarkers) in *APOE ε4 carriers.*

### 3.1.1 *APOE ε4* Genotype and Safety

***Applicant's Analysis***

**ARIA-E and ARIA-H**

For serious or symptomatic ARIA-E, *APOE ε4* genotype was identified as a risk factor, where homozygous and heterozygous carriers have higher risk relative to noncarriers. Given the lower frequency of symptomatic or serious ARIA observed, compared with any ARIA, further covariate and risk factor analyses for symptomatic or serious ARIA are limited.

*APOE ε4* Carrier Status and Risk of ARIA

ARIA-E baseline hazard differed by *APOE ε4* genotype, and by Week 24, it was

- 1.8 times higher in heterozygotes *APOE ε4* compared with noncarriers,
- 3.9 times higher in homozygotes *APOE ε4* compared with noncarriers, and
- 2.1 times higher in homozygotes *APOE ε4* compared with heterozygotes *APOE ε4*

The frequency of ARIA-E (based on MRI and TEAE cluster) was the highest in donanemab-treated homozygote *APOE ε4* carriers.

- homozygote *APOE ε4* carriers (placebo, 3.4%; donanemab, 41.7%)
- heterozygote *APOE ε4* carriers (placebo, 1.9%; donanemab, 24.1%), and
- noncarriers (placebo, 0.7%; donanemab, 14.8%).

The frequency of symptomatic ARIA-E was also the highest in donanemab-treated homozygote *APOE ε4* carriers (placebo, 0.6%; donanemab, 7.7%). The frequency of serious ARIA-E was also the highest in donanemab-treated homozygote *APOE ε4* carriers (placebo, 0%; donanemab, 3.0%).

Exposure-ARIA-E relationship was evaluated in preplanned analyses specified in the PK/PD analysis plan. Findings showed the ARIA-E risk is driven by the baseline hazard, donanemab treatment, *APOE ε4* genotype, average concentration at steady state, number of baseline microhemorrhages, and time components (Population PK/PD report).

Results from a post hoc ARIA risk factor analysis showed *APOE ε4* genotype, baseline microhemorrhages, superficial siderosis-CNS, and white matter disease were associated

with ARIA-E, symptomatic ARIA-E, and ARIA-H. In addition, this post hoc analysis showed that age, baseline weight, and baseline amyloid level were also associated with ARIA risk. However, the magnitude of association with these factors, measured by odds ratio, was smaller compared with baseline MRI abnormality and *APOE ε4* genotype. Baseline tau level was not associated with an increased ARIA risk (Resubmission Safety Update Report, Section 5.5.9.1.4).

Similar results were observed for ARIA-H, with the highest frequency in homozygote carriers (53.6%), followed by heterozygote carriers (30.8%), and noncarriers (18.9%). The frequency of serious ARIA-H was the highest in donanemab-treated homozygous *APOE ε4* carriers (1.2%) compared with none in the placebo-treated participants.

There were no clinically meaningful interactions of non-ARIA-related TEAEs by APOE ε4 carrier status and treatment group on the frequency of common TEAEs (Resubmission Safety Update Report, Sections 5.5.2.5, 5.5.9.1.2.6, and 5.5.9.1.3.5).

***Reviewer's Analysis***

*No additional analyses were conducted regarding APOE ε4 genotype and the risk of both ARIA-E and ARIA-H.*

*The increased risk of both ARIA-E and ARIA-H is also noted in the product labeling (Warnings and Precautions) for the other approved products, lecanemab and aducanumab.*

Please see the Clinical review for complete evaluation of safety findings.

### 3.1.2 *APOE ε4* Genotype and Efficacy:

***Applicant's Analysis***

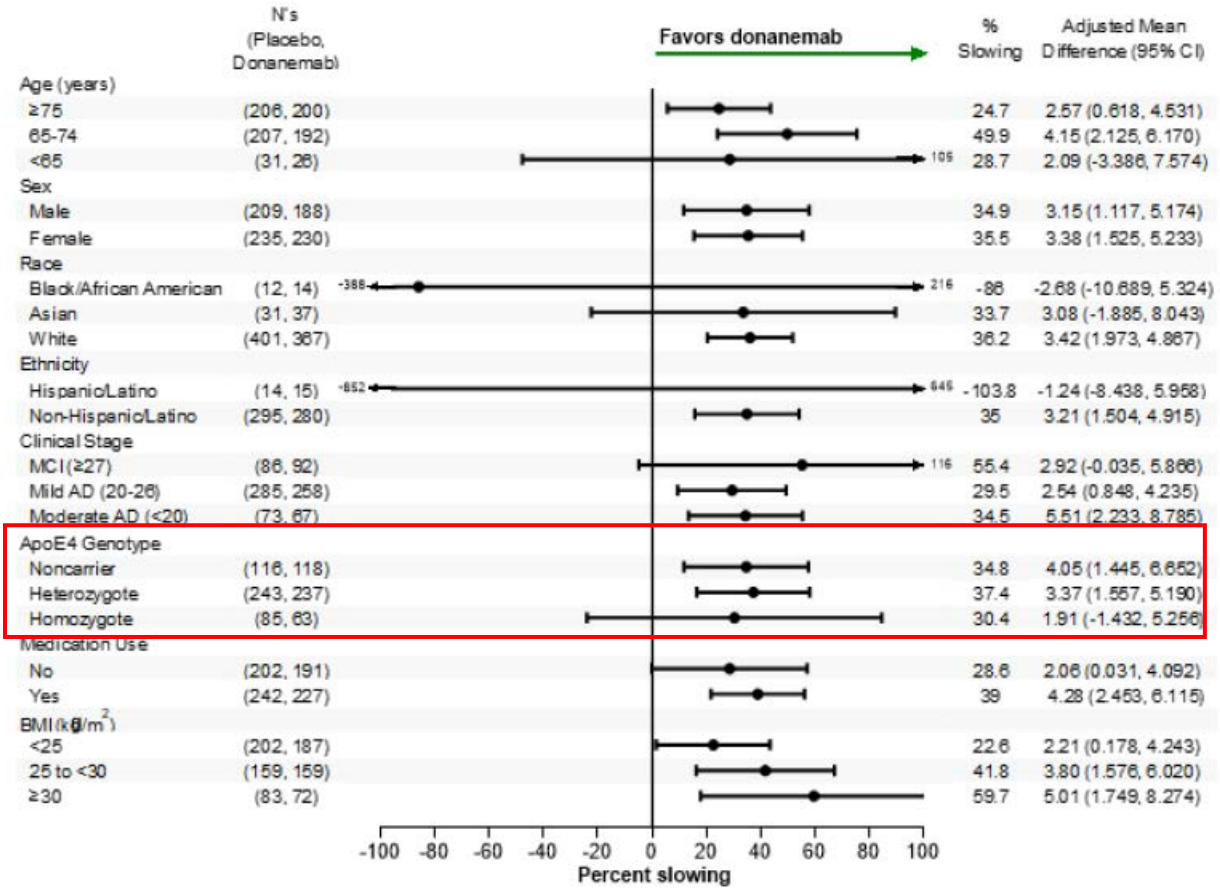
Study AACI met its primary objective, demonstrating a statistically significant slowing of AD clinical decline at 76 weeks, as measured by the iADRS. Positive results for the primary endpoint in the intermediate tau population, overall population, CDR-SB in the intermediate tau population, and CDR-SB in the overall population (**Figure 39** to **Figure 42** below) were also demonstrated across all secondary endpoints measuring cognitive and functional decline, as assessed by the CDR-SB, ADAS-Cog13, and ADCS-iADL.

Study AACI demonstrated that donanemab treatment showed slowing of clinical decline across *APOE ε4* carrier and noncarrier subgroups, as measured across all clinical efficacy scales.

*APOE ε4* carrier status was further categorized into heterozygous carrier (ε2/ε4, ε3/ε4) and homozygous carrier (ε4/ε4). Slowing of clinical decline was observed across heterozygous and homozygous carrier subgroups.

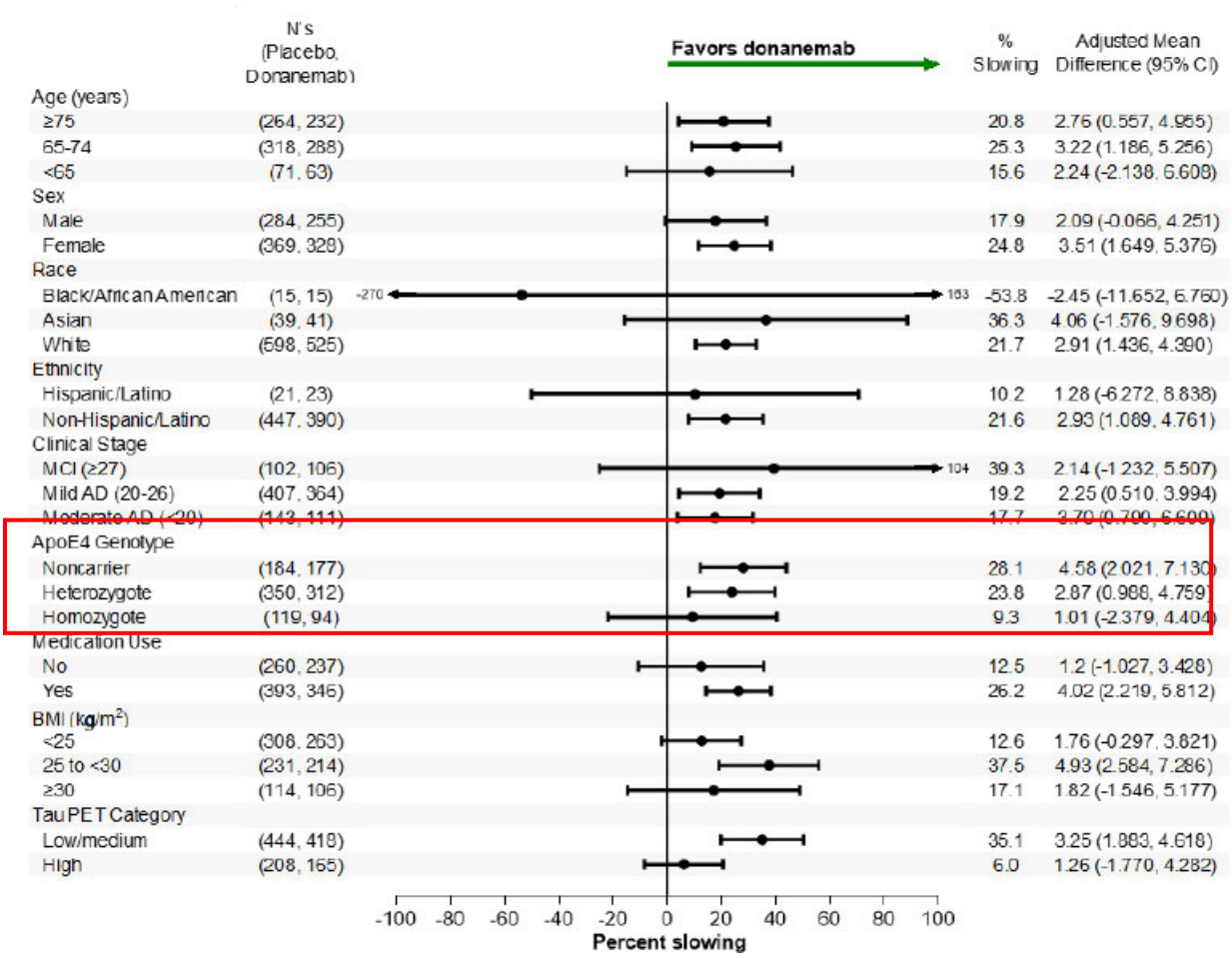
Similar subgroup analyses were performed for the Pooled Subgroup Analysis Set (Studies AACI and AACG) which showed similarly consistent results across *APOE ε4* subgroups.

***Figure 39: iADRS Subgroup analysis by demographic and baseline characteristics, intermediate tau population (AACI-PC period)***



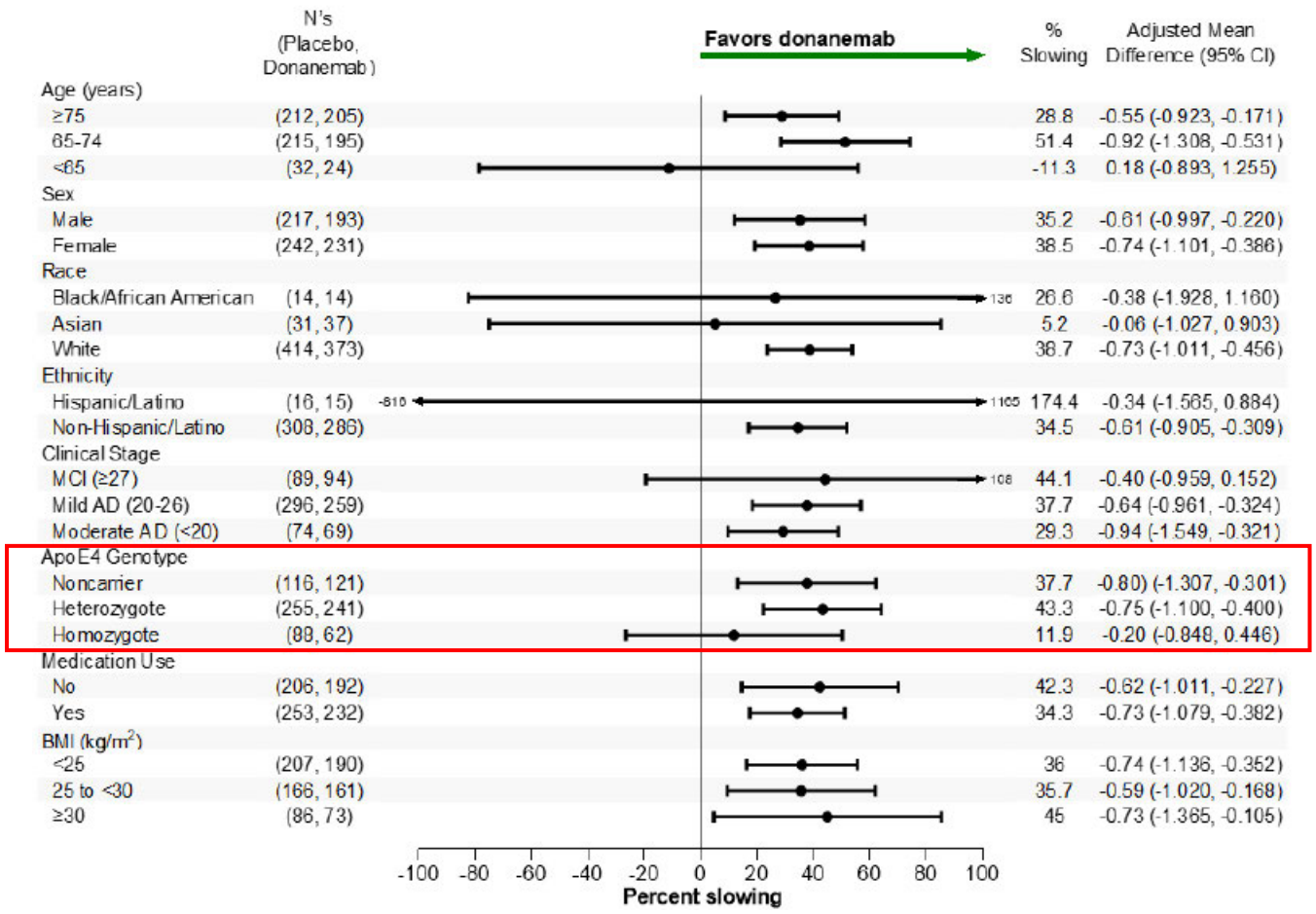

Source: page 176 AACI CSR

***Figure 40: iADRS Subgroup analysis by demographic and baseline characteristics, overall population (AACI-PC period)***



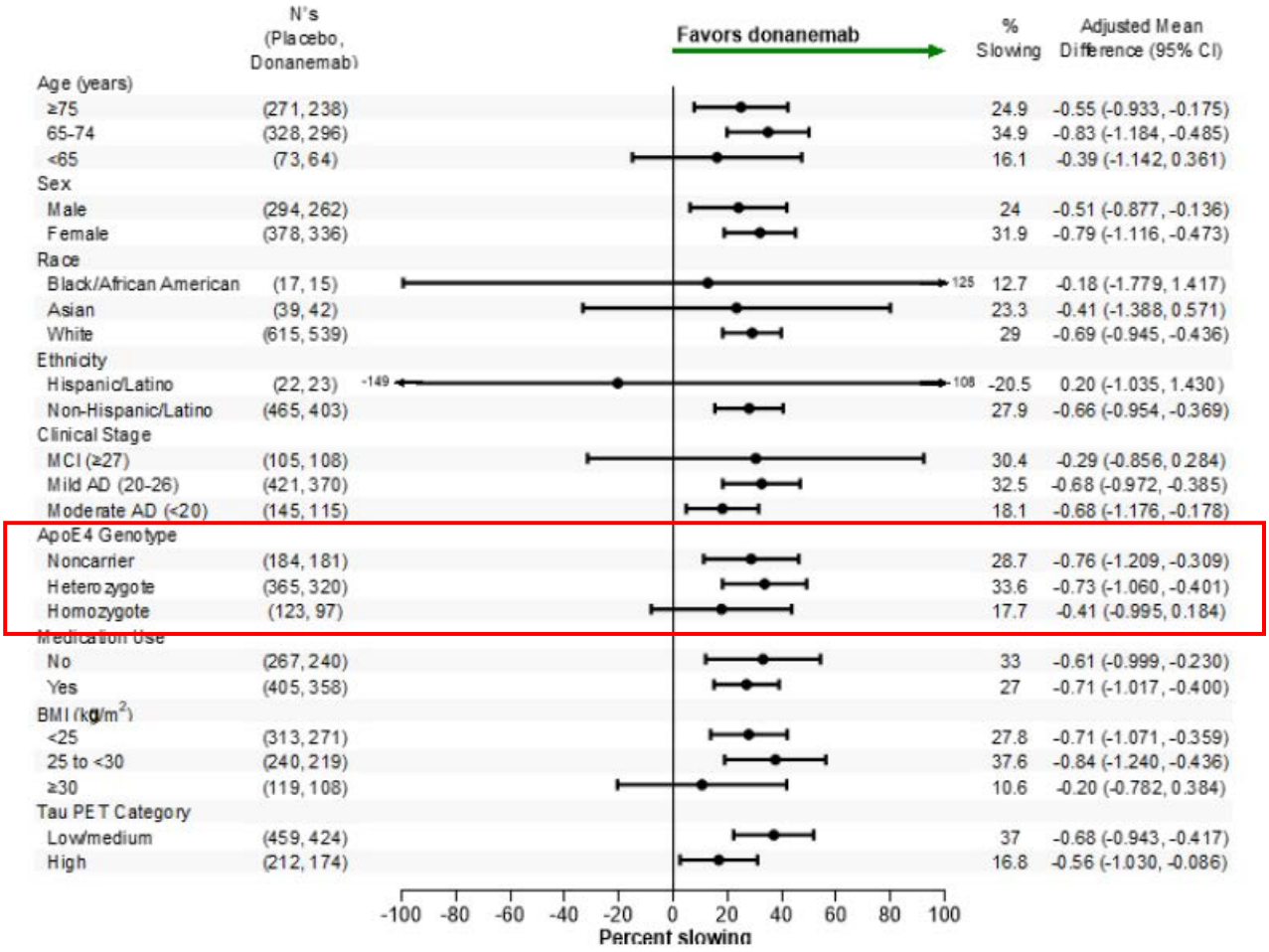

Source: page 177 AACI CSR

***Figure 41: CDR-SB Subgroup analysis by demographic and baseline characteristics, intermediate tau population (AACI-PC period)***




Source: page 178 AACI CSR

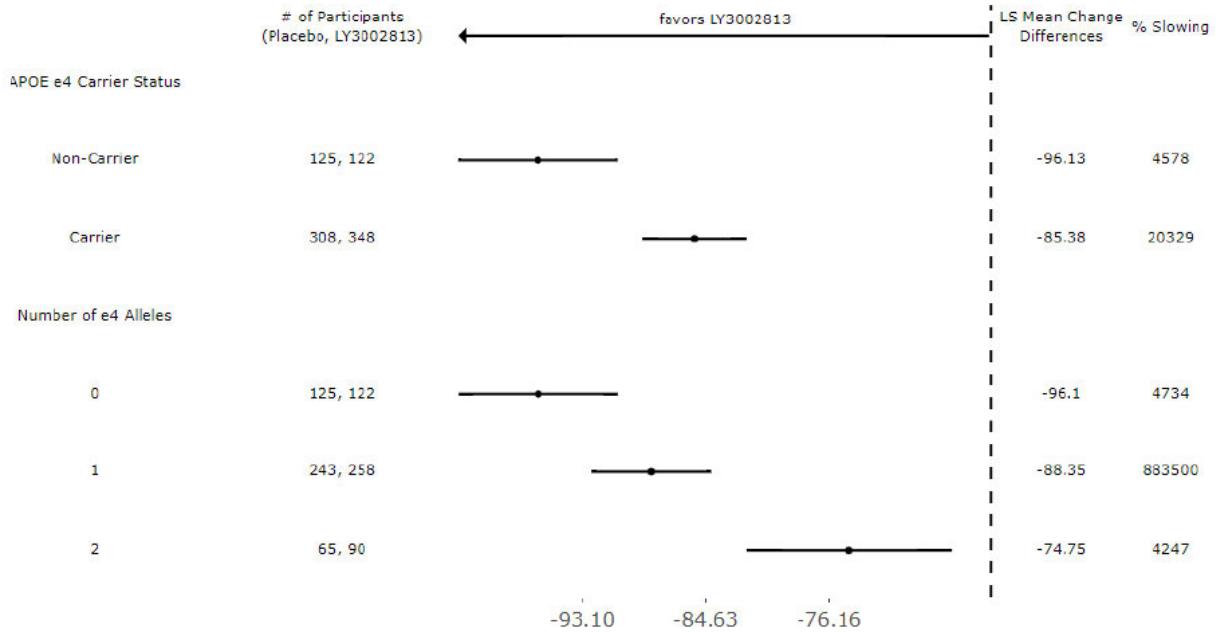
***Figure 42: CDR-SB Subgroup analysis by demographic and baseline characteristics, overall population (AACI-PC period)***




Source: page 179 AACI CSR

The applicant also provided a subgroup analyses of amyloid PET scan by APOE4 carrier status and by number of ε4 alleles (**Figure 43** below).

***Figure 43: MMRM: Subgroup analysis by amyloid PET scan, intermediate population (AACI-PC period)***




Abbreviations: ApoE ε4 = apolipoprotein E allele 4; LS = least squares; MMRM = Mixed Model for Repeated Measures; PC = placebo-controlled; PET = positron emission tomography.

Source: page 181 AACI CSR

### *Reviewer's Analysis*

*APOE ε4 Genotype and Efficacy*

Additional analyses were not performed by the reviewer. This review primarily focused on the efficacy findings in the phase 3 study (AACI). Here, a trend of diminished response to donanemab was observed within the *APOE ε4* homozygous patient subgroup for the primary endpoint iADRS (**Figure 39** and **Figure 40**, above). Furthermore, a similar trend was observed across the secondary endpoint of CDR-SB (**Figure 41** and **Figure 42**). Diminished pharmacodynamic responses measured by amyloid PET scan were also observed in *APOE ε4* homozygotes (**Figure 43**). *APOE ε4* homozygous patients appeared to show a diminished response to donanemab treatment compared to carriers and noncarriers, across primary and secondary clinical endpoints.

Please see the Clinical Review for complete evaluation of efficacy findings.

## 4 Summary and Conclusions

We identify a trend across the various endpoints in the study AACI, that suggest a diminished response to donanemab in *APOE ε4* homozygotes compared to *APOE ε4* heterozygotes and noncarriers.

We find that donanemab is appropriate for the indicated population of patients with MCI due to AD regardless of *APOE ε4* genotype. Additionally, our findings support that *APOE ε4* genotype may influence both the safety and efficacy of donanemab.

## 5 Recommendations

We recommend that the description of the increased risk of both ARIA-E and ARIA-H in *APOE ε4* carriers and homozygotes be included in labeling.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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ANANTHA RAM NOOKALA
02/22/2024 09:17:28 PM

MICHAEL A BEWERNITZ
02/22/2024 11:04:43 PM

MOHSEN RAJABI ABHARI
02/23/2024 08:13:36 AM

YOW-MING C WANG on behalf of XIULIAN DU
02/23/2024 04:49:31 PM
I am signing on behalf of Dr. Xiulian Du as she is currently on leave with no access to the DARRTS.

HOBART ROGERS
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JEFFREY B KRAFT
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YOW-MING C WANG
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VENKATESH A BHATTARAM
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**Office of Clinical Pharmacology (OCP) Review**

| | |
|---|---|
| Applicant | Eli Lilly and Company |
| Product (Generic Name) | Donanemab (LY3002813) |
| Product (Trade Name) | KISUNLA® |
| Link to EDR | \\CDSESUB1\evsprod\BLA761248\0002 |
| BLA Submission | 761248 (Sequence 0002) |
| Dosage Form (Strength) | Lyophilized formulation of 700 mg in a 50-mL vial reconstituted in diluent prior to use. |
| Route of Administration | Intravenous infusion |
| Proposed Dosing regimen | 700 mg administered as an intravenous infusion every four weeks for the first three doses, followed by 1400 mg every four weeks. |
| Proposed Indication | Indicated for the treatment of Alzheimer's disease (AD) |
| Submission Date | 05/18/2022 |
| OCP Review Team | Anantha Ram Nookala, Ph.D., Michael Bewernitz, Ph.D., Mohsen Rajabiabhari, Ph.D., Xiulian Du, Ph.D., Yow-Ming Wang, Ph.D., Atul Bhattaram, 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. |
| OCP Division | Division of Neuropsychiatric Pharmacology (DNP) |
| OND Division | Division of Neurology I (DN1) |

# Contents

# 1. Executive Summary

In this original Biologics License Application (BLA) 761248, the applicant, Eli Lilly and Company is seeking approval of donanemab via accelerated approval pathway for the treatment of Alzheimer's disease (AD). Donanemab (Tradename: KISUNLA®) is a New Molecular Entity (NME) and is not marketed in the US for any indication. It is a recombinant immunoglobulin G1 monoclonal antibody (mAb) that is anticipated to target the N-terminal, third amino acid, pyroglutamate formation (N3pG) amyloid beta epitope present in cerebral amyloid plaques. The original proposed dosing regimen of donanemab is 700 mg diluted in 0.9% sodium chloride to a final concentration of 4 mg/mL to 10 mg/mL and administered as IV infusion over 30 minutes every four weeks for the first three doses. Subsequent infusions are 1400 mg IV infusions over 30 minutes administered every 4 weeks, until the brain amyloid plaque is cleared.

The clinical development program consists of two Phase 1 studies (AACC and AACD) and a Phase 2 registration study (AACG) to evaluate the safety, efficacy, and effect on brain amyloid plaque deposition, and an ongoing Phase 3 trial (AACI). Reduction in brain amyloid has been established as a biomarker reasonably likely to predict clinical benefit in subjects with AD. The applicant is relying on the brain amyloid PET data from a pivotal, multicenter, randomized, double blind, placebo-controlled phase 2 study (AACG) in subjects with evidence of AD neuropathology to support the accelerated approval pathway. A time-dependent decrease in the amyloid PET was observed with donanemab treatment compared to the placebo. The applicant also conducted two phase 1 randomized, double-blind, placebo-controlled dose ranging studies (AACC and AACD). A dose- and time-dependent decrease in amyloid PET was observed and data from this study informed the dose/dosing regimen for the phase 2 trial. The evidence of effectiveness is also supported by exposure-response analysis evaluating the relationship between amyloid PET reduction and reduction of disease progression. Additional mechanistic support for downstream AD pathophysiology is obtained from donanemab-mediated changes in biomarker data, including tau PET, tau phosphorylated at threonine 217 (p-tau217) and glial fibrillary acidic protein (GFAP) in plasma.

The primary focus of this review is to (1) evaluate the acceptability of general dosing recommendations and dose cessation and to explore the need for dose optimization based on extrinsic and intrinsic factors, (2) to evaluate the biomarker changes and correlation with amyloid PET, and (3) to evaluate the impact of immunogenicity on PK, and PD.

## 1.1 Recommendations

The Office of Clinical Pharmacology team reviewed the information submitted under this BLA 761248 and recommends accelerated approval of KISUNLA® indicated for the treatment of Alzheimer's Disease.

Key review issues with specific recommendations and comments are summarized below:

| Review Issues | Recommendations and Comments |
|---|---|
| Pivotal evidence of effectiveness | The evidence of effectiveness for donanemab for the treatment of AD in adults is from one pivotal Phase 2, randomized, multicenter, double-blind, placebo-controlled study (AACG). The evidence of effectiveness was based on reduction in brain amyloid PET in study AACG that is considered to reasonably likely to predict clinical benefit. Additional support of effectiveness is provided by amyloid PET reduction in the Phase 1 study AACD, treatment-response relationships, and mechanistic support for downstream AD pathophysiology from tau PET data, and plasma biomarker (p-tau217 and GFAP) data. |
| General dosing instructions | Administer 700 mg by IV infusion every 4 weeks over (b) (4) 30 minutes for the first three doses. Subsequent doses are 1400 mg IV infusions over 30 minutes every 4 weeks. There is no clinical pharmacology evidence to support dose cessation after achieving a reduction in amyloid PET below a certain value or specific treatment duration.<br><br>All doses are administered intravenously after dilution (b) (4) 0.9% Sodium Chloride Injection, USP. |
| Dosing in patient groups (intrinsic and extrinsic factors) | No dosage adjustments are recommended based on intrinsic and extrinsic factors. There was no significant effect of age, race, sex, renal or hepatic impairment on donenamab exposures. Body weight and ADA titer were identified as covariates to impact donanemab exposures. However, the change in the exposures was not found to have an effect on amyloid PET reduction and therefore, no dose adjustments are warranted. |

| | |
|---|---|
| | Metabolic/transporter mediated interactions or impact of food does not apply for donanemab. |
| Bridge between the “to-be-marketed” and clinical trial formulations | Minor differences were noted between the pivotal clinical trial (lyophilized) and to-be-marketed (solution) donanemab formulations. The applicant performed supportive studies to compare the formulations. OBP confirmed that applicant has provided adequate comparability studies to demonstrate that the to-be-marketed product and the pivotal clinical trial formulation are comparable. Please refer to OBP review for details. |

## 1.2 Post marketing requirements and commitments

None from the OCP review team.

# 2. Summary of Clinical Pharmacology Assessment

## 2.1 Pharmacology and Clinical Pharmacokinetics

### Mechanism of Action

Donanemab is a humanized IgG1 isotype mAb that is anticipated to selectively target the N-terminal, third amino acid, pyroglutamate formation (N3pG) amyloid beta epitope present in cerebral amyloid plaques.

### Absorption

Since donanemab is administered by IV infusion, absorption is not relevant.

### Distribution

The volume of distribution of donanemab is 3.37 liters.

### Metabolism and excretion

Donanemab is expected to be degraded to small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs. Monoclonal antibodies typically do not undergo metabolism by the cytochrome P450 system and unlikely to be affected by drug transporters; therefore, no drug interaction studies were conducted with donanemab.

The mean clearance of donanemab is 0.0249 L/h and the mean terminal half-life was approximately 11.8 days.

#### *Age, Race, Body Weight, and Sex*

No dose adjustments are recommended on the basis of age, race, body weight or sex.

### Specific Populations:

*Patients with Renal or Hepatic Impairment*

No dedicated clinical studies were conducted to evaluate the impact of renal or hepatic impairment on the PK of donanemab. Generally, the IgG monoclonal antibodies undergo elimination via intracellular catabolism and therefore, hepatic impairment is not expected to significantly impact the disposition of donanemab. Furthermore, renal elimination of monoclonal antibodies is generally considered low. Therefore, the impact of renal/hepatic impairment is unlikely to be clinically relevant and no dose adjustments are recommended for donanemab in subjects with renal or hepatic impairment.

### Immunogenicity:

Overall, the immunogenicity database consisted of 129 subjects from phase 2 clinical study from which anti-donanemab antibody (ADA) results were available. Of these subjects, treatment-emergent ADAs (TE-ADAs) were detected in 119 subjects; these subjects are therefore deemed ADA+ and the ADA incidence is 119/129 (92.2%).

Neutralizing antibodies (NAbs) were detected in all the ADA+ subjects (119/119; 100%). All the ADA+ subjects have developed the ADA titers by week 16 and many of the subjects (84/107; 78.5%) have achieved the individual maximum titer by week 24. The presence of TE-ADAs had an effect on various PK measures, such as $C_{min,ss}$ and $AUC_{ss}$. However, the changes in donanemab exposures were found not to affect amyloid PET reduction. Please refer to Appendix 4.2 and Office of Biotechnology Products review for additional details on immunogenicity assessments.

## 2.2 Dosing and Therapeutic Individualization

### *2.2.1 General Dosing*

The general dosing regimen is 700 mg diluted in 0.9% sodium chloride to a final concentration of 4 mg/mL to 10 mg/mL and administered as IV infusion over 30 minutes every four weeks for the first three doses. Subsequent infusions are 1400 mg IV infusions over 30 minutes administered every 4 weeks.

Clinical judgment should be used when considering whether an individual patient's dosing should be continued, reduced, or ceased in the absence of a safety issue otherwise warranting alteration in dosing.

### *2.2.2 Therapeutic individualization*

No therapeutic individualization is necessary for extrinsic/intrinsic factors. Donanemab is administered by intravenous route, and therefore, food-drug interactions are not anticipated. In addition, its CYP enzyme/transporter-based drug-drug interaction liability is considered low (See Section 2.1). No dedicated clinical studies were performed in subjects with renal or hepatic impairment; however, renal/hepatic impairment is not expected to impact the pharmacokinetics of donanemab. Therefore, no dose adjustment is warranted in patients with hepatic/renal impairment.

## 2.3 Outstanding Issues

None.

## 2.4 Summary of Labeling Recommendations

The proposed labeling concepts in Section 12.2 and 12.3 are generally acceptable. However, the review team recommends the following major edits to dosing instructions and plasma biomarkers:

***Dosing instructions***

Donanemab treatment showed significant reduction of amyloid PET burden compared to the placebo. Further, the reductions in amyloid PET observed in patients who achieved amyloid levels <11 centiloids by week 24 were maintained until the end of 76-week treatment period. The reductions in amyloid PET with donanemab depended upon the

baseline value and the subjects who reached amyloid PET <11 centiloids by week 24 had lower amyloid PET at the baseline compared to the subjects who did not reach. (b) (4)

***Labeling recommendations for plasma biomarkers***

**Plasma p-tau217** (b) (4)**:** The bioanalysis method validation has scientific gaps, including insufficient coverage of long-term stability and therefore, quantitative changes in biomarker levels over time cannot be reliably estimated. Although quantitative statements are not acceptable, there was an observed change in plasma p-tau217 (b) (4) with dosing regimen indicated in section 1.1 compared to placebo in Study AACG. The review team believes that the effect of donanemab on plasma p-tau217 (b) (4) in study AACG is unlikely to arise merely due to the deficiencies in the bioanalytical method (please refer to Section 3.3.1, 4.1.2, and 4.1.3 for additional details). Hence, the review team recommends including qualitative description of the data in the label. 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.

# 3. Comprehensive Clinical Pharmacology Review

## 3.1 Overview of the Product and Regulatory Background

Donanemab, also known as LY3002813 is supplied at a concentration of 17.5 mg/mL (350 mg/20 mL) in a single-use glass vial for dilution in 0.9% sodium chloride prior to intravenous infusion. Donanemab is a humanized IgG1 mAb that is composed of 2 identical Ig kappa light chains and 2 identical Ig gamma heavy chains. Donanemab is anticipated to selectively target the N-terminal, third amino acid, pyroglutamate formation (N3pG) amyloid beta epitope present in cerebral amyloid plaques to exert its therapeutic effects in AD.

The clinical development program for donanemab BLA submission consists of six completed or on-going clinical studies. Study AACG is the pivotal study, which is a multicenter, randomized, double blind, placebo-controlled phase 2 study. Study AACC and AACD are completed phase 1 studies that evaluated single (0.1 to 40 mg/kg) and multiple doses (0.1 to 20 mg/kg) in patients with mild cognitive impairment due to AD or mild-to-moderate AD. In addition, an on-going phase 2 study (AACH), and two on-going phase 3 studies (AACN and AACI) in subjects with early symptomatic AD provided safety information of donanemab. Please refer to Clinical Review for details of safety evaluation.

Donanemab received fast track designation and breakthrough therapy designation in July 2018 and June 2021, respectively. A pre-BLA meeting was held with FDA in August 2021 to discuss the accelerated approval pathway based on the biomarker and safety data from Studies AACC, AACD, pivotal Phase 2 Study AACG and additional safety data from Study AACI that would support the BLA of donanemab for the treatment of adult patients with early symptomatic AD with elevated amyloid plaque accumulation.

## 3.2 General Pharmacology and Pharmacokinetic Properties

A summary of pharmacology and PK characteristics of donanemab are summarized in the table below.

| **Pharmacology** | |
|---|---|
| Mechanism of Action | Donanemab is a humanized IgG1 isotype mAb composed of two identical immunoglobulin kappa light chains and two identical immunoglobulin gamma heavy chains. It selectively targets the N-terminal, third amino acid, pyroglutamate formation (N3pG) amyloid beta epitope present in cerebral amyloid plaques to exert its therapeutic effects in AD. |
| **General Information** | |
| Dose Proportionality | Following single doses of donanemab from 10 to 40 mg/kg, exposures increased in an approximate dose proportional manner. At doses of 10 and 20 mg/kg, exposures were approximately dose proportional at steady state. |
| Accumulation | After repeated dosing with 10 mg/kg or 20 mg/kg every 4 weeks, the AUC ratio after dosing at Day 141 to Day 1 was 1.06 and 1.26, respectively, indicative of no donanemab accumulation. |
| Immunogenicity | Anti-drug antibodies were evaluated in serum using Affinity Capture Elution-Bridge assay validated at (b) (4). From the Phase 2 study, TE-ADAs were detected in 92.2% subjects (119 out of 129) at one or more time points in either study. All the ADA positive subjects have tested positive for NAbs. |

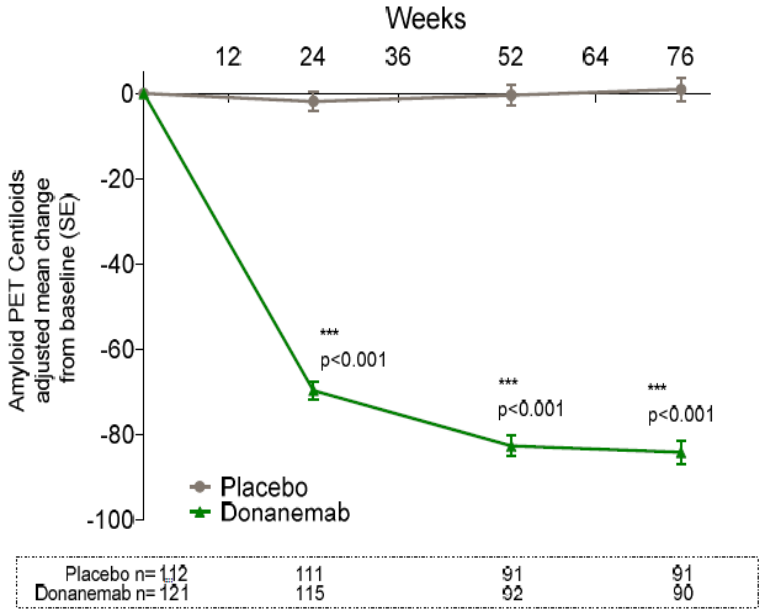
| | |
|---|---|
| | The observed differences in donanemab PK in patients who tested positive for ADA or NAb did not translate to differences in the amyloid PET reduction. |
| Absorption | |
| Tmax | At the end of infusion |
| Distribution | |
| Volume of distribution | The population PK estimate of the central volume of distribution is 3.37 L. |
| Elimination | |
| Terminal Elimination Half-life | The mean terminal half-life is 11.8 days. |
| Metabolism/Excretion | Monoclonal antibodies are not known to be metabolized by the cytochrome P450 system or affected by drug transporters. As a human IgG1 monoclonal antibody, donanemab is expected to be degraded to small peptides and amino acids by ubiquitous proteolytic enzymes in the same manner as endogenous IgG. |

## 3.3 Clinical Pharmacology Questions

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

The primary evidence to support amyloid plaque reduction as an endpoint likely to predict clinical benefit is based on randomized, multicenter, double-blind, placebo-controlled Phase 2 study (15T-MC-AACG) in subjects with early symptomatic AD. The amyloid PET data from study AACG are presented in **Figure 1**.

**Figure 1: Observed Amyloid PET Values by Treatment in Study AACG**

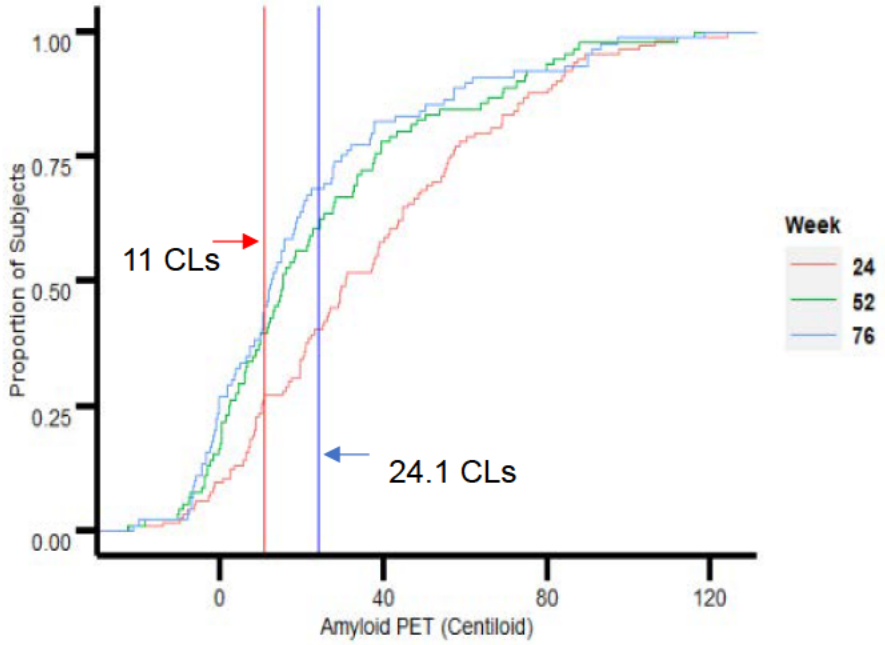



*source: 2-7-2-clin-pharm-sum—us---ad-.pdf, page 29*

The study consisted of a 9-week screening period, followed by a 76-week double-blind treatment period during which donanemab or IV placebo was administered to the subjects randomized in a 1:1 ratio. Subjects enrolled in the study were 60 to 85 years of age and with a gradual and progressive change in memory functions for at least 6 months with a MMSE score of 20 to 28 and have evidence of pathologic tau deposition on a flortaucipir PET. Patients with sufficient amyloid plaque reduction as measured by amyloid PET scans at Week 24 or Week 52 had a double-blinded dose reduction of donanemab for the remaining duration of the double-blind period. Specifically, participants in the donanemab group were titrated down from 1400 mg to 700 mg if amyloid PET levels reached 11 to less than 25 CL, or to placebo if less than 11 CL at any 1 measure, or 11 to less than 25 CL for 2 consecutive measures. Based on the amyloid PET levels, approximately 27% (26/95) and 24% (23/95) of the subjects were titrated down to placebo and 700 mg, respectively at week 28, and approximately 55% (41/75) and 21% (16/75) were titrated down to placebo and 700 mg, respectively at week 56. The proportion of participants that discontinued from the study due to treatment emergent adverse events was higher with donanemab treatment (16%) compared to the placebo group (7.2%). Please refer to clinical safety review for more information. Donanemab treatment resulted in a time-dependent decrease in amyloid PET; a least square mean change of -67.8 centiloids at week 24 ($p<0.001$), -82.3 centiloids at week 52 ($p<0.001$), and -85.1 centiloids at week 76 ($p<0.001$) compared to the placebo group. The proportion of subjects achieving amyloid PET reduction to <11 or <24.1 centiloids (CL) increased with an increase in the treatment duration. With donanemab treatment, 40% (46/115), 60% (55/92), and 68%

(61/90) of the subjects had amyloid PET values <24.1 CL at week 24, 52, and 76, respectively and 24% (27/113) and 39% (36/92) of the subjects had amyloid PET values <11 CL at week 24 and 52, respectively (**Figure 2**). No placebo-treated participants achieved complete amyloid PET values <24.1 CL during the study. There was no difference observed in donanemab-mediated amyloid PET reduction in APOE ε4 carriers versus non-carriers.

**Figure 2: Proportion of Subjects Achieving Amyloid Level <11 or <24.1 by Study Visit**



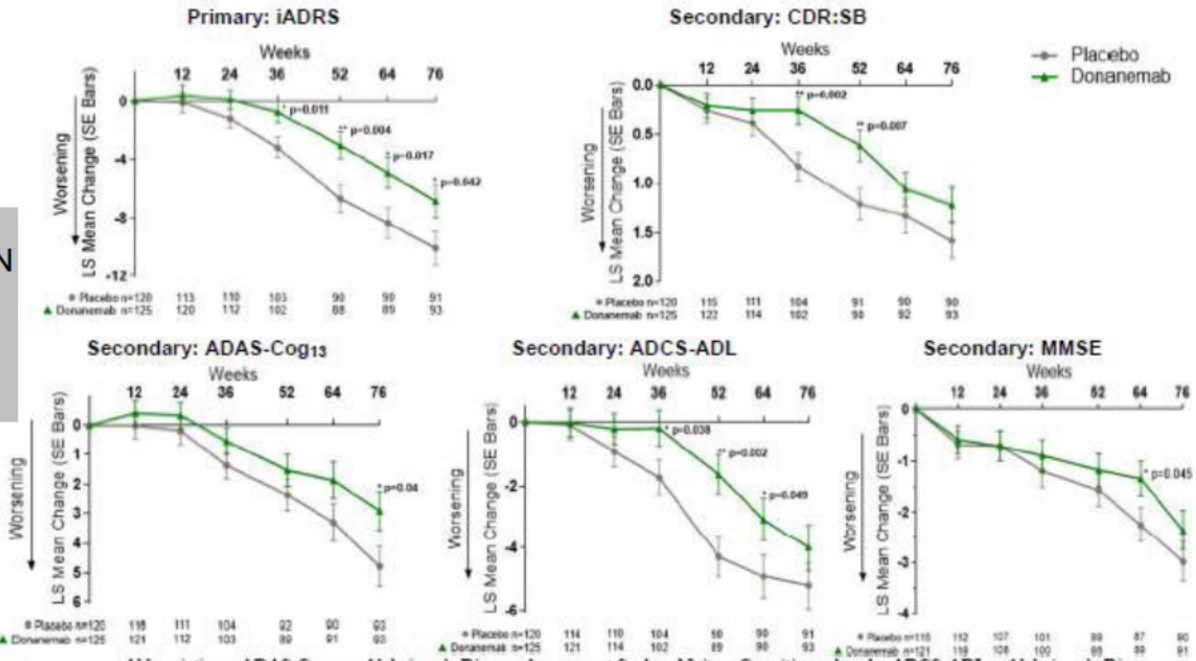

Source: *Reviewer's analysis*

Additional support of donenemab-mediated clinical benefit is obtained from the clinical efficacy measures in study AACG. The Applicant's reports topline results with donanemab providing a numerical benefit over placebo for the primary efficacy endpoint, iADRS[1] and each of the secondary outcomes, including CDR-SB[2], ADAS-Cog13[3], ADCS-iADL[4], and MMSE[5] . Please refer to the clinical review and statistical review for additional details on the pivotal phase 2 efficacy data (see ***Figure 3***).

[1] integrated Alzheimer's Disease Rating Scale
[2] Clinical Dementia Rating Scale – Sum of Boxes
[3] Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale
[4] Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale
[5] Mini-Mental State Examination

APPEARS THIS WAY ON ORIGINAL

**Figure 3: Efficacy Assessments Over Time for Study AACG**



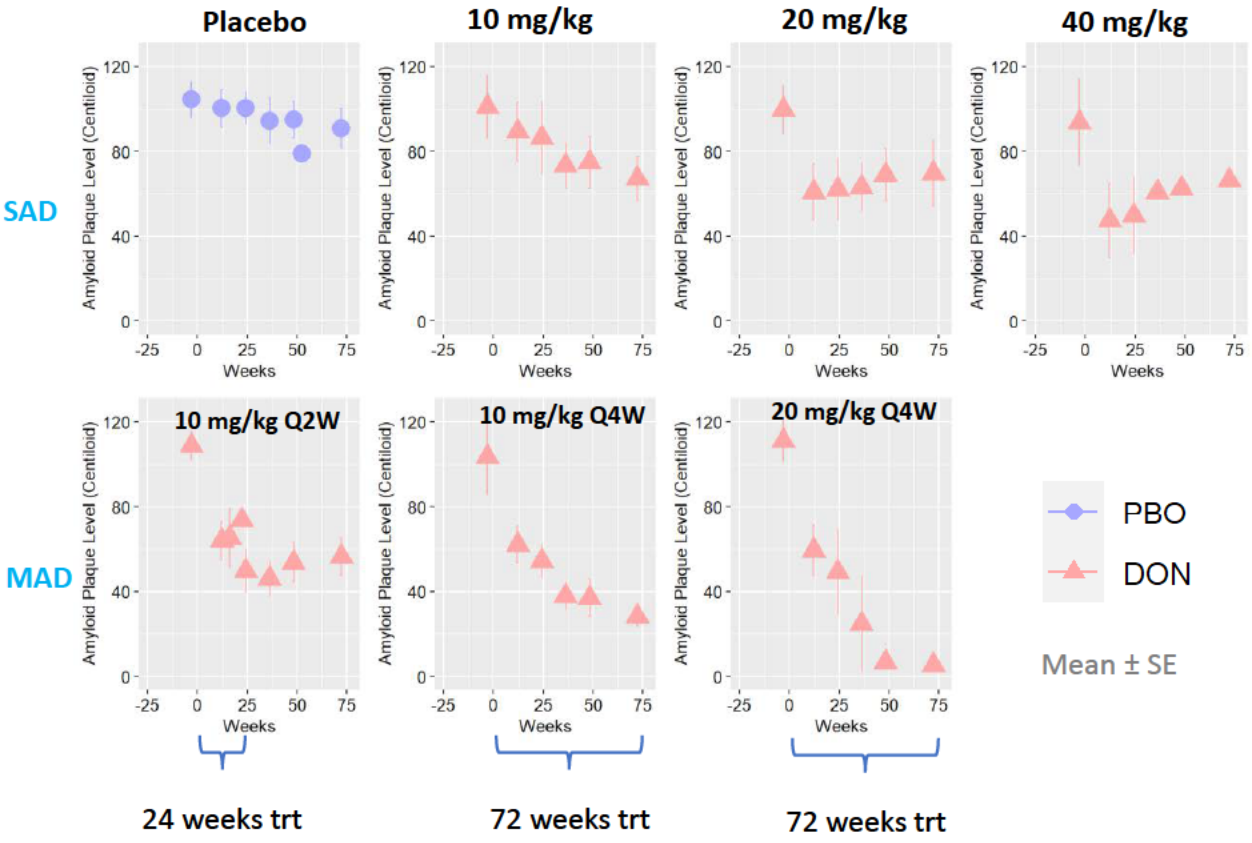

Abbreviations: ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study –Activities of Daily Living subscale; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; iADRS = integrated Alzheimer's Disease Rating Scale; LS = least squares; MMRM = mixed model for repeated measures; MMSE = Mini-Mental State Examination; n = number of participants; SE = standard error.

*Source: Applicant's Summary of Clinical Efficacy; Pg-44*

The evidence of effectiveness is also supported by exposure response analysis evaluating the relationship between amyloid PET and reduction in clinical decline. The results suggested that donanemab-mediated amyloid reduction is associated with the reduction in clinical decline, as measured by iADRS and CDR-SB. The reduction in the clinical decline on both iADRS and CDR-SB compared to placebo was only apparent in APOE ε4-carrier patients. . Refer to pharmacometrics analyses section **4.4.4** for further details on the Applicant's modeling analysis.

Single dose and multiple dose cohorts in the phase 1b study provide additional support in favor of donanemab-mediated amyloid reduction (Study AACD). A single dose of 10 mg/kg, 20 mg/kg, and 40 mg/kg donanemab treatment resulted in a dose-dependent amyloid PET reduction (see **Figure 4**).

**Figure 4: Observed Amyloid Plaque Vs Time by Treatment in Study AACD**




*Each panel represents an arm of study AACD. The placebo group is depicted with blue circles and donanemab arms are depicted with red triangles. The placebo group and single ascending dose (SAD) arms are in the top row. Multiple ascending dose (MAD) arms in the bottom row. Each point represents the mean amyloid level at that time for that arm and the line represents the standard error of the mean. In the 10 mg/kg every two weeks (q2w) arm, subjects were treated for 24 weeks. For the 10 mg/kg every 4 weeks (q4w) and 20 mg/kg q4w arms, the subjects were treated for 72 weeks.*

*Source: Reviewer's analyses.*

Further, the reductions in amyloid PET were maintained for up to 72 weeks. Multiple doses of 10 mg/kg administered Q2W for 24 weeks resulted in a significant amyloid PET reduction that were maintained until 72 weeks. Multiple doses of 10 mg/kg and 20 mg/kg donanemab administered Q4W for 72 weeks showed a dose-dependent reduction in amyloid PET. In addition, by week 72, 50% (5/10) subjects in the 20 mg/kg cohort who received donanemab Q4W had amyloid PET values <24.1 CL compared to 25% (2/8) subjects in the 10 mg/kg cohort. These results support the use of 1400 mg dose (equivalent to 20 mg/kg in a 70 kg individual) in the AACG study.

Overall, the results of amyloid PET reduction from study AACG along with supportive evidence from study AACD and modeling analysis indicate donanemab significantly lowers amyloid PET burden in the brain.

In addition to the data listed above, the applicant provided data from study AACG on tau PET biomarker, tau phosphorylated at threonine 217 (p-tau217) and glial fibrillary acidic protein (GFAP) in plasma, to evaluate donanemab -related effects on potential markers of downstream AD pathophysiology. The results are discussed below.

*Tau PET*

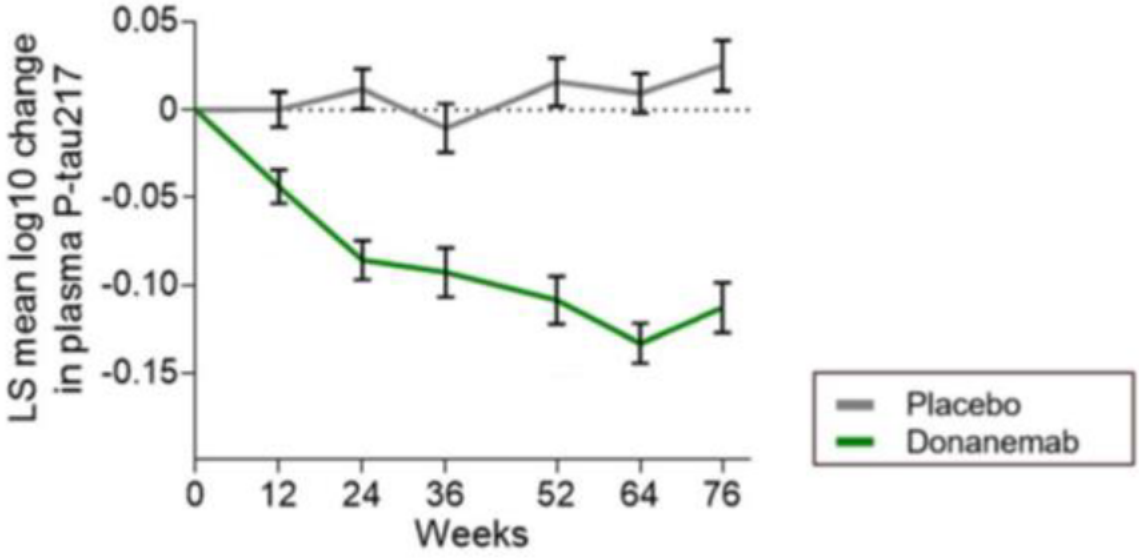
The applicant has evaluated the changes in brain tau PET deposition upon treatment with donanemab. There were no significant differences between treatment groups when comparing the changes in global tau load from baseline to Week 76 using TauIQ method. However, donanemab treatment resulted in a reduction of overall tau deposition and in specific brain regions including, the frontal lobe, parietal lobe, and the lateral temporal lobe compared to the placebo. Please see the clinical review for details on Tau PET results.

*p-tau217*

Published literature showed plasma p-tau217 to correlate with amyloid beta, AD progression, and also discriminate AD from other neurodegenerative diseases[6,7]. A time-dependent decrease in the plasma p-tau217 levels were shown in Study AACG (**Figure 5**); donanemab-treated patients had a 22.4% decrease from baseline to Week 76 while placebo-treated patients had a 7.2% increase. Separation between donanemab and the placebo groups was observed from 12 weeks of treatment and continued until the end of 76-week treatment period. In addition, correlation analysis conducted between change in p-tau217 from baseline at week 76 and change in amyloid PET from baseline at week 76 indicated that a decrease in amyloid PET was associated with a decrease in plasma p-tau217 (**Figure 6**). The association between change in p-tau217 from baseline at week 76 and change in amyloid PET from baseline at week 76 was observed in both APOE ε4-carriers and APOE ε4 non-carriers.

[6] Palmquist S et al. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA. 2020 Aug 25;324(8):772-781.
[7] Mattson-Carlgren N et al. Longitudinal plasma p-tau217 is increased in early stages of Alzheimer's disease. Brain. 2020 Dec 5;143(11):3234-3241.

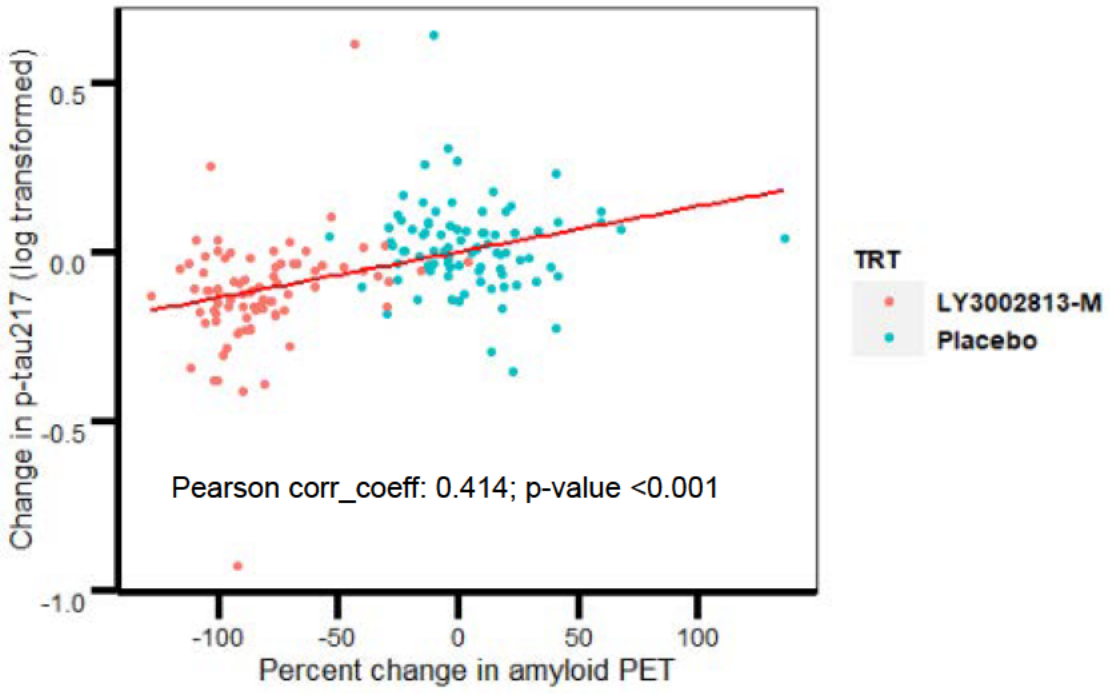
**Figure 5: p-tau217 by Treatment in Study AACG**




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo n= | 119 | 113 | 110 | 103 | 89 | 85 | 86 |
| Donanemab n= | 123 | 119 | 110 | 100 | 90 | 84 | 86 |

*Source: 2-7-3-clin-efficacy-sum.pdf, page 40*

**Figure 6: Assessment of Correlation Between Amyloid PET and p-tau217**




*Source: Reviewer's analysis*

The relationship between p-tau217 and iADRS clinical disease progression was supported by modeling analysis. The results suggested that donanemab-mediated plasma p-tau217 reduction was associated with the reduction in disease progression, as measured by iADRS. This effect is only apparent in APOE ε4-carrier patients; in APOE4 noncarriers, p-tau217 reduction was not associated with a reduction in disease progression as measured by iADRS. Refer to section (**4.4.4 Disease** Progression**)** for further details on the applicant's disease progression modeling analyses.

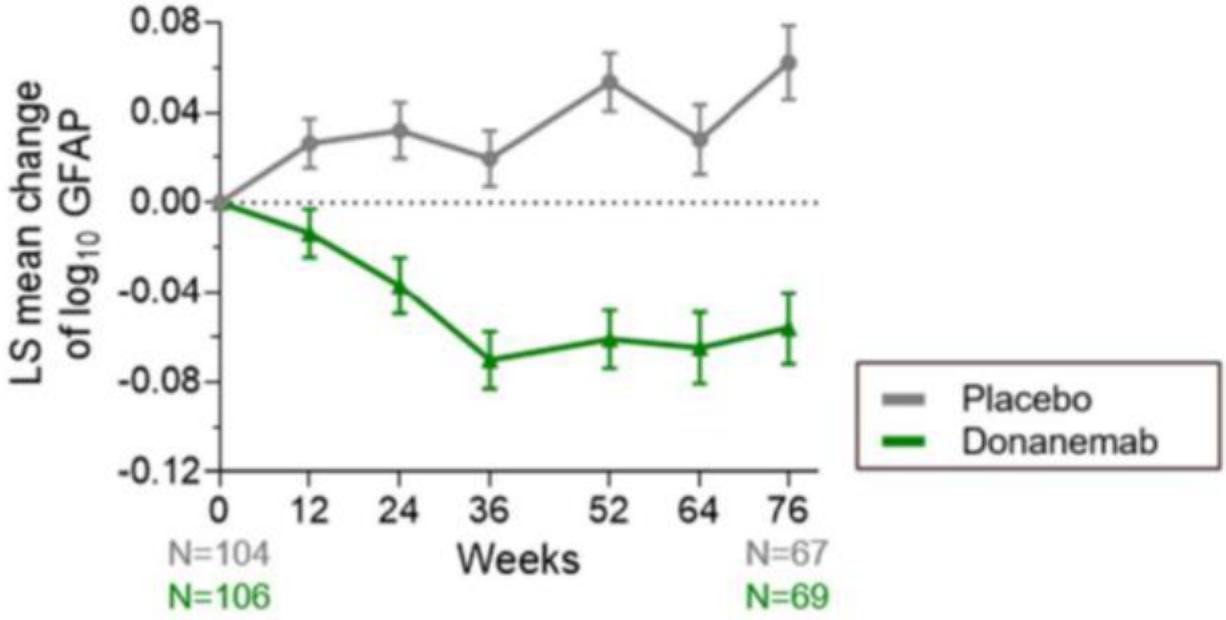
The review team noted that the bioanalytical method validations have not been fully established for plasma p-tau217 and thus all the plasma biomarker analyses presented in this review are considered as exploratory and should be interpreted with caution (refer to Appendix **4.1.2 Bioanalysis** of p-tau217 in human plasma). However, considering totality of evidence such as magnitude of difference (29% difference between the placebo and donanemab groups at week 76), positive correlation between p-tau217 and change in amyloid PET and iADRS clinical disease progression and no apparent correlation between baseline plasma levels of p-tau217 collected at various time points, the review team believes that the effect of donanemab on plasma p-tau217 in study AACG is unlikely to arise merely due to the deficiencies in the bioanalytical method. Hence, the review team recommends including qualitative description of the exploratory data in the label. 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 the label.

*GFAP*

Astrocyte reactivity was previously shown to be present surrounding amyloid beta plaques in the brains of AD patients[8]. Plasma GFAP, a biomarker of astrocyte reactivity has been shown to associate with brain beta amyloid pathology[9]. A time-dependent decrease in the GFAP levels were shown in Study AACG (***Figure 7***). Donanemab-treated patients demonstrated a 12% decrease from baseline to Week 76 while placebo-treated patients had a 15% increase. Separation between donanemab and the placebo groups was observed from 12 weeks of treatment and continued until the end of the treatment period of 76 weeks. However, these data should be interpreted with caution because the observed differences (12-15%) are small relative to bioanalytical assay variability (up to 30%) and physiological variabilities. In addition, correlation analysis conducted between change in GFAP from baseline at week 76 and change in amyloid PET from baseline at week 76 indicated that a decrease in amyloid PET was associated with a decrease in plasma GFAP (***Figure 8***).

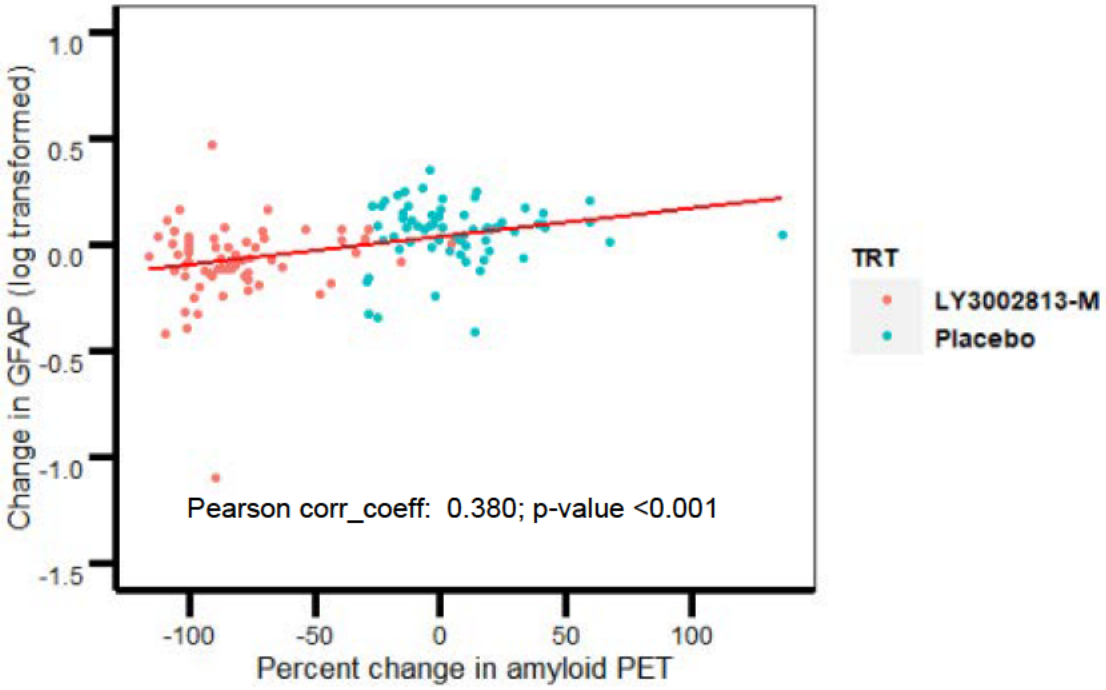
[8] Osborn LM et al. Astrogliosis: An integral player in the pathogenesis of Alzheimer's disease. Prog Neurobiol. 2016;144:121–141.
[9] Pereira JB et al. Plasma GFAP is an early marker of amyloid-b but not tau pathology in Alzheimer's disease. Brain. 2021 Dec 16;144(11):3505-3516.

**Figure 7: GFAP by Treatment in Study AACG**




*Source: 2-7-3-clin-efficacy-sum.pdf, page 41*

**Figure 8: Assessment of Correlation Between Amyloid PET and GFAP**




*Source: Reviewer's analyses*

The review team noted that the bioanalytical method validations have not been fully established for plasma GFAP and thus all the biomarker analyses results presented in this review are considered as exploratory and should be interpreted with caution (refer to Appendix **4.1.3 Bioanalysis** of GFAP in human plasma). However, considering the totality of evidence such as magnitude of difference , slightly positive correlation between GFAP and change in amyloid PET, a trend for an increase in the plasma GFAP concentrations over time in the placebo group, and no apparent correlation between baseline plasma levels of GFAP collected at various times, the review team believes that the effect of donanemab on plasma GFAP in study AACG is unlikely to arise merely due to the deficiencies in the bioanalysis method. Hence, (b) (4) . We note that the plasma GFAP is a relatively a new biomarker and has not been studied widely in AD before.

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

The proposed dosing regimen seems acceptable from clinical pharmacology standpoint. However, the available clinical pharmacology information is not adequate to support treatment cessation after a certain amyloid reduction or treatment period. Details are discussed below.

The applicant is seeking approval of the donanemab dosing regimen which includes 700 mg dose administered as IV infusions for the first three doses followed by 1400 mg infusions every 4 weeks until the brain amyloid plaque is cleared. This dosing regimen with a difference was evaluated in the Phase 2 trial where a dose reduction from 1400 mg to 700 mg or cessation of dosing if sufficient reduction amyloid PET is achieved was adopted. Based on the observed effect of donanemab on amyloid PET reduction in studies AACD and AACG, reduction of brain tau PET and soluble biomarkers, biomarker exposure-response relationships, favorable trends in clinical endpoints, and safety, this regimen is considered effective and well-tolerated.

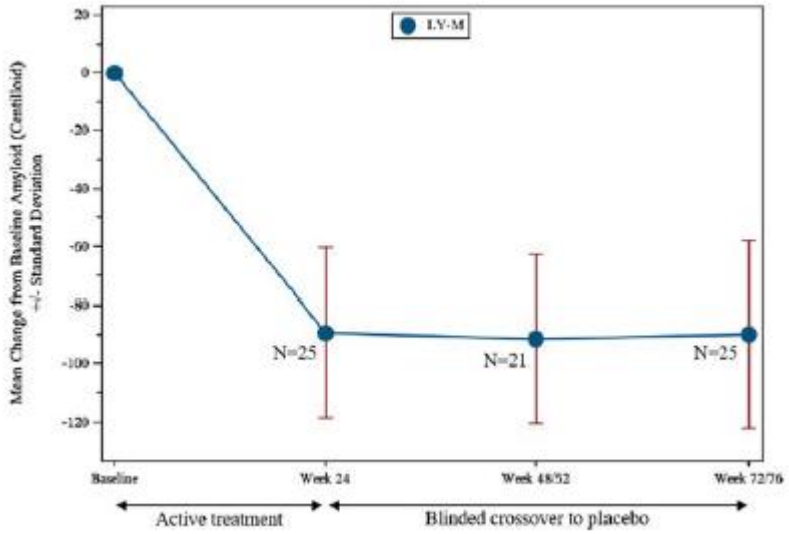
The recommended dose of 1400 mg administered Q4W resulted in mean amyloid PET reduction of -67.8 centiloids at week 24 ($p<0.001$), -82.3 centiloids at week 52 ($p<0.001$), and -85.1 centiloids at week 76 ($p<0.001$) compared to the placebo group. With donanemab treatment, 40% (46/115), 60% (55/92), and 68% (61/90) of the subjects had complete amyloid PET levels <24.1 CL at week 24, 52, and 76, respectively. Additional support for the use of 1400 mg dose is obtained from AACD study where the 20 mg/kg (equivalent to 1400 mg in a 70 kg individual) cohort who received donanemab Q4W for 72 weeks had complete amyloid PET levels <24.1 CL in 50% (5/10) subjects compared

to 25% (2/8) subjects in the 10 mg/kg (see **Figure 4**). Please refer to clinical safety review for details about the adequacy of safety data to support the removal of donanemab down titration from dosing instructions.

The applicant proposed to continue donanemab treatment until brain amyloid is cleared. The review team evaluated the adequacy of treatment cessation proposal. The rationale was based on a very small re-accumulation rate of amyloid deposits in the brain based on the available data. The clinical pharmacology team doesn't have enough information to support accurate estimation of amyloid re-accumulation rate. Further, there is no data to support that additional clinical benefit will not be gained from continuous donanemab treatment.

According to the applicant, single donanemab dose of 20 mg/kg and 40 mg/kg showed amyloid PET reductions that had not returned to baseline by 76 weeks (see **Figure 4**). In study AACG and AACD, subjects who stopped donanemab treatment at week 24 and switched to placebo showed consistent amyloid PET at 24, 52 and 76 weeks (**Figure 9**).

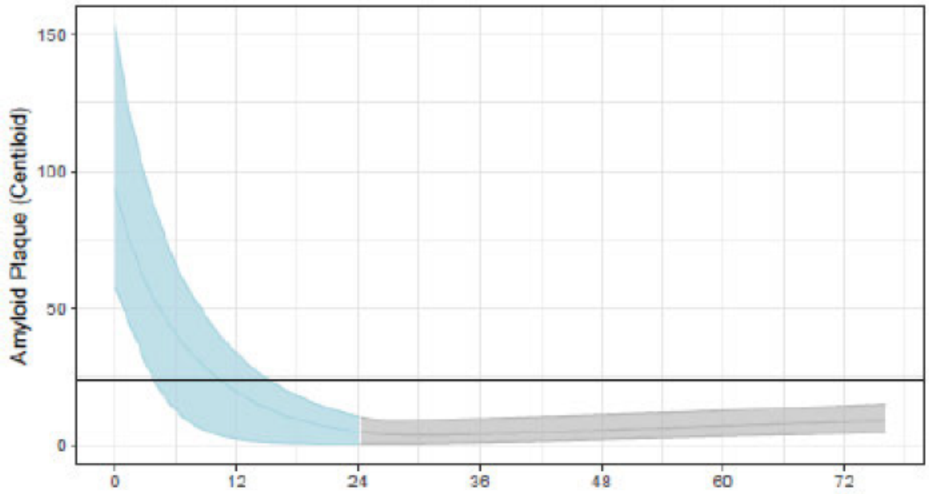
**Figure 9: Amyloid PET in Subjects who Stopped Donanemab Treatment at Week 24**




*Source: Summary of Clinical Efficacy, Pg-34*

The applicant conducted additional PK/PD analysis to simulate the amyloid re-accumulation in patients who achieved amyloid reduction to <11 centiloids and ceased treatment starting at 24 weeks. The results suggest that when ceasing treatment at week 24, in subjects that reached <11 Centiloid, amyloid plaque levels may increase by ~ 3.4 centiloids per year (see **Figure 10**).

**Figure 10: Simulated amyloid plaque level over time in patients achieving <11 amyloid Centiloid units at Week 24**




*Source: Applicant's I5T-MC-AACG Population PK Report, Pg-70*

Even though the amyloid re-accumulation rate estimated from the model is similar to the natural amyloid accumulation rate in AD patients, there is limited observed amyloid PET re-accumulation data beyond 52 weeks after stopping donanemab treatment. Further, though the Applicant ceased donanemab treatment upon achievement of <11 cenitloid (or 11 to 24.1 centiloid on two visits) in study AACG, there is no clear rationale to indicate whether the maximum benefit is attained when amyloid levels reach 11 to 24.1 centiloid. As such, an amyloid-based threshold for ceasing donanemab treatment is not supported by the available data.

(b) (4)

The most commonly reported AEs include Amyloid Related Imaging Abnormality (ARIA) – microhemorrhages and superficial siderosis (ARIA-H), Edema/Effusions (ARIA-E), nausea, infusion related reactions, and vomiting. In study AACG, higher incidences of ARIA-E and ARIA-H were observed; ARIA-E was observed in 26.0% of participants treated with donanemab compared to 0.8% on placebo and ARIA-H was observed in 28.2% of patients treated with donanemab, compared to 8.0% on placebo. The incidence of ARIA-E and ARIA-H were higher in ApoE ε4 carriers by ~4- and 2-fold, respectively when compared to ApoE ε4 non-carriers. Please refer the clinical review for more details.

In conclusion, dosing regimen as indicated in section 1.1 is acceptable from a clinical pharmacology perspective. We defer to the clinical team regarding the adequacy of safety data set for the proposed dose. Overall, based on the limited clinical pharmacology analysis to support treatment cessation, it is not clear whether the maximum benefit has been attained when amyloid levels reach <11 or 11 to 24.1 centiloid on two visits.

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

No. There is no need for alternative donanemab dose or dosing regimen for subpopulation based on the intrinsic factors such as body weight, age, race, sex, BMI, renal or hepatic impairment and extrinsic factor such as ADA status as described below. No dedicated renal and hepatic impairment studies were conducted. Population pharmacokinetic analysis was conducted on data from 177 subjects (46 subjects from Study AACD and 131 subjects from Study AACG) to evaluate the impact of intrinsic and extrinsic factors.

*Body Weight*

Body weight was found to be a statistically significant predictor of donanemab clearance and volume of distribution; increase in the body weight decreased donanemab exposures at steady state. The body weight in the entire PK data was distributed between 40.3 and 123 kg. Final population PK model was used to simulate the steady state concentration-time profile following 1400 mg Q4W in 50 kg ($5^{th}$ percentile) and 98 kg ($95^{th}$ percentile). The Cmax of the 50 kg subject was increased by 93.5% compared to the 98 kg subject (624 vs 322 μg/mL). Subjects were divided into different groups based on the body weight to evaluate if the body weight mediated changes in donanemab exposures had an effect on amyloid reduction (refer to **4.3.1 Reviewer** PK Simulations and ***4.4.1.1 Effect of WT on Amyloid Plaque Reduction*** for additional details). Irrespective of the body weight group, all the subjects showed similar amyloid PET reduction. These results indicate that changes in donanemab exposures across this range of bodyweights are not clinically significant and no dose adjustments are warranted.

*Renal impairment*

No dedicated renal impairment studies were conducted. Based on the population pharmacokinetic analysis, the mean predicted exposures for mild renal impairment patients (n=57) and moderate renal impairment patients (n=41) at steady state were increased by 26% and 49% for AUC,ss, respectively, compared to normal renal function patients (n=14). However, the apparent exposure increases in subjects with renal impairment compared to normal renal function were caused by the differences in body weights rather than differences in renal function. This is because weight is a covariate on donanemab PK, mild renal impairment and moderate renal impairment subjects had 19% and 31% lower body weight compared to normal renal function subjects. In general, renal

elimination of monoclonal antibodies is considered low and no dose adjustment is recommended based on renal impairment..

*Hepatic impairment*

No dedicated hepatic impairment studies were conducted. Based on the population pharmacokinetic analysis, the mean predicted exposures at steady state for mild hepatic impairment patients (n=9) were comparable to normal hepatic function patients (n=122). In general, hepatic elimination of monoclonal antibodies is considered low and given the minimal impact on exposures, no dose adjustment is recommended based on hepatic impairment.

*APOε4 Status*

APOε4 status was evaluated as a covariate in the population pharmacokinetic model. No differences in the donanemab exposures were observed in patients who are APOε4 carriers compared to non-APOε4 carriers. ARIA-E and ARIA-H incidence are greater in APOε4 carriers than non-carriers. However, the clinical team has determined that no dose-adjustment is required based on APOε4 status. Please refer to Clinical safety review for details on ARIA-E.

*Sex*

Based on the population pharmacokinetic analysis, the mean predicted exposures for females (n=55) at steady state were increased by 33% for AUC,ss compared to males (n=57). However, the increase in the exposures were due to the differences in the body weights rather than the sex as identified in the Pop PK covariate modeling. Female subjects had 22% lower body weight compared to male subjects. Further, the amyloid PET reduction and ARIA-E incidence are similar between males and females and therefore, no dose adjustment is recommended.

*Anti-Drug Antibodies*

Development of ADA against donanemab negatively affected donanemab pharmacokinetics. Clearance of donanemab increased proportionally to the logarithm of ADA titer. ADA positive subjects had lower donanemab concentrations compared to ADA negative subjects at all the time points. The geometric mean ratio and the upper limit of the 90% CIs were less than 1 at all the time points except for week 12. To account for worst case scenario, final Pop PK model with subjects maintaining the same ADA titer was used to simulate the impact of ADA on donanemab exposures. At the maximum titer range (>1:81920), median exposure (AUCt,ss) was reduced by 23% and trough concentration at steady state was reduced by 55%, compared with the low titer (<1:5120). Subjects were divided into different groups based on the maximum ADA titer to evaluate if the ADA titer mediated changes in donanemab exposures had an effect on amyloid PET reduction (refer to section 4.2.1 and 4.2.2 for additional details). Irrespective of the

ADA titer group, all the subjects showed similar amyloid PET reduction. However, as single and multiple doses of donanemab showed sustained reductions in amyloid PET, changes mediated by ADA titer may not be immediately reflected on amyloid PET reduction.

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

Since donanemab is administered by intravenous infusion, food-drug interactions are not anticipated.

Donanemab is a monoclonal antibody and is not a cytokine modulator, therefore it is unlikely to influence drug metabolizing enzymes/transporters. Therefore, no drug-drug or transporter-drug interaction studies were conducted in-vitro or in-vivo.

### *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?*

No. The applicant used lyophilized donanemab drug product in the phase 2 trial and is proposing to use a solution formulation as the to-be-marketed formulation. The applicant performed supportive studies to compare the formulations. OBP confirmed that applicant has provided adequate comparability studies to demonstrate that the to-be-marketed product and the pivotal clinical trial formulation are comparable. Please refer to OBP review for details.

# 4 APPENDICES

## 4.1 Summary of Bioanalytical Method Validation

### *4.1.1 Bioanalysis of donanemab in human serum*

For the determination of serum donanemab concentrations, the applicant used an Enzyme-Linked Immunosorbent Assay (ELISA) method. The applicant submitted three validation reports (Reports 8248-152, 8338-154, and 8352-531) to support donanemab quantification in human plasma. The applicant conducted cross-validation assessments between the different methods by analyzing spiked serum controls and incurred serum sample pools. The recovery of the spiked controls and incurred pools was within 30% on comparing different methods and is considered acceptable.

Briefly, the final method used [$Pyr^3$]-β-amyloid (3-40) capture reagent precoated on Nunc Medisorp Microtiter® plates to capture donanemab present in the serum. Bound donanemab was detected by using mouse anti-human IgG-coupled horseradish peroxidase and visualized using 3, 3', 5, 5'–tetramethylbenzidine peroxidase substrate solution. The color development was stopped, and the intensity of the color was measured at 450 nm with a wavelength correction set to 650 nm. The concentration of the samples was obtained from a 5-parameter logistic curve fit of the standard curve with 1/y weighting. This method was developed and validated by (b) (4) . The ELISA method was validated in compliance with the standards set forth in the 2018 FDA Bioanalytical Method Validation guidance. Summary of the validation parameters are presented in the ***Table 1*** below:

**Table 1: Summary of Donanemab Serum Bioanalytical Assay Validation Report**

| | |
|---|---|
| Analyte | LY3002813 (Donanemab) |
| Source and Lot of Reagents | Donanemab drug product, Eli Lilly and Company, Lot RS1009; 4.6 mg/mL |
| Biological Matrix | Human serum |
| Minimum Required Dilution | 1:40 |
| LLOQ | 200 ng/mL |
| ULOQ | 5000 ng/mL |
| MQC | 1500 ng/mL |

| | |
|---|---|
| Cumulative Accuracy (%Bias) of Standards | -1.3% to 2.2% |
| Cumulative Precision (%CV) of Standards | ≤3.0% |
| Cumulative Accuracy (%Bias) of QCs | -1.5% to 5.0% |
| Cumulative Precision (%CV) of QCs | ≤9.7% |
| Total Error QCs | ≤12.3% |
| Selectivity & matrix effect | Evaluated in ten samples of normal human serum and diseased human serum at 200 or 300 ng/mL. All spiked samples had acceptable recoveries (≤20%), and all the blank samples were less than LLOQ. |
| Dilution Linearity and Hook Effect | 3200-fold dilution validated. No hook effect was observed. |
| Hemolysis Effect | Five hemolyzed samples were evaluated unspiked and spiked at 200 or 300 ng/mL. All spiked samples had acceptable recoveries (≤20%), and all the unspiked samples were less than LLOQ. |
| Freeze-thaw stability | 6 freeze-thaw cycles at -70°C |
| Long-term storage | 364 days at -20°C and 631 days at -70°C |
| Lipemic effect | Five lipemic samples were evaluated unspiked and spiked at 200 or 300 ng/mL. All spiked samples had acceptable recoveries (≤20%), and all the unspiked samples were less than LLOQ. |

*Reviewer's comments:*

*The validated assay performance was reviewed for the pivotal phase 2 study. Accuracy and precision of QC samples were ≤15% (and ≤20% at LLOQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits. Further, based on the*

*recoveries and passing rates of spiked controls and incurred serum sample pools, the cross validation was considered acceptable.*

### *4.1.2 Bioanalysis of p-tau217 in human plasma*

For the determination of plasma p-tau217 concentrations, the applicant used a bead-based ELISA method. (b) (4)

(b) (4)

Summary of the validation parameters submitted by the applicant are presented in **Table 2**. Deficiencies were identified in some of the validation parameters which are described below.

**Table 2: Summary of Bioanalytical Method Performance in Plasma – Phospho-Tau 217 (p-tau217) Assay**

| | |
|---|---|
| **Bioanalytical method validation report name, amendments, and hyperlinks** | C078 |
| **Method description** | Method Validation of Measuring P-tau217 via a Digital Immunoassay Method |
| **Materials used for standard calibration curve and concentration** | (b) (4) |
| **Validated assay range** | |
| **Material used for quality controls (QCs) and concentration** | |
| **Minimum required dilutions (MRDs)** | |
| **Source and lot of reagents (LBA)** | |
| **Regression 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** | |
| **Carry over** | |
| | |
| **Assay passing rate** | |
| **Standard curve performance** | |

*Source: Applicant Clinical Summary Appendix; Pg-15, Table APP.2.7.1.7*

*Reviewer's comments:* Below is the list of the deficiencies related to validation parameters.

1. **Inadequate long term stability duration:** (b) (4) [redacted]

2. **Insufficient stability assessment with respect to concentration range:** (b) (4) [redacted]

3. **Insufficient data to support lack of cross-reactivity:** (b) (4) [redacted]

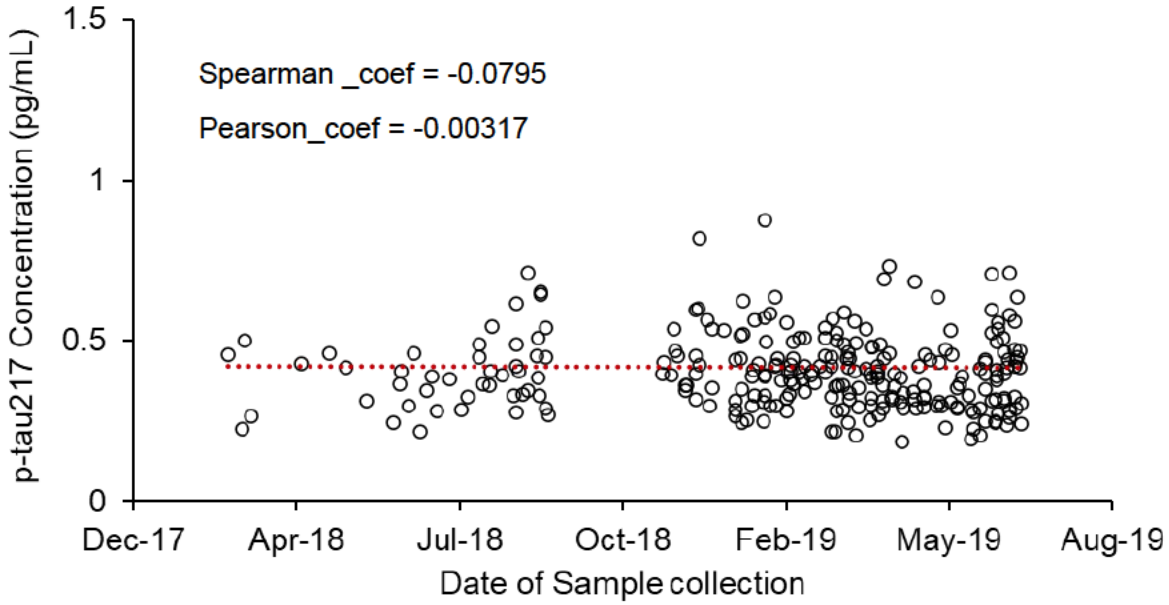
4. **No accuracy data:** (b) (4) [redacted]

5. **Inadequate data to support the use of different matrices for calibrators and actual samples:** (b) (4) [redacted]

(b) (4)

The reviewer conducted exploratory analysis to evaluate the potential impact of long-term storage stability on p-tau217 analysis. The reviewer examined the plasma p-tau217 baseline data in relation to the sample storage duration. According to the applicant's response to IR, the first samples were collected in early 2018 with the bulk of the samples collected throughout 2019 and 2020. Sample analysis for p-tau217 began in May 2021 and were completed by July 2021. The sample storage span varied from 1 – 3.5 years before the analysis. ***Figure 11*** shows that no correlation (Spearman_coeff = -0.0795; Pearson_coeff = -0.00317) was observed between the baseline plasma p-tau217 concentrations and date of sample collection. This exploratory correlation analysis cannot be considered as a substitute for long-term storage stability to justify endorsing quantitative information.

**Figure 11: Correlation between p-tau217 and date of sample collection in baseline samples**




*Source: Reviewer's analysis*

*Summary: In summary, the method validation does not meet the industry standard or comply with recommendations in the FDA Bioanalytical Method Validation guidance and*

*therefore, the integrity of analyte during study conduct cannot be assured. Following to the mid-cycle meeting, the applicant submitted additional long term stability data at* (b) (4) *$^0$C for up to 12 months. However, the established stability period of 12 months is insufficient to support the sample storage duration of approximately 3.5 years.*

### *4.1.3 Bioanalysis of GFAP in human plasma*

For the determination of plasma GFAP concentrations, the applicant used a bead-based ELISA method. (b) (4) Summary of the applicant submitted validation parameters are presented in the ***Table 3*** below. Deficiencies were identified in some of the validation parameters which are described below.

**Table 3: Summary of Bioanalytical Method Performance in Plasma – Glial Fibrillary Acidic Protein (GFAP) Assay**

| Method description | Method Validation of measuring GFAP via a Digital Immunoassay Method (b) (4) |
|---|---|
| Materials used for standard calibration curve and concentration | |
| Validated assay range | |
| Material used for quality controls (QCs) and concentration | |
| Minimum required dilutions (MRDs) | |
| Source and lot of reagents (LBA) | |
| Regression model and weighting | |
| Validation parameters | |
| Standard calibration curve performance during 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 | |
| Carry over | |
| | |
| Assay passing rate | |
| Standard curve performance | |
| QC performance | |

*Source: Applicant Clinical Summary Appendix; Pg-16, Table APP.2.7.1.8*

*Reviewer's comments:* Below is the list of the deficiencies related to validation parameter.

1. **Inadequate long term stability data:** (b) (4)

2. **Insufficient data to support no interference from hemolysis and lipemic plasma:** (b) (4)

3. **Lack of selectivity data:** (b) (4)

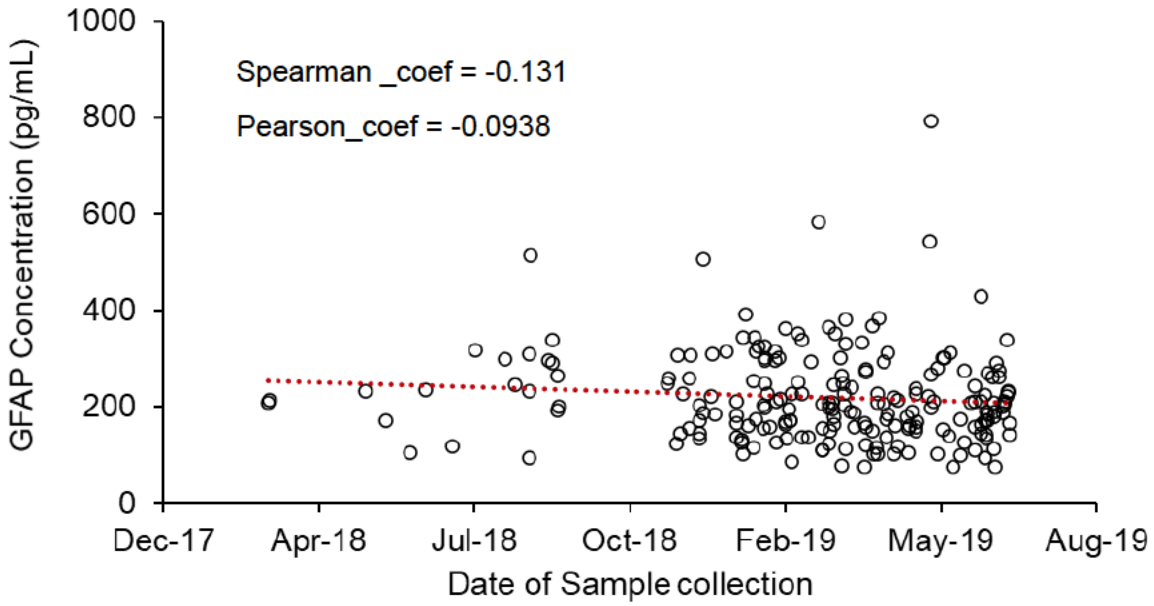
4. **Inadequate accuracy data:** (b) (4)

5. **Insufficient freeze/thaw stability assessment with respect to concentration range:** (b) (4)

The reviewer conducted an exploratory analysis to evaluate the potential impact of long-term storage stability on GFAP analysis. The reviewer examined the plasma GFAP

baseline data in relation to the sample storage duration. According to the applicant response to an IR, the first samples were collected in early 2018 with the bulk of the samples collected throughout 2019 and 2020.

**Figure 12: Correlation between GFAP and date of sample collection in baseline samples**




*Source: Reviewer's analysis*

Based on the chronological order of GFAP validation reports, sample analysis for GFAP began in June 2021 and were completed by November 2021. The sample storage span varied from ~1 – 4 years before the analysis. **Figure 12** shows that no apparent correlation (Spearman_coeff = -0.131; Pearson_coeff = -0.0938) was observed between the baselibe plasma GFAP concentrations and date of sample collection. This exploratory correlation analysis cannot be considered as a substitute for long-term storage stability to justify endorsing quantitative information.

*Summary: In summary, the method validation does not meet the industry standard or comply with recommendations in the FDA Bioanalytical Method Validation guidance and therefore, the integrity of analyte during study conduct cannot be assured.*

## 4.2. Impact of Immunogenicity

For the determination of ADAs, the applicant used an affinity capture and elution bridge immunogenicity assay. The assay was developed at Lilly Research Laboratories (Eli Lilly and Company, Indianapolis, Indiana, USA) and validated at (b) (4)

(b) (4). Various method validation parameters for assessing immunogenicity were considered adequate. Please refer to the immunogenicity assay review by OBP for additional details.

### *4.2.1 Impact of immunogenicity on PK*

To evaluate the impact of immunogenicity on PK, we compared the observed concentrations in ADA+ and ADA- subjects with time-matched PK and ADA data. The average donanemab concentrations (ADA+ and ADA- groups) were calculated at each timepoint and are presented in ***Figure 13***. The results show that the mean concentrations in ADA+ subjects were lower than ADA- subjects. The geometric mean ratio (GMR) of concentration data between ADA+ and ADA- groups and the related 90% CI are presented in the

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**Table *4*: Study AACG - Summary of average concentration by ADA status**

| Visit # | Treatment week (predose) | Total N | donanemab Concentration (µg/mL), geometric mean | | | | GMR (90%CI) **ADA+/ADA-** |
|---|---|---|---|---|---|---|---|
| | | | ADA+ group | N | ADA- group | N | |
| 2 | 0 | 127 | 3.128 | 6 | 4.642 | 121 | 0.67 (01,3.4) |
| 3 | 4 | 131 | 2.004 | 34 | 7.158 | 97 | 0.28 (0.2,0.3) |
| 4 | 8 | 126 | 2.366 | 97 | 10.948 | 29 | 0.21 (0.1,0.3) |
| 5 | 12 | 125 | 22.661 | 114 | 52.865 | 11 | 0.42 (0.1,1.4) |
| 6 | 16 | 117 | 4.469 | 106 | 17.899 | 11 | 0.25 (0.1,0.6) |
| 7 | 20 | 5 | 0.774 | 5 | - | 0 | - |
| 8 | 24 | 111 | 36.740 | 93 | 86.669 | 18 | 0.4 (0.2,0.9) |
| 9 | 28 | 5 | 0.689 | 5 | - | 0 | - |
| 10 | 32 | 2 | 0.845 | 2 | - | 0 | - |
| 11 | 36 | 101 | 2.938 | 84 | 7.491 | 17 | 0.39 (0.2,0.8) |
| 12 | 40 | 1 | | 1 | - | 0 | |
| 15 | 52 | 91 | 10.073 | 76 | 43.478 | 15 | 0.23 (0.1,0.7) |
| 18 | 64 | 1 | - | 0 | BLQ | 1 | - |
| 19 | 68 | 1 | BLQ | 1 | - | 0 | - |

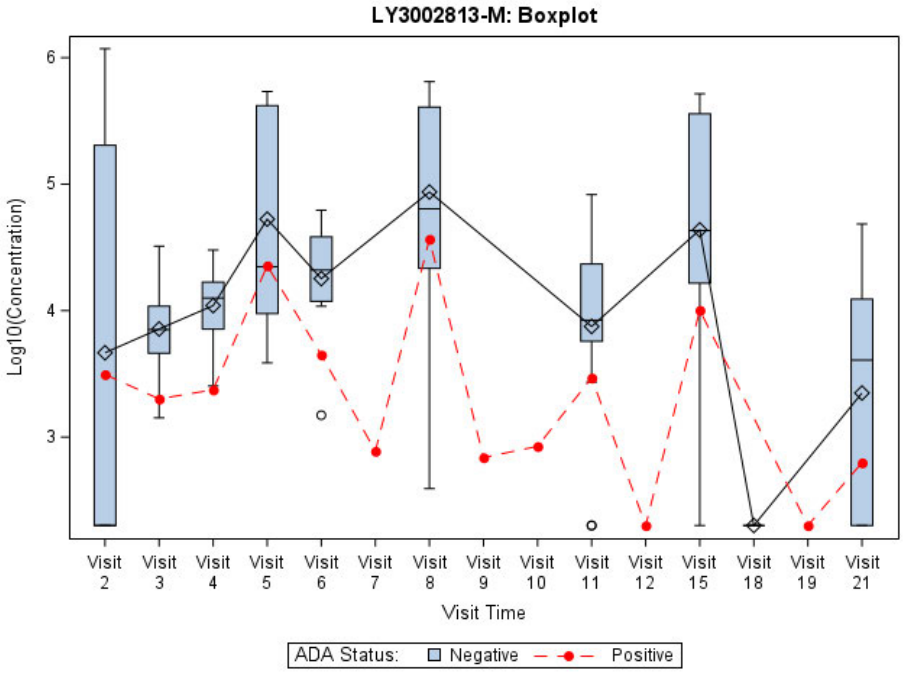
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 21 | 76 | 72 | 0.627 | 53 | 2.229 | 19 | 0.28 (0.1,0.6) |

N: number of subjects; GMR: geometric mean ratio; CI: confidence interval; BLQ: below limit of quantification; ADA status represents the ADA reported for study samples at each study visit

*Source: Reviewer's analysis*

and ***Figure 14***. Subjects in the ADA+ group had lower pre-dose concentrations at all the evaluated time points with lower concentrations in ADA+ group starting from week 4, i.e., at the end of the first dosing interval.

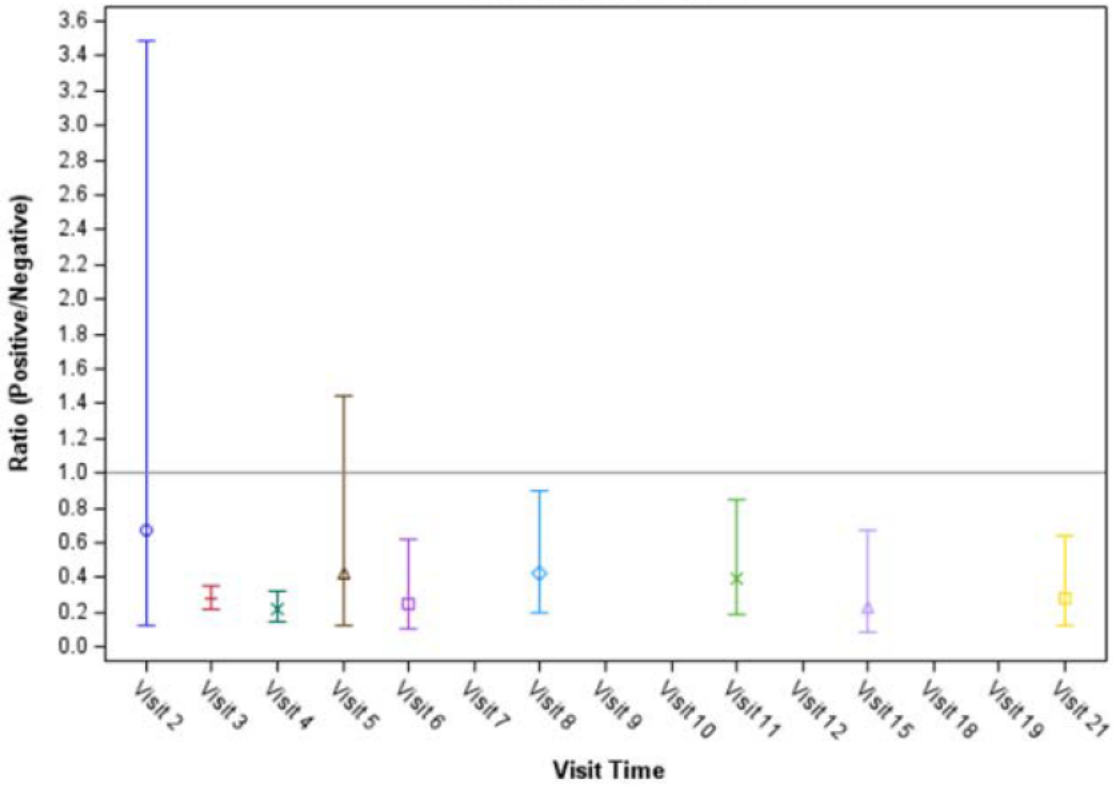
**Figure 13: Donanemab concentrations from ADA positive and ADA negative subjects during the treatment period (72 weeks)**




*The donanemab concentrations at each visit in the ADA negative group are presented in a blue box and the ADA positive group are presented as a line plot. Open rhombus and solid red circle represents the mean donanemab concentrations at each time point.*

Changes in donanemab exposures mediated by ADA titer were also confirmed by modeling and simulations. To account for worst case scenario, the final Pop PK model with subjects maintaining the same ADA titer was used to simulate the impact of ADA on donanemab exposures. There was a significant overlap in the concentrations across different titer cutoff points (<1:5120 and >1:81920). At the maximum titer range (>1:81920), the median exposure (AUCt,ss) was reduced by 23% and trough concentration at steady state was reduced by 55%, compared with the low titer (<1:5120).

**Figure 14: Geometric mean ratio of drug concentration at each visit in ADA+ subjects compared to ADA- subjects**




*Source: Reviewer's analysis*

**Table 4: Study AACG - Summary of average concentration by ADA status**

| Visit # | | Total N | donanemab Concentration (µg/mL), geometric mean | |
|---|---|---|---|---|

| | Treatment week (predose) | | ADA+ group | N | ADA- group | N | GMR (90%CI) **ADA+/ADA-** |
|---|---|---|---|---|---|---|---|
| 2 | 0 | 127 | 3.128 | 6 | 4.642 | 121 | 0.67 (01,3.4) |
| 3 | 4 | 131 | 2.004 | 34 | 7.158 | 97 | 0.28 (0.2,0.3) |
| 4 | 8 | 126 | 2.366 | 97 | 10.948 | 29 | 0.21 (0.1,0.3) |
| 5 | 12 | 125 | 22.661 | 114 | 52.865 | 11 | 0.42 (0.1,1.4) |
| 6 | 16 | 117 | 4.469 | 106 | 17.899 | 11 | 0.25 (0.1,0.6) |
| 7 | 20 | 5 | 0.774 | 5 | - | 0 | - |
| 8 | 24 | 111 | 36.740 | 93 | 86.669 | 18 | 0.4 (0.2,0.9) |
| 9 | 28 | 5 | 0.689 | 5 | - | 0 | - |
| 10 | 32 | 2 | 0.845 | 2 | - | 0 | - |
| 11 | 36 | 101 | 2.938 | 84 | 7.491 | 17 | 0.39 (0.2,0.8) |
| 12 | 40 | 1 | | 1 | - | 0 | |
| 15 | 52 | 91 | 10.073 | 76 | 43.478 | 15 | 0.23 (0.1,0.7) |
| 18 | 64 | 1 | - | 0 | BLQ | 1 | - |
| 19 | 68 | 1 | BLQ | 1 | - | 0 | - |
| 21 | 76 | 72 | 0.627 | 53 | 2.229 | 19 | 0.28 (0.1,0.6) |

N: number of subjects; GMR: geometric mean ratio; CI: confidence interval; BLQ: below limit of quantification; ADA status represents the ADA reported for study samples at each study visit

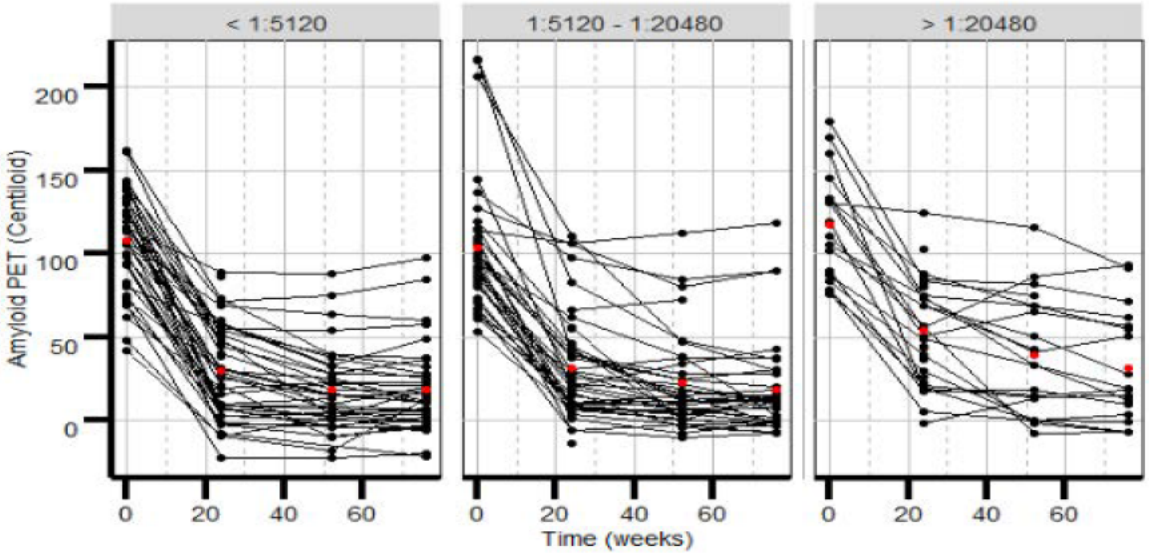
*Source: Reviewer's analysis*

### *4.2.2 Impact of immunogenicity on PD*

To evaluate if the ADA titer mediated changes in donanemab exposures were translated to a reduced PD effect (amyloid PET reduction), the subjects were divided into three different quantiles based on their maximum ADA titer (***Figure 15***). The results indicated that the reduction in amyloid PET was observed irrespective of the observed maximum titer. Additional analyses were also conducted by grouping the subjects based on a) median titer and b) time of appearance of maximum titer i.e., if the maximum titer was

observed before or after dose escalation to 1400 mg at week 12 (***Figure*** and ***Figure 16***). These results indicated that the reduction in amyloid PET was observed irrespective of the observed maximum median titer or observed maximum median titer before or after 12 weeks.

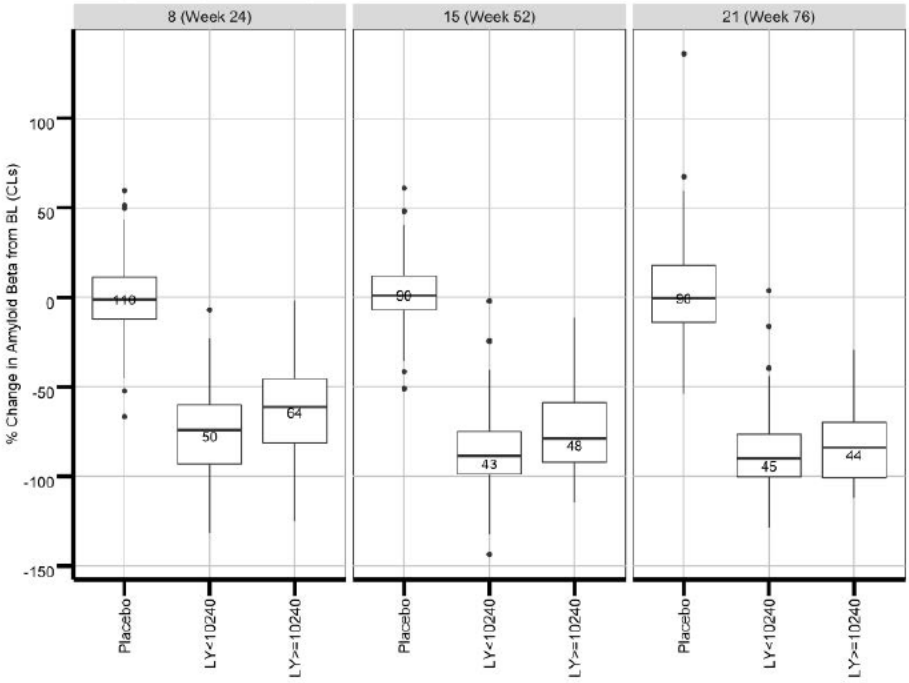
**Figure 15: Changes in Amyloid PET in Individual Subjects by Maximum Titer**




*Amyloid PET values for each subject are presented by individual black lines and solid black circles. The mean on amyloid PET in each group at each time point is represented by a solid red color.*

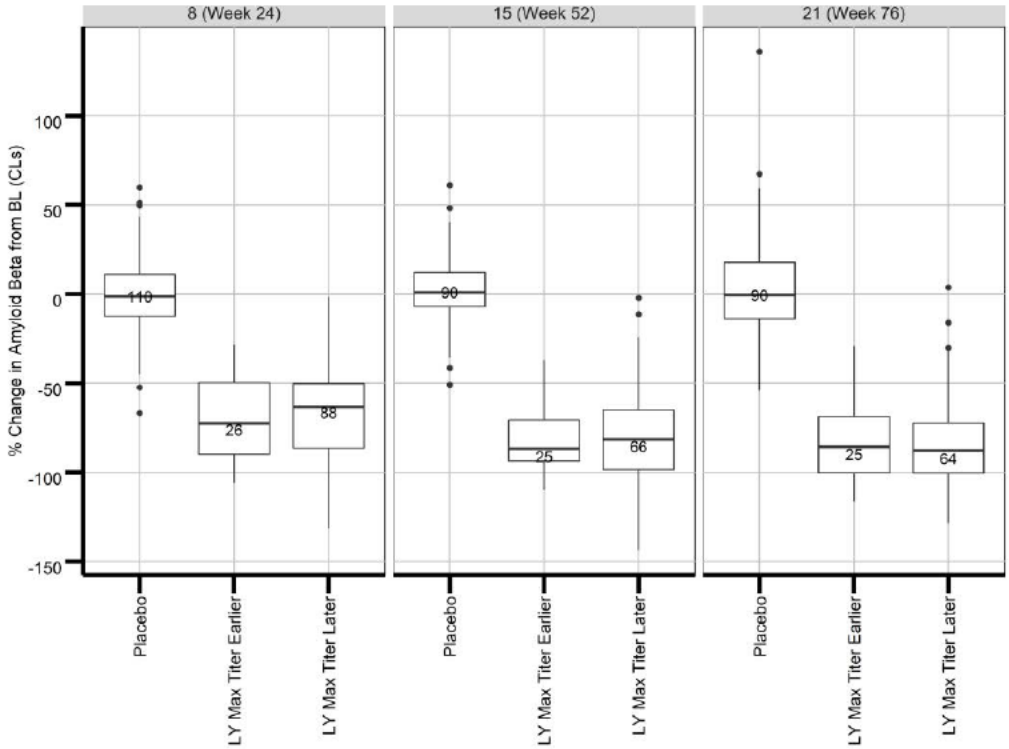
*Source: Reviewer's analysis*

**Figure 16: Changes in Amyloid PET By Median ADA Titer**




*Source: Reviewer's analysis*

**Figure 167: Changes in Amyloid PET by Maximum Titer Observed Before or After 12 weeks**



### *4.2.3 Impact of immunogenicity on Safety and Efficacy*

There is insufficient data to assess whether the observed ADA-associated changes in pharmacokinetics reduces effectiveness. Also, because of the low occurrence of subjects without ADAs, the effect of ADA on the safety of donanemab is unknown.

## 4.3 Population PK Review

The applicant developed a population PK model to describe the pharmacokinetics (PK) of donanemab, characterize the relationship between donanemab PK with demographics and other covariates. The PK dataset includes subjects with early symptomatic AD.

Summary of PK data

In total, the PK dataset consisted of 2578 observations from 177 subjects. The data was obtained from 2 clinical studies:

Phase 1b: AACD: 46 subjects

Phase 2: AACG: 131 subjects

Study details can be found in **3.1 Overview** of the Product and Regulatory Background.

**Population PK Model**

Applicant's modeling approach utilized the rich PK data from phase 1 studies (Study AACC and AACD) to develop the structural model. Next, the data from Study AACG was included along with the data from Study AACD for (re)estimation of model parameters. Based on the previous experience from phase 1 studies, body weight was prospectively included as a covariate in the base model. The applicant evaluated the possible effect of various covariates for their clinical relevance on the disposition of donanemab during the final model development.

The selected base model had two-compartments following intravenous infusion and was parameterized in terms of clearance (CL), volume of distribution of the central (V1) and peripheral compartment (V2), and intercompartment clearance (Q). Interindividual variability was added on clearance, as well as central and peripheral volumes of distribution. Following the completion of stepwise covariate modeling and additional covariate testing outside stepwise covariate modeling, one covariate effect (ADA titer) was found to be statistically significant. The final model included covariate effect of titer change over time on clearance.

Allometric Scaling: Clearance and distributional clearance were scaled allometrically by weight and central and peripheral volumes of distribution were also scaled allometrically with weight, using exponents of 0.8 for clearance terms and 1 for volume terms.

Residual variability: Multiplicative

Covariates: The final model identified ADA titer as a covariate on clearance and body weight normalized to 72 kg as a covariate on clearance and volume using a power model. Fixed power coefficients of 0.8 and 1 were applied to clearance and volume, respectively.

Typical estimates of PK model parameters were CL=0.0249 L/h, V1=3.37 L, V2=3.63 L, and Q=0.0189 L/h with %SE ranging from 3% to 12%. Variance terms highlighted a large inter-individual variability in the population on V2 (84.4 %CV). Inter-individual variability in the population on CL and V1 were limited being 19.6 and 21.8%, respectively.

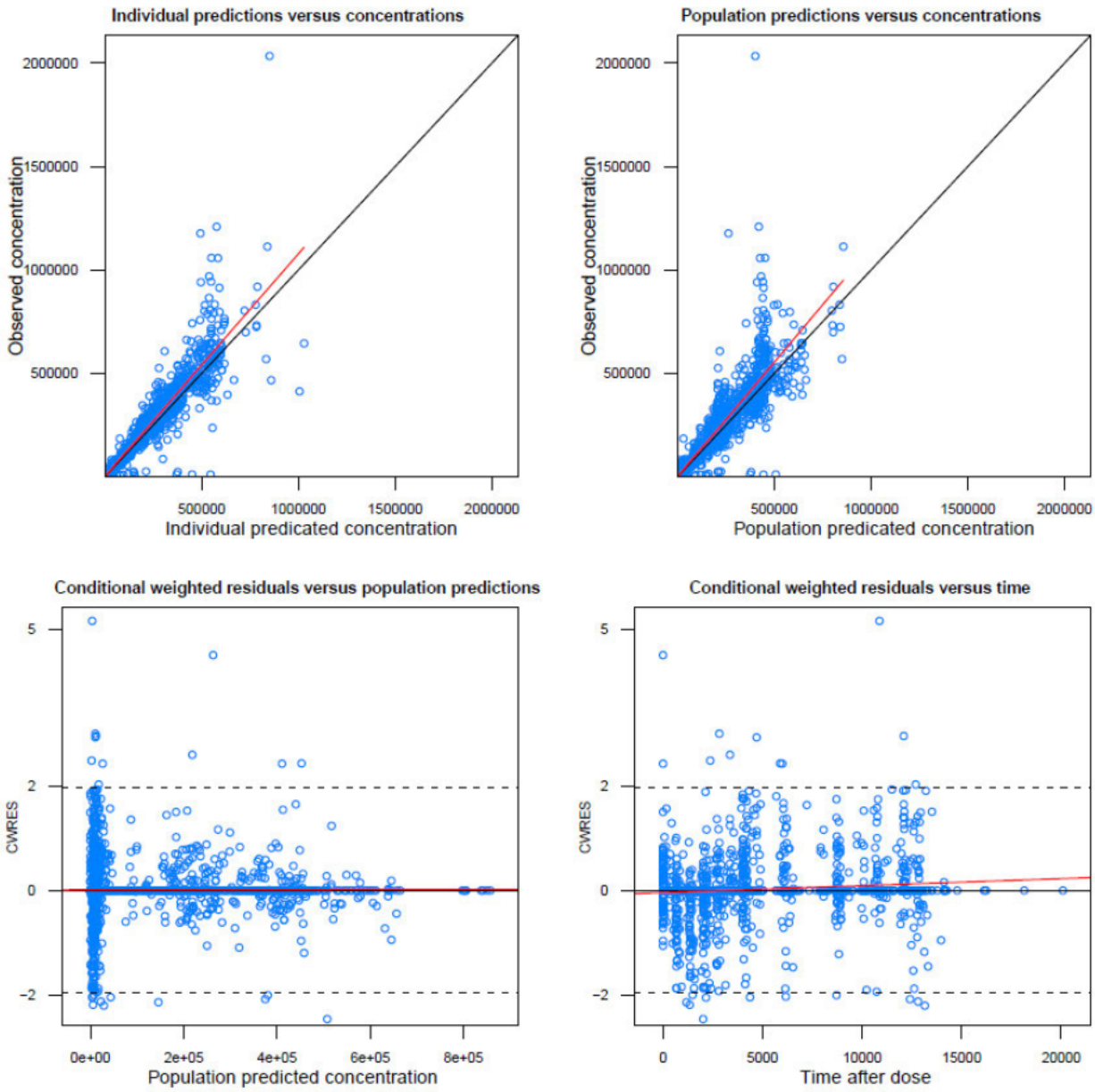
The parameter estimates for the base model and the final model are shown in the ***Table 5*** below.

**Table 5: Pharmacokinetic and Covariate Parameters in Population Model**

| Parameter | Base Model Population Mean (95% CI)[g] | Final Model Population Mean (95% CI)[g] |
|---|---|---|
| CL (L/h)[a] | 0.0275 (0.0258-0.0294) | 0.0249 (0.0234-0.0265) |
| V1 (L)[b] | 3.40 (3.21-3.55) | 3.37 (3.21-3.53) |
| V2 (L)[c] | 3.41 (2.88-4.06) | 3.63 (3.11-4.27) |
| Q (L/h)[d] | 0.0189 (0.0151-0.0248) | 0.0189 (0.0150-0.0233) |
| **Covariate effects** | | |
| *Covariate effect on Cl[e]* | | |
| Effect of titer | NA | 0.0333 (0.0218-0.0554) |
| **Interindividual variability CV% (95% CI)[f]** | | |
| CL | 20.7% (16.8-23.4) | 19.6% (16.4-22.4) |
| V1 | 21.8% (12.7-31.7) | 21.8% (15.5-28.2) |
| V2 | 75.7% (57.9-97.1) | 84.4% (67.6-110) |
| **Residual unexplained variability** | | |
| Proportional (%) | 41.7% (38.4-47.8) | 40.2% (36.6-44.2) |

The model diagnostics are presented in **Figure 17** and **Figure 18**

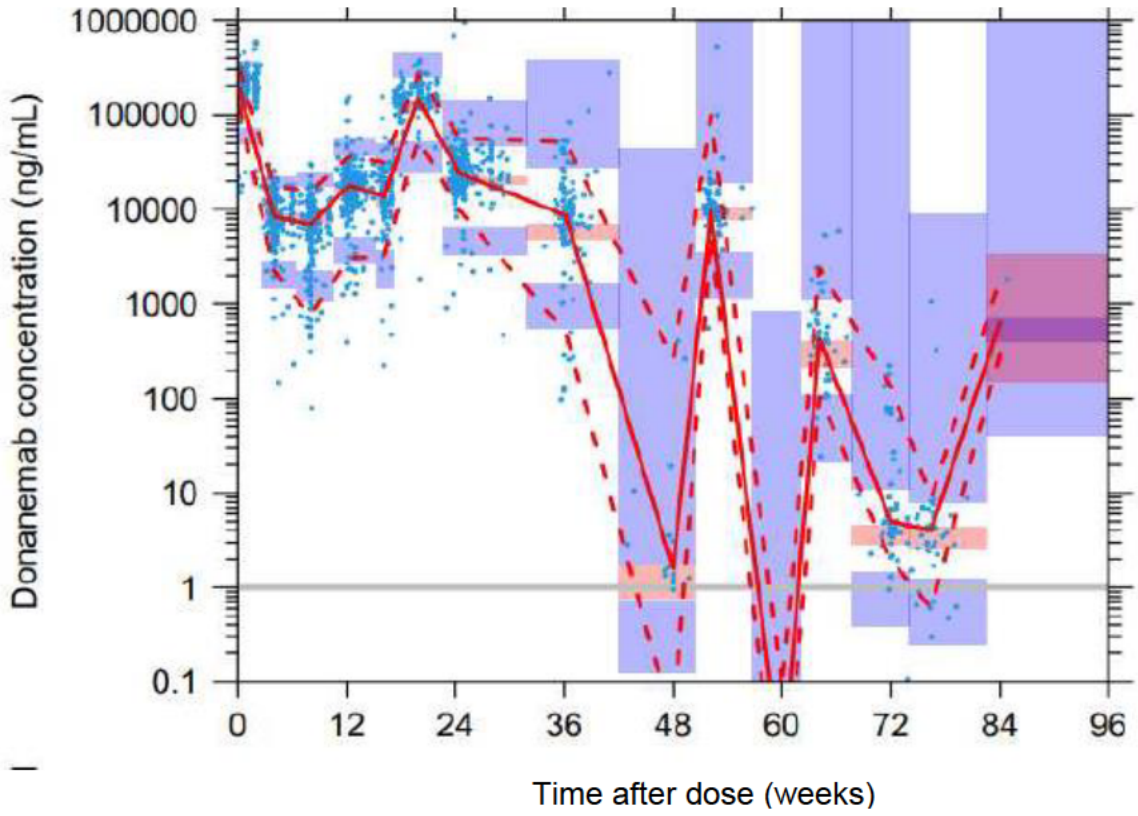
**Figure 17: Diagnostic plots for the Final Population PK Model**




*Blue: data points, Red Line: line of identity. Units: ng/mL*

*Source: Reviewer's independent analysis*

**Figure 18: Visual Predictive Check for the Final Population PK Model**




*Solid red line: median of observed concentrations; dashed red lines: 5th and 95th percentiles of observed concentrations; red shaded area: confidence interval for the median of simulated data; blue shaded areas: 95% confidence intervals (CIs) for the 5th and 95th percentiles of simulated data; blue full circles: individual observed concentration data. The gray horizontal line represents the lower limit of quantification (LLOQ) of 200ng/mL.*

*Source: 5-3-3-5-Pop PK AACD AACG report-.pdf, page 43*

*Reviewer's Comments: The visual inspection of goodness-of-fit diagnostic plots do not suggest the presence of systemic bias and provided an adequate description of the donanemab plasma concentrations. Concentration values associated to CWRES greater than /4/ were 2 representing a small percentage in the whole data set. The visual predictive check indicates that the model can represent the distribution of donanemab exposures reasonably well for the dosing regimen used in Study AACG. Overall, the model is acceptable.*

### *4.3.1 Reviewer PK Simulations*

The reviewer conducted a simulation to assess characterize the effect of body weight on the steady-state Cmax for the proposed dosing. The Applicant's PPK model was used to simulate the PK profile for a typical patient weighing 50 kg and 98 kg, respectively. The

dosing regimen simulated is three administrations of 700 mg once monthly followed by 1400 mg once monthly until steady-state (nine administrations of 1400 mg once monthly used to represent steady-state). The simulated state-state Cmax for 1400 mg once monthly for a 50 kg and 98 kg subject are 624 µg/mL and 323 µg/mL (93% greater for a typical 50 kg subject compared to 98 kg), respectively. Please refer to **4.4.1 Amyloid-Plaque** Reduction for details on the anticipated impact of weight on amyloid plaque.

## 4.4 Exposure-Response Analyses

The Applicant submitted report pop-pk-aacg-report.pdf, titled "Population Pharmacokinetic and Pharmacodynamic Analyses of Studies I5T-MC-AACD and I5T-MC-AACG" submitted to module 5335 in sequence 0002. The exposure-response analyses in the report assess the relationship between exposure and ARIA-E, amyloid PET, P-tau217, and disease progression (via iADRS and CDR-SB). The amyloid PET analyses include data from studies AACD and AACG. The analyses of ARIA-E and disease progression models (iADRS and CDR-SB) include data from AACG.

The individual PK parameters estimates from the population PK analyses (see 4.2.3 Impact of immunogenicity on Safety and Efficacy

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There is insufficient data to assess whether the observed ADA-associated changes in pharmacokinetics reduces effectiveness. Also, because of the low occurrence of subjects without ADAs, the effect of ADA on the safety of donanemab is unknown.

4.3 Population PK Review) were used with the observed dosing history for each subject to obtain drug concentration predictions for inclusion in these analyses. All analyses were performed in the NONMEM version 7.4.2 software package.

### *4.4.1 Amyloid-Plaque Reduction*

The dataset includes n=1147 amyloid plaque observations a total of 304 subjects from studies AACD and AACG. The observed amyloid plaque data are shown for study AACG in **Figure 1** for study AACD in **Figure 4**.

A turnover model (also referred to as an indirect response model) was applied to describe the time-course of amyloid plaque level. The model is parameterized in terms of amyloid plaque elimination half-life and individual subject baseline plaque level. The effect of PK on amyloid plaque levels was coded as a simulating the amyloid plaque degradation rate constant. Covariates tested on the treatment effect parameter include ADA titer and time from diagnosis as continuous linear relationships, and treatment emergent ADA status as well as APOE4 status as categorical relationships. Covariates tested on the baseline amyloid plaque parameter included time from diagnosis as a continuous linear relationship and APOE4 status as a categorical relationship. None of the covariates assessed were statistically significant. Parameter estimates are shown in ***Table 6***.

**Table 6: Parameter Estimates for the Final Amyloid Plaque Reduction Model.**

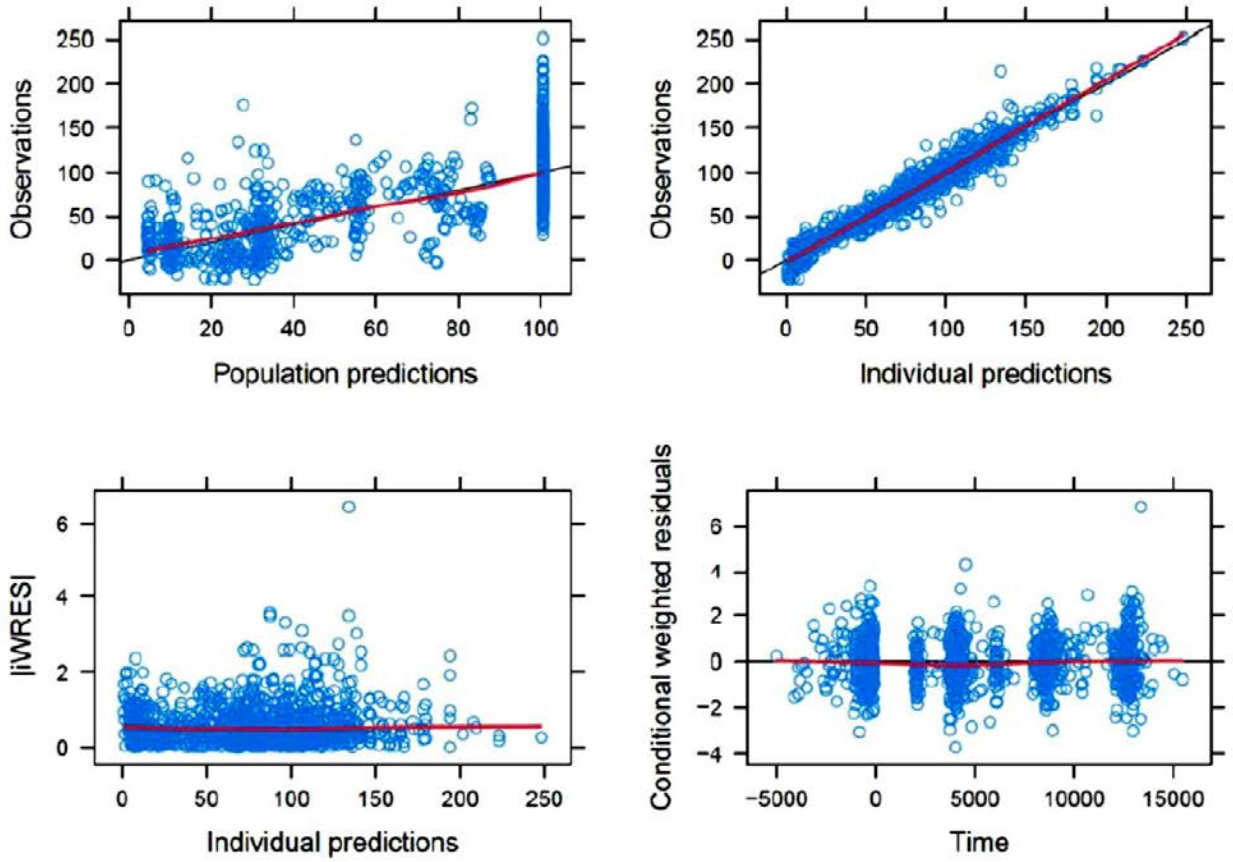
| Parameter | Final model (95% CI)[a] |
|---|---|
| Treatment effect | 38.6 (19.3, 103.6) |
| Plaque removal half-life (hr) | 89200 (47646.1, 206032.4) |
| Baseline amyloid plaque (Centiloid units) | 101 (97.35, 104.63) |
| Threshold concentration associated with treatment effect (µg/mL) | 4.43 (0.956, 10.380) |
| **Interindividual variability CV% (95% CI)** | |
| Treatment effect | 95.2% (75.2, 120.8) |
| Baseline amyloid plaque | 30.9% (27.6, 34.3) |
| **Residual unexplained variability** | |
| Additive (Centiloid) | 12.5 (11.5, 13.8) |

Abbreviations: CI = confidence interval; CV = coefficient of variation.
[a] 95% CI from bootstrap.

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 45 of 176*

Key diagnostic plots are presented in **Figure 19**.

**Figure 19: Diagnostic plots for the amyloid-plaque reduction PKPD model**

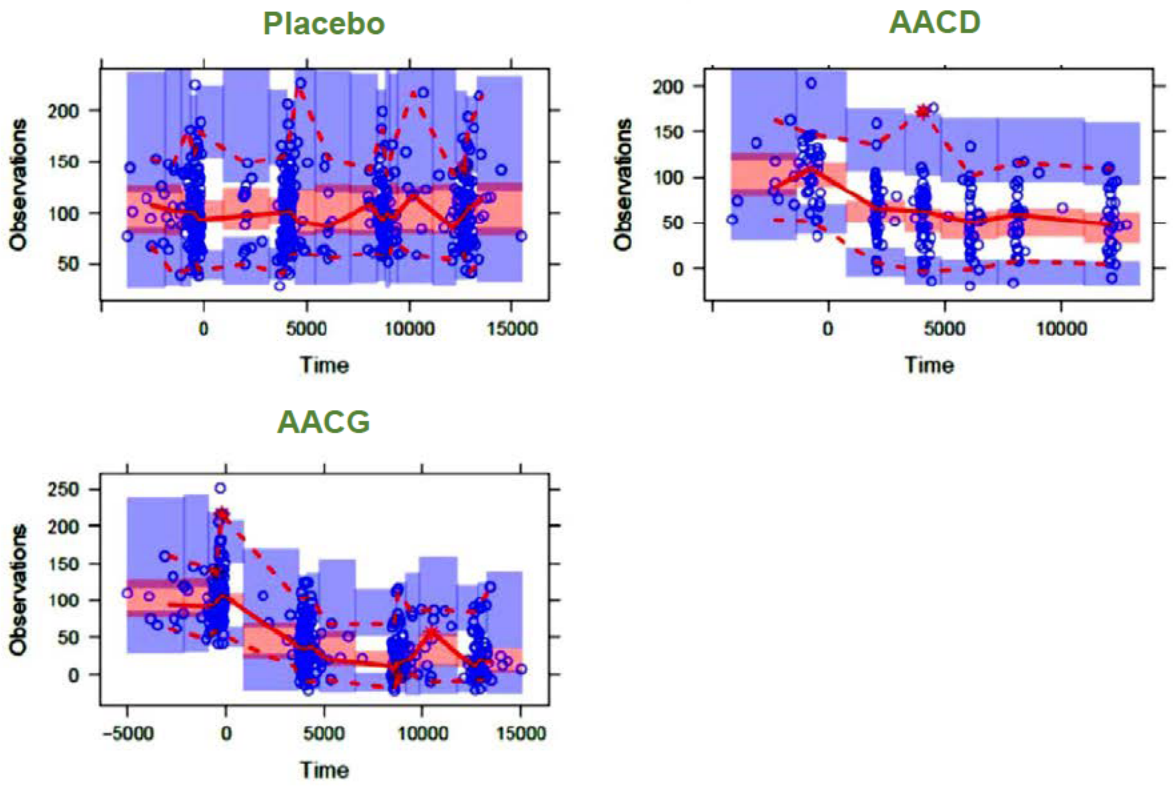



IWRES = individual weighted residual.

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 137 of 176*

A visual predictive check is presented in **Figure 20**.

**Figure 20: Visual predictive check for Final Model of Amyloid Plaque Reduction**

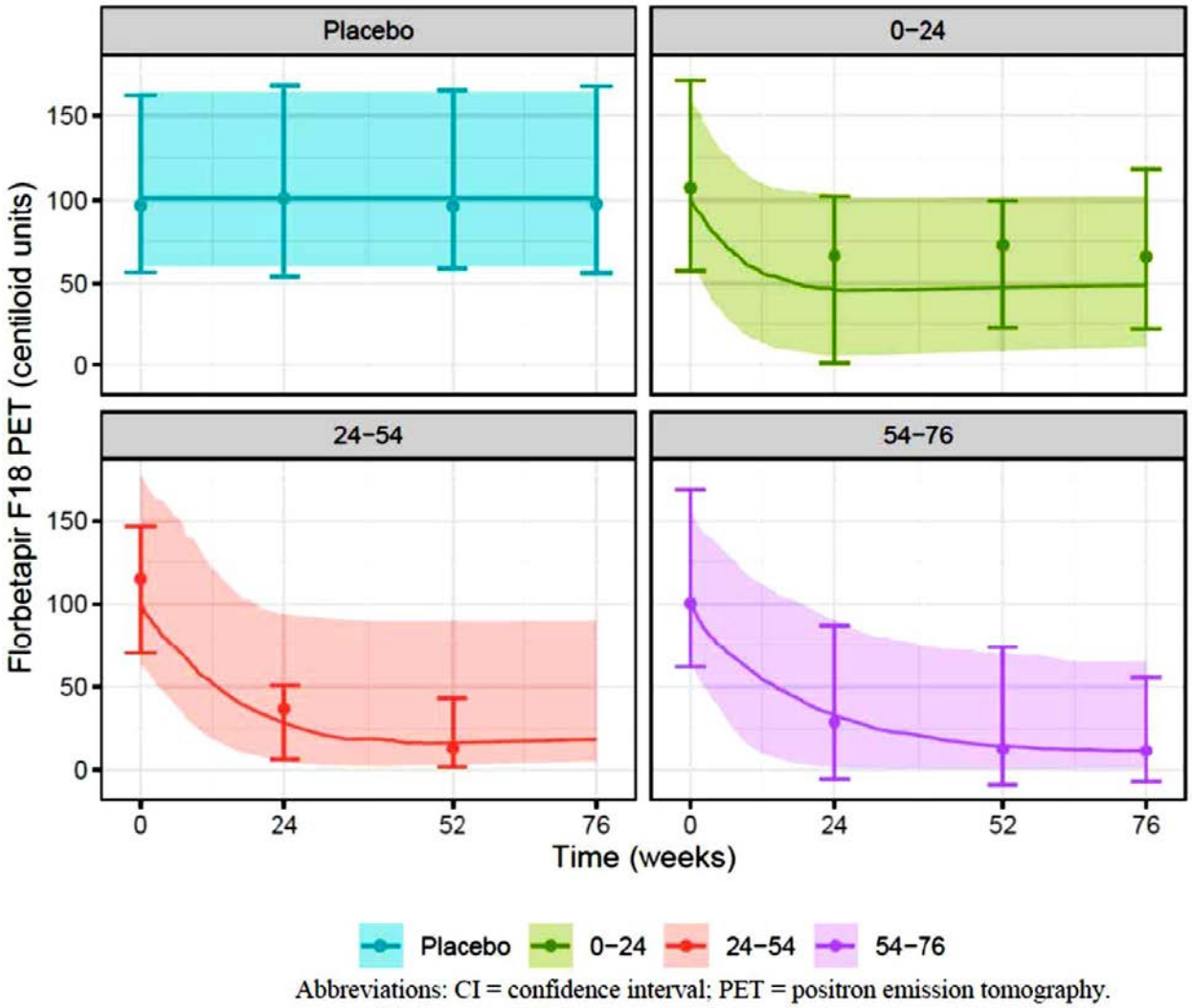



Data and predictions stratified by placebo arm (top left panel), AACD donanemab data (top right panel), and AACG donanemab data (bottom panel).
Observed data: Solid red line: median of observed concentrations; dashed red lines: 5th and 95$^{th}$ percentiles of observed concentrations; blue full circles: individual observed amyloid plaque data.
Simulated data: red shaded area: 95% confidence interval for the median of simulated data; blue shaded areas: 95% confidence intervals for the 5$^{th}$ and 95th percentiles of simulated data;

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 46 of 176*

The Applicant conducted an additional assessment of model performance using data from subjects who discontinued treatment (or were dose reduced to 0 mg) early. The effect of withdrawing treatment after achieving amyloid beta plaque reduction to <11 Centiloid. This scenario includes the subset of subjects that demonstrated < 11 Centiloid levels before Week 24. Subjects were simulated to received 24 weeks of treatment at which time treatment ceases. **Figure 21** shows the anticipated re-accumulation according to the amyloid plaque PKPD model.

**Figure 21: Observed (5th, 50th, 95th percentile) and PKPD Simulated (median and 95% CI) Amyloid Plaque Levels In Subjects With Early Treatment Cessation.**




CI = confidence interval; PET = positron emission tomography. PKPD simulated median and 95% CI of the median represented by solid line and shaded areas, respectively. Observed 5$^{th}$, 50$^{th}$ (median) and 95th percentiles represented by dose and bars, respectively.

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 47 of 176*

[*Reviewer comment: Eta shrinkage is 37% and 7%, for treatment effect and baseline amyloid level, respectively. Epsilon shrinkage 18%. The between subject variability on the treatment effect is high (CV 95%). The residual unexplained variability (12.5 Centiloid) is ~1/3 of the treatment effect size (38.6 Centiloid).*

*The diagnostic plots (**Figure 19**) do not suggest the presence of systematic bias with respect to time after dose or magnitude of concentrations. The VPC (**Figure 20**) demonstrates that the model appears to capture the central tendency of the model more reliably (with 2-3 times smaller confidence interval width) than the extreme values.*

*The Applicant's model for amyloid plaque reduction demonstrates the presence of an exposure dependent effect. Overall, the PKPD model is acceptable.*

**PKPD Simulations of Amyloid Beta**

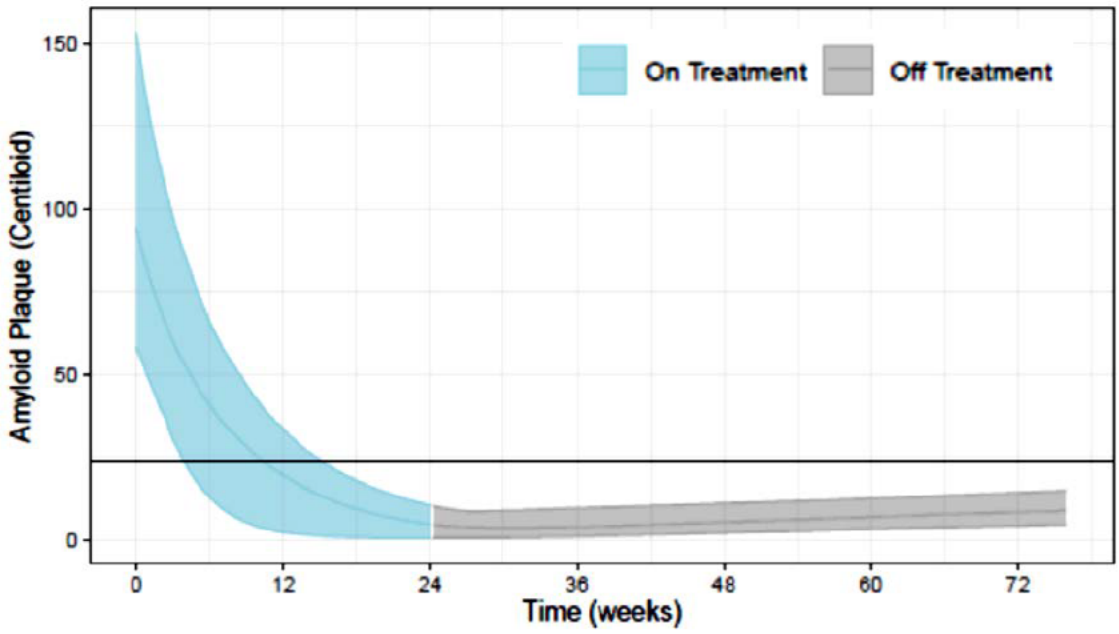
The Applicant utilized the amyloid PKPD model to conduct numerous simulations. For each amyloid PKPD simulation, the applicant utilized the titration and maintenance dosing in Phase 2 study AACG. All simulated subjects started on 700 mg Q4W for the first three doses, followed by 1400 mg Q4W up to Week 76; the dosing amount for each simulated subject was adjusted at Weeks 24 and 52 based on each simulated subject's predicted amyloid plaque level, where if amyloid plaque level <11 Centiloid, then the dose amount was reduced by 1 level from 1400 to 700 mg or from 700 to 0 mg. If amyloid plaque level ≥11 Centiloid at Weeks 24 or 52, then the simulated patient continued receiving the current dose.

**Effect of Immunogenicity**: The Applicant assessed the effect of ADA titer (a covariation donanemab PK) on the predicted amyloid beta profile. The amyloid levels were simulated for donanemab treatment as administered in Phase 2 study AACG (refer to the previous paragraph for details on dosing). The Applicant concludes that while higher ADA titers are associated with increased donanemab clearance, the effect of donanemab on amyloid beta are generally similar in subjects with no ADA titer versus subjects with the highest observed ADA titer assigned at each timepoint in the simulation.

The reviewer conducted independent analyses to assess the Applicant's conclusion regarding the effect of immunogenicity on amyloid levels. The reviewer generated plots of observed amyloid beta time profile for subjects stratified by maximum titer level. Based on these analyses (see **Figure 15**, **Figure** , and **Figure 16**), amyloid plaque removal was observed irrespective of the maximum titer value or whether the maximum titer occurred before or after the dose escalation to 1400 mg at week 12.

**Effect of Withdrawal at Week 24 When < 11 Centiloid Is Achieved**: The Applicant utilized the amyloid-plaque model and applied it to assess the effects of donanemab discontinuation on amyloid-plaque levels. For this analysis the Sponsor used the PPK model, the documented donanemab dosing history for subjects that includes dosing lapses, and the amyloid degradation model to predict the effects of dosing lapse on the amyloid beta profile. The predicted the amyloid-beta profile is compared against the observed amyloid-beta values in **Figure 22**.

**Figure 22: Simulated amyloid plaque level over time using treatment exposure-response model and stratified by participants achieving <11 Centiloid units at Week 24. Duration extending to 76 weeks**




PET = positron emission tomography. The solid line represents the simulated median value, and the shaded area represents the 95% confidence interval of the median. Simulations used titer values over time from the NONMEM dataset with last-observation-carried-forward applied to replicate the time-varying effect of titer on clearance in the PK model. Reference line shows 24.1 Centiloid.

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 70 of 176*

Applicant concludes that in a group of subjects that achieve amyloid levels <11 Centiloid by week 24, withdrawal of donanemab treatment did not result in a substantial increase in amyloid level through the end of the simulation (Week 76).

[*Reviewer comment: The Applicant utilizes a threshold of 24.1 Centiloid to represent complete amyloid clearance. During study AACG, an additional threshold of < 11 Centiloid was also used to determine when treatment could be discontinued.*

*The Applicant's simulations suggest that after attaining amyloid plaque levels < 11 Centiloid by 24 weeks, if donanemab treatment ceases at 24 weeks, that the donanemab levels are expected to increase over time.*

*The Applicant conducted simulations extending to 15 years to determine the time at which subjects increase back to 24.1 Centiloid. However, the amyloid assessments were planned up to 76 weeks with the actual times occurring generally ≤ week 80 (out of 1147 amyloid measurements, only 12 measurements were collected across the population between week 80 and the maximum time, 92 weeks). Overall, it is not clear that the model can reliably predict*

*outcomes as far as out as 15 years. As such, the simulations beyond week 76 will not be further discussed.*]

#### 4.4.1.1 Effect of WT on Amyloid Plaque Reduction

Weight is a covariate on donanemab pharmacokinetics (see

Source: Reviewer's analysis

**Table 4: Study AACG - Summary of average concentration by ADA status**

| Visit # | Treatment week (predose) | Total N | donanemab Concentration (µg/mL), geometric mean | | | | GMR (90%CI) **ADA+/ADA-** |
|---|---|---|---|---|---|---|---|
| | | | ADA+ group | N | ADA- group | N | |
| 2 | 0 | 127 | 3.128 | 6 | 4.642 | 121 | 0.67 (01,3.4) |
| 3 | 4 | 131 | 2.004 | 34 | 7.158 | 97 | 0.28 (0.2,0.3) |
| 4 | 8 | 126 | 2.366 | 97 | 10.948 | 29 | 0.21 (0.1,0.3) |
| 5 | 12 | 125 | 22.661 | 114 | 52.865 | 11 | 0.42 (0.1,1.4) |
| 6 | 16 | 117 | 4.469 | 106 | 17.899 | 11 | 0.25 (0.1,0.6) |
| 7 | 20 | 5 | 0.774 | 5 | - | 0 | - |
| 8 | 24 | 111 | 36.740 | 93 | 86.669 | 18 | 0.4 (0.2,0.9) |
| 9 | 28 | 5 | 0.689 | 5 | - | 0 | - |
| 10 | 32 | 2 | 0.845 | 2 | - | 0 | - |
| 11 | 36 | 101 | 2.938 | 84 | 7.491 | 17 | 0.39 (0.2,0.8) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 12 | 40 | 1 | | 1 | - | 0 | |
| 15 | 52 | 91 | 10.073 | 76 | 43.478 | 15 | 0.23 (0.1,0.7) |
| 18 | 64 | 1 | - | 0 | BLQ | 1 | - |
| 19 | 68 | 1 | BLQ | 1 | - | 0 | - |
| 21 | 76 | 72 | 0.627 | 53 | 2.229 | 19 | 0.28 (0.1,0.6) |

N: number of subjects; GMR: geometric mean ratio; CI: confidence interval; BLQ: below limit of quantification; ADA status represents the ADA reported for study samples at each study visit

*Source: Reviewer's analysis*

### *4.2.2 Impact of immunogenicity on PD*

To evaluate if the ADA titer mediated changes in donanemab exposures were translated to a reduced PD effect (amyloid PET reduction), the subjects were divided into three different quantiles based on their maximum ADA titer (***Figure 15***). The results indicated that the reduction in amyloid PET was observed irrespective of the observed maximum titer. Additional analyses were also conducted by grouping the subjects based on a) median titer and b) time of appearance of maximum titer i.e., if the maximum titer was observed before or after dose escalation to 1400 mg at week 12 (***Figure and*** Figure ***16).*** These results indicated that the reduction in amyloid PET was observed irrespective of the observed maximum median titer or observed maximum median titer before or after 12 weeks.

Amyloid *PET values for each subject are presented by individual black lines and solid black circles. The mean on amyloid PET in each group at each time point is represented by a solid red color.*

Source*: Reviewer's analysis*

*Source: Reviewer's analysis*

*4.2.3 Impact of immunogenicity on Safety and Efficacy*

*There is insufficient data to assess whether the observed ADA-associated changes in pharmacokinetics reduces effectiveness. Also, because of the low occurrence of subjects* without ADAs, the effect of ADA on the safety of donanemab is unknown.

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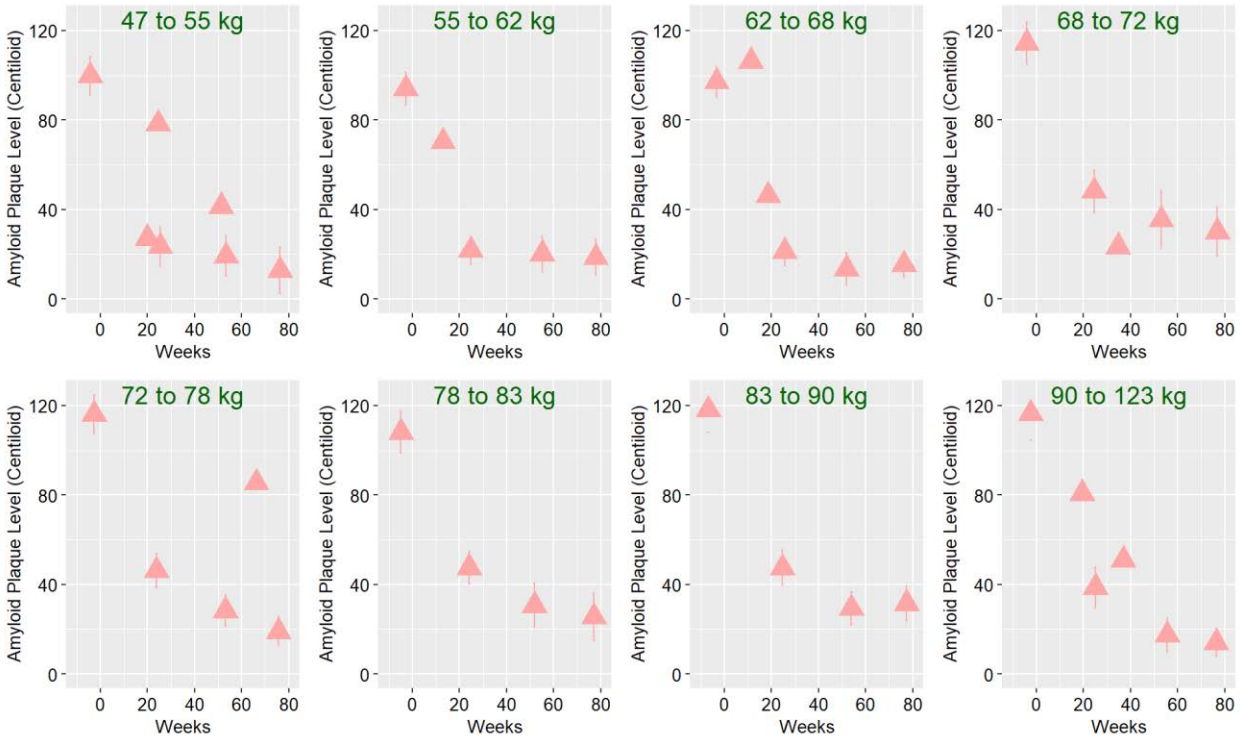
*4.3 Population PK Review* for details). A typical subject weighing 50 kg is expected to have 93% higher $C_{max}$ steady state than a 98 kg subject for the proposed dosing of 1400 mg once monthly (see **4.3.1 Reviewer** PK Simulations). The effect of weight on amyloid plaque profile was assessed graphically in **Figure 23**.

**Figure 23: Observed Amyloid Plaque Profile by Baseline Weight in Study AACG**




*Subjects were binned in 8 quantiles by baseline body weight. Each point represents mean ± standard error amyloid plaque level in centiloids at each timepoint.*

*source: reviewer's analysis*

The data in **Figure 23** do not support the existing of a relationship between weight and amyloid beta plaque reduction in study AACG.

### *4.4.2 ARIA-E*

The ARIA-E events were modeled using a time-to-event framework. These analyses utilized a dataset that included a total of 37 ARIA-E events (37 subjects each with one

event) out of a group of n=254 subjects. In subjects with multiple ARIA-E events, only the first occurrence was included in these analyses. Exponential, Weibull, and Gompertz hazard models were assessed. The probability density function was estimated for individuals that experience ARIA-E at time=t and the probably of not having ARIA-E at time=t was estimated for subjects who did not have an ARIA-E event during the observation period (or were censored).

Covariates assess on the three hazard models were APOE ε4, age of the study participant, time since onset of symptoms of Alzheimer's disease, time since diagnosis of Alzheimer's disease, baseline C-reactive protein, antidrug antibodies, initial rate of plaque removal and sex. A stepwise forward inclusion, backward elimination (stepwise covariate modeling) was implemented. Linear, power, and exponential covariate relationships were evaluated. Covariates were selected based on OFV reduction, clinical relevance, magnitude of effect, and precision of the estimates.

The final model parameter estimates are listed in **Table 7**.

**Table 7: Parameter Estimates for Final PKPD Model for Time-To-First-ARIA-E Event**

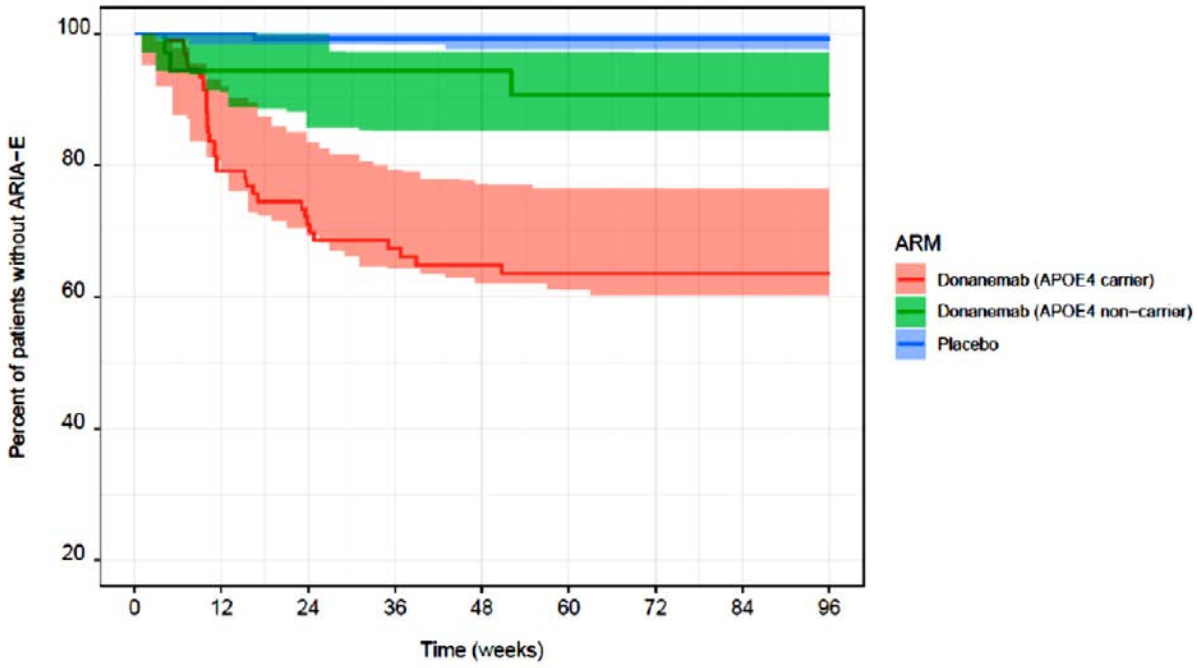
| Parameter | Estimate (%SEE) | Bootstrap (95% CI) |
|---|---|---|
| Baseline hazard | -5.74 (14.0) | (-8.57, -4.46) |
| Weibull Shape | 0.536 (75.2) | (-0.165, 1.64) |
| Gompertz Shape | -0.0859 (45.4) | (-0.210, -0.0264) |
| APOE ε4 carriers on the baseline hazard | -0.225 (28.4) | (-0.406, -0.0736) |
| Placebo treatment on the baseline hazard | 0.827 (30.2) | (0.476, 8.40E+17) |
| $dHaz/dt = e^{(-5.74*(1+\theta_{1placebo})*(1+\theta_{2APOE\ carrier}))} * e^{(-0.0859*t)} * e^{(0.536*Log(t))}$<br>Where Haz is hazard of getting the first event of ARIA-E and<br>$\theta_{1placebo}$ *is* 0.827 *for Placebo*.<br>$\theta_{2APOE\ carrier}$ *is* $-0.225$ *for APOE carriers on drug treatment*. | | |

APOE ε4 = apolipoprotein E4; ARIA-E = amyloid-related imaging abnormalities-edema/effusions, CI=confidence interval; SEE = standard error of estimate.

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 49 of 176*

Key model diagnostics are presented below.

**Figure 24: Visual Predictive check for time-to-first ARIA-E event model**




APOE4 = apolipoprotein E4; ARIA-E = amyloid-related imaging abnormalities-edema/effusions. The solid lines are the Kaplan-Meier plot of the observed data and the shaded areas are the 90% prediction interval for the simulated data.

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 50 of 176*

The Applicant provides the following conclusions:

- For safety measurement ARIA-E, there is a clear donanemab treatment effect. APOE ε4 carrier/noncarrier had different treatment response regarding ARIA-E. APOE ε4 carriers and noncarriers had a 24% and 6%, respectively, likely to develop ARIA-E by Week 24 while placebo treatment had <1%. Donanemab-treated APOE ε4 carriers had 4 times greater likelihood of ARIA-E at Weeks 24 and 96 than donanemab-treated APOE ε4 noncarriers.
- No correlation between donanemab serum concentration and ARIA-E incidence could be determined. The analysis did not identify an exposure limit that was associated with increased risk of ARIA-E. The analysis used data from Study AACG, which examined only a single dosage regimen. The lack of an exposure-response relationship for ARIA-E likely reflects the narrow distribution of exposures in this study.
- Although immunogenicity had an impact on PK, the number of observed ARIA-E events did not provide sufficient power to detect an effect of immunogenicity on ARIA-E incidence at the level of significance required to be included in the model. At $p<0.05$, the data suggests that ADA titer is likely associated with reduced risk of ARIA-E.

[*Reviewer comment: According to* ***Figure 24****, 90% prediction interval (PI) contains the Kaplan-Meier curves for three groups. Compared to the other two groups, the Kaplan-Meier curve for the APOE4 negative group is generally closer to its PI boundary and is outside of it at ~12 weeks and 24 weeks. The relative abundance of APOE4 positive subjects (~74.6% positive) is a factor that likely explains the greater performance in APOE4 positive subjects compared to APOE4 negative subjects.*]

### *4.4.3 p-Tau217*

A turnover model (also known as an indirect response model) was utilized to describe the time-course of plasma P-Tau217. The effect of donanemab on P-Tau217 was coded as a simulating the elimination term for P-tau217. Covariates tested on the treatment effect parameter include ADA titer and time from diagnosis as continuous linear relationships, and treatment emergent ADA status as well as APOE4 status as categorical relationships. Covariates tested on the baseline amyloid plaque parameter included time from diagnosis as a continuous linear relationship and APOE4 status as a categorical relationship. None of the covariates assessed were statistically significant. Parameter estimates are shown in **Table 8**.

**Table 8: Parameter Estimates for the P-tau217 Model**

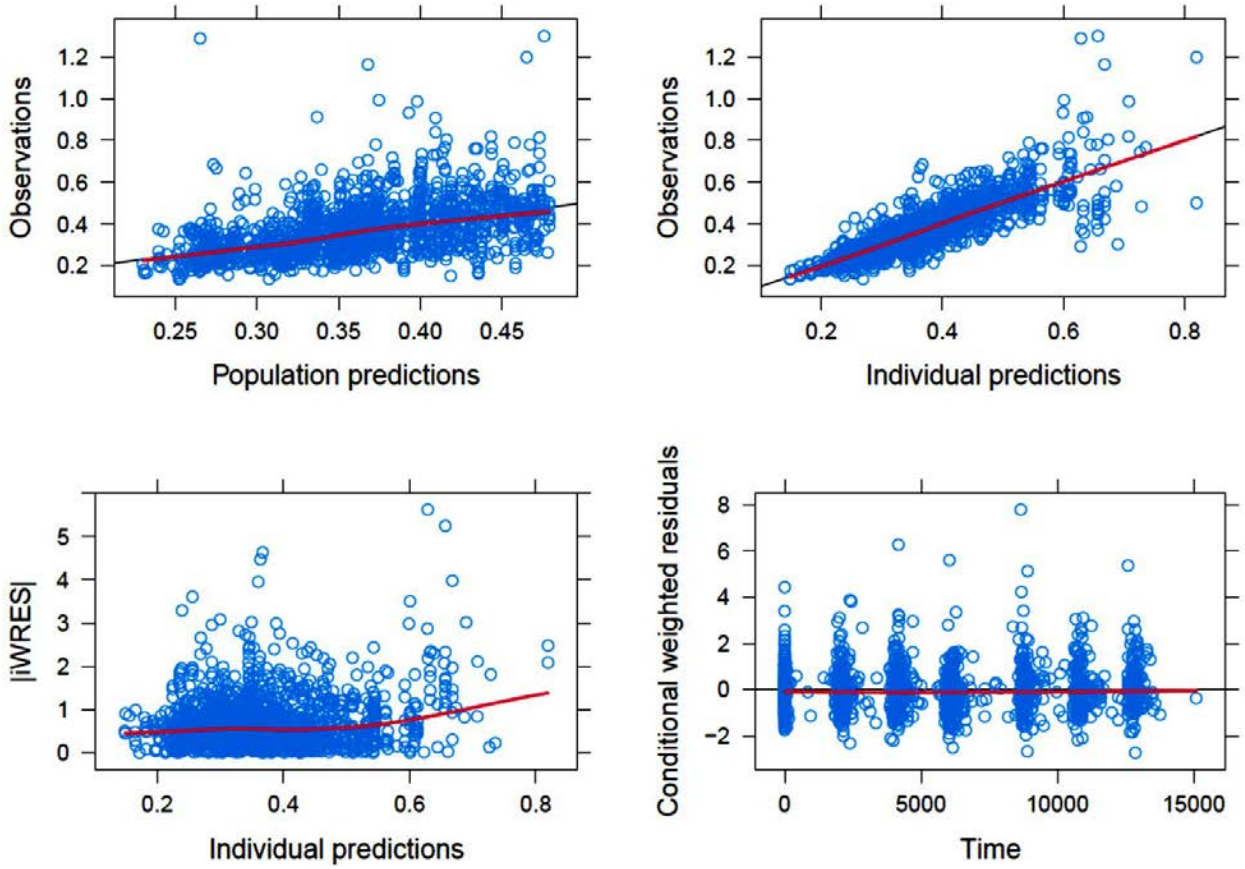
| Parameter | Base Model Population Mean (95% CI)[c] | Final Model Population Mean (95% CI)[c] |
|---|---|---|
| Kin (U/mL/h) | 0.000372 (0.000247, 0.000613) | 0.000355 (0.000237, 0.000584) |
| Baseline P-tau217 Concentration (U/mL) | 0.389 (0.376, 0.403) | 0.384 (0.372, 0.396) |
| Effect of Amyloid Reduction on Kin | 0.273 (0.236, 0.315) | 0.274 (0.231-0.319) |
| **Covariate effects** | | |
| *Covariate effect on Baseline P-tau217 Concentration* | | |
| Effect of Baseline Tau PET SUVr[a] | NA | 0.966 (0.671-1.27) |
| **Interindividual variability CV% (95% CI)[b]** | | |
| Baseline P-tau217 Concentration (U/mL) | 26.0% (23.2-28.6) | 23.4% (20.6-25.6) |
| Treatment Effect | 39.5% (23.3-51.2) | 38.3% (21.4-50.2) |
| **Residual unexplained variability** | | |
| Proportional (%) | 18.6% (16.8-20.5) | 18.6% (16.9-20.7) |

BTAUSUVR = Baseline Tau PET SUVr; CI = confidence interval; CV = coefficient of variation; PET = positron emission tomography; SUVr = standardized uptake value ratio a 0.384* (1 + 0.966*(BTAUSUVR-1.2)) where BTAUSUVR is baseline tau PET SUVr b Inter-individual variability was calculated using the following equation for log-normal distributions of the random effects %CV = 100 × √(e^($OMEGA_N$) − 1), where $OMEGA_N$ is the variance of the parameter. c 95% CI from bootstrap

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 51 of 176*

Key diagnostic plots are shown in the figures below.

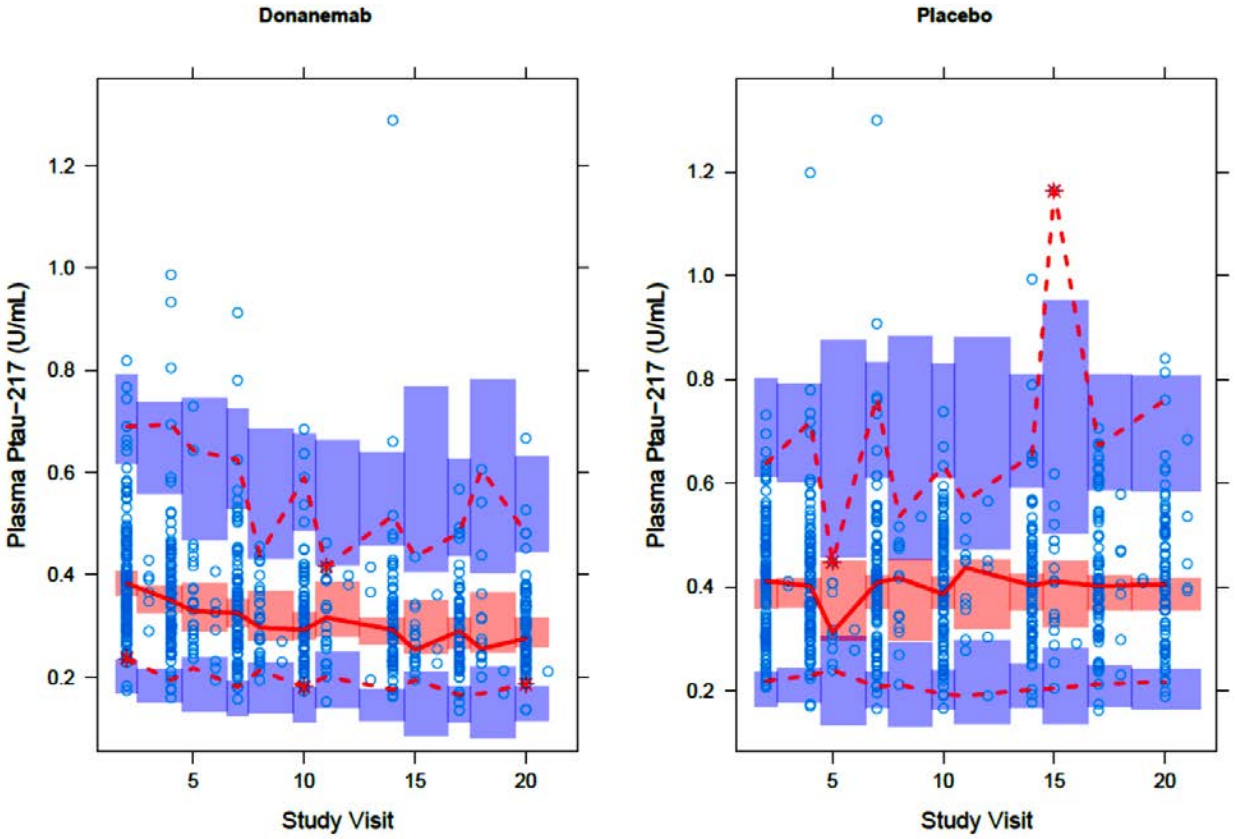
**Figure 25: Basic Diagnostic Plots for the P-tau217 Model**




iWRES = individual weighted residuals

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 165 of 176*

**Figure 26: Visual Predictive Check of the Final P-tau217 Model**




The points are the observed data. The lines are the 5th, 50th, and 95th percentiles of the observed data. The shaded areas are the model-predicted 95% confidence interval of the corresponding percentiles.

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 52 of 176*

[*Reviewer comment: The model demonstrates an effect of donanemab on the lowering P-tau217 levels. The eta shrinkage on the term for drug effect is 61%.*

### *4.4.4 Disease Progression*

The Applicant developed disease separate disease progression models for the iADRS as well as the CDR-SB measures. The model-building approach was identical for both models. Each model was coded to constraint predictions within the acceptable range of values (0 to 18 for CDR-SB and 0 to 146 for iADRS). For each model , numerous logistic models were assessed including the Verhulst logistic model and the Richard's logistic model. Beta regression was used to account for the decreasing variance in residual error as the data approach the boundary values (heteroscedasticity).

Applicant assessed drug exposure through maximum effect models as well as threshold models due to the use of a single dose level was studied. Applicant also assess a treatment effect model. The effect of amyloid PET values (as absolute change from baseline or relative change from baseline) was evaluated as a predictor of disease progression.

Covariate analyses was performed using a stepwise forward inclusion, backward deletion process. Linear, power, and exponential covariate relationships were evaluated. Due to sample size constraints, the forward inclusion and backward deletion criteria were $p<0.01$. Covariate selection was based on OFV reduction, clinical relevance, magnitude of effect, and precision of the estimates. Covariates assessed on both models are presented in **Table 9**.

***Table 9: Covariates Assessed in the disease progression model development for iADRS and CDR-SB***

| Model parameter | Covariates |
|---|---|
| Baseline score | APOE ε4, baseline tau, age of the study participant, time since onset of symptoms of Alzheimer's disease, time since diagnosis of Alzheimer's disease, baseline C-reactive protein, and sex |
| Disease progression | APOE ε4, baseline tau, age of the study participant, time since onset of symptoms of Alzheimer's disease, time since diagnosis of Alzheimer's disease, baseline C-reactive protein, and sex |
| Drug effect | ADA titer, TE ADA status, APOE ε4 genotype, baseline tau, age of the study participant, time since onset of symptoms of Alzheimer's disease, time since diagnosis of Alzheimer's disease, baseline C-reactive protein, and sex |

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 40 of 176*

For both the iADRS and CDR-SB models, the treatment effect is active at any time when the concentration in the central compartment is greater than 1 ng/mL. Otherwise, the treatment effect is inactive. The parameter estimates for the final CDR-SB disease progression model and final iADRS disease progression model are found in **Table 10**.

***Table 10: Parameter Estimates for the Disease Progression Models for iADRS and CDR-SB***

| | iADRS | | CDR | |
|---|---|---|---|---|
| **Parameter** | **Estimate (%SEE)** | **Bootstrap (95% CI)** | **Estimate (%SEE)** | **Bootstrap (95% CI)** |
| Baseline Score[a] | 108 (2.64) | (107, 110) | 3.13 (2.73) | (2.90, 3.35) |
| Disease progression rate (week$^{-1}$) | 0.00346 (4.48) | (0.00287, 0.00399) | 0.00517 (6.44) | (0.00452, 0.00636) |
| Shape factor | 7.25 (Fixed) | - | 3.51 (42.2) | (1.50,13.3) |
| Residual error[b] | 144 (4.02) | (130, 162) | 65.6 (4.01) | (59.6, 74.7) |
| Reduction in disease progression for APOE ε4 carriers (%) | 41.8 (17.4) | (19.5, 62.2) | 28.6 (39.9) | (9.33, 50.1) |
| Effect of age on baseline score[c] | 0.0255 (19.6) | (0.0156, 0.0350) | - | - |
| Effect of age on disease progression[d] | - | - | 0.0246 (36.1) | (0.00484, 0.0492) |
| Effect on baseline tau on baseline score[c] | 1.17 (19.9) | (0.716, 1.63) | - | - |
| Effect on baseline tau on disease progression[d] | - | - | 1.33 (32.2) | (0.377, 2.44) |
| Effect of time from diagnosis of Alzheimer's disease on baseline score[e] | - | - | 0.112 (29.1) | (0.0634, 0.176) |
| Population variability in the baseline score (%CV) | 44.3 (9.22) | (39.0, 49.0) | 61.7 (9.55) | (56.1, 67.7) |

Treatment effect is estimated only for APOE4 carriers and presented as "Reduction in disease progression for APOE ε4 carriers (%)" in this table. AADIAG = time from diagnosis of Alzheimer's disease; APOE4 = apolipoprotein subtype E allele 4; BTau = baseline tau; CI = confidence interval; CV = coefficient of variance; CDR-SB = clinical dementia rating-sum of boxes; iADRS = integrated Alzheimer's disease rating scale; SEE = standard error of the estimate.

- a Estimate as back-transformed from the logit scale.
- b Tau parameter for Beta distribution.
- c Typical logit for baseline iADRS = -1.06 + 1.17*(BTau - 1.2) + 0.0255*(Age – 75.5).
- d Typical disease progression for CDR-SB = 0.00517* (1 + 1.33 *[BTau – 1.2]) *(1 + 0.0246*[Age - 75.5]).
- e Typical logit for baseline CDR-SB = -1.56 + 0.112*(AADIAG – 0.53).

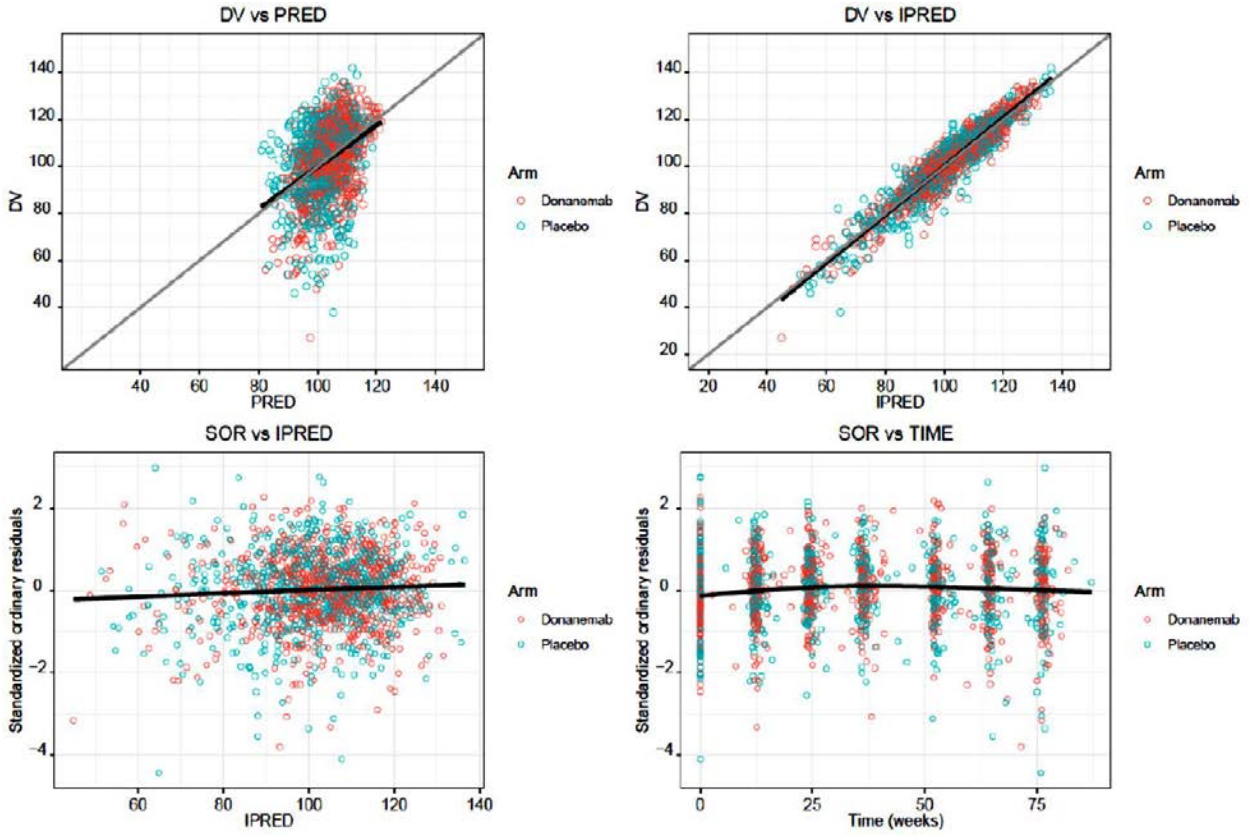
*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 55 of 176*

Diagnostic plots and modeling conclusions can be found in the next sections.

#### *4.4.4.1 iADRS*

Key diagnostic plots for the disease progression model based on iADRS are shown in **Figure 27**.

***Figure 27: Diagnostic Plots for iADRS Disease Progression Model – Treatment Effect***

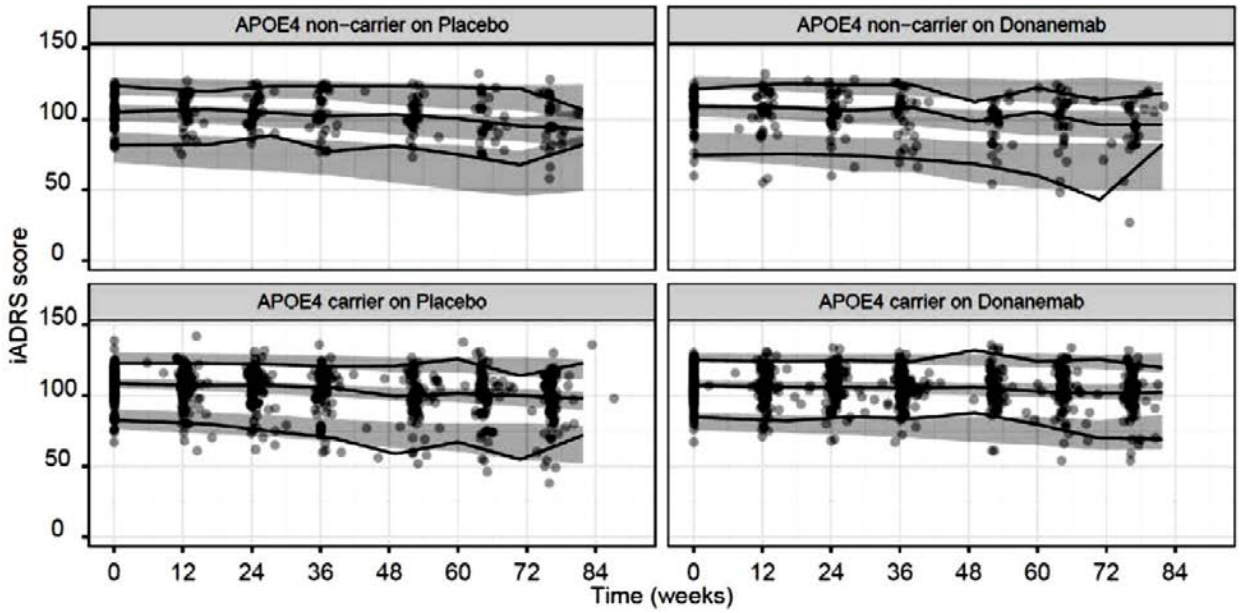



DV = dependent variable; iADRS = integrated Alzheimer's disease rating scale; IPRED = individually predicted value; LOWESS = locally weighted scatterplot smoothing; PRED = population predicted values; SOR = standardized ordinary residuals. LOWESS fit, a smoothed value given by a weighted linear least-squares regression over the span of observations, for data are presented (black line) in addition to a line of identity (gray line on top panel).

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 56 of 176*

The visual predictive check is presented in **Figure 28**.

***Figure 28: Visual Predictive Check for iADRS Disease Progression Model – Treatment Effect***




APOE4 = apolipoprotein subtype E allele 4; iADRS = integrated Alzheimer's disease rating scale. The points are the observed data. The lines are the 5th, 50th, and 95th percentiles of the observed data. The shaded areas are the model-predicted 95% confidence interval of the corresponding percentiles.

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 57 of 176*

The Applicant constructed an alternate disease progression model where amyloid beta or P-tau217 were used as a predictor of iADRS disease progression instead of a treatment effect. The final model retained a treatment effect as it provides a better fit (lower objective function) than amyloid beta or P-tau217. The alternate model is discussed further in **4.4.4.3 Use of Biomarkers As Predictors of Disease Progression** .

[*Reviewer comment: Eta shrinkage for the treatment effect is 2%. Epsilon shrinkage is not applicable as there is no residual variability term in this model.*

*The Applicant's goodness of fit plots (**Figure 27**) do not indicate systematic bias over time or with concentration magnitude.*

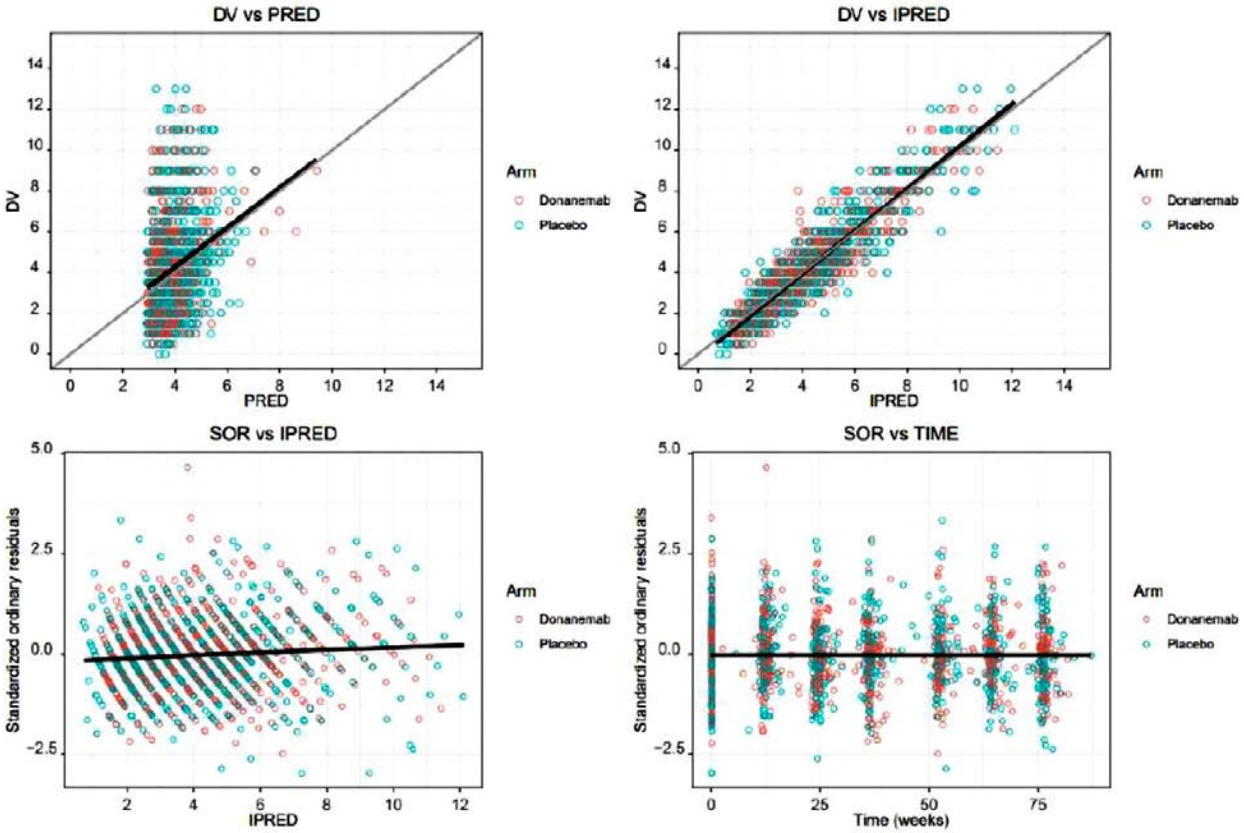
*The visual predictive check (**Figure 28**) indicates that the model describes the central tendency and 95$^{th}$ percentile values well in APOE4 carriers and non-carriers for treatment or placebo. The 95% confidence intervals for the 5$^{th}$ percentile are wider than for the 50$^{th}$ or 95$^{th}$ percentiles in all 4 panels..*

***The Applicant's iADRS disease progression model with a treatment effect is acceptable.***

#### *4.4.4.2 CDR-SB*

Key diagnostic plots for the disease progression model based on CDR-SB are shown in **Figure 29**.

***Figure 29: Diagnostic Plots for CDR-SB Disease Progression Model – Treatment Effect***

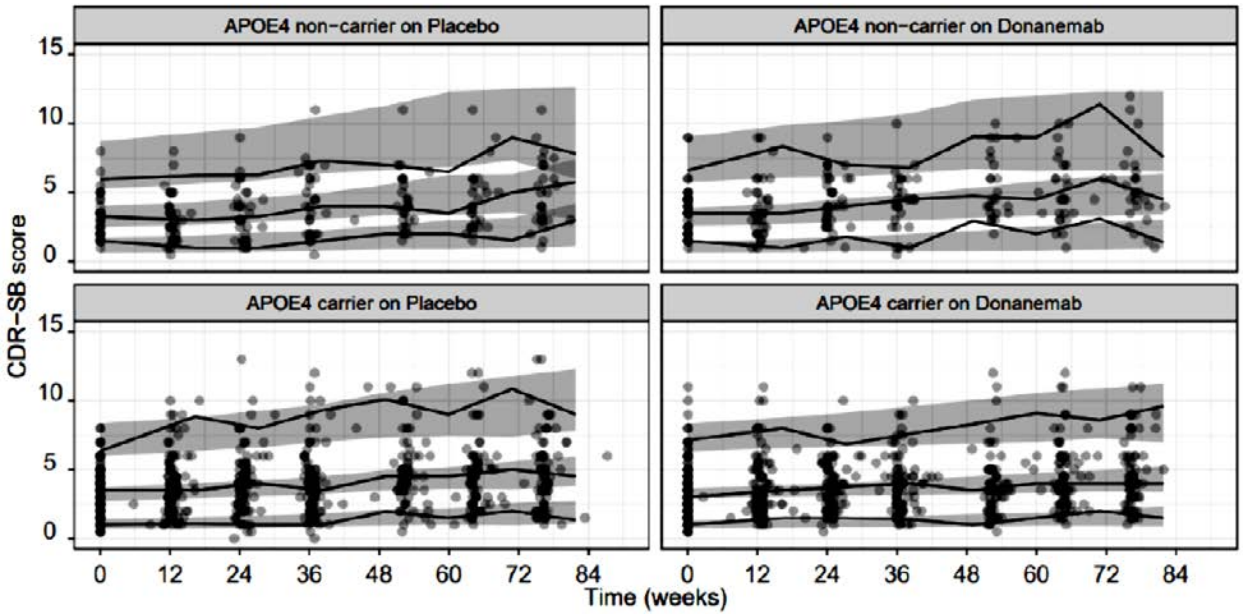



CDR-SB = clinical dementia rating-sum of boxes; DV = dependent variable; IPRED = individually predicted value; LOWESS = locally weighted scatterplot smoothing; PRED = population predicted values; SOR = standardized ordinary residuals. LOWESS fit, a smoothed value given by a weighted linear least-squares regression over the span of observations, for data are presented (black line) in addition to a line of identity (gray line on top panel).

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 58 of 176*

The visual predictive check is presented in **Figure 30**.

**Figure 30: Visual Predictive Check for CDR-SB Disease Progression Model – Treatment Effect**




APOE4 = apolipoprotein subtype E allele 4; CDR-SB = clinical dementia rating-sum of boxes. The points are the observed data. The lines are the 5th, 50th, and 95th percentiles of the observed data. The shaded areas are the model-predicted 95% confidence interval of the corresponding percentiles.

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 59 of 176*

The Applicant constructed an alternate disease progression model where amyloid beta was used as a predictor of CDR-SB disease progression instead of treatment. The final model retained a treatment effect as it provides a better fit (lower objective function) than amyloid beta. The alternate model is discussed further in **4.4.4.3 Use of Biomarkers As Predictors of Disease Progression**.

[*Reviewer comment: Eta shrinkage for the baseline CDR-SB term is 3%. Epsilon shrinkage is 2.4%.*

*The diagnostic plots (**Figure 29**) do not suggest the presence of bias in terms of time after administration or prediction magnitude.*

*The visual predictive check (**Figure 30**) suggests that the model represents the central tendency and 5$^{th}$ percentile values well for treatment or placebo, in APOE4 carriers and non-carriers. The 95% confidence intervals are wider for the 95$^{th}$ percentiles than the 5$^{th}$ or 50$^{th}$ percentile in all 4 panels,.*

***Overall, the Applicant's disease progression model for CDR-SB is acceptable**.*

#### *4.4.4.3 Use of Biomarkers As Predictors of Disease Progression*

The Applicant assessed the ability of amyloid beta to predict disease progression for both iADRS and CDR-SB. While amyloid was a significant predictor of disease progression in iADRS and CDR-SB models that did not include a treatment effect, the objective function value (OFV) decrease is greater for treatment effect alone than for amyloid PET alone (see **Table 11**).

**Table 11: Changes in Objective Function When Using Treatment Effect versus Amyloid To Predict Disease Progression for iADRS or CDR-SB**

| Endpoint | ΔOFV for treatment effect | ΔOFV for amyloid as predictor |
|---|---|---|
| CDR-SB | -9 | -7 |
| iADRS | -25 | -17 |

*Source: sequence 0002, module 5335, pop-pk-aacg-report.pdf, page 53 of 176*

The Applicant assessed the ability of P-tau217 to predict iADRS disease progression. effect. The Applicant reports that use of P-tau217 as a predictor of disease progression with the iADRS scale provides a similar change in OFV as the model using amyloid as a predictor of disease progression. For these reasons, the Applicant's final disease progression models for iADRS and CDR-SB utilized a treatment effect only.

[*Reviewer comment: This modeling result is consistent with a positive relationship between amyloid plaque reduction or P-tau217 reduction and improvement in iADRS or improvement in CDR-SB.* ]

#### *4.4.4.5 Conclusions*

The Applicant provides the following conclusions regarding disease progression modeling for iADRS as well as CDR-SB:

- There is a donanemab treatment effect on the overall population (any APOE4 status) with disease progression reductions for iADRS by 28% and CDR-SB by 20%.
- In APOE4 carriers, donanemab reduced disease progression for iADRS by 42% and for CDR-SB by 28%.
- A concentration-effect relationship for disease progression with iADRS and CDR-SB could not be identified as only 1 dosing regimen was studied in study AACG. This likely reflects the narrow distribution of exposures in this study.

[*Reviewer comment: The Applicant's exposure-response analyses support a treatment effect of donanemab on reducing disease progression in terms of iADRS as well as CDR-SB.* ]

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