The Journal of Prevention of Alzheimer's Disease 12 (2025) 100202

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

Lower baseline amyloid beta burden is associated with greater percent of amyloid beta positron emission tomography reduction and better clinical outcomes in the aducanumab Phase 3 trials ENGAGE and EMERGE in early Alzheimer's disease

Jackson Burton[a,*], Holly M. Brothers[a], R. Matthew Hutchison[a], Jennifer Murphy[a], Tao Sun[a], Gersham Dent[a], Gioacchino Curiale[a], Ken Kowalski[b]

[a] Biogen Inc., Cambridge, MA, USA
[b] Kowalski PMetrics Consulting, LLC, Naples, FL, USA

ARTICLE INFO

Keywords:
Amyloid beta centiloids
Treatment related amyloid clearance
Clinical outcomes
Pharmacokinetics-pharmacodynamics
Exposure-response

ABSTRACT

Background: Aducanumab is a human immunoglobulin G1 anti-amyloid beta antibody for early-stage Alzheimer's disease. After the discontinuation of the aducanumab clinical program and market withdrawal, the Phase 3 data were further assessed to characterize the relationship between baseline amyloid beta load, degree of amyloid beta removal, and subsequent clinical outcomes to provide context for future research.
Objectives: This analysis leveraged modelling techniques to impute missing amyloid beta positron emission tomography values and better understand the relationship between baseline amyloid beta positron emission tomography status, amyloid beta positron emission tomography reduction, and clinical outcomes in the aducanumab Phase 3 ENGAGE and EMERGE (NCT02477800/NCT02484547) studies.
Design: Exploratory data analysis.
Setting: A previously developed model which characterized the relationship between aducanumab exposure and amyloid beta positron emission tomography standard uptake value ratio was updated to impute centiloid values for participants not enrolled in the amyloid beta positron emission tomography substudy. Additional clinically-relevant variables were also summarized.
Participants: 1876 participants with baseline amyloid beta positron emission tomography and clinical endpoints in a pooled ENGAGE/EMERGE dataset at week 78.
Intervention: Aducanumab
Measurements: Amyloid burden measured by centiloids and clinical endpoints.
Results: In older participants whose baseline amyloid beta burden is lower than the average trial population, exposure to aducanumab provides greater clinical benefit across cognitive and functional endpoints.
Conclusions: The relationship between baseline amyloid beta load and treatment benefit in a large population after exposure to an amyloid beta–directed antibody provides insight into which subpopulations are likely to benefit from this class of treatment.

1. Introduction

Amyloid beta (Aβ)-directed antibodies for the treatment of Alzheimer's disease (AD) have demonstrated consistent removal of extracellular neuritic Aβ plaques with sufficient drug exposure as measured using Aβ positron emission tomography (PET). Further, these therapies have demonstrated a strong relationship between Aβ plaque reduction and clinical outcomes [1–4]. Model-based approaches have provided further understanding of the factors and dynamics that influence the relationship between Aβ plaque reduction and slowing of clinical decline, such as the Q-ATN model [5]. Such approaches are critical for identifying which patient populations are most likely to benefit, which stage of disease is best for treatment initiation, and the expected range of outcomes.

A key challenge in characterizing the relationship between Aβ plaque removal and clinical outcomes is the availability of Aβ PET data, given the financial, operational, and patient burden aspects of collecting longitudinal data within substudies of clinical trials. This sparsity of Aβ

* Corresponding author: 5341 E 10th St, Tucson, AZ 85711, USA.
E-mail address: Jackson.Burton@Biogen.com (J. Burton).

https://doi.org/10.1016/j.tjpad.2025.100202
Received 19 February 2025; Received in revised form 29 April 2025; Accepted 7 May 2025

PET information can be addressed through a pharmacometrics model approach in which centiloid values can be imputed based on the observed exposure to Aβ-directed antibody treatment. Such models can be developed and evaluated to ensure concordance between observed and predicted data, as has been done for approved Aβ-directed antibody treatments [6,7]. In the context of exposure-response, these models are often used with population pharmacokinetic (PK) models to fully characterize a dose-exposure–response relationship.

Aducanumab is a human immunoglobulin G1 monoclonal anti-Aβ antibody that selectively targets aggregated forms of Aβ, including soluble oligomers and insoluble fibrils [8,9]. Two identically designed Phase 3 trials, EMERGE and ENGAGE, assessed the efficacy and safety of aducanumab in participants with early AD (mild cognitive impairment due to AD and mild AD dementia) who had confirmed amyloid plaque pathology [2]. In ENGAGE and EMERGE, 31 % and 48 % of patients achieved amyloid negative status at week 78, respectively, and had discordant clinical outcomes. ENGAGE did not meet primary or secondary clinical endpoints while EMERGE was significant across clinical outcomes. Both trials were halted early based on results from a futility analysis of interim data but contain valuable clinical outcome data and longitudinal Aβ PET data.

An approach to accurately impute missing Aβ PET values can provide greater confidence in inferences between treatment-based Aβ reduction and clinical outcomes. With this approach and given the large size of the ENGAGE/EMERGE studies, valuable insights can be generated about the relationships between baseline Aβ level, subsequent Aβ clearance, clinical outcomes, and participant clinical characteristics.

A previously developed population PK (popPK) and popPK-pharmacodynamic (PD) model using aducanumab studies characterized the dose-exposure relationship and exposure-Aβ PET standardized uptake value ratio (SUVR) relationship [10] from data that only included imaging collected with the florbetapir tracer. In the present work, we expanded the original aducanumab popPK-PD model with data from ENGAGE/EMERGE that contained baseline and longitudinal Aβ PET data based on different radiotracers; we subsequently used it to predict centiloid values at week 78 of ENGAGE/EMERGE. This model-based approach allows for imputation of centiloid values at clinical visits where no Aβ PET measurements were taken, increasing the sample size and generating greater confidence in the relationship between Aβ levels and clinical observations for the benefit of the AD scientific community.

2. Methods

2.1. Study data for analysis population

Three datasets referred to hereafter as the "model update dataset," the "non-imputation dataset," and the "imputation dataset" were used in this analysis (see Supplemental Figure 1). The model update dataset was the collection of all available Aβ PET records with corresponding dosing (and placebo) records from aducanumab studies (ENGAGE, EMERGE, PRIME). The imputation dataset was the collection of all available clinical endpoint data for participants with a baseline Aβ PET and complete dosing (and placebo) records from ENGAGE/EMERGE at week 78. The non-imputation dataset was the subset of all participants in the imputation dataset who had both an Aβ PET record and clinical assessments at week 78 of ENGAGE/EMERGE. The PRIME study was used exclusively for the model update as it helped contribute more Aβ PET records to increase precision in parameter estimation. It was not used for the imputation approach due to study design differences. The ENGAGE/EMERGE week 78 endpoint was chosen to provide a placebo-controlled comparator arm for the analysis. The model update dataset was used for updates to the popPK-PD model, which included Aβ PET data during the ENGAGE/EMERGE placebo-controlled period and long-term extensions as well as data from the PRIME study. The clinical outcomes included the primary outcome measure Clinical Dementia Rating scale-Sum of Boxes (CDR-SB), an assessment of both cognition and function in AD, and three secondary clinical outcome measures—the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale–Cognitive Subscale–13 items (ADAS-Cog13), Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory–Mild Cognitive Impairment (ADCS-ADL-MCI), all commonly used measures of Alzheimer's disease stage, cognitive functioning, and independence in daily activities, respectively.

The imputation dataset included both observed clinical endpoints and clinically relevant variables based on imputed centiloid trajectories generated using the updated popPK-PD model at clinical visits. It contained all participants with an ENGAGE/EMERGE baseline Aβ PET, regardless of whether they had enrolled in the Aβ PET substudy. The non-imputation dataset was used for the exploratory data analysis to compare observed clinical outcomes between observed and predicted Aβ PET centiloid quartile groups. Similarities in the exploratory relationships between clinical outcomes and Aβ PET centiloid reductions in the imputation and non-imputation datasets were used to assess and ensure that the imputation in participants with missing centiloid data did not unduly bias the relationships.

Our analysis was expanded from the original aducanumab popPK-PD model with the inclusion of additional Aβ PET records from ENGAGE/EMERGE. The additional baseline and longitudinal Aβ PET records included data from three PET ligands: [18F]-florbetapir, [18F]-florbetaben, and [18F]-flutemetamol. Aβ PET records from these ligands were harmonized to the centiloid scale (see Supplemental Figure 1) [11]. In the updated model dataset, the majority of the additional Aβ PET records were at ENGAGE/EMERGE baseline, and while they did not provide additional longitudinal information for certain model parameters, they did provide a basis to predict changes in centiloid values based on drug exposure from a known baseline. Additional longitudinal Aβ PET records from a Japanese cohort in ENGAGE/EMERGE using [18F]-flutemetamol were also included in this analysis.

Data exclusions were performed for the imputation dataset (and the non-imputation dataset by extension) based on missing data and centiloid values at baseline. Records with at least one missing clinical endpoint were excluded to ensure consistency in sample sizes across endpoints. For both the imputation dataset and the model update dataset, participants with baseline centiloid values < 0 were removed to ensure positivity of the metric for Aβ reduction described later.

2.2. PopPK and poppk-pd model description

Details of both the original PopPK and PopPK-PD models have been published previously [10]. Aducanumab PK was characterized using a linear two-compartment model with first-order elimination. The PD response of Aβ clearance based on aducanumab's mechanism of action was best described by an indirect response model with a stimulatory effect on SUVR elimination rate (i.e., a measure of the rate of removal of Aβ plaques). Covariates included in the original popPK-PD model were the effect of weight on SUVR elimination rate, the effect of age on maximal drug effect, and the effects of apolipoprotein (ApoE) ε4 gene carrier status, MMSE, and age at baseline.

2.3. Updates to popPK-PD model

The PK of aducanumab for ENGAGE/EMERGE participants have been well characterized with the previous popPK model, and no additional model development was performed. The popPK-PD model was updated by re-estimating the parameters using the model update dataset. Comparison of updated parameter estimates to the original model parameter estimates were made and standard model diagnostics were performed following best practices. Further model refinement was explored based on the results of the model diagnostics for the updated model. This was done to ensure that underlying model assumptions were not influencing the centiloid imputations.

2.4. Quantifying aβ plaque levels and aβ reduction

In the previous popPK-PD model, the SUVR was calculated for a composite region of interest, with whole cerebellum as the reference region. The composite region of interest included parts of major cortical regions (frontal, parietal, lateral temporal, sensorimotor, and anterior and posterior cingulate) and served as a summary measure of global cerebral Aβ level. In this work, Aβ PET SUVR records from the different tracers were harmonized to the centiloid scale. The metric used for quantifying reduction in Aβ plaque in this analysis was percent centiloid reduction (PCR), defined as:

$$PCR = -100 * \left(\frac{CENTILOID\_postbaseline - CENTILOID\_baseline}{CENTILOID\_baseline} \right)$$

The rationale for the choice of this metric was to associate Aβ clearance as a percentage of total burden rather than an absolute change. For a fixed drop in centiloids, this metric results in higher values for lower baseline Aβ burden compared with higher burden. Practically, a centiloid value can drop below 0 as this anchor point represents an average Aβ burden observed in a group of healthy control participants and not an absolute floor. While participants with baseline centiloids < 0 were excluded from this analysis to ensure positive scores, centiloid values that dropped below 0 after treatment initiation were retained. This scenario only occurs for observed centiloid measures as the mathematical formulation of the model restricts the lower bound of predicted centiloids to 0.

2.5. Centiloid imputations

The model was used to predict centiloid values for all participants in ENGAGE/EMERGE at week 78 with an Aβ baseline (the imputation dataset). Participants with observed centiloids at week 78 were compared with model-predicted week 78 centiloids as part of the exploratory data analysis comparison described in the next section (the non-imputation dataset). In all cases, predicted centiloid values were used to derive PCR values and were performed in a two-step manner by [1] generating the time course of exposure using the popPK model based on the actual dosing history for each participant and [2] simulating the time course of centiloid values using the popPK-PD model with the predicted exposure as input. For all participants included in the imputation dataset, their individual PK parameters, which had been estimated from the popPK model, were required to generate the simulations. Hence, all participants had individualized centiloid predictions for this analysis.

2.6. Non-Imputed exploratory data analyses

To ensure that the imputation procedure was not biasing the relationship between centiloid reduction and clinical outcomes, we performed a comparison of exploratory data analysis results within the non-imputed dataset. Using the non-imputation dataset, centiloid values were predicted for participants with observed centiloids. PCR values were derived for both observed and predicted centiloids. Quartiles for the observed PCR values were used to partition both observed and predicted centiloids in treated groups, with participants who received placebo kept as a separate group. Using observed quartiles therefore leads to differences in samples sizes for model-predicted centiloids. Within each quartile, means for the observed CDR-SB, ADAS-Cog13, ADCS-ADL-MCI, and MMSE endpoints were computed. Additionally, observed values for amyloid-related imaging abnormalities with edema or effusion (ARIA-E) rates, Aβ negativity, and ApoE-4 genotype proportions were computed in each PCR quartile. Aβ negativity was defined as centiloid ≤ 20. The safety MRI population was used for ARIA analyses and it included all randomized participants in the pool who received at least 1 dose of study treatment and had at least 1 postbaseline MRI assessment during the pooled analysis period. ARIA-E incidences were defined as the incidence of participants who experienced at least one ARIA-E event up to and including the clinical visit of interest. For this comparison and the imputation approach described later, the PCR values were derived without reference to the original treatment arm in ENGAGE/EMERGE, except for the placebo group. Graphical representation to assess the relationship between the four clinical endpoints and PCR quartiles were generated.

Table 1
Comparison of participant characteristics between the original model dataset and the updated model dataset.

	Original Model Dataset		Updated Model Dataset	
	Treated	Placebo	Treated	Placebo
Number of participants	850	275	2037	970
Age, mean, year	70.8	69.3	70.5	70.3
Male, n (%)	404 (48)	140 (51)	980 (48)	458 (47)
Aβ PET centiloids, mean	88.9	85.9	88.2	86.3
Total centiloid records	2682	973	4279	1997
Baseline-only centiloid records	100	16	1187	569
Post-baseline centiloid records	1832	698	2242	1027
ApoE ε4, non-carriers, n (%)	262 (31)	74 (27)	620 (30)	298 (31)
ApoE ε4, heterozygotes, n (%)	442 (52)	143 (52)	1061 (52)	491 (51)
ApoE ε4, homozygotes, n (%)	146 (17)	58 (21)	356 (17)	181 (19)
CDR-GS, (% with 0.5)*	0.52	0.51	0.51	0.51
MCI, n (%)*	653 (77)	220 (80)	1586 (78)	781 (81)
Mild AD, n (%)*	197 (23)	55 (20)	451 (22)	189 (19)
CDR-SB, mean*	2.46	2.53	2.47	2.45
ADAS-Cog13, mean*	21.9	21.4	22.4	22
ADCS-ADL-MCI, mean*	43	42.8	42.8	42.7
MMSE, mean*	26.3	26.5	26.3	26.3

AD, Alzheimer's disease; ADAS-Cog13, Alzheimer's Disease Assessment Scale–Cognitive Subscale–13 items; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory–Mild Cognitive Impairment; ApoE, apolipoprotein; CDR-GS, Clinical Dementia Rating-Global Score; CDR-SB, Clinical Dementia Rating-Sum of Boxes; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron emission tomography.
* Does not include the PRIME study.

2.7. Exploratory data analysis for imputation dataset

The purpose of the imputation approach was to increase the sample size of centiloid records by predicting centiloid trajectories for all participants with missing centiloid data in the imputation dataset, i.e., participants without longitudinal Aβ PET assessments at week 78 of ENGAGE/EMERGE. These imputed centiloid values were combined with the observed centiloids and comprised the imputation dataset as described earlier. Similar to the non-imputed exploratory data analyses, summaries of observed clinical endpoints and variables were computed based on predicted PCR values grouped according to observed PCR quartiles for both treated groups and the placebo group. Additional statistical and graphical summaries were generated to further examine the underlying populations within each PCR quartile.

3. Results

3.1. Analysis population

Aducanumab PK data included in this analysis were used as previously reported [10]. The popPK-PD model update dataset included 3007 participants and 6276 Aβ PET records from three aducanumab studies (PRIME, ENGAGE, EMERGE). Of the 3007 participants, 1756 had baseline records only, and the remaining 1251 participants had a mean of 3.6 Aβ PET assessments with a mean duration of follow-up of 2.4 years. Table 1 shows a comparison between the original model dataset and model update dataset. Both datasets were consistent in baseline characteristics for both placebo and treated participants. The baseline clinical stage and endpoints were only calculated for ENGAGE/EMERGE because only Aβ PET-related data and demographics were included from

PRIME for the model update. The imputation dataset included 1876 participants with week 78 clinical assessments for CDR-SB, ADAS-Cog13, ADCS-ADL-MCI, and MMSE after exclusions; all of these participants had baseline Aβ PET measurements. The non-imputation (observed centiloids) dataset as a subset of the imputation dataset had a total of 659 participants with an Aβ PET and clinical assessment at week 78 of ENGAGE/EMERGE. Approximately 2.8 % of participants were excluded from the analysis due to having a negative centiloid baseline value.

3.2. Updated popPK-PD model

The popPK-PD model was updated by re-estimating the parameters on the model update dataset. Supplemental Table 1 shows a comparison between the parameter estimates for the original and updated popPK-PD models. All relevant significant covariates in the original model remained significant in the model update, while the ApoE ε4 homozygote effect on baseline centiloids remained as a weak effect. Of importance, the previous popPK-PD (SUVR) model identified age on maximum drug effect as a prognostic factor, indicating that higher age is related to greater SUVR reduction. This effect remained significant in the popPK-PD model update as reported previously [7] . Additionally, for both the original and updated popPK-PD models, the ApoE ε4 heterozygote effect on baseline was significant and hence, for completeness, both the ApoE ε4 heterozygote and homozygote effects were included despite the lack of significance of the ApoE ε4 homozygote effect on baseline centiloids. The parameters remained consistent between the original and updated models, indicating similarity between the two datasets. The standard errors for the updated parameter estimates related to longitudinal measures remained consistent, while standard errors for baseline parameters decreased. This observation is expected given that the majority of the additional data included in the update was baseline data. The standard diagnostics for evaluating a pharmacometric model were generated (not shown) and were satisfactory and consistent with the previous popPK-PD SUVR model. During evaluation of the diagnostics of the updated popPK-PD model, it was shown that drug effect parameters depend on baseline centiloids, which violates the assumption that the first-order plaque elimination rate should indicate that PCR is independent of baseline centiloids. However, the individual random effects in the model account for this and does not lead to an impact on the final results.

To substantiate the use of the imputation approach, Supplemental Figure 2 shows the mean change from baseline for CDR-SB, ADAS-Cog13, ADCS-ADL-MCI, and MMSE stratified by the original randomized dose groups (pooled independently of ApoE ε4 carrier status) at week 78 of ENGAGE/EMERGE. Within each dose group, the mean value of PCR was computed for the subset of participants enrolled in the Aβ PET substudy. For each endpoint, there was perfect rank correlation between the PCR values and the mean change from baseline. This motivated examination of the relationship between PCR values and the pooled study populations independent of dose. Hence, this required the use of the popPK-PD model to perform imputations for missing week 78 ENGAGE/EMERGE Aβ PET visits.

3.3. Non-Imputed exploratory data analyses

The popPK-PD model was used to predict centiloid trajectories for the 659 participants with an Aβ PET and clinical assessments at week 78 of ENGAGE/EMERGE. Supplemental Table 2 summarizes the observed clinical endpoints and variables in each PCR quartile and the placebo group at the ENGAGE/EMERGE week 78 visit. Within each quartile, all summarized endpoints and variables are observed, except for mean centiloid values in the predicted group. The means of observed and predicted centiloids are consistent in each quartile and the placebo group. The corresponding summaries of clinical endpoints and variables are consistent between the groups of participants with observed centiloids. More precisely, the largest percent difference between any observed and predicted PCR centiloid group for CDR-SB, ADAS-Cog13, ADCS-ADL-MCI, and MMSE was 7.7 % (52 % < PCR $\leq$ 75 %), 22 % (PCR $\geq$ 75 %), 3.7 % (31 % < PCR $\leq$ 52 %), and 9.8 % (PCR $\geq$ 75 %), respectively. Supplemental Figure 3 shows the relationship between midpoints in each PCR quartile and the mean change from baseline for CDR-SB, ADAS-Cog13, ADCS-ADL-MCI, and MMSE. The observed clinical scores were stratified by the observed and individual predicted centiloid values for each endpoint for comparison, and 95 % confidence intervals were calculated. For all four outcomes, consistent trends were seen between the observed and predicted centiloid values, indicating the model accurately characterized the observed centiloid values. Most importantly, the comparison between the observed and predicted centiloids provided evidence that the imputation approach did not alter the observed relationships between centiloid reduction and clinical outcomes. This supports the approach to impute all missing centiloid values from week 78 of ENGAGE/EMERGE to increase the sample size and confirm trends in the larger trial population.

3.4. Exploratory data analysis for imputation dataset

The popPK-PD model was used to impute centiloid values for participants in the imputation dataset with missing ENGAGE/EMERGE Aβ PET data at week 78, thereby significantly increasing the sample size. All observed week 78 centiloid values were kept. Fig. 1 shows the relationship between midpoints in each PCR group and the mean change from baseline for CDR-SB, ADAS-Cog13, ADCS-ADL-MCI, and MMSE at week 78 of ENGAGE/EMERGE. Table 2 shows the corresponding observed clinical endpoint and variable summaries in each PCR group. Overall, a trend of increasing clinical benefit for PCR groups with higher centiloid reduction was seen for CDR-SB, ADCS-ADL-MCI, and MMSE, while only in the highest PCR group was there an observed benefit with ADAS-Cog13. Clinical benefit was very weak or not apparent for PCR values less than approximately 50 %. Compared with the placebo group, the highest PCR group showed the largest clinical benefit, had the highest percentage of ApoE ε4 non-carriers, and had the lowest ARIA-E incidence, consistent with the known association between ApoE ε4 genotype and ARIA-E incidence [12,13]. In the highest PCR group, the majority of participants were Aβ negative (76 % vs < 13 % in all other PCR groups), with PCR values < 50 % showing no difference in Aβ negativity compared with the placebo group.

The data in Fig. 1 and Table 2 suggest that greater cognitive benefit was seen with greater percent Aβ reduction. To further examine this hypothesis, the baseline characteristics of each PCR group using the observed centiloid quartiles were examined to assess potential population differences. Supplemental Table 3 shows the baseline characteristics for each PCR group and the placebo group. Baseline clinical scores and disease stage were highly consistent across the PCR groups and the placebo group. In contrast, baseline centiloid values, ApoE ε4 genotype status, and age varied across the PCR groups. The most significant difference was in baseline centiloids, which were approximately 25 % lower in the highest PCR group than the other groups. In contrast, all other groups (PCR $\leq$ 75 %), including the placebo group, only differed by at most 8 % in mean baseline centiloids. ApoE ε4 non-carriers decreased from 56 % to 9 % across the highest to lowest PCR groups, respectively, whereas ApoE ε4 homozygotes increased from 6 % to 30 % across the highest to lowest PCR groups, respectively. Age decreased from 74.1 to 66.1 years across the highest to lowest PCR groups, respectively.

The lower Aβ burden in the highest PCR group suggests that the slowing of decline on clinical endpoints may be attributed to slower underlying disease progression, and is dependent upon ApoE ε4 genotype [14–16]. To better examine natural progression, Supplemental Figure 4 shows the change from baseline in clinical scores for participants who received placebo, from the imputation dataset stratified by the median baseline centiloid value of 87.0 across the ENGAGE/EMERGE baseline, week 26, week 50, and week 78 visits. The median centiloid values for the low– and high–baseline centiloid groups were 60.1 and 115.5, re-

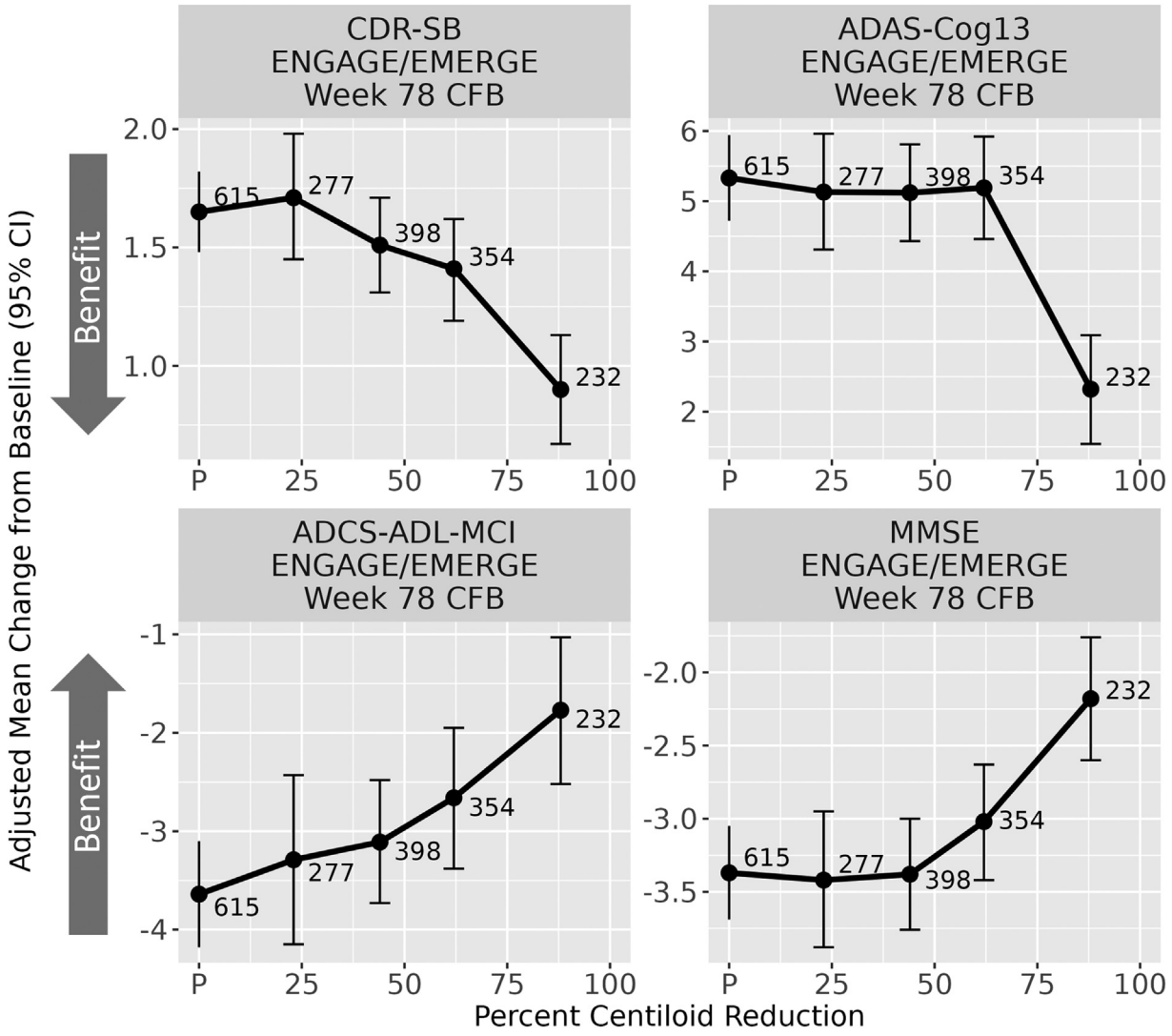

Fig. 1. Observed mean change from baseline across endpoints at week 78 of ENGAGE/EMERGE vs PCR values. Points represent midpoints within each PCR group. Error bars represent the 95 % confidence intervals and numbers at the points represent the number of observations.
ADAS-Cog13, Alzheimer's Disease Assessment Scale–Cognitive Subscale–13 items; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory–Mild Cognitive Impairment; CDR-SB, Clinical Dementia Rating scale-Sum of Boxes; CFB, change from baseline; MMSE, Mini-Mental State Examination; PCR, percent centiloid reduction; P, placebo.

Table 2
Imputation approach results showing observed clinical endpoints and variables at week 78 of ENGAGE/EMERGE based on PCR values.

Observed and imputed centiloids week 78 of ENGAGE/EMERGE, mean	PCR > 75 % 7.44	52 % < PCR ≤ 75 % 36.03	31 % < PCR ≤ 52 % 54.38	PCR < 31 % 70.46	Placebo 89.18
	Observed summaries				
Number of participants	232	354	398	277	615
CDR-SB CFB, mean	0.9	1.41	1.51	1.71	1.65
ADAS-Cog13 CFB, mean	2.32	5.19	5.12	5.13	5.33
ADCS-ADL-MCI CFB, mean	−1.77	−2.66	−3.11	−3.29	−3.64
MMSE CFB, mean	−2.18	−3.02	−3.38	−3.42	−3.37
ARIA-E, n (%)	48 (21)	100 (28)	114 (29)	101 (36)	16 (3)
Aβ negative (< 20 CL), n (%)	176 (76)	46 (13)	8 (2)	6 (2)	10 (2)
ApoE ε4, non-carriers, n (%)	130 (56)	129 (36)	89 (22)	24 (9)	177 (29)
ApoE ε4, heterozygotes, n (%)	89 (38)	183 (52)	233 (59)	169 (61)	310 (50)
ApoE ε4, homozygotes, n (%)	13 (6)	42 (12)	76 (19)	84 (30)	128 (21)

ADAS-Cog13, Alzheimer's Disease Assessment Scale–Cognitive Subscale–13 items; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory–Mild Cognitive Impairment; ApoE, apolipoprotein; ARIA-E, amyloid-related imaging abnormalities with edema or effusion; Aβ, amyloid beta; CDR-SB, Clinical Dementia Rating scale-Sum of Boxes; CFB, change from baseline; CL, centiloids; MMSE, Mini-Mental State Examination; PCR, percent centiloid reduction.

Table 3
Observed baseline characteristics for PCR groups and placebo grouped above and below median baseline centiloid value.

	PCR > 75 %		52 % < PCR ≤ 75 %		31 % < PCR ≤ 52 %		PCR < 31 %		Placebo	
	bCL < 86.4	bCL ≥ 86.4	bCL < 86.4	bCL ≥ 86.4	bCL < 86.4	bCL ≥ 86.4	bCL < 86.4	bCL ≥ 86.4	bCL < 86.4	bCL ≥ 86.4
N	161	71	152	202	161	237	137	140	307	308
Centiloids	49.62	116.25	64.07	119.63	65.89	116	62.32	115.08	60.92	115.48
Age, mean, year	73.1	76.4	71.1	71.7	68.4	68.7	67.2	67	69.7	70.3
Sex, n (%) male	96 (60)	28 (39)	79 (52)	99 (49)	75 (47)	102 (43)	60 (44)	65 (46)	147 (48)	138 (45)
MCI, n (%)	142 (88)	59 (83)	127 (84)	160 (79)	135 (84)	189 (80)	110 (80)	113 (81)	253 (82)	263 (85)
Mild AD, n (%)	19 (12)	12 (17)	25 (16)	42 (21)	26 (16)	48 (20)	27 (20)	27 (19)	54 (18)	45 (15)
ApoEnc, n (%)	96 (60)	34 (48)	49 (32)	80 (40)	33 (20)	56 (24)	13 (9)	11 (8)	97 (32)	80 (26)
ApoEhet, n (%)	59 (37)	30 (42)	77 (51)	106 (52)	93 (58)	140 (59)	81 (59)	88 (63)	138 (45)	172 (56)
ApoEhom, n (%)	6 (4)	7 (10)	26 (17)	16 (8)	35 (22)	41 (17)	43 (31)	41 (29)	72 (23)	56 (18)
CDR-SB, mean	2.38	2.42	2.5	2.52	2.41	2.51	2.22	2.63	2.36	2.59
ADAS-Cog13, mean	21.17	21.62	21.74	21.87	22.27	22.98	22.62	22.66	21.58	22.36
ADCS-ADL, mean	42.63	43.25	42.61	42.96	42.84	43.21	42.82	42.39	42.73	42.8
MMSE, mean	26.7	26.49	26.43	26.33	26.33	26.14	26.31	26.14	26.45	26.26

AD, Alzheimer's disease; ADAS-Cog13, Alzheimer's Disease Assessment Scale–Cognitive Subscale–13 items; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory–Mild Cognitive Impairment; CDR-SB, Clinical Dementia Rating scale-Sum of Boxes; ApoE, apolipoprotein; bCL, baseline centiloids; het, heterozygotes; hom, homozygotes; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; nc, non-carriers; PCR, percent centiloid reduction.

spectively. For all four endpoints, the mean change from baseline values were similar between participants, with baseline centiloids ≥ 87.0 versus those with baseline centiloids < 87.0 for weeks < 78. In contrast, all four endpoints showed less worsening in the low-baseline centiloid group than in the high-baseline centiloid group at week 78. The percent reduction for the endpoints in the low–baseline centiloid group relative to the high–baseline centiloid group at week 78 was 18.3 %, 32.9 %, 19.0 %, and 26.2 % for CDR-SB, ADAS-Cog13, ADCS-ADL-MCI, and MMSE, respectively.

To qualitatively assess the effect of baseline Aβ burden on change in clinical endpoints, Fig. 2 shows the relationship between PCR and clinical endpoints further stratified into two groups, above and below the median baseline centiloid value of 87.0. Across all four clinical endpoints, the greatest slowing of decline was seen in the highest PCR group (> 75 %) for both the low– and high–baseline centiloid groups. The change from baseline in the highest PCR group compared with the placebo group was slightly higher in the low–baseline centiloid group than in the high–baseline centiloid group (45 %, 57 %, 51 %, and 34 % vs 41 %, 46 %, 47 %, and 27 % for CDR-SB, ADAS-Cog13, ADCS-ADL-MCI, and MMSE, respectively). In the low–baseline centiloid group, slowing of decline was seen for PCR > 50 %, while slowing of decline was primarily seen for PCR > 75 % in the high–baseline centiloid group. In the low–baseline centiloid group, PCR < 50 % generally showed greater decline compared with the placebo group across all four endpoints. In contrast, the high–baseline centiloid group in any PCR group showed no worsening compared with the placebo group. The baseline characteristics of each PCR group and the placebo group stratified by the low– and high–baseline centiloid groups are shown in Table 3. Notably, the low–baseline centiloid groups with PCR ≥ 50 % had more clinical benefit than the high–baseline centiloid groups with PCR ≥ 50 %; and, noting that proportions of ApoE ε4 genotype status are less imbalanced in these groups, it suggests that lower baseline Aβ burden is related to greater clinical benefit.

The imputation approach was further assessed by comparing the relationship between PCR and clinical outcomes with baseline centiloid stratification in the non-imputed and imputed datasets shown in Fig. 3. In general, the non-imputed and imputed datasets show consistency in observed clinical outcomes, with the imputed dataset showing higher precision due to the increased sample size. The largest discrepancies are seen for CDR-SB and ADCS-ADL in the high baseline centiloid group for lower PCR values. Because the concordance shown in Supplemental Figure 3 suggests the model is not biasing this relationship and the clinical scores are all observed, there may be underlying differences between the amyloid sub-study and the full trial populations.

4. Discussion

In this work, we performed a post hoc exploratory data analysis to examine the relationship between Aβ reduction measured by percent of centiloid reduction from baseline (PCR) and clinical outcomes based on aducanumab exposure in the ENGAGE/EMERGE Phase 3 studies. A model-based approach enabled imputations of centiloid trajectories at the week 78 visit for participants with missing Aβ PET measurements, thereby increasing the sample size of available centiloid measures for comparison with clinical scores. Observed clinical endpoints and variables were summarized by quartiles of PCR.

The use of percent reduction is less commonly examined compared to other metrics such as change from baseline in amyloid burden or the percentage of participants below an amyloid positivity threshold. Higher PCR will tend to correspond to participants with lower baseline amyloid burden, because less amyloid needs to be removed compared to participants with a higher burden and the same PCR value. The choice of the metric, however, does seem to indicate greater discrimination among treatment benefit, and should be examined in more rigorous settings.

According to the PCR metric, results indicate that the group of participants with the greatest treatment benefit are older, have lower proportions ApoE ε4 carrier status, and have lower Aβ burden at baseline compared with those who receive placebo. The overall results are supported by examining changes in CDR-SB, ADAS-Cog13, ADCS-ADL-MCI, and MMSE at week 78 of ENGAGE/EMERGE versus PCR, and by stratifying by baseline Aβ burden. Baseline characteristics in different PCR groups indicate that lower baseline Aβ burden and influence of an ApoE ε4–age interaction are key factors which determine the degree of clinical benefit. The motivation for examining the effect of baseline Aβ burden on clinical endpoints resulted from observing significantly lower Aβ burden in the highest PCR group. This in part was due to the nature of the metric itself, as lower absolute baseline Aβ required less exposure to therapy to achieve complete reduction. Also, underlying differences in natural disease progression due to baseline Aβ burden was seen in participants who received placebo across all clinical endpoints. Notably, a generally weak trend of clinical worsening relative to the placebo group was observed in the low centiloid group for PCR < 50 %. This is potentially due to a combination of faster underlying progression (due to higher proportions of ApoE ε4 carrier status) and insufficient Aβ removal. However, no such worsening relative to the placebo group was observed for PCR < 50 % in the high baseline centiloid group, despite showing very similar proportions of ApoE ε4 genotype.

An important consideration for this analysis is that the PCR groups are defined by response to treatment, resulting in imbalanced proportions of ApoE ε4 genotypes relative to the placebo group. These differ-

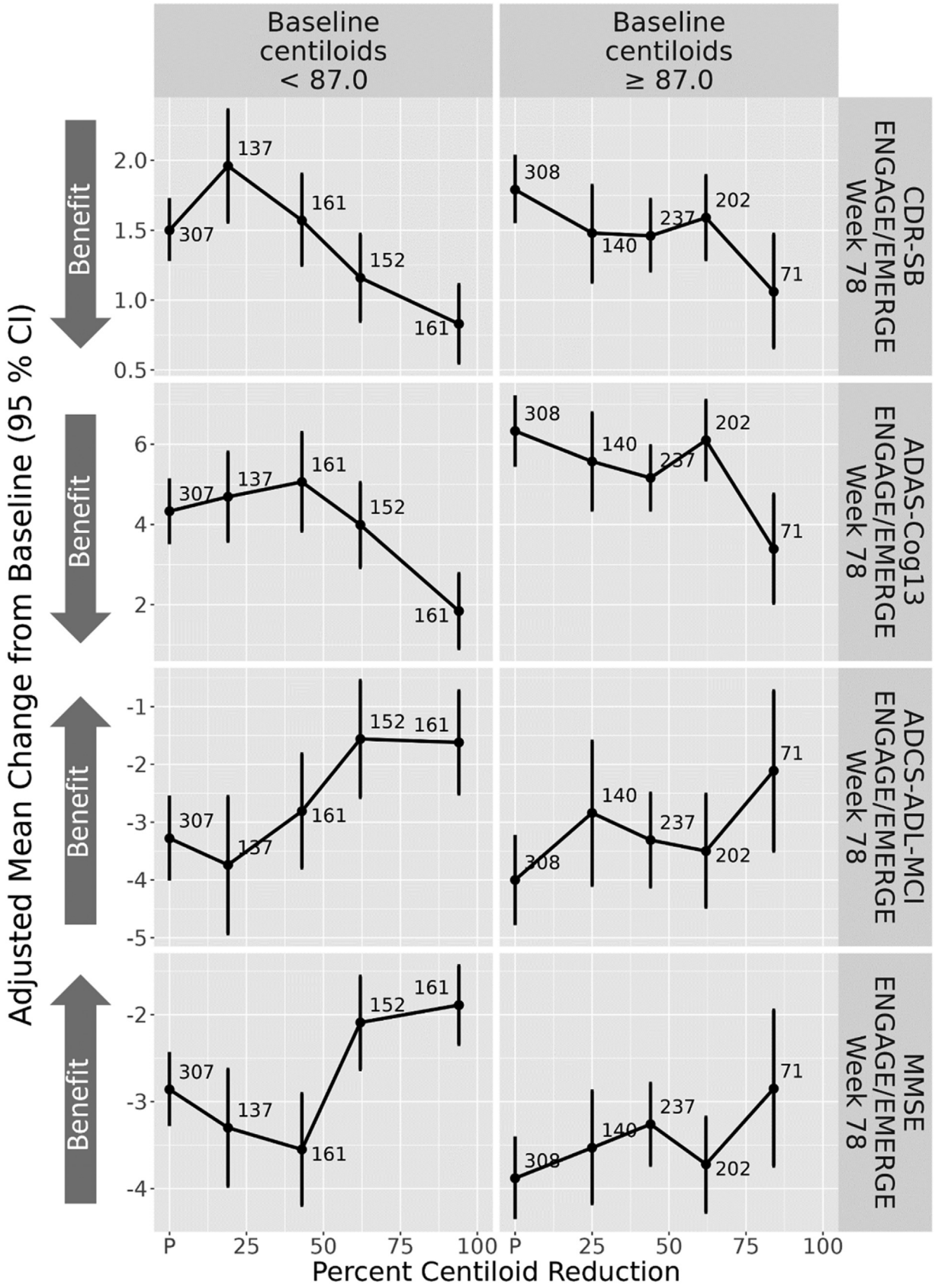

Fig. 2. Observed mean change from baseline across endpoints at week 78 of ENGAGE/EMERGE vs PCR values stratified by the median baseline centiloid value. Points represent midpoints within each PCR group. Error bars represent the 95 % confidence intervals and numbers at the points represent the number of observations. ADAS-Cog13, Alzheimer's Disease Assessment Scale–Cognitive Subscale–13 items; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory–Mild Cognitive Impairment; CDR-SB, Clinical Dementia Rating scale-Sum of Boxes; CFB, change from baseline; MMSE, Mini-Mental State Examination; PCR, percent centiloid reduction; P, placebo.

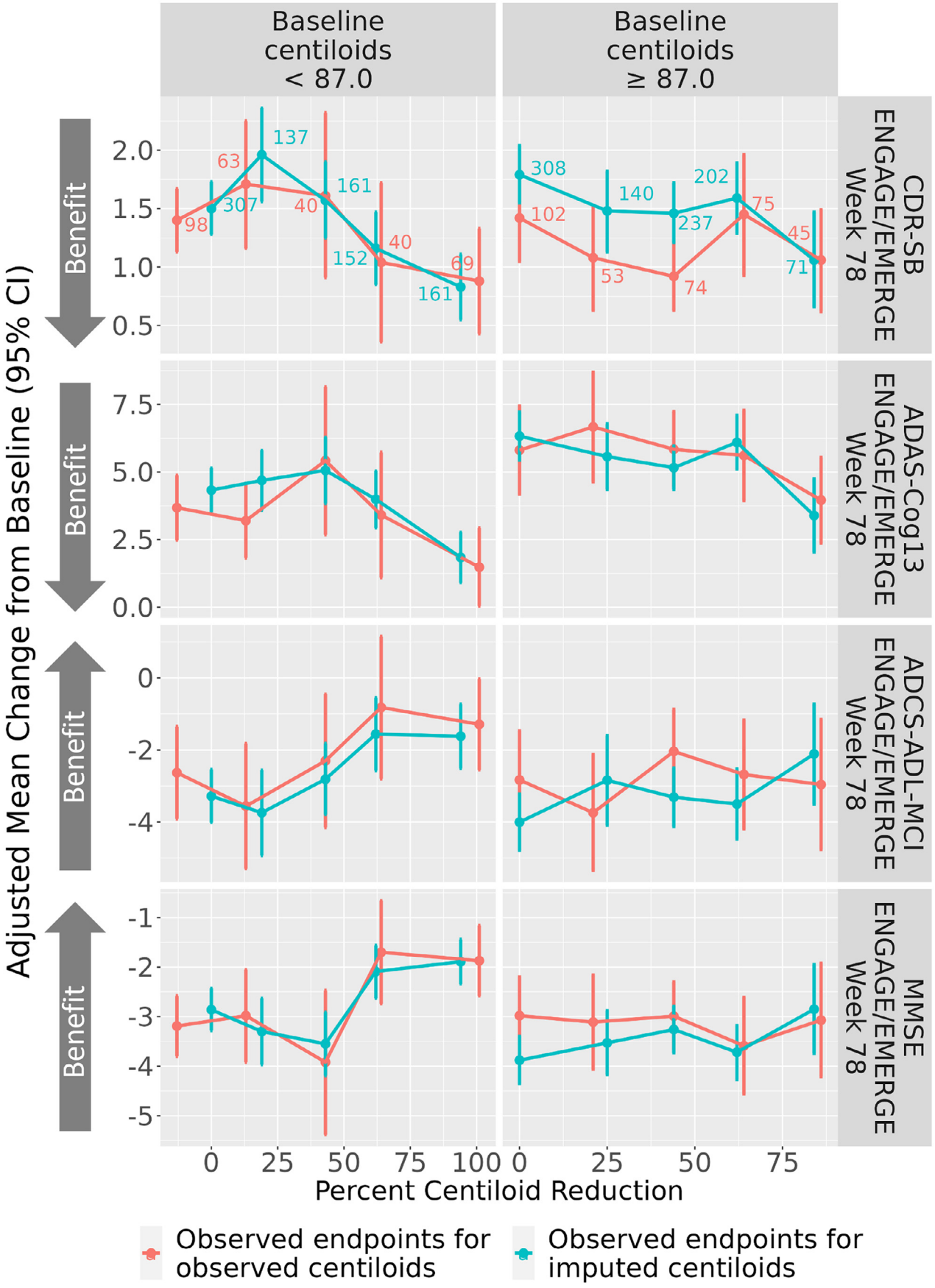

Fig. 3. Observed mean change from baseline across endpoints at week 78 of ENGAGE/EMERGE vs PCR values stratified by the median baseline centiloid value for the non-imputed dataset (red) and the imputation dataset (cyan). Points represent midpoints within each PCR group. Error bars represent the 95 % confidence intervals and numbers at the points represent the number of observations. Numbers of observations across all four endpoints are identical as indicated for CDR-SB.

ences are important given that higher ARIA-E incidence related to ApoE ε4 genotype led to protocol-initiated dose interruptions [2,10], thereby reducing the opportunity to clear Aβ. Comparisons with participants who received placebo are therefore only to help provide insights into the effect of baseline Aβ burden, among other population differences, and they should not be considered as comparisons between randomized populations. The imbalance in ApoE ε4 subpopulations makes it difficult to interpret treatment effect across these groups. Evidence from a previous subgroup analysis of EMERGE and other studies suggests that there may be the same or greater efficacy observed in ApoE ε4 carriers indicating the need for further studies [2,17]. For future work, exposure-response modeling that characterizes the centiloid-clinical outcome relationship would be appropriate as such an analysis could adjust for population imbalances via evaluation of covariate relationships on the parameters of the clinical outcome – PCR relationship. Importantly, this would foundationally characterize placebo progression by simultaneously adjusting for multiple patient features, which would better account for the impact of slower progression when considering the magnitude of clinical benefit.

Another important consideration in this analysis is the underlying model-based methodology. As highlighted earlier, the model formulation requires the assumption on drug effect to be independent of baseline centiloids, but such a dependence was seen. The model is fit-for-purpose for this analysis, but future use of the model to predict PCR changes and/or characterize PCR with clinical outcomes would require an update to the model formulation. Additionally, per the design of the Phase 3 studies, most participants only had a baseline Aβ PET measurement (collected for eligibility), with no post-baseline measurements (collected as part of a substudy). These participants do not contribute to informing model parameters requiring longitudinal assessments. The patient-specific variability therefore cannot be quantified in these participants, and population parameters govern the change in centiloids. A true baseline measurement, however, does enable realistic predictions of Aβ reduction based on actual dose histories. The non-imputation approach showed that the model imputations did not bias the relationship between PCR and clinical endpoints (Supplemental Figure 3) and was further supported by showing consistency between the non-imputed and imputed datasets (Fig. 3). Therefore, given the large sample size of baseline-only Aβ PET, the model-based imputation provided the added advantage of enabling inferences about the relationship of Aβ reduction and clinical outcomes for a much larger participant population at post-baseline assessments.

In this analysis, no use of the original treatment arms nor any subsetting to the target 10 mg/kg dose was made. The rationale to include the lower doses of 3 mg/kg and 6 mg/kg is that these doses help to better characterize the continuous relationship between PCR and change in clinical scores. This was further motivated by examination of the perfect rank correlation between randomized dose and PCR values (Supplemental Figure 2).

The exploratory data analysis, examining baseline Aβ burden (Fig. 2) and its relationship to clinical outcomes, should be viewed as hypothesis generating. However, other analyses on this data have quantified heterogeneity in treatment response related to other clinically relevant variables, including p-tau 181 and hippocampal volume [18].This suggests that, overall, the relationship between Aβ clearance and change in clinical outcomes indicate a complex interaction between demographics and biomarker-based assessments with causal relationships being difficult to verify. More rigorous statistical and/or pharmacometrics analyses can be carried out that characterize the relationship between amyloid reduction and clinical outcomes while controlling factors influencing this relationship.

The overall results suggest that in older participants treated with an Aβ-directed antibody, a lower baseline Aβ burden may be a strong predictor for clinical benefit, although the generalizability of aducanumab is well-established. A potential hypothesis is that when the amyloid burden is low, aducanumab may be more efficient at removing neurotoxic oligomers, which may be key targets in AD pathology. However, it is unclear if there are other unidentified factors that were not measured resulting in the observed differences in clinical outcomes across PCR groups. It is also plausible that a participant who develops AD earlier in life is likely to have a more aggressive form of the disease—i.e., have multiple copies of ApoE ε4 alleles and greater Aβ burden—and will be more difficult to treat successfully with Aβ-directed antibody therapies. Further, ApoE ε4 homozygosity was recently suggested to be a distinct genetic form of AD [19]. Conversely, results from this analysis suggest that participants with onset of AD later in life may have a less aggressive form of the disease, i.e., have no copies of ApoE ε4 alleles and lower Aβ burden, and hence may receive more benefit from Aβ-directed antibody therapies.

In summary, these results provide additional insights into the relationship between Aβ reduction and clinical benefit in a large participant population. Sufficient removal of Aβ plaques in individuals with lower initial Aβ burden may lead to greater clinical benefit. With higher Aβ burden, a higher degree of Aβ reduction appears to be associated with more clinical benefit and suggests that insufficient plaque clearance may not achieve maximum clinical benefit. In both cases, the number of ApoE ε4 alleles play a crucial role. As new data for approved therapies emerge, additional analyses that statistically control for ApoE ε4 carrier status can help determine more precisely how baseline Aβ burden relates to clinical benefit and treatment with Aβ-directed antibody therapies. Nevertheless, this analysis sheds light on a participant sub-population likely to benefit most from Aβ-directed antibody therapies, specifically, those earlier in the disease continuum as measured by Aβ burden who are generally older and are ApoE ε4 non-carriers [14–16,20]. Additionally, given the concordance between cerebrospinal fluid biomarkers and Aβ PET [20], these findings are likely to generalize across Aβ fluid biomarkers. This finding is consistent with learnings from decades of trials targeting Aβ [21] and the current strong focus on early intervention [22]. This analysis can inform future investigations to better understand how amyloid plaque removal relates to clinical outcomes and how these hypothesis-generating observations may provide insight into optimal patient selection for anti-amyloid therapies.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors confirm that they have not used AI or AI-assisted technologies in the writing process or in the preparation of this manuscript.

Funding

This study was funded by Biogen Inc.

Disclosures

J.B., H.B., M.H., J.M., T.S., G.D., and G.C. are employees of Biogen Inc. and may hold stock. K.K. is an employee of Kowalski PMetrics Consulting and received consultancy fees from Biogen Inc.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jackson Burton reports a relationship with Biogen Inc that includes: employment and equity or stocks. Holly M. Brothers reports a relationship with Biogen Inc that includes: employment and equity or stocks. R. Matthew Hutchison reports a relationship with Biogen Inc that includes: employment and equity or stocks. Jennifer Murphy reports a relationship with Biogen Inc that includes: employment and equity or stocks. Tao Sun reports a relationship with Biogen Inc that includes: employment and equity or stocks. Gersham Dent reports a relationship with Biogen Inc that includes: employment and equity or stocks. Gioacchino

Curiale reports a relationship with Biogen Inc that includes: employment and equity or stocks. Ken Kowalski reports a relationship with Kowalski PMetrics Consulting that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Jackson Burton: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Holly M. Brothers:** Writing – review & editing. **R. Matthew Hutchison:** Writing – review & editing. **Jennifer Murphy:** Writing – review & editing. **Tao Sun:** Writing – review & editing. **Gersham Dent:** Writing – review & editing. **Gioacchino Curiale:** Writing – review & editing. **Ken Kowalski:** Writing – review & editing, Methodology, Conceptualization.

Acknowledgments

This study was sponsored by Biogen Inc. Biogen played a role in the design and conduct of the study, as well as the collection, analysis, and interpretation of data. Biogen authors played a role in the preparation of this manuscript. Editorial support, under direction of the author, was provided by Nucleus Global and funded by Biogen Inc.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100202.

References

[1] Wang Y. An insider's perspective on FDA approval of aducanumab. Alzheimers Dement (N Y) 2023;9(2):e12382. doi:10.1002/trc2.12382.
[2] Budd Haeberlein S, Aisen PS, Barkhof F, Chalkias S, Chen T, Cohen S, et al. Two randomized phase 3 studies of aducanumab in early alzheimer's disease. J Prev Alzheimers Dis 2022;9(2):197–210. doi:10.14283/jpad.2022.30.
[3] van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early alzheimer's disease. N Engl J Med 2023;388(1):9–21. doi:10.1056/NEJMoa2212948.
[4] Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. Donanemab in early symptomatic alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. Jama 2023;330(6):512–27. doi:10.1001/jama.2023.13239.
[5] Mazer NA, Hofmann C, Lott D, Gieschke R, Klein G, Boess F, et al. Development of a quantitative semi-mechanistic model of Alzheimer's disease based on the amyloid/tau/neurodegeneration framework (the Q-ATN model). Alzheimers Dement 2023;19(6):2287–97. doi:10.1002/alz.12877.
[6] Gueorguieva I, Willis BA, Chua L, Chow K, Ernest CS, Shcherbinin S, et al. Donanemab population pharmacokinetics, amyloid plaque reduction, and safety in participants with alzheimer's disease. Clin Pharmacol Ther 2023;113(6):1258–67. doi:10.1002/cpt.2875.
[7] McDade E, Cummings JL, Dhadda S, Swanson CJ, Reyderman L, Kanekiyo M, et al. Lecanemab in patients with early Alzheimer's disease: detailed results on biomarker, cognitive, and clinical effects from the randomized and open-label extension of the phase 2 proof-of-concept study. Alzheimers Res Ther 2022;14(1):191. doi:10.1186/s13195-022-01124-2.
[8] Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 2016;537(7618):50–6. doi:10.1038/nature19323.
[9] Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, et al. Addendum: the antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 2017;546(7659):564. doi:10.1038/nature22809.
[10] Kandadi Muralidharan K, Tong X, Kowalski KG, Rajagovindan R, Lin L, Budd Haberlain S, et al. Population pharmacokinetics and standard uptake value ratio of aducanumab, an amyloid plaque-removing agent, in patients with Alzheimer's disease. CPT Pharmacomet Syst Pharmacol 2022;11(1):7–19. doi:10.1002/psp4.12728.
[11] Klunk WE, Koeppe RA, Price JC, Benzinger TL, Devous MD Sr, Jagust WJ, et al. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. Alzheimers Dement 2015;11(1):1–15 e1-4. doi:10.1016/j.jalz.2014.07.003.
[12] Salloway S, Chalkias S, Barkhof F, Burkett P, Barakos J, Purcell D, et al. Amyloid-related imaging abnormalities in 2 phase 3 studies evaluating aducanumab in patients with early alzheimer disease. JAMA Neurol 2022;79(1):13–21. doi:10.1001/jamaneurol.2021.4161.
[13] Filippi M, Cecchetti G, Spinelli EG, Vezzulli P, Falini A, Agosta F. Amyloid-related imaging abnormalities and β-amyloid-targeting antibodies: a systematic review. JAMA Neurol 2022;79(3):291–304. doi:10.1001/jamaneurol.2021.5205.
[14] Kim SJ, Woo SY, Kim YJ, Jang H, Kim HJ, Na DL, et al. Development of prediction models for distinguishable cognitive trajectories in patients with amyloid positive mild cognitive impairment. Neurobiol Aging 2022;114:84–93. doi:10.1016/j.neurobiolaging.2022.02.012.
[15] Karcher H, Savelieva M, Qi L, Hummel N, Caputo A, Risson V, et al. Modelling decline in cognition to decline in function in alzheimer's disease. Curr Alzheimer Res 2020;17(7):635–57. doi:10.2174/1567205017666201008105429.
[16] Narasimhan S, Holtzman DM, Apostolova LG, Cruchaga C, Masters CL, Hardy J, et al. Apolipoprotein E in Alzheimer's disease trajectories and the next-generation clinical care pathway. Nat Neurosci 2024;27(7):1236–52. doi:10.1038/s41593-024-01669-5.
[17] Evans CD, Sparks J, Andersen SW, Brooks DA, Hauck PM, Mintun MA, et al. APOE ε4's impact on response to amyloid therapies in early symptomatic Alzheimer's disease: analyses from multiple clinical trials. Alzheimers Dement 2023;19(12):5407–17. doi:10.1002/alz.13128.
[18] Pang M, Gabelle A, Saha-Chaudhuri P, Huijbers W, Gafson A, Matthews PM, et al. Precision medicine analysis of heterogeneity in individual-level treatment response to amyloid beta removal in early Alzheimer's disease. Alzheimers Dement 2024;20(2):1102–11. doi:10.1002/alz.13431.
[19] Fortea J, Pegueroles J, Alcolea D, Belbin O, Dols-Icardo O, Vaqué-Alcázar L, et al. APOE4 homozygosity represents a distinct genetic form of Alzheimer's disease. Nat Med 2024;30(5):1284–91. doi:10.1038/s41591-024-02931-w.
[20] Hansson O, Seibyl J, Stomrud E, Zetterberg H, Trojanowski JQ, Bittner T, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: a study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimers Dement 2018;14(11):1470–81. doi:10.1016/j.jalz.2018.01.010.
[21] Bullain S, Doody R. What works and what does not work in Alzheimer's disease? From interventions on risk factors to anti-amyloid trials. J Neurochem 2020;155(2):120–36. doi:10.1111/jnc.15023.
[22] Raket LL, Cummings J, Moscoso A, Villain N, Schöll M. Scenarios for the long-term efficacy of amyloid-targeting therapies in the context of the natural history of Alzheimer's disease. Alzheimer's Dement 2024;20(9):6374–83. doi:10.1002/alz.14134.