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ORIGINAL RESEARCH

Application of Meta-analysis to Evaluate Relationships Among ARIA-E Rate, Amyloid Reduction Rate, and Clinical Cognitive Response in Amyloid Therapeutic Clinical Trials for Early Alzheimer's Disease

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Abstract

Background Removal of the extracellular Aβ plaques in the brain is one of the mechanisms to treat Alzheimer's disease (AD). Separate clinical trials for several therapeutic compounds that target amyloid plaque reduction have shown noteworthy correlations among plaque removal, the Amyloid-Related Imaging Abnormalities (ARIA) rate, and clinical efficacy of the treatment. The relationships among therapeutic dose levels, the rate of amyloid removal, and the clinical efficacy deserve further investigation across therapeutic agents, particularly for clinical trials to provide insights for strategies to develop amyloid therapies in Alzheimer's disease.

Methods Published data summaries from clinical trials with amyloid therapies of aducanumab, donanemab, lecanemab, and gantenerumab are evaluated with meta-analyses. Linear mixed models for repeated measurements for visits and random study effects are applied to analyze amyloid centiloid value reduction from baseline and clinical cognition change from baseline for treatment groups according to doses and compounds for the clinical trials. Logistic regression analysis is applied to evaluate the relationship between the amyloid removal rate and the ARIA-Edema (ARIA-E) rate across different dose groups and clinical trials.

Results The extent of amyloid removal varies among therapeutic agents and their dose levels. Across treatment groups and clinical trials, amyloid centiloid value reductions at Weeks 26 and 52 are strongly correlated with both ARIA-E rate over 78 weeks and the clinical efficacy response in the Clinical Dementia-Rating Scale Sum of Boxes (CDR-SB) score change from baseline at Week 78; and the Spearman rank correlations for amyloid reduction at Week 52 are stronger as − 0.79 with the ARIA-E rate over 78 weeks and 0.73 with the Week 78 CDR-SB score change from baseline.

Conclusion Aβ plaques removal in the brain due to amyloid therapy is strongly correlated with a better clinical response in patients with early Alzheimer's disease and a higher ARIA-E rate for the treatment groups and clinical trials in this meta-analysis. These relationships suggest that the balance between the clinical efficacy response and safety in ARIA-E rate is relevant for the choice of doses for amyloid therapies in confirmatory clinical trials.

Keywords Meta-analysis · Amyloid reduction · ARIA-E · CDR-SB · Alzheimer's disease

Introduction

Alzheimer's disease (AD) is a progressive and fatal neurodegenerative disorder and is the most common cause of dementia in the elderly population. An estimator for the global number of people with dementia is 55 million in 2019, and this number is expected to increase to 78 million by 2030 and to 139 million by 2050. The total estimated annual worldwide cost of dementia was over 1.3 trillion US dollars in 2021, and this figure is projected to be 2.8 trillion US dollars by 2030 [1]. More than 6 million adults aged 65 and older in the United States (US) are living with Alzheimer's disease in 2021, and this number is projected to rise to nearly 13 million in 2050 [2]. In 2021, Alzheimer's disease and other dementias are expected to cost the US $355 billion, and this amount could rise to $1.1 trillion by 2050.

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The financial burden of AD globally is potentially huge for human society.

Laboratory and clinical evidence support the concept that an imbalance between the production and clearance of Aβ protein in the brain is an early and often initiating factor in AD [3–5]. Research and clinical studies on Aβ removal and its potential for slowing the progression of cognitive and functional decline in patients with Alzheimer's disease has led to the development of multiple disease-modifying therapies, including monoclonal antibodies directed to bind and remove Aβ plaques in the brain, such as aducanumab [6], lecanemab [7], donanemab [8], and gantenerumab [9]. In June of 2021, the US Food and Drug Administration (FDA) conditionally approved aducanumab (Aduhelm™), through the FDA-Accelerated Approval Program, as the first potentially disease-modifying medicine to treat patients with Alzheimer's disease based on biomarker endpoint results in Phase 3 trials [10]. This Accelerated Approval triggered a worldwide discussion in the amyloid therapeutic area for Alzheimer's disease, and several biopharmaceutical sponsors are developing similar strategies for potential regulatory submissions for their amyloid therapeutic agents including lecanemab [7], donanemab [8], and gantenerumab [9]. From the scientific perspective, a unified analysis of published clinical trials' data in this field may provide some insight to answer important scientific questions concerning amyloid therapies for Alzheimer's disease. For this article, we have extracted currently available, published summary statistics for clinical trials for aducanumab, lecanemab, donanemab, and gantenerumab. We then perform appropriate meta-analyses to assess relationships among such summary statistics for amyloid removal rate, Amyloid-Related Imaging Abnormality-Edema (ARIA-E) rate, and clinical cognitive response as efficacy, and these relationships are potentially informative for understanding the role of dose for amyloid therapies. However, the results for these relationships are not intended to have a causal interpretation nor to pertain to whether the amyloid removal rate might be a surrogate endpoint for clinical cognitive response, mainly because they are based on summary statistics for the clinical trials in the meta-analyses rather than patient-level data.

Methods

Data Extraction Methods for Analysis

Analysis datasets were created from published studies as presented in Table 1. Summary statistics (mean and standard errors, ARIA-E rate) were used for all analyses in this article. Available numerical results of variables of interest (e.g., mean amyloid reduction from baseline and standard error, numerator and denominator for ARIA-E rate, mean Clinical Dementia-Rating Scale Sum of Boxes (CDR-SB) score change from baseline and standard error) were used directly from the published materials. For numerical results that were not available in the published materials, we extracted the needed information from figures or graphs that were available in the published materials using measurement tools built in Nuance Power PDF Advanced© software version 3.0 [11]. Some studies only reported positron emission tomography standardized uptake value ratio (PET SUVR) values and standard errors of SUVR values for amyloid reduction. For these studies, SUVR values and standard errors were converted to amyloid centiloid values and their corresponding standard errors.

Initial Method for ARIA-E Analysis

The sample sizes and numbers of patients with ARIA-E are shown in Table 2 for the dose groups for the four compounds within the clinical trials, and they correspond to 22 treatment groups in all. For the lecanemab G000-201 study, there is initial pooling for the 2.5 mg/kg biweekly and 5 mg/kg monthly groups (since each only has one patient with ARIA-E), and for the aducanumab Prime study, there is

Table 1 Studies Included in the Analysis

Compound	Study	Phase	Treatment Groups	Published Data Source
Aducanumab	Prime (103)	1b	Placebo, 1, 3, 6, 10 mg/kg monthly	Sevigny et al. 2016 Nature [6]
	Engage(301) Emerge(302)	3	Placebo, 6, 10 mg/kg monthly	Biogen aducanumab 2020 BLA submission briefing book and slides [18]
Lecanemab	G000-201	2b	Placebo, 2.5 mg/kg biweekly 5 mg/kg biweekly, 5 mg/kg monthly 10 mg/kg monthly, 10 mg/kg biweekly	Eisai 2018 AAIC BAN2401 presentation slides [19]
Donanemab	Trailblazer-alz	2	Placebo, 700 mg titration to 1400 mg monthly	Mintun et al. 2021 NEJM [8]
Gantenernumab	Scarlet RoAD	3	Placebo, 105 mg, 225 mg monthly	Ostrowitzki et al. 2017 Alzheimer's Research & therapy [9, 20]

Table 2 ARIA-E Rate for Dose Groups Within Clinical Trials for the Four Compounds

Compound	Study	Treatment Group	Schedule (Monthly = M, Biweekly = W)	Dose (mg/kg)	Week	Sample Size	Number of Patients with ARIA-E Events	ARIA-E Rate
Aducanumab	301	10 mg/kg	M	10	78	555	174	0.3135
Aducanumab	301	6 mg/kg	M	6	78	202	42	0.2079
Aducanumab	301	Placebo	M	0	78	545	16	0.0294
Aducanumab	302	10 mg/kg	M	10	78	547	188	0.3437
Aducanumab	302	6 mg/kg	M	6	78	203	41	0.2020
Aducanumab	302	Placebo	M	0	78	548	13	0.0237
Lecanemab	G000-201	10 mg/kg	W	20	72	161	16	0.0994
Lecanemab	G000-201	10 mg/kg	M	10	72	253	25	0.0988
Lecanemab	G000-201	5 mg/kg	M	5	72	51	1	0.0196
Lecanemab	G000-201	5 mg/kg	W	10	72	92	3	0.0326
Lecanemab	G000-201	2.5 mg/k	W	5	72	52	1	0.0192
Lecanemab	G000-201	Placebo	M	0	72	245	2	0.0082
Aducanumab	Prime	10 mg/kg	M	10	48/192	32	13	0.4063
Aducanumab	Prime	6 mg/kg	M	6	48/192	30	11	0.3667
Aducanumab	Prime	3 mg/kg	M	3	48/192	32	2	0.0625
Aducanumab	Prime	1 mg/kg	M	1	48/192	31	1	0.0323
Aducanumab	Prime	Placebo	M	0	48/192	48	0	0.0000
Gantenernumab	Scarlet RoAD	225 mg	M	3	104	260	35	0.1346
Gantenernumab	Scarlet RoAD	105 mg	M	1.5	104	271	18	0.0664
Gantenernumab	Scarlet RoAD	Placebo	M	0	104	226	2	0.0088
Donanemab	Trailblazer-alz	1400 mg	M	20	76	131	35	0.2672
Donanemab	Trailblazer-alz	Placebo	M	0	76	125	1	0.0080

initial pooling of the 1 mg/kg and 3 mg/kg groups (since they, respectively, only have 1 and 2 patients with ARIA-E). There is also initial pooling for the G000-201, Prime, Scarlet RoAD, and Trailblazer-alz clinical trials because all of their placebo groups have ARIA-E event rates that are less than 0.01 (via two or fewer patients with ARIA-E events). Subsequent to these initial poolings, meta-analysis is applied with a logistic regression model that includes study (for 301, 302, and all others) and dose group for the distinct treatment groups. Since study (with $p = 0.79$) is not a statistically significant factor in this model, a simpler model without study is applied. This simpler model invokes pooling of the placebo groups for all of the studies and the pooling of the aducanumab studies 301, 302, and Prime for the 6 mg/kg dose and the 10 mg/kg dose. For the logistic regression model for the 11 distinct dose groups that result from the previously indicated poolings, there is support for the additional pooling of the aducanumab 1 mg/kg and 3 mg/kg groups with the lecanemab 2.5 mg/kg biweekly and 5 mg/kg monthly groups ($p = 0.318$) and the pooling of the lecanemab 5 mg/kg biweekly group with the lecanemab 10 mg/kg monthly group ($p = 0.059$), although the latter pooling has further justification by both of these treatment groups corresponding to a monthly dose of 10 mg/kg. Thus, the initial meta-analyses of the ARIA-E rates for the 22 treatment groups in Table 2 with logistic regression models lead to the following nine dose groups for consideration with the meta-analyses for the amyloid removal rate. These dose groups are presented as the following: Control: pooled placebo groups across all studies; G105: gantenernumab Scarlet RoAD 105 mg dose group; G225: gantenernumab Scarlet RoAD 225 mg group; L2.5BW, L5M, A13: pooled group from lecanemab G000-201 study 2.5 mg/kg biweekly and 5 mg/kg monthly with aducanumab Prime study 1 mg/kg and 3 mg/kg dose groups; A6: pooled group from aducanumab Studies 301, 302, and Prime 6 mg/kg dose groups; A10: pooled group from aducanumab Studies 301, 302, and Prime 10 mg/kg dose groups; L5BW, L10M: pooled group from lecanemab G000-201 study 5 mg/kg biweekly and 10 mg/kg monthly dose groups; L10BW: lecanemab G000-201 study 10 mg/kg biweekly dose group; D: donanemab 1400 mg dose group.

Amyloid Reduction Analysis Method

Amyloid centiloid value change from baseline over time is meta-analyzed with a mixed effects model with repeated measurements for visits and random study effects [12]. The data structure for this analysis is shown in Table 3. As shown

Table 3 Available Visits for Repeated Measurements for Treatment Groups Within Studies

Compound	Study	Treatment Group	Dose Group*	Number of Visits	Visit 1 Weeks	Visit 2 Weeks	Visit 3 Weeks
Aducanumab	301	10 mg/kg	A10	2	26	78	–
Aducanumab	301	6 mg/kg	A6	2	26	78	–
Aducanumab	301	Placebo	Control	2	26	78	–
Aducanumab	302	10 mg/kg	A10	2	26	78	–
Aducanumab	302	6 mg/kg	A6	2	26	78	–
Aducanumab	302	Placebo	Control	2	26	78	–
Aducanumab	Prime	1 mg/kg	L2.5BW, L5M, A13	2	26	54	–
Aducanumab	Prime	10 mg/kg	A10	2	26	54	–
Aducanumab	Prime	3 mg/kg	L2.5BW, L5M, A13	2	26	54	–
Aducanumab	Prime	6 mg/kg	A6	2	26	54	–
Aducanumab	Prime	Placebo	Control	2	26	54	–
Donanemab	Trailblazer-alz	donanemab 1400 mg monthly	D	3	24	52	76
Donanemab	Trailblazer-alz	Placebo	Control	3	24	52	76
Gantenernumab	Scarlet RoAD	105 mg	G105	3	20	60	100
Gantenernumab	Scarlet RoAD	225 mg	G225	3	20	60	100
Gantenernumab	Scarlet RoAD	Placebo	Control	3	20	60	100
Lecanemab	G000-201	10 mg/kg biweekly	L10BW	2	48	72	–
Lecanemab	G000-201	10 mg/kg monthly	L5BW, L10M	2	48	72	–
Lecanemab	G000-201	2.5 mg/kg biweekly	L2.5BW, L5M, A13	2	48	72	–
Lecanemab	G000-201	5 mg/kg biweekly	L5BW, L10M	2	48	72	–
Lecanemab	G000-201	5 mg/kg monthly	L2.5BW, L5M, A13	2	48	72	–
Lecanemab	G000-201	Placebo	Control	2	48	72	–

*Control: pooled placebo groups across all studies; G105: gantenernumab Scarlet RoAD 105 mg dose group; G225: gantenernumab Scarlet RoAD 225 mg group; L2.5BW, L5M, A13: pooled group from lecanemab G000-201 study 2.5 mg/kg biweekly and 5 mg/kg monthly with aducanumab Prime study 1 mg/kg and 3 mg/kg dose groups; A6: pooled group from aducanumab Studies 301, 302, and Prime 6 mg/kg dose groups; A10: pooled group from aducanumab Studies 301, 302, and Prime 10 mg/kg dose groups; L5BW, L10M: pooled group from lecanemab G000-201 study 5 mg/kg biweekly and 10 mg/kg monthly dose groups; L10BW: lecanemab G000-201 study 10 mg/kg biweekly dose group; D: donanemab 1400 mg dose group

there, amyloid centiloid values are available at Week 26 and Week 54 for five of the 22 treatment groups; at Week 26 and Week 78 for six of the 22 treatment groups; at Week 48 and Week 72 for six of the 22 treatment groups; at Week 24, Week 52, and Week 76 for two of the 22 treatment groups; and at Week 20, Week 60, and Week 100 for three of the 22 treatment groups. Also, all 22 treatment groups have amyloid centiloid values at baseline. Since the 22 treatment groups have different schedules for the measurements of amyloid centiloid values, the role of the mixed model is to produce estimates for all of them at Week 26, Week 52, and Week 78 through a structure with potentially different linear trends for baseline to Week 26, Week 26 to Week 52, Week 52 to Week 78, and Week 78 to Week 100. Accordingly, the preliminary model has the following specification:

$$\begin{aligned} y_{ijt} = {} & \alpha + s_i + \beta_0 x_{ij0} + \beta_{0j} x_j + \beta_1 w_{1ijt} \\ & + \beta_2 w_{2ijt} + \beta_3 w_{3ijt} + \beta_{4j} w_{1ijt} x_j \\ & + \beta_{5j} w_{2ijt} x_j + \beta_{6j} w_{3ijt} x_j + \epsilon_{ijt}. \end{aligned}$$

For this model, y_{ijt} is the amyloid centiloid value change from baseline for study $i = 1, 2, 3, 4, 5, 6$ for the studies in Table 1; dose group $j = 1, 2, 3, 4, 5, 6, 7, 8, 9$ as summarized at the end of the previous section; at visit $t = 20, 24, 26, 48, \ldots, 100$ as shown in Table 3; α is the fixed intercept, and s_i is the random effect for study i on the intercept; the random study effects s_i are assumed to have independent $N\left(0, \sigma_s^2\right)$ normal distributions. The baseline amyloid centiloid value is x_{ij0} for dose group j in Study i, and β_0 is its slope; x_j is the indicator variable for dose group j versus

Table 4 Derived Visit Variables w_1, w_2, and w_3 from Actual Visit Weeks for the Linear Model for Amyloid Centiloid Value Change from Baseline

Week	$*\ w_1$ Variable for Coefficient β_1	w_2 Variable for Coefficient β_2	w_3 Variable for Coefficient β_3	Prediction
20	20	20	20	$20\beta_1 + 20\beta_2 + 20\beta_3$
24	24	24	24	$24\beta_1 + 24\beta_2 + 24\beta_3$
26	26	26	26	$26\beta_1 + 26\beta_2 + 26\beta_3$
48	48	26	26	$48\beta_1 + 26\beta_2 + 26\beta_3$
52	52	26	26	$52\beta_1 + 26\beta_2 + 26\beta_3$
54	52	28	26	$52\beta_1 + 28\beta_2 + 26\beta_3$
60	52	34	26	$52\beta_1 + 34\beta_2 + 26\beta_3$
72	52	46	26	$52\beta_1 + 46\beta_2 + 26\beta_3$
76	52	50	26	$52\beta_1 + 50\beta_2 + 26\beta_3$
78	52	52	26	$52\beta_1 + 52\beta_2 + 26\beta_3$
100	52	52	48	$52\beta_1 + 52\beta_2 + 48\beta_3$

*Derivation of w_1, w_2, and w_3:

w_1 = Week if Week ≤ 52; w_1 = 52 if Week > 52.

w_2 = Week if Week ≤ 26, w_2 = 26 if 26 ≤ Week ≤ 52; w_2 = Week-26 if 52 < Week ≤ 78; w_2 = 52 if Week > 78.

w_3 = Week if Week ≤ 26, w_3 = 26 if 26 < Week ≤ 78; w_3 = Week-52 if Week > 78

placebo, and β_{0j} is the corresponding treatment effect relative to placebo; w_{1ijt}, w_{2ijt}, and w_{3ijt} are derived variables as shown in Table 4 for visit weeks for study i and dose group j at Week t, and they have coefficients β_1, β_2, and β_3 such that $(\beta_1 + \beta_2 + \beta_3)$ represents the linear trend between baseline and Week 26, β_1 represents the linear trend between Week 26 and Week 52, β_2 represents the linear trend between Week 52 and Week 78, and β_3 represents the linear trend between Week 78 and Week 100; the $w_{1ijt}x_j$, $w_{2ijt}x_j$, and $w_{3ijt}x_j$ represent interaction terms with the x_js for the corresponding dose groups, and they respectively have corresponding coefficients β_{4j}, β_{5j}, and β_{6j} that represent the influence of the jth dose group relative to placebo on the linear trends that correspond to β_1, β_2, and β_3. The random error terms ε_{ijt} are assumed to have independent $N\left(0, \sigma_{ei}^2\right)$ distributions for the corresponding studies. For the model selection process with backward elimination, there is support for the removal from the model of $\beta_3 w_{3ijt}$, and the interaction terms for $\beta_{5j} w_{2ijt} x_j$ and $\beta_{6j} w_{3ijt} x_j$. Thus, the final model for amyloid centiloid value change from baseline is as follows:

$$y_{ijt} = \alpha + s_i + \beta_0 x_{ij0} + \beta_{0j} x_j + \beta_1 w_{1ijt} + \beta_2 w_{2ijt} + \beta_{4j} w_{1ijt} x_j + \varepsilon_{ijt}\ .$$

The analysis for this model is used to estimate predicted means for amyloid centiloid value change from baseline at Week 26, Week 52, and Week 78 for the 22 treatment groups in Table 3. Since the structure of Table 4 implies that the difference between the predicted mean at Week 78 and that at Week 52 for all 22 treatment groups is $26\beta_2$, the analysis for the relationships for amyloid centiloid value change with ARIA-E and clinical response only addresses the roles for the predicted means of amyloid centiloid value change at Week 26 and at Week 52. Also, graphical displays are produced to describe how well the model predicts the observed means for amyloid reduction at the times for their determination.

Methods for Associations Between ARIA-E and Amyloid Reduction

Two methods are applied to evaluate the relationships between the amyloid reduction rate and the ARIA-E rate. For descriptive purposes, Spearman rank correlations are calculated between the ARIA-E rates in Table 2 for the 22 treatment groups and the predicted means at Week 26 and Week 52 for amyloid reduction from the methods described in the previous section. Additionally, a logistic regression model is applied to evaluate how well the variation among the ARIA-E rates for the 22 treatment groups can be explained by the variation among the predicted means for amyloid reduction at Week 26 and Week 52. The final model for this purpose includes the Week 52 predicted mean for amyloid reduction and an indicator variable which is equal to 1 for Study 301 or Study 302 and equal to 0 for all other studies. The indicator for Study 301 or Study 302 is included in the model because the predicted means for amyloid reduction at Week 52 are from a mixed model that includes study as a random effect; and the indicator variable invokes pooling for Studies 301 and 302 because of the similarity of their ARIA-E rates in Table 2 for placebo, aducanumab 6 mg/kg, and aducanumab 10 mg/kg. Graphical displays are produced to describe how well the logistic regression model explains the variation among the ARIA-E rates for the 22 treatment groups.

Clinical Response Analysis Method

Since the schedules for the measurements of CDR-SB for the 22 treatment groups are the same as those shown in Table 3 for the amyloid centiloid values, the first stage of analysis for CDR-SB change from baseline uses a mixed model with repeated measurements for visits and random study effects in ways that are similar to the previously described use of such models for amyloid centiloid value change from baseline. The structure of the resulting final model is essentially the same as that for the amyloid centiloid value change from baseline, except for the replacement of $\beta_2 w_{2ijt}$ by $\tilde{\beta}_2 \tilde{w}_{2ijt}$, where $\tilde{w}_{2ijt} = 0$ if Week ≤ 52 for the measurement of CDR-SB and $\tilde{w}_{2ijt} = (\text{Week} - 52)$ if Week ≥ 52. From the analysis for this model, predicted means of CDR-SB change from baseline are estimated for Week 26, Week 52, and Week 78 for the 22 treatment groups in Table 3, with those at Week 78 being of primary clinical interest. Also, a graphical display is produced to describe how well this model predicted the observed means for CDR-SB change from baseline at the times for their determination for the 22 treatment groups.

For evaluation of the relationships between amyloid reduction and CDR-SB change from baseline, two methods are applied. For descriptive purposes, the Spearman rank correlation is produced between the predicted means at Week 52 for amyloid reduction and the predicted means at Week 78 for CDR-SB change from baseline for the 22 treatment groups in Table 3. Additionally, the previously described mixed model for CDR-SB change from baseline is modified to have the variables corresponding to dose groups (i.e., the x_j and the $w_{1ijt}x_j$) replaced by the predicted means at Week 52 for amyloid reduction and additionally to include the interactions of that explanatory variable with both the w_{1ijt} and the $\tilde{w}_{2ijt}$ that correspond to weeks for measurements. How well this model explains the variation among the predicted means for CDR-SB change from baseline at Week 78 for the 22 treatment groups is described with a graphical display.

All analyses in this paper are performed using SAS 9.4 software [13]. Example SAS code using PROC MIXED procedure for the meta-analysis is included in Appendix.

Results

A total of 6 studies and 22 treatment groups within them are included in the meta-analyses. Detailed information for the studies and the treatment groups are provided in Tables 1 (and its cited references), 2, and 3.

ARIA-E Analysis Results

The observed ARIA-E rates across treatment groups are shown in the last column of Table 2. Within each study, the ARIA-E rate is dose exposure dependent, i.e., higher ARIA-E rates are evident at higher dose levels. The odds ratios (ORs) and their 95% confidence intervals from the meta-analysis with logistic regression are shown in Table 5 for the comparisons to placebo for each of the other eight dose groups.

Except for the low dose group L2.5BW, L5M, A13, the 95% confidence intervals for the odds ratios of ARIA-E event for the other dose groups, relative to the pooled placebo group, exclude 1. The OR for dose group A10 is 24.75, which is the highest among the dose groups included in this analysis. The OR for the donanemab dose group (D) is more than three times that of the OR for the lecanemab L10BW dose group, even though the total exposure seems similar (i.e., 20 mg/kg for a month) between these two dose groups. The reason for this difference could be the different dose

Table 5 Odds Ratio (OR) of ARIA-E Event for Different Dose Groups

Dose Group	OR Comparing to Pooled Placebo Group	95% Confidence Interval of OR
A10	24.75	(17.24, 35.52)
D	18.26	(10.91, 30.56)
A6	13.81	(9.17, 20.79)
G225	7.79	(4.76, 12.74)
L10BW	5.53	(2.98, 10.25)
L5BW, L10M	4.42	(2.65, 7.40)
G105	3.56	(1.98, 6.41)
L2.5BW, L5M, A13	1.56	(0.60, 4.03)

A10, A6: aducanumab 10 mg/kg, 6 mg/kg dose groups, respectively; D: donanemab 1400 mg; G105, G225: gantenernumab 105 mg and 225 mg dose groups, respectively; L10BW: lecanemab 10 mg/kg biweekly dose group; L5BW, L10M: pooled lecanemab 5 mg/kg biweekly and 10 mg/kg monthly dose groups; L2.5BW, L5M, A13: pooled lecanemab 5 mg/kg monthly and 2.5 mg/kg biweekly dose groups, aducanemab 1 mg/kg and 3 mg/kg dose groups

schedules or the difference between the compounds. The lecanemab L10BW group has a biweekly dosing schedule, and the donanemab D group has a monthly dosing schedule titrated up to 1400 mg after 700 mg in the first 3 doses.

Amyloid Centiloid Value Reduction Analysis Results

The observed means for amyloid centiloid value reduction over time across the 22 treatment groups within the 6 studies are presented in Fig. 1. Within each study, the means for amyloid centiloid value reduction from baseline are dose exposure dependent, i.e., larger means for amyloid centiloid value reduction are evident at higher doses within each study. Also, the cumulative amyloid centiloid value reduction becomes larger over time within each treatment group. Figure 2 shows that the mixed model with repeated measurements for visits and random study effects provides predicted means for amyloid removal with reasonably good fit to the observed means for amyloid removal values. The model predicted means for amyloid reduction for the 9 dose groups at Week 26, Week 52, and Week 78 are presented in Table 6.

Consistent with the trends for the observed means for amyloid reduction, the donanemab D group has the largest predicted mean for amyloid reduction during the first 26 weeks; the aducanumab 10 mg/kg (A10) and 6 mg/kg (A6) dose groups have the second and third largest predicted means for amyloid reduction during the first 26 weeks, followed by the lecanemab 10 mg/kg biweekly group for which the very large standard error is due to the absence of an observed mean amyloid reduction at Week 26 in the G000-201 study. As might be expected, there is no apparent amyloid removal for the control group over time.

Relationship Between the Amyloid Removal Rate and the ARIA-E Rate

The Spearman rank correlation coefficients between the ARIA-E rates and the predicted least-squares (LS) means of amyloid centiloid value reduction at Week 26, Week 52, and the LS mean differences between Week 52 and Week 26 are -0.69, -0.79, and -0.67, respectively, all with $p < 0.001$. For the logistic regression analysis, the simplest model only includes the predicted means for amyloid centiloid value reduction at Week 52 since it nearly is a sufficient explanatory variable for the ARIA-E rate. Figure 3 shows the consistency of the model predicted ARIA-E rates with the observed ARIA-E rates for this logistic regression model. Alternatively, Fig. 4 presents the predicted ARIA-E rates from a logistic regression model that includes study (as pooled 301 and 302 versus the pooled other studies) and

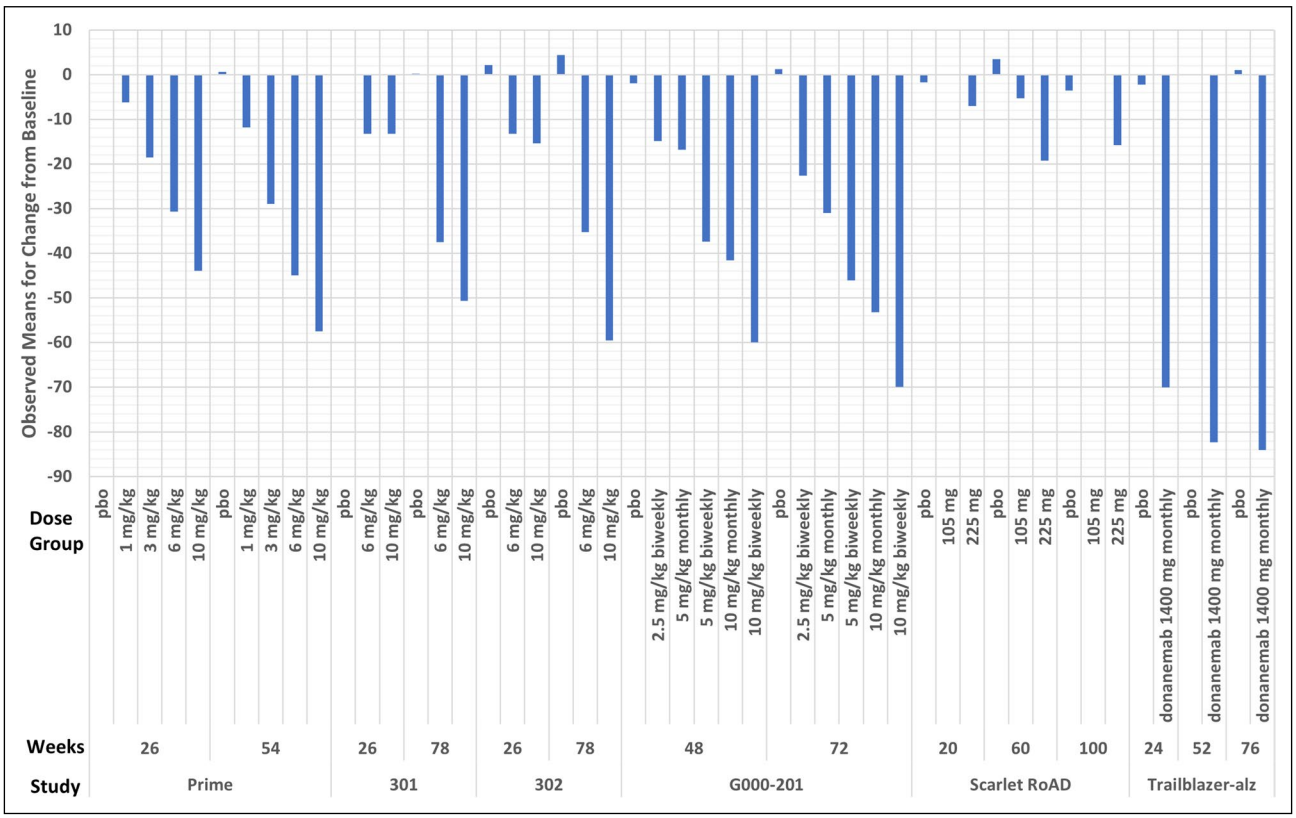

Fig. 1 Observed means for amyloid centiloid value reduction over time across treatment groups in different studies

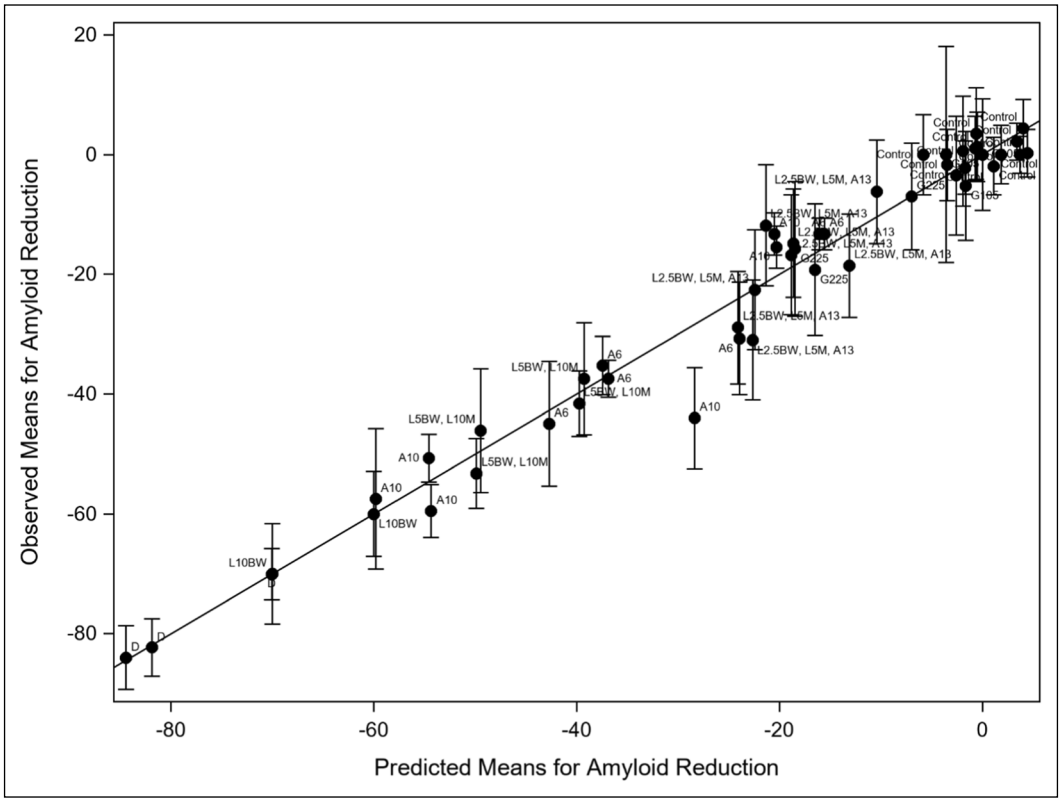

Fig. 2 Consistency of predicted mean amyloid reduction versus observed mean amyloid reduction. Labels for data points represent dose groups. The diagonal line is a reference line where observed equals to predicted values

Table 6 Predicted Means for Amyloid Reduction over Time

	Week 26		Week 52		Week 78	
Treatment	LS Mean	Standard Error	LS Mean	Standard Error	LS Mean	Standard Error
A10	−24.42	3.13	−55.65	3.46	−58.45	3.20
A6	−19.93	3.14	−38.47	3.46	−41.27	3.20
D	−69.63	3.50	−80.39	3.21	−83.19	3.17
G105	1.09	4.64	0.96	4.40	−1.83	4.26
G225	−8.06	4.56	−14.59	4.32	−17.38	4.18
L10BW	−16.49	37.97	−67.52	5.27	−70.31	4.99
L5BW, L10M	5.80	27.61	−46.30	4.19	−49.09	3.83
L2.5BW, L5M, A13	−8.29	4.10	−19.06	2.93	−21.86	3.03
Control	−0.88	2.25	2.66	2.34	−0.14	2.17

the predicted means for amyloid centiloid value reduction at Week 52. As shown in both Figs. 3 and 4, the observed ARIA-E rates for the A6 and A10 dose groups in the PRIME study are outliers. In contrast to the observed ARIA-E rates for the same dose groups (A6 and A10) in the 301 and 302 studies, the observed ARIA-E rates in the PRIME study are not stable due to the small sample sizes. More generally, a clear trend is evident in Figs. 3 and 4 for larger predicted means for amyloid centiloid value reduction at Week 52 to correspond to higher ARIA-E event rates.

Relationship Between Amyloid Removal Rate and Clinical Efficacy Response

The observed means for longitudinal CDR-SB score changes from baseline for the 22 treatment groups are described in Fig. 5 where lower values of CDR-SB score change from

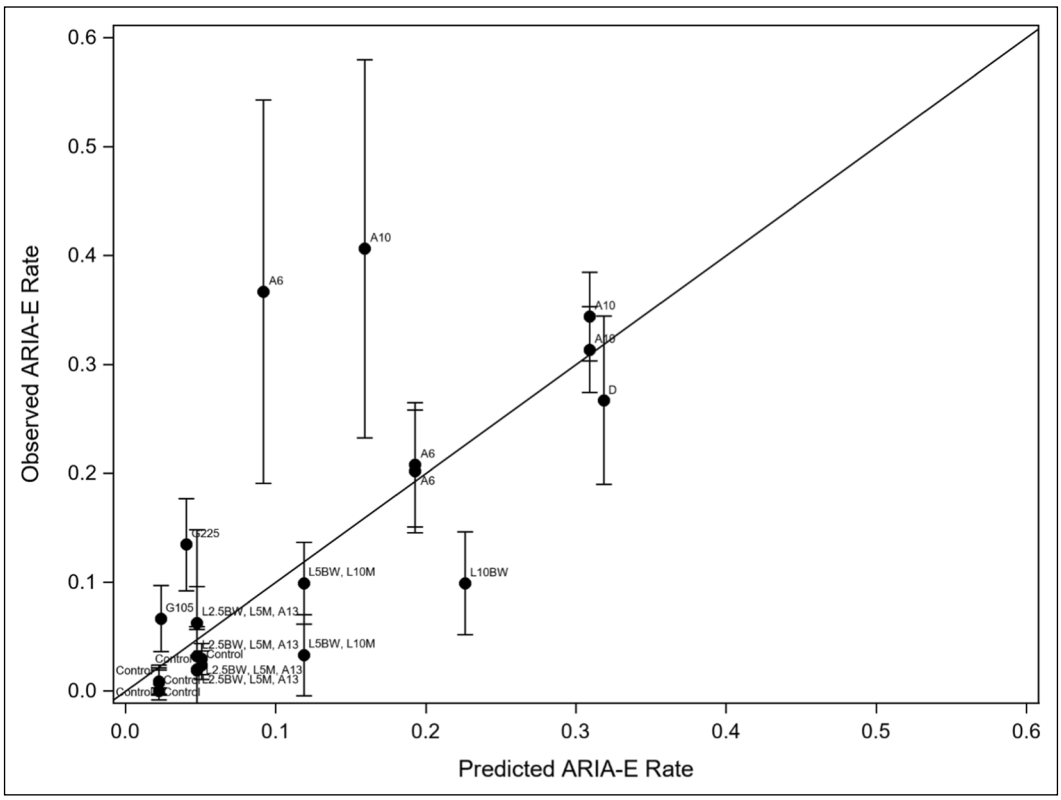

Fig. 3 Consistency of observed ARIA-E rates and predicted ARIA-E rates from the logistic regression model with the predicted mean for amyloid centiloid value reduction at Week 52 as the explanatory variable. Labels for data points represent dose groups. The diagonal line is a reference line where observed is equal to predicted values

baseline are preferable to higher values. An effective treatment is expected to slow the disease progression, with this being equivalent to a smaller observed mean CDR-SB score change from baseline. Thus, a more negative difference between a treated group and the placebo group (as treated – placebo) represents a better treatment effect. As shown in Fig. 6, the mixed model with repeated measurements for visits and random study effects produces predicted means for CDR-SB score change from baseline that tends to increase for all nine dose groups over time. The predicted LS mean CDR-SB score changes from baseline in the control and L2.5BW, L5M, and A13 dose groups have similar increases; and those increases are larger than those for the other dose groups, particularly Groups D, A10, and L10BW for which the increases are clearly smaller than for the control group. The previously noted interpretations are also well supported by the predicted LS means for CDR-SB score changes from baseline at Week 26, Week 52, and Week 78 that are shown in Table 7. How well larger predicted means for amyloid centiloid value reduction at Week 52 correspond to less decline for the predicted means of CDR-SB score changes from baseline at Week 78 is shown in Fig. 7. Dose groups D, A10, and L10BW have the smallest predicted means for CDR-SB score increase at Week 78 relative to the other dose groups, especially relative to the placebo control group. The trends in Fig. 7 indicate that the predicted mean for amyloid centiloid value reduction at Week 52 is strongly correlated with the clinical treatment response at Week 78 as represented by the predicted mean for CDR-SB score change from baseline. The Spearman rank correlation coefficient between the predicted mean for amyloid centiloid value reduction at Week 52 (LS mean) and the predicted mean for CDR-SB score change from baseline at Week 78 (LS mean) is 0.73 ($p < 0.001$) for the 22 treatment groups in Table 3. Thus, larger amyloid reduction at Week 52 (as more negative change from baseline) corresponds to slower cognition decline in CDR-SB score change from baseline.

Discussion and Conclusions

This article reports the results of meta-analyses based on summary statistics extracted from published data for clinical trials in amyloid therapeutics for patients with early Alzheimer's disease. These meta-analyses evaluate the relationships among the amyloid removal rate in terms of amyloid centiloid value reduction, the ARIA-E rate, and the clinical efficacy response in CDR-SB score change from baseline in

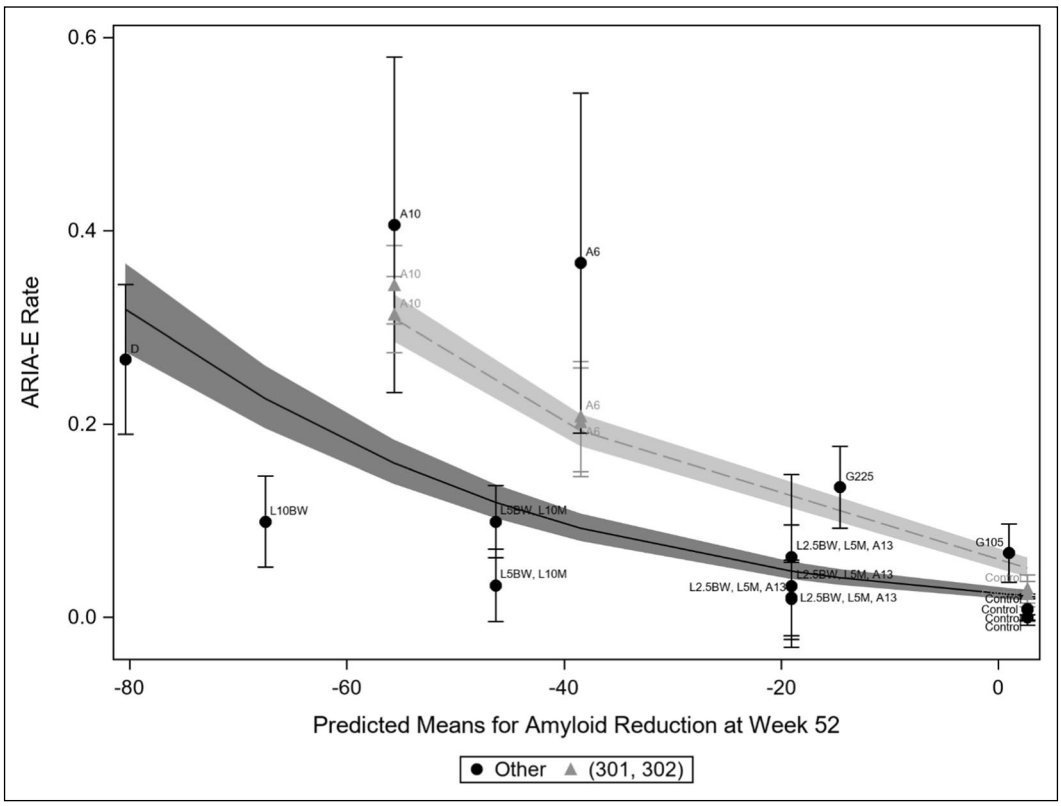

Fig. 4 Prediction of ARIA-E rates from a model that includes predicted mean amyloid reduction at Week 52 and studies in the model. Pooled studies 301 and 302 (gray solid upper triangle) are compared with the other pooled studies (black solid circle)

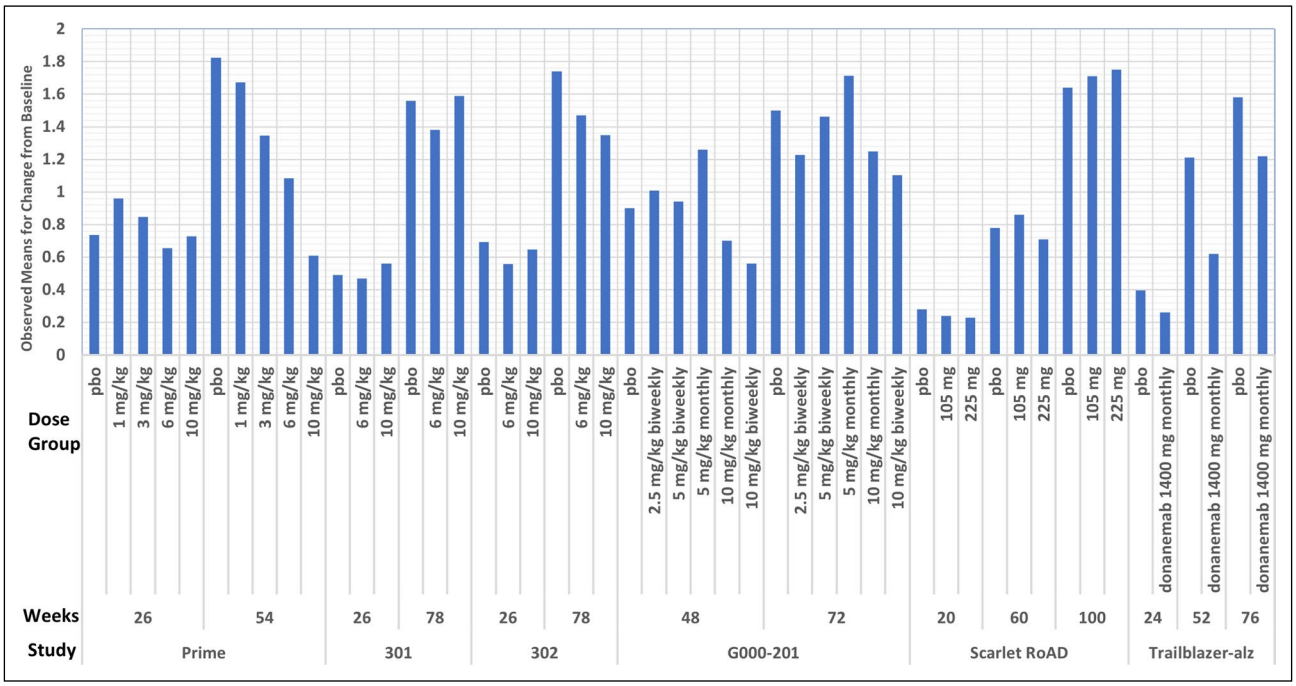

Fig. 5 Longitudinal observed means CDR-SB score change from baseline across treatment groups in different studies

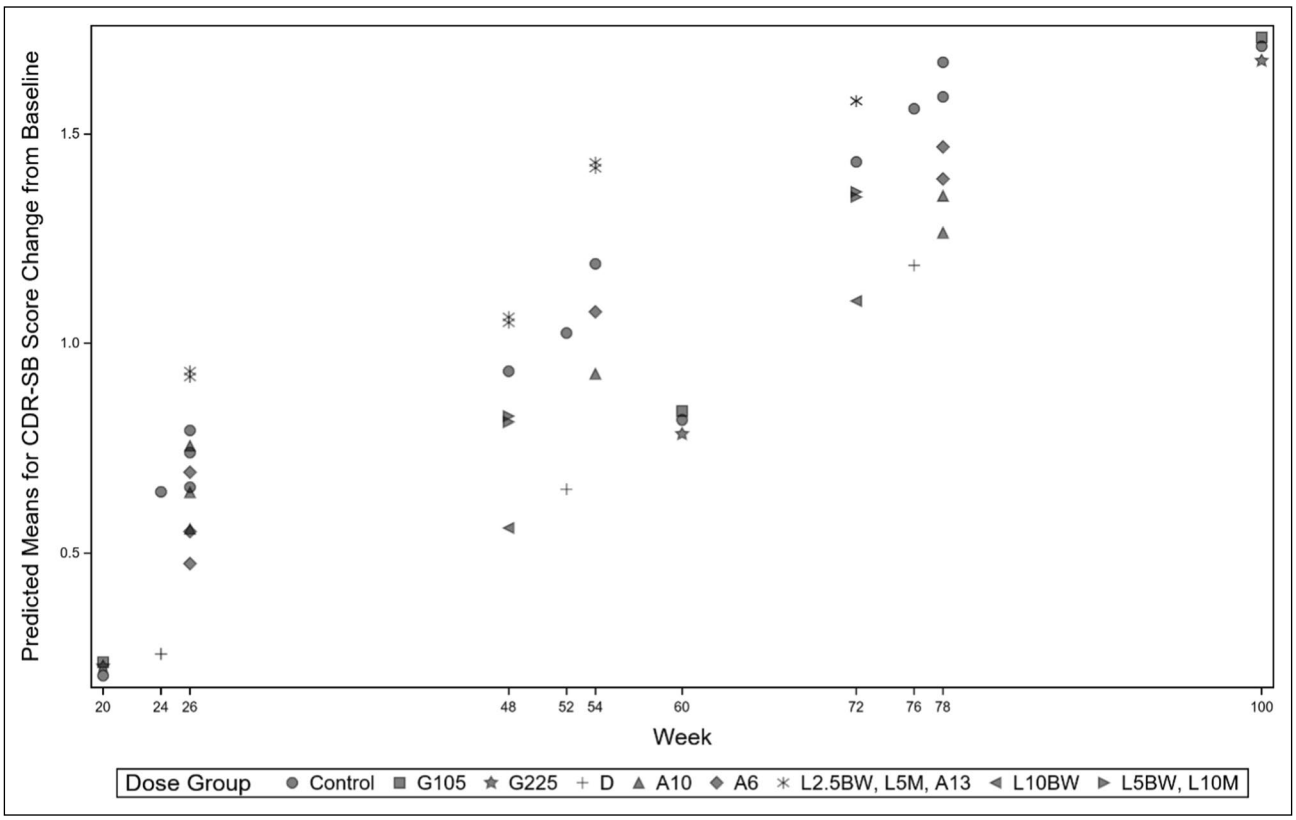

Fig. 6 Predicted means for CDR-SB score change from baseline over time for dose groups

the target patient population. In general, the magnitude and the extent of brain Aβ plaques removal seem to depend on therapeutic agents and their dose exposure levels. For the reported meta-analyses, higher dose levels tend to provide more amyloid removal in terms of the observed means for amyloid centiloid value reduction for each of the therapeutic agents in the corresponding studies. Among the investigated amyloid therapeutic agents in this paper, donanemab and lecanemab 10 mg/kg biweekly have predicted means at Week 52 that correspond to more removal of brain Aβ plaques than the other agents, and their administration is at seemingly similar therapeutic dose exposures. Such predicted means for brain Aβ plaques removal in early Alzheimer's disease patients are strongly correlated with higher rates of ARIA-E events, and the rates of ARIA-E events are larger for larger dose exposures. The predicted means for amyloid removal at Week 52 are also positively correlated with the predicted means for clinical efficacy response assessed at 78 weeks, i.e., more amyloid centiloid value reduction at Week 52 corresponds to better clinical response at Week 78 in terms of CDR-SB score change from baseline. However, for aducanemab at 10 mg/kg, the predicted means for the clinical efficacy response in terms of CDR-SB score change from baseline did not differ as much from placebo at Week 26 as at Week 52 or Week 78, even though the amyloid removal difference was substantial at Week 26. Such considerations suggest that the clinical efficacy response difference from placebo control for a therapeutic dose level of some compounds might be delayed to Week 52 or Week 78 after the appearance of substantial amyloid removal at Week 26.

For the meta-analyses to fit models to the summary statistics from the longitudinal data for amyloid centiloid value reduction and CDR-SB score change from baseline, the numerical values of estimated parameters vary somewhat among orders of data-sorting procedures. This consideration could suggest that the likelihood surface of the meta-analysis for this dataset is relatively flat so that the optimal estimates for parameters could not be obtained. Nevertheless, the predicted means from the mixed models for the amyloid centiloid value reductions and the CDR-SB score change from baseline for the dose groups are relatively similar for the alternative sorting procedures, and so are their interpretations. The analysis results in this paper are based on the dataset with sorting by Study, Treatment group, and Week variables, respectively. This sorting specification satisfies criteria for better model fitting statistics (smaller is better) in terms of Akaike Information Criterion (AIC), AIC corrected for small sample sizes (AICC), and Bayesian Information Criterion (BIC) versus other possible sorting specifications for the dataset.

Table 7 Predicted Means for CDR-SB Score Change over Time Comparing to Control

		Predicted CDR-SB Score Change		Difference from Placebo		
Treatment	Week	LS Mean	Standard Error	LS Means Difference	Standard Error	Descriptive *p* Value
A10	26	0.55	0.07	−0.10	0.06	0.0929
A6		0.46	0.07	−0.19	0.06	0.0033
D		0.24	0.12	−0.41	0.11	0.0015
G105		0.67	0.06	0.02	0.05	0.7048
G225		0.67	0.07	0.02	0.05	0.5902
L10BW		0.03	0.94	−0.62	0.94	0.5171
L5BW, L10M		0.33	0.67	−0.32	0.67	0.6401
L2.5BW, L5M, A13		0.68	0.13	0.03	0.13	0.8170
Control		0.65	0.06	–	–	–
A10	52	0.68	0.07	−0.32	0.06	<.0001
A6		0.80	0.07	−0.20	0.06	0.0017
D		0.60	0.10	−0.40	0.10	0.0003
G105		1.01	0.06	0.01	0.04	0.8442
G225		0.98	0.07	−0.02	0.04	0.6081
L10BW		0.66	0.13	−0.34	0.13	0.0126
L5BW, L10M		0.92	0.10	−0.08	0.10	0.4075
L2.5BW, L5M, A13		1.13	0.08	0.13	0.08	0.1092
Control		1.00	0.06	–	–	–
A10	78	1.26	0.07	−0.32	0.06	<.0001
A6		1.38	0.07	−0.20	0.06	0.0017
D		1.18	0.10	−0.40	0.10	0.0003
G105		1.59	0.06	0.01	0.04	0.8442
G225		1.56	0.07	−0.02	0.04	0.6081
L10BW		1.24	0.13	−0.34	0.13	0.0126
L5BW, L10M		1.50	0.10	−0.08	0.10	0.4075
L2.5BW, L5M, A13		1.71	0.08	0.13	0.08	0.1092
Control		1.58	0.05	–	–	–

A limitation of the results from the meta-analyses presented in this paper is that they are based on published summary statistics that are available from clinical trials information in the public domains. Also, only six studies are included in the analyses, with this scope being limited by the number of amyloid therapeutic agents currently ongoing investigation. As noted for Table 3, the schedules for assessments of amyloid removal and clinical efficacy differ for the six studies, and the extent of such differences increases the variability for the predicted means at unobserved time points. Nevertheless, consistent patterns are noted across different therapeutic agents with respect to relationships among the predicted means for the amyloid removal rate, the ARIA-E rate, and the predicted means for the clinical response in CDR-SB score change over time. Such relationships need further evaluation with additional clinical trials data for amyloid therapeutic agents as they become available in the future, especially from the datasets that will be produced from the currently ongoing large phase 3 clinical trials, such as the donanemab TRAILBLAZER-ALZ 2 study [ClinicalTrials.gov identifier: NCT04437511] [14], the lecanemab CLARITY study [ClinicalTrials.gov identifier:NCT03887455] [15], and the gantenernumab GRADUATE 1 & 2 studies [ClinicalTrials.gov identifier: NCT03443973, NCT03444870] [16, 17]. When available, subject level data from these and other studies may provide very useful information for further investigation of the relationships among the amyloid removal rate, the ARIA-E event rate, and the clinical efficacy response. As indicated at the end of the Introduction, the reported relationships for summary statistics from the studies included in the meta-analyses in this article are not intended to have a causal interpretation, although they are considered to be potentially informative for understanding the roles of the doses for the amyloid therapies in those studies. For future confirmatory studies, they shed light on the relevance for the

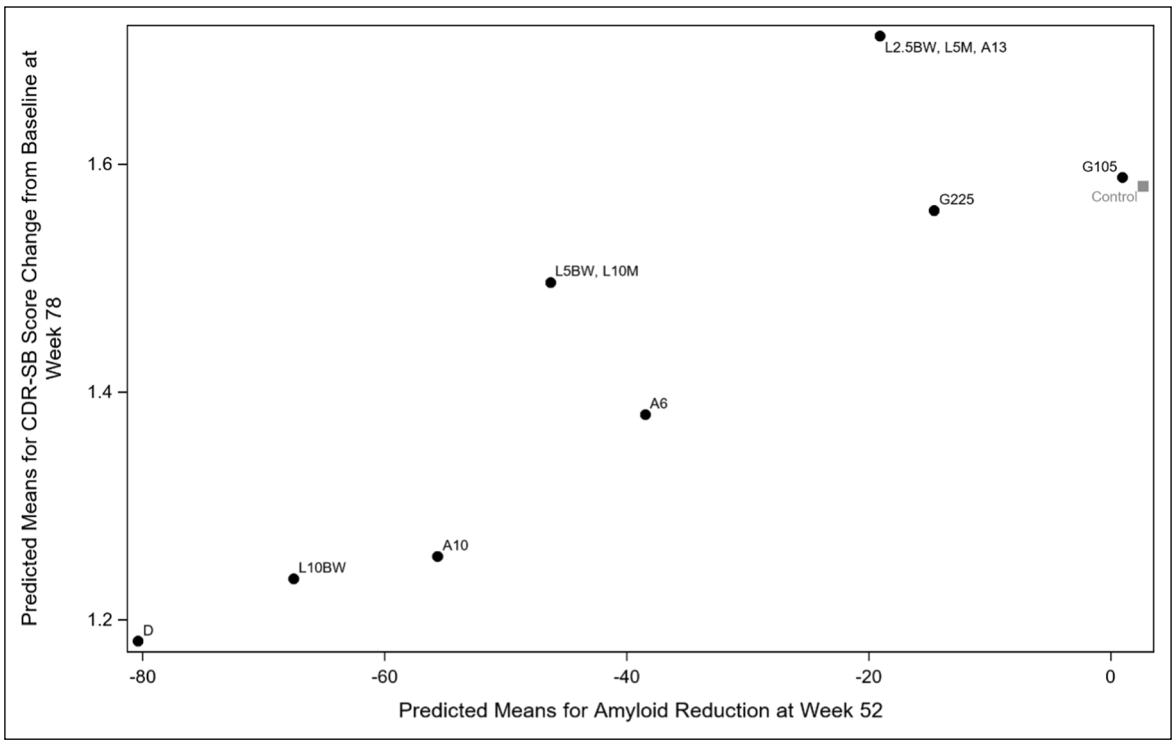

Fig. 7 Predicted means for CDR-SB score change from baseline at Week 78 from the model where the predicted mean of amyloid reduction at Week 52 is an explanatory variable

balance between clinical efficacy response and safety in the ARIA-E rate for the choice of dose for amyloid therapies.

Author Contributions

The data collection, research, and analysis were supported by AbbVie Inc. and University of North Carolina at Chapel Hill (UNC-CH). DW, who is an employee of AbbVie Inc., participated in the extraction of the data, the analysis, writing and interpretation of results, and approval of this manuscript. EKK and GGK participated in the data analysis, interpretation of results, writing, and approval of this manuscript. EKK is a graduate student of UNC-CH. GGK is an employee of UNC-CH and is the Principal Investigator of a collaborative biostatistical agreement between UNC-CH and AbbVie Inc.

Declarations

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest. Nevertheless, the authors acknowledge that AbbVie has an Alzheimer's research program in the same drug class as the medicines in the clinical trials that are addressed by the analyses in this manuscript. In addition, as the manuscript indicates, the data structures and analyses that are necessary to support accelerated approval by a regulatory agency for a medicine for Alzheimer's disease are beyond the scope of this manuscript.

Appendix

1: Example PROC MIXED code for "Amyloid Reduction Analysis Method" in the Methods section.

```
*************************************************************************
* centimeta: input dataset for meta-analysis                            *
* study: class variable for study                                       *
* dose: class variable for dose groups (see Table 3)                    *
* change_centiloid: mean change of centiloid value from baseline        *
* bl_centiloid: mean baseline centiloid value                           *
* o2w1: o2w1 = Week if Week ≤ 52; o2w1 = 52 if Week > 52 (see Table 4)   *
* o2w2: o2w2 = Week if Week ≤ 26; o2w2 = 26 if 26 ≤ Week ≤ 52;          *
*   o2w2 = Week-26 if 52 < Week ≤ 78; o2w2 = 52 if Week > 78 (see Table 4) *
* centiESTwithPrime: input data set including within study variance for change_centiloid *
*   variable                                                            *
*************************************************************************

proc mixed data = centimeta method = ml cl;
class study dose(ref = "Control");
model change_centiloid = bl_centiloid dose o2w1 o2w2 dose*o2w1 / s cl covb;
random int / subject = study s type = un;
repeated / group = study;
parms / parmsdata = centiESTwithPrime eqcons = 1 to 49;
lsmeans dose / at (o2w1 o2w2)=(26 26) pdiff;
lsmeans dose / at (o2w1 o2w2)=(52 26) pdiff;
lsmeans dose / at (o2w1 o2w2)=(52 52) pdiff;
run;
```

2: Example PROC MIXED code for analysis of CDR-SB discussed in "Clinical Response Analysis Method" in the Methods section.

```
*************************************************************************
* cdrsb: input dataset for meta-analysis                                *
* study: class variable for study                                       *
* dose: class variable for dose groups (see Table 3)                    *
* cdrsb_change: mean change of CDR-SB score from baseline               *
* cdrsb_bl: mean baseline CDR-SB score                                  *
* w1: w1 = Week if Week ≤ 52; w1 = 52 if Week > 52                      *
* w2: w2 = 0 if Week ≤ 52; w2 = Week - 52 if Week > 52                  *
* cdrsbESTwithPrime: input data set including within study variance for cdrsb_change *
*   variable                                                            *
*************************************************************************

proc mixed data = cdrsb method = ml cl;
class study dose(ref = "Control");
model cdrsb_change = cdrsb_bl dose w1 w2 w1*dose / s cl covb;

random int / subject = study s type = un;
repeated / group = study;
parms / parmsdata = cdrsbESTwithPrime eqcons = 1 to 49;
lsmeans dose / at (w1 w2)=(26 0) pdiff;
lsmeans dose / at (w1 w2)=(52 0) pdiff;
lsmeans dose / at (w1 w2)=(52 26) pdiff;
run;
```

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