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Original Article

Lecanemab for treatment of individuals with early Alzheimer's Disease (AD) who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes

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ABSTRACT

Background: Lecanemab, an antibody directed at Aβ-protofibrils and plaque, showed meaningful delay in disease progression and biological effects consistent with disease modification in the phase 3 Clarity AD trial.
Objective: The objective of this paper is to present efficacy and safety results in ApoE ε4 non-carriers or heterozygotes population of Clarity AD.
Design: Clarity AD is an 18-month, randomized study (core) in participants with early AD, with an open-label extension phase (OLE) phase.
Setting: Academic and clinical centers.
Participants: All eligible ApoE ε4 participants were randomized 1:1 across 2 treatment groups (placebo and lecanemab 10 mg/kg biweekly); the results presented herein are for the ApoE4 heterozygote or non-carrier participants.
Measurements: Endpoints included change from baseline at 18 months in the global cognitive and functional scale, CDR-SB, amyloid positron emission tomography (PET), Alzheimer's Disease Assessment Scale-Cognitive Subscale 14 (ADAS-Cog14), Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL), and health-related quality-of-life (HRQoL) assessments. Amyloid imaging related abnormalities (ARIA) occurrence was monitored throughout the study by central reading of magnetic resonance imaging. Following 18 months treatment in the Core, eligible participants transitioned to the OLE where they received open-label lecanemab. Clinical outcomes (CDR-SB, ADAS-Cog14, and ADCS-MCI-ADL) were evaluated by examining 'delayed start' (core:placebo followed by OLE:lecanemab) and 'early start' (core: lecanemab followed by OLE:lecanemab) cohorts as well as natural history cohorts. Time to progression to next stage of AD was also evaluated through 36 months.
Results: 1795 participants with early AD were enrolled in Clarity AD, of which 1521 were ApoE ε4 heterozygotes or non-carriers (85 %). Lecanemab significantly reduced clinical decline on CDR-SB at 18 months compared to placebo in the ApoEε4 heterozygotes or non-carriers subgroup. Amyloid PET, ADAS-Cog14, ADCS-MCI-ADL, and HRQoL results were consistent with the CDR-SB findings. In the analysis subgroup, the most common adverse reactions for lecanemab were infusion-related reactions (26 %), ARIA-H (13 %), fall (11 %), headache (11 %),

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and ARIA-E (9 %). In the OLE, lecanemab-treated participants continued to accrue benefit in CDR-SB through 36 months, with continued separation through 36 months relative to the ADNI natural history cohort. Delayed start results follow a parallel trajectory relative to early start results, but do not catch up, confirming a disease modifying effect and reflecting importance of early treatment initiation. Results were similar for ADAS-Cog14 and ADCS-MCI-ADL. Lecanemab reduced the risk of progression to next stage of AD by 28 % on lecanemab as compared to the ADNI natural history cohort.

Conclusion: In the ApoE ε4 heterozygotes or non-carrier subgroup of Clarity AD, lecanemab slowed decline in disease progression and reduced markers of amyloid, with expanding benefit over time.

ClinicalTrials.gov identifier: Clarity AD NCT03887455

1. Introduction

Alzheimer's disease (AD), the most common form of dementia, is defined by neuropathologic changes, such as amyloid-beta (Aβ) plaques comprised of aggregated Aβ and neurofibrillary tangles containing aggregated tau proteins [1–5]. Cognitive impairment result from neuropathologic changes due to synapse and neuronal loss, neurotransmitter deficiencies, inflammation of the neurons, and astrogliosis [2]. In the European Union (EU), approximately 7 million people are currently living with AD, with estimates predicting a rise to 14 million by 2030 [6]. In the United Kingdom (UK), it is estimated that 982,000 people are living with dementia [7] and AD is the cause in 60–70 % of people with dementia in the UK [8].

Growing evidence suggests that amyloid removal slows progression of disease and therapies targeting this process may alter the underlying disease course [3,9–11]. Recently, phase 3 studies have demonstrated that anti-amyloid disease modifying therapies can improve the lives of those with early AD and slow progression of the disease [12–14].

Lecanemab is a novel humanized immunoglobulin G1 monoclonal antibody developed against Aβ protofibrils, as the 'Arctic' mutation in Swedish subjects with familial AD was found to have an increased propensity for aggregation of Aβ to form protofibrils [15,16]. Aβ peptides exist in many different conformational states including monomeric Aβ peptide, soluble Aβ aggregates of increasing size ranging from small dimers and trimers to larger oligomers and protofibrils, and insoluble fibrils. Aβ protofibrils have been implicated in altering synaptic function and mediating neurotoxicity leading to cognitive decline and, ultimately, the dementia observed as AD progresses clinically. Lecanemab was designed to selectively target these large soluble protofibrils relative to monomers (greater than 1000-fold over Aβ monomers), while it also interacts with the insoluble fibrils that are a major component of brain amyloid [15–25].

In two randomized controlled trials, lecanemab has demonstrated a consistent slowing of decline in clinical (global, cognitive, functional, and quality of life) outcomes, and reduction in brain amyloid in early AD [12,26]. Lecanemab was shown to be well tolerated in multiple clinical trials, although an increased rate of amyloid-related imaging abnormalities (ARIA) was observed relative to placebo, especially in individuals who were ApoE ε4 homozygotes [12,26–28]. Lecanemab was recently approved in the UK as well as in the EU for the treatment of mild cognitive impairment (MCI) and mild dementia due to AD in adult participants who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers.

Herein, we present results of the apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers subgroup of Clarity AD, consistent with the approved product labelling in the UK and the EU, as well as other countries (e.g., Canada). This manuscript will include Clarity AD randomized (Core) and open-label extension (OLE) data. This subgroup analysis of the original Clarity AD data was not pre-specified, but was requested by the European authorities (MHRA and EMA) as part of the submission for market authorization approval.

2. Methods

2.1. Trial design and oversight

Overall designs of Clarity AD and Clarity AD OLE have been previously published [12,28–30]. This analysis of only the ApoE ε4 heterozygotes or non-carriers from Clarity AD followed the prior published methods, with several exceptions that will be highlighted below. All analyses presented in this manuscript are subgroup analysis of the original Clarity AD data that were not pre-specified, and therefore, all results should be considered as post-hoc and exploratory. Briefly, Clarity AD was an 18-month global, multicenter, double-blind, placebo-controlled, parallel-group study (Core) with a single-arm OLE in individuals with early AD (Figure S1).

Eligible participants were randomized to placebo or lecanemab 10 mg/kg IV biweekly according to a fixed 1:1 schedule. The randomization of the Core was stratified according to clinical subgroup (MCI due to AD or mild AD dementia [31,32]); presence or absence of concomitant approved AD symptomatic medication at baseline (e.g., acetylcholinesterase inhibitors, memantine, or both); ApoE4 status (ie, carriers or non-carriers); and geographical region (ie, North America, Europe, or Asia Pacific).

The OLE evaluated the long-term safety and tolerability of lecanemab in participants with early AD and whether the long-term effects of lecanemab as measured by the efficacy assessments at the end of the Core Study were maintained over time in the OLE. Any subject who completed the Core study and met OLE eligibility criteria had the option to receive intravenous lecanemab 10 mg/kg biweekly in the OLE for up to 48 months (4 years) in the clinic, until the drug is commercially available in the country where the subject resides, or until the benefit-to-risk assessment from treatment with lecanemab is no longer considered favorable. Some participants initiated OLE treatment or transitioned to a weekly subcutaneous lecanemab formulation. Full eligibility criteria have been previously published [12,28–30]. This manuscript will focus on available OLE data up to 36 months.

The study was conducted in accordance with International Conference on Harmonisation guidelines and ethical principles of the Declaration of Helsinki. The trial was approved by the institutional review board or independent ethics committee at each center and all participants provided written informed consent. An independent Data Safety Monitoring Board (DSMB) consisting of experts in AD and statistics reviewed unblinded safety data during trial conduct. In addition, an independent, blinded medical monitoring team reviewed ARIA, infusion related reactions and hypersensitivity reactions to minimize treatment bias. Clinical assessment raters were independent from study investigators.

2.2. End points

Efficacy endpoints included change from Core Study baseline in CDR-SB, change from baseline in amyloid PET imaging using Centiloids (with either florbetaben, florbetapir, or flutemetamol tracers), Alzheimer's disease Assessment Scale-Cognitive Subscale 14 (ADAS-Cog14; [33]), and Alzheimer's Disease Cooperative Study-Activities of Daily

Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL; [34]).

Since there is no longer a placebo arm in the Clarity AD OLE study, efficacy was compared to an ADNI cohort, with data obtained from the ADNI database (adni.loni.usc.edu). Briefly, a matched observational cohort from ADNI was created a priori during the design of Clarity AD to aid in decision-making for the protocol design. The observational cohort criteria were: (1) baseline diagnosis of "MCI" with global CDR = 0.5 and CDR memory ≥0.5 or baseline diagnosis of "AD" with global CDR = 0.5 or 1.0 and CDR memory ≥0.5; (2) proportion of MCI (60 %) and mild AD (40 %); (3) baseline MMSE scores ≥22; (4) at least 1 of 2 criteria for amyloid positivity; (4a) baseline amyloid PET SUVr florbetapir ≥1.11 or amyloid PET SUVr Pittsburgh compound B (PIB) ≥1.47 or (4b) baseline cerebrospinal fluid (CSF) total tau/amyloid beta (Aβ) >0.222. Using this ADNI cohort, rate of decline at 18 months and variability in the data was estimated for power calculations in Clarity AD. This same ADNI cohort was applied to Clarity AD enrollment criteria, matching expected participant characteristics, during the recruitment of the study. Additional information on the ADNI cohort control can be found in Supplemental Appendix A. Clarity AD OLE efficacy results were also compared to a historical control group composed by data from the Swedish BioFINDER study (NCT01208675). For BioFINDER matching, baseline diagnosis of MCI was used with a global CDR = 0.5 and a baseline MMSE score ≥22. Amyloid positivity was defined by CSF Aβ42/40 ratio (positive if ratio <0.091).

Efficacy was also assessed in the subgroup of participants with lower pathology—considered to represent an early pathologic stage of disease—as defined as having low or no tau (Cutoffs for MK Tau PET: No/Low SUVR <1.06; Intermediate SUVR 1.06–2.91; High SUVR >2.91). Results for this subgroup was summarized as the percentage of participants who had 'no decline' or had 'improvement' from Core baseline at each timepoint.

The safety endpoints were the incidence of adverse events (AEs) and changes in vital signs, ECGs, laboratory safety tests, and magnetic resonance imaging (MRI) safety parameters. ARIA occurrence was monitored throughout the study by central reading of MRI scans performed for safety monitoring.

Biomarker assessments included plasma biomarkers (Aβ 42/40 ratio, p-tau181). For health-related quality of life (HRQoL) assessments, the effects of lecanemab 10 mg/kg administered biweekly compared to placebo in subjects with early AD as measured included the European Quality of Life–5 Dimensions (EQ-5D-5 L; by subject), the Quality of Life in AD (QOL-AD; by subject), and the Zarit Burden Interview ZBI (ZBI) [29], as previously described [29]. EQ-5D-5 L measures 5 dimensions of health (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with 5 levels of severity in each dimension (no limitations, slight problems, moderate problems, severe problems, and inability to perform or extreme limitations).

2.3. Statistical analysis

The statistical analysis for the overall Clarity AD Core study was previously published [12]. All analyses presented in this manuscript are subgroup analysis of the original Clarity AD data that were not pre-specified, and therefore, all results should be considered as post-hoc and exploratory. There are no adjustments for multiplicity and all p values presented are nominal. As requested by the European Medicines Agency, efficacy analyses were conducted for ApoE ε4 non-carriers or heterozygotes participants using control-based multiple imputation (CBMI) method, in which all missing values were imputed with copy-increments (change between visits) using the actual value in placebo group. This methodology (called the EU analysis herein) differs from that used in the Clarity AD primary analysis which used mixed model for repeated measures (MMRM), with no imputation of missing data, meaning that for a participant who drops out of the study, the model assumes that the participant would behave like similar participants in the same treatment group [12]. MMRM results will also be presented (ie, UK analysis).

For the OLE, there was no formal statistical hypothesis testing; all analyses were descriptive, as was previously described [30]. Briefly, efficacy analyses were performed in the modified intention-to-treat population, which was defined as the group of randomly assigned participants who received at least one dose of lecanemab or placebo and who had a baseline assessment and at least one post-dose CDR-SB efficacy measurement. All efficacy analyses of OLE data were conducted with standard MMRM methodology. For the efficacy analyses broken down by Core drug assignment, individuals who were randomized to lecanemab in the Core were considered 'early start' participants relative those who were randomized to placebo in the Core (ie, 'delayed start' participants) since they started lecanemab 18 months earlier than those who started on placebo. Efficacy was compared to the ADNI cohort and a BioFINDER cohort.

Safety analyses were performed for lecanemab-treated period in the safety analysis set. Subjects who received lecanemab in the Core and subjects who received placebo in the Core and lecanemab in the OLE were included. Adverse events were reported descriptively by preferred term and coded according to the Medical Dictionary for Regulatory Activities version 25.

Post-hoc analyses of CDR-SB time to worsening and impact of ARIA on clinical progression were conducted. For CDR-SB time to worsening analysis, progression was defined as CDR-SB Score progressing from MCI (0.5–4) to mild AD dementia (4.5–9) or mild dementia to moderate dementia (9.5–15.5) based on dementia staging on CDR-SB [35]. CDR-SB time to worsening analysis was also conducted for mild AD population including the analysis using the same imputation method as described above. For the impact of ARIA on clinical progression analysis, the probability of worsening of CDR-SB by 3.0 points was compared between participants with and without ARIA over the course of the study. Additional thresholds were evaluated as part of this analysis as well.

3. Results

3.1. Participants

Data presented from the Clarity AD Core includes 1795 participants, 897 randomized to placebo and 898 randomized to lecanemab (859 and 875 participants included in the modified intention-to-treat population for placebo and lecanemab, respectively; Table 1). Of these participants, 1466 and 1521 ApoE ε4 heterozygotes or non-carriers were used in the standard MMRM (UK) and CBMI (EU) methodology populations, respectively (Table 1). Baseline characteristics were generally similar for the EU/UK analyses populations versus the overall Clarity AD population, with the exception of the homozygous ApoE4 carriers who were excluded from the EU/UK analyses population (Table 1).

3.2. Efficacy

Results for the CDR-SB efficacy analyses through 18 months are shown in Fig. 1. Using standard MMRM methodology (UK analysis), lecanemab significantly slowed disease progression compared with placebo on CDR-SB by 33 %, with an adjusted least-squares mean change difference from baseline at 18 months: −0.58; 95 % CI: −0.81 to −0.35; $P < 0.00001$ (Fig. 1A). Significant differences vs placebo were observed at all time points beginning at 3 months. An additional analysis using conservative methods for the handling of missing data (ie, CBMI; EU analysis) gave similar results, slowing progression by 31 % (adjusted mean change from baseline at 18 months: 1.22 with lecanemab and 1.75 with placebo (difference: −0.54; 95 % CI: −0.78 to −0.29] Fig. 1B). Results for a global CDR time to worsening analysis where the shift from MCI to dementia or from mild AD to moderate/severe AD was analyzed showed that lecanemab meaningfully delayed progression to next AD stage through 18 months (hazard ratio = 0.66 (95 %CI: 0.53, 0.81)

Table 1
Baseline Characteristics for Core Clarity AD Study.

	Clarity AD All Participants (MMRM Methodology)		**ApoE ε4 Heterozygotes or Non-carriers Population**			
			EMA Indicated Population (CBMI Methodology)		**United Kingdom Indicated Population** (MMRM Methodology)	
	Placebo (*N* = 875)	**Lecanemab 10 mg/kg biweekly (*N* = 859)**	**Placebo (*N* = 764)**	**Lecanemab 10 mg/kg biweekly (*N* = 757)**	**Placebo (*N* = 743)**	**Lecanemab 10 mg/kg biweekly (*N* = 723)**
Age, mean (standard deviation), years	71.0 (7.8)	71.4 (7.9)	71.5 (8.0)	72.1 (7.9)	71.4 (8.0)	72.1 (7.9)
Female, n (%)	464 (53.0)	443 (51.6)	401 (52.5)	383 (50.6)	390 (52.5)	365 (50.5)
AD Stage						
MCI	544 (62.2)	528 (61.5)	472 (61.8)	466 (61.6)	462 (62.2)	445 (61.5)
Mild dementia	331 (37.8)	331 (38.5)	292 (38.2)	291 (38.4)	281 (37.8)	278 (38.5)
ApoE4 Status						
Noncarrier	275 (31.4)	267 (31.1)	286 (37.4)	278 (36.7)	275 (37.0)	267 (36.9)
Heterozygous	468 (53.5)	456 (53.1)	478 (62.6)	479 (63.3)	468 (63.0)	456 (63.1)
Homozygous	132 (15.1)	136 (15.8)	-	-	-	-
CDR-SB, mean (SD)	3.22 (1.34)	3.17 (1.34)	3.23	3.18	3.22	3.17
Amyloid PET Centiloids, mean (SD)	75.03(41.82)	77.92 (44.84)	73.7	76.3	73.7	76.3
ADAS-Cog14, mean (SD)	24.37 (7.56)	24.45 (7.08)	24.40	24.46	24.40	24.48
ADCS MCI-ADL, mean (SD)	40.9 (6.9)	41.2 (6.6)	40.7	41.2	40.9	41.3

ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale. ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment. ApoE4, apolipoprotein E4. CDR-SB, Clinical Dementia Rating-sum of boxes. MCI, mild cognitive impairment. MMSE, Mini-Mental State Exam. PET, positron emission tomography. SD, standard deviation. Overall population published in van Dyck CH, et al. N Engl J Med. 2023;388:9–21.

Fig. 1C). In the subgroup of participants with mild AD (i.e., CDR-SB 4.5 to 9.0), lecanemab meaningfully delayed progression to moderate AD through 18 months (hazard ratio = 0.58 (95 %CI: 0.31, 1.11); copy increments from reference approach: hazard ratio = 0.52 (95 % CI: 0.29, 0.91).

In the analysis of amyloid PET imaging, lecanemab significantly reduced fibrillar amyloid burden at all time points beginning at 3 months (Fig. 2A). At 18 months, the mean change from baseline in amyloid PET relative to placebo was −59.4 for lecanemab relative to placebo hazard ratio ($p < 0.00001$). The magnitude of the reduction was time-dependent. For ADAS-Cog14 and ADCS MCI-ADL, results were similar to those of the CDR-SB assessment, with lecanemab significantly slowed disease progression beginning at 6 months using both methodologies (Fig. 2). Adjusted mean treatment differences for ADAS-Cog14 at 18 months were 1.6 (95 % CI: −2.56, −0.71; $p = 0.00052$) and −1.5 (95 % CI: −2.49, −0.54; $p = 0.00235$) in the MMRM (UK analysis) and CBMI (EU analysis), respectively (Fig. 2B-2C). For ADCS MCI-ADL, adjusted mean treatment differences at 18 months were 2.23 (95 % CI: 1.34, 3.13; $p < 0.00001$) and 1.94 (1.03, 2.84; $p = 0.00002$) in the MMRM (UK analysis) and CBMI (EU analysis), respectively (Fig. 2D-2E).

In the OLE, lecanemab-treated ApoeE4 non-carriers and heterozygote participants continue to accrue benefit through 36 months for all efficacy endpoints (Figure S2A). Matched ADNI and BioFINDER participants representing the population of those in Clarity AD study show similar degree of decline as the placebo group out to 18 months, supporting that these natural history cohorts are representative of placebo decline. The treatment effects between lecanemab and ADNI as well as BioFINDER cohorts are comparable to the efficacy of lecanemab versus placebo at 18 months, and the treatment effects continue to expand from 18 through 36 months. Of note, the lecanemab delayed start group also shows benefit in OLE relative to control cohorts. Time saved evaluated at 36 months for CDR-SB was 6.8 months and 8.9 months for early-start lecanemab versus the ADNI and BioFINDER controls, respectively (Figure S2B). This represents an increase from 18 months where time saved for early-start lecanemab was 5.2 months relative to ADNI, 6.3 months for BioFINDER, and 6.6 months for placebo Figure S2B). Results for a CDR-SB time to worsening analysis through 36 months showed a meaningfully delayed progression to next AD stage for lecanemab relative to the matched ADNI control (Hazard Ratio = 0.72 (95 %CI: [0.59, 0.87]) (Figure S2C). The proportion of participants that progress to next disease stage during the OLE were 79.1 % in the ADNI cohort and 53.4 % in the lecanemab group. Results out to 36 months in other efficacy endpoints in the OLE were similar to the CDR-SB results (Figure S2D and Figure S2E).

In a subgroup analysis of no/low tau participants representing an early population within the early AD continuum, subjects with no/low tau continued to benefit through 36 months (Figure S3). A majority of participants from subgroup improved or maintained CDR-SB out to 36 months, with 59 % showing no decline and 54 % reporting improvement at 36 months.

3.3. Biomarkers

An overview of results for the assessments of plasma Aβ42/40 ratio and p-tau181, amyloid pathology biomarkers, are summarized in Table S1. Overall, biomarker results were consistent with efficacy findings. Results of analyses of end points involving plasma Aβ42/40 ratio and p-tau181 levels both showed significant improvements when comparing lecanemab with placebo (Table S1). The adjusted mean change from baseline at 18 months were 0.008 ($p < 0.00001$) and −0.825 ($p < 0.00001$) for plasma Aβ42/40 ratio and p-tau181, respectively. Statistically significant differences for lecanemab vs placebo were also observed at 12 months (Table S1).

3.4. Safety

A summary of the incidence of adverse events, including ARIA, is shown in Table 2. Deaths occurred in 0.8 % and 0.9 % of participants in the lecanemab and placebo groups, respectively. No deaths were related to lecanemab or occurred with ARIA during the 18-month randomized trial. Serious adverse events occurred in 14.8 % of participants in the lecanemab group and 11.3 % of participants in the placebo group. The overall incidence of adverse events was 88.1 % and 81.2 % in the lecanemab and placebo groups, respectively. Adverse events leading to drug withdrawal occurred in 5.9 % of participants in the lecanemab group and 3.0 % of participants in placebo group. The frequency of adverse events of special interest in the lecanemab group were infusion reactions (lecanemab:25.8 %; placebo:7.1 %), ARIA-H (combined cerebral microhemorrhages and superficial siderosis; lecanemab:12.9 %; placebo:6.8 %), ARIA-E (lecanemab:8.9 %; placebo:1.3 %). Intracerebral hemorrhage occurred in 0.4 % and 0.1 % of participants in the lecanemab and placebo groups, respectively. Events of ARIA-E were mostly mild-to-moderate, mostly asymptomatic, and occurred within the first 6 months of treatment (Fig. 3), and generally resolved within 4

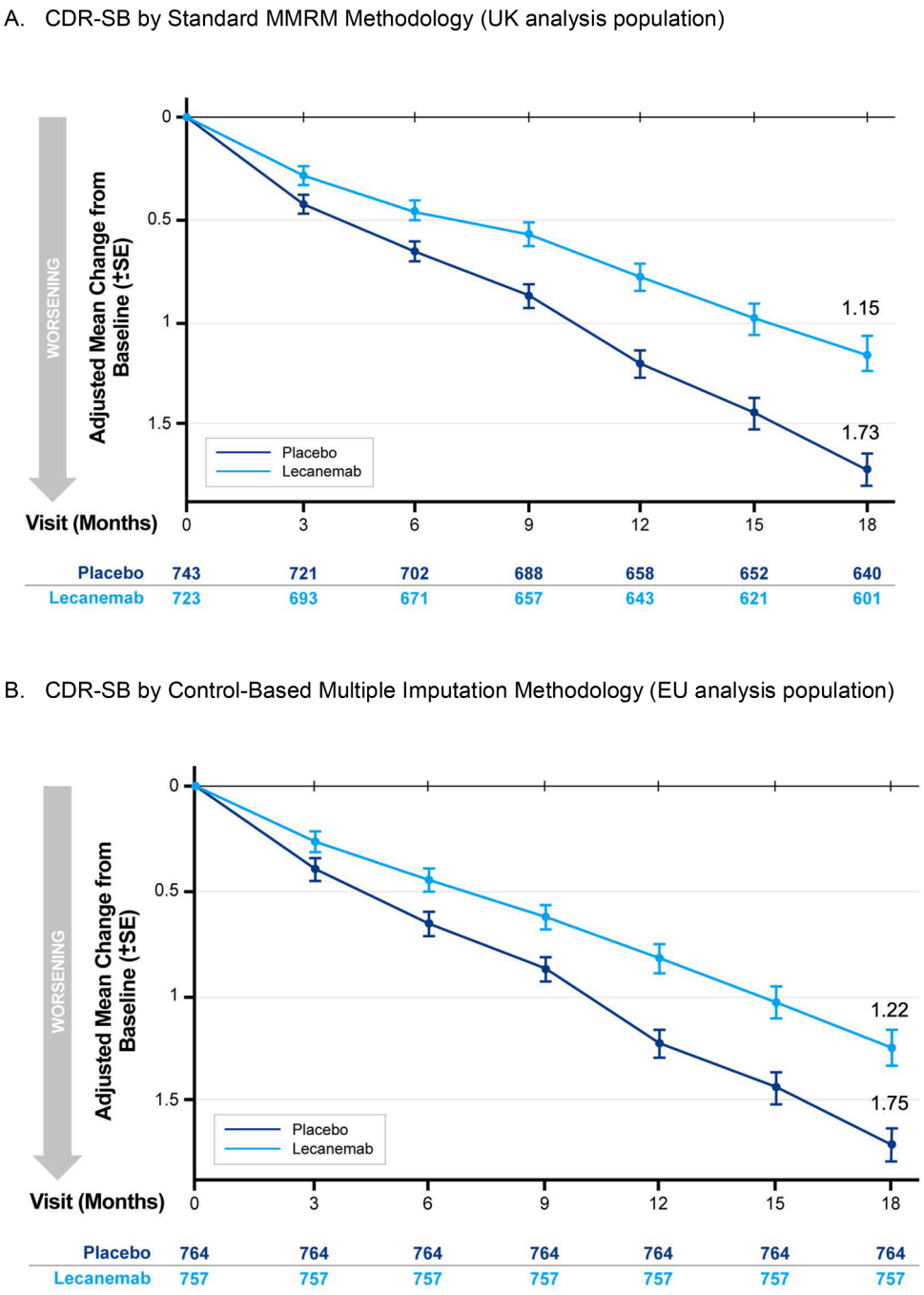


Fig. 1. Efficacy Endpoint Results: CDR-SB. A. CDR-SB by Standard MMRM Methodology (UK analysis population). B. CDR-SB by Control-Based Multiple Imputation Methodology (EU analysis population). C. Global CDR Time to Worsening Analysis.
AD, Alzheimer's disease. CDR, clinical dementia rating. CDR-SB, Clinical Dementia Rating - sum of boxes. CI, confidence interval. LS, least squares. MCI, mild cognitive impairment. SE, standard error.
Note: Based on modified intention-to-treat analysis population. As requested by the European Medicines Agency regulatory authority, efficacy analyses were conducted for ApoE ε4 non-carriers or heterozygotes participants using control-based multiple imputation method, in which all missing values were imputed with copy-increments (change between visits) using the actual value in placebo group. This methodology differs from that used in the Clarity AD primary analysis which used mixed model for repeated measures (MMRM) with missing at random assumption.

months from detection. In a post hoc analysis of time to worsening of CDR-SB by 3 points for the ApoE ε4 heterozygote or non-carrier analysis population, the cognitive outcomes in participants experiencing ARIA were indistinguishable from those without ARIA through 36 months (Figure S4). Results were the same irrespective of the CDR-SB threshold utilized.

In the Clarity AD OLE, lecanemab was also generally well-tolerated, with no new safety signals with longer-term treatment. Adverse events, serious adverse events, and discontinuations due to adverse events decreased year over year (Table S2). ARIA-E was also less frequent after each subsequent year of treatment (<12 months, 9.7 %; ≥12–24 months, 2.5 %; ≥24–36 months, 1.1 %).

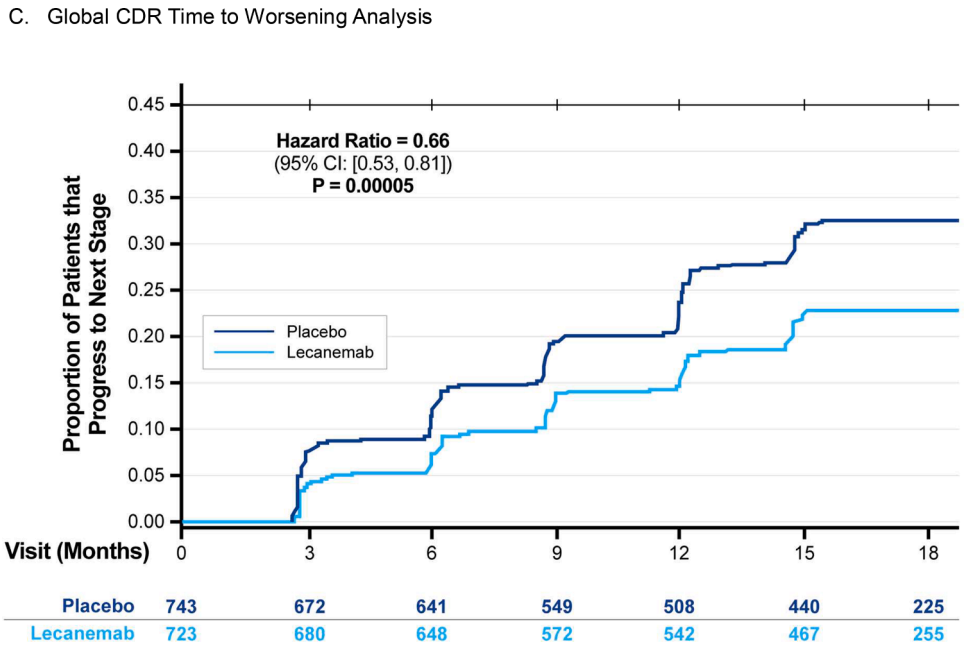


Fig. 1. (*continued*).

3.5. Quality of life

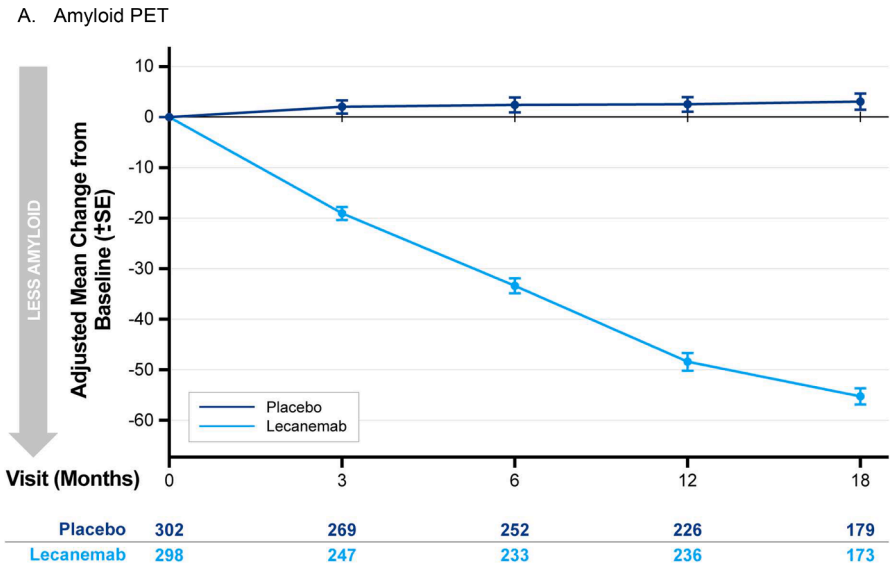
Health-related quality of life results through 18 months in the ApoE ε4 heterozygote and non-carrier population of Clarity AD are summarized in Figure S5. Lecanemab was associated with preservation of quality of life in this subgroup, with participants treated with lecanemab experienced 43 % and 53 % less decline than placebo in EQ-5D-5 L (Health Today Rated by Participant) and QOL-AD (Rated by Participant), respectively (Figure S5). In addition, care partner burden was reduced by 39 % in lecanemab-treated participants vs placebo in the ZBI assessment. HRQoL data out to 36 months for EQ-5D-5 L (health today by subject) and QOL-AD (total score rated by subject as well as by proxy) and ZBI (total score) demonstrated that lecanemab-treated participants continued to benefit out to 3 years relative to the delayed-start group. (Figure S6).

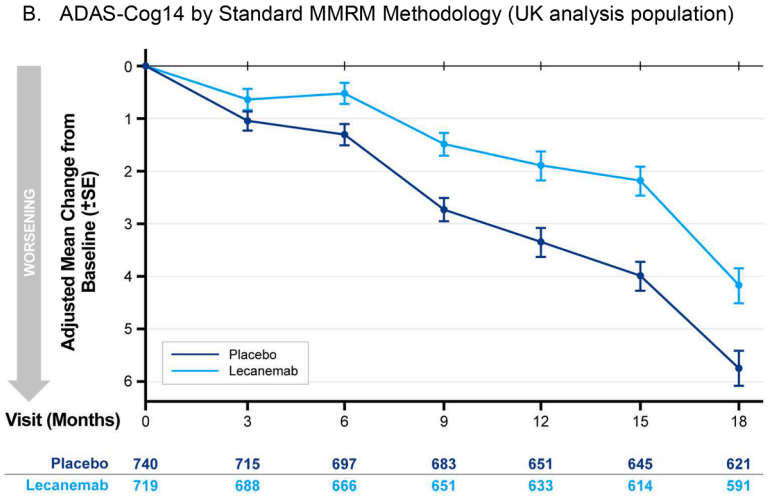
4. Discussion

Lecanemab, an amyloid beta-directed antibody, was recently approved in the UK and the EU for the treatment of participants with MCI and mild dementia due to AD who are ApoE ε4heterozygotes or non-carriers. In this post-hoc and exploratory analysis of the ApoE ε4 heterozygote or non-carrier subgroup of Clarity AD participants, we show lecanemab resulted in less decline than placebo on CDR-SB at 18 months as well as on measures of cognitive function and reduced markers of amyloid at 18 months with expanding over time. Lecanemab maintained the benefits out to 36 months in OLE. Of note in the OLE, delayed start results follow a parallel trajectory relative to early start results, but do not catch up, suggesting a disease modifying effect and reflecting the importance of early treatment initiation. The ADAS-Cog14 and ADCS MCI-ADL results were consistent with the CDR-SB results. The safety profile of lecanemab in this population was consistent with the overall Clarity AD population [12,28,30], with a notable decrease in overall ARIA rate given the exclusion of ApoE ε4 homozygotes as shown previously in analyses evaluating results by carrier status [12,28,30]. The most common adverse reactions for lecanemab in the analysis subgroup were infusion-related reactions, ARIA-H, headache, and ARIA-E.

In this analysis, treatment with lecanemab was associated with preservation of quality of life for participants and caregivers when compared to placebo out to 18 months, consistent with results from the overall population [28,30]. Quality of life assessed out to 36 months appeared to maintain benefits with a consistent rate of decline. The trajectory of quality-of-life results for delayed start participants appeared to improve after initiating lecanemab treatment, although results did not catch up to early start participants, similar to the efficacy assessments. Taken together with the efficacy and safety findings, the quality-of-life findings show consistent results and help define an overall clinically meaningful benefit with lecanemab treatment [36,37]. The treatment benefits of lecanemab on CDR-SB and the other cognitive, functional, and quality of life endpoints are clinically relevant for early AD as the participant is maintained at earlier disease stages of AD where they can function more independently.

Time to event and "time saved" analyses are a suggested approach to communicate the clinical relevance of anti-amyloid treatments, contextualized to the patient's life experiences. Over the 18-month double-blind period, approximately 5–7.5 months were preserved on lecanemab relative to placebo on CDR-SB, ADAS-cog14, and ADCS-MCI-ADL. The time saved expands to 7–9 months on CDR-SB over 36 months relative to natural history. The results support that lecanemab treated patients are maintained at earlier stages of AD where they can function more independently with better quality of life, thereby delaying disability from AD [38]. The time to worsening analysis on global CDR score demonstrate the clinical relevance of the group-level mean differences of the CDR-SB. Transition to the next stage of disease represents a clinically relevant disease milestone. Each stage represents irretrievable loss of independence, functional decline and increasing burden of care. For instance, a patient with MCI (global CDR 0.5) is independent in all activities despite cognitive impairment; a patient with mild AD (global CDR 1) has impairment in complex tasks such as maintaining finances or shopping, but many abilities are preserved; a patient with moderate AD (global CDR 2) is no longer independent in any high-level tasks and needs assistance with basic personal care. At 18 months, there is a 10 % absolute difference in progression to the next stage—33 % of patients on placebo progressed, compared to 23 % of those treated with lecanemab, which represents a 34 % reduction in the risk for progression (hazard ratio 0.64). The reduced risk of progression is maintained over 36 months relative to natural history progression, with a HR of 0.72. For the endpoints, we present results from two different methodologies: standard MMRM and CBMI. These two assessments conducted as part of





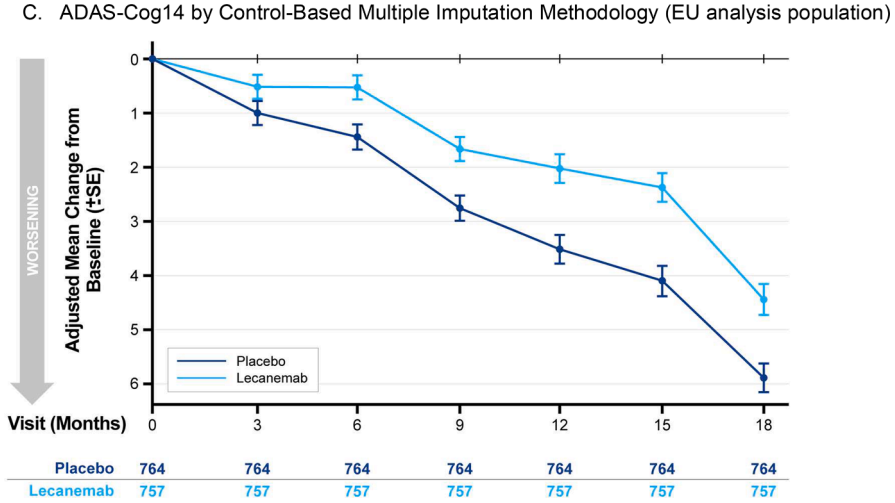
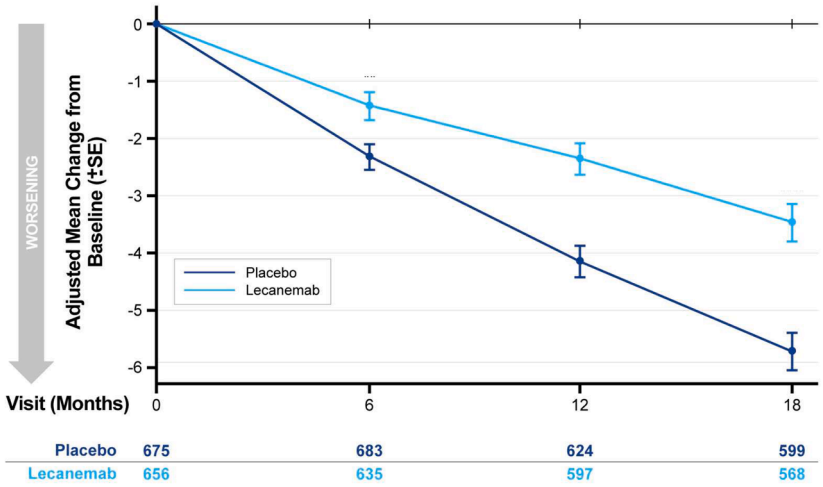


Fig. 2. Amyloid PET, ADAS-Cog14, and ADCS MCI-ADL Endpoint Results. A. Amyloid PET.
After 18 months of treatment, the average amyloid level was 21 Centiloids in the lecanemab treatment group in the amyloid PET substudy, which is below the threshold for amyloid positivity of approximately 30 Centiloids above which participants are considered to have elevated brain amyloid.
Note: Based on pharmacodynamic analysis population (amyloid PET sub-study population).
PET: positron emission tomography. SE: standard error. B. ADAS-Cog14 by Standard MMRM Methodology (UK analysis population).
C. ADAS-Cog14 by Control-Based Multiple Imputation Methodology (EU analysis population).
Note: Based on modified intention-to-treat analysis population. As requested by the European Medicines Agency regulatory authority, efficacy analyses were conducted for ApoE ε4 non-carriers or heterozygotes participants using control-based multiple imputation method, in which all missing values were imputed with copy-

increments (change between visits) using the actual value in placebo group. This methodology differs from that used in the Clarity AD primary analysis which used mixed model for repeated measures (MMRM) with missing at random assumption.
ADAS-Cog14, Alzheimer's Disease Assessment Scale–cognitive subscale. LS, least squares. SE, standard error.
D. ADCS MCI-ADL by Standard MMRM Methodology (UK analysis population).
E. ADCS MCI-ADL by Control-Based Multiple Imputation Methodology (EU analysis population).
Note: Based on modified intention-to-treat analysis population. As requested by the European Medicines Agency regulatory authority, efficacy analyses were conducted for ApoE ε4 non-carriers or heterozygotes participants using control-based multiple imputation method, in which all missing values were imputed with copy-
increments (change between visits) using the actual value in placebo group. This methodology differs from that used in the Clarity AD primary analysis which used mixed model for repeated measures (MMRM) with missing at random assumption. ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment. LS, least squares. SE, standard error.

D. ADCS MCI-ADL by Standard MMRM Methodology (UK analysis population)



E. ADCS MCI-ADL by Control-Based Multiple Imputation Methodology (EU analysis population)

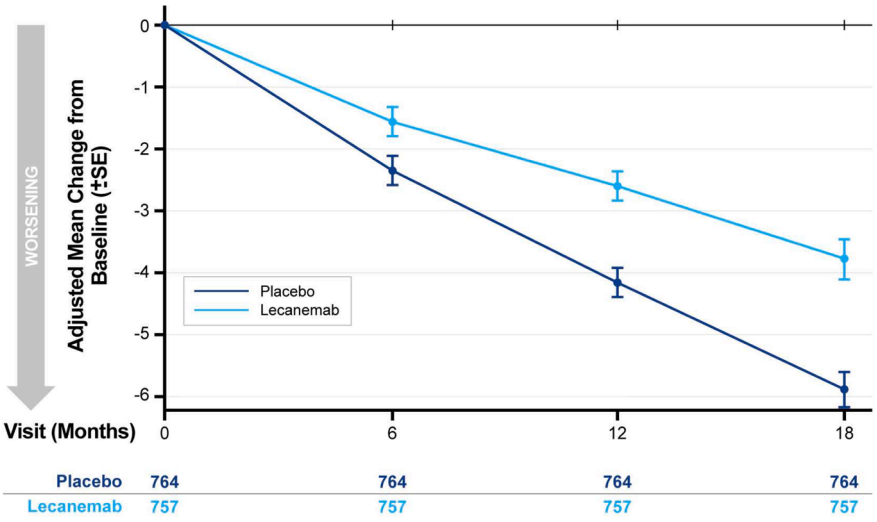


Fig. 2. (*continued*).

the regulatory approval process in Europe and in the UK, with each regulatory body preferring a different methodology. However, in both analyses, the results for the efficacy assessments (ie, CDR-SB, ADAS--Cog14, and ADCS MCI-ADL) were comparable and all showed a consistent significant benefit in favor of lecanemab over placebo.

There are potential limitations in this study. First, this subgroup analysis of the original Clarity AD data was not pre-specified, but was requested by the European authorities (MHRA and EMA) as part of the submission for market authorization approval. Therefore, all results should be considered as post-hoc and exploratory. The duration of the randomized phase of the Clarity AD was 18 months and so no controlled data are available for assessments of longer-term treatment. However, there is now extensive single-arm data from the Clarity AD OLE [28,30]. Although the OLE does not have a randomized control arm, the data show a continuing of benefits with lecanemab treatment, with no new safety signals. Of note, when the OLE lecanemab efficacy data is compared to historical controls from ADNI and BioFINDER, we observe ongoing benefit for participants treated with lecanemab vs the historical control groups. We also see that the participants who had delayed lecanemab treatment (ie, participants who were randomized to placebo in the Core study but then received lecanemab in the OLE) had improved results relative to the historical controls. These longer-term data seem to indicate there is benefit from continued treatment and treatment should be started as early as possible to maximize the benefit.

Table 2
Adverse events.

	ApoE ε4 heterozygotes or non-carriers Population	
	Placebo (*N* = 764)	**Lecanemab (*N* = 757)**
Adverse events (AE)	620 (81.2)	667 (88.1)
severe	47 (6.2)	60 (7.9)
Treatment-related AE	147 (19.2)	314 (41.5)
Serious AE	86 (11.3)	112 (14.8)
Death	7 (0.9)	6 (0.8)
AE leading to study drug dose adjustment	77 (10.1)	166 (21.9)
leading to study drug withdrawal	23 (3.0)	45 (5.9)
leading to study drug dose interruption	58 (7.6)	129 (17.0)
leading to infusion interruption	10 (1.3)	22 (2.9)
AEs of special interest		
ARIA-E	10 (1.3)	67 (8.9)
ARIA-H	52 (6.8)	98 (12.9)
Microhemorrhage	43 (5.6)	78 (10.3)
Superficial siderosis	15 (2.0)	32 (4.2)
Intracerebral hemorrhage	1 (0.1)	3 (0.4)
Infusion-related reactions	54 (7.1)	195 (25.8)

In summary, lecanemab is approved in UK and the EU for treatment in early AD participants who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers. In a post-hoc and exploratory analysis of this subgroup, lecanemab reduced amyloid load in the brain at 18 months and resulted in less decline on global cognition and function compared to placebo. Similarly, measures of cognitive and functional loss were reduced and reduced markers of amyloid and p-tau in plasma. In this population of ApoE ε4 non-carriers and heterozygotes, ARIA adverse events were approximately half as frequent as in the overall population of Clarity AD study. Lecanemab meaningfully delayed progression to next AD stage and had superior effects on several measures of quality of life over placebo. Overall, similar efficacy as overall Clarity AD population was observed, including preservation of HRQoL, with lower risk of ARIA events.

Declaration of the use of generative AI and AI-assisted technologies in scientific writing and in figures, images and artwork

AI was not used to generate any facet of this manuscript.

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CRediT authorship contribution statement

Richard Perry: Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Christopher Kipps:** Writing – review & editing, Writing – original draft, Investigation. **Maria Eugenia Soto Martín:** Writing – review & editing, Writing – original draft, Investigation. **Marco Bozzali:** Writing – review & editing, Writing – original draft, Investigation. **Giancarlo Logroscino:** Writing – review & editing, Writing – original draft, Investigation. **Sarah Trafford:** Writing – review & editing, Writing – original draft, Formal analysis. **Shobha Dhadda:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Michio Kanekiyo:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Amanda Goodwin:** Writing – review & editing, Conceptualization. **Mark Hodgkinson:** Writing – review & editing, Formal analysis. **Steven Hersch:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Michael Irizarry:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Lynn Kramer:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Lutz Froelich:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Richard Perry reports a relationship with Biogen, Eisai, Eli Lilly,

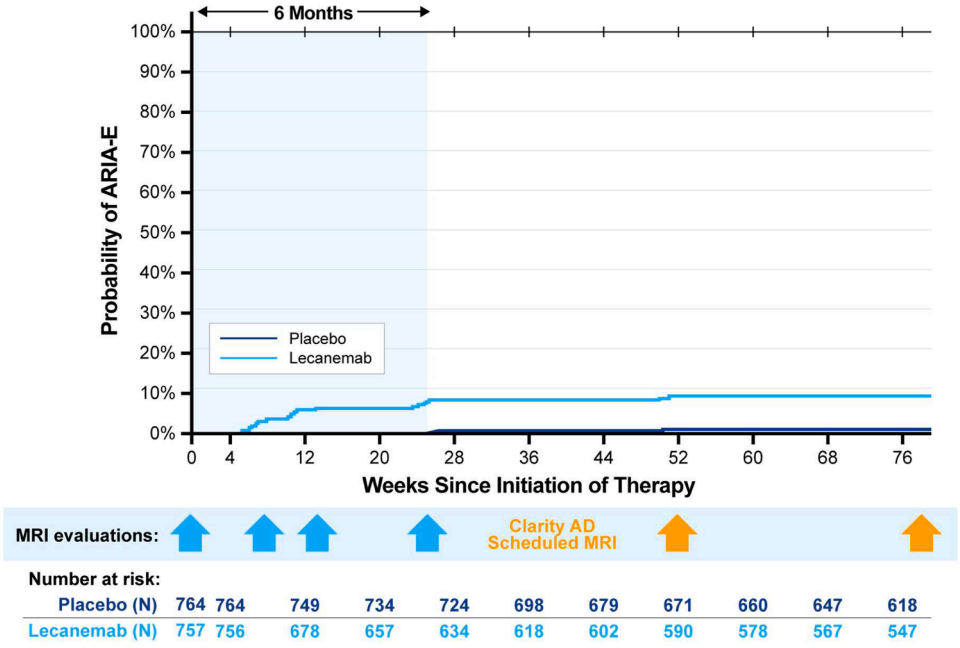

Fig. 3. ARIA-E Timing. AE, adverse event. ApoE4, apolipoprotein E4. ARIA, Amyloid related imaging abnormality. ARIA-E, ARIA with edema. ARIA-H, ARIA with haemosiderin deposits. MRI, magnetic resonance imaging. Overall population published in van Dyck CH, et al. N Engl J Med. 2023;388:9–21.

Hoffman-LaRoche, and Merck Sharp and Dohm that includes: personal consulting fees.

Christopher Kipps has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Maria Eugenia Soto Martín reports a relationship withEisai and Eli Lilly that includes: personal consulting fees.

Marco Bozzali has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Giancarlo Logroscino reports a relationship with Biogen, Eisai, Eli Lilly, Hoffman-LaRoche, and Merck Sharp and Dohm that includes: personal consulting fees. Giancarlo Logroscino reports a relationship with Biogen, Axovant, Alector, Denali, Roche, Eisai, Genentech, Amylyx, PIAM Farmaceutici SpA that includes: investigator for clinical trials.

Sarah Trafford reports a relationship with Eisai that includes: employment.

Shobha Dhadda reports a relationship with Eisai that includes: employment

Michio Kanekiyo reports a relationship with Eisai that includes: employment

Amanda Goodwin reports a relationship with Eisai that includes: employment

Mark Hodgkinson reports a relationship with Eisai that includes: employment

Steven Hersch reports a relationship with Eisai that includes: employment

Michael Irizarry reports a relationship with Eisai that includes: employment

Lynn Kramer reports a relationship with Eisai that includes: employment

Lutz Froelich reports a relationship with Anavex, Avanir/Otsuka, Biogen, BioVie, Bristol-Myers-Squibb, DerCampus, Eisai, Eli Lilly, FOMF, Araclon/Grifols, Janssen Cilag, Johnson&Johnson, Medical Tribune, Medfora, Medscape, Neurimmune, Neuroscios, Noselab, NovoNordisk, PharmatrophiX, Hoffmann-LaRoche, TauRX, Schwabe, StreamUp, Vivoryon that includes: personal consulting fees.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100507.

Data availability

The data are available from the corresponding author upon reasonable request.

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