MSR217

Using Propensity Weighting Methods With Real-World Data and Non-Controlled Extension Data From a Clinical Trial to Estimate Long-Term Treatment Effect: An Example in Alzheimer's Disease

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Background and Objective

- Donanemab is indicated in the UK for the treatment of mild cognitive impairment and mild dementia due to AD in adults that are ApoE ε4 heterozygotes or non-carriers[1]
- Randomised controlled trials rarely provide long-term treatment effect data in time for health technology assessments; therefore, assumptions need to be made on the long-term treatment effect of donanemab to inform a cost-effectiveness model
- To support this, we estimated a three-year treatment effect for donanemab in the UK indicated population using real-world data from the Alzheimer's Disease Neuroimaging Initiative (ADNI)[2] and non-controlled TRAILBLAZER-ALZ 2 trial long-term extension data[3]

Conclusions

- Our analyses provide evidence of maintenance of a donanemab effect beyond the initial placebo-controlled period
  - Importantly, a sustained effect was demonstrated beyond treatment discontinuation
- These analyses provide further evidence for modelling long-term treatment effect in cost-effectiveness models

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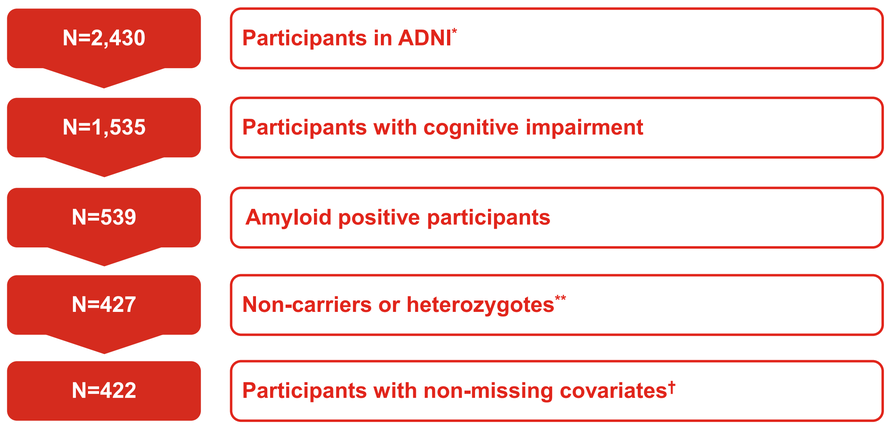
METHODS

- The ADNI database, launched in 2003 as a public–private partnership,[2] was selected to provide an external control to the TRAILBLAZER-ALZ 2 long-term data, as it provides key AD biomarker information and the relevant CDR-SB outcome
  - ADNI individual patient-level data were used
- TRAILBLAZER-ALZ 2 was a 76-week, Phase 3, randomised, double-blind, parallel, multicenter, placebo-controlled trial with an additional 78 weeks of follow-up in which treatment assignment remained double-blinded [3,4]
  - Participants randomised to placebo during the placebo-controlled period were switched to donanemab after 76 weeks (TRAILBLAZER-ALZ 2 placebo group)
  - Participants were switched in a blinded procedure from donanemab to placebo at Weeks 24, 52 and 76 (and later at Weeks 102 and 130) if they met treatment completion criteria* (TRAILBLAZER-ALZ 2 donanemab group)
- In line with the UK donanemab label,[5] only data from amyloid positive ADNI participants** with cognitive impairment were used; for both databases, ApoE ε4 non-carriers and heterozygotes were included
- Treatment effect analysis was performed on the UK eligible subpopulation of the TRAILBLAZER-ALZ 2 long-term extension and the UK indicated subpopulation of the ADNI cohort, as no anticoagulant information is recorded in ADNI
  - However, anticoagulant use was not considered to be a treatment effect modifier based on analyses of TRAILBLAZER-ALZ 2
- PS weights were estimated for the ADNI participants to ensure balance in key demographic and baseline characteristics between the PS-weighted ADNI cohort and the TRAILBLAZER-ALZ 2 placebo group
  - Baseline covariates included in the weighting procedure were age, sex, ApoE ε4 status (non-carrier or heterozygote), CDR-SB score, ADAS-Cog_{13} and MMSE score
  - PS weights were estimated for the ADNI cohort with the ATT estimand using the inverse probability weighting method***
  - Balance was assessed using SMD <0.1 for each covariate and extreme weights were trimmed using the 95th percentile of the weights;[6] the impact on ESS was also assessed
- A first MMRM analysed CDR-SB CfB in the TRAILBLAZER-ALZ 2 placebo group and the weighted ADNI cohort during the first 18 months to check whether the observed decline in the weighted ADNI cohort matched the decline observed in the TRAILBLAZER-ALZ 2 placebo group
- A second MMRM analysed CDR-SB CfB in the TRAILBLAZER-ALZ 2 donanemab group and the weighted ADNI cohort during the full 36 months to estimate the long-term treatment effect
  - The MMRM for CDR-SB CfB included the following covariates: treatment (TRAILBLAZER-ALZ 2 arm vs. weighted ADNI cohort), age, ApoE ε4 status, baseline CDR-SB score, and visit, as well as visit-by-treatment and visit-by-baseline CDR-SB interaction terms
- Sensitivity analyses were conducted to ensure the robustness of the base case, including modifications in weighting method (entropy balancing and GBM) and chosen population (participants with amyloid level <24.1 at Month 6 and those that stopped donanemab at Months 6, 12 or 18 as per the TRAILBLAZER-ALZ 2 protocol based on amyloid clearance)

*Defined as amyloid plaque level <11 Centiloids on any single PET scan or <25 Centiloids on two consecutive PET scans.
**Assessed as having a cerebrospinal fluid total-tau/Aβ42 ratio >0.28.
***Calculated with generalised linear model method using WeightIt package in R version 4.4.2.

KEY RESULT

- Of the 2,430 participants in ADNI, 422 participants with no missing baseline matching met the UK label conditions and were weighted in line with the baseline characteristics of the placebo arm of TRAILBLAZER-ALZ 2 (UK eligible subpopulation)



*ADNI dataset used was ADNIMERGE with cut-off date January 10, 2025. **UK indicated subpopulation.
†Non-missing covariates used in PS model were age, sex, APOE4 ε4 status (non-carrier or heterozygote), CDR-SB score, ADAS-Cog_{13} and MMSE score.

Balance Assessments

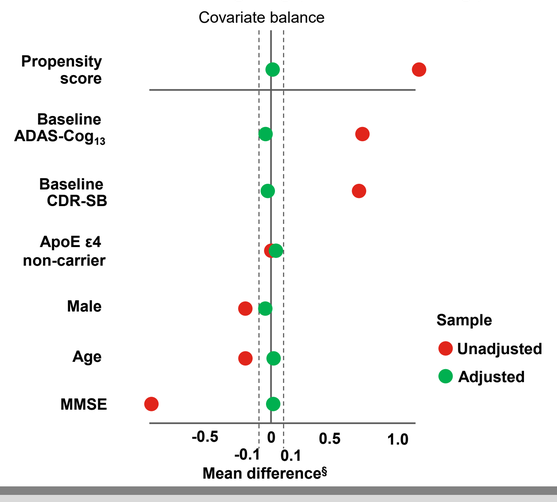
- The propensity-weighted ADNI cohort was well matched with the TRAILBLAZER-ALZ 2 placebo group in terms of diagnosis, baseline demographic and clinical characteristics

Baseline demographic and clinical characteristics before and after weighting (and after trimming*)

Characteristic	TRAILBLAZER-ALZ 2 placebo group N=623**	ADNI cohort before weighting N=422**	ADNI cohort after weighting ESS=212†
Age, years	73.54 (6.07)	74.71 (7.35)	73.44 (8.29)
Male, n (%)	252 (40.4)	246 (58.3)	266.9 (44.0)
ApoE ε4 non-carrier‡, n (%)	214 (34.3)	154 (36.5)	204.4 (33.7)
MMSE	23.62 (2.49)	25.83 (2.78)	23.61 (2.69)
ADAS-Cog_{13}	29.14 (9.01)	23.25 (9.35)	29.63 (9.85)
CDR-SB	3.94 (2.05)	2.67 (1.79)	4.04 (2.03)

Data presented as mean (SD) unless otherwise stated.
*22 patients with a weight ranging from 5.28 to 17.55 were trimmed to the 95% percentile (5.28).
**N = participants with non-missing baseline characteristics to allow for weighting.
†ESS can be interpreted as the number of participants contributing to the analysis based on the size of the weights.
‡Binary variable, as homozygotes were excluded from the UK eligible subpopulation.
§Balance was assessed using SMD <0.1 for each covariate and extreme weights were trimmed using the 95th percentile of the weights.

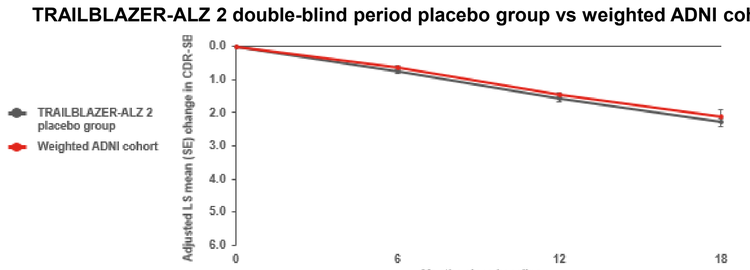
Standardised mean differences for baseline covariates before and after weighting (and after trimming*)



Assessing External Control as a Proxy to Placebo in CDR-SB Progression

- The first MMRM demonstrated the suitability of the weighted ADNI cohort to mimic the pattern of disease progression on CDR-SB change observed in the TRAILBLAZER-ALZ 2 placebo group up to Month 18
  - Assuming the pattern of disease progression of TRAILBLAZER-ALZ 2 placebo group would be the same beyond the 18-month follow-up period, the weighted ADNI cohort represents an acceptable external control group to donanemab

TRAILBLAZER-ALZ 2 double-blind period placebo group vs weighted ADNI cohort up to 18 months



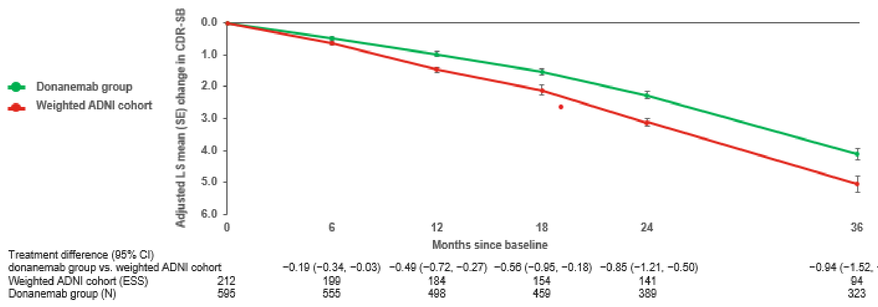
Treatment difference (95% CI)				
TRAILBLAZER-ALZ 2 placebo group vs. weighted ADNI cohort		0.09 (−0.07, 0.26)	0.12 (−0.12, 0.37)	0.19 (−0.26, 0.63)
Weighted ADNI cohort (ESS)	212	199	184	154
TRAILBLAZER-ALZ 2 placebo group (N)	616	571	516	491

UK eligible population for TRAILBLAZER-ALZ 2 and UK indicated population for ADNI. ADNI cohort was weighted using propensity score using average treatment effect on the treated weights; Change from baseline in CD-SB was estimated with MMRM model using ADNI weight.

Base Case Results

- The second MMRM showed an increased treatment effect difference (assessed by CfB in CDR-SB) between the donanemab group and the weighted ADNI cohort from 18 to 36 months*
- The estimated treatment difference (95% CI) for the donanemab group vs the weighted ADNI cohort was statistically significant at all time points up to Month 36**

TRAILBLAZER-ALZ 2 long-term extension donanemab group vs weighted ADNI cohort up to 36 months



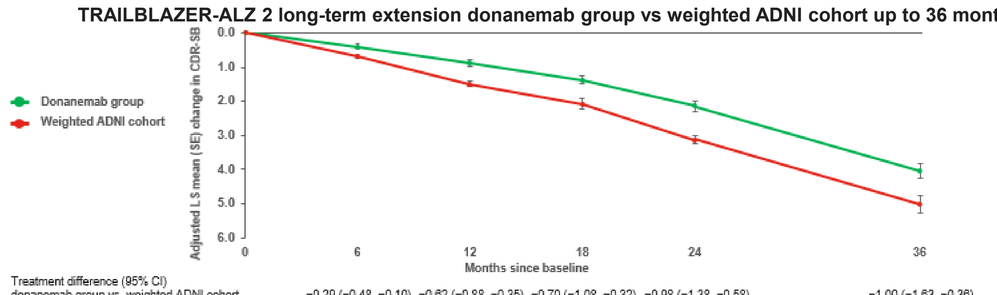
Treatment difference (95% CI)						
donanemab group vs. weighted ADNI cohort		−0.19 (−0.34, −0.03)	−0.49 (−0.72, −0.27)	−0.56 (−0.95, −0.18)	−0.85 (−1.21, −0.50)	−0.94 (−1.52, −0.37)
Weighted ADNI cohort (ESS)	212	199	184	154	141	94
Donanemab group (N)	595	555	498	459	389	323

*This analysis includes a proportion of participants remaining on treatment beyond 18 months in line with the TRAILBLAZER-ALZ 2 long-term extension trial design.
**Based on the assumption that the pattern of disease progression of the TB2 placebo group would be the same as for the weighted ADNI cohort. UK eligible population for TRAILBLAZER-ALZ 2 and UK indicated population for ADNI. ADNI cohort was weighted using propensity score using average treatment effect on the treated weights; CfB in CDR-SB was estimated with MMRM model using ADNI weight.

Results for Participants who Stopped Donanemab* by Month 18

- This MMRM supported the persistence of the long-term benefits of donanemab even after stopping treatment
  - The estimated treatment difference (95% CI) for only those participants in the donanemab group who stopped treatment at 6, 12 or 18 months vs the weighted ADNI cohort remained statistically significant at all time points up to Month 36**

TRAILBLAZER-ALZ 2 long-term extension donanemab group vs weighted ADNI cohort up to 36 months



Treatment difference (95% CI)						
donanemab group vs. weighted ADNI cohort		−0.28 (−0.48, −0.10)	−0.62 (−0.88, −0.35)	−0.70 (−1.08, −0.32)	−0.98 (−1.38, −0.58)	−1.00 (−1.63, −0.36)
Weighted ADNI cohort (ESS)	212	199	184	154	141	94
Donanemab group (N)	298	288	291	290	289	218

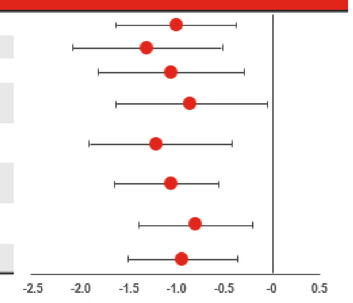
*As per protocol, participants were switched to placebo in a blinded procedure (including in the long-term extension) according to amyloid clearance. UK eligible population for TRAILBLAZER-ALZ 2 restricted to participants that switched to placebo at 6, 12 or 18 months and UK indicated population for ADNI. **Based on the assumption that the pattern of disease progression of the TRAILBLAZER-ALZ 2 placebo group would be the same as for the weighted ADNI cohort. ADNI cohort was weighted to the 'mixed' donanemab group (participants who stopped treatment at 6, 12 or 18 months and participants who did not stop treatment by 18 months) using propensity score using average treatment effect on the treated weights. Change from baseline in CDR-SB was estimated with MMRM model using ADNI weight.

Results – Sensitivity Analyses

- Results were consistent between analyses and lead to similar interpretation regardless of the weighting method used or the population chosen, indicating the robustness of the conclusions

TRAILBLAZER-ALZ 2 long-term extension sensitivity analysis results

Analysis	Number of patients at baseline		ADNI ESS at baseline	Treatment difference (95% CI) in CDR-SB score at 36 months
	TB2	ADNI		
Base case	595	422	212	
Base case with entropy balancing	595	422	237	
Base case with generalised boosted model*	595	422	211	
6-month amyloid clearers (generalised linear model) – base case weighting	190	422	212	
6-month amyloid clearers (generalised linear model) – 6-month clearer only weighting	190	422	227	
6-month amyloid clearers (entropy balancing) – base case weighting	190	422	237	
6-month amyloid clearers (generalised boosted model*) – base case weighting	190	422	211	
Switcher to placebo before Month 18 only (generalised linear model)**	298	422	212	



*Standardised mean differences were <1 for all variables, except for the baseline MMSE with a standardised mean difference of 0.12 with the generalised boosted model method.
**Only the generalised linear model is presented in this poster for the switcher to placebo by 18 months at the latest only.
None of the treatment differences in CDR-SB score between weighted ADNI cohort and placebo group at 18 months were statistically significant.

Limitations

- This analysis was conducted using an external data source to mimic the placebo arm of TRAILBLAZER-ALZ 2 after Month 18; therefore, it is subject to limitations
- The use of ADNI, a US database designed to validate AD biomarkers, may introduce a selection bias due to the research question and may not be a true reflection of clinical practice in the UK
- The results rely on the assumption that the pattern of disease progression observed in the TRAILBLAZER-ALZ 2 placebo group would be the same for the weighted ADNI cohort
- Furthermore, the amyloid Centiloid level, a potential treatment effect modifier, was not included in the propensity weighting calculations due to a high number of missing values in the ADNI database (losing 44% of the participants and among them, no participant with amyloid level had a CDR-SB at Month 18 making the comparison of placebo group vs weighted ADNI cohort not possible)
- Nevertheless, after weighting on baseline variables, it was reassuring that the weighted ADNI cohort had a similar declining disease progression to the TRAILBLAZER-ALZ 2 placebo group from the 18-month randomised double-blind period and can therefore be considered an appropriate comparator

Abbreviations
AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; ADAS-Cog_{13}, 13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale; ApoE ε4, apolipoprotein E ε4; ATT, average treatment effect in the treated; CDR-SB, Clinical Dementia Rating – Sum of Boxes; CfB, change from baseline; CI, confidence interval; ESS, effective sample size; GBM, generalised boosted model; LS, least squares; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Exam; ; N, number of participants; PS, propensity score; SD, standard deviation; SE, standard error; SMD, standardised mean difference; UK, United Kingdom; US, United States.

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