Donanemab in Early Symptomatic Alzheimer's Disease: Efficacy and Safety from the TRAILBLAZER-ALZ 2 Long-Term Extension

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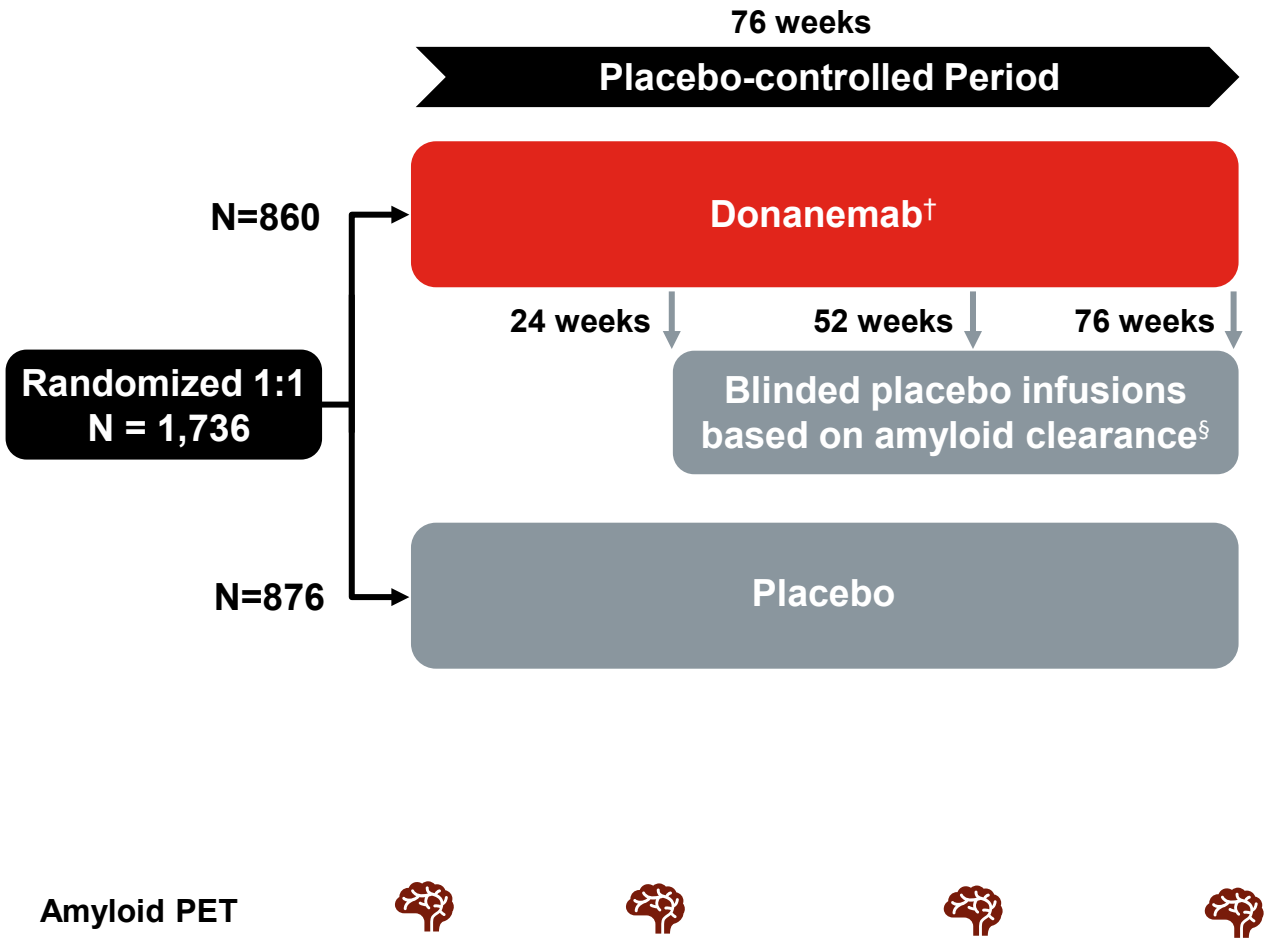
TRAILBLAZER-ALZ 2 DEMONSTRATED BENEFIT OF DONANEMAB WITH LIMITED DURATION DOSING

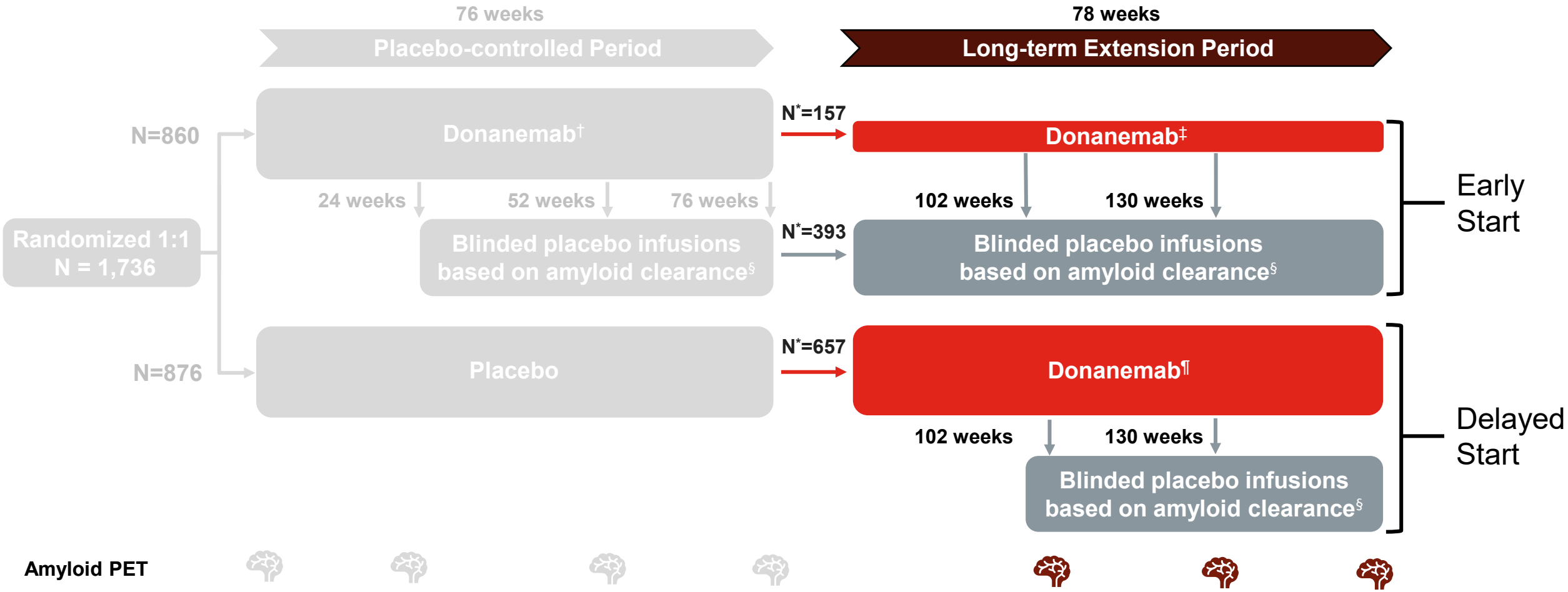


- Reducing treatment duration based on amyloid clearance criteria:
  - 47% of participants completed treatment at 52 weeks‡
  - 69% of participants completed treatment at 76 weeks‡

†700 mg Q4W for the first 3 doses and 1400 mg Q4W thereafter administered intravenously; ‡Percent of participants was calculated at specified visit (not cumulative) and based on amyloid level. Participants may have stopped treatment before the specified visit; §Participants who met prespecified treatment completion criteria based on amyloid PET were switched in a blinded fashion to placebo Q4W (saline infusion).

LTE: long-term extension; MRI: magnetic resonance imaging; N: number of participants; PET: positron emission tomography; PC: placebo-controlled; Q4W: every four weeks.

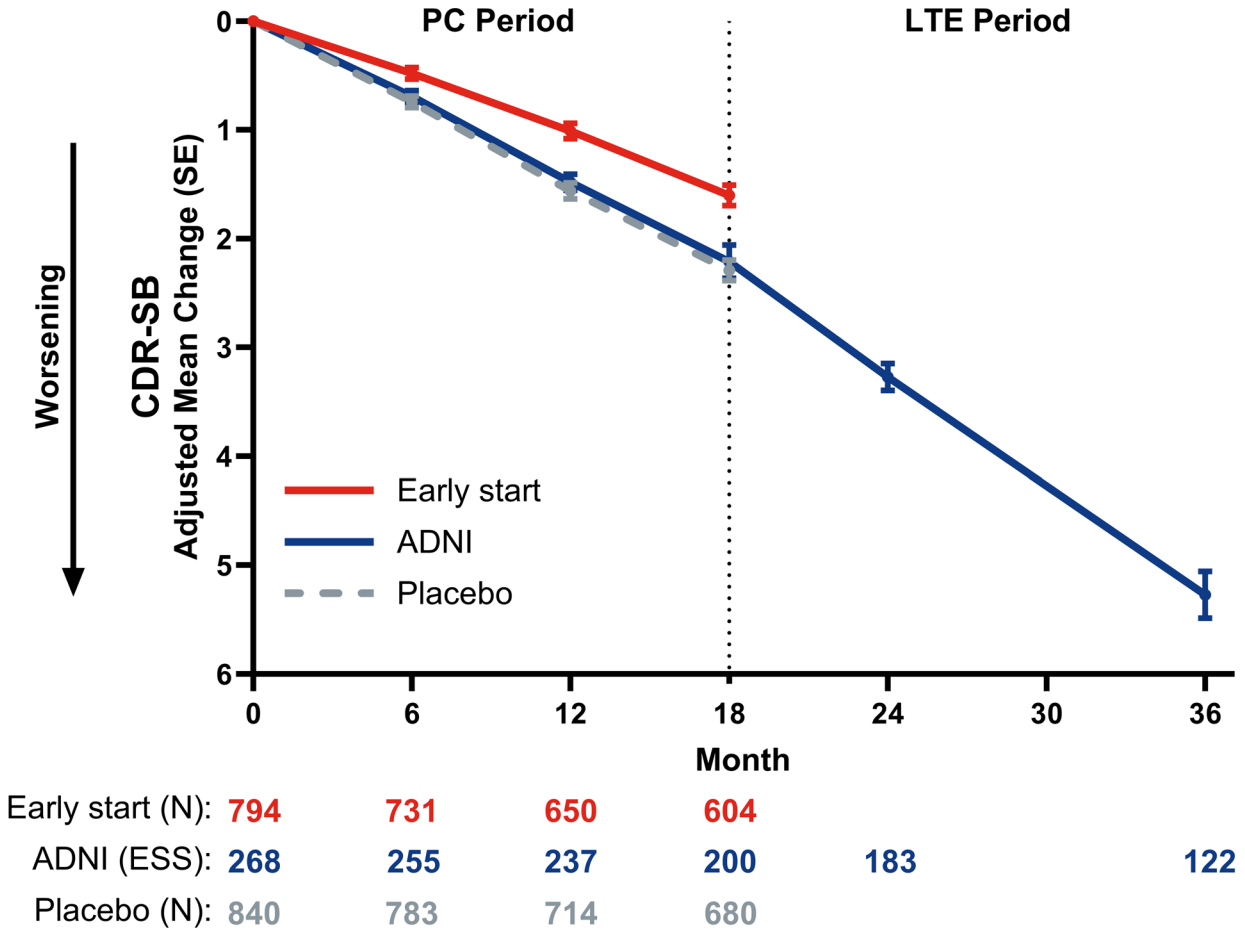
LONG-TERM SAFETY AND EFFICACY EVALUATED IN TRAILBLAZER-ALZ 2 LONG-TERM EXTENSION



*Number of participants receiving at least one infusion in the LTE period; †700 mg Q4W for the first 3 doses and 1400 mg Q4W thereafter administered intravenously; ‡Participants randomized to donanemab during the PC period who did not meet the treatment completion criteria by 76 weeks continued receiving donanemab Q4W; §Participants who met prespecified treatment completion criteria based on amyloid PET were switched in a blinded fashion to placebo Q4W (saline infusion); ¶Participants randomized to placebo Q4W during the PC period were assigned to receive donanemab Q4W starting at Visit 22 (78 weeks after randomization) and followed the same dose titration as participants during the PC period.

LTE: long-term extension; MRI: magnetic resonance imaging; N: number of participants; PET: positron emission tomography; PC: placebo-controlled; Q4W: every four weeks.

EFFICACY: SLOWING OF CLINICAL DECLINE IN EARLY START DONANEMAB VS EXTERNAL ADNI COHORT



- Since there was no placebo group during the LTE period, we compared the donanemab-treated participants to a propensity weighted external ADNI cohort
- During the first 18 months, the ADNI cohort was very well matched to the progression of placebo

Notes: External ADNI cohort was weighted using propensity score using average treatment effect on the treated weights at study entry/baseline; CDR-SB change from baseline were estimated with MMRM model using ADNI weights. Point change differences are early start vs external ADNI cohort.

ADNI: Alzheimer's Disease Neuroimaging Initiative (https://adni.loni.usc.edu/); CDR-SB: Clinical Dementia Rating-Sum of Boxes; ESS: effective sample size; MMRM: Mixed Model for Repeated Measures; N: number of participants; PC: placebo-controlled; SE: standard error.

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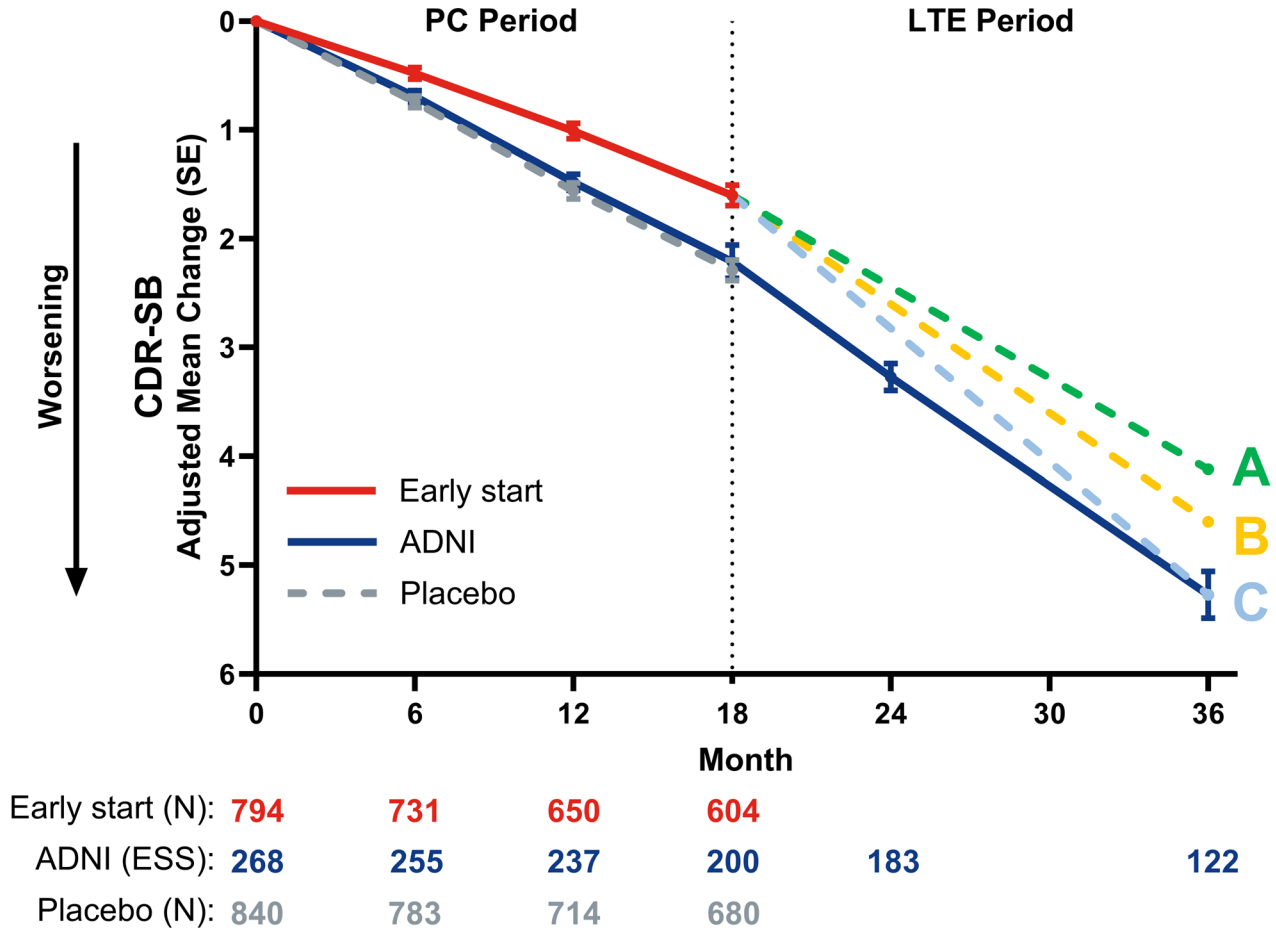

Hypothetical scenarios:

A: Continued widening between drug and comparator, suggesting **increased benefit**, even though most participants had completed treatment

B: Parallel lines suggesting **maintenance of benefit**

C: Converging lines suggesting **waning of treatment effect** once treatment is completed

Notes: External ADNI cohort was weighted using propensity score using average treatment effect on the treated weights at study entry/baseline; CDR-SB change from baseline were estimated with MMRM model using ADNI weights. Point change differences are early start vs external ADNI cohort.

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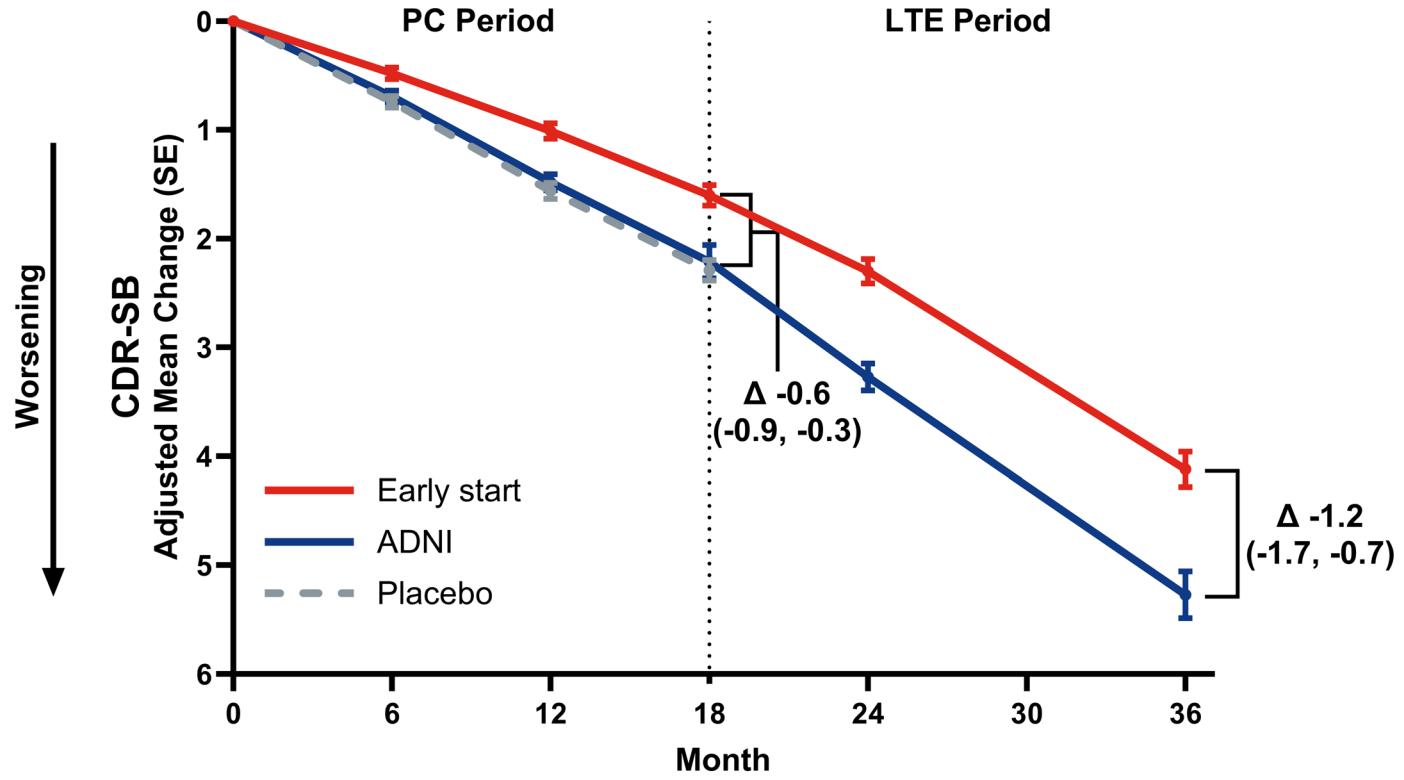


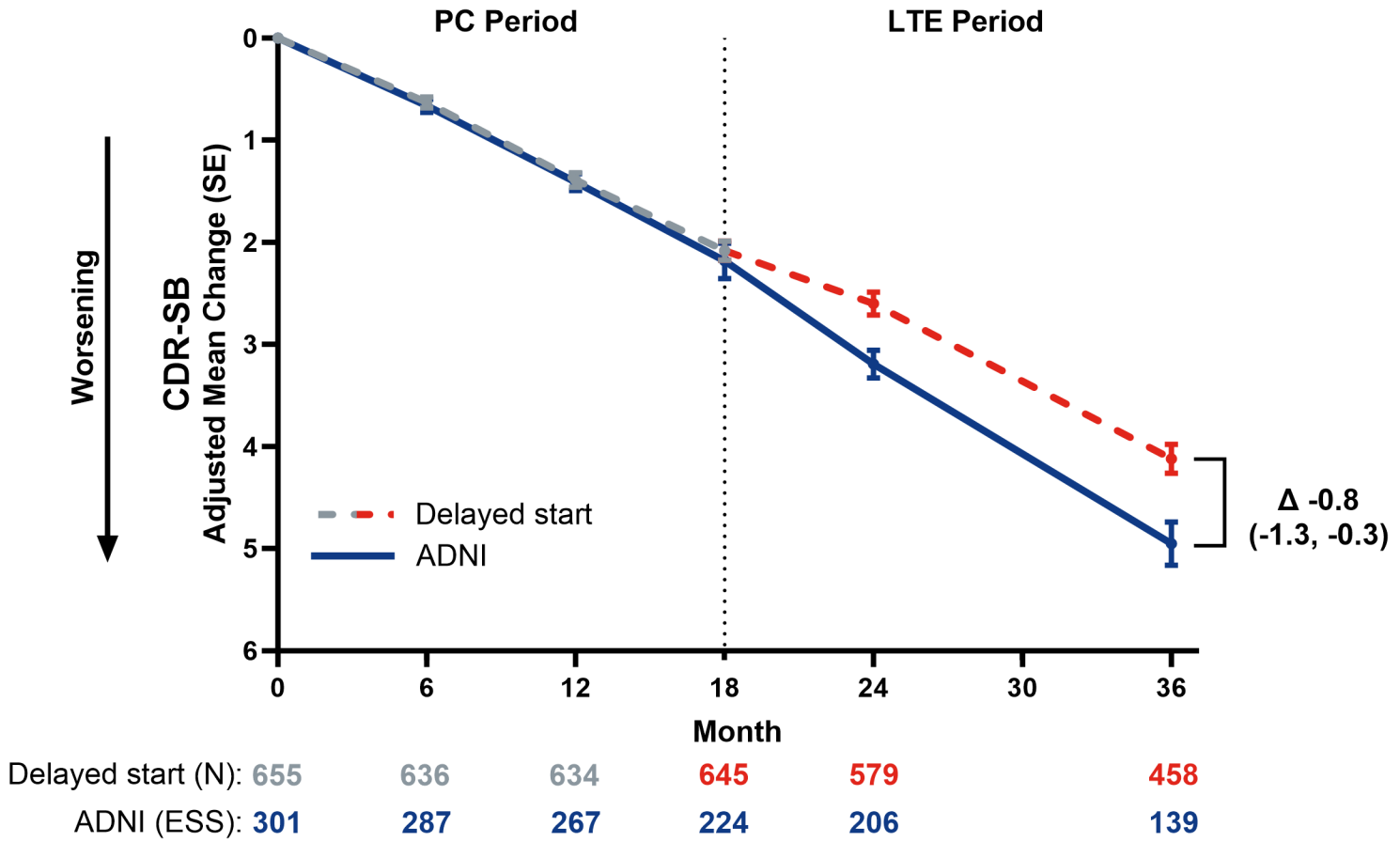
Early start (N):	794	731	650	604	507	417
ADNI (ESS):	268	255	237	200	183	122
Placebo (N):	840	783	714	680		

- Treatment benefit increased even after treatment regimen was completed in most participants
- Donanemab benefit continued to grow over 3 years compared to external ADNI cohort with delta CDR-SB increasing from 0.6 at 18 months to 1.2 at 36 months

Notes: External ADNI cohort was weighted using propensity score using average treatment effect on the treated weights at study entry/baseline; CDR-SB change from baseline were estimated with MMRM model using ADNI weights. Point change differences are early start vs external ADNI cohort.

ADNI: Alzheimer's Disease Neuroimaging Initiative (https://adni.loni.usc.edu/); CDR-SB: Clinical Dementia Rating-Sum of Boxes; ESS: effective sample size; MMRM: Mixed Model for Repeated Measures; N: number of participants; PC: placebo-controlled; SE: standard error.

EFFICACY: DELAYED START PARTICIPANTS ALSO BENEFITED FROM DONANEMAB TREATMENT



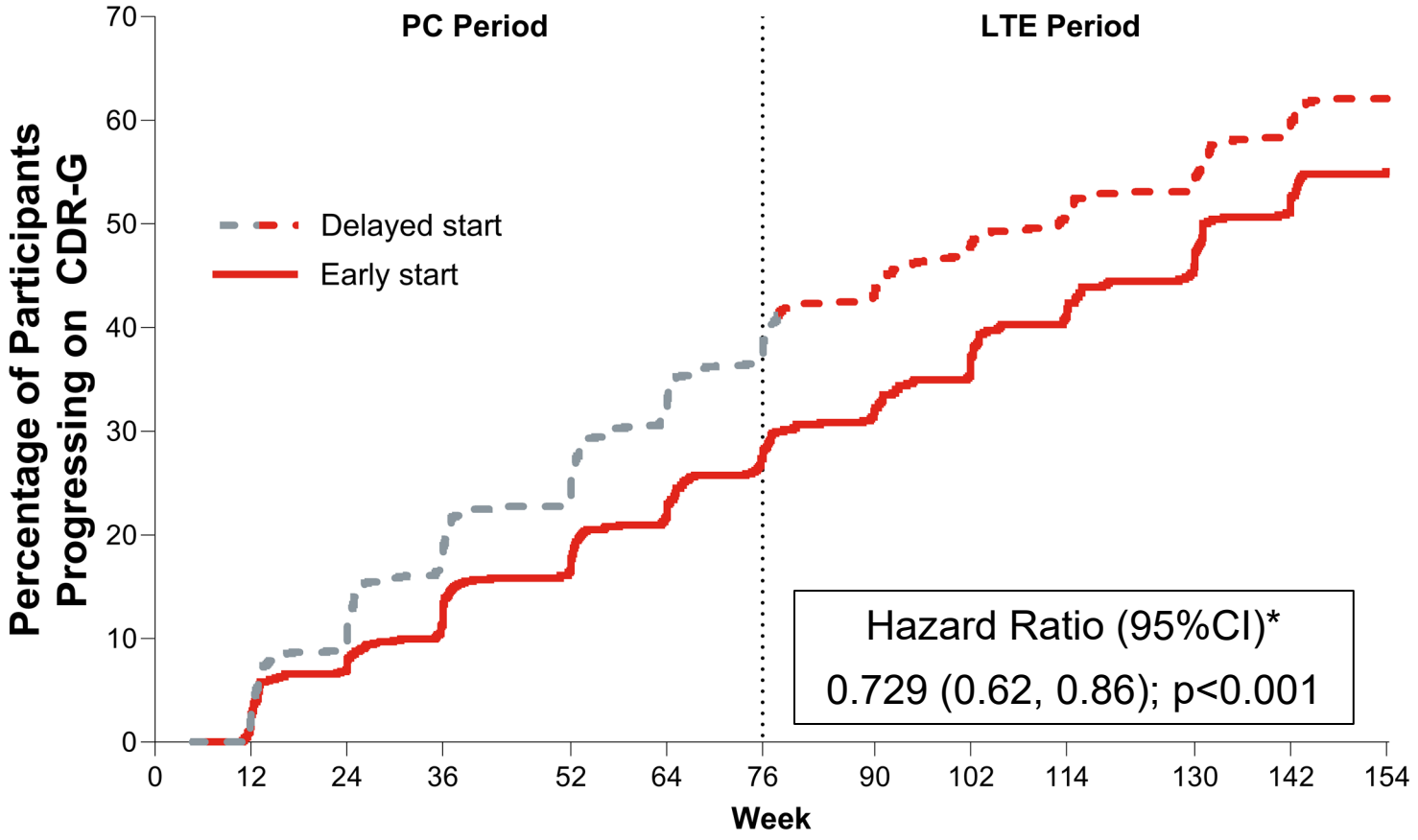
- Nearly half of placebo-treated participants progressed to moderate AD by start of LTE

Key Characteristics at Start of LTE Period	Delayed Start
Age, mean (SD)	**74.9 (6.1)**
MMSE, mean (SD)	**19.8 (5.5)**
MMSE category, n (%)	
MCI (27+)	70 (10.7)
Mild (20-26)	290 (44.1)
Moderate AD (<20)	297 (45.2)
CDR-SB, mean (SD)	**5.7 (3.2)**

Notes: External ADNI cohort was weighted using propensity score using average treatment effect on the treated weights with covariates at study entry/baseline; CDR-SB change from baseline were estimated with MMRM model using ADNI weights.

ADNI: Alzheimer's Disease Neuroimaging Initiative (https://adni.loni.usc.edu/); CDR-SB: Clinical Dementia Rating-Sum of Boxes; ESS: effective sample size; LTE: long-term extension; MCI: mild cognitive impairment; MMRM: Mixed Model for Repeated Measures; MMSE: mini-mental state examination; N: number of participants; PC: placebo-controlled; SD; standard deviation; SE: standard error.

EFFICACY: REDUCED RISK OF PROGRESSION TO NEXT CLINICAL DISEASE STAGE

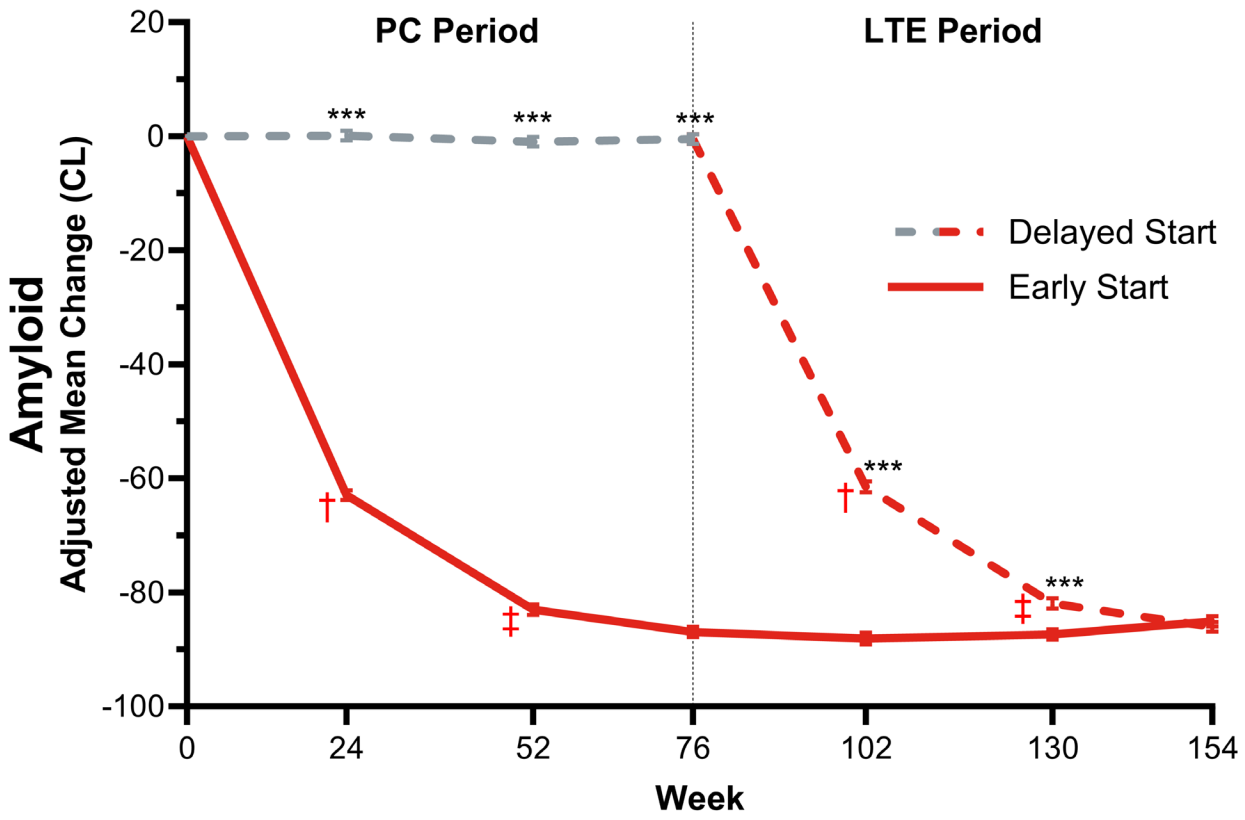


- Early start donanemab group showed 27% reduced risk of progression to next stage of disease compared to delayed start donanemab group
- Disease modification by donanemab was demonstrated by continued treatment differences between the early and delayed start groups

*Hazard Ratio, 95% CI, and p-value are calculated using Cox proportional hazards model. The model was stratified by pooled investigator and baseline tau level and included the following baseline covariates: age, CDR-G, AChEI/Memantine use.

AChEI: acetylcholine esterase inhibitor; CDR-G: Clinical Dementia Rating-Global Score; CI: confidence interval; LTE: long-term extension; PC: placebo-controlled.

AMYLOID REDUCTION CONSISTENT IN DELAYED START TREATMENT



- Amyloid reduction reproduced in the LTE period at similar time points following donanemab initiation

	Early Start	Delayed Start
Pre-treatment, mean CL (SD)	104.02 (34.42)	101.86 (35.67)¶
24 weeks	-62.91 (0.86)	0.13 (0.83)
52 weeks	-83.01 (0.89)	-0.98 (0.86)
76 weeks	-86.96 (0.92)	-0.48 (0.88)
102 weeks	-88.09 (1.03)	-61.47 (0.97)
130 weeks	-87.33 (0.95)	-81.92 (0.90)
154 weeks	-85.06 (0.94)	-86.01 (0.89)

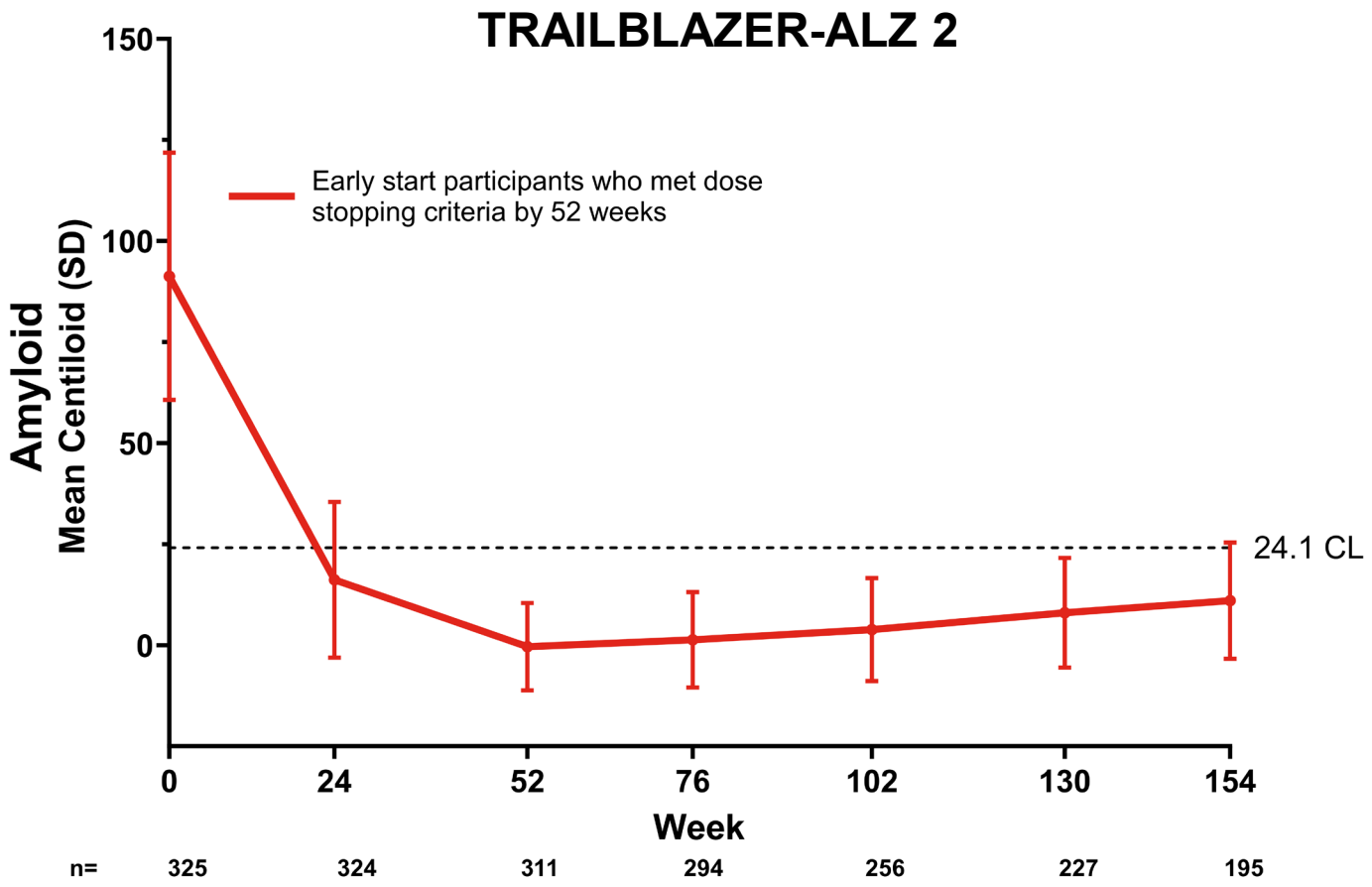
¶Represents amyloid level at 76 weeks
All values are LS mean CL change from baseline (SE) unless otherwise noted.

- Amyloid clearance (<24.1 CL) achieved by >75% of participants§ in both groups 76 weeks after starting donanemab

***p<0.001; †24 weeks from start of donanemab treatment; ‡52 weeks from start of donanemab treatment;
§Among those with an amyloid PET scan at 76 weeks from start of treatment

CL: Centiloid; LS: least squares; SE: standard error.

AMYLOID PLAQUE LEVELS FOR PARTICIPANTS WHO MET TREATMENT COMPLETION CRITERIA BY 52 WEEKS



- Mean amyloid levels remained below 24.1 CL at 3 years for participants who completed donanemab treatment by 52 weeks
- From observed data across four donanemab studies*, amyloid plaque reaccumulation (2.4 CL/year) was comparable to the natural accumulation rate[1,2]

[1]Jagust and Landau. Neurology. 2021. [2]Elhefnawy et al. J Pharmacokinet Pharmacodyn. 2025.
*Includes data from: a Phase 1 study (NCT02624778), TRAILBLAZER-ALZ and TRAILBLAZER-EXT Parts B and C (NCT03367403, NCT04640077) and TRAILBLAZER-ALZ 2 PC, exposure addendum and LTE (NCT04437511).

Note: Treatment completion criteria were met for any participants with amyloid plaque level <11 CL on any single PET scan or ≥11 and <25 on two consecutive PET scans.
CL: Centiloids; n: number of patients at each visit with non-missing values; PET: positron emission tomography.

CONSISTENT SAFETY PROFILE WITH LATER DONANEMAB INITIATION

Treatment Arm	Donanemab initiated in PC period*†	Donanemab initiated in LTE period*‡
Observation Period	PC Period	LTE Period
	N=853; n (%)	N=657; n (%)
Death§	17 (2.0)	7 (1.1)¶
Serious AE	148 (17.4)	129 (19.6)
Study discontinuations due to AE	73 (8.6)	39 (5.9)
Treatment discontinuations due to AE	115 (13.5)	89 (13.5)
Treatment emergent AEs	763 (89.4)	568 (86.5)
Treatment emergent AEs deemed related to study treatment#	414 (48.5)	315 (47.9)

- Similar safety profile between early donanemab treatment initiation and later initiation

*Includes safety analysis population (i.e., all participants who received at least one infusion in the relevant study period).
†TEAE: baseline AEs defined as all AEs starting before the first dose; post baseline starts the day of first infusion and ends at the end of the PC period + 57 days, or data cut-off. Includes additional data incorporated after primary outcome lock.
‡ TEAE: baseline AEs defined as all ongoing AEs on the first LTE dose; post baseline starts the day of first LTE infusion and ends at the earlier of date of study withdrawal/completion, end of the LTE period + 57 days, or data cut-off.
§Deaths are also included as serious adverse events and discontinuations due to adverse events.
¶Includes two previously reported deaths due to ARIA-E and ICH. ICH occurred following thrombolytic administration where MRI the same day showed severe ARIA-E[1]
#Includes events that were considered related to study treatment as judged by the investigator.
Note: Participants may be counted in more than one category.

[1]Zimmer et al. JAMA Neurology. 2025.

AE: adverse event; ARIA-E: amyloid-related imaging abnormality-edema/effusion; ICH: intracranial hemorrhage; LTE: long-term extension; MRI: magnetic resonance imaging; N: number of participants in the analysis population; n: number of participants with at least one event per type; PC: placebo-controlled; TEAE; treatment-emergent adverse event.

ARIA AND INFUSION-RELATED REACTION FREQUENCIES WITH LATER DONANEMAB INITIATION

Treatment Arm	Donanemab initiated in PC period*†	Donanemab initiated in LTE period*‡
Observation Period	PC Period	LTE Period
	N=853; n (%)	N=657; n (%)
ARIA-E§	**205 (24.0)**	**171 (26.0)**
Symptomatic	52 (6.1)	40 (6.1)
SAE of ARIA-E¶	13 (1.5)	9 (1.4)
ARIA-H§	**269 (31.5)**	**261 (39.7)**
Symptomatic	10 (1.2)	3 (0.5)
SAE of ARIA-H¶	4 (0.5)	0 (0.0)
Macrohemorrhage§	**3 (0.4)**	**7 (1.1)**
SAE of Macrohemorrhage¶	1 (0.1)	1 (0.2)
Infusion-related reaction	**75 (8.8)**	**49 (7.5)**
Anaphylactic reaction#	**3 (0.4)**	**4 (0.6)**

- Comparable frequencies of ARIA and infusion-related reactions between early donanemab treatment initiation and later initiation

*Includes safety analysis population (i.e., all participants who received at least one infusion in the relevant study period).
†Includes events that occurred prior to the earlier of date of study withdrawal/completion, end of the placebo-controlled period + 57 days, or data cut-off. Includes additional data incorporated after primary outcome lock.
‡ Includes events that occurred prior to the earlier of date of study withdrawal/completion, end of the extension period + 57 days, or data cut-off are included in this table.
§Based on MRI or TEAE cluster.
¶Based on TEAE cluster.
#Includes anaphylactic reaction and anaphylactic shock.

ARIA: amyloid-related imaging abnormality; ARIA-E: amyloid-related imaging abnormality-edema/effusion; ARIA-H: amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits; LTE: long-term extension; MRI: magnetic resonance imaging; N: number of participants in the analysis population; n: number of participants with at least one event per type; PC: placebo-controlled; SAE: serious adverse event; TEAE: treatment emergent adverse event.

WITH LONGER OBSERVATION, SAFETY PROFILE BEGAN TO APPROXIMATE PLACEBO

Treatment Arm	Placebo initiated in PC period*†	Donanemab initiated in PC period*‡
Observation Period	PC Period	LTE Period
	N=874; n (%)	N=550; n (%)
Death§	11 (1.3)	10 (1.8)
Serious AE	130 (14.9)	101 (18.4)
Study discontinuations due to AE	37 (4.2)	21 (3.8)
Treatment discontinuations due to AE	41 (4.7)	21 (3.8)
Treatment emergent AEs	722 (82.6)	448 (81.5)
Treatment emergent AEs deemed related to study treatment¶	176 (20.1)	101 (18.4)

- During the LTE period, participants who initiated donanemab early began to approximate the safety profile of placebo treated participants

*Includes safety analysis population (i.e., all participants who received at least one infusion in the relevant study period).
†TEAE: baseline AEs defined as all AEs starting before the first dose; post baseline starts the day of first infusion and ends at the end of the PC period + 57 days, or data cut-off. Includes additional data incorporated after primary outcome lock.
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¶Includes events that were considered related to study treatment as judged by the investigator.
Note: Participants may be counted in more than one category.

AE: adverse event; ARIA-E: amyloid-related imaging abnormality-edema/effusion; LTE: long-term extension; MRI: magnetic resonance imaging; N: number of participants in the analysis population; n: number of participants with at least one event per type; PC: placebo-controlled; TEAE; treatment-emergent adverse event.

WITH LONGER OBSERVATION, ARIA FREQUENCY DECREASED

Treatment Arm	Placebo initiated in PC period*†	Donanemab initiated in PC period*‡
Observation Period	PC Period	LTE Period
	N=874; n (%)	N=550; n (%)
ARIA-E§	**18 (2.1)**	**19 (3.5)**
Symptomatic	0 (0.0)	4 (0.7)
SAE of ARIA-E¶	0 (0.0)	1 (0.2)
ARIA-H§	**119 (13.6)**	**105 (19.1)**
Symptomatic	3 (0.3)	1 (0.2)
SAE of ARIA-H¶	0 (0.0)	0 (0.0)
Macrohemorrhage§	**2 (0.2)**	**0 (0.0)**
SAE of Macrohemorrhage¶	1 (0.1)	0 (0.0)
Infusion-related reaction	**4 (0.5)**	**13 (2.4)**
Anaphylactic reaction#	**0 (0.0)**	**0 (0.0)**

- During the LTE period, participants who initiated donanemab early had ARIA and infusion-related reaction frequencies that began to approximate the safety profile of placebo treated participants

*Includes safety analysis population (i.e., all participants who received at least one infusion in the relevant study period).
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SUMMARY

Clinical Efficacy

- Donanemab benefit continued to grow over 3 years (CDR-SB vs ADNI: -1.2 points)
- Delayed initiation of donanemab also provided benefit on CDR-SB
- Early initiation of donanemab reduced risk of progression by 27% on CDR-G

Safety

- No new safety signals observed versus the established safety profile

Biomarkers

- Early and delayed start of donanemab showed robust amyloid reduction (~86 CL)
- Amyloid clearance (<24.1 CL) achieved by >75% of early and delayed start participants with amyloid PET scan 1.5 years after starting donanemab
- Amyloid plaque reaccumulation estimated at 2.4 CL/year

ADNI: Alzheimer's Disease Neuroimaging Initiative (https://adni.loni.usc.edu/); CDR-G: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; CL: Centiloids; PET: positron emission tomography.

CONCLUSION

- Over 3 years, donanemab-treated participants showed increasing clinical benefit despite most participants completing the dosing regimen, with a consistent safety profile
- Participants initiating donanemab after 18 months of placebo demonstrated Alzheimer's disease slowing on donanemab treatment
- The TRAILBLAZER-ALZ 2 long-term extension data reinforce the importance of early intervention and support limited duration, treat-to-target dosing with continued long-term benefits

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