Bridging Community: Collaborative Efforts in Early Detection and Intervention for Alzheimer's Disease

Safety & Efficacy of Approved Amyloid Therapies

Overview of Approved AD DMTs

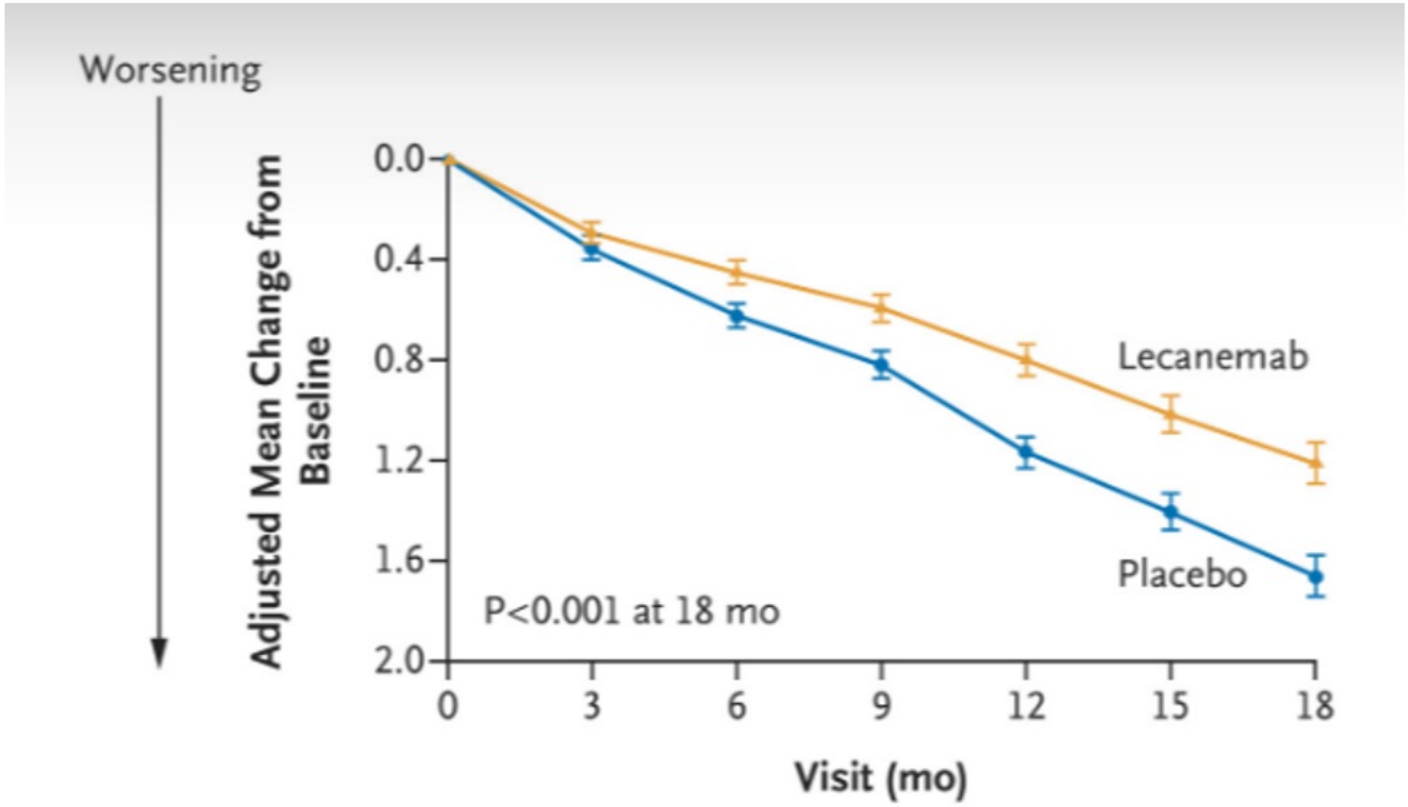
DRUG	TARGET	STATUS	INDICATION	DOSING	EFFICACY IN PHASE 3 RCTs	SAFETY IN PHASE 3 RCTs
Lecanemab	Aβ plaques and protofibrils	Full approval granted in 2023	Early symptomatic AD (MCI or mild dementia)	10 mg/kg IV every 2 weeks	Slowed functional and cognitive decline relative to placebo in patients with MCI or mild dementia due to AD	Infusion-related reactions (26%), ARIA-H (14%), ARIA-E (13%), headache (11%)
Donanemab	Aβ plaques	Full approval granted in 2024		700 mg (first 3 doses) then 1 400 mg IV every 4 weeks until Aβ plaque level is under cutoff	Slowed functional and cognitive decline relative to placebo **and** increased Aβ clearance relative to aducanumab in patients with MCI or mild dementia due to AD	ARIA-E (24%), ARIA-H (20%), headache (14%), infusion-related reaction (9%)

Aβ, amyloid β; ARIA-E, amyloid-related imaging abnormalities with edema; ARIA-H, amyloid-related imaging abnormalities with hemorrhage; IV, intravenous; N/A, not applicable, RCTS, randomized control trial.

van Dyck CH, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med*. 2023;388(1):9-21; Sims JR, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA*. 2023;330(6):512-527; Salloway S, et al. TRAILBLAZER-ALZ 4: topline study results directly comparing donanemab to aducanumab on amyloid lowering in early, symptomatic Alzheimer's disease. *BJPsych Open*. 2023;9(Suppl 1):S67.

Lecanemab

18-month, multicenter, double-blind, phase 3 trial involving persons 50 to 90 years with early AD (MCI or mild dementia due to AD) with evidence of amyloid on PET or by CSF testing



No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

- <u>Primary end point</u>: Score on the Clinical Dementia Rating – Sum of Boxes (CDR-SB)
- Scores for each of six domains identified by patients and caregivers range from 0 to 3, with higher scores indicating greater impairment
  - Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, Personal Care
- Total scores range from 0 to 18, a score of 0.5 to 6 indicating early AD

I, Indicates the adjusted mean changes from baseline, standard errors; P value were derived with the use of a mixed model for repeated measures, with trial group, visit, trial group–by–visit interaction, clinical subgroup, use of medication for symptoms of Alzheimer's disease at baseline, ApoE ε4 carrier status, geographic region, and baseline value–by–visit interaction as fixed effects and baseline value as a covariate.

Van Dyck CH, Swanson CJ, Aisen P et al. Lecanemab in Early Alzheimer's Disease, *N Engl J Med* 2022; Nov 29.

Lecanemab

18-month, multicenter, double-blind, phase 3 trial involving persons 50 to 90 years with early AD (MCI or mild dementia due to AD) with evidence of amyloid on PET or by CSF testing

Primary Efficacy End Point	Lecanemab (N=859)	Placebo (N=875)
Change from baseline to 18 mo in the CDR-SB score		
No. of participants evaluated	859	875
Adjusted mean change	1.21	1.66
Adjusted mean difference vs. placebo (95% CI)	-0.45 (-0.67 to -0.23)	--
P value vs. placebo	<0.001	--

Primary endpoint in modified intention-to-treat population.

Van van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med*. 2023;388(1):9-21.

Lecanemab

18-month, multicenter, double-blind, phase 3 trial involving persons 50 to 90 years with early AD (MCI or mild dementia due to AD) with evidence of amyloid on PET or by CSF testing

Event	Lecanemab (N=898)	Placebo (N=897)
Overall – no. (%)		
Any Adverse Event (AE)	798 (88.9)	735 (81.9)
AE related to lecanemab or placebo†	401 (44.7)	197 (22.0)
Serious AE	126 (14.0)	101 (11.3)
Death	6 (0.7)	7 (0.8)
AE leading to discontinuation of the trial agent	62 (6.9)	26 (2.9)
AE event that occurred in ≥5% of participants in either group		
Infusion-related reaction	237 (26.4)	66 (7.4)
ARIA with microhemorrhages or hemosiderin deposits	126 (14.0)	69 (7.7)
ARIA-E	113 (12.6)	15 (1.7)

Event	Lecanemab (N=898)	Placebo (N=897)
AE event that occurred in ≥5% of participants in either group		
Headache	100 (11.1)	73 (8.1)
Fall	93 (10.4)	86 (9.6)
Urinary tract infection	78 (8.7)	82 (9.1)
COVID-19	64 (7.1)	60 (6.7)
Back pain	60 (6.7)	52 (5.8)
Arthralgia	53 (5.9)	62 (6.9)
Superficial siderosis of CNS	50 (5.6)	22 (2.5)
Dizziness	49 (5.5)	46 (5.1)
Diarrhea	48 (5.3)	58 (6.5)
Anxiety	45 (5.0)	38 (4.2)

*ARIA denotes amyloid-related imaging abnormalities, ARIA-E ARIA with edema or effusions, ARIA-H ARIA with hemosiderin deposits, and Covid-19 coronavirus disease 2019. †The relatedness of adverse events to lecanemab or placebo was determined by the investigators.
CNS, central nervous system.
van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med*. 2023;388(1):9-21.

Lecanemab

18-month, multicenter, double-blind, phase 3 trial involving persons 50 to 90 years with early AD (MCI or mild dementia due to AD) with evidence of amyloid on PET or by CSF testing

ARIA‡	Lecanemab (N=898)	Placebo (N=897)
ARIA-E – no. (%)	113 (12.6)	15 (1.7)
Symptomatic ARIA-E, no. (%)§	25 (2.8)	0
ApoE ε4 noncarrier, no./total no. (%)	4/278 (1.4)	0/286
ApoE ε4 carrier, no./total no. (%)	21/620 (3.4)	0/611
ApoE ε4 heterozygote	8/479 (1.7)	0/478
ApoE ε4 homozygote	13/141 (9.2)	0/133
ARIA-E according to ApoE ε4 genotype, no./total no. (%)		
ApoE ε4 noncarrier	15/278 (5.4)	1/286
ApoE ε4 carrier	98/620 (15.8)	14/611 (2.3)
ApoE ε4 heterozygote	52/479 (10.9)	9/478 (1.9)
ApoE ε4 homozygote	46/141 (32.6)	5/133 (3.8)

ARIA‡	Lecanemab (N=898)	Placebo (N=897)
ARIA-E or ARIA-H, no. (%)	193 (21.5)	85 (9.5)
Concurrent ARIA-E and ARIA-H, no. (%)	74 (8.2)	9 (1.0)

ARIA‡	Lecanemab (N=898)	Placebo (N=897)
ARIA-H – no. (%)	155 (17.3)	81 (9.0)
Microhemorrhage	126 (14.0)	68 (7.6)
Superficial siderosis	50 (5.6)	21 (2.3)
Macrohemorrhage	5 (0.6)	1 (0.1)
Symptomatic ARIA-H§	6 (0.7)	2 (0.2)
Isolated ARIA-H: no concurrent ARIA-E	80 (8.9)	70 (7.8)
ARIA-H according to ApoE ε4 genotype, no./total no. (%)		
ApoE ε4 noncarrier	33/278 (11.9)	12/286 (4.2)
ApoE ε4 carrier	122/620 (19.7)	69/611 (11.3)
ApoE ε4 heterozygote	67/479 (14.0)	41/478 (8.6)
ApoE ε4 homozygote	55/141 (39.0)	28/133 (21.1)

*ARIA denotes amyloid-related imaging abnormalities, ARIA-E ARIA with edema or effusions, ARIA-H ARIA with hemosiderin deposits, and Covid-19 coronavirus disease 2019. ‡ARIA events were based on central review of MRI studies and include events that occurred after the double-blind intervention period. §Symptomatic ARIA-H concurrent with ARIA-E were included under ARIA-E.

van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med*. 2023;388(1):9-21.

Lecanemab

Safety observations + more detailed safety data from the double-blind Core phase and the OLE of the phase 3 Clarity AD in early AD

n/N (%)	Core Placebo (N=897)	Lecanemab (N=898)	Core + OLE Lecanemab (N=1612)
Any AE	735 (81.9)	798 (88.9)	1389 (86.2)
Deaths	7 (0.8)	6 (0.7)	16 (1.0)*
Serious AE	101 (11.3)	126 (14.0)	241 (15.0)
SAE with ARIA-E	0	7 (0.8)	18 (1.1)
SAE with ARIA-H	0	2 (0.2)	10 (0.6)
SAE with infusion-related reactions	0	11 (1.2)	20 (1.2)
Treatment-related AE	197 (22.0)	401 (44.7)	721 (44.7)
AE leading to drug withdrawal	26 (2.9)	62 (6.9)	124 (7.7)

*The 16 deaths included 6 from Core, 9 from OLE, and one death that occurred > 30 days after last dose.
Honig LS, Sabbagh MN, van Dyck CH, et al. Updated safety results from phase 3 lecanemab study in early Alzheimer's disease [published correction appears in *Alzheimers Res Ther*. 2024 Jul 10;16(1):159.

n/N (%)	Core Placebo (N=897)	Lecanemab (N=898)	Core + OLE Lecanemab (N=1612)
ARIA-E	15/897 (1.7)	113/898 (12.6)	219/1612 (13.6)
ARIA-E by APOE4 genotype			
APOE4 noncarrier	1/286 (0.3)	15/278 (5.4)	32/496 (6.5)
APOE4 carrier	14/611 (2.3)	98/620 (15.8)	187/1116 (16.8)
APOE4 heterozygote	9/478 (1.9)	52/479 (10.9)	101/867 (11.6)
APOE4 homozygote	5/133 (3.8)	46/141 (32.6)	86/249 (34.5)
Symptomatic ARIA-E	0	25/898 (2.8)	54/1612 (3.3)
APOE4 noncarrier	0	4/278 (1.4)	8/496 (1.6)
APOE4 carrier	0	21/620 (3.4)	46/1116 (4.1)
APOE4 heterozygote	0	8/479 (1.7)	18/867 (2.1)
APOE4 homozygote	0	13/141 (9.2)	28/249 (11.2)
Recurrent ARIA-E	1 (0.1)	28 (3.1)	46/1612 (2.9)
APOE4 noncarrier	0/286 (0)	1/278 (0.4)	4/496 (0.8)
APOE4 carrier	1/611 (0.2)	27/620 (4.4)	42/1116 (3.8)
APOE4 heterozygote	0/478 (0)	7/479 (1.5)	18/867 (2.1)
APOE4 homozygote	1/133 (0.8)	20/141 (14.2)	24/249 (9.6)

Lecanemab

Safety observations + more detailed safety data from the double-blind Core phase and the OLE of the phase 3 Clarity AD in early AD

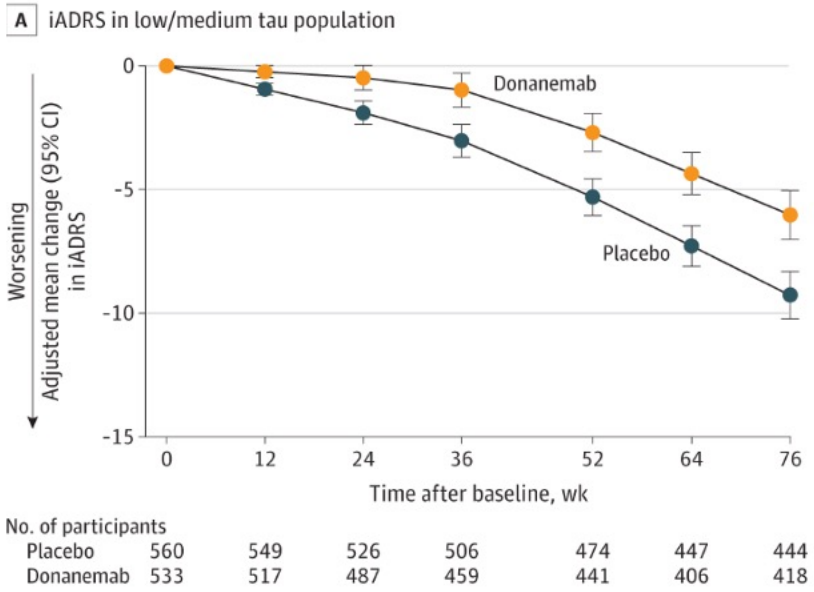
n/N (%)	Core Placebo (N=897)	Lecanemab (N=898)	Core + OLE Lecanemab (N=1612)
ARIA-H	80 (8.9)	152 (16.9)	298/1612 (18.5)
Microhemorrhage	68 (7.6)	126 (14.0)	258/1612 (16.0)
Superficial siderosis	21 (2.3)	50 (5.6)	96/1612 (6.0)
Intracerebral hemorrhage	1 (0.1)	5 (0.6)	8/1612 (0.5)
Symptomatic ARIA-H	2 (0.2)	11 (1.2)	27/1612 (1.7)
ARIA-H by ApoE4 genotype			
ApoE4 noncarrier	11/286 (3.8)	32/278 (11.5)	59/496 (11.7)
ApoE carrier	69/611 (11.3)	120/620 (19.4)	239/1116 (21.4)
ApoE heterozygote	41/478 (8.6)	66/479 (13.8)	140/867 (16.1)
ApoE4 homozygote	28/133 (21.1)	54/141 (38.3)	99/249 (39.8)
Isolated ARIA-H	69 (7.7)	78 (8.7)	146 (9.1)
Microhemorrhage	63 (7.0)	60 (6.7)	119 (7.4)
Superficial siderosis	13 (1.4)	23 (2.6)	39 (2.4)

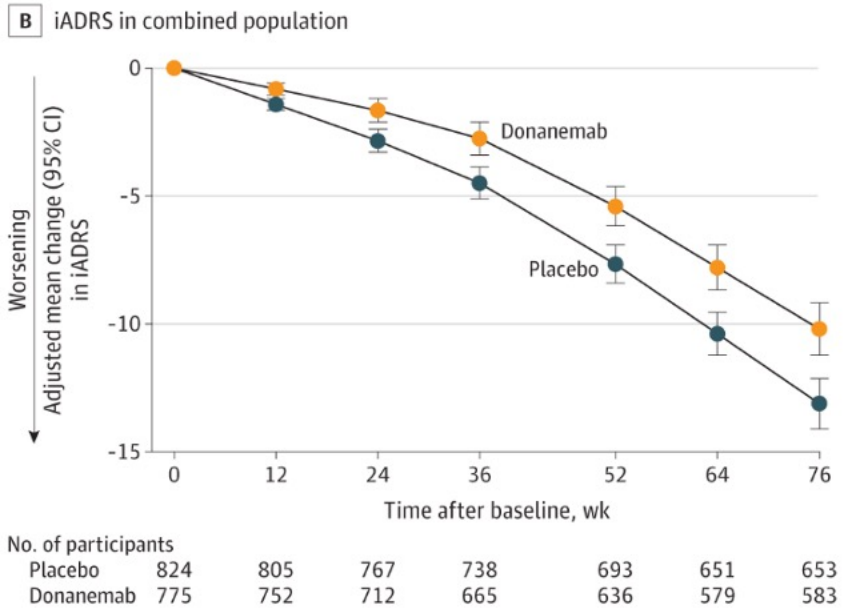
n/N (%)	Core Placebo (N=897)	Lecanemab (N=898)	Core + OLE Lecanemab (N=1612)
Isolate intracerebral hemorrhage	1 (0.1)	4 (0.4)	5 (0.3)
Symptomatic isolated ARIA-H	2 (0.2)	4 (0.4)	6 (0.4)
Isolated ARIA-H by ApoE4 genotype			
ApoE4 noncarrier	10/286 (3.5)	22/278 (7.9)	38/496 (7.7)
ApoE4 carrier	59/611 (9.7)	56/620 (9.0)	108/1116 (9.7)
ApoE4 heterozygote	35/478 (7.3)	39/479 (8.1)	76/867 (8.8)
ApoE4 homozygote	24/133 (18.0)	17/141 (12.1)	32/249 (12.9)

Honig LS, Sabbagh MN, van Dyck CH, et al. Updated safety results from phase 3 lecanemab study in early Alzheimer's disease [published correction appears in *Alzheimers Res Ther*. 2024 Jul 10;16(1):159.

Donanemab

TRAILBLAZER-ALZ 2 was a 76-week, phase 3, randomized, double-blind, parallel, multicenter, placebo-controlled trial among participants with early symptomatic AD and amyloid and tau pathology screened at 277 sites in 8 countries





- <u>Primary end point</u>: Change in the iADRS score from baseline to 76 weeks in either the low/medium tau population or combined (low/medium and high tau) population
- The iADRS is an integrated assessment of cognition and daily function from the 13-item cognitive subscale of the ADAS-Cog13 and ADCS-iADL, measuring global disease severity across the AD continuum as a single summary score

ADAS-Cog13, Alzheimer Disease Assessment Scale; ADCS-iADL, Alzheimer Disease Cooperative Study – Instrumental Activities of Daily Living; iADRS, integrated Alzheimer Disease Rating Scale.

Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA*. 2023;330(6):512-527.

Donanemab

TRAILBLAZER-ALZ 2 was a 76-week, phase 3, randomized, double-blind, parallel, multicenter, placebo-controlled trial among participants with early symptomatic AD and amyloid and tau pathology screened at 277 sites in 8 countries

Outcome[a]	Group	Donanemab		
		Mean (SD)		LSM Change (95% CI)
		Baseline	76 Weeks	
iADRS	Low/medium tau	n=533	n=418	--
	NCS2[c]	105.92 (13.72)	101.31 (18.23)	-6.02 (-7.01 to -5.03)
	MMRM[d]	105.92 (13.72)	101.31 (18.23)	-5.81 (-6.90 to -4.71)
	Combined	n=775	n=583	--
	NCS2[c]	104.55 (13.90)	96.98 (20.87)	-10.19 (-11.22 to -9.16)
	MMRM[d]	104.55 (13.90)	96.98 (20.87)	-10.19 (-11.27 to -9.11)

Outcome[a]	Group	Placebo		
		Mean (SD)		LSM Change (95% CI)
		Baseline	76 Weeks	
iADRS	Low/medium tau	n=560	n=444	--
	NCS2[c]	105.95 (13.42)	98.88 (17.95)	-9.27 (-10.23 to -8.31)
	MMRM[d]	105.95 (13.42)	98.88 (17.96)	-9.61 (-10.67 to -8.56)
	Combined	n=824	n=653	--
	NCS2[c]	103.82 (13.88)	93.82 (20.38)	-13.11 (-14.10 to -12.13)
	MMRM[d]	103.82 (13.88)	93.82 (20.38)	-13.22 (-14.27 to -12.18)

Group	LMS Difference vs placebo (95% CI)	P value vs placebo	Slowing of clinical progression, % (95% CI)[b]
Low/medium tau	--	--	--
NCS2[c]	3.25 (1.88 to 4.62)	< 0.001	35.1 (19.90 to 50.23)
MMRM[d]	3.80 (2.36 to 5.25)	< 0.001	39.6 (23.93 to 55.22)
Combined	--	--	--
NCS2[c]	2.92 (1.51 to 4.33)	< 0.001	22.3 (11.38 to 33.15)
MMRM[d]	3.03 (1.60 to 4.47)	< 0.001	22.9 (11.96 to 33.92)

[a]iADRS range from 0 to 144, with lower scores indicating greater impairment. [b]The percentage of slowing of clinical progression was calculated by dividing the least-squares mean change from baseline treatment differences at 76 weeks by the least-squares mean change from baseline with placebo at 76 weeks and multiplying by 100. The CI is estimated using the Delta method. [c]Gated outcome. [d]For MMRM analyes, 95% CIs for least-squares mean changes were calculated with the normal approximation method.

Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA*. 2023;330(6):512-527.

Donanemab

TRAILBLAZER-ALZ 2 was a 76-week, phase 3, randomized, double-blind, parallel, multicenter, placebo-controlled trial among participants with early symptomatic AD and amyloid and tau pathology screened at 277 sites in 8 countries

Summary of AE by Treatment Group	Donanemab (N=853)[a]	Placebo (N=874)[a]
Overview of AEs, No (%)		
Death[b]	16 (1.9)[c]	10 (1.1)
Death considered related to treatment[d]	3 (0.4)	1 (0.1)
Participants with ≥1 serious AE[e]	148 (17.4)	138 (15.8)
Treatment discontinuations due to AEs	112 (13.1)	38 (4.3)
Study discontinuations due to AEs	69 (8.1)	32 (3.7)
Participants with ≥1 TEAE[f]	759 (89.0)	718 (82.2)

Summary of AE by Treatment Group	Donanemab (N=853)[a]	Placebo (N=874)[a]
TEAEs ≥5% incidence, No (%)		
ARIA-E	205 (24.0)	17 (1.9)
ARIA-H	168 (19.7)	65 (7.4)
COVID-19	136 (15.9)	154 (17.6)
Headache	119 (14.0)	86 (9.8)
Fall	114 (13.4)	110 (12.6)
Infusion-related reaction	74 (8.7)	4 (0.5)
Superficial siderosis of CNS	58 (6.8)	10 (1.1)
Dizziness	53 (6.2)	48 (5.5)
Arthralgia	49 (5.7)	42 (4.8)
Urinary tract infection	45 (5.3)	59 (6.8)
Diarrhea	43 (5.0)	50 (5.7)
Fatigue	42 (4.9)	45 (5.1)

TEAE, treatment-emergent adverse event.

[a]Participants may have been counted in more than 1 category; adverse events population is defined as all participants that received at least 1 infusion. [b]Deaths are also included under serious AEs and discontinuation due to AEs. [c]Includes 1 death that occurred after treatment completion and in the follow-up period. [d]Deaths related to donanemab occurred subsequent to ARIA and the death related to placebo due to arteriosclerosis. [e]Definition of serious AE: results in death, is life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, or based on other medical/scientific judgement. [f]Definition of TEAE: an untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.

Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023;330(6):512-527.

Donanemab

TRAILBLAZER-ALZ 2 was a 76-week, phase 3, randomized, double-blind, parallel, multicenter, placebo-controlled trial among participants with early symptomatic AD and amyloid and tau pathology screened at 277 sites in 8 countries

Summary of AE by Treatment Group	Donanemab (N=853)[a]	Placebo (N=874)[a]
Overview of ARIA[g]		
Microhemorrhage or superficial siderosis present at baseline, No. (%)	124 (14.5)	161 (18.4)
ARIA-E by *APOE* ε4 allele status, No./total No. (%)		
Noncarrier	40/255 (15.7)	2/250 (0.8)
Heterozygous carrier	103/452 (22.8)	9/474 (1.9)
Homozygous carrier	58/143 (40.6)	5/146 (3.4)
Any ARIA, No. (%)[h]	314 (36.8)	130 (14.9)
ARIA-E, No. (%)	205 (24.0)	18 (2.1)
Asymptomatic	153 (17.9)	17 (1.9)
Symptomatic	52 (6.1)	0 (0.1)[i]
ARIA-H, No. (%)	268 (31.4)	119 (13.6)
Microhemorrhage	229 (26.8)	109 (12.5)
Superficial siderosis	134 (15.7)	26 (3.0)
Intracerebral hemorrhage >1 cm	3 (0.4)	2 (0.2)

[g]Based on safety MRI or TEAE cluster (after baseline); *APOE4* is a known risk factor for ARIA-E. [h]Based on MRI. [i]One placebo-treated participant had ARIA-E during the placebo-controlled period; however, the participant developed symptoms during the long-term extension period.

Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023;330(6):512-527.

Donanemab

TRAILBLAZER-ALZ 4, comparison of donanemab to aducanumab on amyloid lowering in early, symptomatic AD

- Achievement of amyloid clearance at 6-month florbetapir F18 PET scans revealed:
  - 37.9% donanemab-treated participants vs.
  - 1.6% aducanumab-treated participants ($p<0.001$)
- Achievement of amyloid clearance (tau subpopulation):
  - 38.5% donanemab-treated participants vs.
  - 3.8% aducanumab-treated participants ($p=0.008$)
- Percent change in brain amyloid levels:
  - Donanemab: −65.2%±3.9% (baseline: 98.29±27.83 CL) and
  - Aducanumab: −17.0%±4.0% (baseline: 102.40±35.49 CL) ($p<0.001$)
- Percent change in brain amyloid levels (tau subpopulation):
  - Donanemab: −63.9%±7.4% (baseline: 104.97±25.68 CL) and
  - Aducanumab: −25.4%±7.8% (baseline: 102.23±28.13 CL) ($p\leq0.001$)

- Reported AEs:
  - 62.0% of donanemab-treated participants and
  - 66.7% of aducanumab-treated participants
- Serious AEs due to ARIA:
  - None in the donanemab arm and
  - 1.4% (one event) in the aducanumab arm

A significantly higher number of participants reached amyloid clearance and amyloid plaque reductions with donanemab versus aducanumab at 6 months

Salloway S, et al. TRAILBLAZER-ALZ 4: topline study results directly comparing donanemab to aducanumab on amyloid lowering in early, symptomatic Alzheimer's disease. *BJPsych Open*. 2023;9(Suppl 1):S67. Pain A et al. TRAILBLAZER-ALZ 4: Directly comparing donanemab to aducanumab on amyloid lowering in early, symptomatic Alzheimer's disease - Results from 12-months. *Alzheimer's Dement*. 2023;19(Suppl. 24):e082529. Salloway S, et al. TRAILBLAZER-ALZ 4: topline study results directly comparing donanemab to aducanumab on amyloid lowering in early, symptomatic Alzheimer's disease. Neurology. 2023;100(Suppl 2:S26.009.