Donanemab

Peripheral and Central Nervous System Drugs Advisory Committee

June 10, 2024

Introductory Comments

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Center for Drug Evaluation and Research

Donanemab

- Monoclonal antibody targeting the N-terminal, third amino acid, pyroglutamate formulation (N3pG) epitope that is present in brain amyloid plaques.
- Proposed indication: Treatment of early symptomatic Alzheimer's disease (e.g., mild cognitive impairment and mild dementia stages)
- Proposed dosing regimen: 700 mg as an intravenous infusion every four weeks for the first three doses, followed by 1400 mg every four weeks, may be stopped when brain amyloid plaque is cleared

Key Regulatory History

- May 2022: Initial BLA submission seeking accelerated approval based on change from baseline in brain amyloid plaque as measured by positron emission tomography (PET) in phase 2 Study AACG
- January 2023: Complete response issued due to inadequate safety database to support the long-term safety of donanemab
- May 2023: Positive topline results reported from Phase 3 study, AACI
- June 12, 2023: BLA resubmitted data from study AACI

Clinical Studies Relevant to Evaluation of Efficacy

	AACG	AACI	AACI Safety Addendum
Study design	Phase 2, randomized, double-blind, placebo-controlled	Phase 3, randomized, double-blind, placebo-controlled	Single-arm, open-label
Population	Mild Cognitive Impairment due to AD or mild AD dementia		
Patients enrolled	131 donanemab, 126 placebo	860 donanemab, 876 placebo	1047 donanemab
Key endpoints	iADRS*, CDR-SB, ADAS-Cog 13, ADCS-iADL, MMSE, amyloid PET	iADRS*, CDR-SB, ADAS-Cog 13, ADCS-iADL, amyloid PET	Safety, amyloid PET, plasma biomarkers
Tau PET enrollment criteria	Inclusion: low/medium Exclusion: no/very low, high	Inclusion: low/medium, high Exclusion: no/very low	no/very low, low/medium, high
Amyloid PET guided dose modification	Dose reduction to 700 mg or switch to placebo	Dose switch to placebo	Dose cessation

* Primary endpoint: AD – Alzheimer's Disease: iADRS – integrated Alzheimer's Disease Rating Scale: CDR-SB – Clinical Dementia Rating-Sum of Boxes: MMSE – Mini-Mental State Examination: ADAS-Cog 13 – Alzheimer's Disease Assessment Scale – Cognitive 13-Item Scale: ADCS-iADL – Alzheimer's Disease Cooperative Study instrumental Activities of Daily Living: PET – positron emission tomography

Evidence of Effectiveness of Donanemab for the Treatment of Alzheimer's Disease

- Study AACI
  - Met primary endpoint on iADRS (less decline compared to placebo) and both components (ADAS-Cog 13 and ADCS-iADL), and also on Clinical Dementia Rating – Sum of Boxes (CDR-SB)
  - Results consistent across prespecified subgroups
- Study AACG
  - Met primary endpoint of iADRS with numerical trends on components (ADAS-Cog, ADCS-iADL); only ADAS-Cog met nominal significance
  - Positive numerical trend on CDR-SB

Unique Trial Design Elements

- Enrichment using tau PET
  - No/very low tau levels on PET excluded from controlled trials, but included in AACI Safety Addendum (biomarker and safety data only)
- Dosing regimen
  - Dosing stopped based on clearance criteria for amyloid on PET

Safety

- Safety database with sufficient exposures to assess long-term safety
- Key safety issues:
  - Amyloid-related imaging abnormalities (ARIA) and intracerebral hemorrhage
  - Infusion-related reactions and hypersensitivity
  - Imbalance in mortality

Questions for the Advisory Committee

- **Discussion:** Discuss whether the available data provide evidence of effectiveness of donanemab for the treatment of Alzheimer's disease in the population enrolled in the clinical trials with mild cognitive impairment and mild dementia.
  - Discuss the support for effectiveness across tau PET subgroups

- **Vote:** Do the available data show that donanemab is effective for the treatment of Alzheimer's disease in the population enrolled in the clinical trials with mild cognitive impairment and mild dementia?

- **Discussion:** Discuss the dosing regimen used in the clinical trials that completed treatment based on reduction of amyloid plaques on PET imaging, and if there are scientific and/or clinical considerations that may factor into a decision to stop or continue dosing with donanemab if approved.

Questions for the Advisory Committee

- **Discussion:** Discuss the overall benefit-risk assessment of donanemab for the treatment of Alzheimer's disease in the population enrolled in the clinical trials with mild cognitive impairment and mild dementia.

- **Vote:** Do the benefits outweigh the risks of donanemab in the treatment of Alzheimer's disease in the population enrolled in the clinical trials with mild cognitive impairment and mild dementia?


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Clinical Overview of Efficacy

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Donanemab

- Mechanism of Action
  - Monoclonal antibody directed against the N-terminal, third amino acid, pyroglutamate formation (N3pG) epitope present in brain amyloid plaques
- Proposed indication
  - Treatment of early symptomatic Alzheimer's disease in patients with mild cognitive impairment or mild dementia stages of disease
- Proposed dosing regimen
  - 700 mg as an intravenous infusion every four weeks for the first three doses, followed by 1400 mg every four weeks, may be stopped once brain amyloid plaque is cleared
- Notable clinical design features
  - Enrichment based on low to high levels of tau as measured by positron emission tomography (PET); excluded patients with no/very low tau
  - Cessation of dosing guided by amyloid PET

Clinical Studies Relevant to Evaluation of Efficacy

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* Primary endpoint: AD – Alzheimer's Disease: iADRS – integrated Alzheimer's Disease Rating Scale: CDR-SB – Clinical Dementia Rating-Sum of Boxes: MMSE – Mini-Mental State Examination: ADAS-Cog 13 – Alzheimer's Disease Assessment Scale – Cognitive 13-Item Scale: ADCS-iADL – Alzheimer's Disease Cooperative Study instrumental Activities of Daily Living: PET – positron emission tomography

Study AACI Primary Endpoint

- Integrated Alzheimer's Disease Rating Scale (iADRS)
  - Composite score that is a sum of ADAS-Cog 13 and ADCS-iADL total scores
- Division expressed concerns with iADRS as primary endpoint in March 2021 and December 2022 meetings with Applicant
  - Concerns with whether iADRS is capable of assessing the effects of the intervention on both cognition and function and not driven by effect on only one component
  - In order to consider the iADRS clinically meaningful, strong positive effects would need to be demonstrated on both components, ADAS-Cog 13 (cognition) and ADCS-iADL (function)
  - As the study had been initiated with CDR-SB as primary endpoint, Division advised Applicant to retain that approach
  - Alternatively, the Division advised that Applicant could specify ADAS-Cog 13 and ADCS-iADL as co-primary efficacy measures

iADRS – integrated Alzheimer's Disease Rating Scale: CDR-SB – Clinical Dementia Rating-Sum of Boxes: ADAS-Cog 13 – Alzheimer's Disease Assessment Scale – Cognitive 13-Item Scale: ADCS-iADL – Alzheimer's Disease Cooperative Study instrumental Activities of Daily Living

Study AACI Disposition

	Placebo	Donanemab
Screened	8240	
Randomized (1:1)	876	860
Received ≥1 dose, n(%)	874 (99%)	853 (99%)
Treatment discontinuation, n(%)	176 (20%)	252 (29%)
Study discontinuation, n(%)	173 (20%)	231 (27%)

n = the number of randomized subjects who discontinued; % = n/Total number of randomized subjects

Study AACI Baseline Characteristics

- Average age 73 years; 57% female; 92% white
- 72% of participants enrolled in the United States
- 61% received concomitant medications for Alzheimer's Disease (AD)
- 70% ApoE4 carriers (54% heterozygotes, 17% homozygotes)
- 68% had low/medium tau
- Baseline demographics and disease characteristics balanced between treatment arms

ApoE – apolipoproterin E

Study AACI Efficacy Results

Overall Population (Week 76)						
	Placebo		Donanemab		Treatment Difference	
Endpoint	n[1] (%)	Change From Baseline, Adjusted Mean (SE)	n[1] (%)	Change From Baseline, Adjusted Mean (SE)	Difference vs. Placebo (95% CI); % Slowing	p-value
iADRS	653 (75%)	-13.1 (0.5)	583 (68%)	-10.2 (0.5)	2.9 (1.5, 4.3); -22%	p<0.001
CDR-SB	672 (77%)	2.4 (0.1)	598 (70%)	1.7 (0.1)	-0.7 (-1.0, -0.5); -29%	p<0.001
ADAS-Cog 13	677 (77%)	6.8 (0.3)	607 (71%)	5.5 (0.3)	-1.3 (-2.1, -0.6); -20%	p<0.001
ADCS-iADL	661 (75%)	-6.1 (0.3)	591 (69%)	-4.4 (0.3)	1.7 (0.8, 2.6); -28%	p<0.001

- Statistically significant reduction in brain amyloid (-86.4 Centiloids, p<0.001)
- Statistically significant results also observed in low/medium tau population

[1] number of randomized participants with a baseline and a Week 76 efficacy score

% Slowing: difference of NCS2 estimates of mean change from baseline between treatment groups at Week 76 divided by NCS2 estimate of mean change from baseline value of the placebo group

iADRS – integrated Alzheimer's Disease Rating Scale: CDR-SB – Clinical Dementia Rating-Sum of Boxes: CI – confidence interval: ADAS-Cog 13 – Alzheimer's Disease Assessment Scale – Cognitive 13-Item Scale: ADCS-iADL – Alzheimer's Disease Cooperative Study instrumental Activities of Daily Living

Study AACG Efficacy Results

- Randomized patients:
  - placebo n=126,
  - donanemab n=131
- Study discontinuation
  - placebo 25%
  - donanemab 28%
- Baseline characteristics
  - 75 years, 47% male, 95% White
  - 100% low/medium tau

	Treatment Difference (Week 76)	
Endpoint	**Difference vs. Placebo (95% CI); % Slowing**	**p-value**
IADRS (primary)	3.2 (0.1, 6.3); 32%	0.04
CDR-SB	-0.4 (-0.8, 0.1); 23%	0.14
ADAS-Cog 13	-1.9 (-3.6, -0.1); 39%	0.04
ADCS-iADL	1.2 (-0.8, 3.2); 23%	0.23

Reduction in brain amyloid (−85.1; 95% CI −92.7, −77.4)

iADRS – integrated Alzheimer's Disease Rating Scale: CDR-SB – Clinical Dementia Rating-Sum of Boxes: ADAS-Cog 13 – Alzheimer's Disease Assessment Scale – Cognitive 13-Item Scale: ADCS-iADL – Alzheimer's Disease Cooperative Study instrumental Activities of Daily Living

Evidence of Effectiveness of Donanemab for the Treatment of AD

- Study AACI
  - Met primary endpoint on iADRS (less decline compared to placebo) and both components (ADAS-Cog 13 and ADCS-iADL), and also on CDR-SB
  - Results consistent across prespecified subgroups
- Study AACG
  - Met primary endpoint of iADRS with numerical trends on components (ADAS-Cog, ADCS-iADL); only ADAS-Cog met nominal significance
  - Positive numerical trend on CDR-SB

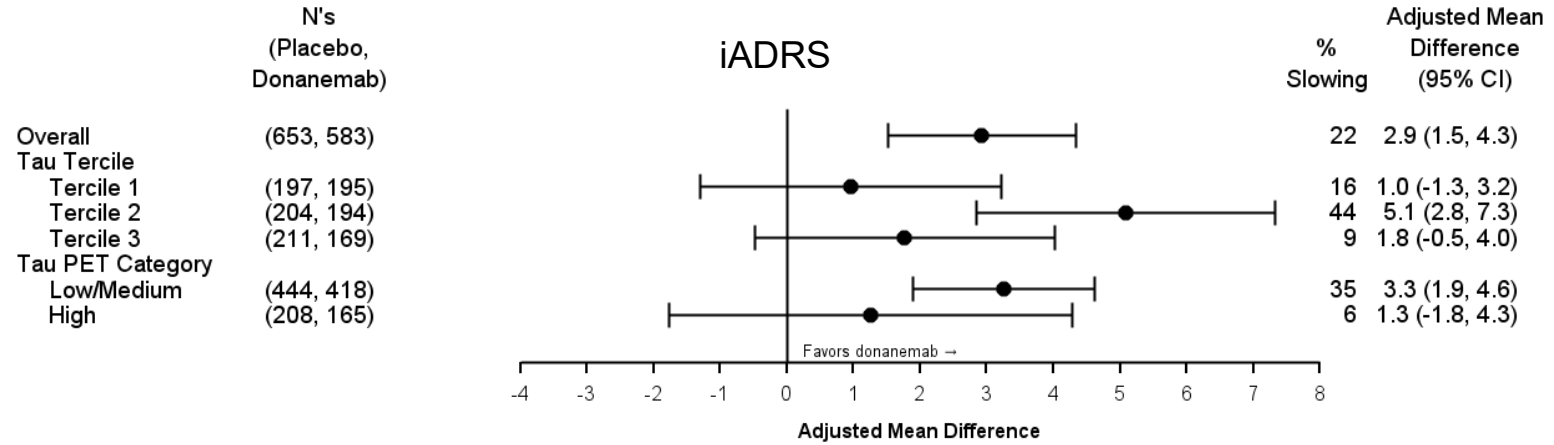
Tau PET Enrichment Strategy for AACI

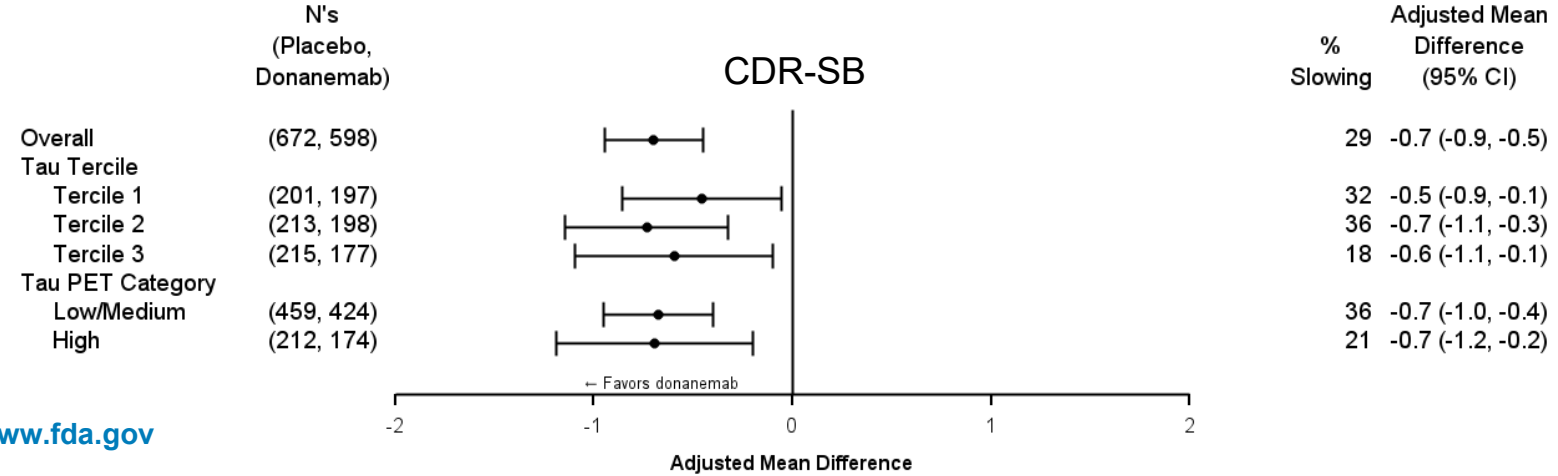
NO/VERY LOW TAU	LOW/MEDIUM TAU	HIGH TAU

• **Criteria**
  • SUVR<1.1 and visual assessment consistent with moderate AD
  • Visual assessment not consistent with AD pattern
 	
• **Minimal tau burden excluded from AACI as hypothesized to be:**
  • Likely to respond to treatment
  • Less likely to progress during study
	• **Criteria**
	  • 1.10≤SUVR≤1.46 and visual assessment consistent with advanced AD
	  • SUVR≤1.46 and visual assessment consistent with moderate AD
	
	• **Moderate tau burden enrolled in AACI as hypothesized to be:**
	  • Likely to respond to treatment
	  • Likely to progress during study
		• **Criteria**
		  • SUVR>1.46 and visual assessment consistent with moderate or advanced AD
		
		• **High tau burden enrolled in AACI as hypothesized to be:**
		  • Likely to respond to treatment, although lower than moderate tau
		  • More likely to progress during study

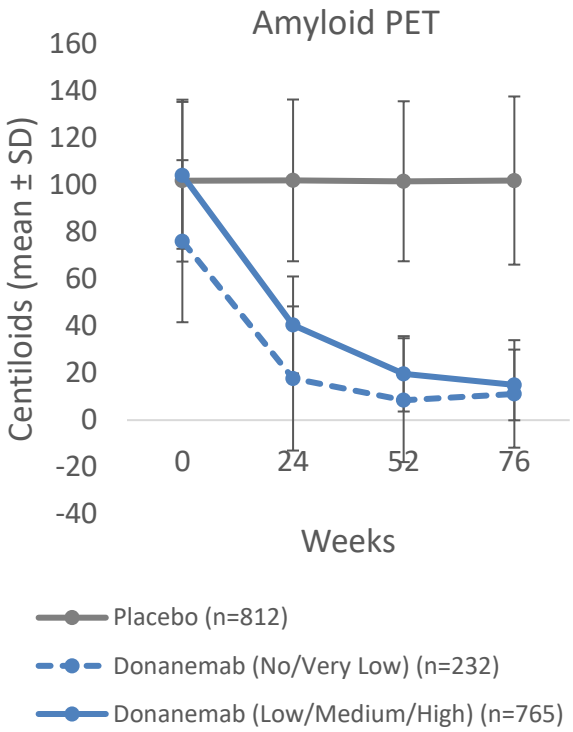
SUVR – Standardized Uptake Value Ratio

Treatment Effect by Baseline Tau in AACI

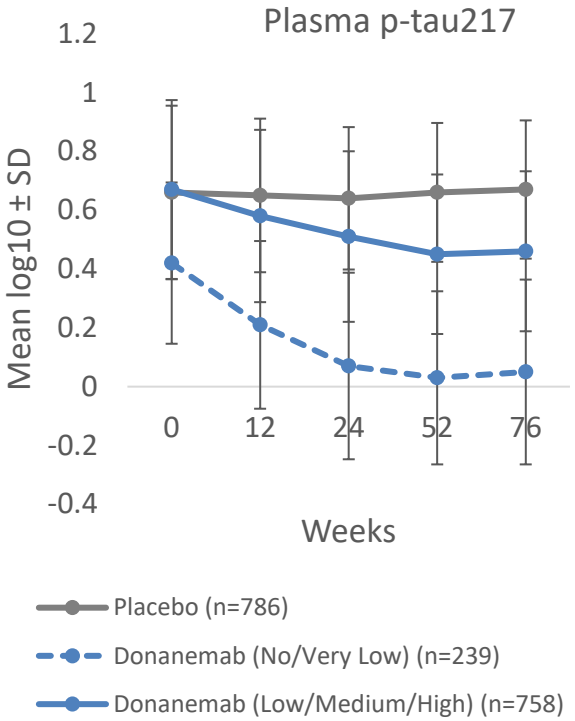


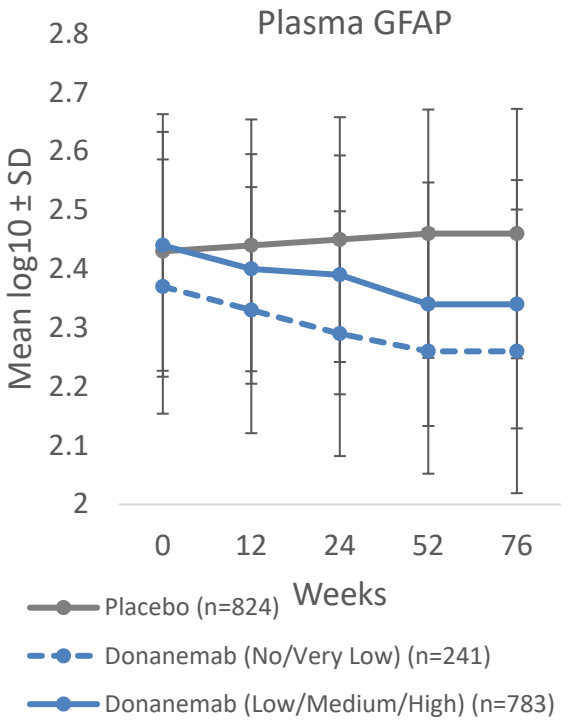


Reduction From Baseline in Amyloid PET in Patients With No/Very Low Tau in Study AACI Safety Addendum



Reduction From Baseline in Biomarkers in Patients With No/Very Low Tau in Study AACI Safety Addendum





GFAP– glial fibrillary acidic protein

Considerations Regarding Effectiveness in Patients With No or Very Low Tau Levels

- Most symptomatic, amyloid positive patients have some degree of tau pathology even if not detectable on tau PET, and course of disease is progressive for all tau levels
- Pharmacodynamic effect on amyloid plaque reduction appears to be independent of baseline tau
  - Reduction in amyloid plaque and other biomarkers demonstrated to be similar in subjects with no or very low tau compared to those with higher tau treated in the safety addendum
- Results of Study AACI suggest larger treatment effect (% slowing) in patients with low/medium tau compared to high tau in Study AACI subgroup analyses
- Treatment effect observed across range of baseline tau levels included in Study AACI
- Clinical benefit from reduction in amyloid plaques likely to be seen across baseline tau levels

Study AACI Dosing Regimen

- Titration
  - 700 mg every 4 weeks for the first 3 doses
  - 1400 mg every 4 weeks thereafter
- Dose switched to placebo
  - Based on amyloid PET levels measured at Weeks 24, 52, and 76
    - <11 Centiloids on PET at any single visit
    - ≥11 to <25 Centiloids on PET at 2 consecutive visits

Dosing in Study AACI and Amyloid Re-Accumulation

- The proportion of subjects meeting dose stopping criteria was 17%, 42%, and 60%, at Weeks 24, 52, and 76, respectively
- 29% of donanemab-treated subjects entering long-term extension were still receiving 1400 mg dose
- Upon dose cessation, amyloid began to re-accumulate at a mean rate of 2.8 Centiloids/year

Uncertainties Regarding Dose Cessation

- Relatively short off-treatment period during Study AACI
- Lack of appropriate comparator group
- Optimal Centiloid threshold for dose cessation
- Potential for re-initiation of dosing based on re-accumulation of amyloid

Efficacy Review Conclusions

- Overall, two positive adequate and well-controlled studies with consistent findings across endpoints
  - Study AACI provides strong and clinically meaningful support for the effectiveness of donanemab for treatment of Alzheimer's disease
    - Persuasive p-values on the primary endpoint and its components
    - Consistent results across multiple clinical and pharmacodynamic endpoints
  - Study AACG also provides evidence of effectiveness
    - Statistically significant results on primary endpoint of iADRS with numerical trends on components (ADAS-Cog, ADCS-iADL) and CDR-SB
- It appears reasonable to generalize the efficacy results from the population studied in Study AACI across the spectrum of tau burden, including patients with no or very low tau
- Residual uncertainty regarding cessation of dosing remains

Clinical Overview of Safety

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Clinical Safety Reviewer
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Center for Drug Evaluation and Research

Exposure to Donanemab Within the Safety Database

- Number of patients exposed to at least one dose of donanemab intravenously across the clinical development program: 2,885

Exposure at Proposed Dose[a]	Study AACI N=853	All-Donanemab Pool[b] N=2802
≥6 months	690 (81%)	1912 (68%)
≥12 months	486 (57%)	1057 (38%)
≥18 months	215 (25%)	432 (15%)

[a]Exposure is based on number of donanemab infusions received by a patient at the time 90-Day Safety Update.
[b]Includes Studies AACG, AACH Part B, the long-term extension period of Study AACI, Safety Addendum of Study AACI, and AACN-Dona

Mortality in AACI

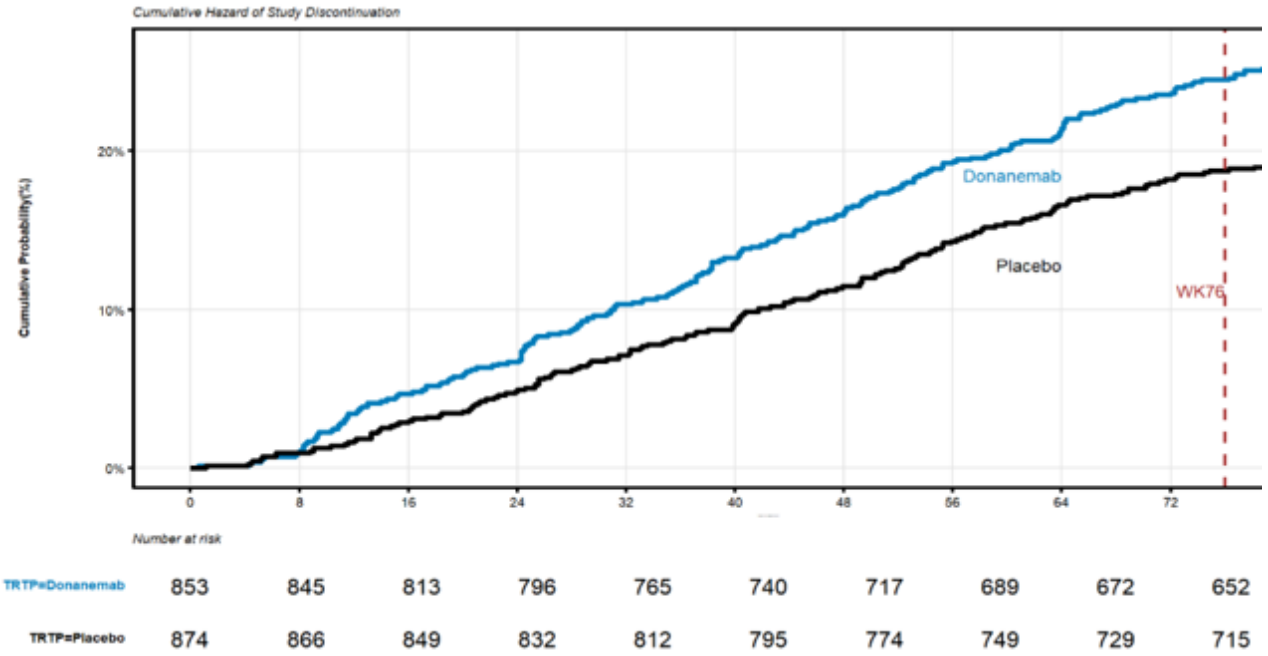
Variable	Donanemab N=853 n, (%[a])	Placebo N=874 n, (%[a])	Risk Difference (95% CI)
Mortality at 76 weeks	17 (2.2%)	10 (1.2%)	1.0% (-0.3%, 2.3%)
Non-ARIA mortality at 76 weeks	14 (1.8%)	10 (1.2%)	0.6% (-0.6%, 1.8%)

Source: FDA, Statistical Memo Addendum using SUBJINFO.XPT in SDN161
Abbreviations: ARIA, amyloid-related imaging abnormalities; CI, confidence interval.
[a]Kaplan-Meier estimates of cumulative incidence
[b]Hazard ratio estimate from Cox Proportional-Hazards model without covariate adjustment

Limitations to Analysis:

- Imbalance in early study discontinuation for donanemab (26%) vs placebo (20%)
- Vital status at Week 76 not captured for discontinuations

Time to Trial Discontinuation in Study AACI



Source: FDA, Statistical Memo Addendum

Adverse Events With Fatal Outcome in AACI

AE With Fatal Outcome	Donanemab N=853 n	Placebo N=874 n
ARIA-E	1	0
ARIA-E and ARIA-H	1	0
Intracerebral hemorrhage[a]	1	0
Subarachnoid hemorrhage	1	0
Dementia Alzheimer's type	1	1
Death	1	1
Covid-19[b]	2	1
Pneumonia	1	2
Sepsis	0	1
Retroperitoneal hemorrhage	1	0
Dehydration	1	0
Completed suicide	2	1
Pulmonary embolism	2	0
Respiratory arrest	1	0
Respiratory failure	1	0
Respiratory fume inhalation disorder	0	1
Arteriosclerosis	0	1
Myocardial infarction	0	1

[a] Occurring in the setting of ARIA-E and ARIA-H
[b] Includes Covid-19 pneumonia

Updated Mortality in AACI

- Missing vital status retrieved in 52% with unknown vital status at the time of the 90-Day Safety Update
- Additional 2 deaths in donanemab-treated patients and 5 deaths on placebo within 76 weeks

Variable	Donanemab N=853 n, (%[a])	Placebo N=874 n, (%[a])
Mortality at 76 weeks	19 (2.3%)	16 (1.9%)

Source: FDA, Statistical Memo Addendum using SUBJINFO.XPT in SDN161
[a]Kaplan-Meier estimates of cumulative incidence

- Limitations to analysis
  - Vital sign data obtained from publicly available information
  - ~ 10% of patients still had missing vital status
  - Information on cause of death lacking

Most Frequent Treatment-Emergent SAEs, Study AACI

Preferred Terms	Donanemab N=853 n (%)	Placebo N=874 n (%)
Any SAE	140 (16.4)	124 (14.2)
ARIA-E	13 (1.5)	0
Covid-19[a]	8 (0.9)	7 (0.8)
Pneumonia	5 (0.6)	3 (0.3)

[a] Includes Covid-19 pneumonia

Most Common Treatment-Emergent Adverse Events (TEAEs) in AACI

Preferred Term	Donanemab N=853 n (%)	Placebo N=874 n (%)
Patients with any TEAE	758 (89)	715 (82)
ARIA-H Microhemorrhage	217 (25)	100 (11)
Amyloid related imaging abnormality-edema/effusion	201 (24)	17 (2)
ARIA-H Superficial siderosis of central nervous system	125 (15)	23 (3)
Headache	115 (13)	86 (10)
Infusion related reaction	74 (9)	4 (0.5)

Events related to ARIA are based on ARIA events reported in the MRI dataset. Other adverse events are based on adverse events reported in the Adverse Event dataset.

Amyloid Related Imaging Abnormalities (ARIA)

- Monoclonal antibodies directed against aggregated forms of beta amyloid can cause ARIA, observed on brain magnetic resonance imaging (MRI).
- It is hypothesized that anti-Aβ antibodies accelerate breakdown and clearance of Aβ, which may disrupt vascular integrity and result in leakage into surrounding tissues with parenchymal or sulcal changes observed on MRI:
  - ARIA-E (edema): vasogenic edema or sulcal effusions
  - ARIA-H (hemosiderin deposition): microhemorrhage or superficial siderosis.

Amyloid Related Imaging Abnormalities (ARIA)

- ARIA can occur spontaneously in patients with AD or cerebral amyloid angiopathy (CAA)
- ARIA-H and ARIA-E can occur together.
- ARIA is usually asymptomatic, although serious and life-threatening events can infrequently occur. When present, reported symptoms associated with ARIA may include, headache, confusion, visual changes, dizziness, nausea, gait difficulty, and focal neurological deficits.

Incidence of ARIA and Intracerebral Hemorrhage > 1 cm in AACI

Events	Donanemab N=853 n (%)	Placebo N=874 n (%)
ARIA-E or ARIA-H	307 (36)	122 (14)
ARIA-E	201 (24)	17 (2)
Symptomatic ARIA-E	52 (6)	0
ARIA-H	263 (31)	111 (13)
Isolated ARIA-H	106 (12)	105 (12)
ARIA-H, Microhemorrhages	217 (25)	100 (11)
ARIA-H, Superficial Siderosis	125 (15)	23 (3)
Intracerebral hemorrhage > 1 cm	4 (0.5)	2 (0.2)

Incidence of ARIA and Cerebral Hemorrhage > 1 cm by ApoE ε4 Status in Study AACI

Event	Non-Carrier		Heterozygotes		Homozygotes	
	DON N=255 n (%)	PBO N=250 n (%)	DON N=452 n (%)	PBO N=474 n (%)	DON N=143 n (%)	PBO N=146 n (%)
ARIA-E or ARIA-H	63 (25)	29 (12)	164 (36)	60 (13)	79 (55)	32 (22)
ARIA-E	40 (16)	2 (0.8)	102 (23)	9 (2)	58 (41)	5 (3)
ARIA-H	48 (19)	27 (11)	142 (31)	54 (11)	72 (50)	30 (20)
Intracerebral hemorrhage > 1 cm[a]	1 (0.4)	0	3 (0.7)	1 (0.2)	0	0

DON: donanemab, PBO: placebo

[a]One placebo-treated patient with intracerebral hemorrhage > 1 cm had unknown ApoE ε4 carrier status

ARIA-H or Intracerebral Hemorrhage by Antithrombotic Use in AACI

Event	Donanemab		Placebo	
	AT use N=349 n (%)	No AT use N=504 n (%)	AT use N=361 n (%)	No AT use N=513 n (%)
ARIA-H	106 (30)	148 (29)	47 (13)	63 (12)
Intracerebral Hemorrhage > 1 cm	2 (0.6)	2 (0.4)	0	2 (0.4)

AT: Antithrombotic

Symptoms of ARIA Can Mimic Ischemic Stroke

- 70-year-old patient, ApoE ε3/ε4 carrier, screening MRI with focal lesions of white matter disease
- 7 days after the 5th dose of donanemab, developed headache and slurred speech; hospitalized for ischemic stroke
- Computed tomography (CT)/CT angiogram/CT perfusion of head/neck with no findings suggestive of ischemia or vessel blockages
- Tenecteplase was administered and altered mental status developed one hour later
- Repeat imaging obtained
  - CT scan showed multiple hemorrhages in the bilateral hemispheres
  - MRI with severe ARIA-E, superficial siderosis; macrohemorrhage in the left temporal, left occipital, left parietal, and right frontal lobes; and bilateral intraventricular hemorrhages
- The patient died due to bilateral intraparenchymal hemorrhage and acute hypoxic respiratory failure four days later

Symptoms of ARIA Can Mimic Ischemic Stroke

- If approved, the Division is considering the following recommendations for labeling:
  - Healthcare providers should be aware that ARIA can present with focal neurologic symptoms that can mimic stroke.
  - Patients who develop symptoms concerning for stroke may require a more extensive evaluation and MRI to assess the etiology of the symptoms.
  - Patients should carry a medical information card indicating that they are being treated with donanemab.
  - Healthcare providers should carefully consider the potential for ARIA and the potential benefits and risks when considering the use of a thrombolytic agent in a donanemab-treated patient with symptoms of stroke.

Cerebral Amyloid Angiopathy (CAA)

- CAA increases the risk for intracerebral hemorrhage and for ARIA.
- Up to 90% of patients with AD are reported to have some degree of underlying CAA;[1,2] risk of severe CAA is highest in ApoE ε4 homozygotes.[3,4]
- Findings suggestive of CAA include prior intracerebral hemorrhage greater than 1 cm, more than 4 microhemorrhages, more than 1 area of superficial siderosis, vasogenic edema, or severe white matter disease.
- Risk of donanemab use in patients with CAA is not well characterized.

1. Love S et al. Insights into the pathogenesis and pathogenicity of cerebral amyloid angiopathy. Frontiers in Bioscience 14, 4778-4792, January 1, 2009.
2. Jäkel L et al. Prevalence of cerebral amyloid angiopathy: A systematic review and meta-analysis. Alzheimers Dement. 2022 Jan;18(1):10-28.
3. Souza et al. Inflammatory Cerebral Amyloid Angiopathy: A Broad Clinical Spectrum. J Clin Neurol 2023;19(3):230-241.
4. Ringman JM et al. Cerebral Amyloid Angiopathy and influence of *APOE* Genotype in Persons with Pathologically Verified Alzheimer Disease. JAMA Neurol 2014; 71:878-883

Safety Summary and Conclusions

- ARIA, intracerebral hemorrhage, infusion-related reactions and hypersensitivity are the main safety signals associated with donanemab.
- Imbalance in mortality was observed that included fatalities related to ARIA and to intracerebral hemorrhage. No known mechanism regarding causality for other deaths.
- Risk of ARIA is higher in ApoE ε4 homozygotes compared to heterozygotes and noncarriers.
- Risk of ARIA and intracerebral hemorrhage in the presence of CAA or with antithrombotic use is not well characterized. Symptoms of ARIA may mimic ischemic stroke. Benefit-risk discussion needs to consider these uncertainties with the potential risks of use with antithrombotic or thrombolytic therapy.
- Risks and uncertainties can be described in prescribing information.
- Prescriber and patient education regarding ARIA, and surveillance for new or worsening neurological symptoms and follow-up with unscheduled MRIs, particularly in ApoE ε4 homozygotes or patients with other risk factors, may mitigate some risks of ARIA associated with donanemab.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