DAY 2
ABSTRACT 1

Donanemab in Early Symptomatic Alzheimer Disease **The TRAILBLAZER-ALZ 2 Randomized Clinical Trial**

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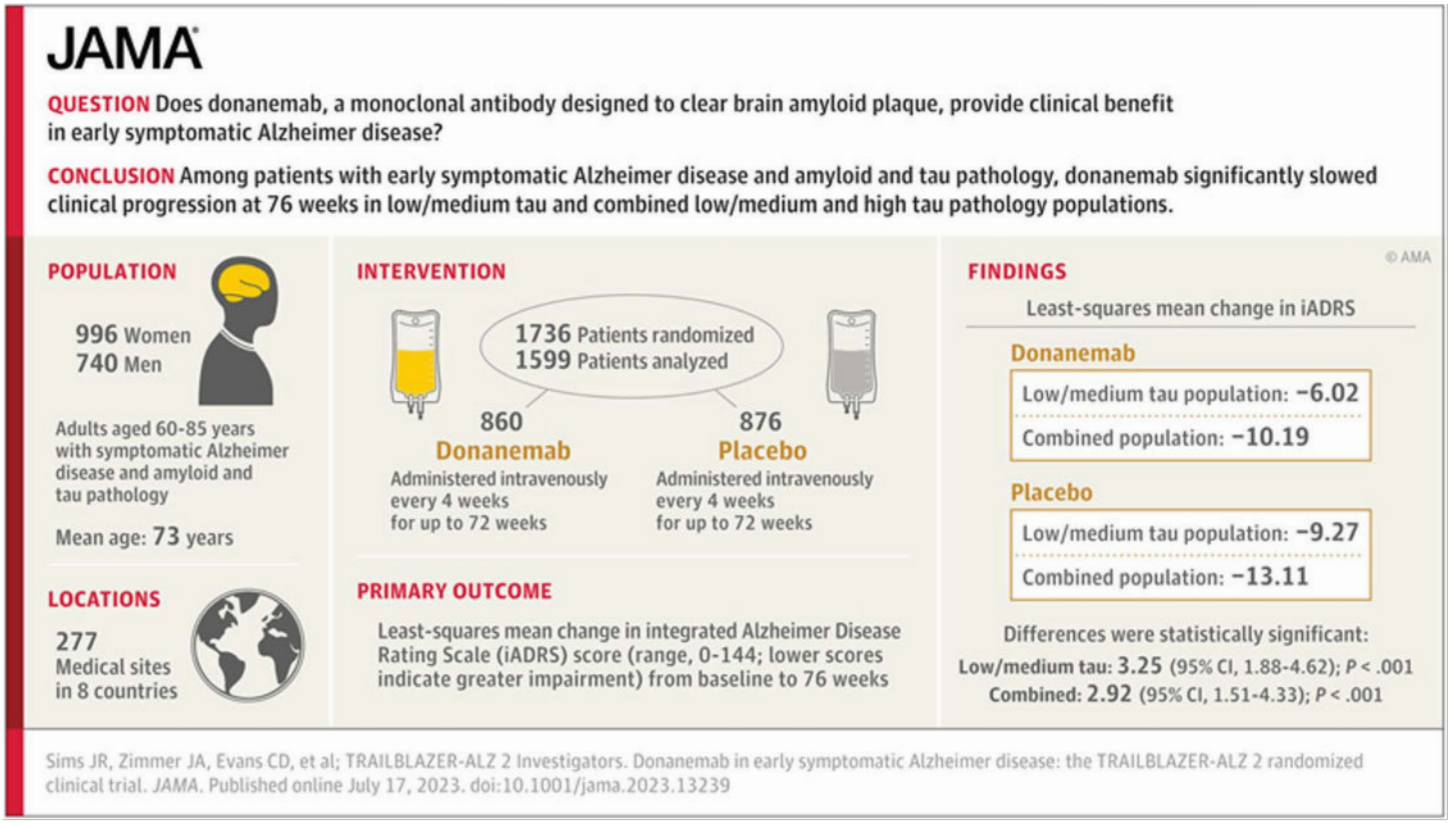

Editorial

Donanemab for Alzheimer Disease—Who Benefits and Who Is Harmed?

Jennifer J. Manly, PhD; Kacie D. Deters, PhD

Editorial

Amyloid-Targeting Monoclonal Antibodies for Alzheimer Disease

Gil D. Rabinovici, MD; Renaud La Joie, PhD

Editorial

Novel Alzheimer Disease Treatments and Reconsideration of US Pharmaceutical Reimbursement Policy

Meredith B. Rosenthal, PhD

Editorial

Ushering in a New Era of Alzheimer Disease Therapy

Eric W. Widera, MD; Sharon A. Brangman, MD; Nathaniel A. Chin, MD

KEY POINTS:

Question Does donanemab, a monoclonal antibody designed to clear brain amyloid plaque, provide clinical benefit in early symptomatic Alzheimer disease?

Findings In this randomized clinical trial that included 1736 participants with early symptomatic Alzheimer disease and amyloid and tau pathology, the least-squares mean change in the integrated Alzheimer Disease Rating Scale score (range, 0-144; lower score indicates greater impairment) at 76 weeks was −6.02 in the donanemab group and −9.27 in the placebo group for the low/medium tau population and −10.19 in the donanemab group and −13.11 in the placebo group in the combined study population, both of which were significant differences.

Meaning Among participants with early symptomatic Alzheimer disease and amyloid and tau pathology, donanemab treatment significantly slowed clinical progression at 76 weeks.

Abstract:

Importance There are limited efficacious treatments for Alzheimer disease.

Objective To assess efficacy and adverse events of donanemab, an antibody designed to clear brain amyloid plaque.

Design, Setting, and Participants Multicenter (277 medical research centers/hospitals in 8 countries), randomized, double-blind, placebo-controlled, 18-month phase 3 trial that enrolled 1736 participants with early symptomatic Alzheimer disease (mild cognitive impairment/mild dementia) with amyloid and low/medium or high tau pathology based on positron emission tomography imaging from June 2020 to November 2021 (last patient visit for primary outcome in April 2023).

Interventions Participants were randomized in a 1:1 ratio to receive donanemab (n = 860) or placebo (n = 876) intravenously every 4 weeks for 72 weeks. Participants in the donanemab group were switched to receive placebo in a blinded manner if dose completion criteria were met.

Main Outcomes and Measures The primary outcome was change in integrated Alzheimer Disease Rating Scale (iADRS) score from baseline to 76 weeks (range, 0-144; lower scores indicate greater impairment). There were 24 gated outcomes (primary, secondary, and exploratory), including the secondary outcome of change in the sum of boxes of the Clinical Dementia Rating Scale (CDR-SB) score (range, 0-18; higher scores indicate greater impairment). Statistical testing allocated α of .04 to testing low/medium tau population outcomes, with the remainder (.01) for combined population outcomes.

Results Among 1736 randomized participants (mean age, 73.0 years; 996 [57.4%] women; 1182 [68.1%] with low/medium tau pathology and 552 [31.8%] with high tau pathology), 1320 (76%) completed the trial. Of the 24 gated outcomes, 23 were statistically significant. The least-squares mean (LSM) change in iADRS score at 76 weeks was −6.02 (95% CI, −7.01 to −5.03) in the donanemab group and −9.27 (95% CI, −10.23 to −8.31) in the placebo group (difference, 3.25 [95% CI, 1.88-4.62]; P < .001) in the low/medium tau population and −10.2 (95% CI, −11.22 to −9.16) with donanemab and −13.1 (95% CI, −14.10 to −12.13) with placebo (difference, 2.92 [95% CI, 1.51-4.33]; P < .001) in the combined population. LSM change in CDR-SB score at 76 weeks was 1.20 (95% CI, 1.00-1.41) with donanemab

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Conclusions and Relevance Among participants with early symptomatic Alzheimer disease and amyloid and tau pathology, donanemab significantly slowed clinical progression at 76 weeks in those with low/medium tau and in the combined low/medium and high tau pathology population.

Trial Registration ClinicalTrials.gov Identifier: NCT04437511