

# Efficacy and Safety of Lanabecestat for Treatment of Early and Mild Alzheimer Disease

## The AMARANTH and DAYBREAK-ALZ Randomized Clinical Trials

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**IMPORTANCE** Alzheimer disease (AD) is a neurodegenerative disorder characterized by cognitive deterioration and impaired activities of daily living. Current treatments provide only minor symptomatic improvements with limited benefit duration. Lanabecestat, a brain-permeable inhibitor of human beta-site amyloid precursor protein–cleaving enzyme 1 (BACE1/β-secretase), was developed to modify the clinical course of AD by slowing disease progression.

**OBJECTIVE** To assess whether lanabecestat slows the progression of AD compared with placebo in patients with early AD (mild cognitive impairment) and mild AD dementia.

**DESIGN, SETTING, AND PARTICIPANTS** AMARANTH (first patient visit on September 30, 2014; last patient visit on October 4, 2018) and DAYBREAK-ALZ (first patient visit on July 1, 2016; last patient visit on September 28, 2018) were randomized, placebo-controlled, phase 2/3 and phase 3 clinical trials lasting 104 weeks and 78 weeks, respectively. AMARANTH and DAYBREAK-ALZ were multicenter, global, double-blind studies conducted at 257 and 251 centers, respectively, located in 15 and 18 countries or territories, respectively. A population-based sample of men and women aged 55 to 85 years who met National Institute on Aging–Alzheimer’s Association criteria for early AD or mild AD dementia was screened using cognitive assessments, and the presence of amyloid was confirmed. Patients were excluded for unstable medical conditions or medication use, significant cerebrovascular pathologic findings, or a history of vitiligo and/or current evidence of postinflammatory hypopigmentation. AMARANTH screened 6871 patients; 2218 (32.3%) were randomized, and 539 patients completed the study. DAYBREAK-ALZ screened 5706 patients; 1722 (30.2%) were randomized, and 76 patients completed the study.

**INTERVENTIONS** Patients were randomized (1:1:1) to once-daily oral doses of lanabecestat (20 mg), lanabecestat (50 mg), or placebo.

**MAIN OUTCOMES AND MEASURES** The primary outcome measure was change from baseline on the 13-item Alzheimer Disease Assessment Scale–cognitive subscale. Secondary outcomes included Alzheimer’s Disease Cooperative Study–Instrumental Activities of Daily Living Inventory, Clinical Dementia Rating, Functional Activities Questionnaire, Mini-Mental State Examination, and Neuropsychiatric Inventory. Efficacy analyses were conducted on the intent-to-treat population.

**RESULTS** Among 2218 AMARANTH patients, the mean (SD) age was 71.3 (7.1) years, and 1177 of 2218 (53.1%) were women. Among 1722 DAYBREAK-ALZ patients, the mean (SD) age was 72.3 (7.0) years, and 1023 of 1722 (59.4%) were women. Both studies were terminated early after futility analysis. There were no consistent, reproducible dose-related findings on primary or secondary efficacy measures. Psychiatric adverse events, weight loss, and hair color changes were reported in a higher percentage of patients receiving lanabecestat than placebo.

**CONCLUSIONS AND RELEVANCE** Treatment with lanabecestat was well tolerated and did not slow cognitive or functional decline.

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**A**lzheimer disease (AD) is manifested by cognitive deterioration and progressive impairment of activities of daily living.<sup>1</sup> The pathologic features of AD are characterized by the formation of amyloid plaques and neurofibrillary tangles.<sup>2</sup> Cleavage of amyloid precursor protein (APP) by proteases known as secretases ( $\beta$  and  $\gamma$ ) gives rise to the group of peptide fragments known as  $A\beta$ , the main components of amyloid plaques. Imbalance between production and clearance of  $A\beta$  leads to formation of  $A\beta$  plaques during early pathogenesis of the disease. Beta-site APP-cleaving enzyme 1 (BACE1/ $\beta$ -secretase) is a type 1 transmembrane aspartic acid protease that cleaves APP at the  $\beta$ -secretase site, after which APP is cleaved by  $\gamma$ -secretase to generate  $A\beta$  peptides.<sup>3,4</sup> Lanabecestat is a brain-permeable inhibitor of human BACE1 (nonselective for BACE1 vs BACE2) that has been shown to reduce levels of  $A\beta$ 1-40 and  $A\beta$ 1-42 in the brain, cerebrospinal fluid (CSF), and plasma in several animal models, as well as in human CSF and plasma.<sup>5-7</sup> Based on previous phase 1 data, it was estimated that the mean reduction in CSF  $A\beta$ 1-42 for the selected dose arms in both studies, lanabecestat, 20 mg, and lanabecestat, 50 mg, was approximately 55% and 75%, respectively.<sup>5</sup>

The primary objective of the AMARANTH and DAYBREAK-ALZ trials was to test the hypothesis that lanabecestat, administered orally at doses of 20 mg and 50 mg daily for 104 weeks and 78 weeks, respectively, would slow the decline of AD compared with placebo in patients with early AD (AMARANTH) and mild AD dementia (DAYBREAK-ALZ). Both studies were deemed to be futile at an interim analysis and terminated early. This article summarizes the results of the data available after early termination.

## Methods

### Study Design

AMARANTH was a phase 2/3, multicenter, randomized, 104-week, double-blind, placebo-controlled, global study of lanabecestat in patients with early AD, defined as the continuum of patients with mild cognitive impairment (MCI) attributable to AD and patients diagnosed as having mild AD dementia. Total planned enrollment was 2202. Patients who completed AMARANTH could elect to enter a separate 104-week delayed-start (DS) extension study,<sup>8</sup> AMARANTH-EXT.<sup>9</sup> DAYBREAK-ALZ was a phase 3, multicenter, randomized, double-blind, global study of lanabecestat in patients with mild AD dementia that included a 78-week placebo-controlled period, followed by a 78-week DS period; during the DS period, all patients receiving placebo were switched to lanabecestat.<sup>8</sup> Total planned enrollment was 1899. The full enrollment of DAYBREAK-ALZ was not achieved before the futility analysis. DAYBREAK-ALZ was initiated after the phase 2 portion of AMARANTH ended (after passing a safety interim), and AMARANTH formally entered into phase 3. Because of their early termination, only the results from the placebo-controlled periods of both studies are reported herein. Both studies included a 60-day screening period and a safety follow-up 4 to 6 weeks after treatment. The protocol,

### Key Points

**Question** Does lanabecestat, a potent inhibitor of the beta-site amyloid precursor protein-cleaving enzyme 1 (BACE1), slow the progression of early Alzheimer disease (AD) and mild AD dementia?

**Findings** In 2 global randomized clinical trials (AMARANTH [n = 2218] and DAYBREAK-ALZ [n = 1722]), daily lanabecestat at both doses tested (20 mg and 50 mg) failed to slow cognitive or functional decline compared with placebo.

**Meaning** In patients with early AD or mild AD dementia, lanabecestat was generally well tolerated but did not slow cognitive or functional decline.

patient information, consent form, and other relevant study documentation were approved by the ethics committees or institutional review boards of each site before study initiation. The study was conducted in accordance with ethical principles originating from the Declaration of Helsinki<sup>10</sup> and was consistent with good clinical practice and applicable regulatory requirements. Before enrollment, all patients provided written informed consent. The trial protocols are available in [Supplement 1](#). This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Patients with a florbetapir positron emission tomography (PET) scan or CSF sample conducted as part of the study screening process could participate in the florbetapir PET imaging and/or the CSF substudy. All randomized patients in both studies also had serial magnetic resonance imaging (MRI) of the brain.

### Patients, Randomization, and Blinding

**Table 1** summarizes the key inclusion and exclusion criteria for both studies. An interactive web and voice response system was used to randomize patients centrally. In AMARANTH, eligible patients were randomized 1:1:1 to once-daily oral doses of 20-mg lanabecestat, 50-mg lanabecestat, or placebo, stratified by disease status at baseline (MCI attributable to AD or mild AD). DAYBREAK-ALZ also incorporated equal randomization between the 3 treatment groups for the 78-week double-blind period.

In AMARANTH, the 20-mg lanabecestat, 50-mg lanabecestat, and placebo tablets were identical. In DAYBREAK-ALZ, the 20-mg lanabecestat and 50-mg lanabecestat tablets were not identical. Blinding of the study treatment was achieved using the double-dummy technique. In both studies, all patients, investigators, and sponsor staff were blinded to treatment allocation with limited exceptions as specified in the protocols. Study treatment was dispensed during site visits, and eligible patients were instructed to take study treatment once daily orally. Adherence to study treatment was assessed by direct questioning and by counting returned tablets at each visit. Patients who consumed at least 80% of their study treatment over the course of the study were considered to be adherent.

### Outcomes

The primary objective in both studies was to evaluate the efficacy of 20-mg lanabecestat and 50-mg lanabecestat

Table 1. Key Inclusion and Exclusion Criteria in AMARANTH and DAYBREAK-ALZ

Variable	AMARANTH	DAYBREAK-ALZ
Phase	2/3	3
Indication	Early AD (MCI due to AD and mild AD dementia)	Mild AD dementia
Secondary outcomes	FAQ, ADCS-iADL, CDR-SB, iADRS, MMSE, NPI, CDR global score	FAQ, ADCS-iADL, CDR-SB, iADRS, MMSE, NPI, CDR global score
Primary outcome measure	ADAS-Cog <sub>13</sub>	ADAS-Cog <sub>13</sub>
Target sample size	734 Per arm or 2202 total	633 Per arm or 1899 total
Power/effect size	>90% Power to detect 0.21 effect size (approximately 25% slowing), assumed 65% mild AD and 35% MCI	99.4% Power to detect 0.27 effect size on ADAS-Cog <sub>13</sub>
Key inclusion criteria		
Age, y	55-85	55-85
AD criteria	Mild AD: meet NIA-AA criteria with a CDR global score of 0.5 or 1, with memory box score $\geq$ 0.5 MCI: meet NIA-AA criteria with a CDR global score of 0.5, with memory box score $\geq$ 0.5	Mild AD: meet NIA-AA criteria with a CDR global score of 0.5 or 1, with memory box score $\geq$ 0.5
MMSE score	20-30	20-26
RBANS DMI	$\leq$ 85	NA
Study partner	Yes	Yes
Amyloid positive	Cerebrospinal fluid, florbetapir amyloid PET, or historical amyloid PET (florbetaben, florbetapir, flutemetamol, NAV-4694, PiB)	Cerebrospinal fluid, florbetapir amyloid PET, or historical amyloid PET
Key exclusion criteria		
Unstable medical conditions or medication use	Yes	Yes
MRI findings	>5 Microhemorrhages, significant cerebrovascular pathology, or other pathologies	>5 Microhemorrhages, significant cerebrovascular pathology, or other pathologies
QTcF, ms	>470	>470
Medical history	Vitiligo and/or current evidence of postinflammatory hypopigmentation or exposure to depigmenting agents	Vitiligo and/or current evidence of postinflammatory hypopigmentation

Abbreviations: AD, Alzheimer disease; ADAS-Cog<sub>13</sub>, 13-item Alzheimer Disease Assessment Scale-cognitive subscale; ADCS-iADL, Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living Inventory; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating-sum of boxes; FAQ, Functional Activities Questionnaire; iADRS, Integrated Alzheimer's Disease Rating Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NA, not applicable; NAV-4694, fluorine 18-labeled flutafuranol; NIA-AA, National Institute on Aging-Alzheimer's Association; NPI, Neuropsychiatric Inventory; PET, positron emission tomography; PiB, Pittsburgh compound B; QTcF, QT interval corrected using Fridericia's formula; RBANS DMI, Repeatable Battery for the Assessment of Neuropsychological Status Delayed Memory Index.

compared with placebo in slowing the decline of AD as measured by change from baseline to the end of double-blind, placebo-controlled periods on the 13-item Alzheimer Disease Assessment Scale-cognitive subscale (ADAS-Cog<sub>13</sub>).<sup>11,12</sup> The ADAS-Cog<sub>13</sub> measures severity of impairment in various cognitive domains (memory, language, orientation, praxis, and executive functioning). The scale has a score range of 0 to 85 points, with higher scores indicating worse performance. The scale is analyzed as a continuous measure.

Secondary objectives included efficacy evaluations of lanabecestat vs placebo on the change from baseline to the end of the placebo-controlled treatment periods on the following functional, cognitive, and clinical outcomes: Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living Inventory (ADCS-iADL),<sup>13,14</sup> Functional Activities Questionnaire (FAQ),<sup>15</sup> Integrated Alzheimer's Disease Rating Scale (iADRS),<sup>16</sup> Clinical Dementia Rating-sum of boxes (CDR-SB),<sup>17</sup> Neuropsychiatric Inventory (NPI),<sup>18,19</sup> and Mini-Mental State Examination (MMSE).<sup>20</sup>

In AMARANTH, a time-to-event analysis was performed to evaluate the efficacy of lanabecestat to prolong time in the current disease state. This was measured by the CDR global score.

Safety and tolerability of lanabecestat were evaluated in both studies using the following key assessments: spontaneously reported adverse events, laboratory tests, vital signs and

body weight, and physical examinations, including neurological examinations and electrocardiograms (ECGs). Additional safety assessments included eye examinations, dermatological examinations, MRI to examine for any possible amyloid-related imaging abnormalities, and administration of the Columbia-Suicide Severity Rating Scale (C-SSRS) to assess any potential suicidality.

Biomarker objectives included evaluation of the effect of lanabecestat on amyloid markers (CSF A $\beta$ 1-42 and A $\beta$ 1-40), amyloid burden (florbetapir PET), and hippocampal volume (MRI). Findings from markers of neurodegeneration (CSF total tau and phosphorylated tau) and soluble A $\beta$  precursor protein (sAPP $\alpha$  and sAPP $\beta$ ) are shown in eFigure 1 and eFigure 2 in Supplement 2.

### Statistical Analysis

Efficacy analyses were conducted in the intent-to-treat population, which included all randomized patients with a baseline and at least 1 postbaseline scale result. Safety was assessed in the safety population (patients who received  $\geq$ 1 dose of study treatment).

The sample sizes in AMARANTH and DAYBREAK-ALZ were calculated to yield greater than 90% power to detect an effect size of 0.21 and 0.27, respectively, in the change from the baseline ADAS-Cog<sub>13</sub> score for each active dose vs placebo. These effect sizes equate to a 2.9-point treatment

difference and 25% slowing of disease progression. The primary outcome measure, change from baseline until the end of the placebo-controlled period in the ADAS-Cog<sub>13</sub> score, was analyzed using a mixed model of repeated measures (MMRM) analysis, with the change from baseline at each scheduled postbaseline visit acting as the dependent variable. Secondary outcomes included ADCS-iADL, CDR, FAQ, MMSE, and NPI. Models included additional covariates for apolipoprotein E (APOE 4) status (carrier or noncarrier), baseline ADAS-Cog<sub>13</sub> total score, concomitant symptomatic AD treatments (yes or no), baseline age, country or territory, and baseline ADAS-Cog<sub>13</sub> total score by visit interaction. AMARANTH also included disease status at baseline. All efficacy MMRM analyses used an unstructured covariance matrix with the exception of the NPI, which used the heterogeneous Toeplitz structure. No adjustments for multiplicity were made.

A Kaplan-Meier analysis was used to compare the amount of time spent in each disease stage until progression to the next stage of disease (as measured by the CDR global score). A stratified log-rank test, stratified by disease severity, was used to compare active treatments with placebo.

All patients who received at least 1 dose of randomized study treatment were included in the safety analysis. Analyses of treatment-emergent adverse events, laboratory results, vital signs, MRI scans, skin and eye examinations, C-SSRS, and ECGs were performed.

Change in total CSF Aβ<sub>1-40</sub> and Aβ<sub>1-42</sub> was assessed by the least squares (LS) mean percentage change from baseline last observation carried forward. Florbetapir PET changes were assessed by analyzing the annualized LS mean change from baseline in florbetapir PET standardized uptake value ratio (SUVr) (with cerebellum as the reference region) and the LS mean change from baseline to end point using Centiloid units.<sup>21</sup> Hippocampal volume changes were assessed by annualizing LS mean change. The LS mean changes were computed using an analysis of covariance model with disease status at baseline (AMARANTH only), baseline biomarker reading, age at baseline, and treatment as model terms; volumetric MRI also includes intracranial volume as a baseline covariate in model changes.

An independent external data monitoring committee reviewed unblinded data during the conduct of the studies. Statistical analyses were performed using a software program (SAS, version 9.4; SAS Institute Inc). All hypotheses were tested at a 2-sided .05 significance level. No adjustments for multiple comparisons were made.

## Results

### Patient Disposition and Baseline Characteristics

Among 2218 AMARANTH patients, the mean (SD) age was 71.3 (7.1) years, and 1177 of 2218 (53.1%) were women. Among 1722 DAYBREAK-ALZ patients, the mean (SD) age was 72.3 (7.0) years, and 1023 of 1722 (59.4%) were women. In AMARANTH, of the 6871 patients who were screened, 2218 (32.3%) met study eligibility criteria and were enrolled and randomized between September 30, 2014, and September 29, 2017; the last patient visit

was on October 4, 2018, and 539 patients completed the study. In DAYBREAK-ALZ, 1722 of 5706 patients (30.2%) were enrolled and randomized between July 1, 2016, and June 11, 2018; the last patient visit was on September 28, 2018, and 76 patients completed the study. Patients were recruited from 257 centers in 15 countries or territories in AMARANTH and from 251 centers in 18 countries or territories in DAYBREAK-ALZ (eAppendix in Supplement 2). A population-based sample of men and women aged 55 to 85 years who met National Institute on Aging-Alzheimer's Association criteria for early AD or mild AD dementia was screened using cognitive assessments, and the presence of amyloid was determined by means amyloid PET scan or Aβ<sub>1-42</sub> measurements in CSF. Patients were excluded for unstable medical conditions or medication use, significant cerebrovascular pathologic findings, or a history of vitiligo and/or current evidence of postinflammatory hypopigmentation. Top reasons for patient exclusion at screening for both studies are summarized in eTable 1 and eTable 2 in Supplement 2. On June 12, 2018, the study sponsor announced that both studies would be discontinued early for futility. At the time of announcement of discontinuation, AMARANTH was fully enrolled and approximately 16 months from completion, and DAYBREAK-ALZ was approximately 90% (1722 of 1899) enrolled. As a result, most discontinuations from both studies were attributable to early termination by the sponsors (Figure 1).

Baseline demographics and clinical baseline characteristics are summarized in Table 2. Across treatment groups in both studies, patient baseline demographics were well balanced with regard to sex, age, race, educational level, body mass index, employment status, family history of AD, and acetylcholinesterase inhibitor use. Baseline imbalances were noted for proportion of patients with Hispanic/Latino ethnicity in AMARANTH and for APOE 4 carrier status in DAYBREAK-ALZ. The mean baseline scores for the primary outcome measure of ADAS-Cog<sub>13</sub> and all the secondary outcome measures were well balanced across treatment groups in both studies.

Adherence was uniformly high (≥97%) across the 2 studies and all treatment arms. The proportion of patients taking at least 80% of their study treatment was 2165 of 2209 (98.0%) for AMARANTH and 1675 of 1714 (97.7%) for DAYBREAK-ALZ.

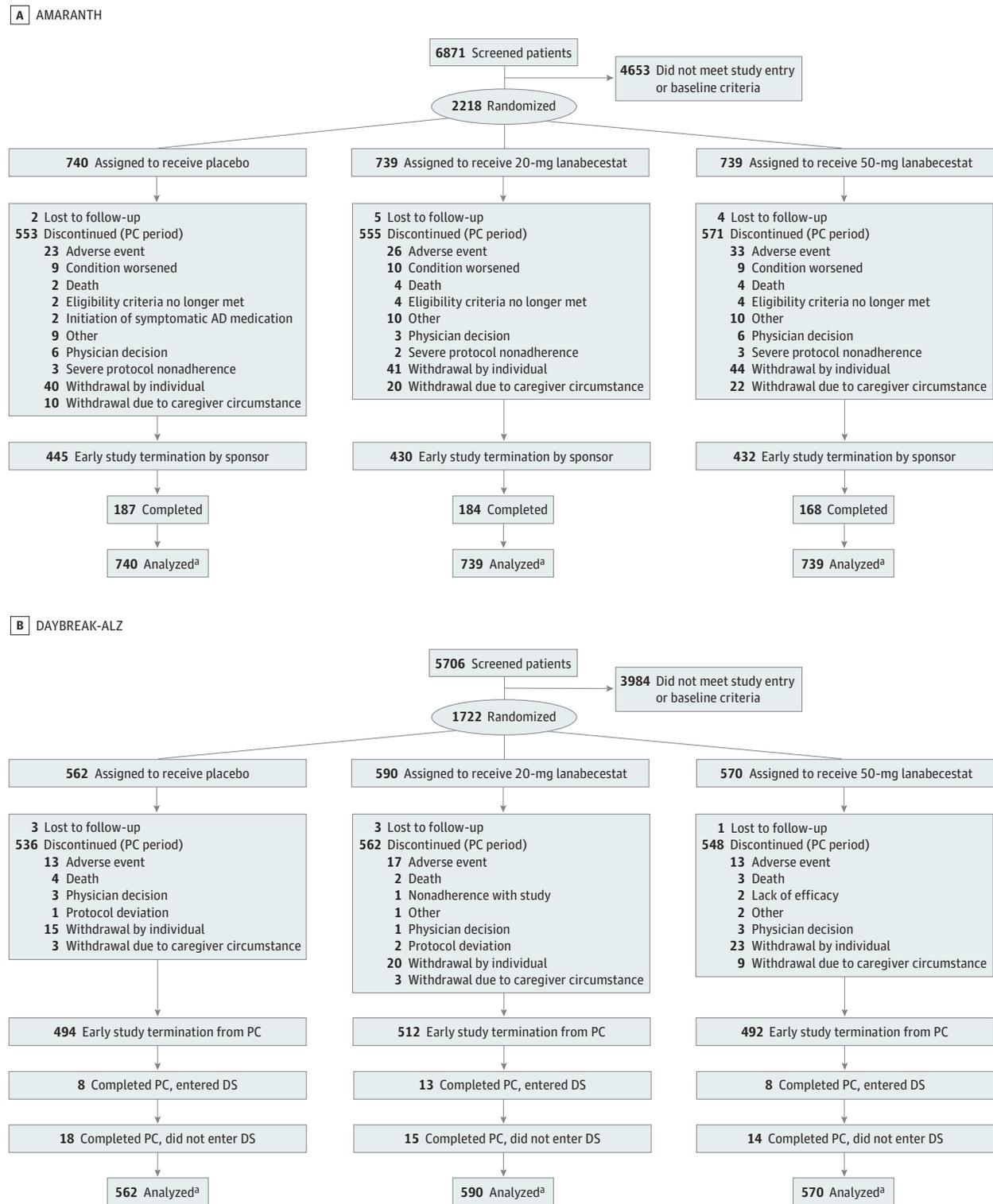
### Primary and Secondary Efficacy Analyses

The LS mean changes from baseline in the ADAS-Cog<sub>13</sub>, ADCS-iADL, and CDR-SB across 104 weeks (AMARANTH) and 78 weeks (DAYBREAK-ALZ) of the placebo-controlled period are shown in Figure 2. The MMRM output for the primary outcome measure is listed in eTable 3 in Supplement 2. No dose-related differences were consistently observed with 20-mg lanabecestat or 50-mg lanabecestat compared with placebo on these outcome measures. The LS mean changes over time for both studies on the MMSE, iADRS, FAQ, and NPI are shown in eFigure 3 in Supplement 2. As demonstrated by the Kaplan-Meier estimate, lanabecestat did not prolong time in each disease state in AMARANTH (censored log-rank *P* = .76) (eFigure 4 in Supplement 2).

### Safety and Tolerability

Because of differences in planned study durations and early termination of both studies, the total exposure in AMARANTH

Figure 1. CONSORT Diagrams of Study Flow



A and B, Most patients did not enter the delayed-start (DS) period because of early study termination. AD indicates Alzheimer disease; CONSORT, Consolidated Standards of Reporting Trials; PC, placebo-controlled.

<sup>a</sup> Intent-to-treat population.

Table 2. Characteristics of Patients at Baseline

Variable	AMARANTH			DAYBREAK-ALZ		
	Placebo (n = 740)	20-mg Lanabecestat (n = 739)	50-mg Lanabecestat (n = 739)	Placebo (n = 562)	20-mg Lanabecestat (n = 590)	50-mg Lanabecestat (n = 570)
<b>Demographics</b>						
Women, No. (%)	398 (53.8)	395 (53.5)	384 (52.0)	348 (61.9)	335 (56.8)	340 (59.6)
Age, mean (SD), y	71.4 (6.9)	71.2 (7.5)	71.2 (7.0)	72.1 (7.1)	72.3 (7.0)	72.6 (7.0)
Race/ethnicity, No. (%) <sup>a</sup>						
Asian	85 (11.5)	85 (11.5)	102 (13.8)	64 (11.4)	76 (12.9)	69 (12.1)
Black or African American	5 (0.7)	5 (0.7)	6 (0.8)	4 (0.7)	5 (0.8)	9 (1.6)
White	598 (80.8)	609 (82.4)	593 (80.2)	387 (68.9)	398 (67.5)	389 (68.2)
Other <sup>b</sup>	52 (7.0)	40 (5.4)	38 (5.1)	107 (19.0)	111 (18.8)	103 (18.1)
Hispanic/Latino, No./total No. (%)	43/669 (6.4)	26/676 (3.8)	24/668 (3.6)	53/469 (11.3)	45/487 (9.2)	55/478 (11.5)
Educational level ≥13 y, No./total No. (%)	397/740 (53.6)	400/738 (54.2)	425/739 (57.5)	307/562 (54.6)	324/590 (54.9)	318/569 (55.9)
BMI, mean (SD)	25.4 (4.3)	25.2 (4.3)	25.2 (4.6)	25.6 (4.6)	25.7 (4.3)	25.4 (4.6)
Full-time employment status, No./total No. (%)	66/737 (9.0)	72/736 (9.8)	77/733 (10.5)	20/562 (3.6)	27/589 (4.6)	19/569 (3.3)
APOE 4 carrier, No./total No. (%)	494/739 (66.8)	511/737 (69.3)	517/739 (70.0)	397/556 (71.4)	387/586 (66.0)	367/564 (65.1)
First-degree family history of AD, No. (%)	305 (41.2)	312 (42.2)	328 (44.4)	209 (37.2)	195 (33.1)	186 (32.6)
AChEI use, No. (%)	495 (66.9)	489 (66.2)	508 (68.7)	372 (66.2)	389 (65.9)	385 (67.5)
<b>Scale score, mean (SD)</b>						
ADAS-Cog <sub>13</sub>	28.6 (7.9)	29.0 (7.7)	28.5 (8.2)	30.4 (7.9)	30.6 (8.3)	30.6 (8.5)
ADCS-ADL	67.5 (7.7)	67.3 (7.6)	67.3 (7.4)	65.9 (8.3)	65.5 (8.2)	65.8 (8.7)
ADCS-iADL	48.9 (7.2)	48.7 (7.1)	48.7 (7.0)	47.4 (7.7)	47.0 (7.5)	47.3 (7.9)
ADCS-bADL	18.7 (0.9)	18.6 (1.0)	18.6 (1.0)	18.5 (1.2)	18.5 (1.3)	18.5 (1.4)
iADRS	105.3 (12.1)	104.6 (12.2)	105.2 (12.4)	101.9 (13.1)	101.5 (12.3)	101.7 (13.3)
MMSE	23.8 (2.6)	23.7 (2.6)	23.7 (2.6)	22.8 (1.9)	22.9 (1.8)	22.8 (1.9)
CDR-SB	3.6 (1.5)	3.6 (1.5)	3.6 (1.5)	3.5 (1.4)	3.6 (1.5)	3.7 (1.6)
RBANS total score	65.5 (11.8)	65.5 (11.5)	66.2 (11.6)	63.3 (12.1)	63.3 (12.5)	63.3 (11.4)
RBANS DMI	55.0 (13.1)	54.8 (13.2)	55.8 (13.8)	53.4 (14.8)	53.2 (15.1)	54.0 (14.6)
FAQ	9.2 (6.1)	9.5 (6.1)	9.1 (5.9)	10.5 (6.5)	10.8 (6.2)	10.8 (6.5)

Abbreviations: AChEI, acetylcholinesterase inhibitor; AD, Alzheimer disease; ADAS-Cog<sub>13</sub>, 13-item Alzheimer Disease Assessment Scale-cognitive subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living; ADCS-bADL, basic items of the Alzheimer's Disease Cooperative Study; ADCS-iADL, Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living Inventory; APOE 4, apolipoprotein E; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CDR-SB, Clinical Dementia Rating-sum of boxes; FAQ, Functional Activities Questionnaire; iADRS, Integrated Alzheimer's Disease Rating Scale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory;

RBANS DMI, Repeatable Battery for the Assessment of Neuropsychological Status Delayed Memory Index.

<sup>a</sup> The investigator classified individuals by patient direct questioning (self-report of the individual). The study sponsor provided predefined options for race and ethnicity to the investigator. Race and ethnicity were assessed to characterize the study population and to allow for post hoc exploratory analyses.

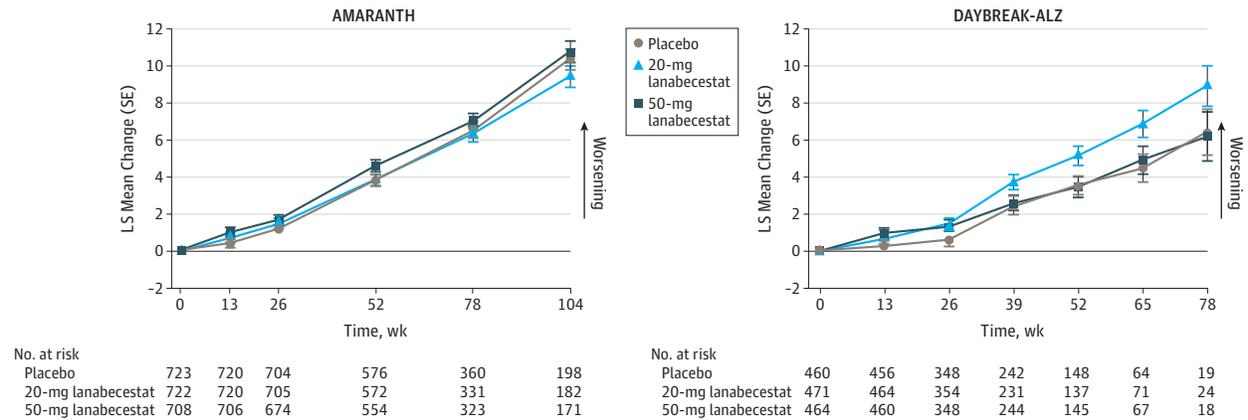
<sup>b</sup> Includes other and missing for AMARANTH and American Indian/Alaska native, Native Hawaiian or other Pacific Islander, multiple, and missing for DAYBREAK-ALZ.

and DAYBREAK-ALZ was 3027 total patient-years and 1121 total patient-years, respectively. An overview of safety observations is summarized in Table 3. The incidence of deaths (range, 0.3% [2 of 738] to 0.9% [5 of 558]) was similar across treatment groups in both studies, with 1 death in each study deemed to be related to lanabecestat by the investigator. In AMARANTH, the incidence of patient discontinuations from the study or study treatment because of adverse events was greater in the 50-mg lanabecestat group (6.7% [49 of 735]) compared with the placebo group (4.2% [31 of 738]). The proportion of patients with at least 1 serious adverse event overall and the proportion of patients with at least 1 serious adverse event in the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) of psychiatric disorders were numerically greater in the 50-mg lanabece-

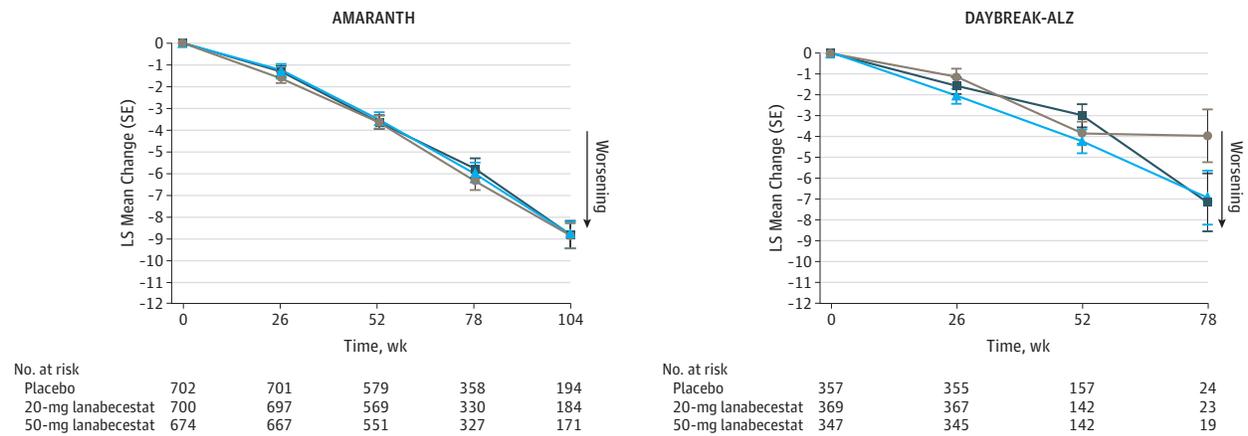
stat group compared with the placebo group in AMARANTH, whereas treatment groups were similar in DAYBREAK-ALZ. However, in both studies, the proportion of patients with at least 1 treatment-emergent adverse event in the psychiatric disorders SOC was numerically greater in both lanabecestat groups compared with the placebo group. In the psychiatric disorders SOC, anxiety and depression (the MedDRA preferred terms) were among the most common treatment-emergent adverse events (Table 3). In addition, the incidence of hair color changes (the MedDRA preferred term) was greater in the 50-mg lanabecestat group (and the 20-mg lanabecestat group in AMARANTH) compared with the placebo group and was most often mild in severity. In DAYBREAK-ALZ, in which greater than expected hair graying or whitening was specifically queried as part of the

Figure 2. Change in Outcome Scores From Baseline in AMARANTH and DAYBREAK-ALZ

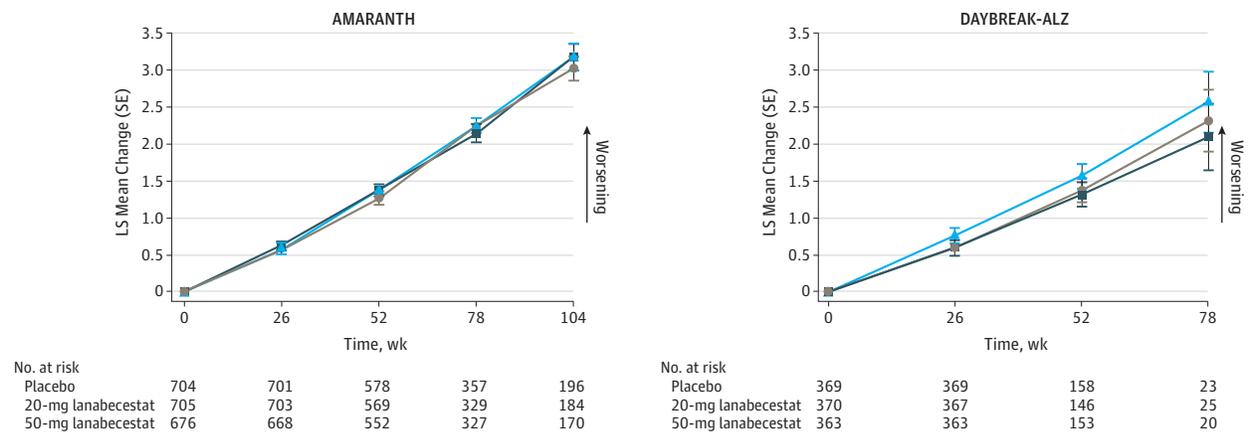
**A** ADAS-Cog<sub>13</sub> (primary outcome)



**B** ADCS-iADL



**C** CDR-SB



A-C, Results are presented as least squares (LS) mean (SE) change from baseline on the 13-item Alzheimer Disease Assessment Scale–cognitive subscale (ADAS-Cog<sub>13</sub>) (higher scores indicate greater cognitive impairment), the Alzheimer’s Disease Cooperative Study–Instrumental Activities of Daily Living Inventory (ADCS-iADL) (lower scores indicate greater functional impairment), and Clinical Dementia Rating–sum of boxes (CDR-SB) (higher scores indicate greater cognitive/functional impairment).

Table 3. Exposure, Deaths, SAEs, Discontinuations Because of Adverse Events, and TEAEs<sup>a</sup>

Variable	AMARANTH			DAYBREAK-ALZ		
	Placebo (n = 738) <sup>b</sup>	20-mg Lanabecestat (n = 736) <sup>b</sup>	50-mg Lanabecestat (n = 735) <sup>b</sup>	Placebo (n = 558) <sup>b</sup>	20-mg Lanabecestat (n = 588) <sup>b</sup>	50-mg Lanabecestat (n = 568) <sup>b</sup>
Exposure, No. (%)						
Time, mean (SD), d	512 (189)	501 (189)	488 (200)	247 (147)	231 (147)	239 (146)
Total patient-years	1034.2	1010.4	982.3	377.2	371.7	371.8
Deaths, No. (%)	2 (0.3)	4 (0.5)	4 (0.5)	5 (0.9)	2 (0.3)	3 (0.5)
Deaths related to treatment, No. (%) <sup>c</sup>						
Cognitive disorder	0	0	1 (0.1)	0	0	0
Sudden cardiac death	0	0	0	0	1 (0.2)	0
SAEs, No. (%)	108 (14.6)	117 (15.9)	147 (20.0)	50 (9.0)	50 (8.5)	46 (8.1)
Most common SAEs, No. (%) <sup>d</sup>						
Fall	6 (0.8)	8 (1.1)	4 (0.5)	1 (0.2)	3 (0.5)	5 (0.9)
Syncope	2 (0.3)	6 (0.8)	7 (1.0)	3 (0.5)	3 (0.5)	3 (0.5)
Dehydration	1 (0.1)	4 (0.5)	5 (0.7)	0	2 (0.3)	1 (0.2)
Chest pain	1 (0.1)	4 (0.5)	4 (0.5)	0	1 (0.2)	0
Delirium	1 (0.1)	2 (0.3)	5 (0.7)	1 (0.2)	1 (0.2)	2 (0.4)
Influenza	0	2 (0.3)	4 (0.5)	0	0	0
Depression	0	0	4 (0.5)	0	0	0
Discontinuation from study or study treatment because of an AE, No. (%)	31 (4.2)	34 (4.6)	49 (6.7)	19 (3.4)	18 (3.1)	16 (2.8)
TEAEs, No. (%)	621 (84.1)	652 (88.6)	642 (87.3)	331 (59.3)	375 (63.8)	354 (62.3)
TEAEs related to study treatment, No. (%) <sup>c</sup>	113 (15.3)	163 (22.1)	172 (23.4)	65 (11.6)	94 (16.0)	102 (18.0)
Most common TEAEs, No. (%) <sup>e</sup>						
Fall	73 (9.9)	75 (10.2)	76 (10.3)	22 (3.9)	34 (5.8)	39 (6.9)
Nasopharyngitis	60 (8.1)	78 (10.6)	76 (10.3)	23 (4.1)	12 (2.0)	19 (3.3)
Diarrhea	39 (5.3)	63 (8.6)	54 (7.3)	17 (3.0)	29 (4.9)	29 (5.1)
Anxiety	34 (4.6)	57 (7.7)	48 (6.5)	12 (2.2)	15 (2.6)	14 (2.5)
Dizziness	43 (5.8)	43 (5.8)	52 (7.1)	24 (4.3)	22 (3.7)	19 (3.3)
Depression	31 (4.2)	36 (4.9)	48 (6.5)	18 (3.2)	16 (2.7)	19 (3.3)
Nausea	32 (4.3)	33 (4.5)	41 (5.6)	20 (3.6)	19 (3.2)	19 (3.3)
Cough	25 (3.4)	46 (6.3)	25 (3.4)	10 (1.8)	16 (2.7)	14 (2.5)
Other safety findings of interest, No./total No. (%) <sup>f</sup>						
SAEs in psychiatric disorders SOC	8 (1.1)	10 (1.4)	20 (2.7)	6 (1.1)	4 (0.7)	6 (1.1)
TEAEs in psychiatric disorders SOC	181 (24.5)	220 (29.9)	246 (33.5)	74 (13.3)	87 (14.8)	98 (17.3)
Hair color changes <sup>g</sup>	1 (0.1)	15 (2.0)	21 (2.9)	0	2 (0.3)	15 (2.6)
Weight decrease $\geq 7\%$	93/731 (12.7)	154/728 (21.2)	180/723 (24.9)	34/539 (6.3)	54/570 (9.5)	79/545 (14.5)

Abbreviations: AE, adverse event; SAEs, serious adverse events; SOC, system order class; TEAEs, treatment-emergent adverse events.

<sup>a</sup> Adverse events are coded in Medical Dictionary for Regulatory Activities 21.1.

<sup>b</sup> Number of randomized patients who received at least one dose of either 20-mg lanabecestat or 50-mg lanabecestat postrandomization.

<sup>c</sup> As judged by investigator.

<sup>d</sup> By preferred term ( $\geq 0.5\%$  in a lanabecestat group and with greater incidence

in a lanabecestat group than a placebo group in  $\geq 1$  study).

<sup>e</sup> By preferred term ( $\geq 5\%$  in a lanabecestat group and with greater incidence in a lanabecestat group than a placebo group in  $\geq 1$  study).

<sup>f</sup> Based on beta-site amyloid precursor protein–cleaving enzyme 1 inhibitor toxicology or clinical data.<sup>8,22</sup>

<sup>g</sup> Medical Dictionary for Regulatory Activities preferred term.

dermatological examination, treatment-emergent hair hypopigmentation was greater in the 50-mg lanabecestat group (3.8% [19 of 497]) compared with the placebo group (1.0% [5 of 494]).

Weight decrease of at least 7% from baseline at any time over the course of the studies occurred at a greater incidence in both studies in the lanabecestat groups compared with the placebo groups. Comparing patients who completed week 104

of the AMARANTH trial, the mean (SD) weight loss was 0 (4.7) kg for placebo,  $-0.8$  (4.6) kg for the 20-mg lanabecestat group, and  $-1.9$  (5.2) kg for the 50-mg lanabecestat group. No other pattern of potentially clinically significant vital signs, laboratory values, or ECG parameters was observed in either study.

Across the studies, 2 patients met criteria for alanine aminotransferase at least 3 times the upper limit of normal and

total bilirubin at least 2 times the upper limit of normal. In one occurrence, not attributed to study drug, the patient was diagnosed as having pancreatic adenocarcinoma approximately 4 months after initiating lanabecestat, 50 mg, daily. The other occurrence was in a patient receiving lanabecestat, 20 mg, for approximately 1 year and was attributed by the investigator to study drug and possibly a concomitant medication (solifenacin succinate, a muscarinic receptor antagonist) and was confounded by alcohol use.

No notable differences were consistently observed across both studies in suicidal ideation or behavior among each lanabecestat treatment group and placebo, as assessed using the C-SSRS (eTable 4 in Supplement 2). In both studies, based on MRI review by a central vendor, the incidence of the amyloid-related imaging abnormalities of edema or effusions and the increase in amyloid-related imaging abnormalities of hemorrhage or hemosiderin deposition were similar among each lanabecestat group and the placebo group (eTable 5 in Supplement 2). No new safety concerns were observed across the follow-up periods of the 2 studies.

### Biomarkers

In AMARANTH, lanabecestat produced substantial dose-related reductions in CSF A $\beta$ 1-40 concentration (58.0% and 73.3% for 20 mg and 50 mg, respectively) and A $\beta$ 1-42 concentration (51.3% and 65.5% for 20 mg and 50 mg, respectively) (eFigure 5 in Supplement 2). For CSF A $\beta$ 1-40, the baseline mean (SD) concentration was 18.85 (6.20) for placebo, 17.25 (5.90) for 20-mg lanabecestat, and 17.40 (5.43) for 50-mg lanabecestat. For CSF A $\beta$ 1-42, the baseline mean (SD) concentration was 603.69 (223.43) for placebo, 602.80 (213.39) for 20-mg lanabecestat, and 599.56 (180.75) for 50-mg lanabecestat. For DAYBREAK-ALZ, insufficient postdose CSF samples were available to allow for a meaningful analysis. In both studies, the annualized LS mean change from baseline of florbetapir PET scan using SUVr was significantly greater with lanabecestat (20 mg and 50 mg) compared with placebo (eFigure 6 in Supplement 2). In AMARANTH, the LS mean (SE) Centiloid change over 2 years was significantly greater with lanabecestat (20 mg and 50 mg) compared with placebo (-13.7 [2.6] and -17.7 [2.7] Centiloids, respectively). However, in DAYBREAK-ALZ, 10 or fewer patients per group had an end-point PET scan, and there were no significant differences between either lanabecestat group and the placebo group (eFigure 7 in Supplement 2). These mean (SE) data for lanabecestat (20 mg and 50 mg, respectively) compared with placebo were -2.2 (13.8) Centiloids ( $P = .87$ ) and -15.2 (15.4) Centiloids ( $P = .34$ ), respectively.

Significantly greater hippocampal volume loss was observed in AMARANTH with the lanabecestat groups (-0.52% and -0.48% for the 20-mg group and 50-mg group, respectively) compared with the placebo group but not in DAYBREAK-ALZ. The mean (SD) annualized change in hippocampal volume is -204.51 (142.63) for placebo, -239.53 (141.90) for 20-mg lanabecestat, and -228.23 (150.18) for 50-mg lanabecestat. The annualized percentage change in volume is -0.52% for 20-mg lanabecestat vs placebo and -0.48% for 50-mg lanabecestat vs placebo. These results are summarized in eFigure 8 and eTable 6 in Supplement 2.

## Discussion

In AMARANTH and DAYBREAK-ALZ, lanabecestat did not slow cognitive or functional decline of AD compared with placebo. Of note, the primary efficacy outcome measure showed numerical worsening at certain time points for the lanabecestat treatment arms, although no clear pattern was discernible between the 2 studies. It is unlikely that this observation was clinically meaningful because none of the functional scales reflected this pattern. In both studies, lanabecestat was generally well tolerated. Treatment-emergent psychiatric adverse events were numerically greater in lanabecestat treatment groups compared with placebo and were consistent with dose dependence. Lanabecestat exposure was also associated with hair color changes and weight loss. In AMARANTH, lanabecestat produced substantial dose-related reductions in CSF A $\beta$ 1-40 and A $\beta$ 1-42 concentrations. Furthermore, in AMARANTH, lanabecestat (20 mg and 50 mg) was associated with greater reduction from baseline in  $\beta$ -amyloid neuritic plaque density compared with placebo, as well as greater hippocampal volume loss.

AMARANTH and DAYBREAK-ALZ trials were designed to recruit 2 different patient populations. AMARANTH enrolled patients with early AD (MCI attributable to AD and mild AD dementia), and DAYBREAK-ALZ enrolled patients with mild AD dementia only. Given the differences in study populations, it was hypothesized that the AMARANTH patients would exhibit less cognitive and functional impairment than the DAYBREAK-ALZ patients. However, the baseline clinical patient characteristics demonstrated a large overlap in scores, which may be associated with a key difference in inclusion criteria between the studies. AMARANTH required all patients to score 85 or less at screening on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Delayed Memory Index, reflecting a performance 1 SD below normal (mean [SD], 100 [15]). A cutoff score of 1 to 1.5 SDs below the mean on cognitive tests is consistent with the performance of an MCI population compared with age and educational level-matched controls.<sup>22</sup> The mean RBANS Delayed Memory Index of approximately 55 in AMARANTH at baseline was 3 SDs below normal, indicating that the AMARANTH population had greater episodic memory deficits than expected for an early AD population. Furthermore, the RBANS total score, a measure of global cognition, was similar between the studies, suggesting that the AMARANTH population had a cognitive profile more closely resembling that of a population with mild AD dementia. In addition, the baseline cognitive scores were similar to those of a previous clinical trial of solanezumab use in a population with mild AD only (EXPEDITION3).<sup>23</sup> Estimates for change over time for the placebo groups on the primary outcome measure, the ADAS-Cog<sub>13</sub>, as well as the ADCS-iADL, are comparable between the 2 lanabecestat studies herein and the solanezumab EXPEDITION3 study, further indicating that AMARANTH and DAYBREAK-ALZ enrolled similar patient populations. This overlap in patient populations likely contributed to the similar results in outcomes observed across the studies.

Off-target effects of BACE1 inhibition on protein processing could contribute to the adverse events seen in the lanabecestat program, as well as in other BACE inhibitors, which may be due to off-target processing. The studies of other BACE inhibitors assessed verubecestat (investigated in patients with mild to moderate AD dementia<sup>24</sup>) and umibecestat (a BACE inhibitor tested for the prevention of AD dementia<sup>25</sup>).

Hair color changes were not unexpected based on preclinical findings.<sup>6,26</sup> The increase in psychiatric adverse events observed herein is possibly attributable to off-target protein processing of neuregulin 1 (Nrg1) because BACE1 cleavage of Nrg1 is presumed to be important for normal psychiatric behaviors.<sup>27</sup> Imbalance in Nrg1 function could have resulted in abnormal psychiatric behaviors as previously demonstrated in mouse models.<sup>28</sup> The psychiatric symptoms observed in AMARANTH and DAYBREAK-ALZ may confound the identification of any potential benefit.

Seizure protein 6 (SEZ6), another BACE1 substrate, helps maintain dendritic spine density and long-term potentiation, with both being impaired in BACE1 knockout mice. Inhibition of SEZ6 processing could manifest as cognitive deficits or neuropsychiatric symptoms in humans. Another substrate, close homologue of LI (CHLI), guides axons to their targets, and stunted growth of mossy fiber axons in the hippocampi of BACE1 conditional knockout mice was observed,<sup>29</sup> providing another possible explanation for off-target effects of BACE1 inhibition and negative effects on cognition. In addition, observed effects on body weight across BACE compounds could be explained by an effect of lowered BACE1 activity on hypothalamic leptin sensitivity.<sup>30</sup>

In AMARANTH and DAYBREAK-ALZ, the proportions of patients with treatment-emergent increase in microhemorrhages were similar among treatment groups, and treatment-emergent vasogenic edema was uncommon overall, with no differences observed among lanabecestat and placebo groups (eTable 4 in Supplement 2). This finding is consistent with previous human and mouse studies<sup>22,31</sup> of BACE inhibitors.

### Strengths and Limitations

Although these studies were terminated early, there were some notable strengths. Baseline characteristics of patients

were well-balanced across 2 large, global, phase 3 studies. Both studies included confirmation of amyloid positivity as a requirement for study entry to increase diagnostic certainty.

Limitations of these studies included an overall lower duration of study treatment exposure than planned because of early study termination. This may have limited the ability to detect subtle changes or treatment effects in efficacy and safety assessments. In addition, although requiring confirmation of amyloid positivity for study inclusion (now implemented in most symptomatic AD studies) increases diagnostic certainty, it could have a negative predictive utility. Including amyloid-positive patients might inadvertently select individuals too late in the disease progression for a disease-modifying treatment of this nature to demonstrate an observable effect in studies of this duration. It has been hypothesized that starting treatment earlier in the disease continuum may prove to be efficacious; however, data presented recently from another BACE trial<sup>32</sup> did not support this hypothesis. Similarly, that previous study shared the design element of amyloid confirmation for inclusion. It remains to be seen whether treatment with a BACE inhibitor in a population that is at risk for A $\beta$  accumulation is effective.

### Conclusions

In patients with early AD or mild AD dementia, lanabecestat was generally well tolerated and did not slow cognitive or functional decline in 2 phase 3 studies (AMARANTH and DAYBREAK-ALZ) despite evidence supportive of target engagement. These results are consistent with previously reported phase 3 studies<sup>22,32</sup> of a BACE inhibitor. Although it appears unlikely that current BACE inhibitors will be an effective disease-modifying treatment for symptomatic AD, future studies are needed to determine if reduction in A $\beta$  production can provide meaningful clinical benefit in earlier stages of the disease continuum or in other high-risk populations.

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