

Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease

Lawrence S. Honig, M.D., Ph.D., Bruno Vellas, M.D., Michael Woodward, M.D., Mercè Boada, M.D., Ph.D., Roger Bullock, M.D., Michael Borrie, M.B., Ch.B., Klaus Hager, M.D., Niels Andreasen, M.D., Ph.D., Elio Scarpini, M.D., Hong Liu-Seifert, Ph.D., Michael Case, M.S., Robert A. Dean, M.D., Ph.D., Ann Hake, M.D., Karen Sundell, B.S., Vicki Poole Hoffmann, Pharm.D., Christopher Carlson, Ph.D., Rashna Khanna, M.D., Mark Mintun, M.D., Ronald DeMattos, Ph.D., Katherine J. Selzler, Ph.D., and Eric Siemers, M.D.

ABSTRACT

BACKGROUND

Alzheimer's disease is characterized by amyloid-beta ($A\beta$) plaques and neurofibrillary tangles. The humanized monoclonal antibody solanezumab was designed to increase the clearance from the brain of soluble $A\beta$, peptides that may lead to toxic effects in the synapses and precede the deposition of fibrillary amyloid.

METHODS

We conducted a double-blind, placebo-controlled, phase 3 trial involving patients with mild dementia due to Alzheimer's disease, defined as a Mini-Mental State Examination (MMSE) score of 20 to 26 (on a scale from 0 to 30, with higher scores indicating better cognition) and with amyloid deposition shown by means of florbetapir positron-emission tomography or $A\beta$ 1-42 measurements in cerebrospinal fluid. Patients were randomly assigned to receive solanezumab at a dose of 400 mg or placebo intravenously every 4 weeks for 76 weeks. The primary outcome was the change from baseline to week 80 in the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; scores range from 0 to 90, with higher scores indicating greater cognitive impairment).

RESULTS

A total of 2129 patients were enrolled, of whom 1057 were assigned to receive solanezumab and 1072 to receive placebo. The mean change from baseline in the ADAS-cog14 score was 6.65 in the solanezumab group and 7.44 in the placebo group, with no significant between-group difference at week 80 (difference, -0.80 ; 95% confidence interval, -1.73 to 0.14 ; $P=0.10$). As a result of the failure to reach significance with regard to the primary outcome in the prespecified hierarchical analysis, the secondary outcomes were considered to be descriptive and are reported without significance testing. The change from baseline in the MMSE score was -3.17 in the solanezumab group and -3.66 in the placebo group. Adverse cerebral edema or effusion lesions that were observed on magnetic resonance imaging after randomization occurred in 1 patient in the solanezumab group and in 2 in the placebo group.

CONCLUSIONS

Solanezumab at a dose of 400 mg administered every 4 weeks in patients with mild Alzheimer's disease did not significantly affect cognitive decline. (Funded by Eli Lilly; EXPEDITION3 ClinicalTrials.gov number, NCT01900665.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Honig at Columbia University Medical Center, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University College of Physicians and Surgeons, 630 W. 168th St. (P&S Unit 16), New York, NY 10032-3795, or at lh456@cumc.columbia.edu.

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THE NEUROPATHOLOGICAL HALLMARKS of Alzheimer's disease include extracellular plaques containing amyloid beta ($A\beta$) and intracellular neurofibrillary tangles containing hyperphosphorylated tau protein,¹ along with synaptic and neuronal losses.² The $A\beta$ hypothesis of the mechanism of Alzheimer's disease proposes that early pathogenesis of the disease results from the overproduction of or reduced clearance of $A\beta$, leading to the formation of oligomers, fibrils, and neuritic $A\beta$ plaques.^{3,4} Treatments that slow the production of $A\beta$ or that increase the clearance of $A\beta$ may slow the progression of Alzheimer's disease. Solanezumab, a humanized immunoglobulin G1 monoclonal antibody that binds to the mid-domain of the $A\beta$ peptide, was designed to increase clearance from the brain of soluble $A\beta$, peptides that may lead to toxic effects in the synapses at a stage before the deposition of the fibrillary form of the protein.

In two completed phase 3 clinical trials (EXPEDITION and EXPEDITION2), solanezumab did not significantly reduce the decline in cognition or function (e.g., activities of daily living and community involvement) in patients who had received a clinical diagnosis of mild-to-moderate Alzheimer's disease.⁵ However, in prespecified pooled secondary analyses, patients with mild Alzheimer's disease who were treated with solanezumab had less cognitive decline by approximately 34% and less functional decline by approximately 18% than did patients who received placebo.⁶ We report the results of a third double-blind, placebo-controlled phase 3 trial (EXPEDITION3), which enrolled only patients who had mild Alzheimer's disease, defined as a Mini-Mental State Examination (MMSE) score of 20 to 26 (on a scale from 0 to 30, with higher scores indicating better cognition), and had biomarker evidence of cerebral beta-amyloid deposition. This trial was intended to further investigate the secondary efficacy analyses from the earlier two trials.

METHODS

PATIENT POPULATION AND TRIAL DESIGN

This international trial included male and female patients, 55 to 90 years of age, who met the diagnostic criteria for probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke

and the Alzheimer's Disease and Related Disorders Association.⁷ The exclusion criteria have been described previously.^{5,6} Unlike the EXPEDITION and EXPEDITION2 trials, the EXPEDITION3 trial included only patients with mild Alzheimer's disease who had biomarker evidence of amyloid-related disease, determined by means of either florbetapir positron-emission tomography (PET) scan or $A\beta$ 1-42 measurements in cerebrospinal fluid (CSF).

Patients were randomly assigned in double-blind fashion to receive intravenous infusions of either solanezumab at a dose of 400 mg or placebo every 4 weeks for 76 weeks. Patients who completed the double-blind period could participate in an optional 24-month open-label period. Concomitant therapy, including treatments for symptoms of dementia (acetylcholinesterase inhibitors and memantine, alone or in combination) and nondrug treatments, was allowed in order to ensure that patients continued receiving the standard of care for Alzheimer's disease. This article includes only the results from the double-blind, placebo-controlled period of the trial. The primary objective of the trial was to test the hypothesis that solanezumab would slow the cognitive decline of Alzheimer's disease, as compared with placebo, in patients with mild dementia due to Alzheimer's disease.

SAFETY ASSESSMENTS

Key safety assessments included routine physical and neurologic examinations, routine clinical laboratory assessment, and the collection of adverse-event data. Magnetic resonance imaging (MRI) was used to detect any evidence of amyloid-related imaging abnormalities for either hemorrhage or hemosiderin deposition (cerebral microhemorrhage or hemosiderosis) or edema or effusions (vasogenic edema). Adverse events that are associated with immunogenicity or antidrug antibodies were evaluated. Additional safety assessments are described in the protocol, available with the full text of this article at NEJM.org.

OUTCOME MEASURES

The primary efficacy measure was the change from baseline to 80 weeks in the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; scores range from 0 to 90, with higher scores indicating greater cognitive impairment).^{8,9} Key second-

ary efficacy measures included scores on the following assessments: the MMSE¹⁰; the Alzheimer's Disease Cooperative Study (ADCS) Activities of Daily Living Inventory (ADCS-ADL; scores range from 0 to 78, with lower scores indicating greater functional impairment); the ADCS instrumental subscale (ADCS-iADL), which assesses complex activities such as using public transportation, managing finances, or shopping (scores range from 0 to 56, with lower scores indicating greater functional loss)^{11,12}; the Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB; scores range from 0 to 18, with higher scores indicating greater impairment)^{13,14}; the Functional Activities Questionnaire (FAQ; scores range from 0 to 30, with higher scores indicating greater functional loss)¹⁵; and the Integrated Alzheimer's Disease Rating Scale (iADRS; scores range from 0 to 146, with lower scores indicating worse performance).¹⁶ Biomarker and neuroimaging methods are described in the Supplementary Appendix, available at NEJM.org.

OVERSIGHT

The trial protocol was approved by the ethics and institutional review boards at all the sites. All the participants provided written informed consent before participation in the trial. The sponsor (Eli Lilly) designed and funded the trial, provided solanezumab and placebo, participated in writing the manuscript, and oversaw contracted research organizations. The first draft of the manuscript was written by the first author and an author who was an employee of the sponsor. Several authors are former employees of the sponsor but were still employees at the time that the manuscript was written. All the statistical analyses that are reported here were performed by the sponsor or by a contract research organization. The statistical analysis plan is available with the trial protocol, and the informed-consent form is provided in the Supplementary Appendix. All the authors attest to the fidelity of the trial to the protocol and to the accuracy and completeness of the data and analysis. All the authors reviewed and approved versions of the manuscript for submission for publication.

STATISTICAL ANALYSIS

Analyses were conducted on the basis of a modified intention-to-treat principle and involved only patients who had outcome measurements both

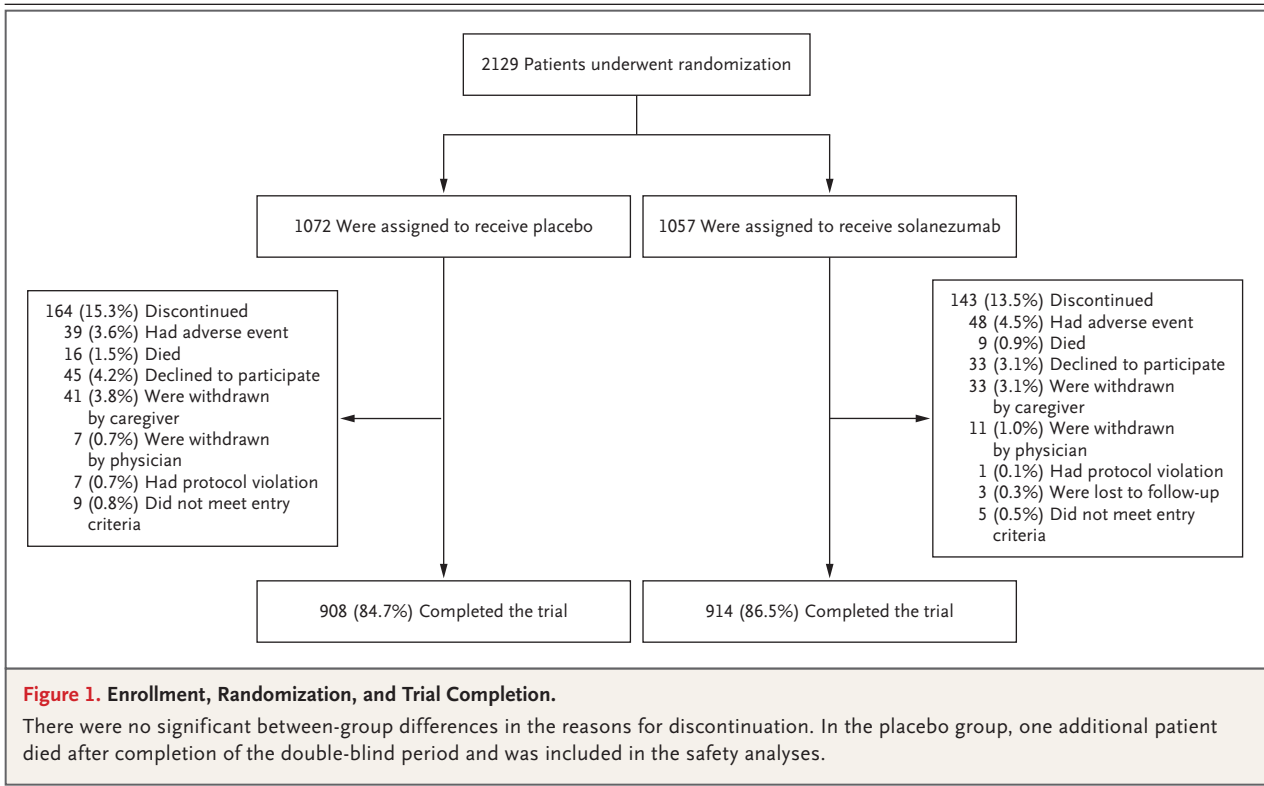
at and after baseline. All the tests of effects were conducted at a two-sided alpha level of 0.05, unless otherwise specified. Patients who did not have a postbaseline measure were not included in the analyses. Additional details, including information about the weighted imputation methods for missing data, are provided in the statistical analysis plan (see the protocol).

Randomization of the patients was stratified according to site and according to the method that was used to determine the presence of amyloid-related disease (florbetapir PET scan or CSF assessment). Fisher's exact test or Pearson's chi-square test was used for trial-group comparisons of categorical data; analysis of variance, with independent factors for treatment and site, was used for continuous data.

The primary outcome, the change from baseline to 80 weeks in the ADAS-cog14 score, was analyzed with the use of a mixed-model repeated-measures analysis, with the change from baseline in the ADAS-cog14 score at each scheduled visit at weeks 12, 28, 40, 52, 64, and 80 after baseline as the dependent variable. The model for the fixed effects included terms for seven effects: the baseline ADAS-cog14 score, site, trial group, visit, trial group–by–visit interaction, concomitant use of acetylcholinesterase inhibitors or memantine (or both) at baseline (yes or no), and age at baseline. Visits were considered to be a categorical variable, with values equal to the visit number at which the scales were assessed.

Each secondary efficacy outcome was assessed with the use of a mixed model with a repeated-measures analysis in the following hierarchical order: ADCS-iADL, MMSE, and FAQ. The CDR-SB score was assessed only at baseline and at the final study visit, so the change in the CDR-SB score was examined with the use of an analysis of covariance model that contained terms for baseline score, site, trial group, concomitant use of acetylcholinesterase inhibitors or memantine (or both) at baseline (yes or no), and age at baseline. The failure, at a two-sided P value of 0.05, of any analysis in the hierarchy would prevent the reporting of significance testing for all the items after the point of failure.

Safety was assessed by the summary and analysis of clinical laboratory results, adverse events, MRI scans, electrocardiograms, and immunogenicity results. Safety analyses for the double-blind period used comparisons between the



solanezumab group and the placebo group. No adjustments for multiple comparisons were made. Analyses comparing the proportion of patients with abnormalities between trial groups during the double-blind period included only patients with both a baseline and a postbaseline observation for each variable. An independent data and safety monitoring committee met periodically to monitor accruing safety data. No interim efficacy analyses were conducted. Statistical methods that were used for biomarker and neuroimaging assessments are provided in the Supplementary Appendix.

RESULTS

TRIAL POPULATION

Of 4101 patients who underwent screening, 2129 underwent randomization between August 12, 2013, and October 13, 2016; a total of 1822 patients (86.5% of the patients in the solanezumab group and 84.7% of those in the placebo group) completed the trial (Fig. 1). There were 210 sites in 11 countries, with each site contributing 1 to 30 patients. There were no significant between-group differences in the baseline characteristics of the patients with respect to age, sex, race,

education, or apolipoprotein E (APOE) ϵ 4 carrier status. The mean (\pm SD) ADAS-cog14 score at baseline was 28.9 ± 8.3 in the solanezumab group, as compared with 29.7 ± 8.5 in the placebo group ($P=0.02$), and the mean MMSE score at the beginning of the trial was 22.8 ± 2.8 and 22.6 ± 2.9 , respectively ($P=0.12$). Additional demographic characteristics of the patients are listed in Table 1.

OUTCOMES

The results of the primary-outcome measure (the ADAS-cog14) were analyzed as the change from baseline over time (Fig. 2A). There was no significant between-group difference at week 80 in the change in score from baseline (change, 6.65 in the solanezumab group and 7.44 in the placebo group; difference, -0.80 ; $P=0.10$) (Table 2).

As a result of the failure to reach significance regarding the primary outcome in the prespecified hierarchical analysis, the secondary outcomes were considered to be descriptive and are reported (as point estimates with confidence intervals) without significance testing. There was a decrease (indicating worsening) in the score on the MMSE, the ADCS-iADL (Fig. 2B), the ADCS-ADL, and the iADRS in the two trial groups and an increase (indicating worsening) in the score on the FAQ

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=1072)	Solanezumab (N=1057)	P Value
Age — yr	73.3±8.0	72.7±7.8	0.07
Female sex — no. (%)	631 (58.9)	600 (56.8)	0.34
Race — no./total no. (%)†			0.76
White	894/986 (90.7)	878/970 (90.5)	
Black	19/986 (1.9)	14/970 (1.4)	
Asian	71/986 (7.2)	75/970 (7.7)	
Multiple or other	2/986 (0.2)	3/970 (0.3)	
APOE ε4 allele — no./total no. (%)	685/1033 (66.3)	712/1027 (69.3)	0.14
Education — yr	13.7±3.8	13.7±3.7	0.91
Duration since symptom onset — yr	4.3±2.6	4.2±2.5	0.41
Duration since diagnosis — yr	1.6±1.7	1.5±1.6	0.13
Acetylcholinesterase inhibitor or memantine use — no. (%)	856 (79.9)	822 (77.8)	0.24
ADAS-cog14 score‡	29.7±8.5	28.9±8.3	0.02
ADCS-iADL score§	45.4±8.1	45.6±7.9	0.44
MMSE score¶	22.6±2.9	22.8±2.8	0.12
FAQ score	10.6±7.1	10.3±6.8	0.36
CDR-SB score**	3.9±2.0	3.9±1.9	0.54

* Plus-minus values are means ±SD. APOE denotes apolipoprotein E.

† Race was reported by the patient.

‡ Scores on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14) range from 0 to 90, with higher scores indicating greater cognitive impairment.

§ The instrumental subscale of the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-iADL) is used to assess complex activities such as using public transportation, managing finances, or shopping; scores range from 0 to 56, with lower scores indicating greater functional loss.

¶ Scores on the Mini-Mental State Examination (MMSE) range from 0 to 30, with higher scores indicating better cognition.

|| Scores on the Functional Activities Questionnaire (FAQ) range from 0 to 30, with higher scores indicating greater functional loss.

** Scores on the Clinical Dementia Rating–Sum of Boxes (CDR-SB) range from 0 to 18, with higher scores indicating greater impairment.

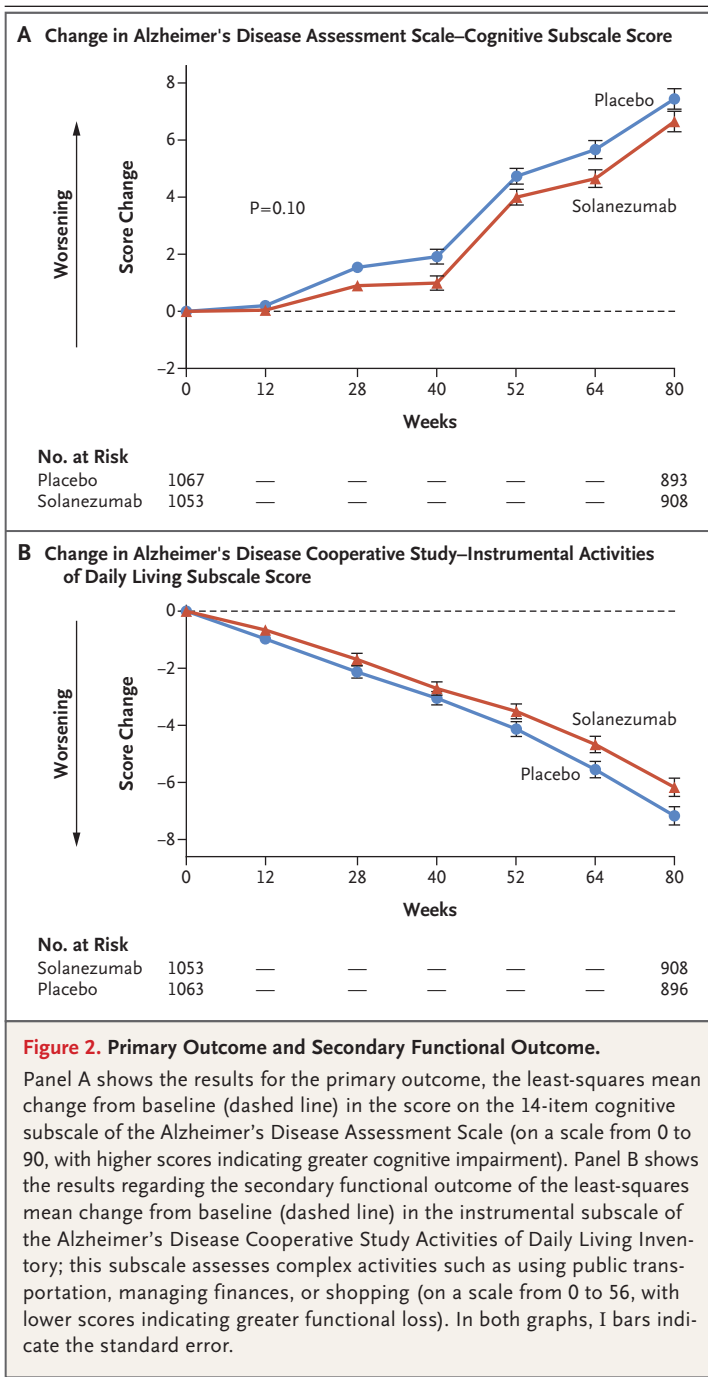
and CDR-SB (Table 2). The raw values, the mean changes at week 80, between-group differences, and 95% confidence intervals for the secondary outcomes are shown in Table 2. The main results of the biomarker and neuroimaging assessments are provided in the Supplementary Appendix. Details of these biologic secondary outcomes have not been fully analyzed.

ADVERSE EVENTS

A total of 891 of 1054 patients (84.5%) in the solanezumab group and 890 of 1067 (83.4%) in the placebo group had at least one adverse event during the double-blind period in the safety population. Four categories of events occurred

significantly more frequently in the solanezumab group: vitamin D deficiency, nasal congestion, spinal osteoarthritis, and dysuria; and two categories occurred more frequently in the placebo group: gait disturbance and somnolence. Table S1 in the Supplementary Appendix lists the adverse events that occurred in 2% or more of the patients during the double-blind period.

In the population of patients who had undergone randomization, 48 of 1057 patients (4.5%) in the solanezumab group and 39 of 1072 (3.6%) in the placebo group had an adverse event that led to discontinuation of the trial. There were no significant between-group differences in the numbers of patients who had a serious adverse



event and those who died. A total of 175 of 1054 patients (16.6%) in the solanezumab group had at least one serious adverse event, as did 202 of 1067 (18.9%) in the placebo group. A total of 112 patients (10.6%) in the solanezumab group and 105 (9.8%) in the placebo group were hospitalized during the trial. There were 9 deaths

(0.9%) among patients receiving solanezumab and 17 (1.6%) among those receiving placebo. Table S2 in the Supplementary Appendix lists the serious adverse events that occurred in 0.5% or more of the patients.

At baseline, before exposure to the trial regimen, 80 of 1034 patients (7.7%) in the solanezumab group and 73 of 1048 (7.0%) in the placebo group had antidrug antibodies. Antidrug antibodies occurred after baseline during the double-blind period in 33 patients (3.2%) in the solanezumab group and in 41 (3.9%) in the placebo group ($P=0.41$). Neutralizing antibodies were present in 4 patients (0.4%) in the solanezumab group and in 6 (0.6%) in the placebo group. Events that were considered to be potentially related to hypersensitivity were observed in 8 patients with antidrug antibodies in the solanezumab group and in 15 in the placebo group.

There was one case of amyloid-related abnormality of edema or effusions on cerebral imaging in the solanezumab group and two cases in the placebo group. The three patients with amyloid-related abnormalities of edema or effusions on imaging were asymptomatic during the placebo-controlled phase of the trial. There were no significant differences between groups in amyloid-related abnormalities on imaging with regard to hemorrhage or hemosiderin deposition.

DISCUSSION

This phase 3 trial of solanezumab administered intravenously at a dose of 400 mg in patients with mild Alzheimer's disease did not show a significant benefit, as compared with placebo, in reducing cognitive decline as measured by the ADAS-cog14 at 80 weeks (primary outcome). Significance testing of the secondary cognitive and functional measures was not reported because of failure of the primary outcome in the hierarchical analysis. The results of this trial may be compared with those of earlier phase 3 trials of solanezumab that involved patients with more advanced disease. Among a limited number of patients who consented to undergo amyloid PET or have CSF assessments in substudies of the EXPEDITION and EXPEDITION2 trials, approximately 25% of the patients with mild Alzheimer's disease did not have evidence of amyloid-related disease.⁶ These patients would not have been expected to have a response to a treatment target-

Table 2. Primary and Key Secondary Outcomes.*

Outcome	Raw Score at Baseline		Raw Score at 80 Wk		Least-Squares Mean Change at 80 Wk		Estimated Difference at 80 Wk (95% CI)	P Value†
	Placebo	Solanezumab	Placebo	Solanezumab	Placebo	Solanezumab		
Primary outcome: ADAS-cog ¹⁴ score	29.70±8.50	28.87±8.26	36.11±14.27	35.09±13.28	7.44±0.36	6.65±0.36	-0.80 (-1.73 to 0.14)	0.10
Secondary outcomes								
MMSE score	22.62±2.89	22.81±2.77	19.09±5.56	19.62±5.30	-3.66±0.16	-3.17±0.15	0.49 (0.10 to 0.88)	—
ADCS-iADL score	45.37±8.14	45.60±7.93	39.01±11.86	39.83±11.41	-7.17±0.32	-6.17±0.32	1.00 (0.17 to 1.83)	—
ADCS-ADL score‡	66.69±9.15	67.02±8.67	59.00±14.61	60.20±13.52	-8.77±0.39	-7.42±0.39	1.35 (0.33 to 2.37)	—
FAQ score	10.60±7.11	10.31±6.81	15.73±8.10	15.35±8.24	5.57±0.21	5.17±0.21	-0.40 (-0.93 to 0.13)	—
CDR-SB score	3.93±1.95	3.88±1.90	6.02±3.38	5.72±3.18	2.21±0.11	1.87±0.10	-0.34 (-0.57 to -0.11)	—
iADRS score§	105.70±13.95	106.73±13.47	93.04±23.71	94.81±22.15	-14.59±0.54	-12.92±0.53	1.68 (0.29 to 3.06)	—

* The plus-minus values for the scores at baseline and at 80 weeks are means (±SD). The estimated difference is the least-squares mean (±SE) change from baseline between the two trial groups at 80 weeks. Differences may not calculate as expected because of rounding. CI denotes confidence interval.
 † As a result of the failure of the prespecified hierarchical analysis regarding the primary outcome, the secondary outcomes were considered to be descriptive and are reported without significance testing.
 ‡ Scores on the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) scale range from 0 to 78, with lower scores indicating greater functional impairment.
 § Scores on the Integrated Alzheimer's Disease Rating Scale (iADRS) range from 0 to 146, with lower scores indicating worse performance.

ing $A\beta$. The inclusion in the current trial of only patients with mild Alzheimer's disease and evidence of amyloid burden was expected to produce treatment outcomes of at least the same magnitude or greater as those seen in the previous trials. The treatment effect in the current trial on the rate of cognitive decline was smaller than that observed in the secondary analyses of the population of patients with mild Alzheimer's disease in the two previous studies.⁶ The reason for the smaller clinical effects is unclear.

There were no significant differences between the solanezumab group and the placebo group with regard to serious adverse events. Concerns about potential cardiac effects of solanezumab arose in the previous phase 3 studies⁶ but did not do so in the current trial. Adverse events that are associated with amyloid-related imaging abnormalities of edema or effusions and hemorrhage or hemosiderin deposition that occurred with other monoclonal antibodies that directly target amyloid plaques¹⁷⁻²⁰ were observed in only one participant receiving solanezumab in the current trial. The low incidence of adverse amyloid-related imaging abnormalities associated with solanezumab is consistent with the reported occurrence of imaging changes that are seen in the placebo groups of other clinical trials.²¹ Therefore, it is possible that the low incidence of adverse amyloid-related imaging abnormalities associated with solanezumab administration may reflect the binding only to soluble $A\beta$, but there is no direct evidence to support this hypothesis.

The percentages of patients who have the APOE $\epsilon 4$ allele were higher in the EXPEDITION3 trial (69.3% in the solanezumab group and 66.3% in the placebo group) than in the EXPEDITION and EXPEDITION2 trials (57.6% overall),⁶ a finding that is likely to be due to the entry requirement for evidence of markers of amyloid-related disease. The completion rate of 85.6% in the current trial was high, with limited early withdrawals from the trial, given that 20 intravenous infusions were required per the protocol over an 18-month period.

There are several possible reasons why the administered dose of solanezumab did not reduce cognitive decline. First, the observed peripheral reductions in soluble free $A\beta$ concentrations may not have been sufficient to reduce deposited cerebral amyloid, neuronal atrophy, or the patho-

biologic events that lead to clinical decline. The so-called peripheral sink hypothesis posits that reducing the free (unbound) fraction of $A\beta$ in plasma would lead to the increased clearance of $A\beta$ from the brain.²² The solanezumab dose that was administered in this trial was associated with a high level of peripheral target engagement, sufficient to reduce free plasma $A\beta$ concentrations by more than 90% (Fig. S1 in the Supplementary Appendix). However, this effect did not produce clinical efficacy. Thus, a reduction in peripheral free $A\beta$ alone is unlikely to lead to clinically meaningful cognitive benefits.

Second, the dose of solanezumab (400 mg, administered every 4 weeks) may have been insufficient to produce a meaningful effect. Solanezumab penetration into the central nervous system (CNS), as measured by cerebrospinal fluid concentrations, is only approximately 0.1 to 0.3% of the concentration measured in plasma. The resultant penetration of CNS antibody in the brain may have been too low to neutralize enough interstitial fluid $A\beta$ to produce a clinically meaningful effect at this dose. The administered dose of solanezumab did not reduce the burden of fibrillar amyloid, as assessed by means of florbetapir PET imaging. A lack of an effect on preexisting amyloid plaques in this trial is consistent with the results from earlier clinical data and nonclinical studies in animals.²³ Antibodies that bind soluble $A\beta$ would be expected to have only marginal effects on preexisting amyloid. Dose-response studies that have been performed with other antibodies that, unlike solanezumab, are directed against deposited amyloid (a mechanism dependent on antibody penetration into the CNS) have shown dose-proportional effects on plaque clearance and possible slowing of clinical decline.²⁰ Studies with these plaque-targeting antibodies have also shown dose-dependent increases in the incidence of CNS-associated adverse events.^{17,20}

Third, the pathological changes in the mild stage of Alzheimer's disease-related dementia may not be amenable to treatment with a drug targeting soluble $A\beta$. Some data from mouse models suggest that neurodegeneration in Alzheimer's disease may reach a point at which it becomes self-propagating²⁴ and not susceptible to intervention. However, it is unclear whether this finding is applicable to human disease or at

what stage it might pertain. Data from ongoing clinical trials involving patients at earlier stages of the continuum of Alzheimer's disease, such as the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) trial (ClinicalTrials.gov number, NCT02008357) and the Dominantly Inherited Alzheimer Network Trial (DIAN-TU; NCT01760005), may address this question.

Fourth, solanezumab was designed to increase the clearance of soluble A β from the brain, predicated on the A β hypothesis of Alzheimer's disease — that the disease results from the overproduction of or reduced clearance of A β (or both). Although the amyloid hypothesis is based on considerable genetic and biomarker data,²⁵ if amyloid is not the cause of the disease, solanezumab would not be expected to slow disease progression.^{26,27} A single study ought not to be viewed as disproving a hypothesis; nevertheless, the amyloid hypothesis will need to be considered in the context of accruing results from this trial and other clinical trials of antiamyloid therapies.

In conclusion, in patients with mild Alzheimer's disease, the results of the EXPEDITION3 trial showed no benefit of solanezumab on the primary outcome of cognitive decline and did not reproduce the secondary analyses of the EXPEDITION and EXPEDITION2 trials. The rationale for further trials with solanezumab with different doses and timing may require examination.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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This article is dedicated to the memory of Roza Hayduk, M.D., former Vice President and Global Medical Head of Neurology trials at Quintiles, whose energetic, thoughtful, and careful devotion to the EXPEDITION trials and other trials in Alzheimer's disease provided what will be a sorely missed leadership role in the conduct of these complex and lengthy studies.

APPENDIX

The authors' affiliations are as follows: the Department of Neurology and Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York (L.S.H.); Gérontopôle, Centre Hospitalier Universitaire Toulouse, Unité Mixte de Recherche INSERM Unité 1027 Université Toulouse III–Paul Sabatier, Toulouse, France (B.V.); Austin Health Continuing Care Clinical Service Unit, Heidelberg, and the University of Melbourne, Melbourne, VIC — both in Australia (M.W.); Fundació ACE, Alzheimer Research Center and Memory Clinic, Institut Català de Neurociències Aplicades, Barcelona (M. Boada); Kingshill Research Centre, Victoria Hospital, Swindon, United Kingdom (R.B.); the Division of Geriatric Medicine, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada (M. Borrie); Clinic for Medicine of the Elderly, Diakovere Henrietenstift, Hannover, Germany (K.H.); Karolinska Institutet Alzheimer's Disease Research Center and Clinical Trial Unit, Geriatric Clinic, Karolinska University Hospital, Huddinge, Sweden (N.A.); the Department of Pathophysiology and Transplantation, Neurology Unit, Dino Ferrari Center, University of Milan, Fondazione Ca' Granda, Istituto di Ricovero e Cura a Carattere Scientifico Ospedale Policlinico, Milan (E. Scarpini); Eli Lilly (H.L.-S., M.C., A.H., K.S., V.P.H., C.C., R.K., M.M., R.D., K.J.S., E. Siemers) and the Department of Pathology and Laboratory Medicine, Indiana University School of Medicine (R.A.D.) — both in Indianapolis; and Avid Radiopharmaceuticals, Philadelphia (M.M.).

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