ORIGINAL ARTICLE

Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease

Rachelle S. Doody, M.D., Ph.D., Ronald G. Thomas, Ph.D., Martin Farlow, M.D., Takeshi Iwatsubo, M.D., Ph.D., Bruno Vellas, M.D., Steven Joffe, M.D., M.P.H., Karl Kieburtz, M.D., M.P.H., Rema Raman, Ph.D., Xiaoying Sun, M.S., and Paul S. Aisen, M.D., for the Alzheimer's Disease Cooperative Study Steering Committee; and Eric Siemers, M.D., Hong Liu-Seifert, Ph.D., and Richard Mohs, Ph.D., for the Solanezumab Study Group

ABSTRACT

BACKGROUND

Alzheimer's disease is characterized by amyloid-beta plaques, neurofibrillary tangles, gliosis, and neuronal loss. Solanezumab, a humanized monoclonal antibody, preferentially binds soluble forms of amyloid and in preclinical studies promoted its clearance from the brain.

METHODS

In two phase 3, double-blind trials (EXPEDITION 1 and EXPEDITION 2), we randomly assigned 1012 and 1040 patients, respectively, with mild-to-moderate Alzheimer's disease to receive placebo or solanezumab (administered intravenously at a dose of 400 mg) every 4 weeks for 18 months. The primary outcomes were the changes from baseline to week 80 in scores on the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog11; range, 0 to 70, with higher scores indicating greater cognitive impairment) and the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale (ADCS-ADL; range, 0 to 78, with lower scores indicating worse functioning). After analysis of data from EXPEDITION 1, the primary outcome for EXPEDITION 2 was revised to the change in scores on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range, 0 to 90, with higher scores indicating greater impairment), in patients with mild Alzheimer's disease.

RESULTS

Neither study showed significant improvement in the primary outcomes. The modeled difference between groups (solanezumab group minus placebo group) in the change from baseline was −0.8 points for the ADAS-cog11 score (95% confidence interval [CI], −2.1 to 0.5; P=0.24) and −0.4 points for the ADCS-ADL score (95% CI, −2.3 to 1.4; P=0.64) in EXPEDITION 1 and −1.3 points (95% CI, −2.5 to 0.3; P=0.06) and 1.6 points (95% CI, −0.2 to 3.3; P=0.08), respectively, in EXPEDITION 2. Between-group differences in the changes in the ADAS-cog14 score were −1.7 points in patients with mild Alzheimer's disease (95% CI, −3.5 to 0.1; P=0.06) and −1.5 in patients with moderate Alzheimer's disease (95% CI, −4.1 to 1.1; P=0.26). In the combined safety data set, the incidence of amyloid-related imaging abnormalities with edema or hemorrhage was 0.9% with solanezumab and 0.4% with placebo for edema (P=0.27) and 4.9% and 5.6%, respectively, for hemorrhage (P=0.49).

CONCLUSIONS

Solanezumab, a humanized monoclonal antibody that binds amyloid, failed to improve cognition or functional ability. (Funded by Eli Lilly; EXPEDITION 1 and 2 ClinicalTrials.gov numbers, NCT00905372 and NCT00904683.)

From the Alzheimer's Disease and Memory Disorders Center, Department of Neurology, Baylor College of Medicine, Houston (R.S.D.); Alzheimer's Disease Cooperative Study, Department of Family and Preventive Medicine (R.G.T., R.R., X.S.), and the Department of Neurosciences (R.G.T., R.R., P.S.A., R.M.), University of California at San Diego, San Diego; Indiana Alzheimer Disease Center, Indiana University (M.F.), and Eli Lilly (E.S., H.L.-S., R.M.) — both in Indianapolis; the Department of Neuropathology, School of Medicine, and the Department of Neuropathology and Neuroscience, School of Pharmacological Science, University of Tokyo, Tokyo (T.I.); Gerontopole, Unité Mixte de Recherche 1027, Centre Hospitalier Universitaire Toulouse, Toulouse, France (B.V.); the Department of Medical Ethics and Health Policy, University of Pennsylvania, Philadelphia (S.J.); and the Center for Human Experimental Therapeutics, University of Rochester Medical Center, Rochester, NY (K.K.). Address reprint requests to Dr. Doody at the Department of Neurology, Alzheimer's Disease and Memory Disorders Center, Baylor College of Medicine, 1977 Butler Blvd., Suite E 5.101, Houston, TX 77030, or at rdoody@bcm.edu.

N Engl J Med 2014;370:311-21.
DOI: 10.1056/NEJMoa1312889

Alzheimer's disease is associated with the accumulation of aggregated amyloid-beta (Aβ) peptide in the cerebral cortex and hippocampus. One approach to reducing brain amyloid involves increasing the clearance of Aβ by means of prolonged treatment with monoclonal antibodies directed against this peptide. In preclinical studies, a murine antibody that targeted the central domain of Aβ and was selective for soluble forms slowed Aβ deposition in a transgenic mouse model[1]; in another transgenic murine model, Aβ–antibody complexes were present in the cerebrospinal fluid (CSF) and plasma, and behavioral deficits were reversed without a decrease in amyloid plaques, as assessed by immunohistochemical analysis.[2] Solanezumab, the humanized analogue of the murine antibody, was tested in clinical phase 1 and 2 studies.[3,4] These studies showed dose-related increases in total (bound plus unbound) plasma Aβ and similar CSF alterations (increased total Aβ and, at the highest dose [400 mg weekly], decreased unbound Aβ1-40 but increased unbound Aβ1-42),[4] findings that suggest solanezumab might have efficacy in Alzheimer's disease through a central effect[5] or through promotion of Aβ efflux from the central nervous system to the peripheral circulation. Eli Lilly conducted two phase 3, randomized, double-blind, placebo-controlled trials (EXPEDITION 1 and EXPEDITION 2), which were analyzed and are reported here by the Alzheimer's Disease Cooperative Study (ADCS) Data Analysis and Publication Committee.

Methods

Patients and Study-Drug Regimens

Both trials involved otherwise healthy patients 55 years of age or older who had mild-to-moderate Alzheimer's disease without depression. Mild-to-moderate Alzheimer's disease was documented on the basis of a score of 16 to 26 on the Mini–Mental State Examination (MMSE; score range, 0 to 30, with higher scores indicating better cognitive function)[6] and the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association.[7] The absence of depression was documented on the basis of a score of 6 or less on the Geriatric Depression Scale (score range, 0 to 15, with higher scores indicating more severe depression).[8] Participants were randomly assigned to receive solanezumab (400 mg) or placebo, administered as an intravenous infusion of approximately 70 ml over a period of 30 minutes, once every 4 weeks for 18 months. Concomitant treatment with cholinesterase inhibitors, memantine, or both was allowed.

Oversight

The study protocol was approved by the institutional review board at each participating institution, and all participants provided written informed consent. (The study protocol is available with the full text of this article at NEJM.org.) The Data Analysis and Publication Committee of the ADCS, an academic consortium funded by the National Institute on Aging, was funded by a contract between Eli Lilly and the University of California at San Diego as a fiduciary for the ADCS. Eli Lilly designed and conducted the study. The manuscript was written by the committee chair and was revised and approved by the voting members of the Data Analysis and Publication Committee, the ADCS steering committee, and all the authors. All the authors vouch for the completeness and veracity of the data and data analysis and for the fidelity of this report to the study protocol, with modifications and additions to the statistical analysis plan as explained in this report and in the Supplementary Appendix, available at NEJM.org.

Safety Assessments

Safety was assessed on the basis of measurements of vital signs and weight, physical examination, serum biochemical measurements, hematologic analysis, measurement of electrolytes, urinalysis, and electrocardiography. Adverse events were assessed at each visit.

Clinical Outcome Measures

Efficacy measures included the 11- or 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog11 [score range, 0 to 70] and ADAS-cog14 [score range, 0 to 90], with higher scores indicating greater cognitive impairment),[9] the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale (score range, 0 to 78, with lower scores indicating worse functioning),[10] the Clinical Dementia Rating–Sum of Boxes (CDR-SB),[11,12] the Neuropsychiatric Inventory (NPI),[13] the Resource Utiliza-

tion in Dementia Lite (RUD-Lite) scale,[14] the European Quality of Life–5 Dimensions (EQ-5D) scale (proxy version),[15] the Quality of Life in Alzheimer's Disease (QOL-AD) scale,[16,17] and the MMSE.[7]

BIOLOGIC MARKERS AND NEUROIMAGING OUTCOME MEASURES

Apolipoprotein E genotypes were determined. Plasma levels of Aβ were assessed at multiple time points, and CSF levels of Aβ^4 and tau protein[18] were measured in a subset of patients. Brain volumetric magnetic resonance imaging (MRI) was performed; amyloid imaging by means of positron-emission tomography (PET) with the use of ^{18}F-florbetapir was performed at baseline and week 80 or at early termination in a subset of patients.

Plasma and CSF concentrations of total (bound and unbound) A$\beta_{1\text{-}40}$ and A$\beta_{1\text{-}42}$ were determined by means of INNOTEST immunoassays (Innogenetics) that were modified and validated for use with biologic specimens containing variable levels of solanezumab, as reported previously.[19]

STATISTICAL ANALYSIS

The statistical analysis plan followed by the Data Analysis and Publication Committee was consistent with the Eli Lilly statistical analysis plans for the two trials, although it differed in some details (see Table S1 in the Supplementary Appendix). Mixed-model repeated-measures analyses were used to assess between-group differences in the modeled change in scores from baseline to week 80. The dependent variable in each analysis was the change from the baseline score. Fixed effects were baseline scores on outcome measures, study-drug assignment (solanezumab or placebo), MMSE score at screening (categorical variable [mild or moderate Alzheimer's disease]), visit and treatment-by-visit interaction, concomitant use of cholinesterase inhibitors or memantine at baseline (yes or no), and age at baseline. The random effect (random intercept) was "participant." Study visit was treated as a categorical variable; an unstructured variance–covariance matrix was used. In addition, a mixed-effects repeated-measures slope analysis model (i.e., visit included as a continuous variable) was used for sensitivity analyses. The primary efficacy analysis was based on the intention-to-treat population, which included all randomly assigned participants for whom there was at least one postbaseline observation. A secondary analysis was performed for all randomly assigned participants who completed the period of treatment with the study medication.

The primary outcomes for EXPEDITION 1 and the original primary outcomes for EXPEDITION 2 were the change in scores on the ADAS-cog11 and the ADCS-ADL scale from baseline to week 80 (end point). Secondary outcomes were the change from baseline in scores on the CDR-SB, MMSE, NPI, EQ-5D scale, RUD-Lite scale, and QOL-AD scale; the values for plasma and CSF levels of Aβ and for CSF levels of tau and phospho-tau; MRI brain volumetric measurements; and evidence of amyloid accumulation on imaging studies performed with ^{18}F-florbetapir–PET. Safety analyses were based on the full intention-to-treat population, and all biomarker analyses were calculated with the use of data from patients with at least one postbaseline value. The baseline characteristics of the study groups were compared with the use of Fisher's exact test for categorical variables and an analysis of variance for continuous variables. An analysis of covariance was used to assess changes from baseline in plasma and CSF biomarkers and in imaging studies. Safety analyses were based on summary listings of adverse events, with Fisher's exact test used for pairwise comparisons. R statistical software, version 2.15.1 (www.r-project.org), was used for all statistical analyses. The R code is provided in Table S1 in the Supplementary Appendix. A P value of less than 0.05 was considered to indicate statistical significance. All statistical testing was two-sided.

In prespecified analyses in EXPEDITION 1, we assessed the treatment effect of solanezumab in patients with mild Alzheimer's disease (MMSE score of 20 to 26 at visit 1) versus patients with moderate Alzheimer's disease (MMSE score of 16 to 19 at visit 1) and the treatment effect in apolipoprotein E (*APOE*) ε4 carriers versus noncarriers. No clear differential treatment effects on efficacy measures were observed between *APOE* ε4 carriers and noncarriers in EXPEDITION 1. However, differential effects on cognitive measures were observed; a benefit of solanezumab treatment was observed in patients with mild Alzheimer's disease but not in patients with moderate Alzheimer's disease or in the combined populations.

On the basis of these findings, and before the EXPEDITION 2 trial was completed, the statistical

analysis plan was revised (and resubmitted to regulatory agencies) for analyses of the EXPEDITION 2 data and for analyses of pooled data from EXPEDITION 1 and 2. For these analyses, the patients with mild Alzheimer's disease were considered the primary-analysis population, and the ADAS-cog14, which was designed as a better measure of cognitive change in patients with mild Alzheimer's disease than the ADAS-cog11, was the single primary outcome measure. The plan also called for assessment of treatment effects in the subgroup of patients with moderate Alzheimer's disease. In addition to the categorical mixed-model repeated-measures analysis, the ADCS performed a mixed-effects model repeated-measures slope analysis as a sensitivity analysis.

RESULTS

ENROLLMENT AND RATES OF STUDY COMPLETION

A total of 1012 patients were enrolled in EXPEDITION 1 (506 in each study group) and 1040 patients were enrolled in EXPEDITION 2 (521 in the solanezumab group and 519 in the placebo group). In EXPEDITION 1, completion rates were 73.1% for patients in each group. In EXPEDITION 2, completion rates were 77.9% for patients in the solanezumab group and 77.1% for those in the placebo group; among patients with mild Alzheimer's disease, completion rates were 78.0% and 79.9%, respectively. The most common reasons for study discontinuation were adverse events and withdrawal of consent, regardless of study or study-group assignment (Fig. 1).

BASELINE CHARACTERISTICS

There were no significant differences in either study between the solanezumab group and the placebo group with respect to age, sex, or educational level; 76.6 to 84.4% of participants in each group were white (Table 1). Across groups, 54.6 to 61.3% of participants were *APOE* ε4–positive, with no significant imbalances. Both studies included patients with mild-to-moderate Alzhei-

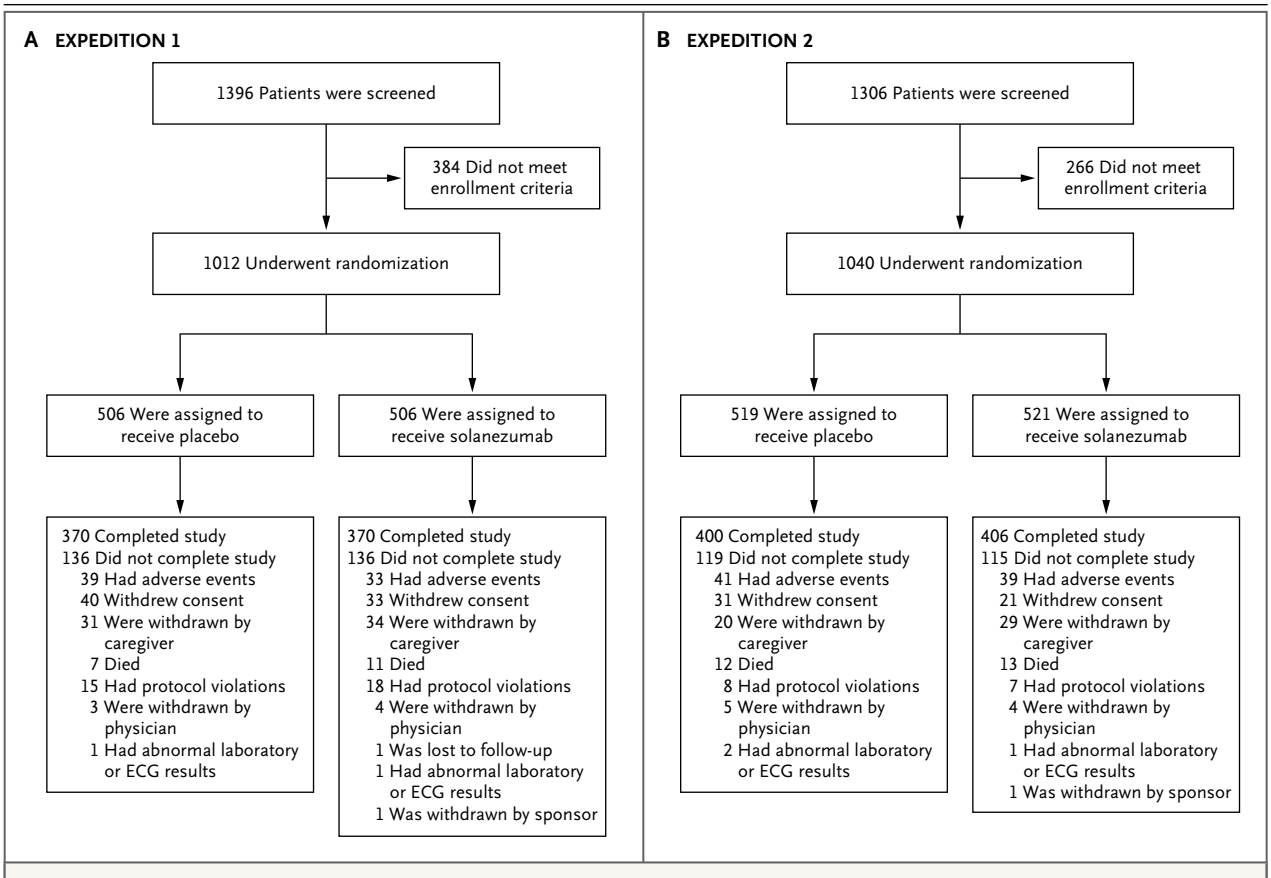

Figure 1. Enrollment, Randomization, and Study Completion in EXPEDITION 1 and EXPEDITION 2.
ECG denotes electrocardiography.

mer's disease, with a mean (±SD) MMSE score of 21±3 in each trial. Approximately 88% of the patients in EXPEDITION 1 and 91% of the patients in EXPEDITION 2 were being treated with cholinesterase inhibitors, memantine, or both at baseline. In EXPEDITION 2, patients with mild Alzheimer's disease (the primary-analysis population in the revised statistical analysis plan) had a mean MMSE score of 23±3, and approximately 89% of these patients were taking cholinesterase inhibitors, memantine, or both at baseline.

COGNITIVE AND CLINICAL OUTCOMES

Primary Outcomes

The results of all primary and secondary analyses are summarized in Tables 2, 3, and 4. Modeled changes from baseline over time in scores on the ADAS-cog11 and the ADCS-ADL scale in the two studies and in scores on the ADAS-cog14 and the ADCS-ADL scale in patients with mild Alzheimer's disease and those with moderate Alzheimer's disease in EXPEDITION 2 are shown in Figures S1 through S8 in the Supplementary Appendix.

In EXPEDITION 1, the mean modeled difference between groups (solanezumab group minus placebo group) in the change from baseline to week 80 was −0.8 points for the ADAS-cog11 score (95% confidence interval [CI], −2.1 to 0.5; P=0.24) and −0.4 points for the ADCS-ADL score (95% CI, −2.3 to 1.4; P=0.64) (Table 2).

In EXPEDITION 2, the mean modeled between-group difference in the change from baseline to week 80 was −1.3 points for the ADAS-cog11 score (95% CI, −2.5 to 0.3; P=0.06) and 1.6 points for the ADCS-ADL score (95% CI, −0.2 to 3.3; P=0.08) (Table 3). Although there were signifi-

Table 1. Demographic and Baseline Clinical Characteristics of the Patients in the Two Solanezumab Studies.*

Characteristic	EXPEDITION 1		EXPEDITION 2			
	Placebo (N=506)	Solanezumab (N=506)	All Patients		Patients with Mild Alzheimer's Disease	
			placebo (N=519)	solanezumab (N=521)	placebo (N=325)	solanezumab (N=322)
Age — yr	74.4±8.0	75.0±7.9	72.4±7.8	72.5±8.0	72.5±7.9	71.5±7.9
Male sex — no. (%)	219 (43.3)	207 (40.9)	233 (44.9)	238 (45.7)	144 (44.3)	159 (49.4)
Race or ethnic group — no. (%)†						
White	427 (84.4)	420 (83.0)	403 (77.6)	399 (76.6)	270 (83.1)	248 (77.0)
Black	25 (4.9)	20 (4.0)	2 (0.4)	7 (1.3)	1 (0.3)	4 (1.2)
Asian	49 (9.7)	65 (12.8)	114 (22.0)	112 (21.5)	54 (16.6)	68 (21.1)
American Indian or Alaska Native	2 (0.4)	0	0	1 (0.2)	0	1 (0.3)
More than one	3 (0.6)	1 (0.2)	0	2 (0.4)	0	1 (0.3)
Education — yr	12.8±3.9	12.6±4.2	11.7±4.2	11.6±4.1	12.2±3.9	11.8±4.0
Antidementia therapy at baseline — no. (%)						
Acetylcholinesterase inhibitor alone	218 (43.1)	229 (45.3)	350 (67.4)	352 (67.6)	219 (67.4)	228 (70.8)
Memantine alone	33 (6.5)	21 (4.2)	35 (6.7)	25 (4.8)	24 (7.4)	9 (2.8)
Acetylcholinesterase inhibitor and memantine	196 (38.7)	197 (38.9)	91 (17.5)	90 (17.3)	52 (16.0)	47 (14.6)
None	59 (11.7)	59 (11.7)	43 (8.3)	54 (10.4)	30 (9.2)	38 (11.8)
MMSE score‡	21±3	21±4	21±3	21±3	23±3	22±3
ADAS-cog11 score§	22±9	22±8	23±10	24±9	19±7	20±7
APOE ε4 carrier — no./total no. (%)	288/470 (61.3)	266/464 (57.3)	281/472 (59.5)	263/463 (56.8)	183/298 (61.4)	155/284 (54.6)

* Plus–minus values are means ±SD.
† Race or ethnic group was self-reported.
‡ Scores on the Mini–Mental State Examination (MMSE) range from 0 to 30, with higher scores indicating better cognitive function.[6]
§ Scores on the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog11) range from 0 to 70, with higher scores indicating greater cognitive impairment.[9]

Table 2. Primary and Secondary Outcomes in EXPEDITION 1, Intention-to-Treat Population.*

Variable	Mean Change from Baseline to Wk 80 (95% CI)		Mean Difference (95% CI)	P Value
	Placebo	Solanezumab		
ADAS-cog11 score†	4.5 (3.3 to 5.8)	3.8 (2.5 to 5.0)	−0.8 (−2.1 to 0.5)	0.24
ADAS-cog14 score‡	5.8 (4.3 to 7.3)	4.5 (2.9 to 6.0)	−1.4 (−2.9 to 0.2)	0.09
ADCS-ADL score†	−8.7 (−10.4 to −7.0)	−9.1 (−10.9 to −7.4)	−0.4 (−2.3 to 1.4)	0.64
CDR-SB score§	1.8 (1.3 to 2.3)	2.0 (1.5 to 2.4)	0.1 (−0.3 to 0.6)	0.51
NPI score¶	0.6 (−1.5 to 2.6)	−0.3 (−2.4 to 1.7)	−0.9 (−2.6 to 0.8)	0.29
MMSE score	−2.0 (−2.8 to −1.2)	−1.4 (−2.2 to −0.6)	0.6 (0.0 to 1.2)	0.06
Free $A\beta_{40}$ in CSF — pg/ml	80.9 (−2100.5 to 2262.3)	−1127.3 (−3272.4 to 1017.9)	−1208.2 (−2132.4 to −283.9)	0.01
Free $A\beta_{42}$ in CSF — pg/ml	−28.5 (−160.0 to 102.9)	−54.4 (−186.7 to 77.9)	−25.8 (−88.3 to 36.6)	0.41
Total $A\beta_{40}$ in CSF — pg/ml	−1902.1 (−6660.1 to 2855.8)	1325.4 (−3162.0 to 5812.9)	3227.6 (1253.6 to 5201.5)	0.002
Total $A\beta_{42}$ in CSF — pg/ml	−242.3 (−1144.4 to 659.7)	471.4 (−436.0 to 1378.8)	713.7 (309.1 to 1118.4)	<0.001

* Mixed-model repeated-measures analyses were used to assess between-group differences (solanezumab group minus placebo group) in the modeled changes from baseline to week 80. The dependent variable was the change from the baseline score at each postbaseline visit during the treatment period. Fixed effects were baseline scores on outcome measures, study-drug assignment (solanezumab or placebo), baseline MMSE score (mild or moderate Alzheimer's disease), visit and treatment-by-visit interaction, concomitant use of cholinesterase inhibitors or memantine at baseline (yes or no), and age at baseline, and the random effect was participant identification. Measurements of amyloid-beta ($A\beta$) in the cerebrospinal fluid (CSF) were available at baseline and follow-up for 25 patients in the placebo group and 20 patients in the solanezumab group. CI denotes confidence interval.

† The primary outcomes were the changes from baseline to week 80 in scores on the ADAS-cog11 and the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale (ADCS-ADL; range, 0 to 78, with lower scores indicating worse functioning).[10]

‡ 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.[9]

§ Scores on the Clinical Dementia Rating–Sum of Boxes (CDR-SB) range from 0 to 18, with higher scores indicating worse functioning.[11,12]

¶ Scores on the Neuropsychiatric Inventory (NPI) range from 0 to 144, with higher scores indicating worse functioning.[13]

Table 3. Primary and Secondary Outcomes in EXPEDITION 2, Intention-to-Treat Population.*

Variable	Mean Change from Baseline to Wk 80 (95% CI)		Mean Difference (95% CI)	P Value
	Placebo	Solanezumab		
ADAS-cog11 score†	6.6 (5.2 to 7.9)	5.3 (4.0 to 6.7)	−1.3 (−2.5 to 0.3)	0.06
ADAS-cog14 score†	7.5 (5.8 to 9.1)	5.9 (4.3 to 7.5)	−1.6 (−3.1 to 0.1)	0.04
ADCS-ADL score†	−10.9 (−12.7 to −9.1)	−9.3 (−11.2 to −7.5)	1.6 (−0.2 to 3.3)	0.08
CDR-SB score	1.9 (1.4 to 2.4)	1.6 (1.2 to 2.1)	−0.3 (−0.7 to 0.2)	0.17
NPI score	3.0 (0.8 to 5.1)	2.8 (0.7 to 5.0)	−0.2 (−1.8 to 1.5)	0.85
MMSE score	−2.8 (−3.6 to −2.0)	−2.1 (−2.8 to −1.3)	0.8 (0.2 to 1.4)	0.01
Free $A\beta_{40}$ in CSF — pg/ml	−649.0 (−2139.5 to 841.5)	−1258.1 (−2695.8 to 179.7)	−609.1 (−1228.4 to 10.2)	0.05
Free $A\beta_{42}$ in CSF — pg/ml	−35.1 (−129.5 to 59.3)	1.0 (−94.1 to 96.2)	36.1 (−1.0 to 73.3)	0.06
Total $A\beta_{40}$ in CSF — pg/ml	−876.4 (−4342.5 to 2589.8)	2156.8 (−1211.9 to 5525.4)	3033.1 (1628.4 to 4437.9)	<0.001
Total $A\beta_{42}$ in CSF — pg/ml	323.8 (86.2 to 561.5)	726.6 (489.4 to 963.9)	402.8 (307.7 to 497.8)	<0.001

* The methods used to analyze between-group differences in outcomes from baseline to week 80 were the same as those used in EXPEDITION 1. Measurements of $A\beta$ in the CSF were available at baseline and follow-up for 32 patients in the placebo group and 44 patients in the solanezumab group.

† The original primary outcomes were the changes from baseline to week 80 in scores on the ADAS-cog11 and the ADCS-ADL scale. After analysis of data from EXPEDITION 1, the primary outcome for EXPEDITION 2 was revised to the change in scores on the ADAS-cog14 in patients with mild Alzheimer's disease.

cant between-group differences in the change in the ADAS-cog11 score at weeks 52 and 64 that favored solanezumab (Fig. S3 in the Supplementary Appendix), there were no significant differences at 80 weeks (end point).

In patients with mild Alzheimer's disease, the modeled between-group difference in the change in the ADAS-cog14 score from baseline to week 80 was −1.7 points (95% CI, −3.5 to 0.1; P=0.06). A significant difference favoring solanezumab was seen at week 64 only (Fig. S5 in the Supplementary Appendix). In patients with moderate Alzheimer's disease, the between-group difference at week 80 was −1.5 points (95% CI, −4.1 to 1.1; P=0.26) (Table 4).

Secondary Outcomes

In EXPEDITION 1, there were no significant treatment-related differences in the change in scores on the MMSE (P=0.06), the CDR-SB (P=0.51), or the NPI (P=0.29) (Table 2), nor were there significant differences in the change in scores on the EQ-5D, RUD-Lite, or QOL-AD scales (Tables S6-1, S6-2, and S6-3, respectively, in the Supplementary Appendix).

In EXPEDITION 2, there was a treatment difference favoring solanezumab in the change in the MMSE score, with a difference of 0.8 points (95% CI, 0.2 to 1.4; P=0.01) (Table 3). There were no significant treatment-related differences in the change in scores on the CDR-SB (P=0.17) or the NPI (P=0.85) (Table 3), nor were there significant differences in the change in scores on the EQ-5D, RUD-Lite, or QOL-AD scales (Tables S6-1, S6-2, and S6-3, respectively, in the Supplementary Appendix).

Among patients in EXPEDITION 2 who had mild Alzheimer's disease, there was a significant treatment effect on the change in the ADCS-ADL score, with a modeled difference between groups of 2.3 points (95% CI, 0.2 to 4.4; P=0.04) at week 80. However, there were no significant treatment-related differences in the change in scores on the MMSE (P=0.10), the CDR-SB (P=0.22), or the NPI (P=0.58) (Table 4), nor were there significant differences in the change in scores on the EQ-5D, RUD-Lite, or QOL-AD scales (Tables S6-1, S6-2, and S6-3, respectively, in the Supplementary Appendix). Among patients with moderate Alzheimer's disease, there was a significant treatment effect on the change in the MMSE score that favored solanezumab, with a

Table 4. Outcomes in Patients with Mild Alzheimer's Disease and in Those with Moderate Alzheimer's Disease at Enrollment in EXPEDITION 2, Intention-to-Treat Population.*

Variable	Mild Alzheimer's Disease				Moderate Alzheimer's Disease				Test for Heterogeneity
	Mean Change from Baseline to Wk 80		Mean Difference (95% CI)	P Value†	Mean Change from Baseline to Wk 80		Mean Difference (95% CI)	P Value†	P Value‡
	placebo	*solanezumab*			*placebo*	*solanezumab*			
ADAS-cog11 score	5.1	3.6	−1.5 (−3.0 to 0.0)	0.05	10.9	10.0	−0.9 (−3.1 to 1.3)	0.43	0.65
ADAS-cog14 score	5.8	4.1	−1.7 (−3.5 to 0.1)	0.06	12.7	11.3	−1.5 (−4.1 to 1.1)	0.26	0.88
ADCS-ADL score	−8.9	−6.6	2.3 (0.2 to 4.4)	0.04	−16.3	−15.8	0.5 (−2.6 to 3.5)	0.77	0.34
CDR-SB score	1.6	1.3	−0.3 (−0.8 to 0.2)	0.22	3.4	3.2	−0.3 (−0.9 to 0.4)	0.44	0.95
NPI score	1.5	1.0	−0.5 (−2.4 to 1.3)	0.58	8.0	8.4	0.4 (−2.5 to 3.4)	0.78	0.60
MMSE score	−2.4	−1.8	0.7 (−0.1 to 1.4)	0.10	−5.8	−4.8	1.0 (0.0 to 1.9)	0.04	0.60

* Methods used to analyze between-group differences (solanezumab group minus placebo group) from baseline to week 80 were the same as those used for the primary analysis. In the placebo group, 325 patients had mild Alzheimer's disease and 194 had moderate Alzheimer's disease; in the solanezumab group, 322 patients had mild Alzheimer's disease and 199 had moderate Alzheimer's disease.
† The P value is for the comparison between the solanezumab group and the placebo group.
‡ The P value is for the comparison between patients with mild Alzheimer's disease and those with moderate Alzheimer's disease.

Table 5. Summary of Adverse Events Occurring during Study Treatment.*

Event	Solanezumab (N=1027)	Placebo (N=1025)
	no. (%)	
Amyloid-related imaging abnormalities		
With edema	9 (0.9)	4 (0.4)
With hemorrhage	50 (4.9)	57 (5.6)
Cardiac disorders	87 (8.5)	66 (6.4)
Cardiac arrhythmias	51 (5.0)	38 (3.7)
Cardiac ischemia	18 (1.8)	12 (1.2)
Eye disorders	67 (6.5)	62 (6.0)
Gastrointestinal disorders	262 (25.5)	278 (27.1)
Diarrhea	73 (7.1)	63 (6.1)
General disorders and administration-site conditions	173 (16.8)	183 (17.9)
Infections and infestations	331 (32.2)	377 (36.8)
Nasopharyngitis	70 (6.8)	76 (7.4)
Upper respiratory tract infection	42 (4.1)	66 (6.4)
Urinary tract infection	71 (6.9)	83 (8.1)
Injury, poisoning, and procedural complications	198 (19.3)	236 (23.0)
Fall	92 (9.0)	107 (10.4)
Need for clinical investigations	131 (12.8)	137 (13.4)
Metabolic and nutritional disorders	116 (11.3)	106 (10.3)
Musculoskeletal and connective-tissue disorders	213 (20.7)	224 (21.9)
Back pain	67 (6.5)	55 (5.4)
Neoplasms: benign, malignant, and unspecified	39 (3.8)	53 (5.2)
Nervous system disorders	281 (27.4)	339 (33.1)
Cerebral microhemorrhage	50 (4.9)	56 (5.5)
Dizziness	58 (5.6)	57 (5.6)
Headache	72 (7.0)	77 (7.5)
Psychiatric disorders	255 (24.8)	288 (28.1)
Anxiety	66 (6.4)	69 (6.7)
Renal and urinary disorders	78 (7.6)	84 (8.2)
Respiratory, thoracic, and mediastinal disorders	138 (13.4)	127 (12.4)
Cough	61 (5.9)	48 (4.7)
Skin and subcutaneous-tissue disorders	126 (12.3)	128 (12.5)
Surgical and medical procedures	54 (5.3)	57 (5.6)
Vascular disorders	90 (8.8)	109 (10.6)

* Adverse events are listed according to the preferred terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 13.1. Events with an incidence of at least 5% in either group are shown. Table S9 in the Supplementary Appendix shows events occurring in at least 2% of patients receiving solanezumab.

between-group difference of 1.0 points (95% CI, 0.0 to 1.9; P=0.04) (Table 4). However, there were no significant treatment-related differences in the change in scores on the CDR-SB (P=0.44) or the NPI (P=0.78) (Table 4), nor were there significant differences in the change in scores on the EQ-5D, RUD-Lite or QOL-AD scales (Tables S6-1, S6-2, and S6-3, respectively, in the Supplementary Appendix).

BIOLOGIC MARKERS AND NEUROIMAGING OUTCOMES

Plasma levels of Aβ_{40} rose between baseline and the first assessment (at week 12) and remained at increased levels through week 80 in the solanezumab groups (P<0.001 in both studies). Plasma levels of Aβ_{42} also rose, with a similar time course, and were sustained through week 80 (P<0.001 in both studies). There were no significant increases in these biologic markers in the placebo groups.

Measurements of Aβ in the CSF were available at baseline and follow-up for 20 patients in the solanezumab group and 25 patients in the placebo group in EXPEDITION 1 and for 44 patients in the solanezumab group and 32 patients in the placebo group in EXPEDITION 2. Levels of free Aβ_{40} decreased in the solanezumab groups, with no appreciable change in the placebo groups (P=0.01 in EXPEDITION 1 and P=0.05 in EXPEDITION 2 for the between-group comparison of the change from baseline) (Tables 2 and 3). Levels of total Aβ_{40} increased in the solanezumab groups (P=0.002 in EXPEDITION 1 and P<0.001 in EXPEDITION 2 for the change from baseline as compared with the placebo groups). Levels of total Aβ_{42} also increased in the solanezumab groups, with no appreciable change in the placebo groups (between-group difference, P<0.001 in both studies), whereas levels of free Aβ_{42} did not change significantly.

There were no significant changes in CSF levels of tau or phospho-tau in the solanezumab group or placebo group in either study. Hippocampal volumes decreased as expected during the 80 weeks in the solanezumab group and the placebo group in both studies, but there were no significant treatment-related differences in either study. Whole-brain volume increased slightly in the solanezumab group and the placebo group in both studies, and the between-group comparisons were not significant.

A total of 169 patients in EXPEDITION 1 (17%)

and 97 patients in EXPEDITION 2 (9%) underwent baseline and follow-up ^{18}F-florbetapir–PET scanning. The composite standardized uptake value ratio for the anterior and posterior right and left cingulate, plus right and left frontal, lateral temporal, and parietal regions, combined and normalized to the whole cerebellum, did not change significantly in the solanezumab group or the placebo group in either study.

ADVERSE EVENTS AND DEATHS

There were no adverse events for which the overall rate was at least 2% and the rate in the combined solanezumab groups was at least twice the rate in the placebo groups. After a review of the serious adverse events, which showed that cardiac diseases were numerically more common in patients who received solanezumab than in those who received placebo (Table S5 in the Supplementary Appendix), we investigated cardiac arrhythmia and cardiac ischemia, even though the between-group differences in these adverse events did not meet our prespecified criteria above. Arrhythmia occurred in 5.0% of patients who received solanezumab and in 3.7% of those who received placebo (P=0.20; ischemia occurred in 1.8% and 1.2% of patients, respectively (P=0.36) (Table 5, and Tables S4 and S9 in the Supplementary Appendix). Because antiamyloid treatments have been associated with amyloid-related imaging abnormalities with edema or hemorrhage,[20] we compared these findings in the combined solanezumab and placebo groups. Amyloid-related imaging abnormalities with edema were observed in 0.9% of patients who received solanezumab and in 0.4% of those who received placebo (P=0.27); amyloid-related imaging abnormalities with hemorrhage were observed in 4.9% and 5.6% of patients, respectively (P=0.49).

The frequency of serious adverse events occurring during the study treatment was low across system or organ classes as listed in the *Medical Dictionary for Regulatory Activities*, version 13.1, with no apparent association between any event and solanezumab treatment (Table S5 in the Supplementary Appendix). There were 19 deaths among patients who received placebo and 24 deaths among those who received solanezumab (Table S7 in the Supplementary Appendix). Examination of all listed causes of death revealed no clear treatment-related pattern.

DISCUSSION

Two randomized, double-blind, placebo-controlled, phase 3 studies of solanezumab treatment were performed in patients with mild-to-moderate Alzheimer's disease. Neither study showed a benefit of solanezumab with respect to the originally designated coprimary outcomes: the changes from baseline in scores on the ADAS-cog11 and the ADCS-ADL scale. On the basis of the results of EXPEDITION 1 and while EXPEDITION 2 was still under way, the statistical analysis plan of EXPEDITION 2 was amended to designate the change in ADAS-cog14 scores in patients with mild Alzheimer's disease as the primary outcome. Solanezumab treatment did not significantly improve ADAS-cog14 scores in the EXPEDITION 2 study in patients with mild Alzheimer's disease, as hoped. Thus, the two phase 3 studies were negative. As predicted on the basis of preclinical data showing that solanezumab does not directly target fibrillar amyloid plaques,[21] this monoclonal antibody therapy was associated with a low incidence of amyloid-related imaging abnormalities with edema or hemorrhage.

It has been proposed that therapies targeting amyloid in patients with Alzheimer's disease must be instituted early in the disease, possibly in presymptomatic stages, to substantially modify the symptoms or course of the disease.[22] However, the revised statistical analysis plan for EXPEDITION 2, which focused on patients with mild Alzheimer's disease, did not show clinical efficacy of solanezumab. It is possible that larger studies of solanezumab in patients with mild Alzheimer's disease or studies of solanezumab in asymptomatic persons with biomarker evidence of brain amyloid accumulation will show efficacy.

Several past attempts to treat Alzheimer's disease by reducing brain amyloid have yielded results suggesting that individual approaches, or antiamyloid drugs as a class, might have a deleterious effect on the symptoms, course, or neuroimaging signs of Alzheimer's disease, including the active immunotherapeutic agent AN1792,[23] high doses of the antiaggregation agent scyllo-inositol,[24] the γ-secretase inhibitor avagacestat,[25] the plaque-binding passive immunotherapeutic agent bapineuzumab (especially in *APOE* ε4 carriers),[26] and the γ-secretase inhibitor semagace-

stat.[27] The results of the current study argue for carefully differentiating among these therapeutic approaches according to the underlying mechanism, rather than for grouping all antiamyloid treatments together.

The solanezumab studies, like others before them, included assessments of biologic and neuroimaging markers associated with disease progression in an attempt to show target engagement, as well as for the purpose of potentially correlating biologic markers with clinical effects. However, the current studies failed to show treatment effects on hippocampal or total brain volumes or on amyloid accumulation with the use of ^{18}F-florbetapir–PET. These results are consistent with the observation that solanezumab does not target fibrillar amyloid. Our PET findings were not conclusive because of the small sample, but sufficient numbers of solanezumab-treated and untreated patients underwent serial MRI to make the failure to detect a slowing of brain atrophy a meaningful finding. Future analyses of MRI data on brain volume and of PET data on amyloid accumulation in a larger population of patients with mild Alzheimer's disease could yield useful exploratory hypotheses.

The changes that we saw in plasma and CSF levels of Aβ are consistent with target engagement of soluble brain amyloid by solanezumab. There were large, sustained increases of Aβ in plasma, which is not surprising because the antibody was directly infused into the blood. The reduction in CSF levels of free (unbound) Aβ_{40} in conjunction with increased CSF levels of total (bound and unbound) Aβ_{40} in patients who received solanezumab suggests that there was movement of Aβ within the central compartment. CSF levels of total Aβ_{42} also increased. It is plausible that these central shifts of Aβ were associated with some transfer of Aβ to the periphery. Alternatively, subtle central shifts of Aβ between compartments that disrupt the equilibrium between fibrillar and soluble Aβ could be hypothesized to lead to a reduction in soluble brain amyloid.

There are several mechanistically different strategies with a good rationale that provide treatment targets for Alzheimer's disease. Antiamyloid treatments include passive and active immunotherapies, antiaggregation approaches, and γ- and β-secretase inhibitors. Other strategies include neurotransmitter-based therapies, metabolic or neurotrophic drugs, regenerative approaches, glial-cell modulators, and anti–tau proteinopathy approaches. Our analyses of data from these two phase 3 solanezumab trials did not show efficacy of this monoclonal antibody. Nonetheless, further studies of solanezumab, in patients with mild Alzheimer's disease or in asymptomatic persons with biomarker evidence of brain amyloid accumulation, are necessary for a thorough test of this particular antiamyloid approach.

Supported by Eli Lilly.

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

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