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Phase 3 solanezumab trials: Secondary outcomes in mild Alzheimer's disease patients

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Abstract

Background: EXPEDITION and EXPEDITION2 were identically designed placebo-controlled phase 3 studies assessing effects of solanezumab, an antiamyloid monoclonal antibody binding soluble amyloid-β peptide, on cognitive and functional decline over 80 weeks in patients with mild-to-moderate Alzheimer's disease (AD). Primary findings for both studies have been published.

Methods: Secondary analyses of efficacy, biomarker, and safety endpoints in the pooled (EXPEDTION + EXPEDITION2) mild AD population were performed.

Results: In the mild AD population, less cognitive and functional decline was observed with solanezumab (n = 659) versus placebo (n = 663), measured by Alzheimer's Disease Assessment Scale Cognitive subscale, Mini-Mental State Examination, and Alzheimer's Disease Cooperative Study–Activities of Daily Living functional scale Instrumental ADLs. Baseline-to-endpoint changes did not differ between treatment groups for Alzheimer's Disease Cooperative Study–Activities of Daily Living functional scale, basic items of the ADCS-ADL, and Clinical Dementia Rating Sum of Boxes. Plasma/cerebrospinal fluid biomarker findings indicated target engagement by solanezumab. Solanezumab demonstrated acceptable safety. Efficacy findings for the moderate AD population are also provided.

Conclusion: These findings describe solanezumab effects on efficacy/safety measures in a mild AD population. Another phase 3 study, EXPEDITION3, will investigate solanezumab's effects in a mild AD population.

Keywords: Mild Alzheimer's disease; Solanezumab; Clinical trial; Phase 3; Cognition; Function; Safety; Monoclonal antibody; EXPEDITION; Target engagement; Amyloid-β peptide; LZAM; LZAN

1. Introduction

Investigational agents that are intended to slow the clinical progression of Alzheimer's disease (AD) have been studied for over a decade; however, none have been successful thus far. Most of these investigational agents were intended to target the amyloid-β (Aβ) peptide or deposited amyloid plaques [1], although clear evidence of target engagement has not been consistently demonstrated [2]. Biomarker evidence of target engagement has been demonstrated for semagacestat, a gamma-secretase inhibitor [3,4] and bapineuzumab, a monoclonal antibody targeting deposited amyloid plaques [5]. Despite evidence for target engagement in the central nervous system, in recent phase 3 trials, semagacestat was unexpectedly shown to cause cognitive worsening [4], whereas bapineuzumab had no effect on cognitive decline [5].

Solanezumab is an IgG1 antiamyloid monoclonal antibody that binds to the mid-domain of the Aβ peptide and

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is thought to increase clearance of soluble Aβ. Preclinical studies using transgenic APP^{V717F} mice demonstrated that administration of the murine anti-Aβ monoclonal antibody from which solanezumab was derived (m266.2) reduced brain amyloid plaque deposition [6,7] and showed strong correlations between plasma Aβ accumulation and plaque deposition. In phase 1 and phase 2 studies of patients with mild-to-moderate AD, evidence of target engagement was demonstrated by dose-dependent increases in plasma and cerebrospinal fluid (CSF) total (bound plus unbound) Aβ [8,9]. The increase in CSF total Aβ is presumably a result of solanezumab movement from plasma to the central nervous system, binding to Aβ in that compartment with accumulation of measureable total Aβ in CSF [8]. Solanezumab administration had more complex effects on free (unbound) isoforms of Aβ in CSF. In the phase 2 study of patients with AD, 12 weeks of solanezumab treatment produced a dose-dependent *increase* in CSF free $Aβ_{1–42}$, the predominant form of Aβ found in amyloid plaque. In contrast, solanezumab produced evidence of a dose-dependent *decrease* in CSF free $Aβ_{1–40}$, a much less abundant form of Aβ in amyloid plaque [9]. The cause of these disparate effects on the free fractions of $Aβ_{1–42}$ and $Aβ_{1–40}$ is not entirely clear. Given that solanezumab has similar affinity for the two Aβ isoforms and the relative abundance of each isoform is different in amyloid plaque (consisting primarily of $Aβ_{1–42}$), we questioned whether solanezumab might be altering equilibria such that concentrations of *free* $Aβ_{1–42}$ in CSF might be different from those of free $Aβ_{1–40}$ after administration of solanezumab because of the relative abundance of $Aβ_{1–42}$ in plaque [2,9].

The first phase 3 studies of solanezumab (EXPEDITION and EXPEDITION2) examined the effect versus placebo on cognitive and functional decline over 80 weeks in patients with mild-to-moderate AD dementia. The original planned coprimary endpoints in both studies were the Alzheimer's Disease Assessment Scale Cognitive subscale ($ADAS\text{-}Cog_{11}$) [10,11] and the Alzheimer's Disease Cooperative Study–Activities of Daily Living functional scale (ADCS-ADL) [12]. Primary outcome findings from these two separate studies, with analyses conducted by the ADCS Data Analysis and Publication Committee, have been described previously [13]. Neither study showed a significant benefit of solanezumab for both originally designated coprimary outcomes.

Key prespecified secondary analyses in the EXPEDITION and EXPEDITION2 statistical analysis plans (SAPs) included subgroup analyses based on disease severity (mild or moderate AD dementia) at baseline; these analyses were performed based on the concept that therapies targeting amyloid should be started early in the AD disease process to substantially modify the course of the disease [14]. In addition, because EXPEDITION and EXPEDITION2 were identical in design, an SAP was developed for a secondary analysis of the pooled data from these two studies, which included analyses of the mild and moderate AD populations separately. After review of the analyses of the pooled mild AD population described in this report, a third phase 3 trial, EXPEDITION3, was initiated to continue to explore the effects of solanezumab in patients with mild AD.

2. Methods

2.1. Study design

The designs of the phase 3 trials, EXPEDITION and EXPEDITION2, have been described previously [13,15,16].

Briefly, both were multinational, randomized, double-blind, placebo-controlled studies of solanezumab 400 mg in outpatients with mild-to-moderate AD. Patients were at least 55 years old and met criteria for probable AD based on National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria [17]. Patients with Mini-Mental State Examination (MMSE) [18] scores of 16 through 26 were allowed to participate. Mild disease was defined as screening visit MMSE scores of 20–26; moderate was defined as screening visit scores of 16–19. Subjects were randomized by investigative site and AD severity (mild/moderate) to ensure an even distribution of severity of disease across treatment groups.

Study medication was given intravenously every 4 weeks through week 76, with final evaluations occurring 4 weeks later at week 80, such that total duration was approximately 18 months. Subjects were allowed to continue on stable doses of standard of care symptomatic medications, such as acetylcholinesterase inhibitors and memantine, for the duration of the study.

After obtaining results from EXPEDITION, but before obtaining results from EXPEDITION2, the SAP for the pooled data set (EXPEDITION plus EXPEDITION2) was modified to consider the mild AD population as primary, with the $ADAS\text{-}Cog_{14}$ as the primary efficacy outcome. The $ADAS\text{-}Cog_{14}$ is an expanded version of the $ADAS\text{-}Cog_{11}$ that includes three additional items to assess executive function and delayed verbal recall; these additional domains may be more likely to be affected in patients with mild AD, thereby increasing the sensitivity of the scale in this population [11].

Other prespecified outcome measures included $ADAS\text{-}Cog_{11}$, ADCS-ADL (total score and subscores for the basic and instrumental ADLs), Clinical Dementia Rating Sum of Boxes (CDR-SB), and MMSE. The $ADAS\text{-}Cog_{14}$, $ADAS\text{-}Cog_{11}$, and ADCS-ADL were administered at baseline and weeks 12, 28, 40, 52, 64, and 80; and the CDR-SB and MMSE were administered at baseline and weeks 28, 52, and 80.

Plasma $Aβ_{1–40}$ and $Aβ_{1–42}$ levels were measured as described previously [19] and brain volumetric magnetic

resonance imaging (vMRI) was performed at multiple time points in all subjects. In those participating in an optional study addendum, CSF free (unbound) and total (bound plus unbound) fractions of $A\beta_{1-40}$ and $A\beta_{1-42}$ and CSF tau and phosphorylated-tau (p-tau) were measured as described previously [9,19,20]. In a second optional study addendum, amyloid burden was assessed by a positron emission tomography (PET) scan using florbetapir F18 [21]. In these addenda, CSF proteins and amyloid burden were measured at baseline and week 80 or early termination.

Proprietary, validated, drug-tolerant assays were used to detect, characterize, and titer treatment-emergent antidrug antibodies.

2.2. Statistical methods

Unless otherwise specified, data were analyzed using the intent-to-treat mild AD population (i.e., all randomized subjects with mild AD in EXPEDITION and EXPEDITION2), and all tests of treatment effects were to be conducted at a two-sided alpha level of 0.05. Baseline for the treatment period was defined as the last observation collected before the first infusion of study medication unless otherwise specified.

Baseline characteristics were summarized by treatment group and overall for all randomized subjects with mild AD. The Cochran-Mantel-Haenszel test, controlling for study, was used for treatment group comparisons of categorical data. For continuous data, analysis of variance, with independent factors for treatment and investigator, was used.

To test the hypothesis that solanezumab slowed cognitive decline compared with placebo in patients with mild AD, we used a mixed model repeated measures (MMRM) analysis for ADAS-Cog_{14}. An MMRM analysis was used for other efficacy outcome measures also. A repeated measures analysis modeling the change from baseline score at each scheduled postbaseline visit as the dependent variable was constructed. The model for the fixed effects included terms for eight effects: baseline score, study, treatment, study-by-treatment interaction, visit, treatment-by-visit interaction, concomitant AChEI and/or memantine use at baseline (yes/no), and age at baseline. Visit was considered a categorical variable with values equal to the visit numbers at which the scales were assessed. The null hypothesis was that the difference between solanezumab versus placebo at the last visit (week 80) equaled zero. To assess the effects of missing data on our conclusions, sensitivity analyses were conducted, including selection modeling and pattern mixture modeling, on the individual study data for the ADAS-Cog_{14} and the instrumental items of the ADCS-ADL (ADCS-iADL).

For assessment of brain amyloid burden, a composite standardized uptake value ratio (SUVR) was derived that included the anterior and posterior cingulate, frontal cortex, temporal cortex, parietal cortex, and precuneus regions normalized to the mean whole cerebellum [22]. Analysis of change in composite SUVR and the changes in CSF analytes ($A\beta_{1-40}$, $A\beta_{1-42}$, total tau, and p-tau) were performed using analysis of covariance models including terms for baseline, study, treatment, study-by-treatment interaction, and baseline age.

Because vMRI (whole brain atrophy and total ventricular volume) and measurement of plasma Aβ ($A\beta_{1-40}$ and $A\beta_{1-42}$) were performed at multiple time points during the studies, each parameter was analyzed separately using an MMRM analysis. Change from baseline score at each postbaseline visit on which the measure was performed was the dependent variable. The model for the fixed effects included the following independent terms: baseline value, study, treatment, visit, treatment-by-visit interaction, study-by-treatment interaction, and age at baseline. Visit was a categorical variable.

All safety analyses were performed using data from all randomized subjects with mild AD in EXPEDITION and EXPEDITION2 who had received at least one dose of study medication. Treatment-emergent adverse events (TEAEs) were defined as adverse events (AEs) that first occurred or worsened on or after baseline. Adverse events were coded according to established MedDRA terms and summarized by MedDRA system organ class (SOC) and preferred term (PT). For TEAEs of special interest (e.g., potential class effects and prior and potential signals identified during safety surveillance), separate analyses were performed using predefined MedDRA standard medical queries (SMQs). For *cardiac arrhythmia*, SMQs used were arrhythmia-related investigations, signs, and symptoms; bradyarrhythmias (including conduction defects and disorders of sinus node function); cardiac arrhythmia terms, nonspecific; supraventricular tachyarrhythmias; tachyarrhythmia terms, nonspecific; and ventricular tachyarrhythmias. For *cardiac ischemic events*, SMQs were acute myocardial infarction and other ischemic heart disease. For *suicidal ideation or behavior*, the SMQ was suicide/self-injury. For *hemorrhagic stroke*, the SMQ was haemorrhagic cerebrovascular conditions. For *infusion-related reactions*, the SMQ was anaphylactic reaction; two additional PTs, infusion-related reaction and urticaria, were also included. Analyses of TEAE data were performed using a Cochran-Mantel-Haenszel test with study as strata.

Magnetic resonance imaging (MRI) of the brain was performed at weeks 0, 12, 28, 52, and 80 (endpoint) or early discontinuation to evaluate possible amyloid-related imaging abnormalities-hemosiderin deposition/hemorrhage (ARIA-H) and/or amyloid-related imaging abnormalities-edema/effusion (ARIA-E). ARIA-H was quantified categorically by number of microhemorrhages (0, 1, 2–5, 6–10, >10). A categorical increase was defined as a shift to a higher category; any increase in number of microhemorrhages from >10 was also considered a categorical increase.

All statistical analyses in this report were performed by Eli Lilly and Company or a contracted research

organization. The analyses in this report were performed independently from those reported previously [13].

3. Results

Flow of subjects with mild AD through the EXPEDITION trials is shown in Fig. 1. A total of 1322 patients with mild AD were randomized in EXPEDITION plus EXPEDITION2. Of these, 521 of the 663 assigned to placebo (79%) completed the study, versus 503 of the 659 assigned solanezumab (76%; $P > .05$).

3.1. Baseline characteristics

Baseline demographic and clinical characteristics of the pooled mild AD population are summarized in Table 1. No differences between the treatment groups were observed for age, gender, or race ($P > .05$). Of note, almost 90% of the study population was taking a concomitant standard of care treatment for AD. Except for expected geographic differences in standard of care practices, baseline demographic and outcome measures for the mild AD population appeared similar in the EXPEDITION and EXPEDITION2 studies (data not shown).

3.2. Efficacy findings

In the pooled mild AD population, less decline from baseline to endpoint was observed in the solanezumab treatment group versus placebo for the ADAS-Cog$_{14}$ (primary efficacy outcome measure for the analyses of the pooled data set), as well as some other prespecified cognitive and functional outcomes (ADAS-Cog$_{11}$, MMSE, and ADCS-iADL; $P < .05$ in all cases; Table 2). For the ADAS-Cog$_{14}$ and MMSE, there was a slowing of decline of 34%; for ADCS-iADL, there was a slowing of decline of 18%. The decline from baseline did not differ between solanezumab and placebo groups in the case of ADCS-ADL, basic items of the ADCS-ADL (ADCS-bADL), and CDR-SB. For each measure, the study-by-treatment interaction was not significant. Sensitivity analyses findings were consistent with these findings and did not affect the conclusions (data not shown). Findings for the pooled moderate AD population are provided in Supplementary Table 1.

Fig. 2 shows the mean change over the course of 18 months of treatment with solanezumab or placebo for cognitive and functional outcomes. For the ADAS-Cog$_{14}$, as well as the ADAS-Cog$_{11}$, significant differences between treatment groups ($P < .05$) were first observed at week 40 and were sustained through endpoint (week 80). For MMSE, the difference between treatment groups reached significance at endpoint ($P < .001$). For the ADCS-iADL, significant differences between treatment groups ($P < .05$) were observed at week 64 and sustained through endpoint. No differences were evident between treatment groups for change from baseline on the ADCS-ADL, the ADCS-bADL subscale or the CDR-SB ($P > .05$). The placebo versus active treatment group differences in the ADAS-Cog$_{14}$ and ADCS-iADL increased over 18 months.

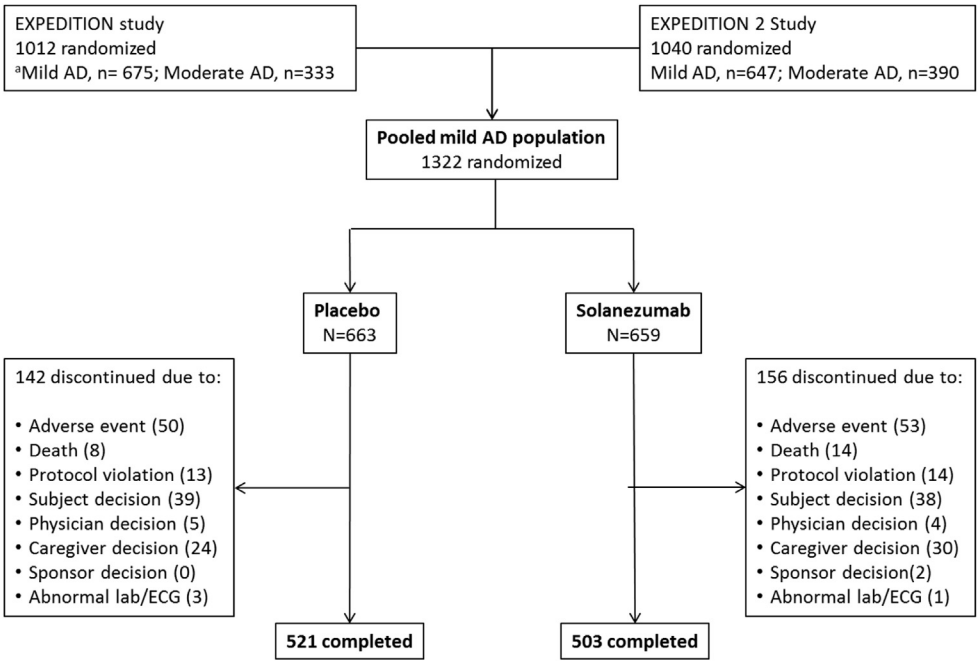


Fig. 1. Flow of study subjects. [a]Disease severity was based on baseline MMSE score (mild, MMSE 20–26; moderate, MMSE 16–19). Baseline MMSE was outside of the study eligibility range (>26) for some randomized subjects, and these individuals were not categorized based on disease severity nor included in pooled mild-AD data set. Abbreviations: MMSE, Mini-Mental State Examination; AD, Alzheimer's disease; lab, laboratory measure; ECG, echocardiogram.

Table 1
Baseline characteristics for the mild AD study population

Baseline characteristic	Placebo* (n = 663)	Solanezumab* (n = 659)	Total (N = 1322)
Age, mean (SD), y	73.3 (7.9)	73.9 (8.1)	73.6 (8.0)
Education, mean (SD), y	12.6 (3.9)	12.4 (4.0)	12.5 (4.0)
Female, n (%)	362 (54.6)	346 (52.5)	708 (53.6)
Race, n (%)			
White	558 (84.2)	530 (80.4)	1088 (82.3)
Black or African American	12 (1.8)	16 (2.4)	28 (2.1)
Asian	91 (13.7)	111 (16.8)	202 (15.3)
Other†	2 (0.3)	2 (0.3)	4 (0.3)
APOE ε4 carriers, n (%)‡	367 (59.8)	329 (55.3)	696 (57.6)
Time since symptom onset, mean (SD), y	4.2 (2.6)	4.3 (2.4)	4.3 (2.5)
Time since diagnosis, mean (SD), y	2.0 (1.9)	1.9 (1.8)	1.9 (1.8)
Standard of Care medication at baseline, n (%)	587 (88.5)	574 (87.1)	1161 (87.8)
Baseline efficacy measures			
MMSE	22.5 (2.8)	22.5 (2.8)	22.5 (2.8)
ADAS-Cog$_{11}$	18.9 (7.0)	19.4 (6.9)	19.1 (6.9)
ADAS-Cog$_{14}$	29.6 (8.8)	30.1 (8.6)	29.9 (8.7)
ADCS-ADL	63.8 (10.8)	63.4 (11.2)	63.6 (11.0)
ADCS-bADL	20.9 (2.1)	21.0 (1.9)	20.9 (2.0)
ADCS-iADL	42.9 (9.5)	42.4 (10.0)	42.7 (9.7)
CDR-SB	4.4 (2.2)	4.4 (2.1)	4.4 (2.1)

Abbreviations: AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive subscale (11 item and 14 item); ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; ADCS-bADL, ADCS-ADL Basic ADLs; ADCS-iADL, ADCS-ADL Instrumental ADLs; CDR-SB, Clinical Dementia Rating Sum of Boxes.

*Number of randomized subjects. For baseline efficacy measures, the number of subjects included in each analysis varies based on the number of subjects with a baseline value for that measure.

†Other comprises American Indian or Alaska Native, and Multiple.

‡Percentage based on number of subjects with *APOE* ε4 status available (placebo, 614; solanezumab, 595).

3.3. Biomarker findings

Plasma levels of both A$\beta_{1–40}$ and A$\beta_{1–42}$ rose between baseline and the first postbaseline assessment (week 2), eventually approximating and remaining roughly 300- to 500-fold higher through week 80 in the solanezumab treatment group compared with placebo ($P < .001$ for both species); no increases in A$\beta_{1–40}$ or A$\beta_{1–42}$ were seen in subjects assigned placebo.

Overall, 185 subjects with mild AD participated in the optional CSF collection addendum. Baseline to endpoint change in level of CSF total (bound plus unbound) A$\beta_{1–40}$ was greater in the solanezumab treatment group (least squares mean change [standard error, SE], 2774.0 pg/mL [468.2]) versus placebo (−721.8 pg/mL [469.7]; $P < .0001$), as was change in level of CSF total A$\beta_{1–42}$ (550.0 pg/mL [62.7] vs. 6.13 pg/mL [62.5]; $P < .0001$). CSF concentration of free (unbound) A$\beta_{1–40}$ decreased more in the solanezumab treatment group (−1053.5 pg/mL [199.1]) than in the placebo group (−314.6 pg/mL [199.4]; $P = .01$). In contrast, change in CSF level of free

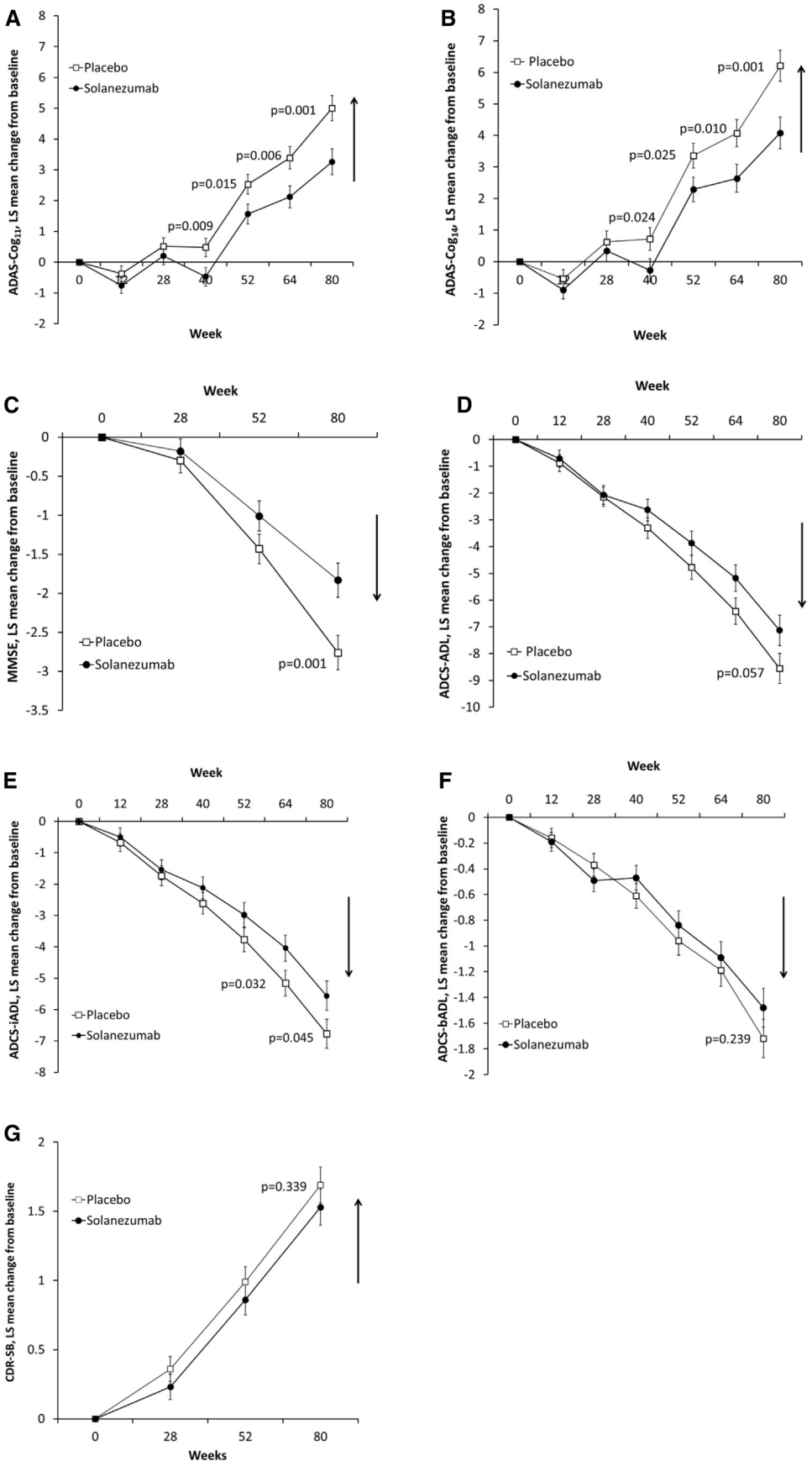
Table 2
Mean change (baseline to endpoint) in prespecified outcome measures for the mild AD study population

Outcome measure†	Least squares mean change (SE)		*P* value	Reduction in decline with solanezumab versus placebo, %
	Placebo* (n = 663)	Solanezumab* (n = 659)		
ADAS-Cog$_{14}$	6.21 (0.49)	4.08 (0.50)	.001	34.3
ADAS-Cog$_{11}$	5.00 (0.41)	3.26 (0.42)	.001	34.8
MMSE	−2.76 (0.22)	−1.83 (0.22)	.001	33.7
ADCS-ADL	−8.55 (0.56)	−7.13 (0.57)	.057	16.6
ADCS-bADL	−1.72 (0.15)	−1.48 (0.15)	.24	14.0
ADCS-iADL	−6.77 (0.46)	−5.56 (0.47)	.045	17.9
CDR-SB	1.69 (0.13)	1.53 (0.13)	.34	9.5

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive subscale (11 item and 14 item); MMSE, Mini-Mental State Examination; ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; ADCS-bADL, ADCS-ADL Basic ADLs; ADCS-iADL, ADCS-ADL Instrumental ADLs; CDR-SB, Clinical Dementia Rating Sum of Boxes.

*Number of randomized subjects. The number of subjects included in each analysis varies based on the number of subjects with a baseline and postbaseline value for that measure.

†Worsening of illness is indicated by increasing score on the ADAS-Cog and CDR-SB but decreasing score on the MMSE and ADCS-ADL.


A
ADAS-Cog11, LS mean change from baseline
Placebo
Solanezumab
p=0.001
p=0.006
p=0.015
p=0.009
Week
B
ADAS-Cog14, LS mean change from baseline
Placebo
Solanezumab
p=0.001
p=0.010
p=0.025
p=0.024
Week
C
MMSE, LS mean change from baseline
Week
Placebo
Solanezumab
p=0.001
D
ADCS-ADL, LS mean change from baseline
Week
Placebo
Solanezumab
p=0.057
E
ADCS-iADL, LS mean change from baseline
Week
Placebo
Solanezumab
p=0.032
p=0.045
F
ADCS-bADL, LS mean change from baseline
Week
Placebo
Solanezumab
p=0.239
G
CDR-SB, LS mean change from baseline
Placebo
Solanezumab
p=0.339
Weeks

$A\beta_{1-42}$ did not differ between the solanezumab treatment group (−21.4 pg/mL [13.2] vs. placebo −35.6 pg/mL [13.4]; $P = .46$). Baseline to endpoint changes in levels of CSF total tau and p-tau did not differ between treatment groups ($P > .05$; Supplementary Table 2).

Of the 251 subjects with mild AD who participated in the optional amyloid imaging addendum and had interpretable baseline scans, 195 (78%) were considered to have positive amyloid burden at baseline based on a centralized visual reading of the PET scans. For these baseline amyloid positive subjects, the treatment group difference in baseline to endpoint change in composite summary SUVR normalized to mean whole cerebellum did not reach statistical significance (LS mean change [SE] placebo: 0.02 [0.017] vs. solanezumab: −0.01 [0.019]; $P = .17$).

Baseline to endpoint changes in whole brain and ventricular volume as measured by vMRI did not differ between treatment groups ($P > .05$; Supplementary Table 3). In both the solanezumab and placebo group, the loss in whole brain volume (atrophy) was approximately 20 cm^3 and ventricular size increased approximately 6.7 cm^3.

3.4. Safety findings

There were no differences between treatment groups in number of reported deaths ($P > .05$; Table 3). At the SOC level, there were no differences between groups in reporting frequency of serious adverse events (SAEs; $P > .05$ vs. placebo) with the exception of cardiac disorders, where events were more frequently reported in the solanezumab versus placebo group (3.8% vs. 1.8%; $P = .028$); the incidence of individual SAEs at the PT level within this SOC was not significantly different between groups. At the PT level, the only SAE for which there was a difference in reporting frequency between treatment groups was noncardiac chest pain which was less frequently reported in the solanezumab treatment group ($P = .046$; Table 3).

Fewer solanezumab- versus placebo-assigned subjects reported TEAEs within the following SOCs: nervous system disorders (27.8% vs. 33.8%; $P = .019$); injury, poisoning, and procedural complications (20.8% vs. 25.5%; $P = .045$); and vascular disorders (8.0% vs. 11.7%; $P = .024$). There were no SOCs for which TEAEs were reported more frequently with solanezumab. TEAEs at the PT level which were reported more frequently with solanezumab were cardiac failure congestive, arthropod sting, emphysema, rash pruritic, and rash papular (Table 3); 14 TEAEs at the PT level (accidental overdose, hemoglobin decreased, major depression, urinary incontinence, hematuria, upper respiratory tract infection, sinusitis, subdural hematoma, procedural pain, lacunar infarction, duodenal ulcer, helicobacter infection, dermatitis allergic, and skin neoplasm excision) were reported more frequently with placebo ($P < .05$).

Table 3
Pooled safety findings for the mild AD study population

Event	Number of events (%) Placebo* (n = 660)	Solanezumab* (n = 654)	P value
Discontinuations due to AE	58 (8.8)	67 (10.2)	.37
Deaths†	8 (1.2)	14 (2.1)	.19
Serious SAEs‡	132 (20.0)	127 (19.4)	.79
Non-cardiac chest pain	4 (0.6)	0	.046
TEAEs‡	551 (83.5)	545 (83.3)	.94
Cardiac failure congestive	0	4 (0.6)	.044
Arthropod stings	0	6 (0.9)	.014
Emphysema	0	4 (0.6)	.044
Rash pruritic	0	6 (0.9)	.014
Rash papular	0	5 (0.8)	.024
Cardiac AEs of interest			
Cardiac ischemia§	10 (1.5)	15 (2.3)	.30
Cardiac arrhythmia§	32 (4.8)	41 (6.3)	.26

Abbreviations: AD, Alzheimer's disease; AE, adverse event; SAE, serious AE; TEAE, treatment-emergent adverse event.

*Number of randomized subjects who received at least one dose of study medication.

†Deaths in the placebo treatment group were reported to be due to cardiac arrest, laryngeal cancer, respiratory arrest, respiratory failure, pneumonia, renal failure chronic, and subarachnoid hemorrhage. Deaths in the solanezumab treatment group were reported to be due to acute myocardial infarction, B-cell lymphoma, cardiac arrest, cardiogenic shock, completed suicide, haemorrhagic stroke, lower respiratory tract infection, myocardial infarction, pneumonia, respiratory failure, septic shock, and unresponsive to stimuli. All causes are listed at the MedDRA preferred term level.

‡Specific events are shown at the MedDRA preferred term level where differences between treatment groups at $P < .05$.

§Comprises relevant SMQs (see Methods section for details).

Treatment-emergent cardiac-related events from the cardiac disorders SOC with a treatment group difference at $P < .10$ were examined and revealed the following: The reported incidences of individual cardiac events (angina pectoris, sinus bradycardia, cardiac failure congestive, and acute myocardial infarction) were ≤1.1% for either treatment group. Only cardiac failure congestive was reported more frequently in the solanezumab versus placebo group ($P = .044$; Table 3). Neither the incidence of cardiac ischemic events nor of cardiac arrhythmias differed between treatment groups ($P > .05$; Table 3).

Neither the overall incidences of events categorized as treatment-emergent infusion-related reactions, suicidal

Fig. 2. LS mean change from baseline in (A) ADAS-Cog11, (B) ADAS-Cog14, (C) MMSE, (D) ADCS-ADL, (E) ADCS-iADLs, (F) ADCS-bADLs, and (G) CDR-SB over the 80-week study period for the mild AD study population. *P* values shown where $P < .05$ for difference between treatment groups at any time point and for difference between groups at 80 weeks. Error bars represent standard error. Arrows show direction for cognitive or functional decline. Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive subscale (11 item and 14 item); MMSE, Mini-Mental State Examination; ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; ADCS-iADL, ADCS-ADL Instrumental ADLs; ADCS-bADL, ADCS-ADL Basic ADLs; CDR-SB, Clinical Dementia Rating Sum of Boxes.

ideation or behavior, or hemorrhagic stroke, nor the incidences of any individual events at the PT level within the relevant SMQs differed between treatment groups ($P > .05$ in all cases).

There were no differences between the treatment groups in the percentage of subjects with ARIA-E or ARIA-H as determined by MRI ($P > .05$). Thirteen subjects (placebo, four; solanezumab, nine) experienced ARIA-E. Six of the 10 for whom the information was available carried at least one *APOE* ε4 allele. The time-to-resolution of ARIA-E varied. Of the placebo-assigned subjects who had ARIA-E, two showed complete resolution and two showed partial resolution during follow-up. For those assigned solanezumab, five showed complete resolution, three showed partial resolution, and one showed no change in ARIA-E severity during follow-up. There were no clinical symptoms clearly associated with ARIA-E for any subject. One subject reported headache and nausea during the time when ARIA-E was present but this resolved within 24 hours after paracetamol treatment before the ARIA-E resolution. At baseline, 248 subjects (19%) had ARIA-H (placebo, 122; solanezumab, 126). Of these, 132 (53%) had only a single ARIA-H. Overall, there was an increase in size of preexisting ARIA-H and/or increase in ARIA-H number in 36 subjects in the placebo group (5.6%) and 40 (6.6%) in the solanezumab treatment group ($P = .55$). There was no difference between treatment groups in the number of categorical increases ($P = .32$).

Treatment-emergent antisolanezumab antibodies were generally transient, of low titer and did not appear to be associated with alteration of drug levels. There were no differences ($P > .05$) between treatment groups at any time point in the frequency of detection of antisolanezumab antibody; the number with antidrug antibodies ranged from 1 (0.2%) to 10 (1.9%) in the placebo group and 2 (0.3%) to 5 (0.9%) in the solanezumab group, depending on visit week. No subjects with treatment-emergent antisolanezumab antibodies experienced TEAEs associated with immune activation.

4. Discussion

While EXPEDITION and EXPEDITION2 did not meet their primary endpoints, results from the secondary analyses of this pooled mild AD population showed less worsening in cognition in those assigned solanezumab versus placebo. This finding pertained to the ADAS-Cog_{14} and other cognitive measures (ADAS-Cog_{11}, MMSE). Solanezumab did not reduce functional decline as assessed using the full ADCS-ADL; however, using the ADCS-iADL, less functional decline was seen in the solanezumab treatment group than placebo ($P = .045$). As evidenced by the lack of interaction between study and treatment for these outcome measures, these effects were generally consistent across the two clinical trials. Solanezumab did not, however, reduce decline as determined by the CDR-SB, a composite measure assessing both cognition and function. Ratings for this instrument are determined after a semistructured interview with the patient and an informant and do not rely directly on psychometric tests. One possible explanation for the lack of treatment separation is that although the CDR-SB has demonstrated good intrarater reliability (and thus is able to detect disease progression), inter-rater reliability varies and intercenter reliability is low (such that the CDR-SB may not be capable of detecting a treatment effect) [23,24]. Furthermore, the CDR-SB consists of just six items, three cognitive and three functional, each of which are rated categorically; the ADAS-cog14 and ADCS-iADL contain 14 and 18 items, respectively. Nevertheless, the reason(s) for the lack of effect of solanezumab on the CDR-SB, while an effect on both the ADAS-cog and ADCS-iADL appeared to be present, are unclear. The CDR-SB is included in the ongoing EXPEDITION3 study, which will provide another opportunity to compare the performance of the CDR-SB to that of other cognitive and functional measures in a large global clinical trial.

No evidence of slowing of cognitive or functional decline with solanezumab was seen in those subjects who had moderate AD at study commencement (Supplementary Table 1). Although therapies targeting amyloid might be more efficacious when started earlier in the disease process [4,14], the reason for such a marked difference in efficacy in the mild and moderate AD populations in the EXPEDITION trials is unclear. Given that progression of AD occurs across a continuum, although these data suggest that there was a greater effect of solanezumab in subjects with an MMSE score of 20–26 at baseline compared with those with a score of 16–19, an absolute conclusion that there is a drug effect in patients with mild AD but not those with moderate AD would appear unlikely.

Across many disease states, the clinical meaningfulness of a therapeutic effect is often judged by the point difference on a particular scale, usually in the context of an improvement in scores. For a treatment that targets the underlying pathophysiology of AD, point differences need to be interpreted in the context of the duration of treatment necessary to achieve that difference because the difference in scores for various outcome measures between active treatment and placebo might be expected to increase over time. Consistent with this hypothesis, for both the ADAS-Cog14 and the ADCS-iADL, which are arguably the most relevant outcome measures for a mild AD population, the solanezumab-placebo difference appears to increase over time, without evidence of an attenuation of the effect through the 18-month course of the trials. Our data (Fig. 2) suggest that the decline in the placebo group over 18 months and differences between active treatment and placebo groups might not be linear. The ongoing EXPEDITION3 study may help to clarify this.

Plasma and CSF biomarker findings in the mild AD study population were similar to those reported previously for phase 2 studies and for the phase 3 mild-to-moderate AD population [9,13]. After solanezumab treatment,

substantial increases in plasma and CSF total (bound plus unbound) $A\beta_{1-40}$ and $A\beta_{1-42}$ were evident, confirming target engagement in the periphery and the central nervous system. Interpretation of changes in CSF free (unbound) fractions of $A\beta_{1-40}$ and $A\beta_{1-42}$ seen with solanezumab treatment is complex and appears to be dependent on treatment duration. In a phase 2 study, 12 weeks of solanezumab administration produced a small nonsignificant, but potentially dose-related *decrease* in free (unbound) $A\beta_{1-40}$ relative to placebo [9]. In the two, larger and longer 80-week phase 3 studies discussed here, solanezumab significantly decreased CSF free $A\beta_{1-40}$ concentrations, confirming the phase 2 findings. In contrast, 12 weeks of solanezumab treatment in the phase 2 study significantly *increased* CSF free $A\beta_{1-42}$ concentrations relative to placebo. Interestingly, the solanezumab-associated increase in CSF free $A\beta_{1-42}$ levels observed after only 12 weeks was no longer evident after 80 weeks of treatment in these two phase 3 studies; however, the free $A\beta_{1-42}$ findings continued to be different from those for the free $A\beta_{1-40}$ findings after either 12 weeks (phase 2 study) or 80 weeks (phase 3 studies). Thus, the solanezumab-associated increase in CSF free $A\beta_{1-42}$ concentrations noted after 12 weeks may be transient and dependent on the duration of solanezumab treatment. It is important to note that although the CSF free $A\beta_{1-42}$ concentration in the solanezumab treatment group was no longer different from that of placebo after 80 weeks of treatment, the CSF free $A\beta_{1-40}$ concentration was significantly reduced in the solanezumab treatment group compared with placebo. The cause of different solanezumab treatment duration-dependent effects on CSF free $A\beta_{1-40}$ and $A\beta_{1-42}$ is not known. We hypothesize that the transient rise in CSF free $A\beta_{1-42}$ concentration (at 12 weeks) may reflect solanezumab treatment-related release of this form of Aβ peptide from amyloid plaque. Because CSF free $A\beta_{1-40}$ showed only a decrease at 12 and 80 weeks, this finding may reflect the considerably smaller amount of this particular Aβ isoform associated with amyloid plaque. Although EXPEDITION 3 will provide an opportunity to replicate the 80-week phase 3 findings reported here, assessment of solanezumab effects on CSF free $A\beta_{1-40}$ and free $A\beta_{1-42}$ over various treatment durations will be required to further test this hypothesis.

A numeric reduction was seen in the florbetapir SUVR in the solanezumab treatment group versus placebo ($P > .05$). A substantially greater number of florbetapir PET scans will be obtained in the EXPEDITION3 trial, providing an opportunity to confirm or refute an effect of solanezumab treatment on amyloid plaque load.

Although plasma and CSF biomarker findings were consistent with target engagement, other biomarker findings did not provide evidence of downstream changes in neurodegeneration. Similar to previously reported for the mild-to-moderate AD population [13], solanezumab did not show an effect on measures postulated as downstream biomarkers of neurodegeneration (vMRI and CSF tau and p-tau) in the mild AD population. Slowing of loss of brain volume has long been discussed as a potential surrogate biomarker for putative disease-modifying treatments for AD [25]. However, to date, only one study of a treatment targeting amyloid, AN1792, has shown a statistically significant treatment effect, in this case *greater* volume loss [26]. In the phase 3 bapineuzumab studies, among *APOE* ε4 carriers there was a numerical increase in the annual rate of loss of brain volume in the bapineuzumab group (19.9 ± 0.50 mL/y) versus placebo (18.7 ± 0.59 mL/y; $P = .13$) but no difference was observed between treatment groups among noncarriers [5]. Thus, as even the desired direction of change for vMRI in studies of treatments targeting amyloid is in question, the lack of effect of solanezumab on vMRI is difficult to interpret. CSF tau and p-tau concentrations are widely reported to be increased in patients with AD. Interestingly, CSF concentrations of tau/p-tau are not elevated for patients with other "tauopathies," such as frontotemporal dementia and progressive supranuclear palsy [27–29]. Findings from phase 3 studies of bapineuzumab did show a small but statistically significant decrease in p-tau in *APOE* ε4 carriers; no effect on these biomarkers was seen in the *APOE* ε4 noncarriers [5]. Thus, in the bapineuzumab trials, small decreases in brain volume and decreases in concentration of CSF tau were observed in actively treated *APOE* ε4 carriers but with a lack of effect on clinical scores; conversely, in the EXPEDITION studies, no drug effect was seen on brain volumes or CSF tau, but a separation in clinical scores was observed in these secondary analyses of the pooled data set. The relationship between concentrations of tau in CSF and in brain may be complex. In the EXPEDITION3 study and other trials, the use of tau PET imaging in addition to determination of CSF concentrations of tau may provide further insights into the relationship between tau concentrations in CSF and brain.

The safety of solanezumab in patients with mild AD was similar to that reported previously for the mild-to-moderate AD population [13]. ARIA-H and ARIA-E, often associated with anti-amyloid therapies [5,30,31], were numerically increased with solanezumab treatment ($P > .05$ vs. placebo) in the mild-to-moderate AD population [13] and in the mild AD population examined here. In the completed EXPEDITION studies, the ARIA-E incidence was approximately 1%, and was not clearly related to symptoms or significantly different from that in the placebo group ($P > .05$). In addition, there were no treatment group differences in either frequency or degree of ARIA-H changes. The frequency of potential infusion-related AEs and treatment-emergent antisolanezumab antibodies did not differ between treatment groups.

There are clear limitations to these analyses. Although analyses of EXPEDITION and EXPEDITION2 pooled dataset were planned before completion of both trials, the analyses reported here are based on secondary outcomes of the studies. To be eligible for study participation, patients were not required to be amyloid positive at baseline based

on either PET or CSF analysis. Based on florbetapir PET scans or CSF measures performed in study addenda, approximately 25% of this mild AD study population probably did not have amyloid at baseline and thus would not likely meet pathologic criteria for AD; whether these findings are generalizable to the overall mild AD study population is not known.

In summary, based on these secondary analysis findings, subjects with mild AD treated with solanezumab in EXPEDITION/EXPEDITION2 may have had a slowing in cognitive decline of approximately 34% (as measured using ADAS-Cog$_{14}$ and MMSE) and a slowing in functional decline of approximately 18% (as measured using the ADCS-iADL). Most subjects in this mild AD population were taking concomitant standard of care treatment; thus, the possible effect of solanezumab seen here is in addition to the effect of currently available symptomatic treatments. Interestingly, in a recent study by Dysken et al. [32] investigating the effect of vitamin E and memantine in veterans with mild-to-moderate AD who were already taking a cholinesterase inhibitor, those given vitamin E alone had a 19% slowing in decline on the full ADCS-ADL; vitamin E had no statistically significant effects on either the ADAS-cog or MMSE. The slowing in functional decline was similar to that which we observed. Discrepancies in the effect on cognitive measures will likely be a subject of future research.

The findings presented here are the first to describe the possible benefits and risks of solanezumab based on secondary analyses of data from patients with mild AD who participated in EXPEDITION or EXPEDITION2. Based on these findings, a third phase 3 study, EXPEDITION3, has been initiated [2]. Enrolling only patients with mild AD and with evidence of amyloid pathology, EXPEDITION3 will continue to explore the possible effects of solanezumab in these patients.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2015.06.1893.

RESEARCH IN CONTEXT

1. Systematic review: Although phase 3 studies of solanezumab in a mild-to-moderate Alzheimer's disease (AD) population (EXPEDITION/EXPEDITION2) did not meet their primary endpoints (Doody et al. [2]), planned subgroup analyses in the mild AD population showed slowing in cognitive (Alzheimer's Disease Assessment Scale Cognitive subscale, Mini-Mental State Examination), and functional (instrumental items of the ADCS-ADLs) decline with solanezumab versus placebo. These findings, in combination with an acceptable safety profile, were sufficient to warrant initiation of a third phase 3 trial in a mild AD population (EXPEDITION3; Karran et al. [2]).
2. Interpretation: This article is the first to provide efficacy, safety, and biomarker results from these planned subgroup analyses in the mild AD population. These results support the amyloid hypothesis of AD pathogenesis and are consistent with an emerging consensus that potential therapies targeting amyloid β may be more effective when used earlier in the disease course.
3. Future directions: Results from EXPEDITION3 may support the findings from these secondary analyses of EXPEDITION/EXPEDITION2.

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