Original Research

The Journal of Prevention of Alzheimer's Disease - JPAD©
Volume 5, Number 1, 2018

Delayed-Start Analyses in the Phase 3 Solanezumab EXPEDITION3 Study in Mild Alzheimer's Disease

H. Liu-Seifert[1], M.G. Case[1], S.W. Andersen[1], K.C. Holdridge[1], P.S. Aisen[2], S. Kollack-Walker[1], E. Siemers[1]

1. Lilly Research Laboratories, Indianapolis, Indiana, USA; 2. Alzheimer's Therapeutics Research Institute, University of Southern California, San Diego, CA, USA

Corresponding Author: Hong Liu-Seifert, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana , USA, liu-seifert_hong@lilly.com, Phone: +1 3174330662

J Prev Alz Dis 2018;5(1):8-14
Published online January 11, 2018, http://dx.doi.org/10.14283/jpad.2018.1

Abstract

OBJECTIVE: A delayed-start design has been proposed to assess a potential disease-modifying effect in investigational drugs for Alzheimer's disease that target the underlying disease process. We extended this methodology to recently obtained data from the EXPEDITION3.

METHODS: EXPEDITION3 was a Phase 3, double-blind study with participants randomized to solanezumab (400 mg) or placebo every 4 weeks for 80 weeks, with an optional extension of active treatment. The delayed-start analysis was designed to determine if a statistically significant treatment difference established during the placebo-controlled period is maintained (at predefined level) during the delayed-start period, which would suggest the active drug has a disease-modifying effect. The delayed-start analysis was assessed across multiple efficacy measures, and includes data from baseline in the placebo-controlled period and up to 9 months in the delayed-start period.

RESULTS: No significant difference was observed between the placebo and solanezumab treatment groups at the end of the placebo-controlled period for the Alzheimer's Disease Assessment Scale-Cognitive 14-item subscale. A significant treatment difference was observed at the end of the placebo-controlled period for the Alzheimer's Disease Cooperative Study-Activities of Daily Living instrumental items, an effect also seen at 6 months in the delayed-start period, and the noninferiority criterion was met. No other efficacy measures met these criteria.

CONCLUSIONS: Delayed-start statistical methodology was used to understand the longitudinal outcomes in EXPEDITION3 and its extension. The small treatment differences observed at the end of the placebo-controlled phase prevented adequate assessment of any putative disease modifying effect.

Key words: Alzheimer's disease, delayed-start analysis, cognition, function.

Introduction

A variety of clinical trial designs have been used in an attempt to distinguish disease-modifying effects from symptomatic effects of drugs in the treatment of Alzheimer's disease (AD) and Parkinson's disease (reviewed in (1-4)). A delayed-start design, also known as randomized-start design, has been proposed as a method to assess a potential disease-modifying effect of investigational drugs for AD that target the underlying disease process (5-9). The delayed-start design consists of a randomized, placebo-controlled period followed by a delayed-start extension period during which all patients receive active treatment. During the delayed-start period, patients and investigators remain blinded to the original treatment randomization during the placebo-controlled period, ensuring that the blind to randomization to either the early-start or delayed-start group is maintained throughout the study duration. If the treatment difference is maintained (i.e. delayed-start patients do not catch up to the early-start patients), this suggests the drug primarily has a disease-modifying effect. If the treatment difference is not maintained (i.e. delayed-start patients catch up to the early-start patients), this suggests the active drug primarily has a symptomatic effect on the disease state. A drug can have both symptomatic and disease-modifying effects.

Solanezumab is a humanized monoclonal antibody that binds to the central region of β-amyloid, and is in development for the treatment of AD. We applied the delayed-start methodology to data from mild AD patients in the Phase 3, placebo-controlled studies EXPEDITION (EXP) and EXPEDITION2 (EXP2), as well as EXPEDITION-EXTENSION (EXP-EXT), an open-label extension study available to patients who had completed EXP or EXP2 (6, 7). In EXP and EXP2, patients were treated with either placebo or solanezumab; in EXP-EXT, all patients were treated open-label with solanezumab. Efficacy and high level safety findings from EXP and EXP2 have been previously published (10, 11).

The initial analysis included pooled data from patients with mild AD in placebo-controlled EXP and EXP2 studies and 6 months of treatment in the open-label extension study, EXP-EXT. This analysis was based on an interim dataset from EXP-EXT, with 240 placebo and 232 solanezumab patients completing 6 months or 28 weeks of treatment in the delayed-start period. Six months was set as the primary time point to assess maintenance of treatment outcome. In this analysis, a significant difference was observed between the solanezumab and placebo treatment groups for the Alzheimer's Disease

Received November 28, 2017
Accepted for publication December 12, 2017

Assessment Scale-Cognitive 14-item subscale (ADAS-Cog_{14}) at the end of the placebo-controlled period (Week 80), and at 6 months in EXP-EXT (Week 108) (6). The treatment difference in cognition between solanezumab and placebo treatment groups observed at the end of the placebo-controlled period was preserved at the end of the delayed-start period within a predefined margin (i.e., noninferiority criterion). Therefore, the results suggested patients who received solanezumab rather than placebo during the placebo-controlled study had a benefit that could not be recovered by patients who began solanezumab later in EXP-EXT. This finding was consistent with what is frequently called a disease-modifying treatment effect.

A subsequent analysis was completed when all participants in EXP-EXT had complete 2 years of treatment or discontinued. In particular, 441 placebo and 441 solanezumab patients completed 6 months of treatment in the delayed-start period (7). The delayed-start analysis was performed on the ADAS-Cog_{14}, the instrumental items from the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-iADL), and other cognitive and functional scales. Results showed a statistically significant difference between placebo and solanezumab for the ADAS-Cog_{14} and the ADCS-iADL at the end of the placebo-controlled period (Week 80), and at 6 months in EXP-EXT (Week 108); the noninferiority criterion was met for both. Therefore, the results of the ADAS-Cog_{14} and the ADCS-iADL provided further support of the possible disease-modifying effects of solanezumab on cognition and functioning. While the results for the 11-item scale of the ADAS-Cog (ADAS-Cog_{11}) were consistent with the ADAS-Cog_{14}, the results for the other efficacy measures were more difficult to interpret, as some but not all of the criteria of the delayed-start analysis were met.

We now extend this methodology to recently obtained data from the EXPEDITION3 (EXP3) clinical trial. The EXP3 study incorporated a delayed-start design into a single protocol providing an opportunity to evaluate further the utility of this method and to understand the treatment effect of solanezumab. We report on findings from a delayed-start analyses across eight different cognitive and/or functional scales. Efficacy and high level safety findings from the double-blind, placebo-controlled period of EXP3 have been accepted for publication (12). After the double-blind, placebo-controlled period of EXP3 was completed, the results showed the study did not meet its primary endpoint as measured by ADAS-Cog_{14}, and therefore, the open-label period of the study was stopped. Results from delayed-start analyses of available data are reported herein.

Methods

EXP3 (Study LZAX, NCT01900665) was a Phase 3, double-blind study with participants randomized to solanezumab (400 mg) or placebo every 4 weeks for 80 weeks, with an optional extension of active treatment. The delayed-start analysis included data from baseline to up to 9 months in the delayed-start period available at the database lock. Eight different cognitive and functional subscales were assessed at 6 months and/or 9 months based on when the measures were collected. The placebo-controlled period extended from baseline (Week 0) out to 18 months (Week 80). The delayed-start period started at Week 80 and extended out to 28 weeks or 6 months (Week 108 from baseline, or the beginning of the placebo-controlled period), or to 40 weeks or 9 months (Week 120 from baseline). Mixed model repeated measures analyses were used to assess the longitudinal outcomes in the delayed-start period.

The delayed-start analysis focused on the primary outcome, the ADAS-Cog_{14}, and a key secondary outcome, the instrumental subscale of the ADCS-iADL. Additional secondary measures included the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), basic items of the ADCS-ADL (ADCS-bADL), integrated Alzheimer's Disease Rating Scale (iADRS), Functional Activities Questionnaire (FAQ), and the Mini-Mental State Examination (MMSE).

The delayed-start analysis was intended to determine whether the treatment difference, if significant at the end of the placebo-controlled period, was maintained (within a predefined margin) during the delayed-start period, by answering the following questions:

Is there a significant difference between treatment groups at the end of the placebo-controlled period (Δ_1)? If YES, then:

Is there a significant difference at the end of the delayed-start period (Δ_2)?

Is the lower limit of 90% confidence interval for the noninferiority test statistic

$\Delta_2 - 0.5\Delta_1 > 0$?

The noninferiority test was carried out by constructing a one-sided 90% confidence interval for Δ_2-$0.5\Delta_1$. If the lower limit of the confidence interval is greater than 0, the null hypothesis is rejected and the noninferiority criterion is met, indicating that at least 50% of the treatment difference observed at the end of the placebo-controlled period had been preserved at the end of the delayed-start period.

The early termination of the delayed-start period may have resulted, in part, in all of the patients essentially appearing to be early "drop-outs", or early termination visits. Therefore, instead of having evenly spaced, scheduled visits or time points for data collection and relatively large patient numbers at those time points, the early termination resulted in additional unplanned visits that had fewer numbers of patients at each time point. Subsequently, the number of data points collected at the protocol-specified, scheduled time points (e.g., every 3 months for the key clinical outcomes) were significantly reduced.

To determine the potential significance and impact of

Table 1. Summary of the Delayed-Start Analyses using 3 Different Methods*

		Scheduled Visits				All Observed Open Label Visits				Visit Interval				
Scale														
Time Point	Treatment Group	LS Mean Change from BL to Endpoint (SE)	p-value	95% CI	Lower Bound of CI (SE)	LS Mean Change from BL to Endpoint (SE)	p-value	95% CI	Lower Bound of CI (SE)	N	LS Mean Change from BL to endpoint (SE)	p-value	95% CI	Lower Bound of CI (SE)
ADAS Cog14														
6 months	DS N=553	10.40 (0.346)	.516	-1.14, 0.57	-0.51 (0.381)	10.94 (0.400)	.414	-1.45, 0.60	-0.51 (0.452)	661	11.66 (0.449)	.224	-1.95, 0.46	-0.22 (0.441)
(Week 108)	ES N=553	10.11 (0.344)				10.51 (0.398)				683	10.91 (0.447)			
9 months	DS N=392	10.93 (0.379)	.332	-0.48, 1.42	na	12.02 (0.496)	.839	-1.43, 1.16	na	464	13.25 (0.526)	.272	-2.22, 0.63	na
(Week 120)	ES N=403	11.40 (0.374)				11.89 (0.491)				480	12.45 (0.523)			
ADAS- Cog11														
6 months	DS N=553	9.20 (0.344)	.298	-1.36, 0.42	-0.33 (0.370)	8.54 (0.338)	.574	-1.11, 0.62	-0.62 (0.435)	661	9.22 (0.337)	.191	-1.44, 0.29	-0.20 (0.350)
	ES N=553	8.72 (0.343)				8.30 (0.336)				683	8.64 (0.333)			
9 months	DS N=392	10.05 (0.415)	.509	-1.46, 0.72	na	8.91 (0.432)	.825	-1.01, 1.26	na	464	10.19 (0.397)	.282	-1.61, 0.47	na
	ES N=403	9.68 (0.411)				9.04 (0.427)				480	9.62 (0.392)			
MMSE														
6 months	DS N=538	-4.88 (0.189)	.607	-0.36, 0.61	-0.37 (0.204)	-4.47 (0.200)	.801	-0.58, 0.45	-0.65 (0.266)	756	-4.76 (0.177)	.365	-0.24, 0.65	-0.26 (0.176)
	ES N=548	-4.76 (0.187)				-4.54 (0.198)				782	-4.55 (0.174)			
ADCS iADL														
6 months	DS N=551	-10.52 (0.402)	.044	0.03, 2.17	0.07 (0.413)	-9.93 (0.358)	.030	0.10, 1.92	0.00 (0.406)	660	-10.17 (0.352)	.020	0.17, 1.96	0.10 (0.365)
	ES N=560	-9.43 (0.400)				-8.92 (0.354)				692	-9.11 (0.346)			
9 months	DS N=395	-11.70 (0.455)	.247	-0.50, 1.94	na	-10.85 (0.474)	.441	-0.67, 1.54	na	465	-11.17 (0.404)	.191	-0.35, 1.75	na
	ES N=407	-10.98 (0.451)				-10.42 (0.422)				482	-10.47 (0.398)			
ADCS ADL Total														
6 months	DS N=551	-11.40 (0.380)	.018	0.19, 2.06	-0.02 (0.419)	-11.54 (0.430)	.029	0.12, 2.32	-0.17 (0.538)	661	-13.13 (0.494)	.029	0.15, 2.80	0.17 (0.491)
	ES N=560	-10.37 (0.375)				-10.32 (0.425)				692	-11.66 (0.490)			
9 months	DS N=395	-12.25 (0.415)	.822	-0.92, 1.16	na	-12.43 (0.537)	.712	-1.14, 1.67	na	465	-14.74 (0.555)	.170	-0.45, 2.55	na
	ES N=408	-12.13 (0.409)				-12.16 (0.529)				483	-13.70 (0.551)			
ADCS bADL														
6 months	DS N=552	-2.14 (0.118)	.056	-0.01, 0.62	-0.05 (0.142)	-2.13 (0.117)	.071	-0.02, 0.60	-0.06 (0.141)	662	-2.18 (0.115)	.039	0.02, 0.62	-0.03 (0.134)
	ES N=560	-1.83 (0.117)				-1.85 (0.117)				692	-1.86 (0.113)			
9 months	DS N=395	-2.27 (0.143)	.839	-0.35, 0.43	na	-2.32 (0.141)	.604	-0.28, 0.47	na	466	-2.36 (0.138)	.524	-0.25, 0.49	na
	ES N=408	-2.23 (0.141)				2.23 (0.139)				483	-2.24 (0.135)			
FAQ														
6 months	DS N=557	7.26 (0.248)	.237	-1.01, 0.25	-0.16 (0.270)	7.31 (0.249)	.191	-1.06, 0.21	-0.12 (0.264)	777	7.28 (0.235)			
	ESN=557	6.88 (0.247)				6.89 (0.248)				791	6.87 (0.233)	.178	-1.00, 0.19	-0.08 (0.225)
iADRS														
6 months	DS N=546	-22.54 (0.757)	.092	-0.29, 3.80	-0.05 (0.748)	-21.25 (0.641)	.089	-0.22, 3.09	-0.29 (0.713)	652	-22.59 (0.747)	.076	-0.19, 3.84	0.04 (0.723)
	ES N=549	-20.79 (0.755)				-19.82 (0.637)				678	-20.77 (0.743)			
9 months	DS N=387	-25.41 (0.887)	.259	-1.02, 3.80	na	-23.51 (0.791)	.482	-1.33, 2.82	na	455	-25.63 (0.865)	.158	-0.66, 4.04	na
	ES N=400	-24.02 (0.883)				-22.77 (0.783)				474	-23.94 (0.859)			

Abbreviations: AD = Alzheimer's disease; BL = baseline; CI = confidence interval; DS = Delayed-Start; ES = Early Start; LS = least squares; na = not applicable; N = number; SE = standard error. *to demonstrate that all 3 methods have consistent results; Scales: ADAS-Cog14 = 14-item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADAS-Cog11 = 11-item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living inventory; ADCS-bADL = basic items of the ADCS-ADL; ADCS-iADL = instrumental items of the ADCS-iADL; FAQ = Functional Assessment Questionnaire; iADRS = integrated Alzheimer's Disease Rating Scale; MMSE = Mini-Mental State Examination; Blue: significant p-values for comparisons between placebo and solanezumab treatment groups; Red: Noninferiority is met; Note: The number of patients (N) is the same for ""Scheduled Visits" and "All Observed Open-Label Visits" analyses, as both included data from Week 108 and Week 120. The N for "By Interval" is different, as it combines data across multiple visits; For scales that include 6- and 9-month data, the 6-month interval is Weeks 96-108, and the 9-month interval is Weeks 112-120; For scales with only 6-month data, the final interval is Weeks 84-108; Normal ranges: ADAS-Cog14: score ranges from 0 to 90, higher score = greater cognitive impairment; ADAS-Cog11: score ranges from 0 to 70, higher score = greater cognitive impairment; MMSE: score ranges from 0 to 30, higher score = better cognition; ADCS-iADL: total score ranges from 0 to 56, lower score = greater functional loss; ADCS-ADL Total: score ranges from 0 to 78, lower score = greater functional loss; ADCS-bADL:scores ranges from 0-19, lower score = greater functional loss; FAQ: score ranges from 0 to 30, higher score = greater functional loss; iADRS: scores range from 0-146, lower score = worse performance.

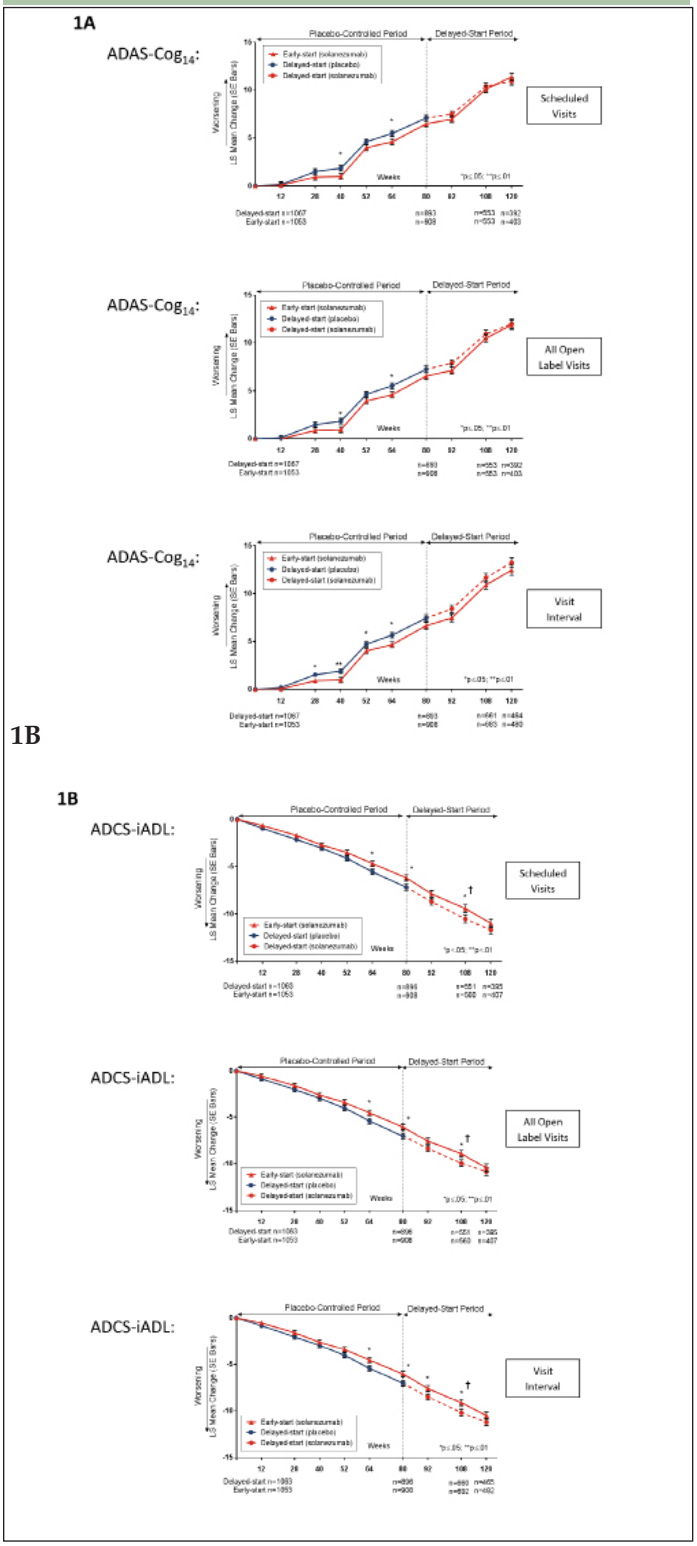
this technical issue, we assessed the outcomes of the delayed-start analysis using three different statistical approaches across eight different scales. These approaches included: 1) "Scheduled Visits", 2) "All Observed Open-Label Visits", and 3) "Visit Interval". The "Scheduled Visits" approach included data from those visits at which scales were scheduled or preplanned for data collection according to study protocol. This approach is consistent with previously reported delayed-start analyses of solanezumab studies (6, 7). The "All Observed Open-Label Visits" approach included data collected from all visits in the model. Any visit at which a scale was administered was analyzed separately. This approach resulted in small patient counts for some of these visits. Lastly, the "Visit Interval" approach included data from all open-label visits. The time intervals were based on scheduled visits that occurred every 3 months, utilizing the last observation made within that interval for each patient. Analyses using these three statistical approaches were pre-specified prior to final database lock.

Results

No significant difference was observed between the placebo and solanezumab treatment groups at the end of the placebo-controlled period as measured by the study's primary outcome, the ADAS-Cog$_{14}$ (Figure 1A). While the noninferiority test is no longer meaningful in this situation, the mixed model repeated measures analyses were carried out to better understand the longitudinal outcomes in the delayed-start period. For the ADAS-Cog$_{14}$, no significant difference was observed between the delayed-start and early-start groups at 6 months or 9 months in the delayed-start period. These findings were consistent across all three statistical approaches – "Scheduled Visits", "All Open-Label Data Visits", and "Visit Interval" (Figure 1A, Table 1).

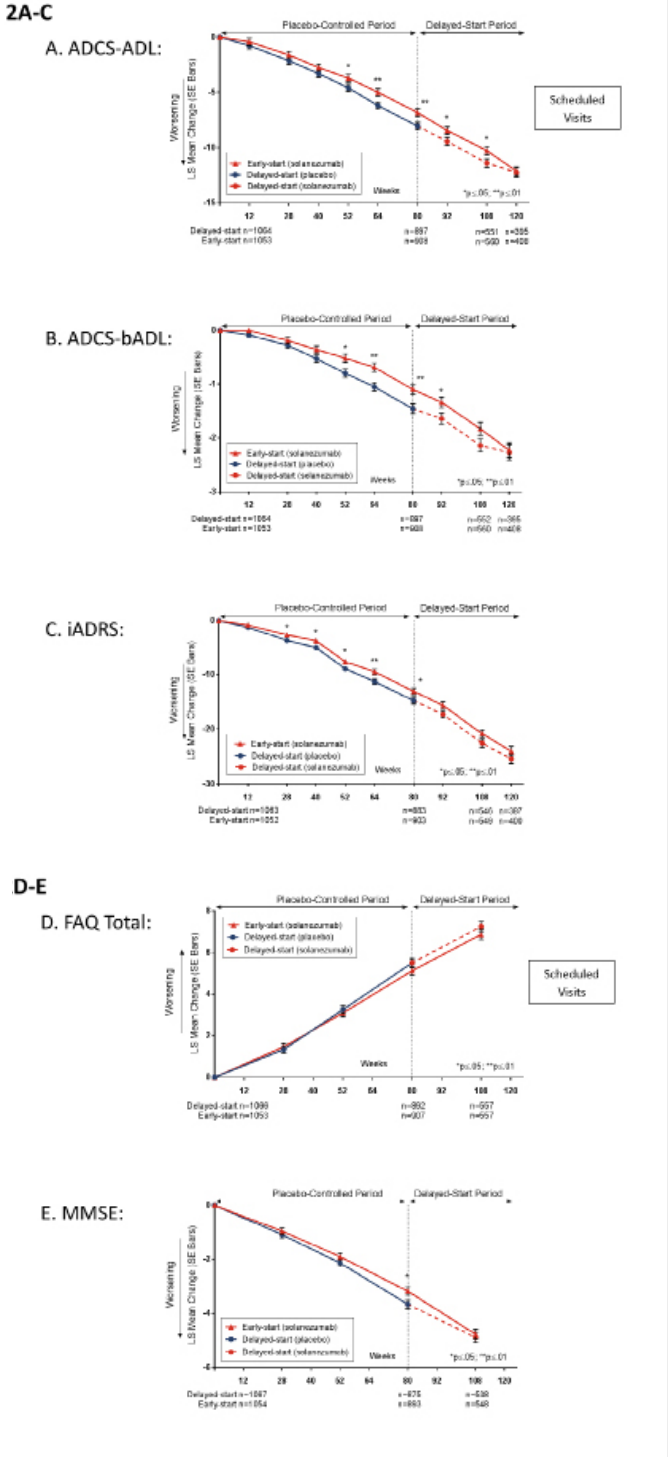
In contrast, a significant difference (unadjusted for multiplicity) was observed between the placebo and solanezumab treatment groups at the end of the placebo-controlled period for the key secondary outcome, the ADCS-iADL (Figure 1B). A significant difference was also observed and the noninferiority criterion was met at 6 months into the delayed-start period. The lower limit of the 90% confidence interval for the test statistic (Δ_2 – 50% X Δ_1) was 0.07 at 6 months. Therefore, the treatment difference in the ADCS-iADL observed between the placebo and solanezumab treatment groups at the end of the placebo-controlled studies was preserved at the end of the delayed-start period within a predefined margin. However, the difference between treatment groups was not maintained at 9 months into the delayed-start period, nor was the noninferiority criterion met at 9 months. These findings were also consistent across all three statistical approaches – "Scheduled Visits", "All Open-Label Data Visits", and "Visit Interval" (Figure 1B, Table 1).

Figure 1. Delayed-start analysis of: A) ADAS-Cog$_{14}$ and B) ADCS-iADL



Results are illustrated for each efficacy measure using the three statistical approaches. † Noninferiority met, p-values shown for endpoint and any values <.05. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Error bars represent standard error. Number of patients shown at baseline, Week 80, and Week 120 for each efficacy measure. Abbreviations: AD = Alzheimer's disease; ADAS-Cog$_{14}$ = 14-item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study Activities of Daily Living inventory, instrumental items; LS = least squares; n = number.

Figure 2. Delayed-start analysis of: A) ADCS-ADL, B) ADCS-bADL, C) iADRS, D) FAQ Total, and E) MMSE Total using the "Scheduled Visits" approach



† Noninferiority met, p-values shown for endpoint and any values <.05. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Error bars represent standard error. Number of patients shown at baseline, Week 80, and Week 120 for each efficacy measure. Abbreviations: AD = Alzheimer's disease; ADAS-Cog$_{14}$ = 14-item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study Activities of Daily Living inventory, instrumental items; LS = least squares; n = number.

Among the remaining secondary measures, a significant difference was observed between the placebo and solanezumab treatment groups at the end of the placebo-controlled period for the ADCS-ADL, ADCS-bADL, iADRS, and MMSE, but not for FAQ. The "Scheduled Visits" approach results for the delayed-start analysis are presented in Figure 2. At 6 months, a significant difference was also observed between the delayed-start and early-start treatment groups for the ADCS-ADL, although the noninferiority criterion was not met at this time point. No significant treatment differences were observed at 6 months or 9 months for other scales assessed, nor was the noninferiority criterion met.

The results were generally consistent regardless of which of the three statistical methods was used (Table 1). The significant difference observed between the delayed-start and early-start treatment groups for ADCS-iADL and meeting the noninferiority criterion at 6 months using the "Scheduled Visits" approach was also observed with the other two statistical approaches – "All Observed Open Label Visits" and "Visit Interval". Similarly, the significant treatment difference between delayed-start and early-start groups observed for the ADCS-ADL at 6 and 9 months in the delayed-start period was evident across all three statistical approaches. The lack of a significant treatment difference and the failure to meet the noninferiority criterion at 6 and 9 months was generally observed for the other efficacy measures across all three statistical approaches. There were two exceptions, including: 1) a significant treatment difference observed for ADCS-bADL evident using the "Visit Interval" approach; and 2) the iADRS meeting the noninferiority criterion at 6 months using the "Visit Interval" approach.

Discussion

In the current analysis, we applied the delayed-start methodology to data from EXP3 to determine if an anticipated significant treatment difference at the end of the placebo-controlled period was maintained (at a predefined level) during the delayed-start period. However, no significant difference was observed between the placebo and solanezumab treatment groups at the end of the placebo-controlled period for ADAS-Cog$_{14}$, the study's primary outcome measure. For the ADCS-iADL, a significant treatment difference was observed between the placebo and solanezumab treatment groups at the end of the placebo-controlled period, and at 6 months in the delayed-start period, and the noninferiority criterion was met. None of the other secondary efficacy measures (i.e. ADCS-ADL, ADCS-bADL, iADRS, FAQ, MMSE) demonstrated a similar treatment profile.

Previous studies (EXP and EXP2) have suggested that solanezumab may have a disease-modifying effect on the progression of AD among patients who began treatment

at the mild AD stage (6, 7). In the second paper, the subsequent analysis included additional data for up to 2 years from the EXP-EXT Study for a total of a 3.5-year period, including 18 months in the placebo-controlled period and 2 years in the delayed-start period (7). For the ADAS-Cog_{14}, the treatment difference was maintained at 6 months (Week 108) and subsequently at Weeks 132 and 160, meeting the noninferiority criterion at Weeks 108 and 132. For the ADCS-iADL, the treatment difference was maintained at 6 months (Week 108) and subsequently at Week 132, meeting the noninferiority criterion at Weeks 108 and 132. Somewhat more variable results were observed for the Clinical Dementia Rating scale-Sum of Boxes (CDR-SB), MMSE and ADCS-bADL demonstrating evidence for significant treatment differences and meeting the noninferiority criterion at some visits, but not in a pattern consistent with that observed for the ADAS-Cog_{14} and ADCS-iADL.

EXP3 demonstrated a smaller treatment difference at the end of the placebo-controlled period consistently across all the clinical measures than was observed in secondary analyses of EXP and EXP2. Honig and colleagues have proposed several possible explanations for the lack of substantial reductions in cognitive decline with solanezumab in EXP3. These possible explanations include: 1) inadequacy of peripheral reductions in soluble free Aβ concentration to reduce deposited amyloid; 2) an insufficient dose of solanezumab; and 3) the possibility that brain neurodegeneration may be too advanced even in patients with mild AD to limit disease progression (12). However, the reasons for the difference in the magnitude of treatment differences between EXP/EXP2 and EXP3 are not fully understood.

Clearly, this smaller treatment difference and the lack of a significant treatment difference at the end of the placebo-controlled period in EXP3 underlies, in part, the failure to replicate earlier findings with regard to the delayed-start analysis. With respect to the delayed-start design, a smaller treatment difference at the end of the placebo-controlled period (Δ_1) would result in a decreased ability to detect significant treatment differences at the end of the delayed-start period (Δ_2). Further, a small Δ_1 would lead to reduced power to meet noninferiority criteria.

To determine the potential impact of early study termination of EXP3 on the delayed-start analyses, we assessed the outcomes of the delayed-start analysis using three different statistical approaches ("Scheduled Visits", "All Observed Open-Label Visits", and "Visit Interval") across 8 different scales. It did not appear that the statistical approach used to assess the delayed-start analyses affected the overall findings significantly. The results were generally similar with respect to differences observed between the placebo and solanezumab treatment groups for each efficacy measure and for those that met the noninferiority criterion across the three statistical approaches with few exceptions. Data suggest that "Visit Interval" approach may have a slightly greater power to detect group difference in the delayed-start period. This may not be surprising given this approach utilized all available patients and their data.

There are several limitations to the current analysis. The delayed-start period of the EXP3 study was terminated early, and this may have resulted in all the patients essentially appearing to be early "drop-outs" and consequently affecting the statistical analysis of data. Therefore, instead of having an analysis with evenly spaced visits for data collection and larger numbers of patients at each time point, the analysis had many more time points for data collection and fewer numbers of patients at each time point. A reduction in patient sample size per visit in the delayed-start period may have decreased statistical power to adequately assess the treatment difference and the noninferiority criterion. In addition, it is important to note that the difference observed between the placebo and solanezumab treatment groups for the ADCS-iADL might be viewed as being only nominally significant since it was not corrected for multiple comparisons.

Conclusion

EXP3 did not meet its primary objective with small treatment differences across clinical measures. Statistical modeling methodology reported previously for delayed-start analysis was applied to EXP3 to understand the longitudinal long-term outcomes. While the ADCS-iADL reached nominal statistical significance at the end of the placebo-controlled period and met noninferiority at the pre-specified 6-month time point in the delayed-start period, the treatment differences were small. The constraints of small treatment differences at the end of the placebo-controlled period and early stopping of the delayed-start period do not allow adequate assessment of any putative disease-modifying effect of solanezumab.

Conflict of interest: Dr. Liu-Seifert, Mr. Case, Mr. Andersen, and Ms. Holdridge are employees of Eli Lilly and Company. Drs. Kollack-Walker and Siemers were employees of Eli Lilly and Company at the time of manuscript preparation. Dr. Aisen serves on a scientific advisory board for Proclara; has served as a consultant to Proclara, Eli Lilly, Merck, Roche, Amgen, Abbvie, Pfizer, Novartis, Janssen, Lundbeck, Biogen, iPerian, Probiodrug, Anavex, Cohbar, Cytox, aTyr, Avanir; and receives research support from Eli Lilly, Janssen, NIA, FNIH, and the Alzheimer's Association.

Ethical standards: Ethical review board approval and informed consent of subjects are reported in the primary publications of the studies noted in this article.

References

1. Xiong C, van Belle G, Miller JP, Morris JC. Designing clinical trials to test disease-modifying agents: application to the treatment trials of Alzheimer's disease. Clin Trials. 2011 Feb;8(1):15-26.
2. Zhang RY, Leon AC, Chuang-Stein C, Romano SJ. A new proposal for randomized start design to investigate disease-modifying therapies for Alzheimer disease. Clin Trials. 2011 Feb;8(1):5-14.
3. Cummings J, Gould H, Zhong K. Advances in designs for Alzheimer's disease clinical trials. Am J Neurodegener Dis. 2012;1(3):205-16.
4. McGhee DJ, Ritchie CW, Zajicek JP, Counsell CE. A review of clinical trial designs used to detect a disease-modifying effect of drug therapy in Alzheimer's disease and Parkinson's disease. BMC Neurol. 2016;16:92. doi:

10.1186/s12883-016-0606-3.
5. Leber P. Slowing the progression of Alzheimer Disease: Methodologic issues. Alzheimer Dis Assoc Disord. 1997;11(Suppl 5):S10-S21.
6. Liu-Seifert H, Andersen SW, Lipkovich I, Holdridge KC, Siemers E. A novel approach to delayed-start analyses for demonstrating disease-modifying effects in Alzheimer's disease. PLoS One. 2015b;10(3):e0119632.
7. Liu-Seifert H, Siemers E, Holdridge KC, et al. Delayed-start analysis: Mild Alzheimer's disease patients in solanezumab trials, 3.5 years. Alzheimers Dement (N Y) 2015a;1(2):111-121.
8. FDA Guidance: Guidance for Industry. Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease. 2013, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338287.pdf. Accessed 24 09 2017 .
9. European Medicines Agency Committee for Medicinal Products for Human Use. Draft guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease and other dementias. Jan 2016 (EMA/CHMP/539931/2014). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/02/WC500200830.pdf. Accessed 6 September 2017.
10. Doody RS, Thomas RG, Farlow M, et al. Alzheimer's Disease Cooperative Study Steering Committee.; Solanezumab Study Group. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med. 2014;370(4):311-21.
11. Siemers E, Sundell K, Carlson C, et al. Phase 3 solanezumab trials: Secondary outcomes in mild Alzheimer's disease patients. Alzheimers Dement. 2016;12:110-120.
12. Honig LS, Vellas B, Woodward M, et al. EXPEDITION3: A Phase 3 trial on the efficacy and safety of solanezumab for mild dementia due to Alzheimer's Disease. N Engl J Med 2017; accepted.