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Featured Article

Delayed-start analysis: Mild Alzheimer's disease patients in solanezumab trials, 3.5 years

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Abstract

Introduction: Solanezumab is an anti-amyloid monoclonal antibody in clinical testing for treatment of Alzheimer's disease (AD). Its mechanism suggests the possibility of slowing the progression of AD.

Methods: A possible disease-modifying effect of solanezumab was assessed using a new statistical method including noninferiority testing. Performance differences were compared during the placebo-controlled period with performance differences after the placebo patients crossed over to solanezumab in the delayed-start period.

Results: Noninferiority of the 14-item Alzheimer's Disease Assessment Scale-Cognitive subscale ($ADAS\text{-}Cog_{14}$) and Alzheimer's Disease Cooperative Study Activities of Daily Living inventory instrumental items (ADCS-iADL) differences was met through 132 weeks, indicating that treatment differences observed in the placebo-controlled period remained, within a predefined margin, after the placebo group initiated solanezumab. Solanezumab was well tolerated, and no new safety concerns were identified.

Discussion: The results of this secondary analysis show that the mild subgroup of solanezumab-treated patients who initiated treatment early, at the start of the placebo-controlled period, retained an advantage at most time points in the delayed-start period.

Keywords: Solanezumab; Delayed-start; Clinical trials; Alzheimer's disease; Anti-amyloid-β antibody

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1. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by a progressive decline in cognitive function. Currently approved treatments attenuate the symptoms of AD but have not been shown to affect the underlying pathology [1]; thus, they are sometimes termed "symptomatic" treatments. Leber (1997) [2] proposed the delayed-start design as a method for demonstrating a disease-modification drug effect; that is, an effect that slows the progression of disease by modifying the underlying biological pathology, rather than only attenuating symptoms.

The delayed-start, also known as randomized-start, study design is one in which patients are randomized to the same active treatment but starting at different times, resulting in two treatment periods: a placebo-controlled period followed by a delayed-start period. During the placebo-controlled period, patients receive either an active treatment or placebo. During the delayed-start period, placebo patients are switched to active treatment and thus become delayed-start patients. Patients on active treatment during the placebo-controlled period continue to receive active treatment during the delayed-start period and are labeled as early-start patients. Thus, in a delayed-start study, patients are randomized at the beginning of the placebo-controlled period to be either early- or delayed-start patients. During the entire length of the study (that is, both the placebo-controlled and delayed-start periods), this randomization to treatment group is blinded to all patients and study personnel. If the treatment difference observed at the end of the placebo-controlled period was preserved at the end of the delayed-start period (that is, delayed-start patients do not "catch up" with the early start patients), the treatment effect is considered consistent with a disease-modifying effect.

There have been very limited published data on delayed-start studies; one example is the Attenuation of Disease Progression with Azilect Given Once-daily (ADAGIO) study, a study of rasagiline conducted to assess possible disease-modification effects in Parkinson's disease. However, the study included some methodological issues and a lack of dose response made the results difficult to interpret [3]. Other studies have reported the long-term use of symptomatic drugs in a framework similar to the delayed-start design, either with or without placebo wash-out periods [4,5]. Although these studies suggested that continued treatment with symptomatic drugs may offer longer term benefit, no quantitative methods were applied to assess whether the differences between early-start and delayed-start patients were due to chance and whether delayed-start patients had caught up with early-start patients within a statistical margin.

We recently proposed a new method for delayed-start analyses that includes comparisons of treatment differences at the beginning and end of the delayed-start period using a noninferiority test. This method uses a single mixed-model repeated measure (MMRM) analysis model including all available data from all randomized patients from the beginning of the placebo-controlled period through the end of the delayed-start period. This new method was developed to mitigate some issues observed with previously applied methods [6], and its application to data from the solanezumab EXPEDITION program represents the first effort of a prespecified statistical delayed-start analysis in an AD study.

1.1. Solanezumab

Solanezumab is an IgG1 anti-amyloid monoclonal antibody that binds to the mid-domain of the amyloid-beta (Aβ) peptide and is thought to increase clearance of soluble Aβ. EXPEDITION and EXPEDITION2 were identical phase 3, 18-month, placebo-controlled studies investigating solanezumab treatment in patients with mild-to-moderate AD. EXPEDITION-EXT is an ongoing open-label extension study offered to patients who completed EXPEDITION or EXPEDITION2, in which all patients receive solanezumab; patients, investigators, and site personnel remain blinded to the original treatment assignment during the placebo-controlled period. Analyses from the two individual placebo-controlled studies did not show a significant benefit of solanezumab for the original coprimary outcomes: the 11-item Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog_{11}) and the Alzheimer's Disease Cooperative Study Activities of Daily Living inventory (ADCS-ADL) in the mild-to-moderate AD population. In EXPEDITION, the treatment benefit for solanezumab at 80 weeks was 0.8 points ($P = .24$) for the ADAS-Cog_{11} and 0.4 points ($P = .64$) for the ADCS-ADL. In EXPEDITION2, the treatment benefit for solanezumab at 80 weeks was 1.3 points ($P = .06$) for the ADAS-Cog_{11} and 1.6 points ($P = .08$) for the ADCS-ADL [7]. However, a key prespecified secondary analysis of the mild AD population in EXPEDITION demonstrated a significant effect of solanezumab on cognition; based on this result, the statistical analysis plan for EXPEDITION2 was changed such that the primary outcome was cognition alone (the 14-item ADAS-Cog [ADAS-Cog_{14}]) in the mild population. This single primary outcome did not reach statistical significance in the smaller mild-only subgroup in EXPEDITION2 ($P = .06$) [7]. When examining the mild subgroup in the larger pooled population from EXPEDITION and EXPEDITION2, the treatment benefit for solanezumab was 2.13 points ($P = .001$) for the ADAS-Cog_{14} and 1.21 points ($P = .045$) for the instrumental items of the ADCS-ADL (ADCS-iADL) [8]. Delayed-start analyses of the first interim data cut for EXPEDITION-EXT (through 20 June 2012, including 240 placebo and 232 solanezumab mild AD patients who had completed 28 weeks of treatment in the delayed-start period), showed a persistent benefit on cognition [6]. That is, the treatment difference in cognition between solanezumab and placebo observed at the end of the placebo-controlled studies was preserved at 28 weeks in the delayed-start period. Safety analyses from the