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Featured Article

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

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Abstract

Introduction: 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.

Discussion: 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

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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 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