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EXPEDITION3: A Phase 3 Trial of Solanezumab in Mild Dementia due to Alzheimer's disease

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Background: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by amyloid beta (Aβ) plaques, neurofibrilliary tangles, and neuronal loss with clinical symptoms including cognitive and functional impairment. Solanezumab, a humanized monoclonal antibody, was studied to determine if it would slow the progression of AD by increasing clearance of soluble Aβ from the brain. *Methods*: EXPEDITION3 was a double-blind, placebo-controlled, Phase 3 global study conducted in 11 countries at 210 sites in patients age 55 to 90 years with mild dementia due to AD (mild AD) (Mini–Mental State Examination [MMSE] score of 20 through 26), with confirmed amyloid pathology based on biomarkers (amyloid positive by F18 florbetapir PET or CSF Aβ1-42), with an optional open-label extension. Patients were randomized to 400-mg solanezumab (N=1057) or placebo (N=1072) administered intravenously every 4 weeks. The primary efficacy outcome was change on the 14-item Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog14) from baseline to Week 80. Key functional measures assessed included the Instrumental activities of the Alzheimer's Disease Cooperatives Study Activities of Daily Living Inventory (ADCS-iADL) and the Functional Activities Questionnaire (FAQ). Additional efficacy measures assessed included the MMSE and the Clinical Dementia Rating scale–Sum of Boxes (CDR-SB). Key safety assessments included adverse event (AE) reporting and magnetic resonance imaging (MRI). Biomarkers included plasma changes in Aβ1-40 and Aβ1-42, CSF changes in total and phosphorylated tau (p-tau), and neuroimaging measures including positron emission tomography (PET) scans using florbetapir F18 and F18 flortaucipir, and volumetric MRI. *Results:* There was no statistically significant difference between treatment groups for the primary endpoint, ADAS-Cog14 (p=.095); numerically there was 11% less decline in cognition in the solanezumab-treated group compared with placebo. For the key secondary endpoints, treatment effects favoring solanezumab were seen on cognitive and functional measures, including 13% less decline on the MMSE (p=.014), 15% less decline on the CDR-SB (p=.004), and 14% less decline on the ADCS-iADL (p=.019). FAQ did not show statistically significant differences (7% less decline, p=.140). Solanezumab-treated patients showed a statistically significant greater increase in plasma Aβ1-40 and Aβ1-42 compared with placebo-treated patients (p<.001 for each biomarker), confirming peripheral target engagement. Changes between treatment groups for florbetapir PET, CSF total tau and p-tau, and flortaucipir PET did not show significant treatment differences. Whole brain atrophy and ventricular enlargement were not statistically different between treatment groups, as demonstrated by volumetric MRI. Safety findings were comparable across study treatment groups with respect to deaths, serious AEs (SAEs), discontinuations due to an AE and treatment-emergent AEs (TEAEs). There were few statistically significant treatment group differences at the individual Preferred Term level for TEAEs and none for any SAEs. *Conclusions:* EXPEDITION3, a Phase 3 trial of solanezumab initiated in a mild AD patient population, did not meet the primary objective of decreasing cognitive decline. Several secondary clinical endpoints, including both cognitive and functional measures, directionally favored solanezumab, but the effect sizes were small. Factors possibly relevant to interpretation of the study results include drug target, disease stage studied, and drug dosage delivered. Solanezumab had a favorable safety profile at the dose studied.