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Efficacy and Safety of Oral Valiltramiprosate in APOE4/4 Homozygotes with Early AD: Topline Results from APOLLOE4 Phase 3 Trial

Background

Valiltramiprosate (ALZ-801) is an oral inhibitor of amyloid oligomer formation. Tramiprosate (active agent in ALZ-801) had shown promising efficacy signals with favorable safety in 1300 APOE4 carriers with AD, with no observed ARIA-E. This trial evaluated Valiltramiprosate in APOE4/4 homozygotes with Early AD.

Methods

This 78-week double-blind, placebo-controlled, two-arm trial that randomized 325 homozygotes (162 to placebo, 163 to 265 mg BID), stratified by MCI (MMSE 27-30) or Mild AD (MMSE 22-26). MRI (1.5/3 Tesla) were conducted every 26 weeks and analyzed by Clario Inc. The clinical outcomes were ADAS-Cog13 (primary), CDR-SB (key secondary) and DAD (disability assessment for dementia, secondary). Hippocampal volume (HV) was the main imaging outcome. MMRM was the primary analysis model.

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Results

Safety population (N=325) was 51% females, 90% Caucasian, mean age 68 years, MMSE 25.6, 39% with MCI (MMSE 27-30) and 30% with baseline microhemorrhages and/or siderosis. In the full analysis set (N=320), the placebo-adjusted least-square mean (LSM) difference in change from baseline (CBL) on ADAS-Cog13 favored drug non-significantly (delta=-0.50; p=0.61, 11% vs placebo CBL); CDR-SB and DAD numerically favored drug by 23% and 29%, but HV favored drug significantly (74 mm^3, nominal p=0.017, 18% less atrophy). Prespecified Mild AD showed small nonsignificant clinical effects favoring placebo, but showed numerical benefit on HV (51 mm^3, 12% p= 0.115). In prespecified MCI, all outcomes favored drug (nominal p-values): ADAS-Cog13= -2.14 (p=0.041; 52%); CDR-SB= -0.65 (p=0.053, 104%); DAD= 6.09 (p=0.016, 96%); and HV= 108 mm^3 (p= 0.004, 26% less atrophy). Nausea (mostly mild) was the most common adverse event; the incidence of ARIA-E was the same as placebo.

Conclusions

In the overall population, ADAS-Cog13 did not achieve significance, but the hippocampus showed a significant 18% slowing of atrophy. The pre-specified Mild AD group showed trends to HV atrophy slowing that did not translate to clinical benefits. The pre-specified MCI group showed significant 28% HV atrophy slowing with meaningful cognitive and functional benefits and positive trends on several secondary clinical outcomes. Overall safety was favorable with no increased ARIA. In the high-risk APOE4/4 population, this positive benefit-risk profile supports valiltramiprosate's potential as an oral disease-modifying treatment for APOE4/4 homozygotes with MCI.

Biography

Dr. Tolar serves as the Founder, President & CEO of Alzheon. Prior to founding Alzheon in June 2013, Dr. Tolar held executive positions in several life sciences companies, where he has successfully established and grew new companies, business areas and product opportunities. Dr. Tolar served as President & CEO of Knome, Inc., where he led the development of human genome interpretation systems and services for academic, pharmaceutical and clinical clients, as President & CEO at NormOxys, Inc., where he built the business for novel cancer therapeutics, and as Chief Scientific Officer and Chief Business Officer at CoMentis, Inc., where he developed the first clinical-stage beta secretase inhibitor platform for Alzheimer's disease and negotiated a collaboration with a potential value of $1.1 billion with Astellas Pharma in 2008. Dr. Tolar held a variety of clinical development and business leadership positions at Pfizer, where he was instrumental in a wide range of business transactions, including acquisition of Rinat Neuroscience for $500 million in 2006, and directed programs through all stages of clinical development and FDA approval including NDA filings.

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