COGNITIVE AND FUNCTIONAL EFFICACY OF TRAMIPROSATE IN APOE4+ PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE: SUB-GROUP ANALYSES OF THE PHASE 3 NORTH AMERICAN AND EUROPEAN TRIALS

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Background:
Current therapeutic options for Alzheimer's disease (AD) provide limited long-term efficacy. The apolipoprotein E4 (APOE4) genotype is the most significant known risk factor for the development and progression of late-onset AD, through a possible increase in β-amyloid (Aβ) deposition. APOE4 positive (APOE4+) subjects, which comprise up to 60% of AD patients, display more aggressive course as well as more homogenous progression and severity of the disease, and are significantly less likely to be misdiagnosed of AD than the general population. Tramiprosate, a small molecule inhibitor of Aβ aggregation, has been shown to prevent amyloid deposition and protect against Aβ-induced neurotoxicity, as well as to significantly reduce CSF $A\beta_{42}$ in AD patients. Tramiprosate was evaluated in two independent multicenter, double-blind, placebo-controlled Phase 3 trials in AD patients conducted in North America and Europe, respectively. We report a subgroup analysis of the merged data from both trials, with the goal to evaluate the efficacy of tramiprosate in APOE4+ patients with AD. This study summarizes the cognitive and functional efficacy data of tramiprosate 100 mg BID and 150 mg BID on the co-primary endpoints ADAS-Cog and CDR-SB. Based on the promising efficacy and safety findings with tramiprosate, Alzheon is developing ALZ-801, a novel, orally available valine conjugate prodrug of tramiprosate with improved pharmaceutical properties, oral absorption and gastrointestinal tolerability.

Methods:
A total of 909 APOE4+ patients (i.e., with either one or two APOE4 alleles) were included in this analysis. Patients were ≥ 50 and < 80 years of age at enrollment, with mild-to-moderate AD (MMSE 16–26), and on a stable dose of acetylcholinesterase inhibitors, alone or with memantine. Patients were randomly allocated to 78-week treatment with placebo (n = 320), tramiprosate 100 mg BID (T100) (n = 307) or 150 mg BID (T150) (n = 282). The primary clinical efficacy endpoints were the changes from Baseline to Week 78 in ADAS-Cog and CDR-SB scores. General Linear Repeated Measures Mixed Effects models adjusting for baseline ADAS-Cog or CDR-SB, site, age, baseline MMSE, race, education, cardiovascular comorbidity, use of antidepressants and vitamin E were used to assess between group differences with respect to the study outcomes.

Results:
For placebo, T100 and T150, respectively, baseline mean (SD) for ADAS-Cog was 21.4 (8.5), 22.1 (8.6) and 21.8 (8.0), for CDR-SB 5.5 (2.6), 5.2 (2.5) and 6.0 (2.6), and for MMSE 21.0 (3.0), 21.0 (3.0) and 21.0 (3.0).

For ADAS-Cog, the results showed a significant treatment group ($F = 5.29$, $P = 0.0051$) and group x time effect ($F = 1.77$, $P = 0.0614$). Significant adjusted differences vs. placebo (i.e., ADAS-Cog delta improvement vs. placebo) were observed for T150 at Week 78: delta = +2.17, $P = 0.0009$; Week 26: delta = +1.22, $P = 0.0248$; Week 52: delta = +1.89, $P = 0.0014$; and Week 65: delta = +1.98, $P = 0.0015$ and overall slope: delta = +8.64, $P = 0.0012$. A trend was observed for the T100 at Week 78: delta = +1.13, $P = 0.0985$.

For CDR-SB, a significant group effect (F = 3.98, P = 0.0190) was observed. Significant adjusted differences vs. placebo (i.e., delta improvement vs. placebo) were observed for T150 at Week 78: delta = +0.63, P = 0.0015; at Week 65: delta = +0.53, P = 0.0053 and overall slope: delta = +1.74, P = 0.0422.

The incidence of adverse events (AEs; mild gastrointestinal) and drop-out rates due to AEs were similar for the three groups, with AE rates 7.5% for placebo, 14.1% for T100 and 15.0% for T150, respectively. Also, the incidence of observed serious AEs (SAEs; any causality) was the same for the three groups: 9.4% for placebo, 9.7% for T100 and 8.7% for T150, respectively.

Conclusion:
The subgroup analysis of the merged North American and European cohorts of the Phase 3 tramiprosate North American and European trials showed that, in the population of APOE4+ patients < 80 years of age, tramiprosate displayed sustained and significant efficacy in AD patients on top of standard of care treatment with acetylcholinesterase inhibitors and/or memantine. The observed efficacy of the top dose of tramiprosate (150 mg, BID) was sustained over the 78-week treatment. In addition, tramiprosate was very well tolerated at both dose strengths and the tolerability and drop-out rate were similar to placebo. The data of this analysis, in combination with the demonstrated high safety and tolerability profile of tramiprosate, support progression of the optimized tramiprosate prodrug ALZ-801 into confirmatory Phase 2/3 program in the APOE4+ Alzheimer's disease population in the near future. ALZ-801 has the promise to be a new, oral, small molecule amyloid-targeting treatment for AD that extends the efficacy of the current standard of care therapy.