Results of a Phase 2 Study of AR1001 in Mild to Moderate Alzheimer's Disease Patients

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Backgrounds

Alzheimer's disease (AD) is a neurodegenerative disease that impacts the lives of more than 6 million patients in the United States alone. Due to the complex nature of AD pathology, it is challenging to develop a clinically meaningful therapeutic agent with a single molecular target or mechanism of action. Polypharmacology, the use of multiple mechanisms or targets in drug development, is an ideal approach to address multifactorial diseases such as AD. AR1001 is a small molecule with multiple mechanisms of action that could ameliorate AD symptoms and slow disease progression. AR1001 improves neurogenesis and inhibits neuron apoptosis through the activation of CREB signaling pathway, while improving synaptic plasticity via the stimulation of Wnt pathway. AR1001 also increases autophagy activity, reducing beta-amyloid (Aβ) and phosphorylated tau burden. AriBio conducted a Phase 2 study of AR1001 in mild to moderate Alzheimer's patients across 21 clinical trial centers in the United States.

Objectives

AR1001, a small molecule, is being investigated as a polypharmacological therapeutic agent for mild to moderate Alzheimer's disease. This Phase 2 study aims to evaluate the safety and efficacy of AR1001 in patients with mild to moderate Alzheimer's disease.

Methods

This double-blind, randomized, placebo-controlled, parallel-group comparison study of AR1001 investigated its safety and efficacy in mild to moderate AD patients. NIAAA (National Institute of Aging and Alzheimer's Associations, 2011) criteria was used for defining AD with MRI or CT imaging consistent with the diagnosis. A total of 210 eligible patients were randomized into placebo, AR1001 10 mg, or AR1001 30 mg groups. AR1001 was administered as a daily oral dose for 26 weeks. After completion of the main phase (first 26 weeks of dosing), patients had the option to participate in the extension phase to receive either 10 mg or 30 mg of AR1001 for another 26 weeks. In the extension phase, subjects from active groups in the main phase continued their doses, and the placebo subjects were randomized into either 10 mg or 30 mg of AR1001. The primary endpoints included Alzheimer's Disease Assessment Scale, Cognitive Subscale, 13-item Version (ADAS-Cog 13) and the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC). Secondary endpoints included the MMSE-2 (Mini-mental status examination), NPI (Neuropsychiatric Inventory), GDS (Geriatric Depression Scale), C-SSRS (Columbia Suicide Severity Rating Scale), and QOL-AD (Quality of Life in Alzheimer's Disease).

Results

A total of 173 (82.4%) subjects completed the Treatment Phase including 61 (87.1%) subjects randomized to AR1001 10 mg, 57 (81.4%) subjects randomized to AR1001 30 mg, and 55 (78.6%) subjects randomized to Placebo. A total of 141 (67.1%) subjects continued into the Extension Phase of the study, including 54 (77.1%) subjects in the AR1001 10 mg group, 48 (68.6%) subjects in the AR1001 30 mg group. The ITT Population included 204 (97.1%) subjects who received at least one dose (AR1001 10 mg or 30 mg or placebo) and had post-dose efficacy measurements. Co-primary Endpoints: At week 52, mean change (SE) of ADAS-Cog 13 from baseline value (week 0) was 1.174 (1.332) in the AR1001 10 mg group 0.759 (1.633) in the AR1001 30 mg group. For ADCS-CGIC, the mean (SE) values at week 52 were 4.11 (0.178) for the AR1001 10 mg group and 4.39 (0.188) for the AR1001 30 mg. There were no significant changes over baseline in secondary endpoints. Meaningful trends were noted in patients receiving AR1001 alone without concomitant administration of approved AD medication such as Aricept. Most notably, subjects receiving 30 mg of AR1001 alone improved 3.5 points (13.9%) on the ADAG-Cog 13 at Week 26 and continued to improve to 5.8 points (31.4%) at Week 52, p-value 0.01 and 0.007, respectively. Patients with mild AD based on the Mini Mental State Examination (MMSE) at screening showed improvement in ADAS-Cog-13 at 52 weeks over baseline, while the moderate AD group showed cognitive decline over 52 weeks. For mild AD patients that received AR1001 alone, the 10 mg group showed 2.4 points (15.1%) and the 30 mg group showed 8.7 points (46.3%, P = 0.001) improvement over baseline at 52 weeks. Other secondary endpoints demonstrated similar trends of better response in mild AD patients and in participants that received AR1001 alone.

Conclusion

AR1001-ADP2-US01 was the first study to assess the safety and efficacy of AR1001 in mild to moderate AD patients. The results support the safety and tolerability of AR1001 for up to one year of treatment. These results also suggest that there may be cognitive benefit to mild AD patients and to those taking AR1001 as a monotherapy. A larger study is recommended to further investigate the efficacy of AR1001 in mild AD patients as well as its effect as a stand-alone therapy without concomitant administration of approved AD medication.