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DRUG DEVELOPMENT

PODIUM PRESENTATIONS

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Results of the DIAN-TU prevention trial of solanezumab and gantenerumab in dominantly inherited AD

Gantenerumab in-depth outcomes

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Abstract

Background: Gantenerumab is a humanized anti-amyloid-beta monoclonal antibody in clinical development for the treatment of several stages of Alzheimer disease (AD). Gantenerumab was evaluated in a phase 2/3 clinical trial program designed to evaluate its efficacy in autosomal dominant AD based on a combination of clinical and biomarker evidence.

Method: The study enrolled both mutation carriers (n=69 with 3:1 randomization of treatment (n=52) vs placebo (n=17)) and non-carriers (n=28, all on placebo) from 15 years before to 10 years after the expected age of onset inclusive. Patients were both asymptomatic (CDR 0 and MMSE $\geq$25) and symptomatic (CDR 0.5-1 and MMSE $\geq$16). There were 41 asymptomatic and 28 symptomatic mutation carriers. The initial dose of gantenerumab was 225 mg monthly administered subcutaneously. The dose was titrated to 1200 mg/month following a protocol amendment based on the increased amyloid lowering seen at higher doses in the gantenerumab program in symptomatic AD. The treatment duration was a minimum of 4 years (range 48-80 months). The primary outcome was change from baseline in the DIAN-TU multivariate cognitive endpoint. Secondary clinical outcomes included the DIAN-TU cognitive composite, Cogstate multivariate cognitive endpoint, CDR SB, and time to CDR progression of $\geq$0.5 points. Change from baseline in amyloid PET was the primary biomarker outcome. Other biomarker outcomes included MRI, tau PET, CSF amyloid, tau and phosphotau, and CSF and plasma neurofilament light (NfL). Safety outcomes including ARIA were compared between drug and placebo groups.

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Result: We will report change from baseline on the DIAN-TU multivariate cognitive endpoint, DIAN-TU cognitive composite, CDR-SB and other secondary efficacy endpoints. We expect significant lowering on amyloid PET with PIB and florbetapir based on the results from recent anti-amyloid antibodies, including Gantenerumab, in sporadic AD. We will also present the results of change in other key imaging and fluid biomarkers. The frequency, duration, and severity of ARIA will be reported and compared with studies in sporadic AD.

Conclusion: This clinical trial was designed to inform future for ADAD and will provide new insights on the role of amyloid reduction in both pre-symptomatic and clinical AD.