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Saturday

Twelve-Month Results from the INFRONT-2 Phase 2 Open-Label Study of Latozinemab (AL001) in Frontotemporal Dementia Participants with *C9orf72* Repeat Expansions

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State of the Art:

Frontotemporal dementia (FTD) is a rare, early-onset form of dementia, and hexanucleotide repeat expansions in the *C9orf72* gene is the most common cause of familial FTD. Scientific evidence suggests a common pathway between C9orf72 and progranulin-mediated disease. Variants of *GRN* that reduce progranulin levels have been linked to shortened survival after disease onset in *C9orf72* repeat expansion carriers. FTD-*C9orf72* patients exhibit TDP-43 pathology, and in nonclinical studies progranulin was shown to reverse and protect against TDP-43 pathology, suggesting that increasing progranulin levels may reduce TDP-43 pathology in humans. Latozinemab is a human monoclonal IgG1 antibody that blocks and downregulates sortilin, a receptor in the primary degradation pathway of progranulin, and is being developed by Alector for the treatment of FTD.

Methodology:

INFRONT-2 is an open-label, Phase 2 study investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of latozinemab administered intravenously every four weeks in FTD-*C9orf72* and FTD-*GRN* mutation carriers. Lumbar punctures and MRI scans were performed at baseline and every 6 months thereafter. Clinical assessments were done every 3 months. Fluid biomarkers were analyzed in plasma and CSF.

Results:
Preliminary safety results of latozinemab in FTD-*C9orf72* participants from INFRONT-2 are presented. Chronic dosing led to a sustained increase in progranulin levels throughout treatment. Preliminary data on clinical assessments and biomarkers will be presented for FTD-*C9orf72* participants who have received latozinemab for up to 12 months.

Conclusions:
Latozinemab increased PGRN levels in plasma and CSF and was generally well tolerated with chronic dosing in the FTD-*C9orf72* population.

Conflicts of interest

All authors are equity stakeholders in Alector, Inc and/or employees of Alector, LLC