International Congress for Ataxia Research, London, UK, November 12-15, 2024

Effect of nomlabofusp administration on tissue frataxin levels, plasma lipid profiles, and gene expression in patients with Friedreich's ataxia

Noreen Scherer[1], Adrienne Clements-Egan[1], Mohamed Hamdani[1], Magdy Shenouda[2], Anik Forest[3], Christine Des Rosiers[3], Gopi Shankar[1], Russell Clayton[1]

[1]Larimar Therapeutics Inc., 3 Bala Plaza East, Suite 506, Bala Cynwyd, PA, USA

[2]Clinilabs, Inc., 4 Industrial Way West, Eatontown, NJ, USA

[3]Montreal Heart Institute, Metabolomics Platform, 5000 Rue Bélanger, Montreal QC H1T 1C8, Canada

Methods

In a Phase 2 placebo-controlled double-blind dose exploration study, adults with Friedreich's ataxia (FRDA) were enrolled into 2 cohorts and randomized 2:1 to receive nomlabofusp 25 mg (Cohort 1) and 50 mg (Cohort 2) or placebo via subcutaneous injection daily for 14 days followed by alternate day administration for 14 days. Tis-sue frataxin concentrations were measured using a hybrid LC-MS/MS assay in buccal and skin cells before, during, and after treatment. Buccal cells were collected before, during, and after treatment for gene expression profiling using the NanoString nCounter system. Blood samples were collected before, during, and after treatment for lipid profiling using high-resolution liquid chromatography quadrupole time-of-flight.

Results

Thirteen (9 nomlabofusp, 4 placebo) and 15 adults with FRDA (10 nomlabofusp, 5 placebo) participated in Cohorts 1 and 2, respectively. In general, nomlabofusp appeared to be well tolerated. Compared with baseline, median frataxin concentration increased by 0.56 pg/mcg and 0.72 pg/mcg in buccal cells and 2.81 pg/mcg and 5.57 pg/mcg in skin cells in Cohorts 1 and 2, respectively, after 14 days of daily administration of nomlabofusp, with no change from baseline observed in subjects receiving placebo. Abnormal lipid profiles were identified in adults with FRDA at baseline with directional dose-dependent normalization observed post nomlabofusp treatment. Prelimi-nary analyses indicated similar observations with abnormal gene expression identified in adults with FRDA.

Discussion

Frataxin deficiency results in metabolic dysfunction in patients with FRDA. Increased tissue frataxin concentrations observed after nomlabofusp administration appear to affect metabolic function as evidenced by normalization of gene expression and lipid profiles.

Conclusion

In patients with FRDA, daily administration of 25 mg and 50 mg nomlabofusp was well tolerated and resulted in increased tissue frataxin concentrations, and directional dose-dependent normalization of lipid profiles and gene expression was observed following treatment with nomlabofusp.