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

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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. Tissue 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. Preliminary 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.