International Congress for Ataxia Research, Atlanta, USA, November 10-13, 2026

Plasma Lipid Profiles in Patients with Friedreich's Ataxia Before and After Treatment with Nomlabofusp

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Background and Objectives

Friedreich's ataxia (FRDA) is an autosomal recessive disorder caused by frataxin (hFXN) deficiency resulting in mitochondrial metabolic dysfunction and characterized by progressive neurologic and cardiac disease. The mitochondrial metabolic dysfunction in FRDA includes reduced fatty acid (FA) β-oxidation and ATP generation, generation of reactive oxygen species and impaired oxidative stress response, and lipid dysregulation.

Nomlabofusp is an investigational protein therapy intended to address the root cause of FRDA by delivering hFXN to patients with FRDA. The objective of this study was to characterize plasma lipid profile alterations and evaluate the effect of nomlabofusp treatment on lipid dysregulation in patients with FRDA.

Methods

Untargeted plasma lipidomic analyses by liquid chromatography tandem mass spectrometry were conducted on plasma samples collected from fasting healthy volunteers (HV) and from subjects with FRDA from 3 nomlabofusp clinical studies. Lipidomic profiles were compared between HV and untreated subjects with FRDA and baseline versus postdose samples of each clinical study. Relationships between changes in plasma lipid profiles and increases in tissue hFXN concentrations with nomlabofusp treatment were also assessed.

Results

Across studies, plasma TG, predominantly with polyunsaturated fatty acid (PUFA) and frequently with odd chain FA, were elevated in FRDA relative to HV. After up to 1 month of nomlabofusp treatment, levels of plasma TGs with these features were reduced. Nomlabofusp dose dependency of lipid changes was observed by Day 28 in a placebo-controlled dose exploration study. In addition, significant inverse correlations were observed between changes in PUFA containing TG and skin hFXN levels.

Discussion and Conclusion

In subjects with FRDA, increased tissue hFXN concentrations associated with nomlabofusp treatment correlated with a decrease of specific plasma TG values towards those observed in HV, suggesting normalization of FRDA-associated lipid dysregulation.