Prediction of tissue frataxin levels with long term administration of nomlabofusp in adults with Friedreich's ataxia using modeling and simulations

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Methods: Plasma nomlabofusp concentrations and skin frataxin concentrations from adults with Friedreich's ataxia (FRDA) before and after short term (< 30 days) subcutaneous administration of 25, 50, 75, and 100 mg nomlabofusp in Phase 1 and 2 clinical studies were used to construct an exposure-response model. Simulations of a population of virtual FRDA patients receiving daily doses of 25, 50, 75 or 100 mg of nomlabofusp were performed (n=100, 100 trials) and skin frataxin profiles over time at each dose were predicted.

Results: The simulations predicted that skin frataxin concentrations should reach steady state at approximately 28 days after daily administrations across all doses. Daily administration of 25, 50, 75, and 100 mg nomlabofusp was predicted to attain a median maximum skin frataxin concentration of 6.22, 9.06, 11.9, and 14.7 pcg/mcg, respectively.

Discussion: In a separate study, the mean skin frataxin concentration in healthy controls with 2 normal frataxin alleles was 16.35 pcg/mcg. Prior published studies indicate that the mean frataxin concentration in asymptomatic heterozygous carriers is 50% of healthy controls. In relation to these findings, 59% of patients with FRDA receiving daily 50 mg nomlabofusp are predicted to achieve skin frataxin concentrations that are equal or above 50% of the concentrations found in healthy controls.

Conclusion: Modeling and simulation using data from short term studies of nomlabofusp administration can be used to predict a potential long term therapeutic dose. Daily administration of 50 mg nomlabofusp is predicted to result in skin frataxin concentrations that are > 50% of concentrations found in healthy controls.