QSP model of Niemann Pick B Disease and Olipudase Alpha ERT is an innovative tool for extending the value of clinical data and disease knowledge, and filling the gap through computer simulation

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Objective: We describe a QSP model supporting late-stage development of olipudase alfa, an enzyme replacement therapy for acid sphingomyelinase deficiency (ASMD). ASMD, clinically known as Niemann-Pick disease types A and B, is a lysosomal storage disorder resulting in sphingomyelin accumulation and other complex lipid abnormalities. This leads to heterogeneous clinical effects affecting multiple organ systems. Through a multi-scale, semi-mechanistic description of ASMD, the QSP model can provide insight into the variability among patient characteristics, clinical disease markers, and treatment response.

Methods: The multi-scale model framework includes mechanistic and empirical sub-models (Figure 1A). These sub-models describe olipudase alfa effects on clinical disease markers, including ceramide, hepatosplenomegaly, and pulmonary decline. The model was informed by natural history, preclinical, and clinical studies for non-neurological ASMD [1,2,3,4].

Results: The model was calibrated using single- and multiple-dose (78 weeks, Q2W) clinical data. By using patient-specific PK profiles and indicators of disease severity, the model reproduced transient and long-term responses of molecular-level markers (Figure 1B), and changes in organ volume and lung function.

Conclusions: The QSP model captures molecular- and organ-level clinical responses to olipudase alfa. By quantifying systemic treatment responses in a heterogeneous disease like ASMD, the model provides insight into how the treatment affects the overall disease burden. The model also provides a platform for studying different dosage regimens and pediatric extrapolation.

References: