PK/PD model of plasma ceramide in patients with acid sphingomyelinase deficiency following enzyme replacement therapy with olipudase alfa.

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Objectives: Plasma ceramide, a catabolite of sphingomyelin, transiently increased in patients with acid sphingomyelinase deficiency (ASMD) who received treatment with olipudase alfa (rhASM), an investigational enzyme replacement therapy. A novel within-patient dose-escalation strategy was employed in a Phase 1b clinical trial of olipudase alfa to successfully control the release of ceramide. Pre-infusion ceramide levels declined with each successive dosing step, and remained below pre-treatment levels at completion of dose escalation. Our objective was to develop a population PK/PD (popPK/PD) model to characterize the time course of plasma olipudase alfa and ceramide in patients with ASMD receiving olipudase alfa.

Methods: The pooled modeling database included 16 adults with nonneuronopathic ASMD who were treated with olipudase alfa – 11 received a single dose (0.03 to 1.0 mg/kg) and 5 were dose-escalated from 0.1 mg/kg to 3 mg/kg. A sequential PK/PD modeling approach using NONMEM software was applied to describe plasma concentrations of olipudase alfa and ceramide. Estimated individual PK parameters were used as an input function on the rate parameter that represented the catabolism of sphingomyelin to ceramide (kASM).

Results: The final model consisted of a 5-compartment popPK/PD model with saturable response on the rate of catabolism as a function of enzyme concentration changing over time. The model adequately described the individual PK and PD time courses observed in single and multiple dose trials. Nearly maximal increase in enzyme rate was achieved at peak concentrations of olipudase alfa following a single dose of >0.1 mg/kg, and repeat doses of olipudase alfa resulted in a cumulative reduction in the predicted sphingomyelin levels.

Conclusions: A popPK/PD model has been developed to characterize the time course of plasma olipudase alfa and ceramide responses in patients with ASMD. The model could be used to guide late stage clinical development of olipudase alfa and to serve as an important tool for pediatric extrapolation.