**Background and objectives**

- **Metachromatic leukodystrophy (MLD)** (GM2/GD2) is an autosomal recessive disease caused by deficiency in the activity of sphingolipid Aβ.
  - Deficient activity of Aβ causes sulfatides to accumulate in the cells of the central and peripheral nervous system, resulting in death of neurons. This leads to progressive deterioration in motor skills and cognitive function, and ultimately premature death.
- MLD is categorized by age of onset as: infantile (<30 months), juvenile (2–18 years), and adult (>18 years).
- There are currently no approved therapies for MLD, and thus management of patients with MLD has been largely symptomatic and supportive care.
  - A new candidate enzyme replacement therapy using recombinant human Aβ (rhAβ), Shire, Lexington, MA, USA, is in phase 3 clinical trial.
  - The aim of this study was to evaluate the effects of rhAβ on sulfatides, CSF composition, and GMFM-88 total score in patients with MLD receiving rhAβ, to assess the clinical effects and determine the optimum dosing regimen.

**Methods**

- **Patient eligibility**
  - Eligible patients with MLD were identified from an open-label, dose-escalation safety evaluation of rhAβ (NCT01510105), and a follow-up safety evaluation and extension study in the same population (NCT01887038). The design of the study is shown in Figure 1.
  - All patients received rhAβ every other week for a maximum of 43 weeks and at least 12 months prior to enrollment in the original dose-escalation study and received 10, 30, and 100 mg rhAβ, respectively. Patients in Cohort 1 who were less than 12 years of age at enrollment and received 100 mg rhAβ that had been manufactured using a revised process.

- **Inclusion criteria for each analysis were as follows.**
  - PK: all patients received at least one dose of rhAβ and at least one rhAβ concentration measurement in serum or CSF.
  - PK/PD: all patients with PK parameter estimates available from the PK analysis and with at least one CSF sulfatide or GMFM-88 total score measurement available.

![Figure 1. Dose-escalation and extension study design](image)

**Disclosures**

- Patents: (n = 2) were equally distributed across the four groups.
- At baseline, mean patient age was 4.9 (standard deviation 2.3) and mean weight was 28.4 (SD, 7.0; range, 11.1–55.1 kg).

**Results**

- **PK/Parameters**
  - The fixed effects were estimated using nonlinear mixed-effects models with the exception of the proportional components of $\gamma$ and $\kappa$ (2008;97:15–21).
  - The precision of the estimated parameters and inter-compartmental clearance, $Q_{CSF}$, were consistent with CSF physiological turnover (approximately 6 hours).
  - The median transit rate constant (expressed as a transit half-life) of 1.19 (range, 0.555–2.09) hours is consistent with CSF physiological turnover (approximately 6 hours).

- **PK/PD relationship**
  - An A50% reduction in sulfatides in the CSF (model-estimated $EC_{50}$, 184 ng/mL rhAβ with a steep Hill slope of 3.59) and concentration-dependent proportional relationship with $\gamma$ (40.2% RSE).
  - The age-based dosing regimen for MLD was explored in patients who were younger than 8 months old and were at least 6 months of age.
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**Conclusions**

- **This analysis shows that delivery of rhAβ via an IDDD may lower the levels of rhAβ in CSF and slow the rate of motor function loss in a dose- and exposure-dependent manner in patients with MLD.**
  - Pharmacokinetic/pharmacodynamic modeling was used to predict the population PK, PK/PD, and E–R relationships to GMFM-88 total score. In all cases, the model provided good characterization of the measurements in the patients receiving rhAβ.
  - Given the small number of patients, the variability observed in rhAβ concentrations in CSF and that CSF concentrations were only observed at one time point, the precision between models varied. However, the model suggested rapid distribution of rhAβ into brain tissue and systemic circulation, but a slow terminal elimination half-life from the CNS.
  - Further studies are required to fully determine the effect of rhAβ on the accumulation of sulfatides in the CNS, motor skills, cognitive function, and overall survival in patients with MLD. The simulation results of the efficacy of rhAβ should be drawn from these data.