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Pharmacokinetic/pharmacodynamic modeling and simulation of recombinant human arylsulfatase A in patients with metachromatic leukodystrophy: a preliminary evaluation

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Background and objectives

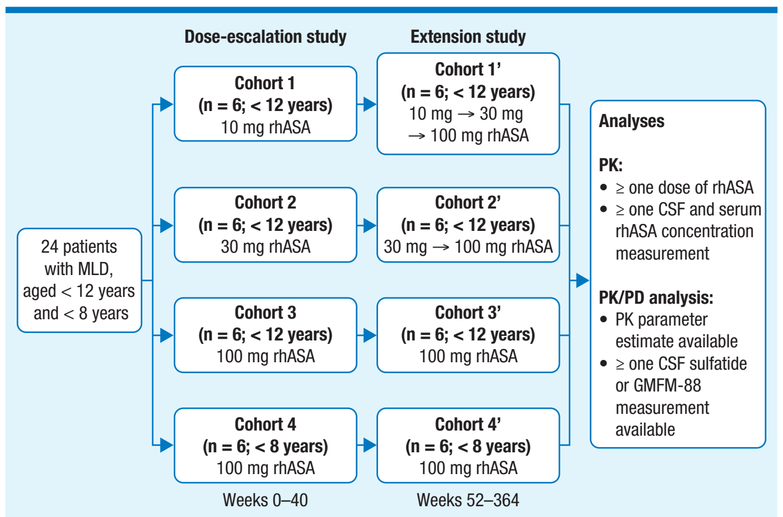
- Metachromatic leukodystrophy (MLD; OMIM 250100) is an autosomal recessive disease caused by deficiency in the activity of arylsulfatase A (ASA).[1,2]
  - Deficient activity of ASA causes sulfatides to accumulate in the cells of the central and peripheral nervous systems, resulting in demyelination of neurons. This leads to progressive deterioration in motor skills and cognitive function, and ultimately premature death.[1]
- MLD is categorized by age of onset as: late-infantile (< 30 months), juvenile (2.5–16 years) and adult (>16 years) forms.[3]
- There are currently no approved therapies for MLD, thus management of patients with MLD has so far been limited to symptomatic treatment and supportive care.[4]
- A new candidate enzyme replacement therapy using recombinant human ASA (rhASA; SHP611, formerly known as HGT-1110) is now under development for MLD.
- The aims of this study were to investigate:
  - the pharmacokinetic/pharmacodynamic (PK/PD) profiles of rhASA following intrathecal administration in patients with MLD
  - the effect of rhASA on sulfatide levels in cerebrospinal fluid (CSF)
  - changes in Gross Motor Function Measure-88 (GMFM-88) total score in patients with MLD receiving rhASA, to assess its 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 rhASA (NCT01510028) and a follow-on safety and evaluation extension study in the same population (NCT01887938). The design of this study is shown in Figure 1.
- All patients received rhASA every other week for up to 338 weeks via an intrathecal drug delivery device (IDDD). Patients in cohorts 1, 2 and 3 were less than 12 years of age at enrollment in the original dose-escalation study and received 10, 30 and 100 mg of rhASA, respectively. Patients in cohort 4 were less than 8 years of age at enrollment and received 100 mg of rhASA that had been manufactured using a revised process.
- Inclusion criteria for each analysis were as follows.
  - PK analysis: all patients received at least one dose of rhASA and with at least one rhASA concentration measurement in serum or CSF.
  - PK/PD analysis: all patients with a PK parameter estimate 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

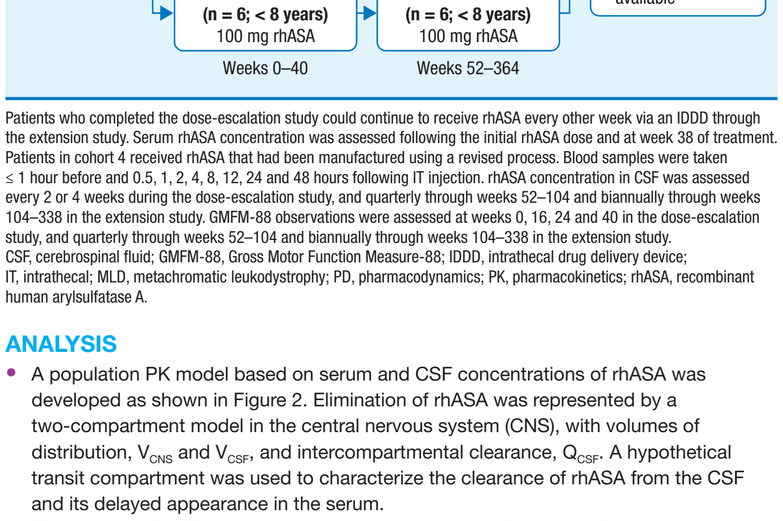


Patients who completed the dose-escalation study could continue to receive rhASA every other week via an IDDD through the extension study. Serum rhASA concentration was assessed following the initial rhASA dose and at week 38 of treatment. Patients in cohort 4 received rhASA that had been manufactured using a revised process. Blood samples were taken ≤ 1 hour before and 0.5, 1, 2, 4, 8, 12, 24 and 48 hours following IT injection. rhASA concentration in CSF was assessed every 2 or 4 weeks during the dose-escalation study, and quarterly through weeks 52–104 and biannually through weeks 104–338 in the extension study. GMFM-88 observations were assessed at weeks 0, 16, 24 and 40 in the dose-escalation study, and quarterly through weeks 52–104 and biannually through weeks 104–338 in the extension study.
CSF, cerebrospinal fluid; GMFM-88, Gross Motor Function Measure-88; IDDD, intrathecal drug delivery device; IT, intrathecal; MLD, metachromatic leukodystrophy; PD, pharmacodynamics; PK, pharmacokinetics; rhASA, recombinant human arylsulfatase A.

ANALYSIS

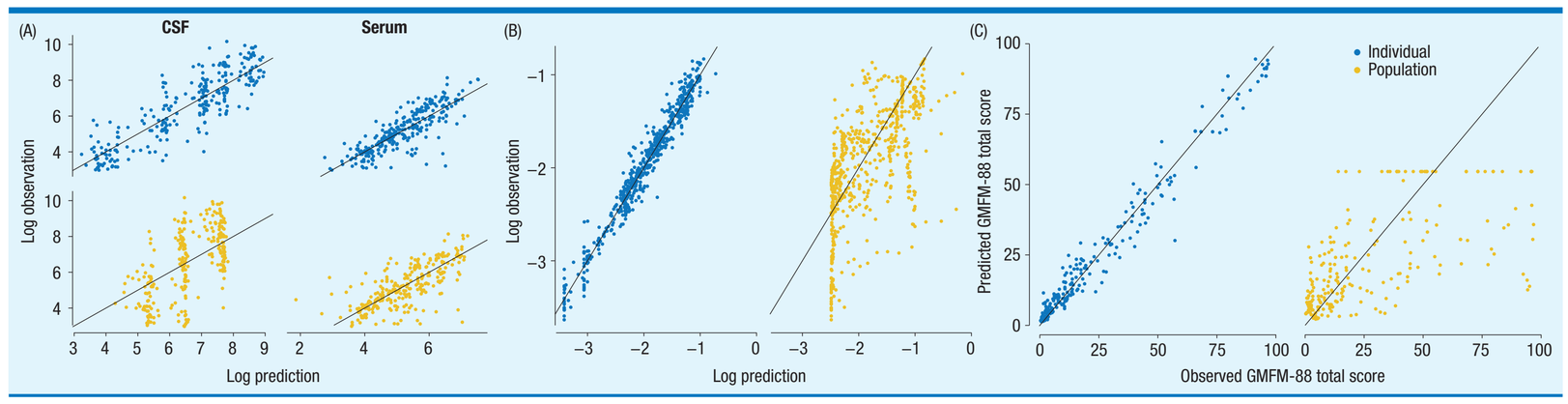
- A population PK model based on serum and CSF concentrations of rhASA was developed as shown in Figure 2. Elimination of rhASA was represented by a two-compartment model in the central nervous system (CNS), with volumes of distribution, V_{CNS} and V_{CSF}, and intercompartmental clearance, Q_{CSF}. A hypothetical transit compartment was used to characterize the clearance of rhASA from the CSF and its delayed appearance in the serum.
- The following PK/PD relationships were modeled: the effect of rhASA on sulfatide concentration measured in CSF and the exposure–response (E–R) relationship of rhASA to GMFM-88 total score.
  - The PK driver for the PK/PD relationship was the patient-specific, time-continuous PK profiles in the CSF and the CNS. PD effects were modeled sequentially and all PK-related parameters were fixed during estimation of PD parameters.
    - The CSF sulfatide measurement time course was characterized using an indirect response PK/PD model, with rhASA modeled as enhancing the elimination of sulfatide.
  - The population PK model-predicted rhASA concentration in the CNS compartment was used as the driver of PD response.
    - The E–R relationship of rhASA exposure to GMFM-88 total score was evaluated using a beta-regression model constrained by a logit link function to restrict the model predictions to lie within the range of 0–100%.

Figure 2. Clinical PK/PD model for rhASA concentrations in CSF, CNS and serum, and the effect on CSF sulfatide concentrations



CL, drug clearance; CMT, compartment; CNS, central nervous system; CSF, cerebrospinal fluid; k_{in}, formation rate of sulfatides; k_{out}, depletion rate constant of sulfatides; K_{trans}, transit rate constant; PK/PD, pharmacokinetics/pharmacodynamics; Q_{CSF}, intercompartmental clearance; rhASA, recombinant human arylsulfatase A.

Figure 3. Model goodness-of-fit plots of rhASA concentrations in CSF and serum (A); sulfatide concentrations in CSF (B); and GMFM-88 total scores (C)



CSF, cerebrospinal fluid; GMFM-88, Gross Motor Function Measure-88; rhASA, recombinant human arylsulfatase A.

- The population PK, PK/PD and E–R models were used to simulate expected rhASA concentration–time profiles and GMFM-88 total scores.
  - Four different dosing scenarios were used.
    - Scenario 1: 100 mg every other week.
    - Scenario 2: 100 mg every week for 12 weeks (initial weekly dosing), then 100 mg every other week.
    - Scenario 3: 150 mg every week for 12 weeks (initial weekly dosing), then 150 mg every other week.
    - Scenario 4: age-adjusted dosing weekly for 12 weeks (initial weekly dosing), then every other week (scenario 4: 80 mg, < 8 months; 120 mg, 8–< 30 months; 150 mg, ≥ 30 months).
  - 750 patient profiles were simulated; 250 randomly sampled uniformly from each age group.
- All data assembly, plots and summary tables were prepared using R (v3.3 or higher; R Foundation; http://www.r-project.org).
- The population PK, PK/PD and E–R modeling analyses and simulations were performed using NONMEM software (v7.3 or higher; ICON Development Solutions, Ellicott City, MD, USA).

Results

PATIENT CHARACTERISTICS

- Patients (n = 24) were equally distributed across the four cohorts.
- At baseline, mean patient age was 44.9 (standard deviation [SD], 22.8; range, 19.0–107.0) months and mean weight was 15.4 (SD, 4.14; range, 10.5–24.8) kg.

PK PARAMETERS

- The fixed effects were estimated with good precision, with the exception of the proportionality coefficients of V_{CSF} (76.1% relative standard error [RSE]), V_{CNS} (121% RSE) and K_{trans} (40.2% RSE).
  - The precision of the estimated inter-individual variability was poor.
- The model suggested rapid distribution of rhASA into brain tissue and systemic circulation: median distributive half-life of rhASA in the CNS was 1.02 (range, 0.394–1.66) hours and median half-life of distribution from the CSF to serum was 1.19 (range, 0.555–2.09) hours. However, median terminal half-life of rhASA in the CNS was approximately 20 days (477 [range, 256–1010] hours) (Table 1).
- 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

- A concentration-dependent reduction in sulfatide in the CSF (model-estimated EC_{50}: 184 ng/mL rhASA with a steep Hill slope of 3.59) and concentration-dependent inhibition in gross motor function loss (model-estimated IC_{50}: 120 ng/mL rhASA, with a shallow Hill slope of 0.554, in brain tissue) were observed.

MODEL FIT

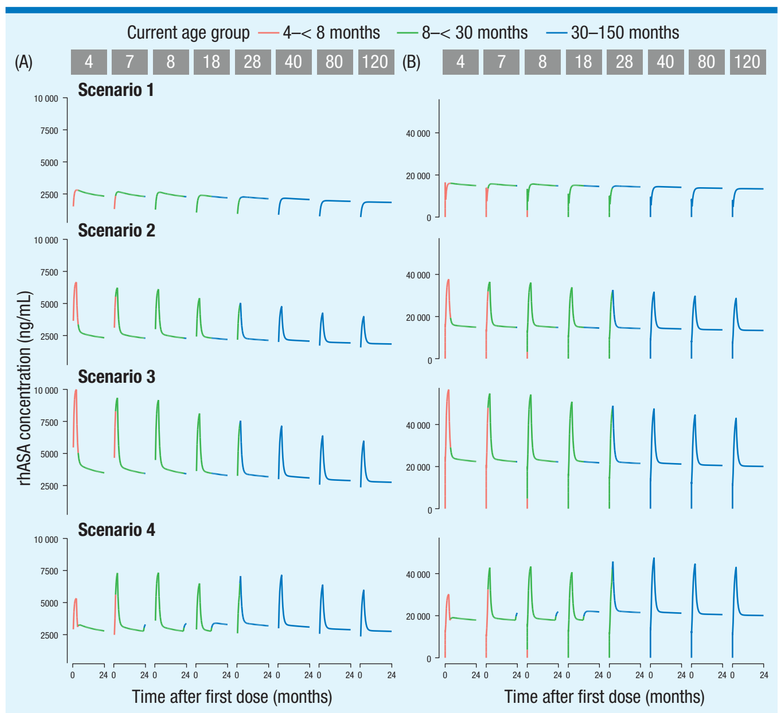
- The goodness-of-fit plots of population- and individual-predicted rhASA concentrations in CSF and serum, sulfatide concentrations in CSF and GMFM-88 total scores are shown in Figure 3A, B and C, respectively.
  - All three models show reasonable characterization of observed rhASA concentrations; precision of the models varied, which may have been caused by the small number of patients included in the study.
- The median simulated pre-dose trough rhASA concentrations in the CSF and CNS for the four simulated dosing scenarios are shown in Figure 4A and 4B, respectively.
  - At 100 mg every other week (scenario 1), it takes approximately 16 weeks to achieve PK steady-state, consistent with the median rhASA elimination half-life of 477 hours.
  - At 100 mg or 150 mg, with weekly dosing for 12 weeks, followed by dosing every other week (scenarios 2 and 3), higher trough concentrations of rhASA were achieved in the CSF and CNS compared with scenario 1.
  - The age-based dosing scenario (scenario 4) showed more consistent steady-state trough concentrations of rhASA over time for all three age groups. However, patients less than 8 months old did not achieve the same high trough concentrations of rhASA during the weekly administration phase as in scenarios 2 and 3.
- The simulations of the GMFM-88 total score show anticipated stabilization over time in some patients (Figure 5), which is consistent with the observed clinical study results.
  - Scenarios 1–3 predicted that some patients in all groups would show an early response to treatment.
  - Scenario 3 predicted the greatest number of patients with GMFM-88 total scores above 35 or 50 at 12 months and 24 months, respectively.
  - The age-based dosing regimen (scenario 4) predicted that fewer patients in the < 8 months and 8–< 30 months groups would respond to treatment than in the > 30 months group.

Table 1. Summary statistics of individual PK parameter estimates

rhASA PK parameter	Mean (SD)	Median (range)
CSF		
Half-life$_{CSF-serum}$, hours	1.28 (0.421)	1.19 (0.555–2.09)
Transit rate$_{CSF-serum}$, 1/hour	0.61 (0.22)	0.58 (0.332–1.25)
Intercompartmental Q_{CNS}, L/hour	0.0028 (0.0002)	0.0028 (0.0025–0.0032)
Distributive half-life$_{CNS}$, hours	1.06 (0.33)	1.02 (0.394–1.66)
Terminal half-life$_{CNS}$, hours	499 (176)	477 (256–1010)
Distribution volume$_{CNS}$, L	1.65 (0.49)	1.58 (0.963–3.17)
Distribution volume$_{CSF}$, L	0.031 (0.018)	0.027 (0.0063–0.099)
Serum		
Clearance$_{systemic}$, L/hour	3.04 (0.60)	2.80 (2.30–4.39)
Elimination half-life, hours	16.5 (5.72)	14.5 (8.83–30.6)
Distribution volume$_{systemic}$, L	73.7 (33.20)	71.5 (32.3–155)

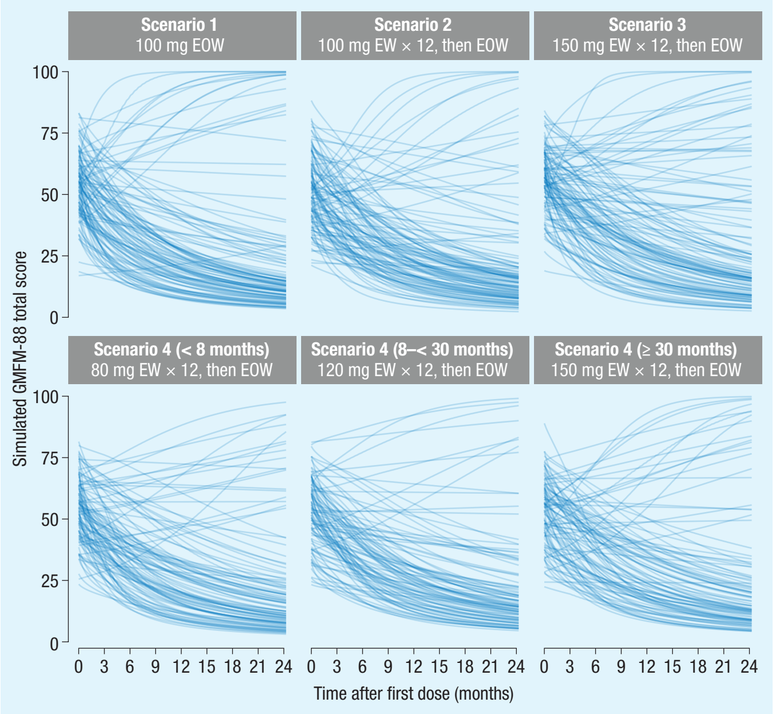
CNS, central nervous system; CSF, cerebrospinal fluid; PK, pharmacokinetic; Q_{CNS}, intercompartmental clearance in the CNS; rhASA, recombinant human arylsulfatase A; SD, standard deviation.

Figure 4. Representative simulated rhASA trough concentrations in the CSF (A) and CNS (B) by dose regimen and baseline age



The four dosing scenarios were as follows: scenario 1, 100 mg every other week; scenario 2, 100 mg every week for 12 weeks, then 100 mg every other week; scenario 3, 150 mg every week for 12 weeks, then 150 mg every other week; scenario 4, age-adjusted dosing weekly for 12 weeks, then every other week (80 mg, < 8 months; 120 mg, 8–< 30 months; 150 mg, ≥ 30 months).
CNS, central nervous system; CSF, cerebrospinal fluid; rhASA, recombinant human arylsulfatase.

Figure 5. Simulated individual-level predicted GMFM-88 total score by dosing scenario



The four dosing scenarios were as follows: scenario 1, 100 mg every other week; scenario 2, 100 mg every week for 12 weeks, then 100 mg every other week; scenario 3, 150 mg every week for 12 weeks, then 150 mg every other week; scenario 4, age-adjusted dosing weekly for 12 weeks, then every other week (80 mg, < 8 months; 120 mg, 8–< 30 months; 150 mg, ≥ 30 months).
EOW, every other week; EW, every week; GMFM-88, Gross Motor Function Measure-88.

Conclusions

- This analysis shows that delivery of rhASA via an IDDD may lower the levels of sulfatides in CSF and slow the rate of motor function loss in a dose- and exposure-dependent manner in patients with MLD.
- Pharmacometric modeling approaches were used to predict the population PK, PK/PD and E–R relationships to GMFM-88 total score. In all cases, the models provided good characterization of the measurements observed in the patients receiving rhASA.
- Given the small number of patients, the variability observed in rhASA concentrations in CSF and that CSF concentrations were only observed at pre-dose time points, the precision between models varied. However, the model suggested rapid distribution of rhASA 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 rhASA on the accumulation of sulfatides in the CSF, motor skills, cognitive function and overall survival in patients with MLD; no clinical conclusions on the efficacy of rhASA should be drawn from these data.

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Disclosures Steven Troy and Margaret Wasilewski are employees of, and have ownership interest in, Shire. CJ Godfrey is an employee of Metrum Research Group.

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References **1.** Gieselmann V. *Acta Paediatrica* 2008;97:15–21. **2.** Gieselmann V, Krageloh-Mann I. *Neuropediatrics* 2010;41:1–6. **3.** Rauschka H *et al. Neurology* 2006;67:859–63. **4.** Gomez-Ospina N. *GeneReviews* 2017. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1130/ (Accessed 21 December 2017).

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