Pharmacokinetics of RLS-0071, a Novel Anti-Inflammatory Peptide, in Newborns With Moderate or Severe Hypoxic Ischemic Encephalopathy

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Background

- Hypoxic ischemic encephalopathy (HIE) is a common cause of infant mortality and life-long neurocognitive disabilities with no currently approved pharmacological treatments available
- RLS-0071 (pegtarazimod) is a novel anti-inflammatory peptide that inhibits complement activation at C1, as well as myeloperoxidase activity and neutrophil extracellular trap formation
- Prior pharmacokinetic (PK) analysis of RLS-0071 in animal and adult human studies demonstrated a two-compartment model with a bi-exponential decline in plasma concentration driven by rapid distribution into tissues
- RLS-0071 is currently being evaluated in the STAR study, a phase 2 randomized placebo-controlled dose-escalation trial in neonates with moderate or severe HIE (NCT05778188)

Objective

To characterize the pharmacokinetics (PK) profile of RLS-0071 in newborns with HIE to assess safety

Methods

Sample Collection and RLS-0071 Detection:

- Participating infants in the STAR study were dosed within 10 hours of birth. RLS-0071 was administered at 3 mg/kg IV (first dosing cohort) and continued every 8 hours for a total of 10 doses
- Blood samples were obtained pre-dose, at the end of first infusion (Cmax), 1 hour post dose (close to the inflection point in the bi-exponential kinetics) and at 8 hours post dose (Cmin)
- RLS-0071 plasma concentration was measured by liquid chromatography/mass spectrometry (LC/MS)

Modeling and Simulation of PK curves:

- Neonatal PK modeling was performed using a two-compartment model and results compared against adult PK profiles derived from the RLS-0071 healthy volunteer Phase 1 trial (NCT05298787)
- To simulate a pediatric population, an adult model was adapted with 30% variability in clearance (CL) and volume of distribution (Vd)
- This model was then applied to neonates weighing 3 kg, with 100 simulations performed by sampling from the ETA distributions of the PK parameters. Simulations were conducted using allometric scaling and assumed a conservative 50% reduction in CL to account for delayed organ maturation and hypothermia

Results

- RLS-0071 plasma concentrations for 10 HIE neonates (8 moderate, 2 severe) following the first dose and multiple doses at 3 mg/kg are summarized in Table 1
- No drug accumulation was observed, and concentrations were within established safe plasma levels in adults
- RLS-0071 PK profile in neonates follows a two-compartment model with a bi-exponential curve consistent with adult kinetics
- HIE infant PK curves for RLS-0071 at the 3 mg/kg/dose were similar to adult human curves at the 2 mg/kg/dose (Figure 1)

Table 1. PK plasma values for RLS-0071 at 3 mg/kg IV Q8hr

	C_{max} (min, max) mcg/ml	C_{min} (min, max) mcg/ml	$AUC_{0\text{-}8hr}$ (min, max) mcg/ml/hr
First Dose	11.7 (1.9, 72.80)	ND	ND
Multiple Doses	10.2 (1.1, 26.7)	0.05 (0.02, 0.10)	7.3 (1.0, 16.5)

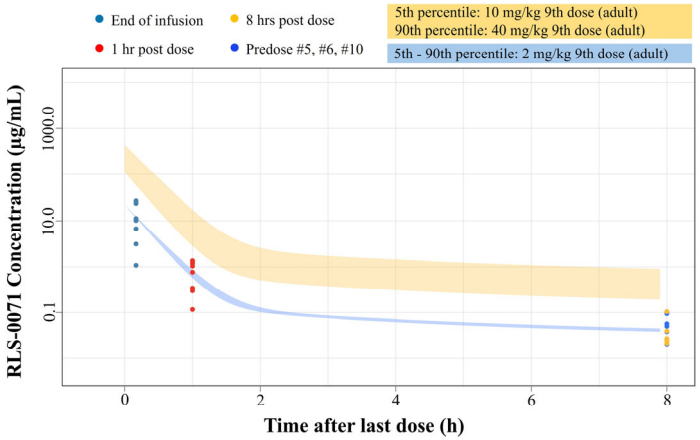

Figure 1. Comparison of pediatric and adult RLS-0071 PK curves after multiple doses. Yellow and blue shaded ribbons represent adult post-hoc simulations. Colored dots represent pediatric data at 3 mg/kg after 10th dose. Predose #5, #6, #10 are plotted at 8 h after 10th dose.

Results

- Simulation results for a single dose and multiple doses at assumed clearance levels are summarized in Table 2
- Assuming a 50% reduction in CL, simulation results predicted that 30% of infants receiving a 3 mg/kg dose of RLS-0071 would reach the target peak concentration (Cmax = 17 mcg/ml), associated with optimal efficacy in the animal model

Table 2. Predicted proportion of participants above threshold of 17 mcg/ml.

CL reduction	Dose (mg/kg)	N_{dose}	n	% above threshold
50% reduction	3	1	100	30
50% reduction	3	10	100	30
50% reduction	10	1	100	99
50% reduction	10	10	100	99
No reduction	3	1	100	1
No reduction	3	10	100	1
No reduction	10	1	100	83
No reduction	10	10	100	83

Conclusions

- The pharmacokinetics of RLS-0071 in HIE neonates followed a bi-exponential profile and was consistent with PK curves in adults
- Following multiple 3 mg/kg IV doses, RLS-0071 plasma levels in neonates were within previously established safety limits
- These results establish a safety and PK profile in HIE neonates that is reassuring for the continued investigation of RLS-0071 in HIE clinical trials

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