Population Pharmacokinetics of Rimeporide: a Sodium-Hydrogen Exchanger (NHE-1) inhibitor for Patients with Duchenne Muscular Dystrophy (DMD)

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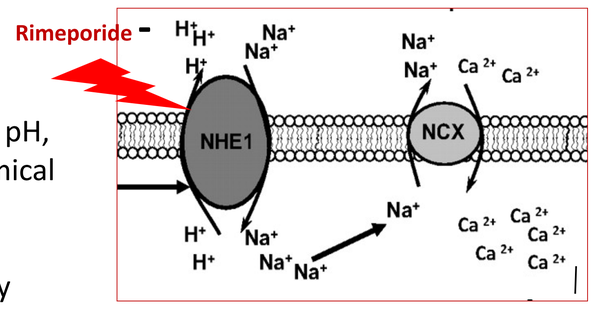
Background and rationale

Duchenne Muscular Dystrophy (DMD)

- DMD is a rapidly progressive and lethal form of muscular dystrophy affecting male children caused by mutations in the dystrophin gene. Currently, there is no cure for this rare disease.
- NA^+/H^+ exchangers (NHE-1) are ubiquitous membrane that regulate pH, and cell volume. NHE-1 inhibitors have many applications in biochemical and physiological research.
- Rimeporide is a novel therapeutic approach for DMD :
  - ✓ Myocytes/cardiomyocytes of DMD patients are characterized by increased intracellular sodium concentrations and edema (Weber et al, 2012).
  - ✓ Increased intracellular pH has also been shown in myocytes of DMD patients (Torriani et al, 2012; Dunn et al, 1992) and is related to disease severity (Wary et al 2012).



Rimeporide mechanism of action, Modified from Stanbouly et al. 2008.

Rimeporide

- Potent, orally administered selective NHE-1 inhibitor in clinical development for the treatment of patients with DMD by ***EspeRare Foundation*** (http://esperare.org/).
- Rimeporide has shown efficacy in two animal models relevant to different clinical manifestations of DMD:
  - ✓ Improvement of specific force, decreased fibrosis and inflammation established in dystrophic mice in skeletal and cardiac muscles.
  - ✓ Improvement in survival in hamsters with dilated cardiomyopathy with improved heart necrosis and fibrosis.
- Rimeporide has the potential to address inflammation, fibrosis and cardiomyopathy which are the 3 major pathogenic events in DMD that lead to a fatal outcome. Rimeporide is applicable to all patients with DMD, regardless of the causative mutation and has the potential to prolong ambulation, delay disease progression and prolong life.

Population Pharmacokinetics of Rimeporide

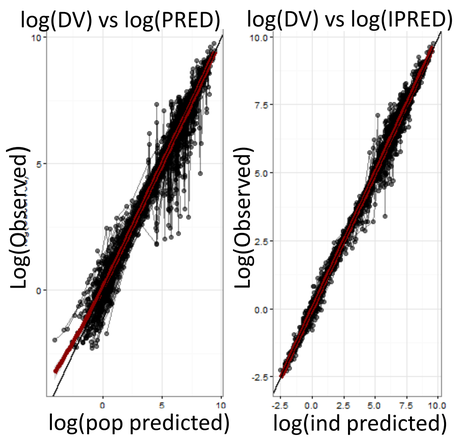
Objectives

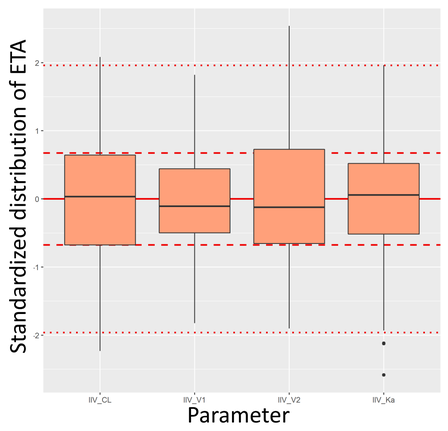
- To build a population PK model for Rimeporide based on adult heathy volunteers data in order to simulate Rimeporide concentrations in young boys suffering from DMD (6 to 14 years old).
- To check the adequacy of the model developed in adults with the concentrations obtained in paediatric patients in an ongoing phase Ib clinical trial.

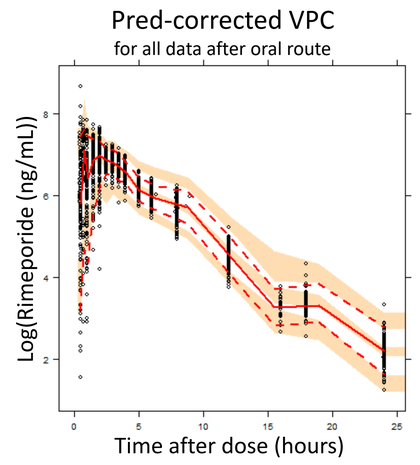
Methods

- Rimeporide plasma concentration, after intravenous and oral administrations in adult healthy volunteers, were obtained from 6 clinical studies, overall **156 subjects for 3302 Rimeporide concentrations**.
- Log-transformed plasma concentrations were modelled with non-linear mixed-effects approaches using NONMEM v7.3.0.

Final PK model in adults healthy volunteers



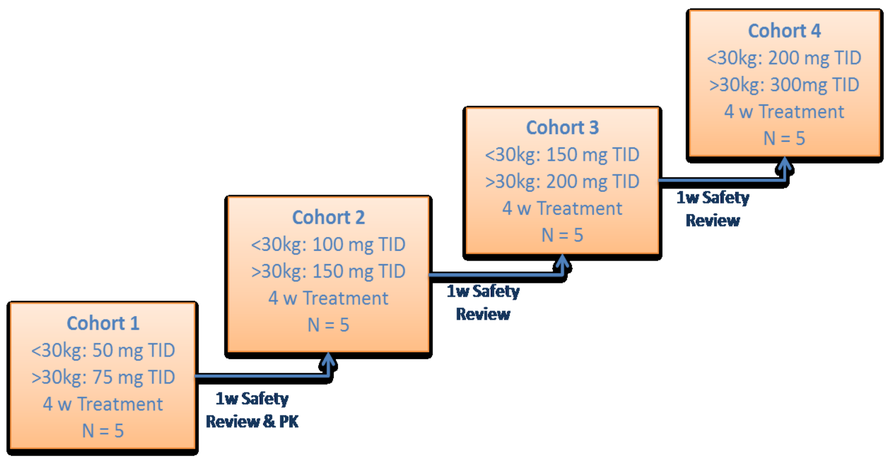




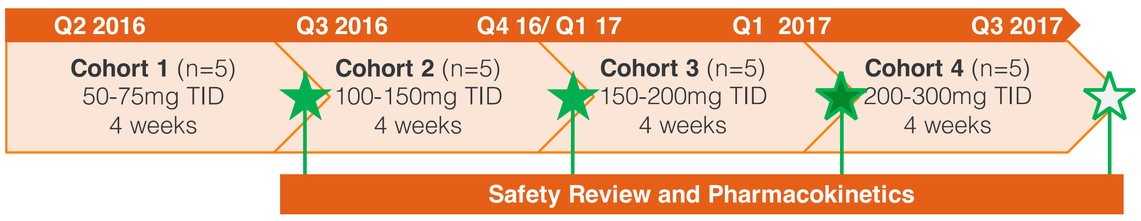
- 3-compartment model for disposition with a 3-transit compartment model for absorption and an absolute bioavailability fixed to 1.
- GOF, Distribution of random effects and pred-corr VPC plots show the good agreement between the model and the observed Rimeporide adults concentrations.

Rimeporide Paediatric Clinical Trial

Ongoing Clinical development in patients with DMD (6 to 14 y)

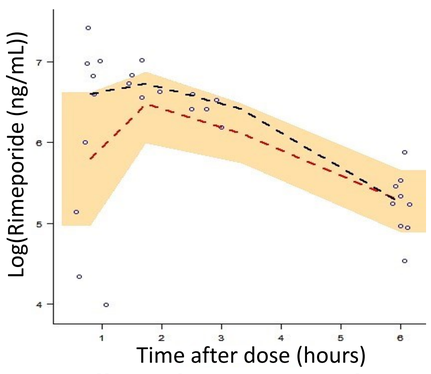


- **Primary objective:** Determine safety & tolerability of Rimeporide after 4 weeks oral treatment three-times a day
- **Secondary objective :** Evaluate the PK profile of Rimeporide in plasma
- **Exploratory objectives:** NMRI indices (T2, Muscle Mass, Fat Fraction) & Serum Biomarkers

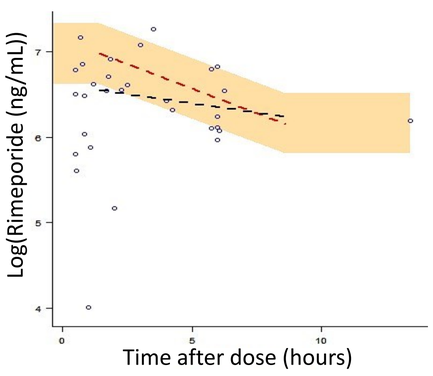


Preliminary PK results for the first 3 cohorts (pred-corr VPC n=1000 replicates)

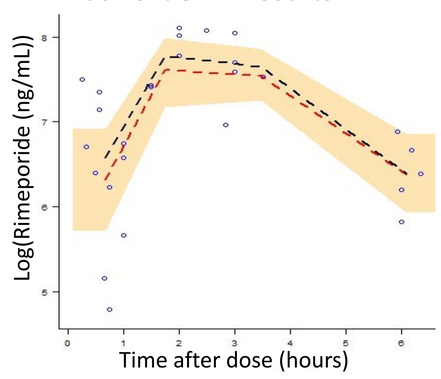
- **Cohort 1 PK results**



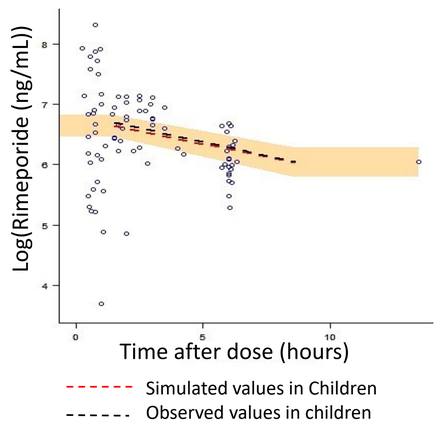
- **Cohort 2 PK results**



- **Cohort 3 PK results**



- **All 3 Cohorts PK results**



- **Covariate effect:** Renal function in children suffering from DMD, was characterized using GFR and Filler formula (***Filler et al, Pediatr Nephrol, 2003***) which uses Cystatin C rather than serum creatinin.
- **Results:** pred-corr Visual Predictive Checks show that the adult healthy volunteers model adequately reflects the PK in children for the 3 available cohorts.
- **Next step:** look at PK data for Cohort 4, and explore potential relationships between Rimeporide PK and NMRI indices and serum biomarkers.

ODD Preclinical PoC 2016 → Phase Ib in DMD patients 2017 → Phase II/III preparation 2018 → Patient recruitment in pivotal study(ies) 2021 → NDA approval

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