Translational Development of Rimeporide, a Sodium-Hydrogen Exchanger (NHE-1) Inhibitor, for Patients with Duchenne Muscular Dystrophy

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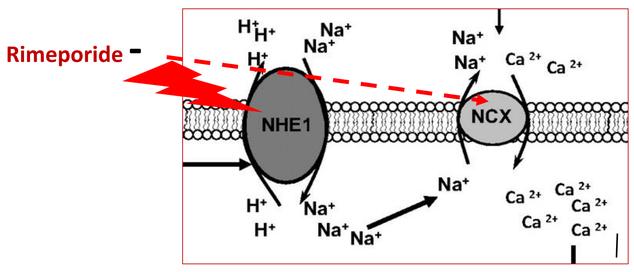
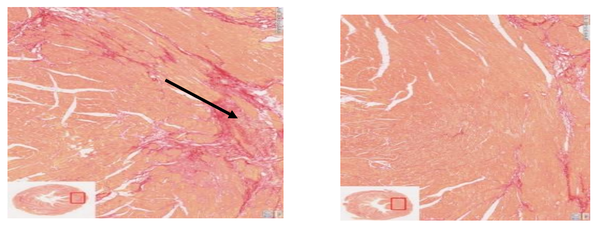
Background and rationale

Background of NHE-1 inhibition in DMD

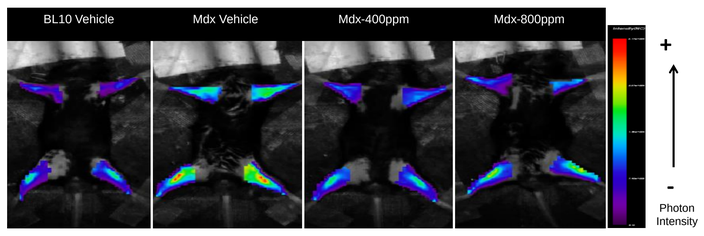


- $[Na^+]_i$ serves as a co-regulator of Ca^{2+} influx through the NCX and NHE-1, (*Burr et al, 2015*)
- $[Na^+]_i$overload was observed in DMD patients (*Weber at al, 2012*), is responsible for edema and a secondary increase in basal Ca^{2+} levels leading to myofiber necrosis and muscles degeneration (*Burr et al, 2015*)
- **NHE-1 inhibitors reduce $[Na+]_i$, & indirectly $[Ca2+]_i$** *(Iwata et al, 2007; Dorchies et al, 2015*), **reduce myocardial necrosis** (*Chahine et al, 2005*), **myofiber fibrosis** (*Nagaraju et al, 2015*), **inflammation** (*Yang et al 2013*) and **prevent early death** *(Bkaily et al, 2015)* in CM hamsters .

Fibrosis and Inflammation in mdx mice

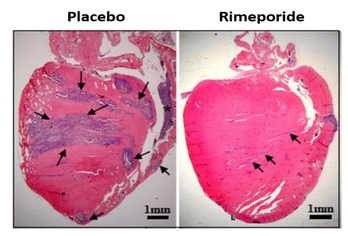


Significant reduction of fibrosis in the heart (above, -29%) & in diaphragm (-19%) , in mdx mice after a 9 M treatment)



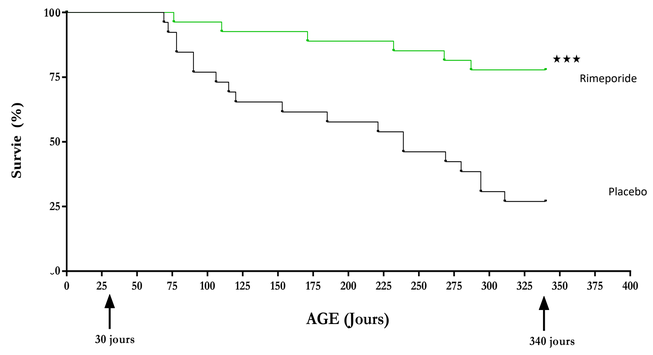
Significant reduction in inflammation in a large panel of skeletal muscles (forelimb & hindlimb) & diaphragm (-38%)

Cardioprotection in CMH Hamsters



Decreased heart necrosis, thrombosis, myolysis

Prevention of early death in cardiomyopathic hamsters



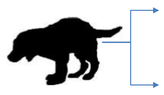
Phase II/III prerequisites

GLP Toxicology studies

Extensive Toxicology package did show that Rimeporide was safe

- Repeated oral toxicity studies up to 26-week in rats and up to 39-week in dogs showed the main target organ in both species to be fundic parietal cells (reversible mild parietal cells alteration)
- No mutagenic activity nor teratogenic potential were shown
- No impairment of male and female fertility
- No skin sensitising properties
- No effect on cardiovascular hemodynamic parameters, no evidence of risk for any pro-arrhythmic effects
- No relevant effects on the central and peripheral nervous system, nor on the gastro-intestinal, renal and respiratory system

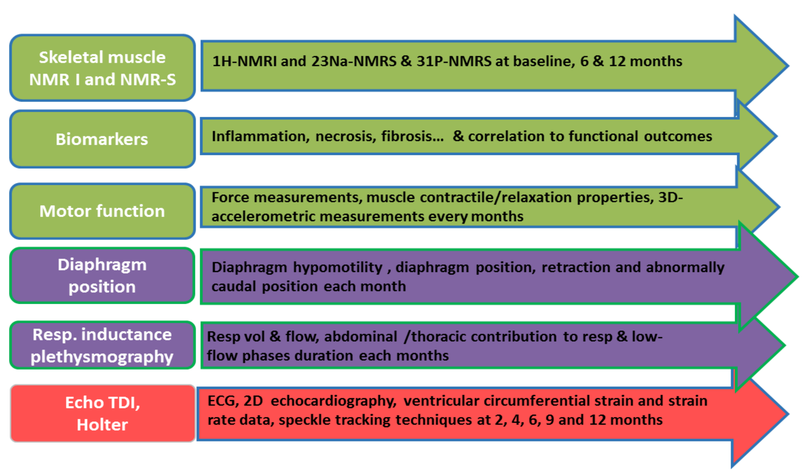
Translational GRMD Dogs studies



GMRD severe

GMRD moderate

- 20 animals (8 severe & 12 moderate)
- Blinded treatment with Rimeporide at 20 mg/kg/d or placebo started from 2 to 12 months
- Objectives:
  - Contribute to the design of the clinical study by guiding dose selection, identifying novel non invasive biomarkers as well as cardiac outcome measures.

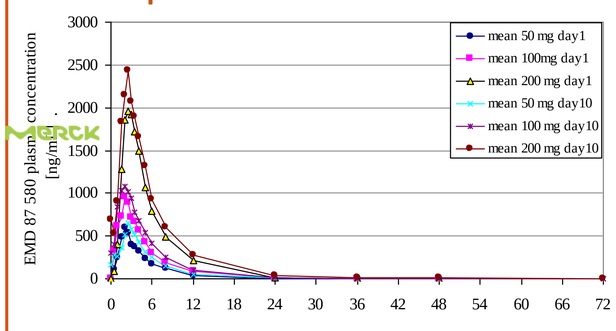


Rimeporide Clinical trial status update

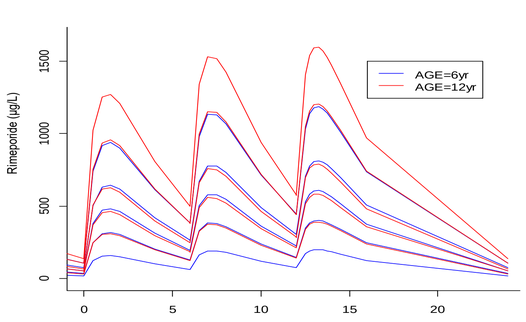
A complete safety & PK in healthy adults and congestive heart failure patients

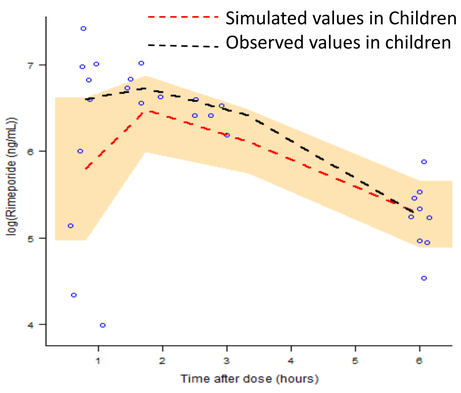
- **Clinical pharmacology studies in over 166 healthy and CHF patients:**
  - Single oral and IV administration
  - Multiple oral doses administration
  - Food interaction
  - Drug Drug Interaction with Digoxin
  - Safety, tolerability, PK in CHF patients with renal insufficiency
- **Adverse events were mild in intensity with no clear dose dependency**
  - headache (≈15%), dizziness (≈ 5%), chest discomfort (≈10%), paresthesias, vaso-vagal attacks, local skin reactions. No clinically relevant changes in vital signs, ECGs, Laboratory.
  - Similar events reported on Placebo and treated patients

- **PK profile in Adults**



Predicted PK profile in Children





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

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

- **Cohort 1 PK results**
  - **In cohort 1**:
  - 5 ambulant DMD patients aged 6 to 10 y, enrolled in France, received oral rimeporide for 4 W
  - No treatment-related adverse events, no significant modification of safety lab & tolerability issues
  - **In cohort 2**: 5 patients (6-10 y) in Italy, Spain & UK completed, safety analysis ongoing
  - **PK:** Visual Predictive Check shows that the adult model, incorporating allometric scaling, adequately reflects the PK in children

ODD — **2015** Scientific Advice — **2016** Biomarkers strategy — **2017** Launch of pivotal study(ies) — **2021** NDA approval

Preclinical PoC — **Phase Ib in DMD patients** — **Phase II/III preparation**

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