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

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Rimeporide: a Na^+/H^+ exchanger inhibitor to protect cardiac AND skeletal muscles in patients with DMD

Rimeporide is a first in class Na^+/H^+ exchanger inhibitor which mediates predictable, measurable, reproducible and clinically relevant anti inflammatory and anti fibrotic effects in cardiac, respiratory and skeletal muscles. Rimeporide is also a potent cardioprotective agent and is expected to be of benefit to prevent the long term accumulation of inflammation and fibrosis in skeletal and cardiac muscles in patients with DMD

Fibrosis

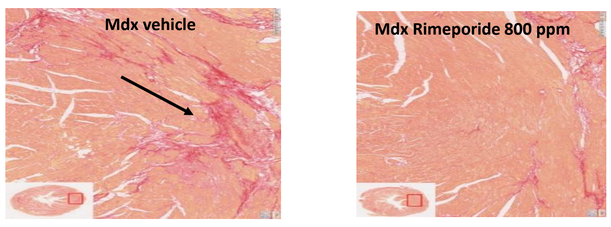


Figure 1: Representative images of the heart from mdx vehicle and mdx 800 ppm Rimeporide treated mice (9 months treatment)

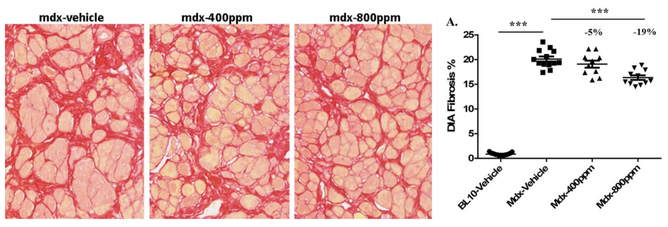


Figure 2: Representative images of the diaphragm from mdx vehicle and mdx 400 & 800 ppm Rimeporide treated mice (9 months treatment) and quantification of area of fibrosis

Inflammation

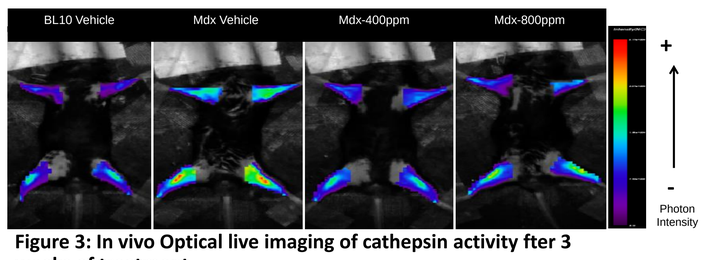


Figure 3: In vivo Optical live imaging of cathepsin activity fter 3 weeks of treatment

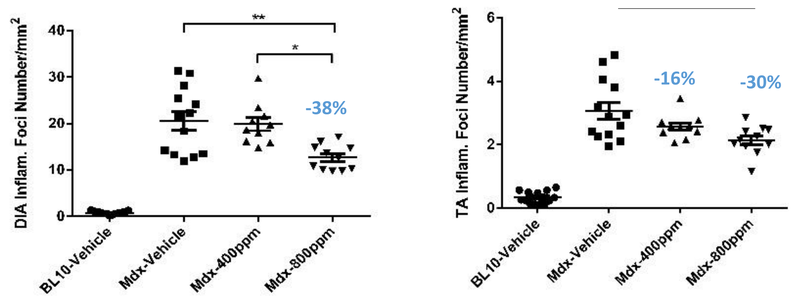


Figure 4: Quantification of inflammation (foci/mm2) in the diaphragm &Tibiliais anterior . *P-value<0.05; **P-value<0.01; ***P-value<0.001. % above each of the bars indicates the percentage change from mdx vehicle

Cardioprotection

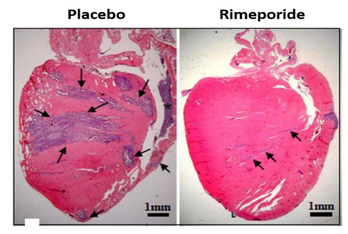


Figure 5: Representative myocardial longitudinal sections of hearts.. 198-day treatment of 30-day-old CMHs with Rimeporide significantly (p<0.001) prevented development of cardiac necrosis.

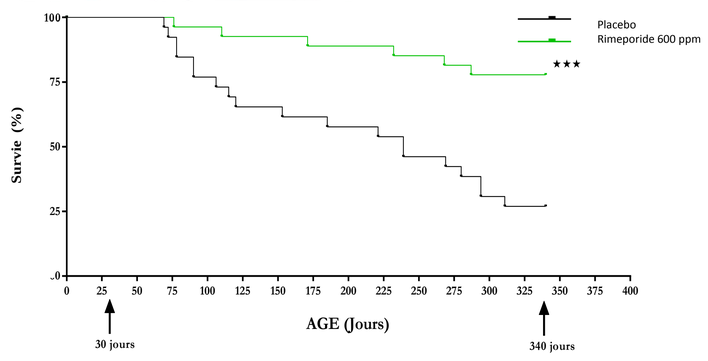


Figure 6: 310 day treatment of 30-day-old CMHs with Rimeporide significantly (p<0.001) improve overall survival

Rimeporide in GRMD dogs: a "translational bridge between mice and humans"

Key objectives of the study

GRMD dogs play a key role in the translational approach to develop candidate therapies for DMD. The rimeporide long term efficacy study in young (2 month) GRMD dogs will contribute to the design of the clinical phase II/III pivotal study by guiding dose selection, identifying novel non invasive biomarkers as well as cardiac outcome measures.

Study Design

- **Controlling GRMD dog phenotypic heterogeneity is essential to improve the robustness of results and enhance the translational value of GRMD dogs studies: Pr Blot's team at the Ecole Nationale Vétérinaire d'Alfort** has developed a method to control the inter-individual phenotypic heterogeneity in GRMD dogs (figure 7). It allows the stratification between moderate GRMD dogs with slow disease progression and severe GRMD dogs with fast disease progression and loss of ambulation before 6 months. Increased percentage of circulating CD4+CD49dHi T-lymphocytes have also been correlated with both disease severity and a more rapid disease progression (Pinto-Mariz et al, 2015, Skeletal Muscle)

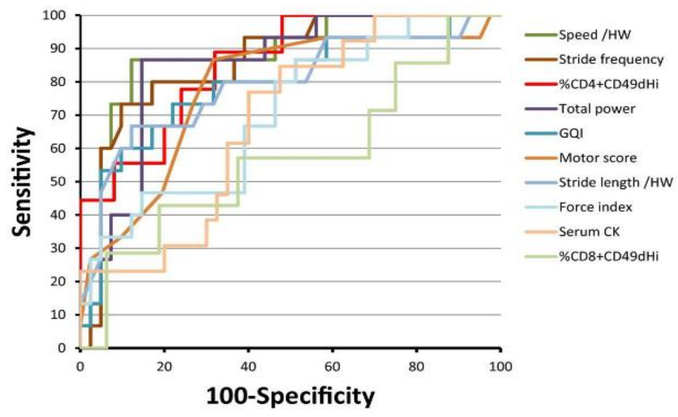
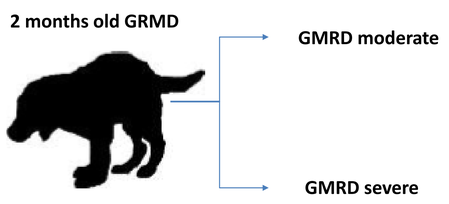


Figure 7 : ROC curve of 10 candidate markers for prediction of the severe GRMD form at 2 months of age (Dis. Mod. Mech. 2014).

Stratification of GRMD Dogs

- At 2 months of age, three selective markers will be used to stratify GRMD : normalized speed, stride frequency and $CD4^+$ $CD49d^{hi}$ lymphocytes proportion with specific cut-off to avoid inclusion of false-positive.

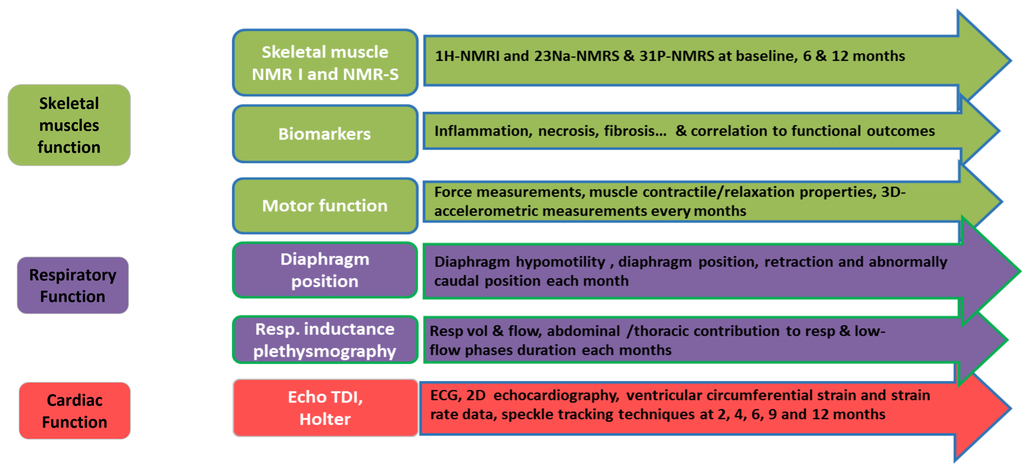


Treatment

- 20 animals will be screened and enrolled
- Treatment will be started at 2 months. Based on previous animal studies a dose of Rimeporide at 15 mg/kg/d was selected.
- Rimeporide or placebo will be given orally for 10 months in a blinded way
- PK profile in dogs showed that a twice a day dosing was sufficient to maintain plasma levels above the expected efficacy range

GMRD Rimeporide N=10 severe/moderate	GMRD placebo N=10 severe/moderate

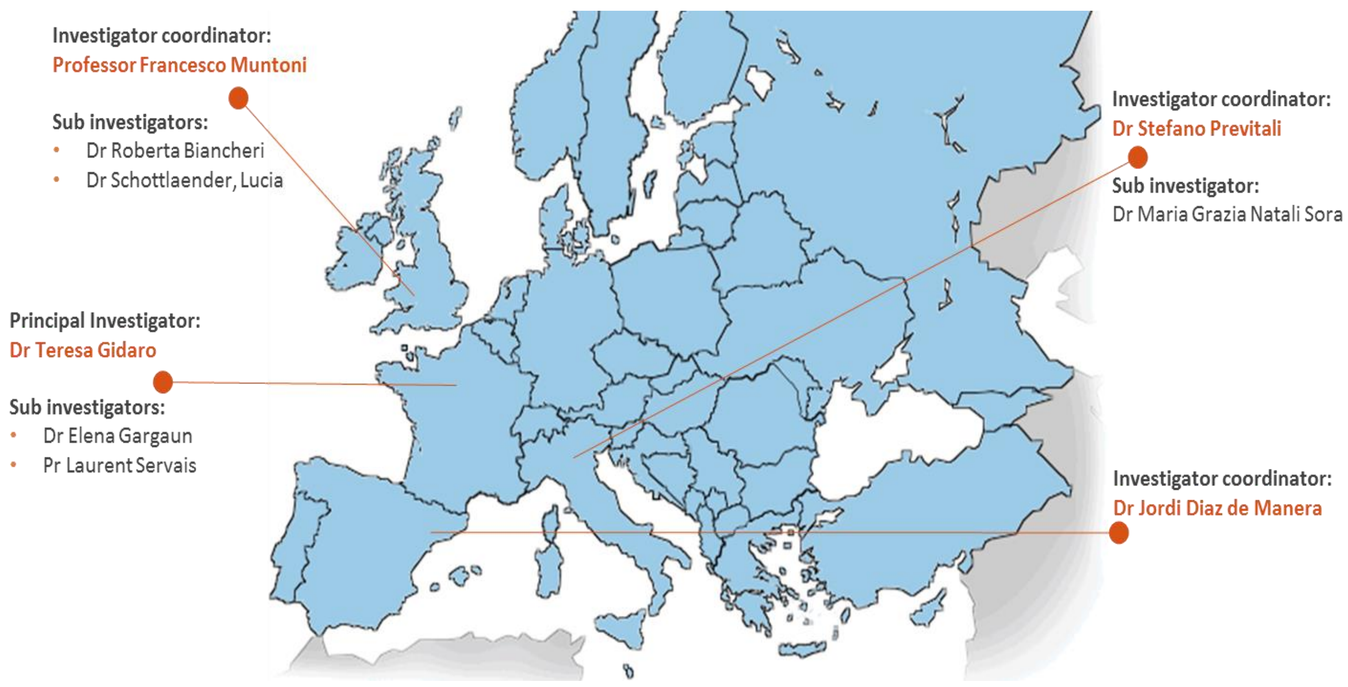
Study Endpoints



Rimeporide multicenter phase Ib trial

Study Design

A multicenter phase Ib, open label, sequential-group study of ascending oral doses of Rimeporide in 6 to 14 years old patients with DMD after 4 weeks of treatment.



Study Objectives & clinical endpoints

Primary Objective:

- To determine the safety and tolerability profile of rimeporide in 6-14 year old patients with DMD

Secondary objective :

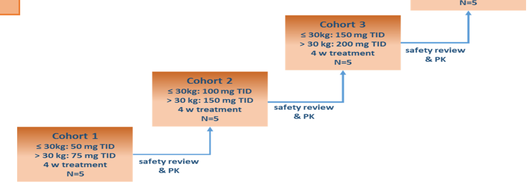
- Evaluate the pharmacokinetic profile of rimeporide in plasma

Exploratory objectives:

- **NMRI indices**: T2, T2 heterogenity, fat fraction, CSA, and muscle-mass index for all patients
- **31P NRMS and 23Na NMRI**: for the patients in Paris only, measure of intracellular pH and Sodium
- **Blood biomarkers**: CK, CRP, TNFα, TGFβ-1, inflammatory cytokines & other exploratory PD biomarkers to monitor muscle damage

Rimeporide Treatments

- 4 weeks of oral treatment
- Weight based dosing (> or < 30kg)
- Capsules of 25 mg or 50 mg



SUMMARY

- **Rimeporide is a muscle-sparing agent that may alleviate long-term accumulated muscle and myocardial damage and inflammation with no restriction on age and genotype. Rimeporide could represent an important therapeutic combination with other treatments that restore or augment dystrophin.**
- **Rimeporide was granted Orphan Drug Designation and received a positive evaluation from the European Medicines Agency in 2015 in a Scientific Advice and in a Biomarkers Qualification Advice.**
- **EspeRare aims to enable Rimeporide's registration for DMD patients by 2020 and extend its use to other rare forms of muscular dystrophyies.**

Acknowledgements:
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