Translational development of Rimeporide for Duchenne Muscular Dystrophy

Action Duchenne, London, October 2014
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R&D Director & co-founder EspeRare
EspeRare: An innovative venture philanthropic model

- EspeRare is a non-profit enterprise to drive patient-centered translational development of new treatments in rare diseases

- EspeRare works with a team of experts in rare diseases to advance new medicines for high unmet need patients
Rimeporide, NHE-1 inhibitor as a new treatment for Duchenne Muscular Dystrophy (DMD)
Rimeporide  Mechanism of action

- Concept: can correction of ionic dysregulation with Rimeporide in patients with Duchenne by inhibition of NHE-1 transporter delay disease progression
Rimeporide has completed a comprehensive nonclinical safety package

- **GLP Tox:**
  - No specific toxicology signal in rodent and non-rodent after acute and long-term studies (chronic and acute, genotox, mutagenicity, fertility..)

- **Safety pharmacology:**
  - No safety findings in cardiovascular, CNS and respiratory organs

- **PK and TPK**
  - ADME in animals

- **Chemistry and manufacturing**
  - Scaled up GMP process for both Drug Substance and Drug product
  - IMPD under preparation
  - Pediatric formulation planned for phase II

Confidential
Rimeporide is safe and well tolerated in healthy adults and heart failure patients

- Clinical pharmacology studies
  - 166 adults received Rimeporide
  - Rimeporide is safe and well tolerated up to 600mg/day
  - PK profile after oral administration:
    - high and dose proportional absorption, distribution to the tissues was rapid. Rimeporide was cleared by the kidney as the unchanged drug
  - No drug drug interactions & no CYP induction/inhibition

- PK modelling and simulation
  - Simulations of plasma concentrations in DMD patients aged from 6 to 12 years supported the development of a three times daily regimen of doses ranging from 25 to 150 mg
Rimeporide from heart failure to Duchenne: the rationale

• Pathophysiological similarities of heart- and skeletal muscle in DMD:
  • increased Na+ levels in the diseased muscles and oedema
  • impaired intracellular Ca++ handling leading to necrosis

• In a mouse model of Duchenne, NHE-1 inhibitor
  • markedly reduced histological muscle damage & preserved muscle performance

• In sarcoglycan deficient dystrophic hamster
  • NHE-1 inhibitor normalized intracellular Ca++ handling and decreased stretch induced CK release
  • protective effects were also shown with the NHE inhibitor EIPA
Rimeporide reduced cardiac necrosis & thrombosis in cardiomyopathic hamsters:

Effects of 198-days treatment of cardiomyopathic hamsters (CMHs) with rimeporide on calcium (A) and sodium (B). Wild= wild type hamster, CM= untreated CMHs, EMD= rimeporide treated CMH, n=3, ***p<0.001.

Representative myocardial longitudinal sections of hearts. Arrows show necrosis and (*) shows mural thrombus. 198 days treatments of 30-day-old CMHs with rimeporide significantly (p<0.001) reduced cardiac necrosis.

Long term preventive studies (198 days)
Chahine et al 2005
**Rimeporide** prolonged overall survival & decreased cardiac necrosis in cardiomyopathic hamsters

**Representative myocardial longitudinal sections of hearts from 340-day-old UM-X7.1 cardiomyopathic hamsters.** Untreated (Placebo) or treated for 310 days with Rimeporide 600 ppm (Rimeporide).

**Long term preventive studies (310 days)**
Rimeporide a short treatment in mdx mice modestly improved functional strengths

In mdx mice: a 3-week treatment leads to consistent (FL&HL) and IVF functional improvements
Rimeporide striking anti-inflammatory response (1)

Optical Imaging
Statistically significant decreased inflammation with Rimeporide

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Rimeporide striking anti-inflammatory response (2): reduction of inflammation foci (H&E staining, Diaph)
Rimeporide a new treatment paradigm for DMD

- Lack of dystrophin
- Calcium influx
- Sodium influx
- Oxidative stress
- Membrane fragility
- Muscle Cell death
- Fibrosis
- Inflammation
- Oedema
- Motor function degeneration
- Respiratory function degeneration
- Cardiomyopathy
- Death
Rimeporide biological effect on non invasive markers

Translatable Predictive and Pharmacodynamic biomarkers

Non invasive biomarker:
31-Phosphorus spectroscopy
23-Na spectroscopy
MRI :T2 and fat infiltration
Rimeporide first pediatric trial

MAD study in Europe
- Ambulatory DMD patients
- 15 days dosing
- Tolerability & Safety
- PK & Biomarkers
- Identify doses for Phase 2

- **Sample size:** 15 males between 6 and 14 years,
- **Sequential dose groups:** subject will participate in only 1 dose cohort.
- **Dose Escalation:** DSMB review of 1-week safety data.

- **Cohort 1**
  - <30kg: 50 mg TID
  - >30kg: 75 mg TID
  - 2w Treatment
  - N = 5

- **Cohort 2**
  - <30kg: 100 mg TID
  - >30kg: 150 mg TID
  - 2w Treatment
  - N = 5

- **Cohort 3**
  - <30kg: 150 mg TID
  - >30kg: 200 mg TID
  - 2w Treatment
  - N = 5
Rimeporide phase Ib study: Clinical sites
Is Rimeporide a Skeletal and/or Cardiac drug?
Development strategy of Rimeporide in Duchenne

- Q1 2014: Preclinical PoC
  - MDX mice data
  - GMP transfer and production
  - Orphan Drug Designation

- Q1 2015: Phase Ib
  - PK, safety and tolerability
  - Proof of Mechanism
  - Biomarker strategy
  - Scientific Advice, PIP and IND preparation

- Q3 2016: Phase II/III
  - Pediatric formulation
  - Dose range finding
  - Long term Safety and efficacy

- Q3 2020: MA
Acknowledgments and questions?