Every child Matters

Fast-forwarding treatments for children with rare diseases

Rimeporide in Duchenne Muscular Dystrophy

January 2017

Photo credits: Ceridwen Hughes, http://www.samebutdifferentcic.org.uk/
The orphan disease market is heterogeneous and complex

- Drug development is a long, complex and costly process
- Despite significant progress in scientific research & technologies, drug development remains inadequate to address medical needs in rare diseases
- Therapeutic development suffers from the heterogeneity & complexity of these diseases & the lack of interest from pharma

Only 5% of rare diseases with approved therapeutic solutions

Source: EspeRare
EspeRare is a unique business model in the orphan disease space.

**Unique Model**

**Solid foundation of efficient translational development based on Pharma know-how**

- **Product** – repositioned drug with secured exclusivity data package
- **Regulatory file** – reduced cost and faster process as SME
- **Market insights** – early market insights thanks to agile organization and information flow

**Benefits from not-for-profit status**

- **Patient engagement** – centered focus (without commercial conflict of interests) on the patient communities
- **Ethical, Social Responsible commitment** – mission-driven positioning for R&D
- **Access** – early advice from regulators, policy makers and unbiased input from KOLs
- **Financial de-risking** – non-diluted funds from philanthropic donations

**Small Biotech capabilities**

**Mission-driven incentives**
Key stakeholders are engaged by our side, to advance treatments for rare diseases

EspeRare secured key collaborations with patient organizations, drug developers & research institutes to source treatment opportunities and to drive universal access to developed medicines.
Our Portfolio

Our portfolio: CHF 8 million invested to date in 5 drug development programs addressing diseases affecting 2 million children

**Rare diseases addressed**
- Duchenne muscular dystrophy
- Pulmonary hypertension
- Duchenne muscular dystrophy
- Focal segmental glomerulosclerosis
- Congenital heart defects

**Preclinical**
- Rimeporide
- Rimeporide
- ER-002
- ER-003

**Phase 1/2**
- FloWatch device (commercial registration)
- Outlicense in 2017
- Preclinical PoC 2017
- Preclinical PoC 2017
- Fundraising
- Market re-launch
**Disease Overview**

- Duchenne Muscular Dystrophy (DMD) is the most common childhood form of muscular dystrophy. It is an X-linked recessive disease affecting males resulting from mutations in the gene encoding the protein dystrophin.
- Lack of dystrophin leads to inflammation and fibrosis in all muscles.
- DMD is rapidly progressing and severe. Children display skeletal muscle weakness by the age of 2–6 years then progressively lose ability to walk. Cardiac and respiratory dysfunction soon follow.
- There is no cure for DMD, nor any drug to delay disease progression.
- There are over 50,000 DMD patients in the US and EU, all of whom would be eligible for a novel therapy.
- The main cause of death is cardiac and respiratory failure in the late 20s.

**Cardiomyopathy and DMD**

- Cardiac dysfunction is nearly ubiquitous in DMD patients, and is the primary cause of premature death.
- Cardiac dysfunction in DMD is characterized by ventricular fibrosis, arrhythmias and conduction abnormalities and dilated cardiomyopathy, as in other muscular dystrophies.
- No specific disease-modifying treatment exists or is in development for DMD cardiomyopathy. Current standard of care are treatments used for common cardiac failure with limited efficacy.
- There is urgency to develop treatments for this severe condition, to extend and improve the quality of life of DMD patients.
Rimeporide

A selective, potent, safe, and first-in-class NHE-1 inhibitor already shown to be safe in human clinical trials

<table>
<thead>
<tr>
<th>Drug type</th>
<th>Small molecule, Na+/H+ exchange-1 (NHE-1) inhibitor</th>
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<tbody>
<tr>
<td>Originator</td>
<td>Merck KGaA, licensed to EspeRare in 2013</td>
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<tr>
<td>Target</td>
<td>Sodium-Proton (Na+/H+) Exchanger (NHE-1) inhibitor (overexpressed in mdx mice)</td>
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<tr>
<td>Target Product Profile</td>
<td>• First in class oral disease modifier</td>
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<td>• Cardioprotective, anti-fibrotic and anti-inflammatory with a more favorable safety profile than steroids</td>
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<td>• All genotypes in DMD, all muscles (cardiac, skeletal and respiratory), broad age range</td>
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<tr>
<td>Indications</td>
<td>• Duchenne Muscular Dystrophy (active development), Becker Muscular Dystrophy, Emery Dreyfuss, cardiomyopathies...</td>
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<td>• Congestive Heart Failure (CHF), development discontinued by Merck KGaA in 2002 in the context of discontinuation of all R&amp;D activities in cardiovascular</td>
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<tr>
<td>Phase of Development</td>
<td>• Was shown to be safe in 150 adults (7 phase I trials) and 20 patients with congestive heart failure</td>
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<td>• Phase Ib in DMD patients ongoing</td>
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Rimeporide inhibits the NHE-1 transporter in mdx myofibers and prevents deleterious calcium and sodium overloads.

**On-target Effect**

- **Rimeporide lowers pH**
- **Rimeporide inhibits intracellular Ca++ entry**
- **Rimeporide reduces Na+ accumulation**
Robust preclinical evidence based on in vivo results and DMD animal models testing

**Anti-inflammatory effect**
in diaphragm & skeletal muscles

**Improvement of specific force**
In skeletal muscle

**Antifibrotic effect**
In skeletal & cardiac muscle

**Cardio-protective effect**
Preventing early death

![Graph showing peak specific force comparison between mdx Control and mdx Rimeporide.](Image)

![Graph showing survival percentage over time between Placebo and Rimeporide.](Image)
A complete Safety package available at the pharmaceutical companies standards

<table>
<thead>
<tr>
<th>Safety pharmacology</th>
<th>Reproductive Toxicology</th>
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<tbody>
<tr>
<td>CNS</td>
<td>Embryofetal toxicity study in rats</td>
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<tr>
<td>Human HERG potassium channel</td>
<td>Dose tolerance in pregnant rats</td>
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<tr>
<td>Repolarisation assay (papillary muscle and cardiomyocytes)</td>
<td>Embryofetal development in rabbits</td>
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<td>QT retrospective analysis</td>
<td>Male fertility study in rats</td>
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<tr>
<td>Cardiovascular hemodynamics in rats &amp; pigs</td>
<td>Female fertility study in rats</td>
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<td>Respiratory</td>
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<th>Chronic GLP Toxicology</th>
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<tr>
<td>13 week oral mice</td>
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<tr>
<td>2 week iv rats</td>
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<tr>
<td>4 week oral Rats</td>
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<tr>
<td>26 week oral Rats</td>
<td></td>
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<tr>
<td>2 week iv dogs</td>
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<td>4 week oral Dogs</td>
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<td>13 week oral Dogs</td>
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<td>39 week oral Dogs</td>
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<th>Local Tolerance</th>
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<td>Maximisation test i guinea pigs</td>
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<tr>
<td>Local tolerance in rabbits after iv</td>
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<td>Ames</td>
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<td>Chromosome abberation test on human lymphocytes</td>
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<td>In vivo micronucleus test in rats</td>
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Rimeporide comes with a comprehensive nonclinical safety package, completed by Merck, with no safety flags

Source: EspeRare
7 Clinical pharmacology studies were conducted:
- Single and Multiple ascending doses studies (oral and iv)
- Food interaction study
- Drug Drug Interaction with Digoxin
- Safety, tolerability, PK in chronic heart failure 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 in placebo and treated patients

Dose linear increase of absorption and plasma concentrations, no effect on CYP 450, no saturation of renal elimination
Study Objectives

- Determine safety and tolerability of rimeporide after 4 weeks oral treatment
- Evaluate the PK profile of rimeporide
- Explore NMRI indices (T2, muscle mass, FF) and serum biomarkers to monitor muscle damage

Design

- 20 ambulant DMD patients (6 to 14 yrs) on stable dose of corticosteroids for at least 6 months
- Multicenter study (UK, France, Italy, Spain)
- Multiple dose escalating study, 4 dose cohorts
- 4 weeks oral treatment with hard gel capsules of 50 mg/weight based
- Independent SMC to approve dose escalation
Study Objectives

- Skeletal muscle NMRI/NMRS, Cardiac MRI
- Biomarkers
- Motor function/muscle biopsies
- Diaphragm position
- Respiratory inductance / plethysmography
- Echocardiography TDI, Holter

Design

- 20 GRMD dogs
  - (8 severe and 12 moderate)
- Treatment from 2 to 12 months
- Dose: 10 mg/kg twice daily oral
- Interim analysis after 6 months of treatment (especially meaningful for the severe phenotype)
- Study Duration: 18 months

Ongoing GRMD dog study

Rimeporide is currently being tested in a long term preventive GRMD dog study to inform the design of phase II studies
Strong Level of Protection

Multiple protection mechanisms including patents, orphan drug protection & pediatric exclusivity

- Orphan Drug Designation
  - Orphan drug designation already granted by the EMA\(^{(1)}\) in 2015 in Europe
  - 10 years market exclusivity
  - Orphan drug designation ongoing for US and Japan
  - Potentially 7 year market exclusivity in the US

- Rare pediatric Disease Designation
  - 2 years SPC in Europe

- Potential Additional Patent Protection
  - A patent application on “novel polymorphic salts and crystalline modifications” filed by Merck in Feb-16
  - A patent application on new slow release formulation is planned
  - Potential 6 months exclusivity extension in the US

Note 1: European Medicines Agency
Source: EspeRare
On track for NDA submission by 2021

**Timeline**

- 2016
  - Phase 1b
  - Long-term preventive study in GRMD
  - Translational biomarker discovery

- 2017
  - Development Plan

- 2018
  - 2019
  - 2020
  - 2021

- Phase 2 Primary Endpoint Cardiovascular
- Phase 3 (at least 2 years)
- Phase 2 Primary Endpoint Muscular
- Slow release formulation
- Orphan drug filing USA
- Pediatric Investigation Plan
- Pre-IND Meeting

**Note 1:** Golden Retriever Muscular Dystrophy
Source: EspeRare
Our priority is to streamline the transition into late clinical development with a partner aligned with our mission to ensure patient access to Rimeporide.

- EspeRare aims to initiate Phase 2/3 clinical development with a commercial partnership in place.
- EspeRare aims to ensure full alignment of potential partner with our commitment to ensure universal patient access and financial return to patient organizations that have supported the program.
- Financial return from the partnering will be entirely dedicated to progress other programs in our portfolio.
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