The first start-up committed to the development of SOCE modulators as a therapy for rare genetic diseases

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Rare Diseases: More Common Than You Think

7,000 different rare diseases

400,000,000 affected people worldwide

(35m in Europe | 3m in Italy)

80% affect children

5% has a drug treatment
Incentives for Companies with Orphan Designations

- 10/12 yrs of market exclusivity
- Protocol assistance from EMA
- Tax breaks
- Research grants

1/3 of all new drug approvals are for rare diseases

Defined Daily Doses, DDD*

Pharmaceutical Expenditure*

Orphan drugs
Non-orphan drugs

*Data referred to year 2015
Our Clinical Focus

**Tubular Aggregate Myopathy**

“A patient should have the right to a pain free life, even if that comes with some risk”

Shannon Larratt

Programmer, writer and artist
Died after a lifelong battle with TAM at the age of 39

- Mobility problems
- Weakness
- Miosis

**York Platelet Syndrome**

- Platelet dysfunction and dysaggregation
- Degeneration
- Bleeding
- Thrombocytopenia

**Stormorken Syndrome**

- Bleeding
- Painful contractures
- Other signs:
  - Small stature
  - Asplenia
  - Ichthyosis
  - Cognitive defects

Global prevalence: 1/200,000

Average cost per patient: 100,000-200,000 €/year; Addressable market: 60-90 M€/year
Common Features of Calcium-Related Rare Diseases

URGENT and UNMET Medical Need
Team

Beatrice Riva, CEO

- PhD
- Pharmacologist
- Post-Doc
- 7 Years in pharmacology
- PhD in pharmacology
- Expert in calcium signaling and molecular pharmacology
- Publications: 6
- Named inventor on patents

Tracey Pirali, CTO

- PhD
- Medicinal Chemist
- Associate Professor
- 15 Years in drug discovery
- PhD in medicinal chemistry
- Expert in click chemistry and multicomponent reactions
- Publications: 32
- Named inventor on patents
ChemICare Solution for Calcium-Related Rare Diseases

**Small molecules designed to:**

- Interfere with Store-Operated Calcium Entry
- Decrease intracellular calcium levels

**Benefits:**

- Calcium to **physiological** levels
- No cytotoxicity at effective concentrations
ChemICare Solution for Calcium-Related Rare Diseases

Efficacy in biopsies of patients affected by TAM

Graph showing the calcium levels over time for patients with and without treatment.
ChemICare Solution for Calcium-Related Rare Diseases

• Alleviating symptoms
• Slowing down disease progression
• Improving the quality of life in patients
### Our Competitors are an Opportunity

<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
<th>Company</th>
<th>Phase</th>
<th>Condition</th>
<th>Status/Note</th>
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<td>CM4620</td>
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<td>CalciMedica</td>
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<td>Acute pancreatitis</td>
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<td>GlaxoSmithKline</td>
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<td>Acute pancreatitis</td>
<td>No information</td>
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</tbody>
</table>
Barriers to Competition

Therapeutic Indications:

1. Rare genetic diseases
2. Cancer, psoriasis and acute pancreatitis
3. Immunodeficiencies, viral infections, inflammatory, autoimmune, haematological and degenerative diseases

Patent Pending - filed on 08/06/16

«Modulators of SOCE, compositions and use thereof»

ITUA20164199 filed on 08-06-2016
PCT/IB2017/053355 filed on 07-06-2017
W0 2017/212414 A1 published on 14-12-2017

Tracey Pirali, Beatrice Riva, Armando A. Genazzani

Positive report

European Patent Office

4 documents cat. "A"
Assets

- Fast synthesis/screening and high degree of parallelization
- One patent and other classes of molecules in development
- Unique mouse model

\[ \text{PolyGene} \quad \text{C57/BL6 KI}^{115F} \]

11 months for generation (Oct 2016 - Sept 2017)

- STIM1 \textit{Knock-In} mouse model for the human mutation c. 343A>T p.I115F
- First reported Stormorken and TAM model
- Heterozygous mouse line

\begin{itemize}
  \item Mice at 4 months
  \item Gastrocnemius muscle of mice at 4 months
  \item Histological evaluation of soleus and quadriceps muscles
\end{itemize}

- Scientific Network
Drug Development Pipeline

2015-17
- Chemical Synthesis
- Transgenic mouse model generation
- In vitro and ex vivo studies

2018
- Transgenic mouse model characterization
- PK & TOX
- In vivo studies

2019
- GLP pre-clinical study
- 2nd round financing: 2M€

New classes of molecules

CLINICAL TRIALS

✓ Research Grants
✓ Business Angels
✓ Competitions
✓ Business Angels and VC
✓ Research Grants

PARTNERSHIPS

MDA, BiolinItaly, START UP INITIATIVE, INazzareno F. Pelosi, HORIZON PHARMA, MUSCULAR DYSTrophy Association, elethon, Shire, Horizon Pharma, Amicus Therapeutics, Savara, Sanofi, Alexion, Pfizer
Society Development Pipeline

- **ChemICare**: Founded as Srls on December 15, 2016.
- **Aurelio Serra**: Became Srl on July 20, 2017.
- **Celia Cordero Sanchez**: Became Srl on October 2, 2017.

**Recent acquisitions in orphan drugs**:
- **Amicus Therapeutics**: 229 M$ cash & stock.
- **Shire**: 5.2 BS stock.
- **NPS Pharma**: 510 M$ cash.
- ** créalta**: MIAMED 6.5 M$ cash & stock + 83 M$ on milestone achievement.
- **SAVARA Pharmaceuticals**: 60 M$ round-financing.
- **SERENDEX Pharmaceuticals**: Partnership Licensing deal.

**Events**:
- **Start CUP**: Pomerano Valley - March 29, 2017.
- **BioinItaly**: September 21, 2017.
- **Meet in Italy**: Life Science 2017.
- **Premio Nazionale Innovazione**: December 1-3, 2016.
- **Partnership Licensing deal**: October 2017.
- **Contact with Sanofi Genzyme**: October 2017.
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The first start-up committed to the development of SOCE modulators as a therapy for rare genetic diseases
Backup
Plus & Minus

**Multidisciplinary network with know-how on:**
- synthetic chemistry (Pirali)
- analytical chemistry (Grosa)
- pharmacology (Riva)
- animal behaviour (Filigheddu)
- TAM, YPS, STMK (Bertini, Tasca, Garibaldi)

**Physical proximity**

**High degree of parallelization**

Fast and straightforward chemical approaches

+ Parallel screening by calcium imaging

Rounds of synthesis/testing that help to be on the right track, avoiding waste of time and resources

**2018 Resources need**

- IP
- In vitro ADMET
- In vivo PK and TOX
- Personnel
- Consumables

**IP support and management expertise**

**Project management and business development expertises**
Fundraising

2018 Resources need

- Personnel
- Consumables
- In vitro ADMET
- In vivo PK and TOX
- IP

IP support and management expertise
Project management and business development expertises

➢ Research Grants

✓ Business Angels/Venture Capitalists
Resources year 2018

Personell (1 for synthesis, 1 for biological studies): 45.000
Consumables: 32.000

IP:
National phases 1° application: 150.000
2° application filing: 9.000

Target Selectivity: 15.000

In vitro ADMET (on 3 hit compounds) 24.000
Solubility 500
Permeability 5.000
CYP450 inhibition 2.500
Metabolic stability (mouse, human) 5.000
Plasma stability (mouse, human) 2.000
Plasma protein binding 1.000
Metabolite identification 3.000
Toxicity (hERG, Ames, etc) 5.000

Preliminary mouse PK and bioavailability (on 3 hit compounds) 25.000

300.000
Contratto di Licenza UPO ChemICare

Licenziante: UPO  
Possiede i diritti patrimoniali di invenzione  
Gestisce pratiche brevettuali (gestione, ecc)

Licenziatario: ChemICare  
Titolari di diritti reali  
Licenza esclusiva: esclusività dei propri diritti di sfruttamento dell’invenzione

Utilizzo invenzione per fini: R&D, produttivi, commerciali direttamente o attraverso società terze per collaborazioni in tutto il mondo

ChemICare

- Può concedere a terzi sub-licenze dei diritti di sfruttamento del brevetto;
- All’UPO deve \textbf{royalty pari al 6 % più IVA} del fatturato netto derivante da vendita, leasing, ecc;
- In caso di concessione di \textbf{sublicenza a terzi}, per ogni accordo \textbf{royalty del 12% + imposte} del fatturato netto;
- Indipendentemente dal fatturato gli importi minimi che deve a UPO sono:
  - 2500 € +IVA x 2018 -> entro 28/02/2019
  - 3000 € +IVA x 2018 -> entro 28/02/2020
  - 4500 € +IVA x 2018 -> entro 28/02/2021
- Può in qualsiasi momento acquistare la totalità dei diritti (previo accordo fra le parti);
- Possiede diritto di prelazione su acquisto del brevetto;
- Può rescindere il contratto se entro il 31/12/2019 la licenza non viene sfruttata (lancio attività, vendita prodotti con copertura brevettuale.

\textbf{TUTTO QUANTO DESCRITTO VALE ANCHE PER CONTESTI I DIFFERENTI DAL SETTORE SPECIFICO DI APPLICAZIONE}
Toxicity Considerations

1. Calcium restored to physiological level → Dose modulation

2. SOCE is the main calcium entry mechanism in T lymphocytes, platelets and skeletal muscle, but a minor and redundant mechanism in other districts (other compensatory mechanisms)

3. No impairment of cell viability up to 100 μM in in vitro studies with ChemICare inhibitors
Scientific Background

Overview of the Pathophysiological Implication of SOCE

**Autoimmune disorders**
- Psoriasis
- Rheumatoid arthritis
- Asthma
- Inflammatory bowel disease
- Systemic lupus erythematosus
- Allergic disorders

**Cancer**
- Cancer cell migration
- Proliferation
- Tumor metastasis
- Angiogenesis
- Apoptosis resistance in prostate cancer cells

**Immunological disorders**
- Immuno deficiencies
- Transplant rejection
- Acute inflammation

**Cardiovascular and Hemostatic disorders**
- Thrombosis
- Atherosclerosis
- Restenosis
- Hypertension
- Platelet dysfunction
- Cardiac myocytes dysfunction

**Metabolic disorders**
- Liver steatosis
- Hepatic insulin resistance
- Type 2 diabetes
- Acute pancreatitis

**Neuromuscular disorders**
- Alzheimer Disease
- Parkinson Disease
- Cerebellar ataxias
- HIV-Associated Dementia
- Duchenne muscular dystrophy (DMD)

**Genetic disorders**
- STIM1/Orai1 Gain-of-function mutations
  - Tubular Aggregate myopathy
  - Stormorken Syndrome
  - York Platelet Syndrome
  - Limb-Girdle Muscular Dystrophy
- STIM1/Orai1 Loss-of-function mutations
  - CRAC-channelopathy
  - SCID-like immunodeficiency
### Scientific Background

<table>
<thead>
<tr>
<th>Mutation</th>
<th>References</th>
<th>Clinical Phenotype</th>
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<tbody>
<tr>
<td>c.216C&gt;G(p.H72Q)</td>
<td>Böhm J. 2013</td>
<td>Tubular aggregate myopathy (TAM)</td>
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<td>c.251A&gt;G(p.D84G)</td>
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<td>Limb-Girdle Muscular Dystrophy</td>
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<td>c.286C&gt;G(p.L96V)</td>
<td>Böhm J. 2014; Tasca G. 2015</td>
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<td>Hedberg C.M. 2014; Tasca G. 2015</td>
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<td>c.911G&gt;A(p.R304G)</td>
<td>Harris E. (unpublished)</td>
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<td>c.290C&gt;G(p.S97C)</td>
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<td>c.734C&gt;T(p.P245L)</td>
<td>Nesin V. 2014; Shahrizaila N. 2004</td>
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<td>c.292G&gt;A(p.G98S)</td>
<td>Böhm J. 2017</td>
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