Santhera Pharmaceuticals

Advancing Mitochondrial Medicine

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Santhera at a glance

- Founded in 2004; Listed on SIX Swiss Exchange (SIX: SANN)
- Best performing biotech/pharma stock in 2014 by Biocentury
- Development stage company with focus on orphan and niche neuromuscular and mitochondrial diseases
- Cash: CHF 14.0 M ($ 15.0 M) (as per 31. March 2015)
- Market Cap: CHF ~455M ($ ~500M)
Pipeline with Idebenone (Raxone®/Catena®) in three indications with high unmet medical need

- **Leber’s Hereditary Optic Neuropathy (LHON):**
  - MAA under review in EU

- **Duchenne Muscular Dystrophy (DMD):**
  - Positive Phase 3 study outcome,
  - NDA/MAA filing in preparation

- **Primary progressive MS (ppMS):**
  - Phase 2 study in collaboration with NIH

Raxone®: trademark in EU
Catena®: alternative trademark
Raxone® in Leber’s Hereditary Optic Neuropathy (LHON)

Leber’s Hereditary Optic Neuropathy (LHON): Marketing Authorization Application (MAA) under review in EU
LHON – an inherited form of blindness

- Inherited form of blindness:
  - Prevalence ~ 2 in 100,000
  - ~ 2,500 patients diagnosed in past 5 years in EU
- Genetic disease with clear diagnosis and family pattern
- Predominantly young males in all ethnic groups affected
- Rapid loss of central vision by functional loss and degeneration of retinal nerve cells
- No treatment available
Clinical presentation of LHON

Normal vision

Vision due to LHON

Days, weeks or few months
Therapeutic objectives

- The therapeutic objective:
  - stabilize the disease
  - promote clinically relevant recovery
- There is a window of opportunity for treatment up to ~ 5 years when retinal ganglion cells are still viable
Vision loss caused by dysfunctional retinal ganglion cells (RGCs)

Retinal ganglion cell (RGC) with high energy demand
LHON – a mitochondrial disease

- mtDNA mutations
- Other risk factors
- ROS
- Energy deficiency

Loss of RGC function

Window of opportunity for treatment: ~5 years from onset of vision loss

Loss of RGC viability by apoptosis
Idebenone elicits functional recovery of retinal ganglion cells
50% of LHON patients treated with Raxone® experience clinically relevant recovery of vision

Data from Expanded Access Program
Raxone® efficacy typically seen within 12 months from treatment start

Data from Expanded Access Program
Temporary Authorization in France
CHMP Decision for Europe awaited

- Authorization for Temporary Use (ATUc) granted in 2014
- Use of Raxone® in hospital-treated patients with LHON
- Supply of Raxone® fully reimbursed by the government program

- Marketing Authorization Application (MAA) for Europe filed in May 2014 (validated in June 2014)
- Decision by EMA’s CHMP expected in 1H 2015
- Market exclusivity due to Orphan Drug protection
European Commercialization Plans

- Chief Commercial Officer for Europe and RoW

- Commercial presence build-up in 4 regional clusters
  - F, BeNeLux
  - D, A, CH, CZ
  - Southern
  - UK, Nordic

- National /regional distribution agreements for other EU countries
Raxone® in Duchenne Muscular Dystrophy (DMD)

Duchenne Muscular Dystrophy (DMD):
Positive Phase 3 study outcome,
NDA/MAA filing in preparation
Medical need for effective treatment of respiratory illness in DMD

- Progressive weakness of respiratory muscles leads to a restrictive pulmonary syndrome.

- Medical complications include ineffective cough, nocturnal hypoventilation, sleep disordered breathing, and ultimately daytime respiratory failure.

- DMD patients develop cardiac and respiratory complications that typically lead to early morbidity and mortality.
Measures of pulmonary function loss in DMD

Figures (B) and (C) courtesy of Dr. Oscar H. Mayer, Division of Pulmonology, The Children's Hospital of Philadelphia, USA.
Use of glucocorticoid steroids and assisted ventilation increase life expectancy in DMD

taken from Goemans et al. (2014) European Neurological Review, 9(1):78–82
…. but there is an urgent medical need for patients unable to take glucocorticoid steroids

- With increasing age, fewer patients tolerate glucocorticoid steroids (side effects)
- Loss of respiratory function enters critical stage in early teenage years
- There is currently no treatment available for this group of DMD patients
Natural history: PEF%p and FVC%p show a linear decline from age 10 onwards

Mitochondrial impairment in DMD
Idebenone - mechanism of action in DMD

B

Loss of dystrophin

Aberrant Ca^{2+} influx

Mitochondrial dysfunction

ROS ↑

ATP ↓

Cell death and muscle degeneration
Efficacy of idebenone on respiratory function in patients with Duchenne muscular dystrophy not using glucocorticoids (DELOS): a double-blind randomised placebo-controlled phase 3 trial

Gunnar M Buyse, Thomas Voit, Ulrike Schara, Chiara S M Straathof, M Grazia D’Angelo, Günther Bernert, Jean-Marie Cuisset, Richard S Finkel, Nathalie Goemans, Craig M McDonald, Christian Rummey, Thomas Meier, for the DELOS Study Group

The Lancet 2015; 385:1748-57
DELOS – patients and treatment

Patients:
- Age 10-18 years
- No selection for mutational status
- Patients had to be off chronic steroids
- 92% of patients were non-ambulatory

Randomized treatment:
- Raxone® (900 mg/d): N=31
- Placebo: N=33
- Mean Age: 14.3 y
- Treatment duration: 12 months
Raxone® delays the loss of respiratory function
Consistency of results

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<th>12 months</th>
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<td>PEF%p</td>
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</table>

favors Raxone®
Fewer patients on Raxone® fell below critical 1 L-threshold in FVC

Changes in Spirometry Over Time as a Prognostic Marker in Patients with Duchenne Muscular Dystrophy

Margaret F. Phillips, Rosaline C. M. Quinlivan, Richard H. T. Edwards, and Peter M. A. Calverley
Pulmonary and Rehabilitation Research Group, University Hospital Aintree, Fazakerley, Liverpool; Muscle Clinic, Robert Jones and Agnes Hunt Orthopaedic and District Hospital, Oswestry, Shropshire, United Kingdom


The time when FVC falls below 1 L is a strong marker of subsequent mortality (5-yr survival 8%).

No. of Patients | Raxone® | Placebo
--- | --- | ---
BL FVC: > 1L but < 1.5 L | 6 | 9
Patients with FVC < 1L during 1y | 1 | 5
Fewer patients on Raxone® experience respiratory tract disease

Graph showing the proportion of patients with URT-related AEs over study weeks. The graph indicates that patients on Raxone® experience fewer respiratory tract disease events compared to those on placebo. The p-value is 0.028, and the hazard ratio is 0.41 (95% CI 0.19-0.91) according to the Cox Proportional Hazards Model.
Combined analysis of Phase 2 and 3 data (patients not using glucocorticoid steroids)

**PEF%p**

Worsening (decrease in PEF%p)  Improvement (increase in PEF%p)

- Idebenone: N=36; Placebo N=36

**FVC%p**

Worsening (decrease in FVC%p)  Improvement (increase in FVC%p)

- 78%  50%  60%
- 92%  75%  75%
- 40%  12%  18%  37%

Jefferies Healthcare Conference │ June 2015
Emerging DMD treatment landscape

~40% of patients age 10y and older are not using steroids

- **Raxone® (idebenone):** Mitochondrial enhancer by Santhera
- **Translarna® (ataluren):** Stop codon read-through by PTC
- **(drisapersen, etiplersen):** Exon-51 skipping by Proensa, Sarepta
Positioning of Raxone® in the treatment of DMD

Clinical:
- First and only treatment for DMD patients not using steroids
  - ~40% of DMD patient population is not using steroids (due to side effects)
- No restriction to specific mutational or disease status
- Oral medication (2 tablets, 3 times/day)
- Extensive data base demonstrates good safety profile

Regulatory:
- Patent protection until March 2026 (EU, JP) and December 2027 (USA)
- Orphan Drug Designation granted in EU and US
- Fast Track Designation granted by FDA
- Regulatory filings for US and EU in preparation
Raxone® in primary progressive MS

Primary progressive MS (ppMS):
Phase 2 study in collaboration with NIH
Phase 2 study in ppMS with Raxone®

- primary progressive MS
  - affects 10-15% of total MS population
  - no approved treatment available
  - mitochondrial pathology

- Phase 2 trial (IPPoMS) in collaboration with NIH ongoing

- Study is fully recruited
- Santhera has exclusive license to granted use patent
Advancing mitochondrial medicine towards a first treatment in

LHON

DMD

ppMS

Thank you for your attention