Raxone® (idebenone) and pulmonary care in DMD

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CEO
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Medical need for effective treatment of respiratory illness in DMD

- Diagnosis
- 5 years
- Glucocorticoids
- Loss Ambulation
- 9 years
- Loss of Respiratory Function
- 14 years
- Need for Assisted Ventilation
- 20 years
- Death
Measures of pulmonary function in DMD

Endpoints listed in *EMA Guideline on DMD*

- **PEF**: peak expiratory flow
- **FVC**: forced vital capacity
- **FEV1**: forced expiratory volume in 1 sec
Constant decline in PEF%p and FVC%p from ~10 years

- Decline starts at ~ 10 years (80% threshold)
- PEF%p and FVC%p follow parallel trajectories
- Linear decline of 5-6%p per year
- Clinically relevant thresholds impact disease management

Source: CINRG Natural history data base (McDonald 2013); N=334
Progressive decline in respiratory function and relevant outcome measures – a vicious cycle

1. Decline in respiratory function
   - Endpoints: PEF, FVC, FEV1

2. Decreased ability to cough effectively and clear airways
   - Endpoints: PEF, PCF

3. Increased risk of serious infections, including pneumonia
   - Endpoints:
     - Bronchopulmonary AEs
     - Systemic antibiotic treatment
     - Rate of hospitalisations for BAEs

BAE: Bronchopulmonary adverse events
FEV1: Forced expiratory volume in the first second
FVC: Forced vital capacity
PCF: Peak cough flow
PEF: Peak expiratory flow
Santhera’s clinical development program with Raxone® (idebenone) in DMD

**GC non-users**
- **DELPHI**
- **DELPHI-E**
- **CINRG DNHS**
- **DELOS**

**Phase 3**
- **PPM Study**

**GC users**

|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|

**GC:** glucocorticoid steroids; **PPM study:** prospectively planned matching study
The Phase III DELOS trial in DMD

Study objective: to assess the efficacy of Raxone (idebenone) on respiratory function
- Randomised, placebo-controlled, N=64
- Patients not using concomitant glucocorticoids
- First trial focusing on respiratory function endpoints

First trial in severely impaired patients in advanced disease stage
- All patients were in respiratory function decline (Baseline PEF%p: 54%, FVC%p: 53%)
- 92% of patients were non-ambulatory
- 59% of patients were unable to raise hand to mouth
DELOS study met primary endpoint

Change from Baseline to Week 52 (hospital spirometry)

<table>
<thead>
<tr>
<th>Endpoint (ITT)</th>
<th>Treatment difference* (mean, 95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEF%p</td>
<td>6.27 %p (0.61, 11.93)</td>
<td>p=0.0306</td>
</tr>
<tr>
<td>PEF (L/min)</td>
<td>28.1 L/min (2.69, 53.50)</td>
<td>p=0.0308</td>
</tr>
</tbody>
</table>

* Mixed Model of Repeated Measures. Data are estimated mean (95%CI)

- DELOS study met prospectively defined primary endpoint (ITT population)
- Outcome for PEF%p confirmed with change for non-normalised PEF (L/min)

**Clinical Relevance:**

Treatment difference for primary endpoint PEF%p equivalent to 1-year decline expected in natural history\(^1,2\)

1. Mayer (2015) : 5.8%
Change in PEF%p during 52-week study period

Weekly home-based assessment of PEF%p by hand-held device support results of hospital-based spirometry
Outcome for the primary endpoint is robust across study populations and analyses methods

Primary Analysis
Analysis Method (3)
Analysis Population (3)
Missing Data (5)
Height Measurement (4)
Normalisation Equation (4)
Precision of Age (5)
Influence of Individuals (11)

In favour of Raxone

Treatment difference for PEF%p at week 52; analyses requested by CHMP
Results in PEF%p are supported by additional respiratory function endpoints

![Graph showing treatment difference from Baseline by study week for PEF%, FVC%, and FEV1%. The graph indicates improvement over time, with values in favor of Raxone.]
Fewer patients treated with Raxone fall below clinically relevant thresholds for FVC%p

<table>
<thead>
<tr>
<th>FVC%p</th>
<th>Disease status according to standard of care guideline</th>
<th>Raxone</th>
<th>Placebo</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50%</td>
<td>Moderate pulmonary insufficiency</td>
<td>20%</td>
<td>44%</td>
<td>0.34 (0.10, 1.18)</td>
</tr>
<tr>
<td>&lt;40%</td>
<td>Signs and symptoms of hypoventilation</td>
<td>17%</td>
<td>20%</td>
<td>0.58 (0.13, 2.60)</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>High risk of hypoventilation</td>
<td>14%</td>
<td>25%</td>
<td>0.59 (0.17, 2.10)</td>
</tr>
<tr>
<td>Any</td>
<td></td>
<td>34%</td>
<td>57%</td>
<td>0.51 (0.23, 1.14)</td>
</tr>
</tbody>
</table>

**Clinical Relevance:**
Falling in FVC%p categories results in increasing need for patient care
Fewer patients treated with Raxone fall below clinically relevant threshold for Peak Cough Flow (PCF)

<table>
<thead>
<tr>
<th>Patients at risk (PCF at BL: &gt;160 L/min)</th>
<th>Raxone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>26</td>
<td>33</td>
</tr>
<tr>
<td>Patients with PCF &lt;160L/min during 1y</td>
<td>1 (4%)</td>
<td>6 (18%)</td>
</tr>
</tbody>
</table>

Clinical Relevance:

When PCF falls below 160 L/min, the cough is no longer effective enough to provide adequate mucociliary clearance.
Fewer patients treated with Raxone experience bronchopulmonary AEs

Patients with bronchopulmonary AEs

<table>
<thead>
<tr>
<th>Patients/Events</th>
<th>Raxone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>6 (19.4%)</td>
<td>17 (51.5%)</td>
</tr>
<tr>
<td>Events</td>
<td>7</td>
<td>28</td>
</tr>
</tbody>
</table>

Duration of bronchopulmonary AEs

<table>
<thead>
<tr>
<th>Patients/Events</th>
<th>Raxone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Days</td>
<td>82</td>
<td>222</td>
</tr>
</tbody>
</table>

Clinical Relevance:

Bronchopulmonary disease, including airway infections, increase the risk of hospitalisation and further weaken respiratory muscle function

Clinical Relevance:

Bronchopulmonary disease, including airway infections, increase the risk of hospitalisation and further weaken respiratory muscle function.

Hazard Ratio* 0.28; p=0.0026

*proportional means regression analysis
Fewer patients treated with Raxone needed systemic antibiotic treatment

**Clinical Relevance:**
Systemic antibiotic use considered clinically relevant

<table>
<thead>
<tr>
<th>Patients/Events</th>
<th>Raxone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>7 (22.6%)</td>
<td>13 (39.4%)</td>
</tr>
<tr>
<td>Events</td>
<td>8</td>
<td>17</td>
</tr>
</tbody>
</table>

**Duration of antibiotic use**

<table>
<thead>
<tr>
<th>Patients/Events</th>
<th>Raxone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Days</td>
<td>65</td>
<td>105</td>
</tr>
</tbody>
</table>

**Hazard Ratio**: 0.52; p=0.1330

*proportional means regression analysis
Fewer patients treated with Raxone experienced hospitalisations due to respiratory complications

Hospitalisations due to respiratory complications

<table>
<thead>
<tr>
<th>Patients/Events</th>
<th>Raxone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>1 (3%)</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>Events</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

Duration of hospitalisation due to respiratory complications

<table>
<thead>
<tr>
<th>Patients/Events</th>
<th>Raxone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Days</td>
<td>3</td>
<td>30</td>
</tr>
</tbody>
</table>

Clinical Relevance:

Hospitalisation interpreted as hard endpoint related to morbidity; increased risk of further complications
# Publications of DELOS Results

<table>
<thead>
<tr>
<th>Title</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idebenone reduces respiratory complications in patients with Duchenne muscular dystrophy</td>
<td>McDonald et al., Neuromuscular Disorders (2016); 26: 473–480</td>
</tr>
<tr>
<td>Treatment effect of idebenone on inspiratory function in patients with Duchenne muscular dystrophy</td>
<td>Buyse et al., Pediatric Pulmonology (2017); 52(4):508–515</td>
</tr>
<tr>
<td>Characterization of pulmonary function in 10-18 year old patients with Duchenne muscular dystrophy</td>
<td>Meier et al., Neuromuscular Disorders (2017); 27: 307–314</td>
</tr>
<tr>
<td>Efficacy of idebenone to preserve respiratory function above clinically meaningful thresholds for Forced Vital Capacity (FVC) in patients with Duchenne muscular dystrophy</td>
<td>Mayer et al., Journal of Neuromuscular Diseases (2017); 4: 189–198</td>
</tr>
</tbody>
</table>
• DELOS met primary endpoint, consistently supported by other respiratory function endpoints
• Outcome of the DELOS trial internally robust
• Observed treatment effect is clinically relevant and translate into patient benefit
• Raxone is generally well tolerated
• Based on existing data Santhera seeks Marketing Authorization in the EU
  “... for slowing the decline of respiratory function in patients with DMD not using glucocorticoids (i.e. patients in whom glucocorticoid treatment is no longer tolerated or is considered inadvisable)”
• Appeal Procedure currently ongoing; outcome expected by end of January 2018
The medical need: Proportion of patients in the EU not using glucocorticoids (age 10-20 years)

Source: TREAT-NMD, November 2016
Glucocorticoids (GCs) delay the onset but not the rate of pulmonary function decline

- GCs delay time to clinically important threshold of pulmonary function decline by ~2-3 years
- Once this threshold of decline is reached, the rate of decline is similar to that seen in patients not using GCs

Source: CINRG Natural history data base
N= 334 patients; data is mean ±SEM
Santhera’s clinical development program with Raxone® (idebenone) in DMD

GC: glucocorticoid steroids; PPM study: prospectively planned matching study
SIDEROS – a Phase 3 trial in patients using glucocorticoids

**Objective:** To assess the efficacy of idebenone compared to placebo, in delaying the loss of respiratory function in DMD patients receiving glucocorticoid steroids (GCs)

**Study conduct:** ~60 centers in Europe, USA and Israel
The SIDEROS study: addressing DMD-associated respiratory impairment.

The SIDEROS study is a phase III clinical trial, evaluating the efficacy of idebenone compared to placebo, in delaying the loss of respiratory function in patients with DMD receiving glucocorticoid steroids.

VIEW TRIAL OVERVIEW
Santhera’s commitment to patients with DMD

• Santhera focuses on the development and registration of Raxone® to slow the loss of respiratory function in patients with DMD
  – under review by CHMP for patients not able to take glucocorticoids
  – SIDEROS study ongoing to provide efficacy data in patients on concomitant glucocorticoid treatment

• Santhera is committed to further investigate the therapeutic potential of Raxone® in DMD

• Santhera is actively working with patient groups to increase awareness for “Respiratory Management in DMD”