Raxone® (idebenone) and pulmonary care in Duchenne Muscular Dystrophy (DMD)

Thomas Meier, PhD

February 2018
Agenda

• Medical need for effective treatment of respiratory illness in DMD

• Understanding respiratory function decline and clinical complications

• The **DELOS** study: Efficacy data for idebenone (Raxone®) in slowing respiratory function decline in DMD patients not using glucocorticoids

• Open for enrolment: the **SIDEROS** study in patients on glucocorticoid treatment

• Raising awareness for respiratory function in DMD
Medical need for effective treatment of respiratory illness in DMD
Medical need for effective treatment of respiratory illness in DMD
Increasing muscle weakness leads to a progressive cycle of respiratory function decline in DMD

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 hospitalizations for BAEs

PEF: Peak expiratory flow
FVC: Forced vital capacity
EV1: Forced expiratory volume in the first second
PCF: Peak cough flow
BAE: Bronchopulmonary adverse events
Respiratory and cardiac failure remain the leading causes of death in patients with DMD

From the total pool of 340 eligible patients, 40 died over the 8 year study period.

CINRG-DNHS: Cooperative International Neuromuscular Research Group–Duchenne Natural History Study.
Understanding respiratory function decline and clinical complications
Respiratory muscle dynamics in patients with DMD

Collaboration with Prof. Andrea Aliverti
DEIB – Politecnico di Milano, IT
Respiratory function decline in patients with DMD: Spirometry measures

PEF: peak expiratory flow
FVC: forced vital capacity
Both PEF%p and FVC%p follow a linear and parallel decline in patients over time

Change in PEF%p and FVC%p with age$^1$)

- $n = 334$

$^1$ Data from CINRG-DNHS showing mean ± SEM absolute percentage point decline from baseline. Mayer OH, et al. US Neurology 2017;13:35–41.
The DELOS study: Efficacy data for idebenone (Raxone®) in slowing respiratory function decline in DMD
DELOS: Efficacy and safety of idebenone to delay respiratory function decline in patients not using glucocorticoids (GCs)

DMD patients not taking GCs  
$n = 64^{1)}$

Assessment schedule

<table>
<thead>
<tr>
<th>Week 13</th>
<th>Week 26</th>
<th>Week 39</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study type: Randomized, placebo-controlled trial

Key eligibility criteria: 10–18 years, off chronic glucocorticoids (GCs) and in respiratory function decline (PEF%p ≤ 80%)

Primary endpoint: Change in PEF%p from baseline to week 52

Other endpoints: Changes in PEF (L/min and %p), FVC (L and %p) and FEV1 (L and %p) and PCF (L/min)

Additional analyses: Time to crossing clinically relevant FVC thresholds, frequency / duration of BAEs and associated hospitalization. Respiratory function (PEF and FEV1) were also assessed independently using the home-based device

Idebenone 300 mg orally 3 times daily ($n = 31^1$)

Placebo orally 3 times daily ($n = 33$)∗

$^{1}$ITT population.

%p: percent predicted; BL: baseline; BAEs: bronchopulmonary adverse events; DMD: Duchenne muscular dystrophy; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; GC: glucocorticoid; ITT: intention to treat; L: liter; L/min: liter per minute; PCF: peak cough flow; PEF: peak expiratory flow; R: randomized.

DELOS patients were non-ambulatory with limited upper limb mobility and established respiratory function decline.

**Ambulatory status**
- 92% non-ambulatory

**Brooke Score**
- ~60% ≥5; unable to raise hand to mouth

**Mean age**
- 14 years
Idebenone slows the decline in respiratory function

Data from weekly home-based assessment of PEF%p

![Graph showing data from weekly home-based assessment of PEF%p for Placebo and Raxone® (idebenone).](image)
Patients in the idebenone group experience fewer respiratory complications and hospitalizations

<table>
<thead>
<tr>
<th></th>
<th>Raxone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bronchopulmonary adverse events (AEs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects (%)</td>
<td>6 (19.4%)</td>
<td>17 (51.5%)</td>
</tr>
<tr>
<td>Events</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Total Days</td>
<td>82</td>
<td>222</td>
</tr>
</tbody>
</table>

**Systemic Antibiotic Use**

<table>
<thead>
<tr>
<th></th>
<th>Raxone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (%)</td>
<td>7 (22.6%)</td>
<td>13 (39.4%)</td>
</tr>
<tr>
<td>Events</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Total Days</td>
<td>65</td>
<td>105</td>
</tr>
</tbody>
</table>

**Hospitalizations (due to respiratory causes)**

<table>
<thead>
<tr>
<th></th>
<th>Raxone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (%)</td>
<td>1 (3%)</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>Events</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Total Days</td>
<td>3</td>
<td>30</td>
</tr>
</tbody>
</table>

Bronchopulmonary Adverse Events

Placebo

Raxone®

Hazard Ratio* 0.28; p=0.0026
The SIDEROS study: Efficacy of idebenone (Raxone®) in patients on glucocorticoid treatment
The SIDEROS study: addressing DMD-associated respiratory impairment.

The SIDEROS study is a phase III clinical trial, evaluating the efficacy of investigational drug idebenone compared to placebo, in delaying the loss of respiratory function in patients with DMD receiving glucocorticoid steroids.
SIDEROS: Efficacy of idebenone to delay respiratory function decline in patients using glucocorticoids (GCs)

DMD patients taking GCs $n \geq 266$

R 1:1

Idebenone 300 mg orally 3 times daily

Placebo orally 3 times daily

Assessment schedule (Week) BL 4 13 26 39 52 65 78

Study type: Randomized, placebo-controlled trial

Key eligibility criteria: $\geq 10$ years, chronic use of systemic GCs and in respiratory function decline (FVC%p 35%-80% at baseline)

Primary endpoint: Change in FVC%p from baseline to week 78

Other endpoints: Changes in PEF%p, time to loss of 10% in FVC and change in inspiratory flow reserve

Additional analyses: Change in peak cough flow (PCF), blood oxygen saturation and EtCO$_2$, Bronchopulmonary illness, Antibiotic use

EtCO$_2$ = End tidal CO2 level, using Capnography
SIDEROS trial

- Currently the largest ongoing clinical trial in DMD
- Ambulant and non-ambulant patients eligible for enrolment
- ~60 clinical trial sites in Europe, US and Israel
- Full reimbursement of travel cost
- All participants who complete SIDEROS are offered to participate in open-label SIDEROS Extension trial
Disease Awareness Campaigns:

Raising awareness for respiratory function in DMD
Respiratory function awareness in the DMD Patient Community

Series of five white board videos

• Focus groups of patients, caregivers, and physicians
• Identified topics of importance
• Available as a community resource (advocacy groups, physicians & companies)

Educational webinars for families & physicians planned for late March / early April 2018
Santhera’s respiratory function awareness campaigns

Dedicated website providing information on respiratory function care

- US website: [www.takeabreathdmd.com](http://www.takeabreathdmd.com)
- European website: [www.breatheduchenne.com](http://www.breatheduchenne.com)
Santhera’s commitment to provide help for patients with DMD

- Collaborate with international experts to better understand respiratory function decline in patients with DMD; helpful to plan clinical trials
- Successful phase III DELOS trial demonstrated that idebenone slows decline in respiratory function in patients unable to take glucocorticoids (GCS)
- Ongoing Phase III SIDEROS trial in ambulant and non-ambulant patients who are using glucocorticoids – study open for enrolment!
- Active contribution to raise awareness of the respiratory diseases component of DMD
- Santhera aims to make idebenone (Raxone®) available to patients with DMD as soon as possible