Efficacy of Raxone® (idebenone) on respiratory outcome in patients with DMD

Dr. Thomas Meier

5. April 2016
Agenda

- Raxone® (idebenone) - development pipeline
- Medical need for treatment of respiratory function loss in DMD
- Mitochondrial impairment in dystrophin-deficient muscle
- Idebenone - mode of action in DMD
- Clinical development program with Raxone®: DELOS Phase 3 trial
- Positioning of Raxone® in the treatment of DMD
- SIDEROS trial in patients on glucocorticoids
Pipeline with Raxone® (idebenone) in three indications with high unmet medical need

- **Leber’s Hereditary Optic Neuropathy (LHON):** Approved 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
Clinical progression of DMD

Loss of ambulation

Loss of respiratory function
Assisted ventilation
Nocturnal ventilation

Age 7 15 23 32

DMD Survival Rate

age 0-7 age 8-15 age 16-23 age 24-31 age 32-40

Courtesy: Nathalie Goemans.
University Hospitals Leuven, Belgium
Medical need for effective treatment of respiratory illness in DMD

• Progressive weakness of respiratory muscles leads to a loss of respiratory function (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.
Patients’ treatment preference of pulmonary function

Patient-Centered Benefit-Risk Study: Pulmonary Treatment for Duchenne Muscular Dystrophy

- Patient-centered benefit-risk survey conducted by PPMD in a community engaged approach
- Focus on treatment priorities for disease aspects not directly related to skeletal muscle function (best-worst scaling methodology, 4 different survey activities)
- 155 participants (85% patients/caregivers with DMD)
- Treatment of pulmonary disease (cough, prevention of airway infections) was highly prioritized as patient/caregiver preference
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
Progressive decline in PEF%p and FVC%p between 10 and 20 years of age

- Almost linear decline in respiratory function from age ~10 years
- PEF%p and FVC%p follow parallel/overlapping trajectories
- Decline established at ~80%
- Decline in expiratory function predicts morbidity (e.g. need for assisted ventilation) and mortality
- PEF selected as primary endpoint of pivotal DELOS trial

Source: Natural history data base from Cooperative International Neuromuscular Research Group (CINRG) ; N= 334 patients
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
40% of prevalent cases are not using glucocorticoid steroids

Santhera model based on survival data\(^1\) and reported steroid use\(^2\)

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2) Henricson et al., Muscle Nerve 2013
Mitochondrial impairment in DMD

Loss of dystrophin

Ca$^{2+}$ Ca$^{2+}$
Ca$^{2+}$

Ca$^{2+}$ Ca$^{2+}$
Ca$^{2+}$ Ca$^{2+}$
Ca$^{2+}$ Ca$^{2+}$
Ca$^{2+}$

Lipid metabolism

mitochondrial dysfunction

ROS

Inflammation

Energy production

Cell Death and Muscle degeneration
Idebenone mode of action in dystrophic muscle

Loss of dystrophin

Idebenone reduces ROS levels

Ca^{2+} Ca^{2+} Ca^{2+} Ca^{2+} Ca^{2+} Ca^{2+} Ca^{2+} Ca^{2+} Ca^{2+}

Mitochondrial dysfunction

ROS

Lipid metabolism

Energy production

Cell Death and Muscle degeneration

Idebenone increases energy output

Inflammation
Clinical development program with Raxone®
Clinical development program with Raxone®

Phase 2: DELPHI (2005-2007)

Idebenone as a novel, therapeutic approach for Duchenne muscular dystrophy: Results from a 12 month, double-blind, randomized placebo-controlled trial

Gunnar M. Buyse a,*, Nathalie Goemans a, Marleen van den Hauwe a, Daisy Thijs b, Imelda J.M. de Groot c, Ulrike Schara d, Berten Ceulemans e, Thomas Meier f, Luc Mertens b

Phase 3: DELOS (2009-2014)

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 Coisset, Richard S Finkel, Nathalie Goemans, Craig M McDonald, Christian Rummey, Thomas Meier, for the DELOS Study Group

The Lancet 2015; 385:1748-57
Phase 3 DELOS trial – 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
• Established respiratory function decline (< 80% PEF%p)

Randomized treatment:

• Raxone® (900 mg/d): N=31
• Placebo: N=33
• Mean Age: 14.3 y
• Treatment duration: 12 months

Respiratory function was assessed by:

• spirometry at hospital visits (every 3 months)
• at weekly intervals with portable device used at the patient’s home
Assessment of respiratory function

**Spirometer – At Hospital Visit Only**

Test performed with physiotherapist

- Peak Expiratory Flow (PEF)
- Forced Vital Capacity (FVC)
- Peak Cough Flow (PCF)
- Inspiratory Flow Reserve (IFR)

**ASMA-1™ - Hospital Visit & Weekly Home Testing**

- Peak Expiratory Flow (PEF)
- Forced Expiratory Volume (FEV1)

At each clinic visit, the patient returns the device, the physiotherapist downloads, saves and prints all the stored readings from the home testing.
Assessment of pulmonary function in DELOS
Assessment of pulmonary function in DELOS

Primary analysis in patients with <20% difference between both measurements for PEF:

mITT: N=57 (30 Catena®/Raxone®; 27 Placebo)
Primary endpoint: Change in PEF%p
(hospital-based spirometry)

<table>
<thead>
<tr>
<th>Difference</th>
<th>3.90</th>
<th>8.32</th>
<th>7.60</th>
<th>6.27</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>0.10</td>
<td>&lt;0.001</td>
<td>0.02</td>
<td>0.03</td>
</tr>
</tbody>
</table>

71% reduction in loss of PEF%p

p=0.22

p<0.001
Progression in absolute PEF [L/min]
(hospital-based spirometry)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>13 Weeks</th>
<th>26 Weeks</th>
<th>39 Weeks</th>
<th>52 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raxone®</td>
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<td></td>
<td></td>
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<tr>
<td>Placebo</td>
<td></td>
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</table>

| Difference   | 14.1     | 33.6     | 32.7     | 28.1     |
| p-value      | 0.18     | 0.002    | 0.02     | 0.03     |
Change in PEF%p (measured by ASMA-device)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change from Baseline (±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0</td>
</tr>
<tr>
<td>13 Weeks</td>
<td>-2.68 (±0.5)</td>
</tr>
<tr>
<td>26 Weeks</td>
<td>-4.97 (±0.5)</td>
</tr>
<tr>
<td>39 Weeks</td>
<td>-3.98 (±0.5)</td>
</tr>
<tr>
<td>52 Weeks</td>
<td>-7.24 (±0.5)</td>
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</table>

Difference

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raxone®</td>
<td>2.68</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.97</td>
</tr>
<tr>
<td></td>
<td>3.98</td>
</tr>
<tr>
<td></td>
<td>7.24</td>
</tr>
</tbody>
</table>

p-value

<table>
<thead>
<tr>
<th>Treatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raxone®</td>
<td>0.15</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>0.03</td>
</tr>
</tbody>
</table>

80% reduction in loss of PEF%p
Change in FVC\%p

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
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<th>26 Weeks</th>
<th>39 Weeks</th>
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<tr>
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<td></td>
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<tr>
<td>Placebo</td>
<td></td>
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</tr>
</tbody>
</table>

Difference | 3.27 | 4.72 | 4.97 | 3.27

p-value | 0.02 | 0.002 | 0.02 | 0.08

37% reduction in loss of FVC\%p
Progression in absolute FVC [L]

| Difference | 0.09 | 0.16 | 0.16 | 0.13 |
| p-value    | 0.04 | 0.003 | 0.005 | 0.05 |
Idebenone slows the loss of respiratory function

Consistency of results

DELOS data presentation
Inspiratory function is impaired in DMD patients

- Reduced $V'I$, max (FVC)
- Reduced inspiratory flow reserve (IFR)

De Bruin et al., 2001. Inspiratory low reserve in boys with DMD. Pediatric Pulmonology 31:451-457
Raxone® also preserves inspiratory function

**Maximum Inspiratory Flow: V’I,max (FVC)**

<table>
<thead>
<tr>
<th></th>
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<th>13</th>
<th>26</th>
<th>39</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference (95% CI)</td>
<td>0.23 (0.02, 0.49)</td>
<td>0.27 (0.01, 0.54)</td>
<td>0.34 (0.08, 0.60)</td>
<td>0.30 (-0.01, 0.62)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.034</td>
<td>0.046</td>
<td>0.012</td>
<td>0.061</td>
<td></td>
</tr>
</tbody>
</table>

**Inspiratory Flow Reserve (IFR, %)**

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<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>13</th>
<th>26</th>
<th>39</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference (95% CI)</td>
<td>3.71 (-2.10, 9.51)</td>
<td>4.52 (-0.58, 9.63)</td>
<td>6.16 (-0.12, 12.44)</td>
<td>5.78 (0.28, 11.27)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.225</td>
<td>0.091</td>
<td>0.055</td>
<td>0.040</td>
<td></td>
</tr>
</tbody>
</table>
Fewer patients on Raxone® fell below critical thresholds for Peak Cough Flow (PCF)

"When the PCF falls below 160 L/min, the cough is no longer effective enough to provide adequate mucociliary clearance“ 1,2,3

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Raxone®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCF at BL: &gt;160 L/min</td>
<td>26</td>
<td>33</td>
</tr>
<tr>
<td>Patients with PCF &lt; 160L/min during 1y</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

Analysis of ITT population

2. Bach JR et al., Chest (1997), 112:1024-1028
3. Tzeng AC et al., Chest (2000), 118: 1390-1396
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. QUPHILIAN, RICHARD H. T. EDWARDS, and PETER M. A. CAVENDER
Pharmacy and Benfiddahion Research Group, University Hospital, Birmingham, England; Mayo Clinic, Scottsdale, Ariz.; and Agios Hosp in Orthopædic and Gynæcol Hospital, Coventry, England. United Kingdom


Post-hoc analysis

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Raxone®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL FVC: &gt; 1L but &lt; 1.5 L</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Patients with FVC &lt; 1L during 1y</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Analysis of ITT population

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

DELOS data presentation
Raxone® delays time to 10% relative decline in FVC%p

hazard ratio = 0.46
(95%CI 0.26-0.81)
Fewer patients on Raxone® experience bronchopulmonary disease (e.g. airway infections)

<table>
<thead>
<tr>
<th></th>
<th>Raxone®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

Duration of antibiotic use (d)

<table>
<thead>
<tr>
<th></th>
<th>Raxone®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>11.7</td>
<td>7.9</td>
</tr>
<tr>
<td>Median</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Total Days</td>
<td>82</td>
<td>222</td>
</tr>
</tbody>
</table>

Hazard Ratio* 0.28; p=0.0026

Bronchopulmonary disease classified as treatment emergent adverse events:

**Included**: larynx, airways, alveoli (bronchitis, influenza, laryngitis, pneumonia, upper respiratory tract infection, viral infection, respiratory failure, cough, dyspnoea);

**Excluded**: pharynx and nose (influenza like illness, pyrexia, otitis media, rhinitis allergic, rhinorrhea, sleep apnoea syndrome)

*proportional means regression analysis
Patients on Raxone® use less antibiotics for the treatment of bronchopulmonary disease

<table>
<thead>
<tr>
<th>Raxone®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (%)</td>
<td>7 (22.6%)</td>
</tr>
<tr>
<td>Events</td>
<td>8</td>
</tr>
</tbody>
</table>

Duration of antibiotic use (d)

<table>
<thead>
<tr>
<th>Raxone®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>8.1</td>
</tr>
<tr>
<td>Median</td>
<td>8</td>
</tr>
<tr>
<td>Total Days</td>
<td>65</td>
</tr>
</tbody>
</table>

Hazard Ratio* 0.52; p=0.1330

*proportional means regression analysis
Summary of DELOS outcome

• The Phase 3 trial met its primary and secondary endpoints
• Demonstrated a consistent treatment effect for Raxone® on expiratory and inspiratory function
• Provides supportive evidence for efficacy in clinically relevant responder analyses
• Demonstrates clinically relevant impact of bronchopulmonary disease and antibiotic use
Positioning of Raxone® in the treatment of DMD

• There is a sizeable proportion of patients who cannot tolerate steroids at the time when respiratory function loss becomes evident

• There is an urgent unmet medical need to slow down the decline of respiratory function in these patients

• “Slowing down the accumulation and the progression of disability” recognized as clinically relevant (EMA guideline on DMD)

• Available data demonstrate that the investigational drug Raxone® slows down loss of respiratory function in patients not using steroids

• Raxone® was tested in patients without restriction to specific mutational or disease status (no competition to alternative treatment approaches)
SIDEROS - a new Phase 3 trial in patients using steroids

- **Objective**: To assess the efficacy of idebenone (Raxone®) compared to placebo, in slowing the loss of respiratory function in patients with DMD receiving glucocorticoids (GCs)

- **Endpoints**: Change in FVC%p (primary), change in other respiratory function outcomes (PEF%p, FEV1 etc.)

- **Patients**: ~260 DMD patients using stable GCs who have started to decline on respiratory function (at baseline 30% ≤ FVC%p ≤ 80%)

- **Randomization**: 1:1 to receive idebenone (900 mg/d) or placebo

- **Stratification for steroid regimen**

- **Treatment duration**: 78 weeks

- **Study conduct**: approx. 50 centers in Europe and US

- **Status**: Protocol completed, feasibility study completed

- **Study start**: 2Q2016; Study end: 3Q2019

- **Extension study**: Open label extension phase offered to trial participants
Advancing mitochondrial medicine towards treatments for

- LHON
- DMD
- ppMS

Thank you for your attention