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

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Agenda

• Understanding respiratory function decline-DMD, including need for a targeted treatment
• **DELOS** study: Efficacy and safety for idebenone in slowing respiratory function decline-DMD
• Open for enrollment: the **SIDEROS** study
• US Expanded Access Program (EAP)
• Raising awareness for respiratory function in DMD
Understanding Respiratory Function Decline-DMD
Urgent medical need for new therapies in DMD

• Increasing respiratory muscle weakness in DMD leads to:
  – Decreased lung volumes and flow rates
  – Decreased ability to cough effectively and clear airways from mucus
  – Increased risk of respiratory infections

• As respiratory function declines, assisted ventilation is required
• There are no approved pharmacological therapies for treating respiratory decline
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

Data from CINRG-DNHS showing mean ± SEM absolute percentage point decline from baseline.

The DELOS study: Overview
DELOS: Effect of idebenone to delay respiratory function decline in boys not using glucocorticoids (GCs)

DMD patients not taking GCs, n = 64

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

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

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

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

<table>
<thead>
<tr>
<th>Ambulatory status</th>
<th>Brooke Score</th>
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<tr>
<td>92% non-ambulatory</td>
<td>~60% ≥5; unable to raise hand to mouth</td>
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Mean age

14 years
DELOS: Effect of idebenone on respiratory function

Data from weekly home-based assessment of PEF%p
Effect of idebenone on respiratory complications and hospitalizations

<table>
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<tr>
<th></th>
<th>Idebenone</th>
<th>Placebo</th>
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<tr>
<td><strong>Bronchopulmonary adverse events (AEs)</strong></td>
<td></td>
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<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>
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</table>

| **Systemic Antibiotic Use** |           |         |
| Subjects (%)               | 7 (22.6%) | 13 (39.4%) |
| Events                      | 8         | 17      |
| Total Days                  | 65        | 105     |

| **Hospitalizations** (due to respiratory causes) |           |         |
| Subjects (%)               | 1 (3%)    | 4 (12%) |
| Events                      | 1         | 6      |
| Total Days                  | 3         | 30     |

**Hazard Ratio* 0.28; p=0.0026**
The SIDEROS study: Effects of idebenone in patients on glucocorticoid treatment
ENROLLING FOR SIDEROS: Effects of idebenone on respiratory function in patients using glucocorticoids (GCs)

DMD patients taking GCs \( n \geq 266 \)

<table>
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<tr>
<th>Study type:</th>
<th>Randomized, placebo-controlled trial</th>
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<tr>
<td>Key eligibility criteria:</td>
<td>( \geq 10 ) years, chronic use of systemic GCs and in respiratory function decline (FVC%p 35%-80% at baseline)</td>
</tr>
<tr>
<td>Primary endpoint:</td>
<td>Change in FVC%p from baseline to week 78</td>
</tr>
<tr>
<td>Secondary endpoints:</td>
<td>Changes in PEF%p, time to loss of 10% in FVC and change in inspiratory flow reserve</td>
</tr>
<tr>
<td>Other endpoints:</td>
<td>Change in peak cough flow (PCF), blood oxygen saturation and EtCO(_2), Bronchopulmonary illness, Antibiotic use</td>
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EtCO\(_2\) = End tidal CO2 level, using Capnography
SIDEROS trial

- Currently the largest ongoing clinical trial in DMD
- Ambulant and non-ambulant patients
- 65 sites sites in US, Europe and Israel
- 23 sites in US
- All completers are offered enrollment to the open-label SIDEROS Extension trial

See poster presentation with information on study centers
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.

VIEW TRIAL OVERVIEW
US Expanded Access Program: *BreatheDMD*

**A US Expanded Access Program (EAP) in patients with DMD***

**Up to 250 DMD patients**

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<tr>
<th>Population</th>
<th>DMD patients ≥ 10 years in respiratory decline</th>
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<td>Objective</td>
<td>Provide access to treatment with idebenone for patients with DMD in the US</td>
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<tr>
<td>Treatment</td>
<td>Idebenone 300mg orally 3 times daily</td>
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<td>Assessments</td>
<td>Safety, tolerability, effectiveness and QoL data</td>
</tr>
<tr>
<td>Status</td>
<td>Enrolling</td>
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- **Up to 35 sites across the US**
- **States with active sites depicted in red**

**Centers and locations**

Please visit [www.breathedmd.com](http://www.breathedmd.com) for more information

*Patients must NOT be eligible for SIDEROS/other ongoing trials with idebenone in DMD*
Regulatory strategy

Patients with DMD not using glucocorticoids

- Successful Phase 3 DELOS trial as basis for regulatory dossier
- Additional natural history data to establish clinical relevance of treatment effect
- Additional open-label data with idebenone
- Best approval pathway in US and EU under consideration

Patients with DMD using glucocorticoids

- Top-line data available H2 2020
- Positive SIDEROS Study may allow for expansion of label to all patients in respiratory decline, irrespective of GC use status

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<tr>
<th>Santhera Pipeline</th>
<th>Drug</th>
<th>Preclin.</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Filing</th>
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<tr>
<td>Duchenne Muscular Dystrophy (GC non-users)</td>
<td>Idebenone*</td>
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GC: Glucocorticoid
Disease Awareness Activities:
Raising awareness for respiratory function in DMD
Respiratory 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)
Santhera’s respiratory awareness campaigns

Dedicated website providing information on respiratory function care

- US website: www.takeabreathdmd.com
- European website: www.breatheduchenne.com
Santhera’s commitment to the DMD community

• Collaborate with clinical experts and patients to better **understand** respiratory function decline in DMD

• Successful phase III **DELOS** trial demonstrated that idebenone slows decline in respiratory function in patients not taking glucocorticoids (GCS)

• Ongoing Phase III **SIDEROS** trial in patients who are using glucocorticoids – study open for enrolment!

• US Expanded Access Program (EAP) open for enrolment!

• Active contribution to **raise awareness** of the respiratory disease component of DMD

• Santhera aims to **make** idebenone **available** to patients with DMD as soon as possible