

**Background**

In DMD, progressive muscle weakness leads to sequential loss of function, one of the most serious of which is respiratory function decline. This typically begins while patients can still walk, and accelerates after loss of ambulation, eventually resulting in the need for assisted ventilation.

Natural history studies have demonstrated that the risk and severity of respiratory morbidity, including hospitalizations due to respiratory causes, increases with declining respiratory function. Treatment with idebenone in the Phase III DELOS trial (in DMD patients with established respiratory function decline [FVC%] at baseline [BL], and not taking glucocorticoids), significantly reduced the loss of peak respiratory flow, measured as % predicted (PFT) (p = 0.003 vs. 0.48% to 2.57% at week 52 (an absolute difference of 6.29% (p = 0.012)).

Post hoc analyses of the DELOS trial showed that more patients in the placebo group compared to the idebenone group experienced bronchopulmonary adverse events (BAEs) (i.e., airway inflamed [inhaled] (calculated by patient): %HR: 0.33; p = 0.016 and for all BAEs: %HR: 0.28, p = 0.002), indicated a clear idebenone treatment effect.

In addition, the number of serious adverse events leading to hospital admissions due to respiratory causes was higher in the placebo group as was the use of antibiotics typically prescribed to treat bronchopulmonary complications.

Here we report data collected from a retrospective cohort study (SYROS) in DMD patients who completed the DELOS trial and were treated with idebenone (900 mg/day) under Expanded Access Programs (EAPs) in four countries (Belgium, Germany, Netherlands and Switzerland).

**Aims**

- To evaluate the effect of long-term idebenone treatment on the rate of respiratory function decline, and also in reducing the frequency of, and time taken to reach, respiratory morbidity-associated events in a real-world study.

**Methods**

SYROS is a long-term real-world study in 18 former DELOS patients who transitioned to idebenone under Expanded Access Programs (EAPs) in four countries (Belgium, Germany, Netherlands and Switzerland). Patients had provided consent and signed a Data Release Agreement.

Collection of long-term data from EAPs

- Patients who had taken idebenone as part of an EAP after DELOS.
- Patients who had provided consent and signed a Data Release Agreement.

Key inclusion criteria

- Patients had taken idebenone as part of an EAP after DELOS.
- Patients had provided consent and signed a Data Release Agreement.

Comparison of patients in DELOS trial vs. those in the SYROS study

- Significant differences in baseline characteristics (i.e., sex distribution, age at BL FVC%, FVC% at BL and age at the first respiratory event).

**Results**

- **Efficacy of long-term idebenone treatment on clinically relevant outcomes**
  - When comparing the annual change in FVC% for patients on long-term idebenone treatment compared with the preceding Off-Idebenone period (N = 11), idebenone reduced the rate of decline by approximately 50% (7.4%; 95% CI: -9.1, -5.8 for Off-Idebenone period vs -3.8%; 95% CI: -4.8, -2.8 for On-Idebenone period).
  - During the On-Idebenone periods, 6 patients (33.3%) reported a total of 8 BAEs (i.e. 0.05 events per person year of follow-up).
  - During the Off-Idebenone periods, 3 patients (16.6%) reported 3 events (i.e. 0.02 events per person year of follow-up).

- **The rate of hospitalizations due to respiratory infections or related disorders were smaller for the Off-Idebenone periods (0.06 events per person year) compared with Off-Idebenone periods (0.15 events per person year), although interpretation is limited by the small number of events reported.**

- **Hospitalizations due to any reason were also lower in the On-Idebenone periods compared to the Off-Idebenone periods (0.29 versus 0.48 events per person year).**

**Conclusion**

- In this long-term analysis (up to 6 years), the reduced rate of decline in respiratory function observed in prior studies was translated into a smaller number of bronchopulmonary complications and hospitalization for respiratory events, as well as an increased time to experiencing a 10% relative decline in FVC% and decreased reliance on systemic antibiotics.
- This is in line with the results of the DELOS trial, that showed fewer patients in the idebenone group compared to the placebo group experienced BAEs and serious adverse events leading to hospital admissions due to respiratory causes.
- Real-world data suggests that maintaining long-term treatment with idebenone continues to slow respiratory function decline, thus reducing the occurrence and severity of clinically relevant respiratory morbidity.
- These results are an early indication of the long-term benefits of slowing the rate of respiratory function decline, and the disease-modifying potential of idebenone.

**References**


**Acknowledgements**

DELOS and SYROS Study Groups. All patients and carers who participated in their studies.

**Conflict of interest**

O.H. Mayer, L. Severin, C. Straathof, U. Schara, T. Voit, E. Mercuri and G. Buyse act as advisors to Santhera Pharmaceuticals (Switzerland) Ltd and have participated in prior/current studies with idebenone in DMD. G. Buyse is co-inventor of relevant patent applications. M. Leinonen is an employee of Santhera Pharmaceuticals (Switzerland) Ltd.

**Table 1.** Summary of demographics, disease status and respiratory function data for the DELOS and SYROS ITT populations. Data are reported at BL of both DELOS and SYROS populations.

<table>
<thead>
<tr>
<th>N (%)</th>
<th>DELOS ITT population (N = 18)</th>
<th>SYROS ITT population (N = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, median, (minimum-maximum))</td>
<td>14.3 (2.7)</td>
<td>13.3 (2.7)</td>
</tr>
<tr>
<td>PFT (mean, median, (minimum-maximum))</td>
<td>9.7 (1.5)</td>
<td>10.3 (2.5)</td>
</tr>
<tr>
<td>FVC% (mean, median, (minimum-maximum))</td>
<td>9.5 (7.2, 14.3)</td>
<td>9.8 (7.8, 12.8)</td>
</tr>
<tr>
<td>52-week change in FVC% (mean, median, (minimum-maximum))</td>
<td>15 (8.5, 25)</td>
<td>14.3 (2.7)</td>
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**Table 2.** Reasons for and frequency of hospitalization.

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>N (%)</th>
<th>On-Idebenone</th>
<th>Off-Idebenone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory infection or related disorder</td>
<td>4</td>
<td>0.25</td>
<td>2.60</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>0.55</td>
<td>1.30</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>0.78</td>
<td>3.90</td>
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**Table 3.** Summary of cumulative frequency of BAEs under idebenone treatment.

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>N (%)</th>
<th>On-Idebenone</th>
<th>Off-Idebenone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total frequency</td>
<td>15</td>
<td>0.81</td>
<td>2.40</td>
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<tr>
<td>Number of patients with at least one BAE</td>
<td>11</td>
<td>0.61</td>
<td>3.30</td>
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**Figure 1.** Kaplan-Meier analysis of time to first decline in FVC% by treatment period. N = 10 for Off-Idebenone periods; N = 18 patients for On-Idebenone periods.

**Figure 2.** Mean cumulative function estimates (proportional means regression model) for cumulative frequency of BAEs by treatment. N = 14 for Off-Idebenone periods; N = 18 patients for On-Idebenone periods.

**Figure 3.** Kaplan-Meier analysis of time to first decline in FVC% by treatment period.