Background

- Respiratory function decline, a predominant cause of early mortality in DMD, is caused by the underlying weakness and degeneration of the respiratory muscle groups – notably the diaphragm, intercostal and chest wall muscles – leading to impaired inspiratory and expiratory effort.1, 2

- Treatment with idebenone in the Phase III DELOS trial (in DMD patients with established respiratory function decline (<80%p) at baseline (BL), and not taking glucocorticoids), significantly reduced the loss of weak expiratory flow, measured as % predicted (PEF%p) from BL, from -8.48% to -2.57% at week 52 (an absolute difference of 5.7% (p = 0.031)).3

- 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).

Objectives

- To evaluate the long-term evolution of the respiratory function during idebenone treatment, compared to the evolution during idebenone-free periods.

SYROS Study

Key inclusion criteria:

- Patients had completed the DELOS trial (clinicaltrials.gov ID: NCT01278784).4
- Patients had taken idebenone as part of an EAP after DELOS.
- Patients had provided consent and signed Data Release Agreement.

Collection of long-term data from EAP:

- Patients were managed according to routine clinical practice in the EAP.
- Data from DELOS and SYROS were used to evaluate evolution of respiratory function.
- Comparisons were made between treated and untreated periods:
  - On-On comparison: any period when patients received idebenone, either during DELOS or during the EAP.
  - Off-On comparison: idebenone-free periods, either during DELOS (in placebo arm) and/or during completion of DELOS and start of idebenone treatment in the EAP.
  - The primary endpoint was the annual change in forced vital capacity % predicted (FVC%p) in both Off-idebenone and On-idebenone periods.
- Annual rates of change in FVC%p and PEF%p were estimated using random coefficient regression models along with the mean slope: the red dotted line) are shown for change in FVC%p (A, B) (N = 11). Slopes for the Off-idebenone and On-idebenone groups are shown for FVC%p in (A) and for PEF%p in (B) (along with the mean slope: the red dotted line) are shown for change in FVC%p (A, B) (N = 11). Slopes for the Off-idebenone and On-idebenone groups are shown for FVC%p in (A) and for PEF%p in (B).

The mean idebenone exposure in the EAPs was 4.2 years (range 2.4 to 6.1 years) in the DELOS and 5.3 years (1.8 to 8.9 years) in the SYROS trial (Table 1).

Table 1. Summary of demographics, disease status and respiratory function data for the DELOS and SYROS patient populations. Data are reported at baseline of DELOS.

<table>
<thead>
<tr>
<th>Age range (year), mean (SD), median, (minimum-maximum)</th>
<th>DELOS-OTT population N = 11</th>
<th>SYROS-OTT population N = 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 14 (12.7) 14.6 (12.0) 14.9</td>
<td>13.3 (12.7) 12.6 (12.0) 13.8</td>
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<tr>
<td>Prior glucocorticoid use, n (%)</td>
<td>28 (43.8) 36 (59.3) 26 (65.6)</td>
<td>7 (13.6) 11 (20.2) 11 (20.2)</td>
</tr>
<tr>
<td>Time since last glucocorticoid use, years (mean, median, (minimum-maximum))</td>
<td>3.7 (2.3) 3.5 (2.6) 3.5</td>
<td>4.1 (3.8) 4.2 (3.4) 4.2</td>
</tr>
<tr>
<td>Ambulatory status, n (%)</td>
<td>5 (7.8) 6 (20.2) 6 (21.2)</td>
<td>10 (18.1) 15 (27.3) 15 (27.3)</td>
</tr>
<tr>
<td>Age at loss of ambulation, years (mean, median, (minimum-maximum))</td>
<td>59 (7.5) 6 (2.2) 6 (2.2)</td>
<td>50 (7.5) 6 (2.2) 6 (2.2)</td>
</tr>
<tr>
<td>FVC%p (mean, median, (minimum-maximum))</td>
<td>52.8 (18.1) 51.3 (22.6) 51.3</td>
<td>61.5 (22.6) 61.5 (22.6) 61.5</td>
</tr>
<tr>
<td>PEF%p (mean, median, (minimum-maximum))</td>
<td>5.6 (8.1) 5.6 (8.1) 5.6</td>
<td>5.6 (8.1) 5.6 (8.1) 5.6</td>
</tr>
</tbody>
</table>

- The mean idebenone exposure in the EAPs was 4.2 years (range 2.4 to 6.1 years) in the ITT population (N = 18).

- In total, the exposure to idebenone treatment was 84 person years, consisting of 8 person years in the DELOS study and 76 person years in the EAPs.

Analysis by treatment periods

- On-On comparison: annual change of respiratory function was assessed for patients treated with idebenone in DELOS who continued long-term idebenone treatment during the EAP (patients 1-7, Figure 1).
- Minor treatment interruptions were accepted (continued arrows in grey areas).

- Off-On comparison: annual change of respiratory function was assessed for patients on long-term idebenone treatment compared to the preceding Off-idebenone period (patients 8-18, Figure 1).

Results

Treatment with idebenone reduced the long-term annual rate of decline of FVC%p by 50%

- When comparing the annual change in FVC%p for the “Off-On” idebenone group (N = 11), long-term treatment with idebenone reduced the rate by approximately 50% from -7.4% (95% CI: -9.1, -5.8) for the Off-idebenone period to -3.8% (95% CI: -4.8, -2.8) for the On-idebenone period (Figure 2).

- Individual slope estimates from the random coefficient regression model also highlight the consistent FVC%p rate decrease when comparing slopes from the Off-idebenone periods (Figure 3A) to those from the On-idebenone periods (Figure 3B).

- The annual change in PEF%p was similarly reduced from -5.9% (95% CI: -8.0, -3.9) for the Off-idebenone periods to -1.9% (95% CI: -3.2, -0.7) for the On-idebenone periods (N = 9).

- For the “On-On” idebenone group, the annual rate of decline in FVC%p remained low with continued treatment for both On-idebenone periods from DELOS and in the EAPs with estimated rates of -0.7% (95% CI: -3.7, 2.2) and -3.9% (95% CI: -5.4, -2.3), respectively (N = 7). Similar results were seen for PEF%p, with 1.3% (95% CI: -3.3, 5.8) and -1.3% (95% CI: -3.4, 0.8), respectively (N = 6).

Sustained long-term efficacy, and a 68% reduction in the risk of respiratory complications

- In a secondary analysis, annual rates of FVC%p decline (Figure 4) were compared using two-year bins to assess the temporal evolution of respiratory function.

- Continued long-term treatment with idebenone resulted in a stable reduction in respiratory function decline for up to 6 years.

- Further comparisons were made to matched untreated patients for each 2-year bin from the CINRG-DNHS and to evaluable data during the Off-idebenone periods in DELOS/SYROS for years 1-2 (Figure 4), both of which demonstrated consistently higher rates of respiratory function decline in untreated patients compared to patients treated with idebenone.

- Similar outcomes were observed for PEF%p (data not shown).

- The risk of bronchopulmonary adverse events (BAEs) was reduced by 68% during the On-idebenone periods versus Off-idebenone (Figure 5), leading to fewer hospitalizations due to respiratory causes (0.06 vs 0.15 events per person year).

- In line with a reduced frequency of BAEs, patients during On-idebenone periods required less systemic use of antibiotics compared to Off-idebenone periods (0.15 vs 0.04 events per person year).

Conclusions

- SYROS demonstrates that long-term treatment with idebenone results in a consistent and sustained reduction in the rate of respiratory function decline, an effect that was maintained for up to 6 years.

- Furthermore, there was a reduced risk of experiencing patient-relevant outcomes, such as BAEs or hospitalizations due to respiratory causes.

- Idebenone holds disease-modifying therapeutic potential over the long-term, adding to data from previously published studies.5-10

References


Conflict of interest

G. Buyse is co-inventor of relevant patent applications.
G. Buyse, J. Mercuri, C. McDonald, T. Voit and O.H. Mayer are paid consultants for Santhera and/or are investigators in prior/current studies with idebenone in DMD.

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