**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 leading to impaired inspiratory and expiratory efforts.
- Progressive respiratory insufficiency requires the use of non-invasive ventilation, often progressing to invasive ventilation, following the loss of ambulation.
- Treatment with idebenone in the Phase III DELOS trial (N = 64) in DMD patients with established respiratory function decline (≤80%) at baseline (BL), and not taking glucocorticoids (GCs), significantly reduced the loss of peak expiratory flow, measured as % predicted (PEF%) from BL, from -14.8% to -2.5% at week 52 (an absolute difference of 6.27% [p = 0.031]).

Here we report data collected from a retrospective cohort study (SYROS) in DMD patients (N = 18) 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) for up to 6 years.

**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:NCT01027884).
  - Taken idebenone as part of an EAP after DELOS.
- Provided consent and signed a Data Release Agreement.

**Collection of long-term data from EAP**

- Data from DELOS and SYROS were used to evaluate respiratory function.
- Comparisons were made between treated and untreated periods:
  - **On-idebenone** = any period when patients received idebenone, either during DELOS or during the EAP.
  - **Off-idebenone** = idebenone-free periods, either during DELOS (i.e. placebo group) and/or after completion of DELOS and start of idebenone treatment in the EAP.
- The primary endpoint was the comparison of annual changes in forced vital capacity (% predicted (FVC%) between Off-idebenone and On-idebenone periods.
- Annual rates of change in FVC% and PEF% were estimated using random coefficient regression models accounting for prospectively planned analyses.
- Changes during treatment periods were also compared to a matched (BL FVC%) external cohort from the CINRG Duchenne Natural History Study (CINRG DHNS).
- Data on bronchopulmonary adverse events (BAEs) and hospitalizations were also collected.
- Demographics and respiratory function status was comparable between patients of DELOS and SYROS (Table 1).

**Analysis by treatment periods**

- **On-** vs **Off-idebenone comparison**: annual change of respiratory function was assessed for treated DELOS patients who continued long-term treatment with idebenone during the EAP (patients 1 – 7, Figure 1). Minor treatment interruptions (less than 10% of the overall treatment exposure) were accepted.
- **Off-idebenone 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% by 50%**
  - When comparing the annual change in FVC% for the "Off-On" idebenone group (N = 11), long-term treatment 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 2A).
  - Similarly, annual change in FEP% was -5.9% (95% CI: -8.0, -3.9) for Off-idebenone periods (N = 9) and -1.9% (95% CI: -3.2, -0.7) for the On-idebenone periods (Figure 2B).
- Individual slope estimates highlight the change in FVC% rates when comparing Off-idebenone (Figure 3A) and On-idebenone periods (Figure 3B).
- For the "On-" idebenone group, the annual rate of decline in FVC% remained low with continued treatment for treated periods (DELOS and SYROS), 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%, 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% decline (Figure 4) were compared using 2-year bins to assess the temporal evolution of respiratory function.
  - Continued long-term treatment with idebenone resulted in a reduction in respiratory function decline year-on-year for up to 6 years.
  - Further comparisons were made to matched, untreated patients for each 2-year bin from the CINRG DHNS and to evaluative data during the Off-idebenone periods in DELOS/SYROS for years 1-2 (Figure 4), both of which demonstrated consistently lower rates of respiratory function decline when treated with idebenone.
  - Similar outcomes were observed for PEF% (data not shown).
- The risk of BAEs was reduced by 68% comparing the On-idebenone period vs 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 reduced systemic use of antibiotics compared to Off-idebenone periods (0.04 vs 0.15 events per person year of follow-up).

**Conclusions**

- Data from the SYROS study indicates that long-term treatment with idebenone results in the continued, consistent, and sustained reduction in the rate of respiratory function decline, measured as annual change in FVC% and PEF%.
- The slower decline in respiratory function was accompanied by a reduced risk of experiencing patient-relevant outcomes, such as BAEs or hospitalizations leading to respiratory causes.
- Taken in combination with previously published results, these data indicate that idebenone has the potential to slow long-term respiratory function decline and potentially extend the time taken for patients to reach clinically relevant milestones, such as the need for assisted ventilation.

**References**


**Conflict of interest**

- G. Buyse is co-inventor of relevant patent applications.
- G. Buyse, I. Mercier, C. McDonald, T. Vocke, L. Servais and S. Mayer are paid consultants for Santaris Pharmaceuticals (Switzerland) Ltd and/or are investigators in current(randomized) trials with idebenone in DMD.

**ADDeLS, SYROS and CINRG Study Groups.**