**Consistent long-term effect of idebenone in reducing respiratory function decline in patients with Duchenne Muscular Dystrophy (DMD)**

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**Background**

- Respiratory function decline in DMD is caused by progressive weakening of respiratory muscles and inevitably results in the need for assisted ventilation.
- Respiratory failure remains a leading cause of death in patients with advanced DMD.
- Loss of respiratory function starts early in the disease course usually preceding loss of ambulation, reaching the lower limit of normal (defined as 80% predicted) around 10 years of age.
- Glucocorticoid (GC) treatment, the current standard of care in DMD, delays the onset of respiratory function decline by around 2 – 3 years; however, once established, decline continues at the same rate in GC users and non-users.
- The efficacy of idebenone in slowing respiratory function decline in DMD has been reported in two randomized, placebo-controlled trials: the Phase II DELPHI trial and the Phase III DELOS trial over 52 weeks.
- Long-term data from the SYROS study in patients treated for up to 6 years is presented at this meeting (poster number 7).
- Here we present a comparison of efficacy from DELPHI and DELOS and their corresponding long-term extensions, DELPHI-Extension (DELPHI-E) and SYROS.

**Objectives**

- The objective was to evaluate the consistency of long-term efficacy of idebenone in reducing the rate of respiratory function decline in the two independent, randomized, placebo-controlled studies (DELPHI, DELOS) and their corresponding long-term data collections, DELPHI-E and SYROS.

**Methods**

**DELPHI + DELPHI-E** (Figure 1A)

- DELPHI was a randomized, double-blind, placebo-controlled 52-week Phase II trial in 21 patients and included patients irrespective of baseline respiratory function and GC use status.
- DELPHI-E was an open-label, 2-year extension study for patients who had completed the DELPHI study.
- For this analysis and in accordance to international consensus, only data from 11 patients with abnormal respiratory function (FVC%p <80%) at baseline were analyzed (Table 1).

**DELOS + SYROS** (Figure 1B)

- DELOS was a randomized, double-blind, placebo-controlled 52-week Phase III trial in 64 patients with abnormal respiratory function at baseline who were not taking GCs.
- SYROS was a long-term real-world study in 18 former DELOS patients who were treated with idebenone under Expanded Access Programs (EAPs) for up to 6 years (Table 1).
- The changes in FVC%p were compared between idebenone and placebo with a mixed model for repeated measures (double-blind trials) and long-term changes estimated with random coefficient regression models (extension studies) and compared to corresponding untreated periods or to a matched external cohort from the CINRG-DMD Natural History Study (CINRG DNHS).

**Results**

**Treatment with idebenone showed consistent and sustained reductions in annual rates of respiratory function decline**

- When comparing DELPHI (FVC <80% subgroup) and the 18 DELOS patients who participated in SYROS, the estimated change at 52 weeks vs placebo as measured by FVC%p was consistent at 7.6% vs 7.8% (Figure 2).
- The annual change in FVC%p during long-term treatment in DELPHI-E for 2 years and SYROS for an average of 4 years was also consistent at -4.5% vs -3.8% (Figure 2).
- In a temporal analysis of efficacy over time:
  - For years 1-2, the annual rate of change in FVC%p was similar for DELPHI-E and SYROS at -4.5% vs -5.4%.
  - For years 1-2, the annual rate of change in FVC%p was similar for DELPHI-E and SYROS at -4.5% vs -5.4%.
  - For years 2-6 in SYROS, the annual change in FVC%p was consistently lower than in the matched untreated external controls (Figure 3, idebenone – orange bars, CINRG matched controls – black bars).
- Consistent outcomes were also observed for PEF%p (data not shown).

**Conclusion**

- Analysis of efficacy from two randomized, placebo-controlled trials and their respective long-term data collections have demonstrated consistent and robust outcomes.
- Furthermore, a temporal analysis of efficacy has shown sustained and consistent efficacy year-on-year when compared with matched external controls from natural history.
- Idebenone holds disease-modifying therapeutic potential over the long term, adding to data from previously published studies.

**References**


**Conflict of interest**

O.H. Mayer, L. Servais, C. McDonald, T. Voit, E. Mercuri and G. Buyse act as advisors to Santhera Pharmaceuticals and have participated in prior/current studies with idebenone in DMD.

G. Buyse is co-inventor of relevant patent applications.

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