Consistent long-term effect of idebenone in reducing respiratory function decline in advanced 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,[1] reaching the lower limit of normal (defined as 80% predicted) around 10 years of age.[2]
- 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.[2,3]
- 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[4] and the Phase III DELOS trial over 52 weeks.[5-9]
- 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.[4]
- **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,[10] 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.[5]
- **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).[3]

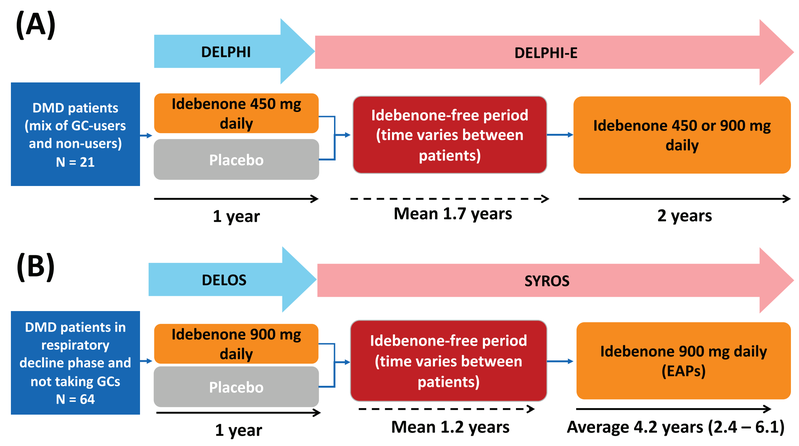

Figure 1. Design summary of the Phase II DELPHI + DELPHI-E (A), and the Phase III DELOS + SYROS (B).

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% compared to -8.1% for the matched external control and -7.9% for untreated SYROS patients over the same period (**Figure 3, red box**).
  - 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).

Table 1. Demographic and baseline characteristics of patients from the Phase II DELPHI study and the subgroup of SYROS patients from the Phase III DELOS study.

	DELPHI Subgroup FVC%p <80%		SYROS: Subgroup of DELOS patients	
Parameter	Idebenone (N = 8)	Placebo (N = 3)	Idebenone (N = 8)	Placebo (N = 10)
Age (years), mean (SD)	14.4 (1.6)	11.6 (3.0)	12.6 (2.9)	13.8 (2.7)
Non-ambulatory, N (%)	6 (75.0)	2 (66.7)	5 (62.5)	10 (100.0)
Baseline GC use status **User, N (%)** **Non-User, N (%)**	 4 (50.0) 4 (50.0)	 0 (0.0) 3 (100.0)	 0 (0.0) 8 (100.0)	 0 (0.0) 10 (100.0)
Baseline FVC%p, mean (SD)	59.3 (14.4)	51.7 (15.5)	61.1 (14.0)	56.9 (20.5)
Baseline PEF%p, mean (SD)	59.3 (19.9)	52.0 (27.1)	60.7 (4.8)	56.8 (13.1)

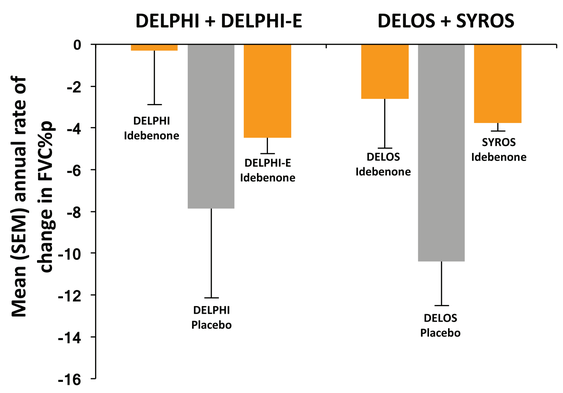

Figure 2. Annual rates of change for FVC%p in idebenone treated (orange) and untreated periods (grey) from DELPHI, DELPHI-E, DELOS and SYROS.

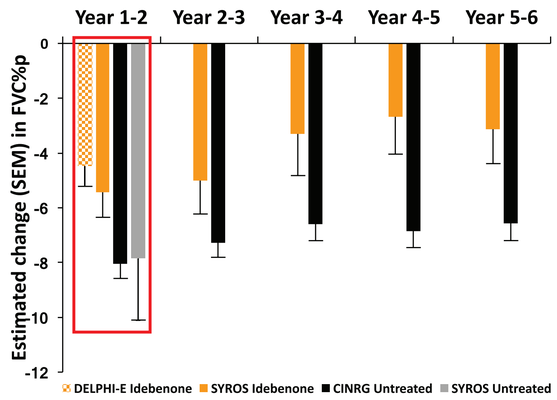

Figure 3. Analysis of annual rate of change for FVC%p by 2-year bins: comparison of periods in the DELPHI-E study (checked) and SYROS study where patients were idebenone treated (orange) or untreated (grey). Annual rate of change in FVC%p from matched patients from the CINRG natural history study (black).

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.[5-9]

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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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