Consistent long-term effect of idebenone on the rate of 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 insufficiency which, following the loss of ambulation, is the second irreversible disease milestone in DMD that greatly impacts the patient's quality of life and remains a leading cause of death.
- Loss of respiratory function starts early in the disease course, usually preceding loss of ambulation[1] and reaching the lower limit of normal (defined as 80% predicted) around 10 years of age.[2]
- 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[3] and the Phase III DELOS trial over 52 weeks.[4-8]
- Long-term data from the SYROS study in patients treated for up to 6 years is presented at this meeting (poster number 138).
- Here we present a comparison of efficacy for patients participating in the DELPHI and DELOS studies who continued treatment in corresponding long-term data collections, DELPHI-Extension (DELPHI-E) and SYROS.

Objectives

- The objective was to evaluate the consistency of efficacy of idebenone in reducing the long-term rate of respiratory function decline from 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, enrolled irrespective of baseline respiratory function and glucocorticoid (GC) use status.[3]
- **DELPHI-E** was an open-label, 2-year extension study for patients who had completed the DELPHI study.
- For this analysis, in accordance to international consensus,[9] only data from 11 patients with abnormal respiratory function (<80% of predicted) at baseline were included (**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 (PEF%p <80%) who were not taking GCs.[4]
- **SYROS** was a data collection in 18 former DELOS patients who were treated with idebenone under Expanded Access Programs (EAPs) for up to 6 years (**Table 1**) under real-world conditions.
- Annual rates of change in FVC%p were compared between idebenone and placebo with a mixed model for repeated measures (double-blind trials) and long-term changes were estimated with random coefficient regression models (extension studies) and compared to corresponding untreated periods, and/or to a matched external cohort from the CINRG Duchenne Natural History Study (CINRG DNHS).

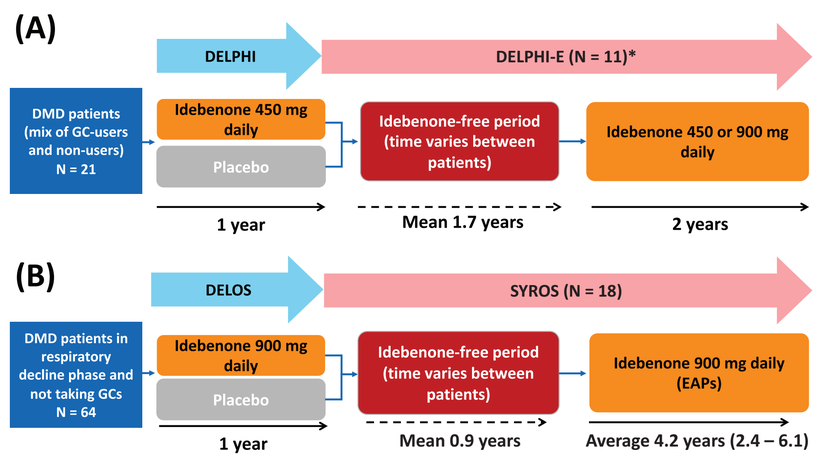

*Figure 1. Design summary of the Phase II DELPHI + DELPHI-E (A), and the Phase III DELOS + SYROS (B). *For this analysis, only data from 11 patients with abnormal respiratory function (<80% of predicted) at baseline were included. GC: glucocorticoid.*

Results

Treatment with idebenone resulted in consistent and sustained reductions in annual rates of respiratory function decline across both randomized trials and long-term programs

- When comparing DELPHI (FVC <80% subgroup) and the 18 DELOS patients who continued in SYROS, the estimated change at 52 weeks for idebenone vs. placebo, as measured by FVC%p, was consistent at -0.3% vs -7.9% and -2.6% vs -10.4% for each study, respectively (**Figure 2**).
- The annual change in FVC%p during long-term treatment in DELPHI-E for 2 years and SYROS for an average of 4.2 years, was also consistently low at -4.5% vs -3.8%, respectively (**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%		DELOS Subgroup of SYROS patients	
Parameter	Idebenone (N = 8)	Placebo (N = 3)	Idebenone (N = 8)	Placebo (N = 10)
Age (years), mean (SD)	14.4 (1.6)	11.6 (3.1)	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)

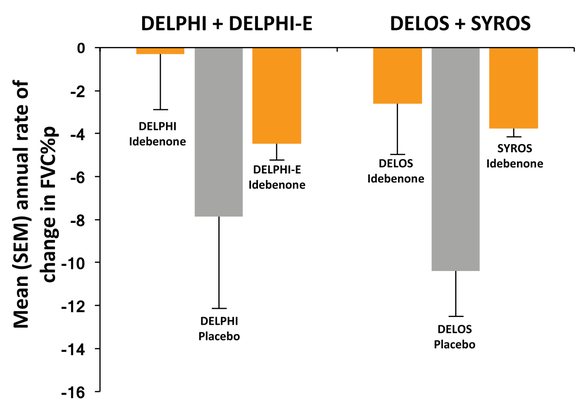

Figure 2. Annual rates of change for FVC%p in idebenone treated (orange) and untreated periods (grey) from DELPHI, DELPHI-E, DELOS and SYROS.

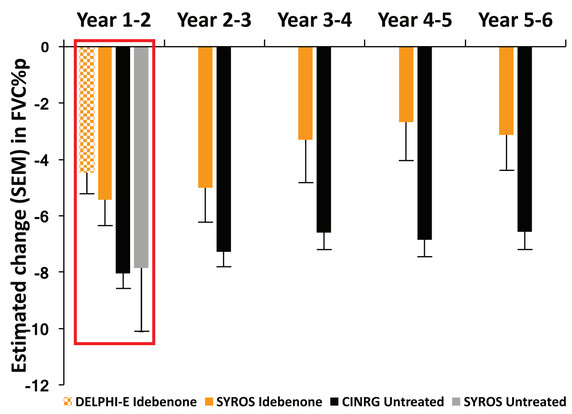

Figure 3. Analysis of annual rate of change for FVC%p by 2-year bins: comparison of periods in the DELPHI-E study (checked) and SYROS study where patients were idebenone treated (orange) or untreated (grey). Annual rate of change in FVC%p from matched patients from the CINRG DNHS (black).

Conclusions**

- Analysis of efficacy from two randomized, placebo-controlled trials and their respective long-term data collections have demonstrated a robust and consistent treatment effect with idebenone in reducing the rate of respiratory function decline.
- Furthermore, a temporal analysis of efficacy has shown sustained treatment benefit year-on-year with idebenone when compared with untreated patients and matched, untreated, external controls from a natural history study for up to 6 years.
- Taken together, these results show that idebenone has the potential to slow long-term respiratory function decline and, thereby, extend the time for patients to reach clinically relevant milestones such as the need for assisted ventilation.

References

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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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**Idebenone has not yet been approved for the treatment of DMD by any national health regulatory agency, including the European Medicines Agency (EMA).

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