Evaluating the effect of long-term idebenone treatment on respiratory morbidity in patients with Duchenne muscular dystrophy (DMD)

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Poster accompanying oral presentation at ERS 28th Sep – 2nd Oct, 2019. Presentation included in session: Rare and ultra-rare diseases and the lungs: updates and new perspectives; 2nd Oct; 19601

Background

- In DMD, progressive muscle weakness leads to sequential loss of function, one of the most serious of which is respiratory function decline.[1] This typically begins while patients can still walk, and accelerates after loss of ambulation, eventually resulting in the need for assisted ventilation.
- Natural history studies have demonstrated that the risk and severity of respiratory morbidity, including hospitalizations due to respiratory causes, increases with declining respiratory function.[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 peak expiratory flow, measured as % predicted (PEF%p) from BL, from -8.84% to -2.57% at week 52 (an absolute difference of 6.27% [p = 0.031]).[3]
- Post hoc analyses of the DELOS trial showed that more patients in the placebo group compared to the idebenone group experienced bronchopulmonary adverse events (BAEs) including airway infections (hazard ratios, calculated "by patient": HR: 0.33, p = 0.0187 and for "all BAEs" HR: 0.28, p = 0.0026, indicated a clear idebenone treatment effect).[4]
- In addition, the number of serious adverse events leading to hospital admissions due to respiratory causes was higher in the placebo group, as was the use of antibiotics typically prescribed to treat bronchopulmonary complications.[4]
- **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).**

Aims

- To evaluate the effect of long-term idebenone treatment on the rate of respiratory function decline, and also in reducing the frequency of, and time taken to reach, respiratory morbidity-associated events in a real-world study.

Methods

- SYROS is a long-term real-world study in 18 former DELOS patients who transitioned to idebenone under Expanded Access Programs (EAPs) following a variable untreated period.

Key inclusion criteria

- Patients had completed the DELOS trial (clinicaltrials.gov ID: NCT01027884).[3]
- Patients had taken idebenone as part of an EAP after DELOS.
- Patients had provided consent and signed a Data Release Agreement.

Collection of long-term data from EAPs

- Patients were managed according to routine clinical practice.
- Data on time to clinically relevant worsening (defined as time to first relative decline of at least 10% in forced vital capacity percent predicted (FVC%p) from BL) was collected. This analysis was conducted by evaluating the time to event during the longest consecutive Off-Idebenone and On-Idebenone periods.
- Data on frequency of BAEs (classified as adverse events that involve the larynx, trachea, bronchi, lower airways or lung),[4] hospitalizations and systemic antibiotic use were also collected.
- Comparisons were made between idebenone-treated and untreated periods.
- Demographics and respiratory function status were comparable between patients of the DELOS and SYROS trial (**Table 1**).

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

	DELOS ITT population N = 64	SYROS ITT population N = 18
Age, years mean (SD) median, (minimum-maximum)	 14.3 (2.7) 14.0, (10.1, 19.0)	 13.3 (2.7) 12.9, (10.1, 18.5)
Prior glucocorticoid use, n (%) Non-user Previous user	 28 (43.8) 36 (56.3)	 7 (38.9) 11 (61.1)
Time since last glucocorticoid use, years n mean (SD) median, (minimum, maximum)	 36 3.7 (2.1) 3.5, (0.9, 8.9)	 11 4.1 (1.9) 4.2, (1.3, 6.9)
Ambulatory Status, n (%) Ambulatory Non-ambulatory	 5 (7.8) 59 (92.2)	 3 (16.7) 15 (83.3)
Age at loss of ambulation, years n mean (SD) median, (minimum, maximum)	 59 9.7 (1.5) 9.5, (7.2, 14.3)	 15 10.0 (1.7) 9.8, (7.8, 12.8)
FVC%p mean (SD) median, (minimum, maximum)	 52.8 (18.1) 53.0, (22.6, 96.4)	 58.7 (17.6) 61.5, (22.6, 96.4)

Results

Efficacy of long-term idebenone treatment on clinically relevant outcomes

- When comparing the annual change in FVC%p for patients on long-term idebenone treatment compared to the preceding Off-Idebenone period (N = 11), idebenone reduced the rate of decline by approximately 50% (-7.4%; 95% CI: -9.1, -5.8 for Off-Idebenone period vs -3.8%; 95% CI: -4.8, -2.8 for On-Idebenone period). This reduction was maintained over a period of up to 6 years (mean of 4 years).
- Time to 10% relative decline from BL in FVC%p is considered an important functional status-related milestone and is used as such an endpoint in other respiratory diseases.[5]
- The median time to the first 10% FVC%p decline during the Off-Idebenone period was 0.63 years compared with 1.72 years during the On-Idebenone period (HR: 0.44), indicating that idebenone treatment prolonged the time to a 10% decline in FVC%p (**Figure 1**).

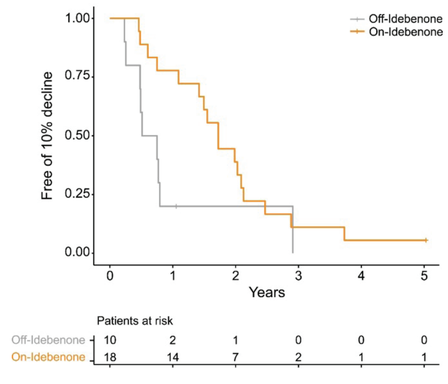

Figure 1. Kaplan-Meier analysis of time to first decline in FVC%p by treatment period. N = 10 for Off-Idebenone periods; N = 18 patients for On-Idebenone periods.

- We next investigated whether long-term treatment with idebenone could also influence the occurrence of BAEs, which constitute clinically relevant complications in patients with DMD.
- During the Off-Idebenone periods, 5 patients (35.7%) reported 9 BAEs, i.e. 0.33 events per person year of follow-up.
- During the On-Idebenone periods, 6 patients (33.3%) reported 8 BAEs, i.e. 0.10 events per person year of follow-up, representing a clear reduction in BAEs under idebenone treatment.
- The cumulative frequency of the BAEs as a function of time (**Figure 2**) demonstrated clearly diverging trajectories for the cumulative occurrence of BAEs between the On-Idebenone and Off-Idebenone treatment periods (HR: 0.32).

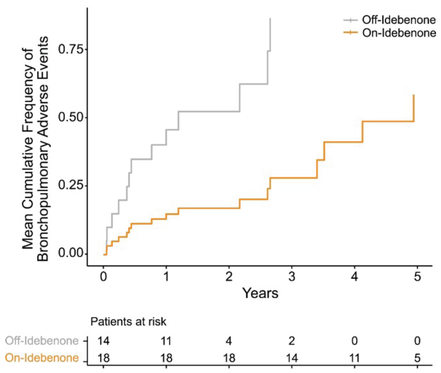

Figure 2. Mean cumulative function estimates (proportional means regression model) for cumulative frequency of BAEs by treatment. N = 14 for Off-Idebenone periods; N = 18 patients for On-Idebenone periods.

- In line with a reduced frequency of BAEs, we also observed that patients during On-Idebenone periods required reduced use of systemic antibiotics. During the Off-Idebenone periods, 3 patients (21.4%) reported 4 events of antibiotic use (i.e. 0.15 events per person year of follow-up), which was higher than systemic antibiotic use reported for On-Idebenone periods with 3 patients (16.7%) reporting 3 events (i.e. 0.04 events per person year of follow-up).
- As previous data from the DELOS trial also showed that idebenone treatment reduced the rate of hospitalizations due to respiratory infections or other respiratory causes when compared to patients receiving placebo,[4] it was of interest to assess the efficacy of idebenone on the risk of hospitalization due to respiratory causes also in the longer term.
- **Table 2** provides a summary of events by category, the event rates per person year and number of patients during the Off-Idebenone and On-Idebenone periods.

Table 2. Reasons for and frequency of hospitalization.

Reason for hospitalization	Off-Idebenone period N = 14			On-Idebenone period N = 18		
	Number of events	Event rate (event/ person year)	N (%)	Number of events	Event rate (event/ person year)	N (%)
Respiratory infection or related disorder	4	0.15	2 (14.3)	5	0.06	5 (27.8)
All hospitalizations	13	0.48	5 (35.7)	24	0.29	12 (66.7)

- The rate of hospitalizations due to respiratory infections or related disorders were smaller for the On-Idebenone periods (0.06 events per person year) compared with Off-Idebenone periods (0.15 events per person year), although interpretation is limited by the small number of events reported.
- Hospitalizations due to any reason were also lower in the On-Idebenone periods compared to the Off-Idebenone periods (0.29 versus 0.48 events per person year).

Conclusion

- In this long-term analysis (up to 6 years), the reduced rate of decline in respiratory function observed in prior studies[3,4,6,7] translated into a smaller number of bronchopulmonary complications and hospitalization for respiratory events, as well as an increased time to experiencing a 10% relative decline in FVC%p and decreased reliance on systemic antibiotics.
  - This is in line with the results of the DELOS trial, that showed fewer patients in the idebenone group compared to the placebo group experienced BAEs and serious adverse events leading to hospital admissions due to respiratory causes.[4]
- Real-world data suggests that maintaining long-term treatment with idebenone continues to slow respiratory function decline, thus reducing the occurrence and severity of clinically-relevant respiratory morbidity.
- These results are an early indication of the long-term benefits of slowing the rate of respiratory function decline, and the disease-modifying potential of idebenone.

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Acknowledgements

DELOS and SYROS Study Groups. All patients and carers who participated in these studies.

Conflict of interest

O.H. Mayer, L. Servais, C. Straathof, U. Schara, T. Voit, E. Mercuri and G. Buyse act as advisors to Santhera Pharmaceuticals (Switzerland) Ltd and have participated in prior/current studies with idebenone in DMD.
G. Buyse is co-inventor of relevant patent applications.
M. Leinonen is an employee of Santhera Pharmaceuticals (Switzerland) Ltd.

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Job number: NP-HQ-DMD-PUL-0016 Date of preparation: August 2019