Long term analysis of the rate of respiratory function decline in patients with Duchenne muscular dystrophy (DMD) in a real-world setting: The SYROS study

Laurent Servais[a,b], Oscar H Mayer[c], Craig McDonald[d] for the CINRG DNHS study group, Chiara Straathof[e], Ulrike Schara[f], Thomas Voit[g], Eugenio Mercuri[h], and Gunnar Buyse[i] for the DELOS and SYROS study groups

[a]MDUK Oxford Neuromuscular Centre, Oxford, UK, [b]Centre de Réfèrence Neuromusculaire, Liège, Belgium, [c]Children's Hospital of Philadelphia (CHOP), Philadelphia, USA, [d]UC Davis Health, Davis, USA, [e]Leiden University Medical Center, Leiden, The Netherlands, [f]University Hospital, Essen, Germany, [g]UCL Great Ormond Street Institute of Child Health, London, UK, [h]Universita Cattolica del Sacro Cuore, Rome, Italy, [i]University Hospitals Leuven, Leuven, Belgium

Poster presented 20th September 2019 at EPNS; Poster Session 11: Neuromuscular; Poster: 138

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 effort.[1-4]
- 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%p) at baseline (BL), and not taking glucocorticoids (GCs), 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]).[5]
- 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).[5-9]
  - Taken idebenone as part of an EAP after DELOS.
  - Provided consent and signed a Data Release Agreement.

Collection of long-term data from EAP

- Patients were managed according to routine clinical practice.
- 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 between 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%p) between Off-Idebenone and On-Idebenone periods.
- Annual rates of change in FVC%p and PEF%p were estimated using random coefficient regression models according to prospectively planned analyses.
- Changes during treatment periods were also compared to a matched (BL FVC%p) external cohort from the CINRG Duchenne Natural History Study (CINRG DNHS).
- 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**).

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)	14.3 (2.7)	13.3 (2.7)
median, (minimum-maximum)	14.0, (10.1, 19.0)	12.9, (10.1, 18.5)
Prior GC use, n (%)		
Non-user	28 (43.8)	7 (38.9)
Previous user	36 (56.3)	11 (61.1)
Time since last GC use, years		
n	36	11
mean (SD)	3.7 (2.1)	4.1 (1.9)
median, (minimum, maximum)	3.5, (0.9, 8.9)	4.2, (1.3, 6.9)
Ambulatory Status, n (%)		
Ambulatory	5 (7.8)	3 (16.7)
Non-ambulatory	59 (92.2)	15 (83.3)
Age at loss of ambulation, years		
n	59	15
mean (SD)	9.7 (1.5)	10.0 (1.7)
median, (minimum, maximum)	9.5, (7.2, 14.3)	9.8, (7.8, 12.8)
FVC%p		
mean (SD)	52.8 (18.1)	58.7 (17.6)
median, (minimum, maximum)	53.0, (22.6, 96.4)	61.5, (22.6, 96.4)
PEF%p		
mean (SD)	53.8 (11.8)	58.5 (10.2)
median, (minimum, maximum)	56.9, (29.1, 79.1)	59.1, (30.1, 77.7)

- The mean idebenone exposure in the EAPs was **4.2 years** (range 2.4 to 6.1) in the ITT population (N = 18).
- In total, the exposure to idebenone treatment was 84 person years, consisting of 8 person years in the DELOS study and 76 person years in the EAPs.

Analysis by treatment periods

- "On-On" 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-On" 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**).

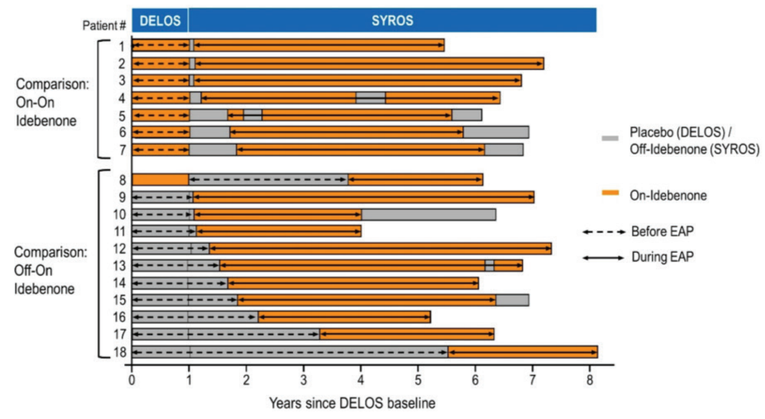

Figure 1. Periods analyzed for annual change in FVC%p (primary efficacy outcome). Treatment periods: On-Idebenone (orange) and Off-Idebenone (grey) over time (years since DELOS BL). Arrows indicate the longest consecutive evaluation period (On or Off) before and during the EAPs.

Results

Treatment with idebenone reduced the long-term annual rate of decline of FVC%p by 50%

- When comparing the annual change in FVC%p 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 PEF%p 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%p rates when comparing Off-Idebenone (**Figure 3A**) and On-Idebenone periods (**Figure 3B**).
- For the "On-On" Idebenone group, the annual rate of decline in FVC%p 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%p, with 1.3% (95% CI: -3.3, 5.8) and -1.3% (95% CI: -3.4, 0.8), respectively (N = 6).

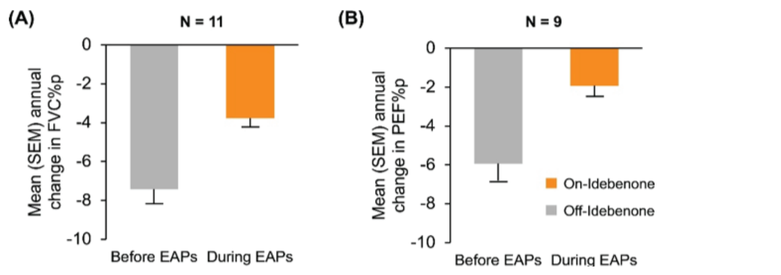

Figure 2. Annual rate of change for FVC%p (A; N = 11) and PEF%p (B; N = 9) between Off-Idebenone and On-Idebenone treatment periods. Data are estimated mean (SEM) from the random coefficient regression model.

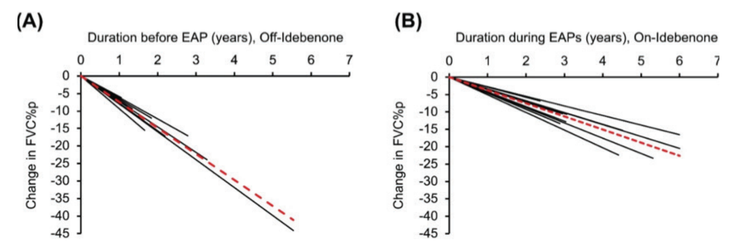

Figure 3. Individual slope estimates from the random coefficient regression model for FVC%p. The individual estimates (along with the mean slope: the red dotted line) are shown for change in FVC%p (A, B) (N = 11). Slopes for the Off-Idebenone periods are shown in (A) and for On-Idebenone periods in (B).

Sustained long-term efficacy, and a 68% reduction in the risk of respiratory complications

- In a secondary analysis, annual rates of FVC%p 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 DNHS and to evaluable 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%p (data not shown).
- The risk of BAEs was reduced by 68% comparing the On-Idebenone periods 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).

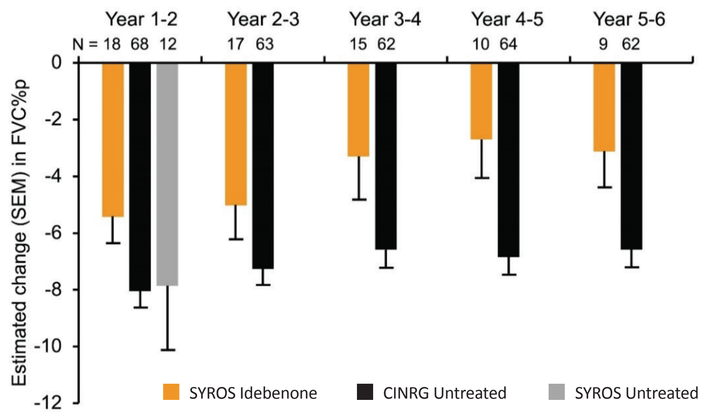

Figure 4. Comparison of annual rates of change in FVC%p for patients during On-Idebenone and Off-Idebenone periods and matched groups of untreated patients. Annual rates of decline are calculated from the longest consecutive On-Idebenone periods of the SYROS/DELOS studies (orange bars). Data from Off-Idebenone periods (SYROS/DELOS) are shown for the first 2-year bin (grey bars). Patients for the untreated natural history (CINRG DNHS) comparator groups (black bars) were matched based on BL FVC%p. Data are estimated means (SEMs) from random coefficient regression models.

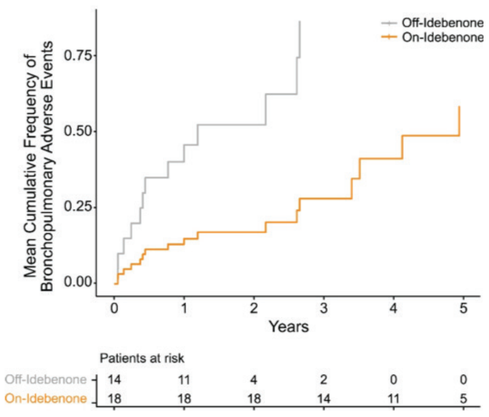

Figure 5. Kaplan-Meier analysis (proportional means regression model) for cumulative frequency of BAEs by treatment.

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%p and PEF%p.
- The slower decline in respiratory function was accompanied by a reduced risk of experiencing patient-relevant outcomes, such as BAEs or hospitalizations due to respiratory causes.
- Taken in combination with previously published results,[5-9] 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

1. Mayer OH, et al. *US Neurology* 2017;13:35-41; 2. Hahn A, et al. *Arch Phys Med Rehabil* 1997;78:1-6; 3. LoMauro A, et al. *Ther Clin Risk Manag* 2015;11:1475-88; 4. Lo Mauro A, et al. *Eur Respir J* 2010;35:1118-25; 5. Buyse GM, et al. *Lancet*, 2015;385:1748-57. 6. Buyse GM, et al. *Pediatr Pulmonol*, 2017; 52:508-515. 7. McDonald CM, et al. *Neuromuscul Disord*, 2016;26:473-80. 8. Mayer OH, et al. *J Neuromuscular Diseases*, 2017;4:189-98; 9. Meier T, et al. *Neuromuscul Disord,* 2017;27:307-14.

Conflict of interest

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

G. Buyse, E. Mercuri, C. McDonald, T. Voit, L. Servais and O.H. Mayer are paid consultants for Santhera Pharmaceuticals (Switzerland) Ltd and/or are investigators in prior/current studies with idebenone in DMD.

Acknowledgements

DELOS, SYROS and CINRG Study Groups.

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

Job number: NP-HQ-DMD-PUL-0007 Date of preparation: September 2019