Long term efficacy: Idebenone reduces the rate of both inspiratory and expiratory functional loss in Duchenne muscular dystrophy (DMD)

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Background

- Forced vital capacity (FVC) measurement is the standard for assessing longitudinal change in respiratory function in DMD.
- Dynamic measures of inspiration such as Inspiratory Flow Reserve (IFR) provide valuable information about the progression of pulmonary involvement.[1]

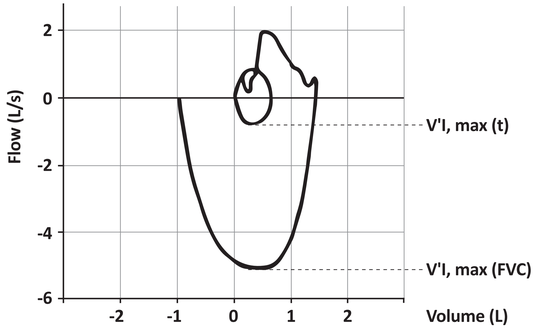

Figure 1. The largest value during tidal breathing (V'I, max (t)) and the largest value of inspiratory flow during the maximum effort maneuver (V'I, max (FVC)) are determined. The inspiratory flow ratio is calculated as V'I, max (t) / V'I, max (FVC) and the Inspiratory Flow Reserve (IFR%) is calculated as 1 - (V'I, max (t) / V'I, max (FVC)) and expressed as percentage. In addition, the difference V'I, max (FVC) - V'I, max (t) can be expressed as absolute IFR (L/S).

- Absolute Inspiratory Flow Reserve (IFR) is calculated as V'I, max (FVC) - V'I, max (t), where V'I, max (t) is the maximum inspiratory flow during tidal breathing and decreases over the course of the disease (**Figure 1**).[1,2]
- Inspiratory Flow Reserve (IFR%) is calculated as 1 - (V'I, max (t) / V'I, max (FVC)) and decreases over the course of the disease (**Figure 1**).[1,2]
- Idebenone is a short chain benzoquinone that restores mitochondrial ATP production and is a powerful catalytic antioxidant[3] that has been shown to preserve respiratory muscle function and slow the rate of respiratory function decline in DMD.
- In the Phase III DELOS trial, DMD patients in respiratory function decline (PEF%p <80% at baseline), not taking glucocorticoids, showed a statistically significant treatment difference of 6.27% for idebenone vs placebo for PEF%p from baseline to week 52.[4]
- IFR% increased by 2.8% (95% CI: -1.3, 6.8) in patients receiving idebenone vs -3.0% (95% CI: -6.8, 0.7) on placebo.[2]
- **Here, we report long-term respiratory function data including IFR 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 long-term evolution of respiratory function, including IFR, during idebenone treatment compared to idebenone-free periods.

SYROS Study

- Patients had taken idebenone as part of an EAP after the DELOS trial (clinicaltrials.gov ID: NCT01027884), signed Data Release Agreement forms and were managed according to routine clinical practice during the EAP.
- Data from DELOS and SYROS were used to evaluate the long-term evolution of respiratory function, including IFR of patients treated with idebenone. Comparisons were made between treated and untreated periods:
  - On-Idebenone: 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 treatment in the EAP.
- Data on bronchopulmonary adverse events and hospitalizations were also collected.
- At DELOS baseline, patients in the SYROS ITT (N = 18) were younger, 13.3 (10.1 – 18.5) vs 14.3 (10.1 – 19.0) in the DELOS ITT cohort (N = 64) but were comparable in other demographic parameters and respiratory function status.[4]
- The mean idebenone exposure during EAPs in the SYROS ITT population (N = 18) was 4.2 years (range 2.4 to 6.1).
- Before the EAPs, the mean duration of follow-up for the 11 patients who were Off-Idebenone was 2.1 years (range 1.1 to 5.5), while mean exposure On-Idebenone was 1.0 years (range 1.0 – 1.0) in 7 patients prior to starting the EAP.
- Of the 18 patients included in SYROS, 6 provided evaluable IFR and V'I, max (FVC) data allowing comparison of changes from Off-Idebenone periods to On-Idebenone treatment periods.
- The mean duration of periods for IFR assessments was 3.3 years (2.0 – 4.5 years) for On-Idebenone, and 1.7 years (1.0 – 3.3 years) for Off-Idebenone.

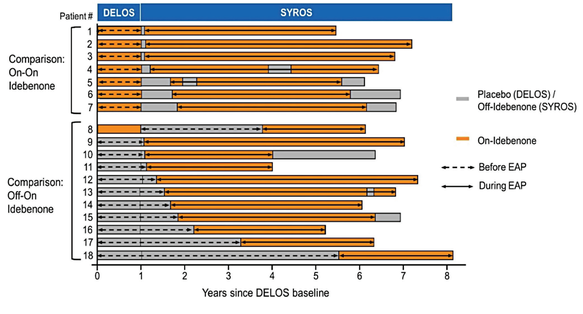

Figure 2. Periods analyzed for annual change in FVC%p (primary efficacy outcome). Treatment periods On-Idebenone (orange) and Off-Idebenone (grey) over time (years since DELOS baseline). Arrows indicate the longest consecutive evaluation period (On or Off) before and during the EAPs.

Results

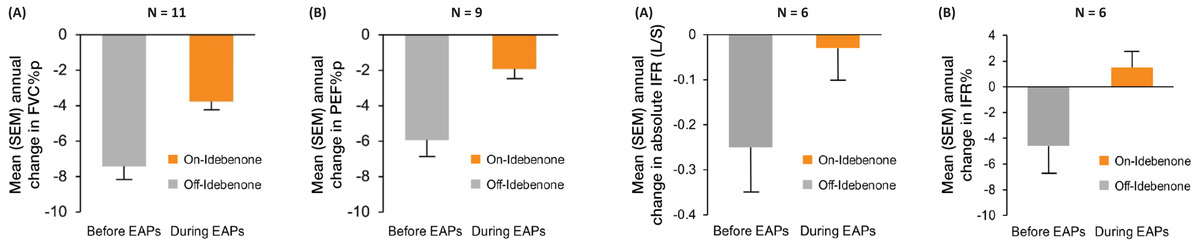

*Figure 3. Annual rate of change for FVC%p (**A**) and PEF%p (**B**) between Off-Idebenone and On-Idebenone treatment periods. Data are estimated mean (SEM) from the random coefficient regression model.*

*Figure 4. Annual rate of change for IFR expressed as absolute IFR (L/S) (**A**) and IFR% (**B**) between Off-Idebenone and On-Idebenone treatment periods. Data are estimated mean (SEM) from the random coefficient regression model.*

Long-term reduction in the annual rate of decline of FVC%p, PEF%p and absolute IFR, and improved IFR%

- Long-term treatment with idebenone resulted in a 50% reduction in the annual rate of change of FVC%p 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 3A**) and from -5.9% (95% CI: -8.0, -3.9) for the Off-Idebenone period to -1.9% (95% CI: -3.2, -0.7) for the On-Idebenone period for PEF%p (**Figure 3B**). Comparable reductions were noted for FEV1 (data not shown).
- The estimated annual rate of change in absolute IFR was reduced from -0.25 L/S (95% CI: -0.50, 0.00) during Off-Idebenone periods to -0.03 L/S (95% CI: -0.21, 0.15) during On-Idebenone periods (**Figure 4A**), and an improvement of IFR% from -4.6% (95% CI: -10.0, 0.9) during Off-Idebenone periods to 1.5% (95% CI: -1.8, 4.8) during On-Idebenone periods was observed (**Figure 4B**).

Reduced risk of respiratory complications and hospitalization due to respiratory causes

- During the SYROS study, the risk of developing bronchopulmonary adverse events was reduced by 68% during the On-Idebenone periods vs Off-Idebenone periods, leading to fewer hospitalizations due to respiratory causes (0.06 vs 0.15 events per person year).

Conclusion

- The SYROS study provides evidence of the long-term reduction in rates of decline for global (FVC), inspiratory (absolute IFR/IFR%) and expiratory (PEF, FEV1) measures of respiratory function over an average of 4 years of treatment and are consistent with observations from the pivotal Phase III DELOS trial.
- Treatment with idebenone over more than 3 years slowed the loss of absolute IFR and improved IFR%, indicating a relative preservation of inspiratory function consistent with effects seen on other respiratory outcome measures.
- Other patient-relevant benefits included a reduction in the risk of bronchopulmonary adverse events and fewer hospitalizations due to respiratory causes.
- 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.

References

1. De Bruin, et al. *Pediatr Pulmonol,* 2001;31:451-57.
2. Buyse GM, et al. *Pediatr Pulmonol,* 2017;52:508-515.
3. Buyse GM, et al. *European Neurological Review,* 2015;10:189-94.
4. Buyse GM, et al. *Lancet,* 2015;385:1748-57.

Acknowledgments

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

Conflict of interest

O.H. Mayer and G. Buyse are paid consultants for Santhera Pharmaceuticals (Switzerland) Ltd and/or are investigators in prior/current studies with idebenone in DMD.
M. Leinonen and S. Hasham are employees of Santhera Pharmaceuticals (Switzerland) Ltd.
G. Buyse is co-inventor of relevant patent applications.

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