Long term efficacy: Idebenone reduces the rate of both inspiratory and expiratory functional loss in 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, 20611

Background

- Forced vital capacity (FVC) measurement is the standard for assessing longitudinal change in respiratory function in DMD.
- Dynamic measures of inspiratory such as Inspiratory Flow Reserve (IFR) provide valuable information about the progression of pulmonary involvement.1
- Inspiratory Flow Reserve (IFR) is calculated as V'I, max (t) / V'I, max (FVC) and the Inspiratory inspiratory flow during the maximum effort maneuver (V'I, max (FVC)) are determined.
- Figure 1. Inspiratory flow ratio is calculated as V'I, max (t) / V'I, max (FVC) and the Inspiratory inspiratory flow during the maximum effort maneuver (V'I, max (FVC)) are determined.
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Aims

- To evaluate the long-term evolution of respiratory function, including IFR, during idebenone treatment compared to idebenone-free periods.
- Patients had taken idebenone as part of an EAP after the DELOS trial (clinicaltrials.gov ID: NCT010277884), 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 status: 1
- 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 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 inspiratory flow during the maximum effort maneuver (V'I, max (FVC)) are determined.

Figure 2. Periods analyzed for annual change in FVC (primary efficacy outcome) of 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

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

- Long term treatment with idebenone resulted in a 50% reduction in the annual rate of decline of FVC from -4.4% (95% CI: -6.5, -2.1) to -2.2% (95% CI: -3.6, -0.8) during On-Idebenone periods vs 3.5% (95% CI: -1.6, 8.5) for the Off-Idebenone period (Figure 3A and Figure 3B). Comparable reductions were noted for PEF1 (2.0 – 4.5 years) for On-Idebenone, and 1.7 years (1.0 – 3.3 years) for Off-idebenone.
- 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.

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 (%s) (A) and IFR% (B) between Off-idebenone and On-idebenone treatment periods. Data are estimated mean (SEM) from the random coefficient regression model.

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.

Acknowledgments

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

References


SYROS Study

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).

Figure 3. Mean (SEM) annual change in FVC (%p) and PEF (%p) ± 1 SEM during On-Adebenone and Off-Idebenone periods. Data are estimated mean (SEM) from the random coefficient regression model.

Figure 4. Mean (SEM) annual change in IFR in On-Idebenone (A) and Off-Idebenone (B).