Effect of Idebenone on Bronchopulmonary Adverse Events and Hospitalizations in Patients with Duchenne Muscular Dystrophy (DMD)

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Background

Duchenne Muscular Dystrophy (DMD) is the most common form of muscular dystrophy, resulting in progressive loss of respiratory muscle strength.[1–3] As a result, patients with DMD are typically at a higher risk for bronchopulmonary adverse events (BAEs).[2,3] These BAEs include upper and lower respiratory tract infections and related complications, where patients often require antibiotics or hospitalization.[4–6]

Idebenone (Raxone®) is in development as a treatment to help manage the respiratory aspects of DMD.[7-10] Idebenone is formulated as an oral tablet and in clinical trials in DMD, is administered as 300 mg three times daily (with meals). Idebenone is a short-chain benzoquinone, capable of stimulating mitochondrial electron flux and cellular energy production, resulting in increased ATP production and decreased reactive oxygen species (ROS).[8]

Objectives

- Evaluate the impact of idebenone on the incidence and duration of BAEs, systemic use of antibiotics and the number and duration of hospitalizations due to respiratory complications in patients with DMD.[9]
- We can achieve this by further, post-hoc analyses of the dataset from the randomized, placebo-controlled Phase 3 trial (DELOS).[8]

Methods

- In the Phase 3, placebo-controlled trial (DELOS), idebenone decreased loss of respiratory function, measured by percent predicted changes in: Peak Expiratory Flow (PEF%p), Forced Vital Capacity (FVC%p) and Forced Expiratory Volume in 1 second (FEV1%p) over 52 weeks in DMD patients aged 10–18 years not using concomitant glucocorticoids (GCs).[8]
- In a post-hoc analysis, we assessed the incidence and duration of BAEs, systemic use of antibiotics and the number and duration of hospitalizations due to respiratory complications.[9]
- Clinically relevant BAEs (evaluated by an independent pulmonologist, in a blinded manner) included: pneumonia, upper respiratory tract infection, respiratory failure, and acute respiratory failure.[9]

Results

- Six patients (19.4%) on idebenone reported 7 BAEs compared with 17 patients (51.5%; p=0.0096) on placebo who reported 28 BAEs **(Table 1)**[9]
- Total duration of these events was 82 days for idebenone compared to 222 days for placebo **(Table 1)**[9]
- Hospitalizations due to respiratory complications were reported for 1 patient on idebenone (duration: 3 days) compared with 4 patients in the placebo group (cumulative duration: 30 days) **(Table 1)**[9]
- The hazard ratio (HR) for the time to first BAE was 0.327 (95% CI: 0.129, 0.830; p=0.0187) in favor of idebenone[9]
- When allowing for multiple BAEs per patient, the HR was 0.281 (95% CI: 0.123, 0.642; p=0.0026) in favor of idebenone **(Figure 1)**[9]
- For systemic antibiotic use, 7 patients (22.6%) reported 8 episodes of antibiotic use for such events for idebenone compared with 13 patients (39.4%) reporting 17 episodes for placebo. The resulting HR for time to first use of antibiotics was 0.52 (95% CI: 0.207, 1.304; p = 0.1631), favoring idebenone **(Table 2)**[9]
- The cumulative frequency of use of antibiotics (allowing for multiple use per patient) resulted in a HR of 0.52 (95% CI: 0.226, 1.217; p = 0.1330), in favor of idebenone **(Table 2 and Figure 2)**[9]

Table 1. Number (%) of patients experiencing bronchopulmonary events (BAEs), including those resulting in hospitalization[9]

Analysis	Idebenone	Placebo
Subjects	6 (19.4%)	17 (51.5%)
Total number of BAEs	7	28
Cumulative days with BAEs	82	222
Subjects hospitalized	1	4
Days in hospital	3	30

Figure 1. Mean cumulative frequency of BAEs[9]

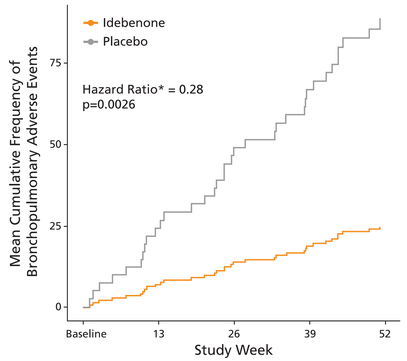

Figure 2. Mean cumulative frequency of antibiotic use[9]

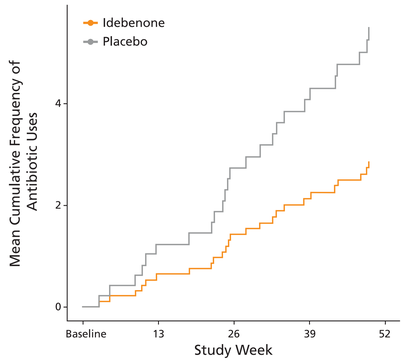

Table 2. Number (%) of patients receiving antibiotics and duration of antibiotic use[9]

Analysis	Idebenone	Placebo
Subjects	7 (22.6%)	13 (39.4%)
Events	8	17
Total days of antibiotic use (d)	65	105

Conclusion

- The results of this post-hoc analysis indicate that the protective effect of idebenone on pulmonary function was associated with reduced incidence of BAEs, reduced need for systemic antibiotic treatment and less hospitalizations in 10-18 year old patients with DMD not using GC.[9]

References

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Acknowledgments

DELOS Study Group

Conflict of interest

O. Mayer, C. McDonald and G. Buyse are paid consultants for Santhera and also participated in prior/current studies with idebenone in DMD.
G Buyse is co-inventor of relevant patent applications
T. Meier and M. Leinonen are employees of Santhera Pharmaceuticals

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