Comparison of home-based versus hospital-based spirometry measurements in Duchenne muscular dystrophy (DMD)

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Background

• Respiratory function decline in Duchenne muscular dystrophy (DMD) is caused by weakening of respiratory muscles and leads to a high disease burden and early mortality.1,2
• Loss of respiratory function starts early in the disease course (usually preceding loss of ambulation), reaching the lower limit of normal (defined as 80% predicted) around 50 years of age.3
• Early detection of respiratory function decline and early intervention may improve clinical outcomes. Recent standard of care guidelines recommend an anticipatory approach in monitoring respiratory function, allowing for timely implementation of supportive strategies.4
• Recent publications have demonstrated that peak expiratory flow, as percent of predicted (PEF%p), starts to decline earlier than forced vital capacity (FVC%Ip) and therefore may be a more sensitive measure of global respiratory function.5,6
• The utility of home-based monitoring of respiratory function with a hand-held device (HHD) was assessed for the first time in the Phase III DELOS study.9

Objectives

• Comparison of the respiratory function measurements of PEF and forced expiratory volume in 1 second (FEV1) using a HHD with those obtained by hospital-based spirometry measures in patients with DMD taking part in the randomized, controlled, Phase III DELOS trial.

Methods

• Respiratory function data were prospectively collected from 64 DMD patients enrolled in DELOS.
• Patients were aged 10–18 years old, and not taking concomitant glucocorticoids. All patients were required to have established respiratory function decline (PEF ≤80%p) at baseline (BL).
• Patients were treated with idebenone (900 mg/day) or placebo.
• Spirometry was conducted during hospital visits at BL and at 3 month intervals thereafter over the 52-week study period.8
• Patients also measured PEF%p and FEV1%p weekly for the first time in the Phase III DELOS study.

Results

• Overall adherence in the weekly use of the HHD was very good, reaching approximately 76% in both treatment groups (Table 1).
• Patients also measured PEF%p and FEV1%p weekly at home using the HHD (type ASMA-1).

Table 1. Adherence with the HHD device.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean compliance (SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idebenone (n = 31)</td>
<td>76.5% (22.0)</td>
</tr>
<tr>
<td>Placebo (n = 33)</td>
<td>75.5% (21.1)</td>
</tr>
<tr>
<td>Total (n = 64)</td>
<td>75.9% (21.5)</td>
</tr>
</tbody>
</table>

*Percentage of weeks treated (treatment compliance). **Weeks in study with at least one home-based measurement.

Home-based respiratory function data is consistent with hospital-based spirometry data

• Home-based respiratory monitoring showed inter-week variability consistent with that seen during hospital-based monitoring.
• Despite this, the trajectories of home-based respiratory data were very similar to in-clinic spirometry results (Figure 1).
• Similar to in-clinic results, weekly HHD data indicated a stabilization of PEF%p in the idebenone group vs. placebo (Figure 1).

Both home- and hospital-based spirometry results confirmed a treatment benefit in favor of idebenone

• Weekly changes in PEF%p measured at home compared well with those from hospital-based measurements, showing a 5.60% (p = 0.0011) overall treatment difference in favor of idebenone across all weekly visits, compared to a 6.27% difference at last visit using standard hospital-based spirometry (p = 0.031) (Table 2).
• Weekly changes in FEV1%p measured at home also compared well with those from hospital-based measurements, showing a 5.46% (p = 0.0046) overall treatment difference in favor of idebenone across all weekly visits, compared to a 6.42% difference at last visit using standard hospital-based spirometry (p = 0.0230) (Table 2).

Table 2. Comparison of weekly PEF%p and FEV1%p data measured by the ASMA-1 HHD as compared to those measured by hospital-based spirometry.

<table>
<thead>
<tr>
<th>Assessment method</th>
<th>Group</th>
<th>PEF%p at BL</th>
<th>Change from BL to week 52 (95% CI)</th>
<th>Treatment difference week 52 (95% CI)</th>
<th>Treatment difference overall (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEF%p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital-based spirometry</td>
<td>Idebenone (n = 31)</td>
<td>53.5 (10.3)</td>
<td>-2.57 (-6.68,1.54)</td>
<td>6.27 (0.61, 11.93)</td>
<td>6.52 (1.98, 11.06)</td>
</tr>
<tr>
<td>Placebo (n = 33)</td>
<td>54.2 (13.2)</td>
<td>-8.84 (-12.73, -4.95)</td>
<td>NA*</td>
<td>NA*</td>
<td>NA*</td>
</tr>
<tr>
<td>Home-based spirometry (all individual weekly measurements)</td>
<td>Idebenone (n = 33)</td>
<td>55.6 (12.6)</td>
<td>NA*</td>
<td>NA*</td>
<td>NA*</td>
</tr>
<tr>
<td>Placebo (n = 31)</td>
<td>52.8 (14.7)</td>
<td>NA*</td>
<td>NA*</td>
<td>NA*</td>
<td>NA*</td>
</tr>
<tr>
<td>Hospital-based spirometry</td>
<td>Idebenone (n = 33)</td>
<td>53.6 (16.1)</td>
<td>-4.23 (-6.82, -0.35)</td>
<td>6.42 (0.92, 11.92)</td>
<td>6.96 (2.90, 11.01)</td>
</tr>
<tr>
<td>Placebo (n = 31)</td>
<td>49.5 (10.6)</td>
<td>-1.65 (-4.14, -0.87)</td>
<td>NA*</td>
<td>NA*</td>
<td>NA*</td>
</tr>
<tr>
<td>Home-based spirometry (all individual weekly measurements)</td>
<td>Idebenone (n = 33)</td>
<td>56.1 (15.2)</td>
<td>NA*</td>
<td>NA*</td>
<td>NA*</td>
</tr>
<tr>
<td>Placebo (n = 31)</td>
<td>49.5 (19.0)</td>
<td>NA*</td>
<td>NA*</td>
<td>NA*</td>
<td>NA*</td>
</tr>
</tbody>
</table>

*Home-based data was only assessed across the entire 52-week study period, as opposed to a change between two timepoints (BL and week 52).

Conclusion

• Loss of respiratory function is a major cause of early morbidity and mortality in patients with DMD.2 Regular assessment of respiratory function is recommended but compliance is generally poor.1,7
• Several recent publications have indicated that PEF%p may be a more sensitive and earlier marker of respiratory function decline compared to FVC%Ip.5,6
• Our results suggest that PEF%p can be reliably assessed with a home-based device, and results were comparable to the hospital-based spirometry in the DELOS Phase III study.
• More frequent home-based monitoring may provide a useful tool for assessing the long-term rate of decline. Its role in detecting acute respiratory exacerbations was not investigated in the DELOS study and should be studied further.

References


Conflict of interest

C. Rummey is a consultant statistician for Santhera Pharmaceuticals.
O.H. Mayer, T. Voit and G. Buyse are paid consultants for Santhera Pharmaceuticals and are investigators in prior/current studies with idebenone in DMD.
G. Buyse is co-inventor of relevant patent applications.
M. Leinonen, S. Hasham and T. Meier are employees of Santhera Pharmaceuticals.

Acknowledgments

DELOS Study Group.

Figure 2. Weekly mixed model of repeated measures estimates compared with hospital-based spirometry results by DELOS treatment group (BL: baseline; SE: standard error.)

Figure 1. Study period.
Assessing idebenone’s impact on respiratory function in Duchenne muscular dystrophy (DMD): Meta-analysis of two clinical trials

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Background

- Respiratory function decline in Duchenne muscular dystrophy (DMD) is caused by weakening of respiratory muscles and leads to a high disease burden and early mortality.1,2
- Loss of respiratory function starts early in the disease course (usually preceding loss of ambulation), reaching the lower limit of normal (defined as 80% predicted) around 10 years of age.3,4
- Glucocorticoid (GC) treatment, the current standard of care, delays the onset of respiratory function decline by around 2 years; however, once established, decline continues at the same rate in GC users and non-users.5
- Secondary mitochondrial dysfunction is believed to be a major contributor to muscle decline in DMD, resulting in poor muscle regeneration,6,7 energetic deficit,8 oxidative damage, increased inflammation9,10 and muscle cell necrosis.11,12
- Idebenone, a synthetic, short chain benzoquinone, supports ATP synthesis, leading to an improved neosynthesis of reactive oxygen species and supporting ATP synthesis, leading to an improved energy balance.13
- The efficacy of idebenone in slowing respiratory function decline in DMD has been investigated in two randomized, placebo-controlled trials: the Phase II DELPHI trial6 and the Phase III DELOS trial.7

Objectives

- The objective of this study was to evaluate the impact of idebenone on respiratory function decline, peak expiratory flow and forced vital capacity, expressed as a percentage of the predicted value (PEF%p and FVC%p, respectively) in patients with DMD, from a pooled analysis of data from the Phase II DELPHI and the Phase III DELOS trials.6

Methods

- DELPHI was an exploratory trial and included patients irrespective of baseline respiratory function and GC use status (Table 1).6
- In DELOS, patients were required to have a baseline PEF për <80% predicted. The interaction with use of GCs was not known and use was therefore not permitted (Table 2).
- For the meta-analysis, DELPHI patients not in the respiratory function decline phase (i.e. patients with baseline PEF%p >80%) were excluded.
- Change in PEF%p and FVC%p from baseline to month 12 was analyzed using a mixed model for repeated measures, with study as a random effect; treatment group, visit and their interaction as fixed factors, and baseline value as a covariate.

Results

- 12 out of 21 patients in DELPHI were in the respiratory decline phase, had a baseline PEF%p ≤80% and were combined with the DELPHI study population (9 patients were not in the respiratory decline phase and were thus excluded). The overall population for this analysis included 76 patients (DELPHI: 12; DELOS: 64, Table 1). A subgroup of 72 patients were not using GCs.

Table 1. Demographic and baseline characteristics of patients from the DELOS trial (all patients) and DELPHI trial (subset of patients in respiratory function decline phase).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DELOS</th>
<th>DELPHI subset with baseline PEF%p ≤80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>13.5 (2.7)</td>
<td>8.0 (2.5)</td>
</tr>
<tr>
<td>Non-ambulatory, n (%)</td>
<td>28 (90.3)</td>
<td>31 (93.3)</td>
</tr>
<tr>
<td>Baseline FVC%p (%), mean (SD)</td>
<td>50.4 ±14.3</td>
<td>50.4 ±14.3</td>
</tr>
<tr>
<td>Baseline FVC%p (%), mean (SD)</td>
<td>59.3 ±15.8</td>
<td>50.4 ±14.0</td>
</tr>
</tbody>
</table>

A consistent treatment benefit was observed in favor of idebenone irrespective of glucocorticoid use

- Across all patients in established respiratory function decline (PEF%p ≤80%) irrespective of their GC status, the treatment difference vs. placebo in PEF%p from baseline to month 12 was 8.0% (p = 0.003) (Figure 2A). When omitting GC users, this difference was 7.7% (p = 0.005) (Figure 2B).
- For FVC%p, the treatment difference was 3.6% (p = 0.046) (Figure 2C) in all patients, with a comparable difference of 3.5% (p = 0.051) when omitting GC users (Figure 2D).

Figure 2. Treatment difference (mean with 95% confidence interval (CI)) in favor of idebenone on PEF%p (A + B) and FVC%p (C + D) in patients in the respiratory function decline phase (baseline PEF%p ≤80%, baseline FVC%p ≤80%).

Conclusion

- Respiratory function decline, and eventual failure, are leading causes of morbidity and mortality in later stages of DMD.1,2
- Recent data published from natural history has shown that GCs delay the onset of reaching the lower limit of normal (≤80%p), but once reached, the rate of decline is similar to those not having used GCs. The DELOS study is the only Phase III study to have shown a statistically significant reduction in the rate of respiratory function decline.7
- This meta-analysis of two randomized trials, the Phase II DELPHI and Phase III DELOS trials, demonstrates a consistent treatment effect in patients in the respiratory function decline stage irrespective of GC status, and further supports the clinical utility of idebenone in slowing the progression of respiratory function decline.

References


Acknowledgments

DELOS and DELPHI Study Groups.

Conflict of Interest

C. Rummy is a consultant statistician for Santhera Pharmaceuticals.
M. Leinonen, T. Meier and S. Hasham are employees of Santhera Pharmaceuticals.
T. Voit, D.H. Mayer and G. Buyse are paid consultants for Santhera Pharmaceuticals and also participated in prior/current studies with idebenone in DMD.
G. Buyse is co-inventor of relevant patent applications.
Phase III DELOS study

The Phase III DELOS study (see patient demographics in Table 1) has previously reported a statistically significant and clinically relevant reduction in the rate of respiratory function decline of 6.27% as measured by PEF%p in patients not taking glucocorticoids (GCs).11

The primary analysis compared the change in PEF%p from baseline to end of study (EOS; week 52).

Secondary analyses were conducted in DMD and forced expiratory volume in 1 second (FEV1%p) over the same time course.

Results

Consistent treatment benefits of idebenone across all respiratory function measures

- All three methods provide consistent evidence for beneficial effects of idebenone, across all primary and secondary respiratory function parameters investigated, confirming the previously observed treatment differences.

Objectives

- To carry out sensitivity analyses of the DELOS trial results using additional, well established statistical models to assess the efficacy of idebenone across three measures of respiratory function: PEF%p, FVC%p and FEV1%p for the 52-week study period.

Methods

- Method 1: Mixed model for repeated measures (MMRM) to estimate treatment difference at EOS only. Treatment group, visit and treatment group by visit interactions were fixed factors, and the baseline was a covariate (Figure 3). This was the pre-specified primary analysis method of the DELOS trial.

- Method 2: MMRM to estimate treatment difference across all post-baseline visits (weeks 13–52) (Figure 3).

- Method 3: A random coefficient regression model (slope analysis) to estimate the rate of decline of all individuals (Figure 3).

Conclusion

- DELOS is the only Phase III study to have shown a statistically significant and clinically relevant reduction in the rate of respiratory function decline in patients not taking GCs.11

- This sensitivity analysis demonstrated the robustness of the treatment effect seen in the primary analysis, and also shows consistent benefit across a range of secondary respiratory function measures.

- These data further support the potential for idebenone to result in clinically meaningful reductions in the rate of respiratory decline.

References


Acknowledgments

DELOS Study Group.

Conflict of interest

O.H. Mayer, T. Voit and G. Buyse are paid consultants for Santhera Pharmaceuticals and are investigators in prior/current studies with idebenone in DMD.

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

M. Leinonen, T. Meier and S. Hasham are employees of Santhera Pharmaceuticals.

C. Rummey is a consultant statistician for Santhera Pharmaceuticals.
Evaluating the effects of baseline variables on the respiratory function benefit of idebenone in Duchenne muscular dystrophy (DMD)

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1Santhera Pharmaceuticals, Pratteln, Switzerland; 2UCL Great Ormond Street Institute of Child Health, London, UK; 3Children’s Hospital of Philadelphia (CHOP), Philadelphia, USA; 4University Hospitals Leuven, Leuven, Belgium

Background

- In Duchenne muscular dystrophy (DMD), progressive weakness of respiratory muscles leads to life-threatening respiratory complications.
- Respiratory function decline becomes linear from around the age of 10. After this point, peak expiratory flow and forced vital capacity, expressed as a percentage of the predicted value (PEF%p and FVC%p), decline by 5–9% on average per year until around the age of 18.
- Glucocorticoid (GC) treatment, the current standard of care, delays the onset of respiratory function decline by around 2 years; however, once established, decline continues at the same rate in GC users and non-users (Figure 1).1

- Mitochondrial dysfunction significantly contributes to muscle decline in DMD, resulting in poor muscle regeneration,10 energetic deficit,11 oxidative damage, increased inflammation12 and muscle cell necrosis.13
- Idebenone is an investigational medication for the treatment of DMD, administered as oral tablets. Idebenone is thought to act on the mitochondria, potentially increasing energy output and decreasing oxidative stress.3,4
- DELOS is a randomized, double-blind, placebo-controlled 52-week study in 64 patients with DMD, aged 10–18 years (Figure 2A). All patients were not taking GCs at baseline (either naïve to GCs or had used previously), and had a baseline PEF%p between 30–80%.6 In this trial, patients received either placebo or idebenone (300 mg/day) (Figure 2B).

Objectives & Methods

- We evaluated the impact of a number of baseline variables on the observed treatment benefit of idebenone on PEF%p.
- The DELOS study is the first and only randomized, Phase III trial to show a statistically significant between-group treatment difference in PEF%p vs. placebo.7 The 6.27% difference observed in favor of idebenone is equivalent to the annual loss reported in several natural history studies8 and represents a clinically relevant reduction in the rate of decline.
- Respiratory failure is one of the main causes of death in late-stage DMD.7

Results

The observed treatment benefit of idebenone on PEF%p was consistent across all subgroups

- We evaluated the impact of a number of baseline variables on the observed treatment benefit of idebenone on PEF%p. In the intention to treat (ITT) efficacy analysis, the between-group difference for PEF%p at week 52 (primary endpoint) was 6.27% (p = 0.031) in favor of idebenone.7 This treatment difference was consistently maintained in all the subgroups studied (Figure 3). No significant interactions between the treatment group and any covariate tested was observed, indicating that none of these baseline characteristics had a significant influence on the treatment difference observed.

Conclusion

- This subgroup analysis demonstrates that there were no significant interactions between the observed treatment difference in the idebenone vs. placebo groups, and the specified baseline characteristics of prior GC use, age, PEF%p, weight, height and ambulatory status.
- The treatment difference between idebenone and placebo was consistent in all subgroups.
- These data further support the efficacy and clinical utility of idebenone in DMD patients not taking GCs and in established respiratory decline, a population for which no other treatment is currently licensed.

References


Conflict of Interest

S. Hasham, M. Leinonen and T. Meier are employees of Santhera Pharmaceuticals. O.H. Mayer, T. Voit and G. Buyse are paid consultants for Santhera Pharmaceutical and are investigators in prior/current studies with idebenone in DMD. G. Buyse is co-inventor of relevant patent applications.

Acknowledgments

DELOS Study Group.
Impact of idebenone on respiratory burden, including risk of bronchopulmonary complications, in Duchenne muscular dystrophy (DMD)

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1Children’s Hospital of Philadelphia (CHOP), Philadelphia, USA; 2Santhera Pharmaceuticals, Pratteln, Switzerland; 3UCL Great Ormond Street Institute of Child Health, London, UK; 4University Hospitals Leuven, Leuven, Belgium

Background

• In Duchenne muscular dystrophy (DMD), progressive muscle weakness leads to sequential loss of function, one of the most serious consequences 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

• Mitochondrial dysfunction in DMD causes a secondary energy deficit, oxidative damage and muscle cell necrosis.3-5

• Idebenone, a synthetic short chain benzoquinone, restores mitochondrial function, leading to decreased oxidative stress and improved ATP synthesis.4,6

• In the Phase III, placebo-controlled DELOS trial, idebenone significantly reduced the rate of respiratory function decline vs. placebo over a 52-week evaluation period.5

Objectives

• To assess if idebenone treatment increases the time to crossing clinically relevant thresholds, thereby reducing the frequency of clinically relevant events.

Methods

• Data from the DELOS trial, which enrolled 64 DMD patients aged 10–18 years, in respiratory decline (defined as peak expiratory flow %p <80%) and not taking concomitant glucocorticoid therapy, were assessed in a number of pre-planned and post-hoc analyses.5

• Clinically relevant thresholds for forced vital capacity, expressed as a percentage of the predicted value (FVC%p) were compiled following a review of standard of care guidelines and expert opinion (Table 1).2,4

• The time to crossing a clinically relevant threshold of FVC%p (≤50%, ≤40%, ≤30% or any of the three thresholds) was analyzed.5

• The frequency of bronchopulmonary adverse events (BAEs) and the rates and duration of hospitalization due to respiratory causes were separately analyzed.6

Results

Idebenone reduced the risk of crossing clinically relevant FVC%p thresholds

• Compared to the placebo group, idebenone-treated patients took longer to fall below the clinically relevant FVC%p threshold of 50% (hazard ratio = 0.34, (95% CI: 0.10–1.18) (Figure 1).

<table>
<thead>
<tr>
<th>FVC%p category</th>
<th>Patient status</th>
<th>Medical recommendation/standard of care</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50%</td>
<td>Moderate pulmonary insufficiency</td>
<td>Special precautions during surgery (e.g., suction surgery); recommended postoperative use of non-invasive ventilation</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>Signs and symptoms of hyperventilation</td>
<td>Volume recruitment; sleep lung inflation techniques; manual and mechanical assisted cough techniques</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>High risk of hyperventilation</td>
<td>Nocturnal ventilation; mandatory postoperative use of non-invasive ventilation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Idebenone (n = 36)</th>
<th>Placebo (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients hospitalized due to respiratory causes</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Events</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

Figure 1. Kaplan-Meier analysis for the time to crossing the 50% FVC%p threshold.

A similar trend was observed for the length of time each treatment group remained above any clinically relevant FVC%p threshold (50, 40 or 30%) (hazard ratio = 0.51, 95% CI: 0.23 – 1.14) (Figure 2).

Figure 2. Kaplan-Meier analysis for the time to crossing the 50%, 40% or 30% FVC%p threshold.

Idebenone reduced the risk of bronchopulmonary adverse events

• The cumulative frequency of all BAEs recorded during the one-year study period showed a lower rate in the idebenone group compared to placebo. (hazard ratio = 0.28, 95% CI: 0.12 – 0.64) (Figure 3).

• A similar trend was observed for the length of time each treatment group remained above any clinically relevant FVC%p threshold (50, 40 or 30%) (hazard ratio = 0.34, 95% CI: 0.10–1.18) (Figure 1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Idebenone (n = 36)</th>
<th>Placebo (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total days hospitalized due to respiratory causes</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

Figure 3. Frequency of bronchopulmonary adverse events (BAEs).

Hospitalizations due to respiratory causes were reduced in patients treated with idebenone

• Patients treated with idebenone required fewer and shorter episodes of hospitalization due to respiratory causes when compared to patients on placebo (Tables 2 & 3).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Idebenone (n = 36)</th>
<th>Placebo (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients hospitalized due to respiratory causes</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Events</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

Conclusion

• As patients cross clinically relevant thresholds of 50%, 40% and 30% FVC%p they are increasingly at risk of hospitalizations due to respiratory causes thus requiring increasingly intensive medical intervention.5

• More patients treated with idebenone remained above clinically relevant thresholds of FVC%p, experienced fewer occurrences of hospitalization due to respiratory causes, and required fewer and shorter episodes of hospitalization.

• These exploratory data further support the efficacy and clinical utility of idebenone in patients not taking glucocorticoids to delay the time to reaching clinically relevant thresholds and reducing the incidence, number and severity of respiratory complications.

References


Acknowledgments

DELOS Study Group.

Conflict of interest

O.H. Mayer, T. Voit and G. Buyse are paid consultants for Santhera Pharmaceuticals and are investigators in prior/current studies with idebenone in DMD.

G. Buyse is co-inventor of relevant patent applications. M. Leinonen, S. Hasham and T. Meier are employees of Santhera Pharmaceuticals.