Comparing Home-Based Respiratory Function Monitoring to Hospital-Based Spirometry in Duchenne Muscular Dystrophy (DMD)

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Poster presented at WSS 2nd - 6th October Poster session: DMD therapeutics II. Poster: P134

Background

- Respiratory function decline in DMD is caused by progressive weakening of respiratory muscles and leads to high respiratory morbidity and early mortality.
- Loss of respiratory function starts early—usually preceding loss of ambulation—and decreases below the lower limit of normal (80% predicted) around 10 years of age.
- Recent publications have demonstrated that peak expiratory flow, as percent of predicted (PEF%p), starts to decline earlier than forced vital capacity (FVC%p) and therefore may be a more sensitive measure of global respiratory function.
- Recent standard of care guidelines recommend increased frequency in monitoring respiratory function following the loss of ambulation, allowing for timely implementation of supportive strategies that could improve clinical outcomes.
- The ability to self-monitor respiratory function accurately and regularly at home could greatly aid in this proactive approach.

The Phase III DELOS study

- The Phase III, placebo-controlled DELOS trial has previously reported a statistically significant and clinically relevant reduction in the rate of respiratory function decline of 6.27%, measured as PEF%p in patients not taking glucocorticoids.
- The utility of home-based monitoring of respiratory function with a hand-held device (HHD) was also assessed for the first time in DELOS patients.

Objectives

- To compare the respiratory function measurements of PEF%p and forced expiratory volume in 1 second (FEV1%p) obtained using a HHD with those obtained by hospital-based spirometry measures in patients with DMD taking part in the 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 lung function already below the lower limit of normal (PEF ≥ 80%) 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.
- Patients also measured PEF%p and FEV1%p weekly at home using the HHD (type ASMA-1, Vitagraph).

Results

DELOS patients were non-ambulatory with limited upper limb mobility and established respiratory function decline.

- The mean age of DELOS participants was 14.3 years.
- At BL, most patients were already facing significant respiratory impairment, with a mean PEF%p of 53.8%.
- A majority (92%) were also non-ambulatory and showed signs of upper limb weakness (50% had a Brooke’s score of 2).

Table 1. Baseline characteristics of the DELOS population by treatment group

<table>
<thead>
<tr>
<th></th>
<th>Idebenone (n = 31)</th>
<th>Placebo (n = 33)</th>
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</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>13.5</td>
<td>15.0</td>
</tr>
<tr>
<td>Previous glucocorticoid use (%)</td>
<td>55</td>
<td>58</td>
</tr>
<tr>
<td>Mean PEF%p</td>
<td>53.5</td>
<td>54.2</td>
</tr>
<tr>
<td>Non-ambulatory (%)</td>
<td>99</td>
<td>94</td>
</tr>
<tr>
<td>Brooke score</td>
<td>5.5</td>
<td>6.6</td>
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</table>

Patients were generally comfortable carrying out home-based assessment of respiratory function.

- During this study a total of 2689 weekly PEF measures were collected.
- Overall adherence to the weekly use of the HHD was very good at 75% overall.
- Adherence was around 80% in the first quarter in both treatment groups, and remained relatively stable at approximately 75% in the idebenone group throughout the study period. In the placebo group, adherence dropped to 71% in Q3 and eventually to 67% in Q4 (Figure 1).

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

- The 52-week changes in PEF%p assessed by the HHD and traditional hospital-based spirometry matched very well.
- There were only 8 patients for whom the change in PEF%p over the study period deviated by > 20% between home and hospital-based data (Figure 2).

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 = 0.002) 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 at home 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 = 0.023) (Table 2).

The assessment method Group (n) PEF%p at BL Change from BL to week 52 (95% CI) Treatment difference week 52 (95% CI) Treatment difference overall (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Idebenone (n = 31)</th>
<th>Placebo (n = 33)</th>
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<tbody>
<tr>
<td>Hospital-based spirometry</td>
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<tr>
<td>PEF%p</td>
<td>53.5 (10.9)</td>
<td>54.2 (13.2)</td>
<td>-2.57 (-6.68, 1.54)</td>
<td>(0.92, 11.92)</td>
<td>6.52 (1.98, 11.06)</td>
<td>p = 0.0056</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td>5.84 (12.7, 4.95)</td>
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<tr>
<td>Home-based spirometry (all individual weekly measurements)</td>
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<tr>
<td>PEF%p</td>
<td>55.6 (12.6)</td>
<td>52.8 (14.7)</td>
<td>NA*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td>NA*</td>
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<td>Hospital-based spirometry</td>
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<tr>
<td>PEF%p</td>
<td>53.6 (16.1)</td>
<td>49.5 (20.6)</td>
<td>2.3 (-8.21, 0.25)</td>
<td>(-8.21, 0.25)</td>
<td>6.42 (0.92, 11.92)</td>
<td>p = 0.0114</td>
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<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td>-10.65 (-14.43, 6.87)</td>
<td></td>
<td>6.96 (2.90, 11.01)</td>
<td>p = 0.0011</td>
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<tr>
<td>Home-based spirometry (all individual weekly measurements)</td>
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</tr>
<tr>
<td>PEF%p</td>
<td>56.1 (15.2)</td>
<td>54.6 (19.0)</td>
<td>NA*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td>NA*</td>
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Discussion

- Regular assessment of respiratory function is recommended for patients with DMD, but compliance is generally poor.
- Several recent publications have indicated that PEF%p may be a more sensitive and earlier marker of respiratory function decline compared to FVC%p.
- Our results demonstrate, for the first time, that PEF%p can be easily and reliably assessed with a home-based device, and results were comparable to the hospital-based spirometry from the DELOS Phase III study.
- Data collected at home confirmed the previously observed treatment benefit seen in DELOS; a relative preservation of PEF%p over the study in patients taking idebenone.
- Several recent publications have indicated that PEF%p is a more sensitive and earlier marker of respiratory function decline.
- More frequent home-based monitoring may provide a useful tool for assessing the long-term rate of respiratory function decline. Its role in detecting acute respiratory exacerbations was not investigated in the DELOS study and should be studied further.

Acknowledgments

DELOS Study Group

Conflict of interest

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

References


Figure 1. Weekly and quarterly adherence to the HMD respiratory function testing during the 52-week study period

Figure 2. Scatterplot for individual patients (n = 64) for change in PEF%p from baseline to week 52 by assessment method
A Phase III Clinical Study Assessing the Efficacy and Safety of Idebenone in Patients with Duchenne Muscular Dystrophy (DMD) taking Concomitant Glucocorticoids (SIDEROS)

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1Santhera Pharmaceuticals, Pratteln, Switzerland; 2Clinical Data Science GmbH, Basel, Switzerland; 3UCI, National Hospital for Neurology and Neurosurgery, London, UK; 4UOC Neuropsychiatria Infantile, Rome, Italy; 5Children’s Hospital of Philadelphia (CHOP), Philadelphia, US; 6University Hospitals Leuven, Leuven, Belgium, for the SIDEROS Study Group

Poster presented at WMS 2nd - 6th October. Poster session: DMD therapies I. Poster: P.122

Background
• Respiratory function decline in DMD is caused by progressive weakening of respiratory muscles, and leads to a high disease burden and early mortality.1-3
• Secondary mitochondrial dysfunction is believed to be a major contributor to muscle decline, resulting in poor muscle regeneration,4-6 energetic deficit,7,8 oxidative damage, increased inflammation9,10 and muscle cell necrosis.11,12
• Idebenone, a synthetic short chain benzoquinone, restores mitochondrial function by reducing the neosynthesis of reactive oxygen species and recovering ATP synthesis, leading to an improved cellular energy balance.13

As part of an extensive clinical development program, Santhera Pharmaceuticals is developing idebenone as a potential treatment for respiratory function decline in patients with DMD (Figure 1).

In the Phase III, 52-week, randomized, placebo-controlled DELOS trial, the effects of oral idebenone tablets (900 mg/day) on respiratory function were investigated in DMD patients aged 10 – 18 years who were not taking concomitant glucocorticoids (GCs).

Results showed that idebenone significantly slowed the rate of respiratory function decline, as demonstrated by a statistically significant difference of 6.27% compared to placebo in peak expiratory flow, expressed as percent predicted (PEF%) in addition to benefits seen on other respiratory outcome measures.14

SIDEROS – Design and objectives

• SIDEROS is a Phase III, randomized, placebo-controlled study investigating the safety and efficacy of idebenone in 266 DMD patients taking GCs (Figure 2) in over 60 centers in the US (23), EU (37) and Israel (1) (Figure 3).

• Patients are randomized (1:1) to receive either idebenone (900 mg/day) or placebo taken 3 times daily, with meals. The treatment duration is 78 weeks. Patients who complete SIDEROS can participate in an open label extension study where all participants receive idebenone.

• SIDEROS is one of only a few trials available for non-ambulatory patients with DMD.

Key inclusion criteria are:
• Documented diagnosis of DMD (severe dystrophinopathy)
• Forced vital capacity, as percent of predicted (FVC%p), ≤ 80% and > 35%
• Minimum of 10 years old at screening
• Chronic use of systemic GCs (prednisone or deflazacort) for DMD related conditions continuously for at least 12 months prior to baseline (BL) and without any dose adjustments in last 6 months
• Ability to provide reliable and reproducible repeat PEF results within 15% of the screening assessment at BL
• Immunized with pneumococcal polysaccharide vaccine, as well as yearly immunized with inactivated influenza vaccine
• Ambulatory and mutational status are not inclusion criteria for this study

Key endpoints include:
• Primary endpoint: change from BL to Week 78 in FVC%p, assessed by clinic-based spirometry measurements
• Other assessments include peak expiratory flow (PEF), forced expiratory volume in 1 second (FEV1), peak cough flow (PCF), inspiratory flow rate (IFR), blood oxygen saturation levels, end-tidal CO2 readings, occurrence of bronchopulmonary adverse events, use of systemic antibiotics and hospitalizations due to respiratory causes

IDEBONE is being studied as part of an extensive clinical development program

Figure 1. Overview of the clinical development program of idebenone. DELPHI-E: DELPHI Extension; SIDEROS- E: SIDEROS Extension

SIDEROS - A Phase III double-blind study with idebenone in patients with DMD taking GCs

(A)

≥ 265 patients using GCs

1:1

B)

Population DMD patients ≥ 10 years in respiratory function decline (FVC%p ≤ 80% and > 35%)

Study design Interventional, placebo-controlled, Phase III RCT

Treatments Parallel group assignment to idebenone 300 mg orally 3 times daily or placebo

Treatment duration 78 weeks

Key endpoint Change from BL in FVC%p at Week 78

Status Recruiting

60 clinical trial sites currently recruiting

10 EU countries

1 non-eu country

18 states across US

Acknowledgments

5. Hasham and R. Drake are employees of Santhera Pharmaceuticals. C. Rummey is a consultant statistician for Santhera Pharmaceuticals.
6. R. Quinilvan, E. Mercuri, O.H. Mayer and G. Buysse are paid consultants for Santhera and are investigators in prior/current studies with idebenone in DMD
7. G. Buysse is co-inventor of relevant patent applications

SIDEROS Study Group

For more information, please see www.siderosdmd.com or www.clinicaltrials.gov posting (NCT02814019).

Santhera Pharmaceuticals is the sponsor of the SIDEROS study

References
Duchenne muscular dystrophy (DMD) is characterized by muscle weakness, wasting, and degeneration starting in early childhood.[1,2] DMD is caused by a mutation in the dystrophin gene that leads to an absence of functional dystrophin protein.[3] In the United States, the estimated prevalence of DMD is approximately 1.02 per 10,000 male persons, though as it is a rare disease, it may be underestimated.[4]

The associated muscle weakening leads to increased disability, with initial symptoms presenting as difficulty walking, climbing stairs, and frequently falling.[5] DMD is incurable, and treatment is limited to supportive measures. Children with DMD will typically utilize corticosteroids, as these have found to slow disease progression, and other support devices such as wheelchairs, ventilators, and cough assist devices.[6,8] The real-world healthcare utilization of this condition is not well represented in the literature, and inclusion criteria for DMD patients often differs, and sample sizes remain small.[2,6]

Further, a previous cost of illness study obtained data via patient survey, which is less accurate than administrative claims.[7] This study aims to describe the healthcare resource use (HCRU) of male patients in the commercial insurance and Medicaid populations, using a large administrative claims database.

### Methods

#### Study Sample
- As a specific International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) for DMD is not available, the code 359.1 (hereditary progressive muscular dystrophy (HPMD)) was used.
- Patients were required to have at least two diagnoses for hereditary progressive muscular dystrophy (ICD-9-CM: 359.1) between 9/30/2011-9/30/2014, the diagnoses within 18 months of each other.

#### Study Design
- A retrospective, observational cohort design was used to describe male patients presumed to have DMD that were identified in an administrative claims database.
- Patients were stratified based on age at first captured diagnosis of DMD during the study period, into mutually exclusive categories of males aged 6-10, 11-14, 15-18, and 19-25 years.
- Clinical characteristics, treatment patterns, and healthcare utilization were assessed in the 12 months following the diagnosis date.
- A control cohort was established of healthy male patients of the same ages with commercial or Medicare insurance without a claim for DMD between 9/30/2011-9/30/2015, who have at least 12 months of continuous enrollment.

#### Data Sources
- This study utilized two distinct U.S. insurance claims data from the MarketScan® Commercial Claims and Encounters Database and the MarketScan® Multi-State Medicaid databases (IBM Watson Health, Ann Arbor, MI).

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### Results

#### Table 1. Clinical Characteristics, Commercial Cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cohort A</th>
<th>Cohort B</th>
<th>Cohort C</th>
<th>Cohort D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractures (%)</td>
<td>31 (15.2)</td>
<td>37 (19.7)</td>
<td>32 (17.1)</td>
<td>27 (18.1)</td>
</tr>
<tr>
<td>Sleep issues (%)</td>
<td>31 (15.2)</td>
<td>29 (15.8)</td>
<td>26 (14.1)</td>
<td>21 (14.8)</td>
</tr>
<tr>
<td>Arthritis (%)</td>
<td>33 (16.8)</td>
<td>32 (17.1)</td>
<td>30 (16.7)</td>
<td>25 (17.8)</td>
</tr>
<tr>
<td>Cough (%)</td>
<td>34 (17.4)</td>
<td>30 (16.1)</td>
<td>28 (15.3)</td>
<td>22 (15.4)</td>
</tr>
<tr>
<td>Oxygen (%)</td>
<td>10 (5.2)</td>
<td>12 (6.5)</td>
<td>10 (5.5)</td>
<td>8 (5.6)</td>
</tr>
<tr>
<td>Ventilation (%)</td>
<td>20 (10.3)</td>
<td>16 (8.6)</td>
<td>15 (8.3)</td>
<td>12 (8.4)</td>
</tr>
</tbody>
</table>

#### Table 2. Utilization and Expenditure, Commercial and Medicaid Cohorts

<table>
<thead>
<tr>
<th>Utilization Measures</th>
<th>Cohort A</th>
<th>Cohort B</th>
<th>Cohort C</th>
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<tbody>
<tr>
<td>Emergency room visits</td>
<td>37 (18.6)</td>
<td>33 (17.9)</td>
<td>30 (16.7)</td>
<td>25 (17.8)</td>
</tr>
<tr>
<td>Average visits per person, mean (SD)</td>
<td>18.6 (9.8)</td>
<td>18.6 (9.8)</td>
<td>18.6 (9.8)</td>
<td>18.6 (9.8)</td>
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<tr>
<td>Physician office visits</td>
<td>200 (67.5)</td>
<td>200 (67.5)</td>
<td>200 (67.5)</td>
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</tr>
</tbody>
</table>

#### Conclusion

DMD results in significant burden to patients with DMD; based on this claims analysis, patients presumed to have DMD had higher annual HCRU costs when compared with non-DMD age-matched cohort.

#### References


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### Conflict of interest

Oscar Henry Mayer is a paid consultant for Santhera Pharmaceuticals and is an investigator in prior/current studies with idebenone in DMD. John Karafilitidis was an employee of Santhera Pharmaceuticals. Brian Griffin and Kate Higgins are employees of IBM Watson Health; this claims initiative performed by IBM Watson Health was funded by Santhera Pharmaceuticals.