2 SYNOPSIS

Name of Sponsor: Santhera Pharmaceuticals (Switzerland) Ltd.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Idebenone	Volume:	
Name of Active Ingredient: Idebenone	Page:	

Study Title: A Phase III double-blind, randomised, placebo-controlled study of the efficacy, safety and tolerability of idebenone in 10 – 18 year old patients with Duchenne Muscular Dystrophy			
Trial Acronym: DELOS			
ClinicalTrials.gov Identifier: NCT01027884			
Eudract No.:	2009-012037-30	**US IND No.:**	103801
Investigator(s) and Study Centre(s): A total of 23 centers in 10 countries (Belgium, Germany, The Netherlands, Switzerland, France, Sweden, Austria, United States, Italy and Spain) participated in this study. Seventeen centers in 10 countries enrolled patients.			
Publication (reference):	Not applicable		
Study Period: 27 July 2009 (first subject screened) to 14 January 2014 (last subject completed)			

Phase of Development: III

Objectives:

Primary

- To assess the efficacy of idebenone, compared to placebo, in improving respiratory function or delaying the loss of respiratory function in patients with Duchenne Muscular Dystrophy (DMD)

Secondary

- To assess the efficacy of idebenone, compared to placebo, in improving respiratory function or delaying the loss of respiratory function using measures other than those used for the primary endpoint
- To assess the efficacy of idebenone, compared to placebo, in improving skeletal muscle strength/ motor function or delaying the loss of skeletal muscle strength/ motor function
- To assess the efficacy of idebenone, compared to placebo, in improving quality of life or delaying the loss in quality of life
- To assess the safety and tolerability of idebenone in patients with DMD

Tertiary

- To assess the effect of idebenone on biochemical markers reflecting cardiac overload or cardiac degeneration
- To assess the efficacy of idebenone on exploratory respiratory parameters

Methodology:

The study was a randomized, double-blind, placebo-controlled, multicenter, parallel group study in patients aged 10 to 18 years with DMD. A group sequential design was used in this study. Initially only glucocorticoid non-users were to be randomized into the study. Glucocorticoid users might have been randomized into the study depending on a decision to open enrolment to the "glucocorticoid users" subgroup following the final analysis of randomized "glucocorticoid non-user" subgroup. However, the study protocol was amended and the study was terminated after completion of the analysis of the "glucocorticoid non-user" subgroup. Only information related to the glucocorticoid non-user subgroup is included in this report.

Patients were treated as out-patients. They were randomized in a 1:1 ratio to treatment with either idebenone 900 mg/day or placebo for a period of 52 weeks. Their participation in the study lasted approximately 15 months (17 months allowing for visit windows): 6-8 weeks for the screening phase, 52 weeks for the treatment period and a 4-week follow-up phase. The patient made weekly respiratory assessments at home throughout the screening and treatment phases.

The study included up to 8 visits. A Screening Visit took place 6 to 8 weeks prior to randomization. Eligible patients were randomized to study treatment at Visit 1/Baseline. Groups were balanced for percent predicted peak expiratory flow (PEF; <40% and 40-80%). Patients were assessed after 4 weeks (Visit 2), 13 weeks (Visit 3), 26 weeks (Visit 4), 39 weeks (Visit 5) and 52 weeks (Visit 6; end of study treatment). Eligible patients were randomized to study treatment. A follow-up visit (Visit 7) took place 4 weeks after Visit 6 or

after premature discontinuation of study medication.

Number of Subjects (Planned and Analyzed):

Planned: 60 not using glucocorticoids to achieve a minimum of 30 evaluable not using glucocorticoids.

Screened: 96

Enrolled: 67 with 65 randomized and 2 allocated treatment (idebenone: 32; placebo: 35); one randomized patient was not treated with study medication.

Safety population: 66 (idebenone: 32; placebo: 34)

Intent-to-Treat (ITT) population: 64 (idebenone: 31; placebo: 33)

Modified ITT (mITT) population: 57 (idebenone: 30; placebo: 27)

Diagnosis and Main Criteria for Inclusion:

Patients aged 10 to 18 years with a diagnosis of DMD or severe dystrophinopathy and clinical features consistent of typical DMD at diagnosis (i.e., documented delayed motor skills and muscle weakness by age 5 years) who were able to provide reliable and reproducible repeat PEF measurements (within 15% of the first assessment, i.e. Baseline vs. Screening) and able and willing to comply with the requirements of the study were eligible for inclusion. Patients dependent on assisted ventilation or with DMD-related hypoventilation for which assisted ventilation was needed, those with a percent predicted PEF (PEF%p) >80% at Baseline, or the presence of other non-DMD respiratory illness that affect PEF or symptomatic heart failure and/or symptomatic ventricular arrhythmias were excluded. No previous use of idebenone was permitted or use of coenzyme Q10 or vitamin E (if taken at a dose of 5 times above the daily physiological requirement) within 30 days prior to Baseline. To comply with the definition of “glucocorticoid non-user”, the following was not permitted: chronic use of systemic glucocorticoid therapy for DMD related conditions within 12 months of Baseline, more than 2 rounds of acute systemic glucocorticoid burst therapy (of ≤2 weeks duration) for non-DMD related conditions within the 12 months prior to Baseline, use of any round of systemic glucocorticoid burst therapy of longer than 2 weeks duration within the 12 months prior to Baseline, and use of systemic glucocorticoid burst therapy less than 8 weeks prior to Baseline.

Test Product, Dose and Mode of Administration, Batch Number:

Idebenone was formulated as film-coated 150 mg tablets. Patients took 2 x 150 mg tablets orally 3 times daily with meals (total dose 900 mg daily).

Packaging batch number: 204574/1 (drug product batch number 0609B005) Expiry Date: 03/2011

Packaging batch number: 202367/2 (drug product batch number 0917B013) Expiry Date: 05/2014

Packaging batch number: 202367/3 (drug product batch number 0836B001) Expiry Date: 09/2013

Packaging batch number: 202367/4 (drug product batch number 0929B014) Expiry Date: 07/2014

Duration of Treatment:

52 weeks

Reference Therapy, Dose and Mode of Administration, Batch Number:

Placebo tables were identical in appearance to idebenone tablets. Patients took 2 tablets orally 3 times daily with meals.

Packaging batch number: 204574/1 (drug product batch number 0639B007) Expiry Date: 10/2011

Packaging batch number: 202367/2 (drug product batch number 0639B007) Expiry Date: 10/2011

Packaging batch number: 202367/3 (drug product batch number 1031B002) Expiry Date: 08/2015

Packaging batch number: 202367/4 (drug product batch number 1031B002) Expiry Date: 08/2015

Criteria for Evaluation:

Efficacy:

The following efficacy assessments were made:

- Pulmonary Function Tests at Screening and Baseline and Weeks 13, 26, 39, and 52
  - PEF measured by spirometry measured and by the ASMA-1 device at hospital visits
  - Forced vital capacity (FVC)
  - Peak cough flow (PCF)
  - Maximum expiratory pressure (MEP) and maximum inspiratory pressure (MIP)
  - Inspiratory flow reserve (IFR)
  - PEF and forced expiratory volume in 1 second (FEV_1) measurements made by the patient at home once per week using the ASMA-1 device
- Upper and lower extremity myometry at Baseline and Screening and Weeks 13, 26, 39, and 52
- Motor function using the Brooke Upper Extremity Scale and the Vignos Lower Extremity Scale at Baseline and Screening and Weeks 13, 26, 39, and 52
- Change in health-related quality of life (HRQOL) as measured by the PedsQL™ Paediatric Quality of Life Inventory at Baseline and Weeks 13, 26, 39, and 52.
- Change in fatigue as measured by the PedsQL™ Multidimensional Fatigue Scale at Baseline and Weeks 13, 26, 39, and 52.
- Clinical Global Impression of Efficacy and Tolerability
- Satisfaction with treatment
- Number of patients needing assisted ventilation, requiring acute hospitalization for complications associated with disease progression, requiring initiation of the use of a brace or spinal jacket, and number starting, stopping or changing glucocorticoid treatment.
- Cardiac biomarkers (brain natriuretic peptide [pro-BNP] and cardiac troponin-I [cTnI] at Screening/Baseline and Weeks 13, 26, 39, and 52.

Safety:

Safety was assessed at every visit by evaluation of adverse events (AEs), physical examination, vital signs, clinical laboratory evaluation of hematological and biochemical parameters (blood and urine samples). Electrocardiograms (ECGs) and transthoracic echocardiography were performed at Screening or Baseline, Week 26 and Week 52.

Statistical Methods:

The sample size was calculated based on the results of the Phase II double-blind, randomized, placebo-control study, SNT-II-001 (DELPHI trial). The study was primarily powered for comparison of idebenone versus placebo in the total randomized cohort in PEF%p at Week 52. However, it was expected that there would be a significant interaction between the treatment effect and use of glucocorticoids. In the subset of randomized patients not using glucocorticoids the effect size was expected to be 15% (SD=14%) in accordance with pilot data from a Phase II study (DELPHI). With 15 patients per group, a power of 80% would be achieved.

It was initially planned to randomize 34 glucocorticoid non-using DMD patients to ensure 30 provided Month 12 data. However, as the PEF testing scheme was changed in Amendment 3 and since it was not expected that pre- and post-Amendment 3 data would be comparable, the sample size was increased to allow the randomization of 40 post-Amendment 3 glucocorticoid non-using patients. Following a blinded analysis it was found that the variability in the data from the glucocorticoid non-using patients randomized pre- and post-Amendment 3 was very similar. This allowed pre- and post-Amendment 3 data to be combined and analyzed in the planned futility analysis. Based on Week 24 and Week 52 data from 34 patients randomized pre-Amendment 3 and Week 24 data from 11 patients randomized post-Amendment 3 it was estimated the study would have 80% power to detect a difference of 10.3% in the subset of glucocorticoid non-using patients.

Based on a futility analysis the Data and Safety Monitoring Board (DSMB) recommended that the study be continued as planned. Thereafter the decision was made to limit the study population to glucocorticoid non-users and the protocol was amended accordingly.

Four populations were defined for this study: the safety population, the ITT population, the mITT population, and the Per-Protocol (PP) population. The safety population included all patients who received at least one dose of the study medication. Patients were analyzed according to the treatment actually received. The ITT population included all randomized patients (excluded siblings who were allocated to treatment assignment rather than randomized) who received at least one dose of the study medication and had at least one post-Baseline assessment of PEF. Patients were analyzed as randomized. The mITT population was the same as the ITT population excluding 7 patients prior to unblinding. The PP population included all patients from the ITT population who completed the study and who had no major protocol deviation.

For the primary efficacy endpoint, the change from Baseline to Week 52 in PEF%p, the estimated treatment difference between idebenone and placebo was calculated using a Mixed Model for Repeated Measurements (MMRM). All available PEF data from all post-Baseline visits were used as response variables in the model.

The treatment group, visit and the interaction between the treatment group and visit were used as fixed factors in the model and the Baseline assessment as a covariate. The difference between idebenone and placebo at Week 52 was estimated based on the MMRM model using contrasts. The unstructured covariance structure was used for the estimation.

Most secondary respiratory function endpoints and muscle strength/muscle function endpoints were also analyzed using MMRM if appropriate. The annual rate of change in percent predicted using data from home-based assessments using the ASMA-1 device was calculated by fitting an individual linear regression line for each patient for the time of the study, i.e. an intercept and slope was estimated for each patient. The slopes were then analyzed using the ANCOVA method with treatment as factor and the calculated intercept value used as a covariate. For responder analyses, responder rates were compared between the treatment groups using the Cochran-Mantel-Haenszel test.

Clinical Global Impression of Efficacy and Tolerability and satisfaction with treatment variables were categorized and the categories were compared between treatments using the Cochran-Mantel-Haenszel test. For event counts, the number of patients for each count were compared between idebenone and placebo using the Cochran-Mantel-Haenszel test. Cardiac biomarkers were analyzed using MMRM as described for the primary endpoint.

Summary of Results:

Efficacy:

For the primary endpoint of the study, the change from Baseline to Week 52 in PEF%p analyzed using the mITT population, at Baseline, the mean PEF%p was similar for idebenone and placebo (53.1% and 54.3%, respectively). In the placebo group PEF%p declined statistically significantly between Baseline and Week 52 by an estimated mean of 9.01% compared to a non-significant decline in the idebenone group of 3.05%, resulting in a 66% relative difference. The estimated difference between treatments of 5.96% (95% CI: 0.16, 11.76) was statistically significant in favor of idebenone (p=0.0443) at Week 52 as well as at other time points. Similar results were seen for this endpoint analyzed using the ITT Population. In the placebo group PEF%p declined statistically significantly between Baseline and Week 52 by 8.84% compared to a non-significant decline in the idebenone group of 2.57%, resulting in a 71% relative difference. The estimated difference between treatments of 6.27% (95% CI: 0.61, 11.93) was statistically significant in favor of idebenone (p=0.0306). Since results for the ITT population were similar to those for the mITT population, all further efficacy analyses were primarily presented using the ITT population (mITT analyses were also performed and presented in post-text tables).

Results for absolute PEF supported those observed for PEF%p. At Week 52 the estimated difference between treatments was 28.09 L/min (95% CI: 2.69, 53.50) and was statistically significant in favor of idebenone (p=0.0308).

Secondary and tertiary measures of respiratory function generally supported the result of the primary endpoint. For the annual rate of change in PEF%p, assessed by home-based pulmonary function test using the ASMA-1 device, in the placebo group PEF%p declined statistically significant between baseline and Week 52 by 9.32% compared to a non-significant decline in the idebenone group of 2.48%. The estimated difference between treatments of 6.84% (95% CI: -0.15, 13.83; p=0.0548). At Week 52, the estimated mean differences in percent predicted FVC (FVC%p; 3.27%; 95% CI: -0.43, 6.97; p=0.0819) and absolute FVC (0.13 L 95% CI: -0.00, 0.27; p=0.0503) both showed a trend in favor or idebenone. Significant differences between treatments in favor of idebenone were observed for all other time points for both parameters. Significant differences in favor of idebenone were seen at Week 52 for both percent predicted FEV_1 (FEV_1%p; p=0.0292) and absolute FEV_1 (p=0.0124). For FEV_1%p, the estimated mean difference was 8.29% (95% CI: 0.88, 15.70) and for FEV_1 the estimated difference between treatments was 0.33 L (95% CI: 0.07, 0.58). For PEF, FVC and FEV_1, either assessed as percent predicted or as absolute values, the proportion of patients not worsening was higher for idebenone than for placebo for each parameter. There was no difference between idebenone and placebo for effects on PCF. IFR results were generally similar to those observed at Baseline at all time points.

Idebenone treatment effects observed with continuous variables were supported by responder analyses counting the number of patients falling below clinically relevant thresholds for FVC (1 L) and PCF (160 L/min). Although the study was not formally powered to detect differences, there were fewer patients in

the idebenone group than in the placebo group falling below these thresholds.

There was no apparent effect of idebenone treatment compared with placebo on maximum mouth pressures measured by MEP and MIP. At Week 52, the estimated difference between treatments for percent predicted MEP was 1.22% (95% CI: -2.41, 4.85) and for MEP was 1.87 cm H_2O (95% CI: -3.59, 7.34). The estimated difference between treatments for percent predicted MIP was -1.89% (95% CI: -7.16, 3.37) and for MIP was -1.73 cm H_2O (95% CI: -7.53, 4.07).

Similarly no effects on upper limb muscle strength as measured by HHM or muscle function, assessed using the Brooke Upper Limb Extremity Scale were observed. Since 92% of patients were non-ambulatory, lower limb muscle strength and function were not assessed.

There was a trend for fewer respiratory tract infections in patients treated with idebenone compared with placebo. There were 14 patients in the idebenone group and 23 patients in the placebo group who reported respiratory tract infections (p=0.076). More patients reported infections of the upper respiratory tract in the placebo group (20 patients) than in the idebenone group (11 patients) and this difference approached statistical significance (p=0.051). The hazard ratio for experiencing AEs classified as upper respiratory tract infections, calculated using a Cox Proportional Hazards model, favored idebenone over placebo (Hazard Ratio 0.41; 95% CI: 0.19-0.91; p=0.028).

No beneficial effects of idebenone on quality of life as measured by the PedsQL™ Quality of Life Inventory was observed. At Week 52, there was no significant difference between treatments for either child/teen reports or parent reports.

Similarly, no beneficial effects of idebenone on fatigue as measured by the PedsQL™ Multidimensional Fatigue scale were observed; the estimated mean difference between treatments in Total Score was in favor of placebo. Based on child/teen reports it was -6.76 (95% CI: -11.8, -1.70; p=0.0097) and based on parent reports was -6.14 (95% CI: -12.8, 0.56 p=0.0719).

There were no significant differences between treatments in the Clinical Impression of Efficacy and Tolerability or in satisfaction with treatment.

There were no significant differences between treatments in cardiac biomarkers.

Safety:

Of the 66 patients included in the safety analyses, 62 (93.9%) experienced at least one AE: 30 (93.8%) in the idebenone group and 32 (94.1%) in the placebo group. The most commonly reported AEs in the idebenone group were nasopharyngitis and diarrhea. Diarrhea was reported by a higher proportion of patients in the idebenone group than in the placebo group (8 patients [25.0%] and 4 patients [11.8%], respectively) whereas nasopharyngitis was reported by similar proportions of patients in the two treatment groups (8 patients [25.0%] in the idebenone group and 9 patients [26.5%] in the placebo group). Headache was also commonly reported in both treatment groups (6 patients [18.8%] in the idebenone group and 7 patients [20.6%] in the placebo group). The only other AEs reported in at least 5 patients in the idebenone group were gastroenteritis

(5 patients [15.6%] in the idebenone group and 1 patient [2.9%] in the placebo group) and pyrexia (5 patients [15.6%] in the idebenone group and 3 patients [8.8%] in the placebo group). Bronchitis, constipation, upper respiratory tract infection and rhinitis were each reported by 6 patients in the placebo group but by 4 or fewer patients in the idebenone group.

Adverse events considered to be drug-related were reported by 16 patients (24.2%), 7 patients (21.9%) in the idebenone group and 9 patients (26.5%) in the placebo group. The only treatment-related AEs reported by more than 1 patient in the idebenone group were diarrhea (reported by 2 patients [6.3%] in the idebenone group and 2 patients [5.9%] in the placebo group) and chromaturia (reported by 3 patients [9.4%] in the idebenone group and no patients in the placebo group). The majority of AEs were of mild or moderate intensity and only 5 patients (1 [3.1%] treated with idebenone and 4 [6.1%] treated with placebo) experienced AEs of severe intensity. All severe AEs were considered by the investigator to be unrelated to study treatment.

No patients died during the study period. Seven patients (2 [6.3%] treated with idebenone and 5 [14.7%] treated with placebo) experienced serious adverse events (SAEs) during the study. The only SAE reported in more than 1 patient was pneumonia (3 events in 2 patients treated with placebo). In the idebenone group 1 patient experienced sleep apnea syndrome and 1 patient experienced urticaria. In the placebo group, 1 patient experienced 2 episodes of pneumonia, 1 patient experienced pneumonia and respiratory failure, 1 patient experienced dehydration, vomiting, nasopharyngitis and pyrexia, 1 patient experienced pulmonary microemboli, and 1 patient experienced 2 episodes of worsening tendinous contracture, acute respiratory failure, and a femur fracture. None of the SAEs reported were considered by the investigator to be related to study treatment.

Four patients were discontinued from study treatment prematurely due to AEs, 2 in each treatment group. None of the AEs that led to premature discontinuation from the study were considered by the investigator to be related to study treatment. The AEs that led to discontinuation were sleep apnea syndrome and diarrhea in the idebenone group and supraventricular arrhythmia and respiratory failure with pneumonia in the placebo group.

There was no evidence observed for a clinically relevant effect of idebenone on any hematological or clinical chemistry parameter. No clinically relevant, treatment-related findings were observed for vital signs or physical examinations. There was no evidence observed for an effect over time on ECG and transthoracic cardiology parameters assessed after treatment with idebenone.

CONCLUSIONS:

This study met its primary objective and demonstrated that idebenone slowed the decline in respiratory function in DMD patients not using concomitant glucocorticoids. The positive findings in flow (PEF) and volume (FVC, FEV_1) parameters were consistent for analyses of the percent predicted results as well as the non-normalized outcomes and were supported by clinically relevant responder analyses.

Idebenone at a dose of 900 mg/day administered for up to 52 weeks was safe and well-tolerated. The nature and frequency of AEs were generally similar to those observed with placebo. The results suggest that idebenone can be used safely for the treatment of patients with DMD.

Publication:

Buyse GM et al. (2015). Efficacy of idebenone on respiratory function in patients with Duchenne muscular dystrophy not using glucocorticoids (DELOS): a double-blind randomised placebo-controlled phase 3 trial. Lancet, 385(15), 1748–57.

Final Report Date:

24 April 2015