CLINICAL STUDY REPORT 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 II open-label extension study to obtain long-term safety, tolerability and efficacy data of idebenone in the treatment of Duchenne Muscular Dystrophy.
Extension to study SNT-II-001

Trial Acronym: DELPHI Extension

ClinicalTrials.gov Identifier: NCT00758225

Eudract No.: 2007-007752-34	**US IND No.:** Not applicable

Investigator(s) and Study Centre(s): Dr Gunnar Buyse, Leuven, Belgium

Publication (reference): Not applicable

Study Period:
15 September 2008 (first subject in study) to
10 January 2011 (last subject completed)

Phase of Development: II

Objectives:

- To gather long-term data on the safety and tolerability of idebenone in DMD patients
- To explore the effect of idebenone after longer term administration on respiratory, cardiac and motor functions, and skeletal muscle strength/function.

Methodology:
The study was an open-label, single centre uncontrolled study for patients with DMD who had completed the DELPHI study (SNT-II-001). Patients were treated as out-patients. Their participation in the study lasted approximately 27 months: up to 2 months for the screening phase, 24 months for the treatment phase and a 1 month follow-up phase.

The study included up to 9 visits. A Screening Visit took place a maximum of 4 weeks prior to the Baseline Visit for patients who did not fulfill inclusion and exclusion criteria concerning wash-out of coenzyme Q10 or idebenone, unstable doses of ACE-inhibitors or glucocorticosteroids, abnormal clinical laboratory values. Beginning at the Baseline Visit (Visit 1), the patient received study medication to take at home and underwent regular assessments in the clinic after 4 weeks (Visit 2), 12 weeks (Visit 3) and 6 months (Visit 4), 12 months (Visit 5), 18 months (Visit 6) and 24 months (Visit 7). At Visit 7, the study medication was discontinued. All patients attended a final follow-up 28-35 days after study medication withdrawal.

Efficacy assessments (respiratory, cardiac and motor functions, skeletal muscle strength/function, and cardiac biomarkers) were made at Baseline and every 6 months thereafter. Safety assessments were performed after enrolment at 12 weeks and at 6, 12, 18 and 24 months and at the Follow-up Visit. At Week 4 the patient returned to the clinic for a safety assessment which included clinical laboratory evaluations, adverse events (AEs), concomitant medication, and patient compliance. If the patient could not come to the clinic for this visit, a trained study nurse was to visit the patient at his home.

Number of Subjects (Planned and Analyzed):

Planned: Maximum of 21 patients (the number of patients who completed SNT-II-001)

Entered: 19 patients

Safety Population: 19 patients

Intent-to-Treat (ITT) population: 19 patients

Per Protocol (PP) population: 19 patients

Diagnosis and Main Criteria for Inclusion:

Patients with a diagnosis of DMD, who had completed the DELPHI study (SNT-II-001) with a body weight ≥25 kg, and eligible to participate (as confirmed by the investigator) were enrolled in the study. Patients were allowed to be using corticosteroids and angiotensin-converting enzyme (ACE) inhibitors if they had been on a stable dose for 2 months prior to inclusion.

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

Idebenone was formulated as film-coated 150 mg tablets. Patients ≤45 kg in weight took 1 x 150 mg tablets orally 3 times daily with meals (total daily dose 450 mg daily). Patients >45 kg in weight took 2 x 150 mg tablets orally 3 times daily with meals (total dose 900 mg daily).

Batch number: SNT-II-001-E-01 (Bulk batch 0717B001) Expiry Date: April 2011

Batch number: SNT-II-001-E-02 (Bulk batch 0717B001) Expiry Date: April 2011

Duration of Treatment:

24 months

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

Not applicable

Criteria for Evaluation:

Efficacy:

The following assessments were performed at the Baseline visit and Months 6, 12, 18 and 24:

- Respiratory Function Testing
- Motor Function Measure (MFM) scale
- Quantitative Muscle Testing (QMT)
- Hand-Held Myometry (HHM)
- Echocardiography and Color Doppler Myocardial Imaging (CDMI)
- Cardiac biomarkers: brain natriuretic peptide (pro-BNP) and cardiac troponin-1 (cTn1)

Safety:

Safety was assessed by evaluation of adverse events (AEs), physical examination, vital signs, electrocardiograms (ECG), and clinical laboratory evaluations of hematological and biochemical parameters (blood and urine samples) and urine pregnancy tests for women of childbearing potential. Safety assessments were made at Months 3 (without ECG), 6, 12, 18 and 24 and at the Follow-up Visit. In addition, AEs and clinical laboratory evaluations were monitored at Week 4.

Statistical Methods:

The sample size of 21 patients for this study was based on the number of patients who had completed the DELPHI study (SNT II 001).

Three populations were defined for this study: the safety population, the ITT population, and the PP population. The ITT population included all patients who received at least one dose of the study medication and for whom an efficacy assessment was available. The safety population included all patients as in the ITT population, since all patients received at least one dose of the study medication and also had a safety assessment available. The PP population included all patients from the ITT population who had no major protocol deviation (a protocol deviation that was considered to have a major impact on the efficacy results).

Efficacy:

The efficacy variables were presented for the ITT population. The efficacy data was integrated with the DELPHI study data and both change from DELPHI study Baseline and DELPHI-E Baseline were calculated and presented with summary statistics. Data from the DELPHI study was not included in the formal statistical analyses. For cardiac and respiratory data changes from Baseline to Months 6, 12, 18 and 24 were calculated and presented with summary statistics. In addition, a repeated measures analysis of covariance (RMANCOVA) model was fitted, to estimate the changes from Baseline. The model included visit as a fixed factor and Baseline value and age at Baseline as covariates. The MFM, QMT, HHM and cardiac biomarker data were analyzed using the same method. In addition, the change rate between the off-medication period (time between the last visit in the DELPHI study and enrolment into DELPHI-E) and on-medication period (during DELPHI-E) for selected cardiac parameters and PEF % predicted, FVC % predicted and MIP % predicted were analyzed using a random regression coefficient model.

Safety*:*

The safety population was used for all analyses of safety variables. The treatment-emergent AEs (i.e., events which started or worsened during the study treatment) were tabulated by system organ class (SOC) and preferred term. In addition, the treatment-emergent AEs were presented and evaluated by seriousness, severity and relationship to study treatment. Deaths and life-threatening events, other SAEs, AEs leading to premature discontinuation and AEs leading to dose adjustment were also summarized.

For each laboratory parameter, descriptive statistics for both absolute values and change from baseline values were presented. Abnormalities were presented in a frequency table and all clinically significant values as evaluated by the investigator were listed.

Vitals signs and ECG parameters (heart rate, PR, QRS, QT, QTcB, QTcF) were summarized by standard descriptive statistics for absolute values and for the changes from Baseline. Abnormalities were presented in a frequency table.

Summary of Results:

Demographic Results:

The mean age of the 19 patients recruited was 15.1 years. All patients were male and all were Caucasian/white. Of the 19 patients, 7 patients were ≤45 kg in weight. All 19 patients had a history of DMD, with 15 (78.9%) being wheelchair-bound. The mean time off medication from the end of the DELPHI study to the start of the DELPHI-E study was 619.1 days (range 447 to 769 days).

Efficacy:

Cardiac Function

During the 24-month study treatment period, the different cardiac parameters remained stable with no clinically important changes. Cardiac remodeling was studied using LV end diastolic diameter

and LV inferolateral (posterior) wall thickness. No clinically important changes were observed during the study period.

Global cardiac function was studied using FS and EF. During the 24-month study period, no significant decline in FS and EF was observed in the patients on treatment.

Due to the lack of a control group, it is uncertain whether this stability in global function is due to drug treatment. However, the natural course of DMD is typically characterized by a progressive increase in cardiac dysfunction (certainly over longer time periods, such as the 24 months of this study), and especially in the older (second decade of life) patients as in the current study.

Regional myocardial function was studied by analyzing end-systolic strain in the inferolateral wall of the LV, which previously has been shown to be reduced in DMD patients. No significant decrease in strain values during the 24-month treatment period was observed in this study. The rate of change in this parameter during DELPHI-E was smaller than during the preceding off-medication period, but did not reach statistical significance.

Cardiac biomarkers for LV dilatation and increased filling pressures (pro-BNP) as well as the biomarker used to study cardiac myocyte damage (cTnI) were unchanged during the study period.

Respiratory Function

During the 24 months of idebenone treatment, there was a significant decline in FVC % predicted and FEV_1 as markers for restrictive lung disease. Most of this decline was apparent in the first 12 months and less so in the second year of the treatment period. At the DELPHI-E study Baseline, the mean FVC % predicted was 61.3%, at Month 12 it was 52.0%, and at Month 24 it was 48.8% for a rate of change in FVC percent predicted of

-6.34% per year.

In the natural course of DMD, changes in respiratory strength parameters (MIP and PEF) precede changes in FVC and FEV_1. At the DELPHI-E study Baseline, the mean MIP % predicted was 27.7% and the mean PEF % predicted 66.1%. Interestingly, in this study MIP remained stable and PEF did not show a significant deterioration during the 24 months of idebenone treatment. For MIP, the stability during this study was significantly different from its 7.83% per year decline during the off-idebenone period preceding the study.

The rate of change in PEF % predicted was a decline of -2.89% per year which was not statistically significant. The rate of change during the off-medication period was slightly higher at -3.25%.

Motor Function and Muscle Strength

During the study, there was a significant decline in the total MFM score as well as in the D1 (standing and transfers) and D2 (axial and proximal motor capacity) subscores. In contrast, the D3 (distal motor capacity) subscore remained stable over the 24-month period.

With HHM, the arm score increased over the 24-month treatment period with a significant improvement for elbow extensor strength and a trend to improvement for elbow flexor strength. Although the increase in arm score as measured with HHM contrasts the expected natural history evolution, this finding was not replicated in the strength assessments by QMT. There was also a trend to improvement in knee extensor strength.

With QMT, the total upper limb score decreased over the 24-month treatment period where the decline in the total upper limb score was caused predominantly by a decline in hand grip strength.

Safety:

No patients died during the study period. Eight SAEs were reported. None of these SAEs were considered by the investigator to be treatment related and none led to permanent premature study discontinuation.

Of the 19 patients included in the safety analyses, 17 (89.5%) experienced at least one AE. The most

commonly reported AEs were upper respiratory tract infection reported by 8 patients (42.1%) and gastrointestinal infection reported by 5 patients (26.3%). Headaches and respiratory tract infections were both reported by 4 patients (21.1%). The majority of AEs were of mild or moderate intensity and only 2 patients experienced AEs of severe intensity. The severe AEs were pneumonia and cardio pulmonary failure in one patient and scoliosis in the other. None of these AEs were considered related to idebenone treatment. Nine AEs considered to be drug-related were reported by 7 patients (36.8%). The AE considered to be possibly related was nausea and the AEs considered unlikely to be related were cough, abdominal pain, cardiomyopathy, cystitis, dyspepsia, fungal infection, headache and migraine. All treatment-related AEs were of mild severity and none was reported by more than one patient. No patients were discontinued from study treatment prematurely due to AEs.

There was no evidence observed for a clinically relevant effect of idebenone on any hematological or clinical chemistry parameter and no clinically relevant, treatment-related findings were observed for vital signs. No clinically significant ECGs were obtained at any timepoint after the start of study treatment.

CONCLUSIONS:

Efficacy Conclusions:

The results of this study are in agreement with the randomized, placebo-controlled DELPHI study, although the interpretation of findings in the DELPHI-E study are complicated by the absence of a direct control group. Results indicate that during the 24 month study period:

- Cardiac function in the patients participating in the study remained unchanged. No changes in cardiac remodeling (LV dimensions and wall thickness) were observed. No changes in global LV function were observed. EF and FS were stable with a temporary improvement after 6 months of treatment. No changes in regional myocardial function were observed with no further decline in radial strain in the inferolateral wall, which may be of medical relevance. No changes in cardiac biomarkers (pro-BNP and cTnI) were observed.
- Respiratory strength measures remained stable (MIP) or did not decrease significantly (PEF). There was a significant decline in restrictive lung disease parameters (such as FVC). The stability of MIP during DELPHI-E was significantly different from its decline during the off-medication period preceding DELPHI-E.
- Peak Expiratory Flow (PEF) and Maximum Inspiratory Pressure (MIP) stabilized in idebenone-treated patients not using glucocorticoids. No additive therapeutic effect of idebenone was apparent in patients already treated with glucocorticoids.
- Motor function (as assessed by MFM total score) declined significantly, although the MFM D3 (distal motor capacity) subscore remained stable over the 24 month period.
- No clear indication for a beneficial effect of 24 months of idebenone treatment on muscle strength (as measured by QMT and HHM) was observed in these advanced disease stage DMD patients, but some significant improvements were observed on some muscle groups both in the upper and lower limb. The interpretation of the study results is complicated by the absence of a direct control group and by the fact that the findings with HHM and QMT do not fully overlap/match.
- Although the interpretation of all DELPHI-E findings are complicated by the absence of a direct control group, any observed stabilization over a long time frame (such as the 24 months in this study) especially in the age range (disease stage) of this study's population, are unlikely to be in line with the expected natural disease evolution.

Safety Conclusions:

- Idebenone at a dose of 450 or 900 mg/day administered to patients with DMD for 24 months was safe and well-tolerated.
- No potential safety signal emerged from the review of vital signs, laboratory and ECG data.

Final Report Date: 15.11.2013