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: Catena®	Volume:	
Name of Active Ingredient: Idebenone	Page:	

Study Title:

A Phase IIIb double-blind, randomized, placebo-controlled study of **P**atient **R**eported **O**utcomes in Friedreich's Ataxia patients after withdrawal from **T**reatment with **I**debenone

Trial Acronym:

PROTI

ClinicalTrials.gov Identifier:

NCT01303406

Eudract No.: 2010-023388-16	**US IND No.:** Not applicable

Investigator(s) and Study Centre(s):

7 centers (1 in the United Kingdom, 1 in the Netherlands, 4 in Germany and 1 in Austria) provided data. A total of 11 centers were eligible for participation in the study.

Publication (reference): Not applicable

Study Period:
29 April 2011 (first subject screened) to
19 July 2012 (last subject completed)

Phase of Development: IIIb

Objectives:

Primary

- To establish whether patients can correctly determine which treatment assignment they received during the randomized phase of the trial

Key Secondary

- To compare the rate of withdrawal from the PROTI study of patients who have been withdrawn from treatment with high-dose idebenone with the rate of withdrawal of patients continuing to receive high dose idebenone.

Secondary

- To compare Patient Reported Outcomes (PROs) and performance measures in FRDA patients who

have been withdrawn from treatment with high-dose idebenone and to compare these outcomes and performance measures with those from patients continuing to receive high dose idebenone.

Methodology:

The study was a randomized, double-blind, placebo-controlled, parallel group, multicenter, withdrawal study which included patients who had received high-dose idebenone in the MICONOS Extension Study (MES, SNT-III-001-E). Patients who had completed Visit 5 (Month12) and/or Visit 6 (Month 18) and/or Visit 7 (Month 24) of the MES and who were considered eligible by the Investigator participated in this study. Patients were treated as out-patients. Patients enrolled in the study at Visit 5 or Visit 6 of the MES were able to re-enter the PROTI study. Patient participation in the study lasted up to 2 months for each cycle of the study.

Each cycle of the study included 2 visits. The Baseline visit (Visit 1) took place at Visit 5, Visit 6 or Visit 7 of the MES. Patients who fulfilled inclusion/exclusion criteria were randomized in a 1:1 ratio to blinded administration of either oral high dose idebenone or placebo. Randomization was done by center and by ambulatory status. Sufficient medication was provided to last until the end of the study (Visit 2 or Early withdrawal visit). Patients who entered the PROTI study a second time were assigned to the alternative study medication from that they had received during their previous cycle in the study.

Clinical performance measures and neurological assessments (International Cooperative Ataxia Rating Scale [ICARS], 9-Hole Peg Test [9 HPT], Modified Fatigue Impact Scale [MFIS], speech capability) were conducted at Visit 1/Baseline and Visit 2 or Early withdrawal visit. Patients also completed a Patient Reported Outcomes (PRO) Status Questionnaire at Visit 1/Baseline and Visit 2 or Early withdrawal visit. At Visit 2 or Early withdrawal visit, a PRO Change Questionnaire was completed and a Clinical Global Impression of Change (CGI-C) assessment and assessment of on-study treatment assignment was completed by both the patient and the Investigator.

Safety assessments were performed at Visit 1/Baseline and included physical examination, vital signs, routine electrocardiograms (ECGs), and safety blood/urine assessments; all these measurements were part of the routine visit assessments of the MES. At Visit 2 or Early withdrawal visit, the patient returned to the clinic for a safety assessment which included safety blood/urine assessments, adverse events (AEs), vital signs, ECG and physical examination.

An interim analysis of the study was performed with a cut-off date of 13 January 2012.

Number of Subjects (Planned and Analyzed):

Planned: Maximum of 80 patients (the number of eligible patients in the MES)
Randomized and analyzed: 29 patients

Diagnosis and Main Criteria for Inclusion:

Patients with a diagnosis of FRDA, who had completed Visit 5 (Month 12), Visit 6 (Month 18) or Visit 7 (Month 24) in the MES, with a body weight ≥25 kg, and who in the opinion of the Investigator were able to comply with the requirements of the study. A negative pregnancy test was required for women of child-bearing potential.

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

Idebenone was formulated as film-coated 150 mg tablets. High dose idebenone was administered in a body weight adjusted manner. Specifically, patients ≤45 kg in weight took 3 x 150 mg tablets orally 3 times daily with meals (total daily dose 1350 mg daily). Patients >45 kg in weight took 5 x 150 mg tablets orally 3 times daily with meals (total dose 2250 mg daily).

Batch number: 205719/1 Expiry Date: September 2013

Duration of Treatment:

Up to 2 months

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

Film-coated placebo tablets, identical in appearance to idebenone tablets. Patients ≤45 kg in weight took 3 tablets orally 3 times daily with meals. Patients >45 kg in weight took 5 tablets orally 3 times daily with meals.
Batch number: 1031B002 Expiry Date: August 2015

Criteria for Evaluation:

Efficacy:

- Patient and Investigator assessment of treatment assignment (Visit 2 or Early withdrawal visit)
- PRO Status Questionnaire (Visit 1/Baseline visit and Visit 2 or Early withdrawal visit)
- PRO Change Questionnaire (Visit 2 or Early withdrawal visit)
- ICARS
- MFIS
- 9-HPT
- Speech assessments
- CGI-C

Safety:

Safety was assessed by evaluation of AEs, physical examination, vital signs, ECG, and clinical laboratory evaluations of hematological and biochemical parameters (blood and urine samples) and urine pregnancy tests for women of childbearing potential.

Statistical Methods:

The sample size of 80 patients for this study was based on the number of eligible patients who might complete Visit 5 (Month 12), Visit 6 (Month 18), or Visit 7 (Month 24) of the MES. This was the maximum number of patients who could participate in the PROTI study.
Two populations were defined for this study: the safety population and the Intent-to-treat (ITT) population. A per protocol (PP) population was to be defined if needed. However, as there were no major protocol deviations no PP population was defined. The safety population included all randomized 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 who received at least one dose of the study medication. Patients were analyzed as randomized regardless of protocol violations.
The method by O'Brien and Fleming was used to control the overall probability of type I error for the interim and final analyses. By using this method, the overall type I error of 0.05 is maintained when the required p-value for the interim analysis is adjusted to 0.0052 and for the final analysis it is adjusted to 0.048.

Efficacy:
Efficacy data were analyzed for the ITT population using three approaches:

- Design 1: Parallel design using only data from the first treatment cycle. This was considered the primary analysis set (N=29; 16 in the idebenone group and 13 in the placebo group).
- Design 2: Crossover design. This analysis set comprised patients who completed both Cycle 1 and Cycle 2 and were treated with both treatments (N=7).
- Design 3: Parallel design using data from both treatment cycles and considering observations from the same patient as independent (N=36; 21 in the idebenone group and 15 in the placebo group).

The primary endpoint, the comparison of the proportions of patients randomized to idebenone and placebo which assessed that they received idebenone treatment, was analyzed using logistic regression. The key secondary endpoint, early withdrawal due to recurrence or worsening of FRDA symptoms, was also to be analyzed using logistic regression.

For Designs 1 and 3, secondary endpoints MFIS, 9-HPT, speech assessments and ICARS were analyzed using an analysis of covariance (ANCOVA) model with the Baseline value as a covariate. In a separate analysis, ambulatory status and Baseline were covariates. In the crossover approach, these endpoints were analyzed using an analysis of variance (ANOVA). Other secondary endpoints (CGI-C, Investigator's assessment of treatment assignment, change questionnaire, status questionnaire) were analyzed using logistic regression analyses for Designs 1 and 3. Analyses were to be performed using McNemar's Test for Design 2, but due to the small number of patients who received both treatments, no statistical testing was performed.

Safety:

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 but not by treatment. 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, and AEs leading to premature discontinuation were also summarized. Other safety endpoints were summarized.

Summary of Results:

Efficacy:

For the primary endpoint, using data from the first treatment cycle only (Design 1, the primary analysis set), there was no statistically significant difference between idebenone and placebo in the proportion of patients who assessed that they received idebenone. 8 patients (50.0%) in the idebenone group correctly assessed that they received idebenone and 6 patients (46.2%) in the placebo group incorrectly assessed that they received idebenone. The odds ratio for idebenone versus placebo was 1.17 (95.2% CI: 0.27, 5.12; p=0.8369).

Analyses of the primary endpoint for patients who completed both Cycles 1 and 2 and using all data from Cycles 1 and 2 treating observations from the same patient as independent (Design 3) also demonstrated no statistically significant difference between treatments; the odds ratio for idebenone versus placebo was 1.65 (95.2% CI: 0.43, 6.39; p=0.4645). For the crossover design (Design 2), 5 patients (71.4%) correctly assessed they received idebenone while they were being treated with idebenone and 4 patients (57.1%) incorrectly assessed they received idebenone while receiving placebo.

Ambulatory patients appeared to be more likely to correctly assess that they had received idebenone treatment than non-ambulatory patients but logistic regression analysis including ambulatory status in the model revealed no significant effect of ambulatory status. For the primary analysis set, for the comparison of ambulatory versus non-ambulatory patients the odds ratio was 1.54 (95.2% CI: 0.35, 6.76; p=0.5675) and for the comparison of idebenone versus placebo the odds ratio was 1.19 (95.2% CI: 0.27, 5.27; p=0.6166).

No patients were withdrawn prematurely due to recurrence or worsening of FRDA symptoms (key secondary endpoint).

No significant differences were observed between treatments for other efficacy endpoints including Investigator's assessment of treatment assignment, MFIS, 9-HPT, CGI-C and speech assessments (although for the AIDS speech capability test which was only performed in the UK center, there was a statistically significant difference between treatments in favor of idebenone). For ICARS, the mean difference (-2.2 points) between idebenone and placebo for the analysis using observed cases (Design 1) was not statistically significant but for ambulatory patients the mean difference between treatments (-6.4 points) was statistically significant (p=0.0121). The ICARS analysis using last observation carried forward showed a significant difference in favor of idebenone for all patients (mean difference -3.4 points, p=0.0365) and for ambulatory patients (mean difference -8.3 points, p=0.0002). For the Change and Status questionnaires, the

majority of patients reported no worsening in all categories, irrespective of whether they were randomized to idebenone or placebo.

Safety:

No patients died during the study period. 1 patient, treated with idebenone, reported 2 SAEs. Neither of these SAEs (fractured femur and dislocated hip) was considered by the Investigator or the Sponsor to be treatment related and they did not lead to premature study discontinuation. No patients were discontinued from study treatment prematurely due to AEs.

Adverse events were reported by 16 patients (76.2%) during treatment with idebenone and by 10 patients (66.7%) during treatment with placebo in either Cycle 1 or Cycle 2. The most commonly reported AEs were falls, nasopharyngitis and fatigue. Nasopharyngitis and fatigue were reported more frequently for idebenone than placebo (5 patients [23.8%] versus 2 patients [13.3%] for nasopharyngitis; 5 patients [23.8%] versus 1 patient [6.7%] for fatigue). Falls were reported by similar proportions in each treatment group (5 patients [23.8%] for idebenone and 4 patients [26.7%] for placebo). Diarrhea, gastroenteritis and speech disorder were each reported by 2 patients (9.5%) in the idebenone group and no patients in the placebo group. No other AEs were reported by more than 1 patient in either treatment group.

All AEs were of mild or moderate intensity and no patients experienced AEs of severe intensity. Adverse events considered to be drug-related were reported by 7 patients (33.3%) treated with idebenone and 6 patients (40.0%) treated with placebo. Fatigue (4 patients [19.0%] treated with idebenone and 1 patient [6.7%] treated with placebo) and falls (4 patients [19.0%] treated with idebenone and 2 patients [13.3%] treated with placebo) were the AEs most commonly considered by the Investigator to be treatment-related. No other AEs were considered to be related to treatment in more than 1 patient in either treatment group.

There were no notable differences between idebenone and placebo in clinical laboratory evaluations, vital signs or ECGs.

CONCLUSIONS:

The number of patients included in this study was lower than planned limiting the conclusions that can be drawn. The study provides no data to support that FRDA patients can correctly determine their treatment assignment (idebenone or placebo) over a 2-month period. No differences were observed between treatments for most efficacy endpoints. However, changes in ICARS in favor of idebenone, although numerically small, were observed, particularly in ambulatory patients. It is possible that FRDA patients with a long disease duration and who have received idebenone treatment for a prolonged time may not be able to perceive the small changes in ICARS over a short time period (2 months) to the extent that they can correctly determine their treatment status.

Idebenone treatment was well-tolerated and no specific safety issue was identified during the study.

Final Report Date:
16 September 2013