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

Study Title:

A Phase III Open-Label, Single-Group Extension Study to Obtain Long-Term Safety and Tolerability Data of Idebenone in the Treatment of Friedreich's Ataxia Patients (SNT-III-001-E)
Extension of Study SNT-III-001

Trial Acronym:

MICONOS-E

ClinicalTrials.gov Identifier:

NCT00993967

Eudract No.: 2007-001646-40 **US IND No.:** N/A

Investigator(s) and Study Center(s):

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12-center study (UK, Austria, Germany, Belgium, Netherlands and France).

Publication (reference): Not applicable

Study Period:

01 June 2007 (first subject screened) to
07 July 2012 (last subject completed)

Phase of Development: 3

Objectives:

- To gather long-term data on the safety and tolerability of idebenone in Friedreich's Ataxia patients.
- To explore the effect of idebenone after longer term administration on neurological symptoms and signs as assessed by the International Cooperative Ataxia Rating Scale (ICARS) and the Friedreich's Ataxia Rating Scale (FARS)

Methodology:

The study (SNT-III-001-E) was an open-label, single-group, multi-center Extension Study for patients with Friedreich's Ataxia, who completed Week 52 of the Main Study SNT-III-001 and who were considered eligible by the investigators to receive long-term idebenone treatment. Subjects were treated with idebenone (1350 mg/day or 2250 mg/day for patients weighing ≤45 kg or >45 kg, respectively) 3 times daily for up to 24 months. In case of poor tolerability, dose reduction to 450 mg/day or 900 mg/day, respectively, were allowed. In addition, subjects were allowed to suspend their participation in SNT-III-001-E in order to participate in SNT-III-004 (Patient Reported Outcomes after withdrawal from Treatment with Idebenone, PROTI) study, and then re-enter SNT-III-00-E if still eligible.

The study visits for SNT-III-001-E were as follows: Visit 1 (Baseline), Visit 2 (Week 4 ± 7 days), Visit 3 (Week 12 ± 7 days), Visit 4 (Month 6 ± 14 days), Visit 5 (Month 12 ± 14 days), Visit 6 (Month 18 ± 14 days) and Visit 6.1[a] (Month 20 – 21 ± 14 days) and Visit 7 (Month 24 ± 14 days or 6 months ± 14 days post Visit 6.1[a], whichever was latest).

Visit 1/Baseline should have coincided with the Visit 7/Week 52 of study SNT-III-001. At this visit informed consent was obtained from the subject and/or parents/legal guardian, and inclusion/exclusion criteria were assessed. Baseline assessments were those that were performed at Visit 7/Week 52 of SNT-III-001. Sufficient study medication to last until the next visit was dispensed to the subject. The first dose of study medication should have been taken on the day of the visit. Whenever possible, no interruption of study medication intake should have taken place. The subject was asked to complete a Patient Diary throughout the entire study. Safety assessments (physical examination, measurement of vital signs, electrocardiogram (ECG), safety blood and urine analysis, and urine pregnancy test for women of childbearing potential) were performed at each visit. Neurological assessments (ICARS and FARS) were done at Visit 1/ Baseline, Visit 5/Month 12 and Visit 7/Month 24. Information about AEs or SAEs were collected throughout the study period and followed up until resolution or until the last study visit. Information on concomitant medications was also sought at each study visit.

Subjects completing Visit 5/Month 12, Visit 6/Month 18 and Visit 7/Month 24, were offered the opportunity to enrol in the PROTI randomized withdrawal study provided the PROTI study was approved and open for recruitment at their site when the subject attended for the relevant visit. Subjects could re-enter SNT-III-001-E at the same SNT-III-001-E study visit at which they were randomized in the PROTI trial after completing a Visit 2/Early termination visit of PROTI, if they remained eligible and consented to the re-entry into SNT-III-001-E. This was to ensure that eligible subjects received at least 24 months of idebenone treatment in SNT-III-001-E and a full six months of active treatment between two potential PROTI cycles.

Patients re-entering this study from the PROTI study should repeat the last visit assessments conducted under this study prior to re-entry and distribution of study medication and patient diary. However, patients completing Visit 2/Early termination visit of the PROTI study and re-entering this study should have

[a] UK sites only - For patients who had re-entered the study after a PROTI cycle

completed all of the visit assessments required under this protocol, except the FARS assessment, at Visit 2/Early termination visit of the PROTI study. Where this is the case, the PROTI results should be used to complete the CRF for the repeat of the last visit of this study, leaving only the FARS assessment to be conducted where required. Where this is not the case, all visit assessments required under this protocol should be conducted.

Number of Subjects (Planned and Analyzed):

Planned: Subjects completing SNT-III-001 (Visit 7/Week 52), up to a maximum of 232 subjects.

Actual number completed SNT-III-001: 212 subjects

Treated in SNT-II-001-E: 200 (94%)

(previous treatment groups in SNT-III-001 were: 51 on placebo; 47 on 180/360 mg/day idebenone, 49 450/900 mg/day idebenone, 53 on 1350/2250 mg idebenone)

Analyzed for Efficacy:

Completed Cases Population: 139 subjects

Analyzed for Safety:

Safety Population: 200 subjects

(See Statistical Methods section for definitions of the analysis populations)

Diagnosis and Main Criteria for Inclusion:

The subject was not included in the study if any of the following inclusion criteria did not apply:

- Completion of 52 weeks in study SNT-III-001
- Body weight ≥ 25kg
- Negative urine pregnancy test
- Eligible to participate in the present Extension Study as confirmed by the investigator

The subject was not included in the study if any of the following exclusion criteria applied:

- Safety or tolerability issues arising during the course of SNT-III-001 which in the opinion of the investigator precluded further treatment with idebenone
- Clinically significant abnormalities of haematology or biochemistry including, but not limited to, elevations greater than 1.5 times the upper limit of AST (SGOT), ALT (SGPT) or creatinine
- Parallel participation in another clinical drug trial
- Pregnancy or breast-feeding
- Abuse of drugs or alcohol

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

Idebenone was formulated as film-coated tablets of 150 mg strength. Idebenone was administered orally three times daily (t.i.d.) with meals. Subjects were allocated medication by body weight (under/equal 45 kg or above 45 kg) to ensure that all subjects received roughly the same dose independent of body weight (see below). Subjects received 1350/2250 mg/day, which corresponded to the High Dose used in the preceding Main Study (SNT-III-001). The investigator could decide to reduce the dose to 450/900 mg/day (corresponding to the Mid Dose in the preceding Main Study) in the case of poor tolerability.

Weight (kg)	Idebenone dose (High Dose)	Reduced idebenone dose (if poor tolerability) (Mid Dose)
≥25 kg to ≤45 kg	1350 mg/day (3 x 150 mg tablet, t.i.d.)	450 mg/day (1 x 150 mg tablet, t.i.d.)
>45 kg	2250 mg/day (5 x 150 mg tablet, t.i.d.)	900 mg/day (2 x 150 mg tablet, t.i.d.)

Batch numbers:
0609B005, 0717B001, 0813B008, 0836B001, 0917B013 for bulk 150 mg idebenone tablets

Duration of Treatment:

Up to 30 months open-label treatment with idebenone or until marketing approval/reimbursement of idebenone was achieved in the respective countries, whichever was shorter.

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

Not applicable

Criteria for Evaluation:

Safety:

- Measures of safety and tolerability:
  Nature and frequency of AEs, haematological and biochemical parameters, physical examinations and vital signs, and ECGs

Efficacy:

- Absolute change in scores from Baseline to Month 12, and to Month 24 assessed by International Cooperative Ataxia Rating Scale (ICARS) and Friedreich's Ataxia Rating Scale (FARS)

Statistical Methods:

Sample size calculation was not relevant to this open-label Extension Study design.

Two populations were defined for this study: the Safety Population and the Completed Cases (CC) Population. The Safety Population included all subjects who received at least one dose of the study medication and for whom a safety assessment was available. The CC Population included all subjects who had an efficacy assessment on the last visit (Visit 7, 2 years) of the study.

For this uncontrolled, single arm, open-label study, safety and neurological data were collected up to 24 months. ICARS and FARS results were summarized descriptively using mean and standard deviation (SD) with no formal hypothesis testing. For the analysis of long term efficacy, the rates of decline in Total ICARS were compared to results from a recently published cross sectional study (**Metz et al., 2013**).

Categorical data were presented in contingency tables with frequencies and percentages. Unless otherwise specified, statistical tests were conducted with a two-sided alternative. The p-values were reported as well as two-sided 95% confidence intervals (CI) for point estimates of the differences. Statistical significance was to be declared for p-values below 0.05.

Disposition of subjects were summarized by center and overall, and demographic and Baseline characteristics overall. Medical history, concomitant diseases (coded using the Medical Dictionary for Regulatory Activities, MedDRA version 12), and prior and concomitant treatments (coded using the Anatomical Therapeutic Chemical [ATC] classification) were tabulated.

All adverse events (AEs) were coded using MedDRA version 12. Treatment-emergent AEs were tabulated by system organ class (SOC) and preferred term, as well as by severity and by causality to the study treatment. Deaths and life-threatening events, other serious AEs, AEs leading to a premature discontinuation and AEs leading to dose adjustment were also summarized. AEs were summarized only for the Extension Study. AEs were also summarized by original treatment group from the Main Study and for the overall group. Summary statistics for haematological and biochemical parameters, vital signs and weight, and ECG were presented for both absolute values and for the change from Main Study Baseline and Extension Study Baseline. Physical examination (by body system) was summarized in frequency tables by visit and original treatment group.

Summary of Results:

Demographics:

200 out of the 212 subjects (94.3%) who completed the preceding Main Study SNT-III-001 were enrolled into the Extension Study, SNT-III-001-E. One-hundred and thirty nine subjects (69.5% of enrolled patients) completed this Extension Study. The overall main reason for dropping out was withdrawal of consent, and only 8 patients dropped out because of AEs (4%). The overall mean (SD) age of subjects in the study was 32.0 (13.68) years, ranging from 9-71 years, with the majority being adult subjects (CC Population).

Efficacy:

Patients completing the MICONOS Extension Study, over the study period of two years, declined by 1.44 points per year in total ICARS, which is well below the anticipated natural history rate for this type of population of FRDA patients. Different subgroup analyses were performed with respect to disease stage (FRDA onset/diagnosis more or less than 20y ago) and disease severity (onset/diagnosis below or over 14 years of age).

It could be shown that especially patients still at a progressive stage of the disease, and also in patients that have a milder form of the disease show a benefit from idebenone treatment. The rate of change in 48 patients that had been diagnosed after 14 years of age and with a disease history shorter than 20 years was 1.05 points in Total ICARS per year in this study, which is only about 50% of the rate of progression in a comparable population, namely 1.80 points per year, as recently published in a cross sectional study (Metz et al., 2013).

For patients already more severely affected at Baseline (disease history longer than 20 years) or patients showing a more severe form of the disease (diagnosis before 14y of age) no clear benefit by idebenone treatment could be shown.

Analysis of the Efficacy data revealed no meaningful differences between patients receiving differing doses or Placebo during the preceding MICONOS study. This was true for the TOTAL ICARS and ICARS subscales as well as TOTAL FARS.

Safety:

Idebenone was safe and well-tolerated at the dose of 2250 mg/day in subjects with FRDA, aged 9-71 years old. AEs were reported by 94.0% of the subjects during the study. Most AEs were mild or moderate in severity, with 49 patients (24.5%) reporting SAEs. There was one death during the study with the causality deemed unrelated to study treatment.

CONCLUSIONS:

In conclusion, this two year open label Extension Study has suggested some possible benefit of idebenone treatment in specific subgroups of FRDA patients, especially younger and less severely affected subjects. In other subgroups no clear benefits could be shown. One possible interpretation in the inability to show beneficial effects in other subgroups may be attributed to the limitations of the ICARS instrument to assess disease progression in the total FRDA population. In addition, recruitment bias may have also influenced the study outcome.

In addition, this study proved again the well-established safety profile of idebenone at a dose of 2250mg/day.

Final Report Date:

31 October 2013