Clinical Study Report Synopsis

Study Title:	A Phase III Double-Blind, Randomised, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of Idebenone in the Treatment of Friedreich's Ataxia Patients
Protocol Number:	SNT-III-001
Study Acronym:	MICONOS (<u>M</u> itochondrial protection with <u>I</u> debenone in <u>C</u> ardiac <u>O</u> r
	Neurological Qutcome Study)
EudraCT Number:	2005-004083-22
Name of Test Article:	Idebenone
Indication:	Friedreich's ataxia
Phase:	3
Design:	Double-Blind, Randomized, Placebo-Controlled
First Subject Enrolled:	28 April 2006 (first screened)
Last Subject Completed:	29 January 2010 (last visit)
Principal Investigators (PI):	Prof. N. Wood (Coordinating PI) The National Hospital, University College London, Queen Square, London, WC 1N 3BG, UK
Sponsor:	13-centre study (UK, Austria, Germany, Belgium, Netherlands & France) Santhera Pharmaceuticals (Switzerland) Ltd, Hammerstrasse 49; 4410 Liestal, Switzerland. Phone: Fax:
Responsible Medical Officer:	
Date of Report:	29 November 2010
Previous Versions:	None

Study Objectives:

Primary Objective:

• To compare the efficacy of 12 months' treatment with three different doses of idebenone with that of placebo¹ on neurological impairment as assessed by the International Cooperative Ataxia Rating Scale (ICARS).

Secondary Objective:

Neurological

• To compare the efficacy of 12 months' treatment with three different doses of idebenone with that of placebo¹ on neurological function as assessed by the Friedreich's Ataxia Rating Scale (FARS).

Cardiological

- To compare the effect of 12 months' treatment with three different doses of idebenone with that of placebo on the proportion of subjects improving on left ventricular peak systolic strain rate (LVPSSR) or showing a reduction in left ventricular mass index (LVMI) with no worsening in strain rate (SR)².
- To compare the effect of 12 months' treatment with three different doses of idebenone with that of placebo on myocardial function assessed by SR and strain imaging².
- To compare the efficacy of 12 months' treatment with three different doses of idebenone with that of placebo on exercise capacity (measured as peak workload) using a modified exercise test.

Tertiary Objectives:

- To assess changes in clinical global function as measured by the Clinical Global Impression of Change (CGIC) indices.
- To assess changes in Health-Related Quality Of Life (HRQOL) indices.
- To assess safety and tolerability following 12 months' treatment with three different doses of idebenone.
- To explore the relationship between plasma levels of three different doses of idebenone and measures of efficacy and safety.

Methodology:

This was a double-blind, randomized, placebo-controlled, parallel-group study in 13 centers with subjects randomized to one of three treatment arms of idebenone or placebo for a period of 52 weeks. Subjects were stratified according to body weight (above and below/equal 45 kg),

¹ Where appropriate as defined in the SAP, the combined mid and high dose groups were to be compared to the combined placebo and low dose groups

² In the statistical analysis sub-population presenting cardiac involvement as defined by the FRDA-CM criteria

cardiac involvement (presence or absence of hypertrophic cardiomyopathy [HCM]) and the ability to walk at Baseline. A minimum of 60 subjects able to walk at Baseline were to be randomized.

The study had 8 visits, a Screening visit followed by 7 study visits: Screening (≤ 8 weeks before randomization), Visit 1 (Baseline/randomization), Visit 2 (Week 4 ± 7 days), Visit 4 (Week 12 ± 7 days), Visit 5 (Week 24 ± 2 weeks), Visit 6 (Week 36 ± 2 weeks), Visit 7 (Week 52 ± 2 weeks) and Visit 8 (Follow-up/Week 56 + 2 weeks). Visit 3/Week 8 was cancelled with Protocol Amendment 4.

At the Screening visit subjects gave informed consent and were screened for medical history, inclusion/exclusion criteria, detailed safety assessments (physical examination, vital signs [heart rate, blood pressure, respiratory rate], routine electrocardiogram [ECG], safety blood and urine samples for biochemistry, hematology and urinalysis and pregnancy tests for women of childbearing potential), and neurological assessments (ICARS and FARS). Inclusion and exclusion criteria were checked again at Baseline (Visit 1) before subjects were randomized to treatment. Subjects took first dose of study medication on the morning of Day 1 (day after Visit 1/Baseline) and continued to receive study medication for up to 52 weeks (Visit 7).

Neurological assessments (ICARS and FARS) were repeated at Baseline, Week 24, Week 52 and Week 56 (Follow-up), cardiac assessments (ECG, echocardiography, Color Doppler Myocardial Imaging [CDMI], cardiac magnetic resonance imaging [MRI] and modified exercise test) were conducted within 2 weeks prior to Baseline, and at Week 24 and Week 52, HROOL were conducted at Baseline, Week 24 and Week 52, and CGIC was assessed at Week 24 and Week 52. Where feasible cardiac MRI and echocardiography were conducted in a single center in each country to reduce variability. Detailed safety assessments and pregnancy tests were conducted at every study visit, along with recording of concomitant medication. Adverse events (AEs) were recorded at every study visit except Baseline, and treatment compliance was assessed at every study visit except Week 56. Subjects completed a Patient Diary daily throughout the study. Blood samples for pharmacokinetic (PK) assessment of idebenone (IDE), QS10, idebenone together with idebenone conjugates (IDE+IDE-C), QS10 together with QS10 conjugates (QS10+QS10-C), QS6 together with QS6 conjugates (QS6+QS6-C), and QS4 together with QS4 conjugates (QS4+QS4-C) were determined at Baseline, Week 12, Week 24 and Week 52.

Subjects were able to enroll into an open-label extension study (SNT-III-001-E) after completion of this study if considered eligible by the Investigator. Subjects who enrolled in the extension study did not have to perform the follow-up visit (Visit 8).

Number of Subjects (planned and analyzed): Planned: 232 Randomized and Treated: 232 Analyzed for Efficacy: Intent-To-Treat (ITT): 227; According-to-Protocol (ATP): 208 Analyzed for Safety Safety Population: 232 (See Statistical Methods section for definitions of the analysis populations)

Diagnosis and Main Criteria for Inclusion:

Subjects with documented diagnosis of Friedreich's ataxia (FRDA) with confirmed FRDA mutations and meeting all of the following **inclusion criteria** were eligible for enrolment in the study:

8 years of age or older at Baseline (or 16 years of age or older at Baseline [valid for site of A Brice, F-Paris only]), body weight \geq 25kg; subjects who in the opinion of the Investigator were able to comply with the requirements of the study, including swallowing the medication, and negative urine pregnancy test at Screening and at Baseline (women of childbearing potential).

Subjects who met the following criteria were **excluded** from the study:

Treatment with idebenone or Coenzyme Q10 (CoQ10) within the past one month, pregnancy and/or breast-feeding, clinically significant abnormalities of clinical hematology or biochemistry including, but not limited to, elevations greater than 1.5 times the upper limit of normal (ULN) of aspartate aminotransferase (AST), alanine aminotransferase (ALT) or creatinine, and past or present history of abuse of drugs or alcohol.

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

Idebenone was formulated as film-coated tablets of 60 mg and 150 mg strength. Subjects randomized to idebenone were assigned to one of three dose groups (Group A, B or C – summarized in the table below). Idebenone was administered orally three times daily (t.i.d.) with meals. Within each dose group 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.

Weight (kg)	Group A Idebenone	Group B Idebenone	Group C Idebenone
\geq 25 kg to \leq 45	180 mg/day	450 mg/day	1350 mg/day
kg	(1 x 60 mg tablet, t.i.d.)	(1 x 150 mg tablet,	(3 x 150 mg tablet,
		t.i.d.)	t.i.d.)
>45 kg	360 mg/day	900 mg/day	2250 mg/day
	(2 x 60 mg tablet, t.i.d.)	(2 x 150 mg tablet,	(5 x 150 mg tablet,
		t.i.d.)	t.i.d.)

Batch numbers:

Batches 0523B011, 0538B005, 0538B006, 0538B007, 0618B013 and 0618B012 for bulk 60 mg idebenone tablets.

Batches 0501B005, 0501B008, 0545B026, 0545B025, 0501B007, 0618B001, 0618B002, 0609B005, and 0836B001 for bulk 150 mg idebenone tablets.

Duration of Treatment: The total duration of participation in this study was approximately 15 months, which included the following phases:

Screening: 2 months; Treatment: 12 months; Follow-up: 1 month*

*Subjects who enrolled in the extension study did not have to perform the follow-up visit.

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

Placebo was provided as tablets that were the same size and appearance as the idebenone tablets

Batch numbers: Batches 0503B003, 0503B004, 0538B008 and 0639B006 for bulk placebo tablets.

CRITERIA FOR EVALUATION

Efficacy:

Primary endpoint:

• Absolute change in ICARS scores from Baseline assessment to Week $52^{3,4}$.

Secondary endpoints:

Neurological

- Proportion of subjects improving (responding) on ICARS by a clinically relevant margin of at least 2.5 ICARS points at Week 52^{3,4}.
- Absolute change in FARS scores from Baseline assessment to Week $52^{3,5}$.

Cardiological

- Proportion of subjects improving on LVPSSR or showing a reduction in LVMI (measured by MRI) with no worsening in SR at Week 52, in the sub-population presenting cardiac involvement as defined by the Friedreich's ataxia cardiomyopathy (FRDA-CM) criteria.
- Change in peak systolic longitudinal SR (PSLSR) and strain (PSLS) from Baseline to Week 52, in the sub-population presenting cardiac involvement as defined by the FRDA-CM criteria.
- Change in peak workload from Baseline to Week 52, assessed by modified exercise test, in all subjects for which these data were available.

Tertiary endpoints:

Neurological

- Absolute change in ICARS scores from Baseline assessment to Week 24³.
- Absolute change in FARS scores from Baseline to Week 24³.

Cardiological

The following endpoints were assessed in a sub-population presenting cardiac involvement as

³ Where appropriate as defined in the SAP, the combined mid and high dose groups was to be compared to the combined placebo and low dose groups

⁴ Where the subject populations were not normally distributed for ICARS the responder analysis was to be used as the primary endpoint

⁵ The exact same combined groups were to be used as for the analysis of the ICARS

defined by the FRDA-CM criteria.

- Proportion of subjects improving on LVPSSR or showing a reduction in LVMI with no worsening in SR at Week 24.
- Change in PSLSR and PSLS from Baseline to Week 24.
- Change in LVMI (measured by MRI) from Baseline to Week 52.
- Percent change in velocity of circumferential fiber shortening (Vcf), compared to Baseline (planned but not done).
- Percent change in diastolic function compared to Baseline, as assessed by isovolumic relaxation time (IVRT), deceleration time (DT), the difference between transmitral A wave duration and the duration of the A wave reversal in the pulmonary vein trace, transmitral E/A ratio and E/E' ratio as indices of left atrial pressure.
- Percent change in atrial volumes (both left and right), compared to Baseline (planned but not done).

CGIC and HRQOL

- CGIC compared to Baseline.
- Improvement of HRQOL assessed by SF-36 or SF-10, and Friedreich's Ataxia Impact Scale (FAIS) compared to Baseline.

Additional efficacy endpoints

Neurological

- Change in ICARS subscores (speech subscore of greatest interest), ICARS subscores "A-F and H" excluding "G", FARS subscores, and functional tests (25-foot timed walk [25FTW], 9-hole peg test [9HPT], PATA⁶) from Baseline to Week 24 and Week 52, and change in ICARS from Baseline to the average of Week 24 and Week 52 estimated with repeated measures analysis.
- Proportion of subjects showing a 2.5 point or greater improvement on ICARS at Week 24.
- Proportion of subjects on ICARS showing no change or any improvement, a 5-point or greater improvement, a 10% improvement, any worsening, and a 2.5 ICARS point worsening at Week 24 and Week 52, and proportion of subjects improving from Baseline to Week 24 and not worsening between Week 24 and Week 52.
- Proportion of subjects with an improvement of 2.5 ICARS or more with any improvement or no worsening on CGIC and with any improvement or no worsening on the FAIS at Week 24 and Week 52.
- Proportion of subjects who, at Week 24 and at Week 52 in at least one ICARS item (dysmetria of saccade excluded), improved from the maximal possible score present at Baseline, worsened to the maximal possible score, worsened from the minimal possible

⁶ The number of times 'PATA' is said in 10 seconds

score present at Baseline or improved to the minimal possible score.

• Number of ICARS subscores and ICARS items in which subjects improve, remain the same or worsen at Week 24 and at Week 52.

Cardiological

The following endpoints were to be assessed in a sub-population presenting cardiac involvement as defined by the FRDA-CM criteria, except endpoints relative to the exercise test:

- Proportion of subjects in which the PSLSR improves between Baseline and Week 24 and 52. The following definitions were used to define "improvement" in SR: any improvement (change from Baseline ≤0/sec); improvement of ≥0.2/sec (change from Baseline ≤-0.2/sec); improvement of ≥0.3/sec (change from Baseline ≤-0.3/sec).
- Proportion of subjects with abnormal LVPSSR (defined as >-1.2/s) at Baseline versus Week 24 and 52.
- Change in peak workload from Baseline to Week 24, and change in peak heart rate (HR), peak Borg-Fatigue scale and peak Borg-Dyspnea scale from the exercise test from Baseline to Week 24 and 52.
- Change in LVMI (measured by MRI) from Baseline to Week 24.
- Change in LVMI (measured by echocardiography) from Baseline to Week 24 and Week 52.
- Proportion of subjects showing a reduction in LVMI with no worsening in LVPSSR from Baseline to Week 24 and 52.
- Proportion of subjects improving on LVPSSR or showing a reduction in LVMI measured by MRI with no worsening in SR at Week 24.
- Proportion of subjects with a reduction in LVMI by at least 10% compared to Baseline (both measured by MRI and echocardiography) at Week 24 and 52.
- Change in relative wall thickness (RWT), ejection fraction (EF, by MRI and echocardiography), and LVM (by MRI and echocardiography) from Baseline to Week 24 and Week 52.
- Proportion of subjects with an abnormal RWT (>0.375 for children, >0.43 for adults) at Baseline who presented with normal RWT at Week 24 and 52.

Safety: Safety was assessed at each visit by evaluation of AEs (not Visit 1/Baseline), physical examinations, vital signs, ECG, clinical laboratory evaluation of hematological and biochemical parameters (blood and urine samples) and urine pregnancy test for women of childbearing potential.

Pharmacokinetics: Plasma concentrations of idebenone and its main metabolites were measured in blood samples taken at Baseline (pre-dose), Week 12, Week 24 and Week 52, using validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) methods.

Statistical Methods:

Continuous data were summarized using the number of subjects (n), mean, the standard deviation (SD), the standard error of the mean (SEM), the median, lower quartile (Q1) and upper quartile (Q3), the minimum and the maximum. Categorical data were presented in contingency tables or absolute and relative frequencies (n and %).

The primary analysis compared the combined group receiving mid/high dose of idebenone (450/900 mg/day and 1350/2250 mg/day idebenone) against the comparator group. Since it was expected that the low dose (180/360 mg/day idebenone) was not efficacious on the neurological endpoints (ICARS and FARS), the combined placebo and low dose groups were to be used as the comparator for these neurological endpoints in the case where the placebo group was non-inferior to the low dose group. The placebo group was to be considered as non-inferior to low dose group if the difference in estimated mean change from Baseline was less than or equal to 1 ICARS point between these groups. If the difference between placebo and low dose group was to be only the placebo group. For the secondary cardiological endpoints, the low dose group might be expected to be efficacious. For this reason, all idebenone doses were to be compared to placebo for analysis of the cardiological endpoints.

The absolute change from Baseline to Visit 7/Week 52 in ICARS scores were to be compared between active treatment group (combined mid/high dose) and comparator group using pairwise tests from an analysis of covariance (ANCOVA) model with treatment, body weight category, and walking status at Baseline as factors and Baseline value as covariate. A two-sided alpha level of 5% was used for hypothesis testing. The primary analysis was performed using the ITT population (all randomized subjects who received at least one dose of the study medication, had a confirmed diagnosis of FRDA, did not take idebenone within one month pre-Screening or between Screening and Visit 1, and were not under idebenone treatment at Baseline according to available PK results at Visit 1) on data imputed using last observation carried forward (LOCF) method.

Secondary and tertiary endpoints were analyzed using the same method as for the primary endpoint. Results were summarized using the ITT and ATP populations (all subjects from the ITT population with no major protocol violations).

If parametric assumptions were not met, a responder analysis (the proportion of subjects who had an improvement of at least 2.5 points in ICARS from Baseline to Week 52) was to be used as the primary analysis instead of the parametric methods. Where the assumptions of the parametric statistical methods were met, the responder analysis was to be a key secondary endpoint.

To explore the dose response relationship for change from Baseline in ICARS a trend analysis was performed in the ITT population. This analysis was based on a non-decreasing trend test using Jonckheere statistics at a 5% alpha level for each parameter. A similar trend analysis was also carried out for secondary endpoints where applicable.

Sensitivity and additional efficacy analyses

- Change from Baseline to Week 52 for ICARS total score excluding all items for each subject which have maximal severity score at Baseline.
- Subgroup analyses of efficacy endpoints (e.g. age at Baseline [various], gender, weight at Baseline, center, country, cardiac involvement [various] at Baseline, ICARS [various] and FRDA classification at Baseline, walking status at Baseline and time of randomization. The following subgroup analyses were also planned but not eventually done: disease duration, age of disease onset, prior use of idebenone, and for exercise tests a subset analysis for subjects with no change in leg/arm ergonometry between visits).
- Center and treatment-by-center interaction analysis for change in ICARS from Baseline to Week 52, and ICARS responder analysis.
- Repeated measures analysis of ICARS.
- Rasch analysis of FAIS (planned but not done).
- Relationship (Pearson's correlation coefficient and scatterplots) between the change from Baseline and Week 52 for the following parameters: change in ICARS and FARS, change in SF-36 (Question 2) and CGIC, change in FAIS (Items 1 to 5) and change in total ICARS and change in total FARS, change in FAIS (category 2–speech) and change in the speech subscore of ICARS or FARS, change in FAIS (category 4–walking) and change in the ICARS or FARS subscore addressing upright stability, change in peak workload and peak HR, change in peak workload and peak Borg-Fatigue scale or peak Borg-Dyspnea scale, change in peak Workload versus change in cardiac SR and strain (using the average "filtered" and "raw" data set).

All safety parameters were assessed in the Safety Population (all randomized subjects who received at least one dose of trial medication and for whom a safety assessment was available).

RESULTS AND CONCLUSIONS

Demographic Results:

A total of 232 subjects were randomized in a 1:1:1:1 ratio, with 57 subjects randomized to 180/360 mg/day idebenone, 56 randomized to 450/900 mg/day idebenone, 60 subjects randomized to 1350/2250 mg idebenone and 59 subjects randomized to placebo, with all subjects being included in the Safety population and 227 subjects being included in the ITT population. One subject (Subject 204-007) randomized to the 1350/2250 mg/day idebenone treatment group mistakenly received 450/900 mg/day idebenone, and thus for the Safety Population has been assigned to the 450/900 mg idebenone treatment group. This explains the difference between the numbers of subjects in the Safety population for these two treatment groups (n=57 for 450/900 mg/day idebenone and n=59 for 1350/2250 mg/day idebenone) and those randomized (n=56 for 450/900 mg/day idebenone and n=60 for 1350/2250 mg/day idebenone).

There was a broad range of disease severity (Baseline ICARS scores of 3 to 96) and ages (8 to 70 years) of subjects enrolled into the study, with low and high ICARS scores observed in both the younger and older subjects. Due to a high degree of variability in ICARS scores observed between Screening and Visit 1 ($S \rightarrow V_1$) (ranging from -10 to +12 points for individual subjects), the mean of these two assessments was used as Baseline ICARS. The $S \rightarrow V_1$ variability in ICARS appeared not to be correlated with Screening ICARS score.

Summary of Demographics and Other Baseline Characteristics (Safety Population)

Demographic and	nd Treatment Groups						
Other Baseline Characteristics	Placebo (N=59)	IDE 180/360 mg/day (Low Dose) (N=57)	Combined Placebo and Low Dose (N=116)	IDE 450/900 mg/day (Mid Dose) (N=57)	IDE 1350/2250 mg/day (High Dose) (N=59)	Combined Mid and High Dose (N=116)	Total (N=232)
Age, yrs at							
Screening,							
available obs. (n)	59	57	116	57	59	116	232
mean (SD)	30.4 (13.3)	30.9 (13.7)	30.7 (13.4)	31.6 (13.1)	30.9 (13.6)	31.2 (13.3)	30.9 (13.3)
median	29.0	29.0	29.0	28.0	29.0	28.5	29.0
min-max	8-65	8-70	8-70	13-63	8-68	8-68	8-70
n (%)							
0-17 yrs	12 (20.3)	9 (15.8)	21 (18.1)	7 (12.3)	10 (16.9)	17 (14.7)	38 (16.4)
<u>></u> 18 yrs	47 (79.7)	48.(84.2)	95 (81.9)	50 (87.7)	49 (83.1)	99 (85.3)	194 (83.6)
18-25 yrs	12 (20.3)	15 (26.3)	27 (23.3)	17 (29.8)	16 (27.1)	33 (28.4)	60 (25.9)
26-35 yrs	13 (22.0)	15 (26.3)	28 (24.1)	12 (21.1)	12 (20.3)	24 (20.7)	52 (22.4)
36-45 yrs	17 (28.8)	10 (17.5)	27 (23.3)	11 (19.3)	13 (22.0)	24 (20.7)	31 (22.0)
>45 yrs	5 (8.5)	8 (14.0)	13 (11.2)	10 (17.5)	8 (13.0)	18 (15.5)	51 (15.4)
Sex, no. (%)							
available obs. (n)	59	57	116	57	59	116	232
male	27 (45.8)	34 (59.6)	61 (52.6)	32 (56.1)	32 (54.2)	64 (55.2)	125 (53.9)
female	32 (54.2)	23 (40.4)	55 (47.4)	25 (43.9)	27 (45.8)	52 (44.8)	107 (46.1)
Daga no (0/)							
Race, no. (%)	50	57	116	57	50	116	222
Caucasian/White	56 (04 0)	54 (94 7)	110 (94.8)	56 (08 2)	56 (94.9)	112 (96.6)	232
Black	0	0	0	0	1 (17)	1 (0.9)	1 (0.4)
Oriental	1(17)	1(18)	2 (17)	0	1(1.7)	1 (0.9)	3 (1.3)
Hispanic	0	0	2(1.7)	0	0	0	0
Other	2 (3.4)	2 (3.5)	4 (3.4)	1 (1.8)	1 (1.7)	2 (1.7)	6 (2.6)
						(··· /	
Height, cm at							
Screening	E.C.	EC	112		59	112	225
available obs. (n)	20	56	112	55	58	113	225
mean (SD)	168.1 (12.3)	169.1 (11.8)	168.6 (12.0)	1/1.2 (10.1)	168.2 (11.6)	170.0	109.1 (11.5)
min may	131 104	133 102	131 104	172.0	135 102	135 105	131-195
mm-max	131-194	155-192	131-194	150-195	155-192	133-195	151-195
Weight, kg at BL							
available obs. (n)	58	57	115	57	59	116	231
mean (SD)	65.6 (17.2)	64.0 (17.6)	64.8 (17.3)	67.1 (16.5)	64.1 (14.7)	65.6 (15.6)	65.2 (16.5)
median	65.0	60.9	63.0	66.0	65.0	65.0	65.0
min-max	27.0-101.0	25.0-120.0	25.0-120.0	32.1-105	26.8-98.0	26.8-105.0	25.0-120.0
≤45 kg, no. (%)	5 (8.5)	6 (10.5)	11 (9.5)	4 (7.0)	5 (8.5)	9 (7.8)	20 (8.6)
>45 kg, no. (%)	54 (91.5)	51 (89.5)	105 (90.5)	53 (93.0)	54 (91.5)	107 (92.2)	212 (91.4)
BML kg/m ² at							
BL							
available obs. (n)	56	56	112	55	58	113	225
mean (SD)	23.1 (4.5)	22.3 (4.9)	22.7 (4.7)	22.8 (4.2)	22.5 (3.9)	22.6 (4.0)	22.7 (4.4)
median	22.4	21.8	22.1	22.8	22.9	22.8	22.5
min-max	13.8-35.2	14.1-39.2	13.8-39.2	14.3-33.1	13.3-30.3	13.3-33.1	13.3-39.2
Disease duration,							
months							
available obs. (n)	59	55	114	55	59	114	228
mean (SD)	178.0 (119.7)	190.1 (124.7)	183.8 (121.8)	160.4 (92.4)	184.8 (117.6)	173.0 (106.4)	178.4 (114.2
	145.0	180.4	158.4	143.8	155.8	150.1	155.7
median						0.507	0 100
median min-max	3-532	11-608	3-608	2-411	5-527	2-527	2-608

Baseline Neurological and Cardiac Characteristics	Placebo (N=58)	IDE 180/360 mg/day (Low Dose) (N=55)	Combined Placebo and Low Dose (N=113)	IDE 450/900 mg/day (Mid Dose) (N=55)	IDE 1350/2250 mg/day (High Dose) (N=59)	Combined Mid and High Dose (N=114)	Total (N=227)
Ability to Walk (Stratification factor) available obs. (n) Able to walk, n (%)	58 29 (50.0)	55 28 (50.9)	113 57 (50.4)	55 28 (50.9)	59 31 (52.5)	114 59 (51.8)	227 116 (51.1)
Ability to Walk (ICARS G13) available obs. (n) Able to walk, n (%)	58 29 (50.0)	55 25 (45.5)	113 54 (47.8)	55 27 (49.1)	59 29 (49.2)	114 56 (49.1)	227 110 (48.5)
Cardiac Involvement (Stratification factor) available obs. (n) HCM	49 30 (61.2)	46 26 (56.5)	95 56 (58.9)	46 28 (60.9)	50 31 (62.0)	96 59 (61.5)	191 115 (60.2)
Cardiac Involvement (defined by FRDA-CM) available obs. (n) Present	57 42 (73.7)	54 41 (75.9)	111 83 (74.8)	55 40 (72.7)	59 41 (69.5)	114 81 (71.1)	225 164 (72.9)
Cardiac hypertrophy at Baseline (echo- cardiography LVMI) available obs. (n) Present	51 13 (25.5)	52 15 (28.8)	103 28 (27.2)	48 13 (27.1)	56 18 (32.1)	104 31 (29.8)	207 59 (28.5)
ICARS at BL ¹ available obs. (n) median min-max n (%) $0 \le 33$ $> 33 \le 66$ $> 66 \le 100$ mild to mod (≤ 54) severe (> 54)	58 49.9 (21.5) 52.5 13.0-96.0 18 (31.0) 22 (37.9) 18 (31.0) 30 (51.7) 28 (48.3)	55 49.0 (22.5) 52.0 8.0-92.0 19 (34.5) 21 (38.2) 15 (27.3) 29 (52.7) 26 (47.3)	113 49.4 (21.9) 52.5 8.0-96.0 37 (32.7) 43 (38.1) 33 (29.2) 59 (52.2) 54 (47.8)	55 47.5 (19.8) 50.0 4.0-76.5 16 (29.1) 27 (49.1) 12 (21.8) 31 (56.4) 24 (43.6)	59 49.1 (22.0) 49.5 3.0-94.0 16 (27.1) 25 (42.4) 18 (30.5) 35 (59.3) 24 (40.7)	114 48.3 (20.9) 49.8 3.0-94.0 32 (28.1) 52 (45.6) 30 (26.3) 66 (57.9) 48 (42.1)	227 48.9 (21.4, 50.5 3.0-96.0 69 (30.4) 95 (41.9) 63 (27.8) 125 (55.1) 102 (44.9)
FARS at BL ¹ available obs. (n) mean (SD) median min-max	58 60.6 (23.6) 63.3 19-107	54 59.3 (26.5) 59.0 9-111	112 60.0 (24.9) 62.3 9-111	54 55.9 (23.2) 56.2 7-93	59 58.3 (25.4) 57.5 8-110	113 57.1 (24.3) 56.5 7-110	NC

Other Baseline Efficacy Characteristics of the ITT Population

¹Calculated Baseline = average between Screening and Baseline (Visit 1); obs: observations; IDE: Idebenone; FRDA-CM: Friedreich's ataxia cardiomyopathy; LVMI: Left ventricular mass index; BL: Baseline; SD: Standard deviation; HCM: Hypertrophic cardiomyopathy; ICARS: International Cooperative Ataxia Rating Scale; FARS: Friedreich's ataxia Rating Scale; NC: Not calculated

Efficacy Results:

Primary efficacy variable: Change in ICARS from Baseline to Week 52

Analysis of the primary endpoint, the change in the total ICARS from Baseline to Week 52 in the ITT population revealed that the ICARS scores for all idebenone treatment groups worsened by between 1.2 and 1.7 points (versus a worsening of 1.1 points with placebo) and the difference did not reach statistical significance for either the 450/900 mg/day (mid dose) or 1350/2250 mg/day idebenone (high dose) or for the combined mid and high dose groups

compared to either placebo or to the combined placebo and low dose (180/360 mg/day idebenone) groups. Similar results were noted in ATP population.

Absolute	Change	From	Baseline	to	Week	52	in	ICARS	(ITT)	Population –	LOCF
Method)											

ICARS	Placebo	Idebenone 180/360 mg/day (Low Dose)	Combined Placebo and Low Dose	Idebenone 450/900 mg/day (Mid Dose)	Idebenone 1350/2250 mg/day (High Dose)	Combined Mid and High Dose
Baseline ¹	49.9	49.0	49.4	47.5	49.1	48.3
Mean Change from BL to Week 52	1.1	1.6	1.4	1.7	1.2	1.4
SD	6.76	5.85	6.31	6.64	5.22	5.93
SEM	0.89	0.79	0.59	0.90	0.68	0.55
P-value ² vs Placebo vs Placebo/Low dose		0.857		0.860 0.921	0.953 0.862	$0.945 \\ 0.965$
Ν	58	55	113	55	59	114

¹ Baseline is defined as the sum of mean of scores obtained at Screening and Visit 1 (Baseline) for each item; ² From the difference in the least square means based on an ANCOVA model; BL: Baseline; SD: standard deviaton; SEM: standard error of mean; vs: versus.

ICARS responder analysis

Secondary endpoint: The ICARS responder analysis did not demonstrate a statistically significant difference at Week 52 between any of the idebenone treatment groups and placebo at the 2.5-point ICARS margin, or in the analyses for any improvement or for a 5-point margin.

ICARS Responder Analysis at Week 52: Percentage of Subjects Improving by 2.5 Points or More (ITT Population – LOCF Method)

ICARS Responder Analysis	Placebo	Idebenone 180/360 mg/day (Low Dose)	Combined Placebo and Low Dose	Idebenone 450/900 mg/day (Mid Dose)	Idebenone 1350/2250 mg/day (High Dose)	Combined Mid and High Dose
No. (%) Subjects Improving by ≥ 2.5 points	18 (31.0)	10 (18.2)	28 (24.8)	13 (23.6)	14 (23.7)	27 (23.7)
P-value ¹ vs placebo vs placebo/Low Dose		0.099		0.390 0.988	0.372 0.999	0.304 0.993
Ν	58	55	113	55	59	114

¹From a logistic regression with treatment, body weight category and walking status at Baseline as explanatory variables

Other ICARS responder endpoints: Tertiary and additional related endpoints and subgroup analyses did not reveal any new findings in favor of idebenone versus placebo, other than for a few isolated assessments showing no consistent pattern or trend.

Other ICARS results

Temporal pattern of change: ICARS scores marginally improved from Baseline to Week 24 in all treatment groups except 450/900mg/day idebenone, and then deteriorated from Week 24 to Week 52 for all groups.

Subscores and other tertiary and additional analyses: Analyses of the subscores on the ICARS did not reveal any consistent difference in favor of idebenone in any of the subscores, including speech, between the Baseline and Week 52 assessments. Other tertiary and additional neurological endpoints and analyses associated with absolute change in ICARS, including pre-specified sensitivity and most subgroup analyses did not reveal any consistent pattern in favor of idebenone versus placebo.

However, post-hoc sensitivity analyses did reveal that the $S \rightarrow V_1$ variability in ICARS score could have had a significant impact on the primary outcome measure. Since subjects with large variability of ≥ 4 ICARS points (+ or -) always appeared to decline from Baseline ICARS, it might be concluded that the setting of the Baseline (mean of Screening and Visit 1) and, therefore, the outcome has been unduly influenced by the better of the two assessments. A further post-hoc sensitivity analysis showed that for subjects with low $S \rightarrow V_1$ variability of <2 points subjects randomized to combined placebo/low dose (n=44) deteriorated (score increased) by approximately 2.5 points for the combined mid/high dose group (n=45).

A high level of variability in the rate of progression of FRDA in these subjects was illustrated in a post-hoc analysis comparing the historical rate of progression with the change in ICARS observed in the study from Baseline to Week 52. There was a broad range of both historical rates of progression and change in ICARS during the study but there was no discernible correlation between these variables for any dose group.

One subgroup analysis with noteworthy findings was the analysis for change in ICARS according to time of randomization which revealed that, overall, subjects enrolled early into the study tended to deteriorate to a lesser extent than those recruited later, irrespective of their drug assignment. An apparent drug effect was however, clearly discernable in subjects recruited late into the study. The outcome for the placebo group changed from -2.21 ICARS points (improvement) for the subjects recruited early to 5.07 ICARS points (worsening) for those recruited late. The idebenone group did not, however, deteriorate to the same extent over the course of the study, with subjects randomized late into the combined mid and high dose groups declining by 3.03 ICARS points. Further analysis of these data revealed a progressive treatment benefit for the combined mid and high dose groups versus placebo for those subjects recruited later into the study, with differences between groups ranging from -2.0 to -6.0 ICARS points during the final third of the recruitment period.

Results on the Friedrich's Ataxia Rating Scale (FARS)

Secondary endpoint: Similarly, the absolute change in FARS between Baseline and Week 52 showed no statistically significant difference between any idebenone treatment group and placebo with all treatment groups worsening by between 0.9 and 1.4 points.

Subscores and subgroup analyses: The change in FARS subscores between Baseline and Week 52 for the four treatment groups also did not show any statistical significant difference in favor of idebenone versus placebo. Subgroup analysis of absolute change in FARS did not reveal any consistent pattern or trend between treatment groups with no statistically significant differences noted other than in a few isolated cases.

Cardiac results

Due to methodological problems, inconsistencies and current lack of consensus amongst SR experts and the core laboratories undertaking the SR analyses, the interpretation of the SR data has proved extremely problematic. Thus the data presented here for SR represent Santhera's current analysis of the data provided by the core reading laboratory based on expert advice. These data will however be the subject of further analysis in due course and an updated, standalone report generated.

Secondary endpoints: There were no statistically significant differences between placebo and idebenone treatment groups for all the secondary cardiac endpoints in subjects presenting with FRDA-CM. This included proportion of subjects improving on LVPSSR or showing a reduction in LVMI with no worsening in SR at Week 52, change in PSLSR and PSLS from Baseline to Week 52 (assessing myocardial function), and change in peak workload from Baseline to Week 52 (assessed in all subjects) which measured exercise capacity using a modified exercise test.

The proportion of subjects improving on LVPSSR or showing a reduction in LVMI with no worsening in SR was 44.1% for the placebo group compared with 50.0%, 51.4% and 30.3% with 180/360 mg/day, 450/900 mg/day and 1350/2250 mg/day idebenone, respectively.

Other cardiac endpoints: LVMI (MRI/Du Bois) increased (i.e. deteriorated) in all idebenone treatment groups from Baseline to Week 52 ranging from increases of 1.80 to 4.45 g/m² while mean values in the placebo group decreased (i.e. improved) by 0.14 g/m^2 , with the difference between placebo and 180/360 mg/day idebenone reaching statistical significance in favor of placebo (p=0.016), and p-values for the other idebenone treatment groups versus placebo approached statistical significance (p=0.092 and p=0.065). A similar pattern was seen when the De Simone method was used for LVMI (MRI). In contrast mean values for LVMI (by echocardiography using Du Bois or De Simone) improved in all treatment groups from Baseline to Week 52, with the improvement with placebo being generally slightly more than with 180/360 mg/day idebenone, although there were no statistically significant differences observed. As would be expected the difference between MRI and echocardiography measurement of LVMI was also reflected in the LVM mean data.

There were no statistically significant differences observed between treatment groups for EF in the LOCF analyses but in the observed cases (OC) analysis the difference between the change in EF from Baseline to Week 52 for 1350/2250 mg/day idebenone and placebo (3.2% increase versus 1.1% increase, respectively) reached statistical significance (p=0.033). The only finding of note for the RWT analysis was for the 180/360 mg/day group which had a higher proportion of subjects switching from abnormal to normal RWT from Baseline to Week 52 (25.8% versus 6.1%, p=0.047) and from Baseline to Week 24 (22.6% versus 3.0%, p=0.044). There were no statistically significant differences between groups for diastolic function other than an isolated case in the 450/900 mg/day idebenone group at Week 24 where DT was increased from Baseline by 8.40% compared with a 0.60% decrease with placebo (p=0.034).

Subgroup analyses: Overall there were no findings of note between treatment groups for the subgroup analyses for the proportion of subjects improving on LVPSSR or showing a reduction in LVMI with no change in SR, and for change in PSLSR, PSLS and peak workload, with no consistent pattern or trend and only isolated cases where p<0.05.

CGIC and HRQOL

There no statistically significant findings observed across treatment groups for SF-10, and SF-36, and only one isolated case for a CGIC subscore, where a higher proportion of subjects on 180/360 mg/day idebenone improved at Week 52 on coordination of lower limb and/or gait and/or stance than in the placebo group (17.4% versus 2.3%, respectively, p=0.042). Subjects in one or more idebenone treatment groups performed less well at Week 52 than placebo for some FAIS subscores including activities of daily living (ADL)/complex tasks subscore, combined subscores 1-5, change in self perception (at Week 24 only), proportion of subjects improving on speech/swallowing subscore (at Weeks 24 and 52) and on self perception subscore, lower limb functioning subscore and ADL/complex tasks) subscore, with differences between groups reaching statistical significance. The only parameter for which idebenone performed statistically better than placebo was in the OC analysis for the mood subscore where 56.9% of subjects on 1350/2250 mg/day idebenone showed an improvement at Week 52 compared with 40.2% of subjects in the combined placebo/low dose group (p=0.035).

Other tests

No statistically significant differences between treatments in favor of idebenone were seen for peak HR, peak Borg-Fatigue scale, peak Borg-Dyspnea scale and functional tests (25FTW, 9HPT, PATA).

Pharmacokinetic Results:

Mean plasma idebenone concentrations at Weeks 12, 24 and 52 for the ITT population ranged from 0.173 ng/ml to 0.345 ng/ml for the 180/360 mg/day idebenone group, 0.896 ng/ml to 1.647 ng/ml for the 450/900 mg/day idebenone group and 4.099 ng/ml to 4.369 ng/ml for the 1350/2250 mg/day idebenone group, with an approximate 2.6-8.5 fold difference between 180/360 mg/day and 450/900 mg/day idebenone and a 2.6-4.6 fold difference between

450/900 mg/day idebenone and 1350/2250 mg/day idebenone, indicating a higher but approximately dose-proportional exposure to idebenone. In general, similar shaped concentration versus time profiles were observed for IDE+IDE-C, QS10, QS10+QS10-C, QS6+QS6-C and QS4+QS4-C, although mean plasma concentrations at all time points were higher than those for idebenone, with IDE+IDE-C and QS4+QS4-C showing the highest maximum mean values (180/360 mg/day idebenone: 1250.6 ng/ml and 1399.7 ng/ml, respectively; 450/900 mg/day idebenone: 4083.3 ng/ml and 4585.6 ng/ml, respectively; 1350/2250 mg/day idebenone: 9341.3 ng/ml and 8570.7 ng/ml, respectively). Detectable levels of idebenone and/or metabolites were measured in blood samples of two subjects on placebo.

Safety Results:

Idebenone was safe and well-tolerated at doses of up to 2250 mg/day in subjects with FRDA, aged 8-70 years old. AEs were reported by 88.1% of the subjects receiving 1350/2250 mg/day idebenone, 91.2% of those on the 450/900 mg/day idebenone and 96.5% on 180/360 mg/day idebenone, compared to 93.2% of the subjects on placebo. Most AEs were mild or moderate in severity, with a similar frequency being reported by idebenone- and placebo-treated subjects (mild: 46.8% versus 47.5%, respectively); moderate: 34.1% versus 35.6%, respectively). Severe AEs were less common, and also reported at a similar frequency by idebenone- and placebo-treated subjects (11.0% versus 10.2%, respectively). AEs considered by the Investigator to be related to treatment were reported at similar frequency in placebo- and idebenone-treated subjects (54.2% versus 52.6%), with no noteworthy differences noted between the three idebenone treatment groups (50.9%, 54.4% and 52.5%).

There were no subjects who died due to an AE. Two subjects (3.4%) on placebo and 5 subjects (2.9%) in the idebenone treatment groups discontinued treatment permanently due to at least one AE. The higher frequency of AEs leading to study drug discontinuation in the 180/360 mg/day idebenone group (4 subjects [7.0%]) was mainly due to the occurrence of pregnancy in two subjects in this group. Serious adverse events (SAEs) were experienced by 7 subjects (12.3%) on 180/360 mg/day idebenone, 4 subjects (7.0%) on 450/900 mg/day idebenone and 8 subjects (13.6%) on 1350/2250 mg/day idebenone, compared to 7 subjects (11.9%) on placebo (although only 6 subjects [10.2%] on placebo reported treatment-emergent SAEs, with the seventh subject experiencing his only SAE prior to starting study medication). Overall, the nature and frequency of the reported SAEs were similar across all study groups, with no noteworthy findings detected following review of these data.

The nature, severity and frequency of the AE observed in the MICONOS study were very similar in subjects treated with idebenone and subjects receiving placebo. The distribution of all AEs, regardless of causality, observed in 5% or more of the subjects in any of the treatment groups are shown in the Table overleaf. Most of the AEs were reported in the Infections and Infestations, Gastrointestinal, Musculoskeletal and Nervous System Disorders System Organ Classes (SOCs).

The most frequently reported AEs across the three idebenone treatment groups in order of decreasing frequency were nasopharyngitis (68 subjects, 39.3%), headache (51 subjects,

29.5%), diarrhea (36 subjects, 20.8%), nausea (26 subjects, 15.0%), back pain (23 subjects, 13.3%), vomiting (21 subjects, 12.1%), cough (19 subjects, 11.0%), influenza and oropharyngeal pain (17 subjects each, 9.8%), pain in extremity (16 subjects, 9.2%), and abdominal pain upper (15 subjects, 8.7%). Overall, the frequency of AEs in the active treatment groups was comparable or lower than that observed in the placebo group, with the main exceptions of vomiting, diarrhea, bronchitis, nasopharyngitis, musculoskeletal pain and back pain; only this latter one appears somewhat correlated to the dose regimen.

Summary of AEs Reported by ≥5% in any of Treatment Groups – Safety Population

MedDRA SOC	Number (%) of Subjects Reporting AE								
Preferred Term	Placebo (N=59)	Idebenone 180/360 mg/day (N=57)	Idebenone 450/900 mg/day (N=57)	Idebenone 1350/2250 mg/day (N=59)	Total Idebenone (N=173)				
At least one AE in any SOC	55 (93.2)	55 (96.5)	52 (91.2)	52 (88.1)	159 (91.9)				
Blood & Lymphatic System Disorders	3 (5.1)	1 (1.8)	2 (3.5)	2 (3.4)	5 (2.9)				
Cardiac Disorders	8 (13.6)	7 (12.3)	5 (8.8)	7 (11.9)	19 (11.0)				
Palpitations	2 (3.4)	1 (1.8)	1 (1.8)	3 (5.1)	5 (2.9)				
Tachycardia	2 (3.4)	3 (5.3)	0	1 (1.7)	4 (2.3)				
Ear & Labyrinth Disorders	4 (6.8)	4 (7.0)	5 (8.8)	1 (1.7)	10 (5.8)				
Vertigo	3 (5.1)	1 (1.8)	2 (3.5)	0	3 (1.7)				
Endocrine Disorders	1 (1.7)	0	3 (5.3)	0	3 (1.7)				
Eye Disorders	2 (3.4)	4 (7.0)	3 (5.3)	1 (1.7)	8 (4.6)				
Gastrointestinal Disorders	28 (47.5)	26 (45.6)	32 (56.1)	22 (37.3)	80 (46.2)				
Diarrhea	8 (13.6)	10 (17.5)	16 (28.1)	10 (16.9)	36 (20.8)				
Nausea	9 (15.3)	6 (10.5)	8 (14.0)	12 (20.3)	26 (15.0)				
Vomiting	2 (3.4)	9 (15.8)	5 (8.8)	7 (11.9)	21 (12.1)				
Abdominal pain upper	6 (10.2)	3 (5.3)	6 (10.5)	6 (10.2)	15 (8.7)				
Abdominal pain	7 (11.9)	4 (7.0)	5 (8.8)	2 (3.4)	11 (6.4)				
Toothache	3 (5.1)	1 (1.8)	6 (10.5)	4 (6.8)	11 (6.4)				
Dyspepsia	2 (3.4)	0	4 (7.0)	1 (1.7)	5 (2.9)				
Flatulence	3 (5.1)	0.	0	1 (1.7)	1 (0.6)				
General Disorders & Administration Site Conditions	9 (15.3)	9 (15.8)	10 (17.5)	11 (18.6)	30 (17.3)				
Fatigue	5 (8.5)	5 (8.8)	2 (3.5)	2 (3.4)	9 (5.2)				
Edema peripheral	1(1.7)	0	3 (5.3)	3 (5.1)	6 (3.5)				
Pyrexia	3 (5.1)	1 (1.8)	3 (5.3)	0	4 (2.3)				
Influenza like illness	0	1 (1.8)	0	3 (5.1)	4 (2.3)				
Infections & Infestations	37 (62.7)	36 (63.2)	40 (70.2)	37 (62.7)	113 (65.3)				
Nasopharyngitis	21 (35.6)	22 (38.6)	25 (43.9)	21 (35.6)	68 (39.3)				
Influenza	5 (8.5)	7 (12.3)	6 (10.5)	4 (6.8)	17 (9.8)				
Bronchitis	1 (1.7)	3 (5.3)	3 (5.3)	4 (6.8)	10 (5.8)				
Sinusitis	4 (6.8)	2 (3.5)	1 (1.8)	3 (5.1)	6 (3.5)				
Gastroenteritis	2 (3.4)	1 (1.8)	2 (3.5)	3 (5.1)	6 (3.5)				
Upper respiratory tract infection	2 (3.4)	2 (3.5)	1 (1.8)	3 (5.1)	6 (3.5)				
Cystitis	1 (1.7)	1 (1.8)	4 (7.0)	1 (1.7)	6 (3.5)				
Rhinitis	3 (5.1)	2 (3.5)	0	1 (1.7)	3 (1.7)				
Urinary tract infection	0	0	2 (3.5)	3 (5.1)	5 (2.9)				
Tracheitis	3 (5.1)	0	0	0	0				

Santhera Pharmaceuticals (Switzerland) Ltd Idebenone

SNT-III-001 SYNOPSIS Page 18 of 20

MedDRA SOC	Number (%) of Subjects Reporting AE									
Preferred Term	Placebo (N=59)	Idebenone 180/360 mg/day (N=57)	Idebenone 450/900 mg/day (N=57)	Idebenone 1350/2250 mg/day (N=59)	Total Idebenone (N=173)					
Injury, Poisoning &	14 (23.7)	13 (22.8)	16 (28.1)	12 (20.3)	41 (23.7)					
Procedural Complications										
Fall	7 (11.9)	4 (7.0)	7 (12.3)	2 (3.4)	13 (7.5)					
Joint sprain	3 (5.1)	0	2 (3.5)	2 (3.4)	4 (2.3)					
Procedural pain	1 (1.7)	0	0	3 (5.1)	3 (1.7)					
Investigations	5 (8.5)	6 (10.5)	5 (8.8)	12 (20.3)	23 (13.3)					
N-terminal prohormone BNP	0	0	0	3 (5.1)	3 (1.7)					
Metabolism & Nutrition Disorders	5 (8.5)	4 (7.0)	1 (1.8)	4 (6.8)	9 (5.2)					
Musculoskeletal & Connective Tissue Disorders	19 (32.2)	18 (31.6)	25 (43.9)	20 (33.9)	63 (36.4)					
Back pain	6 (10.2)	3 (5.3)	11 (19.3)	9 (15.3)	23 (13.3)					
Pain in extremity	5 (8.5)	4 (7.0)	7 (12.3)	5 (8.5)	16 (9.2)					
Arthralgia	3 (5.1)	4 (7.0)	5 (8.8)	2 (3.4)	11 (6.4)					
Musculoskeletal pain	0	4 (7.0)	1 (1.8)	1 (1.7)	6 (3.5)					
Muscle spasms	5 (8.5)	1 (1.8)	2 (3.5)	2 (3.4)	5 (2.9)					
Musculoskeletal stiffness	2 (3.4)	3 (5.3)	0	2 (3.4)	5 (2.9)					
Myalgia	3 (5.1)	1 (1.8)	0	0	1 (0.6)					
Nervous System Disorders	27 (45.8)	22 (38.6)	23 (40.4)	23 (39.0)	68 (39.3)					
Headache	23 (39.0)	16 (28.1)	20 (35.1)	15 (25.4)	51 (29.5)					
Dizziness	2 (3.4)	4 (7.0)	2 (3.5)	1 (1.7)	7 (4.0)					
Hypoesthesia	1 (1.7)	0	0	3 (5.1)	3 (1.7)					
Psychiatric Disorders	5 (8.5)	3 (5.3)	2 (3.5)	4 (6.8)	9 (5.2)					
Renal & Urinary Disorders	6 (10.2)	5 (8.8)	0	2 (3.4)	7 (4.0)					
Hematuria	0	3 (5.3)	0	0	3 (1.7)					
Reproductive System and Breast Disorders	8 (13.6)	5 (8.8)	1 (1.8)	2 (3.4)	8 (4.6)					
Dysmenorrhea	5 (8.5)	1 (1.8)	1 (1.8)	1 (1.7)	3 (1.7)					
Respiratory, Thoracic & Mediastinal Disorders	14 (23.7)	17 (29.8)	8 (14.0)	11 (18.6)	36 (20.8)					
Cough	6 (10.2)	11 (19.3)	2 (3.5)	6 (10.2)	19 (11.0)					
Oropharyngeal pain	7 (11.9)	5 (8.8)	6 (10.5)	6 (10.2)	17 (9.8)					
Skin & Subcutaneous Tissue Disorders	6 (10.2)	7 (12.3)	13 (22.8)	4 (6.8)	24 (13.9)					
Rash	3 (5.1)	3 (5.3)	1 (1.8)	1 (1.7)	5 (2.9)					
Pruritus	1 (1.7)	0	3 (5.3)	2 (3.4)	5 (2.9)					
Surgical & Medical Procedures	2 (3.4)	3 (5.3)	1 (1.8)	6 (10.2)	10 (5.8)					
Foot operation	0	0	0	3 (5.1)	3 (1.7)					
Vascular Disorders	3 (5.1)	2 (3.5)	3 (5.3)	5 (8.5)	10 (5.8)					

AE: Adverse event; MedDRA: Medical Dictionary for Regulatory Activities; SOC: System Organ Class; BNP: brain natriuretic peptide; AEs coded using MedDRA dictionary version 12.1

Laboratory parameters appeared fundamentally similar across all study groups, with no evidence of drug-related, clinically significant abnormalities. A noteworthy pattern concerning leukocytes was detected, i.e. a slight but consistent decrease compared to Baseline in all idebenone study groups. The decrease affected mainly the 450/900 mg/day group at Visit 2 (Week 4) and 4 (Week 12), was generally irrelevant (the mean was always within normal range) and did not worsen over time. In none of the subjects was the decrease considered clinically "notable" (i.e. $<2 \times 10^9$ /l). No noteworthy findings were identified during the review of vital signs, physical examination and ECG parameters.

Conclusions:

There were no statistically significant differences noted between placebo (or combined placebo/low dose when used) and idebenone treatment groups for the primary efficacy variable (change in ICARS from Baseline to Week 52) or for the secondary efficacy variables (Baseline to Week 52 analysis for ICARS responders [≥2.5 margin], change in FARS, LVPSSR responders or subjects showing a reduction in LVMI with no worsening in SR, change in PSLSR, change in PSLS and change in peak workload).

The same was true for majority of the tertiary efficacy variables (Change from Baseline to Week 24 analyses of primary and secondary variables, and SF-36 and SF-10 [HRQOL assessments]). However, statistically significant differences in favor of 180/360 mg/day idebenone over placebo were noted for the CGIC subscore coordination of lower limb and/or gait and/or stance at Week 52, and statistically significant differences in favor of placebo over one or more idebenone treatment groups were noted for the change in some of the FAIS subscores and the change in LVMI (MRI, Du Bois method). There were no statistically significant differences in diastolic function parameters from Baseline to Week 52 or from Baseline to Week 24, other than for the change in DT from Baseline to Week 24 (8.4% increase with 450/900 mg/day idebenone versus 0.6% decrease with placebo).

Although there were some isolated cases where statistically significant differences were observed between placebo and idebenone treatment groups for the additional efficacy endpoints, or for the pre-specified sensitivity and exploratory analyses (such as the subgroup analyses), there was no consistent pattern or trend for the majority of analyses supporting a superior effect of any idebenone treatment group over the placebo treatment group. The only noteworthy exceptions to this were trends seen in favor of idebenone versus placebo or placebo/low dose in the subgroup analyses for change in ICARS from Baseline to Week 52 by time of randomization (in subjects recruited late into the study) and in the post-hoc analysis of subgroups with low $S \rightarrow V_1$ variability of <2 points. There was a broad range of both historical rates of progression and change in ICARS during the study but there was no discernible correlation between these variables for any dose group.

Mean idebenone plasma concentrations were approximately 2.6-8.5-fold greater in subjects who received 400/900 mg/day idebenone compared with those who received 180/360 mg/day idebenone, and 2.6-4.6-fold greater in subjects who received 1350/2250 mg/day idebenone compared with those who received 450/900 mg/day idebenone, indicating a higher but approximately dose-proportional exposure to idebenone.

In general, similar shaped concentration versus time profiles were observed for IDE+IDE-C and the other metabolites/conjugates, although mean plasma concentrations were higher than those for idebenone, with IDE+IDE-C and QS4+QS4-C showing the highest mean values.

Idebenone was safe and well tolerated at doses up to 2250 mg/day. The only AEs potentially associated with the treatment appeared to be minor gastrointestinal disorders of mild to moderate severity, usually not requiring treatment discontinuation.

It would appear that inherent variability in the presentation of FRDA as evidenced by the ICARS score and other factors (insensitivity of the ICARS to change over short periods of time, subjects with long disease duration, variability in disease progression, and time of randomization effects) have adversely affected the outcome of this trial.

Date of Report: 29 November 2010