Clinical Study Report Synopsis

Study Title:	A single visit, observational, follow-up study of patients with Leber's Hereditary Optic Neuropathy following participation in SNT-II-003 trial
Study Acronym	RHODOS-OFU
Study Number:	SNT-II-003-OFU
EudraCT Number:	2011-001034-42
US IND Number:	N/A
ClinicalTrials.gov Identifier:	NCT01421381
Study Phase:	N/A (Observational study)
Study Design:	Single visit, observational study, with historic comparison
Product Name:	None
Indication:	Leber's Hereditary Optic Neuropathy (LHON)
Study Initiated (first patient enrolled):	21 September 2011
Study Completed (last patient completed):	16 November 2011
Principal Investigator(s):	Prof Patrick Chinnery Institute of Genetic Medicine, Newcastle University, Central Parkway, Newcastle upon Tyne, NE1 3BZ, United Kingdom Prof Thomas Klopstock Friedrich Baur Institut Neurologische Klinik und Poliklinik, Ludwig-Maximilians-Universität München, Ziemssenstrasse 1a, D-80336 Munich, Germany Dr Jacinthe Rouleau Hôpital Notre-Dame (CHUM), Unité de recherche, Clinique Ophtalmologie, Pavillon Deschamps, RC, Porte IR 1190, 1560 rue Sherbrooke Est, Montreal, Quebec, H2L 4M1, Canada
Sponsor:	Santhera Pharmaceuticals (Switzerland) Ltd. Hammerstrasse 49, CH-4410 Liestal, Switzerland Tel: [redacted] Fax: [redacted]
Responsible Medical Officer (Core Clinician):	Senior Clinical Research Physician
Version:	1.0
Final Date:	1 May 2012

Objectives:

Primary objective:

- To assess the current logarithm of the minimum angle of resolution (logMAR) visual acuity (VA) of LHON patients who participated in the SNT-II-003 trial and compare this to their logMAR visual acuity at Visit 2/Baseline and Visit 5/Week 24 or last treatment visit of SNT-II-003

Secondary objectives:

- To assess the current Health-Related Quality of Life (HRQoL) status of patients who participated in the SNT-II-003 trial and compare this with the result from Visit 2/Baseline and Visit 5/ Week 24 or last treatment visit of SNT-II-003
- To investigate whether any medical procedure or medication undertaken or received since the patient's last visit of SNT-II-003 may have affected the natural history of LHON

Tertiary objectives:

- To collect information from all participating patients concerning the natural history of the disease from onset of disease to enrolment in SNT-II-003 and since completion of SNT-II-003 and to determine the change over time in visual acuity from onset of vision loss to entry into SNT-II-003

Methodology:

Patients who previously participated in study SNT-II-003 were approached by their local Investigator to attend a visit to ascertain the current status of their visual acuity. Patients who agreed to participate in the present study attended a single visit at which Informed Consent was obtained from the patient and, if applicable, their parents/legal guardian prior to any study-specific procedures taking place.

Inclusion criterion was assessed and eligible patients were included in the study.

The patient's current medical status was assessed and any medical conditions were assessed for seriousness and a potential causal and temporal relationship with SNT-II-003 study medication. A fundoscopic examination as well as an assessment of vital signs was performed. The visual acuity was assessed using the same procedure as during SNT-II-003. Past and current medication since the end of patient's participation in SNT-II-003 was also recorded.

Change in HRQoL was assessed by the patients themselves.

Information pertaining to the natural history of LHON was collected from all participating patients. Where possible/feasible, this included gathering this information from the patient's referring physician to provide a complete record of the progression on disease since onset.

Number of Patients (Planned and Analyzed):

Planned: Up to 85 patients who previously received idebenone (55) or placebo (30) in SNT-II-003.

Completed: 60 patients (Previous treatment in SNT-II-003: idebenone: 41 patients; placebo: 19 patients)

Analyzed for Safety: 60 patients (Previous treatment in SNT-II-003: idebenone: 41 patients; placebo: 19 patients)

Analyzed for change in visual acuity (Total Efficacy Population, i.e. patients with valid VA data): 58 patients (Previous treatment in SNT-II-003: idebenone: 39 patients; placebo: 19 patients)

Diagnosis and Main Criteria for Inclusion:

Previous participation in study SNT-II-003 (RHODOS)

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

No treatment.

Duration of Treatment:

N/A

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

N/A

Criteria for Evaluation:

Efficacy:

The following assessments were performed at the single observational visit.

- Visual acuity (logMAR assessed by Early Treatment Diabetic Retinopathy Study [ETDRS] chart)
- HRQoL assessed by Visual Functioning 14 questionnaire (VF-14)
- Past/current medication, supplements and idebenone
- Natural history of LHON

Safety:

The current medical status of the patients was established at the single observational visit. Any current medical conditions were assessed to determine seriousness. Serious adverse events (SAEs) were recorded in the electronic case report form (eCRF). The Investigator assessed any SAEs for causality and any event judged by the Investigator as having a reasonable suspected causal and temporal relationship with the study medication administered during SNT-II-003 was to be reported to the Sponsor. A fundoscopic examination and an assessment of vital signs, including heart rate (HR), blood pressure (BP) in sitting position, respiratory rate and body weight, were performed.

Statistical Methods:

The primary goal of this study was to evaluate the change in visual acuity in LHON patients following the end of their participation in the SNT-II-003 study.

The efficacy analysis variables were:

Primary endpoint:

- Change in best logMAR visual acuity (*Best Visual Acuity[VA]*) compared to Visit 2/Baseline and Visit 5/Week 24 or last treatment visit of SNT-II-003

Secondary endpoints:

- Change in logMAR visual acuity of individual eyes (*Change in VA of Both Eyes*) compared to Visit 2/Baseline and Visit 5/Week 24 or last treatment visit of SNT-II-003
- Change in logMAR visual acuity of a patient's best eye (*Change in VA of the Best Eye*) compared to the same eye at Visit 2/Baseline or Visit 5/Week 24 or last treatment visit of SNT-II-003.
- Change in HRQoL assessed by VF-14 questionnaire compared to Visit 2/Baseline and Visit 5/Week 24 or last treatment visit of SNT-II-003

Tertiary endpoint:

- Descriptive history of change in visual acuity since onset of LHON.

Sample size and power considerations were not applicable to this observational study design. The sample size was based solely on the number of patients enrolled in the SNT-II-003 trial.

All patients who participated in the SNT-II-003 observational follow-up (SNT-II-003-OFU) study were included in the safety analysis (Safety Population). Patients with valid visual acuity assessments in SNT-II-003 and who participated in the SNT-II-003-OFU were included in the efficacy analysis (Total Efficacy Population).

The study data were tabulated by treatment group during SNT-II-003 (and by visit) with appropriate descriptive summary statistics. For categorical variables numbers and percentages were calculated. Continuous variables were summarized using means, medians, standard error of means (SEM), standard deviations (SD) and ranges. In all statistical analyses, a two-sided p-value of less than 0.05 was considered statistically significant unless stated otherwise.

If the assumptions of the parametric statistical methods were not fulfilled, corresponding non-parametric methods or suitable transformations were to be considered.

Efficacy:

The primary endpoint, the change in best logMAR visual acuity (*Best VA*) compared to Visit 2/Baseline and Visit 5/Week 24 or last treatment visit of SNT-II-003, was analyzed using a mixed model for repeated measures (MMRM). The model included the Baseline value of SNT-II-003 as a covariate. The fixed factors include the stratification factors of study SNT-II-003 (mtDNA [mitochondrial deoxyribonucleic acid] mutation and time since onset of symptoms less than or at least one year), visit, treatment group during SNT-II-003 and the

interaction between the visit and treatment group. The response data consisted of all post-Baseline visits of SNT-II-003 (Weeks 4, 12 and 24) and of the present study.

The changes from Baseline of SNT-II-003 to each visit were calculated for both treatment groups of SNT-II-003 based on the MMRM. Furthermore, the change from Week 24 of SNT-II-003 to the present study as well as the changes within the treatment groups and the difference between the groups was calculated.

The secondary efficacy endpoints (*Change in VA of Both Eyes*, *Change in VA of the Best Eye*, and change in HRQoL assessed by VF-14 questionnaire) were analyzed using similar methods as used for the primary endpoint. The tertiary endpoint (descriptive history of LHON) was specified as an exploratory analysis and descriptive analyses were to be applied.

This was an exploratory study and, therefore, no formal statistical hypotheses were tested. The changes in the endpoints from Baseline of SNT-II-003 and Week 24 (or last treatment visit of SNT-II-003) to the present study were compared between the patients who received idebenone in SNT-II-003 versus those who received placebo in order to explore if the difference detected in SNT-II-003 between the groups had been maintained or not.

Responder analyses were conducted for the proportion of patients (or eyes) with improvement in VA from "off-chart" to "on-chart" and reading at least one full line (i.e. logMAR $\leq$1.6). Fisher's exact test was applied for the comparison of treatment groups as assigned during SNT-II-003 at each time point.

Visual acuity endpoints were also analyzed in patient subgroups:

- patients carrying either the G11778A or G3460A mtDNA mutation
- patients carrying either the G11778A or G3460A mtDNA mutation with onset of symptoms $\leq$1 year at Baseline of SNT-II-003,

In addition, for the Total Efficacy Population and the sub-populations listed above, sensitivity analyses were conducted for which natural history confounder Patient 23 was excluded.

Time elapsed from the last visit of study SNT-II-003 to SNT-II-003-OFU was also explored descriptively for the *Best VA* endpoint.

Safety*:*

SAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and listed. Current medical conditions were coded using MedDRA and tabulated. Vitals signs and fundoscopic examination were summarized using standard descriptive statistics.

Summary of Results:

Demographic Results:

Sixty patients (70.7 %) participating in SNT-II-003 were enrolled into this study, of whom 58 patients provided VA data and were included in the Total Efficacy Population. Baseline demographic characteristics (derived at start of SNT-II-003) for the patients in the Total Efficacy Population of the SNT-II-003-OFU were well-matched across the groups randomized to idebenone and placebo treatment during SNT-II-003. The mean (± SD) age of patients at the time of enrolment into SNT-II-003 was 33.4 (±14.9) years; by the time of the SNT-II-003-OFU visit it was 36.5 (± 15.0) years.

The majority of patients recruited were male (50 patients [86.2 %]) and almost all patients (56 patients [96.6 %]) were Caucasian/white. The proportion of patients who were current smokers was comparable across treatment groups (idebenone: 43.6%; placebo: 42.1%).

The median time since Week 24 of the Study SNT-II-003 to SNT-II-003-OFU was 30.1 months (mean [±SD]: 30.5 [±4.9] months; range: 20.9 to 42.5 months) for the Total Efficacy Population (N=58).

The mean (±SD) time since onset of vision loss at the Baseline visit of SNT-II-003 was 22 (±16) months for the idebenone group and marginally higher at 25 (±18) months for the placebo group. The proportion of patients at Baseline of SNT-II-003 with onset of symptoms less than one year was slightly higher (but not statistically significant [p=0.57 Fisher Exact Test]) in the idebenone treatment group (16 patients, 41.0%) than in the placebo group (6 patients, 31.6%). At the time of enrolment in SNT-II-003-OFU, the mean (±SD) time since onset of symptoms (i.e. vision loss) was 57 (±17) months and 62 (±20) months for the idebenone and placebo groups, respectively.

The most common mtDNA mutation was G11778A (found in 28 patients [71.8%] in the idebenone group and 13 patients [68.4%] in the placebo group). There were 5 patients (12.8%) in the idebenone group and 4 patients (21.1%) in the placebo group with the G3460A mutation and 6 patients (15.4%) in the idebenone group and 2 patients (10.5%) in the placebo group with the T14484C mutation. The proportion of patients with either the G11778A or the G3460A mutation was comparable across treatment groups (84.6% versus 89.5%). In the Total Efficacy Population, the mean (±SD) visual acuity at Baseline of SNT-II-003 for the two eyes pooled was logMAR 1.72 (±0.641) for the idebenone group and logMAR 1.66 (±0.552) for the placebo group.

In summary, there were no notable differences or changes in patient demographics when study subjects were separated by SNT-II-003 treatment group and compared to Baseline of SNT-II-003, from which it can be concluded that no demographic selection bias was introduced.

Efficacy Results:

Comparative Natural History

Graphical presentations of the trajectories of all reported historical VA data including the data from the SNT-II-003 and SNT-II-003-OFU visits were produced on a patient-by-patient basis, with the trajectories showing logMAR values for each eye since the onset of symptoms in the first eye. **Individual Patient Narratives** include these graphical representations of the trajectories together with relevant medical information for each

patient. From the 60 patients enrolled in SNT-II-003-OFU, 37 patients provided interpretable VA data from their disease history. The analysis of individual patients' natural history and trajectory of change in visual acuity from the time before enrolment into the randomized intervention study SNT-II-003 clearly showed that visual acuity of LHON patients typically deteriorates very rapidly within a few months from onset of symptoms. These findings are in agreement with data from the published literature indicating that patients experience profound vision loss within 2-4 months from symptom onset.

Comparative analyses of these data revealed patients with natural histories clearly deviating from the expected, disease-typical course with confounding influence on data interpretation, such as:

- Patients with stable discordant VA (i.e. patients in whom the least affected eye did not progress to blindness as expected from the disease-typical natural history). There were three patients enrolled in SNT-II-003 who had long-term (1.7 to 5 years) stable discordant VA (i.e. with logMAR 0.2 difference in VA between eyes). Such patients would clearly influence the outcome of analyses assessing the potential of idebenone to prevent vision loss;
- Patients with marked improvement in VA immediately prior to enrolment into SNT-II-003. There was one such patient identified who unduly biased the outcome of VA endpoints both in the SNT-II-003 and SNT-II-003-OFU studies.

These patients present with confounding natural histories, who on medical grounds should be excluded from VA analyses.

Influence of Time Between Week 24 of SNT-II-003 and the SNT-II-003-OFU:

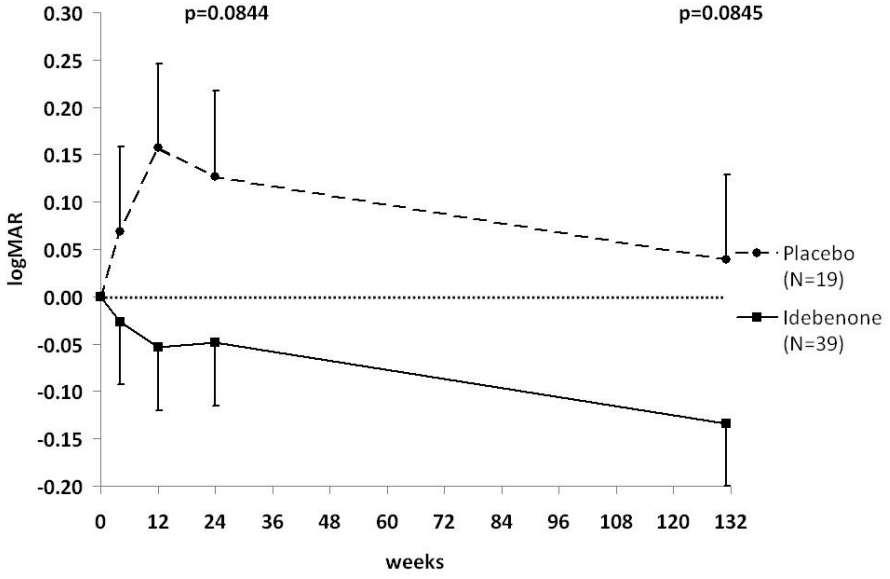
There was no correlation (Scatter plot) between the outcomes for the *Change in Best VA* (from Week 24 of SNT-II-003 to SNT-II-003-OFU) and the time elapsed between the two visual acuity assessments, which varied between 20.9 and 42.5 months. In addition, when patients were divided into two subgroups according to whether the time elapsed from the Week 24 visit of SNT-II-003 to the SNT-II-003-OFU was less or more than the median time elapsed, the *Change in Best VA* between Week 24 of SNT-II-003 and SNT-II-003-OFU was comparable for treatment groups within the two subgroups. Based on these analyses, it was concluded that the variable time between the end of treatment (Week 24) of SNT-II-003 and the SNT-II-003-OFU visit did not introduce a bias into the visual acuity efficacy outcome. Therefore, it was justified to treat the SNT-II-003-OFU visit as a single categorical event in all statistical analyses. The median time of 30 months (131 weeks) from Week 24 of SNT-II-003 to SNT-II-003-OFU was used for illustration purposes in graphs (such as Figure A and B below).

Primary Efficacy Endpoint (*Change in Best VA)*:

For the patients in the Total Efficacy Population, there was a worsening in *Best VA* between Baseline and Week 24 for patients receiving placebo in the SNT-II-003 study (mean change logMAR +0.127, corresponding to a worsening of 6 letters) which was in contrast to the improvement seen in the idebenone group (mean change logMAR -0.048, corresponding to a 2-letter improvement) (Figure A). The difference between treatment groups at Week 24 was logMAR -0.175, equivalent to 8 letters favoring idebenone (p=0.0844). To see whether

the effects observed at Week 24 were maintained after completion of the SNT-II-003 study, and after discontinuation of treatment, *Best VA* was measured at the SNT-II-003-OFU visit which took place at a median time of 30 months after Week 24. *Best VA* at the SNT-II-003-OFU visit was slightly worse than at Baseline in patients in the placebo group (mean change in logMAR +0.039, corresponding to a worsening of 1 letter) whereas *Best VA* improved in the idebenone group (mean change in logMAR -0.139, corresponding to an improvement of 6 letters). This resulted in an 8-letter difference (logMAR -0.173) between treatment groups at the SNT-II-003-OFU visit (p=0.0845).

Figure A **Change Over Time in *Best VA* – Total Efficacy Population (N=58)**



Data are estimated means ± SEM calculated from MMRM model

Separated by treatment group during SNT-II-003, the change in *Best VA* from Week 24 of SNT-II-003 to the SNT-II-003-OFU visit was logMAR -0.085, improvement by 4 letters (p=0.125) for the idebenone group and logMAR -0.088, improvement by 4 letters (p=0.276) for the placebo group, indicating that in the period after treatment discontinuation *Best VA* in patients in both treatment groups developed almost identically (i.e. in parallel).

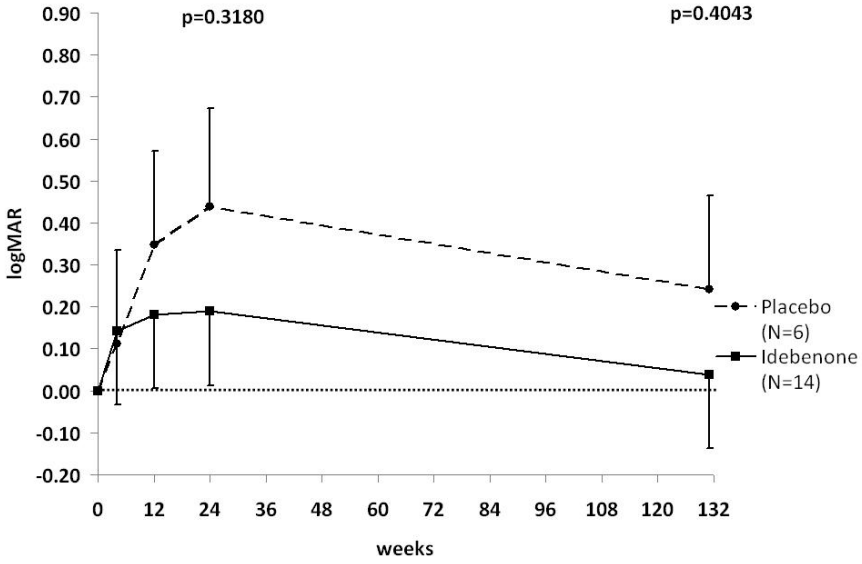
The improvement in *Best VA* in both treatment groups was not dependent on the time since study medication discontinuation in SNT-II-003, but was, however, only observed in patients who were newly diagnosed (i.e. onset of disease ≤ 1 year) at the time of enrolment into SNT-II-003. In contrast, patients with long-standing disease at the time of enrolment did not present with any improvement in *Best VA* subsequent to SNT-II-003.

Subgroup Analysis of *Change in Best VA:*

As analyses by mutation were pre-specified in the SNT-II-003 study, the change in *Best VA* was also analyzed in this study for the subgroup of patients with the G11778A or G3460A mtDNA mutation. The outcome of this analysis essentially showed the same result as for the

Total Efficacy Population. In the subgroup of patients with onset of symptoms of ≤1 year at Baseline of SNT-II-003 and mutations G11778A or G3460A the *Best VA* deteriorated from Baseline of SNT-II-003 to Week 24 in both treatment groups with a more pronounced worsening in the placebo group (Figure B). The mean treatment difference at Week 24 was logMAR -0.249, equivalent to 12 letters favoring idebenone (p=0.3180). By the time of the SNT-II-003-OFU visit *Best VA* had improved in both treatment groups from the Week 24 values, with a treatment difference for the change from Baseline to the SNT-II-003-OFU also favoring idebenone (treatment difference of logMAR -0.203, corresponding to 10 letters, p=0.4043).

Figure B **Change Over Time in Best Visual Acuity in Subset of Patients with Onset of Symptoms of ≤1 Year at Baseline of SNT-II-003 and Mutations G11778A or G3460A (N=20)**



Data are estimated means ± SEM calculated from MMRM model

Sensitivity Analyses of *Change in Best VA* Excluding Patient 23

The treatment differences for the analysis of *Change in Best VA* excluding Patient 23 based on medical grounds, favored idebenone at Week 24 (logMAR -0.242, corresponding to a 12-letter difference) and at the SNT-II-003-OFU (logMAR -0.230, corresponding to an 11-letter difference). These treatment differences were greater than those observed for the primary analysis, and reached statistical significance for both Week 24 (p=0.0140) and the SNT-II-003-OFU visit time points (p=0.0176).

Similarly, in the analysis of *Change in Best VA* in the subgroup of patients with onset of symptoms of ≤1 year at Baseline of SNT-II-003, with mutations G11778A or G3460A and with Patient 23 excluded, medically important treatment differences in favor of idebenone at Week 24 (logMAR -0.512; 25 letters; p=0.0248) and the SNT-II-003-OFU (logMAR -0.386; 14 letters; p=0.0751) were reached.

Sensitivity Analyses of *Change in Best VA* Excluding Patients who used Idebenone Between end of SNT-II-003 and SNT-II-003-OFU:

There were only five patients who reported the use of idebenone subsequent to the end of SNT-II-003. Sensitivity analyses excluding these patients showed that they had no apparent influence on the overall study outcomes. Since the dose and duration of use were not generally available, no conclusions could be drawn from their individual VA outcomes.

Secondary Endpoints:

Change in VA of Both Eyes

Considering eyes as independent, the *VA of Both Eyes* from patients in the idebenone group consistently improved from Baseline up to Week 24 in the Total Efficacy Population whilst in patients receiving placebo it deteriorated. At Week 24, the mean difference between treatment groups was logMAR -0.133, corresponding to a 6-letter difference in favor of idebenone (p=0.0594). Between Week 24 and SNT-II-003-OFU the *VA of Both Eyes* further improved in the idebenone group and remained stable in the placebo group. At the SNT-II-003-OFU, the mean treatment difference was logMAR -0.228 (corresponding to an 11-letter difference in favor of idebenone) which was statistically significant (p=0.0011), and larger than the treatment difference observed at the end of SNT-II-003 (i.e. Week 24).

Although treatment differences in *Change in VA of Both Eyes* at Week 24 of SNT-II-003 and the SNT-II-003-OFU visit were in favor of idebenone for the analysis in the subgroup of patients with onset of symptoms of ≤1 year at Baseline of SNT-II-003, with mutations G11778A or G3460A, they were not statistically significant. The treatment effect for the analyses of *Change in VA of Both Eyes* for the Total Efficacy Population but excluding Patient 23 from Baseline to Week 24 of SNT-II-003 was 9 letters (p=0.004) and to SNT-II-003-OFU was 14 letters (p<0.0001). For the subgroup of patients excluding Patient 23 with onset of symptoms of ≤1 year at Baseline of SNT-II-003 and mutations G11778A or G3460A the treatment effect in favor of idebenone from Baseline to Week 24 was 19 letters (p=0.0095) and to SNT-II-003-OFU was 20 letters (p=0.0035).

Similar results were obtained for the exploratory analysis of *Best Recovery in VA*. The mean changes from Baseline to SNT-II-003-OFU were logMAR -0.305 (improvement of 15 letters) for the idebenone group compared with logMAR -0.147 (improvement of 7 letters) for the placebo group. At the SNT-II-003-OFU, the treatment difference was logMAR -0.158, corresponding to a 7-letter difference in favor of idebenone (p=0.086).

Change in VA of the Best Eye

The *Change in VA of the Best Eye* at Baseline in the two treatment groups mirrored that observed for the *Change in Best VA* (primary endpoint) and for *VA of Both Eyes*, in that at Week 24 deterioration from Baseline was observed in the placebo group and an improvement from Baseline was observed in the idebenone group. This was followed by a slight improvement in *VA of the Best Eye* in both treatment groups between Week 24 and SNT-II-003-OFU. The treatment differences for mean changes in *VA of the Best Eye* from Baseline to Week 24 and from Baseline to SNT-II-003-OFU were both in favor of idebenone and statistically significant at the SNT-II-003-OFU (logMAR -0.221 [11-letter

difference], p=0.0362) with a strong trend at Week 24 (logMAR -0.189 [9-letter difference], p=0.0766).

As with the other VA endpoints, treatment differences in *Change in VA of the Best Eye* at Week 24 and the SNT-II-003-OFU were in favor of idebenone for the analysis in the subgroup of patients with onset of symptoms of ≤1 year at Baseline of SNT-II-003, with mutations G11778A or G3460A, but they did not reach statistically significance.

The treatment effect for the analyses of *Change in VA of the Best Eye* for the Total Efficacy Population but excluding Patient 23 from Baseline to Week 24 of SNT-II-003 was 12 letters (p=0.0147) and to SNT-II-003-OFU was 14 letters (p=0.0056). For the subgroup of patients excluding Patient 23 with onset of symptoms of ≤1 year at Baseline of SNT-II-003 and mutations G11778A or G3460A, the treatment effect in favor of idebenone from Baseline to Week 24 was 26 letters (p=0.0278) and to SNT-II-003-OFU was 29 letters (p=0.0128).

Summary of Results from all VA Endpoints:

The group of patients who derived VA benefit from idebenone treatment in SNT-II-003 has maintained this benefit, despite the long intervening period without therapy. Specifically, the group of patients who have previously received idebenone still had consistently better VA compared to the group of patients previously receiving placebo, which appears to be consistent with the extremely rare rate of recurrences of visual failure in patients, both with or without visual recovery (**Newman, 2005**). This overall outcome was seen with all visual acuity endpoints and subgroup analyses, emphasizing the robustness of the finding.

Responder Analyses : "Off-chart" to "On-chart":

Long-term follow-up data were available at the SNT-II-003-OFU visit for 5 of the 7 patients who had improved from "off-chart" vision at Baseline of SNT-II-003 to "on-chart" vision at the Week 24 of the SNT-II-003 (considered a medically meaningful improvement in vision). Indeed, these 5 patients still had "on-chart" vision at SNT-II-003-OFU. One patient read 3 letters, whilst 4 patients still were able to read at least one full line "on-chart".

In the subgroup of patients with "off-chart" vision at Baseline of SNT-II-003 for whom SNT-II-003-OFU data were available, a higher proportion of patients in the idebenone group (9 patients, 50%) than in the placebo group (2 patients, 25%) regained vision to the extent that at least one eye recovered to "on-chart" visual acuity by the SNT-II-003-OFU visit (p=0.3945, Fisher's test). Applying the same analysis to all eyes instead of patients resulted in a statistically significant difference between the previous idebenone group and the previous placebo group at SNT-II-003-OFU (40.9 % for idebenone; 10.5% for placebo; p=0.0199).

Interestingly, patients who improved from "off-chart" to "on-chart" vision in the idebenone group had shorter disease duration (16.8 months) at the time of treatment start compared to patients who remained with "off-chart" VA (26.9 months). This finding is in line with findings by **Carelli et al. (2011)** indicating that idebenone-mediated recovery of vision already lost is associated with shorter disease history prior to treatment initiation

Change in HRQoL Assessed by VF-14 Questionnaire:

Overall, the changes between VF-14 recorded during SNT-II-003 and SNT-II-003-OFU were small and differences between idebenone and placebo groups were not statistically significant.

Safety Results:

The single-visit SNT-II-003-OFU visit revealed no new safety signal in LHON patients previously enrolled into the idebenone or placebo groups of SNT-II-003.

There was one SAE (hypertensive emergency) in a patient with history of hypertension, over 3 years after the end of idebenone treatment during SNT-II-003. This SAE was classified by the Investigator as unrelated to previous use of idebenone.

CONCLUSIONS:

Efficacy Conclusions:

The results from the single visit SNT-II-003-OFU study indicate that the benefit obtained from treatment with idebenone during the 6-month randomized, controlled SNT-II-003 study was maintained following discontinuation of therapy. This persistence of idebenone treatment for visual acuity outcomes is seen for both, the prevention of vision loss as well as for recovery of vision in severely affected patients.

Both the idebenone and placebo group showed a very similar slight improvement in the *Best VA* between Week 24 of SNT-II-003 and the SNT-II-003-OFU visit. However, improvement was confined to patients with short history of disease, likely representing a learning effect in newly-diagnosed patients. Notably, patients randomized to idebenone treatment showed a significant improvement when considering VA in both eyes and for the best recovery in VA in any eye. No such improvements were seen in the placebo group. The results were supported by responder analyses, demonstrating that idebenone can lead to recovery of visual acuity in severely affected patients, who were able to improve from "off-chart" to "on-chart" vision and that this effect is maintained even after discontinuation of treatment.

Detailed review of individual patients' natural histories prior to enrolment into SNT-II-003 and for the time until the SNT-II-003-OFU visit revealed patients with natural histories clearly deviating from the expected, disease-typical course with confounding influence on data interpretation.

In summary, the VA outcomes from the SNT-II-003 and SNT-II-003-OFU studies clearly demonstrate long-term persistence of the idebenone-mediated improvement in VA in patients with LHON. Individual natural history data identified patients with confounding natural histories, who on medical grounds should be excluded from VA analyses.

Safety Conclusions:

The single-visit SNT-II-003-OFU visit revealed no new safety signal in LHON patients previously enrolled into the idebenone or placebo groups of SNT-II-003.

Final Report Date: 1 May 2012