Case Record Survey

Synopsis

Historical Case Record Survey of Visual Acuity Data from Patients with Leber's Hereditary Optic Neuropathy (LHON)

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Synopsis

Survey Title	Historical Case Record Survey (CRS) of Visual Acuity Data from Patients with Leber's Hereditary Optic Neuropathy (LHON)
Disease	Leber's Hereditary Optic Neuropathy (LHON)
Survey Objectives	1. To establish the clinical course (natural history) and visual acuity (VA) outcomes in patients with a genetically confirmed diagnosis of LHON. 2. To generate a natural history group of idebenone naive patients to serve as comparator group for the open-label study SNT-IV-005 by combining data from this CRS and CRS data collected previously (as reported in SNT-IR-006, NCT01892943)
Participating Sites	CRS data will be collected from expert clinical study sites that maintain records of VA assessments for LHON patients that may participate in the SNT-IV-005 study and/or the Post Authorisation Safety Study (PASS; SNT-IV-003). Additionally, data collected in the previous CRS (SNT-IR-006) will be updated where possible by collecting subsequent VA assessments through chart abstraction.
Survey Endpoints	<u>Primary endpoint</u>: In eyes with a VA assessment made ≤1 year after the onset of symptoms 1. Proportion of eyes with clinically relevant recovery of VA from Baseline or in which Baseline VA better than 1.0 logarithm of the minimal angle of resolution (logMAR) was maintained at 12 months (primary time point) (where Baseline is the first VA assessment after onset of symptoms. At 12 months (the primary time point) means the VA observation closest to 12 months after Baseline within the window of 12±3 months) <u>Secondary Endpoints: In eyes with a VA assessment made ≤1 year after the onset of symptoms</u> 1. Proportion of eyes with clinically relevant recovery of VA from Baseline at 12 months 2. Proportion of eyes in which Baseline VA better than 1.0 logMAR was maintained at 12 months 3. Proportion of patients with clinically relevant recovery of VA in at least one eye or in which Baseline VA better than 1.0 logMAR was maintained in at least one eye at 12 months 4. Proportion of eyes/patients with "Off-chart" VA at Baseline in whom VA improves to better than or equal to 1.60 logMAR at 12 months

5. Proportion of eyes/patients with VA in the categories of better than 1.0 logMAR, 1.0 to 1.68 logMAR and above 1.68 logMAR at Baseline, 12 months and 24 months
6. Proportion of eyes with clinically relevant recovery of VA from Baseline or in which Baseline VA better than 1.0 logMAR was maintained at 24 months

(where Baseline is the first VA assessment after onset of symptoms. At 12 months (the primary time point) means the VA observation closest to 12 months after Baseline within the window of 12±3 months. At 24 months means the VA observation closest to 24 months after Baseline within the window of 24±3 months)

<u>Secondary Endpoints: In eyes with a VA assessment made >1 year after the onset of symptoms</u>

1. Proportion of eyes with clinically relevant recovery of VA from Baseline or in which Baseline VA better than 1.0 logMAR was maintained at 12 months
2. Proportion of eyes with clinically relevant recovery of VA from Baseline at 12 months
3. Proportion of eyes in which Baseline VA better than 1.0 logMAR was maintained at 12 months
4. Proportion of patients with clinically relevant recovery of VA in at least one eye or in which Baseline VA better than 1.0 logMAR was maintained in at least one eye at 12 months
5. Proportion of eyes/patients with “Off-chart” VA at Baseline in whom VA improves to better than or equal to 1.60 logMAR at 12 months
6. Proportion of eyes/patients with VA in the categories of better than 1.0 logMAR, 1.0 to 1.68 logMAR and above 1.68 logMAR at Baseline, 12 months and 24 months
7. Proportion of eyes with clinically relevant recovery of VA from Baseline or in which Baseline VA better than 1.0 logMAR was maintained at 24 months

(Where Baseline is any assessment made >1 year after onset of symptoms for which a follow-up VA assessment within 12±3 months is available. At 24 months means the VA observation closest to 24 months after any Baseline within the window of 24±3 months)

Inclusion Criteria

Case Records from patients will be collected from <u>ALL</u> patients of the participating sites who fulfil the following prospectively defined inclusion criteria:

1. age ≥ 12 years

2. the onset of symptoms is dated after 1999 and is well documented (at least month of onset of symptoms is known for each eye)
3. at least two VA assessments are available within 5 years of onset of symptoms and prior to idebenone use
4. have a genetic diagnosis for LHON for one of the following mitochondrial DNA (mtDNA) mutations: G11778A, G3460A, T14484C

Exclusion Criteria

1. any participation in an interventional clinical trial after the onset of symptoms
2. any other cause of visual impairment (e.g. glaucoma, diabetic retinopathy, AIDS related visual impairment, cataract, macular degeneration, etc.) or any active ocular disorder (uveitis, infections, inflammatory retinal disease, thyroid eye disease, etc.) during the data collection period

Study Design

A multi-country, multi-centre, historical case record survey which will collect data on the VA of eligible patients from existing medical records

Number of patients

Data will be collected from as many case records as possible during the case record survey collection period. A minimum of 89 eligible patients with onset of symptoms ≤1 year prior to Baseline is required for sufficient statistical power for comparison to perform the cross analysis with SNT-IV-005 study.

Statistical Methods

Descriptive statistics will be used to analyse the data from this CRS. The primary analysis will be to describe the changes in VA from Baseline (see SNT-IV-005 study protocol for details), to the VA at 12 months after the Baseline (the primary time point) and at 24 months after Baseline.
Data will be pooled with previously collected (and updated) CRS data (as reported in SNT-IR-006, NCT01892943) to allow comparison to the VA outcome of Raxone®- treated patients from the open-label study SNT-IV-005.

Data to be collected

- Month and year of birth
- Gender
- Results of genetic assessment of LHON specific mtDNA mutations
- Relevant medical history
- LHON history including date of onset of first symptoms (in each eye)
- All VA test results available from date of onset until any use of idebenone
- Method and eye chart used (e.g. ETDRS, Snellen, Counting Fingers etc.) for VA at each assessment
- Idebenone use (date of first intake, date of stop/ongoing, dose)