Case Record Survey

Data Evaluation and Statistics

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

SNT-CRS-002

Version 1.0

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Data Evaluation and Statistics

General Considerations

Statistical analysis and generation of all tables, listings and figures will be performed by using SAS® (SAS Institute, North Carolina), version 9.2 or higher. The analyses of the data collected within this CRS will be descriptive.

A comprehensive Statistical Analysis Plan (SAP) will detail the most appropriate statistical methodology and analyses to be performed in accordance with the study design and objectives. The SAP will also detail for each individual methods of VA assessment (e.g. ETDRS, Snellen, Counting Fingers etc.) and their conversion in logMAR.

The Full Analysis Set (FAS) will be comprised of all enrolled patients providing a patient data release agreement to participate in the study, where it is required by local regulation. If a patient withdraws his agreement to participate, the patient's data collected before the data release agreement withdrawal will remain in the dataset.

All analyses will be performed on the FAS unless otherwise specified in the SAP.

Continuous variables will be reported as mean, median, standard deviation, maximum, and minimum. Categorical variables will be summarized as absolute frequency and percentage. Confidence intervals at 95% may be obtained for the means and/or percentages as required.

As this study aims to provide a descriptive approach, no covariates will be taken into consideration.

The VA data collected under this CRS protocol (SNT-CRS-002) will be merged with natural history data previously collected in CRS (SNT-IR-006) and will be analysed and reported descriptively. Patient's agreement will be provided by signing a data release agreement form wherever required by local authority.

Primary and Secondary Analysis

The primary endpoint will be analysed for each VA assessment made ≤1 year after the onset of symptoms and a subsequent VA assessment made 12±3 months thereafter (a Baseline and outcome "pair"), by tabulating the proportion of eyes meeting the primary endpoint at 12±3 months after Baseline. For any Baseline with more than 1 subsequent observation within the 12±3 month window, the observation conducted closest to 12 months after Baseline will be used, but must fall within the 12±3 month window.

In case there are several such pairs, for the purpose of the analysis of the present protocol, the pair with the Baseline assessment closest to 6 months will be selected for the analysis. It should be noted that this will not match exactly the definition of control group for study SNT-IV-005, as the definition of this control group depends on the data collected in study SNT-IV-005.

The binary secondary endpoints for VA assessment made ≤1 year after the onset will be analysed with similar methods as the primary endpoint.

For the secondary endpoint in VA assessments made >1 year after the onset of symptoms, all available eyes in the combined CRS dataset will be considered, regardless of whether the eye

in question was used for the analysis of the primary endpoint or not. All VA assessments data collected >1 year after the onset of symptoms are considered as potential Baseline values. If a potential Baseline value does not have a follow-up VA assessment within 12±3 months, it will be excluded. The remaining potential Baseline values will be categorized in the following time since onset bins: between >1-2 years, >2-3 years, >3-4 years or >4-5 years. If there are several potential Baseline values for a pair from the same eye in the same bin, the Baseline value closest to the midpoint of the bin will be selected. It should be noted that different pairs from the same eye can be used multiple times, both for the analysis of the primary endpoint (only once) and for the analysis of VA values with Baseline >1 year after the onset of symptoms (not more than once within each of the four bins defined above).Each eye and VA assessment in each bin will be considered as independent observations.

The 12±3 month VA outcomes data for patients in the merged CRS with a VA assessment made ≤1 year after the onset of symptoms at a time matching the mean of those of the LHON patients treated with Raxone® in the open-label study SNT-IV-005 will be compared. These comparative analyses will be described in a separate statistical analysis plan. The principle for matching of patients for time since onset at Baseline is described in the SNT-IV-005 protocol.

Sample Size Calculation

The assumptions used to estimate the number of eyes required for this CRS for comparison with the outcomes of the SNT-IV-005 study are described in section 1.2 (Survey Rationale). The sample size required for the analysis comparing data from the combined surveys and data from SNT-IV-005 was calculated assuming that 40% of the eyes in patients treated with Raxone® will be classified as responders compared to 24% in the natural history control group. A total of 89 patients providing data from 178 eyes in each group (natural history control group and Raxone®-treated patients in SNT-IV-005) are required to provide a power of 90% to detect a statistically significant difference between the two groups using a two-sided significance level of 0.05. As data from 51 patients (102 eyes) are already available from the case record survey reported in SNT-IR-006, valid VA data from at least 38 patients (76 eyes) are still needed. The sample size calculation was done with nQuery Advisor version 7.0 using Table PTT0-1.The sample size calculation assumes an expected 24% responder rate in the natural history control group. This estimate is based on the data from SNT-IR-006. The estimate of responder rate in the control group will be checked once the planned enrolment of the present study has been completed. In case the responder rate in the control group is different from 24%, a sample size re-calculation using the updated control group estimate will be considered.