Long-term (over 24 months) treatment with idebenone may continue to improve visual function response in patients with Leber’s Hereditary Optic Neuropathy (LHON)

Background

- LHON is characterized by rapid, bilateral loss of central vision. In over 90% of cases, it is the result of one of three primary mitochondrial DNA mutations.
- The only approved treatment for LHON in Europe is idebenone (150 mg tablets) at a dose of 900 mg/day. It has been shown to be efficacious and safe in a large proportion of patients.
- Current guidelines for the management of LHON recommend that patients with LHON be treated for at least 1 year to assess response to therapy, and that treatment should be continued for 2 years once a plateau is reached in terms of improvement.

Objectives

- To present visual acuity (VA) outcome data from an international Expanded Access Program (EAP) of idebenone in a sub-group of patients treated for a minimum of 24 months

Methods

- Patients with confirmed mtDNA mutations were treated with idebenone under Named Patient Regagements, and followed in routine clinical practice
- Long-term (LT) efficacy cohort: patients carrying a primary mutation, having initiated treatment within 1 year from onset of VA loss (OVL) and a treatment duration of ≥24 months
- Efficacy was assessed as evidence of clinically relevant recovery (CRR) from nadir at the last visit (VA improvement from off-chart to reading 5 ETDRS letters, or an on-chart improvement of 10 letters, at baseline and at 6, 12, 18, 24, and 30 months

Results

Treatment duration

Patients were treated for a median of 35.7 (range 24.5–59.5) months

Response to treatment

- 26/34 (76.5%) of LT patients experienced a CRR (Table 2). Of these, 42% of initial CRIs occurred within 6 months and 42% between 12 months and last visit (range: 2.5–26.5 months) (Figure 1 and Table 2)

- Over three-quarters of patients with a CRR (77%) had CRR in both eyes
- The median VA improvement from nadir at initial CRI was 18 ETDRS letters, increasing to 31 letters at last visit. The maximum final gain in VA achieved by a patient was 50 ETDRS letters (18 lines) (Table 2). Best median VA scores (expressed as LogMAR; see footnote for Snellen equivalents) were 1.30, 1.34 and 1.15 at baseline, 6–9 months and ≥24 months, respectively (Table 3)
- At 30 months, 55% (35.9%) of LT patients had a best VA of ≤0.1 logarithm (better than 20/200) (Figure 2), of these, 10 patients (25% of the total population) had a best VA of ≥0.5 logarithm (better than 20/63) (data not shown)
- The proportion of patients whose VA was off-chart was 17.5% at baseline, increasing to 35% at 6–9 months and improving again to 20% at 24–30 months (Figure 2)
- In eyes with CRR, nadir had already occurred at baseline for 65%; in the remaining 35% of eyes, median time to nadir was 6.3 months. The maximum time to nadir in eyes with CRR was 13.3 months (Table 4)
- 16 eyes with VA that was off-chart at nadir went on to achieve a CRR (Figure 3) Safety signals observed in the LT treatment cohort were consistent with the overall EAP population

Conclusions

- A steady improvement in VA can be observed in patients who maintain idebenone treatment, with two-thirds of patients experiencing an initial CRI only by 12 months after treatment initiation
- Response to therapy can be rapid (as early as 2.5 months), but it can also occur later than 26.5 months in a sizeable proportion of patients
- Transient deterioration in vision during the first 9 months of idebenone therapy should not be considered as treatment failure, as these results show that improvements can occur up to 30 months

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=40</th>
<th>Mean (±SD)</th>
<th>Median (Q1–Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, years</td>
<td>25 (±1)</td>
<td>25 (22–30)</td>
<td></td>
</tr>
<tr>
<td>Months to OVL</td>
<td>22.5 (±14.5)</td>
<td>23 (13–37)</td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>mtDNA (mtH, mtN, n/a)</td>
<td>33/4/3</td>
<td>33/4/3</td>
<td></td>
</tr>
<tr>
<td>Prior visual acuity (VA) at baseline</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>VA in the involved eye</td>
<td>0.6 (±0.4)</td>
<td>1.0 (0.6–1.1)</td>
<td></td>
</tr>
<tr>
<td>VA in the uninvolved eye</td>
<td>0.6 (±0.4)</td>
<td>0.6 (0.4–0.8)</td>
<td></td>
</tr>
</tbody>
</table>

*Table 2: Patients with CRI from nadir in LT population (patients with ≥24 months of treatment, n=40)

Figure 1: Months in treatment at first CRI (by subject)

Figure 2: Best VA during follow-up

Figure 3: VA over time in eyes with CRR

Table 2

<table>
<thead>
<tr>
<th>Patients with CRI from nadir, n=40</th>
<th>n=40</th>
<th>Mean (±SD)</th>
<th>Median (Q1–Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months to OVL</td>
<td>22.5 (±14.5)</td>
<td>23 (13–37)</td>
<td></td>
</tr>
<tr>
<td>Days from nadir at first visit, LogMAR (100 letters)</td>
<td>203 (±80)</td>
<td>11 (3.5–22)</td>
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</tr>
<tr>
<td>Best gain from nadir at last visit, LogMAR (100 letters)</td>
<td>203 (±80)</td>
<td>11 (3.5–22)</td>
<td></td>
</tr>
</tbody>
</table>

*Table 3: Best VA during follow-up (n=40)

Table 4: Types of CRI at nadir in LT population (eyes with ≥24 months of treatment, n=40)

<table>
<thead>
<tr>
<th>Type of CRI</th>
<th>n=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision loss (VL)</td>
<td>n/a</td>
</tr>
<tr>
<td>Vision reduction (VR)</td>
<td>n/a</td>
</tr>
<tr>
<td>Visual field defect (VF)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

References


Acknowledgements

The authors would like to thank all patients and health care professionals participating in this Expanded Access Program for their contribution in collecting the data. If you have any questions about this data, please contact Dr. Xavier Lloria (xavier.lloria@santhera.com)

Conflict of interest

Xavier Lloria and Magda Silva are regular employees of Santhera Pharmaceuticals (Switzerland) Ltd. Thomas Klopstock has been investigated by Santhera sponsored trials, has served on the Scientific Advisory Board and received speaker honoraria from Santhera. Claudia Catarino has received speaker honoraria from Santhera Pharmaceuticals (Switzerland) Ltd.

Footnotes

- LogMAR-Snellen equivalents
  - 0.00 = 20/20
  - 0.10 = 20/25
  - 0.20 = 20/32
  - 0.30 = 20/40
  - 0.40 = 20/50
  - 0.50 = 20/63
  - 0.60 = 20/80
  - 0.70 = 20/100
  - 0.80 = 20/160
  - 0.90 = 20/200
  - 1.00 = chart (counts fingers)