Idebenone is effective and well tolerated in Leber’s Hereditary Optic Neuropathy (LHON): Long term results of real world clinical practice

Lloria, X1; Catario C2; Silva M1; Klopstock T2

1Santhera Pharmaceuticals, Medical Affairs, Liestal, Switzerland; 2 Friedrich-Baur-Institute, Department of Neurology, Munich, Germany

Poster presented at EUNOS annual congress Sept 10-13, 2017, Session II: Affected Visual System, Poster PA75

Background

LHON causes severe visual impairment and is often misdiagnosed as it is very rare.

• LHON is a mitochondrial disease that predominantly affects young men and causes severe, painless, rapid, bilateral loss of central vision.1

• In over 90% of cases, LHON is caused by one of three mitochondrial DNA mutations which lead to functional loss of Retinal Ganglion Cells (RGCs) and subsequent visual impairment.2

• Rates of spontaneous recovery are low.3

• Idebenone dose elicits effects from complex I to complex III of the mitochondrial respiratory chain, increasing ATP production and reducing lipid peroxidation and oxidative stress.4-5

Therapeutic Goals in LHON:

• The therapeutic goal of treatment with idebenone is to prevent further deterioration of visual acuity in patients with good residual vision and promote recovery in patients who have experienced significant vision loss.6

• Data from the RHODOS clinical trial and the previously reported data (March 2015 cut-off) from the ongoing Expanded Access Program (EAP)7-9 has demonstrated idebenone can achieve both Clinically Relevant Recovery (CRR) and Clinically Relevant Stabilisation (CRS) in patients with LHON.

• Key learnings from these studies indicated that the proportion of responders and magnitude of benefit increase with continued treatment.10

Objectives

• To investigate the benefit of longer term treatment on the proportion of responders and magnitude of benefit in real-world practice in the EAP with a June 2017 cut-off date.

Methods

• Patients received treatment through a Named Patient Scheme under routine clinical practice.

• Population: confirmed mDNA mutation; less than 12 m since onset of vision loss in the last affected eye.

• Endpoints:
  • CRS (Clinically Relevant Stabilisation): maintenance VA < 1.0 logMAR at last visit
  • CRR (Clinically Relevant Recovery): VA improvement from “off-chart” to at least 5 letters “on-chart”, or “on-chart” improvement at least 10 letters

Results

• A total of 111 patients received idebenone at 38 sites in 10 different countries.

• 78% (n = 87) of the patients had the one of the three main mitochondrial mutations, had disease onset < 12 months in the most recent visit and provided BL and post-BL measures. They made up the efficacy population (EP).

• Demographic distribution (mutation, gender, age) of these patients was generally representative of the known disease characteristics of LHON.

• 3% patients had childhood onset (< 12 years of age).

Table 1. Demographics & general data

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>G11778A</th>
<th>G3460A</th>
<th>T14484C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in the EP</td>
<td>87 (100%)</td>
<td>54 (62.1%)</td>
<td>17 (19.5%)</td>
<td>16 (18.4%)</td>
</tr>
<tr>
<td>Treatment duration [m]</td>
<td>23.6 ± 14.7</td>
<td>23.5 ± 15.2</td>
<td>24.9 ± 12.8</td>
<td>23.8 ± 15.3</td>
</tr>
<tr>
<td></td>
<td>2.4 ± 15.1</td>
<td>3.2 ± 16.3</td>
<td>4.4 ± 8.3</td>
<td>2.4 ± 16.0</td>
</tr>
<tr>
<td>Male</td>
<td>71 (81.6%)</td>
<td>45 (83.3%)</td>
<td>13 (75.6%)</td>
<td>13 (81.3%)</td>
</tr>
<tr>
<td>Age at onset [y]</td>
<td>31.4 ± 13.3</td>
<td>33.3 ± 17.5</td>
<td>28.4 ± 16.8</td>
<td>28.1 ± 16.9</td>
</tr>
<tr>
<td></td>
<td>6.6 ± 7.9</td>
<td>12.1 ± 7.8</td>
<td>6.6 ± 6.4</td>
<td>8.5 ± 16.2</td>
</tr>
<tr>
<td>Time since onset at Baseline [m]</td>
<td>4.6 ± 3.0</td>
<td>3.0 ± 11.5</td>
<td>4.3 ± 2.7</td>
<td>5.9 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>0.6 ± 11.4</td>
<td>0.3 ± 11.5</td>
<td>0.3 ± 9.3</td>
<td></td>
</tr>
</tbody>
</table>

• 18 additional patients were included in this 2017 cut-off versus the 2015 cut-off analysis.

• The distribution by gender and mutation is maintained with a slight increase in patients below 18 years of age.

• Mean treatment duration was 23.8 months (range 2.4 to 59.5 m).

Change of VA on treatment

• The majority of patients had severe vision loss (>1.0 logMAR) at presentation (Figure 1).

• The mean VA at BL was 1.23 logMAR indicating patients had clinically significant visual impairment and advanced disease.

• 63 patients had a severe vision loss and 24 patients were below <1.0 logMAR.

• At nadir average vision loss was more than 2 lines from BL (0.26 logMAR).

• At Last Visit (LV) average vision recovered by 3 lines (-0.31 logMAR) from nadir.

Clinically relevant recovery (CRR) from nadir

• CRR at last observation (Figure 2) was achieved in 47.1% patients treated with idebenone across all mutation types.

• The degree of CRR was mutation dependent, 75% in T14484C, 47.1% in G3460A, 38.9% in G11778A.

Figure 2. Patients with Clinically Relevant Recovery (CRR) from nadir by mutation

• By 12 months the 19 patients who did not have a CRR (21.8%) experienced significant vision loss.

• At the time of first CRR the average magnitude of recovery was more than four lines (-0.45 logMAR).

• Recovery increased with continued treatment; average magnitude was >7 lines (-0.72 logMAR) at LV.

• All 3 mutations experienced recovery, T14484C 11 lines, G3460A 6 lines and G11778A 5 lines.

• Mean time to CRR was 10 months with T14484C (7.8 m), G3460A (9.1 m) and G11778A (11.5 m).

• A third of CRR occurred after 12 months post BL (14/41 pts) with some as late as 28.2 months (range 9.9 to 58 months).

Change of VA on treatment

• Of the 24 patients with a VA <1.0 logMAR at least one eye at BL (Figure 1) by 12 months the 19 patients who did not have a CRR (21.8%) were already censored.

• 6 patients had a CRR but were withdrawn from study or lost to follow up early and therefore may not have experienced the full magnitude of benefit

• 2 patients withdrawn from therapy (3.0, 4.4 months)

• 4 patients lost to follow up (9, 9.9, 10.7, 11.6 months)

Figure 3. Kaplan-Meier estimates of time to initial CRR as an event

Time to initial observation of CRR

• Kaplan-Meier estimate of CRR (as event) in idebenone treated patients is 64.3%.

• At 6 months the estimate for patients with CRR is 25% and the median time to CRR was 21.8 months.

• 28 patients experienced CRR in both eyes.

• In some cases CRR (as measured by eyes) occurred later than 30 months post baseline.

Table 2 gives the CRS results and cumulative percentages for each mutation type.

Table 2. CRS results and cumulative percentages for each mutation type

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Time to CRR (months)</th>
<th>CRS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T14484C</td>
<td>7.8 ± 1.1</td>
<td>75%</td>
</tr>
<tr>
<td>G3460A</td>
<td>9.1 ± 1.2</td>
<td>47.1%</td>
</tr>
<tr>
<td>G11778A</td>
<td>11.5 ± 2.0</td>
<td>38.9%</td>
</tr>
</tbody>
</table>

• These data confirm the efficacy and safety of idebenone in the management of LHON.

Conclusion

• Treatment with idebenone resulted in both stabilisation of good residual VA and significant recovery of lost vision.

• Patients experienced a response to therapy up to 2 years after starting therapy.

• Maintaining treatment after the initial response (CRR) resulted in continued improvement.

• These data confirm the efficacy and safety of idebenone in the management of LHON.

Conflict of interest

XLL and MS are regular employees of Santhera Pharmaceuticals. TK has been investigator in Santhera sponsored trials, has been serving on the Scientific Advisory Board and received speaker honoraria from Santhera. CC has received speaker honoraria from Santhera.

Acknowledgments

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.

References