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

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Background

- LHON is characterised by rapid, bilateral loss of central vision.[1] In over 90% of cases, it is the result of one of three primary mitochondrial DNA mutations[2]
- The only approved treatment for LHON in Europe is idebenone (150 mg tablets) at a dose of 900 mg/day.[3*] It has been shown to be efficacious and safe in a large proportion of patients[4]
- Current guidelines for the management of LHON recommend that patients with LHON are treated for at least 1 year to assess response to therapy, and that treatment should be continued for 1 year once a plateau is reached in terms of improvement[5]

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 Regulations, 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, 9, 12, 15, 18, 24 and 30 months

Results

Treatment duration

Patients were treated for a median of 35.7 (range 24.5–59.5) months *(Table 1)*

Response to treatment

- 26/40 (65%) of LT patients experienced a CRR *(Table 2)*. Of these, 42% of initial CRRs 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 CRR was 14 ETDRS letters, increasing to 31 letters at last visit. The maximum final gain in VA achieved by a patient was 90 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 24–30 months, respectively *(Table 3)*
- At 30 months, 15/40 (37.5%) of LT patients had a best VA of <1.0 logMAR (better than 20/200) *(Figure 2)*; of those, 10 patients (25% of the total population) had a best VA of ≤0.5 logMAR (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

Safety signals observed in the LT treatment cohort were consistent with the overall EAP population

Discussion

- In the majority of patients in this LT population, the nadir of their visual function occurred at a time point between baseline and 9 months
- A total of 65% of patients achieved a CRR during follow-up. Of these, 42% occurred between 12 months and last visit (maximum time to CRR: 26.5 months from baseline), demonstrating that some patients benefit from a longer treatment duration than that recommended in current guidelines
- After start of treatment, some further loss of visual acuity can be observed, but that does not preclude the chance of an eventual CRR
- Once CRR is achieved, patients continued to recover and improve in VA, with the median gain in vision versus nadir improving from 14 letters at initial CRR to 31 letters at last visit. Some patients whose VA was off-chart at nadir went on to achieve a CRR by last visit, and some patients achieved gains in vision of up to 18 lines

Conclusions

- **A steady improvement in VA can be observed in patients who maintain idebenone treatment, with two-thirds of patients experiencing an initial CRR 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

Patient demographics in LT population (patients with ≥24 months of treatment, n=40)

Characteristic	
Male, n (%)	**33** (82.5%)
Age at baseline, years	
Median (Q1–Q3)	**22.1** (15.9–37.3)
Min–Max	6.9–65.8
Mutation	
G11778A, n (%)	**22** (55.0%)
G3460A, n (%)	**9** (22.5%)
T14484C, n (%)	**9** (22.5%)
Most recent affected eye, months since onset	
Median (Q1–Q3)	**4.0** (2.1–6.9)
Min–Max	0.3–11.5
Time in treatment, months	
Median (Q1–Q3)	**35.7** (29.2–42.0)
Min–Max	24.5–59.5

Table 2

Patients with CRR from nadir in LT population (patients with ≥24 months of treatment, n=40)

CRR outcomes	
Patients with CRR from nadir, n/N (%)	**26/40** (65.0%)
Months in treatment at first CRR	
Median (Q1–Q3)	**9.1** (3.5–17.5)
Min–Max	2.5–26.5
Gain from nadir at time of first CRR (ETDRS letters)	
Median (Q1–Q3)	**14** (11–22)
Min–Max	10–60
Best gain from nadir at last visit (ETDRS letters)	
Median (Q1–Q3)	**31** (16–54)
Min–Max	10–90

Figure 1

Months in treatment at first CRR (by subject)

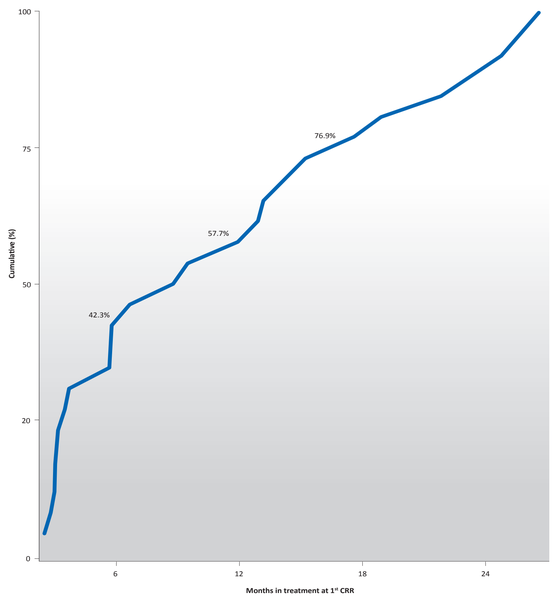

Figure 2

Best VA during follow-up

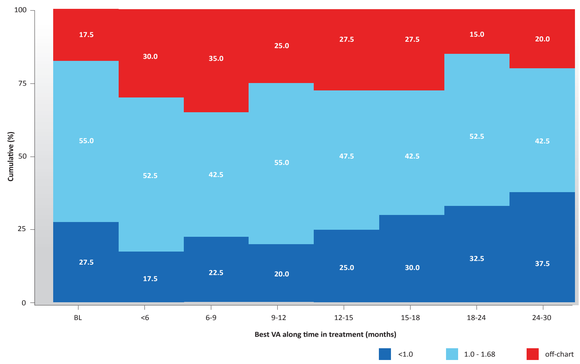

Table 3

Best VA during follow-up (n=40)

	Baseline	<6 months	6–9 months	9–12 months	12–15 months	15–18 months	18–24 months	24–30 months
Median (Q1–Q3)	1.30 (0.95–1.55)	1.36 (1.13–1.80)	1.34 (1.01–1.80)	1.40 (1.02–1.74)	1.34 (0.97–1.80)	1.31 (0.78–1.80)	1.18 (0.69–1.61)	1.15 (0.55–1.59)
Min–Max	-0.12–1.80	0.26–1.80	0.00–1.80	0.00–1.80	0.00–1.80	0.00–1.80	0.00–1.80	-0.10–1.80

Figure 3

VA over time in eyes with CRR

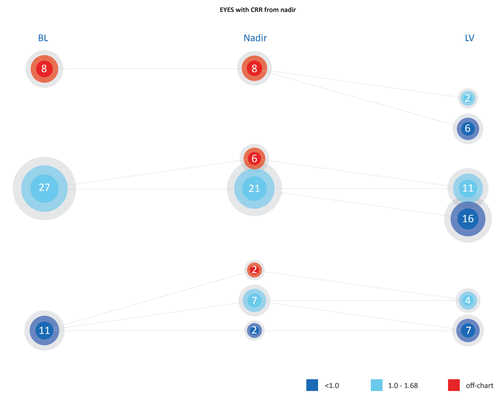

Table 4

Eyes with CRR from nadir in LT population (eyes with ≥24 months of treatment, n=40)

Eyes with CRR	
Eyes with CRR from nadir, n/N (%)	**46/80** (57.5%)
Time of nadir since start of treatment	
Already at baseline	**26** (65.0%)
Post-baseline (n=20)	
Median (Q1–Q3)	6.3 (3.5–9.5)
Min–Max	3.0–13.3

CRR: Clinically Relevant Recovery; **LV:** Last Visit; **BL:** baseline; **VA:** Visual Acuity; VA shown as logMAR (see footnote for Snellen equivalents); off-chart VA were imputed to 1.8 logMAR (approximately 20/1200). Selection criteria for best VA per observation period: if it exists at least one visit during the observation period, then the best VA of the last assessment is used; if no visit exists during the observation period but the patient is still in treatment, the last best VA value is carried forward.

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Conflict of interest

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

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LogMAR–Snellen equivalents[6]

LogMAR	Snellen	LogMAR	Snellen	LogMAR	Snellen
-0.10	20/16	0.40	20/50	0.90	20/160
0.00	20/20	0.50	20/63	1.00	20/200
0.10	20/25	0.60	20/80	1.30	20/400
0.20	20/32	0.70	20/100	1.60	20/800
0.30	20/40	0.80	20/125	2.00	20/2000

Raxone®, Santhera Pharmaceuticals (Deutschland) GmbH, idebenone 150 mg tablets

* In the European Union, Raxone® is indicated for the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON)

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