Evaluating long-term real-world data (RWD) from patients with Leber's hereditary optic neuropathy (LHON) in light of the recommendations of the International Consensus statement

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Background

- LHON is a rare mitochondrial genetic disorder that results in severe, bilateral central vision loss in both eyes. Idebenone, the only approved treatment for LHON in Europe, has been shown to be efficacious in treating LHON regardless of genetic mutation[1]
- An International Consensus[2] on the disease management and treatment of LHON with idebenone recommends:
  1. A minimum treatment duration of 12 months before evaluating efficacy
  2. That efficacy should be evaluated as improvement of two lines of visual acuity (VA) on Early Treatment Diabetic Retinopathy Study (ETDRS) charts (or from off-chart to on-chart)
  3. Idebenone should be discontinued in non-responder patients
  4. Idebenone treatment should be maintained for 12 months after VA improvement has stabilized
  5. Idebenone treatment is currently not recommended in patients in the chronic stages of the disease.

Objectives

- To compare the practical clinical application of the International Consensus statement based on long-term real-world data (RWD) obtained from an Expanded Access Program (EAP)

Methods

- A retrospective evaluation of LHON patients treated with idebenone* (900 mg/day) in 38 international sites under routine clinical practice was conducted in order to assess the VA response to idebenone in real-world clinical practice, in two cohorts: a subacute/dynamic[2] cohort (SD Cohort) and a chronic[2] cohort (C Cohort)
- Male or female patients treated with idebenone under the EAP were included. Patients were eligible if their most recent eye onset was <12 months (SD Cohort) or ≥12 months (C Cohort), and there was confirmation of one primary mutation and available post-baseline data
- Efficacy was evaluated as clinically relevant recovery (CRR; best-corrected VA [BCVA] improvement from off-chart to reading 5 ETDRS letters, or 10 ETDRS letters on-chart improvement), time to initial response and response magnitude over time *(Table 1)*.

Results

Response to treatmen in subacute/dynamic patients (SD Cohort)

- 41 of 87 patients (47 %) experienced a CRR from nadir.
  - 44 % CRRs occurred up to 6 months
  - 22 % CRRs occurred between 6 and 12 months
  - 34 % CRRs occurred after 12 months
- Of the 46 non-responders, 41.3 % discontinued before 12 months
- Estimated 64 % patients with a CRR up to 26.5 months *(Figure 1)*
- Estimated 50 % patients with a CRR by 21.8 months *(Figure 1)*
- The maximum final gain in VA achieved by a patient in was 90 ETDRS letters *(Table 3)*
- Some eyes deteriorated to a nadir after starting therapy, but eventually showed response after maintained treatment *(Figure 2)*
- In patients with CRR, the average magnitude of response increased from 22 letters at time of 1st CRR to 36 letters at the last visit *(Figure 3)*

Safety

- Safety signals were consistent with previously observed results[3]

Response to treatmen in chronic patients (C Cohort)

- 67 % patients experienced a CRR *(Figure 4)*
- 66 % of CRRs occurred up to 7 months *(Figure 4)*
- 1st CRR occurred between 3.1 and 18.5 months *(Figure 4)*
- The maximum final gain in VA achieved by a patient in was 50 ETDRS letters (10 lines) *(Table 3)*

Discussion

- Although the EAP started long before the International Consensus was published, its international real-world setting, together with the wide population treated and the long duration of therapy, offer a unique opportunity to benchmark the applicability of the Consensus
- The EAP collected data in patients whose most recent eye had disease onset less than 12 months before starting treatment, corresponding to the subacute/dynamic phase in the International Consensus
- Response to treatment may take more than 12 months on therapy before patients achieve CRR
- Despite treatment initiation, some patients may show initial deterioration of the VA, which can show recovery with maintained therapy
- Early discontinuation (due to initial deterioration of VA or lack of perceived improvement by the physician or patient) may prevent patients from achieving a CRR
- Early discontinuation before VA improvement has reached a plateau may limit the potential magnitude of improvement achieved
- The C Cohort consisted of patients whose most recent eye was beyond 12 months since onset, corresponding to the chronic phase in the International Consensus. Of the patients in C Cohort, 67% showed a CRR, of which in 66% it could be first observed as early as 7 months after therapy initiation

Table 1

Efficacy evaluation

Efficacy parameters			
Efficacy criteria	**Definition**	**Time point**	**Reference value**
CRR	VA improvement: **either** from off-chart to reading 5 letters, **or** 10 letters on-chart improvement	Last available observation	Nadir BCVA
Time to initial CRR	Treatment duration	First occurrence of CRR	From baseline (1st visit after symptom onset)
Magnitude of response	Improvement in BCVA	First occurrence of CRR and last available observation	Nadir BCVA
VA	BCVA in logMAR units, determined at baseline and follow-up visits		

Table 2

Patients demographic and baseline data

	SD Cohort (n=87)	C Cohort (n=9)
Male, n (%)	**71** (81.6%)	**6** (66.7%)
Age at baseline, years	6.9 – 80.1	11.0 – 73.3
Mutation		
G11778A, n (%)	**54** (62.1%)	**7** (77.8%)
G3460A, n (%)	**17** (19.5%)	**1** (11.1%)
T14484C, n (%)	**16** (18.4%)	**1** (11.1%)
Most recent affected eye, months since onset	0.3 – 11.5	13.5 – 133.7
Time in treatment, months	2.4 – 59.5	7.7 – 54.3

Minimum and maximum are presented for continuous variables

Table 3

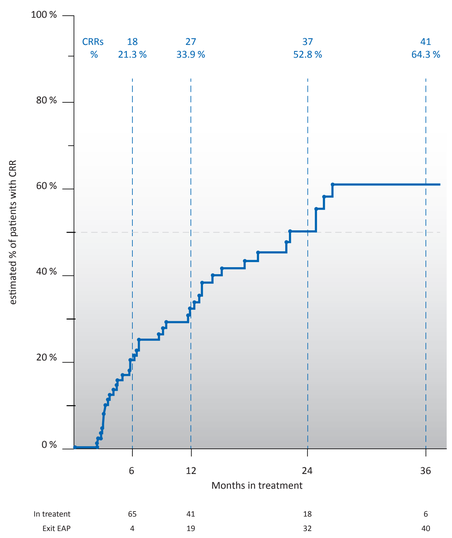
Magnitude of Improvement from Nadir in Best Visual Acuity at 1st CRR and at Last visit

	SD Cohort (n=87)	C Cohort (n=9)
Gain from nadir at 1st CRR (ETDRS letters)	10 – 81	10 – 15
Gain from nadir at last visit (ETDRS letters)	10 – 90	10 – 50

Minimum and maximum are presented

Figure 1

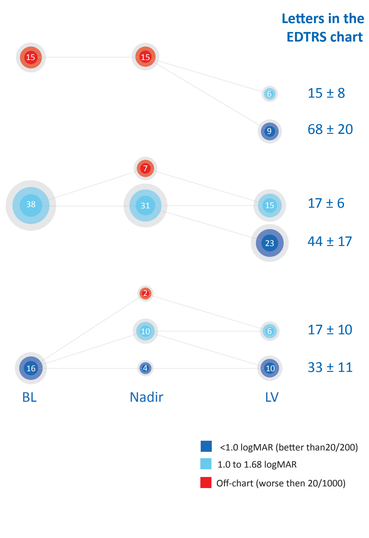
Kaplan-Meier estimates of CRR from nadir in the SD cohort



Median time to CRR: 21.8 months

Figure 2

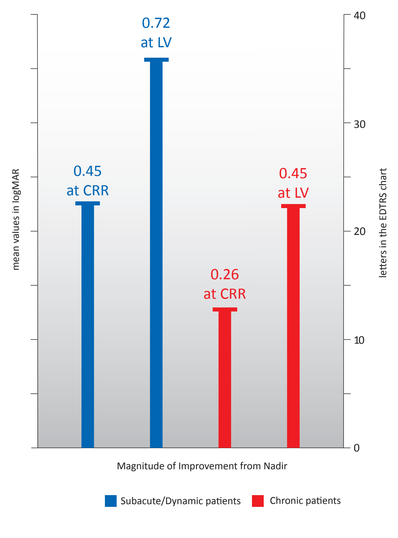
Change over time in Blindness Categories in Eyes with CRR from nadir (SD cohort, n=69 eyes)



Values present mean ± standard deviation of letters in ETDRS chart

Figure 3

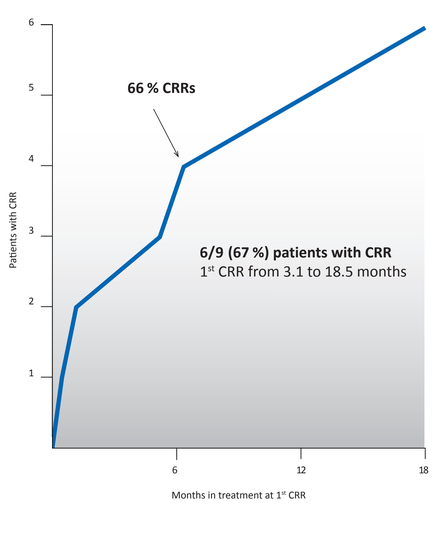
Magnitude of Improvement from Nadir in Best Visual Acuity at 1st CRR and at Last visit (ETDRS chart: mean logMAR and letters)



VA shown as logMAR (see footnote for Snellen equivalents); off-chart VA were imputed to 1.8 logMAR (approximately 20/1250);Only patients with a CRR were considered

Figure 4

Months in treatment at 1st CRR (by patient)



Conclusions

- **In general, our Real World Data support the guidance of the International Consensus statement**
- **However, our data suggest that early discontinuation may prevent a patient achieving a response and also may limit the magnitude of treatment benefit, and that some patients with >12 months since disease onset could also benefit from treatment with idebenone**
- **Therefore, we suggest that the following adjustments to the International Consensus could help improve patient response:**
  - Initial efficacy assessment should not occur before 18–24 months after treatment initiation
  - Initial deterioration after treatment initiation should not be interpreted as failure and treatment should be maintained
  - Treatment maintenance until maximal response has stabilized should be stressed in the International Consensus. Criteria for confirmation of stabilization should also be defined
  - Where Snellen charts are used to monitor vision, response criteria should be based on the equivalent logMAR values
- **The safety profile of idebenone in this long-term analysis is consistent with that seen in previously reported studies**

BCVA: best-corrected visual acuity; **BL:** baseline; **C:** chronic; **CRR:** Clinically Relevant Recovery; **EAP:** Expanded Access Program; **logMAR:** logarithm of the minimum angle of resolution; **SD:** subacute/dynamic; **SD cohort:** patients in subacute/dynamic stage at Baseline; **LV:** Last Visit; **VA:** Visual Acuity; VA shown as logMAR (see footnote for Snellen equivalents); off-chart VA were imputed to 1.8 logMAR (approximately 20/1250). 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.

References

1. Klopstock T, et al. Brain 2011:134;2677–86
2. Carelli V, et al. J Neuro-Ophthalmol 2017;37:371–81
3. Raxone® EPAR. European Medicines Agency, September 2015
4. Elliot DB. Ophthalmic Physiological Optics 2016;36:355–8

LogMAR–Snellen equivalents[4]

LogMAR	Snellen	LogMAR	Snellen	LogMAR	Snellen
-0.10	20/16	0.50	20/63	1.30	20/400
0.00	20/20	0.60	20/80	1.60	20/800
0.10	20/25	0.70	20/100	1.68	20/960
0.20	20/32	0.80	20/125	2.00	20/2000
0.30	20/40	0.90	20/160		
0.40	20/50	1.00	20/200		

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

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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