Clinical experience with Idebenone (Raxone®) in the treatment of patients with Leber's hereditary optic neuropathy (LHON)

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Introduction: LHON

• LHON is one of the most frequent mitochondrial disorders, with a prevalence around 2-3 per 100.000.

• Clinical presentation typically with subacute/acute painless bilateral loss of central vision over weeks to months.

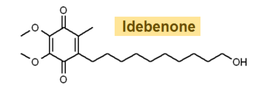
• Prognosis for restoration of vision is poor.

Three point mutations of the mitochondrial DNA cause >95% of the LHON cases:

. m.11778G>A - gene *MT-ND4* - 69%
. m.3460G>A - gene *MT-ND1* - 13%
. m.14484T>C - gene *MT-ND6* - 14%

in genes encoding subunits of Complex 1 of the mitochondrial respiratory chain.
=> leading to decreased ATP production
=> dysfunction and apoptosis of retinal ganglion cells.

Idebenone



- Synthetic short-chain benzoquinone molecule.
- Mechanisms of action: antioxidative action; stimulates mitochondrial electron transport, by bypassing complex I of the mitochondrial respiratory chain.
- Existing evidence of efficacy and safety of idebenone for treatment of early stages of LHON include one placebo-controlled RCT (RHODOS, Klopstock et al., 2011) and a large open-label study (Carelli et al., 2011).

Aims:

- To evaluate the efficacy and safety of Idebenone Raxone® in LHON, using a multicentre Expanded-Access Program (EAP).

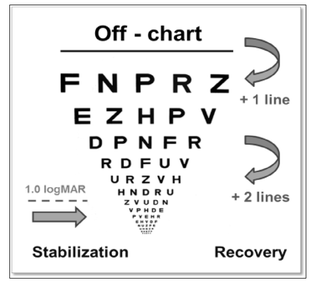
Methods:

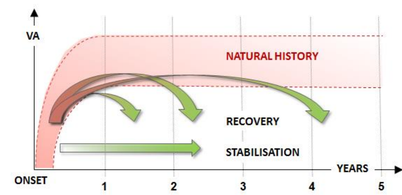
- Multicentre expanded-access program (EAP) in 36 medical centres worldwide.
- Enrollment from November 2011 to September 2015. March 2015 taken as cut-off for analysis.
- Patients enrolled with a recent diagnosis of LHON (<12 months of symptoms).
- Patients were treated with idebenone 900 mg/day orally.
- At baseline and at every 3 months of follow-up, a clinical visit was performed, which included: clinical evaluation; collection of safety data using standardized report forms, and visual acuity (VA) tests using ETDRS chart (logMAR).

- **Clinically relevant recovery** (CRR)

defined in relation to the lowest recorded VA (nadir), when a patient:
1) previously „on-chart" could read 10 letters more, or
2) previously „off-chart" could now read ≥5 letters ("on-chart").

- Responder analyses performed for all patients with ≥3 months of follow-up (at least one follow-up visit).





Results:

- 93 patients were enrolled in the EAP.

Country	Patients	%	Sites
Germany	49	53%	6
United Kingdom	11	12%	10
Australia, New Zealand	8	9%	5
PL, SE, SP, TU, CH	12	13%	9
USA	13	14%	6
total	**93**	**100%**	**36**

Demographics at Baseline Visit:

- 69 patients included in the responder analyses.

Baseline demographics		Efficacy Population	
Patients	*N (%)*	69	(100.0%)
Mutation, N (%)	*G11778A*	43	(62.3%)
	G3460A	13	(18.8%)
	T14484C	13	(18.8%)
Sex, N (%)	*female*	14	(20.3%)
	male	55	(79.7%)
Age [years]	*mean (SD)*	30.7	(17.1)
	median (range)	23.6	6.9 - 80.1
Time since onset in 1st eye [months]	*mean (SD)*	6.3	(3.9)
	median (range)	5.1	(0.9 - 16.7)

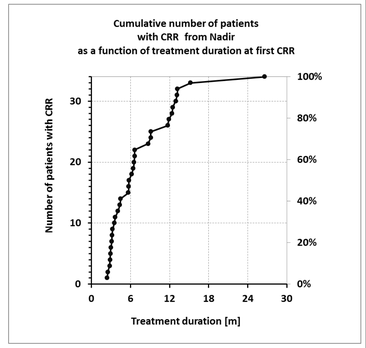
Responder rate:

- Clinical relevant recovery in **49%** of patients.
- Recovery rate dependent on mutation: largest for patients carrying the T14484C mutation.

CRR from Nadir to last observation in the Efficacy Population		Patients all	Patients CRR		Literature data, natural history
All patients	*N (%)*	69	34	(49.3%)	
Mutation	*G11778A*	43	17	(39.5%)	4 - 23%
	G3460A	13	6	(46.2%)	14 - 25%
	T14484C	13	11	(84.6%)	37 - 71%

Treatment duration at first recovery for responders (patients with CRR):

- The majority of responders experienced their first recovery after 6 months of treatment.
- First recovery after more than 12 months of treatment possible.



Discussion:

• This EAP represents the largest collection of LHON patients treated with Idebenone so far and is therefore a valuable information source on "real world" experience in treatment of patients with LHON with Idebenone Raxone.

• Idebenone is well-tolerated and effective in LHON in both clinical recovery and stabilization of VA.

• The highest responder rate was seen in patients carrying the T14484C mutation, while patients with G3460A and G11778A mutations had lower rates of clinical significant recovery.

The magnitude of VA recovery increases with treatment duration:

- Mean recovery, last follow-up: 9 lines (46 letters).

Average Recovery for Eyes with CRR	N	letters	logMAR	SD
at the 6 month visit	15	23	-0.47	0.31
at the 12 month visit	15	31	-0.62	0.48
at last observation (avg 21m)	15	46	-0.93	0.42

Prevention of VA loss:

- Assessed by analysis of VA stabilization in the subgroup of patients with VA < 1.0 logMAR at start of treatment:
  12/21 patients (**57.1%**) stable at last follow-up.

Efficacy Population	Baseline VA < 1.0 logMAR	Last Obs. VA < 1.0 logMAR	
	N	N	%
All Patients	21	12	(57.1%)
G11778A	14	8	(57.1%)
G3460A	3	1	(33.3%)
T14484C	4	3	(75.0%)

Conflict of interest: GM is regular employee of Santhera Pharmaceuticals (Liestal, Switzerland). TK has been a principal investigator or investigator on industry-sponsored trials funded by Santhera Phamaceuticals, has been serving on the scientific advisory board for Santhera Pharmaceuticals and has received speaker honoraria and travel costs from Santhera Pharmaceuticals. CC has received travel costs from Santhera Pharmaceuticals.

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