Treatment of visual impairment in patients with Leber's Hereditary Optic Neuropathy (LHON) using idebenone (Raxone®)

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Background

LHON is a rare primary mitochondrial disease

LHON, the most common mitochondrial genetic disorder, causes rapid and painless loss of vision generally leading to lifelong blindness in most patients (Yu-Wai-Man *et al.*, 2011; Newman, 2012). The prevalence is about 2 per 100,000 population (Mascialino *et al.*, 2012) and typically affects otherwise healthy young men. At least 90% of patients carry one of three mitochondrial DNA mutations (G11778A, G3460A and T14484C) in the genes coding for complex I of the electron transport chain (Yu-Wai-Man *et al.*, 2011; Meyerson *et al.*, 2015), resulting in impaired cellular ATP synthesis and generation of superoxide free radicals.

Dysfunction of retinal ganglion cells (RGCs) leads to the development of a characteristic central scotoma and loss of visual acuity (VA) (Meyerson *et al.*, 2015). Typically, one eye is affected initially with the second eye following a similar course within weeks to months (Yu-Wai-Man *et al.*, 2011). After reaching the nadir, typically within 1 year, VA generally remains stable thereafter. Dysfunctional RGCs may still remain viable (Howell, 1998) for up to several years, representing a window of opportunity for therapeutic intervention. A small proportion of patients show spontaneous improvement, most often in patients with the T14484C mutation (Meyerson *et al.*, 2015).

At a later stage of the disease, apoptotic death of RGCs results in bilateral 'legal' blindness (VA >logMAR 1.0) for life, with the majority of patients being off-chart (Yu-Wai-Man *et al.*, 2011; Raxone® EPAR, 2015).

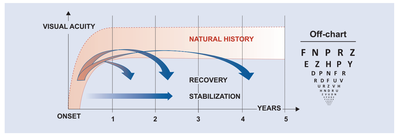
Raxone® for the treatment of LHON

Raxone® (idebenone) is the first and only approved treatment for visual impairment in adolescents and adults with LHON (Lyseng-Williamson, 2016).

Treatment objectives in LHON are:

1. Clinically relevant stabilization (CRS): prevention of further VA loss in patients with good residual VA at baseline
2. Clinically relevant recovery (CRR): recovery of VA in patients at a more advanced disease stage

Figure 1. Schematic of LHON natural history and therapeutic goals



Idebenone is a potent mitochondrial enhancer

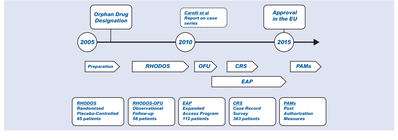
Idebenone, a synthetic short-chain benzoquinone, is a potent antioxidant and an inhibitor of lipid peroxidation, protecting cell membranes and mitochondria from oxidative damage. It also restores electron flow by bypassing deficient complex I and donating electrons directly to complex III, thus increasing production of ATP in the mitochondrial electron transport chain (Haefeli *et al.*, 2011; Giorgio *et al.*, 2012; Erb *et al.*, 2012).

Treatment benefits of idebenone in patients with LHON have been previously reported in single case studies, case series and in patient cohorts (reviewed by Gueven & Faldu, 2013).

Data from over 500 patients collected to date

- N=85 – RHODOS randomized, placebo-controlled clinical trial
  - LHON patients aged 14-64 years, with onset of vision loss ≤5 years prior to enrolment, randomized 2:1 to Raxone 900mg/day or placebo
- N=112 – Expanded Access Program
  - Real-world patient access program in 10 countries and 33 centers, with onset of vision loss within 1 year prior to enrolment
- N=383 – Case Record Survey
  - LHON natural history study

Figure 2. Timeline for idebenone studies and marketing approval in LHON



Randomized controlled trial (RHODOS)

RHODOS: the only RCT in LHON

RHODOS is the first and only randomized, placebo-controlled trial (RCT) of idebenone in LHON patients to date (Klopstock *et al.*, 2011).

Demographics (age, gender and mutation distribution) were typical of patients with LHON from natural history studies and were similar between groups (Table 1).

Table 1. Patient demographics in RHODOS

	Idebenone 900mg/day (n=55)[a]	Placebo (n=30)[a]
Age, mean ± SD [median] (range) (years)	33.8 ± 14.8 [30.0] (14-63)	33.6 ± 14.6 [28.5] (14-66)
Gender Male, n (%) Female, n (%)	47 (85.5) 8 (14.5)	26 (86.7) 4 (13.3)
Mutation, n (%) G11778A T14484C G3460A	37 (67.3) 11 (20.0) 7 (12.7)	20 (66.7) 6 (20.0) 4 (13.3)
Time since onset of vision loss, mean ± SD [median] (range) (months)	22.8 ± 16.2 [17.8] (3-62)	23.7 ± 16.4 [19.2] (2-57)

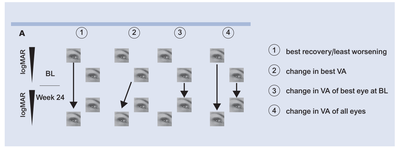
[a]n=82 (n=53 for idebenone; n=29 for placebo) for all VA data.

The efficacy variable was the logarithm of the minimal angle of resolution (logMAR), determined using Early Treatment Diabetic Retinopathy Study (ETDRS) eye charts.

Pre-specified VA endpoints demonstrate a beneficial trend with idebenone treatment

The primary endpoint was the best recovery/least worsening of VA from baseline to Week 24. This and the three secondary outcomes are shown graphically below (Figure 3).

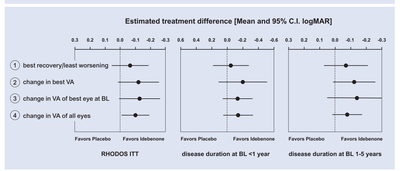
Figure 3. RHODOS study endpoints



Although the primary outcome did not reach significance, there was a clear trend across all endpoints towards a benefit of treatment with idebenone. The clinically most relevant endpoint, 'patients' change in best VA', demonstrated a stronger trend (p=0.086) towards benefit compared with placebo.

In further analysis, patients with <1 year of disease duration appeared to achieve similar VA gains to those with 1-5 years of disease duration (Figure 4).

Figure 4. RHODOS outcomes for the overall ITT population and sub-populations of patients with disease duration <1 year and 1-5 years



Responder analyses in the ITT population

For the purpose of the responder analyses, responders were defined as those patients who experienced either a clinically relevant stabilization or clinically relevant recovery.

Clinically relevant stabilization (CRS) was defined as the maintenance of VA below 1.0 logMAR, the threshold for legal blindness (Figure 5).

In patients with good residual vision at baseline (best VA ≤0.5 logMAR; n=8), all of those treated with idebenone (n=6) remained below 1.0 logMAR at 6 months. In contrast, corresponding placebo-treated patients (n=2) deteriorated to ≥1.0 logMAR at 6 months (p=0.036 between treatment groups) in line with what would be expected from natural history studies (Klopstock *et al.*, 2011; Raxone® SmPC, 2015).

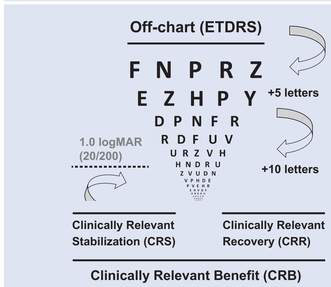
Clinically relevant recovery (CRR) captures meaningful improvement in VA

In line with criteria reported in the literature (Carelli *et al.*, 2011), a definition of CRR of VA as an efficacy measure (Figure 5) was used in a pre-defined analysis.

Definition of CRR used in pre-defined analysis:

- CRR for "off-chart" VA: the ability to read at least 5 letters (equivalent to 1 line) "on-chart" in a patient who was off-chart at baseline
- CRR for "on-chart" VA: the ability to read at least 10 additional letters (equivalent to 2 lines) on-chart

Figure 5. Clinically relevant recovery or stabilization



Three times as many patients experienced CRR vs. placebo in the ITT population after 6 months

In the ITT population, there was a 3-fold increase in the proportion of patients achieving a CRR in the idebenone group compared with the placebo group: 30.2% (16/53) vs. 10.3% (3/29).

Improvements in VA were not limited to patients with recent disease onset: a 2-3 fold increase in the proportion of patients with CRR was seen in those with disease duration <1 year and 1-5 years. The proportions of patients with a CRR in those with <1 year disease duration were: idebenone 21.1% (4/19), placebo 10% (1/10). For those with disease duration 1-5 years, the proportions with a CRR were: idebenone 35.3% (12/34), placebo 10.5% (2/19).

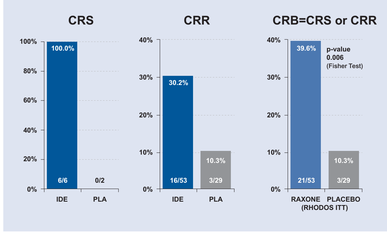
Only patients treated with idebenone recovered from off-chart VA at baseline compared with placebo. One in four patients (28.0%, 7/25) had a CRR from off-chart to at least 5 letters on-chart after 6 months' idebenone treatment, compared with 0% (0/13) for placebo. For patients with on-chart VA status at baseline, 32.1% (9/28) receiving idebenone had a CRR of at least 10 letters (2 lines on an eye chart), compared with 18.8% (3/16) for those receiving placebo.

Pooled responder analysis in the RHODOS ITT

Both CRR and CRS are clinically relevant outcomes, since stabilization of good residual vision is just as important to the patient as recovery of poor vision. To measure the overall benefit of idebenone treatment, a pooled analysis (based on data from the SmPC) combined patients with a CRR or a CRS to give a composite outcome: clinically relevant benefit (CRB).

A significantly higher proportion of idebenone-treated patients achieved CRB compared with placebo-treated patients after 6 months: 39.6% vs. 10.3%; p=0.006 between treatment groups (Figure 6).

Figure 6. Proportions of patients with CRS, CRR, and the composite endpoint (CRS + CRR) of clinically relevant benefit (CRB) after 6 months' treatment in the RHODOS ITT



Expanded Access Program (EAP)

Expanded Access Program (EAP) confirmed clinically relevant benefits in real-world setting

Due to heightened interest from the RHODOS study and unsolicited requests from physicians to treat patients that followed, Santhera established an Expanded Access Program (EAP) across 10 countries and 33 sites. LHON patients with disease duration of <1 year were given idebenone on a named patient basis. At the clinical cut-off in March 2015, data from 69 patients with one of the three major mutations and a post-baseline assessment were analyzed.

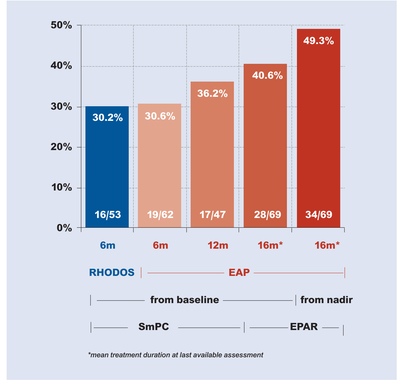
EAP patient demographics were generally representative of LHON natural history characteristics in terms of age at symptoms onset, mutation carried, and gender distribution. Patients were enrolled within 1 year of second eye involvement and were treated with 900mg daily for 16 months on average.

CRR was observed in almost 50% of patients

After 6 months of treatment, the proportion of patients in the EAP with a CRR was 30.6%, compared with 30.2% in RHODOS at the same time point (Figure 7), confirming the results of RHODOS in the real world.

This proportion of patients experiencing a CRR increased with longer treatment duration from 30.6% at 6 months to almost 50% at 16 months from nadir (Figure 7).

Figure 7. Proportions of patients with CRR by treatment duration



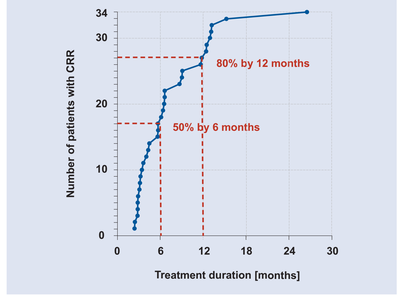
Patients on treatment may initially worsen to their natural nadir, albeit to a lesser extent compared with untreated patients, before a CRR may be seen with a recovery of VA (Raxone® EPAR, 2015).

The number of patients with CRR increases with treatment duration

Cumulative time to start of CRR was found to increase with treatment duration (total number of patients with CRR=100%), from 50% at 6 months to 80% at 12 months (Figure 8), after which fewer patients will start to recover VA with time.

In the EAP, 57.1% (12/21) of patients with VA below 1.0 logMAR at baseline showed CRS and maintained VA below this threshold at last observation (Lyseng-Williamson, 2016).

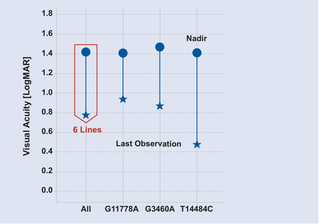
Figure 8. The cumulative number of patients achieving first CRR as a function of treatment duration



On average patients gained 6 lines in VA, with the magnitude of VA recovery increasing with treatment duration

In patients who achieved a CRR, the average gain in VA was 6 lines at the last observation (at a mean of 16.2 months). Patients carrying the T14484C mutation showed greater improvements in VA than those carrying each of the other two major mutations (Figure 9).

Figure 9. Average VA at nadir and last observation for patients with CRR, by mutation type



Data from individual eyes that showed CRR after 6 months and also had follow-up data at 12 months (n=15) demonstrated that the magnitude of VA improvement increased with treatment duration. The average VA gain of 23 letters at 6 months increased to 31 letters after 12 months of idebenone treatment, and 46 letters at the last assessment (Table 2).

Table 2. Gains in VA for patients who had CRR at 6 months and also follow-up at 12 months

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

CRR pooled analysis of all studies

Pooled analysis shows higher proportion of patients with CRR comparing idebenone-treated with untreated patients

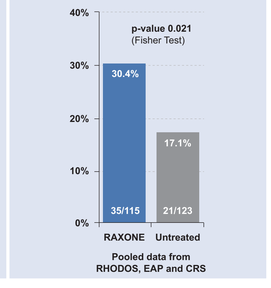
A pooled analysis of responders with a CRR (off-chart to on-chart or at least 2 lines on-chart to on-chart) was carried out across all three studies: RHODOS, EAP and the Case Record Survey (Table 3) (Raxone® SmPC, 2015).

Table 3. Pooled analysis of patients with CRR after 6 months across RHODOS, EAP and Case Record Survey (data from Raxone® SmPC, 2015)

RHODOS (ITT)	RHODOS Raxone® (N=53)	RHODOS Placebo (N=29)
Responders (N, %)	16 (30.2%)	3 (10.3%)
EAP and Case Record Survey	**EAP Raxone® (N=62)**	**Case Record Survey-untreated (N=94)**
Responders (N, %)	19 (30.6%)	18 (19.1%)
Pooled Data	**RHODOS & EAP Raxone (N=115)**	**RHODOS Placebo & Case Record Survey-untreated (N=123)**
Responders (N, %)	35 (30.4%)	21 (17.1%)

The analysis of 6-month data shows that the overall proportion of patients with a CRR is almost double with idebenone treatment (30.4%, 35/115), than with placebo/untreated (17.1%, 21/123); p=0.021 between treated and untreated (pooled data) (Figure 10).

Figure 10. Proportion of patients with CRR after 6 months (pooled data)



Safety

Idebenone is well tolerated with a consistent safety profile and no new safety signals

In RHODOS, the incidence of AEs and treatment-related AEs was low and similar between idebenone and placebo groups. The most common AEs in the idebenone group (difference vs. placebo) were: nasopharyngitis (+8.8%), headache (+3.6%), cough (+10.9%) and diarrhea (-9.1%). The majority of AEs were mild or moderate in intensity.

In the EAP a total of 17 AEs were reported from 10 patients. Mild diarrhea was the most frequently reported AE. Most AEs were classified as mild (n=11), with the remainder being moderate (n=4) or unknown (n=2) (Raxone® EPAR, 2015).

Conclusions

Consistent evidence for benefit of idebenone treatment in LHON

Evidence from the RHODOS study and the Expanded Access Program demonstrated that idebenone *has the potential* to achieve two important therapeutic goals, namely:

1. Stabilize VA below the level of legal blindness in approximately 50% of patients with good residual VA at start of therapy
2. Promote a clinically relevant recovery of VA approximately 50% of patients

Furthermore, data from the EAP suggest the number of patients experiencing recovery, and the magnitude of recovery, increase with longer treatment duration.

The safety assessment in the EAP was comparable to that seen in the placebo-controlled RHODOS study.

- The nature and frequency of AEs reported in patients receiving Raxone® were similar to those observed with placebo
- No new potential safety signal emerged from the review of vital signs, laboratory and ECG data

Literature & Acknowledgments

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Conflict of interest

SH and GM are employees of Santhera Pharmaceuticals (Liestal, Switzerland). TK has been a principal investigator or investigator on industry-sponsored trials, has served on the scientific advisory board and has received speaker honoraria and travel costs (all from Santhera Pharmaceuticals). CC has received travel costs from Santhera Pharmaceuticals.

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