Responder analysis of chronic Leber's hereditary optic neuropathy (LHON) patients to idebenone in a placebo controlled, randomized clinical trial (RHODOS)

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Poster presented at the 14th EUNOS, June 16–19, 2019. Porto, Portugal. PO53

Background

- LHON is a mitochondrial genetic disorder causing severe, bilateral central vision loss[1]
- Idebenone,* the only approved treatment for adolescent and adult patients with LHON in Europe, has been shown to be efficacious in treating LHON regardless of genetic mutation[2] and time since onset (SO) of symptoms
- An International Consensus[3] on the disease management and treatment of LHON with idebenone recommends treating patients whose disease duration is less than 12 months since onset at treatment start, yet consider that the data are insufficient when it comes to supporting the treatment of patients whose disease duration is >1 year SO
- RHODOS, a double-blind, randomized (2:1), placebo controlled clinical trial,[4] evaluated the efficacy and safety of idebenone (900 mg/day) versus placebo in LHON patients over 24 weeks

Objectives

- To report the response outcome to idebenone in the subgroup of patients in RHODOS whose time SO was >1 year

Methods

- RHODOS included patients between 14 and 64 years of age with a confirmed primary mutation and vision loss due to LHON within 5 years
- This *post-hoc* response analysis compared response outcome in patients treated with idebenone versus those given placebo, in the subpopulation of chronic patients (those with >1 year SO at baseline)
- Efficacy was evaluated as a clinically relevant recovery (CRR) at week 24 (last visit) from baseline *(Table 1)*
  - Patients were only considered to have achieved CRR if they still showed a response at last visit
- Patients received treatment/placebo up to 6 months

Results

Patient demographics

- 34 patients were treated with idebenone and 19 received placebo *(Table 2)*
- Gender, mutation and time since onset (SO) were equally balanced between groups *(Table 2)*
- Idebenone-treated patients were younger than placebo-treated patients (61.8% vs 52.6% patients ≤35 years old; *Table 2*)

Response to treatment: patients

- Three times more idebenone-treated patients than placebo-treated patients achieved CRR (35.3% vs 10.5%; p=0.0596; *Figure 1*)
- Four idebenone-treated patients achieved CRR in both eyes *(Tables 3 and 4)*
- CRR was first observed between 1 and 6 months post-baseline *(Table 3, Figure 2)*
- CRR was first observed between 1.4 and 4.4 years SO *(Table 3)*

Response to treatment: eyes

- CRR was observed in 23.5% of idebenone-treated eyes and 5.3% of placebo-treated eyes (p=0.0163; *Figure 1*)
- 56.3% of idebenone-treated eyes with CRR were off-chart at baseline *(Table 4)*
- A gain of 11 to 48 letters was observed in idebenone-treated eyes with CRR (Table 4, *Figure 3*)
- The two placebo-treated eyes that achieved CRR improved by 11 and 26 letters *(Table 4, Figure 3)*

Safety

- Safety signals observed were consistent with previously published results[2]

Discussion

- In the RHODOS 6-month treatment study, chronic LHON patients were able to achieve a CRR
- CRR was observed in three times as many idebenone-treated patients as placebo-treated patients (35.3% vs 10.5%). This difference trended towards significance (p=0.0596)
- In terms of response by eyes, the difference between idebenone and placebo was significant (p=0.0163)
- Over half of eyes (56.3%) treated with idebenone who were off-chart at baseline had a CRR, versus none treated with placebo
- The magnitude of improvement was up to 48 ETDRS letters in idebenone-treated patients
- In patients with chronic LHON who achieved CRR, this was reached as early as one month after treatment commenced in both idebenone- and placebo-treated patients

Table 1

Efficacy evaluation

Efficacy parameters			
VA	BCVA in logMAR units, determined at baseline and follow-up visits		
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 observation (24 weeks)	Baseline BCVA
Time to initial CRR	Treatment duration	First occurrence of CRR	From baseline (first visit after symptom onset)
Magnitude of response	Improvement in BCVA at CRR	Last available observation (24 weeks)	Baseline BCVA

Table 2

Demographic and baseline data in patients with time since onset of symptoms >1 year

	Idebenone (n=34)	Placebo (n=19)
Male, n (%)	**28** (82.4%)	**16** (84.2%))
Age at baseline, years		
≤35 years	**21** (61.8%)	**10** (52.6%)
>35 years	**13** (38.2%)	**9** (47.4%)
Mutation		
G11778A, n (%)	**21** (61.8%)	**12** (63.2%)
G3460A, n (%)	**5** (14.7%)	**3** (15.8%)
T14484C, n (%)	**8** (23.5%)	**4** (21.1%)
Time since onset of symptoms, months		
Median (Q1-Q3)	**28.5** (18.1 – 39.5)	**30.6** (19.3 – 42.2)
Min - Max	12.7 – 61.6	14.2 – 56.5

Median (Q1 – Q3) minimum and maximum are presented for continuous variables

Table 3

Patients with CRR

Patients with CRR from baseline	Idebenone (n=12)	Placebo (n=2)
Months in treatment at 1st CRR		
Mean ± SD	2.81 ± 1.99	3.42 ± 3.25
Min – Max	0.89 – 6.21	1.12 – 5.72
Months since symptoms onset at 1st CRR		
Mean ± SD	30.56 ± 11.12	34.23 ± 12.50
Min – Max	16.79 – 53.16	25.40 – 43.07

SD: standard deviation; mean ± standard minimum and maximum are presented for continuous variables

Table 4

Eyes with CRR

Eyes with CRR from baseline	Idebenone (n=16)	Placebo (n=2)
Gain in ETDRS letters at last visit		
Median (Q1-Q3)	**20** (12 – 24)	-
Min - Max	11 – 48	11 and 26
VA blindness category at baseline		
Off-chart	**9** (56.25%)	**0** (0.00%)
1.0 to 1.68 logMAR	**4** (25.00%)	**1** (50.00%)
< 1.0 logMAR	**3** (18.75%)	**1** (50.00%)
VA blindness category at last visit		
1.0 to 1.68 logMAR	**12** (75.00%)	**1** (50.00%)
< 1.0 logMAR	**4** (25.00%)	**1** (50.00%)

Median (Q1 – Q3) minimum and maximum are presented for continuous variables. Off-chart VA were imputed to 1.8 logMAR (approximately 20/1250); see footnote for Snellen equivalents

Figure 1

Proportion of eyes and patients with CRR from baseline

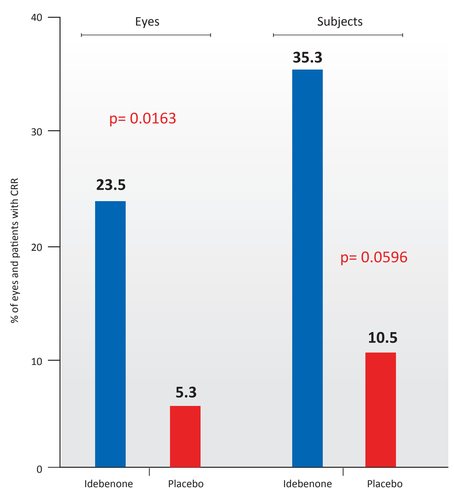
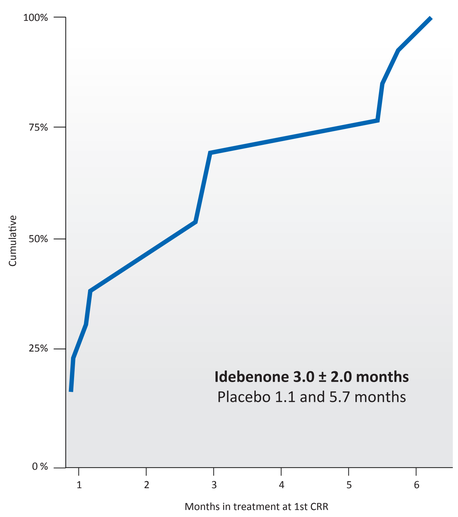


Figure 2

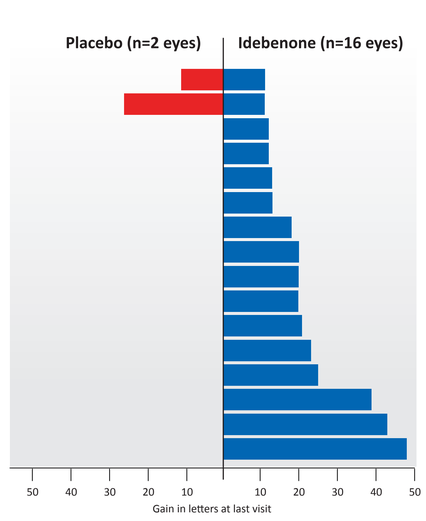
Months in treatment at first CRR



Values are presented as mean ± standard deviation; only 2 eyes in placebo group had a CRR

Figure 3

Magnitude of recovery in eyes with CRR



Magnitude of improvement evaluated in ETDRS letters

Conclusions

- **Idebenone treatment induced CRR in a larger proportion of patients/eyes than placebo in chronic LHON**
- **This demonstrates that some patients with time since onset beyond 12 months could benefit from treatment with idebenone**
- **Therefore, we suggest that adjustments to the International Consensus could be considered to support treatment with idebenone in chronic LHON patients**
- **The safety profile of idebenone in this responder 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 20/1200). 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.

Acknowledgements

The authors would like to thank all patients and health care professionals participating in this study for their contribution in collecting the data.
If you have any questions about the data presented in this poster please contact Dr. Xavier Llòria (Xavier.Lloria@santhera.com)

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

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LogMAR–Snellen equivalents[5]

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® (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)

Job code: NP-HQ-LHON-RAX-0011

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