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ORIGINAL ARTICLE

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Idebenone Treatment in Patients with OPA1-Dominant Optic Atrophy: A Prospective Phase 2 Trial

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ABSTRACT

The aim of this study was to evaluate the therapeutic effect of idebenone in patients with OPA1-dominant optic atrophy (DOA). Sixteen patients with genetically confirmed OPA1-DOA were treated with 900 mg idebenone daily for 12 months. The primary endpoint was the best recovery/least deterioration of visual acuity. Secondary endpoints were the changes of visual acuity, colour vision, contrast sensitivity, visual field, peripapillary retinal nerve fibre layer thickness (pRNFLT), and visual-related quality of life. For the primary endpoint, a significant increase was observed for the right eye ($p = .0027$), for the left eye ($p = .0111$) and for the better-seeing eye ($p = .0152$). For visual fields, a significant improvement was observed for the left eye between baseline and 9 months ($p = .0038$). Regarding pRNFLT, a significant decrease was found for the left eye between baseline and 3 months ($p = .0413$) and between baseline and 6 months ($p = .0448$). In the visual function questionnaire, a significant improvement was observed in the subscale general vision ($p = .0156$) and in the composite score ($p = .0256$). In conclusion, best recovery of visual acuity improved, even though the amount of improvement was small. Furthermore, a maintenance of visual function after 12 months of idebenone intake could be observed as well as a significant improvement in vision-related quality of life.Whether this effect is due to idebenone treatment, the placebo effect, or is explainable by the natural progression of DOA, remains unclear.

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Introduction

Dominant optic atrophy (DOA) is a disease of the retinal ganglion cells[1–4] with a prevalence between 1 in 10 000 and 1 in 50 000.[3,5–7] Currently, there is no approved therapy for DOA.[8] The hallmark of this disease is an insidious onset of bilateral vision loss during childhood, but visual impairment may remain subclinical until adolescence. This is followed by a slow progression in some families, while in others, vision may remain stable. Rapid deterioration of visual acuity is rare.[5–7,9–14] Other clinical features are bitemporal optic atrophy in the early stages followed by total optic atrophy later, reduced colour vision as well as caecocentral, central, or paracentral scotomas in the visual field. Also, pseudo-cupping or excavation of the optic discs can be observed. Phenotypic expression is characterised by large intra- and interfamilial varieties ranging from asymptomatic carriers to patients classified as legally blind.[3–7,9–12,14,15]

In most cases, DOA is caused by a mutation in the OPA1 gene (MIM 165500).[1–4] OPA1 regulates different mitochondrial functions including mitochondrial fusion, cristae derangement, and regulation of apoptosis controlled by cytochrome c. Dysregulation of these processes has been postulated to cause defective oxidative phosphorylation and reduced adenosine triphosphate (ATP) synthesis by complex I.[16,17] Furthermore, an augmented production of reactive oxygen species has been observed in DOA.[17] It is assumed that the retinal ganglion cells are affected by reduced ATP synthesis and increased oxidative stress.[18]

Ubiquinone, also called coenzyme Q_{10}, is a long-chain quinone that plays an important role in the transport of electrons in the respiratory chain as

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a lipophilic electron carrier. It is able to bypass mitochondrial complex I and can transfer electrons directly to complex III.[4,18,19] In contrast to coenzyme Q_{10}, idebenone is less lipophilic and is analogous to the short chain of coenzyme Q_{10}. Due to this biochemical characteristic, idebenone can pass the mitochondrial membrane better than coenzyme Q_{10}.[18,19] Because of its high affinity to absorb electrons, idebenone also functions as an antioxidant, scavenging reactive oxygen species.[17,19] Those two functions tackle the two biochemical problems that OPA1 defects create. Currently, idebenone is approved as Raxone® for the treatment of Leber's hereditary optic neuropathy (LHON) by the European Medicines Agency.[20] LHON and DOA share some similarities such as the clinical presentation and the dysfunction in complex I of the respiratory chain.[1,21] Because of the common features between LHON and DOA, the mitochondrial dysfunctions caused by OPA1 mutations, and the beneficial biochemical functions of idebenone, it is assumed that idebenone has a therapeutic effect in DOA patients.[16]

To this day, two studies have described the use of idebenone in patients with OPA1-DOA. The first publication was a prospective study by Barboni et al. on seven patients.[1] The second one was a retrospective analysis by Romagnoli et al. on 87 patients, 50 of whom were treated with idebenone.[17] Romagnoli et al. reported the effect of idebenone on visual acuity only.[17] In both studies, varying doses of idebenone were used (Barboni et al. used 270–1000 mg/day,[1] Romagnoli et al. used 135-675mg/day[17]). Both described a favourable effect of idebenone.

However, no structured study about the long-term effects of idebenone as treatment for DOA patients with OPA1 mutations has been carried out as of yet. The aim of this study was to observe the therapeutic effect of 900 mg idebenone daily over 12 months in patients with OPA1-DOA.

Materials and methods

Study design and patients

In this prospective, monocentric clinical trial of a registered pharmaceutical product not according to its label (phase 2), patients with OPA1-DOA were treated with 900 mg idebenone (Raxone® 150 mg, Santhera Pharmaceuticals, 3 × 2 film-coated tablets taken with food), the approved dosage for LHON,[20] for 12 months according to recommendations in LHON to assess treatment response.[22]

Subjects with OPA1-DOA were informed about the trial during routine clinical visits at the Department of Ophthalmology, Medical University of Graz, Austria. Trial participation was offered to all subjects. The first 16 subjects that were interested in study participation and fitted the criteria were enrolled. Inclusion and exclusion criteria are depicted in Table 1.

The study was designed according to the Declaration of Helsinki, approved by the Ethics Committee of the Medical University of Graz (EC number: 32-250 ex 19/20) and the Federal Agency for Safety and Health Care in Austria (reference number: 13371525). Furthermore, 9 September 2020, the trial was registered at the European Union Clinical Trials Register (EudraCT number:

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
• Genetically confirmed OPA1 mutation
• Age of 12 years or more
• Intention and ability to take part in the trial and control visits
• Agreement to the treatment with idebenone
• Written informed consent
Exclusion criteria
• Glaucoma or any other optic neuropathy other than dominant optic atrophy
• Baseline best-corrected visual acuity less than counting fingers
• Hereditary diseases like galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
• Allergies or hypersensitivities to the active substance or to any of the ingredients contained in idebenone
• Possible drug interactions
• High-grade hepatic or renal impairment
• Other diseases which limit the compliance required for trial participation
• Pregnancy or lactation at baseline or a planned pregnancy within the next 12 months
• Previous treatment with idebenone
• Participation in other pharmaceutical product or medicine-related trials in the previous 3 months

2019-001493-28). Informed consent was given by all participants.

Endpoints and examinations

The primary endpoint of this study was the best recovery of visual acuity from baseline to 12 months. In patients without recovery, stabilisation or least deterioration of visual acuity was evaluated as recovery. Secondary endpoints were the changes of visual acuity, visual field, colour vision, contrast sensitivity, peripapillary retinal nerve fibre layer thickness (pRNFLT) on optical coherence tomography (OCT), and visual performance-related quality of life within a 12-month period. All visual function endpoints were determined for the right eye and for the left eye. Furthermore, we evaluated all parameters for the better-seeing eye assuming that it has a higher probability to regenerate visual function under idebenone treatment.

Before inclusion, participants underwent all examinations at least once. A full medical history was taken including pre-existing conditions, medications, and the age of onset of vision loss. Other reasons for optic atrophy, for example intracerebral or intraorbital expanding lesions, were ruled out by magnetic resonance imaging of the brain and orbits.

Examinations were performed at baseline and then at 3-monthly intervals (±10 days) according to current recommendations for LHON treatment.[22] At each visit, all primary and secondary endpoints were evaluated. Furthermore, at each follow-up visit the medical history, adverse events, and reactions were evaluated. Compliance of medication intake was checked by counting the remaining tablets at each follow-up visit.

Best-corrected visual acuity (BCVA) was measured using illuminated Early Treatment Diabetic Retinopathy Study (ETDRS) charts according to guidelines.[23,24] During each visit, refraction was checked and, if necessary, updated.[24] The smallest line with one or no errors was converted to the logarithm of the minimum angle of resolution (logMAR). Colour vision was tested with the Ishihara plates at a distance of 75 cm with 38 plates presented in a well-illuminated location; 21 of them counted for the test, and the remaining 17 were placebo plates. The participant had to give the answer in 3 seconds for every plate (forced-choice). The sum of the correct answers was documented as fraction (n/21). Contrast sensitivity was evaluated using Pelli Robson charts at a distance of 1 m in a well-illuminated location according to the examination guidelines.[25] The triplet with the poorest contrast, in which at least two out of three optotypes were recognised, was documented as a logarithm. The change of visual field was assessed through mean deviation (MD) of the 30-2 programme of Octopus 900 (Haag-Streit Switzerland).

A peripapillary 12° scan centred at the optic nerve head with 100 ART (automatic real time) was performed using spectral-domain OCT (Heidelberg Engineering GmbH, Germany, Spectralis Family Acquisition Module Software Version 6.16.8.0) to measure the pRNFLT.[26] Baseline scans were used as reference location for follow-up scans. The retinal nerve fibre layer was segmented by the built-in segmentation software and, if necessary, corrected by a single reviewer. For the comparison of follow-up visits, global pRNFLT was analysed.

To assess the visual performance-related quality of life, the German version of the National Eye Institute 25-Item Visual Function Questionnaire (Version 2000) was used.[27,28] The questionnaire was completed within an interview at baseline and at the 12-month visit. It was evaluated according to the description.[29]

Every 3 months peripheral venous blood was analysed to observe the effect of idebenone on full blood count, liver, and kidney parameters, as well as electrolytes. Furthermore, childbearing women underwent pregnancy tests monthly according to the Medicinal Products Act BGBl. I Nr. 35/2004 of the republic of Austria.[30]

Statistical analysis

The sample size was limited due to the orphan disease status of OPA1-DOA. The number of participants was determined by the expected number of patients presented at the Department of Ophthalmology of Graz. The planned number of participants was 16, and the expected drop-out-rate was about 10%.

For statistical analysis, the better-seeing eye was defined as the eye with the lower logMAR BCVA at baseline. If both eyes had equal BCVA, then the eye with the lower MD in visual field was determined as the better-seeing eye.

Categorical data were presented with quantity and percent, continuous data with mean, standard deviation (SD) or median, minimum, and maximum.

Changes over time for the primary endpoint were estimated via a mixed model accounting for repeated measures (baseline, follow-up) and included time, eye, time–eye interaction as fixed effects, and a random intercept for subject. *P* values and the corresponding 95% confidence intervals (CIs) for the differences in means (follow-up – baseline value), overall, and within eye were estimated by least squares means (LSM). The secondary endpoints were analysed via a mixed model with repeated measures (baseline, 3-, 6-, 9-, and 12 months) and included time, eye, time–eye interaction as fixed effects, and a random intercept for subject and eye. For repeated measures, a first-order autoregressive [AR(1)] covariance structure was modelled.

Additionally, analyses were repeated by including only one eye (the better-seeing eye at baseline). Mixed models including time as a fixed effect, a random intercept for subject and an AR(1) covariance structure for the time points were used.

The *p* values for the comparison of the questionnaire results from baseline to 12 months were obtained by Wilcoxon signed-rank test. *P* values below .05 were defined as statistically significant. No imputation of missing data was applied. SAS version 9.4 (Cary, NC, USA) was used for statistical analysis.

Results

Eleven male (69%) and five female (31%) white Caucasian participants were included between 1 October 2020 and 4 May 2021. The follow-up period ended on 26 April 2022. Characteristics of our study population showed variability in age and baseline BCVA corresponding to descriptions of other studies (Table 2).

For the primary endpoint (best recovery/least deterioration), a significant change of the least square mean difference (LSMD) of −0.08 logMAR (95% CI: −0.12, −0.03; $p = .0027$) was observed for the right eye (Table 3). Further significant improvement could be shown for the left eye (Table 4) as well as for the better-seeing eye (Table 5) with a LSMD of −0.06 logMAR (95% CI: −0.11, −0.01; $p = .0111$) and −0.05 logMAR (95% CI: −0.09, −0.01; $p = .0152$), respectively (Figure 1a).

For the secondary endpoint of change of BCVA within a 12-month period (Figure 1b), no significant change was observed for the right eye (Table 3), the left eye (Table 4) or for the better-seeing eye (Table 5).

For the visual field of the left eye (Table 4), between baseline and the 9-month visit a significant improvement with a LSMD of −1.66

Table 2. Demographic, genetic, and baseline clinical data.

Patient	Gender	Age at baseline (years)	Age at onset of vision loss (years)	BCVA at baseline (logMAR)		Mutation	
				OD	OS		
1	male	37	11	0.7	0.6	c.1879A>T	p.Arg627Ter
2	male	19	6	0.2	0.2	c.1780C>T	p.Arg594*
3	female	43	20	0.3	0.1	c.2232dupT	p.Ile745Tyrfs*16
4	female	57	NVL	0.1	0.3	c.2708_2711delTTAG	p.Val903Glyfs*3
5	male	31	13	0.6	0.5	c.2131C>T	p.Arg711Ter
6	male	62	22	0.2	0.5	c.2708_2711delTTAG	p.Val903Glyfs*3
7	male	28	10	0.1	0.2	c.116_119del	p.Ser39Ilefs*9
8	female	22	14	0.3	0.3	c.2708_2711delTTAG	p.Val903Glyfs*3
9	male	54	16	0.7	0.4	c.687T>A	p.Tyr229Ter
10	male	19	6	0.7	0.6	c.687T>A	p.Tyr229Ter
11	female	37	4	0.9	1.2	c.1313A>G	p.Asp438Gly
12	female	14	2	1	1.3	c.1313A>G	p.Asp438Gly
13	male	62	18	0.3	0.3	c.2708_2711delTTAG	p.Val903Glyfs*3
14	male	53	18	0.7	0.6	c.2708_2711delTTAG	p.Arg904Aspfs*2
15	male	55	43	1.1	1.1	c.(32 + 1_33–1)_(678 + 1_679–1)del, c.(32 + 1_33–578)_(678 + 1_679–1)del	
16	male	16	9	0.4	0.4	c.(32 + 1_33–578)_(678 + 1_679–1)del	

BCVA = best-corrected visual acuity; NR = NVL = perceived no vision loss; OD = right eye; OS = left eye.

Table 3. Visual function data for the right eye.

Time	*n*	Median (Min, Max)	Mean ± SD	LSMD (95% CI)	*p* value
Visual acuity: best recovery/least deterioration (logMAR)					
Baseline	16	0.50 (0.10, 1.10)	0.52 ± 0.32	-	
Follow-up	16	0.40 (0.00, 1.00)	0.44 ± 0.32	−0.08 (−0.12, −0.03)	.0027*
Visual acuity within a 12-month period (logMAR)					
Baseline	16	0.50 (0.10, 1.10)	0.52 ± 0.32	-	
3 months	16	0.50 (0.10, 1.30)	0.53 ± 0.34	0.01 (−0.04, 0.06)	.8011
6 months	15	0.50 (0.10, 1.10)	0.55 ± 0.30	0.00 (−0.05, 0.06)	.8876
9 months	15	0.50 (0.10, 1.00)	0.53 ± 0.29	−0.01 (−0.06, 0.04)	.7164
12 months	15	0.60 (0.00, 1.10)	0.52 ± 0.35	−0.02 (−0.07, 0.03)	.3825
Visual field (dB)					
Baseline	15	3.40 (0.20, 12.80)	4.41 ± 3.27	-	
3 months	15	4.00 (0.00, 15.30)	4.73 ± 3.87	0.33 (−0.72, 1.37)	.5370
6 months	14	3.05 (0.60, 12.90)	4.36 ± 3.35	−0.19 (−1.26, 0.88)	.7263
9 months	13	2.20 (0.40, 9.90)	3.09 ± 2.97	−0.83 (−1.93, 0.26)	.1351
12 months	14	3.20 (−0.60, 13.80)	4.31 ± 3.93	−0.24 (−1.31, 0.83)	.6582
Colour vision (*n*/21)					
Baseline	16	1.50 (0.00, 13.00)	3.81 ± 4.42	-	
3 months	16	1.00 (0.00, 18.00)	3.56 ± 4.75	−0.25 (−1.13, 0.63)	.5747
6 months	15	2.00 (0.00, 20.00)	3.80 ± 5.47	−0.16 (−1.13, 0.81)	.7405
9 months	15	2.00 (0.00, 20.00)	4.07 ± 5.28	0.11 (−0.87, 1.09)	.8279
12 months	15	2.00 (0.00, 19.00)	4.25 ± 5.08	0.29 (−0.69, 1.27)	.5575
Contrast sensitivity (log)					
Baseline	16	1.20 (0.45, 1.50)	1.11 ± 0.31	-	
3 months	16	1.13 (0.60, 1.35)	1.13 ± 0.23	0.02 (−0.1, 0.13)	.7462
6 months	15	1.20 (0.30, 1.65)	1.16 ± 0.34	0.07 (−0.06, 0.20)	.3189
9 months	15	1.35 (0.45, 1.50)	1.19 ± 0.28	0.10 (−0.04, 0.23)	.1624
12 months	15	1.05 (0.45, 2.00)	1.12 ± 0.40	0.03 (−0.11, 0.16)	.6762
Peripapillary retinal nerve fibre layer thickness (µm)					
Baseline	15	60.00 (45.00, 70.00)	58.47 ± 8.02	-	
3 months	15	60.00 (46.00, 69.00)	58.40 ± 8.14	−0.07 (−0.71, 0.57)	.8367
6 months	13	59.00 (48.00, 68.00)	59.23 ± 7.36	0.25 (−0.57, 1.07)	.5487
9 months	14	58.50 (43.00, 69.00)	57.57 ± 8.46	−0.38 (−1.26, 0.50)	.3984
12 months	14	58.50 (44.00, 68.00)	57.36 ± 8.24	−0.58 (−1.5, 0.34)	.2109

*p value < .05.

CI = confidence interval; logMAR = logarithm of the minimum angle of resolution; LSMD = least square mean difference; Max = maximum; Min = minimum; SD = standard deviation.

dB (95% CI: −2.77, −0.55; $p = .0038$) was observed. Between baseline and the other follow-up visits, the change in visual field was not significant (Figure 1c).

For colour vision and contrast sensitivity, no significant change was found (Tables 3–5, Figure 1d,e).

Analysing pRNFLT (Figure 1f), we found a significant decrease in the left eye between baseline and the 3-month visit with a LSMD of −0.67 µm (95% CI: −1.31, −0.03; $p = .0413$) as well as between baseline and the 6-month visit with a LSMD of −0.83 µm (95% CI: −1.63, −0.02; $p = .0448$). This significant decrease disappeared between baseline and the other follow-up visits (Table 4).

Regarding the visual performance-related quality of life, the highest deficits of our participants were documented in subscale general vision, role difficulties, and driving at baseline. After 12 months of idebenone therapy, the participants perceived an improvement in all areas. A significant increase was noticed only for the subscale general vision from a median 60.0 (Minimum [Min] 20.0, Maximum [Max] 80.0) to a median 80.0 (Min 40.0, Max 80.0; $p = .0156$). Improvement of all subscales led to a significant increase in the composite score after 12 months of idebenone treatment from 83.6 (Min 45.9, Max 95.5) to 92.5 (Min 57.8, Max 97.6; $p = .0256$) (Table 6).

Compliance regarding study medication intake was high. The median pill intake was >95% from baseline to the 12-month visit. Observed adverse events were headache (two participants), anorexia (one participant), anaemia (two female participants), elevation of liver parameters (two participants), sore throat (one participant), and heartburn (one participant). Adverse reactions and serious adverse events were not observed.

One participant (6.25%) was lost to follow-up after the first 3 months. The remaining 15 participants completed the study. Octopus perimetry was unobtainable in two right eyes and one left eye due to insufficient visual function. At the 9-month visit, another participant was unable to perform Octopus

Table 4. Visual function data for the left eye.

Time	*n*	Median (Min, Max)	Mean ± SD	LSMD (95% CI)	*p* value
Visual acuity: best recovery/least deterioration (logMAR)					
Baseline	16	0.45 (0.10, 1.30)	0.54 ± 0.36	-	
Follow-up	16	0.40 (0.10, 1.30)	0.48 ± 0.38	−0.06 (−0.11, −0.01)	.0111*
Visual acuity within a 12-month period (logMAR)					
Baseline	16	0.45 (0.10, 1.30)	0.54 ± 0.36	-	
3 months	16	0.40 (0.20, 1.30)	0.55 ± 0.38	0.01 (−0.04, 0.06)	.6145
6 months	15	0.40 (0.10, 1.30)	0.52 ± 0.41	−0.04 (−0.09, 0.01)	.1546
9 months	15	0.40 (0.10, 1.30)	0.54 ± 0.40	−0.02 (−0.07, 0.03)	.5064
12 months	15	0.40 (0.10, 1.30)	0.52 ± 0.38	−0.04 (−0.09, 0.01)	.1537
Visual field (dB)					
Baseline	14	5.10 (0.80, 11.00)	4.81 ± 2.48	-	
3 months	14	3.40 (1.30, 8.30)	4.08 ± 2.10	−0.74 (−1.82, 0.35)	.1807
6 months	13	3.10 (−1.00, 10.80)	4.08 ± 3.28	−0.83 (−1.94, 0.27)	.1383
9 months	13	2.60 (−0.60, 9.40)	3.26 ± 2.81	−1.66 (−2.77, −0.55)	.0038*
12 months	13	3.90 (−0.40, 10.80)	3.90 ± 3.01	−1.02 (−2.13, 0.09)	.0711
Colour vision (*n*/21)					
Baseline	16	1.00 (0.00, 15.00)	3.50 ± 4.63	-	
3 months	16	2.00 (0.00, 16.00)	4.19 ± 5.31	0.69 (−0.19, 1.57)	.1245
6 months	15	1.00 (0.00, 21.00)	3.87 ± 5.95	0.22 (−0.75, 1.19)	.6565
9 months	15	1.00 (0.00, 15.00)	3.67 ± 4.69	0.02 (−0.96, 1.00)	.9718
12 months	15	3.00 (0.00, 15.00)	4.22 ± 4.97	0.57 (−0.41, 1.56)	.2494
Contrast sensitivity (log)					
Baseline	16	1.35 (0.45, 1.50)	1.20 ± 0.28	-	
3 months	16	1.28 (0.30, 1.50)	1.18 ± 0.33	−0.02 (−0.13, 0.10)	.7462
6 months	15	1.35 (0.60, 1.65)	1.26 ± 0.31	0.07 (−0.06, 0.20)	.2819
9 months	15	1.35 (0.15, 1.65)	1.17 ± 0.41	−0.02 (−0.15, 0.12)	.7852
12 months	15	1.35 (0.30, 2.00)	1.19 ± 0.45	0.00 (−0.13, 0.14)	.9441
Peripapillary retinal nerve fibre layer thickness (µm)					
Baseline	15	62.00 (46.00, 83.00)	60.73 ± 10.15	-	
3 months	15	60.00 (45.00, 83.00)	60.07 ± 10.05	−0.67 (−1.31, −0.03)	.0413*
6 months	14	58.50 (44.00, 83.00)	59.43 ± 10.31	−0.83 (−1.63, −0.02)	.0448*
9 months	14	60.00 (45.00, 81.00)	59.36 ± 10.06	−0.87 (−1.75, 0.01)	.0532
12 months	14	60.50 (45.00, 81.00)	59.43 ± 10.20	−0.78 (−1.70, 0.13)	.0937

*p value < .05.

CI = confidence interval; logMAR = logarithm of the minimum angle of resolution; LSMD = least square mean difference; Max = maximum; Min = minimum; SD = standard deviation.

perimetry with his right eye. Regarding pRNFLT, both eyes of one participant were excluded because of vitreous detachment with traction to the optic nerve head. Furthermore, at the 6-month visit, another right eye was excluded because of insufficient OCT quality.

Discussion

This is the first study describing the therapeutic effect of a standardised dose of idebenone in OPA1-DOA participants with defined follow-up visits. Limited awareness about the disease among ophthalmologists and the absence of a collective subject registry in Austria and Europe renders sample size calculation and recruitment difficult. The positive results about the effect of idebenone on visual function in OPA1-DOA subjects from Barboni et al.[1] and Romagnoli et al.[17] encouraged us to make idebenone accessible to all participants and to design our study without a control group.

In the last decades, several studies describing the natural history of OPA1-DOA have been conducted. The rate of visual acuity deterioration varies between 24% and 100%.[2,3,7,12,15,17] Yu-Wai-Man et al. observed a mean rate of vision loss of 0.032 logMAR/year[3] and 0.070 logMAR/year.[2]

To our knowledge, a spontaneous improvement of visual acuity has only been described in the two retrospective studies by Cohn et al.[15] and Romagnoli et al.[17] and in a single-case presentation of a subject with an LHON-like phenotype harbouring the c.740 G>A mutation.[31] A closer look to the retrospective studies reveals some limitations in data collection. They used different observation periods, the method of visual acuity testing was not described,[17] or differing visual acuity charts were used.[15] In the study by Cohn et al., data from previous ophthalmological records were partially included. Additionally, Cohn et al. were uncertain about the validity of their results and could not rule out a learning effect in children.[15]

Table 5. Visual function data for the better-seeing eye.

Time	*n*	Median (Min, Max)	Mean ± SD	LSMD (95% CI)	*p* value
Visual acuity: best recovery/least deterioration (logMAR)					
Baseline	16	0.40 (0.10, 1.10)	0.46 ± 0.32	-	
Follow-up	16	0.40 (0.00, 1.20)	0.41 ± 0.35	−0.05 (−0.09, −0.01)	.0152*
Visual acuity within a 12-month period (logMAR)					
Baseline	16	0.40 (0.10, 1.10)	0.46 ± 0.32	-	
3 months	16	0.40 (0.10, 1.30)	0.49 ± 0.36	0.03 (−0.02, 0.08)	.2342
6 months	15	0.40 (0.10, 1.20)	0.50 ± 0.33	0.02 (−0.04, 0.07)	.5560
9 months	15	0.40 (0.10, 1.20)	0.50 ± 0.33	0.02 (−0.04, 0.07)	.5527
12 months	15	0.40 (0.00, 1.20)	0.46 ± 0.37	−0.02 (−0.08, 0.03)	.3823
Visual field (dB)					
Baseline	15	4.50 (0.20, 11.00)	4.73 ± 2.90	-	
3 months	15	4.00 (0.00, 15.30)	4.74 ± 3.71	0.01 (−1.03, 1.04)	.9898
6 months	14	3.40 (0.70, 12.90)	4.66 ± 3.66	−0.21 (−1.33, 0.91)	.7085
9 months	13	2.70 (0.40, 9.40)	3.22 ± 2.82	−1.03 (−2.19, 0.12)	.0787
12 months	14	3.75 (−0.60, 13.80)	4.49 ± 3.90	−0.38 (−1.51, 0.75)	.5071
Colour vision (*n*/21)					
Baseline	16	2.00 (0.00, 13.00)	3.81 ± 4.32	-	
3 months	16	2.00 (0.00, 18.00)	3.81 ± 4.72	0.00 (−0.96, 0.96)	1.0000
6 months	15	1.00 (0.00, 20.00)	3.73 ± 5.57	−0.23 (−1.26, 0.80)	.6571
9 months	15	2.00 (0.00, 20.00)	4.07 ± 5.38	0.11 (−0.93, 1.14)	.8369
12 months	15	4.00 (0.00, 19.00)	4.42 ± 5.01	0.46 (−0.57, 1.50)	.3738
Contrast sensitivity (log)					
Baseline	16	1.35 (0.45, 1.50)	1.15 ± 0.31	-	
3 months	16	1.20 (0.60, 1.50)	1.15 ± 0.27	0.00 (−0.12, 0.12)	1.0000
6 months	15	1.20 (0.30, 1.65)	1.20 ± 0.34	0.08 (−0.07, 0.22)	.2814
9 months	15	1.35 (0.45, 1.50)	1.20 ± 0.29	0.02 (−0.13, 0.17)	.8246
12 months	15	1.05 (0.45, 2.00)	1.15 ± 0.41	0.02 (−0.13, 0.17)	.7979
Peripapillary retinal nerve fibre layer thickness (µm)					
Baseline	15	60.00 (46.00, 83.00)	60.00 ± 10.09	-	
3 months	15	59.00 (45.00, 83.00)	59.60 ± 10.45	−0.40 (−1.03, 0.23)	.2086
6 months	14	57.00 (44.00, 83.00)	59.21 ± 10.79	−0.36 (−1.10, 0.38)	.3290
9 months	14	58.00 (45.00, 81.00)	59.00 ± 10.21	−0.57 (−1.33, 0.20)	.1456
12 months	14	58.50 (45.00, 81.00)	58.79 ± 10.15	−0.78 (−1.55, 0.00)	.0501

*p value < .05.
CI = confidence interval; logMAR = logarithm of the minimum angle of resolution; LSMD = least square mean difference; Max = maximum; Min = minimum; SD = standard deviation.

In our study, all participants were familiar with the study examinations and had experienced them at least once before. Therefore, a learning effect seems improbable.

Summarising natural history data, most studies describe a stabilisation or slow progression of visual impairment over many years. In LHON, an improvement of 0.2 logMAR on ETDRS charts is accepted as a clinically relevant recovery.[22,32]

For the primary endpoint of our study, a small increase of visual acuity was found (LSMD: right eye −0.08 logMAR [Table 3], left eye −0.06 logMAR [Table 4] and better-seeing eye −0.05 logMAR [Table 5]). However, the aforementioned threshold for clinically relevant recovery was not reached. Within the 12-month period (secondary endpoint), no significant improvement in visual acuity could be observed. Nevertheless, from baseline to the 12-month visit mean visual acuity was stable without deterioration (LSMD: right eye −0.02 logMAR, left eye −0.04 logMAR, better-seeing eye −0.02 logMAR). In comparison with Yu-Wai-Man et al.'s reported rates of visual decrease of 0.032[3] and 0.070[2] logMAR/year, maintenance of visual acuity may be a success. Romagnoli et al. observed a change of the median visual acuity in the best-seeing eyes from 0.52 to 0.51 logMAR in the idebenone treated group (observation time of 4.2 ± 2.3 years). In the untreated group, the median visual acuity was unchanged at 0.52 logMAR after an observation period of 3.4 ± 2.5 years.[17] In our results, the median visual acuity in the better-seeing eye was 0.40 logMAR at baseline and at the 12-month follow-up (Table 5). Although our study participants were observed for only 12 months, our median visual acuity results are comparable with the data of the untreated and treated groups of Romagnoli et al.[17] Barboni et al. were able to show an improvement of mean visual acuity in the right eye from 0.7 logMAR to 0.5 logMAR after 16.4 months of idebenone treatment.[1] In our study, the mean visual acuity in the right eye remained stable after 12 months of treatment (0.52 logMAR at baseline and at the 12-month

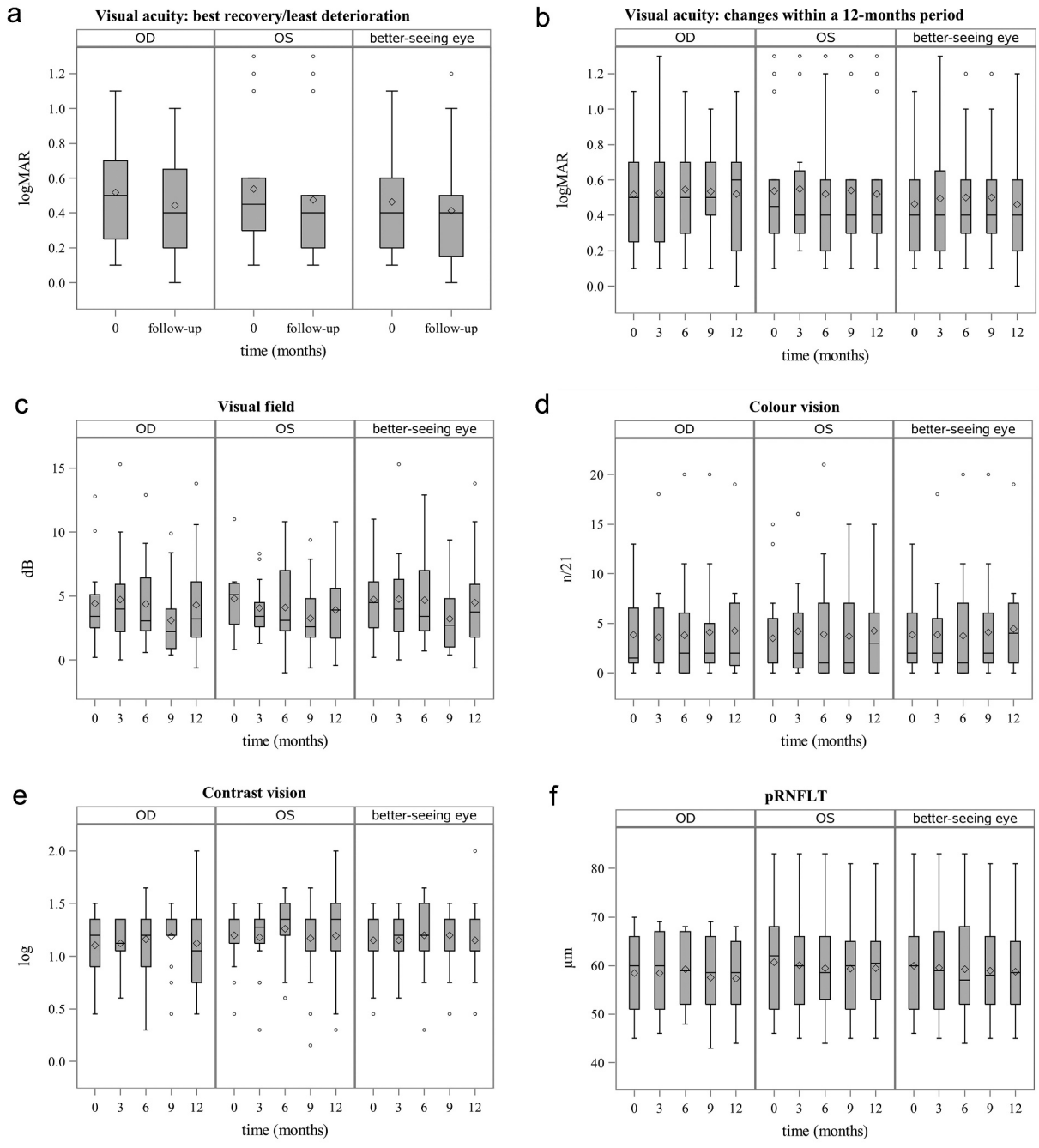

Figure 1. Box plots showing change of visual function within a 12-month period of idebenone treatment. (a) Best recovery or least deterioration of visual acuity. (b) Change of visual acuity. (c) Change of visual field. (d) Change of colour vision. (e) Change of contrast sensitivity. (f) Change of peripapillary retinal nerve fibre layer thickness. Solid lines represent median values and the symbols 'o', '+' and ' ×' within the boxes represent mean values for OD (right eye), OS (left eye) and the better-seeing eye and 'o', '+' and ' ×' outside depict outliers. logMAR = logarithm of the minimum angle of resolution; pRNFLT = peripapillary retinal nerve fibre layer thickness.

visit [Table 3]). In the left eye, the mean visual acuity in the Barboni et al. study was unchanged at 0.6 logMAR after 16.4 months,[1] while we had similar stable results, only changing from 0.54 logMAR to 0.52 logMAR after the 12-month follow-up (Table 4).

A significant improvement of the visual field of the left eye was found between baseline and the 9-month visit. Also, between baseline and the other follow-up visits, the visual field improved, but without a significant change. A trend towards improvement with increasing treatment duration

Table 6. National Eye Institute Visual Function Questionnaire.

Scale Name	Baseline Median (Min, Max)	12-months Median (Min, Max)	Difference Median (Min, Max)	*p* value*
General Health	75.0 (50.0, 100.0)	75.0 (50.0, 100.0)	0.0 (−50.0, 0.0)	.2500
General Vision	60.0 (20.0, 80.0)	80.0 (40.0, 80.0)	0.0 (0.0, 20.0)	.0156*
Ocular Pain	100.0 (37.5, 100.0)	100.0 (87.5, 100.0)	0.0 (0.0, 50.0)	.0625
Near Activities	91.7 (33.3, 100.0)	91.7 (25.0, 100.0)	0.0 (−16.7, 16.7)	.8105
Distance Activities	79.2 (37.5, 100.0)	87.5 (45.8, 100.0)	4.2 (−20.8, 33.3)	.0898
Vision Specific:				
Social Functioning	100.0 (37.5, 100.0)	100.0 (37.5, 100.0)	0.0 (−12.5, 50.0)	1.0000
Mental Health	87.5 (75.0, 93.8)	87.5 (57.3, 100.0)	0.0 (−25.0, 25.0)	.7871
Role Difficulties	68.8 (25.0, 100.0)	100.0 (25.0, 100.0)	0.0 (−50.0, 50.0)	.6328
Dependency	100.0 (58.3, 100.0)	100.0 (58.3, 100.0)	0.0 (−33.3, 41.7)	.3750
Driving	62.5 (0.0, 91.7)	79.2 (0.0, 100.0)	4.2 (−8.3, 91.7)	.0625
Colour Vision	100.0 (50.0, 100.0)	100.0 (75.0, 100.0)	0.0 (−25.0, 25.0)	1.0000
Peripheral Vision	100.0 (25.0, 100.0)	100.0 (2.0, 100.0)	0.0 (−50.0, 25.0)	.8125
Composite Score	83.6 (45.9, 95.5)	92.5 (57.8, 97.6)	3.7 (−6.5, 13.8)	.0256*

*p value < .05, calculated with Wilcoxon signed-rank test.
Max = maximum; Min = minimum.

was detectable. In view of the slow disease progression, prolonged treatment duration may be necessary to confirm this positive trend.

Colour vision deficits of our study population are consistent with colour vision abnormalities described in natural history studies.[3,5–7,9–13,15,33,34] An improvement of colour vision after idebenone treatment could not be observed in our study. However, Barboni et al. showed an improvement of more than 5/15 Ishihara plates in three out of seven OPA1-DOA participants taking idebenone.[1]

Recently, significantly reduced contrast sensitivity in OPA1-DOA subjects (mean 1.21 log) compared with healthy controls has been documented.[35] These deficits are consistent with our baseline characteristics (right eye: mean 1.11 log, left eye: mean 1.20 log, better-seeing eye: 1.15 log). Idebenone therapy had no influence on the change of contrast sensitivity in our data.

Regarding pRNFLT, we found a significant decrease in the left eye between baseline and 3 and 6 months. However, this decrease in the mean global pRNFLT was smaller than 1 µm and did not persist in the later follow-up.

Similar to other hereditary eye diseases, a decreased quality of life has been detected in OPA1-DOA subjects.[35] Eckmann-Hansen et al. found a mean composite National Eye Institute Visual Function Questionnaire −39 score of 69.7,[35] which is comparable to our baseline median composite score. After 12 months of idebenone treatment, the quality of life ameliorated in our study, particularly general vision improved significantly. In an open-label trial such as our study, it is not possible to distinguish if the increase in quality of life after 12 months is caused by the treatment with idebenone or due to a placebo effect. Although we found pathological colour vision and visual field defects in our data, participants were not impaired in their daily lives. An explanation could be that they had developed coping mechanisms to compensate for their impairments in everyday life. Nevertheless, the prospect of a pharmaceutical treatment is important for subjects' mental well-being, particularly in such a rare, hereditary disease.

A dose of 900 mg idebenone was well tolerated, and there was no need to interrupt treatment. Observed adverse events were mild, and almost all of them were documented previously in the product information.

Our study has some limitations. We included a small group of subjects. Nevertheless, our sample size is the second largest reported to date of OPA1-DOA subjects taking idebenone. Examiners were not blinded, and some participants were not able to perform all examinations at every follow-up. We planned our study without a control group and compared the results with baseline data. The development of a collective patient registry in Austria and Europe would facilitate recruitment and planning of an adequately powered, placebo-controlled trial. Another problem for power calculation is the absence of clinically standardised endpoints. A detailed natural history study could lead to the definition of meaningful endpoints as a basis

for evaluation of therapeutic effects of future treatments. Furthermore, the National Eye Institute 25-Item Visual Function Questionnaire was not designed for the use in patients with inherited optic neuropathies. Some questions are irrelevant for patients with OPA1-DOA (e.g. ocular pain). Potential limitations may arise from the scoring system by converting an ordinal into a continuous scale.

In conclusion, we observed an improvement in best recovery of visual acuity with idebenone treatment, but this improvement did not reach the level of clinically relevant recovery set for LHON. Nevertheless, visual function of idebenone treatment was maintained and vision-related quality of life improved significantly. Whether this effect is due to idebenone treatment, placebo-effect or explainable by the natural progress of OPA1-DOA requires further research. A randomised, placebo-controlled, and double-blind study over at least 2 years could solve this issue.

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