Journal of Neuro-Ophthalmology

Real World Clinical Experience with Idebenone in the Treatment of Leber's Hereditary Optic Neuropathy

--Manuscript Draft--

Manuscript Number:	
Full Title:	Real World Clinical Experience with Idebenone in the Treatment of Leber's Hereditary Optic Neuropathy
Short Title:	LHON treatment with Idebenone in clinical practice
Article Type:	Original Contribution
Keywords:	Idebenone; Leber's hereditary optic neuropathy; LHON; visual acuity; real world data; retrospective
Corresponding Author:	Thomas Klopstock, M.D. Ludwig-Maximilians-Universitat Munchen GERMANY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Ludwig-Maximilians-Universitat Munchen
Corresponding Author's Secondary Institution:	
First Author:	Claudia B. Catarino, MD, PhD
First Author Secondary Information:	
Order of Authors:	Claudia B. Catarino, MD, PhD
	Bettina von Livonius, MD
	Constanze Gallenmüller, MD
	Rudrani Banik, MD
	Selma Matloob, MBChB, MRCOphth,
	Madhura A. Tamhankar, MD
	Lorena Castillo, MD
	Nils Dahlgren, MD
	Christoph Friedburg, MD, FEBO
	Christopher A. Halfpenny, MBBS, PhD
	John A. Lincoln, MD, PhD
	Ghislaine L. Traber, MD
	Gölge Acaroglu, MD
	Graeme C. M. Black, DPhil, FRCOphth
	Carlos Doncel, MD
	Clare L. Fraser, MBBS, MMed
	Joanna Jakubaszko, MD, PhD
	Klara Landau, MD, FEBO
	Stefan J. Langenegger, MD, FEBO
	Francisco J. Muñoz Negrete, MD, PhD
	Nancy J. Newman, MD

	Joanna Poulton, MD, MRCPCH
	Elisabetta Scoppettuolo, MBBS, FRCOphth
	Prem Subramanian, MD, PhD
	Ahmed T. Toosy, MBBS, FRCP
	Mariona Vidal, MD
	Andrea L. Vincent, MBChB, MD
	Marcela Votruba, BM BCh, FRCOphth
	Marcin Zarowski, MD, PhD
	Adam Zermansky, MBChB, FRCP
	Claudia Priglinger, MD
	Felice Lob, MD
	Günther Rudolph, MD
	Oskars Mikazans, MA
	Xavier Llòria, MD
	Magda Silva
	Günther Metz, PhD
	Thomas Klopstock, M.D.
Order of Authors Secondary Information:	
Manuscript Region of Origin:	GERMANY
Abstract:	Background : Leber's hereditary optic neuropathy (LHON) leads to bilateral central vision loss. In a clinical trial setting, idebenone has been shown to be safe and to provide a trend towards improved visual acuity, but long-term evidence of effectiveness in real world clinical practice is sparse. Methods: Open-label, multicenter, retrospective, non-controlled analysis of long-term visual acuity and safety in 111 LHON patients treated with idebenone (900 mg/day) in an expanded access program. Eligible patients had a confirmed mitochondrial DNA mutation and had experienced onset of symptoms (most recent eye) within 1 year prior to enrolment. Data on visual acuity and adverse events were collected as per normal clinical practice. Efficacy was assessed as the p roportion of patients with either a Clinically Relevant Recovery (CRR) or stabilization (Clinically Relevant Stabilization, CRS) of visual acuity. In the case of CRR, time to and magnitude of recovery over time were also assessed. Results : At time of analysis, 87 patients had provided longitudinal efficacy data. Average treatment duration was 25.6 months. CRR was observed in 46.0% of patients. Analysis of treatment effect by duration showed that the proportion of patients with recovery, as well as the magnitude of recovery increased with treatment duration. Average gain in best corrected visual acuity for responders was 0.72 logarithm of the minimal angle of resolution, equivalent to more than seven lines on the Early Treatment Diabetic Retinopathy Study chart. Furthermore, 50% of patients who had a visual acuity below 1.0 logMAR in at least one eye at initiation of treatment successfully maintained their vision below this threshold by last observation. Idebenone was well tolerated, with the majority of adverse events classified as minor. Conclusions : These data demonstrate the benefit of idebenone treatment in recovering lost vision and maintaining good residual vision in a real-world setting. Together, these findings indicate that idebenone treatment should be initiated early and be maintained for at least 24 months to maximize efficacy. Safety results were consistent with the known safety profile of idebenone.

Real World Clinical Experience with Idebenone in the Treatment of Leber's Hereditary Optic Neuropathy

(Running title: **LHON treatment with Idebenone in clinical practice**)

Abstract

Background: Leber's hereditary optic neuropathy (LHON) leads to bilateral central vision loss. In a clinical trial setting, idebenone has been shown to be safe and to provide a trend towards improved visual acuity, but long-term evidence of effectiveness in real world clinical practice is sparse.

Methods: Open-label, multicenter, retrospective, non-controlled analysis of long-term visual acuity and safety in 111 LHON patients treated with idebenone (900 mg/day) in an expanded access program. Eligible patients had a confirmed mitochondrial DNA mutation and had experienced onset of symptoms (most recent eye) within 1 year prior to enrolment. Data on visual acuity and adverse events were collected as per normal clinical practice. Efficacy was assessed as the **p**roportion of patients with either a Clinically Relevant Recovery (CRR) or stabilization (Clinically Relevant Stabilization, CRS) of visual acuity. In the case of CRR, time to and magnitude of recovery over time were also assessed.

Results: At time of analysis, 87 patients had provided longitudinal efficacy data. Average treatment duration was 25.6 months. CRR was observed in 46.0% of patients. Analysis of treatment effect by duration showed that the proportion of patients with recovery, as well as the magnitude of recovery increased with treatment duration. Average gain in best corrected visual acuity for responders was 0.72 logarithm of the minimal angle of resolution, equivalent to more than seven lines on the Early Treatment Diabetic Retinopathy Study chart. Furthermore, 50% of patients who had a visual acuity below 1.0 logMAR in at least one eye at initiation of treatment successfully maintained their vision below this threshold by last observation. Idebenone was well tolerated, with the majority of adverse events classified as minor.

Conclusions: These data demonstrate the benefit of idebenone treatment in recovering lost vision and maintaining good residual vision in a real-world setting. Together, these findings indicate that idebenone treatment should be initiated early and be maintained for at least 24 months to maximize efficacy. Safety results were consistent with the known safety profile of idebenone.

30

Real World Clinical Experience with Idebenone in the Treatment of Leber's Hereditary Optic Neuropathy

(Running title: **LHON treatment with Idebenone in clinical practice**)

Authors:

Claudia B. Catarino, MD, PhD, [1, 2]

[1]Department of Neurology, Friedrich-Baur-Institute, University Hospital of the Ludwig-Maximilians-University, Munich, Germany; [2]German Center for Neurodegenerative Diseases (DZNE), Munich, Germany

Bettina von Livonius, MD, [3]

[3]Department of Ophthalmology, University Hospital of the Ludwig-Maximilians-University Munich, Germany

Constanze Gallenmüller, MD, [1]

[1]Department of Neurology, Friedrich-Baur-Institute, University Hospital of the Ludwig-Maximilians-University, Munich, Germany

Rudrani Banik, MD, [4]

[4]New York Eye and Ear Infirmary of Mount Sinai, New York, NY, USA

Selma Matloob, MBChB, MRCOphth, [5]

[5]Ophthalmology Department, Waikato Hospital, Hamilton, New Zealand

Madhura A. Tamhankar, MD, [6]

[6]Scheie Eye Institute, University of Pennsylvania, Philadelphia, PA, USA

Lorena Castillo, MD, [7]

[7]Institut Català de Retina, Barcelona, Spain

Nils Dahlgren, MD, [8]

[8]Södersjukhuset, Stockholm, Sweden

Christoph Friedburg, MD, FEBO, [9]

[9]Augenklinik, Universitätsklinikum Giessen, Giessen, Germany

Christopher A. Halfpenny, MBBS, PhD, [10]

[10]University Hospital Southampton, Southampton, UK

John A. Lincoln, MD, PhD, [11]

[11]McGovern Medical School, UTHealth, Houston, TX, USA

Ghislaine L. Traber, MD, [12]

[12]Department of Ophthalmology, University Hospital and University of Zurich, Zurich, Switzerland

Gölge Acaroglu, MD, [13]

[13]Neuro-ophthalmology Associates, Ankara, Turkey

Graeme C. M. Black, DPhil, FRCOphth, [14, 15]

[14]Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, St Mary's Hospital, Manchester, UK

[15]Division of Evolution and Genomic Sciences, Neuroscience and Mental Health Domain, School of Health Sciences, Faculty of Biology, Medicines and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

Carlos Doncel, MD, [16]

[16]Ophtalmology Unit, Hospital de Poniente, El Ejido, Almería, Spain

Clare L. Fraser, MBBS, MMed, [17]

[17]Save Sight Institute, University of Sydney

Joanna Jakubaszko, MD, PhD, [18]

[18]Wroclaw Medical University, Ophthalmology Clinical Centre SPEKTRUM, Poland

Klara Landau, MD, FEBO, [12]

[12]Department of Ophthalmology, University Hospital and University of Zurich, Zurich, Switzerland

Stefan J. Langenegger, MD, FEBO, [12]

[12]Department of Ophthalmology, University Hospital and University of Zurich, Zurich, Switzerland

Francisco J. Muñoz-Negrete, MD, PhD, [19]

[19]University Hospital Ramon y Cajal, IRYCIS, Madrid, Spain

Nancy J. Newman, MD, [20]

[20]Emory University School of Medicine, Atlanta GA, USA

Joanna Poulton, DM, MRCPCH, [21]

[21]Nuffield Dept Obstetrics and Gynaecology, University of Oxford, The Women's Centre, Oxford

Elisabetta Scoppettuolo, MBBS, FRCOphth, [22]

[22]Department of Ophthalmology, East Kent Hospitals University Foundation Trust, UK

Prem Subramanian, MD, PhD, [23]

[23]Neuro-Ophthalmology Division, University of Colorado School of Medicine, CO, USA

Ahmed T. Toosy, MBBS, FRCP, [24]

[24]Queen Square MS Centre, Department of Neuroinflammation, UCL Institute of Neurology, University College London, London, UK

Mariona Vidal, MD, [25]

[25]Hospital Sant Joan de Déu Barcelona, Barcelona, Spain

Andrea L. Vincent, MBChB, MD, [26]

[26]Eye Department, Greenlane Clinical Centre, Auckland, New Zealand

Marcela Votruba, BM BCh, FRCOphth, [27]

[27]School of Optometry and Vision Sciences, Cardiff University, Cardiff, UK

Marcin Zarowski, MD, PhD, [28]

[28]Department of Developmental Neurology, Poznan University of Medical Sciences, Poznan, Poland

Adam Zermansky, MBChB, FRCP, [29]

[29]Manchester Centre for Clinical Neuroscience, Salford Royal NHS Foundation Trust, U.K

Claudia Priglinger, MD, [3]

[3]Department of Ophthalmology, University Hospital of the Ludwig-Maximilians-University Munich, Germany

Felice Lob, MD, [3]

[3]Department of Ophthalmology, University Hospital of the Ludwig-Maximilians-University Munich, Germany

Günther Rudolph, MD, [3]

[3]Department of Ophthalmology, University Hospital of the Ludwig-Maximilians-University Munich, Germany

Oskars Mikazans, MA [1]

[1]Department of Neurology, Friedrich-Baur-Institute, University Hospital of the Ludwig-Maximilians-University, Munich, Germany

Magda Silva, [30]

[30]Santhera Pharmaceuticals, Pratteln, Switzerland

Xavier Llòria, MD, [30]

[30]Santhera Pharmaceuticals, Pratteln, Switzerland

Günther Metz, PhD, [30]

[30]Santhera Pharmaceuticals, Pratteln, Switzerland

Thomas Klopstock, MD.[1, 2, 31]

[1]Department of Neurology, Friedrich-Baur-Institute, University Hospital of the Ludwig-Maximilians-University, Munich, Germany; [2]German Center for Neurodegenerative Diseases (DZNE), Munich, Germany; [31]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

Corresponding author:

Prof. T. Klopstock

Department of Neurology, Friedrich-Baur-Institute,

University Hospital of the Ludwig-Maximilians-Universität

Ziemssenstr. 1a, 80336 Munich, Germany

E-mail: thomas.klopstock@med.uni-muenchen.de

Tel: +49-89-4400-57400

Conflict of interest

M. Silva, G. Metz and X. Llòria are regular employees of Santhera. T. Klopstock has received research support, consultancy fees, speaker honoraria and travel funds from GenSight Biologics and Santhera Pharmaceuticals, unrelated to this paper.

Keywords

Idebenone, Leber's hereditary optic neuropathy, LHON, visual acuity, real world data, retrospective

Disclosure of funding

Neither physicians nor authors received funding for managing patients, collecting data or write the paper. Statistical analysis was funded by Santhera Pharmaceuticals

Word count: 2501

PRÉCIS

Idebenone treatment can result in both stabilization of residual visual acuity and recovery of lost vision, with a treatment duration of at least 2 years needed to maximize the probability of recovery.

Abstract

Background: Leber's hereditary optic neuropathy (LHON) leads to bilateral central vision loss. In a clinical trial setting, idebenone has been shown to be safe and to provide a trend towards improved visual acuity, but long-term evidence of effectiveness in real world clinical practice is sparse.

Methods: Open-label, multicenter, retrospective, non-controlled analysis of long-term visual acuity and safety in 111 LHON patients treated with idebenone (900 mg/day) in an expanded access program. Eligible patients had a confirmed mitochondrial DNA mutation and had experienced onset of symptoms (most recent eye) within 1 year prior to enrolment. Data on visual acuity and adverse events were collected as per normal clinical practice. Efficacy was assessed as the **p**roportion of patients with either a Clinically Relevant Recovery (CRR) or stabilization (Clinically Relevant Stabilization, CRS) of visual acuity. In the case of CRR, time to and magnitude of recovery over time were also assessed.

Results: At time of analysis, 87 patients had provided longitudinal efficacy data. Average treatment duration was 25.6 months. CRR was observed in 46.0% of patients. Analysis of treatment effect by duration showed that the proportion of patients with recovery, as well as the magnitude of recovery increased with treatment duration. Average gain in best corrected visual acuity for responders was 0.72 logarithm of the minimal angle of resolution, equivalent to more than seven lines on the Early Treatment Diabetic Retinopathy Study chart. Furthermore, 50% of patients who had a visual acuity below 1.0 logMAR in at least one eye at initiation of treatment successfully maintained their vision below this threshold by last observation. Idebenone was well tolerated, with the majority of adverse events classified as minor.

Conclusions: These data demonstrate the benefit of idebenone treatment in recovering lost vision and maintaining good residual vision in a real-world setting. Together, these findings indicate that idebenone treatment should be initiated early and be maintained for at least 24 months to maximize efficacy. Safety results were consistent with the known safety profile of idebenone.

Introduction

Leber's hereditary optic neuropathy (LHON) is a form of blindness due to retinal ganglion cell (RGC) dysfunction,[1] caused by mutations in mitochondrial DNA (mtDNA) which affect complex I (NADH-ubiquinone oxidoreductase) of the mitochondrial respiratory chain.[2, 3] Although rare (estimated prevalence of 1 in 27,000-45,000), it affects all ages and gender, causing rapid and severe, bilateral (usually sequential), painless loss of central vision.[4-7] Spontaneous recovery is rare.[8-11] Idebenone is a synthetic short-chain benzoquinone that bypasses the dysfunctional complex I, and restores mitochondrial function, thus increasing ATP production and reducing lipid peroxidation and oxidative stress.[12-14]

The first randomized, double-blind, placebo-controlled trial of idebenone in LHON patients (Rescue of Hereditary Optic Disease Outpatient Study (RHODOS)) demonstrated a trend towards improved best corrected visual acuity (BCVA) in the idebenone-treated intent-to-treat (ITT) population compared with placebo.[15] Idebenone (RAXONE®, idebenone 150 mg tablets, Santhera Pharmaceuticals, Pratteln, Switzerland) is since 2015 the first and currently only approved treatment for adults and adolescents with LHON[1].

In 2011, the manufacturer set up an international Expanded Access Programme (EAP) to provide special access to idebenone, within local regulations, provided they had a genetically confirmed LHON and disease duration of less than 12 months since onset of vision loss (most recently affected eye). All requests for access to idebenone were unsolicited, and the manufacturer was not involved in any clinical decision. Here, we describe the EAP patient

[1] In the European Union and some other countries.

population and report on clinical outcomes and safety, following ongoing long-term treatment with idebenone in clinical practice.

Methods (see also Supplemental Data A)

Idebenone dose and duration of therapy were entirely at the discretion of the treating physician. Patient follow-up was in accordance with routine clinical practice, typically at 3-monthly intervals.

For each participant, data on visual acuity (VA) and adverse events (AEs) was collected. BCVA was generally assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) charts with logarithm of the minimal angle of resolution (logMAR) values, or converted from standard Snellen notation to logMAR for analysis purposes.[16] Clinically Relevant Stabilization of BCVA (CRS) was defined as a patient having a logMAR of <1.0 at baseline (below the threshold of severe vision loss/legal blindness in the United States[17]) in at least one eye which was maintained in this eye at their last follow-up visit (LV). A Clinically Relevant Recovery of BCVA (CRR) was defined as an improvement from off-chart (i.e. unable to read any letters on an ETDRS chart from 1 meter; > 1.68 logMAR) to on-chart by at least one full line (five letters); or an improvement in on-chart BCVA by at least two lines (10 letters; 0.2 logMAR). The time to initial observation of a CRR was taken as the criterion for an event-based analysis, and the magnitude of recovery is reported as the best recovery observed for a patient. Safety and pregnancy information was collected according to the applicable pharmacovigilance (PV) requirements.

Ethics approval was obtained by the Ethical Committee of the Ludwig-Maximilian University of Munich in accordance with the declaration of Helsinki.

Results

At the time of data cut-off (June 2018), 111 patients from 38 sites in 10 countries, had received at least one dose of idebenone and were included in the safety population (SP). Of those, 87 patients carrying one of the three major LHON mtDNA mutations, having onset within the 12 months previous to treatment start and providing post-baseline BCVA data were included in the Efficacy Population (EP). Mean treatment duration was 25.6 months (2.4 to 70.4) (Table 1).

Patient demographics were generally representative of the known disease characteristics of LHON. Three patients, all G11778A carriers, reportedly had one eye declared unaffected at baseline, namely, a 14 year-old male, a 16 year-old male and a 21 year-old female.

Clinically Relevant Stabilization of BCVA

In the EP, 24/87 subjects had a BCVA at baseline <1.0 logMAR in at least one eye, 50% (12/24) of which experienced CRS (Table 1 and 2). For patients with CRS, mean BCVA improved from 0.47 logMAR at baseline to 0.29 logMAR at LV.

Of the three patients with one unaffected eye at baseline, the 16 year-old patient deteriorated to off-chart BCVA in both eyes after 6 months of therapy, with no recovery thereafter. However, both the 14 year-old male patient and the 21 year-old female patient still had normal BCVA at LV after 12 months follow-up. These two patients also had CRR in the fellow eye, which had presented with BCVA worse than 1.0 logMAR at start of treatment.

Clinically Relevant Recovery of BCVA from Nadir (Table 3).

40/87 patients (46.0%) (by eyes, 67/173; 38.7%)[2] had CRR from nadir to LV. Time to *initial* observation in patients with CRR varied between 2.5 to 26.5 with a mean of 9.5 months (Fig. 1). The magnitude of recovery of patient's best recovering eye, averaged 0.45 logMAR at *initial* observation of CRR and increased to 0.72 logMAR by the LV. This increase of the magnitude of response with longer treatment duration is confirmed when the magnitude of CRR was analyzed specifically in 22 eyes that had demonstrated CRR by 6 months and for which 12 month and beyond follow-up data were available (Fig. 2, right). Eyes that eventually achieve a CRR and important VA improvement can, nevertheless, show some degree of transient deterioration into a nadir, despite treatment start (Fig. 2, left and Supplemental Data B: Table. 4). Eyes can show CRR regardless of VA category achieved at nadir. For 173 eyes in 87 patients (one patient's eye had vision loss attributed to another ocular pathology), at nadir 86 (49.7%) were off-chart; 76 (43.9%) had BCVA 1.0 – 1.68 logMAR; and 11 (6.4%) had BCVA below 1.0 logMAR. For eyes that at nadir were off-chart, 24.4% had a CRR, compared with 53.9% from those between 1.0 – 1.68 logMAR and 45.5% of those better than 1.0 logMAR at nadir (Supplemental Data B: Table 4).

The overall outcome resulting from the shift of patients across BCVA categories is visualized in Fig. 3.

Safety

The cumulative exposure to idebenone in the SP was 1,981 patient-months. Although patient adherence data are not available, prescribed idebenone doses were recorded. The majority of

[2] The proportion of eyes with CRR is lower than the proportion of patients with CRR as not all patients experienced recovery in both eyes.

patients were treated with idebenone (150 mg tablets) at a daily dose of 900 mg (300 mg TID).

In the 111 patients treated with idebenone, 65 AEs (60.7% mild; 4.5% moderate; 4.5% severe) had been reported in 32 patients. The most common AEs were gastrointestinal (n = 17), with diarrhea the most frequent (n = 5). Nine serious AEs were reported in seven patients (all considered "not related" to treatment). Three case with fatal outcome, unrelated to idebenone use, was reported. Nine patients discontinued treatment due to AEs.

Discussion

The data from this EAP provide unique and novel insights into the efficacy and safety of idebenone treatment in LHON in a real world setting. Patients with LHON experience rapid vision loss, thus two therapeutic goals may be defined depending on the stage of progression. For patients who have suffered a relevant degree of vision loss, the aim is to improve BCVA as much as possible, at least to CRR. For patients with relevant residual vision, stabilization of BCVA is important, particularly if 'severe vision loss' has not yet been reached (CRS). Achieving either goal, CRR or CRS, may be considered a Clinically Relevant Benefit (CRB) for patients.

Clinically Relevant Stabilization

Vision loss in untreated patients is rapid,[5] with over 70% of eyes progressing to a BCVA worse than 1.0 logMAR (20/200 Snellen) within three months.[4, 18] Accordingly, only 27.6% patients had a BCVA better than 1.0 logMAR at baseline (mean 4.6 months after symptom onset) (Table 1). While it is to be expected that most patients would further progress if untreated, with treatment, half of those (12/24, 50.0%) maintained a BCVA below this

threshold after an average follow-up time of 24.3 months. Interestingly, the mean BCVA for these patients improved from 0.47 to 0.29 logMAR, corresponding to nine letters on the ETDRS chart. Compared to the natural disease-course, early idebenone treatment provides an opportunity to prevent severe vision loss over a timespan when further BCVA deterioration would be expected for most patients.[19]

In most cases, the journey to LHON diagnosis after symptom onset takes weeks or months, usually not allowing for treatment inititation until the second eye becomes affected. Notably, in the EAP, only three patients had one unaffected eye at treatment start, two of which maintained this status at LV. While the numbers are low, this contrasts with a previous case series, in which all six patients starting idebenone treatment with an unaffected eye subsequently experienced BCVA decrease in these eyes.[8] While this is a good indication of a favorable effect, the small numbers mean it remains to be seen whether idebenone can indeed prevent onset of symptoms, i.e. in patients starting treatment "in-between" onset in the eyes. This can be further explored once better referral and earlier diagnosis result in widespread early treatment of the disease.

Clinically Relevant Recovery

Vision loss in patients with LHON is mostly permanent.[19] However, in the EAP, almost one in two patients (40/87, 46.0%) treated with idebenone experienced CRR after a mean treatment duration of 9.48 months. This is comparable to the 45.5% (20/44) responder rate for idebenone-treated patients in a case series using similar criteria to define recovery,[8] and of 42.9% (6/14) reported for a smaller patient cohort treated with idebenone and vitamin B2.[9] Both of these retrospective studies reported lower rates of recovery, 32.2%[8] and 28.6%,[9] for the untreated, in-study control groups. While the EAP did not have a control group, a recently

conducted, large retrospective case record survey provided rates of CRR using identical criteria as in the EAP.[20, 21] Here, 31.1% of untreated patients (23/74) experienced CRR, a proportion again in line with the untreated groups of the two cohort studies.[8, 9]

Rate of Recovery as a Function of Treatment Duration

This EAP provides a large dataset in patients treated for an average of more than 2 years (in RHODOS was 6 months).

In the EAP, time from start of therapy to initial observation of CRR varies from 2.5 months to 26.5 months (Table 3). This provides evidence for a benefit of longer idebenone treatment in LHON, as only 45.0% of the total responders had experienced their first recovery by 6 months. The responder rate increased with treatment duration up to 12 months, but 33% patients experienced CRR later, with some only showing initial improvement after 24 months of treatment. (Fig. 1).

Magnitude of Recovery as a Function of Treatment Duration

Evaluating the impact of continued therapy *after an initial CRR has been observed* is very relevant. At the initial CRR, the average magnitude of best recovery by subject was 23 letters, which increased to 36 letters (7 lines ETDRS) by LV. This effect was also observed for individual eyes with CRR (n = 67) where after first worsening to a nadir, later improved at initial observation of CRR and further at LV (mean recovery of 35 letters from nadir) (Fig. 2, left). Finally, in a subset of eyes demonstrating early CRR (within 6 months), the magnitude

of CRR continued to increase with prolonged treatment, from 21 letters after 6 months to 50 letters by LV (average treatment duration of 35 months).

Rate of Recovery and Outcome as a Function of Vision Loss During Therapy

An interesting question to address is whether the results of therapy are dependent on the degree of BCVA loss, both in terms of responder rate and to a change in categorical BCVA outcomes, as defined by BCVA thresholds related to quality of life.[17]. At treatment start, 27.6% patients presented with a BCVA <1.0 logMAR and 19.5% were already off-chart, highlighting the rapid vision loss described elsewhere.[11, 19, 22] Visual outcomes showed some further worsening after treatment intitation, reaching a nadir. At the final available assessment, however, visual outcomes were markedly improved compared to nadir, with more than a tripling of patients with BCVA <1.0 logMAR from nadir (9.2%) to LV (32.2%) and a reduction in off-chart patients (44.8% to 32.2%) (Fig. 3). In line with a case series using idebenone[8], our results also show that the probability of therapeutic success is maximized by early treatment initiation, as indicated by a higher responder rate in less affected eyes (CRR of 24.4% vs 53.9% for eyes off-chart and on-chart at nadir, respectively (Supplemental Data B)

Also, for responders, the magnitude of improvement can be very marked, regardless of the severity at nadir.

Impact of LHON Mutation on the Reported Analyses

The most frequent mitochondrial gene variant causing LHON, G11778A, is considered to correlate with the most severe prognosis, whereas the T14484C mutation is typically associated with a milder phenotype and the G3460A mutation has an intermediate prognosis.

[2, 10, 22] The largest subgroup of patients in the EAP were G11778A . They experienced a slightly lower rate of CRS than the entire cohort, a lower rate of CRR, a smaller magnitude of recovery by the LV and longer treatment duration to recovery.As expected, although with small number of patients, T14484C patients had the highest rate of CRS and CRR, the largest magnitude of recovery and the shortest treatment duration before CRR while the corresponding rates for patients with the G3460A mutation mostly fell in between the other two mutations (Table 1, 2, 3).

With the obvious limitations resulting from varying observation duration and definitions of treatment response,[10, 15, 23-27] rates of spontaneous recovery of VA have been documented in several studies and can be as low as 4% for the G11778A mutation. [23-27] In the RHODOS placebo group, spontaneous recovery across all mutations occurred in 10.3% of patients over 6 months.[15] Overall, the CRR rate observed in our data exceeds the reported rates of spontaneous recovery.

Idebenone was well tolerated, with a good safety profile, in line with results from the RHODOS trial.[15] No new safety signals have been observed.

Although our analysis has the inherent limitations from the retrospective nature of the data and a lack of control group, it provides however an important view of long term response and tolerability of idebenone in patients within the first year of disease onset in the second eye in a real world setting.

Conclusions

Our results suggest that the overall outcome of idebenone treatment indicates a better long-term prognosis than expected from limited natural history data. Although treatment

response is observed despite severity of visual impariment, early treatment intitation improves the chances of response.

A treatment duration of at least 18-24 months is needed to maximize the probability of CRR as a certain degree of transient deterioration to a nadir may occur despite therapy initiation and that continued treatment after initial CRR provides further benefit. The risk balance of idebenone 900 mg/day is in line with the previously published clinical trial.

References

1. Gueven N. Optic Neurodegeneration: Time to Act. *Biol Med.* 2014;01

2. Fraser JA, Biousse V, Newman NJ. The neuro-ophthalmology of mitochondrial disease. *Surv Ophthalmol.* 2010;55:299-334

3. Mackey DA, Oostra RJ, Rosenberg T, Nikoskelainen E, Bronte-Stewart J, Poulton J, Harding AE, Govan G, Bolhuis PA, Norby S.. Primary pathogenic mtDNA mutations in multigeneration pedigrees with Leber hereditary optic neuropathy. *Am J Hum Genet.* 1996;59:481-485

4. Carelli V, Carbonelli M, de Coo IF, Kawasaki A, Klopstock T, Lagrèze WA, La Morgia C, Newman NJ, Orssaud C, Pott JWR, Sadun AA, van Everdingen J, Vignal-Clermont C, Votruba M, Yu-Wai-Man P, Barboni P.. International Consensus Statement on the Clinical and Therapeutic Management of Leber Hereditary Optic Neuropathy. *J Neuroophthalmol.* 2017;37:371-381

5. Yu-Wai-Man P, Griffiths PG, Chinnery PF. Mitochondrial optic neuropathies - disease mechanisms and therapeutic strategies. *Prog Retin Eye Res.* 2011;30:81-114

6. Barboni P, Savini G, Valentino ML, La Morgia C, Bellusci C, De Negri AM, Sadun F, Carta A, Carbonelli M, Sadun AA, Carelli V. Leber's hereditary optic neuropathy with childhood onset. *Invest Ophthalmol Vis Sci.* 2006;47:5303-5309

7. Newman NJ. Treatment of hereditary optic neuropathies. *Nat Rev Neurol.* 2012;8:545-556

8. Carelli V, La Morgia C, Valentino ML, Rizzo G, Carbonelli M, De Negri AM, Sadun F, Carta A, Guerriero S, Simonelli F, Sadun AA, Aggarwal D, Liguori R, Avoni P,

Baruzzi A, Zeviani M, Montagna P, Barboni P.. Idebenone treatment in Leber's hereditary optic neuropathy. *Brain.* 2011;134:e188

9. Mashima Y, Kigasawa K, Wakakura M, Oguchi Y.. Do idebenone and vitamin therapy shorten the time to achieve visual recovery in Leber hereditary optic neuropathy? *J Neuroophthalmol.* 2000;20:166-170

10. Spruijt L, Kolbach DN, de Coo RF, Plomp AS, Bauer NJ, Smeets HJ, de Die-Smulders CE.. Influence of mutation type on clinical expression of Leber hereditary optic neuropathy. *Am J Ophthalmol.* 2006;141:676-682

11. Yu-Wai-Man P, Votruba M, Moore AT, Chinnery PF. Treatment strategies for inherited optic neuropathies: past, present and future. *Eye (Lond).* 2014;28:521-537

12. Giorgio V, Petronilli V, Ghelli A, Carelli V, Rugolo M, Lenaz G, Bernardi P.. The effects of idebenone on mitochondrial bioenergetics. *Biochim Biophys Acta.* 2012;1817:363-369

13. Haefeli RH, Erb M, Gemperli AC, Robay D, Courdier Fruh I, Anklin C, Dallmann R, Gueven N.. NQO1-dependent redox cycling of idebenone: effects on cellular redox potential and energy levels. *PLoS One.* 2011;6:e17963

14. Heitz FD, Erb M, Anklin C, Robay D, Pernet V, Gueven N.. Idebenone protects against retinal damage and loss of vision in a mouse model of Leber's hereditary optic neuropathy. *PLoS One.* 2012;7:e45182

15. Klopstock T, Yu-Wai-Man P, Dimitriadis K, Rouleau J, Heck S, Bailie M, Atawan A, Chattopadhyay S, Schubert M, Garip A, Kernt M, Petraki D, Rummey C, Leinonen M,

Metz G, Griffiths PG, Meier T, Chinnery PF. A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy. *Brain.* 2011;134:2677-2686

16. Kniestedt C, Stamper RL. Visual acuity and its measurement. *Ophthalmol Clin North Am.* 2003;16:155-170, v

17. Colenbrander A. 2002. Visual Standards: Aspects and ranges of vision loss with emphasis on population surveys. In *Presented 29th International Congress of Ophthalmology*

18. Metz G, Coppard N, Petraki D, Meier T, Klopstock T, Sahel J. . A Case Report Survey (CRS) on the Natural History of Visual Acuity in Leber's Hereditary Optic Neuropathy (LHON). *Acta Ophthalm*, 2014, Volume92, Issues253 Poster presented at: 2014 European Association for Vision and Eye Research Conference, Nice (France) September 2014.

19. Newman NJ, Biousse V, Newman SA, Bhatti MT, Hamilton SR, Farris BK, Lesser RL, Turbin RE.. Progression of visual field defects in leber hereditary optic neuropathy: experience of the LHON treatment trial. *Am J Ophthalmol.* 2006;141:1061-1067

20. Silva M, Llòria X, Catarino C, Klopstock T. Natural History Findings from a Large Cohort of Patients with Lebers Hereditary Optic Neuropathy (LHON): New Insights into the Natural Disease-Course. *Acta Ophthalmologica.* 2018;96, S261

21. Raxone®. 2015. Summary of Product Characteristics (SmPC). European Medicines Agency

22. Yu-Wai-Man P, Griffiths PG, Hudson G, Chinnery PF.. Inherited mitochondrial optic neuropathies. *J Med Genet.* 2009;46:145-158

23. Johns DR, Heher KL, Miller NR, Smith KH.. Leber's hereditary optic neuropathy. Clinical manifestations of the 14484 mutation. *Arch Ophthalmol.* 1993;111:495-498

24. Johns DR, Smith KH, Miller NR. Leber's hereditary optic neuropathy. Clinical manifestations of the 3460 mutation. *Arch Ophthalmol.* 1992;110:1577-1581

25. Riordan-Eva P, Sanders MD, Govan GG, Sweeney MG, Da Costa J, Harding AE.. The clinical features of Leber's hereditary optic neuropathy defined by the presence of a pathogenic mitochondrial DNA mutation. *Brain.* 1995;118 (Pt 2):319-337

26. Stone EM, Newman NJ, Miller NR, Johns DR, Lott MT, Wallace DC.. Visual recovery in patients with Leber's hereditary optic neuropathy and the 11778 mutation. *J Clin Neuroophthalmol.* 1992;12:10-14

27. Macmillan C, Kirkham T, Fu K, Allison V, Andermann E, Chitayat D, Fortier D, Gans M, Hare H, Quercia N, Zackon D, Shoubridge EA.. Pedigree analysis of French Canadian families with T14484C Leber's hereditary optic neuropathy. *Neurology.* 1998;50:417-422

Figure 1. Time to Initial Observation of Clinically Relevant Recovery (CRR)

Cumulative percentage of total number of patients with CRR, as a function of time on treatment to initial CRR, (n = 40). All mutations,

Figure 2. Magnitude of Mean BCVA Recovery Over Time in Eyes with CRR

Magnitude of best corrected visual acuity (BCVA) recovery in eyes with clinically relevant recovery (CRR). ***Left:*** Average BCVA observed at baseline (BL), nadir, initial observation of CRR and at the last observation visit (LV) for all eyes that experienced CRR (n=67). ***Right:*** Improvement of BCVA over time, at given treatment durations, in those eyes that experienced CRR within 6 months of treatment initiation and where follow-up data were available (n=22). All mutations. All off-chart VA values were imputed to 1.8 logMAR. Error bars indicate the 95% CI.

Figure 3. Shift of Patients, over treatment time, across Categories of BCVA (Efficacy Population, n= 87)

Bar chart for distribution of patients based on blindness categories for best corrected visual acuity (BCVA) at baseline (BL), at nadir, and at last observation visit (LV). All mutations.

Table 1 – Patient Demographics and baseline (BL) values [a]. Efficacy Population (EP) by mutation [b]

	All	G11778A	G3460A	T14484C
Patients in the EP	87/87 (100%)	54/87 (62.1%)	17/87 (19.5%)	16/87 (18.4%)
Treatment duration [months] [c]	25.6 ± 16.9 (2.4 – 70.4)	24.9 ± 17.4 (3.2 – 70.4)	27.7 ± 16.7 (4.4 – 61.0)	25.5 ± 16.0 (2.4 – 53.8)
Gender male	71/87 (82%)	45/54 (83%)	13/17 (77%)	13/16 (81%)
Age at onset [years]	31.4 ± 17.3 (6.6 – 78.9)	33.3 ± 17.5 (12.1 – 78.9)	28.4 ± 16.8 (6.6 – 64.5)	28.1 ± 16.9(8.5 – 56.2)
Adolescent at onset (age 12-17 years)	22/87 (25.3%)	11/54 (20.4%)	6/17 (35.3%)	5/16 (31.3%)
Childhood onset (< 12 years of age)	3/87 (3.4%)	0/54 (0%)	1/17 (5.9%)	2/16 (12.5%)
Time since onset at baseline [e] [months]	4.6 ± 3.0 (0.3 – 11.5)	4.3 ± 2.7 (0.4 – 11.4)	5.9 ± 3.7 (0.3 – 11.5)	4.4 ± 2.8 (0.9 – 9.3)
Interval of onset between eyes [f] [g] [months]	1.7 ± 2.5 (0.0 – 12.6)	1.8 ± 2.5 (0.0 – 10.0)	1.9 ± 3.1 (0.0 – 12.6)	0.9 ± 1.3 (0.0 – 4.7)
BCVA at baseline [logMAR]	1.23 ± 0.52 (-0.18 – 1.8)	1.22 ± 0.59 (-0.18 – 1.8)	1.37 ± 0.38 (0.40 – 1.80)	1.12 ± 0.39 (0.28 – 1.80)
Baseline BCVA off-chart [h]	17/87 (20%)	13/54 (24%)	3/17 (18%)	1/16 (6%)
Baseline BCVA from 1.0 to 1.68 logMAR	46/87 (53%)	25/54 (46%)	11/17 (65%)	10/16 (63%)
Baseline BCVA <1.0 logMAR	24/87 (28%)	16/54 (30%)	3/17 (18%)	5/16 (31%)

Values are given as n (%) or mean ± standard deviation and minimum – maximum (in parentheses); percentages may not total 100% due to rounding; BCVA = best corrected visual acuity; CRR = clinically relevant recovery; CRS = clinically relevant stabilization; logMAR = logarithm of the minimal angle of resolution

[a] data cut-off: June 2018; [b] For information on EP flow see Supplemental Data A; [c] Treatment duration was not pre-determined and was decided by the treating physician according to his/her criteria as per routine clinical practice; [d] BCVA off-chart values are imputed to 1.8 logMAR see Supplemental Data A; [e] Time since onset: time from symptoms onset to start of treatment (baseline) in the most recently affected eye; [f] Three patients were reported by the treating physician to have one asymptomatic eye at baseline; [g] Time between onset of 1st and 2nd affected eye; [h] Off-chart values: not reading any letter on the ETDRS chart at 1m (i.e. >1.68 logMAR) (Supplemental Data A);

Table 2 – Clinically Relevant Stabilization (CRS) for subset of patients with BCVA at baseline <1.0 logMAR. Efficacy Population (EP) [a] [b] by mutation

	All	G11778A	G3460A	T14484C
BCVA stabilization: Patients with CRS [c]	12/24 (50%)	7/16 (44%)	1/3 (33%)	4/5 (80%)
BCVA at baseline [d] [logMAR]	0.47 ± 0.36 (-0.18 – 0.96)	0.31 ± 0.34 (0.18 – 0.88)	0.94	0.62 ± 0.28 (0.28 – 0.96)
BCVA at last observation [d] [logMAR]	0.29 ± 0.29 (-0.16 – 0.8)	0.35 ± 0.34 (-0.16 – 0.8)	0.34	0.17 ± 0.29 (-0.14 – 0.42)
Treatment duration [d] [months]	30.1 ± 19 (9.9 – 67.8)	25.5 ± 20.6 (10.7 – 67.8)	40.0	35.8 ± 18.6 (9.9 – 53.8)

Values are given as n (%) or mean ± standard deviation and minimum – maximum (in parentheses); Percentages may not total 100% due to rounding; BCVA = best corrected visual acuity; CRS = clinically relevant stabilization; logMAR = logarithm of the minimal angle of resolution

[a] Data cut-off: June 2018; [b] For information on EP flow see Supplemental Data A; [c] CRS: BCVA had to be maintained in an eye with BCVA <1.0 logMAR at start of the treatment; [d] Calculations only consider patients with CRS (12 patients);

Table 3 – Clinically Relevant Recovery (CRR) by patient. Efficacy Population (EP) [a] [b] by mutation

	All	G11778A	G3460A	T14484C
BCVA Recovery: Patients with CRR [c]	40/87 (46.0%)	21/54 (39%)	7/17 (41%)	12/16 (75%)
Time to initial CRR [months]	9.5 ± 7.0 (2.5 – 26.5)	11.2 ± 7.8 (2.5 – 26.5)	7.3 ± 3.4 (2.5 – 12.9)	7.8 ± 6.8 (3.0 – 25.6)
Magnitude of recovery at initial CRR				
logMAR	0.45 ± 0.31 0.20 - 1.62	0.39 ± 0.32 0.20 - 1.62	0.39 ± 0.20 0.22 - 0.76	0.60 ± 0.30 0.22 - 1.20
Number of letters ETDRS	22 ± 15 (10 – 81)	19 ± 16 (10 – 81)	19 ± 10 (11 – 38)	30 ± 15 (11 – 60)
Magnitude of recovery at last observation				
logMAR	0.72 ± 0.46 0.20 - 1.80	0.52 ± 0.39 0.20 - 1.76	0.61 ± 0.31 0.24 - 1.10	1.12 ± 0.40 0.46 - 1.80
number of letters ETDRS	36 ± 23 (10 – 90)	26 ± 19 (10 – 88)	30 ± 15 (12 – 55)	56 ± 20 (23 – 90)

Values are given as n (%) or mean ± standard deviation and minimum – maximum (in parentheses); percentages may not total 100% due to rounding; BCVA = best corrected visual acuity; CRR = clinically relevant recovery; ETDRS = Early Treatment Diabetic Retinopathy Study; logMAR = logarithm of the minimal angle of resolution

[a] Data cut-off June 2018; [b] For information on EP flow see Supplemental Data A; [c] CRR is improvement from off-chart BCVA to on-chart by the equivalent of at least one full line on an ETDRS chart (five letters) or an improvement in on-chart BCVA by the equivalent of at least two lines (10 letters).

Table 4 –Clinically Relevant Recovery (CRR) by Individual Eyes as a Function of BCVA at Nadir. Efficacy Population (EP) [a] [b]

VA category at nadir	Eyes	Eyes with CRR [c] within category	Eyes with CRR and BCVA [logMAR] at last observation		
			BCVA >1.0	>0.5 BCVA <1.0	BCVA ≤0.5
Off-chart	86/173 (49.7%)	21/86 (24%)	14	2	5
From 1.0 to 1.68 logMAR	76/173 (44%)	41/76 (54%)	12	13	16
Below 1.0 logMAR	11/173 (6%)	5/11 (46%)	na	0	5
All [d]	173/173 (100%)	67/173 (39%)	26	15	26

Values are given as n (%); Percentages may not total 100% due to rounding; BCVA = best corrected visual acuity; CRR = clinically relevant recovery; logMAR = logarithm of the minimal angle of resolution; na = not applicable

[a] Data cut-off June 2018; [b] For information on EP flow see Supplemental Data A; [c] CRR is improvement from off-chart BCVA to on-chart by the equivalent of at least one full line on an ETDRS chart (five letters) or an improvement in on-chart BCVA by the equivalent of at least two lines (10 letters) at LV; [d] One patient had vision loss in one eye not related to LHON.

Fig. 1

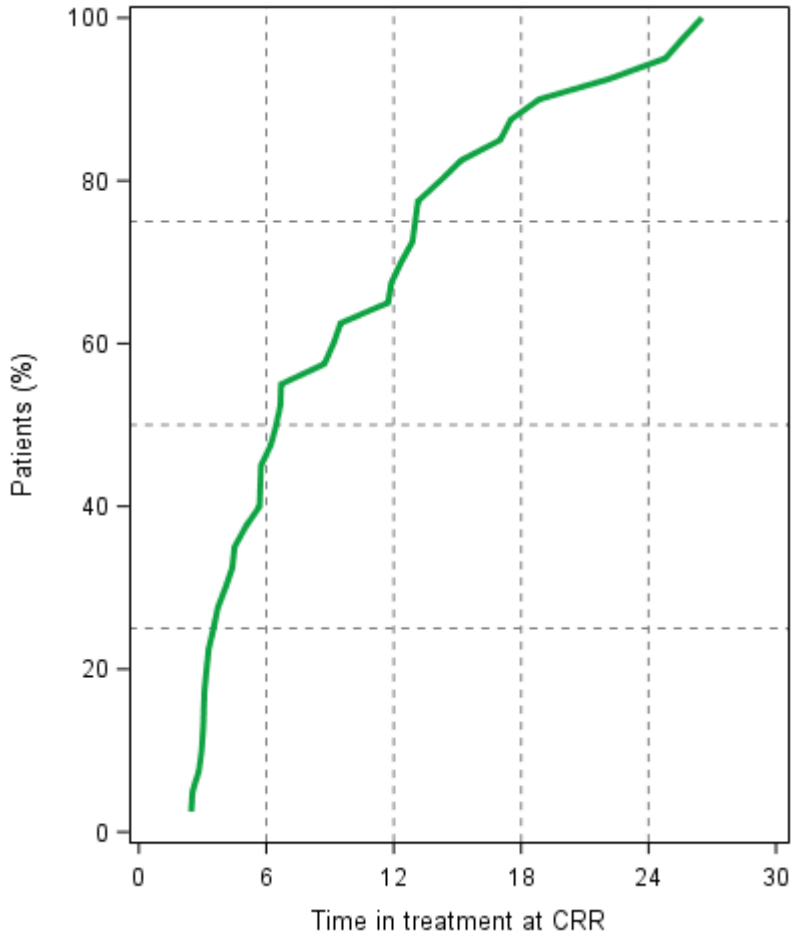

100
80
60
40
20
0
Patients (%)
0
6
12
18
24
30
Time in treatment at CRR

Fig.2

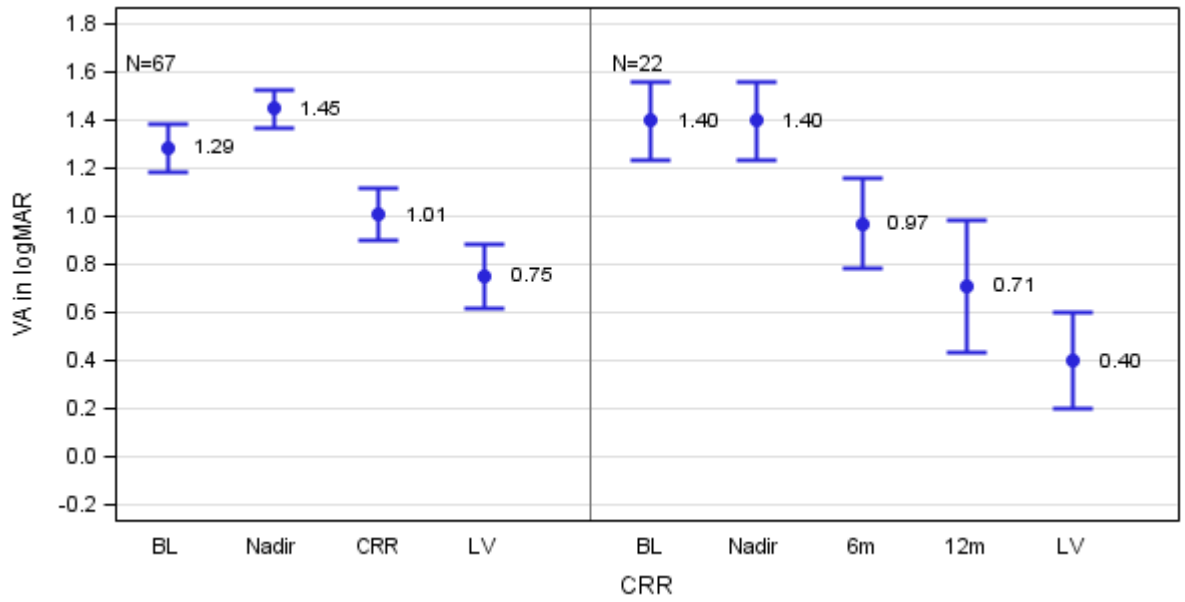
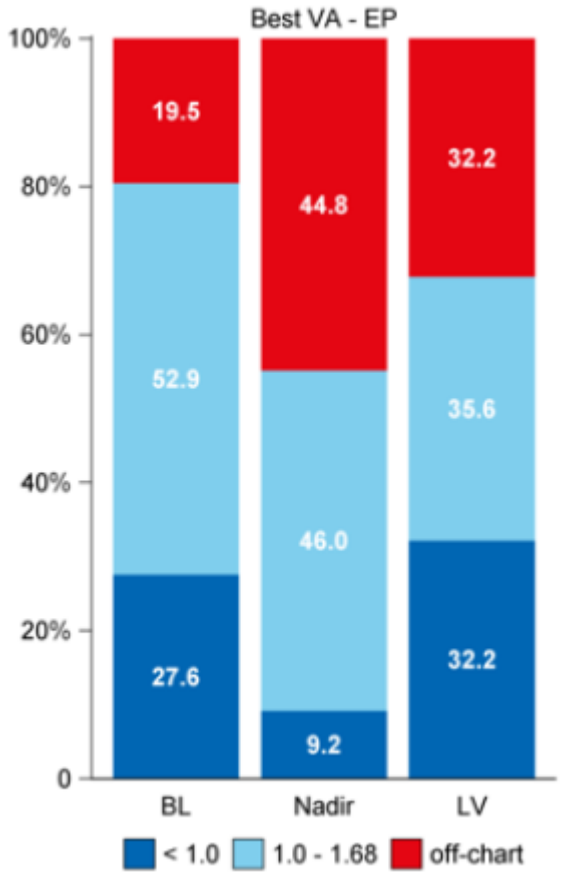

1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
VA in logMAR
N=67
1.29
1.45
1.01
0.75
N=22
1.40
1.40
0.97
0.71
0.40
BL
Nadir
CRR
LV
BL
Nadir
6m
12m
LV
CRR

Fig. 3


Best VA - EP
100%
80%
60%
40%
20%
0
19.5
52.9
27.6
44.8
46.0
9.2
32.2
35.6
32.2
BL
Nadir
LV
< 1.0
1.0 - 1.68
off-chart

Supplemental Data: A

CLINICAL SITES

A total of 111 patients had been enrolled by treating physicians at 38 different sites in 10 countries. Most enrolling sites were in Europe (N=27), followed by the US (N=6) and Australia/New Zealand (N=5).

DATA

Data collection

Data was collected from available medical records, by means of Case Record Forms (CRF):

- Demographic data (age, gender)
- Date of onset of symptoms on each eye
- Genetic confirmation (mutation)
- Best Corrected Visual Acuity (BCVA) (see below)
    - At start of treatment (Baseline)
    - At follow-up visits
- Date of each visit
- Dose
- Adverse events

Statistical Methods

There was no planned sample size as all requests for access to Raxone® for eligible patients which were bona fide and unsolicited had been granted. All treating physicians were approached and invited to contribute data from their treated patients.

Efficacy criteria was based in the Responder Analyses (CRR, CRS and CRB) (see below) with Best Corrected Visual Acuity (BCVA) as efficacy variable. BCVA was assessed using ETDRS (Early Treatment Diabetic Retinopathy Study) charts with logMAR (logarithm of the minimal angle of resolution) values as units. In cases where VA was assessed using Snellen fraction/units, logMAR values where calculated using standard conversion methods. [3] [4]

If VA was > 1.68 logMAR or off-chart (regardless of being assessed as counting fingers, hand motion, light perception or no-light perception) it was imputed to 1.8 logMAR in order to standardize visual acuity data from different physicians. The value 1.8 logMAR was based on the CRR definition: it is considered a CRR any off-chart VA that recovers to at least 1.6 logMAR (being 1.6 logMAR the equivalent to reading one full line in the ETDRS chart).

Continuous data was summarised using the mean, standard deviation, median, 1st and 3rd quartiles, minimum and maximum. Categorical data was presented in contingency tables with frequencies and percentages.

CRR was summarised by means of descriptive statistics and Kaplan-Meier estimates, presented with the 95% confidence interval (using the Greenwood formula) and reverse Kaplan-Meier

[3] Kniestedt C & Stamper RL Visual acuity and its measurement. Ophthalmol Clin North Am. 2003;16:155-70, v.
[4] Kaiser P. Prospective evaluation of visual acuity assessment: a comparison of Snellen versus ETDRS charts in clinical practice (an AOS thesis) Trans Am Ophthalmol Soc 2009;107:311-324

curves. Unless stated otherwise data was analysed using the observed cases or missing data were imputed with the last available observation carried forward (LOCF).

PATIENT DISPOSITION/ANALYSIS POPULATIONS

Data from a total of 111 patients was collected. The following populations were defined for the analysis of safety and efficacy data:

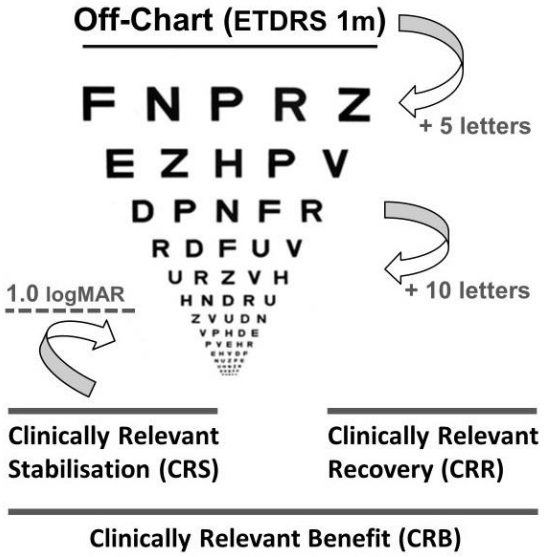
- Safety Population (SP): used for analysis of safety information. It includes all patients enrolled in the EAP who received at least one dose of Raxone® (111 patients).
- Efficacy Population (EP): is defined as the sub-population of the SP who carried one of the 3 major LHON-causative mtDNA mutations, who had time since onset at Baseline of less than 12 months in the most recently affected eye and for whom post-Baseline VA efficacy data was available (87 patients).

DEFINITIONS

- **Nadir**: Nadir is defined as the value when VA reaches its worst point (highest logMAR value). Time of nadir is the first time that nadir is reached, which can take place at baseline, or during the course of the treatment.

- **CRR (Clinically Relevant Recovery)**: It is defined as an improvement:

- from "off-chart" (the equivalent of CF, HM, LP or NLP) VA to at least 1.6 logMAR value or
- of at least 0.2 logMAR value within "on-chart"



As response criteria, **all eyes/patients** qualified as responders (that is, that have CRR) are only considered so when the criteria is evident at the **last available observation (last visit)**. If a patient/eye shows a CRR at a visit during follow-up, but not at the last visit, **it is not considered as a responder**, and no CRR is accounted for.

CRR can be observed when last observation is compared to the *baseline* value (*CRR from Baseline*) or when last observation is compared to the *nadir* (*CRR from Nadir*).

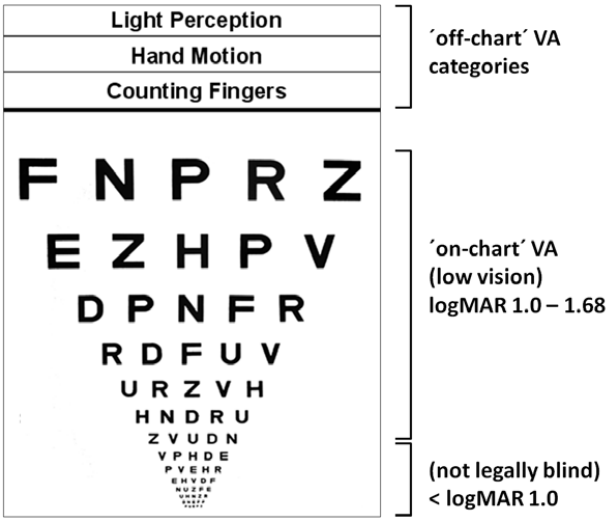
When evaluating CRR in **patients** it is considered that:

- a patient has a CRR if at least one eye has a CRR;
- time of CRR is the time when the 1st CRR occurred;
- improvement of VA at CRR is the improvement observed at the time of 1st CRR;
- improvement of VA at last visit is the best improvement observed in both eyes.

- **CRS (Clinically Relevant Stabilisation of residual VA)**: is defined as a patient having a logMAR of <1.0 at Baseline (below the threshold of severe vision loss, legal blindness in the United States) in at least one eye and maintaining a logMAR of <1.0 in that eye at their last follow-up assessment. A patient has a CRS if at least one eye has a CRS.

- **Magnitude of Improvement**: "Magnitude of improvement from baseline" is defined as the difference between VA logMAR at the visit and VA logMAR at baseline. "Magnitude of improvement from nadir" is defined as the difference between VA logMAR at the visit and VA logMAR at nadir.
  - A decrease in logMAR of 0.02 (-0.02) is equivalent to an improvement in reading ability of one letter (+1 letter) and an increase in logMAR of 0.02 (+0.02) is equivalent to the deterioration in reading ability of one letter (-1 letter).

- **Visual Impairment Categories**: Both at eye and subject level, BCVA values (in logMAR) were classified in three categories (This classification allows to observe changes related to quality of life relevant to the patient's function.)
  - **Off-chart:** not reading any letter on the ETDRS chart at 1m (i.e. >1.68 logMAR)
  - **From 1.0 to 1.68 logMAR:** not reading any letter on the ETDRS chart at 4m (i.e. >1.00 logMAR) but being able to read at least one letter on the ETDRS chart at 1m (i.e. 1.68 logMAR)
  - **<1.0 logMAR:** Being able to read at one or more letters on the ETDRS chart at 4m.



Supplemental Data: B

ANALYSES OF CLINICALLY RELEVANT RECOVERY (CRR) IN INDIVIDUAL EYES AS A FUNCTION OF BCVA AT NADIR

The final BCVA outcome at last observation (LV) was analyzed for eyes with CRR, compared to blindness category at nadir (Table 4). Of 21 eyes that were off chart at nadir and subsequently experienced CRR, 14/21 (66.7%) reached a full line on-chart, 7/21 (33.3%) experienced improvement of more than six lines, reaching a BCVA <1.0, five of which achieved a BCVA ≤0.5 logMAR. For those eyes with a BCVA between 1.0 – 1.68 logMAR at nadir (n = 41), the majority (29; 70.7%) improved to <1.0 logMAR, with 16 improving to ≤0.5 logMAR. Lastly, all eyes with BCVA at nadir <1.0 logMAR (n = 5) had a BCVA ≤0.5 logMAR at last observation. Overall, 67 eyes (38.7%) experienced CRR. Out of these 41/67 (61.2%) had a BCVA <1.0 logMAR at last observation, with 26/67 (38.8%) reaching ≤0.5 logMAR.

TABLE 4

Table 1 – Patient Demographics and baseline (BL) values [a]. Efficacy Population (EP) by mutation [b]

	All	G11778A	G3460A	T14484C
Patients in the EP	87/87 (100%)	54/87 (62.1%)	17/87 (19.5%)	16/87 (18.4%)
Treatment duration [months] [c]	25.6 ± 16.9 (2.4 – 70.4)	24.9 ± 17.4 (3.2 – 70.4)	27.7 ± 16.7 (4.4 – 61.0)	25.5 ± 16.0 (2.4 – 53.8)
Gender male	71/87 (82%)	45/54 (83%)	13/17 (77%)	13/16 (81%)
Age at onset [years]	31.4 ± 17.3 (6.6 – 78.9)	33.3 ± 17.5 (12.1 – 78.9)	28.4 ± 16.8 (6.6 – 64.5)	28.1 ± 16.9(8.5 – 56.2)
Adolescent at onset (age 12-17 years)	22/87 (25.3%)	11/54 (20.4%)	6/17 (35.3%)	5/16 (31.3%)
Childhood onset (< 12 years of age)	3/87 (3.4%)	0/54 (0%)	1/17 (5.9%)	2/16 (12.5%)
Time since onset at baseline [e] [months]	4.6 ± 3.0 (0.3 – 11.5)	4.3 ± 2.7 (0.4 – 11.4)	5.9 ± 3.7 (0.3 – 11.5)	4.4 ± 2.8 (0.9 – 9.3)
Interval of onset between eyes [f] [g] [months]	1.7 ± 2.5 (0.0 – 12.6)	1.8 ± 2.5 (0.0 – 10.0)	1.9 ± 3.1 (0.0 – 12.6)	0.9 ± 1.3 (0.0 – 4.7)
BCVA at baseline [logMAR]	1.23 ± 0.52 (-0.18 – 1.8)	1.22 ± 0.59 (-0.18 – 1.8)	1.37 ± 0.38 (0.40 – 1.80)	1.12 ± 0.39 (0.28 – 1.80)
Baseline BCVA off-chart [h]	17/87 (20%)	13/54 (24%)	3/17 (18%)	1/16 (6%)
Baseline BCVA from 1.0 to 1.68 logMAR	46/87 (53%)	25/54 (46%)	11/17 (65%)	10/16 (63%)
Baseline BCVA <1.0 logMAR	24/87 (28%)	16/54 (30%)	3/17 (18%)	5/16 (31%)

Values are given as n (%) or mean ± standard deviation and minimum – maximum (in parentheses); percentages may not total 100% due to rounding; BCVA = best corrected visual acuity; CRR = clinically relevant recovery; CRS = clinically relevant stabilization; logMAR = logarithm of the minimal angle of resolution

[a] data cut-off: June 2018; [b] For information on EP flow see Supplemental Data A; [c] Treatment duration was not pre-determined and was decided by the treating physician according to his/her criteria as per routine clinical practice; [d] BCVA off-chart values are imputed to 1.8 logMAR see Supplemental Data A; [e] Time since onset: time from symptoms onset to start of treatment (baseline) in the most recently affected eye; [f] Three patients were reported by the treating physician to have one asymptomatic eye at baseline; [g] Time between onset of 1st and 2nd affected eye; [h] Off-chart values: not reading any letter on the ETDRS chart at 1m (i.e. >1.68 logMAR) (Supplemental Data A);

Figure_1

Click here to access/download;Figure;Figure 1 for Catarino et al_Real world experience_20190530.tif

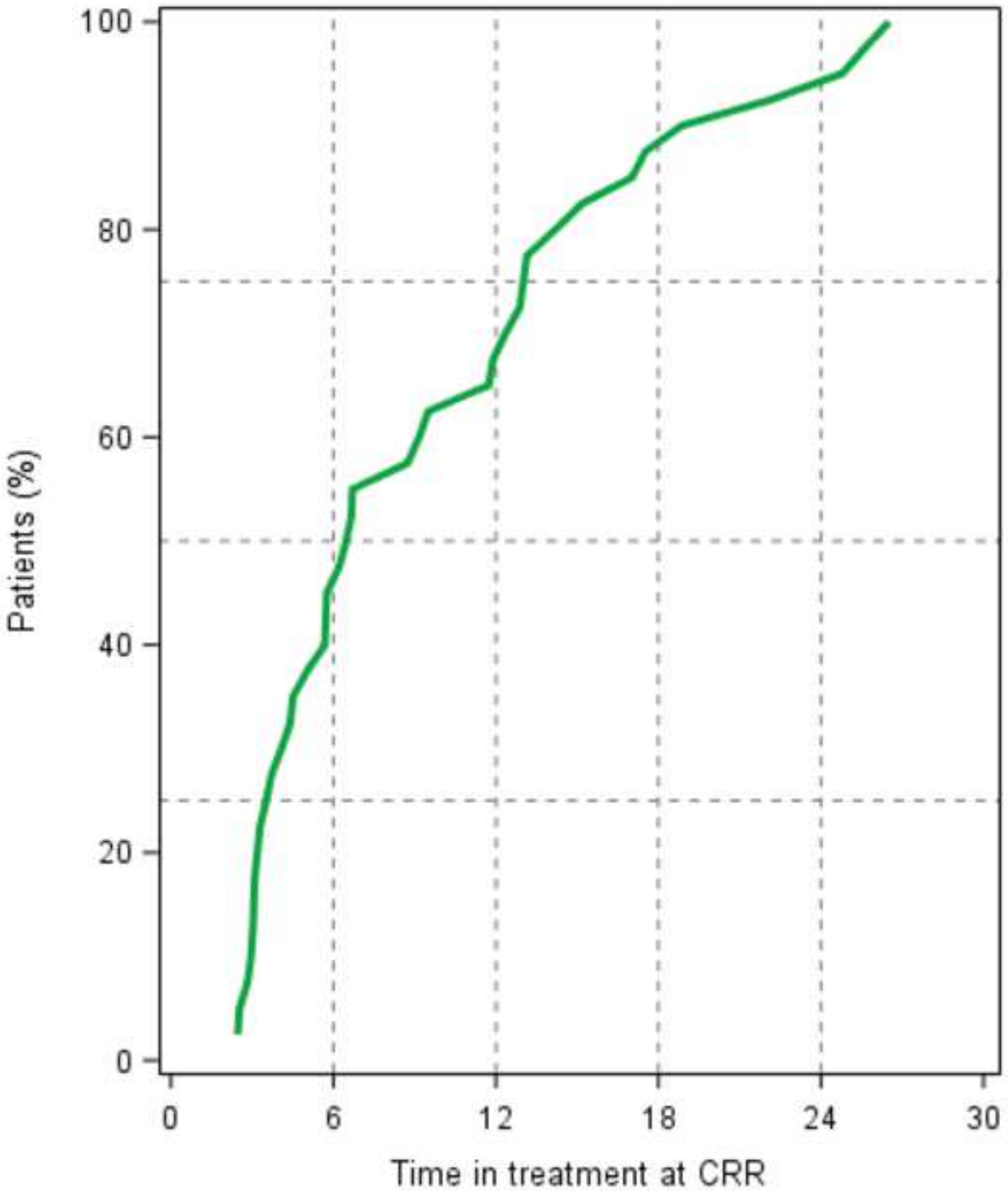


Table 2 – Clinically Relevant Stabilization (CRS) for subset of patients with BCVA at baseline <1.0 logMAR. Efficacy Population (EP)[a] [b] by mutation

	All	G11778A	G3460A	T14484C
BCVA stabilization: Patients with CRS [c]	12/24 (50%)	7/16 (44%)	1/3 (33%)	4/5 (80%)
BCVA at baseline [d] [logMAR]	0.47 ± 0.36 (-0.18 – 0.96)	0.31 ± 0.34 (0.18 – 0.88)	0.94	0.62 ± 0.28 (0.28 – 0.96)
BCVA at last observation [d] [logMAR]	0.29 ± 0.29 (-0.16 – 0.8)	0.35 ± 0.34 (-0.16 – 0.8)	0.34	0.17 ± 0.29 (-0.14 – 0.42)
Treatment duration [d] [months]	30.1 ± 19 (9.9 – 67.8)	25.5 ± 20.6 (10.7 – 67.8)	40.0	35.8 ± 18.6 (9.9 – 53.8)

Values are given as n (%) or mean ± standard deviation and minimum – maximum (in parentheses); Percentages may not total 100% due to rounding; BCVA = best corrected visual acuity; CRS = clinically relevant stabilization; logMAR = logarithm of the minimal angle of resolution

[a] Data cut-off: June 2018; [b] For information on EP flow see Supplemental Data A; [c] CRS: BCVA had to be maintained in an eye with BCVA <1.0 logMAR at start of the treatment; [d] Calculations only consider patients with CRS (12 patients);

Figure_2

Click here to access/download;Figure;Figure 2 for Catarino et al_Real world experience_20190530.tif

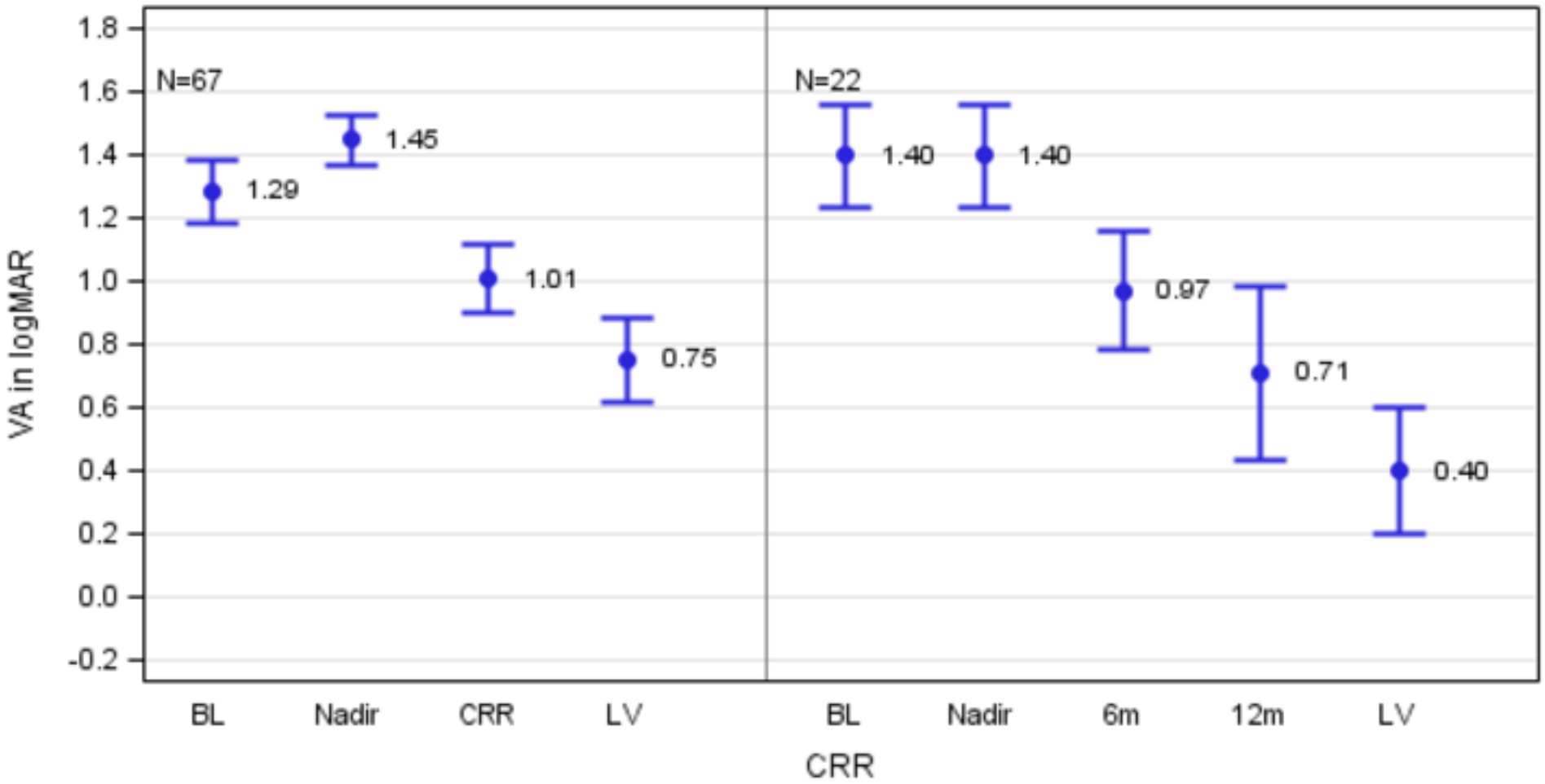


Table 3 – Clinically Relevant Recovery (CRR) by patient. Efficacy Population (EP)[a] [b] by mutation

	All	G11778A	G3460A	T14484C
BCVA Recovery: Patients with CRR [c]	40/87 (46.0%)	21/54 (39%)	7/17 (41%)	12/16 (75%)
Time to initial CRR [months]	9.5 ± 7.0 (2.5 – 26.5)	11.2 ± 7.8 (2.5 – 26.5)	7.3 ± 3.4 (2.5 – 12.9)	7.8 ± 6.8 (3.0 – 25.6)
Magnitude of recovery at initial CRR				
logMAR	0.45 ± 0.31 0.20 - 1.62	0.39 ± 0.32 0.20 - 1.62	0.39 ± 0.20 0.22 - 0.76	0.60 ± 0.30 0.22 - 1.20
Number of letters ETDRS	22 ± 15 (10 – 81)	19 ± 16 (10 – 81)	19 ± 10 (11 – 38)	30 ± 15 (11 – 60)
Magnitude of recovery at last observation				
logMAR	0.72 ± 0.46 0.20 - 1.80	0.52 ± 0.39 0.20 - 1.76	0.61 ± 0.31 0.24 - 1.10	1.12 ± 0.40 0.46 - 1.80
number of letters ETDRS	36 ± 23 (10 – 90)	26 ± 19 (10 – 88)	30 ± 15 (12 – 55)	56 ± 20 (23 – 90)

Values are given as n (%) or mean ± standard deviation and minimum – maximum (in parentheses); percentages may not total 100% due to rounding; BCVA = best corrected visual acuity; CRR = clinically relevant recovery; ETDRS = Early Treatment Diabetic Retinopathy Study; logMAR = logarithm of the minimal angle of resolution

[a] Data cut-off June 2018; [b] For information on EP flow see Supplemental Data A; [c] CRR is improvement from off-chart BCVA to on-chart by the equivalent of at least one full line on an ETDRS chart (five letters) or an improvement in on-chart BCVA by the equivalent of at least two lines (10 letters).

Figure_3

Click here to access/download;Figure;Figure 3 for Catarino et al_Real world experience_20190530.tif

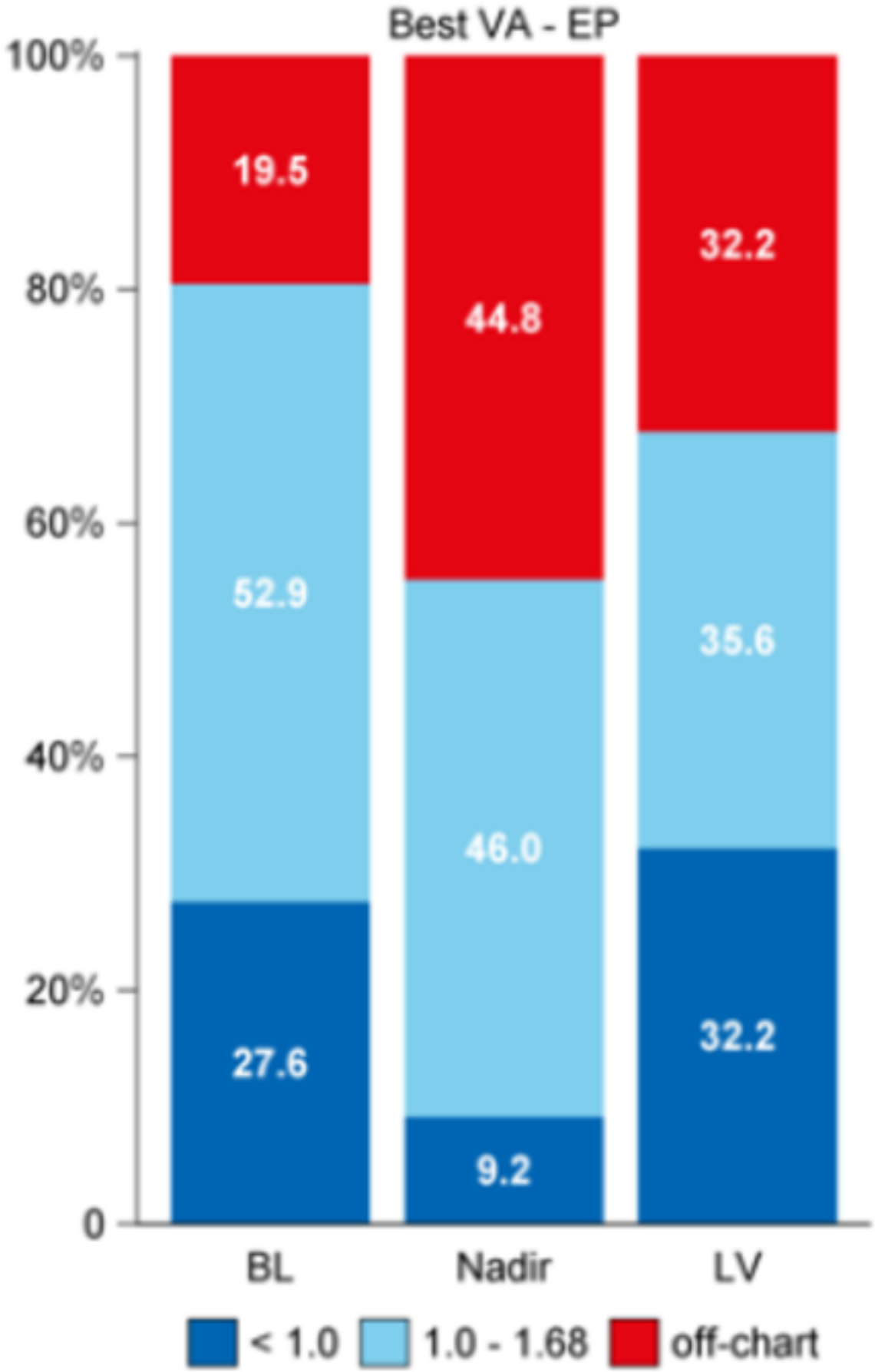


Table 4 –Clinically Relevant Recovery (CRR) by Individual Eyes as a Function of BCVA at Nadir. Efficacy Population (EP) [a] [b]

VA category at nadir	Eyes	Eyes with CRR [c] within category	Eyes with CRR and BCVA [logMAR] at last observation		
			BCVA >1.0	>0.5 BCVA <1.0	BCVA ≤0.5
Off-chart	86/173 (49.7%)	21/86 (24%)	14	2	5
From 1.0 to 1.68 logMAR	76/173 (44%)	41/76 (54%)	12	13	16
Below 1.0 logMAR	11/173 (6%)	5/11 (46%)	na	0	5
All [d]	173/173 (100%)	67/173 (39%)	26	15	26

Values are given as n (%); Percentages may not total 100% due to rounding; BCVA = best corrected visual acuity; CRR = clinically relevant recovery; logMAR = logarithm of the minimal angle of resolution; na = not applicable

[a] Data cut-off June 2018; [b] For information on EP flow see Supplemental Data A; [c] CRR is improvement from off-chart BCVA to on-chart by the equivalent of at least one full line on an ETDRS chart (five letters) or an improvement in on-chart BCVA by the equivalent of at least two lines (10 letters) at LV; [d] One patient had vision loss in one eye not related to LHON.