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Supplemental information

Therapeutic benefit of idebenone in patients with Leber hereditary optic neuropathy: The LEROS nonrandomized controlled trial

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Supplemental Information

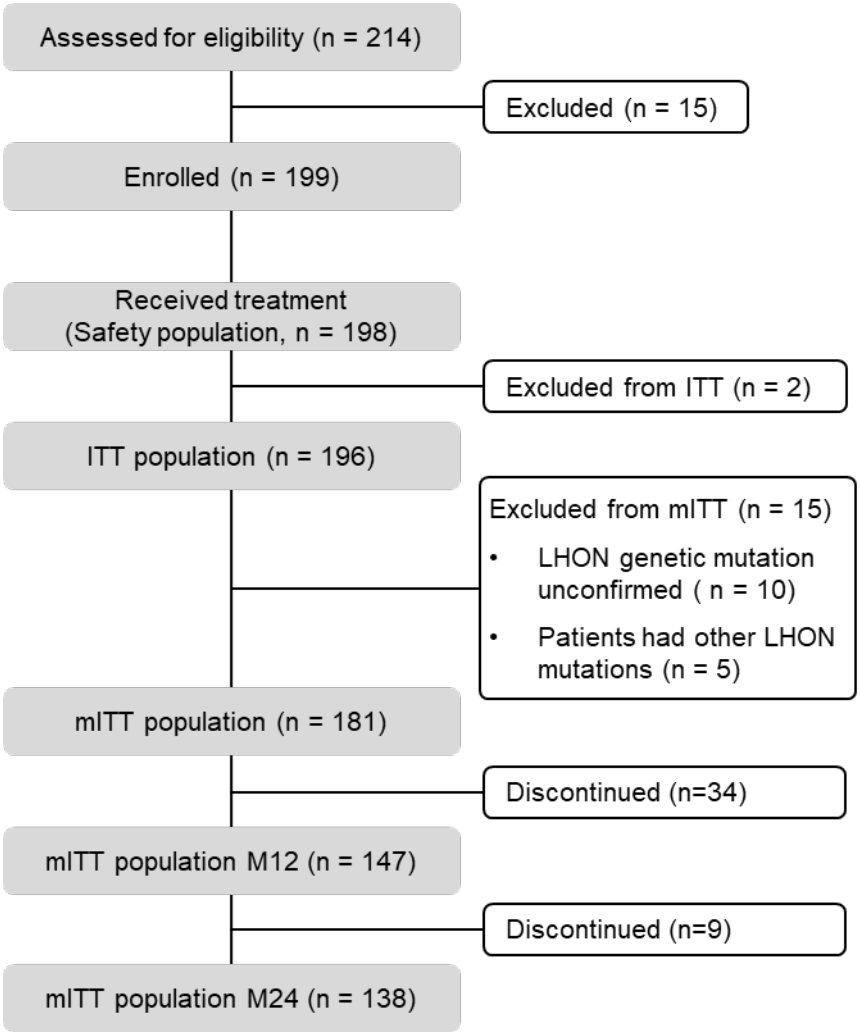

Figure S 1. Disposition of idebenone treated patients, related to Results and STAR Methods
ITT: Intention-To-Treat; LHON: Leber hereditary optic neuropathy; mITT: modified ITT; VA: visual acuity.

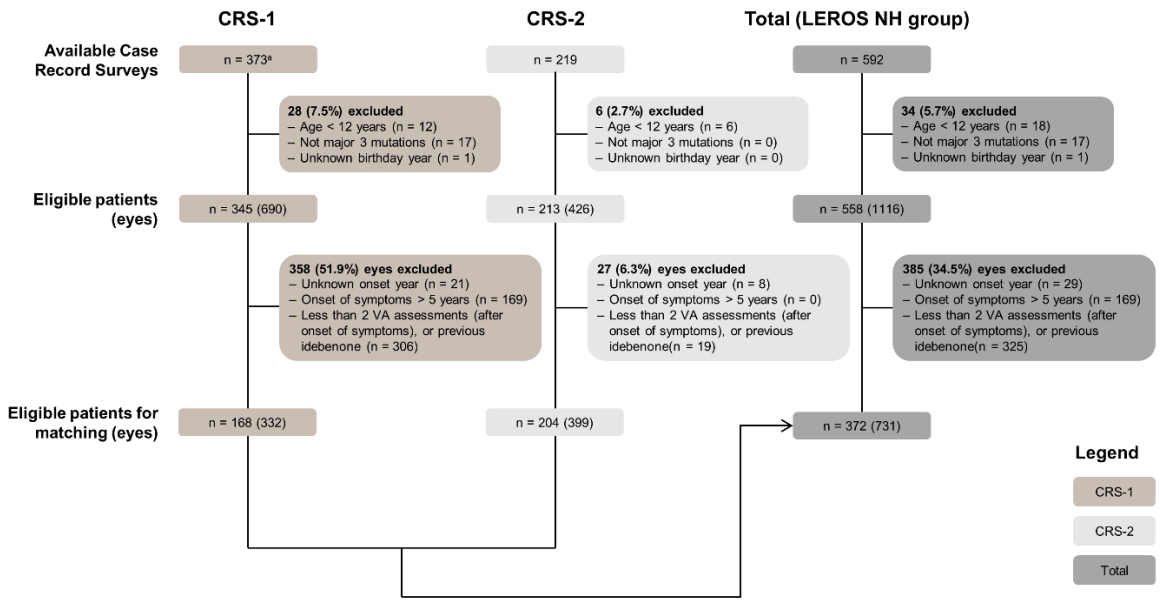

Figure S 2. Disposition of patients in the Natural History control group, related to STAR Methods
[a]Of 383 available record surveys, 10 were of patients included in CRS-2 and were removed from CRS-1. CRS: Case Record Survey; NH: Natural History.

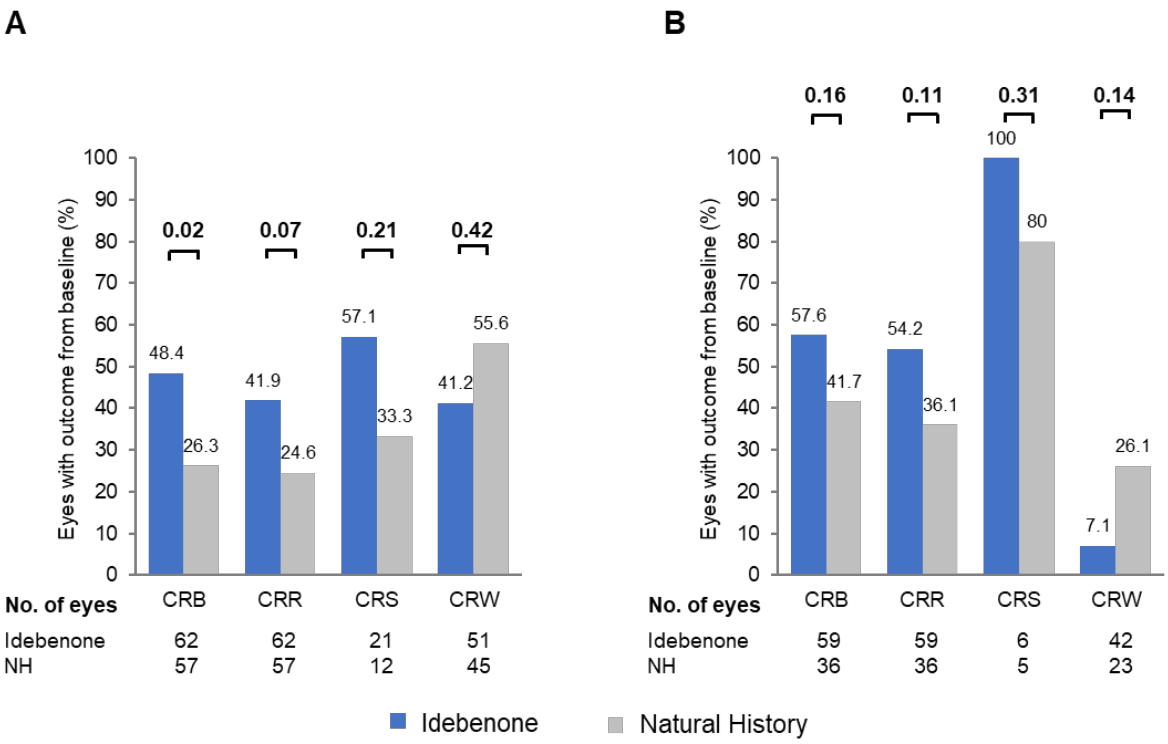

Figure S 3. Responder outcomes at 24 months in (A) subacute eyes (< 6 months after onset at baseline) and (B) dynamic eyes (6 – 12 months after onset at baseline) (mITT vs matched NH). Related to Figure 1
CRB: clinically relevant benefit; CRS: clinically relevant stabilization; CRR: clinically relevant recovery; CRW: clinically relevant worsening; mITT: modified Intention-To-Treat cohort; NH: Natural History cohort.

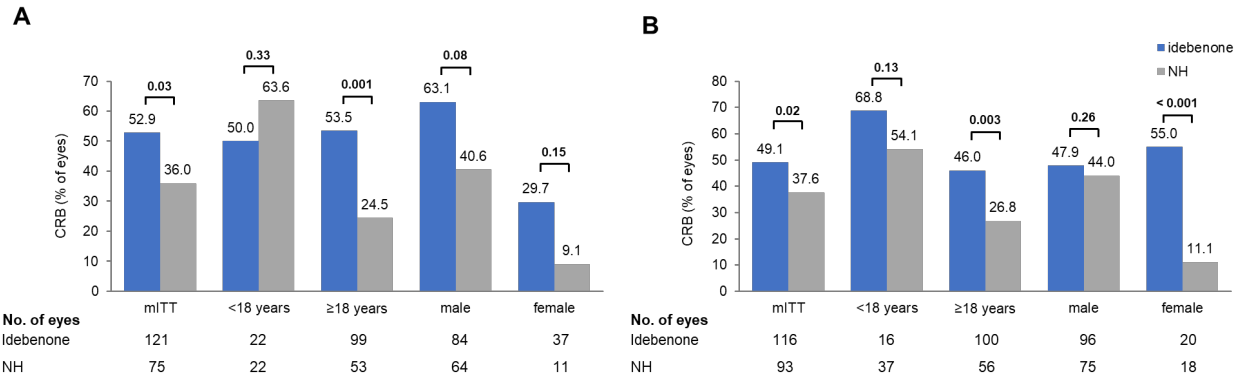

Figure S 4. CRB from baseline by age group at first symptom onset and by gender in (A) subacute/dynamic and (B) chronic eyes at 24 months (mITT vs matched NH). Related to Figure 1
Idebenone had a significant therapeutic benefit in adult eyes (≥18 years) at 24 months (subacute/dynamic [53.5% vs 24.5%, p=0.001]; chronic [46.0% vs 26.8%, p=0.003]). In patients <18 years at symptom onset, the rate of CRB was comparably high in both treated and untreated eyes (subacute/dynamic [50.0% vs 63.6%, p=0.33]; chronic [68.8% vs 54.1%, p=0.13]). Subgroup analyses of CRB by ***gender*** demonstrated a therapeutic benefit of idebenone at 24 months in eyes of female patients in the chronic phase. In the subacute/dynamic phase there was a non-significant trend toward a positive treatment effect in both ***genders***. In subacute/dynamic eyes, the difference in rates was larger in eyes of male patients, whereas this was reversed in the chronic phase. CRB: clinically relevant benefit; mITT: modified Intention-To-Treat cohort; NH: Natural History cohort.

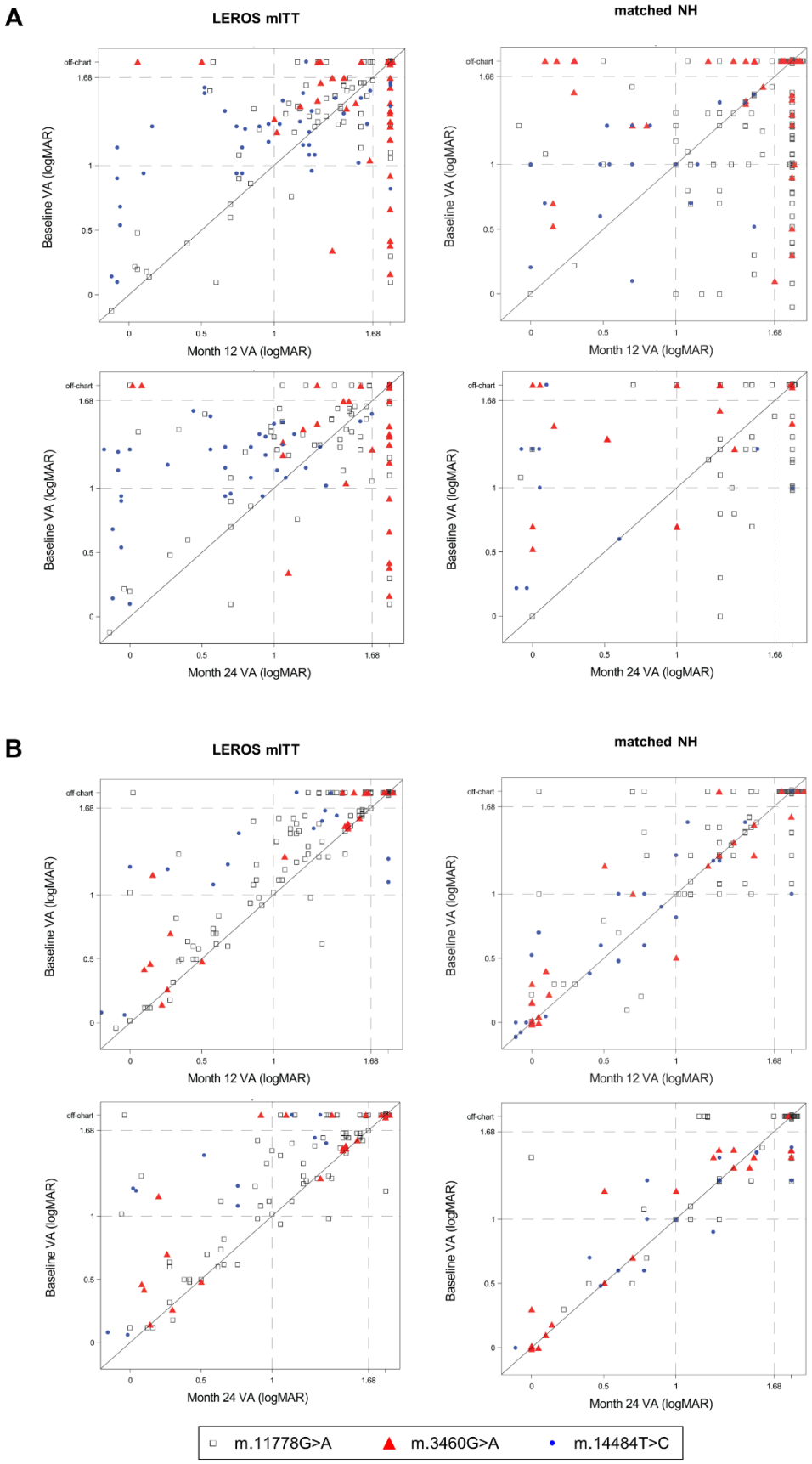

Figure S 5. Visual acuity of individual eyes at baseline versus 12 or 24 months in (A) subacute/dynamic eyes, and (B) chronic eyes (mITT and matched Natural History groups). Related to Figure 4
Off-chart VA was defined as 1.8 logMAR. mITT: modified intention-to-treat; NH: Natural History; VA: visual acuity.

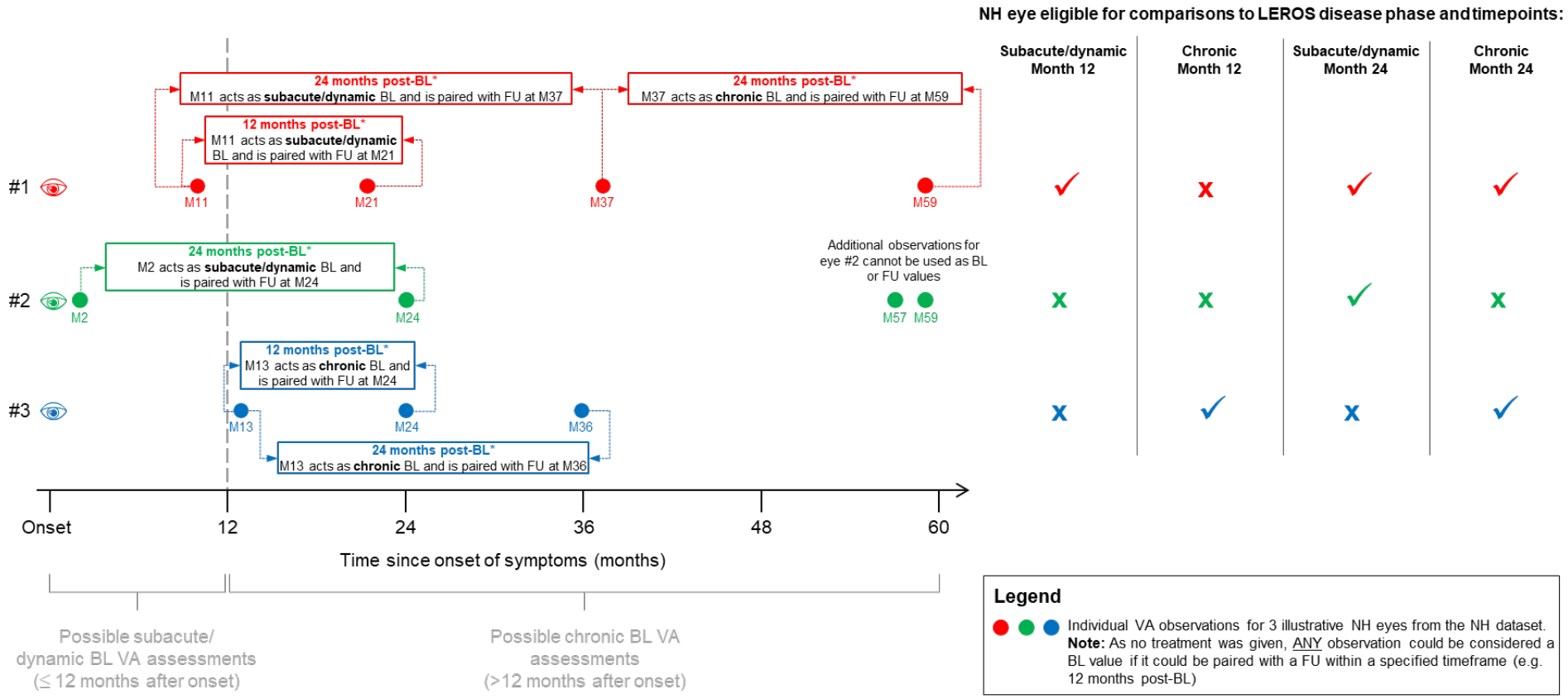

Figure S 6. Illustration of matching subacute/dynamic eyes in the Natural History group to the idebenone-treated LEROS mITT population, related to STAR Methods

* 12 or 24 months post-BL ± 3 months.

BL: baseline; FU: follow-up; NH: Natural History; M: Month; VA: visual acuity.

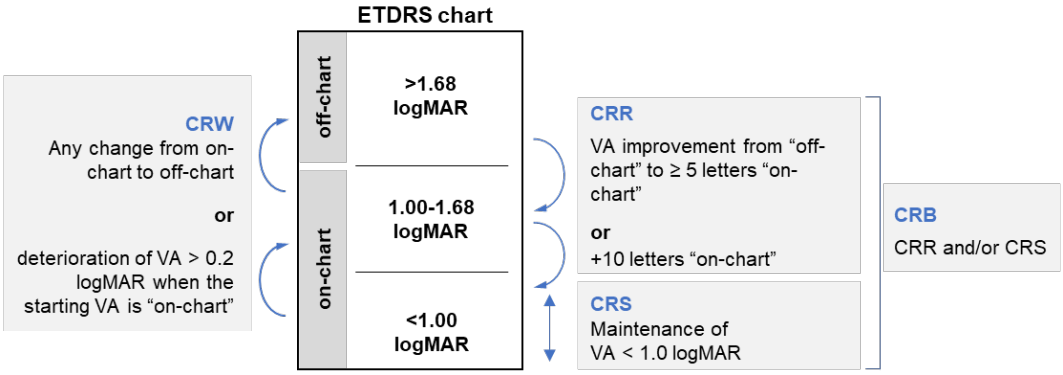

Figure S 7. Definition of outcome measures, related to STAR Methods
CRB: clinically relevant benefit; CRR: clinically relevant recovery; CRS: clinically relevant stabilization; CRW: clinically relevant worsening; ETDRS: Early Treatment Diabetic Retinopathy Study; VA: visual acuity.

Table S 1. Patient characteristics in the different Natural History subsets, related to Table 1
In line with literature reports, around 80% of patients were male with a median age of first symptom onset around 24 – 26 years. [1] The proportions of the three major mutations were also as expected with m.11778G>A found in 73% of patients, followed by 14% carrying the m.3460G>A mutation, and 13% the m.14484T>C mutation in patients eligible for matching.(Yu-Wai-Man et al. 2009) At first symptom onset, 4.6% of patients eligible for matching were <12 years of age and 15.6% were adolescent (12 to <18 years). The majority of patients were adults, with 46.5% in the age group of 18 to <35 years and 33.3% in the age group of 35 years or older. For over 50% of patients eligible for matching at least 5 visits with VA assessments were recorded. Nevertheless, the number of visits was relatively low, leading to a strong reduction of patients with possible baseline-visit pairs for the outcome analyses. Only 36.0% (n=134) of patients eligible for matching had a suitable VA pair at 12 months, and 18.5% (n=69) at 24 months.

Characteristic	(A) Total NH population	(B) Patients with ≥ 2 visits prior to idebenone	(C) Patients in (B) with known onset year and ≤ 5 years since onset	(D) Patients in (C) with one of major 3 mutations	(E) Patients eligible for matching (Patients in (D) aged ≥ 12 years and year of birth known)
Patients, N	**592**	**419**	**391**	**383**	**372**
Gender, n (%)					
Female	124 (20.9%)	85 (20.3%)	78 (19.9%)	76 (19.8%)	**74 (19.9%)**
Male	462 (78.0%)	333 (79.5%)	312 (79.8%)	306 (79.9%)	**297 (79.8%)**
Missing	6 (1.0%)	1 (0.2%)	1 (0.3%)	1 (0.3%)	**1 (0.3%)**
Mutation, n (%)					
m.11778G>A	404 (68.2%)	295 (70.4%)	279 (71.4%)	279 (72.8%)	**273 (73.4%)**
m.3460G>A	95 (16.0%)	59 (14.1%)	55 (14.1%)	55 (14.4%)	**52 (14.0%)**
m.14484T>C	76 (12.8%)	54 (12.9%)	49 (12.5%)	49 (12.8%)	**47 (12.6%)**
Other	17 (2.9%)	11 (2.6%)	8 (2.0%)	-	**-**
Age (years) at 1st symptom onset (years), N	581	413	390	382	**372**
Mean (SD)	28 (14.6)	29 (14.6)	29 (14.6)	29 (14.6)	**30 (14.3)**
Median (Q1; Q3)	24 (17; 37)	25 (18; 38)	25 (18; 39)	26 (18; 39)	**26 (18; 39)**
Min – max	4, 78	4, 75	4, 75	4, 75	**4, 75**
Age group at 1st symptom onset, n (%)					
<12 years	44 (7.4%)	33 (7.9%)	28 (7.2%)	27 (7.0%)	**17 (4.6%)**
12 ≤ years <18	102 (17.2%)	69 (16.5%)	60 (15.3%)	58 (15.1%)	**58 (15.6%)**
18 ≤ years <35	270 (45.6%)	183 (43.7%)	177 (45.3%)	173 (45.2%)	**173 (46.5%)**
≥ 35 years	165 (27.9%)	128 (30.5%)	125 (32.0%)	124 (32.4%)	**124 (33.3%)**
Missing	11 (1.9%)	6 (1.4%)	1 (0.3%)	1 (0.3%)	**-**
Number of visits per patient with VA assessment, N	587	419	391	383	**372**
Mean (SD)	4 (3.5)	5 (3.6)	6 (3.6)	5 (3.6)	**5 (3.6)**
Median (Q1; Q3)	3 (2; 6)	4 (3; 7)	5 (3; 7)	5 (3; 7)	**5 (3; 7)**
Range	1, 31	2, 31	2, 31	2, 31	**2, 31**
1	109 (18.4%)	-	-	-	**-**
2	104 (17.6%)	79 (18.9%)	70 (17.9%)	70 (18.3%)	**68 (18.3%)**
3	94 (15.9%)	81 (19.3%)	74 (18.9%)	74 (19.3%)	**70 (18.8%)**
4	56 (9.5%)	50 (11.9%)	47 (12.0%)	46 (12.0%)	**45 (12.1%)**
5	58 (9.8%)	55 (13.1%)	53 (13.6%)	52 (13.6%)	**50 (13.4%)**
>5	166 (28.0%)	154 (36.8%)	147 (37.6%)	141 (36.8%)	**139 (37.4%)**

SD: standard deviation; Q: quartile; VA: visual acuity.

Table S 2. Follow-up time and time in NH patient population, related to Table 1

	Patients eligible for matching (N=372)
Follow-up time (months)	
Mean (SD)	47.9 (72.41)
Median (Q1; Q3)	14.7 (4.6; 67.6)
Range	0.1 – 514.1
Time since onset of symptoms to first visit (years)	
Mean (SD)	0.4 (0.91)
Median (Q1; Q2)	0.1 (0.0; 0.4)
Range	0.0 – 11.2
≤1 year since onset, n (%)	337 (90.6)
>1 year since onset, n (%)	35 (9.4)

Q: quartile; SD: standard deviation; VA: visual acuity.

Table S 3. Visual acuity reporting formats in the Natural History dataset eligible for matching, related to STAR Methods

	Patients eligible for matching (N=372)
Type of VA recording, F	3999
logMAR, f (%)	509 (12.7)
Off-chart[a], f (%)	804 (20.1)
Decimal, f (%)	579 (14.5)
Snellen, f (%)	2052 (51.3)
Other, f (%)	55 (1.4)

[a] Counting fingers or worse. Off-chart VA was converted to 1.8 logMAR.
F: frequency; f: frequency; VA: visual acuity.

Table S 4. Patient baseline demographics and characteristics in subacute/dynamic and chronic patients (ITT), related to Table 1

Characteristic	Subacute/dynamic patients (N=109)	Chronic patients (N=87)	ITT (N=196)
Mutation, n (%)	109	87	196
m.11778G>A	55 (50.5)	57 (65.5)	112 (57.1)
m.3460G>A	20 (18.3)	15 (17.2)	35 (17.9)
m.14484T>C	24 (22.0)	10 (11.5)	34 (17.3)
Other	2 (1.8)	3 (3.4)	5 (2.6)
No identified mutation	8 (7.3)	2 (2.3)	10 (5.1)
Male, n (%)	78 (71.6)	66 (75.9)	144 (73.5)
Childbearing potential, N	31	21	52
Yes, n (%)	22 (71.0)	13 (61.9)	35 (67.3)
Race, N	109	87	196
Black or African American, n (%)	6 (5.5)	2 (2.3)	8 (4.1)
White, n (%)	36 (33.0)	18 (20.7)	54 (27.6)
Other[a], n (%)	67 (61.5)	67 (76.9)	134 (68.3)
Height (cm), N	104	85	189
Mean (SD)	172.19 (10.47)	170.44 (12.11)	171.41 (11.24)
Min – max	123.50 – 195.01	107.18 – 190.50	107.18 – 195.01
Weight (kg), N	104	85	189
Mean (SD)	74.54 (15.72)	72.74 (15.79)	73.73 (15.73)
Min – max	43.40 – 119.75	34.10 – 115.21	34.10 – 119.75
Age (years), N	109	87	196
Mean (SD)	34.05 (15.06)	34.06 (15.49)	34.06 (15.21)
Min – max	12.56 – 79.23	12.13 – 76.88	12.13 – 79.23
Age at 1st symptom onset (years), N	109	87	196
Mean (SD), years	33.42 (14.98)	31.43 (15.58)	32.53 (15.24)
Min – max	12.05 – 78.17	8.75 – 75.75	8.75 – 78.17
Months since most recent symptom onset, N	109	87	196
Mean (SD)	5.32 (3.04)	30.30 (14.22)	16.41 (15.78)
Min – max	0.07 – 11.86	12.06 – 57.95	0.07 – 57.95
Number of symptomatic eyes per patient, N	109	87	196
One, n (%)	8 (7.3)	3 (3.4)	11 (5.6)
Two, n (%)	101 (92.7)	84 (96.6)	185 (94.4)
Simultaneous onset in both eyes, N	109	87	196
n (%)	41 (37.6)	37 (42.5)	78 (39.8)
Delta onset[b] (months), N	65	47	112
Mean (SD)	4.49 (5.43)	2.57 (2.42)	3.69 (4.51)
Min – max	0.03 – 27.96	0.30 – 11.86	0.03 – 27.96

[a]Other races included 1 (0.9%) Chinese in the subacute/dynamic LHON cohort, and 2 (2.3%) American Indian or Alaska Native, 1 (1.1%) Asian Indian, and 1 (1.1%) Filipino in the chronic LHON cohort. For 66 (60.6%) patients in the subacute/dynamic and 63 (72.4%) in the chronic LHON cohort the race was not specified.[b]Delta onset is the time gap between symptom onset between a patient's two eyes. Eyes that have equal dates onset were not accounted in the calculation of the delta. ITT: intention-to-treat; LHON: Leber hereditary optic neuropathy; max: maximum; min: minimum; SD: standard deviation.

Table S 5. Responder analysis outcomes in subacute/dynamic and chronic eyes (mITT vs matched NH group), related to Figure 1
The sensitivity analysis takes into consideration additional covariates of age at first symptom onset and time since symptom onset, in addition to treatment, mutations, and gender.

	All (mITT)							
	12 months				**24 months**			
	ide, n/N (%)	**NH**, n/N (%)	***p*-Value; OR [95% CI]**	***Sensitivity analysis* *p*-Value; OR [95% CI]**	**ide**, n/N (%)	**NH**, n/N (%)	***p*-Value; OR [95% CI]**	***Sensitivity analysis* *p*-Value; OR [95% CI]**
SUBACUTE/DYNAMIC EYES								
CRB	60/142 (42.3)	40/193 (20.7)	0.002; 2.29 [1.35; 3.88]	0.008; 2.10 [1.22; 3.64]	64/121 (52.9)	27/75 (36.0)	0.030; 2.08 [1.07; 4.10]	0.048; 1.96 [1.01; 3.89]
CRR	47/142 (33.1)	35/193 (18.1)	0.087; 1.65 [0.93; 2.92]	0.215; 1.45 [0.80; 2.62]	58/121 (47.9)	25/75 (33.3)	0.068; 1.86 [0.96; 3.66]	0.113; 1.73 [0.88; 3.44]
CRS	20/31 (64.5)	9/40 (22.5)	<0.001; 7.32 [2.34; 25.91]	0.001; 7.80 [2.17; 33.84]	18/27 (66.7)	6/13 (46.2)	0.096; 5.23 [0.76; 52.91]	0.037; 12.53 [1.15; 375.2]
CRW	30/103 (29.1)	76/130 (58.5)	<0.001; 0.33 [0.18; 0.61]	0.023; 0.45 [0.22; 0.89]	24/93 (25.8)	25/49 (51.0)	0.005; 0.30 [0.12; 0.70]	0.009; 0.29 [0.11; 0.74]
CHRONIC EYES								
CRB	72/143 (50.3)	59/153 (38.6)	0.009; 1.93 [1.18; 3.17]	0.009; 1.94 [1.18; 3.21]	57/116 (49.1)	35/93 (37.6)	0.018; 2.05 [1.13; 3.79]	0.022; 2.05 [1.11; 3.87]
CRR	47/143 (32.9)	30/153 (19.6)	0.003; 2.24 [1.30; 3.93]	0.006; 2.16 [1.25; 3.80]	37/116 (31.9)	15/93 (16.1)	0.001; 3.15 [1.55; 6.77]	0.005; 2.84 [1.36; 6.24]
CRS	32/34 (94.1)	36/38 (94.7)	0.894; 0.85 [0.06; 10.23]	0.919; 0.86 [0.04; 15.18]	26/28 (92.9)	22/23 (95.7)	0.870; 0.75 [0.01; 20.38]	0.908; 0.55 [0.00; 3372]
CRW	4/81 (4.9)	15/89 (16.9)	0.006; 0.22 [0.06; 0.66]	0.016; 0.26 [0.07; 0.78]	2/68 (2.9)	12/60 (20.0)	<0.001; 0.08 [0.01; 0.34]	<0.001; 0.09 [0.01; 0.40]

CI: confidence interval.; CRB: clinically relevant benefit; CRR: clinically relevant recovery; CRS: clinically relevant stabilization; CRW: clinically relevant worsening; ide: idebenone; mITT: modified Intention-To-Treat; NH: Natural History cohort; OR: odds ratio.

Table S 6: Logistic regression Type III tests of Fixed Effects for CRB at 12 and 24 months in subacute/dynamic and chronic eyes by mutation (mITT vs matched NH group), related to Figure 1

Interaction model	Month 12 *p*-values	Month 24 *p*-values
Subacute/dynamic eyes		
Interaction treatment and major 3 mutations	0.0015	0.0078
Treatment	0.0788	0.4529
Mutations	<.0001	<.0001
Gender	0.1726	0.0021
Chronic eyes		
Interaction treatment and major 3 mutations	0.0242	0.0260
Treatment	0.5716	0.9798
Mutations	<.0001	0.0232
Gender	0.3358	0.3243

Table S 7. Responder analysis outcomes in subacute/dynamic and chronic eyes by mutation (mITT vs matched NH group), related to Figure 1

	m.11778G>A						m.3460G>A						m.14484T>C					
	12 months			24 months			12 months			24 months			12 months			24 months		
	Ide, n/N (%)	**NH**, n/N (%)	***p*-Value; Odds Ratio [95% CI]**	**Ide** n/N (%)	**NH**, n/N (%)	***p*-Value; Odds Ratio [95% CI]**	**Ide**, n/N (%)	**NH**, n/N (%)	***p*-Value; Odds Ratio [95% CI]**	**Ide**, n/N (%)	**NH**, n/N (%)	***p*-Value; Odds Ratio [95% CI]**	**Ide**, n/N (%)	**NH**, n/N (%)	***p*-Value; Odds Ratio [95% CI]**	**Ide**, n/N (%)	**NH**, n/N (%)	***p*-Value; Odds Ratio [95% CI]**
SUBACUTE/DYNAMIC EYES																		
CRB	25/68 (36.8)	13/138 (9.4)	<0.001; 6.01 [2.85; 13.24]	27/60 (45.0)	8/47 (17.0)	<0.001; 5.30 [2.12; 14.49]	12/32 (37.5)	14/34 (41.2)	1.0; 1.00 [0.36; 2.77]	9/26 (34.6)	11/18 (61.1)	0.24; 0.47 [0.12; 1.67]	23/42 (54.8)	13/21 (61.9)	0.60; 0.75 [0.25; 2.18]	28/35 (80.0)	8/10 (80.0)	0.98; 1.02 [0.13; 5.52]
CRR	14/68 (20.6)	10/138 (7.2)	0.005; 3.54 [1.48; 8.75]	23/60 (38.3)	7/47 (14.9)	0.002; 4.51 [1.75; 12.84]	12/32 (37.5)	14/34 (41.2)	0.99; 1.00 [0.36; 2.77]	9/26 (34.6)	11/18 (61.1)	0.22; 0.45 [0.12; 1.61]	21/42 (50.0)	11/21 (52.4)	0.87; 0.92 [0.32; 2.64]	26/35 (74.3)	7/10 (70.0)	0.77; 1.27 [0.23; 5.87]
CRS	12/15 (80.0)	3/28 (10.7)	<0.001; 37.03 [7.13; 283.2]	9/12 (75.0)	1/6 (16.7)	<0.001; 127E4 [6.84; N.E.]	0/6 (0.0)	2/6 (33.3)	0.10; 0.00 [N.E.; 1.81]	0/6 (0.0)	2/4 (50.0)	0.09;0.00 [N.E.; 1.70]	8/10 (80.0)	4/6 (66.7)	0.63; 1.78 [0.15; 20.80]	9/9 (100.0)	3/3 (100.0)	N.E.; 1.0 [N.E.; N.E.]
CRW	10/45 (22.2)	64/92 (69.6)	<0.001; 0.13 [0.05; 0.28]	10/41 (24.4)	20/30 (66.7)	<0.001; 0.11 [0.03; 0.34]	14/20 (70.0)	9/17 (52.9)	0.28; 2.10 [0.54; 8.59]	13/17 (76.5)	3/10 (30.0)	0.05; 5.63 [1.02; 38.94]	6/38 (15.8)	3/21 (14.3)	0.88; 1.12 [0.26; 5.83]	1/35 (2.9)	2/9 (22.2)	0.07; 0.10 [0.00; 1.19]
CHRONIC EYES																		
CRB	50/105 (47.6)	24/102 (23.5)	<0.001; 2.93 [1.63; 5.40]	36/82 (43.9)	11/51 (21.6)	0.008; 2.85 [1.31; 6.56]	10/23 (43.5)	16/26 (61.5)	0.24; 0.51 [0.16; 1.58]	10/23 (43.5)	16/24 (66.7)	0.12; 0.40 [0.12; 1.28]	12/15 (80.0)	19/25 (76.0)	0.81; 1.21 [0.26; 6.60]	11/11 (100.0)	8/18 (44.4)	<0.001; 462E4 [4.86; N.E.]
CRR	29/105 (27.6)	17/102 (16.7)	0.06; 1.90 [0.97; 3.78]	20/82 (24.4)	7/51 (13.7)	0.13; 2.03 [0.82; 5.54]	7/23 (30.4)	6/26 (23.1)	0.52; 1.52 [0.42; 5.64]	7/23 (30.4)	5/24 (20.8)	0.43; 1.70 [0.45; 6.78]	11/15 (73.3)	7/25 (28.0)	0.006; 6.86 [1.73; 32.34]	10/11 (90.9)	3/18 (16.7)	<0.001; 46.98 [5.90; 1065]
CRS	24/26 (92.3)	9/9 (100.0)	0.23; 0.00 [N.E.; 4.00]	18/20 (90.0)	4/4 (100.0)	0.45; 0.00 [N.E.; 13.59]	6/6 (100.0)	12/13 (92.3)	0.29; 30790 [0.11; N.E.]	6/6 (100.0)	12/12 (100.0)	N.E.; 1.29 [N.E.; N.E.]	2/2 (100.0)	15/16 (93.8)	0.7156; 14525 [0.01; N.E.]	2/2 (100.0)	6/7 (85.7)	0.54; 44571 [0.02; N.E.]
CRW	2/55 (3.6)	11/44 (25.0)	0.002; 0.11 [0.02; 0.46]	2/45 (4.4)	6/19 (31.6)	0.004; 0.10 [0.01; 0.49]	0/15 (0.0)	3/21 (14.3)	0.05; 0.00 [N.E.; 1.00]	0/15 (0.0)	3/23 (13.0)	0.05; 0.00 [N.E.; 1.03]	2/11 (18.2)	1/24 (4.2)	0.17; 5.55 [0.47; 129.9]	0/8 (0.0)	3/18 (16.7)	0.21; 0.00 [N.E.; 3.29]

CRB: clinically relevant benefit; CRR: clinically relevant recovery; CRS: clinically relevant stabilization; CRW: clinically relevant worsening; ide: idebenone; mITT: modified Intention-To-Treat; N.E.: not estimable; NH: Natural History cohort.

Table S 8. Visual acuity (logMAR) at baseline and in the 12- and 24-month cohorts (by eyes; mITT vs matched NH group), related to Figure 4

	Total		m.11778G>A		m.3460G>A		m.14484T>C	
	Idebenone	**NH**	**Idebenone**	**NH**	**Idebenone**	**NH**	**Idebenone**	**NH**
Subacute/dynamic eyes, 12 months								
N	142	193	68	138	32	34	42	21
VA at baseline, logMAR								
LS-Means (SE)	1.29 (0.04)	1.26 (0.05)	1.29 (0.06)	1.27 (0.05)	1.35 (0.09)	1.46 (0.09)	1.23 (0.08)	1.02 (0.11)
95% CI	1.20; 1.38	1.17; 1.36	1.17; 1.42	1.18; 1.37	1.18; 1.53	1.28; 1.64	1.07; 1.38	0.80; 1.23
VA at 12 months								
LS-Means (SE)	1.20 (0.04)	1.32 (0.05)	1.25 (0.06)	1.57 (0.04)	1.49 (0.08)	1.27 (0.08)	0.99 (0.08)	0.84 (0.11)
95% CI	1.12; 1.29	1.23; 1.42	1.13; 1.36	1.48; 1.66	1.32; 1.65	1.10; 1.43	0.84; 1.14	0.64; 1.05
Difference, logMAR (*p*-value)[a]	-0.12 (0.03)		-0.33 (<0.001)		0.22 (0.06)		0.14 (0.25)	
Subacute/dynamic eyes, 24 months								
N	121	75	60	47	26	18	35	10
VA at baseline, logMAR								
LS-Means (SE)	1.26 (0.05)	1.30 (0.07)	1.31 (0.06)	1.36 (0.07)	1.29 (0.09)	1.45 (0.12)	1.18 (0.09)	1.03 (0.15)
95% CI	1.17; 1.36	1.17; 1.43	1.19; 1.43	1.21; 1.50	1.11; 1.48	1.22; 1.68	1.01; 1.35	0.73; 1.33
VA at 24 months, logMAR								
LS-Means (SE)	1.11 (0.05)	1.14 (0.08)	1.22 (0.07)	1.53 (0.08)	1.48 (0.10)	0.95 (0.13)	0.77 (0.09)	0.57 (0.17)
95% CI	1.00; 1.22	0.98; 1.29	1.08; 1.35	1.37; 1.69	1.28; 1.68	0.70; 1.20	0.58; 0.95	0.23; 0.90
Difference, logMAR (*p*-value)[a]	-0.03 (0.75)		-0.32 (0.002)		0.53 (0.001)		0.20 (0.29)	
Chronic eyes, 12 months								
N	143	153	105	102	23	26	15	25
VA at baseline, logMAR								
LS-Means (SE)	1.16 (0.06)	1.11 (0.06)	1.35 (0.06)	1.49 (0.06)	1.31 (0.11)	0.82 (0.11)	1.25 (0.14)	0.71 (0.11)
95% CI	1.04; 1.27	1.00; 1.22	1.23; 1.46	1.38; 1.60	1.09; 1.53	0.61; 1.04	0.97; 1.53	0.49; 0.92
VA at 12 months, logMAR								
LS-Means (SE)	1.11 (0.03)	1.21 (0.03)	1.17 (0.03)	1.27 (0.03)	1.16 (0.06)	1.20 (0.06)	0.97 (0.08)	1.17 (0.06)
95% CI	1.05; 1.18	1.15; 1.28	1.10; 1.23	1.21; 1.34	1.04; 1.29	1.07; 1.33	0.82; 1.13	1.04; 1.30
Difference, logMAR (*p*-value)[a]	-0.10 (0.004)		-0.10 (0.02)		-0.04 (0.68)		-0.20 (0.05)	
Chronic eyes, 24 months								
N	116	93	82	51	23	24	11	18
VA at baseline, logMAR								
LS-Means (SE)	1.20 (0.07)	1.18 (0.07)	1.34 (0.07)	1.54 (0.08)	1.32 (0.11)	0.82 (0.11)	1.21 (0.17)	1.00 (0.13)
95% CI	1.07; 1.33	1.04; 1.31	1.21; 1.47	1.38; 1.69	1.10; 1.54	0.60; 1.04	0.88; 1.54	0.75; 1.25
VA at 24 months, logMAR								
LS-Means (SE)	1.07 (0.04)	1.24 (0.04)	1.15 (0.04)	1.26 (0.05)	1.11 (0.06)	1.24 (0.07)	0.75 (0.09)	1.27 (0.07)
95% CI	0.99; 1.15	1.16; 1.31	1.08; 1.23	1.17; 1.36	0.98; 1.24	1.11; 1.37	0.57; 0.94	1.13; 1.42
Difference, logMAR (*p*-value)[a]	-0.17 (<0.001)		-0.11 (0.04)		-0.13 (0.16)		-0.52 (<0.001)	

[a]Difference in LS-means VA in change from baseline between idebenone-treated eyes and matched eyes in the NH group. A negative difference indicates a relative improvement in visual acuity in treated eyes compared to the Natural History group.

CI: confidence interval; LS: least squares; mITT: modified Intention-To-Treat cohort; NH: Natural History cohort; SE: standard error; VA: visual acuity.

Table S 9. Safety population baseline demographics, related to Table 1

	Safety population (N=198)
Gender, N	198
Male, n (%)	146 (73.7)
Female, n (%)	52 (26.3)
Childbearing potential, N	52
Yes, n (%)	35 (67.3)
No, n (%)	17 (32.7)
Mutation, N	198
m.11778G>A, n (%)	112 (56.6)
m.3460G>A, n (%)	35 (17.7)
m.14484T>C, n (%)	34 (17.2)
Other, n (%)	5 (2.5)
Negative, n (%)	12 (6.1)
Race, N	198
Black or African American, n (%)	9 (4.5)
White, n (%)	54 (27.3)
Other[a], n (%)	135 (68.2)
Height at baseline (cm), N	191
Mean (SD)	171.3 (11.3)
Min – max	107.2 – 195.0
Weight at baseline (kg), N	191
Mean (SD)	73.6 (15.7)
Min – max	34.1 – 119.8
Age at baseline (years), N	198
Mean (SD)	34.2 (15.2)
Min – max	12.13 – 79.2

[a]Other races included 2 (1.0%) American Indian or Alaska Native, 1 (0.5%) Asian Indian, 1 (0.5%) Chinese, and 1 (0.5%) Filipino. For 130 (65.7%) patients the race was not specified.
max: maximum; min: minimum; SD: standard deviation.

Table S 10. Summary of treatment-emergent adverse events (safety population), related to Table 2

	Events	Patients	Days in Treatment	
	f (%) (F=891)	n (%) (N=198)	Mean (SD)	Min – Max
Any TEAEs	891 (100.0)	154 (77.8)	247.0 (234.9)	1.0 – 1027.0
Product-related TEAEs	101 (11.3)	49 (24.7)	120.4 (178.5)	1.0 – 757.0
Severe TEAEs	25 (2.8)	13 (6.6)	325.0 (252.5)	19.0 – 742.0
Serious TEAEs not leading to death	44 (4.9)	27 (13.6)	291.4 (239.7)	14.0 – 742.0
TEAEs (special interest)	79 (8.9)	36 (18.2)	353.5 (291.3)	1.0 – 1027.0
TEAEs leading to permanent study treatment discontinuation	18 (2.0)	10 (5.1)	241.3 (264.6)	14.0 – 742.0
TEAEs leading to death	1 (0.1)	1 (0.5)	517.0 (-)	517.0 – 517.0

max: maximum; min: minimum; SD: standard deviation; TEAE: treatment-emergent adverse event.

REFERENCES

1. Yu-Wai-Man, P.; Griffiths, P. G.; Hudson, G.; Chinnery, P. F. (2009): Inherited mitochondrial optic neuropathies. In *J Med Genet* 46 (3), pp. 145–158. DOI: 10.1136/jmg.2007.054270.