

Voretigene Neparvovec (reassessment after the deadline: inherited retinal dystrophy)

Resolution of: 15 September 2022
Entry into force on: 15 September 2022
Federal Gazette, BAnz AT 19 10 2022 B3

Valid until: unlimited

Therapeutic indication (according to the marketing authorisation of 22 November 2018):

Luxturna is indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.

Therapeutic indication of the resolution (resolution of 15 September 2022):

See therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Voretigene neparvovec is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells

Extent of the additional benefit and significance of the evidence of voretigene neparvovec:

Hint for a considerable additional benefit

Study results according to endpoints:¹

Adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells

¹ Data from the dossier assessment of the G-BA (published on 1. July 2022), unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Advantages in the endpoints of mobility test, light sensitivity and visual field
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↔	Overall, no advantages or disadvantages in the overall rates. In detail, disadvantages for AE SOC "blood and lymphatic system disorders" and PT "leukocytosis"
<p>Explanations:</p> <p>↑: statistically significant and relevant positive effect with low/unclear reliability of data</p> <p>↓: statistically significant and relevant negative effect with low/unclear reliability of data</p> <p>↑↑: statistically significant and relevant positive effect with high reliability of data</p> <p>↓↓: statistically significant and relevant negative effect with high reliability of data</p> <p>↔: no statistically significant or relevant difference</p> <p>∅: There are no usable data for the benefit assessment.</p> <p>n.a.: not assessable</p>		

301 study: randomised, controlled, open-label phase III study: Voretigene neparvovec vs monitoring wait-and-see approach

Mortality

301 study Endpoint	Voretigene neparvovec		Monitoring wait-and-see approach		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Overall survival/ mortality					
no deaths ^a					

Morbidity

301 study Endpoint	Voretigene neparvovec				Monitoring wait-and-see approach				Intervention vs control
	N ^b baseline (N year 1)	Score at baseline MV (SD) <i>Median (min; max)</i>	Score in year 1 ^c MV (SD)	Change to baseline MV (SD) <i>Median (min; max)</i>	N ^b baseline (N year 1)	Score at baseline MV (SD) <i>Median (min; max)</i>	Score in year 1 ^c MV (SD)	Change to baseline MV (SD) <i>Median (min; max)</i>	Changed ^d [95% CI] Exact p value ^e
Multi-luminance mobility test (MLMT) (ITT population)									
Change in MLMT score ^f for both eyes (bilateral)	21 (21)	3.1 (1.7) <i>n.d.</i>	5.2 (1.7)	1.8 (1.1) 2 (0; 4)	10 (10)	2.9 (1.6) <i>n.d.</i>	3.6 (1.4)	0.2 (1.0) 0 (-1; 2)	1.6 [0.7; 2.4]; 0.001 ^g SMD ^x according to Hedges' g: 1.50 [0.66; 2.34]

301 study Endpoint	Voretigene neparvovec				Monitoring wait-and-see approach				Intervention vs control
	N at baseline (N year 1)	Score at baseline MV (SE) <i>Median (min; max)</i>	Score in year 1 MV (SE)	Change to baseline MV (SE) <i>Median (min; max)</i>	N at baseline (N year 1)	Score at baseline MV (SE) <i>Median (min; max)</i>	Score in year 1 MV (SE)	Change to baseline MV (SE)	Mean change ^h [95% CI] p value
Full field stimulus threshold test (FST)^{ij} (ITT population)									
White light (log ₁₀ (cd *s/m ²)) ^k	20 ^j (19)	-1.3 (0.1)	-3.4 (0.3)	-2.1 (0.3)	9 ⁱ (9)	-1.7 (0.1)	-1.6 (0.4)	0.04 (0.4)	-2.1 [-3.2; -1.0]; < 0.001 SMD ^l according to Hedges' g: -1.52 [-2.41; -0.63]

301 study Endpoint	Voretigene neparovvec				Monitoring wait-and-see approach				Intervention vs control
	N at baseline (N year 1)	Score at baseline MV (SE)	Score in year 1 MV (SE)	Change to baseline MV (SE)	N at baseline (N year 1)	Score at baseline MV (SE)	Score in year 1 MV (SE)	Change to baseline MV (SE)	Mean change ^h [95% CI] p value
Blue light (log10(cd*s/m ²))	20 ^m (17 ⁿ)	-1.6 (0.1)	-3.6 (0.3)	-2.0 (0.3)	9 ^m (9 ⁿ)	-2.0 (0.2)	-1.9 (0.4)	0.1 (0.5)	-2.1 [-3.3; -0.9]; 0.001
Red light (log10(cd*s/m ²))	20 ^m (17 ⁿ)	-1.2 (0.1)	-2.5 (0.2)	-1.3 (0.2)	9 ^m (9 ⁿ)	-1.7 (0.2)	-1.5 (0.3)	0.2 (0.2)	-1.5 [-2.1; -0.9]; < 0.001
Visual acuity^o (logMAR) (ITT population)									
ETDRS/HOTV eye chart	21 (20)	1.2 (0.1)	1.0 (0.2)	-0.2 (0.1)	10 (9)	1.3 (0.2)	1.3 (0.3)	0.01 (0.1)	-0.2 [-0.4; 0.1] ^p ; Exact p value ^q : 0.1703

301 study Endpoint	Voretigene neparovvec		Monitoring wait-and-see approach		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk difference [95% CI] p value
Visual acuity (ITT population)					
Improvement in visual acuity (≥ 10 letters ETDRS)	21	6 (28.6) ^{ad}	10	0 (0.0)	n.d. 0.071
Improvement in visual acuity (≥ 15 letters ETDRS)	21	4 (19.0) ^{ae}	10	0 (0.0)	n.d. 0.268

301 study Endpoint	Voretigene neparvovec				Monitoring wait-and-see approach				Intervention vs control
	N at baseline	Score at baseline	Score in year 1B ^c	Mean change to baseline	N at baseline	Score at baseline	Score in year 1B ^c	Mean change to baseline	Difference change ^s [95% CI] ^t p value
	(N year 1)	MV (SD)	MV (SD)		(N year 1)	MV (SD)	MV (SD)		
Visual field measurement using perimetry^r (ITT population)									
Goldmann: III4e (sum score) ^u	20 ^v (19)	332.9 (413.3)	673.9 (423.7)	302.1 (289.6)	10 (9)	427.1 (372.0)	397.8 (367.3)	-76.7 (258.7)	378.8 [145.5; 612.0]; 0.006 SMD ^w according to Hedges' g: 1.27; 95% CI [0.41; 2.12]
Humphrey: Fovea Sensitivity (dB)	20 (19)	22.4 (6.8)	25.8 (9.1)	2.4 (9.7)	10 (9)	17.6 (8.9)	21.1 (8.9)	2.3 (5.3)	0.04 [-7.1; 7.2]; 0.176
Humphrey: Average macula limit (dB)	20 (19)	16.1 (5.5)	24.0 (8.0)	7.7 (6.2)	10 (9)	14.4 (8.0)	15.8 (7.4)	-0.2 (1.7)	7.9 [3.5; 12.2]; < 0.001 SMD ^w according to Hedges' g: 1.45; 95% CI [0.61; 2.29]

Health-related quality of life

301 study Endpoint	Voretigene neparvovec		Monitoring wait-and-see approach		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Visual function questionnaire					
No suitable data submitted.					

Side effects

301 study Endpoint	Voretigene neparvovec ^y		Monitoring wait-and-see approach ^y		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] ^z p value ^{aa}
Side effects (in year 1 after baseline) (safety population)					
AE	20	20 (100)	9	9 (100)	-
Severe AEs ^{ab}	20	3 (15.0)	9	0 (0.0)	n.d. ^{ac} ; 0.532
SAE	20	2 (10.0)	9	0 (0.0)	n.d. ^{ac} ; 1.000
AEs that led to study discontinuation	20	0 (0.0)	9	0 (0.0)	n.a.

301 study MedDRA system organ class Preferred term	Voretigene neparvovec ^y		Monitoring wait-and-see approach ^y		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] ^z p value ^{aa,ac}
AEs with an incidence ≥ 15% in one of the study arms within one year after baseline (safety population)					
Blood and lymphatic system disorders	20	9 (45.0)	9	0 (0.0)	n.d. ^{ac} 0.027
Leukocytosis	20	9 (45.0)	9	0 (0.0)	n.d. ^{ac} 0.027
Eye disorders	20	10 (50.0)	9	1 (11.1)	4.50 [0.95; 124.40]; 0.096
Cataract	20	3 (15.0)	9	0 (0.0)	n.d. ^{ac} 0.532
Gastrointestinal disorders^{af}	20	12 (60.0)	9	3 (33.0)	1.80 [0.76; 9.21] 0.245
Nausea ^{ag}	20	6 (30.0)	9	1 (11.1)	n.d. ^{ah}
Vomiting	20	8 (40.0)	9	2 (22.2)	n.d. ^{ah}
General disorders and administration site conditions	20	10 (50.0)	9	1 (11.1)	4.50 [0.95; 124.40] 0.096 ^{ah}
Fever	20	7 (35.0)	9	1 (11.1)	n.d. ^{ah}

301 study MedDRA system organ class Preferred term	Voretigene neparovvec ^y		Monitoring wait-and- see approach ^y		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] ^z p value ^{aa,ac}
Infections and infestations^{ai, aj}	20	11 (55.0)	9	4 (44.4)	1.24 [0.57; 6.56] 0.700 ^{ah}
Nasopharyngitis ^{ak}	20	7 (35.0)	9	2 (22.2)	n.d.
Upper respiratory tract infection	20	2 (10.0)	9	3 (33.3)	0.30 [0.03; 1.65] 0.287
Injury, poisoning and procedural complications	20	5 (25.0)	9	2 (22.2)	1.13 [0.26; 7.34] 1.000
Investigations	20	7 (35.0)	9	1 (11.0)	3.15 [0.60; 82.84] 0.372
Increased intraocular pressure	20	4 (20.0)	9	0 (0.0)	n.d. 0.280
Nervous system disorders	20	10 (50.0)	9	3 (33.3)	1.50 [0.60; 6.61] 0.453
Headache ^{al}	20	7 (35.0)	9	2 (22.2)	n.d. ^{ah}
Renal and urinary disorders	20	3 (15.0)	9	1 (11.1)	1.35 [0.15; 34.78] 1.000
Haematuria	20	3 (15.0)	9	1 (11.1)	1.35 [0.15; 34.78] 1.000
Reproductive system and breast disorders	20	3 (15.0)	9	0 (0.0)	n.d. 0.532
Respiratory, thoracic and mediastinal disorders^{am}	20	10 (50.0)	9	5 (55.6)	0.90 [0.43; 2.49] 1.000 ^{ah}
Cough ^{an}	20	6 (30.0)	9	1 (11.0)	n.d. ^{ah}
Oropharyngeal pain ^{ao}	20	6 (30.0)	9	4 (44.0)	n.d. ^{ah}

a: Survey was carried out within the framework of safety.

b: Missing values at year 1 of subjects who dropped out before application of the test medication were imputed with 0.

c: Primary endpoint.

d: The difference of the observed mean changes from baseline was calculated. For the calculation of the 95% CI, the pharmaceutical company used a mixed model that includes terms for the treatment and the study visit (or time and treatment according to the external SAP). Specific information on the statistical model, for example on the covariance structure, could not be identified.

e: A Wilcoxon rank sum test with exact two-sided p value was used to examine the change at year 1 between the treatment groups compared to baseline.

f: A higher score in the mobility score means an improvement in the MLMT.

g: A p value of 0.002 is given in the dossier.

h: The mean change and p value were calculated using an MMRM with the terms treatment, study visit and treatment*study visit.

i: It was analysed averaged over both eyes for both treatment groups.

j: The more negative the value, the better the light sensitivity.

k: Secondary endpoint.

l: SMD according to Hedges' g was calculated for the endpoint FST with white light post hoc for Module 4.

m: According to the pharmaceutical company, the analysis should be performed on the ITT population. It remains unclear why data are missing for one subject in each of the two treatment groups.

n: Information on why year 1 results were reported by only 17 subjects in the intervention group and 9 subjects in the control group could not be identified.

o: It was analysed averaged over both eyes for both treatment groups.

p: The mean change and p value were calculated using an MMRM with the terms treatment, study visit and treatment*study visit.

q: A p value of 0.175 is given in the dossier.

r: It was analysed averaged over both eyes for both treatment groups.

s: The difference of the observed mean changes from baseline was calculated. A mixed model including treatment and study visit terms was used to calculate the 95% CI.

t: The two-sided p value was calculated post hoc using the Wilcoxon rank sum test. No imputations for missing values were performed.

u: Size of the stimulus III4e: Size: 4 mm², luminance: 315 cd/m²

v: For one subject in the intervention group, no reliable test results could be determined at baseline for both perimetry tests.

w: The SMD and Hedges' g were calculated post hoc for the dossier.

x: The SMD was calculated post hoc for the dossier Module 4 according to Hedges' g and Olkin.

y: Different start of the survey time point between the two groups: The survey started in the intervention group from the first injection and in the control group from the baseline investigation.

z: Effect estimator calculated post hoc using four-field table. The CI was calculated with an exact method.

aa: p value calculated post hoc using Fischer's exact test.

ab: According to the study protocol, a study-individual severity classification was made by the principal investigator.

ac: No effect estimators were calculated by the pharmaceutical company.

ad: Percentage self-calculated in relation to the ITT population. In the dossier Module 4, 33.3% of subjects with an improvement of at least 10 letters is given.

ae: Percentage self-calculated in relation to the ITT population. In the dossier Module 4, 22.2% of subjects with an improvement of at least 15 letters is given.

af: The information differs between the dossier Module 4 and the study report for SOC "Gastrointestinal disorders". The effect estimators shown in the table are taken from the previous benefit assessment. According to Module 4, AEs occurred in 13 subjects (65.0%) in the original intervention group and 3 subjects (33.3%) in the control group. The relative risk was 1.95 [95% CI: 0.84; 12.91] and the p value 0.226.

ag: The information differs between the dossier Module 4 and the study report for the PT "Nausea": According to Module 4, AEs occurred in 7 subjects (35.0%) in the original intervention group and 1 subject (11.1%) in the control group. The relative risk was 3.15 [95% CI: 0.60; 82.84] and the p value 0.371.

ah: In case of discrepancies between the current dossier Module 4 and the study report, the results from the previous procedure were reported.

ai: The information differs between dossier Module 4 and study report for SOC "Infections and infestations". The effect estimators shown in the table are taken from the previous benefit assessment. According to Module 4, AEs occurred in 12 subjects (60.0%) in the original intervention group and 5 subjects (55.6%) in the control group. The relative risk was 1.08 [95% CI: 0.56; 3.47] and the p value 1.000.

aj: According to the study report, lower respiratory tract infections occurred in only 1 subject (5.0%). However, in the dossier Module 4, 2 subjects (10.0%) are mentioned.

ak: The information differs between dossier Module 4 and study report for PT "Nasopharyngitis": According to Module 4, AEs occurred in 7 subjects (35.0%) in the original intervention group and 3 subjects (33.3%) in the control group. The relative risk was 1.05 [95% CI: 0.34; 6.56] and the p value 1.000.

al: The information differs between the dossier Module 4 and the study report for the PT "Headache": According to Module 4, AEs occurred in 8 subjects (40.0%) in the original intervention group and 2 subjects (22.2%) in the control group. The relative risk was 1.80 [95% CI: 0.54; 14.86] and the p value 0.431.

am: The information differs between the dossier Module 4 and the study report for SOC "Respiratory, thoracic and mediastinal disorders". The effect estimators shown in the table are taken from the previous benefit assessment. According to Module 4, AEs occurred in 13 subjects (65.0%) in the original intervention group and 6 subjects (66.7%) in the control group. The relative risk was 0.98 [95% CI: 0.54; 2.45] and the p value 1.000.

an: The information differs between the dossier Module 4 and the study report for the PT "Cough": According to Module 4, AEs occurred in 9 subjects (45.0%) in the original intervention group and 2 subjects (22.2%) in the control group. The relative risk was 2.03 [95% CI: 0.64; 15.92] and the p value 0.412.

ao: The information differs between the dossier Module 4 and the study report for the PT "Oropharyngeal pain": According to Module 4, AEs occurred in 7 subjects (35.0%) in the original intervention group and 4 subjects (44.4%) in the control group. The relative risk was 0.79 [95% CI: 0.30; 2.94] and the p value 0.694.

Abbreviations used:

dB = decibel; ETDRS = Early Treatment of Diabetic Retinopathy Study; FST = Full-field Stimulus Testing; ITT = Intention-To-Treat; year 1B = year 1 after treatment of the second eye in the intervention group; year 1C = year 1 after baseline in the control group; n.d. = no data available; CI = confidence interval; logMAR = logarithm of the minimum angle of resolution; MedDRA = Medical Dictionary for Regulatory Activities; MLMT = Multi-Luminance Mobility Test; MMRM = Mixed Model for Repeated Measures; MV = mean value; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; PT = preferred term; pU = pharmaceutical company; RR = relative risk; SAP = statistical analysis plan; SD = standard deviation, SE = standard error; SMD = standardised mean difference, SOC = system organ class; SAE = serious adverse event; AE = adverse event; vs = versus

LTFU study: non-randomised observational study (follow-up of patients from 301 study who received voretigene neparvovec until the data cut-off from 30 June 2020)

Mortality

LTFU study Endpoint	Original intervention group		Original control group	
	N	Patients with event n (%)	N	Patients with event n (%)
Overall survival/ mortality				
no deaths ^a				

Morbidity

LTFU study Endpoint	Original intervention group				Original control group			
	N at baseline ^b	N Year 1 ^c	N Year 3 ^c	N Year 5 ^c	N at baseline ^b	N Year 1 ^c	N Year 3 ^c	N Year 5 ^c
	Score at baseline ^b	Score at year 1 ^c	Score at year 3 ^c	Score at year 5 ^c	Score at baseline ^b	Score at year 1 ^c	Score at year 3 ^c	Score at year 5 ^c
	MV (SD) Median (min; max)	MV (SD) Median (min; max)	MV (SD) Median (min; max)	MV (SD) Median (min; max)	MV (SD) Median (min; max)	MV (SD) Median (min; max)	MV (SD) Median (min; max)	MV (SD) Median (min; max)
Multi-luminance mobility test (MLMT)^d (mITT population)								
MLMT score for both eyes (bilateral) ^e	20 3.3 (1.4) 3 (-1; 5)	20 5.2 (1.7) 6 (-1; 6)	20 5.1 (1.7) 6 (-1; 6)	18 4.9 (1.8) 6 (-1; 6)	9 3.6 ^f (1.4) ^f 4 ^f (1; 5) ^f	9 5.7 (1.0) 6 (3; 6)	8 6.0 (0.0) 6 (6; 6)	7 6.0 (0.0) 6 (6; 6)
Change (visit - baseline)	-	20 1.9 (1.0) 2 (0; 4)	20 1.8 (1.0) 2 (0; 3)	18 1.6 (1.1) 1.5 (1; 3)	-	9 2.1 (1.6) 2 (0; 5)	8 2.4 (1.5) 2 (1; 5)	7 2.4 (1.6) 2 (1; 5)

LTFU study Endpoint	Original intervention group				Original control group			
	N at baseline _b	N Year 1 ^c	N Year 3 ^c	N Year 5 ^c	N at baseline _b	N Year 1 ^c	N Year 3 ^c	N Year 5 ^c
	Score at baseline _b	Score at year 1 ^c	Score at year 3 ^c	Score at year 5 ^c	Score at baseline _b	Score at year 1 ^c	Score at year 3 ^c	Score at year 5 ^c
	MV (SD)	MV (SD)	MV (SD)	MV (SD)	MV (SD)	MV (SD)	MV (SD)	MV (SD)
Full-field stimulus threshold test (FST)^{g,i} (mITT population)								
White light (log ₁₀ (cd *s/m ²))	19 -1.3 (0.4)	20 -3.4 (1.5)	20 -3.3 (1.3)	18 -3.2 (1.3)	9 -1.6 ^h (0.5) ^h	9 -4.5 (1.5)	8 -4.5 (1.2)	7 -4.1 (1.3)
White light Change (visit - baseline)	-	19 -2.1 (1.6)	19 -2.0 (1.4)	17 -2.0 (1.5)	-	9 -2.9 (1.5)	8 -2.9 (1.1)	7 -2.6 (1.2)
Blue light (log ₁₀ (cd *s/m ²))	19 -1.7 (1.6)	17 -3.7 (1.6)	19 -3.7 (1.5)	18 -3.7 (1.4)	9 -1.9 (0.4)	9 -4.9 (1.5)	8 -5.0 (1.2)	7 -4.6 (1.5)
Blue light Change (visit - baseline)	-	17 -2.0 (1.8)	19 -2.1 (1.7)	17 -2.1 (1.6)	-	9 -3.0 (1.5)	8 -3.1 (1.1)	7 -2.8 (1.5)
Red light (log ₁₀ (cd *s/m ²))	19 -1.3 (0.4)	17 -2.6 (0.9)	19 -2.6 (0.8)	18 -2.5 (0.8)	9 -1.5 (0.5)	9 -3.2 (0.8)	8 -3.3 (0.7)	7 -3.0 (0.8)
Red light Change (visit - baseline)	-	17 -1.3 (0.9)	19 -1.3 (0.8)	17 -1.3 (0.8)	-	9 -1.6 (1.0)	8 -1.8 (0.7)	7 -1.6 (0.8)
Visual acuity^{i,j} (logMAR) (mITT population)								
ETDRS and HOTV eye chart, Holladay off-chart	20 1.1 (0.4)	20 1.0 (0.5)	20 1.0 (0.6)	18 1.1 (1.8)	9 1.0 ^k (0.3) ^k	9 0.9 (0.3)	8 0.9 (0.3)	7 0.8 (0.3)

LTFU study Endpoint	Original intervention group				Original control group			
	N at baseline _b	N Year 1 ^c	N Year 3 ^c	N Year 5 ^c	N at baseline _b	N Year 1 ^c	N Year 3 ^c	N Year 5 ^c
	Score at baseline _b	Score at year 1 ^c	Score at year 3 ^c	Score at year 5 ^c	Score at baseline _b	Score at year 1 ^c	Score at year 3 ^c	Score at year 5 ^c
	MV (SD)	MV (SD)	MV (SD)	MV (SD)	MV (SD)	MV (SD)	MV (SD)	MV (SD)
Change (visit - baseline)	-	20 -0.2 (0.3)	20 -0.2 (0.4)	18 0.0 (0.6)	-	9 -0.1 (0.2)	8 -0.1 (0.2)	7 -0.1 (0.3)
Visual field measurement using perimetryⁱ (MITT population)								
Goldman n: III4e (sum score) ^l	19 ^m 350.4 (416.9)	20 673.9 (423.7)	19 625.9 (413.3)	16 533.4 (428.5)	9 397.8 ⁿ (367.3) ⁿ	9 592.1 (296.6)	8 579.1 (247.8)	7 506.9 (219.8)
Change (visit - baseline)	-	19 320.1 (289.6)	18 282.2 (256.5)	15 166.6 (208.7)	-	9 194.3 (244.7)	8 157.9 (325.3)	7 188.9 (222.3)
Humphrey: Fovea Sensitivity (dB)	19 23.3 (5.5)	20 25.8 (9.1)	20 26.6 (8.1)	17 25.7 (8.1)	9 21.5 ^o (8.9) ^o	9 24.7 (9.4)	8 26.8 (4.1)	7 25.6 (9.4)
Change (visit - baseline)	-	19 2.4 (9.7)	19 3.0 (8.7)	16 1.2 (8.1)	-	9 3.2 (11.5)	8 4.7 (77.0)	7 4.7 (6.9)
Humphrey: Mean macula limit (dB)	19 16.6 (5.3)	20 24.0 (8.0)	20 22.9 (6.9)	18 21.7 (7.1)	9 15.8 ^p (7.4) ^p	9 21.0 (11.9)	8 23.0 (8.8)	7 23.3 (5.5)
Change (visit - baseline)	-	19 7.7 (6.2)	19 6.5 (5.8)	17 4.8 (6.7)	-	9 5.2 (9.9)	8 6.8 (6.4)	7 8.2 (5.2)

Health-related quality of life

LTFU study Endpoint	Original intervention group		Original control group	
	N	Patients with event n (%)	N	Patients with event n (%)
Visual function questionnaire				
No suitable data submitted.				

Side effects

LTFU study Endpoint	Original intervention group ^q			Original control group ^q		
	N	Patients with event n (%)		N	Patients with event n (%)	
		until year 1B ^s	until year 5 ^{v,w}		until year 1B ^s	until year 5 ^{v,w}
Side effects^r (injection given in first eye by year 1B^s or by year 5^{v,w}) (safety population)						
AE	20	20 (100.0)	20 (100.0)	9	9 (100.0)	9 (100.0)
Severe AE ^t	20	3 (15.0)	4 (20.0)	9	0 (0.0)	0 (0.0)
SAE	20	2 (10.0)	4 (20.0)	9	0 (0.0)	1 (11.1)
AEs that led to study discontinuation	20	0 (0.0)	0 (0.0)	9	0 (0.0)	0 (0.0)
AEs of special interest ^u	20	n.d.	n.d. ^x	9	n.d.	n.d. ^x

LTFU study MedDRA system organ class Preferred term	Original intervention group ^q			Original control group ^q		
	N	Patients with event n (%)		N	Patients with event n (%)	
		until year 1B	until year 5 ^w		until year 1B	until year 5 ^w
AEs^r with an incidence ≥ 15% in one of the study arms by year 1B^q or year 5^{q,w} (safety population)						
Blood and lymphatic system disorders	20	9 (45.0)	9 (45.0)	9	2 (22.2)	2 (22.2)
Leukocytosis	20	9 (45.0)	9 (45.0)	9	2 (22.2)	2 (22.2)
Eye disorders	20	10 (50.0)	11 (55.0)	9	6 (66.7)	6 (66.7)
Cataract	20	3 (15.0) ^y	5 (25.0)	9	0 (0.0)	1 (11.1)
Retinal deposits	20	0 (0.0)	0 (0.0)	9	3 (33.0)	3 (33.3)
Gastrointestinal disorders	20	12 (60.0)	12 (60.0)	9	5 (55.6)	5 (55.6)

LTFU study MedDRA system organ class Preferred term	Original intervention group ^a			Original control group ^a		
	N	Patients with event n (%)		N	Patients with event n (%)	
		until year 1B	until year 5 ^w		until year 1B	until year 5 ^w
Nausea	20	6 (30.0)	6 (30.0)	9	4 (44.4)	4 (44.4)
Vomiting	20	8 (40.0)	8 (40.0)	9	2 (22.2)	2 (22.2)
General disorders and administration site conditions	20	10 (50.0)	10 (50.0)	9	2 (22.2)	2 (22.2)
Fever	20	7 (35.0)	7 (35.0)	9	2 (22.2)	2 (22.2)
Infections and infestations	20	11 (55.0)	11 (55.0)	9	3 (33.3)	3 (33.3)
Nasopharyngitis	20	7 (35.0)	7 (35.0)	9	1 (11.1)	1 (11.1)
Injury, poisoning and procedural complications	20	5 (25.0)	5 (25.0)	9	2 (22.2)	2 (22.2)
Investigations	20	7 (35.0)	7 (35.0)	9	2 (22.2)	2 (22.2)
Increased intraocular pressure	20	4 (20.0)	4 (20.0)	9	1 (11.1)	1 (11.1)
Musculoskeletal and connective tissue disorders	20	1 (5.0)	1 (5.0)	9	2 (22.2)	2 (22.2)
Nervous system disorders	20	10 (50.0)	10 (50.0)	9	6 (66.7)	6 (66.7)
Headache	20	7 (35.0)	7 (35.0)	9	6 (66.7)	6 (66.7)
Psychiatric disorders	20	2 (10.0)	2 (10.0)	9	2 (22.2)	2 (22.2)
Anxiety	20	0 (0.0)	0 (0.0)	9	2 (22.2)	2 (22.2)
Renal and urinary disorders	20	3 (15.0)	3 (15.0)	9	0 (0.0)	0 (0.0)
Haematuria	20	3 (15.0)	3 (15.0)	9	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	20	3 (15.0)	3 (15.0)	9	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	20	10 (50.0) ^z	10 (50.0)	9	4 (44.4)	4 (44.4)
Cough	20	6 (30.0)	6 (30.0)	9	2 (22.2)	2 (22.2)
Inflammation of the nasal mucosa	20	2 (10.0)	2 (10.0)	9	2 (22.2)	2 (22.2)
Oropharyngeal pain	20	6 (30.0)	6 (30.0)	9	1 (11.1)	1 (11.1)
Skin and subcutaneous tissue disorders	20	2 (10.0) ^{aa}	1 (5.0)	9	4 (44.4)	4 (44.4)

a: Survey was carried out within the framework of safety.

b: Baseline is defined as the examination before the first injection. In the original intervention group, this corresponded to the time of the baseline examination at the start of the 301 study. In the original control group, the visit at year 1C of the 301 study was defined as baseline for the efficacy endpoints.

c: Year x after treatment of the second eye

d: A higher score in the mobility score means an improvement in the MLMT.

e: The values for the visits were only reported in the dossier Module 4.

f: The value at study baseline (baseline at the start of the 301 study) was an average of 3.3 (SD 0.9) or a median of 3 (min; max: 2; 5).

g: The more negative the value, the better the light sensitivity. Only the observed values were reported.

h: The value at study baseline (baseline at the start of the 301 study) was -1.7 (SD 0.4) on average.

i: It was analysed averaged over both eyes for both treatment groups.

j: Visual acuity was presented for both eye charts together (ETDRS, HOTV eye chart) and off-chart analyses (according to Holladay), if applicable.

k: The value at study baseline (baseline at the start of the 301 study) was an average of 1.0 (SD 0.3) or a median of 3 (min; max: 2; 5).

l: Size of the stimulus III4e: Size: 4 mm², luminance: 315 cd/m².

m: For 1 subject in the intervention group, no reliable test results could be determined at baseline.

n: The value at study baseline (baseline at the start of the 301 study) was on average 474.5 degrees (SD 361.0).

o: The value at study baseline (baseline at the start of the 301 study) was 19.2 (7.8) on average.

p: The value at study baseline (baseline at the start of the 301 study) was 15.8 (7.4) on average.

q: In Module 4, AEs are given for the period between injection into the first eye until year 1B and injection into the first eye until year 5 (= time of the last injection + 1,825 days). However, no data on (median) observation periods could be identified. For the original intervention group, the mean observation period was 406.6 days (SD: 20.4) between day of first injection and year 1 after second injection.

r: According to the SAP (22 June 2016), in the LTFU study, a complete assessment of AEs was only planned up to year 1B, but not as part of a long-term assessment for the entire observation period; from year 1B onwards, only specific AEs, namely SAEs, AEs possibly or probably related to the administration of the test preparation, and new or deteriorating AEs in one of the 4 categories (oncological, haematological, neurologic events and/or autoimmune diseases) were to be recorded in the CRF. As of study protocol version 2 (15 June 2018), it is only stated that the documentation of AEs focuses on specific AEs. It remains unclear to what extent or from when no complete assessment of AEs took place in the LTFU study.

s: For the original intervention group, the period "injection given in the first eye until year 1B" corresponds to the observation period of the 301 study. During this period, a complete assessment of the AEs was planned. For the original control group, AEs are recorded from the start of the LTFU study (from injection into the first eye).

t: Study-individual classification of severity grade: If possible, according to the study protocol, a severity grade classification (grade 1-4) should be made in orientation of the WHO toxicity scale. In addition, the pharmaceutical company has defined severity grades for ophthalmological AEs based on this classification.

u: New or deteriorating AEs of the 4 categories mentioned above were defined as AEs of special interest post hoc in the interim study report 2020.

v: In Module 4, calculated post hoc: year 5 corresponds to the time of the last injection + 1,825 days.

w: For the original intervention group, the observation period from the 301 study (from injection in the first eye) is included in the presentation "injection given in the first eye until year 5". For the original control group, AEs are recorded from the start of the LTFU study (from injection into the first eye).

x: According to the 2020 interim study report, 2 AEs (paraesthesia in 1 subject in the original control group; convulsions in 1 subject in the original intervention group) that were not classified as AESIs in the previous interim study reports were labelled as such in the new study report.

y: According to dossier Module 4, the AEs according to PT "cataract" was observed in only 1 subject (5.0%).

z: According to dossier Module 4, the AEs SOC "Respiratory, thoracic and mediastinal disorders" was observed in 9 subjects (45.0%).

aa: According to dossier Module 4, the AEs SOC "Skin and subcutaneous tissue disorders" was observed in only 1 subject (5.0%).

Abbreviations used:

AESI = adverse events of special interest; dB = decibel; ETDRS = Early Treatment of Diabetic Retinopathy Study; FST = Full-field Stimulus Testing; Year 1B = year 1 after treatment of the second eye in the intervention group; n.d. = no data available; logMAR = logarithm of the minimum angle of resolution; LTFU = Long-Term Follow-up; MedDRA = Medical Dictionary for Regulatory Activities; mITT = modified Intention-To-Treat; MLMT = Multi-Luminance Mobility Test; MV = mean value; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; PT = preferred term; pU = pharmaceutical company; RR = relative risk; SAP = statistical analysis plan; SD = standard deviation, SE = standard error; SMD = standardised mean difference, SOC = system organ class; SAE = serious adverse event; AE = adverse event; vs = versus

2. Number of patients or demarcation of patient groups eligible for treatment

Adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells

approx. 100 - 530 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Luxturna (active ingredient: voretigene neparvovec) at the following publicly accessible link (last access: 22 August 2022):

https://www.ema.europa.eu/en/documents/product-information/luxturna-epar-product-information_en.pdf

Treatment with voretigene neparvovec should only be initiated and monitored by retinal surgeons experienced in performing macular surgery.

In accordance with the requirements of the European Medicines Agency (EMA) regarding additional risk minimisation measures, the pharmaceutical company must provide training material for medical professionals (e.g., retinal surgeons- and pharmacists) and a patient identification card. The training material contains, in particular, instructions for preparing and performing intraocular, subretinal application of voretigene neparvovec in a surgical setting under anaesthesia. The patient card shall be provided in specific formats, including large print format and audio file.

The Risk Management Plan (RMP) details that the training material for medical professionals contains relevant information on the preparation, storage and use of voretigene neparvovec including a description of the materials as well as subretinal administration.

To minimise safety risks associated with treatment with voretigene neparvovec, the aim is to ensure that treatment facilities preparing and administering voretigene neparvovec treatment comply with the criteria approved by the EMA and to be implemented in accordance with the risk management plan. The personnel involved in the administration (i.e.

vitreoretinal surgeons and pharmacists) have participated in a mandatory training programme on the use of voretigene neparvovec to ensure the correct use of voretigene neparvovec to minimise the risks associated with its administration and/or the administration procedure (increased intraocular pressure, retinal tear, macular disease, cataract, intraocular inflammation and/or infection associated with the procedure and retinal detachment, third party transmission).

The criteria for treatment facilities should include the following:

- Presence of a specialised ophthalmologist with expertise in the care and treatment of patients with inherited retinal dystrophy.
- Attendance or affiliation with a retinal surgeon experienced in subretinal surgery and competent to administer voretigene neparvovec.
- An anti-inflammatory concomitant medication should be prescribed according to the product information.
- The interval for the treatment of the second eye should be planned according to the product information.

4. Treatment costs

Annual treatment costs:

Adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells

Designation of the therapy	Annual treatment costs/ patient (for both eyes)
Medicinal product to be assessed:	
Voretigene neparvovec	€ 702,100.00
Vitrectomy including subretinal injection	approx. € 6,250.38 ²
Pre and postoperative immunomodulatory treatment with prednisone	€ 18.34
Additionally required SHI services	non-quantifiable ³

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 01 September 2022)

² Shown are the costs for an inpatient procedure.

³ Due to the individual specification of the intervals for control examinations by the attending physician, the costs incurred cannot be quantified.