

Supplementary Table S1. Study schedule excerpt

Period	Screening Period	Duration of Investigational Drug Administration							
Timing of Implementation	Pre-Registration	Start Date of Administration	Week 4	Week 13	Week 26	Week 39	Week 52	Week 65	Week 78
Medication Confirmation			○	○	○	○	○	○	○
ETRS visual acuity test		○							○
HFA 10-2	○ ^{*1}			○	○	○	○	○	○ ^{*1}
HFA 30-2		○ ^{*1}							○ ^{*1}
OCT		○							○
Fundus photography	○								○

*1: If reliable data cannot be obtained, a single retest will be conducted within two weeks. Exceeding the allowable limits is acceptable for the retest. However, for the pre-registration Humphrey Visual Field Test (10-2), retesting should also be conducted before registration, whereas for the pre-dosing Humphrey Field Test (30-2), retesting should be conducted before the start of dosing.

ETDRS, Early Treatment Diabetic Retinopathy Study; HFA, Humphrey visual field test 30-2; OCT, Optical coherence tomography.

Supplementary Table S2. Presumed causative genes

Presumed causative gene, n patients (%)	TK-98 (n = 45 patients)	Placebo (n = 25 patients)	Total (n = 70 patients)
Confirmed cases of causative genes	17 (37.8)	13 (52.0)	30 (42.9)
<i>EYS</i>	8 (17.8)	9 (36.0)	17 (24.3)
<i>RHO</i>	2 (4.4)	0 (0.0)	2 (2.9)
<i>PDE6B</i>	1 (2.2)	1 (4.0)	2 (2.9)
<i>RP1L1</i>	2 (4.4)	0 (0.0)	2 (2.9)
<i>RPGR</i>	1 (2.2)	1 (4.0)	2 (2.9)
<i>USH2A</i>	1 (2.2)	1 (4.0)	2 (2.9)
<i>CNGA1</i>	1 (2.2)	0 (0.0)	1 (1.4)
<i>NR2E3</i>	0 (0.0)	1 (4.0)	1 (1.4)
<i>PRPH2</i>	1 (2.2)	0 (0.0)	1 (1.4)
Not determined	3 (6.7)	2 (8.0)	5 (7.1)
Unclear	25 (55.6)	10 (40.0)	35 (50.0)

Presumed causative genes of the full analysis set (FAS). *EYS*, eyes shut homolog; *RHO*, rhodopsin; *PDE6B*, phosphodiesterase 6B; *RP1L1*, RP1 like 1; *RPGR*, retinitis pigmentosa GTPase regulator; *USH2A*, usherin; *CNGA1*, cyclic nucleotide-gated channel subunit alpha 1; *NR2E3*, nuclear receptor subfamily 2 group E member 3; *PRPH2*, peripherin 2.

Supplementary Table S3. Baseline characteristics of the patients in the PPS population

Characteristic	TK-98 (n = 44 patients)		Placebo (n = 25 patients)		Total (n = 69 patients)		Intergroup comparison
	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	p
Sex, n patients (%)							
Female	23 (52.3)		14 (56.0)		37 (53.6)		0.806
Male	21 (47.7)		11 (44.0)		32 (46.4)		
Age at time of inclusion, y	51.3 ± 11.6	53.0 (21, 77)	51.6 ± 14.2	50.0 (26, 75)	51.4 ± 12.5	52.0 (21, 77)	0.913
MD value* at the time of allocation (average for binocular cases), dB	-14.70 ± 4.88	-14.36 (-23.14, -5.12)	-14.67 ± 5.12	-13.08 (-23.96, -5.91)	-14.69 ± 4.93	-13.98 (-23.96, -5.12)	0.981
Unilateral and binocular cases							0.054
Unilateral	1 (2.3)		4 (16.0)		5 (7.2)		
Binocular	43 (97.7)		21 (84.0)		64 (92.8)		
Genetic form, n patients (%)							0.434
Autosomal dominant	10 (22.7)		2 (8.0)		12 (17.4)		
Autosomal recessive	17 (38.6)		12 (48.0)		29 (42.0)		
X-linked	1 (2.3)		1 (4.0)		2 (2.9)		
Sporadic	16 (36.4)		10 (40.0)		26 (37.7)		
Presumed causative gene, n patients (%)							
Confirmed cases of causative genes	16 (36.4)		13 (52.0)		29 (42.0)		0.218
<i>EYS</i>	8 (18.2)		9 (36.0)		17 (24.6)		0.146
Time from onset of first subjective symptoms†, y	28.6 ± 13.2	29.5 (3, 59)	27.0 ± 12.3	25.0 (9, 67)	28.0 ± 12.8	28.0 (3, 67)	0.618

Baseline characteristics of the patients in the per protocol set (PPS). *Calculated using mean deviation (MD) values observed up to 3 years prior to the time of observation at the start of the study (including the time of observation at the start of the pretreatment period). †Time since onset of any of the following symptoms: night blindness, narrowing of the field of vision, loss of vision, or photophobia. dB, decibel; *EYS*, eyes shut homolog; SD, standard deviation.

Supplementary Table S4. Baseline characteristics of the eyes in the PPS population

Characteristic	TK-98 (n = 87 eyes)		Placebo (n = 46 eyes)		Total (n = 133 eyes)		Intergroup comparison
	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	p
Lens, n eyes (%)							0.004
Phakia	75 (86.2)		29 (63.0)		104 (78.2)		
Pseudophakia	12 (13.8)		17 (37.0)		29 (21.8)		
Humphrey visual field test 10-2							
TPS, dB	1229.2 ± 329.6	1212.0 (615, 1901)	1245.3 ± 363.7	1284.0 (586, 1836)	1238.6 ± 339.5	1222.0 (586, 1901)	0.659
MD value, dB	-14.8 ± 4.9	-14.5 (-23.7, -5.0)	-14.4 ± 5.2	-13.9 (-24.0, -5.6)	-14.6 ± 5.0	-14.2 (-24.0, -5.0)	0.549
MD slope*, dB/y	-0.11 ± 0.92	-0.27 (-1.98, 3.44)	-0.52 ± 1.05	-0.45 (-4.27, 1.21)	-0.21 ± 0.92	-0.37 (-3.46, 3.44)	0.071
Humphrey visual field test 30-2							
TPS, dB	482.4 ± 350.7	358.0 (80, 1628)	458.2 ± 306.8	343.0 (101, 1223)	478.1 ± 336.3	361.5 (80, 1628)	0.838
Ellipsoid zone length, μm	1557.4 ± 1362.3	1460.5 (0.0, 5042.5)	2028.0 ± 1308.2	1913.5 (0.0, 5861.0)	1720.2 ± 1357.6	1649.5 (0.0, 5861.0)	0.057
Visual acuity (ETDRS)							
Readable letter count	65.7 ± 17.0	71.0 (17, 86)	69.1 ± 15.1	73.0 (9, 87)	67.3 ± 15.7	72.0 (17, 87)	0.120
LogMAR	0.34 ± 0.30	0.26 (-0.12, 1.18)	0.28 ± 0.27	0.22 (-0.06, 1.38)	0.32 ± 0.28	0.24 (-0.12, 1.18)	0.114
Preserved retinal area, mm ²	18.7 ± 15.0	14.8 (1.6, 58.1)	17.8 ± 12.6	14.5 (2.3, 41.9)	18.4 ± 14.1	14.6 (1.6, 58.1)	0.739

Baseline characteristics of the eyes in the per protocol set (PPS). *Calculated using mean deviation (MD) values observed up to 3 years prior to the time of observation at the start of the study (including the time of observation at the start of the pretreatment period). dB, decibel; TPS, total point score; ETDRS, Early Treatment Diabetic Retinopathy Study; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation.

Supplementary Table S5. Number of valid Humphrey visual field tests (10-2)

Number of valid tests	TK-98 (n = 88 eyes)	Placebo (n = 46 eyes)
	n (%)	n (%)
7	69 (78.4)	37 (80.4)
6	11 (12.5)	7 (15.2)
5	4 (4.5)	2 (4.3)
4	3 (3.4)	0 (0.0)
3	1 (1.1)	0 (0.0)
2	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)
0	0 (0.0)	0 (0.0)

The number of times a valid test result was obtained out of 7 visual field tests (10-2) set in the trial.

Supplementary Table S6. Secondary outcome measurements in the PPS population

		TK-98					Placebo					Intergroup comparison	
	Case	Eye	Mean ± SD	Median (Range)	Least-squares mean ± SE	Case	Eye	Mean ± SD	Median (Range)	Least-squares mean ± SE	Difference in Least-squares mean (95% CI)	p	
Humphrey visual field test 10-2													
TPS, dB	CA	44	87	-47.9 ± 59.4	-39.7 (-183.6, 117.5)	-47.5 ± 8.3	25	44	-35.4 ± 63.4	-37.1 (-192.7, 113.4)	-37.8 ± 11.3	-9.8 (-37.7, 18.2)	0.488
	CR	44	87	-4.2 ± 5.4	-4.0 (-19.0, 9.9)	-4.2 ± 0.8	25	44	-3.6 ± 6.6	-2.9 (-29.8, 7.3)	-3.7 ± 1.1	-0.5 (-3.2, 2.1)	0.686
MD value, dB	CA	44	87	-0.67 ± 0.91	-0.60 (-2.93, 1.90)	-0.66 ± 0.13	25	44	-0.52 ± 0.99	-0.57 (-3.18, 1.72)	-0.57 ± 0.17	-0.09 (-0.52, 0.34)	0.675
	CR	44	87	-5.2 ± 7.6	-4.2 (-26.3, 13.0)	-5.1 ± 1.2	25	44	-3.8 ± 9.6	-4.4 (-28.1, 27.7)	-4.1 ± 1.6	-1.0 (-4.9, 2.9)	0.621
Humphrey visual field test 30-2													
TPS, dB	CA	44	85	-37.8 ± 57.6	-21.7 (-241.9, 47.4)	-38.0 ± 7.5	25	43	-21.9 ± 57.9	-19.7 (-237.9, 145.6)	-20.1 ± 10.3	-17.8 (-43.1, 7.5)	0.165
	CR	44	85	-6.4 ± 10.8	-5.4 (-30.9, 29.5)	-6.3 ± 1.4	25	43	-6.4 ± 12.9	-5.4 (-40.3, 20.6)	-6.1 ± 2.0	-0.2 (-5.0, 4.6)	0.934
Visual acuity (ETDRS)													
Readable letter count	CA	44	87	-1.1 ± 2.9	-0.7 (-13.9, 4.0)	-1.1 ± 0.3	25	44	-0.7 ± 2.8	-0.7 (-8.5, 6.6)	-0.8 ± 0.5	-0.3 (-1.4, 0.8)	0.631
	CR	44	87	-2.3 ± 7.3	-1.3 (-38.5, 15.5)	-2.2 ± 0.8	25	44	-0.8 ± 4.6	-0.9 (-12.2, 12.7)	-1.0 ± 1.0	-1.3 (-3.9, 1.3)	0.322
LogMAR	CA	44	87	0.026 ± 0.072	0.013 (-0.079, 0.396)	0.026 ± 0.008	25	44	0.019 ± 0.062	0.013 (-0.132, 0.198)	0.020 ± 0.011	0.006 (-0.022, 0.033)	0.679
	CR	44	87	16.6 ± 57.1	4.0 (-39.6, 330.2)	12.0 ± 4.3	25	44	20.1 ± 56.5	8.3 (-31.5, 337.6)	17.1 ± 6.0	-5.2 (-19.8, 9.5)	0.485
Ellipsoid zone length, μm	CA	44	87	-77.1 ± 66.5	-72.0 (-371.2, 0.0)	-77.5 ± 9.0	25	46	-95.6 ± 78.3	-80.4 (-344.1, 0.0)	-95.5 ± 12.2	17.9 (-12.4, 48.2)	0.241
	CR	41	74	-8.7 ± 9.2	-4.8 (-46.4, -0.6)	-9.4 ± 1.3	25	44	-6.9 ± 7.7	-4.0 (-33.2, -0.1)	-7.4 ± 1.7	-2.0 (-6.2, 2.3)	0.362
Preserved retinal area, mm ²	CA	44	84	-0.92 ± 0.88	-0.64 (-3.57, -0.01)	-0.93 ± 0.14	25	46	-0.96 ± 1.19	-0.36 (-5.29, -0.01)	-0.97 ± 0.18	0.05 (-0.41, 0.51)	0.843
	CR	44	84	-5.5 ± 4.4	-4.1 (-22.0, -0.1)	-5.5 ± 0.5	25	46	-4.9 ± 3.7	-3.7 (-13.8, -0.3)	-4.9 ± 0.7	-0.6 (-2.4, 1.1)	0.483

Main second outcome measurements in the per protocol set (PPS) population. All changes (amount of change, CA) were changes per year. The change rate (CR) is the amount of change divided by the absolute value of the initial measurement and multiplied by 100. The least squares mean is the mean of each group estimated in a mixed-effects model that accounts for binocular correlation. Because cataract progression was observed in two eyes in the placebo group, these eyes were excluded from the analysis of the visual field and visual acuity tests in the PPS population. TPS, total point score; dB, decibel; MD, mean deviation; ETDRS, Early Treatment Diabetic Retinopathy Study; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation; SE, standard error; CI, confidence interval. The p-values represent the results of a two-tailed test of the null hypothesis "the difference between the least squares means of the two groups is zero" at a significance level of $\alpha = 0.05$.

Supplementary Table S7. Adverse events in the eyes

Event	TK-98 (n = 45 patients)	Placebo (n = 25 patients)	Difference (95% CI)	p
	n (%)	n (%)		
Blepharitis	1 (2.2)	0 (0.0)	2.2 (-22.3, 26.5)	1.000
Cataract	0 (0.0)	3 (12.0)	-12.0 (-35.7, 12.5)	0.042
Chalazion	1 (2.2)	0 (0.0)	2.2 (-22.3, 26.5)	1.000
Conjunctivitis	1 (2.2)	1 (4.0)	-1.8 (-26.1, 22.6)	1.000
Allergic conjunctivitis	1 (2.2)	0 (0.0)	2.2 (-22.3, 26.5)	1.000
Superficial Punctate Keratopathy	1 (2.2)	0 (0.0)	2.2 (-22.3, 26.5)	1.000
Foreign body	0 (0.0)	1 (4.0)	-4.0 (-28.2, 20.5)	0.357
Macular edema	3 (6.7)	0 (0.0)	6.7 (-18.0, 30.7)	0.548
Decrease in visual acuity	5 (11.1)	1 (4.0)	7.1 (-17.5, 31.0)	0.410
Worsening of visual field	39 (86.7)	21 (84.0)	2.7 (-21.8, 26.9)	0.737
Epiretinal membrane	2 (4.4)	0 (0.0)	4.4 (-20.1, 28.6)	0.534
Total	39 (86.7)	22 (88.0)		

Adverse events corresponding to eye damage, regardless of severity, in the safety analysis set (SAF) population. "Decrease in visual acuity" was defined as worsening of 0.3 logarithm of the minimum angle of resolution (logMAR) or greater compared to the beginning of the study. "Worsening of visual field" addressed negative mean deviation slopes on the Humphrey 10-2 tests during the study period. The p-value was based on the Fisher's exact test. CI, confidence interval.