Subretinal AGTC-501 Gene Therapy for XLRP: 24-Month Interim Results of the Phase 2 SKYLINE Trial

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Key Takeaways
Phase 2 SKYLINE 24-Month Interim Analysis

- XLRP is a severe, aggressive, inherited retinal disease characterized by progressive photoreceptor degeneration; the majority of XLRP is due to mutations in the RPGR gene
- AGTC-501 is an investigational gene therapy for XLRP with a proprietary capsid designed for high transduction of a codon-optimized, full-length RPGR gene
- AGTC-501 shows robust improvements in retinal sensitivity as assessed by MAIA microperimetry to 24 months
- AGTC-501 was generally safe and well tolerated with no ocular SAEs deemed related to AGTC-501
- Follow-up is ongoing through 5 years to assess long-term safety and durability of response

MAIA = macular integrity assessment; SAE = Serious Adverse Event; TEAE: Treatment Emergent Adverse Events

X-Linked Retinitis Pigmentosa (XLRP)

Progressive photoreceptor degeneration that leads to blindness with no treatment options

Severe, aggressive, inherited retinal disease characterized by progressive photoreceptor degeneration[1]

Majority of XLRP is due to mutations in the RPGR gene[2]

Affects primarily young males with estimated prevalence of 3.4-4.4 per 100,000 males in US/Europe/Australia with RPGR mutations[3]

Early symptoms include night blindness and peripheral vision loss, progressing to central vision loss and legal blindness by median age of 45[1]

Childhood → 20-30s → 40-50s

Early	Mid-Stage	Late Stage
Night blindness, early changes in peripheral vision[2]	Increasing loss in peripheral vision[4]	Tunnel vision, central VA loss[6]
Difficulties in low light environments[2]	Difficulties driving, running into objects, difficulty with daily tasks[1,5]	Legal blindness, significant impact on daily life, loss of autonomy[1,4,5]

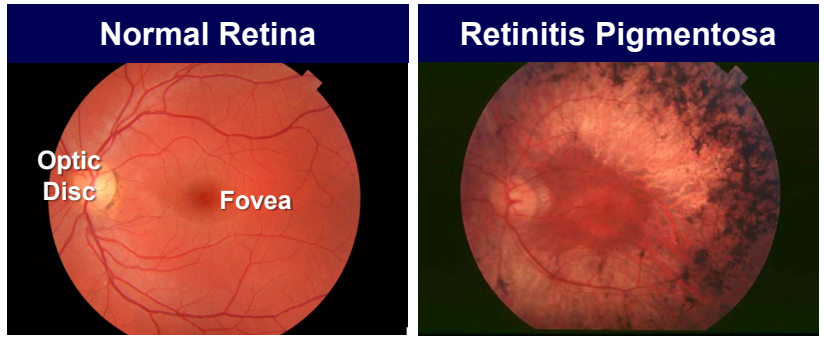
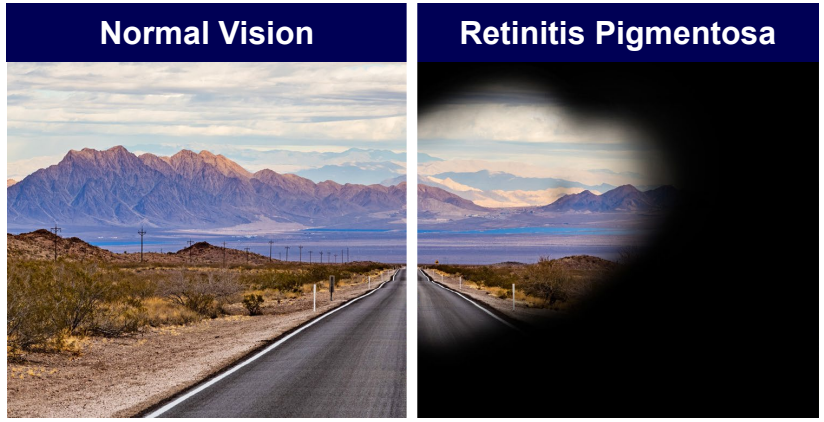


Image by Mikael Häggström[7]

Image from Hamel[8]

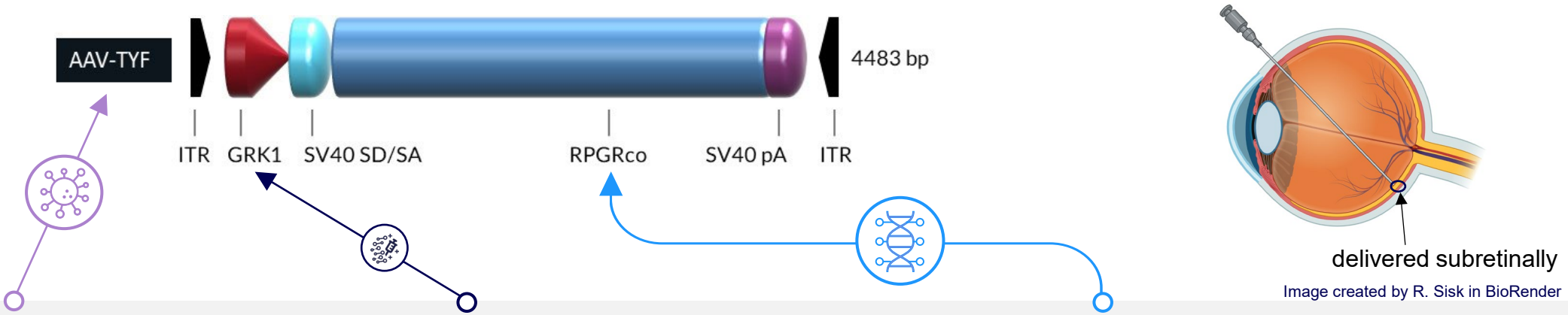


VA=visual acuity

1. Chivers M, et al. *Clinicoecon Outcomes Res*. 2021;13:565-572. 2. Churchill JD, et al. *Invest Ophthalmol Vis Sci*. 2013;54(2):1411-1416. 3. Vinikoor-Imler LC, et al. Ophthalmic Genet. 2022 Oct;43(5):581-588 4. Di Iorio V, et al. *Invest Ophthalmol Vis Sci*. 2020;61(14):36. 5. Senthil MP, et al. *Eye (Lond)*. 2017;31(5):741-748. 6. O'Neal TB, et al. Retinitis Pigmentosa. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519518/ 7. Research Gate. Medical gallery of Mikael Haggstrom 2014. Accessed September 10, 2024. https://www.researchgate.net/publication/274290673_Medical_gallery_of_Mikael_Haggstrom_2014 8. Hamel C. *Orphanet J Rare Dis*. 2006;1:40.

Overview of AGTC-501 Gene Therapy for XLRP

Proprietary capsid designed for high transduction of codon-optimized, full-length transgene



CAPSID

Proprietary capsid AAV2tYF for high transduction

PROMOTER

Photoreceptor specific GRK1 promoter

CODON-OPTIMIZED GENE

Codon-optimized, stable, full-length RPGRORF15 gene

As a full-length RPGR gene therapy, AGTC-501 has a higher probability of restoring natural function of both rods and cones, possibly yielding greater visual improvement[1,2]

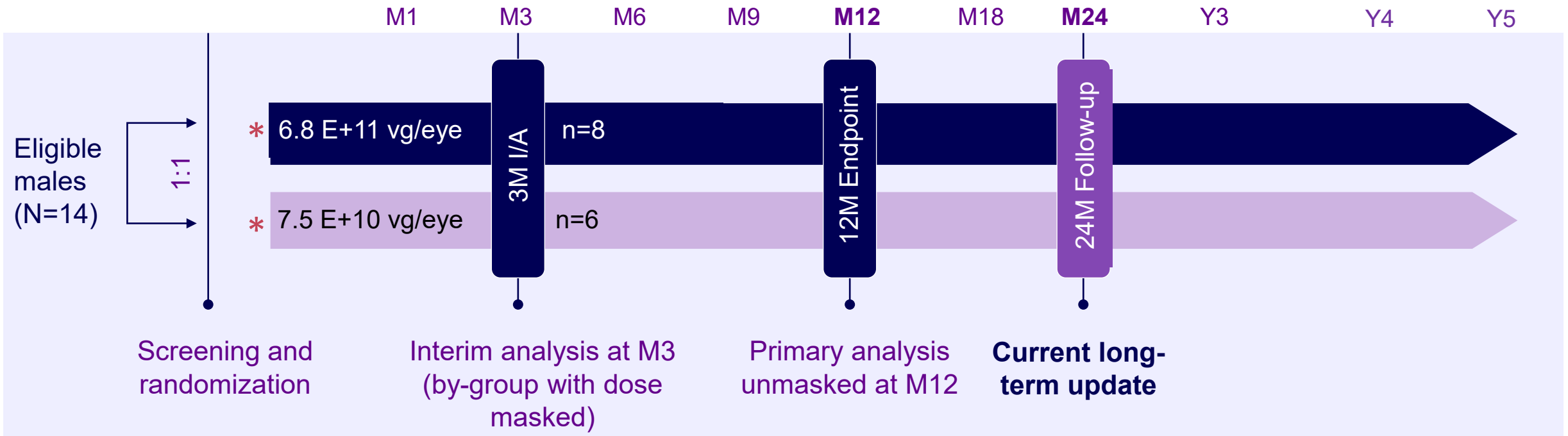
Received Innovative Medicine Designation (ILAP) in the UK, Priority Medicine (PRIME) in the EU, and Fast Track in the US

RPGR=retinitis pigmentosa GTPase regulator; AAV=adeno-associated virus; GRK1=rhodopsin kinase

1. Cehajic-Kapetanovic J, et al. *Proc Natl Acad Sci U S A*. 2022;119(49):e2208707119. 2. Wu Z, et al. *Hum Mol Genet*. 2015;24(14):3956-3970.

Phase 2 SKYLINE Study Design

Randomized, Controlled, Multicenter Study to Evaluate the Safety, Efficacy, and Tolerability of AGTC-501 in Patients with XLRP caused by *RPGR* mutations



FPI: 13 April 2021; 5-year follow-up post treatment

*All patients centrally dosed

XLRP = X-linked Retinitis Pigmentosa; vg/eye = vector genomes / eye; FPI = First Patient In

Key Eligibility Criteria

	Inclusion	Exclusion
Ocular Study eye must meet all ocular inclusion criteria	• BCVA between 35 and 75 letters (ETDRS chart) at each screening visit • Detectable baseline mean macular sensitivity measured by MAIA microperimetry, between 1-12 dB • Detectable EZ line in both eyes	• Variable baseline mean macular sensitivity >2 dB between last 2 microperimetry screening assessments • Myopia (spherical equivalent) exceeding -10 diopters or pathologic myopia in study eye
General	• Males aged 8 – 50 years with clinical diagnosis of XLRP	

BCVA = Best Corrected Visual Acuity; ETDRS = Early Treatment of Diabetic Retinopathy Study; XLRP = X-linked Retinitis Pigmentosa; MAIA = macular integrity assessment

Phase 2 SKYLINE Endpoints

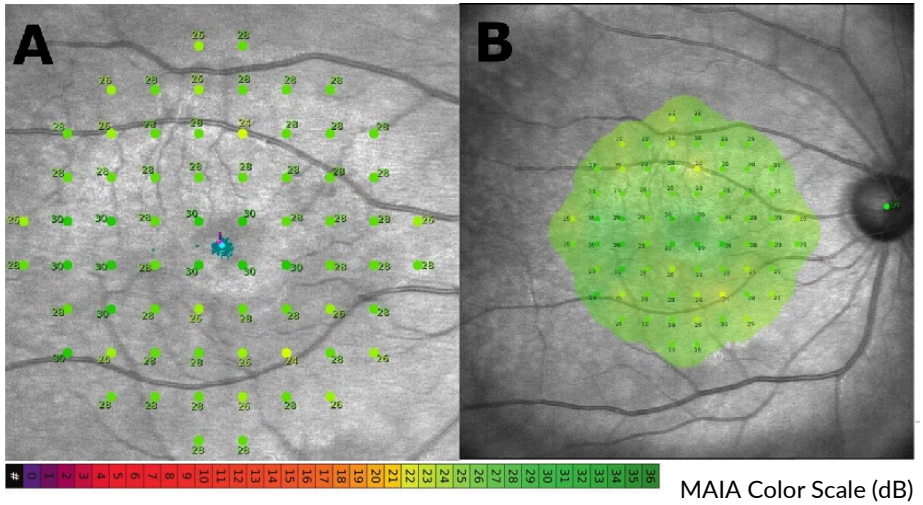
Primary Efficacy Endpoint

- Proportion of response by microperimetry between study and fellow eye at Month 12:
  - Response defined as ≥ 7 dB improvement in ≥ 5 loci (microperimetry via MAIA)

Secondary Endpoints

- Change from baseline (CFB) at Month 12 in:
  - Mean sensitivity by microperimetry (MAIA)
  - Full-field light sensitivity Threshold (FST) – White, Red and Blue
  - Maze (mobility score assessed by the Ora-VNC™ mobility course)
    - defined as “improvement of ≥2 luminance levels”
  - BCVA (ETDRS)
- Safety

Images adapted from Josan[1]



Microperimetry example of a healthy patient

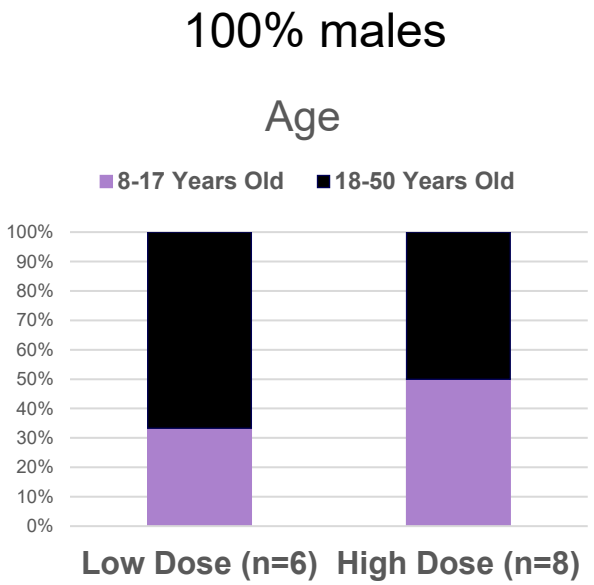
ETDRS = Early Treatment of Diabetic Retinopathy Study; BCVA = Best Corrected Visual Acuity; MAIA = macular integrity assessment; VNC = Visual Navigation Challenge

1. Josan AS, et al. *Transl Vis Sci Technol. 2021*;10(7):12, https://doi.org/10.1167/tvst.10.7.12

Phase 2 SKYLINE Demographics and Baseline Characteristics

Groups were well matched

N = 14



	Low Dose (n=6)	High Dose (n=8)
Mean (SD)	**22.8 (6.52)**	**22.1 (8.68)**
Range	**17, 33**	**13, 36**

Endpoints	Low Dose (7.5 E+10 vg/eye) (N=6)		High Dose (6.8 E+11 vg/eye) (N=8)	
	SE	FE	SE	FE
BCVA (ETDRS letters)	**68.3 (3.20)** 63, 73	**73.2 (1.72)** 71, 75	**66.5 (6.52)** 57, 74	**71.1 (5.14)** 64, 77
Ora-VNC Mobility Passing Score (1-16)	**13.2 (2.56)** 10, 16	**13.8 (2.48)** 11, 16	**11.4 (2.62)** 6, 14	**11.5 (1.20)** 9, 13
Mean Sensitivity (whole grid)[1] (dB)	**5.23 (2.608)** 2.6, 10.0	**4.94 (2.902)** 2.1, 10.5	**4.05 (2.279)** 1.5, 7.6	**3.97 (2.073)** 2.1, 8.1
Full-Field Light Sensitivity Threshold (FST) - White (dB)	**-41.72 (12.748)** -52.0, -17.4	**-42.48 (11.968)** -50.7, -19.9	**-21.75 (9.423)** -31.2, -8.3	**-26.29 (11.332)** -39.8, -11.4
Statistics presented are mean (SD), range				

SE = Study eye (treated); FE = Fellow eye (untreated); ETDRS = Early Treatment of Diabetic Retinopathy Study; BCVA = Best Corrected Visual Acuity; VNC = Visual Navigation Challenge; vg/eye = vector genomes / eye

1. Microperimetry by MAIA

Ocular Serious Adverse Events (SAEs) at Month 24

No Ocular SAEs were deemed Related to AGTC-501

Ocular Serious Adverse Events (SAE)	Low Dose (7.5 E+10 vg/eye) (n=6)		High Dose (6.8 E+11 vg/eye) (n=8)		All Patients (n=14)	
	Study Eye	Fellow Eye	Study Eye	Fellow Eye	Study Eye	Fellow Eye
# of Patients with Any SAE	2	0	0	0	2	0
Glaucoma*	1	0	0	0	1	0
Visual impairment**	1	0	0	0	1	0

*Related to protocol required corticosteroids; severe; treated with medication; resolved by Study Day 181
**Related to injection procedure; ongoing

vg/eye = vector genomes / eye

Ocular Treatment-emergent Adverse Events (TEAEs) Related to AGTC-501 at Month 24

Ocular Treatment-emergent Adverse Event (TEAE)	Low Dose (7.5 E+10 vg/eye) (n=6)		High Dose (6.8 E+11 vg/eye) (n=8)		All Patients (n=14)	
	Study Eye	Fellow Eye	Study Eye	Fellow Eye	Study Eye	Fellow Eye
# of Patients with Any Ocular TEAE Related to AGTC-501	3	0	2	0	5	0
Vitritis	1	0	2	0	3	0
Eye pain	1	0	0	0	1	0
Metamorphopsia	1	0	0	0	1	0
Photopsia	1	0	0	0	1	0
Visual acuity reduced	1	0	0	0	1	0

- Overall, ocular treatment-emergent adverse events (TEAEs) were mostly non-serious, mild or moderate in severity, and rates were similar between high dose and low dose groups

- Ocular TEAEs related to AGTC-501 were considered mild or moderate in severity
  - Most ocular TEAEs related to the injection procedure were considered mild or moderate in severity

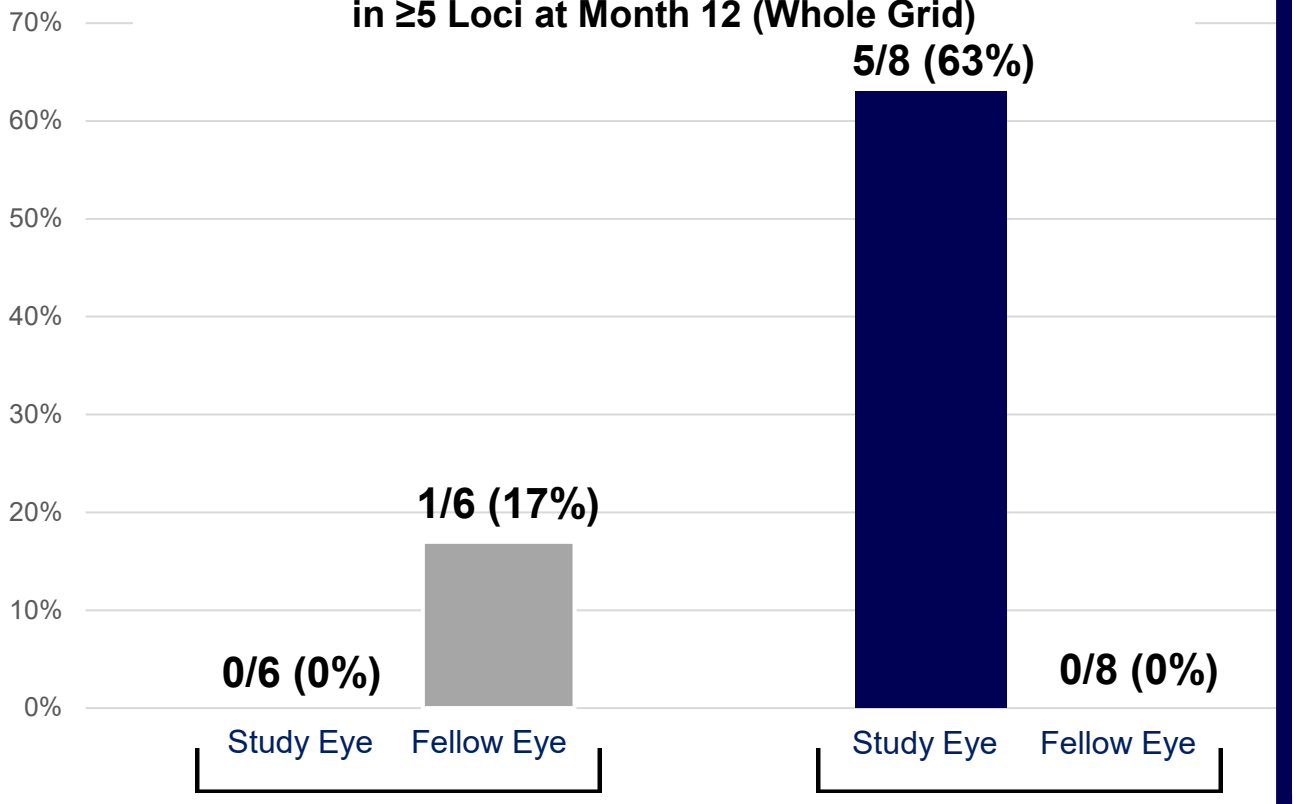
vg/eye = vector genomes / eye

Phase 2 SKYLINE Efficacy Summary at Month 24

Greater response rate seen in the high dose study eyes compared to low dose and fellow eyes, consistent from Month 12 to Month 24

Responder Rate Month 12

Patients (%) Achieving a ≥7 dB Improvement from Baseline in ≥5 Loci at Month 12 (Whole Grid)



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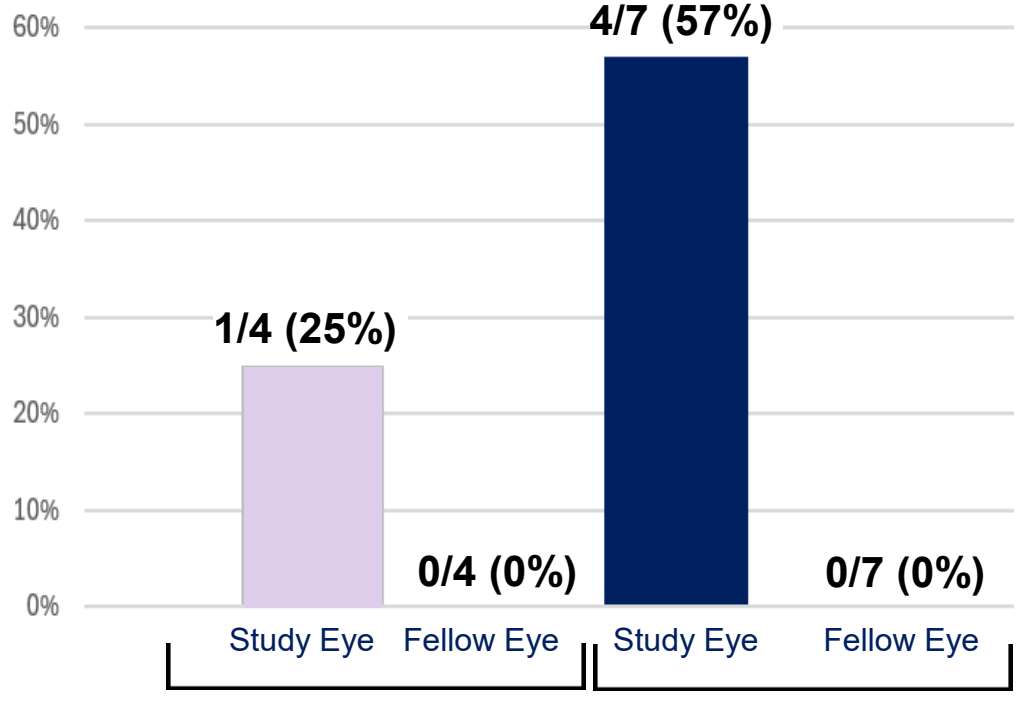
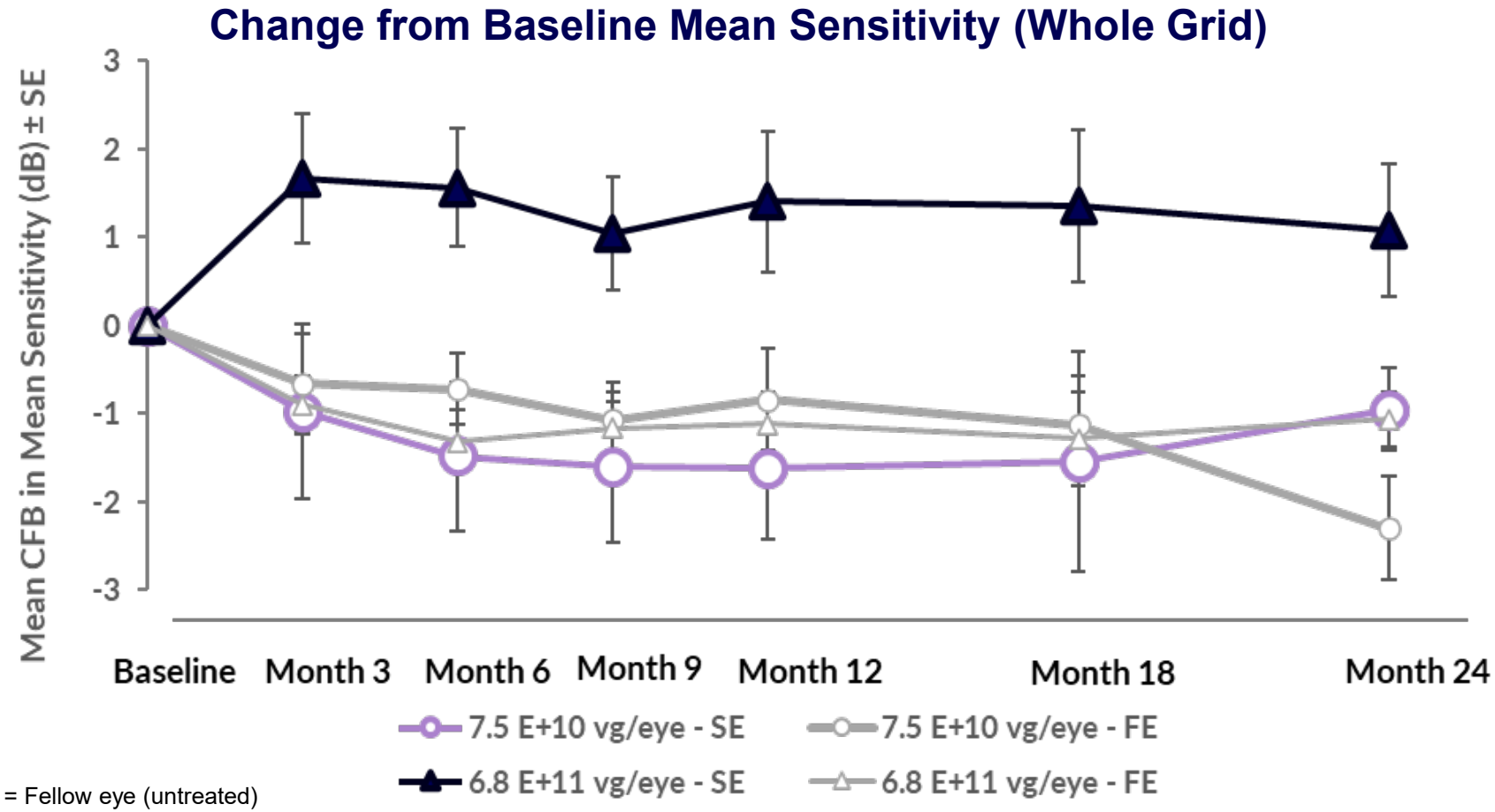


Note: **3 participants (1 high dose and 2 low dose) missed scheduled Month 24 visits**

Phase 2 SKYLINE Efficacy Summary at Month 24

Robust Improvement in Retinal Sensitivity from Baseline Demonstrated
1. Within the high dose group, between study eye and fellow eye
2. Between high dose and low dose groups

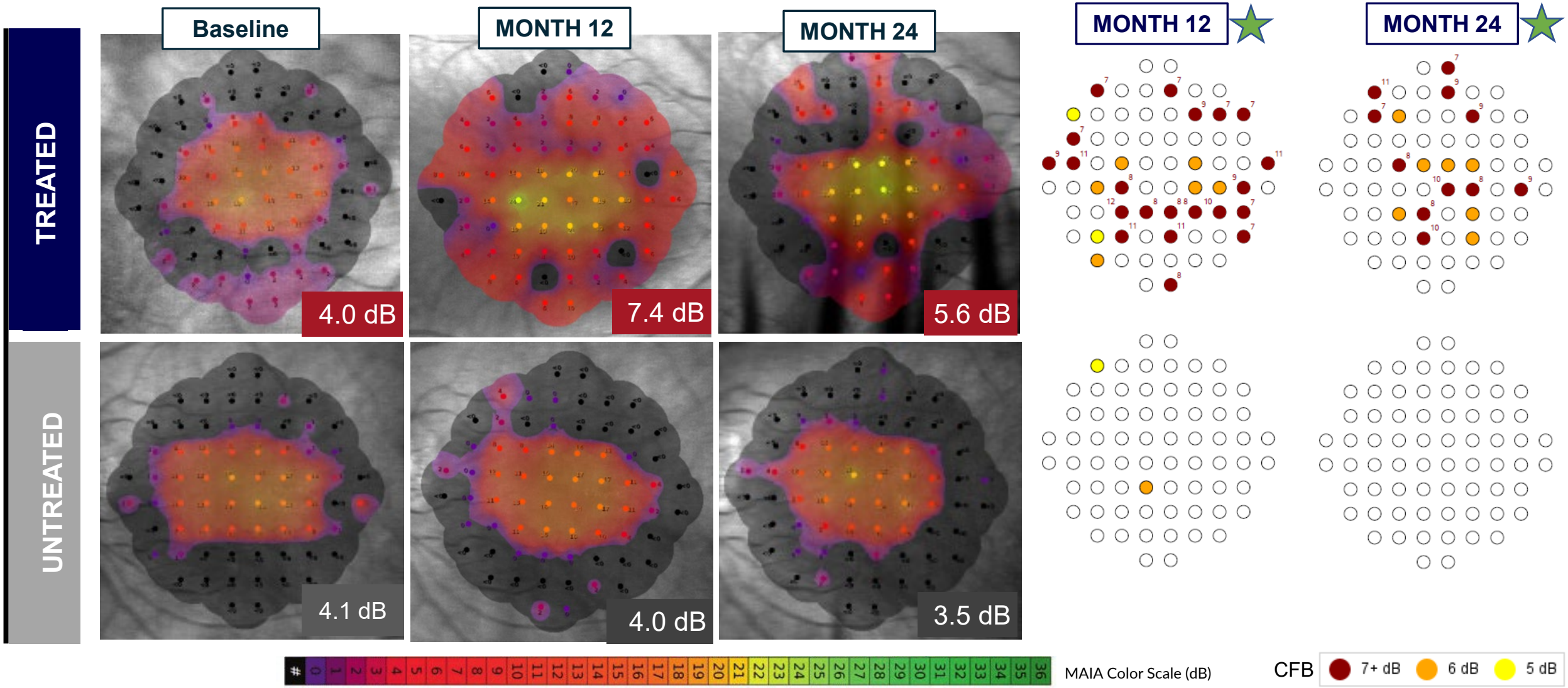


SE = Study eye (treated); FE = Fellow eye (untreated)
Mean Sensitivity = Microperimetry by MAIA

Example of Responding Eye per Microperimetry

≥7 dB in ≥5 loci

Age	Treatment	Study Eye	Type of Mutation
14	6.8 E+11 vg/eye	OD	hemizygous missense variant (VUS) in the RPGR gene. NM_001034853.2(RPGR):c353A>C(p.Gln118Pro)

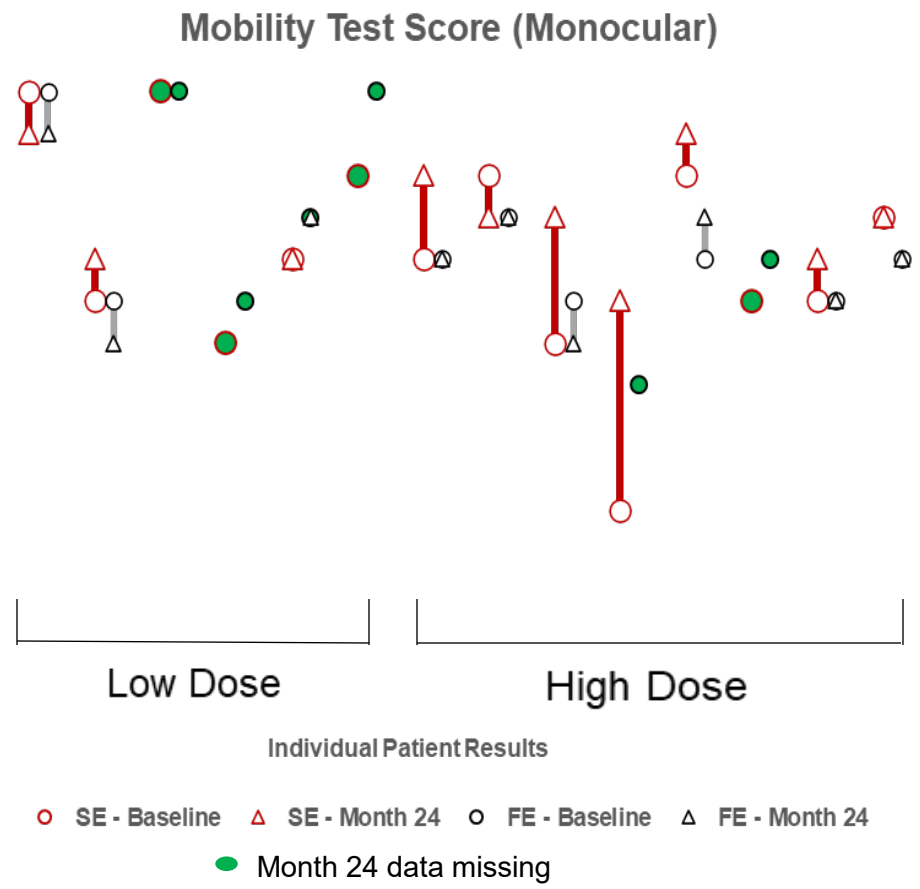


CFB = Change from Baseline; SE = Study eye (treated); FE = Fellow eye (untreated)

Secondary Efficacy Endpoint: Mean CFB in Mobility Maze Score at Month 24

Positive trends in high dose group

	Light Level (lux)	Score
LCVNC	0.35	16
	1	15
	3	14
	8	13
	22	12
	63	11
	178	10
	500	9
HCVNC	0.35	8
	1	7
	3	6
	8	5
	22	4
	63	3
	178	2
	500	1



- Mobility maze test demonstrates positive trends
  - 6/10 treated eyes showed at least one level improvement in maze test
  - 1/9 of the untreated eyes showed one level improvement

n=10 participants, 19 eyes at Month 24
SE, study eye (treated); FE, fellow eye (untreated); LCVNC, Low-Contrast Visual Navigation Challenge; HCVNC, High-Contrast Visual Navigation Challenge; CFB = Change from Baseline

Conclusions
Phase 2 SKYLINE 24-Month Interim Analysis

Data show continued robust improvements in visual function

AGTC-501 was generally safe and well-tolerated

- To date, AGTC-501 data show robust improvements in retinal sensitivity as assessed by MAIA microperimetry
- No Ocular SAEs were deemed related to AGTC-501 and ocular TEAEs were mostly non-serious and mild to moderate in severity
- Follow-up is ongoing through 5 years to assess long-term safety and durability of response
- The benefit-risk profile supports on-going clinical development for the treatment of patients with XLRP caused by RPGR mutations

MAIA = macular integrity assessment; SAE = Serious Adverse Event; TEAE: Treatment Emergent Adverse Events