Subretinal AGTC-501 Gene Therapy for XLRP: 12-Month Interim Safety & Efficacy Results of the Phase 2 SKYLINE Trial

Mark Pennesi, MD, PhD, FARVO

Director, Ophthalmic Genetics

Retina Foundation Dallas, Texas

Professor of Ophthalmology

Professor of Molecular and Medical Genetics, Paul H. Casey Ophthalmic Genetics Division

Casey Eye Institute, Oregon Health & Science University

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Co-authors

Robert Sisk, MD - Cincinnati Eye Institute, Cincinnati, Ohio

David Birch, PhD - Texas Retina Associates, Dallas, Texas

Paul Yang, MD, PhD - Oregon Health Sciences University, Portland, Oregon

Anne Fulton, MD – Boston Children's Hospital, Boston, Massachusetts

Aleksandra Rachitskaya, MD - Cleveland Eye Institute, Cleveland, Ohio

Lejla Vajzovic, MD – Duke Eye Center, Durham, North Carolina

Darin Curtiss, PharmD – Beacon Therapeutics

Nadia Waheed, MD, MPH – Beacon Therapeutics

X-Linked Retinitis Pigmentosa

Progressive photoreceptor degeneration that leads to blindness with no treatment options

Severe, aggressive, inherited retinal disease characterized by progressive photoreceptor degeneration

Orphan Disease @ 1:40,000 affecting young males[1]

17K patients in U.S./EU5[1]

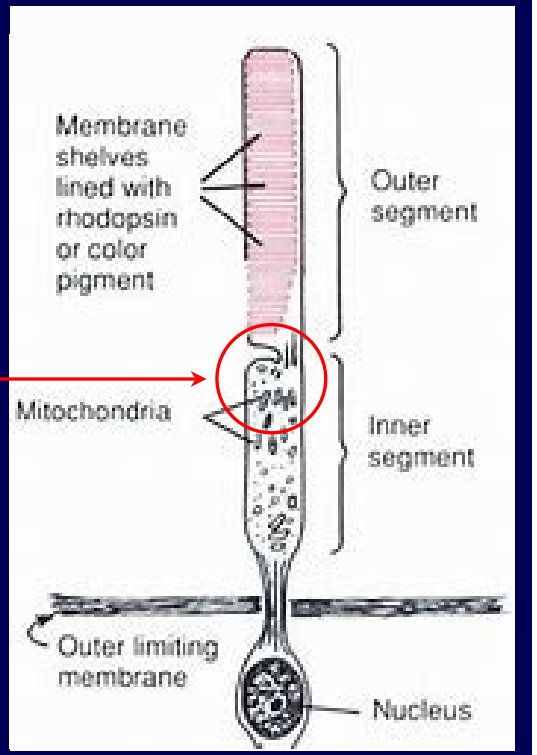
Due to mutation in $RPGR_{orf15}$ gene, which is responsible for long-term photoreceptor viability

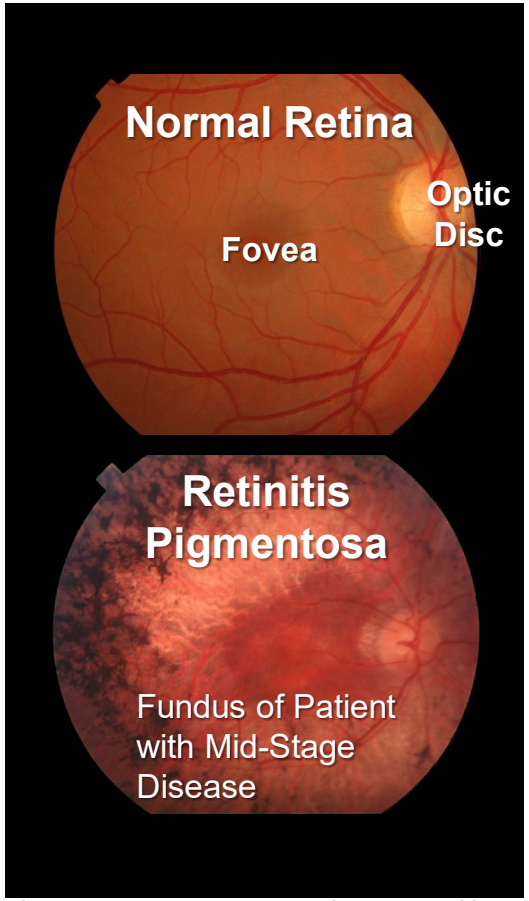
Legally blind by median age of 45[2]

RPGR localized in cilium, the connective body between inner and outer segment of photoreceptors

Disease progression

- Early - Night blindness
- Mid - Peripheral vision loss
- Late - Central vision loss





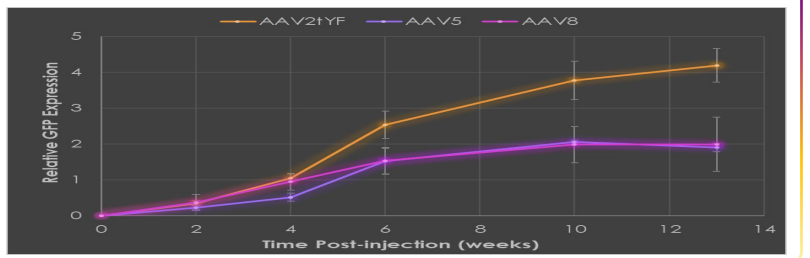
1. Vinikoor-Imler LC, et al. Ophthalmic Genet. 2022 Oct;43(5):581-588 2. Chivers M, et al. Clinicoecon Outcomes Res. 2021;13:565–572

AGTC-501 Targets XLRP

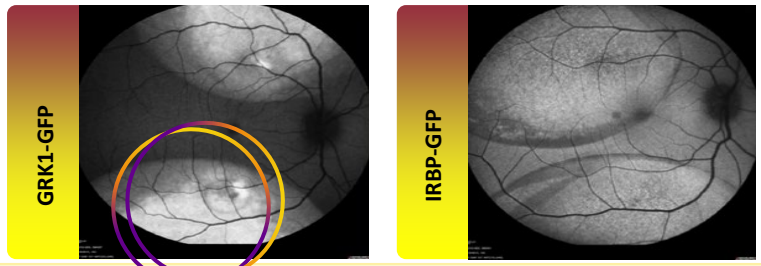
Delivering functional copy of *RPGR* gene using a sub-retinally administered AAV vector

AAV-TYF
ITR
GRK1
SV40 SD/SA
RPGRco
SV40 pA
ITR
4483 bp

CAPSID
AAV2tYF



PROMOTER



CODON OPTIMISED GENE

Model	In-life	Procedure	Result
XLPRA2 dog 9E10+ vg/eye	8–6 weeks	**DNA & RNA** PCR/RT-PCR Sanger sequencing	✓ Sequence confirmed ✓ Stable RPGR, no mutations
Rd9 mouse 4E9+ vg/eye	6 weeks	**RNA & Protein** RT-PCR Sanger sequencing SDS-PAGE/WB	✓ Sequence confirmed ✓ Stable RPGR, no mutations ✓ RPGRco protein correct size ✓ RPGRco glutamylation analysis

Three main advantages:

1. Engineered capsid that results in high and durable transduction
2. Photoreceptor-specific promoter
3. Codon-optimized $RPGR^{ORF15}$ gene encoding full length protein

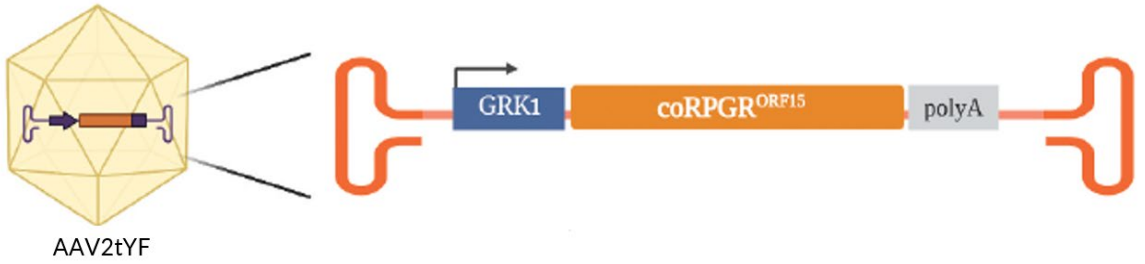
Potential Therapeutic Benefits of Using Full-Length RPGR

AGTC-501 is expected to restore the natural function of photoreceptors

Beacon uses a stable, full-length RPGR^{ORF15} gene therapy vector, not a truncated RPGR^{ORF15}

AGTC-501 expresses the full-length RPGR protein and undergoes full glutamylation during post-translational modification

As a full-length RPGR gene therapy, AGTC-501 therefore has a higher probability of restoring the natural function of cone photoreceptors, possibly yielding greater visual improvement[1,2]



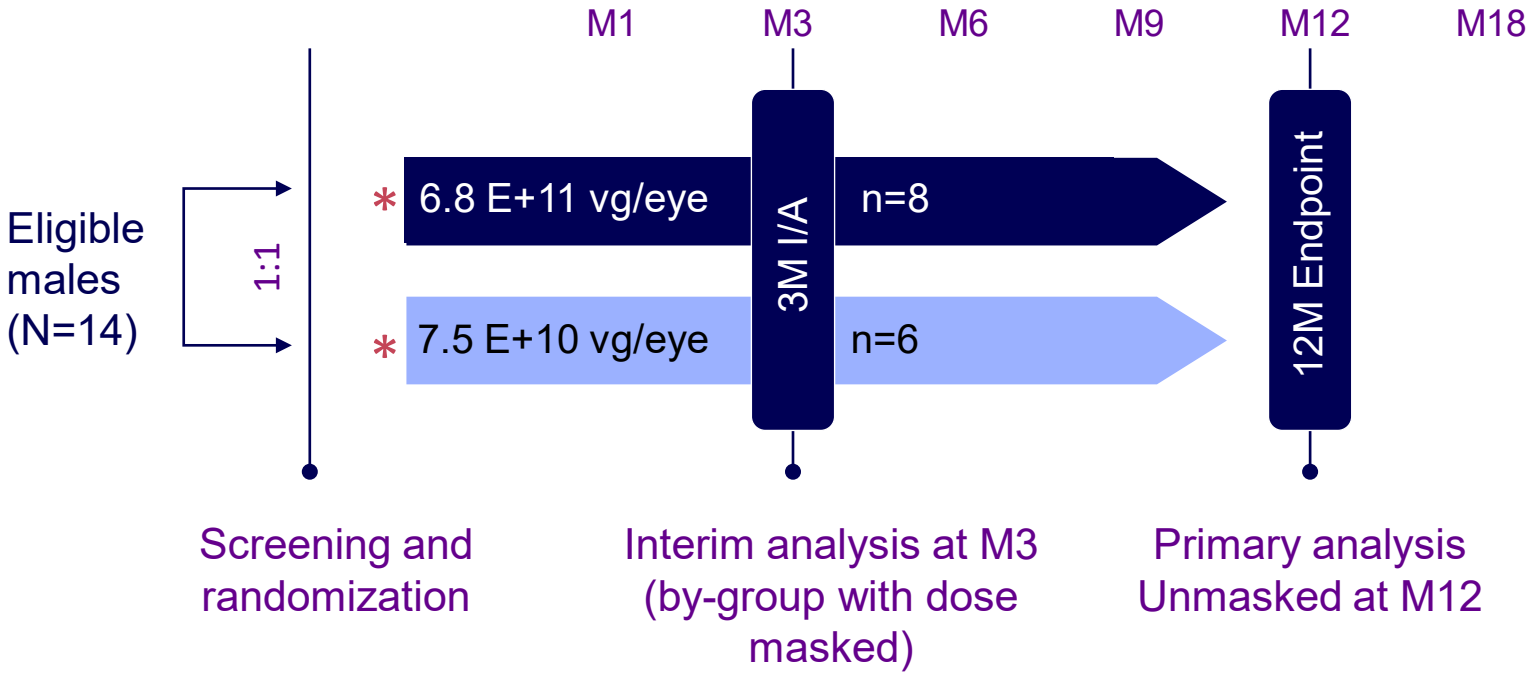
1. Pawlyk B, et al. Gene Ther. 2016;23, 196–204; 2. Sun X, et al. Proceedings of the National Academy of Sciences. 2016;113(21): E2925-E2934

AGTC-501 Clinical Development Program

	Name	Status	Phase	Patients	Data availability	Conclusions
ONGOING	HORIZON	• **Ongoing** – enrollment complete *(since Apr-18)*	• **Phase 1/2** *Dose escalation*	• 29 patients	• >24-month data available	• Favorable safety profile (no SUSARs / SAEs) • Enabled dose selection for Skyline
ONGOING	SKYLINE	• **Ongoing –** enrollment complete *(since Apr-21)*	• **Phase 2**	• 14 patients	• 12-month data available	• Endpoints of microperimetry, mobility maze test, FST, and visual acuity all met
ONGOING	DAWN	• **Ongoing -** enrolling	• **Phase 2** *Open label dose confirmation study*	• Patients previously treated in full length RPGR gene therapy study	N/A	N/A
PLANNED	VISTA	• **Planned**	• **Phase 2/3** *US & EU*	• XLRP patients	N/A	N/A

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

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

Key Inclusion Criteria

- Males aged 8 – 50 years with clinical diagnosis of XLRP
- 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

Key Exclusion Criteria

- 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

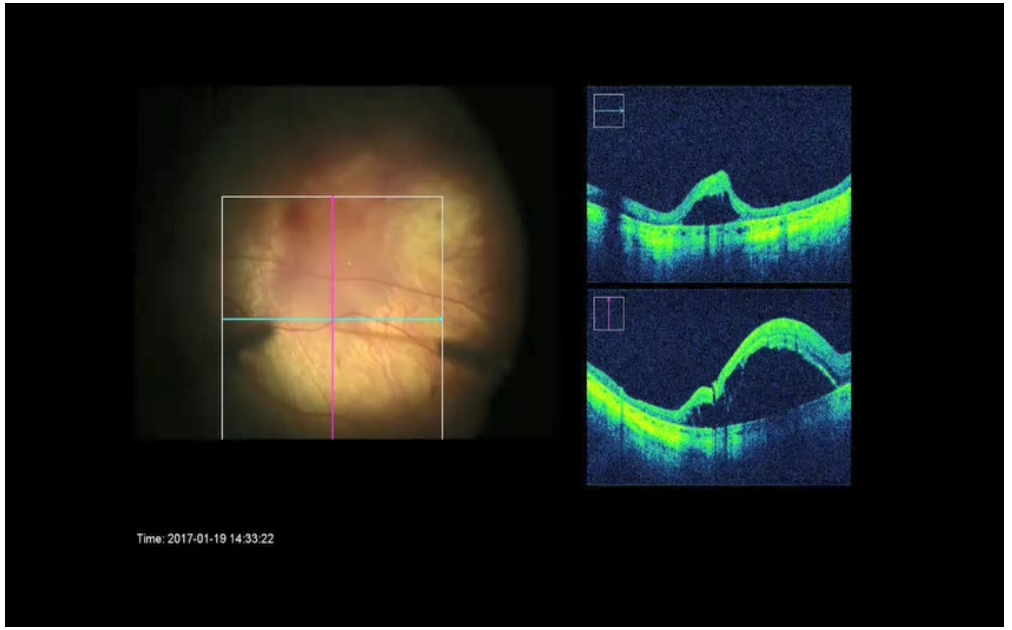
Phase 2 SKYLINE Endpoints

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

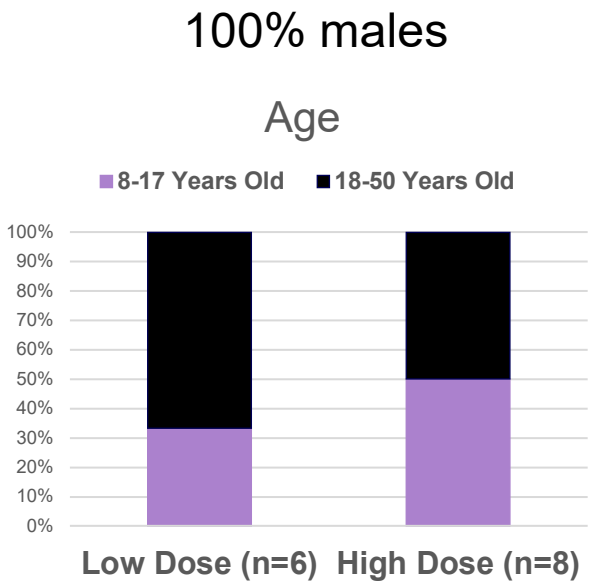


CFB = Change from Baseline; ETDRS = Early Treatment of Diabetic Retinopathy Study; BCVA = Best Corrected Visual Acuity;
MAIA = macular integrity assessment; VNC = Visual Navigation Challenge

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 (N=6)		High Dose (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

1. Microperimetry by MAIA

Ocular Serious Adverse Events (SAEs) at Month 12

No Ocular SAEs were Deemed Related to AGTC-501

Ocular Serious Adverse Events (SAE)	Low Dose (n=6) N		High Dose (n=8) n		All Patients (n=14) n	
	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

Ocular Treatment-emergent Adverse Events (TEAEs) Related to AGTC-501 at Month 12

Ocular Treatment-emergent Adverse Event (TEAE)	Low Dose (n=6)		High Dose (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

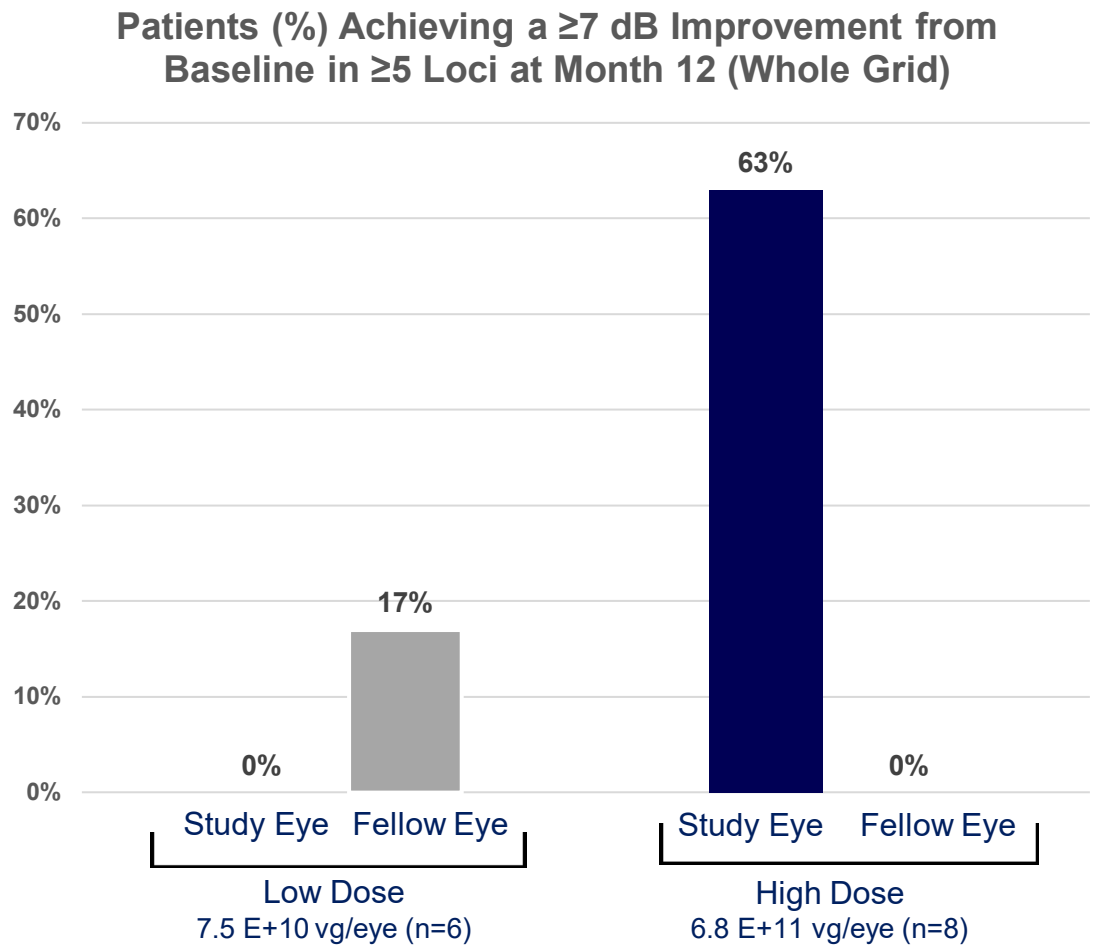
- Ocular treatment-emergent adverse events (TEAEs) were mostly non-serious, mild or moderate in severity, and rates were similar between high dose and low dose groups

- All 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

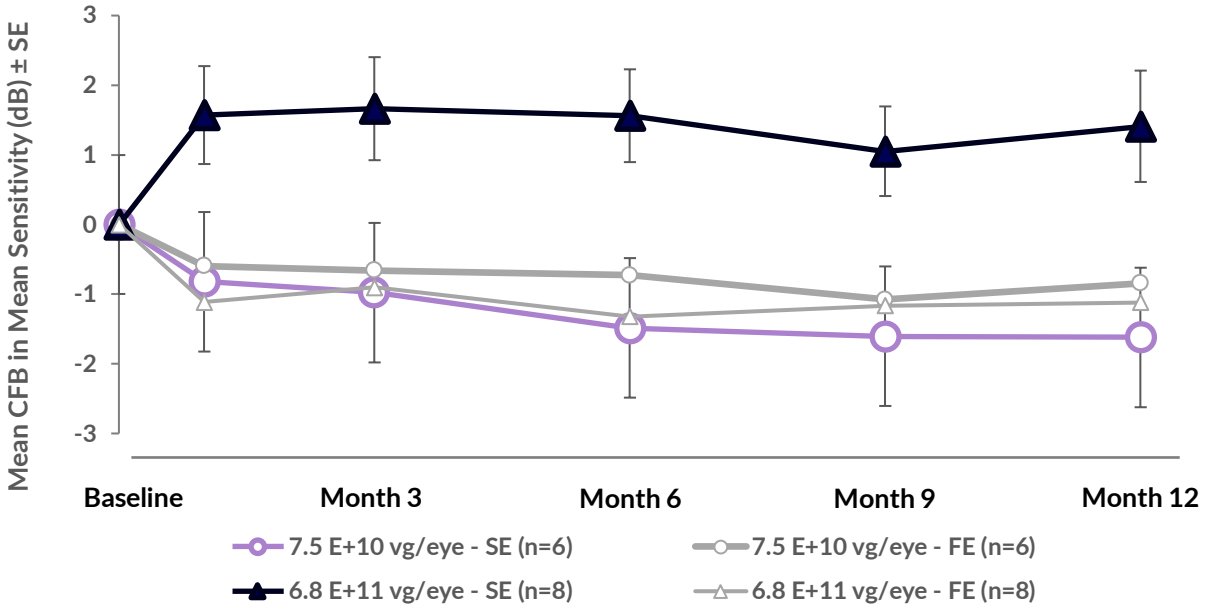
Phase 2 SKYLINE Efficacy Summary at Month 12

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

Responder Rate Month 12



Change from Baseline Mean Sensitivity (Whole Grid)



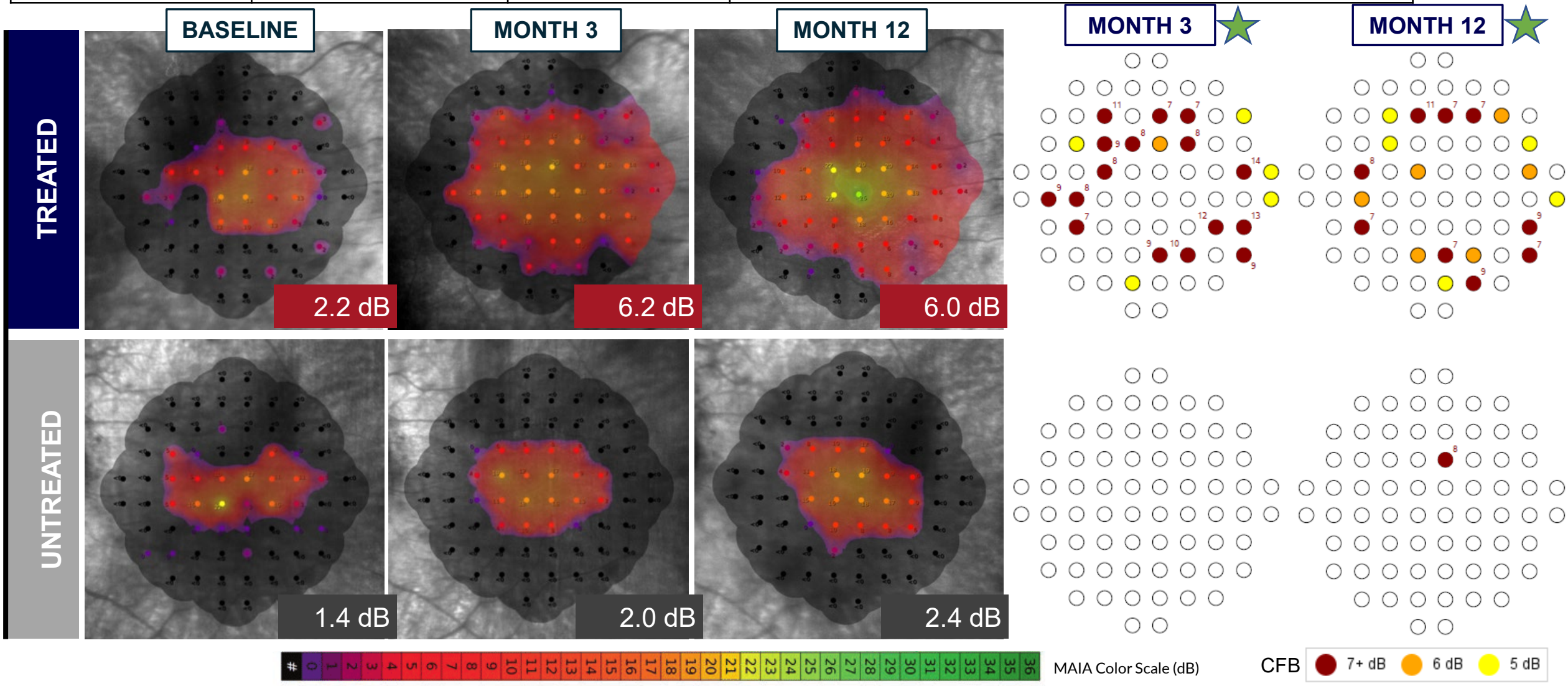
Microperimetry mean sensitivity is an agreed upon registrational endpoint for Europe

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

Example 1: Responding Eye per Microperimetry

★ ≥7 dB in ≥5 loci

Age	Treatment	Study Eye	Type of Mutation
16	6.8 E+11 vg/eye	OD	c.151delA(p.Thr51ProfsTer17) in exon 2

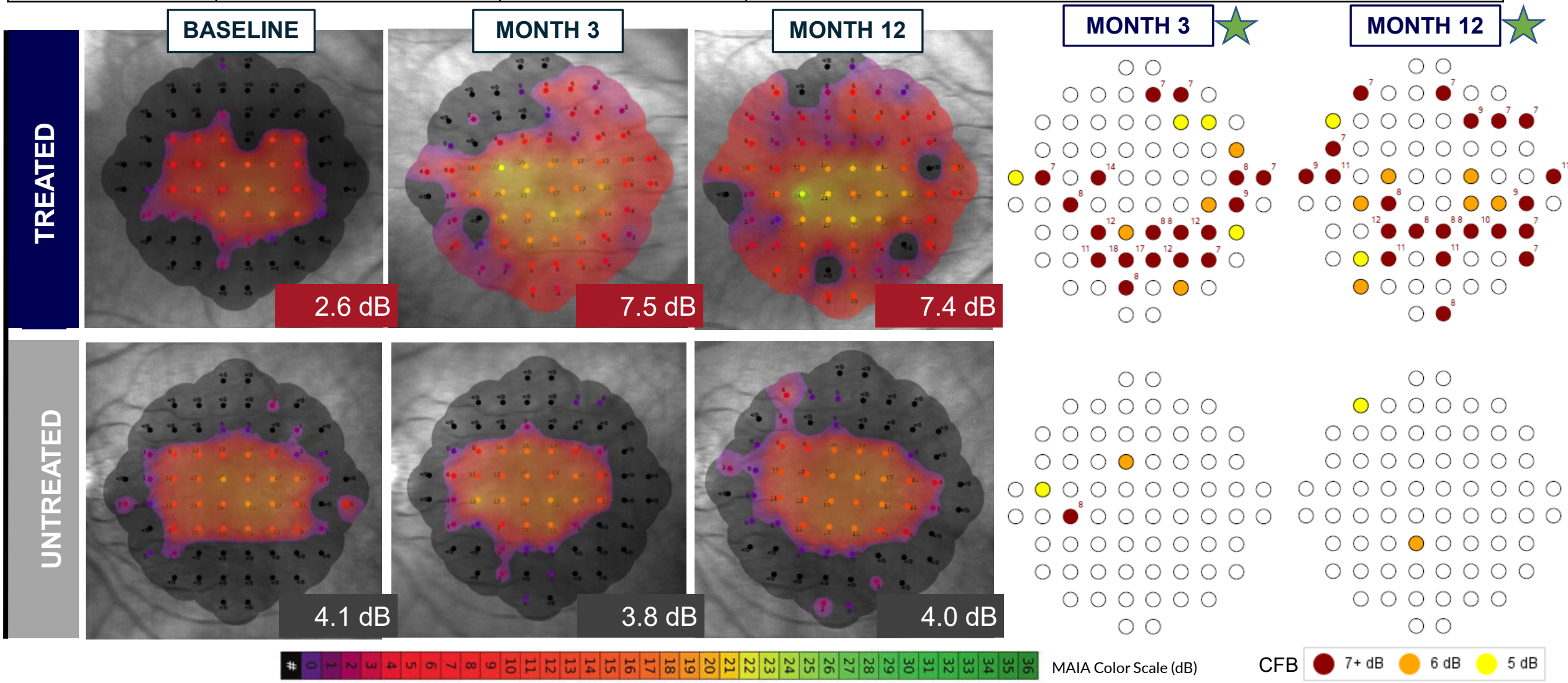


CFB = Change from Baseline; SE = Study eye (treated); FE = Fellow eye (untreated)

Example 2: Responding Eye per Microperimetry

≥7 dB in ≥5 loci

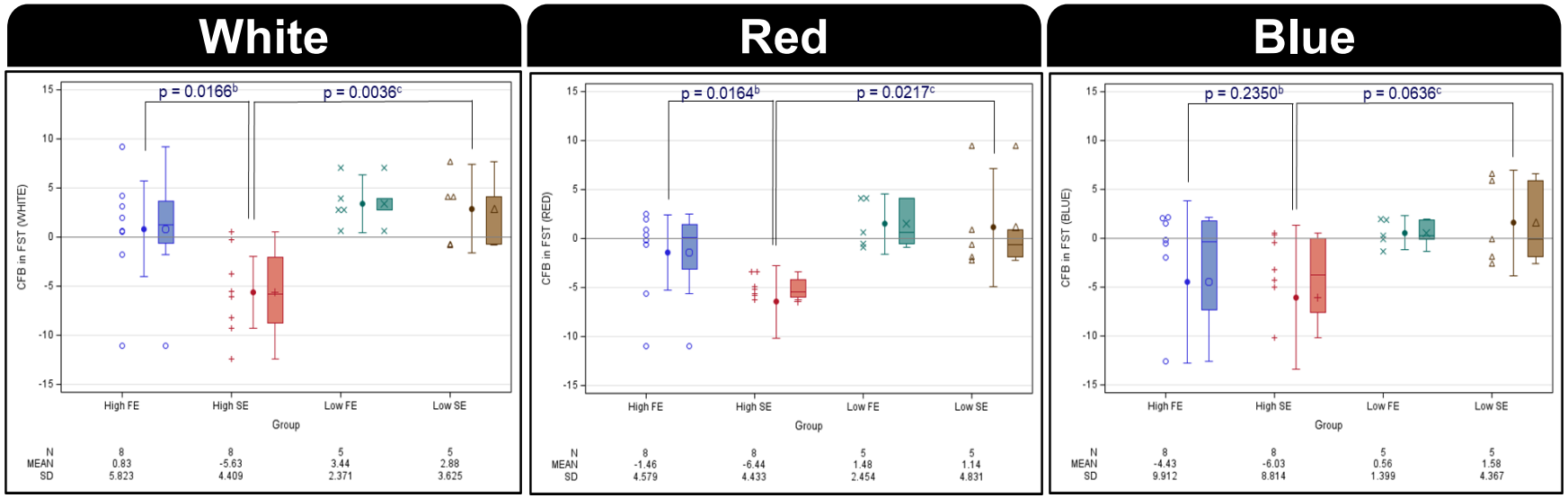
Age	Treatment	Study Eye	Type of Mutation
14	6.8 E+11 vg/eye	OD	hemizygous missense variant (VUS) in the RPGR gene. NM_001034853.2(RPGR):c353A>C(p.Gln118Pro)



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

Secondary Efficacy Endpoint: Mean CFB in Full-Field Light Sensitivity Threshold (FST) at Month 12

Strong Trends in High Dose Group in Full-Field Light Sensitivity (FST)



N=13[a]

[a] n=5 in low dose group; n=8 in high dose group

[b] paired t-test

[c] two-sample t-test with unequal variance

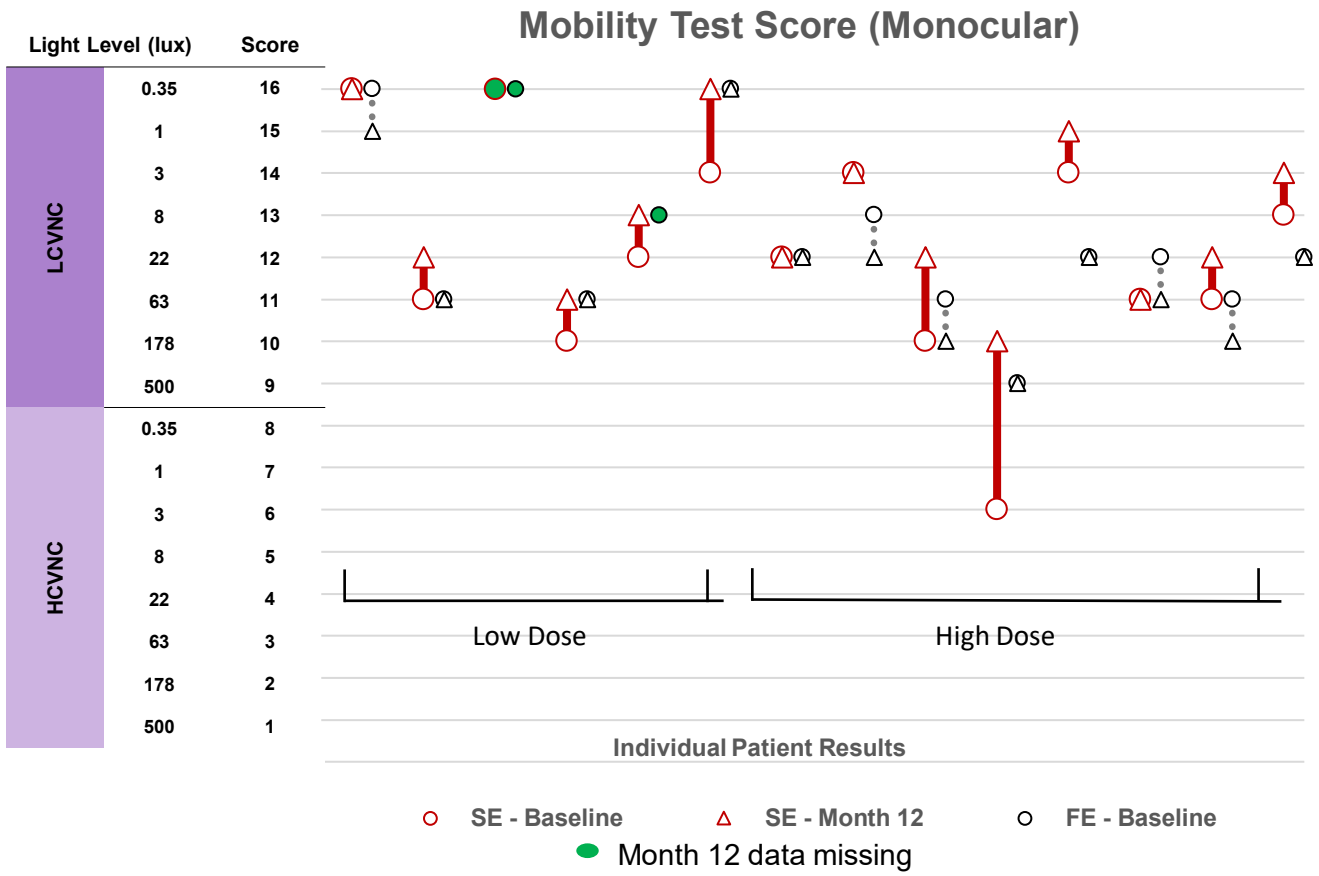
Vertical bar represents the 95% confidence interval of the mean

- Red and White light FST showed statistically significant improvement in the high dose treated eyes compared to both the low dose and the untreated control eyes, while blue light FST showed a strong trend
- This is also consistent with the results obtained with the multi-luminance mobility maze

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

Secondary Efficacy Endpoint: Mean CFB in Mobility Maze Score at Month 12

Positive trends in High Dose Group



- Mobility maze test demonstrates positive trends
  - 9/14 treated eyes showed at least one level improvement in maze test
  - 0/14 of the untreated eyes showed at least one level improvement and 5/14 of the untreated eyes showed at least one level worsening

n=14 patients, 25 eyes
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
SKYLINE 12-month Analysis

Data show robust improvements in visual function

AGTC-501 was generally safe and well-tolerated

- To date, AGTC-501 data show robust improvements in visual function including retinal sensitivity as assessed by MAIA microperimetry and full-field stimulus threshold (FST)
- The benefit-risk profile is favorable and supports continued clinical development for the treatment of patients with XLRP caused by RPGR mutations