Subretinal Gene Therapy laru-zova (AGTC-501) for X-linked Retinitis Pigmentosa (XLRP): Phase 2 DAWN Preliminary Month 6+ Results

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X-Linked Retinitis Pigmentosa (XLRP)

Progressive photoreceptor degeneration that leads to blindness with no treatment options, affecting patients in the prime of their lives

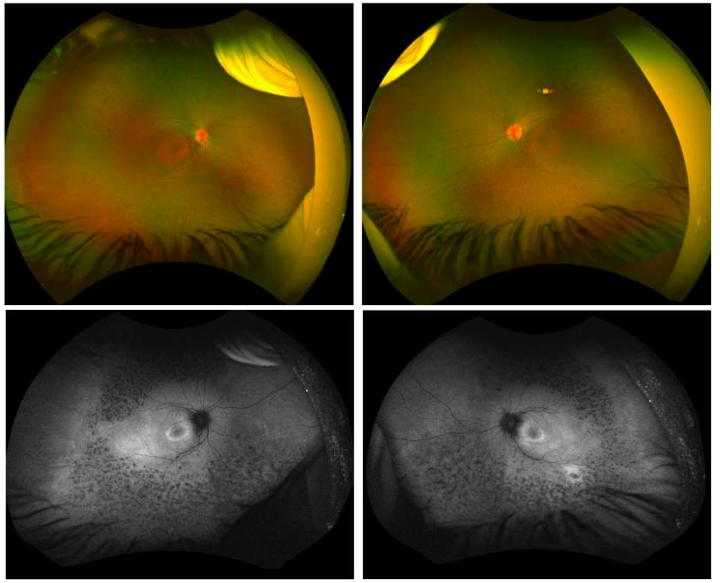
Rare inherited retinal disease characterized by progressive photoreceptor degeneration[1]

70-90% of XLRP is due to mutations in the *RPGR* gene[2]

Affects primarily **young males with estimated prevalence of 1:25,000 males in US/Europe/Australia** having *RPGR* mutations[4]

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[3]	Increasing loss in peripheral vision[5]	Tunnel vision, central VA loss[7]
Difficulties in low light environments[3]	Difficulties driving, running into objects, difficulty with daily tasks[1,6]	Legal blindness, significant impact on daily life, loss of autonomy[1,5,6]



Images from M Pennesi

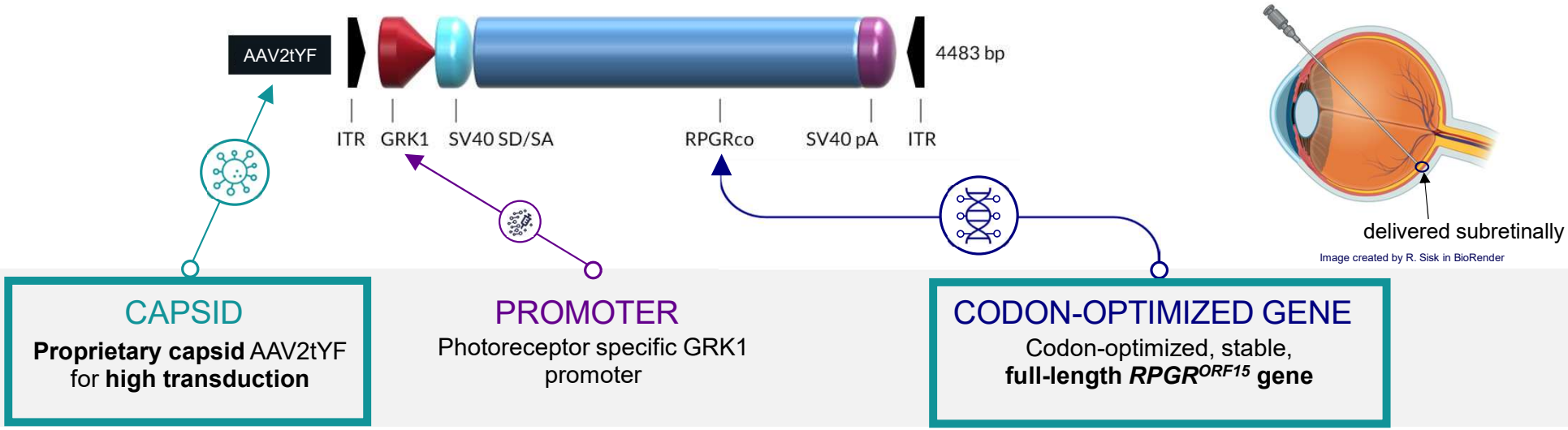
Images from a 12 year old male patient with XLRP

VA = visual acuity

1. Chivers M, et al. *Clinicoecon Outcomes Res*. 2021;13:565-572. 2. Nguyen XT, et al. *Int J Mol Sci.* 2020;21(3):835. 3. Churchill JD, et al. *Invest Ophthalmol Vis Sci.* 2013;54(2):1411-1416. 4. Vinikoor-Imler LC, et al. *Ophthalmic Genet.* 2022 Oct;43(5):581-588 5. Di Iorio V, et al. *Invest Ophthalmol Vis Sci.* 2020;61(14):36. 6. Senthil MP, et al. *Eye (Lond).* 2017;31(5):741-748; 7. O'Neal TB, et al. Retinitis Pigmentosa. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519518.

Overview of laru-zova (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 *RPGR*^{ORF15} gene**

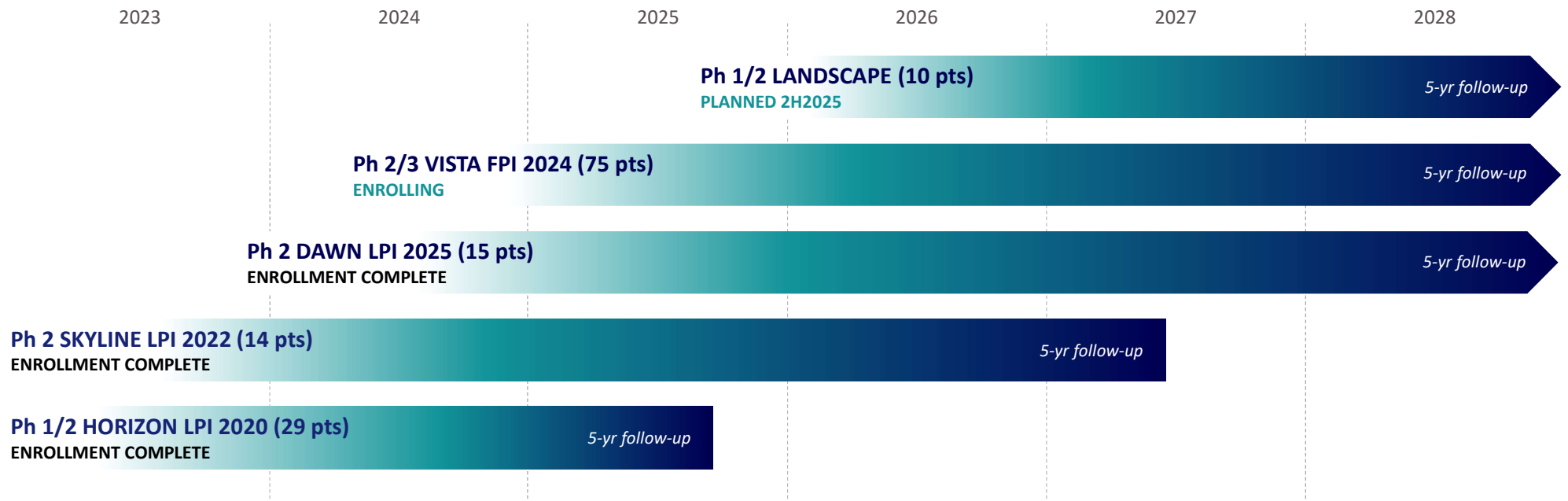
As a **full-length *RPGR* gene therapy**, laru-zova has a greater potential to restore natural function of both rods and cones, possibly yielding greater visual improvement[1,2]

Received ILAP (UK), PRIME (EU), RMAT (US) and Fast Track (US) designations

XLRP = X-linked retinitis pigmentosa; RPGR = retinitis pigmentosa GTPase regulator; AAV = adeno-associated virus; GRK1 = rhodopsin kinase; ILAP = Innovative Medicine Designation; PRIME = Priority Medicines; RMAT = Regenerative Medicine Advanced Therapy.

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.

laru-zova (AGTC-501) Clinical Development Program



LPI = last patient in; FPI = first patient in

Phase 2 DAWN Study Design: Fellow Eye Treatment in Previously-Treated Participants

Non-randomized, open-label, multicenter study comparing two doses of laru-zova (AGTC-501) in the fellow eye of previously treated male participants with XLRP caused by mutations in the *RPGR* gene

FPI: November 2023; 5-year follow-up post treatment[1]

Primary outcome

- Number and proportion of Grade 3 or higher ocular or non-ocular treatment-emergent AEs or SAEs

Secondary outcomes

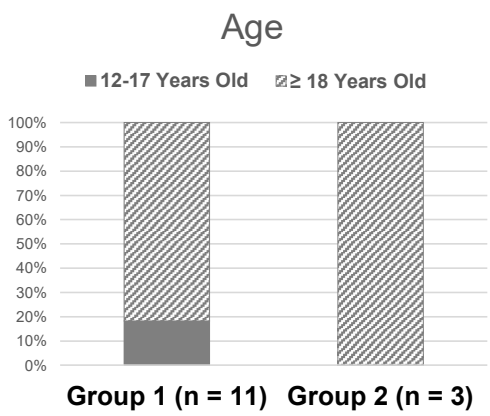
- Changes from baseline (CFB) to Month 12 in:
  - LLVA, BCVA, mean sensitivity via microperimetry (MAIA), LLD, FST
  - Ora-VNC™ mobility course score, MObility Standardized Test-Virtual Reality mobility course score
  - MRDQ, EZ area

XLRP = X-linked retinitis pigmentosa; RPGR = retinitis pigmentosa GTPase regulator; vg = vector genomes; FPI = first patient in; AE = adverse event; SAE = serious adverse event; MAIA = macular integrity assessment; FST = full field stimulus threshold; BCVA = best corrected visual acuity; LLVA = low-luminance visual acuity; LLD = low luminance deficit; EZ = ellipsoid zone; MRDQ = Michigan Retinal Degeneration Questionnaire.

1. NCT06275620. ClinicalTrials.gov. Accessed August September 6, 2024. https://clinicaltrials.gov/study/NCT06275620

DAWN Group Demographics and Baseline Characteristics

N = 14, 100% males[3]



	Group 1 (n = 11)	Group 2 (n = 3)
Mean ± SD	**27.4** ± 11.0	**26.0** ± 11.27
Range	16, 50	19, 39

	Group 1 High Dose: 6.8 E+11 vg/eye (n = 11)[3]	Group 2 Low Dose: 3.7 E+11 vg/eye (n = 3)
Previous Trial Participation		
Phase 1/2 (HORIZON)	**7**	**0**
Phase 2 (SKYLINE)	**3**	**3**
Biogen XIRIUS trial	**1**	**0**
Time Between Doses (months)	**51.9**[2] 28.7, 66.4	**31.6** 29.9, 32.6

Baseline Characteristics	Study Eye	Fellow Eye*	Study Eye	Fellow Eye*
BCVA (ETDRS letters)	**67.9** ± 6.44 57, 76	**70.8** ± 6.94 59, 80	**74.3** ± 1.53 73, 76	**78.3** ± 6.35 71, 82
LLVA (ETDRS letters)	**46.5** ± 13.13 24, 62	**56.4** ± 8.58 40, 70	**53.3** ± 5.77 50, 60	**66.3** ± 6.03 60, 72
LLD (ETDRS letters)	**21.5** ± 8.79 12, 38	**14.5** ± 5.26 5, 22	**21** ± 4.36 16, 24	**12** ± 2.65 10, 15
Mean Sensitivity (whole grid)[1](dB)	**2.37** ± 1.110 1.3, 4.5	**3.30** ± 1.887 0.6, 6.3	**2.47** ± 1.079 1.7, 3.7	**4.57** ± 0.723 4.1, 5.4

Statistics presented are mean ± SD, range

**Fellow Eye = eyes previously treated with a full-length AAV vector-based gene therapy targeting RPGR protein*

vg = vector genomes; ETDRS = Early Treatment of Diabetic Retinopathy Study; BCVA = best corrected visual acuity; LLVA = low luminance visual acuity; LLD = low luminance deficit.
1. Microperimetry by MAIA; 2. Excludes one participant in Biogen trial. 3. Excludes one participant not yet treated at time of data analysis

Ocular TEAEs were generally non-serious and mild or moderate in severity

Ocular TEAEs	Group 1 High Dose (n = 11)		Group 2 Low Dose (n = 3)	
	Study Eye	Fellow Eye	Study Eye	Fellow Eye
Number of participants with at least one ocular TEAE	11	3	3	1
Mild	8	2	1	0
Moderate	3	1	1	1
Severe	0	0	1	0
Number of participants with at least one ocular SAE	0	0	1	0
Number of participants at least one AESI	3	0	1	0
Number of participants with at least one ocular TEAE related to:				
Surgical procedure	11	0	2	0
Protocol required corticosteroids	6	0	2	1
laru-zova	1	0	0	0

Majority of TEAE's were related to the surgical procedure or protocol required steroids and have resolved

TEAE = treatment emergent adverse event; SAE = serious adverse event; AESI = adverse event of special interest; High Dose = 6.8 E+11 vg/eye; Low Dose = 3.7 E+11 vg/eye.
All patients received a peri- and post-operative corticosteroid regimen

Ocular TEAEs were generally non-serious and mild or moderate in severity

		Group 1 High Dose (n = 11)		Group 2 Low Dose (n = 3)	
	Preferred Term	**Study Eye**	**Fellow Eye***	**Study Eye**	**Fellow Eye***
Ocular SAEs	Glaucoma**	0	0	1	0
Ocular TEAEs occurring in > 2 participants	Conjunctival Hemorrhage	8	0	1	0
	Glaucoma	6	0	2	1
	Ocular Discomfort	7	0	0	0
	Conjunctival Hyperemia	5	0	0	0
	Cataract Subcapsular	2	2	2	0
	Eye Pain	2	0	2	0
	Metamorphopsia	3	0	1	0
	Vitreal Cells	3	0	0	0

No SUSARs, retinal detachments or endophthalmitis reported

**Fellow Eye = eyes previously treated with a full-length AAV vector-based gene therapy targeting RPGR protein*
***Severe and serious; related to protocol-required corticosteroids*

TEAE = treatment emergent adverse event; SAE = serious adverse event; High Dose = 6.8 E+11 vg/eye; Low Dose = 3.7 E+11 vg/eye;
SUSAR = suspected unexpected serious adverse reaction.
All patients received a peri- and post-operative corticosteroid regimen.

Adverse Events of Special Interest and Adverse Events of Ocular Inflammation

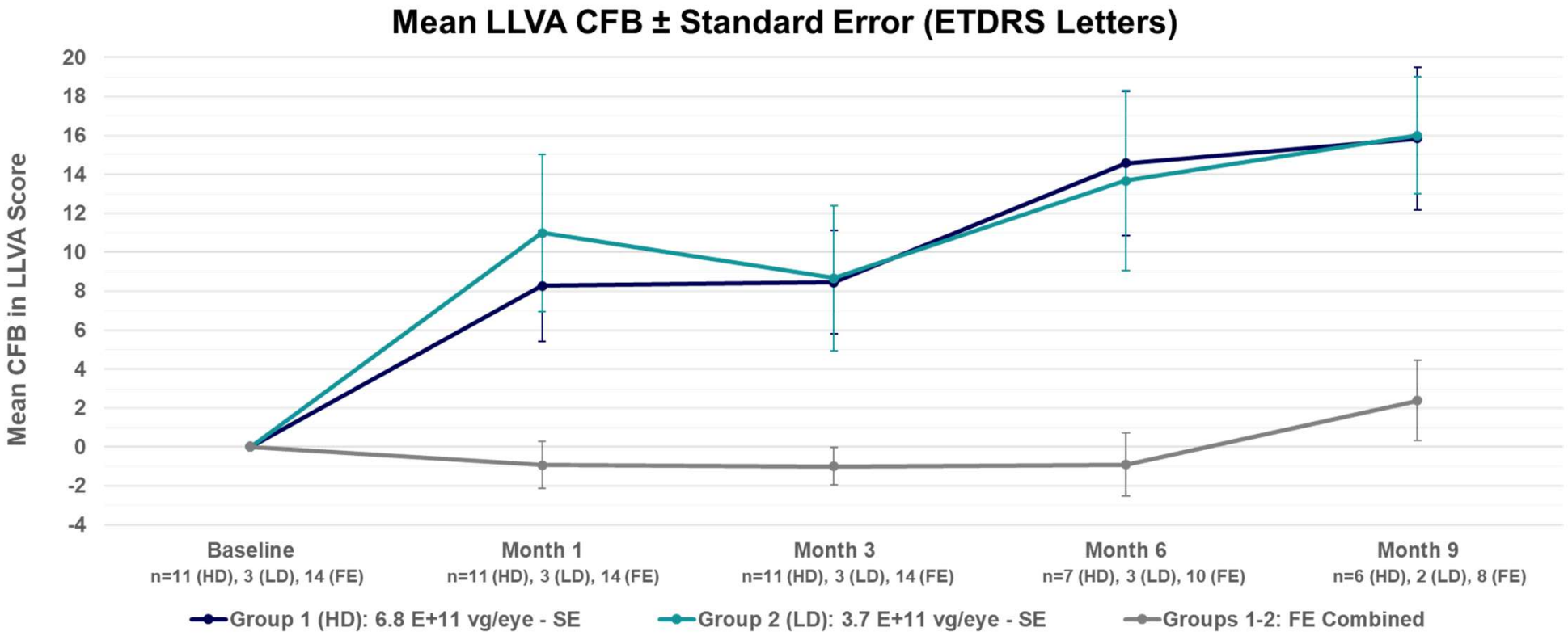
AESIs (PT)	Group 1 High Dose (n = 11)		Group 2 Low Dose (n = 3)	
	Study Eye	Fellow Eye	Study Eye	Fellow Eye
Retinal depigmentation	1	0	0	0
Retinal pigmentation	1	0	0	0
Injection site atrophy	0	0	1	0
Retinal exudates	1	0	0	0
Iridocyclitis	1	0	0	0

Ocular Inflammation (PT)	Group 1 High Dose (n = 11)		Group 2 Low Dose (n = 3)	
	Study Eye	Fellow Eye	Study Eye	Fellow Eye
Vitreal cells	3	0	0	0
Anterior chamber cell	2	1	0	0
Punctate keratitis	1	1	1	0
Uveitis	1	0	0	0
Iridocyclitis	1	0	0	0
Iritis	0	1	0	0

Majority of ocular inflammation was mild and transient in nature

PT = preferred term; AESI = adverse event of special interest; High Dose = 6.8 E+11 vg/eye; Low Dose = 3.7 E+11 vg/eye.
All patients received a peri- and post-operative corticosteroid regimen

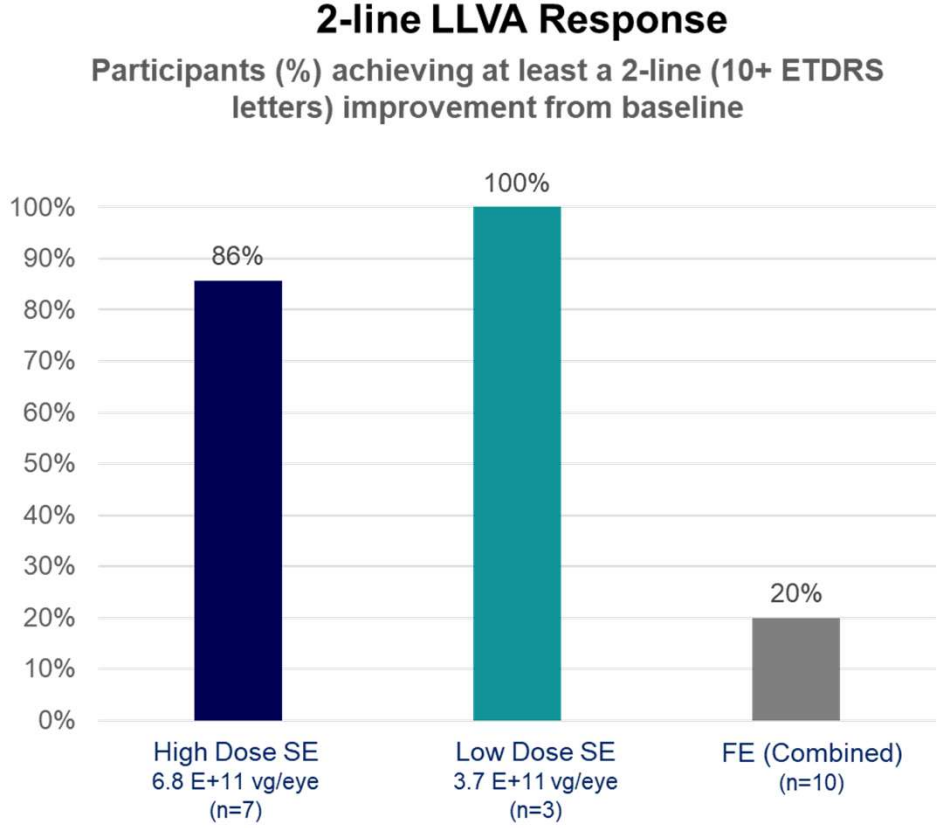
Early improvement in mean LLVA in DAWN Study Eyes

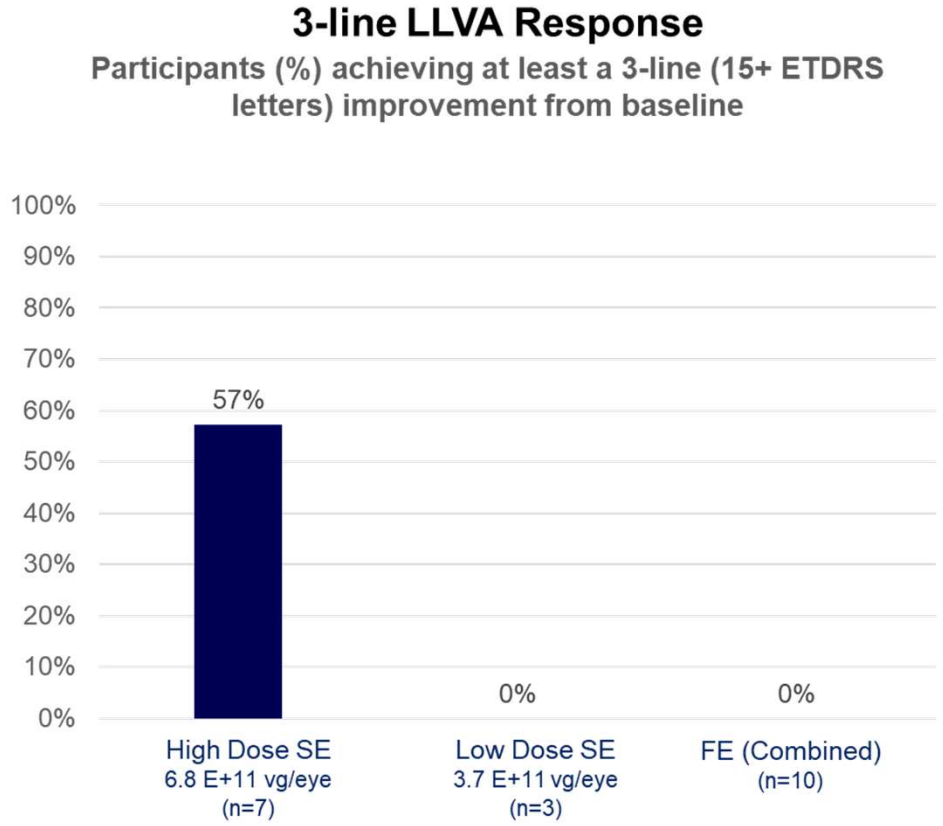


CFB = change from baseline; ETDRS = Early Treatment of Diabetic Retinopathy Study; LLVA = low luminance visual acuity;
SE= study eye (newly treated); FE = fellow eye (previously treated); HD = high dose; LD = low dose

Low Luminance Visual Acuity (LLVA) Response at Month 6+

Greater 2- and 3-line improvements in study eyes compared to previously treated fellow eyes

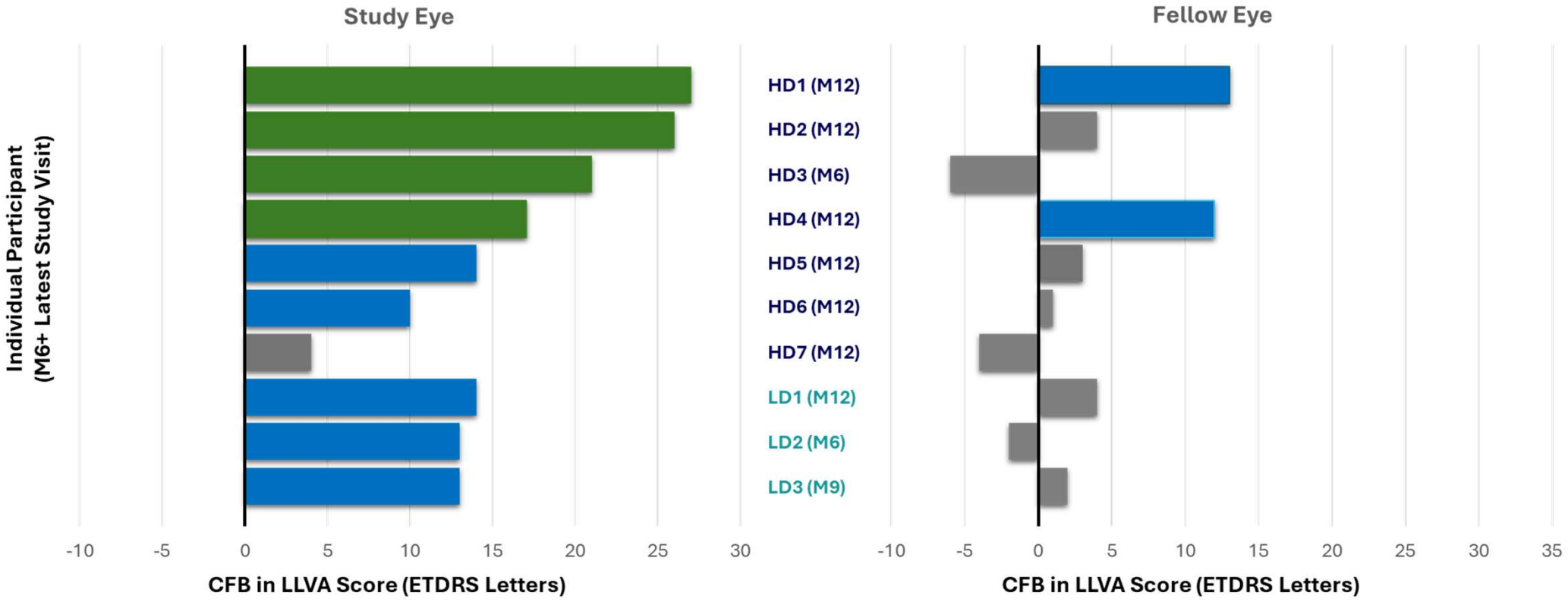




Month 6+ = participants that have reached the Month 6 or beyond follow-up visit; data used from most recent follow-up visit
SE = Study eye (newly treated); FE = Fellow eye (previously treated); ETDRS = Early Treatment of Diabetic Retinopathy Study

Change in Low Luminance Visual Acuity (LLVA) at Month 6+

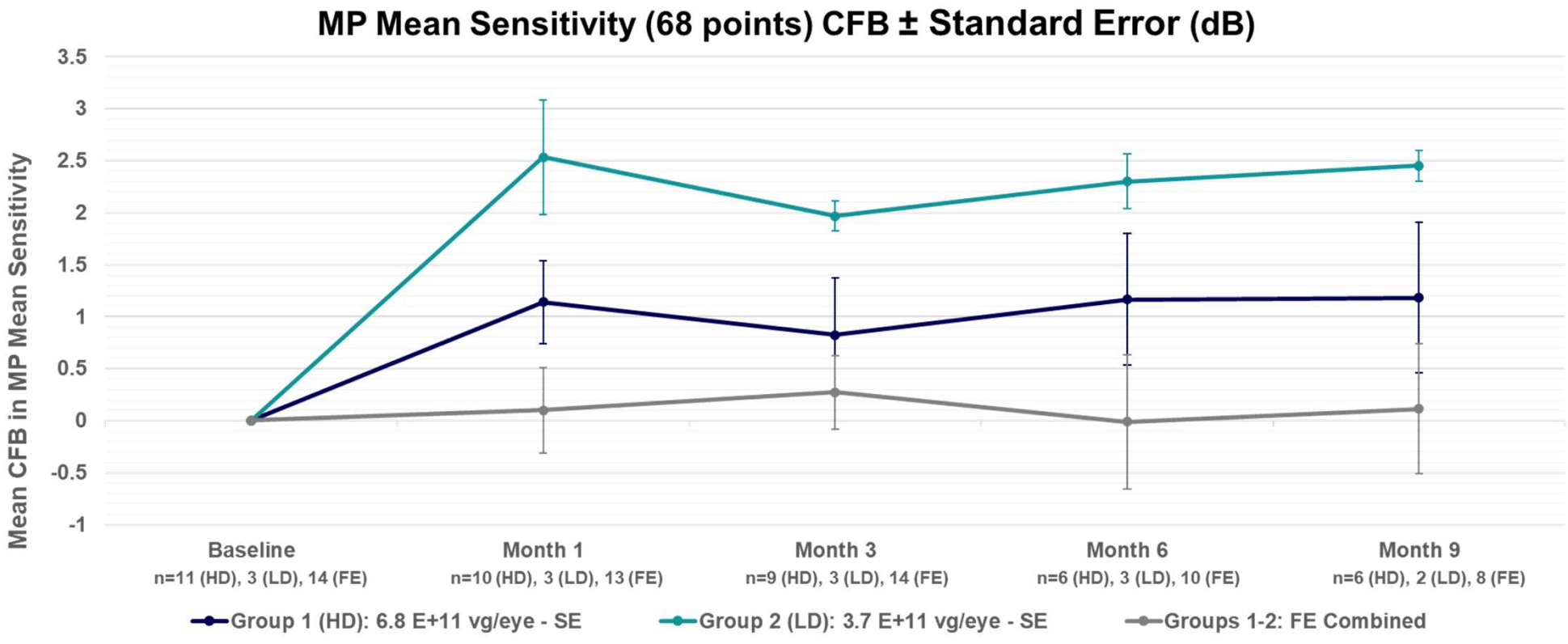
Greater 2- and 3-line improvements in study eyes compared to previously treated fellow eyes



Month 6+ = participants that have reached the Month 6 or beyond follow-up visit; data used from most recent follow-up visit (last visit date shown in parentheses above)
CFB = change from baseline; ETDRS = Early Treatment of Diabetic Retinopathy Study; HD = high dose; LD = low dose

Microperimetry: Change in Mean Sensitivity

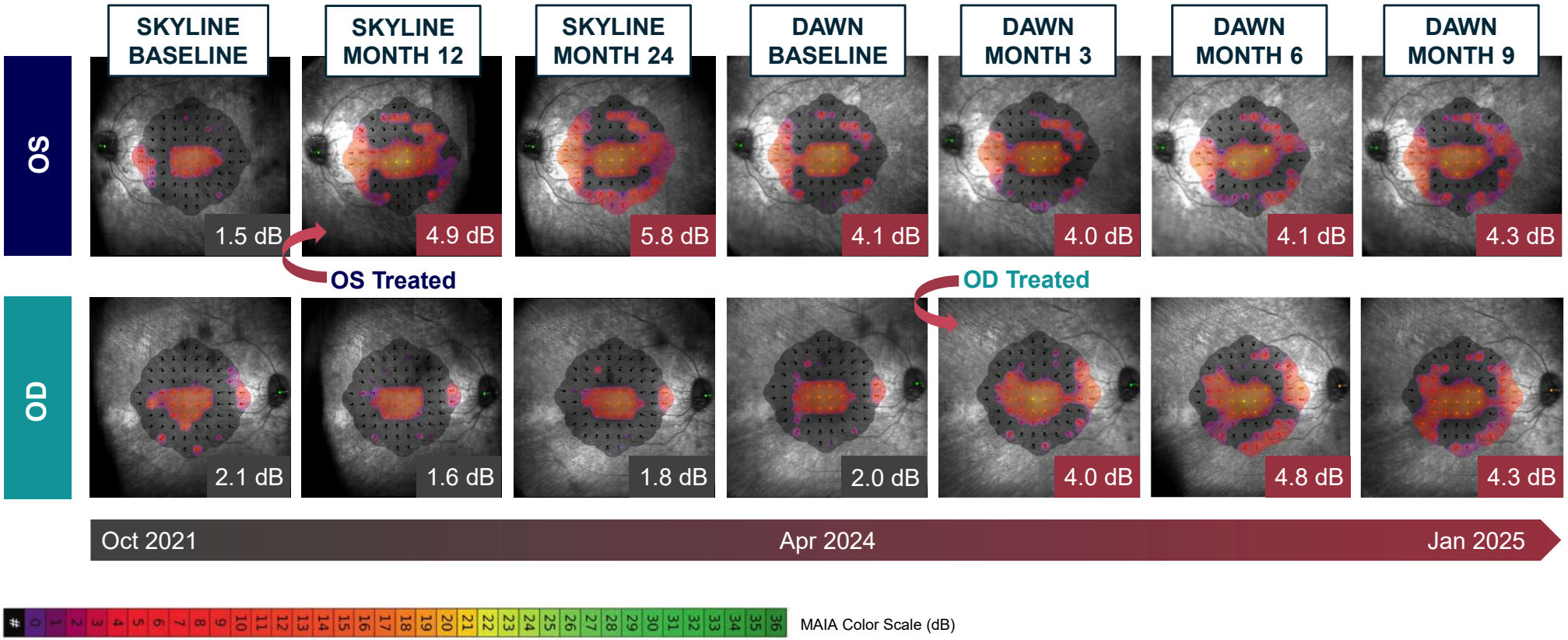
Early and sustained improvement in mean sensitivity



CFB = change from baseline; MP = microperimetry; SE = study eye (newly treated); FE = fellow eye (previously treated); HD = high dose; LD= low dose
Data was excluded from analysis at an individual timepoint if fixation loss was >20%

Case Example: Microperimetry Response Over Time

Age	Laru-zova Dose	SKYLINE Study Eye	DAWN Study Eye
37	6.8 × e^{11} vg/eye OS 3.7 × e^{11} vg/eye OD	OS	OD



Conclusions: Phase 2 DAWN Month 6+ Interim Analysis

laru-zova (AGTC-501) was well-tolerated by all open-label participants

Data show promising improvements in visual function

- To date, laru-zova has been well-tolerated in the Phase 2 DAWN study
  - Ocular TEAEs were generally non-serious and mild to moderate in severity
- Data show promising early improvements in low luminance visual acuity (LLVA), a critical measure of visual function
- The benefit-risk profile supports on-going clinical development for the treatment of patients with XLRP caused by *RPGR* mutations

TEAE = treatment emergent adverse event; XLRP = X-linked retinitis pigmentosa; RPGR = retinitis pigmentosa GTPase regulator

Thank you to all investigators, surgeons and site staff, along with the study participants and their families in the DAWN study

ARVO 2025, Salt Lake City, Utah

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