Subretinal Gene Therapy laru-zova for X-linked Retinitis Pigmentosa (XLRP): Phase 2 DAWN Trial, Preliminary Month 9+ Results

Rajiv Anand, MD[1,2], David Birch, PhD[2], Mark E. Pennesi, MD, PhD[2,3], Sandeep Grover, MD[4], Robert A. Sisk, MD[5], Anne Fulton, MD[6], Efren Gonzalez, MD[6], Aleksandra Rachitskaya, MD[7], Paul Yang, MD, PhD[3], Andreas Lauer, MD[3], Darin Curtiss, PharmD[8]

1. Texas Retina Associates, Dallas, TX; 2. Retina Foundation of the Southwest, Dallas, TX; 3. OHSU Casey Eye Institute. Portland, OR; 4. University of Florida, Jacksonville, FL; 5. Cincinnati Eye Institute, Cincinnati, OH; 6. Boston Children's Hospital, Boston, MA; 7. Cleveland Eye Institute, Cleveland, OH; 8. Beacon Therapeutics, Cambridge, MA

Speaker Disclosures:

Beacon Therapeutics (C, F)

C= Consultant, F=Clinical trial/research support

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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

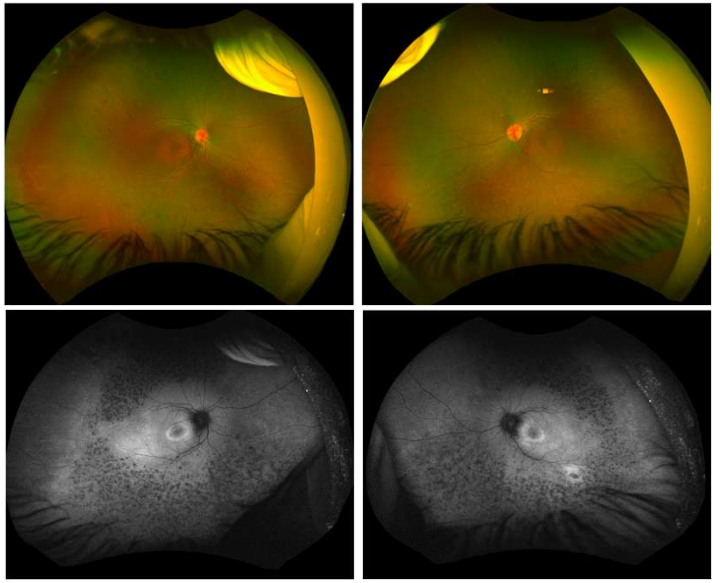
Rare inherited retinal disease characterized by progressive photoreceptor degeneration[1]

>70% 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

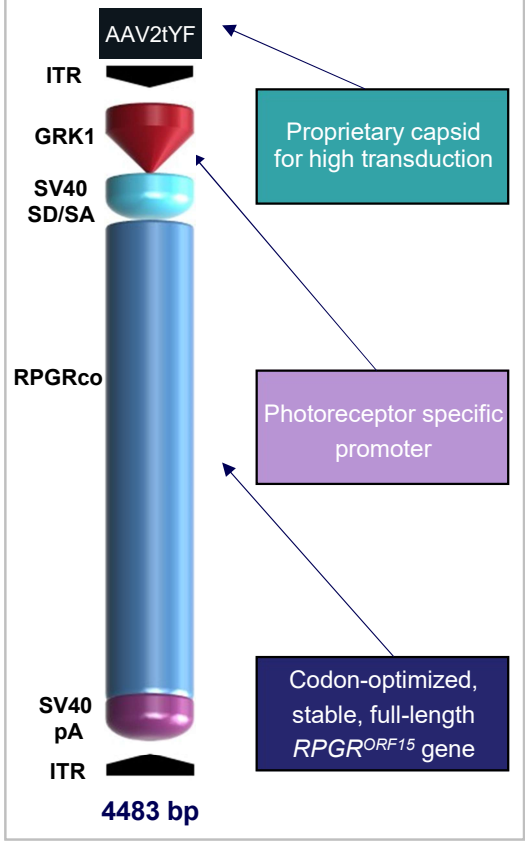
Images from a 12 year old male patient with XLRP

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.

laru-zova

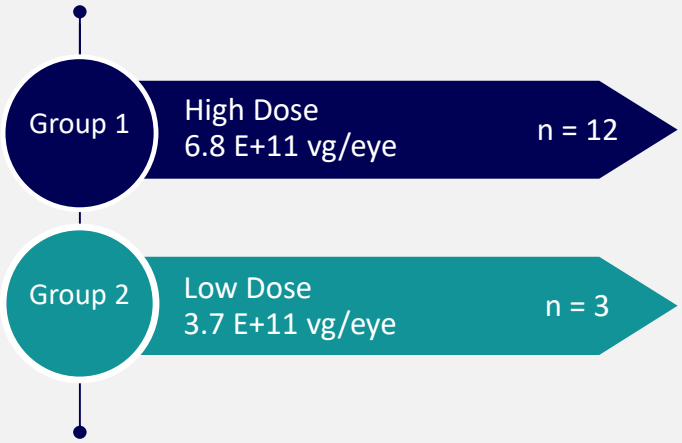
Subretinally delivered functional copy of *RPGR* gene for XLRP



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

Screening M1 M3 M6 M9 M12 M24 Y3, Y4, Y5



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 visual function and functional vision measures, including low luminance visual acuity (LLVA), mean sensitivity via microperimetry, and mobility course scores

5-year follow-up post treatment[1]

Most participants were previously treated in the 1st eye with laru-zova in Phase 1/2 HORIZON and Phase 2 SKYLINE studies

XLRP = X-linked retinitis pigmentosa; RPGR = retinitis pigmentosa GTPase regulator; vg = vector genomes; AE = adverse event; SAE = serious adverse event; 1. NCT06275620. ClinicalTrials.gov. Accessed August September 6, 2024. https://clinicaltrials.gov/study/NCT06275620

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

- **No SUSARs, retinal detachments or endophthalmitis reported**
- **Majority of TEAE's were related to the surgical procedure or protocol-required steroids and have resolved**
- **Majority of ocular inflammation was mild and transient in nature**

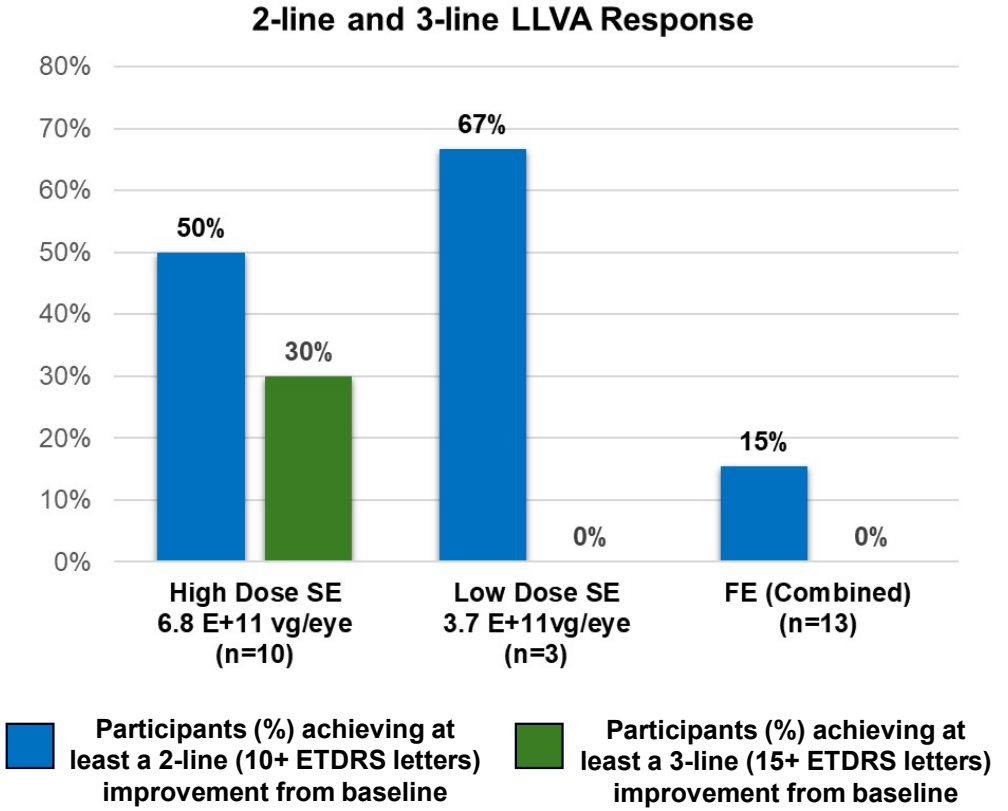
		Group 1 High Dose (n = 12)		Group 2 Low Dose (n = 3)	
	Preferred Term	**Study Eye**	**Fellow Eye***	**Study Eye**	**Fellow Eye***
Ocular SAEs	Glaucoma** *(reported as steroid induced ↑ IOP)*	1	0	1	0
Ocular TEAEs occurring in > 2 participants	Glaucoma *(reported as steroid induced ↑ IOP)*	8	0	2	1
	Conjunctival Hemorrhage	8	0	2	0
	Conjunctival Hyperemia	7	0	0	0
	Ocular Discomfort	7	0	0	0
	Cataract Subcapsular	4	4	2	0
	Anterior chamber cell	4	1	1	0
	Eye Pain	3	0	2	0
	Vitreal Cells	4	0	1	0
	Vision blurred	3	1	1	0
	Epiretinal membrane	4	0	0	0
	Metamorphopsia	3	0	1	0
	Dry eye	2	1	1	0
	Eye irritation	3	0	0	0
	Eyelid ptosis	2	0	1	0
	Injection site atrophy	2	0	1	0

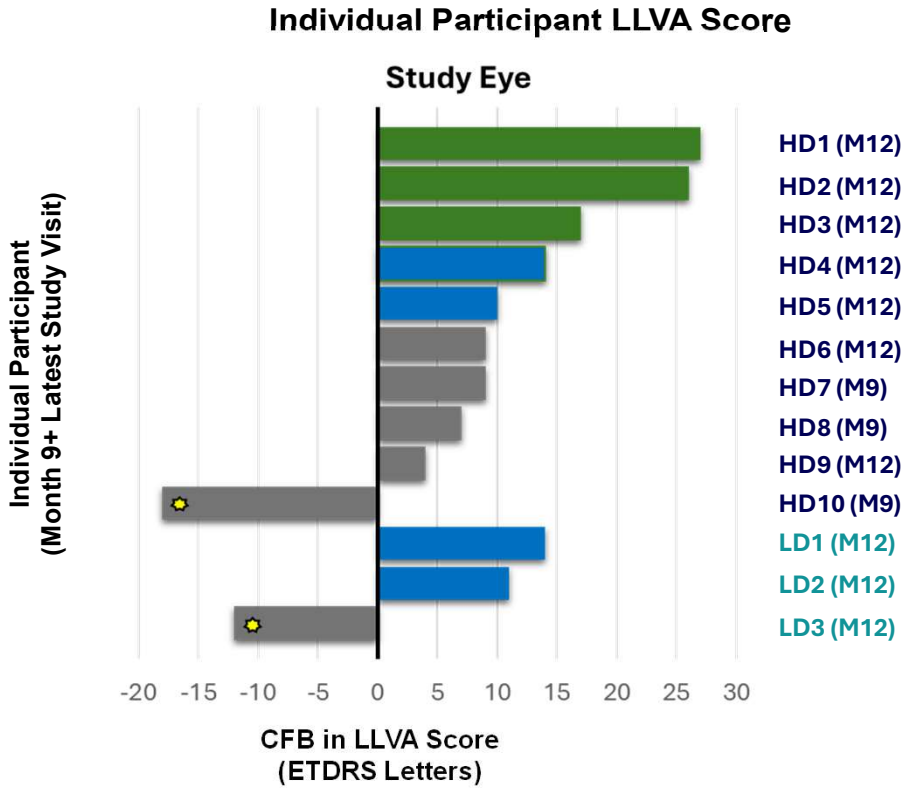
**Fellow Eye = eyes previously treated with an AAV vector-based full-length RPGR gene therapy*
***Related to protocol-required corticosteroids*

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.

Low Luminance Visual Acuity (LLVA) Response at Month 9+

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





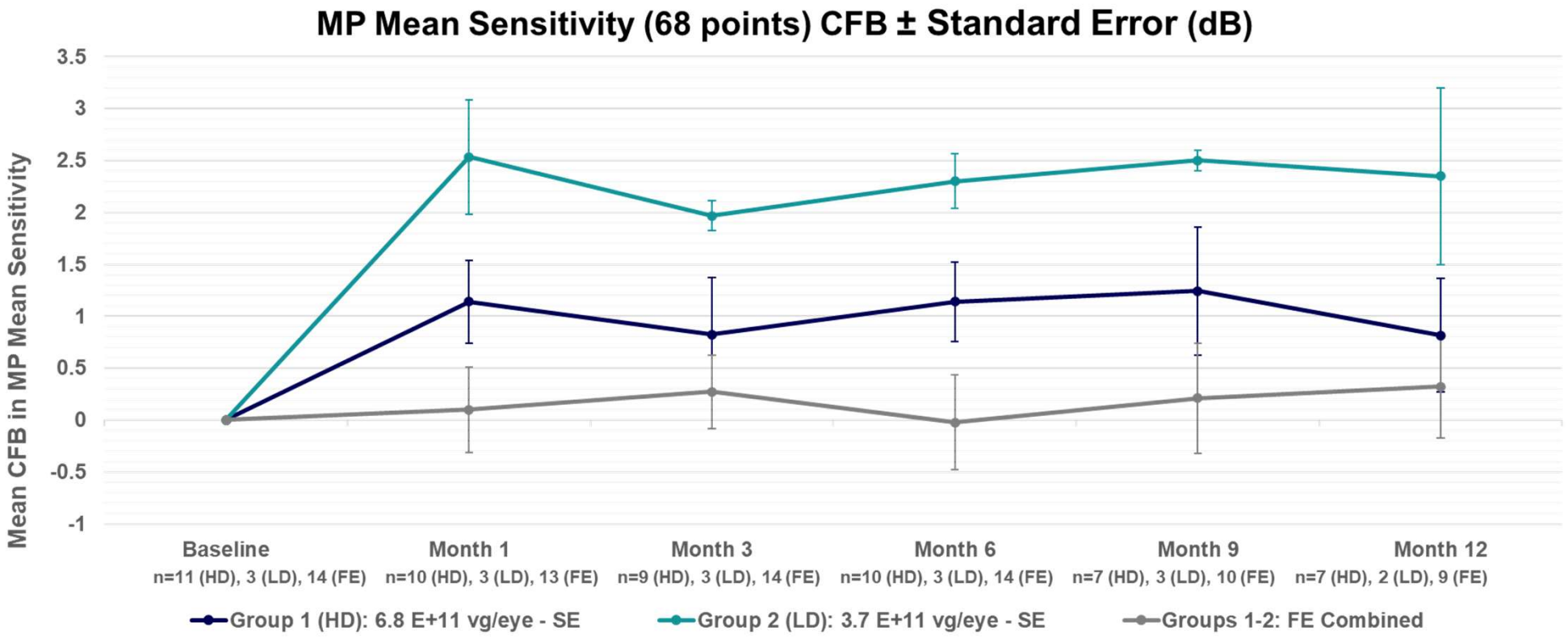
Both participants had worsening cataract in study eye; vision declined 3+ lines from prior visit

Month 9+ = participants that have reached the Month 9 or beyond follow-up visit; data used from most recent follow-up visit up to Month 12

SE = Study eye (newly treated); FE = Fellow eye (previously treated); ETDRS = Early Treatment of Diabetic Retinopathy Study, CFB = change from baseline; HD = high dose; LD = low dose

Microperimetry: Change in Mean Sensitivity

Early and sustained improvement in mean sensitivity

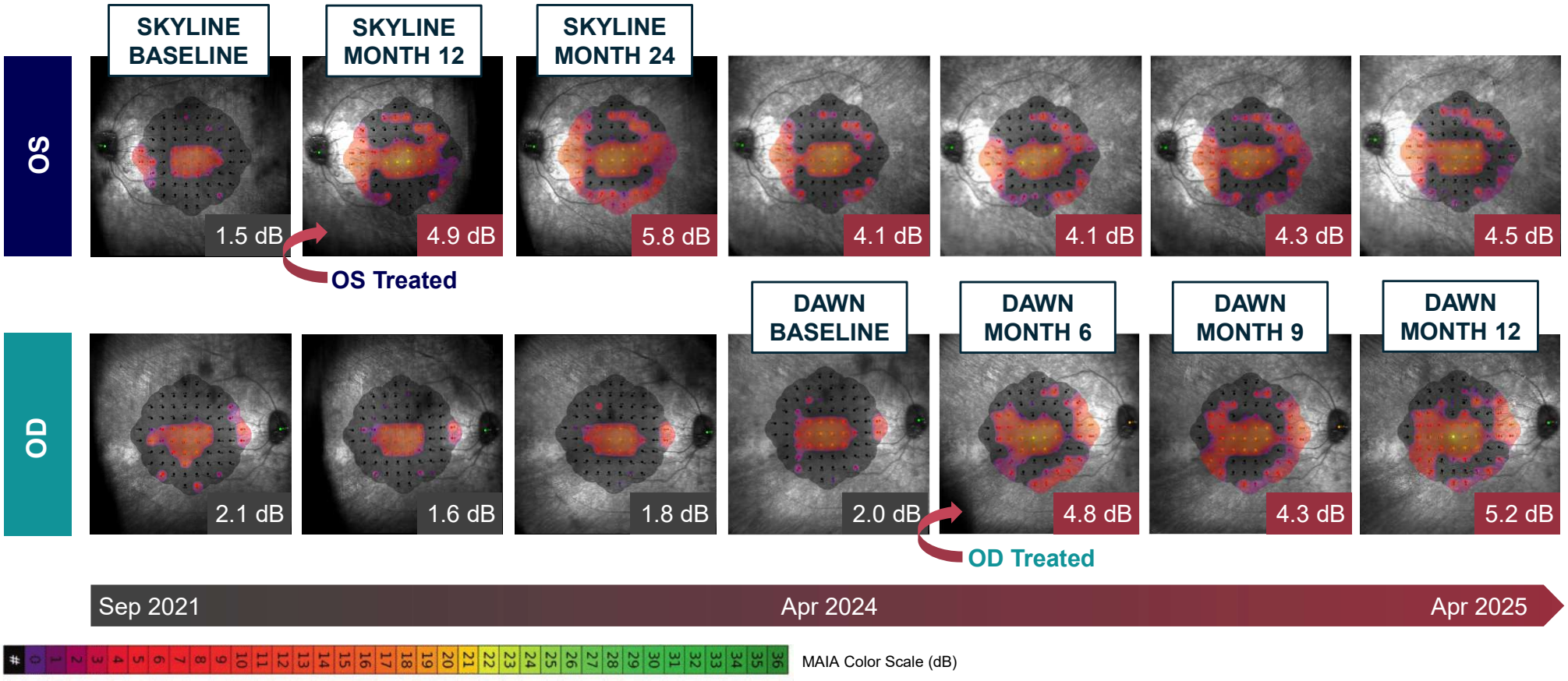


Data was excluded from analysis at an individual timepoint if fixation loss was >20%
CFB = change from baseline; MP = microperimetry; SE = study eye (newly treated); FE = fellow eye (previously treated); HD = high dose; LD= low dose

Case Example: Microperimetry Response Over Time

Age	Laru-zova Dose	SKYLINE Study Eye	DAWN Study Eye
36	6.8 × e^{11} vg/eye OS 3.7 × e^{11} vg/eye OD	OS	OD

3+ years follow-up to date across 2 studies



Conclusions: Phase 2 DAWN Month 9+ Interim Analysis

laru-zova was well-tolerated by all 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
- Pivotal VISTA study recently completed enrollment in June 2025, with results expected in second half of 2026

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