Subretinal laru-zova Gene Therapy for XLRP: 36-Month Results of the Randomized, Controlled, Multicenter Phase 2 SKYLINE Trial

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Speaker Disclosures:

4D Molecular Therapeutics (F), AAVantarde Bio (C), Adverum (C), Ascidian Therapeutics (F), Astellas (C), Atsena Therapeutics (F), Beacon Therapeutics (C, F), Biogen (F), BlueRock Therapeutics (C), Editas Medicine (F), Endogena (C), Foundation Fighting Blindness (C, F), Janssen (C), MeiraGTx (C), Nanoscope Therapeutics (C), Ocugen (F), PYC Therapeutics (F), Sanofi (F), Sepul Bio (F), Sparing Vision (F), Spark Therapeutics (F), SpliceBio (F), TeamedOn (C).

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]

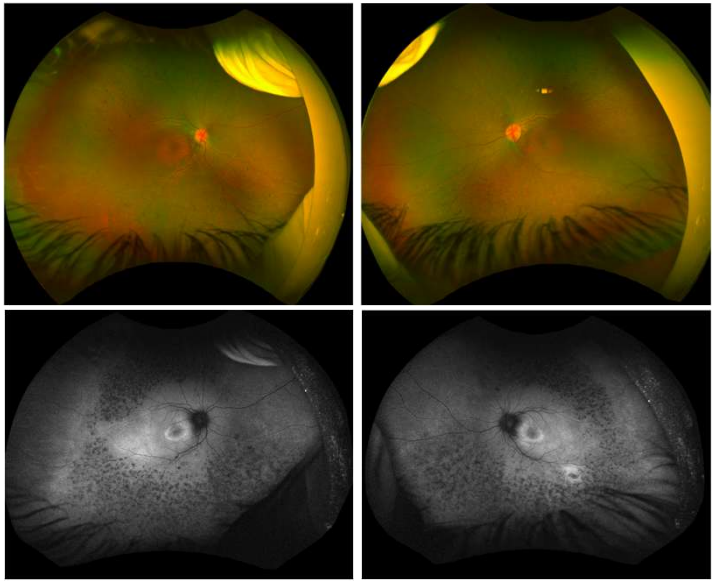
>70% of XLRP is due to mutations in the *RPGR* gene[2]

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

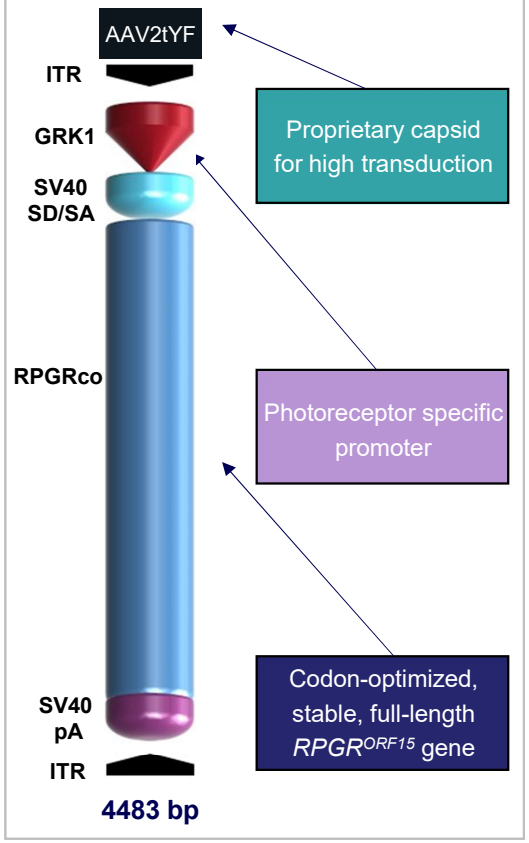
Images from a 12 year old male patient with XLRP

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.

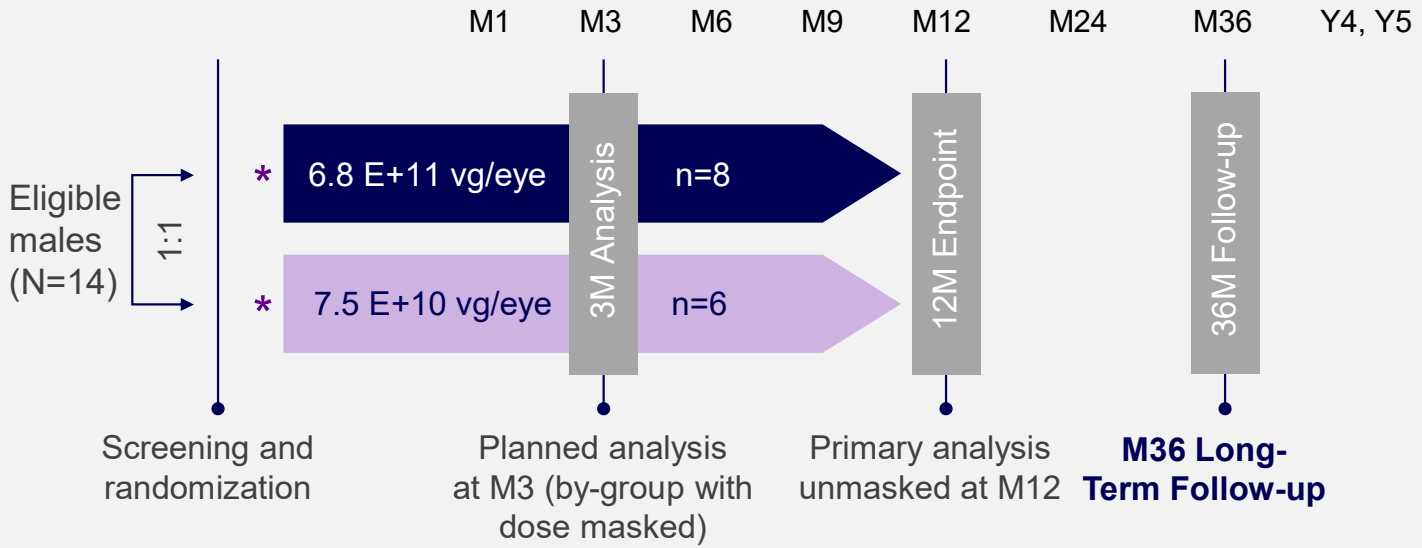
laru-zova

Subretinally delivered functional copy of *RPGR* gene for XLRP



Phase 2 SKYLINE Study Design

Randomized, Controlled, Multicenter Study to Evaluate the Safety, Efficacy, and Tolerability of laru-zova in Male Participants with XLRP caused by mutations in the *RPGR* gene



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

Primary Outcome

- Proportion of response by microperimetry between study and fellow eye at Month 12

Secondary Objectives

- Evaluate changes in functional vision as well as other visual function and structure assessments
- Evaluate safety and tolerability of laru-zova through M12 and obtain long-term safety data for 5 years

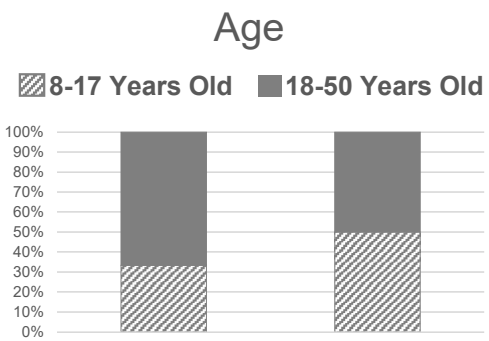
*All participants centrally dosed

XLRP = X-linked retinitis pigmentosa; RPGR = retinitis pigmentosa GTPase regulator; vg = vector genomes; FPI = first patient in. M = Month

1. NCT06333249. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06333249?lead=Beacon%20Therapeutics&rank=1#participation-criteria. 2. Data on file, Beacon Therapeutics (USA), Inc.

Phase 2 SKYLINE Demographics and Baseline Characteristics

Groups were well matched



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

N = 14
100% males

Endpoints	Low Dose (7.5 E+10 vg/eye) (N=6) SE	Low Dose (7.5 E+10 vg/eye) (N=6) FE	High Dose (6.8 E+11 vg/eye) (N=8) SE	High Dose (6.8 E+11 vg/eye) (N=8) FE
BCVA (ETDRS letters)	**68.3** (3.20) 63, 73	**73.7** (1.75) 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 TEAEs were mostly non-serious and mild or moderate in severity

		Low Dose 7.5 E+10 vg/eye (n=6)		High Dose 6.8 E+11 vg/eye (n=8)	
	Preferred Term	**Study Eye**	**Fellow Eye**	**Study Eye**	**Fellow Eye**
Ocular SAEs	Glaucoma*	1	0	0	0
	Visual impairment**	1	0	0	0
Ocular TEAEs Related to laru-zova	Vitritis***	1	0	2	0
	Visual acuity reduced	2	0	0	0
	Eye pain	1	0	0	0
	Metamorphopsia	1	0	0	0
	Photopsia	1	0	0	0

No ocular SAEs were deemed related to laru-zova
Ocular TEAEs related to laru-zova were considered mild or moderate in severity

**Related to protocol required corticosteroids; severe; treated with medication; resolved by Study Day 181*
***Related to injection procedure; ongoing*
****All started POD1 with 0.5-2+ vitreous cells and were resolved by M4*

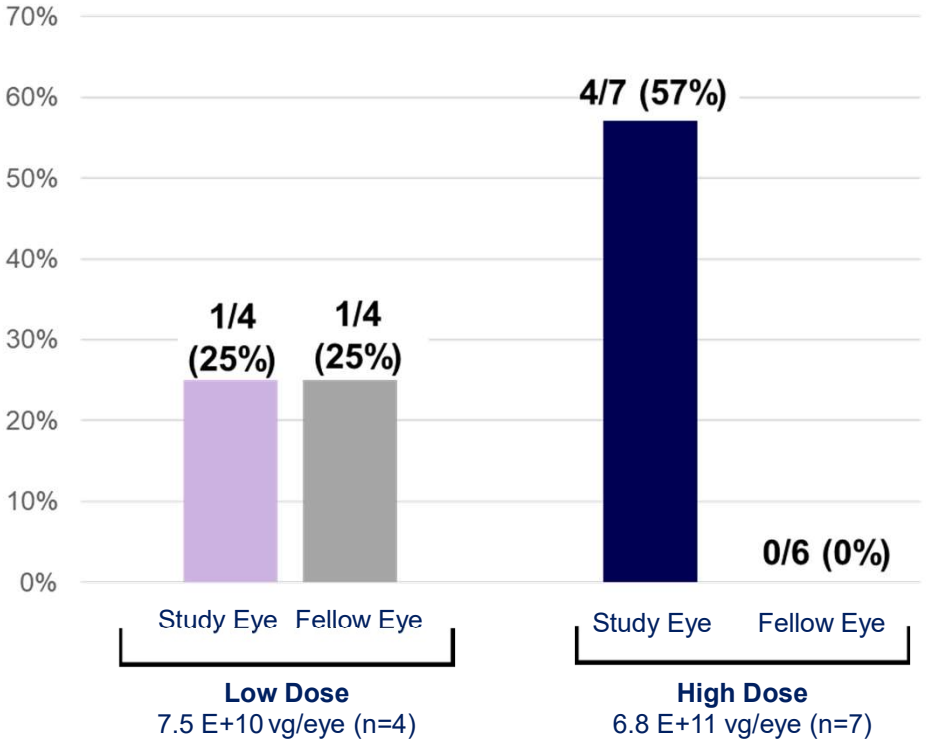
TEAE = treatment emergent adverse event; SAE = serious adverse event; vg/eye = vector genomes / eye.

Phase 2 SKYLINE Efficacy Summary at Month 36

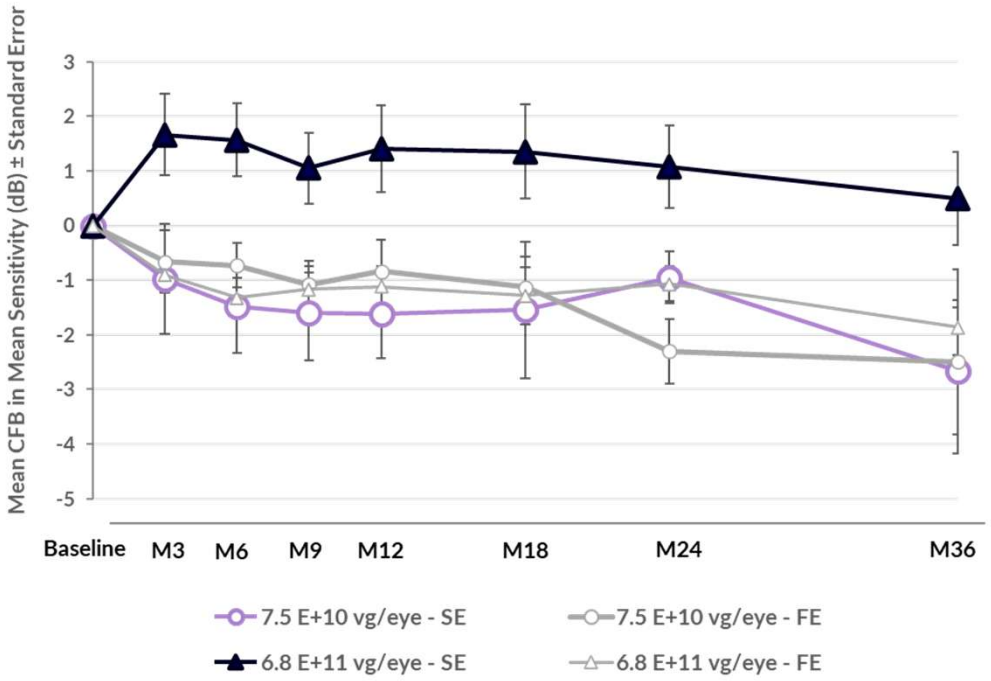
Greater response rate seen in the high dose study eyes compared to low dose and fellow eyes, consistent from Month 12 to Month 36

Responder Rate Month 36

Patients (%) Achieving a ≥7 dB Improvement from Baseline in ≥5 Loci at Month 36 (Whole Grid)



Change from Baseline Mean Sensitivity (Whole Grid)



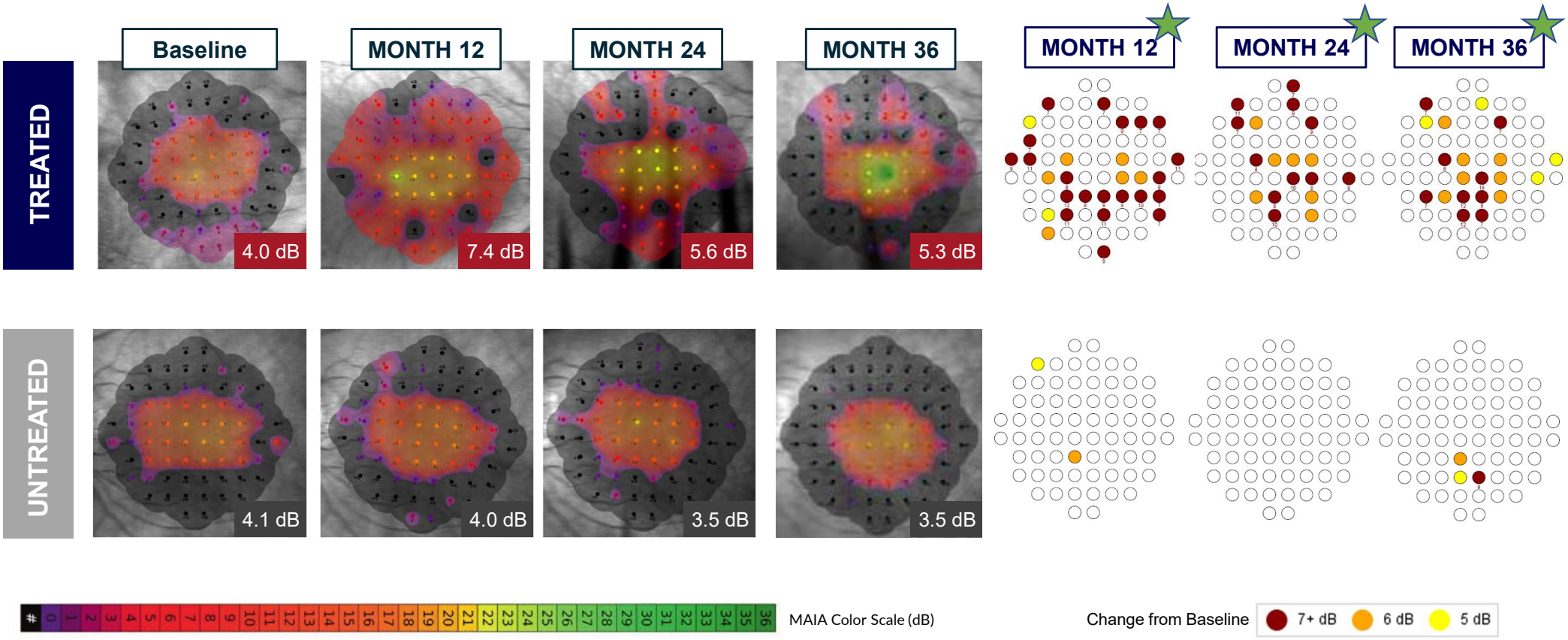
Note: 2 participants in the low dose group missed the M36 visit; 1 participant in the high dose group only had microperimetry data available for the fellow eye at M36 due to cataract; 6 (5 in high dose and 1 low dose) participants rolled over to the DAWN study in which the fellow eye was treated with laru-zova; 2 participants in the high dose group have missing data for the fellow eye due to treatment prior to M36.

SE = Study eye
FE = Fellow eye

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)



Conclusions
Phase 2 SKYLINE 36-Month Analysis

Data show sustained improvements in visual function

Laru-zova was well-tolerated by participants

- High dose treatment group showed sustained improvements in retinal sensitivity through 36M
- No ocular SAEs were deemed related to laru-zova 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; 6 participants have rolled over into DAWN study with laru-zova treatment in fellow eye
- The benefit-risk profile supports on-going clinical development for the treatment of patients with XLRP caused by *RPGR* mutations

SAE = Serious Adverse Event; TEAE: Treatment Emergent Adverse Event; XLRP = X-linked retinitis pigmentosa; RPGR = retinitis pigmentosa GTPase regulator