PO4688 - 0633

SUBRETINAL GENE THERAPY LARU-ZOVA FOR X-LINKED RETINITIS PIGMENTOSA (XLRP)

Phase 2 SKYLINE Trial Post-Hoc Microperimetry Scotomatous vs. Nonscotomatous Analysis

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X-linked retinitis pigmentosa (XLRP)

is an early-onset inherited retinal disease (IRD), characterized by the progressive loss of rod and cone photoreceptors[1-5]

There are no treatment options for XLRP

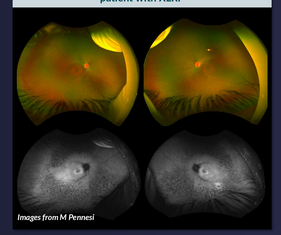
Primarily affecting males, symptoms begin in childhood and progress to central vision loss and legal blindness by median age of 45[3]

Early-Stage: Childhood
- Early changes in peripheral vision
- Night blindness
- Difficulties in low light environments

Mid-Stage: Ages 20–30 yrs
- No longer safe to drive
- Difficulty reading, completing chores, playing sports

Late-Stage: Ages 40–50 yrs
- Tunnel vision; progressive loss of visual acuity
- Loss of reading ability
- Increased difficulty navigating unfamiliar areas

Images from a 12-year old male patient with XLRP



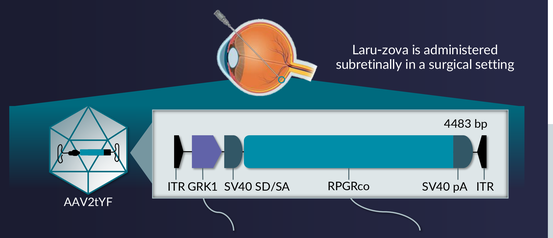
Images from M Pennesi

RPGR gene mutations underlie ≥70% of XLRP cases[2]

- *RGPR*-related XLRP is characterized by early peripheral rod degeneration, followed by later-onset cone dysfunction
- Loss of RPGR function likely disrupts protein transport, impairing phototransduction in the outer segment, ultimately resulting in photoreceptor dysfunction and death[6,7]

Laru-zova (laruparetigene zovaparvovec)

is an investigational gene therapy designed to deliver a functional, full-length copy of the *RPGR*^{ORF15} gene



Proprietary capsid for high transduction of rods and cones

Photoreceptor-specific **GRK1 promoter** targets only rods and cones

Codon-optimized, stable, full-length *RPGR*^{ORF15} gene for expressing high levels of RPGR^{ORF15} protein

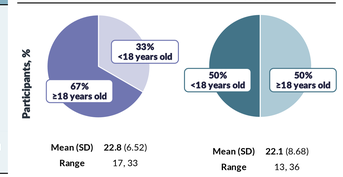
Laru-zova has the potential to restore the natural function of both rods and cones in XLRP caused by *RPGR* mutations

Participants

Baseline characteristics, mean (SD) range	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	**73.7** (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),[a] 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 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

[a] *Microperimetry by MAIA*

Age



SKYLINE enrolled 14 participants averaging ≈22 years old

Month 36 Safety Summary

	Preferred Term	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
Ocular SAEs	Glaucoma[a]	1	0	0	0
	Visual impairment[b]	1	0	0	0
Ocular TEAEs related to laru-zova	Vitritis[c]	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

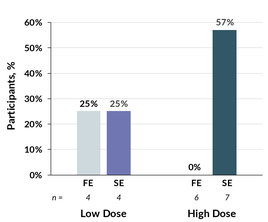
[a] *Related to protocol required corticosteroids; severe; treated with medication; resolved by Study Day 181.* [b] *Related to injection procedure; ongoing.* [c] *All started POD1 with 0.5-2+ vitreous cells and were resolved by M4.*

Ocular TEAEs were mostly non-serious and mild/moderate in severity; all ocular SAEs were deemed related to surgical injection procedure or prophylactic corticosteroid regimen

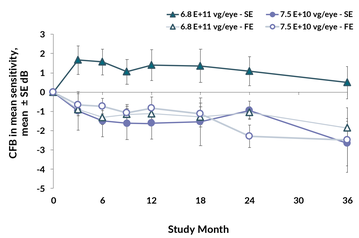
Microperimetry Analyses (whole grid)

- SKYLINE evaluated the change from baseline in mean sensitivity using microperimetry
- A **responder** was defined as a participant who achieved ≥7 dB improvement from baseline in ≥5 loci

Month 36 Responder Rate



Change from Baseline in Mean Sensitivity



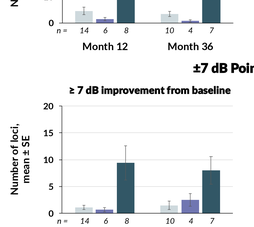
Note: 2 low dose group participants missed the Month 36 visit; 1 high dose participant had only fellow eye microperimetry data available at Month 36 due to cataract. 6 (5 high dose and 1 low dose) participants rolled over to DAWN in which the fellow eye was treated with laru-zova; 2 high dose participants have missing data for the fellow eye due to treatment prior to Month 36.

High-dose study eyes had greater response rate compared to low dose and fellow eyes, with retinal sensitivity improvement sustained from Month 12 to Month 36

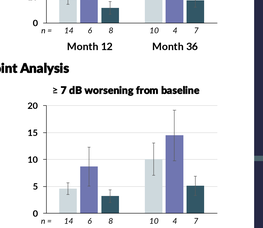
Points Changing from Scotomatous, Nonscotomatous (post-hoc)

- A post-hoc analysis evaluated the number of points on the 68-point microperimetry grid that changed from scotomatous (SC), defined as no light detected at a specific point via microperimetry, to non-scotomatous (NSC); and NSC to SC
- **High-dose eyes had a positive mean shift at Month 36 to more NSC points** when compared to baseline, while low-dose eyes and combined untreated FEs had a negative mean shift, indicating more SC points at Month 36 when compared to baseline

Scotomatous → Nonscotomatous *(improvement)*

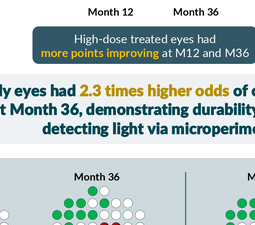


Nonscotomatous → Scotomatous *(worsening)*

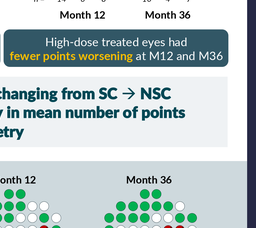


±7 dB Point Analysis

≥ 7 dB improvement from baseline



≥ 7 dB worsening from baseline



High dose
Low dose
Fellow eye (combined)

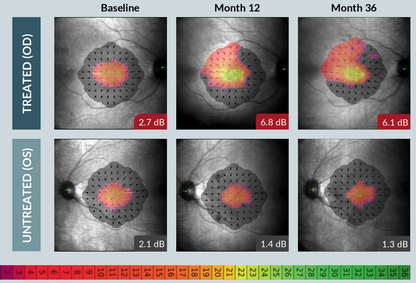
High-dose treated eyes had **more points improving** at M12 and M36

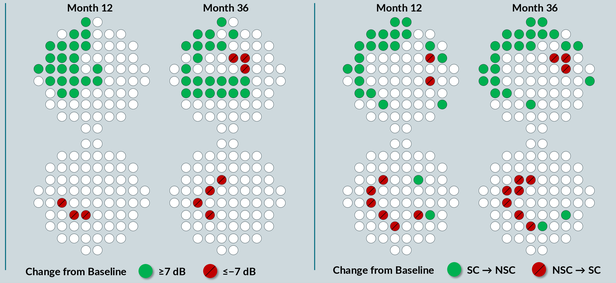
High-dose treated eyes had **fewer points worsening** at M12 and M36

High-dose study eyes had 2.3 times higher odds of changing from SC → NSC than NSC → SC at Month 36, demonstrating durability in mean number of points detecting light via microperimetry

Patient Case: Example of Responding Eye via Microperimetry

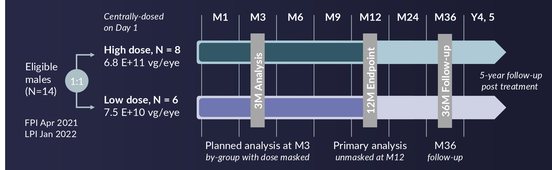
- 13 years old
- 6.8 E+11 vg/eye (OD)





SKYLINE

A phase 2 randomized, controlled, multicenter clinical trial evaluating 2 doses of subretinal laru-zova in male participants with XLRP caused by *RPGR* gene mutations



Primary Outcome

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

Secondary Outcomes

- Changes in visual function and functional vision
- Safety and tolerability

SKYLINE Results Summary

Sustained improvements in visual function with high-dose laru-zova

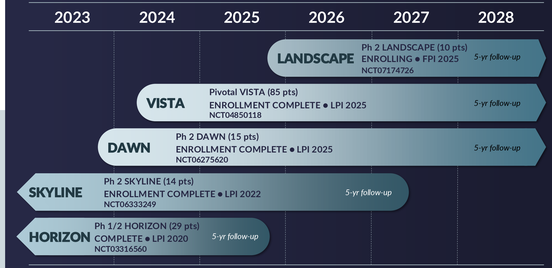
- At the Month 12 primary endpoint, improvement in retinal sensitivity was seen in the high-dose study eyes when compared to fellow eyes
- Retinal sensitivity improvements were **sustained through Month 36 in the high-dose study eyes**
- This post-hoc analysis shows durability in the mean number of points detecting light via microperimetry for the high-dose study eyes at Month 36

Laru-zova was generally well-tolerated by participants

- Ocular TEAEs were mostly non-serious and mild to moderate in severity
- All ocular SAEs were deemed related to surgical injection procedure or prophylactic corticosteroid regimen

Clinical Development Program

Comprehensive program to deliver a potential first-in-class therapy to patients with XLRP



SKYLINE results support continued development of laru-zova; VISTA pivotal results expected H2 2026

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For more information, please reach out to: medical@beacontx.com

References

1. Birch DG, et al. *Transl Vis Sci Technol*. 2023;12(6):5. **2.** Nguyen XT, et al. *Int J Mol Sci*. 2020;21(3):835. **3.** Chivers M, et al. *Clinicoecon Outcomes Res*. 2021;13:565-572. **4.** Branham K, et al. *Ophthalmic Genetics*. 2025;1-7. **5.** Prem Senthil M, et al. *Eye (Lond)*. 2017;31(5):741-748. **6.** Martinez-Fernandez de la Camara C, et al. *Expert Opin Emerg Drugs*. 2022;27(4):431-443. **7.** Pechnikova NA, et al. *J Clin Med*. 2025;14(3):898.

Abbreviations

AAV2tYF, AAV2 capsid variant with three surface tyrosine residues changed to phenylalanine; **BCVA,** best-corrected visual acuity; **CFB,** change from baseline; **dB,** decibel; **ETDRS,** Early Treatment Diabetic Retinopathy Study; **FE,** fellow eye; **FPI,** first patient in; **H,** half; **IRD,** inherited retinal disease; **ITR,** inverted terminal repeat; **LPI,** last patient in; **M,** month; **MAIA,** macular integrity assessment; **NSC,** nonscotomatous; **ORF15,** open reading frame 15; **pA,** polyadenylation signal; **RPGR,** retinitis pigmentosa GTPase regulator; **RPGRco,** codon-optimized human RPGR complementary DNA; **SA,** splice acceptor; **SAE,** serious adverse event; **SD,** splice donor; **SV40,** simian virus 40; **SC,** scotomatous; **SE,** study eye; **TEAE,** treatment-emergent adverse event; **vg,** vector genome; **XLRP,** X-linked retinitis pigmentosa; **Y,** year.

Study Disclosures

Laru-zova is an investigational product; it has not been approved by the FDA. Conclusive evidence of efficacy and safety of laru-zova will require further investigation in additional clinical trials.

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Author Disclosures

All authors are employees (E) of Beacon Therapeutics (USA), Inc.