Subretinal Gene Therapy laru-zova (AGTC-501) for X-Linked Retinitis Pigmentosa (XLRP) Phase 2 Multicenter Study (DAWN): Preliminary 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

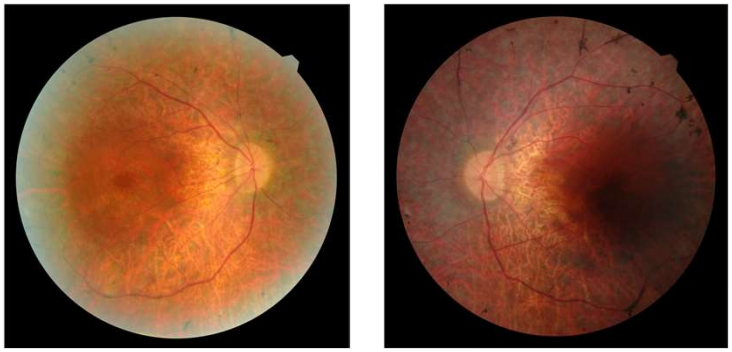
Severe, aggressive, inherited retinal disease characterized by progressive photoreceptor degeneration[1]

Majority 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** with RPGR mutations[3]

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[2]	Increasing loss in peripheral vision[4]	Tunnel vision, central VA loss[6]
Difficulties in low light environments [2]	Difficulties driving, running into objects, difficulty with daily tasks[1,5]	Legal blindness, significant impact on daily life, loss of autonomy[1,4,5]



Images from PE. Stanga

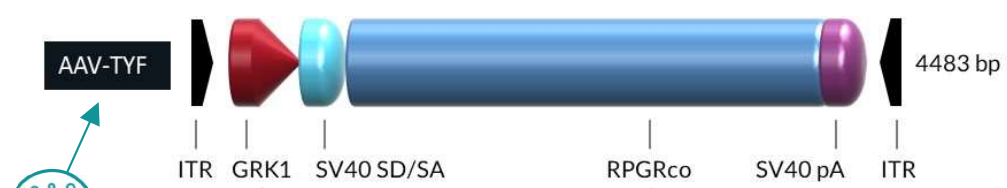
Two color fundus images of a 46 year old male XLRP patient

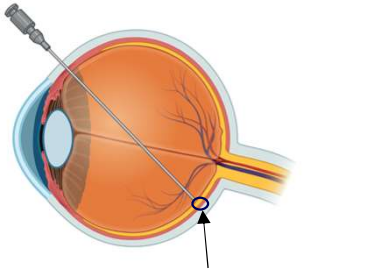
VA = visual acuity

1. Chivers M, et al. *Clinicoecon Outcomes Res.* 2021;13:565-572. 2. Churchill JD, et al. *Invest Ophthalmol Vis Sci.* 2013;54(2):1411-1416. 3. Vinikoor-Imler LC, et al. *Ophthalmic Genet.* 2022 Oct;43(5):581-588 4. Di Iorio V, et al. *Invest Ophthalmol Vis Sci.* 2020;61(14):36. 5. Senthil MP, et al. *Eye (Lond).* 2017;31(5):741-748

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]

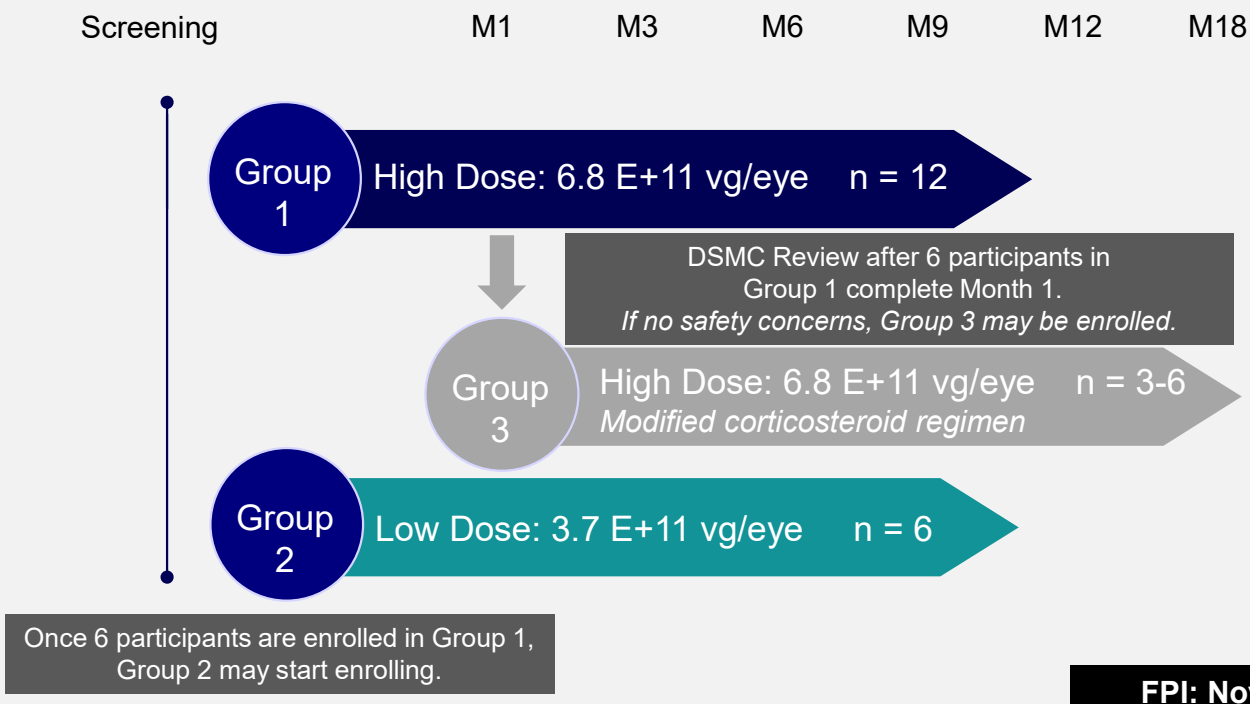
Received Innovative Medicine Designation (ILAP) in the UK, Priority Medicine (PRIME) in the EU, and Fast Track in the US

XLRP = X-linked retinitis pigmentosa RPGR = retinitis pigmentosa GTPase regulator; AAV = adeno-associated virus; GRK1 = rhodopsin kinase

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.

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



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 microperimetry (MAIA), FST
  - Ora-VNC™ mobility course score, MObility Standardized Test-Virtual Reality mobility course score
  - MRDQ

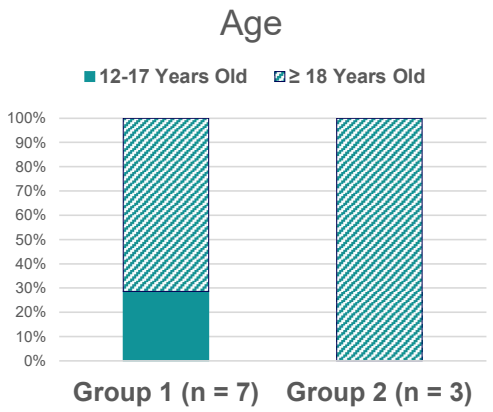
FPI: November 2023; 5-year follow-up post treatment[1]

XLRP = X-linked retinitis pigmentosa; RPGR = retinitis pigmentosa GTPase regulator; vg = vector genomes; FPI = first patient in; AE = adverse event; SAE = serious adverse event; Grade 3 or higher AEs = severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated, disabling, limiting self care activities of daily living; MAIA = macular integrity assessment; FST = full field stimulus threshold; BCVA = best corrected visual acuity; LLVA = low-luminance visual acuity

1. NCT06275620. ClinicalTrials.gov. Accessed October 17, 2024. https://clinicaltrials.gov/study/NCT06275620

Phase 2 DAWN: Demographics and Baseline Characteristics

N = 10, 100% males



Mean (SD)	**28.3 (12.98)**	**26.0 (11.27)**
Range	**16, 50**	**19, 39**

Baseline Characteristics	**Group 1 High Dose: 6.8 E+11 vg/eye (n = 7)**		**Group 2 Low Dose: 3.7 E+11 vg/eye (n = 3)**	
	Study Eye	**Fellow Eye***	**Study Eye**	**Fellow Eye***
BCVA (ETDRS letters)	**65.6 (8.58)** 55, 76	**68.6 (7.04)** 59, 78	**74.3 (1.53)** 73, 76	**78.3 (6.35)** 71, 82
LLVA (ETDRS letters)	**45.6 (13.46)** 24,62	**55.9 (8.88)** 40, 70	**53.3 (5.77)** 50, 60	**66.3 (6.03)** 60, 72
LLD (ETDRS letters)	**20 (10.66)** 2, 34	**12.7 (5.38)** 5, 19	**21 (4.36)** 16, 24	**12 (2.65)** 10, 15
Mean Sensitivity (whole grid)[1](dB)	**1.93 (0.743)** 1.3, 3.5	**3.36 (2.057)** 1.3, 6.3	**2.85 (1.202)** 2.0, 3.7	**4.75 (0.919)** 4.1, 5.4
Previous Trial				
Phase 1 / 2 (HORIZON)	**3**		**0**	
Phase 2 (SKYLINE)	**3**		**3**	
Biogen trial	**1**		**0**	
Time Between Doses (months)	**44.02[2]** 32.9, 62.8		**31.6** 29.9, 32.6	

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.
1. Microperimetry by MAIA; 2. Excludes one participant in Biogen trial

Phase 2 DAWN Safety: Ocular Treatment Emergent Adverse Events (TEAEs) at Month 3

Ocular TEAEs were mostly non-serious, mild or moderate in severity

No study agent-related TEAEs, including no study agent-related ocular inflammatory AEs

No SUSARs, retinal detachments or endophthalmitis reported

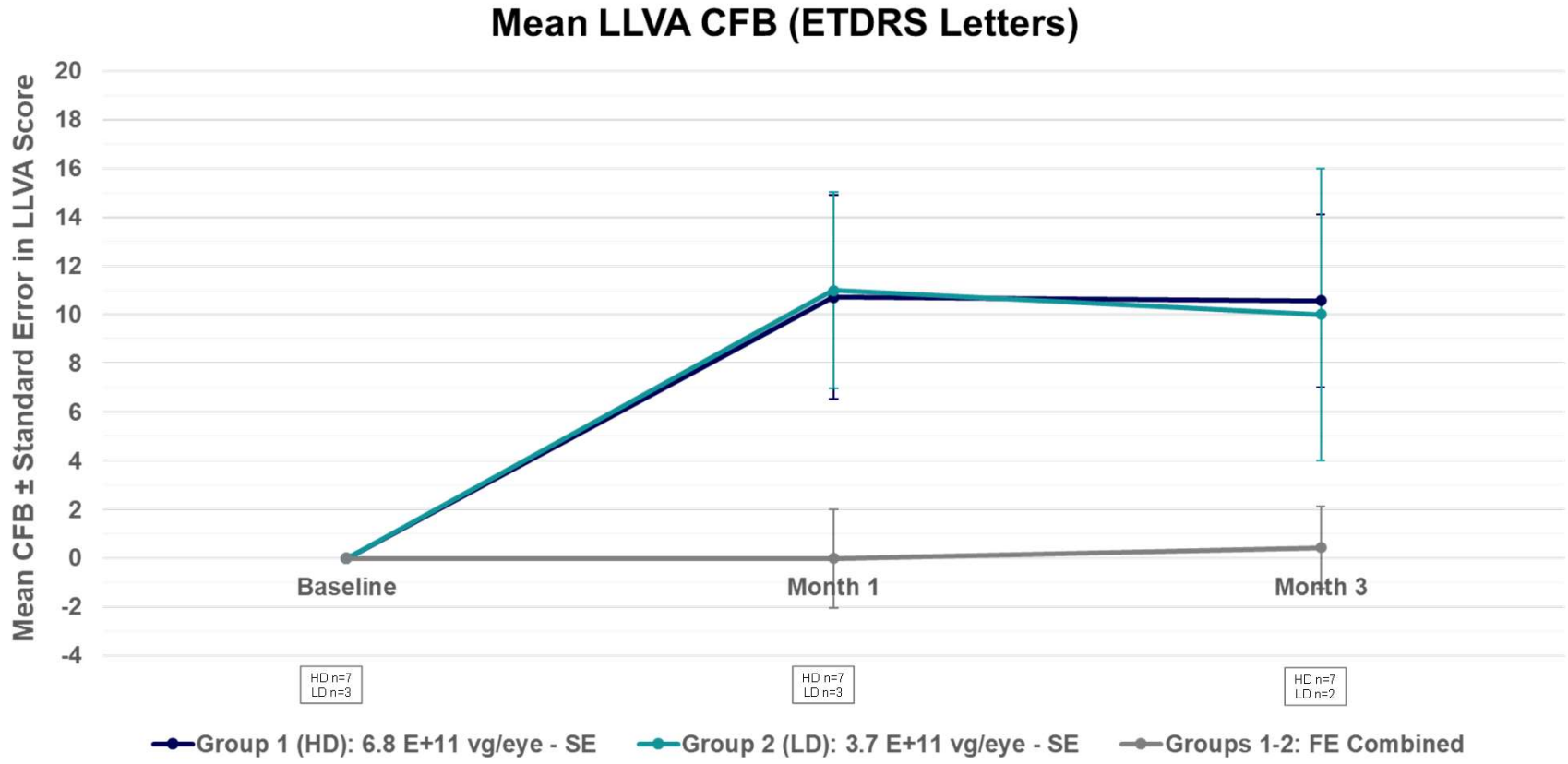
	Ocular TEAE	Group 1 High Dose: 6.8 E+11 vg/eye (n = 7)		Group 2 Low Dose: 3.7 E+11 vg/eye (n = 3)		All Patients (n = 10)	
		Study Eye	Fellow Eye*	Study Eye	Fellow Eye*	Study Eye	Fellow Eye*
Serious	Glaucoma**	0	0	1	0	1	0
Moderate	Eye pain, injection-related	2	0	2	0	4	0
	Eye pain, corticosteroid-related	1	0	0	0	1	0
	IOP increased	1	0	2	1	3	1
	Vision blurred	1	0	0	0	1	0

**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*
All patients received standard dose corticosteroid regimen

AE = adverse event; SUSAR = suspected unexpected serious adverse reaction; vg = vector genomes

Phase 2 DAWN Efficacy
Mean Low Luminance Visual Acuity (LLVA) to Month 3

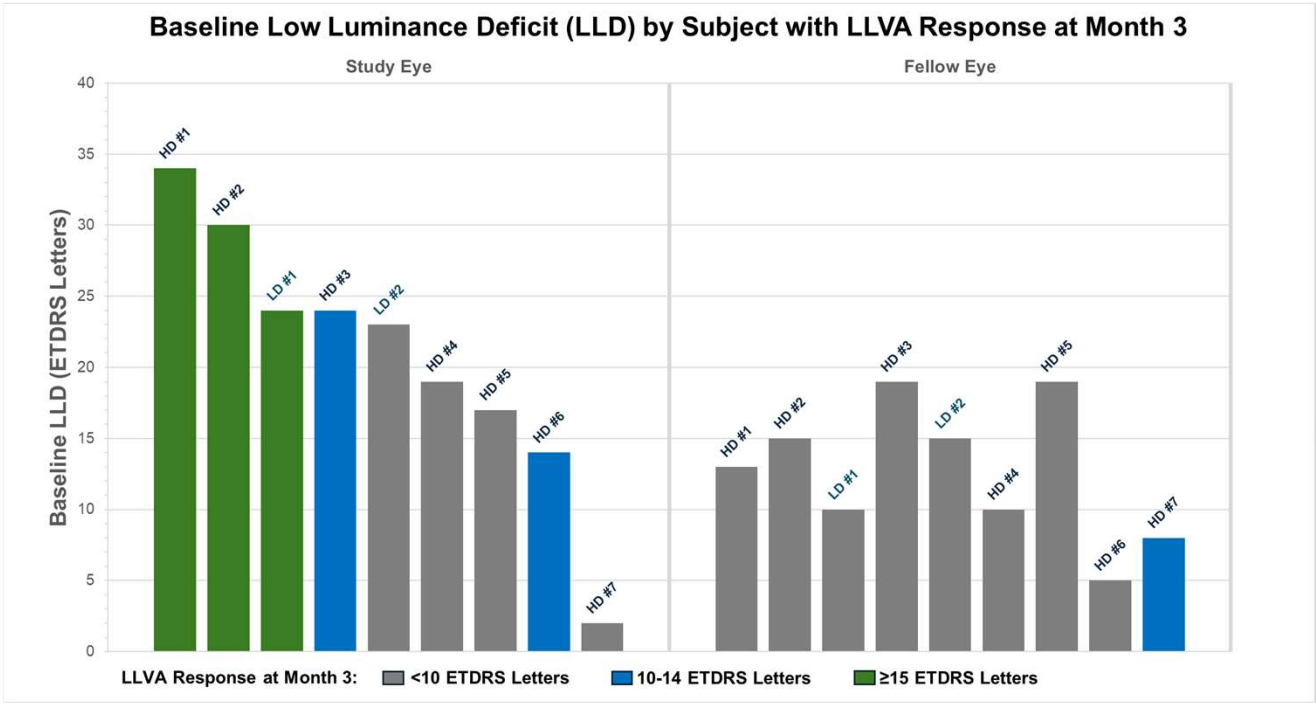
Early improvement in mean LLVA in DAWN Study Eyes

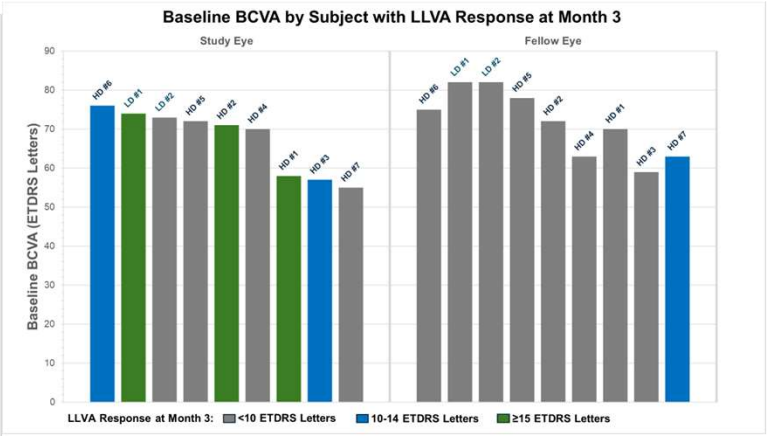


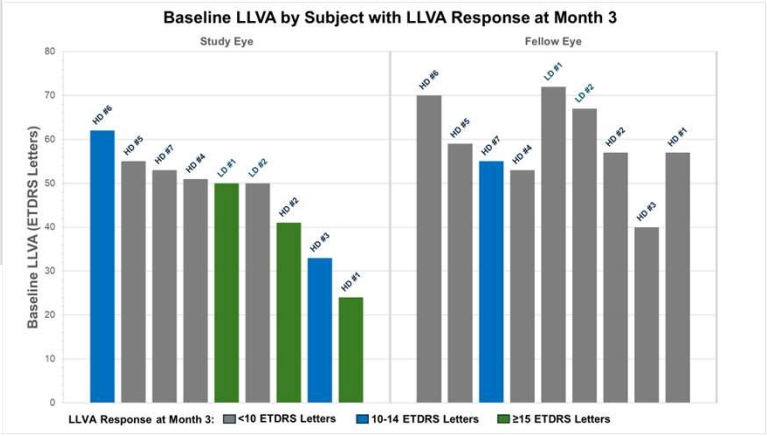
CFB = change from baseline; ETDRS = Early Treatment of Diabetic Retinopathy Study; vg = vector genomes; SE = study eye (newly treated); FE = fellow eye (previously treated); HD = high dose; LD = low dose

Phase 2 DAWN Efficacy

Higher baseline low luminance deficit (LLD) may be a predictor of low luminance visual acuity (LLVA) response at Month 3







When looking at LLVA response (defined as a ≥ 15 or ≥ 10 letter gain) across treated eyes, early data suggests higher baseline LLD may be a predictor of LLVA Response

CFB = change from baseline; ETDRS = Early Treatment of Diabetic Retinopathy Study; LLVA = low luminance visual acuity; HD = Group 1, high dose; LD = Group 2, low dose

Conclusions: Phase 2 DAWN 3-Month 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
  - No study agent-related TEAEs, ocular SAEs or ocular inflammatory AEs were reported
  - Ocular TEAEs were mostly 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
- Higher baseline low luminance deficit (LLD) may be a predictor of LLVA response at Month 3
- 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; SAE = serious adverse event; XLRP = X-linked retinitis pigmentosa RPGR = retinitis pigmentosa GTPase regulator