Beacon Therapeutics
Subretinal Gene Therapy laru-zova (AGTC-501) for X-Linked Retinitis Pigmentosa (XLRP)

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Overview of laru-zova (AGTC-501) Gene Therapy for XLRP

Proprietary capsid designed for high transduction of codon-optimized, full-length transgene

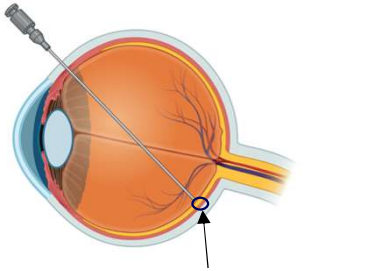

Image created by R. Sisk in BioRender

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.

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laru-zova (AGTC-501) Clinical Development Program

	Name	Status	Phase	Participants	Data availability
ONGOING	HORIZON	• **Ongoing** – enrollment complete *(since Apr-18)*	• **Phase 1/2** *Dose escalation*	• 29 participants	• 36-month data available, recently presented at Euretina 2024 meeting
	SKYLINE	• **Ongoing –** enrollment complete *(since Apr-21)*	• **Phase 2**	• 14 participants	• 24-month data available, recently presented at AAO 2024 meeting
	DAWN	• **Ongoing –** enrolling	• **Phase 2** *Open label dose confirmation study*	• Participants previously treated in full length *RPGR* gene therapy study	• 3-month data available for first 9 participants
	VISTA	• **Ongoing –** enrolling	• **Phase 2/3** *Global, randomized, masked*	• Participants with XLRP	N/A

XLRP = X-linked retinitis pigmentosa; RPGR=retinitis pigmentosa GTPase regulator.

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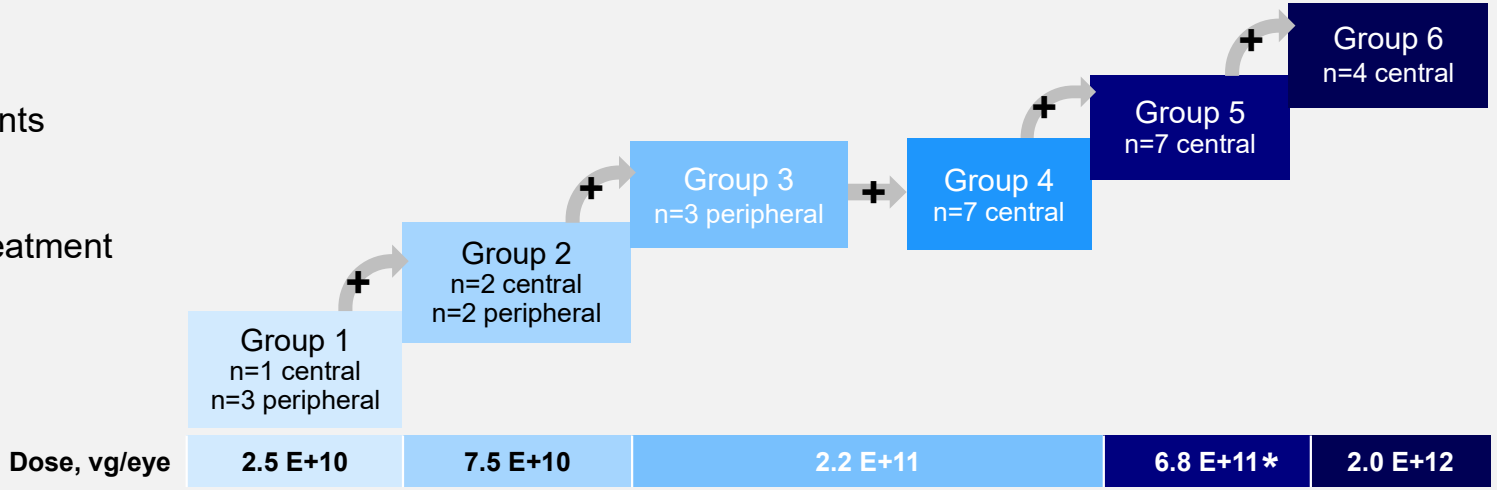
Phase 1/2 HORIZON Study Design

OPEN-LABEL, DOSE ESCALATION STUDY TO EVALUATE THE SAFETY AND EFFICACY OF LARU-ZOVA (AGTC-501) IN MALE PARTICIPANTS WITH XLRP CAUSED BY MUTATIONS IN THE *RPGR* GENE

- 29 eligible male participants
- 4 US sites
- FPI April 2018
- 5 years follow-up post treatment



Cohorts sequentially dosed based on approval by DSMC (+)

**Dose selected for Phase 2 and Phase 2/3*

Primary objective is to evaluate the safety of laru-zova and the secondary objective is to evaluate changes in visual function

FPI=First Participant In; DSMC=Data Safety and Monitoring Committee; XLRP = X-linked retinitis pigmentosa; RPGR = retinitis pigmentosa GTPase regulator; vg = vector genomes

1. NCT03316560. ClinicalTrials.gov. Last Updated May 20, 2024. https://clinicaltrials.gov/study/NCT03316560. 2. Data on file, Beacon Therapeutics (USA), Inc.

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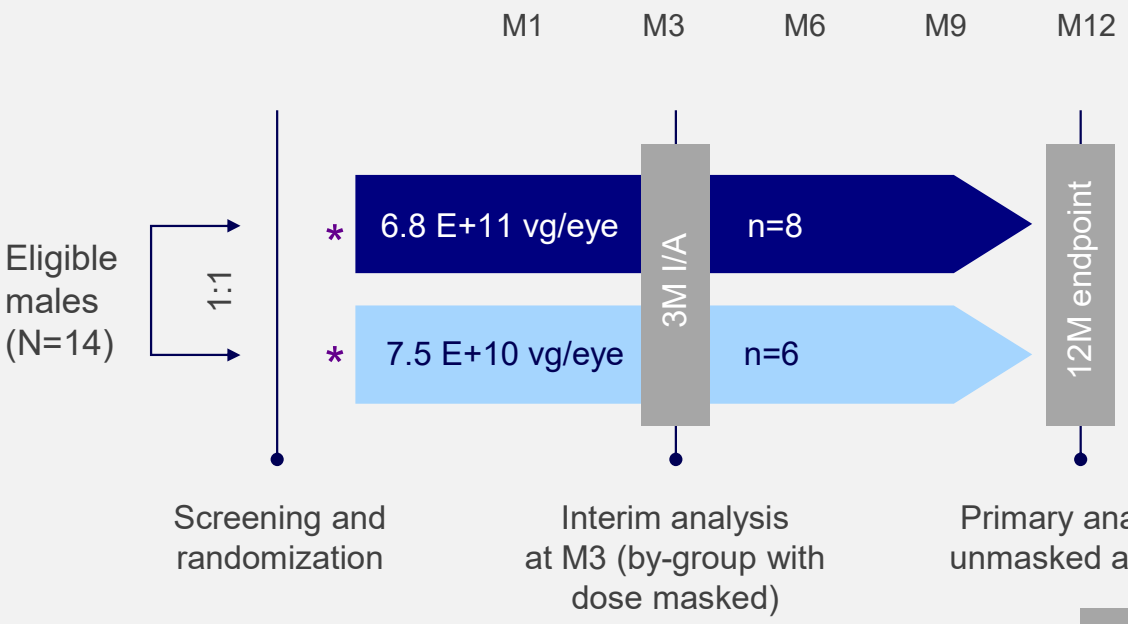
Phase 2 SKYLINE Study Design

RANDOMIZED, CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY, EFFICACY, AND TOLERABILITY OF LARU-ZOVA (AGTC-501) IN MALE PARTICIPANTS WITH XLRP CAUSED BY MUTATIONS IN THE *RPGR* GENE



Primary Outcome

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

Secondary Objectives

- Evaluate changes in functional vision as assessed by mobility VNC course, 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

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

*All participants centrally dosed

VNC=Visual Navigation Challenge; XLRP = X-linked retinitis pigmentosa; RPGR = retinitis pigmentosa GTPase regulator; vg = vector genomes; FPI = first patient in.

1. NCT06333249. ClinicalTrials.gov. Accessed September 5, 2024. https://clinicaltrials.gov/study/NCT06333249?lead=Beacon%20Therapeutics&rank=1#participation-criteria. 2. Data on file, Beacon Therapeutics (USA), Inc.

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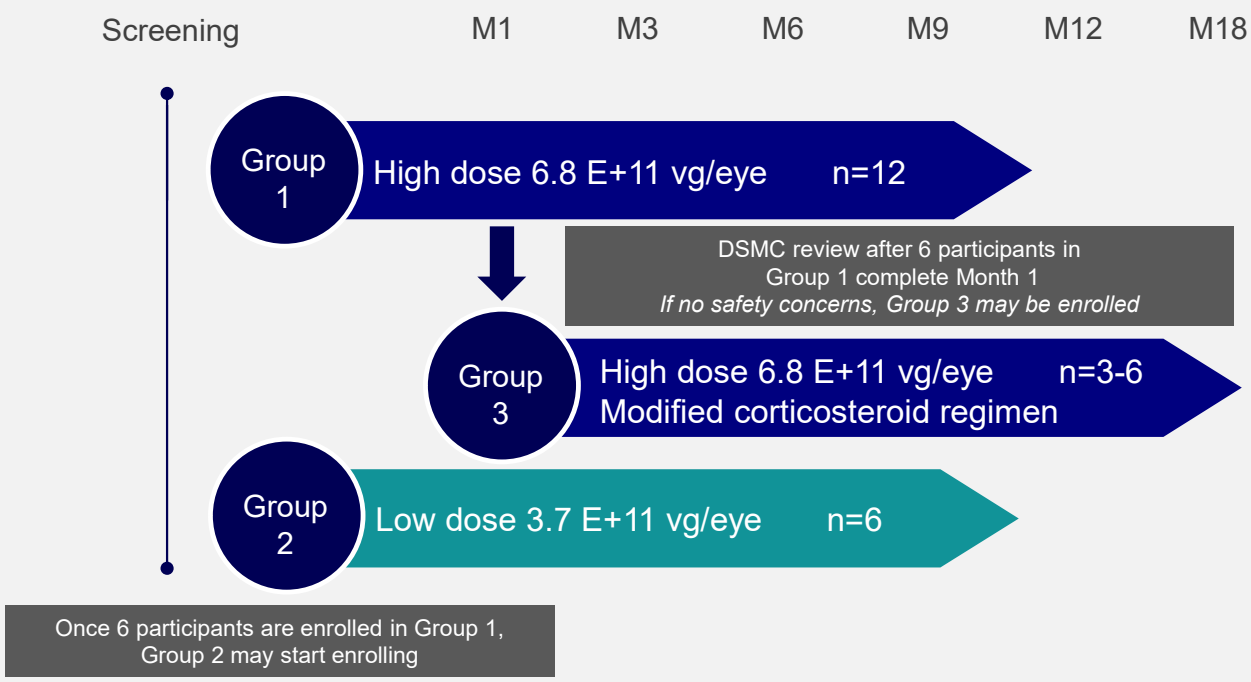
Phase 2 DAWN Study Design

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

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

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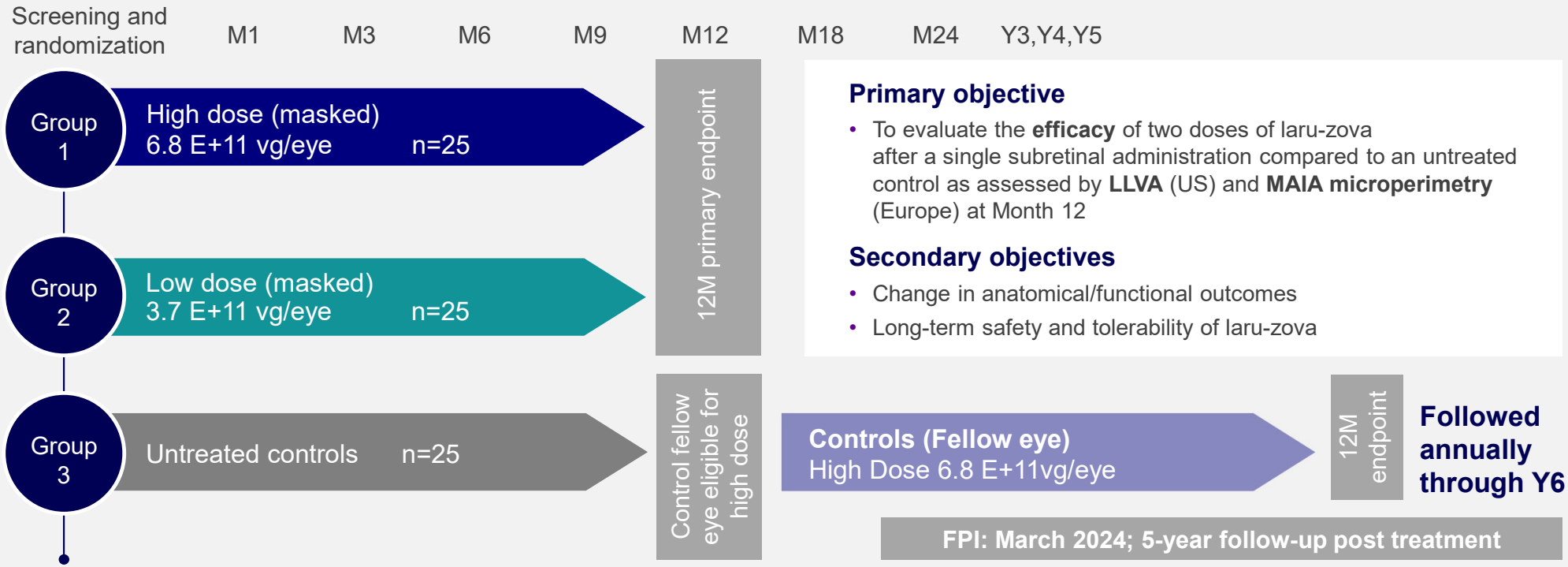
Phase 2/3 VISTA Study Design

RANDOMIZED, CONTROLLED, MASKED, MULTICENTER STUDY EVALUATING THE EFFICACY, SAFETY, AND TOLERABILITY OF TWO DOSES OF LARU-ZOVA (AGTC-501) COMPARED TO UNTREATED CONTROL GROUP IN MALE PARTICIPANTS WITH XLRP CAUSED BY MUTATIONS IN THE *RPGR* GENE



Primary objective

- To evaluate the **efficacy** of two doses of laru-zova after a single subretinal administration compared to an untreated control as assessed by **LLVA** (US) and **MAIA microperimetry** (Europe) at Month 12

Secondary objectives

- Change in anatomical/functional outcomes
- Long-term safety and tolerability of laru-zova

XLRP = X-linked retinitis pigmentosa; RPGR = retinitis pigmentosa GTPase regulator; vg = vector genomes; FPI = first patient in; MAIA = macular integrity assessment; LLVA = low-luminance visual acuity.

1. NCT04850118. ClinicalTrials.gov. Accessed September 6, 2024. https://www.clinicaltrials.gov/study/NCT04850118 2. Data on file, Beacon Therapeutics (USA), Inc.

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Safety

Phase 1/2 HORIZON Safety Summary at Month 36

Grade 3 or Higher Ocular TEAEs

MedDRA Preferred Term	Centrally Dosed (N=21)	Peripherally Dosed (N=8)	All Participants (N=29)
Retinal detachment†	1 (5%)	3 (38%)	4 (14%)
Cataract nuclear	0	1 (12.5%)	1 (3%)
Conjunctival hyperaemia	1 (5%)	0	1 (3%)
Glaucoma†	1 (5%)	0	1 (3%)
Intraocular pressure increased	1 (5%)	0	1 (3%)
Lens disorder	1 (5%)	0	1 (3%)
Retinal depigmentation**	1 (5%)	0	1 (3%)
Visual acuity reduced†	1 (5%)	0	1 (3%)
—Any Grade 3 or Higher Ocular AE—	5 (24%)	4 (50%)	8 (28%)

Statistics presented: n (%) of participants. Multiple events of the same category in a participant are counted only once.
†Reported as serious AE; **Related to study agent.

- **No clinically significant safety events related to the study agent**
- **No SUSARs and no endophthalmitis reported**
- **Majority of TEAEs were non-serious**
- **7 ocular SAEs reported; none related to study agent**
  - 4 SAEs of retinal detachment all deemed related to study injection procedure
    - 3 of the retinal detachments occurred in peripherally dosed participants
  - 1 SAE of glaucoma, deemed related to perioperative steroids
  - 1 SAE of subcapsular cataract related to study injection procedure
  - 1 SAE of visual acuity reduced related to the study injection procedure

Kaplan-Meier survival curves demonstrate that approximately 73% of ocular TEAEs occurred within 3 months and the majority of TEAEs resolved within a month of onset

SUSAR=suspected unexpected serious adverse reaction; TEAE=treatment emergent adverse event; SAE = serious adverse reaction

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Phase 2 SKYLINE Safety Summary at Month 24

No ocular SAEs were deemed related to study agent

- **There were two SAEs of glaucoma and visual impairment in the low dose group, and none in the high dose group**
- Overall, TEAEs were mostly non-serious, mild or moderate in severity, and rates were similar between groups
  - **Ocular TEAEs related to study agent were considered mild or moderate in severity (shown on right)**
  - Most ocular TEAEs related to the injection procedure were considered mild or moderate in severity

Ocular TEAE	Low dose (7.5 E+10 vg/eye) (n=6)		High dose (6.8 E+11 vg/eye) (n=8)		All participants (n=14)	
	Study Eye	Fellow Eye	Study Eye	Fellow Eye	Study Eye	Fellow Eye
# of Participants with Any Ocular TEAE Related to Study Agent	3	0	2	0	5	0
Vitritis	1	0	2	0	3	0
Eye pain	1	0	0	0	1	0
Metamorphopsia	1	0	0	0	1	0
Photopsia	1	0	0	0	1	0
Visual acuity reduced	1	0	0	0	1	0

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

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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 Participants (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 participants received standard dose corticosteroid regimen

TEAE=treatment emergent adverse event; SUSAR=suspected unexpected serious adverse reaction; AE = adverse event; vg = vector genomes.

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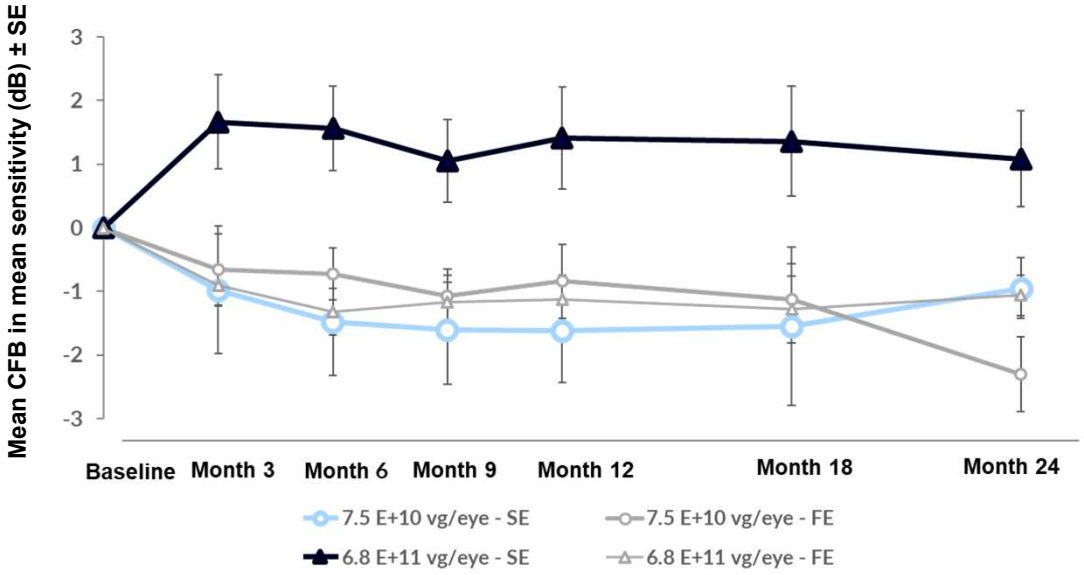
Efficacy

Phase 2 SKYLINE Efficacy Summary at Month 24

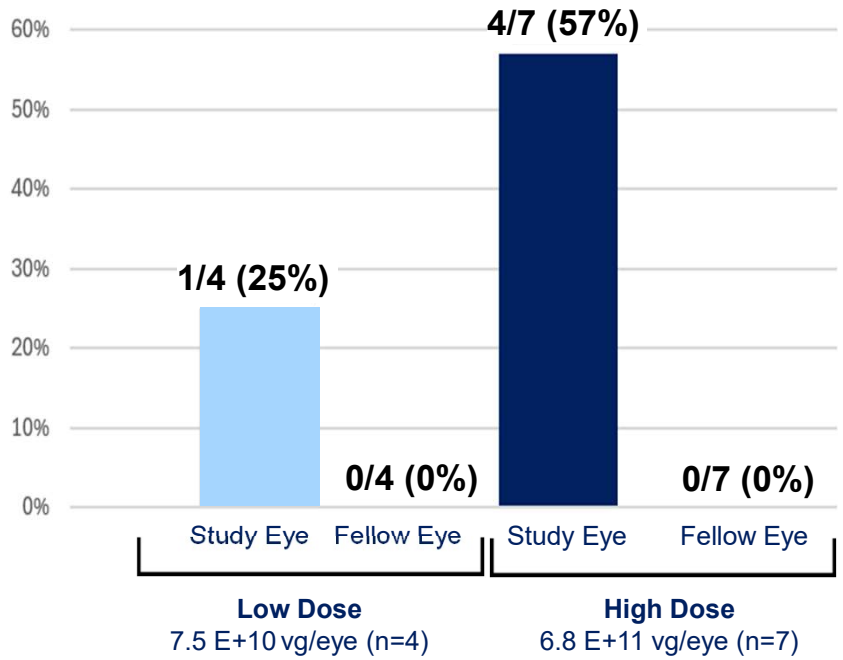
Greater response seen in the high dose study eyes compared to low dose and fellow eyes, consistent from Month 12 to Month 24

Change from Baseline Mean Sensitivity (Whole Grid)



Responder Rate

Participants (%) Achieving a ≥7 dB Improvement from Baseline in ≥5 Loci at Month 24 (Whole Grid)



Note: **3 participants (1 high dose and 2 low dose) missed scheduled Month 24 visits**

SE=study eye (treated); FE=fellow eye (untreated); CFB = change from baseline; vg = vector genomes.
Mean Sensitivity = Microperimetry by MAIA

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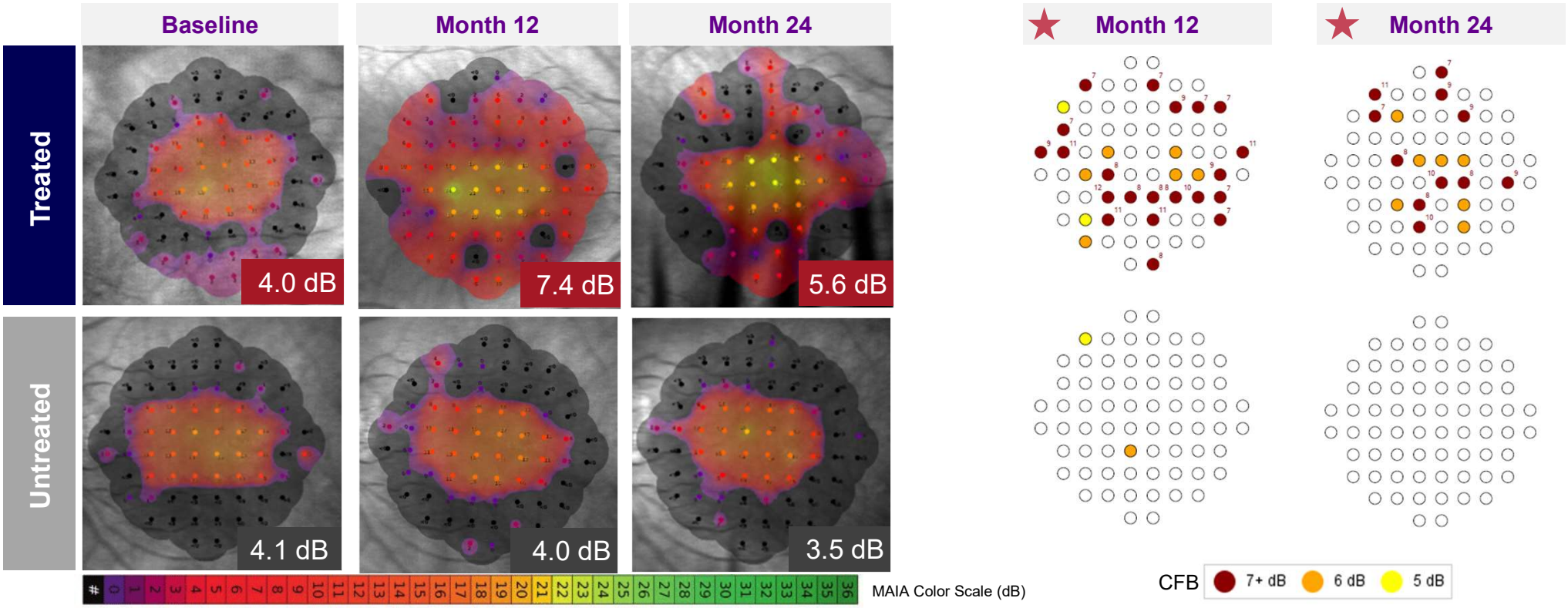
Example of Responding Eye per Microperimetry

★ ≥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)



RPGR = retinitis pigmentosa GTPase regulator; MAIA = macular integrity assessment.

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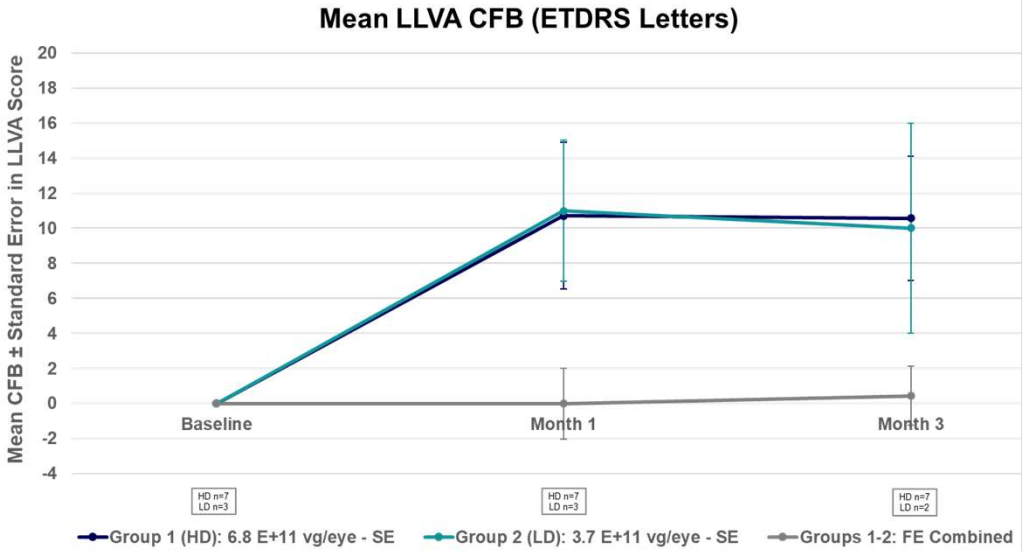
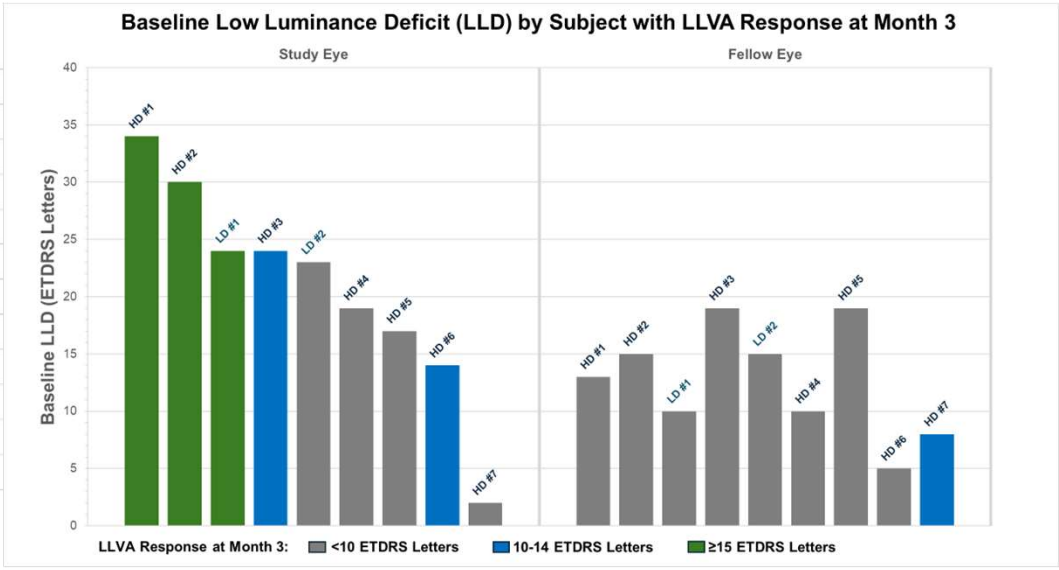
Phase 2 DAWN Efficacy: LLVA at Month 3

Early improvement in mean LLVA in DAWN Study Eyes





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; LLD = low luminance deficit; SE = study eye (newly treated); FE = fellow eye (previously treated); HD = high dose; LD= low dose

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Conclusions

Data has shown improvements in retinal sensitivity, and early improvements in LLVA emerging from the DAWN study

laru-zova (AGTC-501) has been well-tolerated across all studies to date with safety data up to 3 years post treatment

- No ocular SAEs have been deemed related to study agent to date
- The benefit-risk profile supports on-going clinical development for the treatment of patients with XLRP caused by *RPGR* mutations
- Pivotal, phase 2/3 VISTA trial is currently enrolling and designed to evaluate the effectiveness of laru-zova compared to an untreated control

LLVA = low luminance visual acuity; SAE = Serious Adverse Event; XLRP = X-linked retinitis pigmentosa; RPGR = retinitis pigmentosa GTPase regulator.

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