Subretinal Gene Therapy Drug AGTC-501 for X-Linked Retinitis Pigmentosa (XLRP) Phase 1/2 Multicenter Study (HORIZON): 36-Month Interim Results

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Disclosures:

4D Molecular Therapeutics (C, F), AAVantarde Bio (C), Acucela (F), Adverum (C), Astellas (C), Atsena (F), Beacon Therapeutics (F), Biogen (F), BlueRock Therapeutics (C), Editas (F), Eluminex Biosciences (C), Endogena (F), Foundation Fighting Blindness (C, F), Iveric Bio (F), Janssen (C), MeiraGTx (C), Nanoscope Therapeutics (C), Ocugen (F), PYC (F), Reneuron (F), Sanofi (F), Spark (F), TeamedOn (C).

C= Consultant, F=Clinical trial/research support

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X-Linked Retinitis Pigmentosa

Progressive photoreceptor degeneration that leads to blindness with no treatment options

Severe, aggressive, inherited retinal disease characterized by progressive photoreceptor degeneration

Orphan Disease @ 1:40,000 affecting young males[1]

17K patients in U.S./EU5[1]

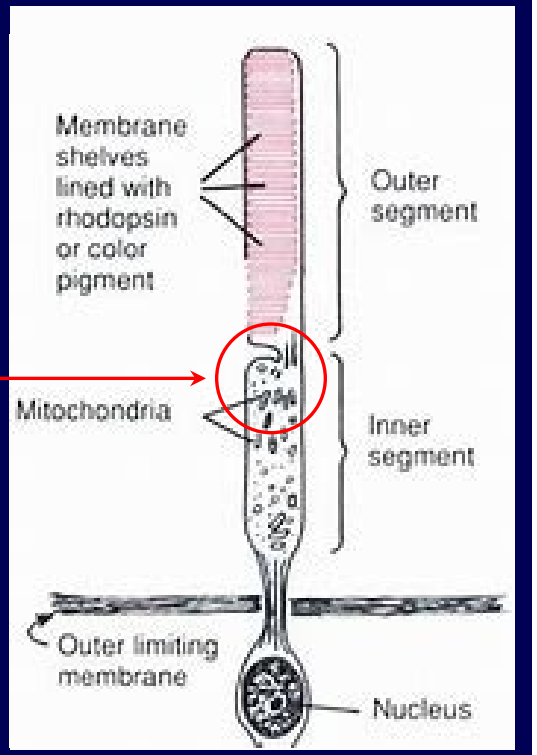
Due to mutation in $RPGR_{orf15}$ gene, which is responsible for long-term photoreceptor viability

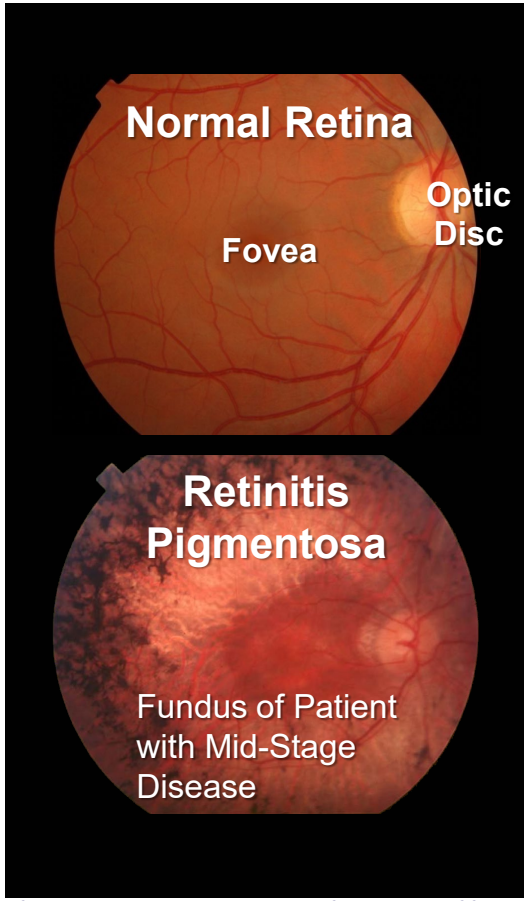
Legally blind
median age of 45[2]

RPGR localized in cilium, the connective body between inner and outer segment of photoreceptors

Disease progression

- Early - Night blindness
- Mid - Peripheral vision loss
- Late - Central vision loss

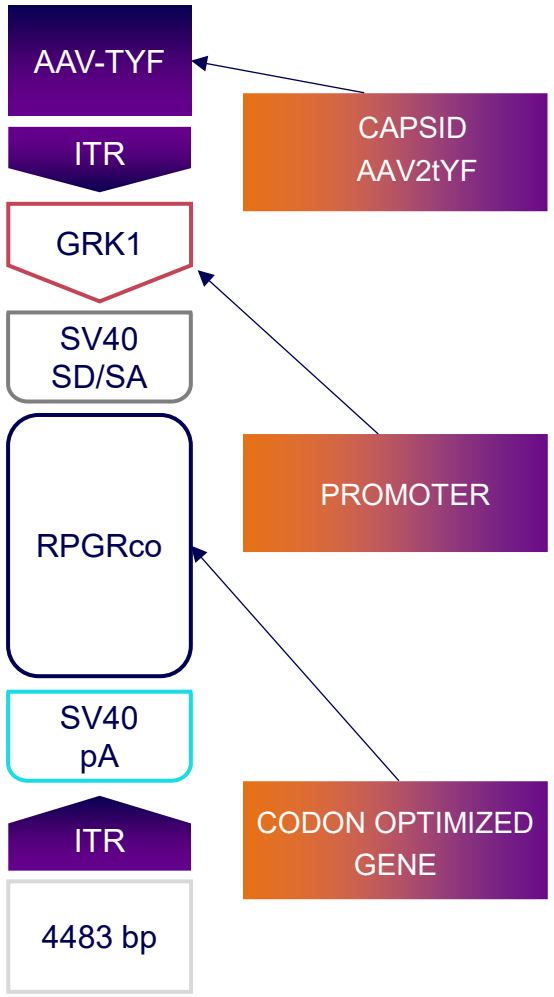




1. Vinikoor-Imler LC, et al. Ophthalmic Genet. 2022 Oct;43(5):581-588 2. Chivers M, et al. Clinicoecon Outcomes Res. 2021;13:565–572

AGTC-501

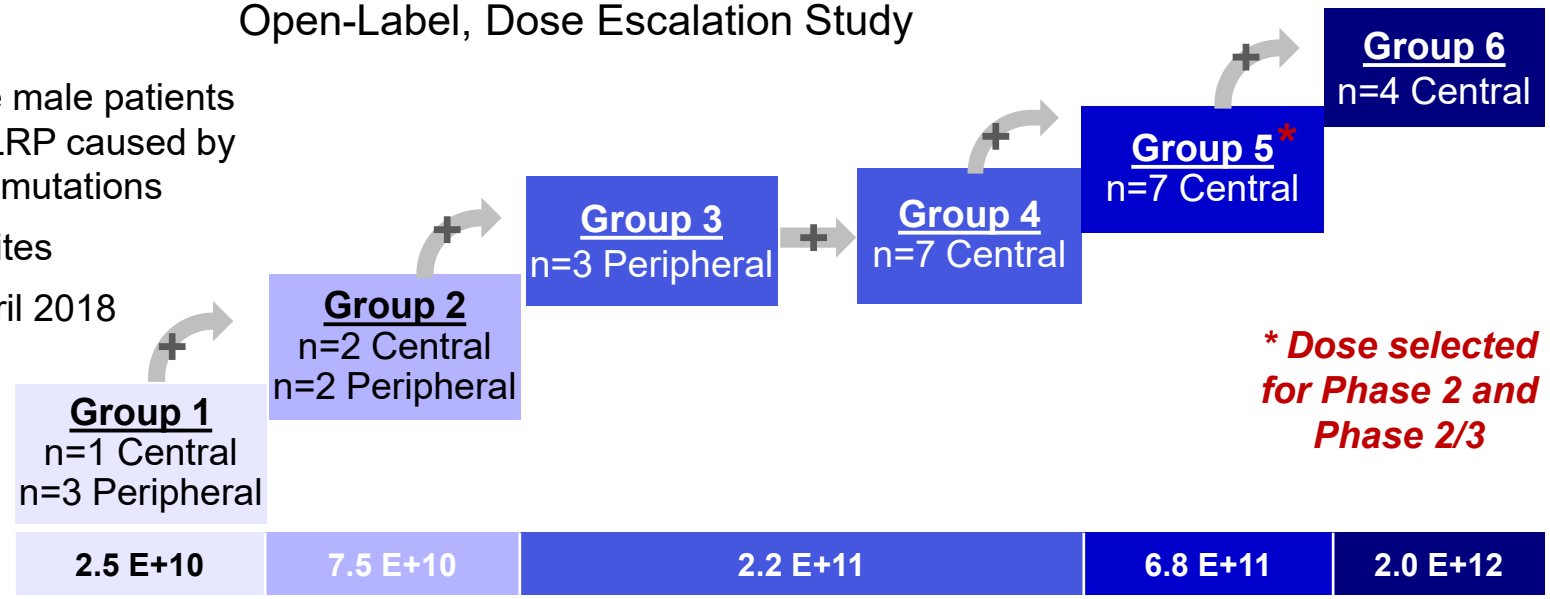
Subretinally delivered functional copy of RPGR gene for XLRP



Phase 1/2 HORIZON Study Design

Open-Label, Dose Escalation Study

- Eligible male patients with XLRP caused by RPGR mutations
- 4 US sites
- FPI April 2018



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

Cohorts sequentially dosed based on approval by DSMC ( )

	Objectives	Endpoints
Primary	Safety	Grade 3 or higher ocular or systemic TEAEs within 36 months
Secondary	Changes in Visual Function	Microperimetry, BCVA, Static perimetry (light and dark adapted), and FST

XLRP = X-Linked Retinitis Pigmentosa; DSMC = Data Safety Monitoring Committee; FPI = First Participant In; vg = Vector Genomes; TEAE = Treatment Emergent Adverse Event; BCVA = Best Corrected Visual Acuity; FST = Full-Field Light Sensitivity Threshold.

Phase 1/2 HORIZON Safety Summary

Centrally Dosed (n=21) + Peripherally Dosed (n=8) at 36 Months

No clinically significant safety events related to the study agent

- **No SUSARs and no endophthalmitis reported**
- **Majority of treatment-emergent adverse events (TEAEs) were non-serious**
- **7 ocular SAEs were 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 patients
  - 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 Event

Phase 1/2 HORIZON Grade 3 or Higher Ocular AEs

Centrally Dosed (n=21) + Peripherally Dosed (n=8) at 36 Months

MedDRA Preferred Term	Group 2 Centrally (N=2)	Group 4 Centrally (N=7)	Group 5 Centrally (N=7)	Group 6 Centrally (N=4)	Centrally Dosed (N=21*)	Peripherally Dosed (N=8)	All Participants (N=29)
Retinal detachment†	1 (50%)	0	0	0	1 (5%)	3 (38%)	4 (14%)
Cataract nuclear	0	0	0	0	0	1 (12.5%)	1 (3%)
Conjunctival hyperaemia	0	1 (14%)	0	0	1 (5%)	0	1 (3%)
Glaucoma†	0	1 (14%)	0	0	1 (5%)	0	1 (3%)
Intraocular pressure increased	0	0	1 (14%)	0	1 (5%)	0	1 (3%)
Lens disorder	0	1 (14%)	0	0	1 (5%)	0	1 (3%)
Retinal depigmentation**	0	0	0	1 (25%)	1 (5%)	0	1 (3%)
Visual acuity reduced†	0	1 (14%)	0	0	1 (5%)	0	1 (3%)
—Any Grade 3 or Higher Ocular AE—	1 (50%)	2 (29%)	1 (14%)	1 (25%)	5 (24%)	4 (50%)	8 (28%)

Statistics presented: n (%) of participants. Multiple events of the same category in a participant are counted only once.
*Including n=1 in Group 1;
†Reported as serious AE.
**Related to study agent.

Majority of Grade 3 or higher ocular AEs were related to study injection procedure. Retinal depigmentation was possibly related to study agent and also possibly related to the injection procedure

AEs of retinal depigmentation, visual acuity reduced, and cataract nuclear are ongoing. All other Grade 3 or higher AEs have resolved.

AE = Adverse Event

Phase 1/2 HORIZON Post-hoc Analysis of Microperimetry Results in High Dose Groups

Among patients treated in HORIZON Groups 4, 5, & 6, there were 10 patients who met the criteria for this post-hoc analysis using inclusion criteria for Phase 2 SKYLINE study:

- BCVA 35-75 letters
- Presence of a detectable EZ line in both eyes
- Baseline mean sensitivity on MAIA microperimetry of 1-12 dB

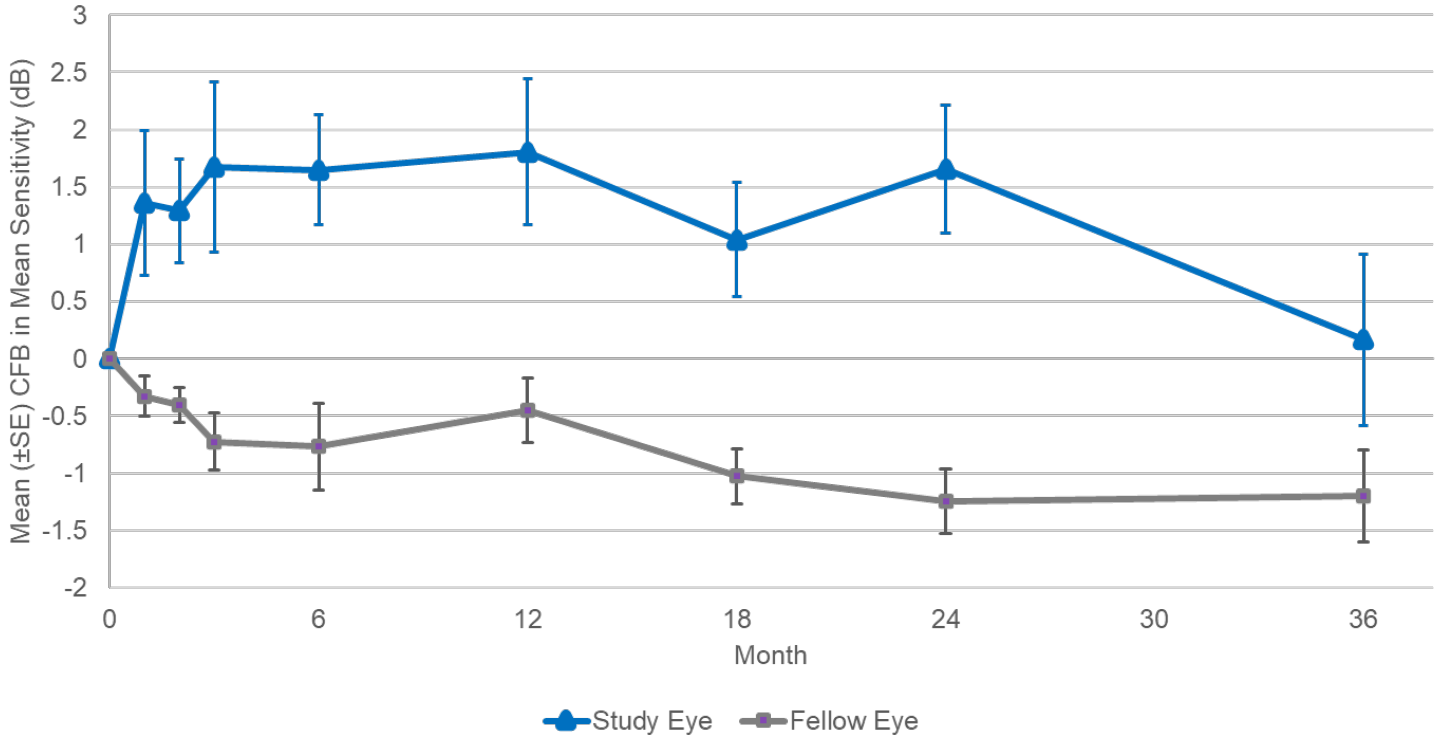
Collective microperimetry results from these patients were compared from baseline to Month 36 and between treated and untreated eyes to Month 36

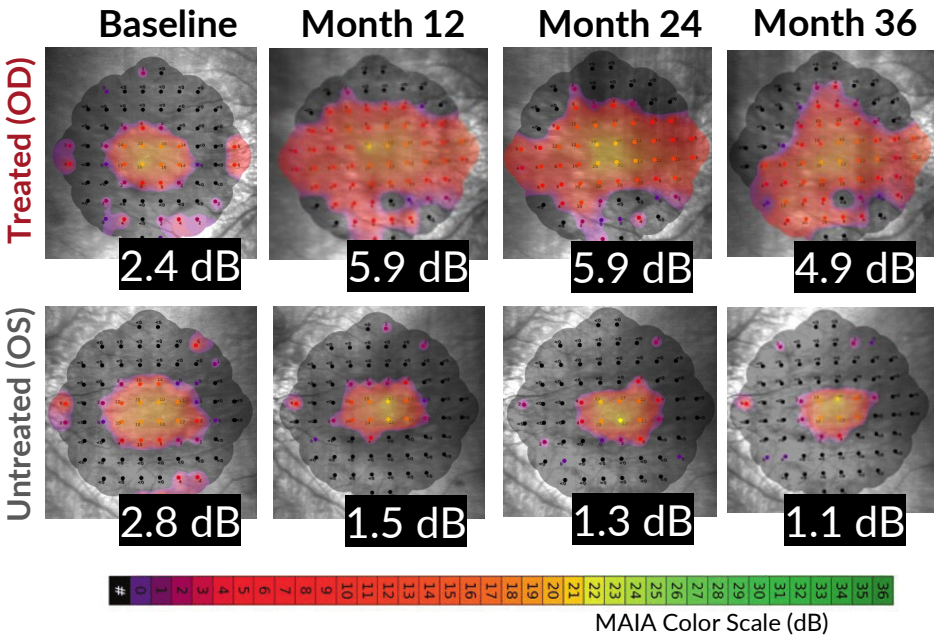
BCVA = Best-Corrected Visual Acuity; EZ = Ellipsoid Zone; MAIA = Macular Integrity Assessment

Phase 1/2 HORIZON Post-hoc Efficacy Summary at Month 36

Differences in retinal sensitivity between study eye and fellow eye maintained

Change from Baseline Mean Sensitivity (Whole Grid): Group 4+5+6 (n=10)





Microperimetry Mapping for a High Dose Responder

Mean (95%) difference in study eye-fellow eye

Month 3 (n=6)	Month 6 (n=7)	Month 12 (n=8)	Month 18 (n=8)	Month 24 (n=7)	Month 36 (n=8)
2.49 (0.36, 4.61) P=0.0299	2.26 (0.52, 4.0) P=0.019	2.28 (0.54, 4.02) P=0.0172	2.29 (0.52, 4.07) P=0.0185	2.95 (1.42, 4.49) P=0.0033	1.12 (-0.8, 3.04) P=0.2094

Nominal p-values

Conclusions
Phase 1/2 HORIZON 36-month Post-hoc analysis

AGTC-501 was generally safe and well-tolerated

Data shows differences in visual function maintained over fellow eye

- No SUSARs or endophthalmitis were reported in 29 patients enrolled in HORIZON, and no SAEs were deemed related to study agent.
- Follow-up is ongoing through 5 years to assess long-term safety and durability of response
- The benefit-risk profile supports on-going clinical development for the treatment of patients with XLRP caused by RPGR mutations
- Open-label Phase 2 fellow eye dose confirmation trial (DAWN) and Phase 2/3 trial (VISTA) enrolling

SUSAR = Suspected Unexpected Serious Adverse Reaction; SAE = Serious Adverse Event; XLRP = X-linked Retinitis Pigmentosa