Phase 1/2 Clinical Trial of Intravitreal 4D-125 AAV Gene Therapy in Patients with Advanced XLRP:

Interim Safety & Preliminary Clinical Activity

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FINANCIAL DISCLOSURES

- **Cagri G Besirli, MD, PhD (presenter)**
  - Research: 4DMT, MeiraGTx, Janssen Pharmaceuticals, Spark Therapeutics, Regeneron, Genentech
  - Consultant: MeiraGTx, Janssen Pharmaceuticals, iRenix Medical
  - Equity ownership/Royalty: iRenix Medical, ONL Therapeutics

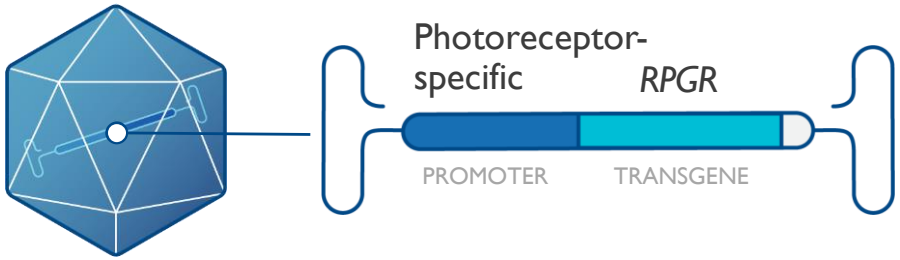
Key Takeaways for 4D-125 Preliminary Phase 1/2 Clinical Data

DATA CUT-OFF: SEPTEMBER 1, 2021

- 4D-125 was well-tolerated
- No dose-limiting toxicities, serious adverse events or chronic inflammation
- Evidence of clinical activity observed in the **treated eye vs. the untreated eye** in evaluable patients on **three clinical activity endpoints**:
  - Increased **mean retinal sensitivity** by microperimetry in treated vs. untreated eye
  - Increased **number of loci gaining ≥ 7 dB sensitivity** by microperimetry in treated vs. untreated eye
  - Increased preservation of **ellipsoid zone area** by SD-OCT in treated vs. untreated eye (progression decreased)

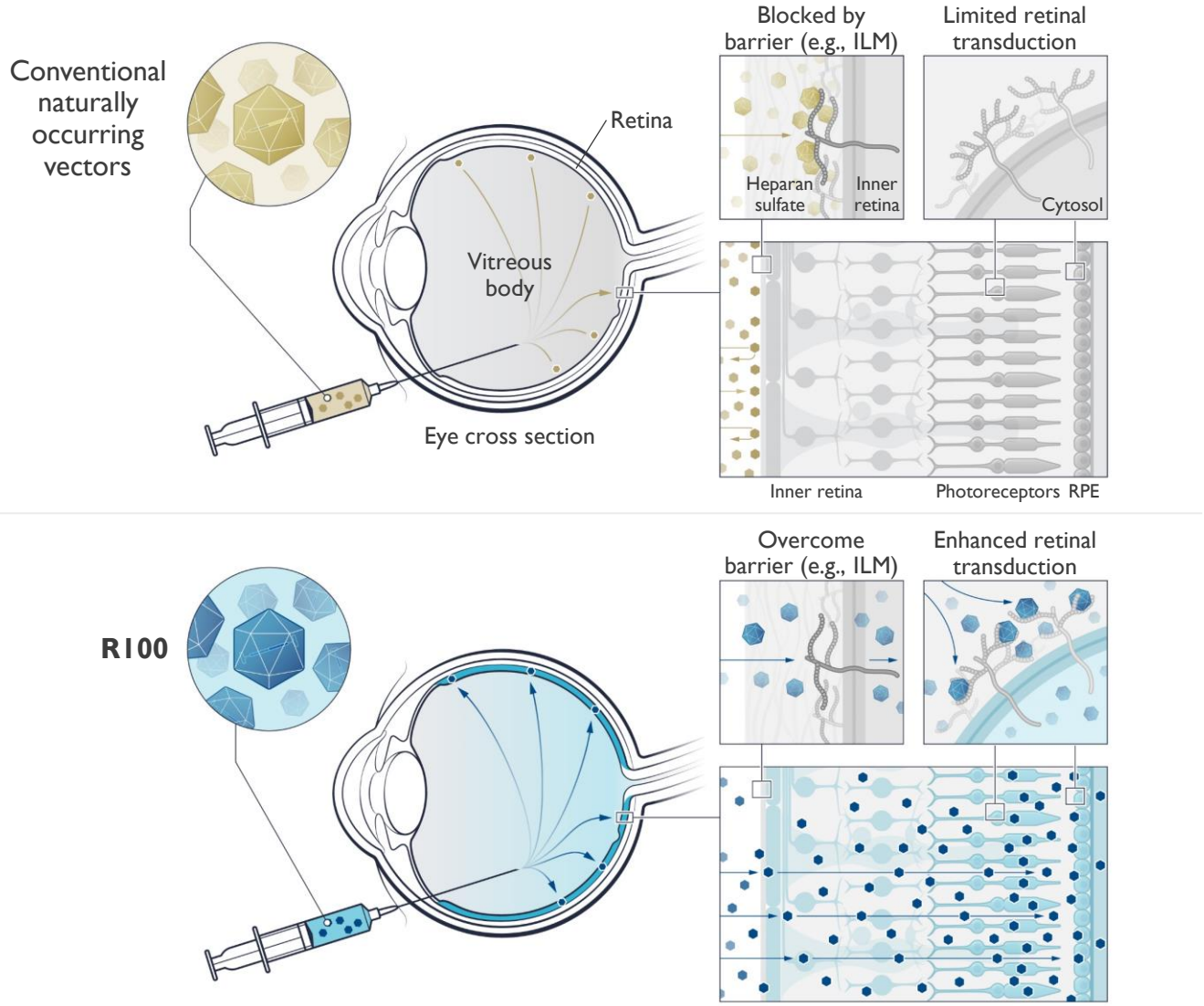
4D-125: R100 Capsid for IVT Delivery of *RPGR* Transgene

INTRAVITREAL DELIVERY ENABLES TREATMENT OF BROAD RANGE OF PATIENTS, INCLUDING EARLIER STAGE



PRODUCT DESIGN

- **Vector:** R100
- **Transgene:** *RPGR*
- **Promoter:** Photoreceptor-specific

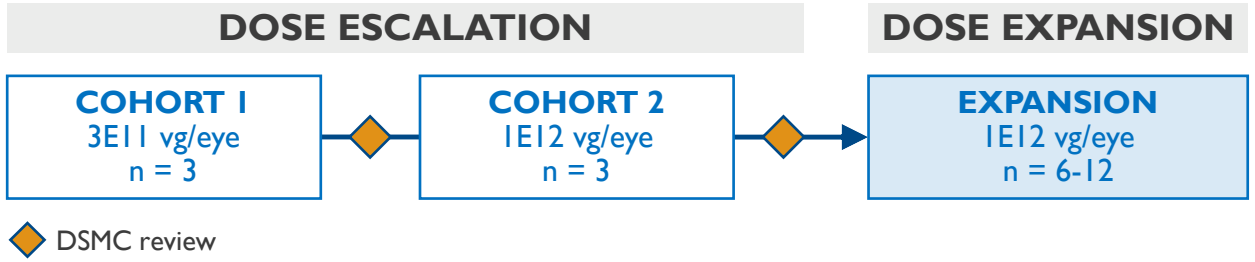


Abbreviations: ILM, inner limiting membrane; RPE, retinal pigment epithelium.

4D-125 Study Design

OPEN-LABEL, PHASE 1/2 TRIAL IN ADULTS WITH XLRP

STUDY DESIGN



ASSESSMENT SCHEDULE

Visit	Baseline	Day 14	Mon 2	Mon 4	Mon 6	Mon 9	Mon 12	Mon 15	Mon 18	Mon 21	Mon 24
Visit Window (days)	-7 to Day 1 (Pre-Dose)	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7
Microperimetry (avg. retinal sensitivity & pointwise)	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
OCT – EZA	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆

◆ Biomarkers assessed by Independent Reading Center

KEY INCLUSION CRITERIA

- Male ≥18 years of age
- Hemizygous RPGR mutation
- Clinical diagnosis of non-syndromic retinitis pigmentosa
- Measurable ellipsoid zone line (EZL) on macular SD-OCT
- >1 nonzero point on microperimetry (dose-escalation) OR
- ≥1dB mean retinal sensitivity on microperimetry (dose-expansion)

PRIMARY ENDPOINT

- Incidence and severity of TEAEs and SAEs, including clinically significant changes in safety parameters

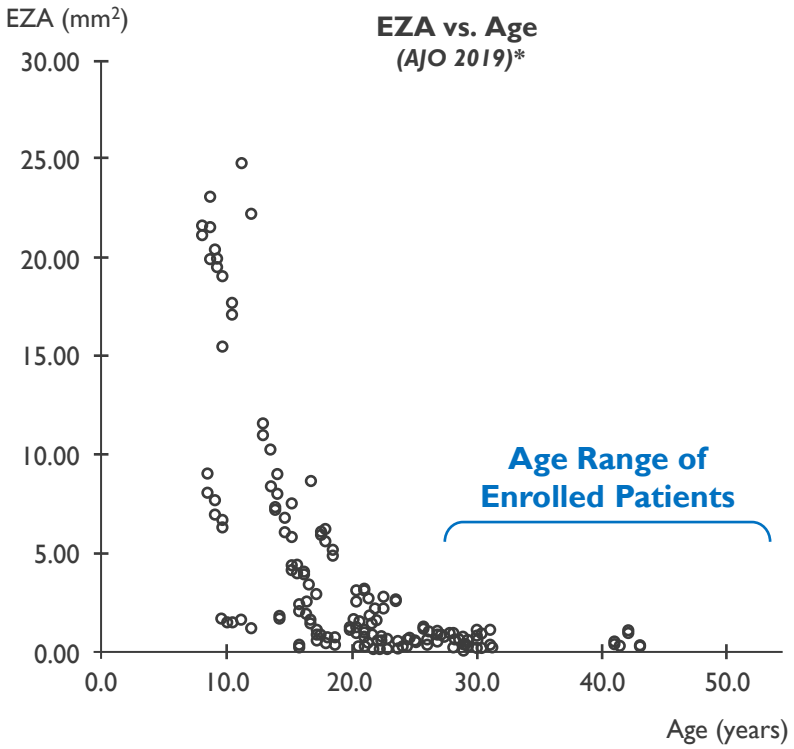
KEY SECONDARY ENDPOINTS

- Change from baseline in EZ area loss by SD-OCT over 12 months
- Change from baseline in visual field sensitivity by microperimetry over 12 months

Baseline Characteristics

ADVANCED STAGE ADULT PATIENTS; PATIENTS 3 & 5 EVALUABLE FOR CLINICAL ACTIVITY

Patient	Age	Follow-up (months)	Adult / Pediatric	Evaluable?	Ellipsoid Zone Area (mm^2)		Mean (SD) Retinal Sensitivity by Microperimetry (dB)	
					Treated Eye	Untreated Eye	Treated Eye	Untreated Eye
Cohort 1 (3×10^{11} vg/eye)								
1	42	13	Adult	Not Evaluable	3.93	6.13	Not Evaluable	Not Evaluable
2	47	12	Adult	Not Evaluable	Not Evaluable	1.03	1.1 (0.14)	Not Evaluable
3	49	12	Adult	**Evaluable**	**3.63**	2.66	**2.55 (0.78)**	3.15 (0.07)
Cohort 2 (1×10^{12} vg/eye)								
4	56	10	Adult	Not Evaluable	Not Evaluable	Not Evaluable	Not Evaluable	Not Evaluable
5	36	9	Adult	**Evaluable**	**1.68**	1.15	**2 (0.14)**	1.5 (0.14)
6	36	9	Adult	Not Evaluable	Not Evaluable	5	Not Evaluable	Not Evaluable
Dose Expansion (1×10^{12} vg/eye)								
7	27	5	Adult	Limited F/U	1.76	2.3	4.05 (0.35)	5.45 (0.64)
8	32	1	Adult	Limited F/U	17.28	16.6	19.80 (0.28)	19.85 (0.5)



- Evaluable patients defined as having measurable EZA and retinal sensitivity in both treated and untreated eyes with at least 6 months follow-up

*Graph: Tee JJL, Yang Y, Kalitzeos A, Webster A, Bainbridge J, Michaelides M. Natural History Study of Retinal Structure, Progression, and Symmetry Using Ellipsoid Zone Metrics in RPGR-Associated Retinopathy. Am J Ophthalmol. 2019 Feb;198:111-123. PMID: 30312579

Safety & Tolerability

DATA CUT-OFF: SEPTEMBER 1, 2021; N=8 (SAFETY & TOLERABILITY)

- 4D-125 was well-tolerated
- No serious adverse events
- No dose-limiting toxicities
- No significant change in visual acuity (BCVA)
- No chronic inflammation
- Transient, self-limited, grade 1+ anterior chamber* and/or vitreous** cells observed in **2/8 patients** at a **single protocol-defined assessment timepoint**

*National Institutes of Health Grading System for Vitreous Cells [Mahendradas, Khanna, Kawali, & Shetty, 2014]

**Standardization of Uveitis (SUN) Nomenclature Grading Scheme [SUN Working Group 2005 (Jabs et al., 2005)]

Ocular Inflammation: Self-limited, Single Timepoint

ANTERIOR CHAMBER CELL*

	BL	D14	M2	M4	M6	M9	M12
Cohort 1 (3×10^{11} vg/eye)							
Patient 1	0	0	0.5	0	0	N/A	0
Patient 2	0	0	0	0	0	N/A	0
Patient 3	0	0	0	0	0	1	
Cohort 2 (1×10^{12} vg/eye)							
Patient 4	0	0	0	0	0	N/A	
Patient 5	0	0	0	0	0		
Patient 6	0	0	0	1	0	0	
Dose Expansion (1×10^{12} vg/eye)							
Patient 7	0	0	0	0			
Patient 8	0	0.5†					

*Standardization of Uveitis (SUN) Nomenclature Grading Scheme [SUN Working Group 2005 (Jabs et al., 2005)]

†Observed at Day 28

Ocular Inflammation: Self-limited, Single Timepoint

VITREOUS CELL*

	BL	D14	M2	M4	M6	M9	M12
Cohort 1 (3×10^{11} vg/eye)							
Patient 1	0	0	0.5	0	0	N/A	0
Patient 2	0	0	0	0	0	N/A	0
Patient 3	0	0	0	0	0	0	
Cohort 2 (1×10^{12} vg/eye)							
Patient 4	0	0	0	0	0	N/A	
Patient 5	0	0.5	0	0	0		
Patient 6	0	0.5	0	1	0	0	
Dose Expansion (1×10^{12} vg/eye)							
Patient 7	0	0	0	0			
Patient 8	0	0					

*National Institutes of Health Grading System for Vitreous Cells
(Mahendradas, Khanna, Kawali, & Shetty, 2014)

4D-125 XLRP Biomarker Data: Preliminary Evidence of Activity

BASELINE TO LAST VISIT; N=2 EVALUABLE & WITH AT LEAST 6 MONTHS FOLLOW-UP

		Optical Coherence Tomography (OCT) [Ellipsoid Zone Area – % Change]		Microperimetry [Mean Retinal Sensitivity (db)]		Microperimetry [# of Loci with ≥ 7db Improvement]	
Patient	Last Assessment	Treated Eye	Untreated Eye	Treated Eye	Untreated Eye	Treated Eye	Untreated Eye
Cohort 1 (3×10^{11} vg/eye)							
1	Month 12	-1.0%	-2.1%	Not Evaluable	Not Evaluable	Not Evaluable	Not Evaluable
2	Month 12	Not Evaluable	-10.7%	-0.3	Not Evaluable	0	Not Evaluable
3	Month 9	**-12.4%**	-16.2%	**+1.65**	+0.25	**+6**	+1
Cohort 2 (1×10^{12} vg/eye)							
4	Month 6	Not Evaluable	Not Evaluable	Not Evaluable	Not Evaluable	Not Evaluable	Not Evaluable
5	Month 6	**-20.2%**	-28.7%	**+0.9**	+0.1*	**+3**	0*
6	Month 9	Not Evaluable	-7%	Not Evaluable	Not Evaluable	Not Evaluable	Not Evaluable

*Month 4 – Patient 5 unable to fixate in untreated eye at m6

Conclusions & Next Steps

- 4D-125 was well-tolerated with no dose-limiting toxicities, serious adverse events or chronic inflammation
- Evidence of clinical activity observed in the **treated eye vs. the untreated eye** in evaluable patients (2/2 pts) on **three clinical activity endpoints**
- Continuing enrollment patients at high dose (1E12 vg/eye) in expansion cohort, including less advanced patients

Acknowledgements

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