Ph1/2 AAV5-*RPGR* (Botaretigene Sparoparvovec) Gene Therapy Trial in *RPGR*-associated X-linked Retinitis Pigmentosa (XLRP)

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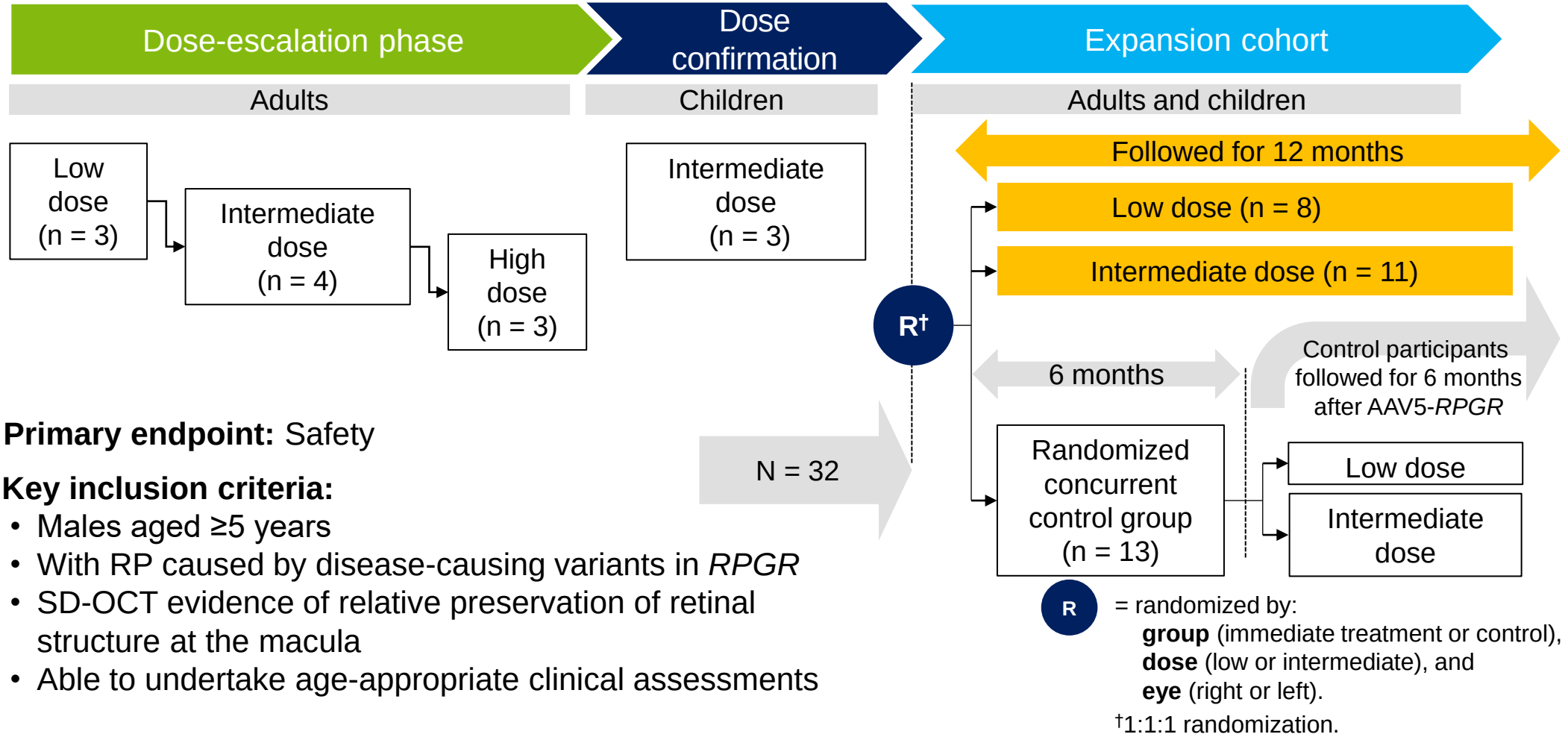
Michel Michaelides, MD (presenter)

- **Consultant:** Acucela, Stargazer Pharmaceuticals, 2C Tech, MeiraGTx, Janssen Pharmaceuticals
- **PI:** Acucela, ProQR, MeiraGTx
- **Equity ownership:** MeiraGTx

MGT009: Phase 1/2 Trial of AAV5-*RPGR*

Open-label study of an AAV5-*RPGR* gene therapy (NCT03252847) conducted at 5 sites in the **US and UK**



Primary endpoint: Safety

Key inclusion criteria:

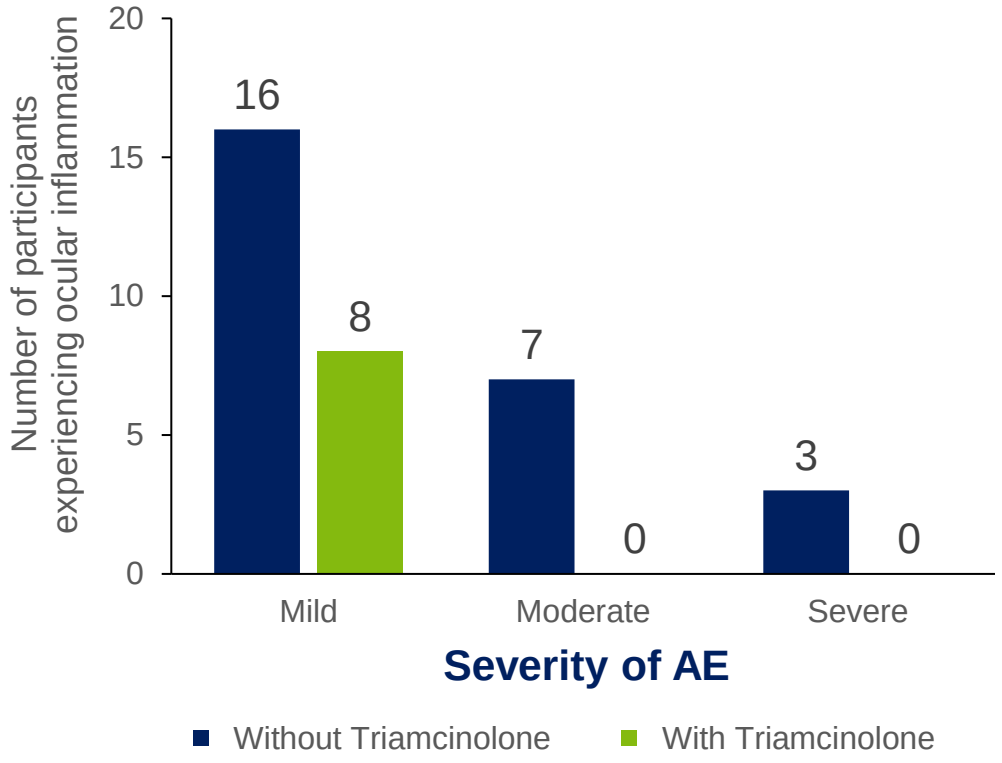
- Males aged ≥5 years
- With RP caused by disease-causing variants in *RPGR*
- SD-OCT evidence of relative preservation of retinal structure at the macula
- Able to undertake age-appropriate clinical assessments

RPGR, retinitis pigmentosa GTPase regulator; RP, retinitis pigmentosa; SD-OCT, spectral domain optical coherence tomography.

Clinical Safety in MGT009

- Doses for the expansion cohort were selected based upon the balance of safety and activity observed in the dose-escalation phase of the study
- AAV5-*RPGR* gene therapy demonstrated an AE profile that is anticipated and manageable
- Most AEs were related to the surgical delivery procedure, transient, and resolved without intervention
- Dose-escalation phase SAEs (previously reported)[1]:
  - 1 retinal detachment: related to study procedure and resolved with treatment, with no sequelae
  - 1 panuveitis (low dose)
- Dose-expansion phase SAE
  - 1 increased intraocular pressure, resolved on treatment
- No dose-limiting events
- Following the implementation of a modified prophylactic steroid regimen for the expansion phase, there was a reduction in inflammation-related AEs in the expansion phase of the study

Number of participants with ocular inflammation-related AEs by severity of AE



AE, adverse event; *RPGR*, retinitis pigmentosa GTPase regulator; SAE, serious adverse event.

1. Michaelides M, et al. Presented at the American Academy of Ophthalmology (AAO) Annual Meeting; November 13-15, 2020; Virtual.

Improvement in MRS in Pooled Low and Intermediate Doses Across All Adult Cohorts at 6 Months Observed: Static Perimetry and Microperimetry

Parameter	Dose	Dose escalation + expansion[§]			Sensitivity analysis applying phase 3 criteria[†,#]		
		N	LS mean change	Treated – concurrent control difference (±95% CI)[‡]	N	LS mean change	Treated – concurrent control difference (±95% CI)[‡]
Static perimetry MRS10°	Pooled low + intermediate	24	2.41	1.96 (0.59, 3.34)*	22	2.56	2.42 (0.91,3.93)***
	Concurrent control	13	0.45		11	0.14	
Microperimetry MRS-Scotopic Red	Pooled low + intermediate	15	0.88	1.06 (0.05, 2.07)*	15	0.88	1.06 (0.05, 2.07)*
	Concurrent control	7	–0.15		7	–0.15	

[§]Full analysis set population (observed data). Includes participants randomized to intermediate and given high dose.
[†]Participants excluded when applying phase 3 criteria.
[#]Sensitivity analysis dataset is the same dataset as for the full analysis. Microperimetry was not available at all sites.
[‡]Adjusted for baseline, 2-sided nominal *P* value.
*Nominal *P* value <0.05.
***Nominal *P* value <0.001.

CI, confidence interval; LS, least squares; MRS, mean retinal sensitivity.

Improvement in Pointwise Responder Analysis of Static Perimetry in Pooled Low and Intermediate Doses Across All Adult Cohorts

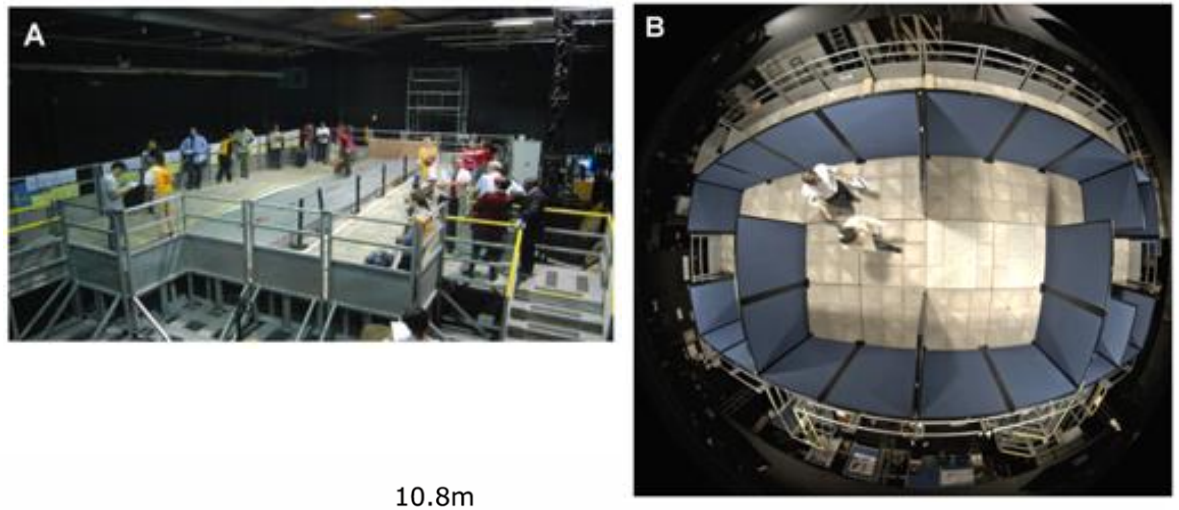
Week	Week 26†	Week 52‡
Full analysis set§		
Pooled low + intermediate	6/23 (26%)	11/23 (48%)
Concurrent control	2/10 (20%)	
Sensitivity analysis¶		
Pooled low + intermediate	5/21 (24%)	10/21 (48%)
Concurrent control	0/8 (0%)	

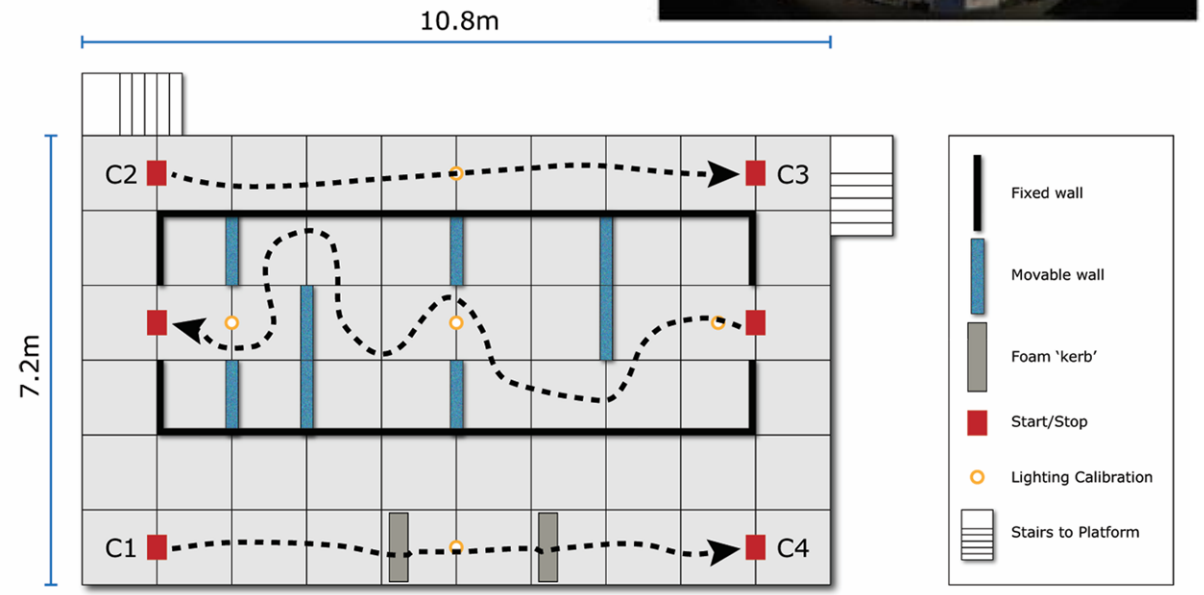
RPGR, retinitis pigmentosa GTPase regulator.
†Week 26: number of participants who completed assessments at both week 26 and week 13. Week 52: number of participants who completed assessments at week 52 and ≥1 visit prior to week 52.
‡For concurrent control participants, this table only summarizes data prior to AAV5-hRKp.*RPGR* administration and serves as a control group. These participants were treated after week 26. There are no week 52 data for these participants.
§Full analysis set (observed data). Included participants randomized to intermediate and given high dose.
¶Participants excluded when applying phase 3 criteria.

Responder criteria: at least a 7 dB improvement from baseline in ≥5 individual loci, with the same 5 loci showing improvement at 2 time points following treatment.

Functional Vision Assessment: Mobility Maze[1]

Dose-escalation Phase





- **To view the maze assessment please click here**

Participant 01-007 Maze assessment shown at 9-month time point.

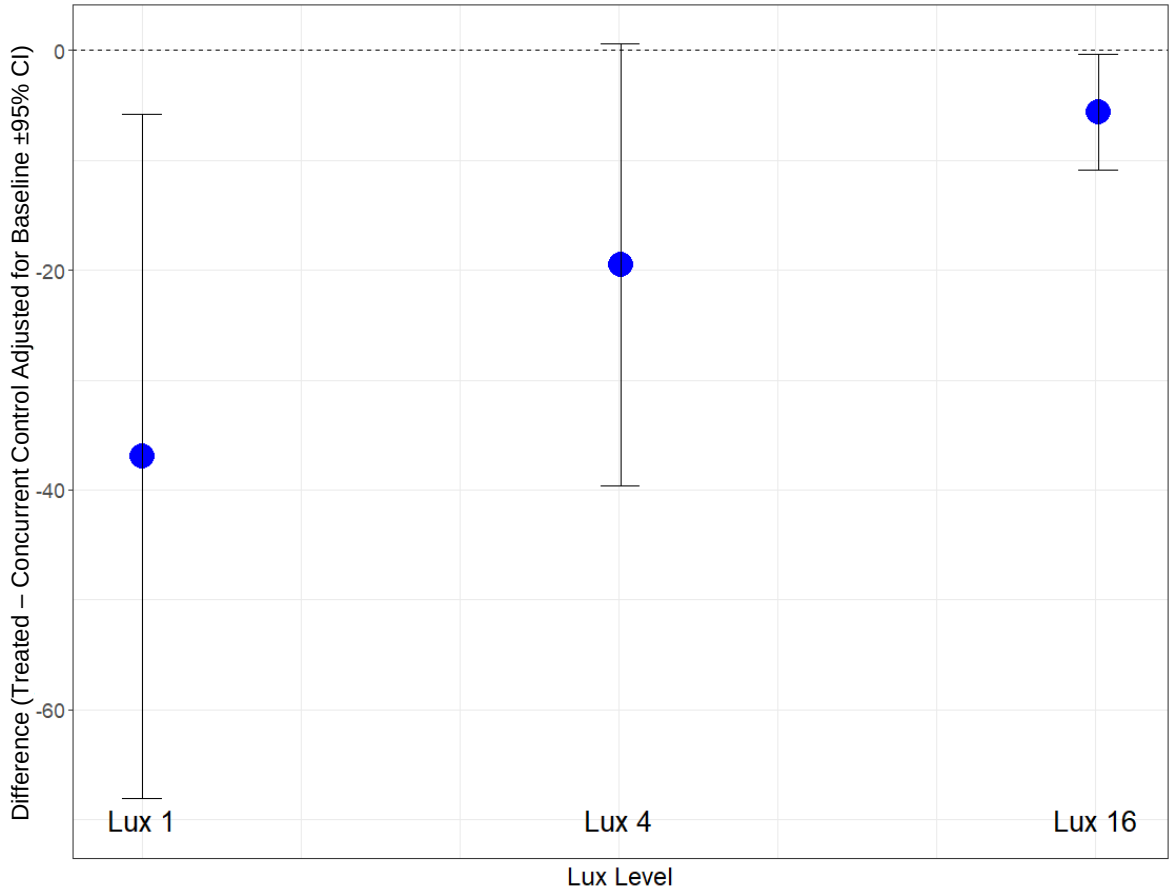
- Light level: 1 lux
- Baseline performance: 61.7 seconds with 2 errors
- 9-month performance: 16.4 seconds with no errors

1. Michaelides M, et al. Presented at the American Academy of Ophthalmology (AAO) Annual Meeting; November 13-15, 2020; Virtual.

Significant Improvement in Walk Time at Week 26 Compared to Baseline

Pooled Dose-escalation and Dose-expansion Treatment Difference Compared to Control at 6 Months (Change From Baseline ±95% CI)

Improvement



	Lux 1	Lux 4	Lux 16
Treatment difference (Rx-c)	–37s*	–19s	–6s*

Nominal *P* value for the full analysis *P* <0.05 shown here.
All 3 lux levels had nominal *P* values <0.01 after application of phase 3 criteria.

CI, confidence interval.

Conclusions

- AAV5-*RPGR* gene therapy demonstrated an adverse event profile that is anticipated and manageable
- Efficacy assessments in this proof-of-concept study demonstrated that eyes treated with AAV5-*RPGR* improved in retinal sensitivity and functional vision in comparison with randomized controls at 6 months
  - Sensitivity analysis on applying the phase 3 criteria further corroborated the endpoints selected for phase 3
  - In addition, all domains in the LLQ-PRO trended positively, and the extreme lighting domain was nominally significant (nominal P <0.01), which is consistent with VMA findings
- Further development of this therapy is warranted
- A phase 3 study of AAV5-*RPGR* is underway (**NCT04671433)**

LLQ, low luminance questionnaire; PRO, patient-reported outcome; *RPGR*, retinitis pigmentosa GTPase regulator; VMA, visual mobility assessment.

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MCW, Medical College of Wisconsin; NHS, National Health Service; OHSU, Oregon Health and Science University; UCL, University College London.