



MEIRAGTx

ASRS Data Review Conference Call

AAV-RPGR Gene Therapy for RPGR-Associated X-Linked Retinitis Pigmentosa: 6-month Results From a Phase 1/2 Clinical Trial

July 17, 2020

Forward Looking Statements

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MeiraGTx Broad Clinical Pipeline

Product	Indication	Preclinical	Phase 1/2	Phase 3
Ocular				
AAV-RPGR* 	X-linked RP	PRIME, Fast Track, Orphan Drug		
AAV-RPE65	RPE65-Associated Retinal Dystrophy	RPDD, Orphan Drug		
AAV-CNGB3* 	Achromatopsia	RPDD, PRIME, Fast Track, Orphan Drug		
AAV-CNGA3* 	Achromatopsia	RPDD, Orphan Drug		
AAV-AIPL1	LCA4	Compassionate use under MHRA Specials License		
A006	Wet AMD			
Neurodegenerative Disease				
AAV-GAD	Parkinson's Disease			
Salivary Gland				
AAV-AQP1	Xerostomia	Orphan Drug		
	Sjögren's Syndrome			

*Co-development program with Janssen Pharmaceuticals pursuant to a collaboration agreement.

Six-Month Dose Escalation Data from Ongoing Phase 1/2 Study of AAV-RPGR in Patients with XLRP

Significant vision improvement six months after treatment

- Meaningful improvement from baseline in retinal sensitivity across multiple metrics and modalities in low and intermediate dose cohorts
- Statistically significant improvement from baseline compared to untreated eyes evident at six months post treatment in low and intermediate dose cohorts
- Initial signs of efficacy at three months, with improvements generally sustained or increased at six months

AAV-RPGR was generally well tolerated, with a favorable safety profile

- Most AEs were ocular, anticipated due to the surgical procedure, transient and resolved without intervention

**Data support advancing
AAV-RPGR into Phase 3
clinical trial**





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X-Linked Retinitis Pigmentosa due to RPGR-Deficiency

- **Retinitis Pigmentosa (RP)**
 - Group of IRDs which represents the most common genetic cause of blindness
- **Disease progression**
 - Progressive photoreceptor cell death
 - Loss of night vision
 - Visual field constriction, with progression to tunnel vision
 - Central visual field loss
- **X-Linked RP (XLRP) is the most severe form of RP**
 - Early onset
 - Rapid progression
 - Severe visual impairment by 30s to 40s
- **Disease-causing variants in *RPGR* account for up to 80% of XLRP and up to 15-20% of all cases of RP^{1,2,3}**
 - ~20,000 cases in U.S., EU5 + Japan
 - RPGR plays a key role in the structure and function of rod and cone photoreceptors

1. Wang DY. Gene mutations in retinitis pigmentosa and their clinical implications. *Clin Chim Acta* 2005;351:5–16.

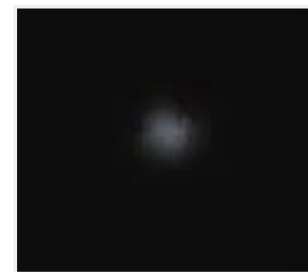
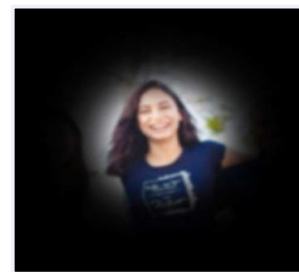
2. Bader I. X-linked retinitis pigmentosa: RPGR mutations in most families with definite X linkage and clustering of mutations in a short sequence stretch of exon ORF15. *Invest Ophthalmol Vis Sci* 2003;44:1458–1463.

3. Tee JJ. RPGR-associated retinopathy: clinical features, molecular genetics, animal models and therapeutic options. *Br J Ophthalmol* 2016; pii: bjophthalmol-2015-307698.

XLRP Patient Experience

Most challenging symptoms for patients

- Loss of night vision or difficulty seeing in dimly lit conditions such as restaurants
- Loss of peripheral vision → frequently running into things, bumping into doorways, tripping over things on the ground
- Progressive vision loss, and associated loss of independence, with no currently available treatments to improve vision or slow progression of disease



Quality of life significantly impaired

- Progressive loss of vision impacts physical, emotional and social functioning, including reduced mobility and ability to perform daily activities^{1,2}
- Patients become increasingly reliant on caregivers over time with reduced independence and ability to engage socially with others³
- RP patients experience lower education levels, employment rates, productivity and income levels^{1,3,4-7}

1. Hartong DT. Retinitis Pigmentosa. *Lancet* 2006;368(9549):1795-1809.

2. Jangra D. Psychosocial adjustment to visual loss in patients with retinitis pigmentosa. *Ophthalmic Genetics* 2007;28:25-30.

3. Lloyd A. Estimation of impact of RPE65-mediated inherited retinal disease on quality of life and the potential benefits of gene therapy. *Br J Ophthalmol* 2019;103(11):1610-1614.

4. Mojon-Azzi SM. Impact of low vision on employment. *Ophthalmologica* 2010;224(6):381-388.

5. Harrabi H. Visual difficulty and employment status in the world. *PLoS One* 2014;9(2):e88306.

6. Sherrod CE. Association of vision loss and work status in the United States. *JAMA Ophthalmol* 2014;132(10):1239-1242.

7. Bertelsen M. Socio-economic characteristics of patients with generalized retinal dystrophy in Denmark. *Acta Ophthalmol* 2015;93(2):134-140.

Gene Therapy for the Treatment of XLRP: AAV-RPGR

Developed to deliver stable gene sequence to rod and cone photoreceptors, driving expression of functional RPGR protein, resulting in rescue of photoreceptor function and consequently improving vision



- **Optimized *RPGR* ORF15 transgene**

- Selective deletion in highly repetitive purine-rich region of *RPGR* ORF15 stabilizes the transgene while still resulting in expression of functional protein with correct photoreceptor localization¹

- **AAV5 capsid**

- Efficiently delivers vector genome to both rods and cones

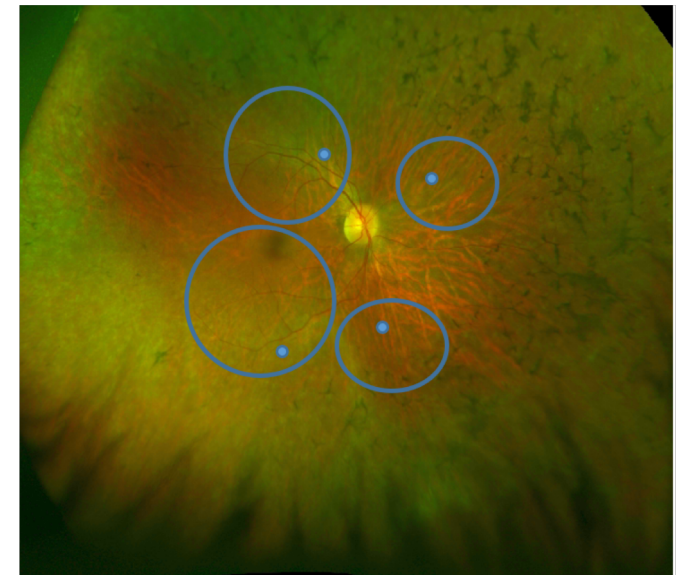
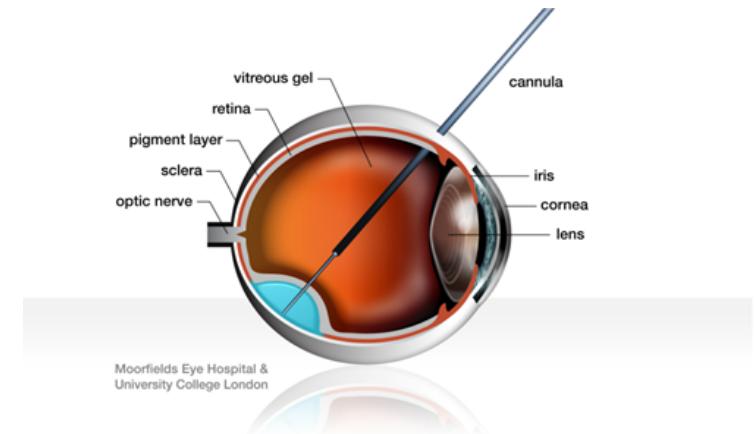
- **Human rhodopsin kinase promoter (hRKp)**

- Photoreceptor-specific promoter restricts expression of transgene to photoreceptor cells

1. Pawlyk BS. Photoreceptor rescue by an abbreviated human RPGR gene in a murine model of X-linked retinitis pigmentosa. *Gene Ther* 2016;23:196–204.

AAV-RPGR Intraocular Administration

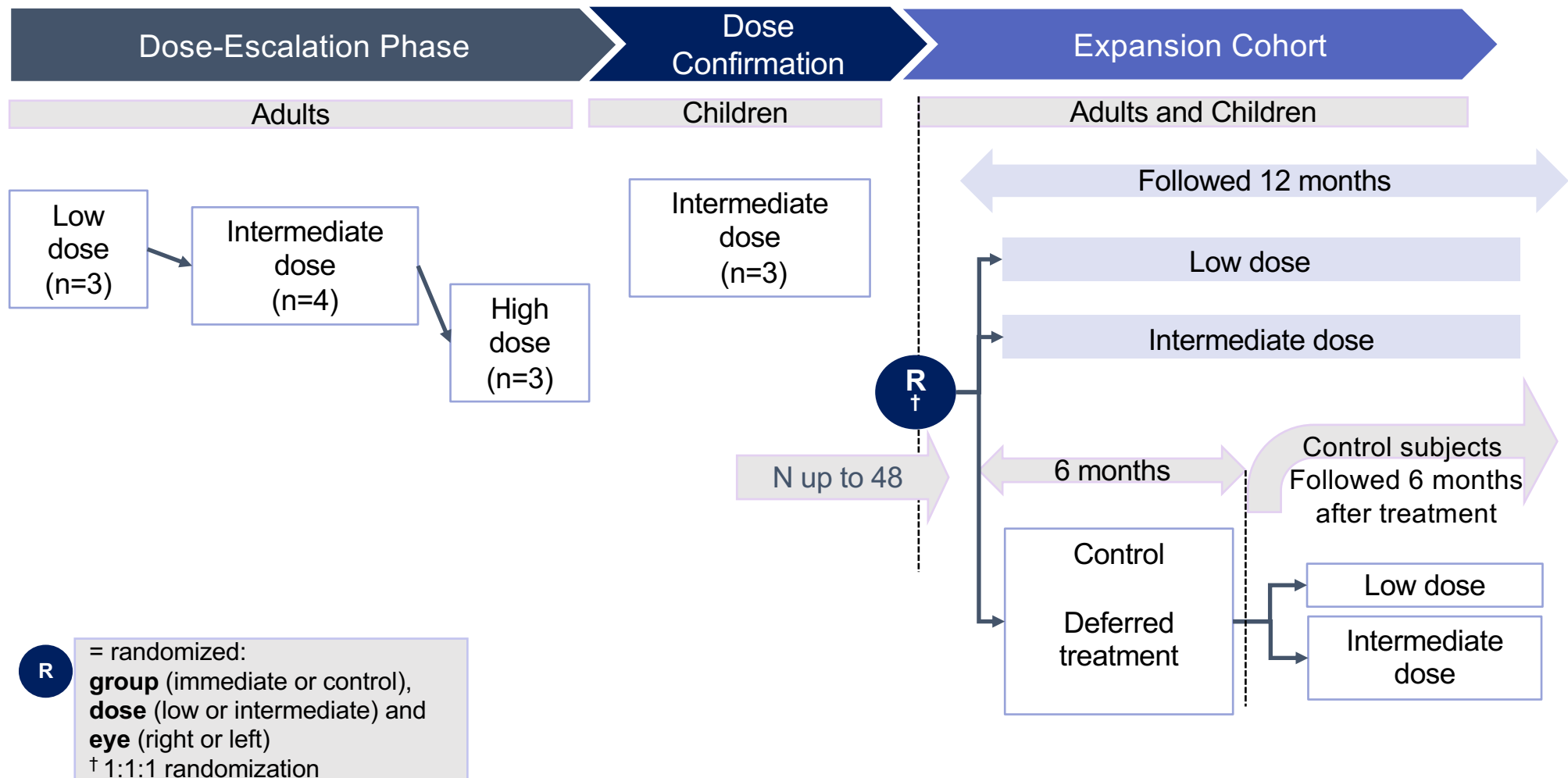
- Gene therapy approaches for the treatment of retinal diseases are attractive due to the accessibility and relatively immune-privileged status of the eye and because administration can be limited to low doses and a single intervention
- AAV-RPGR delivered via subretinal injection
- Central retina targeted, including foveal detachment
- Multiple retinotomies permitted to enable safe and effective coverage of largest possible area of rescuable retina



*0.5ml total volume distributed in
4 subretinal blebs*

MGT009: Ongoing Phase 1/2 Trial of AAV-RPGR

Multicenter open-label Phase 1/2 trial of an AAV5-RPGR gene therapy (NCT03252847)
conducted at 5 sites across the United States and United Kingdom



MGT009 Eligibility and Endpoints

- **Key inclusion criteria:**

- Males aged 5 years or older
- 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

- **Primary endpoint:**

- Safety and tolerability

- **Secondary endpoints** assessing retinal sensitivity, visual function, functional vision and quality of life measurements

Retinal Sensitivity Endpoint

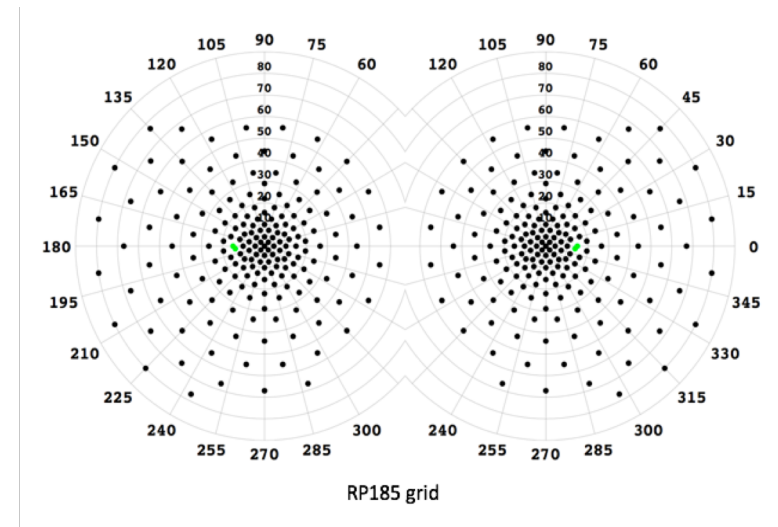
Perimetry performed at baseline (three measurements), three, six, nine and 12 months to assess baseline visual function and change over time

Modalities

- Octopus 900 full-field static perimetry
- MAIA fundus-guided microperimetry (10-2 grid)

Metrics

- Mean retinal sensitivity
- Visual field modeling and analysis (VFMA) derived hill-of-vision
- Pointwise analysis



- Customized grid used in the *RPGR* trial and natural history study
- 185 test points with central condensation and good peripheral coverage extending 55.5° nasally and superiorly, 67° inferiorly and 80° temporally

Dose-Escalation Population

Cohorts	Age (years) Mean (range)	Visual Acuity Mean (range)	Number	Ethnic Origin
Total	24 (18, 30)	69 (52, 83)	10	8 White 1 Black 1 Other
Low dose	27 (24, 30)	62 (52,70)	3	3 White
Intermediate dose	25 (19, 29)	72 (60, 77)	4	3 White 1 Other
High dose	21 (18, 24)	73 (59, 83)	3	2 White 1 Black

Clinical Safety in MGT009 Dose-Escalation Phase

- **Safety data obtained to date has ocular and systemic safety profiles that are anticipated and manageable**
 - Half of AEs that occurred were ocular in nature related to the surgical delivery procedure, transient and resolved without intervention
- **Two SAEs**
 - 1 retinal detachment: related to surgical procedure and resolved without sequelae
 - 1 panuveitis
- **No dose-limiting events**
- **Inflammatory responses were observed in 2 out of the 3 patients in the high dose cohort, which were effectively treated with extension of steroid cover**
 - Inflammatory responses may have been associated with decreased activity of AAV-RPGR in these patients

AEs, adverse events; SAEs, serious adverse events.

Statistically Significant Improvement in Retinal Sensitivity in Low and Intermediate Dose Cohorts

Parameter	Treated-Untreated Eye Difference (90% CI adjusted for baseline)
Mean Retinal Sensitivity (dB)	
Low Dose Cohort	0.69 (−0.28, 1.66)
Intermediate Dose Cohort	1.02 (0.75, 1.31)*
High Dose Cohort	−1.00 (−1.87, 0.38)
Central Visual Field Progression Rate (Central 30° Hill-of-Vision [V30], dB-sr/y)†	
Low Dose Cohort	1.10 (0.10, 2.10)*
Intermediate Dose Cohort	1.26 (0.65, 1.86)*
High Dose Cohort	−0.81 (−1.52, 0.47)

Response was treated-untreated eye adjusted for baseline (double-delta)

* Statistically significant effects at a one-sided 5% level

† Currently, at least 6 months of data and up to one year of data

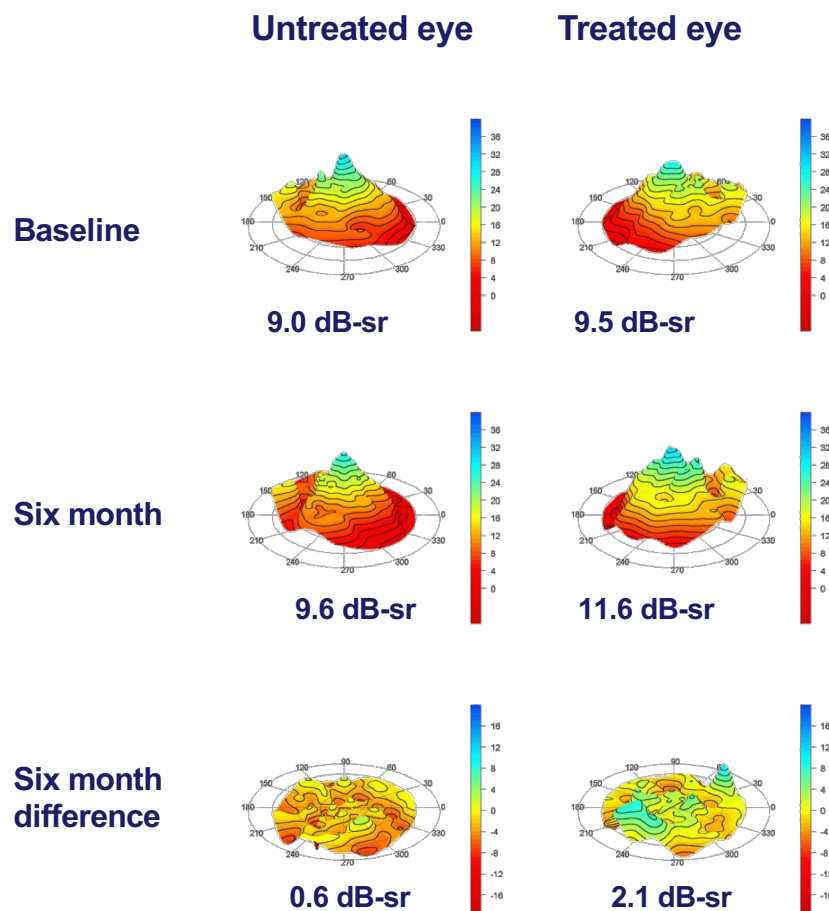
Excludes one subject with panuveitis in the low dose

Octopus 900
Static Perimetry

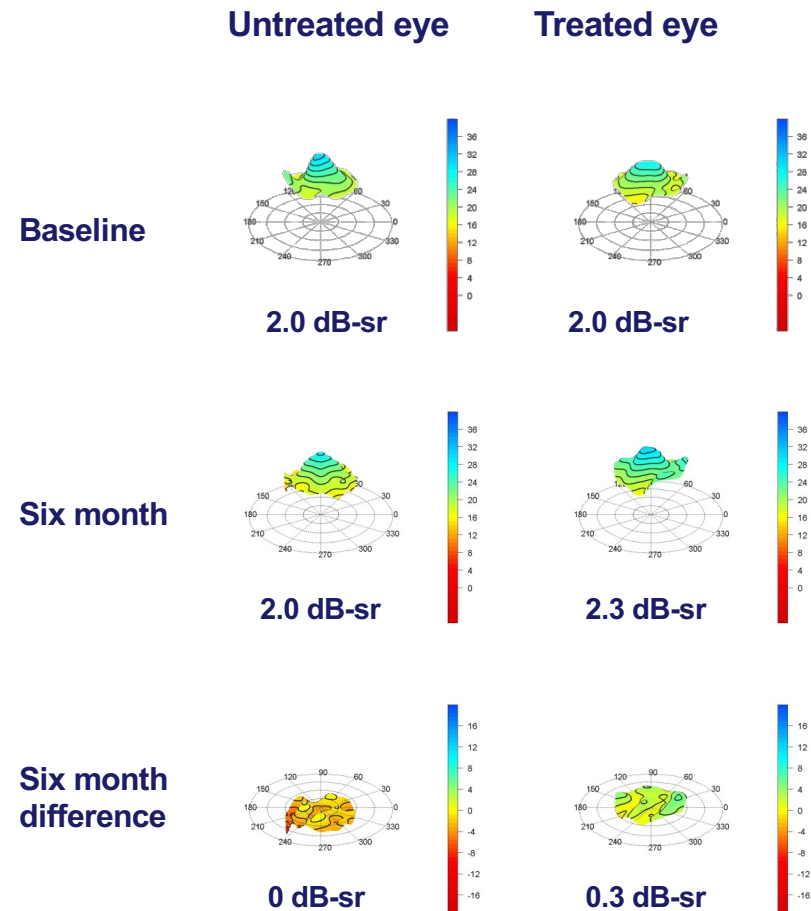


Subject 01-007 – Improved Retinal Sensitivity

VFMA-Derived Central 30° Hill-of-Vision (V30)

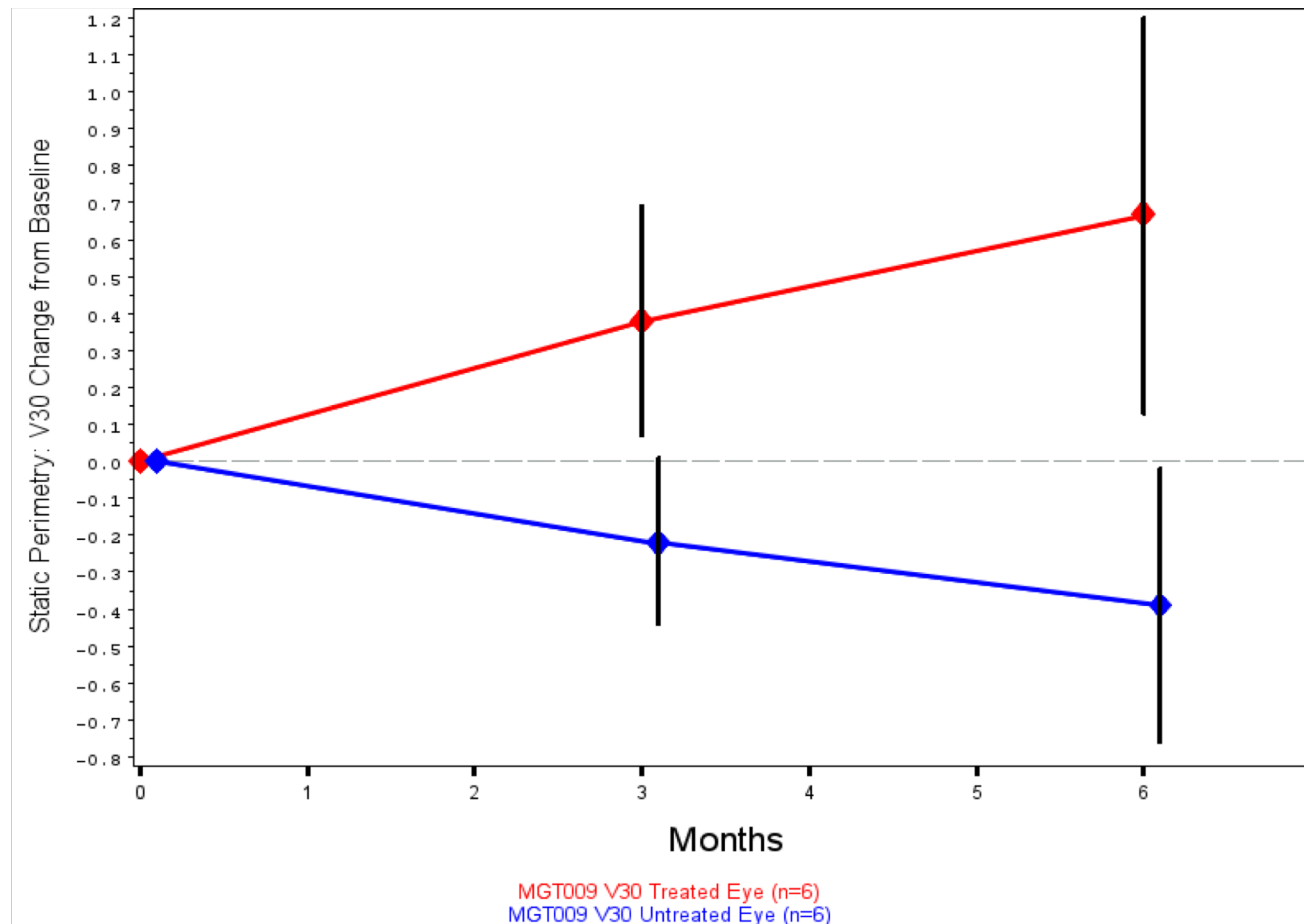


VFMA-Derived Central 10° Hill-of-Vision (V10)



VFMA, visual field modeling and analysis.

Statistically Significant Improvement in Central Retinal Sensitivity Observed in Treated Eyes



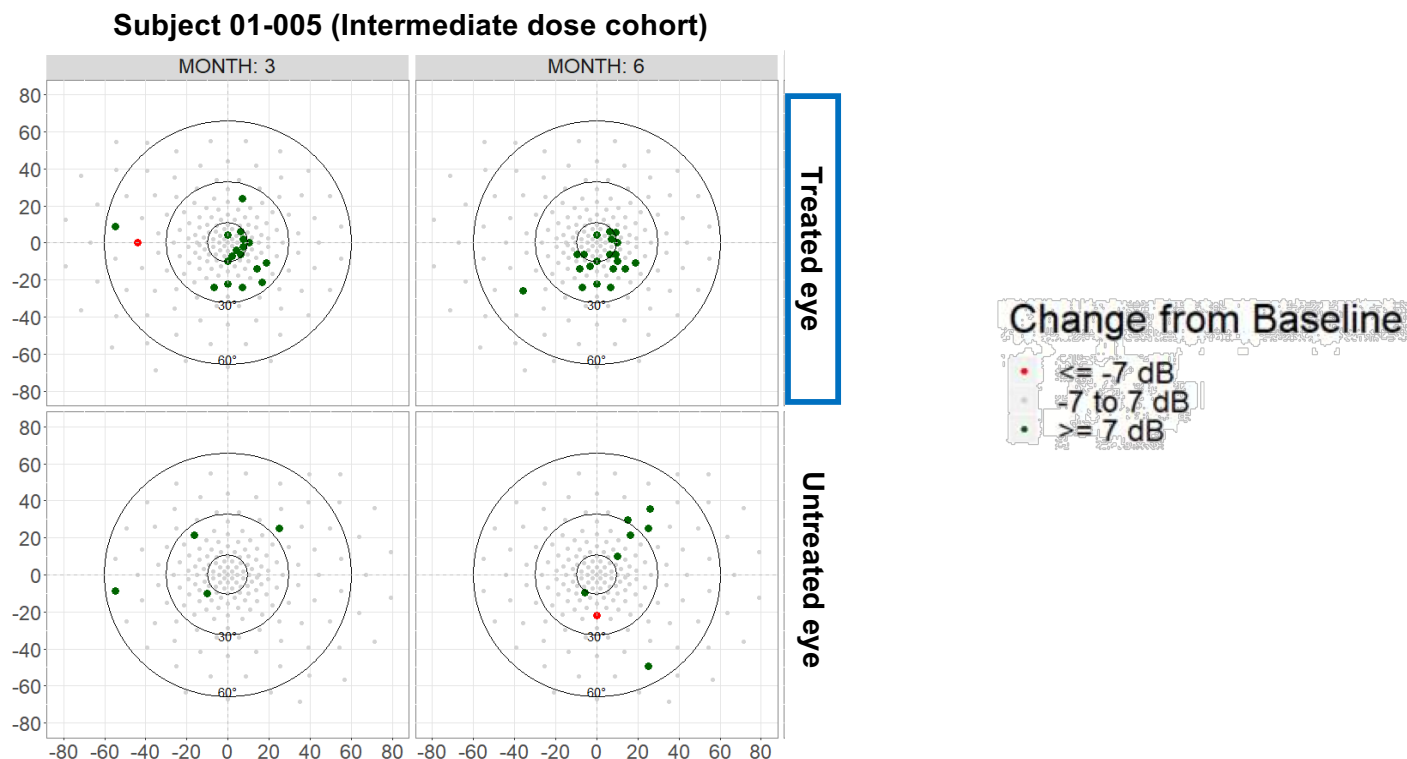
Low and Intermediate Dose Subjects (n=6)*

- Central retinal sensitivity increased in the treated eye group vs. baseline (0.67 dB-sr [90% CI: 0.13, 1.20]), while it decreased in the untreated eye group (−0.39 dB-sr [−0.76, −0.02])
- Statistically significant difference between treated and untreated eyes (1.06 dB-sr; $P < 0.05$)

*Excludes one subject with panuveitis in the low dose

Evidence of Retinal Sensitivity Improvement Using Pointwise Analysis

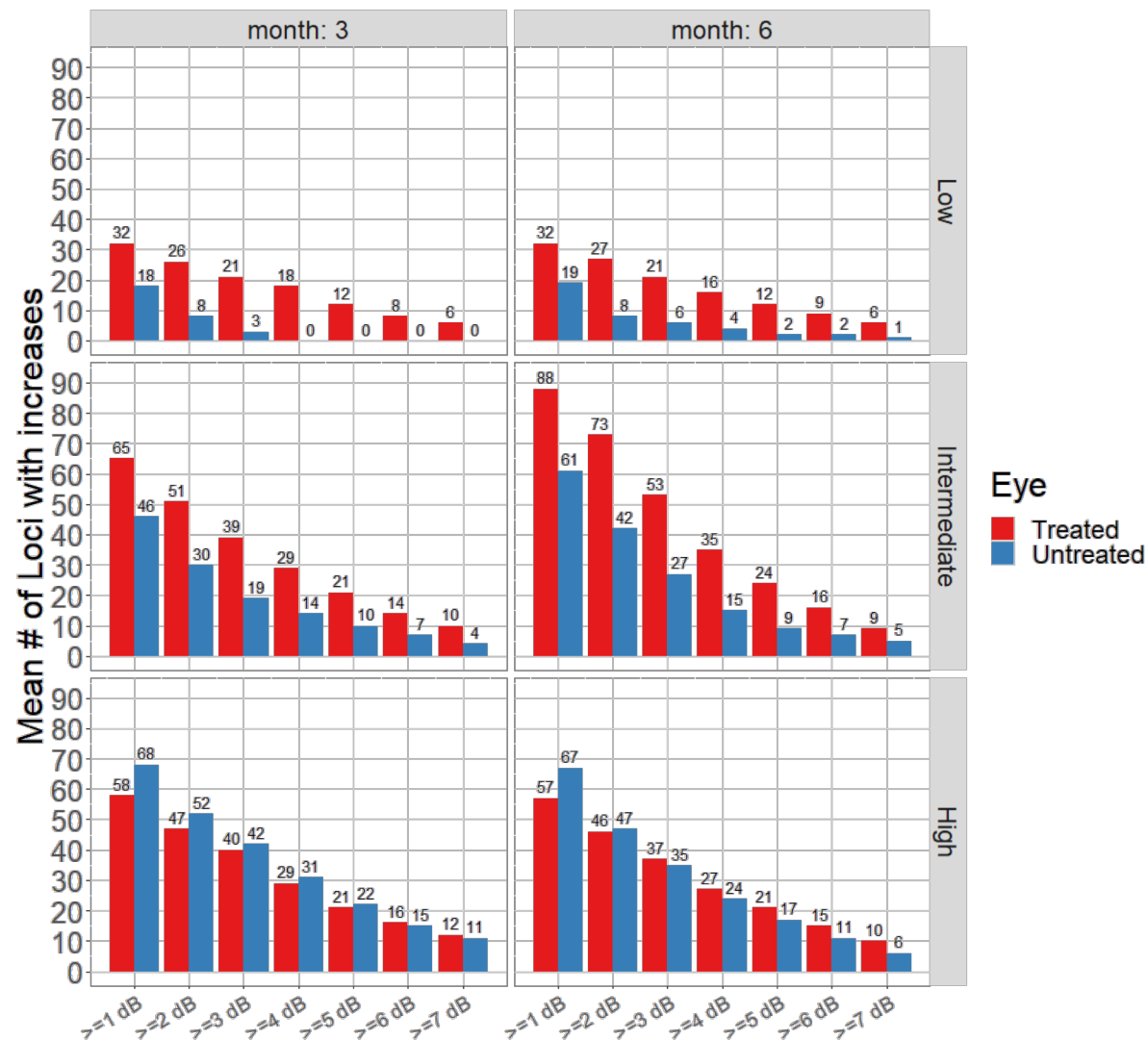
Representative Example of Pointwise Analysis



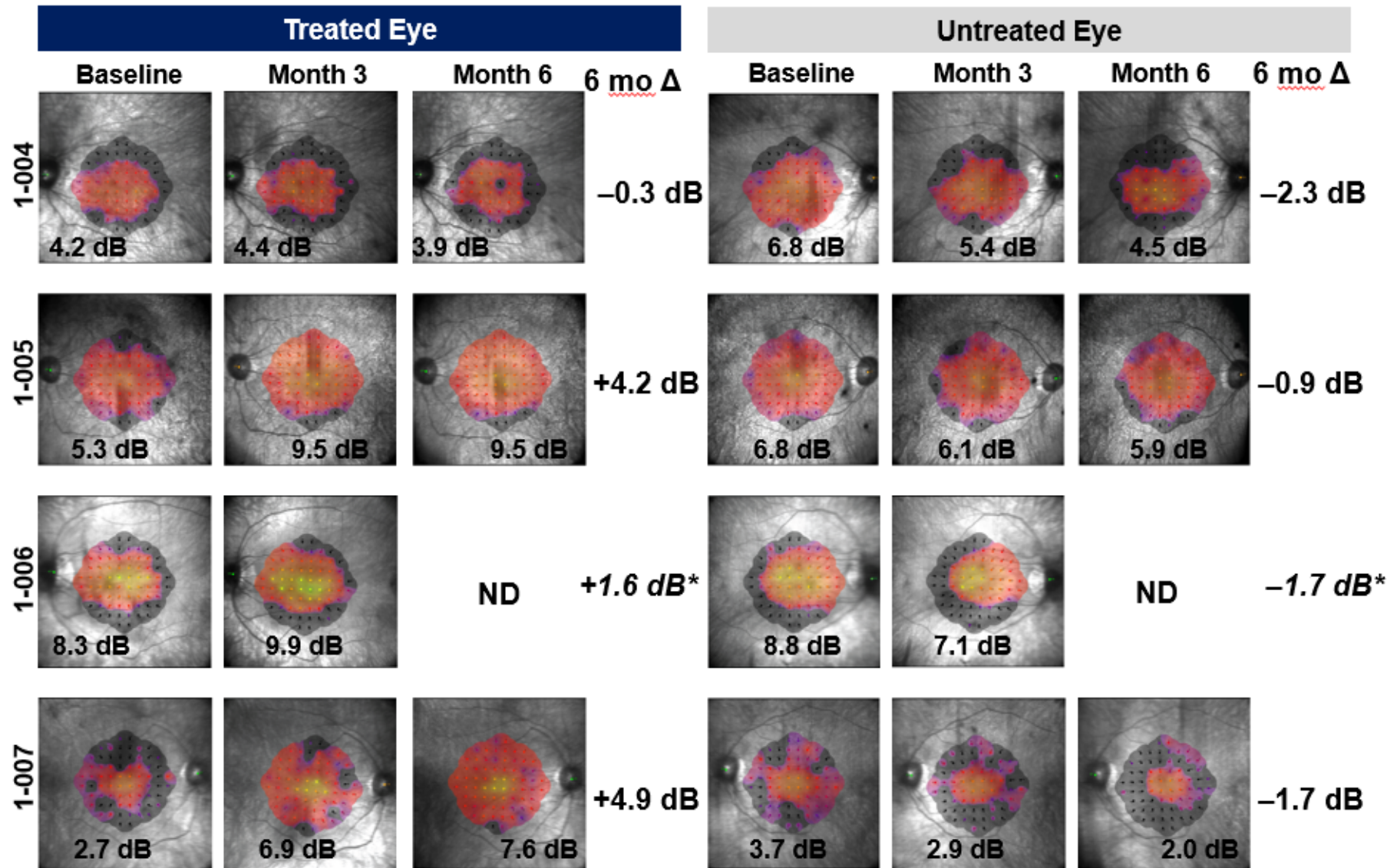
FDA definition of clinically meaningful improvement in diseases characterized by visual field loss: ≥ 5 loci improving ≥ 7 dB

Increased Retinal Sensitivity in Treated Eyes in Low and Intermediate Dose Cohorts

- In low and intermediate dose cohorts, efficacy signals were observed at first post-treatment assessment at three months, with improvements sustained or increased at six months
- No improvement compared to untreated eyes demonstrated in high dose cohort



Retinal Sensitivity Improvements on Mesopic Microperimetry: Intermediate Dose Cohort



*3 month change from baseline. Subject did not complete 6 month microperimetry assessment

Conclusions

- **Low and intermediate dose cohorts achieved clinically meaningful improvements in retinal sensitivity, evident across multiple metrics (mean sensitivity, volumetric, and pointwise) and modalities (full-field static perimetry and microperimetry)**
 - In low (n=3) and intermediate (n=4) dose cohorts, 5/7 subjects demonstrated improvement or stability in retinal sensitivity in the treated eye at six months
 - Efficacy signals were observed at first post-treatment assessment at three months, with improvements sustained or increased at six months
- **Safety data obtained to date suggest that AAV-RPGR is generally safe and well tolerated, the majority of the adverse events were anticipated due to the surgical procedure**
- **Given the robust safety and efficacy signals observed, these doses are being further explored with analyses at additional data time-points in the ongoing randomized, controlled dose-expansion phase of the study**

Acknowledgements

- Patients and families
- Referring clinicians and collaborators
- Trial managers, coordinators, and technicians
- Reading centers in Belfast, Oregon Health and Science University and Medical College of Wisconsin





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