Humoral Immune Response to AAV5-*RPGR* (Botaretigene Sparoparvovec) Gene Therapy in *RPGR*-associated X-linked Retinitis Pigmentosa

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Presented at the Association for Research in Vision & Ophthalmology (ARVO) Annual Meeting; April 23-27, 2023; New Orleans, LA.

Background

- XLRP is a severe form of retinitis pigmentosa that leads to progressive vision loss[1]
- AAV5-*RPGR* (botaretigene sparoparvovec) is being developed as a subretinal gene therapy for patients with XLRP caused by mutations in the *RPGR* gene
- Immunogenicity is a potential concern with AAV-based gene therapies[2]

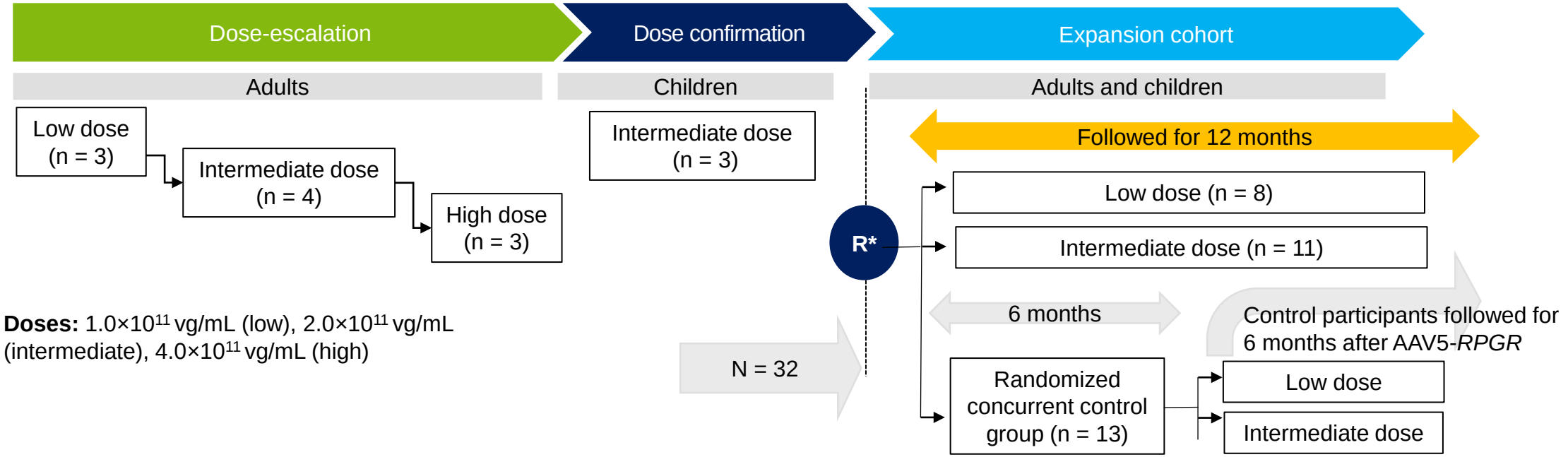
Objective: To summarize immunogenicity data following treatment with AAV5-*RPGR* gene therapy in participants with *RPGR*-XLRP in a phase 1/2 trial

AAV, adeno-associated virus; *RPGR*, retinitis pigmentosa GTPase regulator; XLRP, X-linked retinitis pigmentosa.

1. Megaw RD, et al. *Exp Eye Res*. 2015;138:32-41. 2.Whitehead M, et al. *Biol Rev Camb Philos Soc*. 2021;96(4):1616-1644.

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

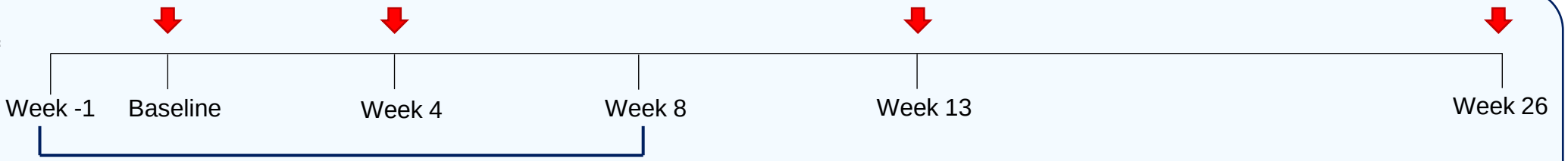
Open-label study of an AAV5-*RPGR* gene therapy (NCT03252847) conducted at 5 sites in the **United States** and the **United Kingdom**



Doses: 1.0×10^{11} vg/mL (low), 2.0×10^{11} vg/mL (intermediate), 4.0×10^{11} vg/mL (high)

Sample collection for the assessment of

- **Antibodies to AAV5**
- **Neutralizing antibodies to AAV5**
- **Antibodies to RPGR**



AAV, adeno-associated virus; R, randomization; *RPGR*, RP GTPase regulator (gene); RPGR, RP GTPase regulator (protein);
*1:1:1 randomization by group (immediate treatment or control), dose (low or intermediate), and eye (right or left).

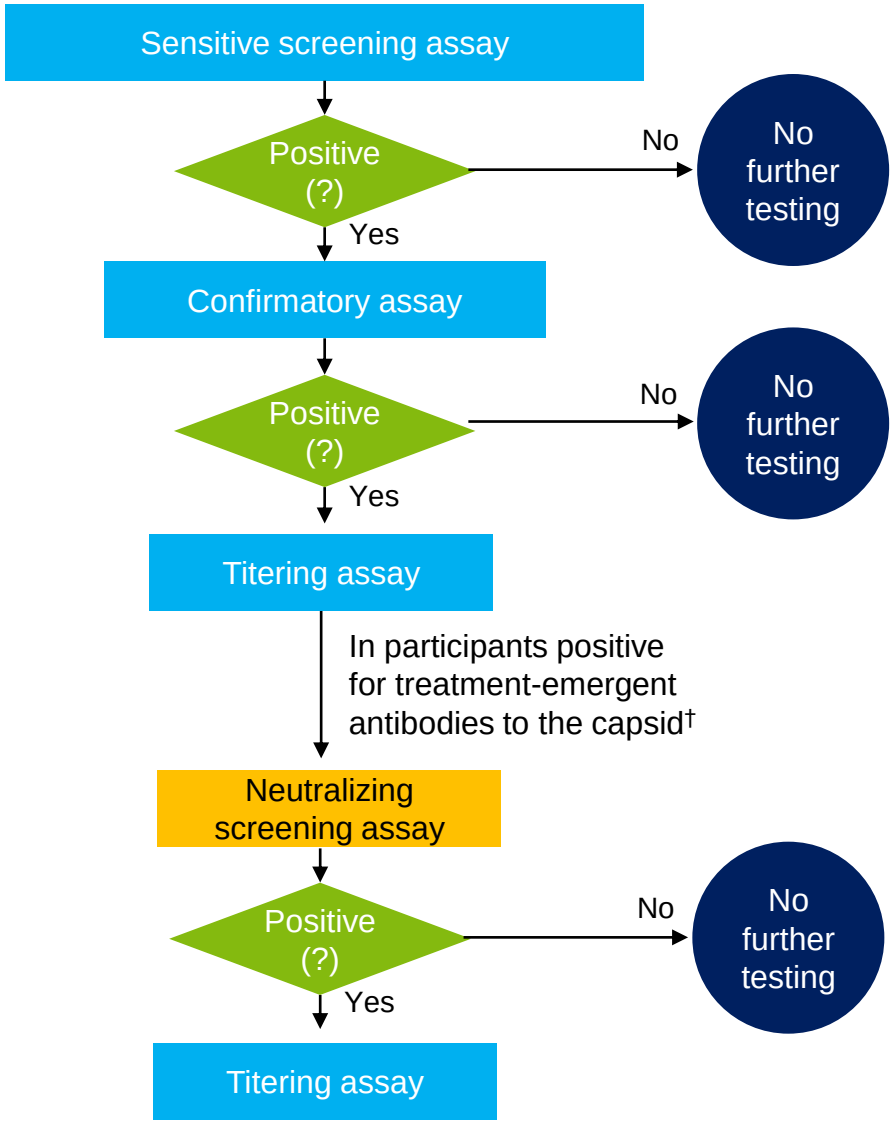
Methods

- Titers were only quantified on samples that were confirmed positive
- Neutralizing antibodies to the capsid were only assessed in participants identified as treatment-emergent positive for antibodies to the capsid
- **Participants positive for treatment-emergent antibodies were defined as those with either**
  - A positive sample at baseline (before administration) and a 4-fold increase of titer from baseline at any time point through Week 26 (after administration) *or*
  - A negative sample at baseline (before administration) and ≥1 positive sample at any time point through Week 26 (after administration) ie, treatment-induced antibodies

Minimum Required Dilutions

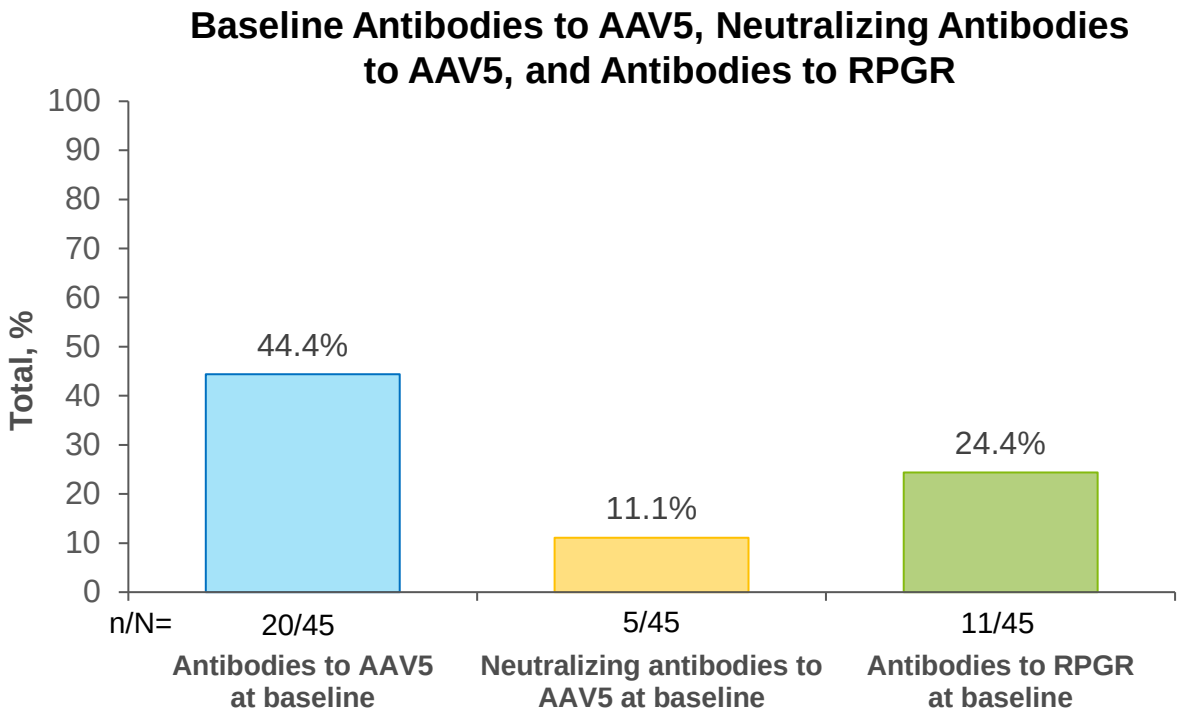
Antibodies to AAV5	Neutralizing Antibodies to AAV5	Antibodies to RPGR
1:10	1:10.5	1:7*

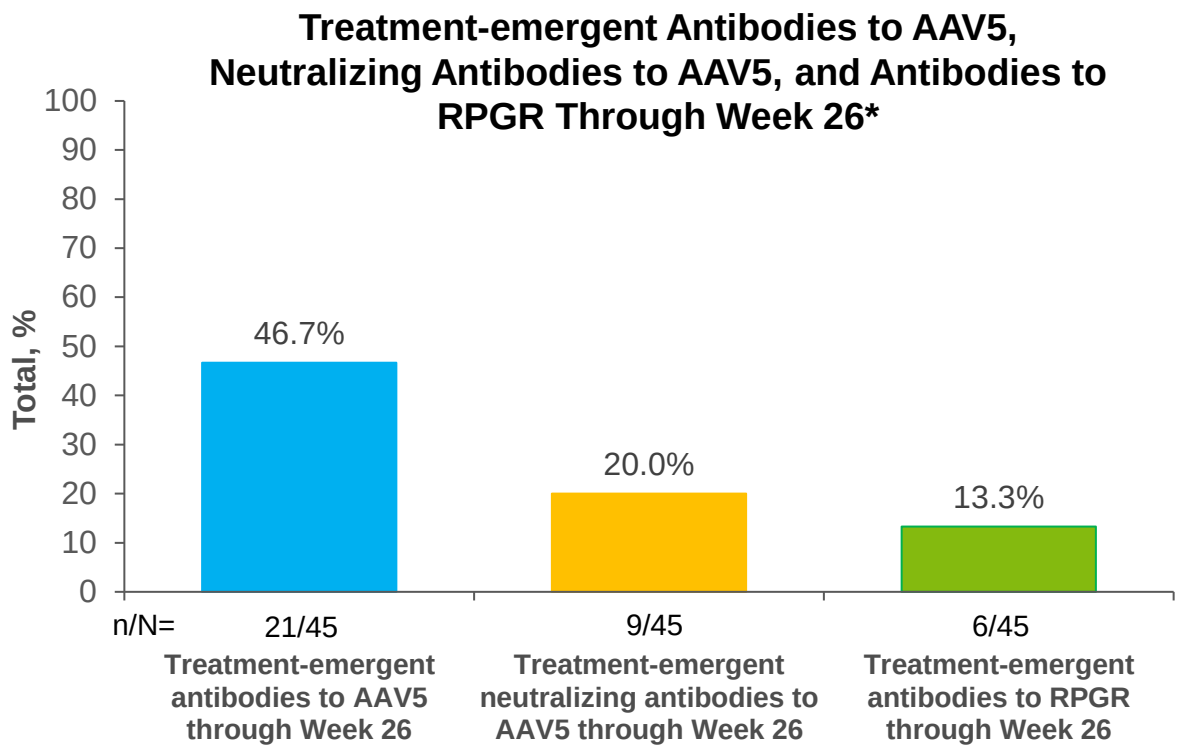
Multitiered Approach Used for Assessment of Antibodies[1]



AAV, adeno-associated virus; RPGR; retinitis pigmentosa GTPase regulator.
*Due to sample volume scarcity, the lowest achievable titer in this analysis was 1:14.
†Neutralizing antibodies to the RPGR protein were not assessed.
1. US Food and Drug Administration. Immunogenicity testing of therapeutic protein products—developing and validating assays for anti-drug antibody detection. Guidance for industry. https://www.fda.gov/media/119788/download. Accessed March 10, 2023.

Summary of Immunogenicity Results



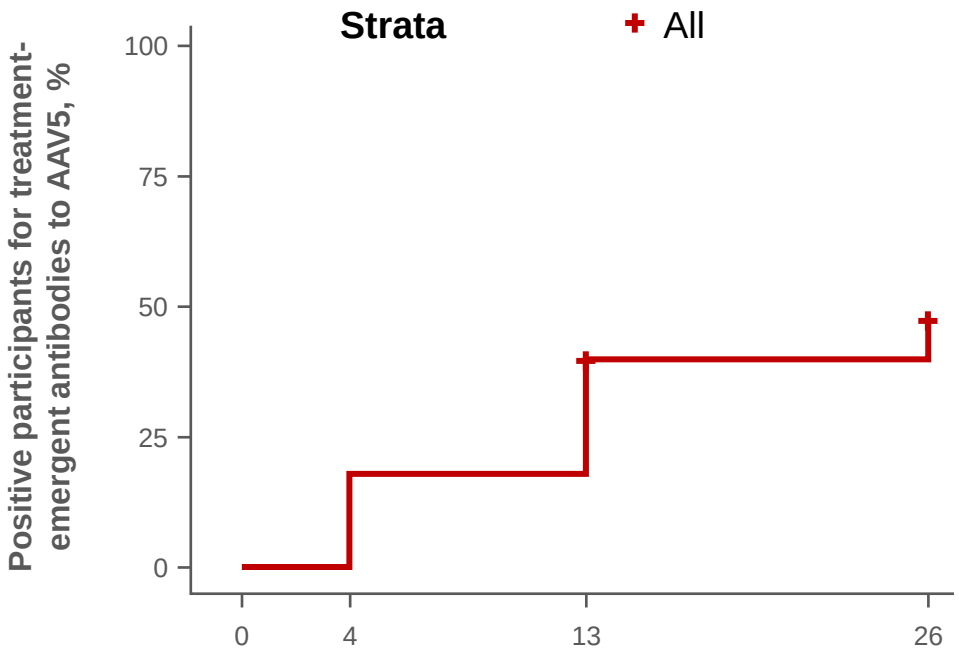


Dose						
Low (n=18), n	8	3	3	7	2	1
Intermediate (n=23), n	8	2	6	12	6	4
High (n=4), n	4	0	2	2	1	1

AAV, adeno-associated virus; RPGR, retinitis pigmentosa GTPase regulator.
*Participants positive for treatment-emergent antibodies are defined as participants with either a positive sample at baseline (before administration) and a 4-fold increase in titer from baseline at any time point through Week 26 (after administration) or a negative sample at baseline (before administration) and at least 1 positive sample at any time point through Week 26 (after administration), ie, treatment-induced antibodies

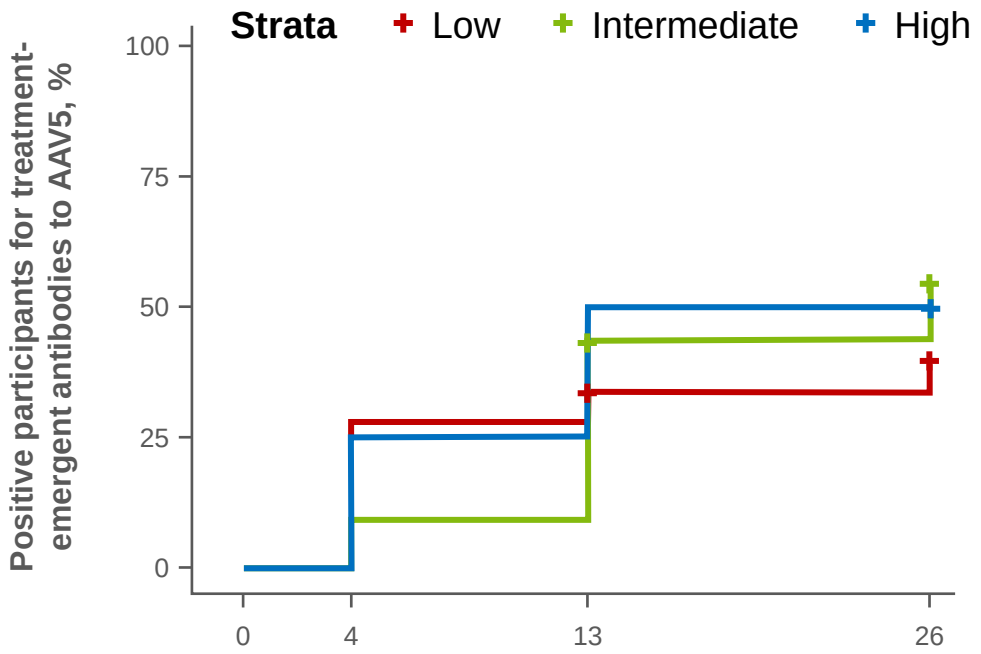
Time to Treatment-emergent Antibodies to AAV5 Capsid

All 45 Participants



Cumulative No. of Events				
All	0	8	18	21

Stratified by Dose Level



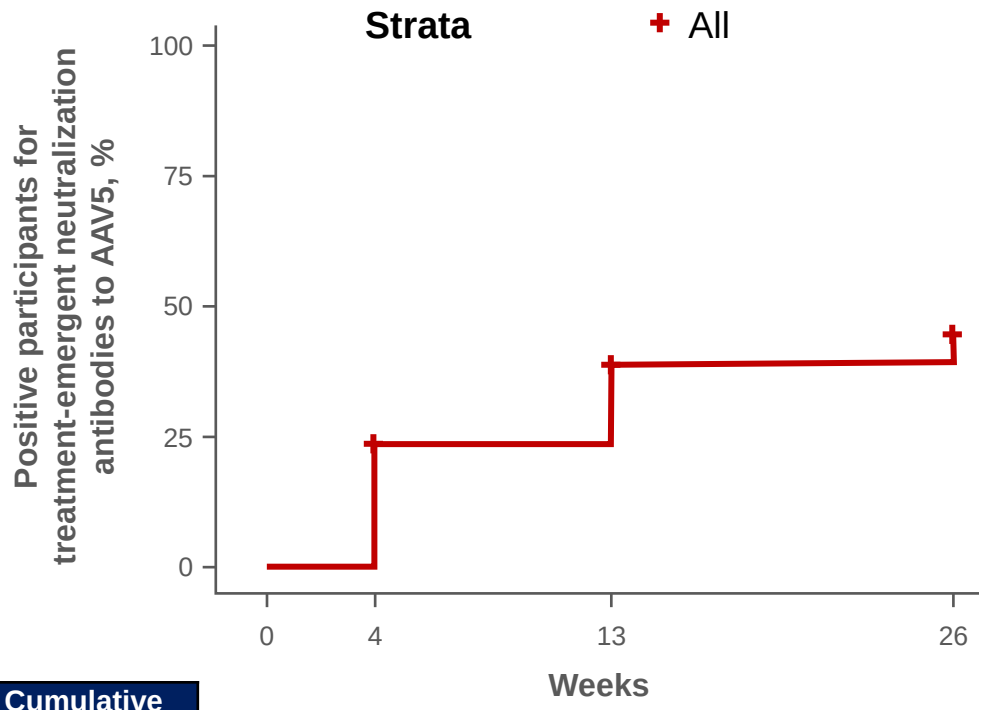
Cumulative No. of Events				
Low (n=18)	0	5	6	7
Intermediate (n=23)	0	2	10	12
High (n=4)	0	1	2	2

Doses: 1.0×10^{11} vg/mL (low), 2.0×10^{11} vg/mL (intermediate), 4.0×10^{11} vg/mL (high)

AAV, adeno-associated virus.

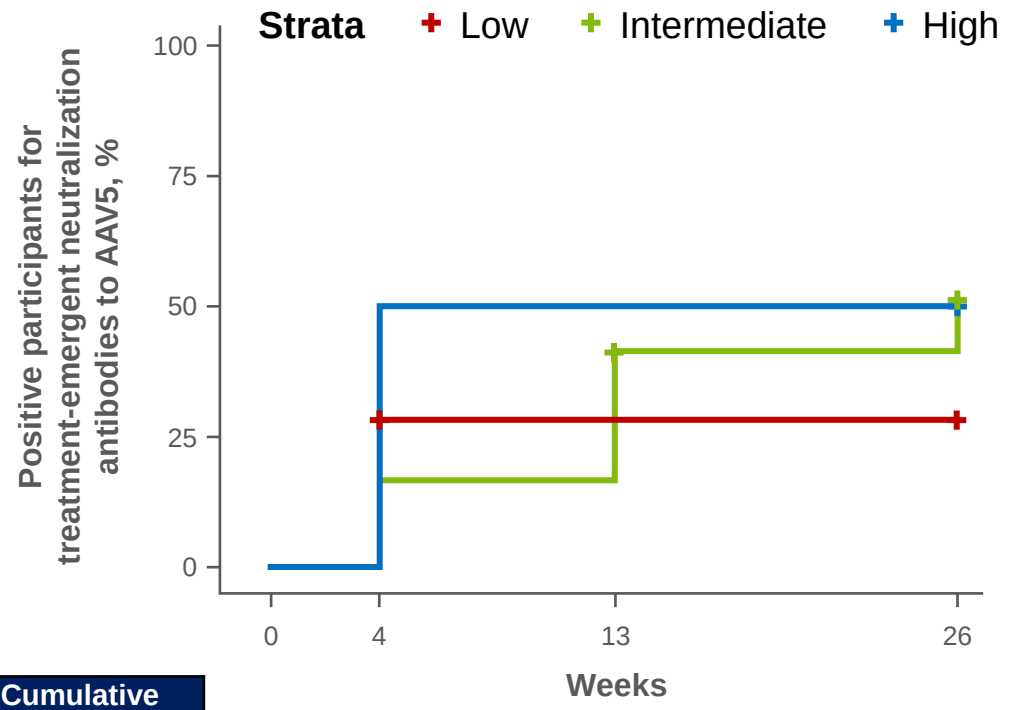
Time to Treatment-emergent Neutralizing Antibodies to AAV5 Capsid

All 21 Positive for Treatment-emergent Antibodies to AAV5 Participants



Cumulative No. of Events				
All	0	5	8	9

Stratified by Dose Level



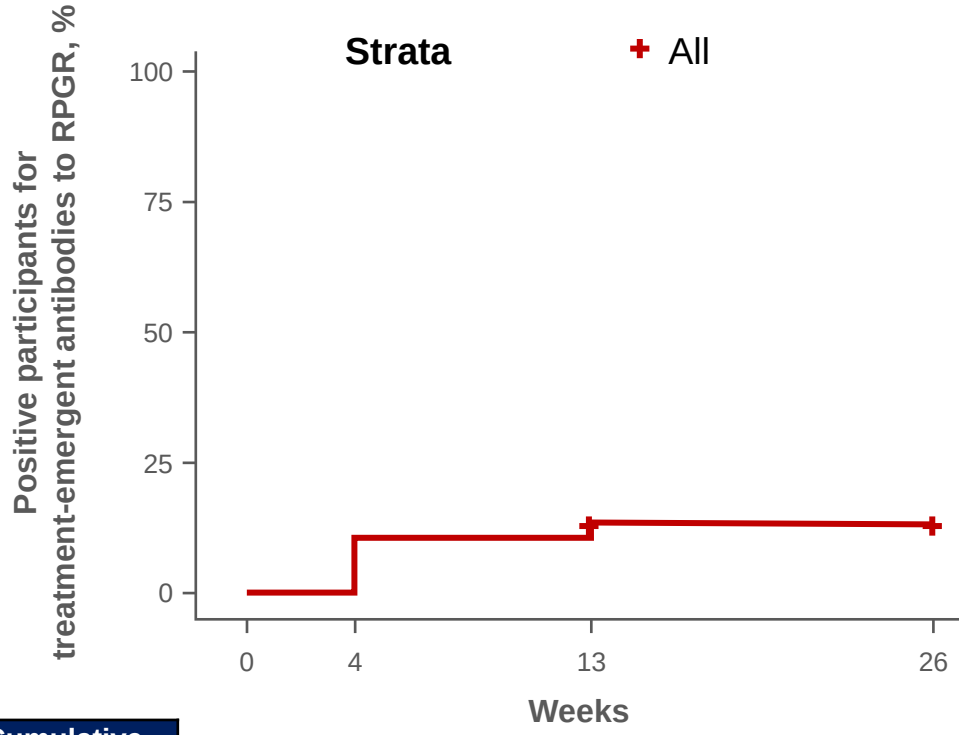
Cumulative No. of Events				
Low (n=18)	0	2	2	2
Intermediate (n=23)	0	2	5	6
High (n=4)	0	1	1	1

Doses: 1.0×10^{11} vg/mL (low), 2.0×10^{11} vg/mL (intermediate), 4.0×10^{11} vg/mL (high)

AAV, adeno-associated virus.

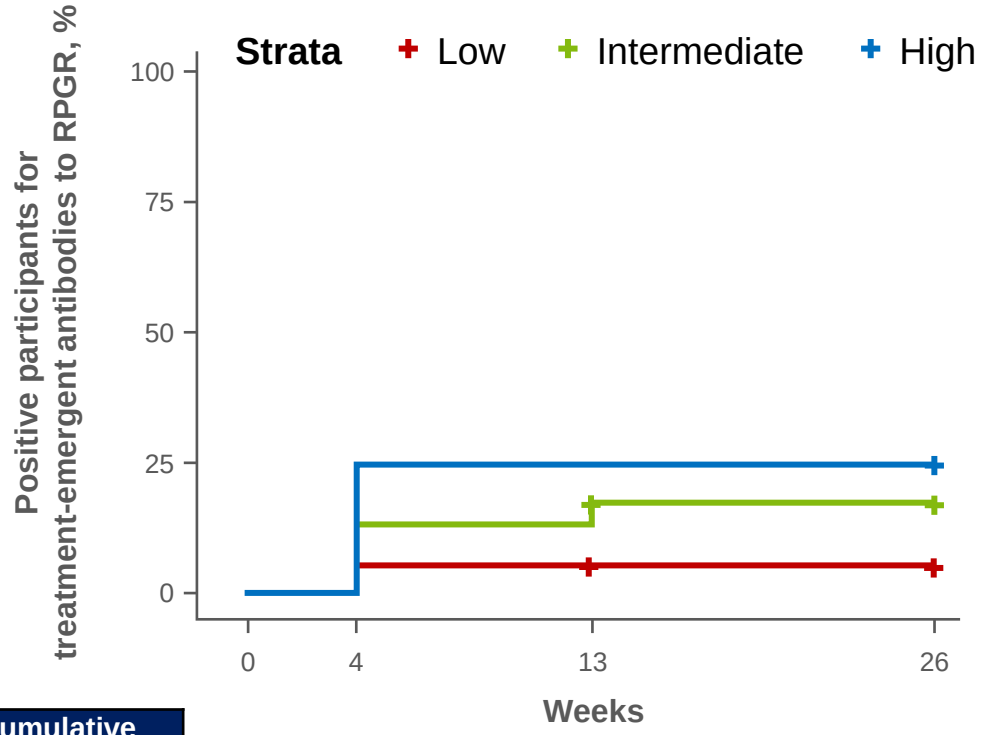
Time to Treatment-emergent Antibodies to RPGR

All 45 Participants



Cumulative No. of Events				
All	0	5	6	6

Stratified by Dose Level



Cumulative No. of Events				
Low (n=18)	0	1	1	1
Intermediate (n=23)	0	3	4	4
High (n=4)	0	1	1	1

Doses: 1.0×10^{11} vg/mL (low), 2.0×10^{11} vg/mL (intermediate), 4.0×10^{11} vg/mL (high)

RPGR; retinitis pigmentosa GTPase regulator.

Conclusions

- There was no apparent association between treatment-emergent antibody status and dose
- Findings did not seem to deviate from those reported for voretigene neparvovec[1-3]

1. US Food and Drug Administration. LUXTURNA® Biologics License Application Clinical Review Memorandum. https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Clinical-Review--December-16--2017---LUXTURNA.pdf. Accessed March 13, 2023.
2. Whitehead M, et al. *Biol Rev Camb Philos Soc*. 2021;96(4):1616-1644. 3. Verdara HC, et al. *Mol Ther*. 2020;28(3):723-746.

Acknowledgments

- **Participants and families**
- **Referring clinicians and collaborators**
- **Trial managers, coordinators, and technicians**
- **Reading centers** in Belfast, OHSU, and MCW
- **Other supporting institutions:** Kellogg Eye Center (University of Michigan), Moorfields Eye Hospital (NHS Foundation Trust), UCL Institute of Ophthalmology, The Leeds Teaching Hospital (NHS Trust), Mass Eye and Ear (Mass General Brigham)
- **Trial funding:** MeiraGTx and Janssen

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