The Development of Voretigene Neparvovec, a Gene Therapy for Biallelic *RPE65* Mutation Associated Inherited Retinal Disease: A Case Study for Retinal Gene Therapy

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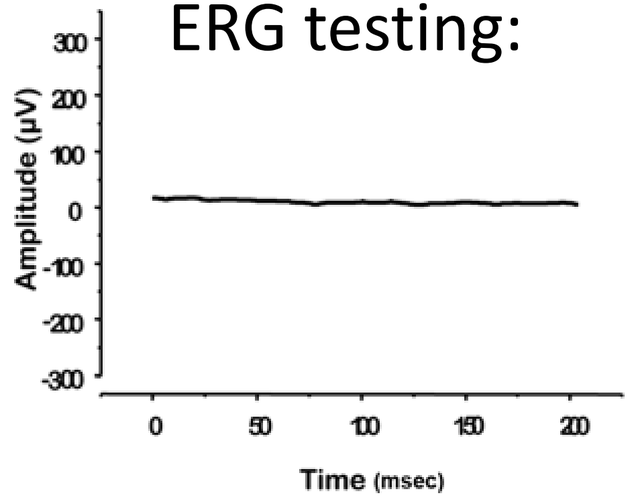
Biallelic *RPE65* mutation-associated retinal dystrophy

- Rare autosomal recessive disease with many clinical descriptors: Leber congenital amaurosis (LCA2), retinitis pigmentosa (RP20)
  - About 8-16% cases of LCA, 1% of RP[1]
- Early onset retinal degeneration; nyctalopia an early symptom
- Some vision early in life, significant impairment by second decade
- Genetically engineered mice and naturally occurring dog models of disease

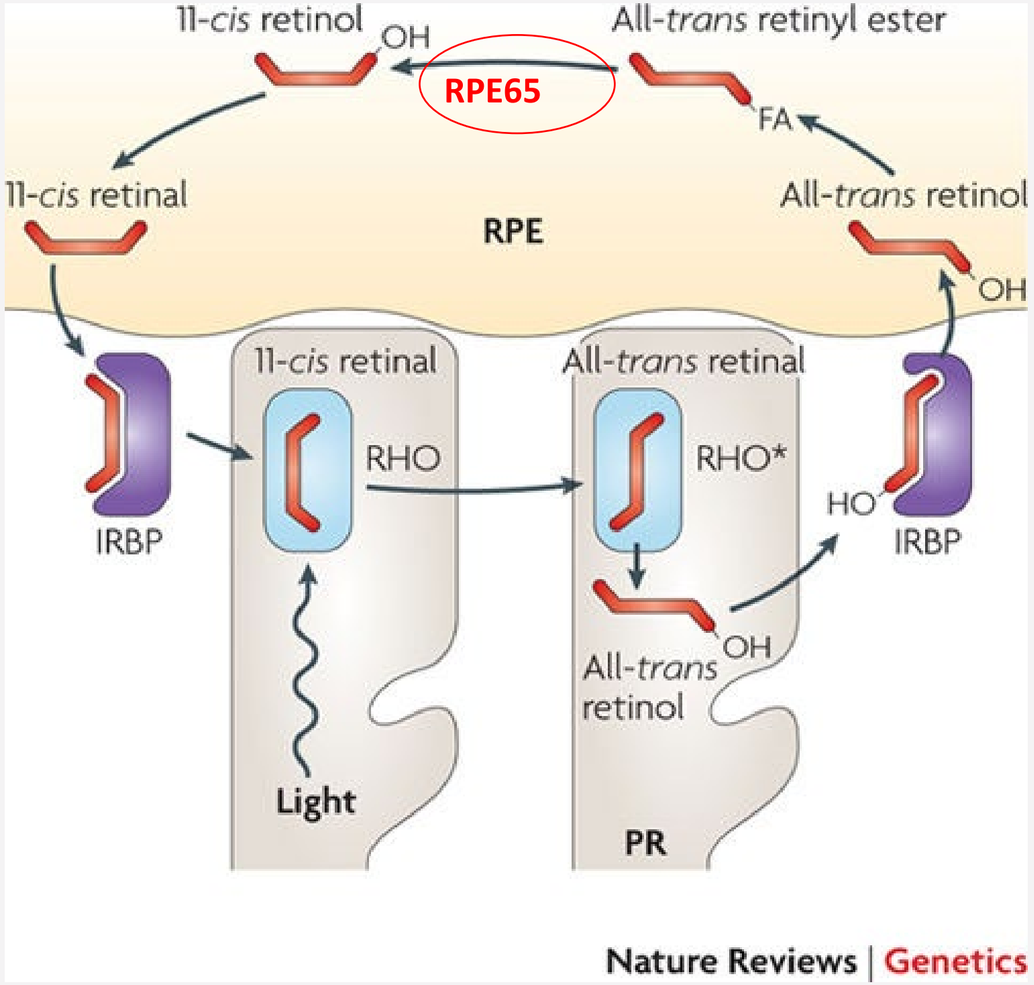
ERG testing:



Nystagmus

[1]Based on incidence/prevalence from Genetics Home Reference and commissioned market research.
Image courtesy of Jean Bennett, MD, PhD.
Russell S, et al. Lancet 2017; 390(10097):849-60

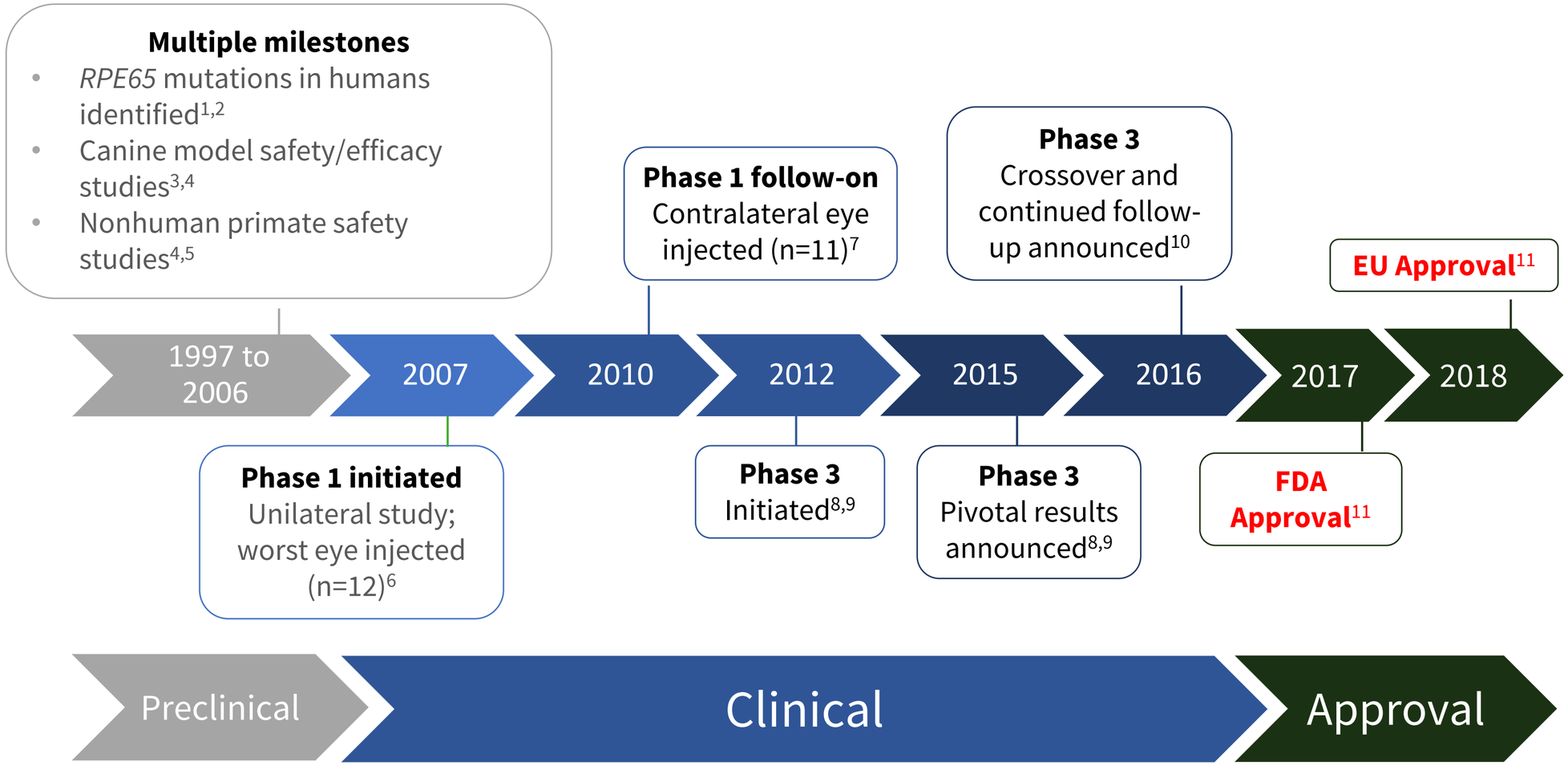
Mechanism of Action of *RPE65* Gene Therapy



PR, photoreceptor; RPE, retinal pigment epithelium;

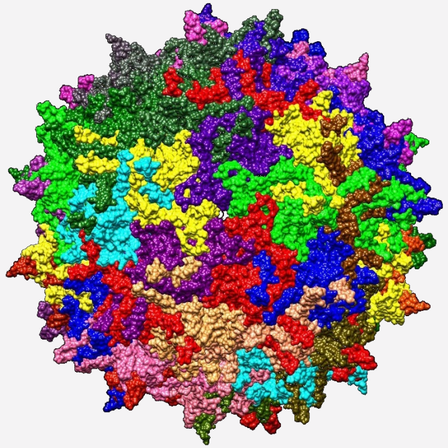
Wright AF, et al. Nat Rev Genet 2010; 11(4):273-84.

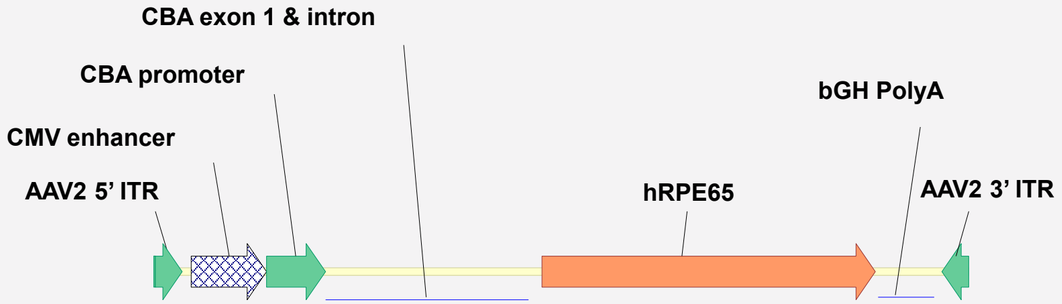
Voretigene Neparvovec-rzyl: Development History



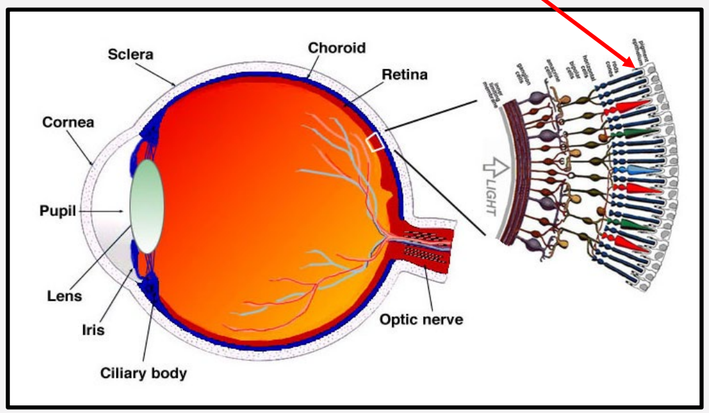
1. Marlhens et al. Nat Genet 1997; 17:139-141. 2. Gu et al. Nat Genet 1997; 17:194-197. 3. Narfström et al. Invest Ophthalmol Vis Sci 2003; 44:1663-1672. 4. Data on File. Spark Therapeutics, Inc. Philadelphia, PA. 5. Jacobson et al. Human Gene Ther 2006; 17:845-858. 6. Maguire et al. Lancet 2009; 374:1597-1605. 7. Bennett et al. Lancet 2016; 388:661-72. 8. Maguire et al. Presentation at: American Academy of Ophthalmology Meeting 2015; November 14-17, 2015; Las Vegas, NV. 9. Russell et al. Presentation at: Retina Society 48th Annual Scientific Meeting; October 7-11, 2015; Paris, France. 10. Spark Therapeutics. http://ir.sparktx.com/news-releases/news-release-details/spark-therapeutics-announces-new-positive-data-continuation. Accessed December 3, 2018. 11. Spark Therapeutics. http://ir.sparktx.com/news-releases/news-release-details/european- commission-approves-spark-therapeutics-luxturnar. Accessed December 3, 2018.

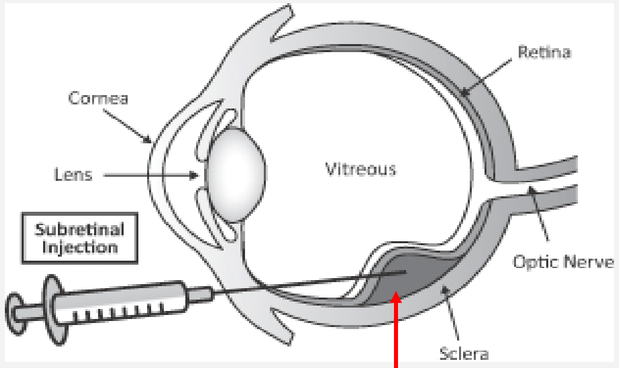
Voretigene neparvovec-rzyl is an AAV2-hRPE65 vector developed for subretinal injection





Subretinal injection
between RPE and PR layer





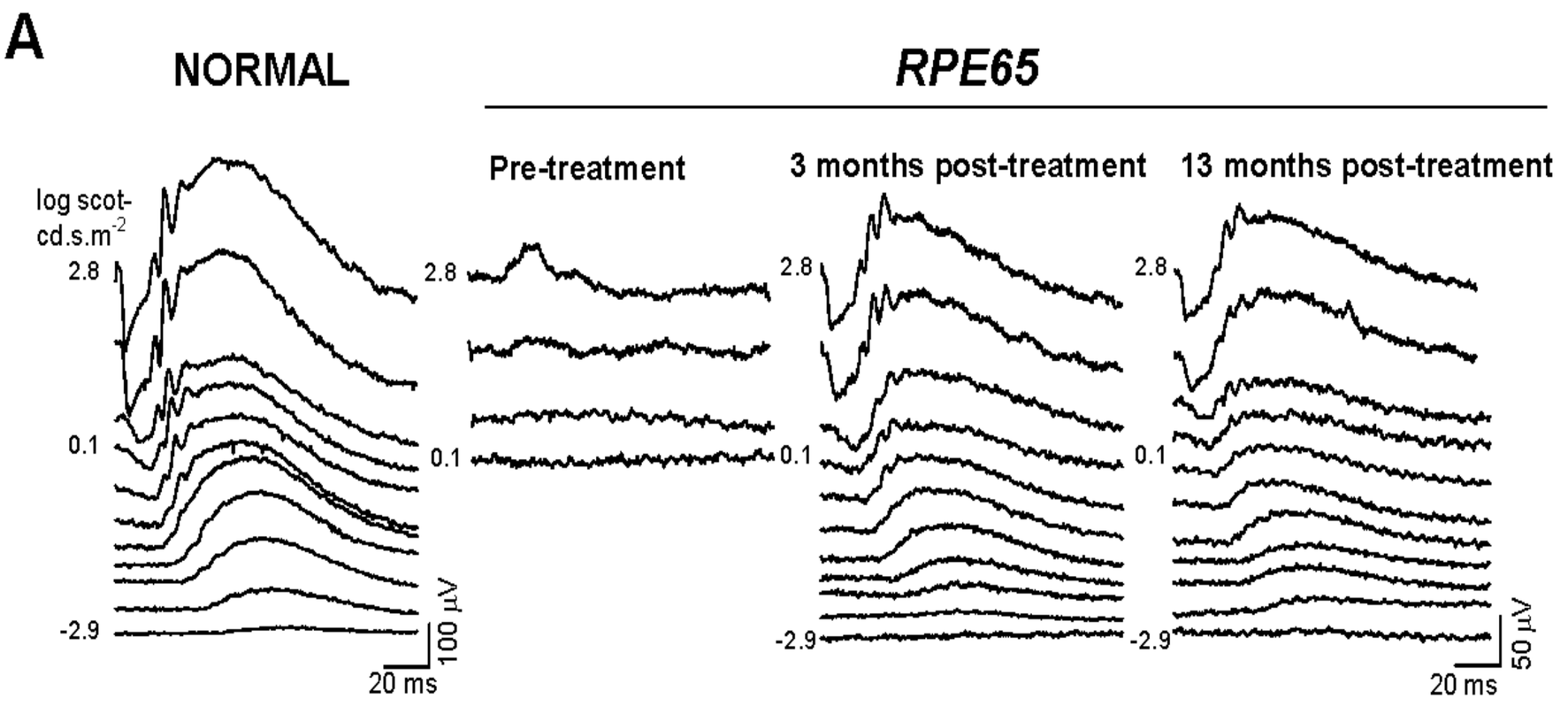
Bleb (~25-30% of retina)

https://commons.wikimedia.org/wiki/File:Adeno-associated_virus_serotype_AAV2.jpg
http://webvision.med.utah.edu/book/part-i-foundations/simple-anatomy-of-the-retina/
http://mmg-233-2014-genetics-genomics.wikia.com/wiki/File:Injection.jpg

Non-Clinical Studies in *RPE65* Mutant Dogs

https://speakingofresearch.com/2009/09/08/blind-dogs-lead-researchers-to-treatments/

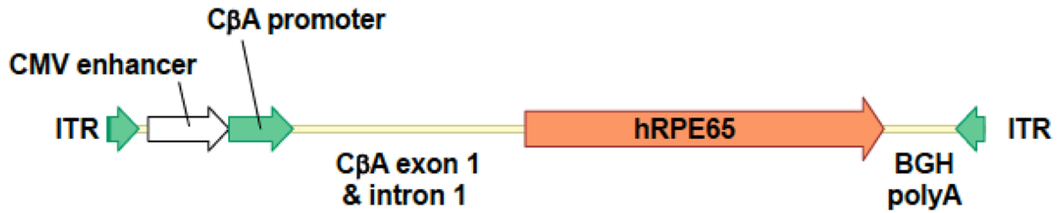
Restored ERG Response



Acland GM, et al. Presented at: Association for Research in Vision and Ophthalmology Annual Meeting, 2002.

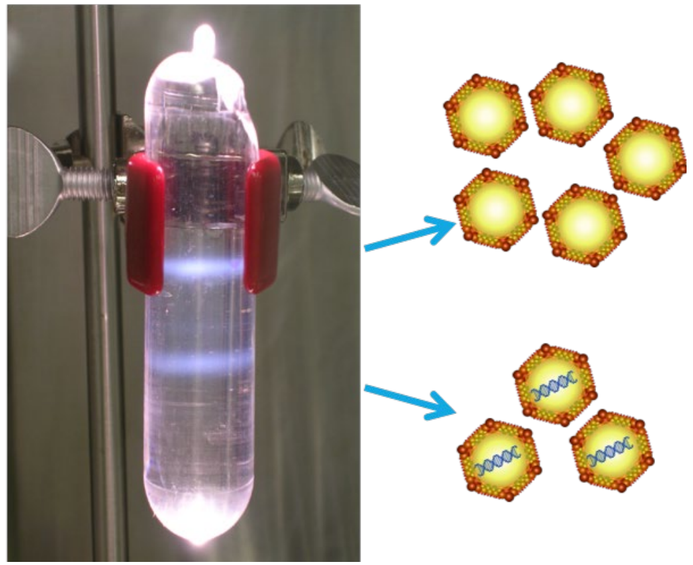
Optimization of Vector Creating Voretigene Neparvovec-rzyl

Optimized construct
- Kozak sequence

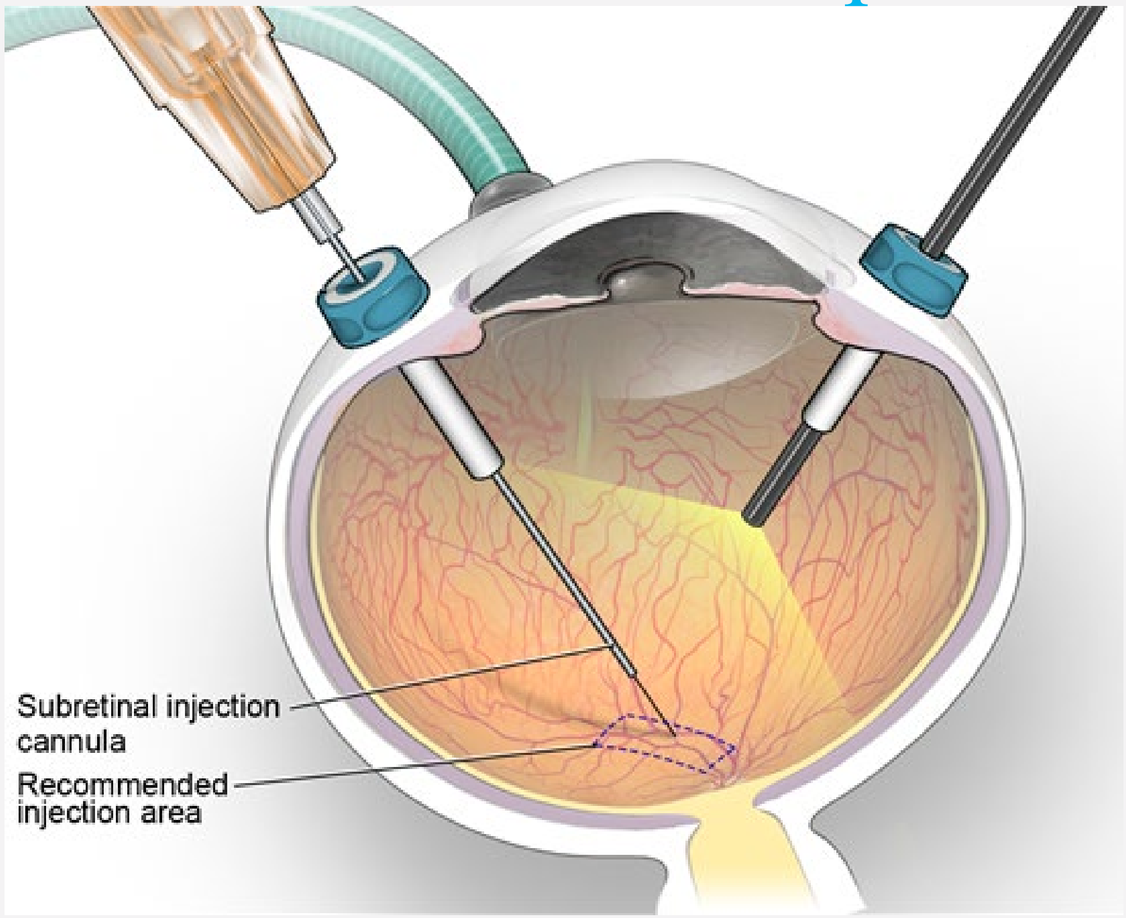


vg/mL: vector genomes per milliliter

Optimized final formulation
- Removed empty capsids
- Added surfactant

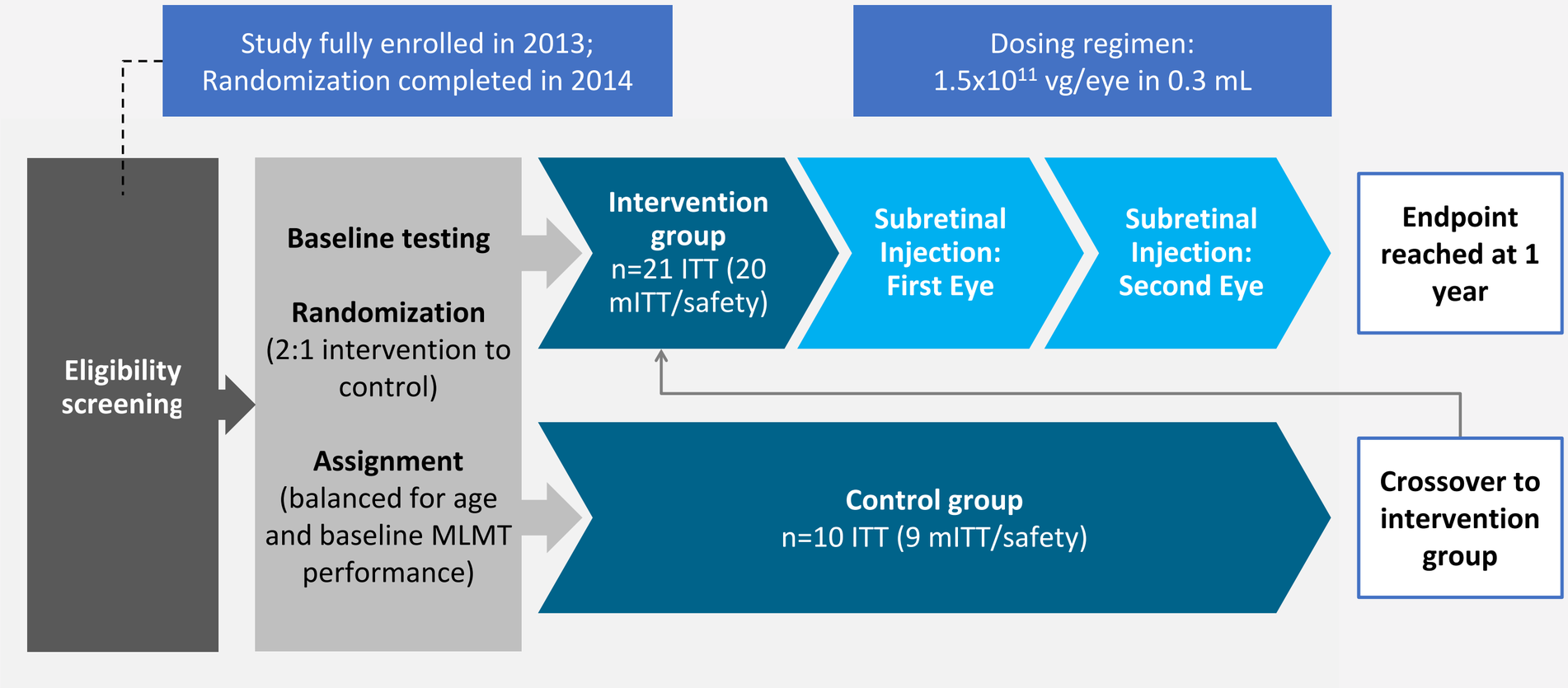


Subretinal injection of voretigene neparvovec-rzyl



- Maguire AM, et al. N Engl J Med 2008; 358:2240-2248.

Phase 3 trial design: Multi-center, open-label, randomized controlled crossover design

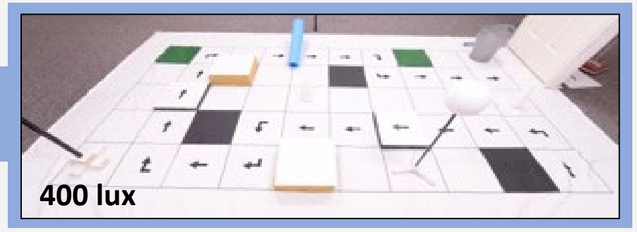


ITT, intent-to-treat population; mITT, modified intent-to-treat population; MLMT, multi-luminance mobility test; vg, vector genome;

- Russell S, et al. Lancet 2017; 390(10097):849-60.

MLMT: Designed to detect changes in functional vision across a range of light levels

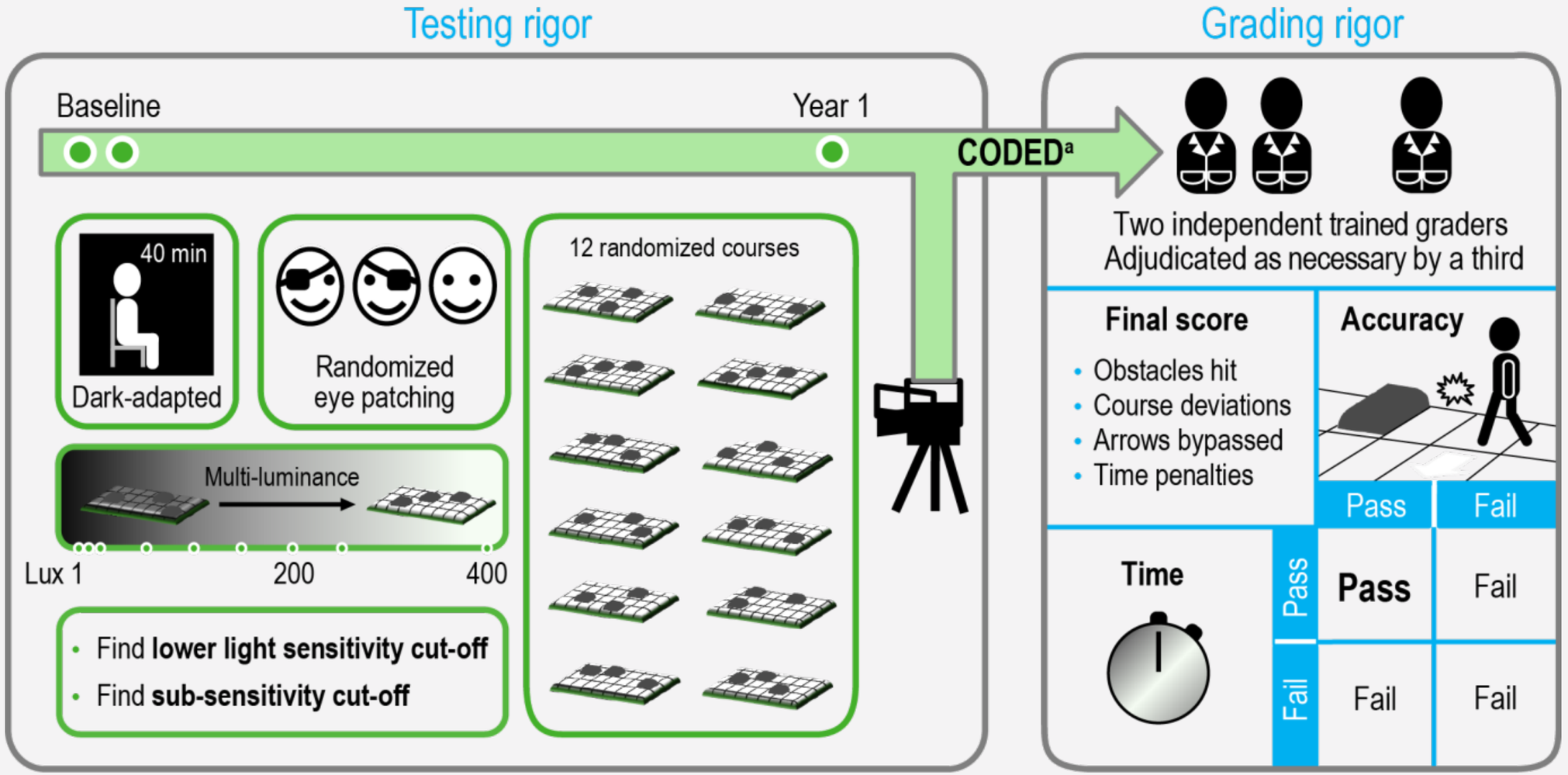
Light Levels	Examples
1 lux	Moonless summer night; Indoor nightlight
4 lux	Cloudless night with half moon; Parking lot at night
10 lux	1 hour after sunset in city; Bus stop at night
50 lux	Outdoor train station at night; Inside of lighted stairwell
125 lux	30 minutes before sunrise; Interior of train / bus at night
250 lux	Interior of elevator or office hallway
400 lux	Office environment or food court



Light meter: National Institute of Standards and Technology-calibrated,
Extech model #EA33 light meters used to provide examples and to set / verify specified light levels used for mobility testing

- Chung DC, et al. Clin Exp Ophthalmol 2018; 46(3):247-259.

Standardizing and Quantifying the MLMT



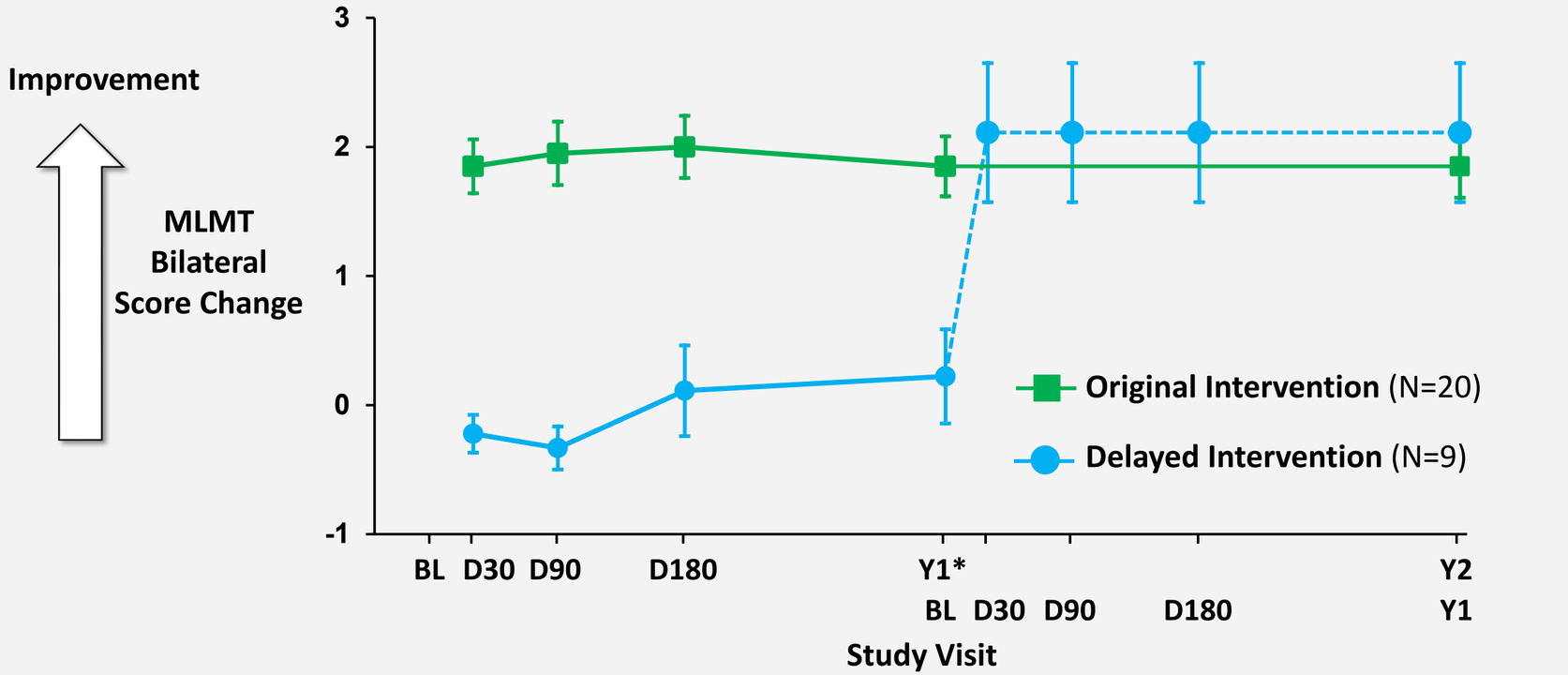
- Chung DC, et al. Clin Exp Ophthalmol 2018; 46(3):247-259.

Phase 3: Efficacy Endpoints and Results

Assessment	Measurement	Difference (95% CI) (Intervention-Control)	p value
Primary Endpoint			
MLMT performance	Bilateral, score change	1.6 (0.72, 2.41)	**p = 0.0013**
Secondary Endpoints			
FST testing	Averaged over both eyes, log10(cd.s/m^2)	-2.11 (-3.19, -1.04)	**p = 0.0004**
MLMT performance	Assigned first eye, score change	1.7 (0.89, 2.52)	**p = 0.0005**
Visual acuity	Averaged over both eyes, LogMAR (Holladay)	-0.16 (-0.41, 0.08)	**p = 0.17**
Additional Endpoint			
Visual field	Goldmann III4e sum total degrees, averaged over both eyes	378.7 (145.5, 612.0)	**Nominal p = 0.0059**
	Humphrey macula threshold, dB, averaged over both eyes	7.9 (3.5, 12.2)	**Nominal p = 0.0005**

- Russell S, et al. Lancet 2017; 390(10097):849-60.

Phase 3 Primary Endpoint: MLMT Improvement at Year 1

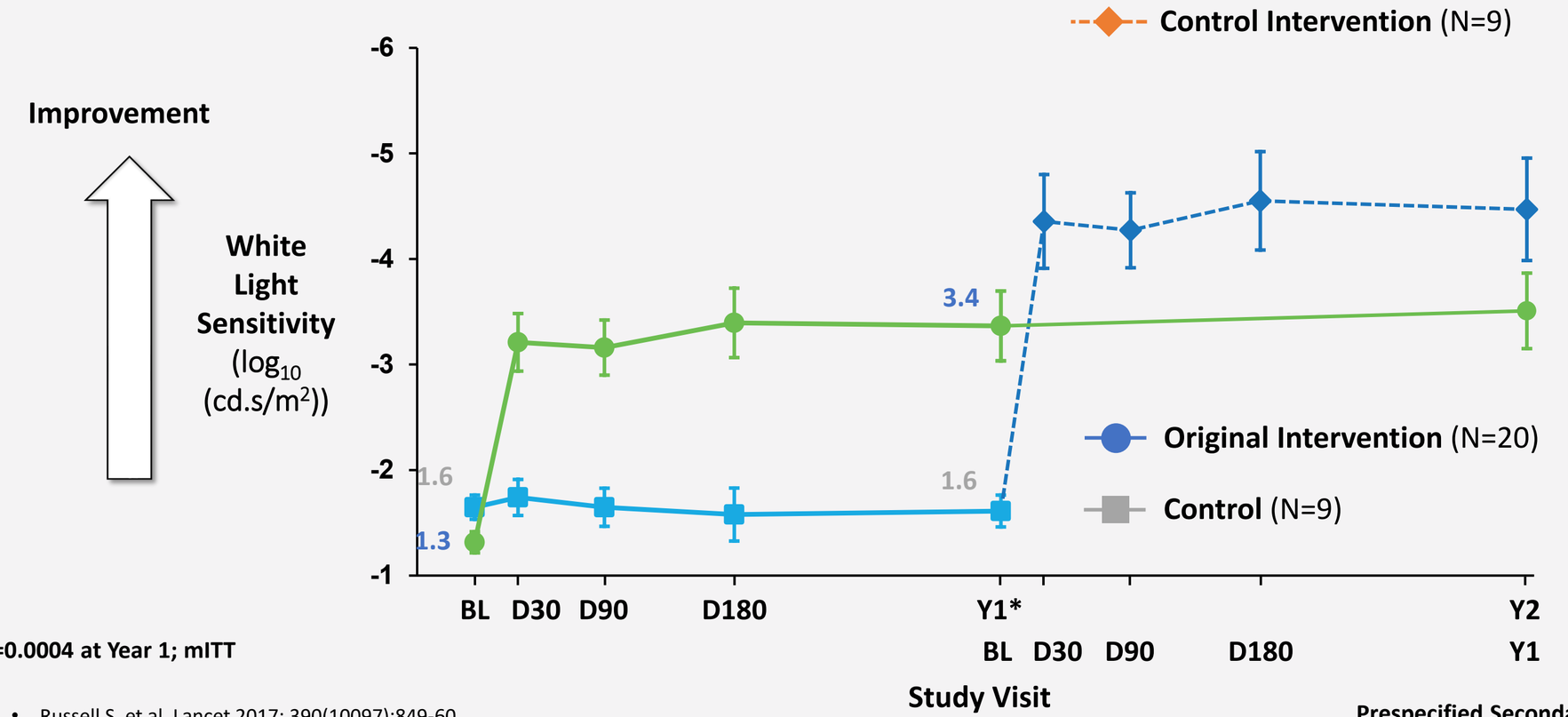


Data presented as mean ± SE. For the DI group, change is relative to injection baseline after Year 1. OI population DI population

Russell S, et al. Lancet 2017; 390(10097):849-60.

Russell S, et al. Poster presented at: the Association for Research in Vision and Ophthalmology Annual Meeting; May 7-11, 2017; Baltimore, MD

Phase 3: Secondary endpoint (FST at Year 1) >100-fold improvement in white light sensitivity



*** p=0.0004 at Year 1; mITT**

Prespecified Secondary Endpoint

- Russell S, et al. Lancet 2017; 390(10097):849-60.
- Russell S, et al. Poster presented at: the Association for Research in Vision and Ophthalmology Annual Meeting; May 7-11, 2017; Baltimore, MD

Safety in Phase 3 Study

- Most frequently reported ocular treatment-emergent adverse events (≥10% subjects) through 2-4 years after vector administration (Intervention and Control/Intervention population):
  - Increased intraocular pressure, 7 events in 5 (17%) subjects
  - Cataract, 10 events in 5 (17%) subjects
  - Retinal tear, 3 events in 3 (10%) subjects
  - Retinal deposits, 3 events in 3 (10%) subjects
- Ocular serious adverse events:
  - One subject in the Control/Intervention group
    - Loss of foveal function assessed as related to the administration procedure
  - One subject with retinal detachment 4 years post administration
- No deleterious immune responses occurred

- Maguire AM, et al. Presentation at: The American Academy of Ophthalmology (AAO) Annual Meeting, Retina Subspecialty Day; November 10, 2017; New Orleans, LA.

Observations

- The first gene therapy for a genetic disease approved in the US
- The first gene therapy for an ocular disease approved
- Novel endpoint designed, validated and successfully used in pivotal trial
- Subretinal injections have a favorable safety profile
- AAV vectors have a favorable safety profile