Clinical Trial of Elamipretide Topical Ophthalmic Solution for the Treatment of Leber's Hereditary Optic Neuropathy

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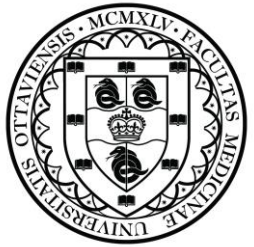

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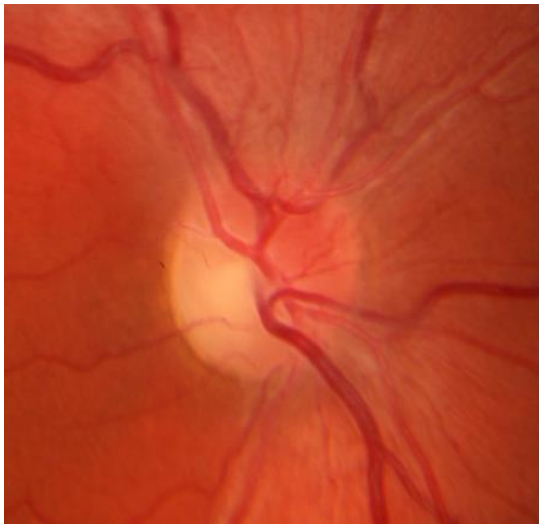
Disclosures

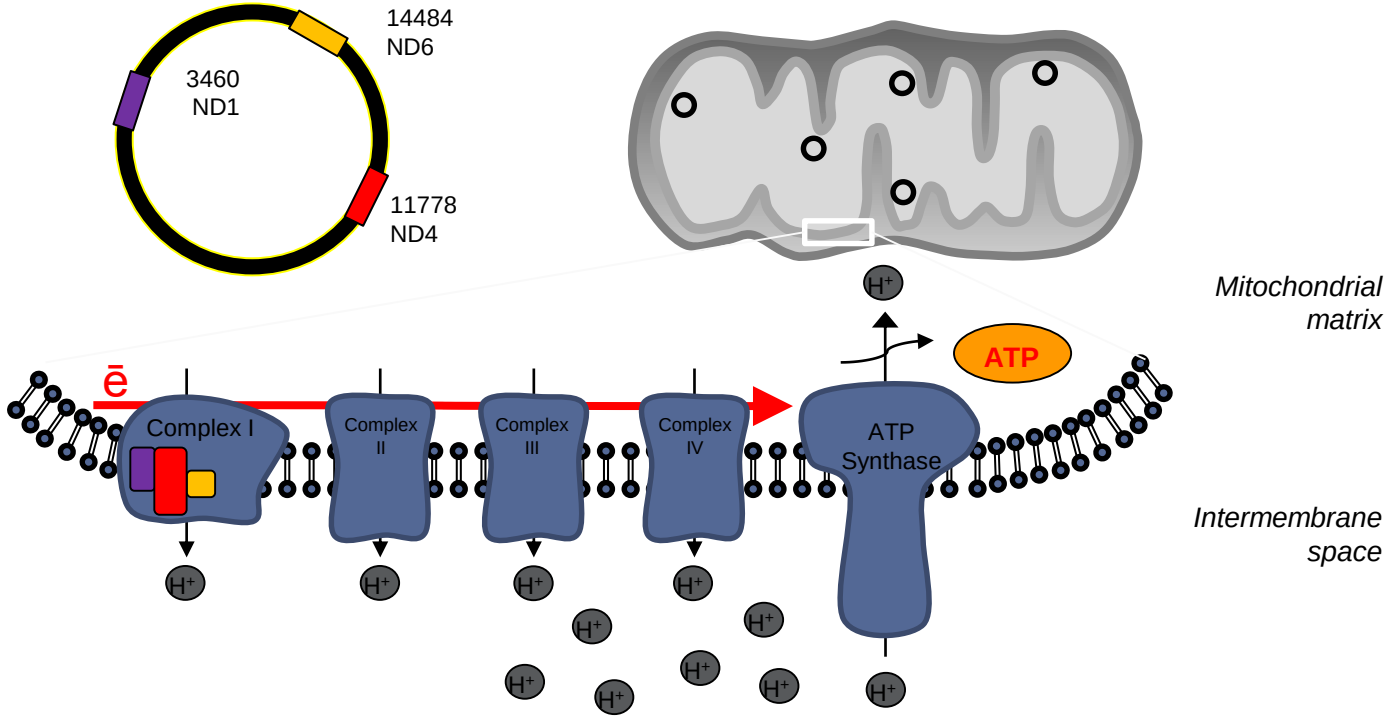
- Industry sponsored study by Stealth Biotherapeutics
- Consultant for GeneSight Biologics
- Research Support from UMDF, GeneSight, BioElectron

Leber's Hereditary Optic Neuropathy

- Subacute vision loss in one eye
  - Fellow eye involved in 3-9 weeks
- Dyschromatopsia, central scotoma
- Pseudo disc edema with telangectasia
- Evolves optic atrophy and count fingers vision
- Mitochondrial Disease
  - mt11778, mt3460, mt14484



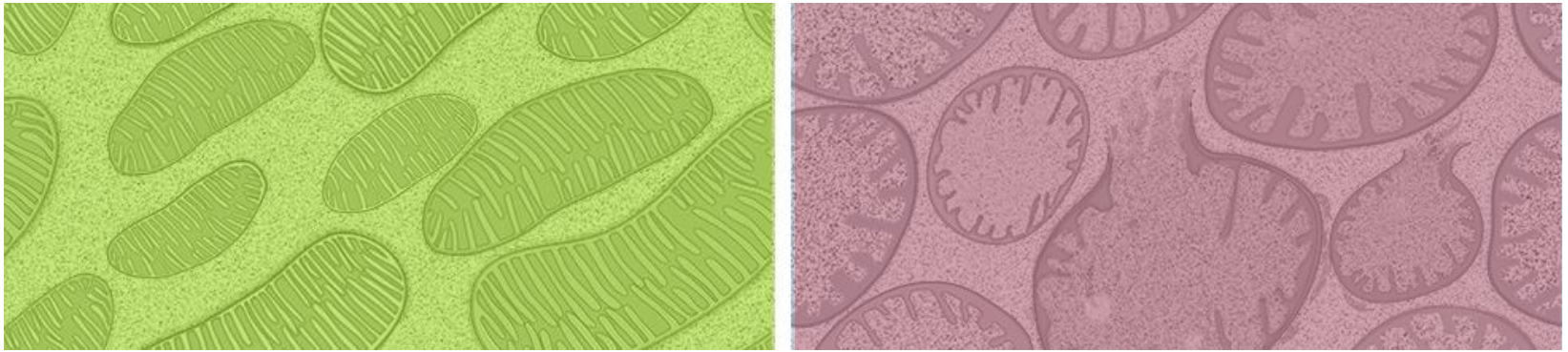
Electron Transport Chain



Cusp of Treatment

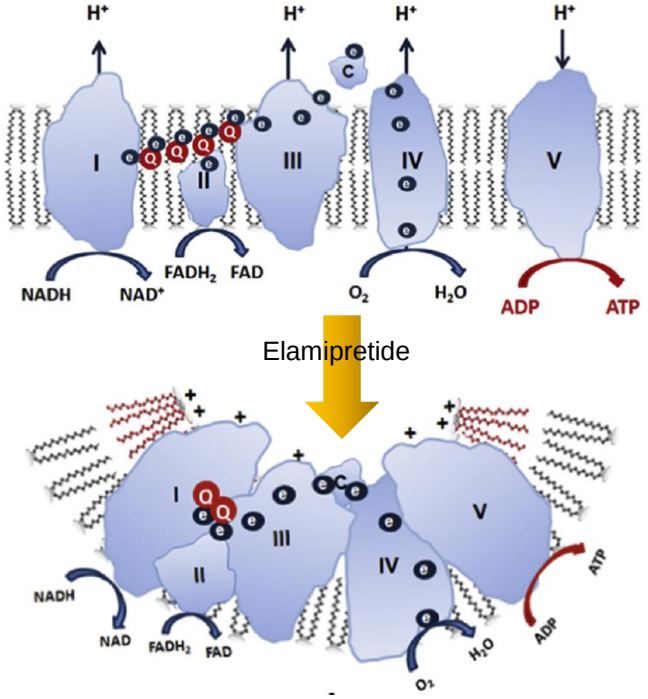
- Antioxidants
  - Idebenone (Raxone, Santhera)
  - EPI-743 (BioElectron)
- AAV-Vectors
  - scAAV2 (University of Miami)
  - GS010 (GenSight Biologics)
  - rAAV2-ND4 (Hauzhong University of Science and Technology)
- Others
  - Elamipretide (Stealth Biotechnology)

Mitochondria



Elamipretide

- Improves inner mitochondrial membrane formation of Super Complexes
- Increases respiration efficiency/ATP Production
- Decreases free electrons and ROS production



Szeto, H. H. and S. Liu (2018) Arch Biochem Biophys **660**: 137-148.

Phase IIB Randomized Double Masked Clinical Trial

- Topical 1% Elamipretide
- 12 Patients
- Primary Endpoint
  - Safety
- Secondary Endpoint
  - Visual Acuity
  - RNFL and RGCT Thickness
  - Color vision
  - Contrast Sensitivity
  - NEI VFQ-39

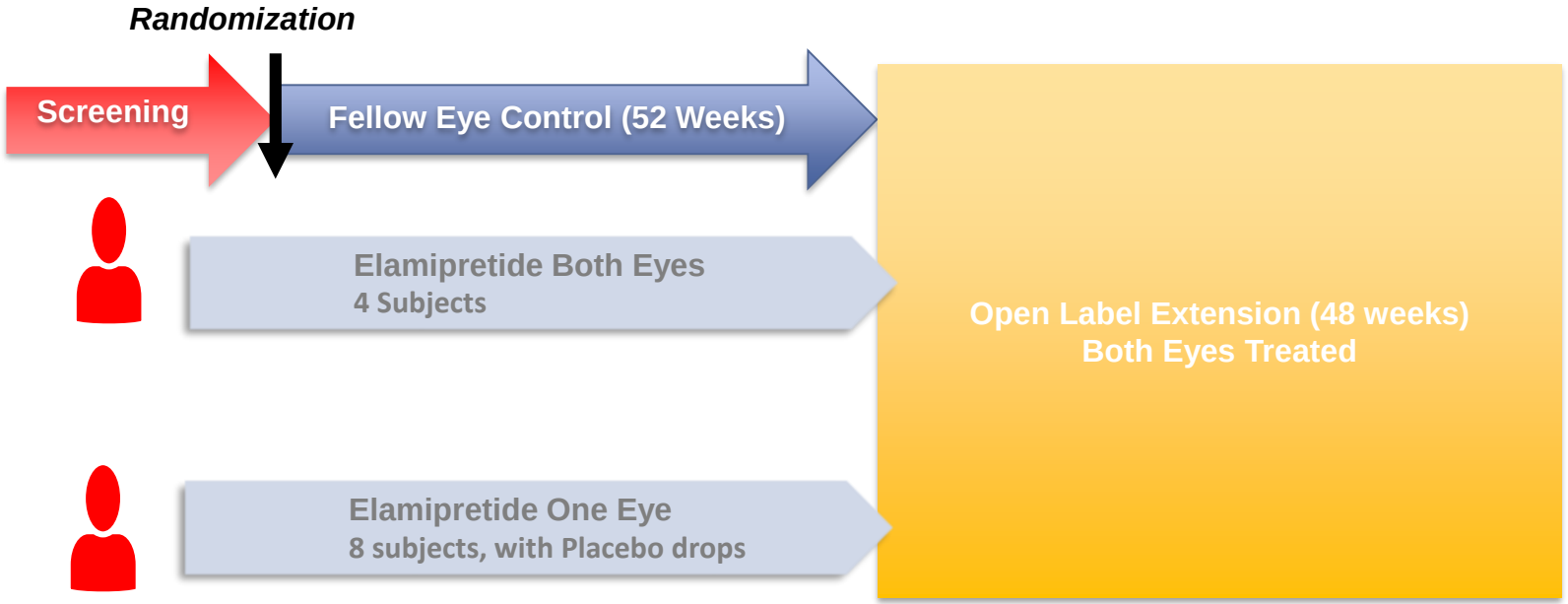
Phase IIB Randomized Double Masked Clinical Trial

Inclusion Criteria

- Adults ≥18 and ≤ 50 years old at the time of loss of vision in the second eye.
- m.11778G>A mutation
- Loss of vision in both eyes of ≥1 year and ≤10 years
- Clinically stable visual function
- Able to satisfactorily complete testing required for the trial
- Women of childbearing potential must agree to use birth control

Exclusion Criteria

- Any other ocular pathology requiring treatment with prescription topical ophthalmic drops
- Cup to disc ratio of > 0.8 in either eye
- Media opacity, suboptimal pupillary dilatation, or refractive error that interferes with adequate retinal imaging
- Known to be immunocompromised or receiving systemic immunosuppression
- Participation in other investigational drug or device clinical trials within 30 days
- Women who are pregnant or lactating


Randomization
Screening
Fellow Eye Control (52 Weeks)
Elamipretide Both Eyes
4 Subjects
Elamipretide One Eye
8 subjects, with Placebo drops
Open Label Extension (48 weeks)
Both Eyes Treated

Demographic and Baseline Characteristics	Single Eye (N=8)	Bilateral (N=4)
Age	35.4	30.0
Gender (n)		
Male	7	3
Female	1	1
Duration of positive mtDNA testing (years)	3.52	4.31
VFQ-39	55.8	49.6
	Vehicle eyes (N=8)	Elamipretide-treated eyes (N=16)
BCVA (Letters ETDRS)	15.6	14.1
HVF (dB)	-22.6	-22.5
Color Discrimination – number of plates	0.0	0.9
Contrast Sensitivity	0.08	0.16
RNFL Thickness (µm)	56.0	59.8
RGCL Thickness (µm)	49.4	50.8

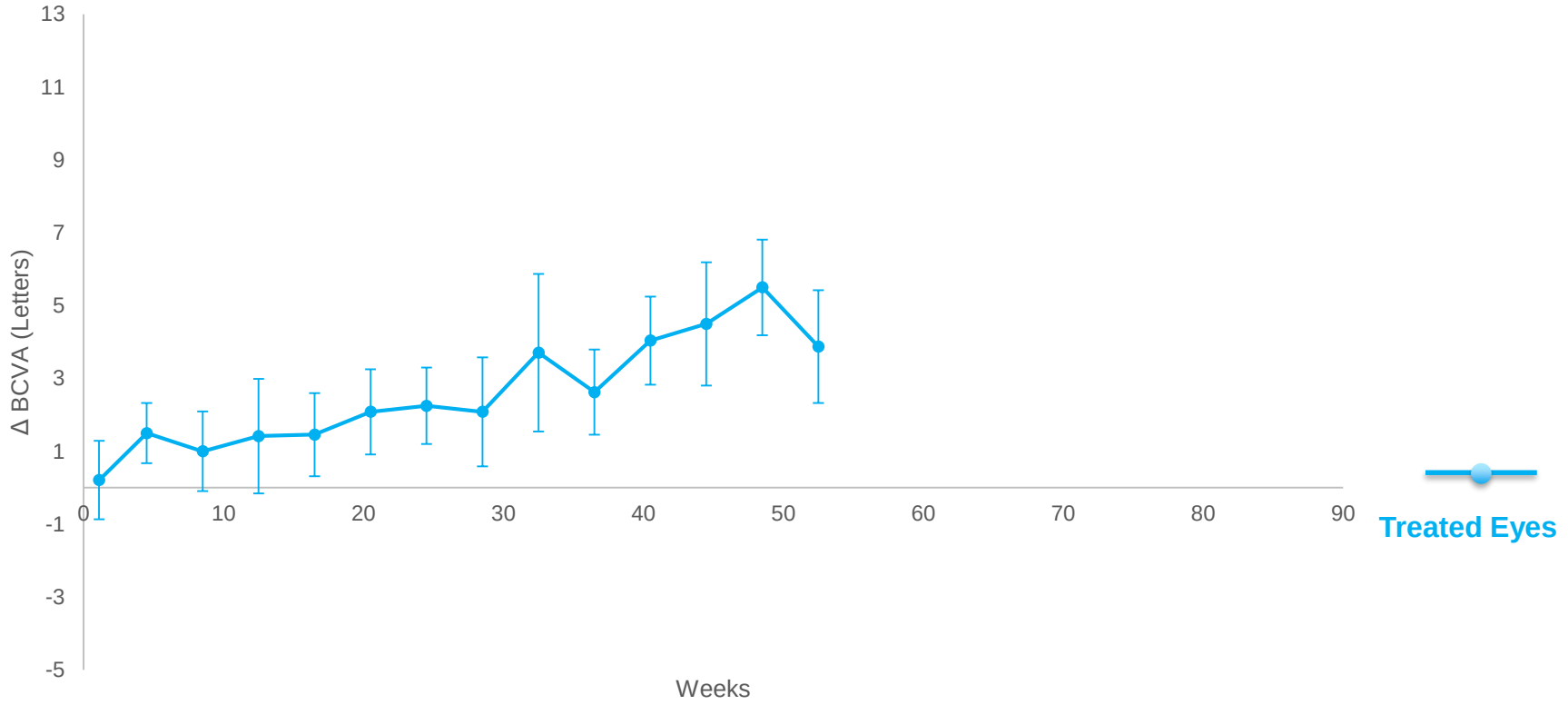
Primary Outcome Measure

- No Serious Adverse Events Reported

Adverse Events	Placebo (n=8)	Elamipretide (n=16)	Total (n= 24)
≥ one ocular AE	5 (63%)	11 (69%)	16 (67%)
Hyperemia	2 (25%)	2 (12.5%)	4 (16.7%)
Punctate keratitis	1 (12.5%)	3 (18.8%)	4 (16.7%)
Dry eye	0	3 (18.8%)	3 (12.5%)
Irritation	2 (25%)	4 (25%)	6 (25%)
Lacrimation	0	2 (12.5%)	2 (8.3%)

Secondary Outcome Measure

Best Corrected Visual Acuity



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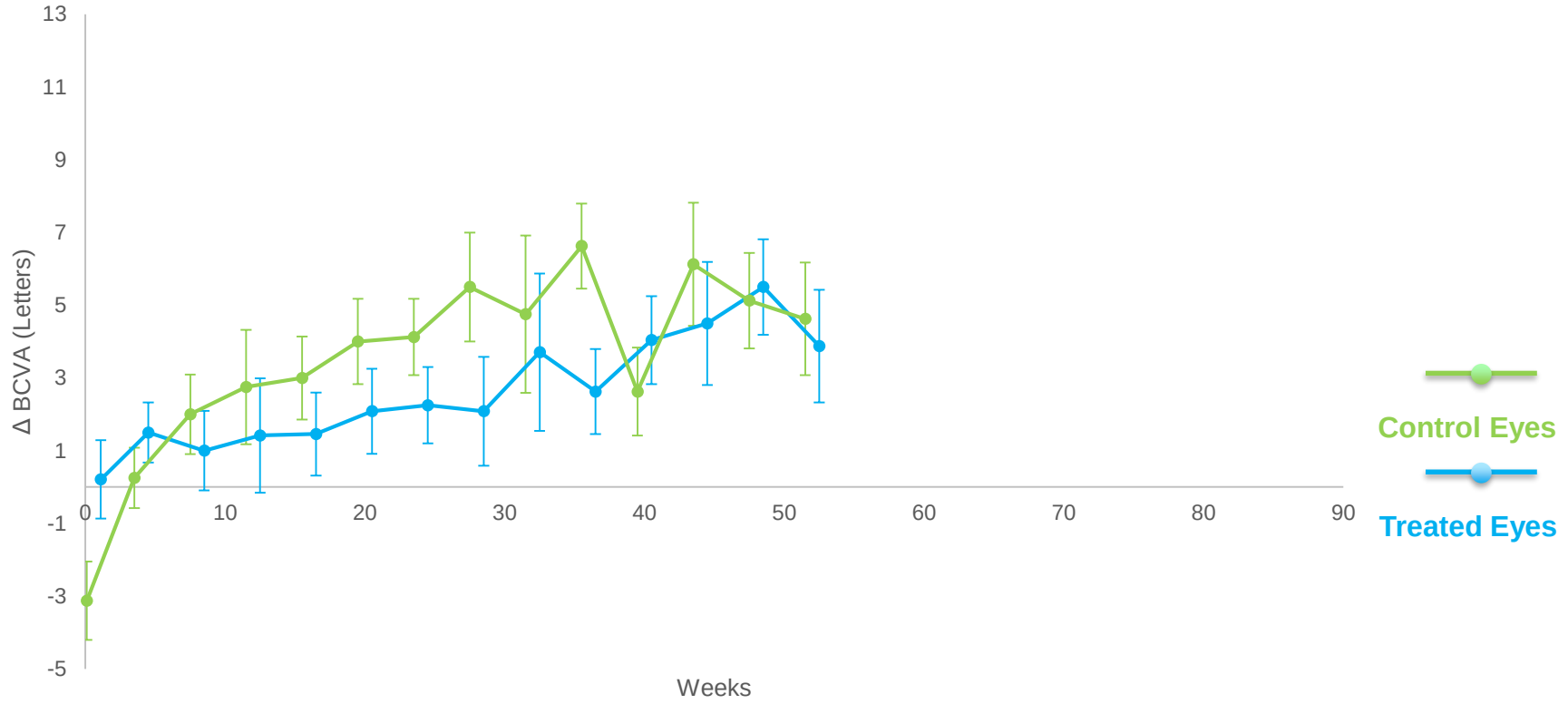

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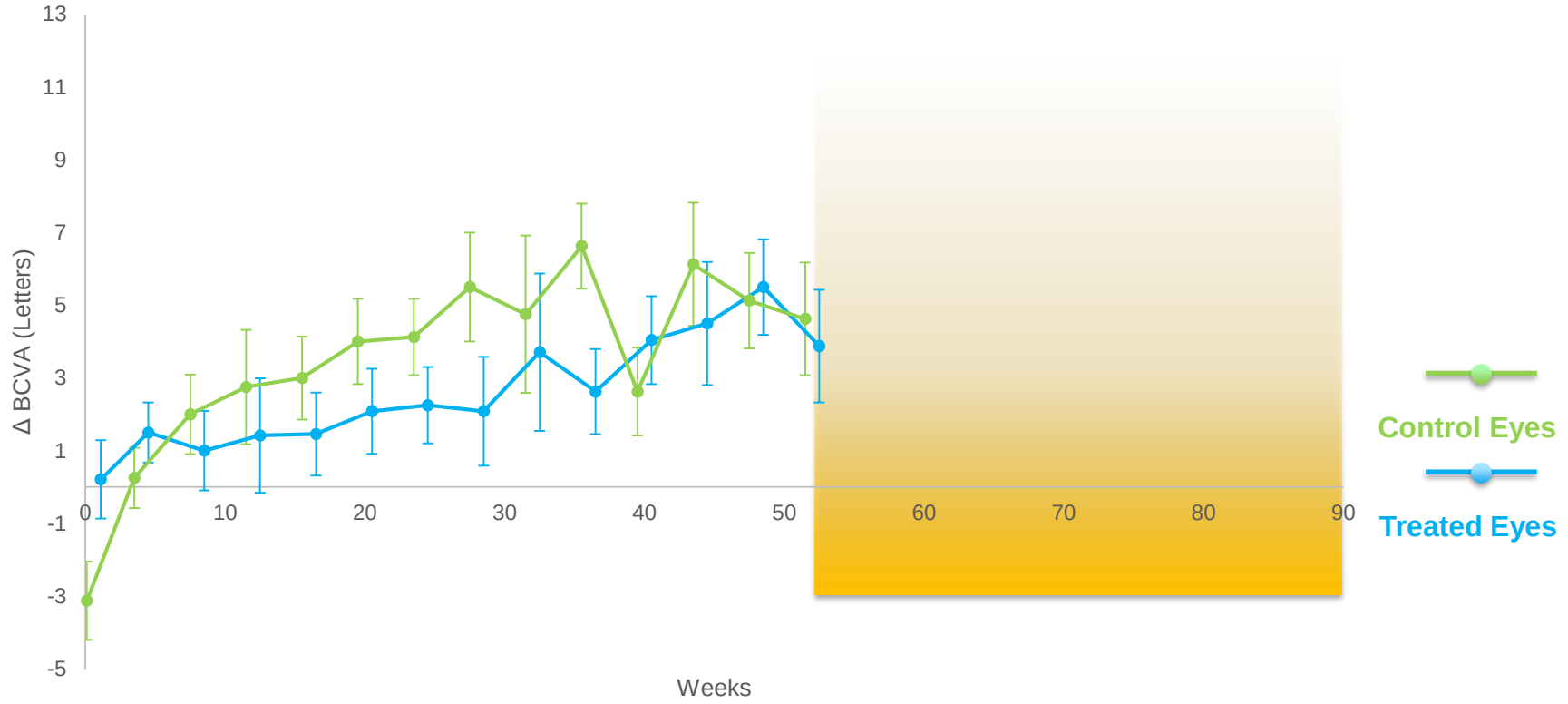

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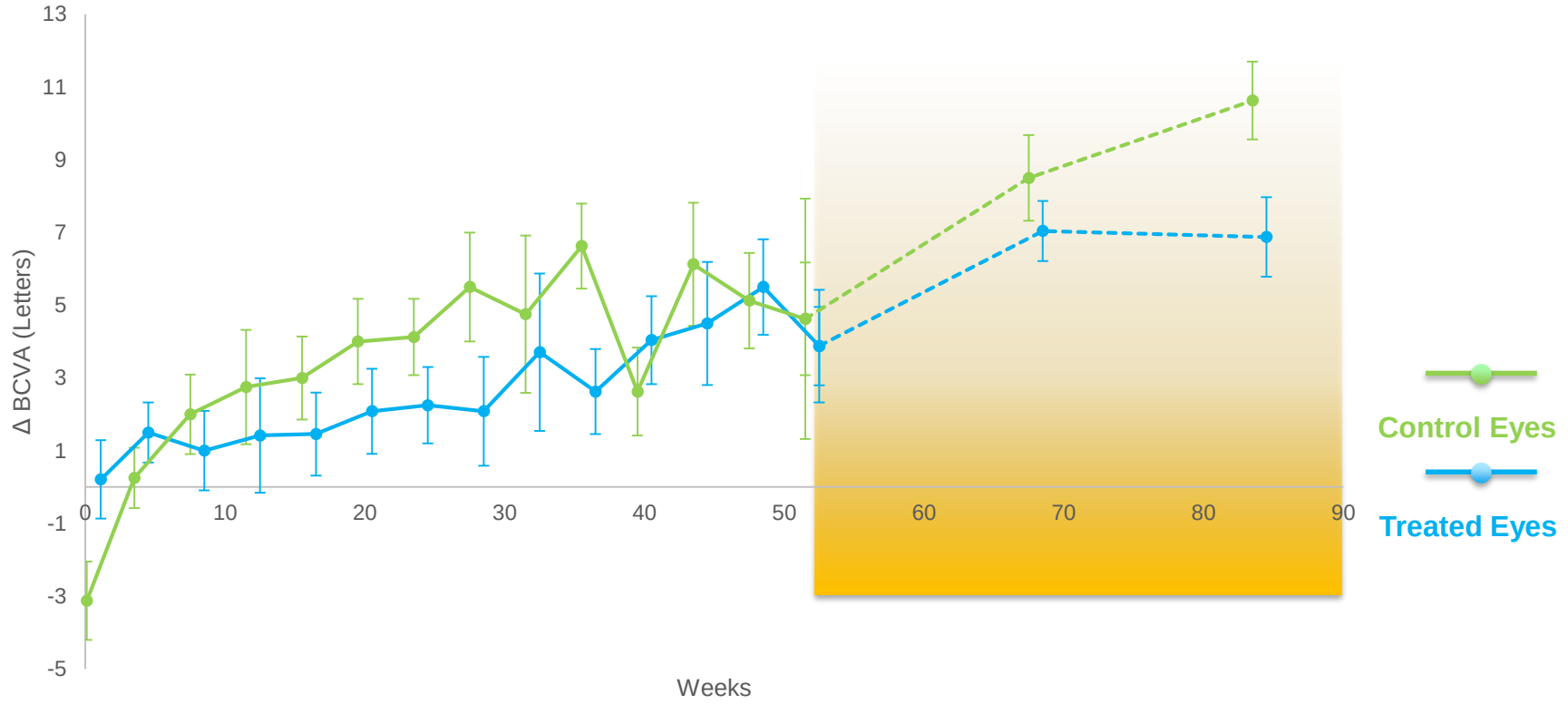

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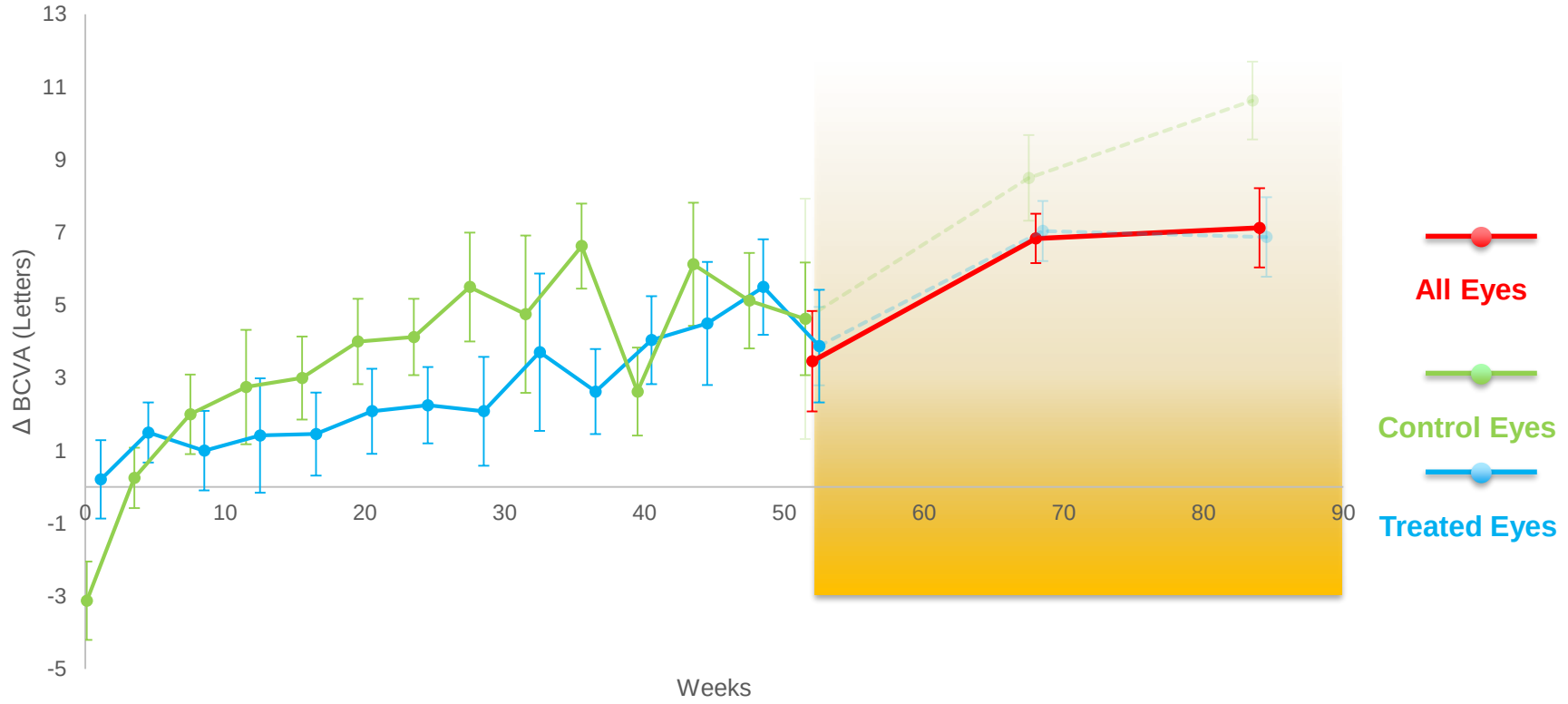

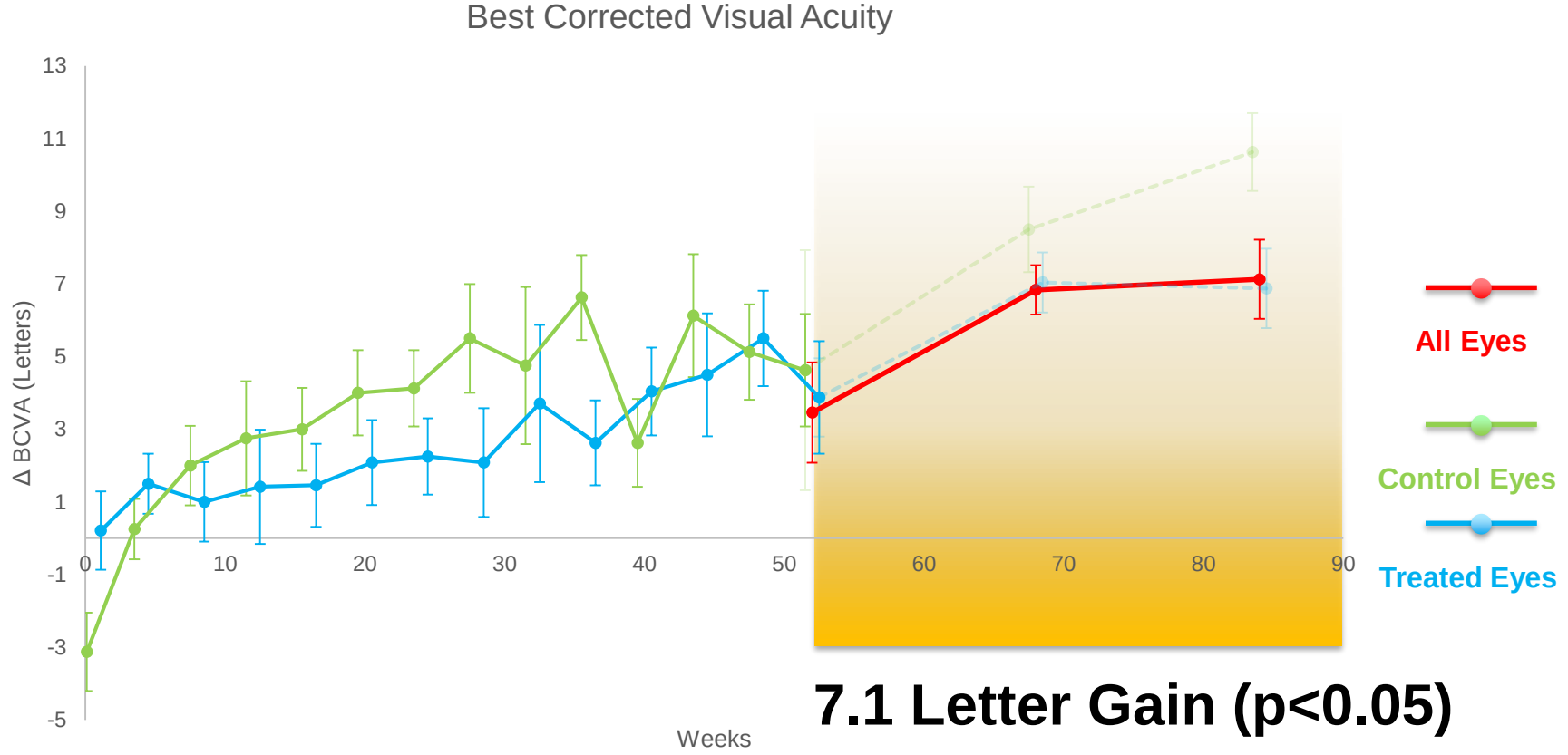

7.1 Letter Gain (p<0.05)

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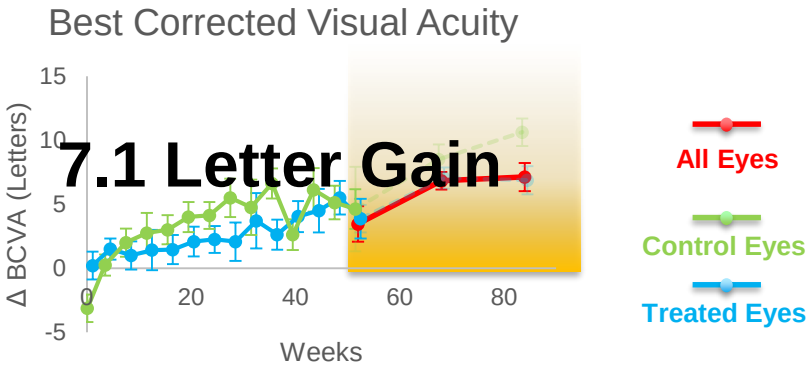


7.1 Letter Gain

0.181 Gain (p<0.005)

4.6 dB Gain (p<0.025)

5.2 dB Gain (p=0.054)

Secondary Outcome Metrics

Outcome	Fellow Eye Control				Open Label Extension	
	Placebo	Elamipretide	Effect	P-Value	Effect v Baseline	P-Value
BCVA (Letters)	*1.3*	*1.9*	*0.6*	*0.43*	*7.1*	*0.050*
Automated Visual Field (MD)	*1.0*	*1.8*	*0.8*	*0.02*	*4.6*	*0.025*
Central Visual Field (MD)	*0*	*1.8*	*1.8*	*<0.001*	*5.2*	*0.054*
Color Discrimination (Plates)	*0.3*	*0.5*	*0.2*	*0.08*	*1.6*	*0.004*
Contrast Sensitivity	*0.09*	*0.035*	*-0.055*	*0.002*	*0.181*	*0.005*
RNFL Thickness	*-3.9*	*-2.0*	*-1.9*	*0.43*		
RGCL Thickness	*-4.5*	*-3.0*	*-1.5*	*0.12*		
Quality of Life (NEI VFQ-39)			*6.0*	*0.006*		

Results

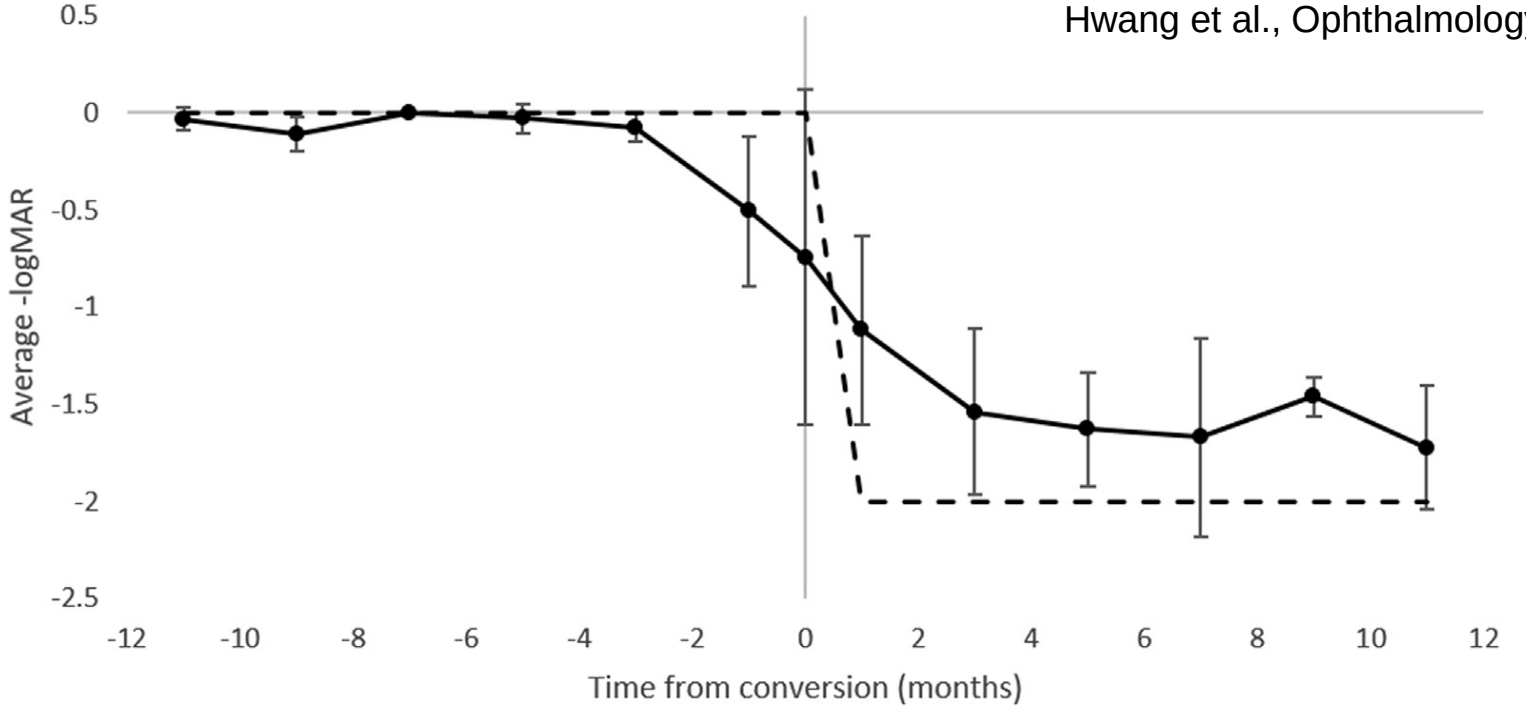
- No serious adverse events were reported
- There was an improvement in:
  - Mean Deviation
  - Color Discrimination
  - Contrast Sensitivity
  - VFQ-39

Challenges

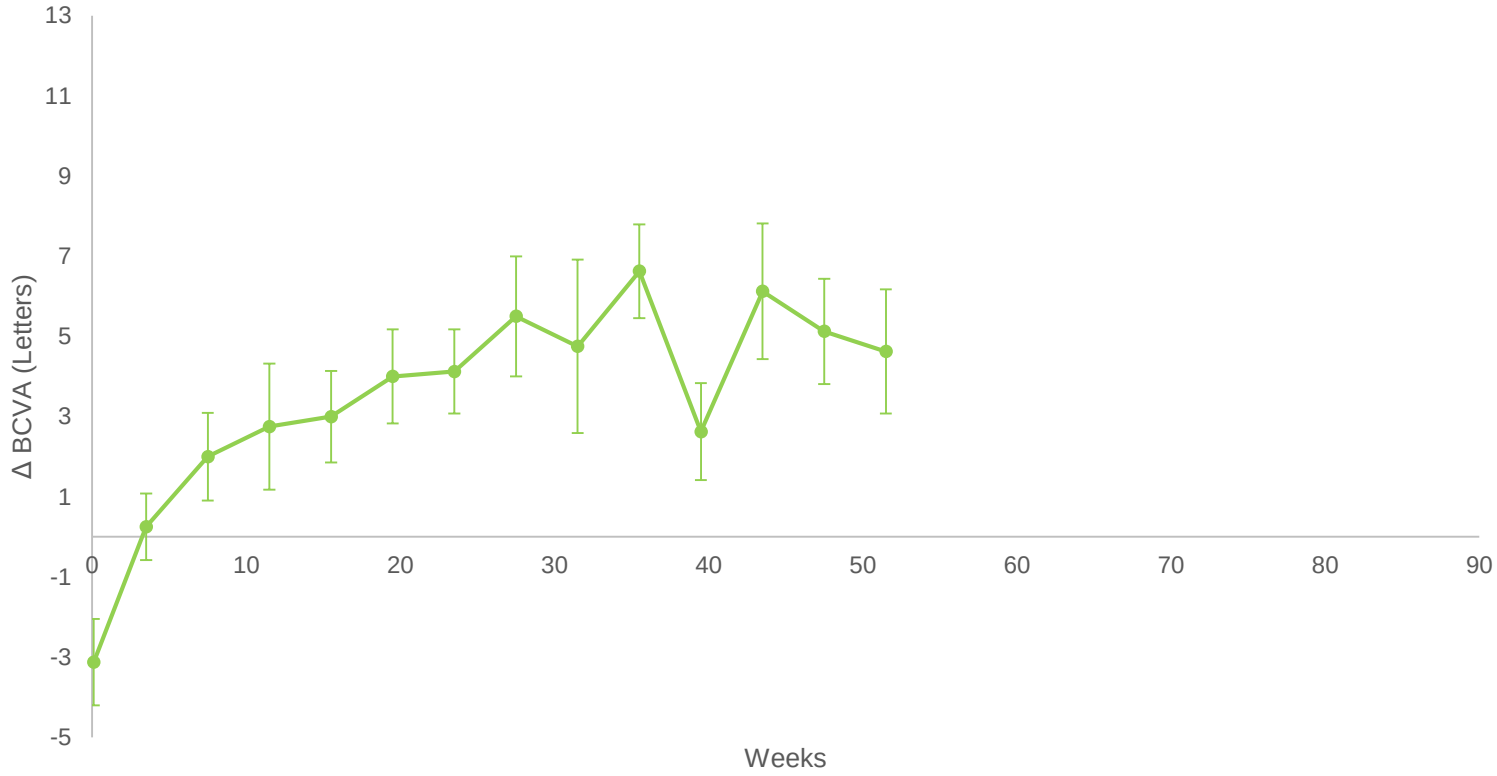
- Two Questions – One Study
- Delayed improvement in visual function

Average Visual Acuity

Hwang et al., Ophthalmology 2017



Best Corrected Visual Acuity



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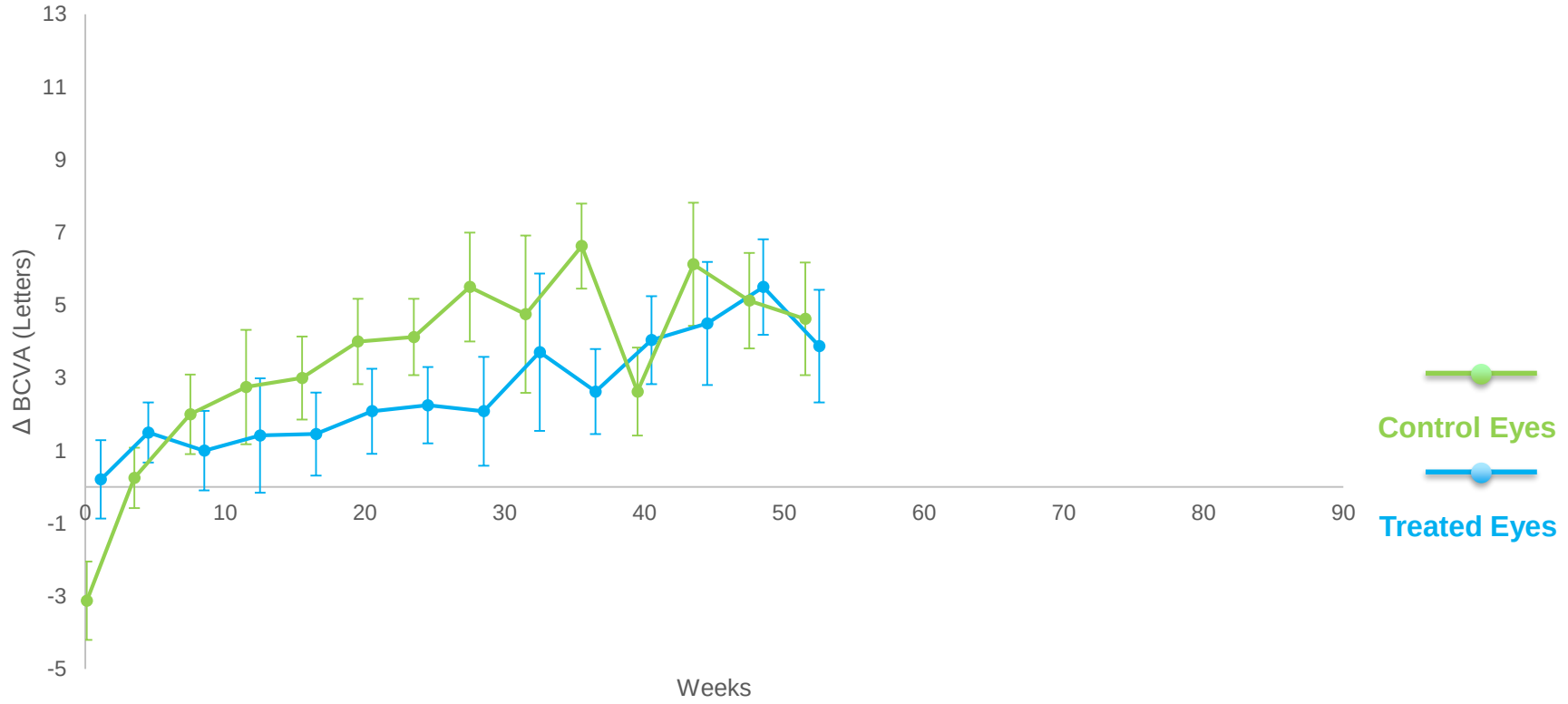

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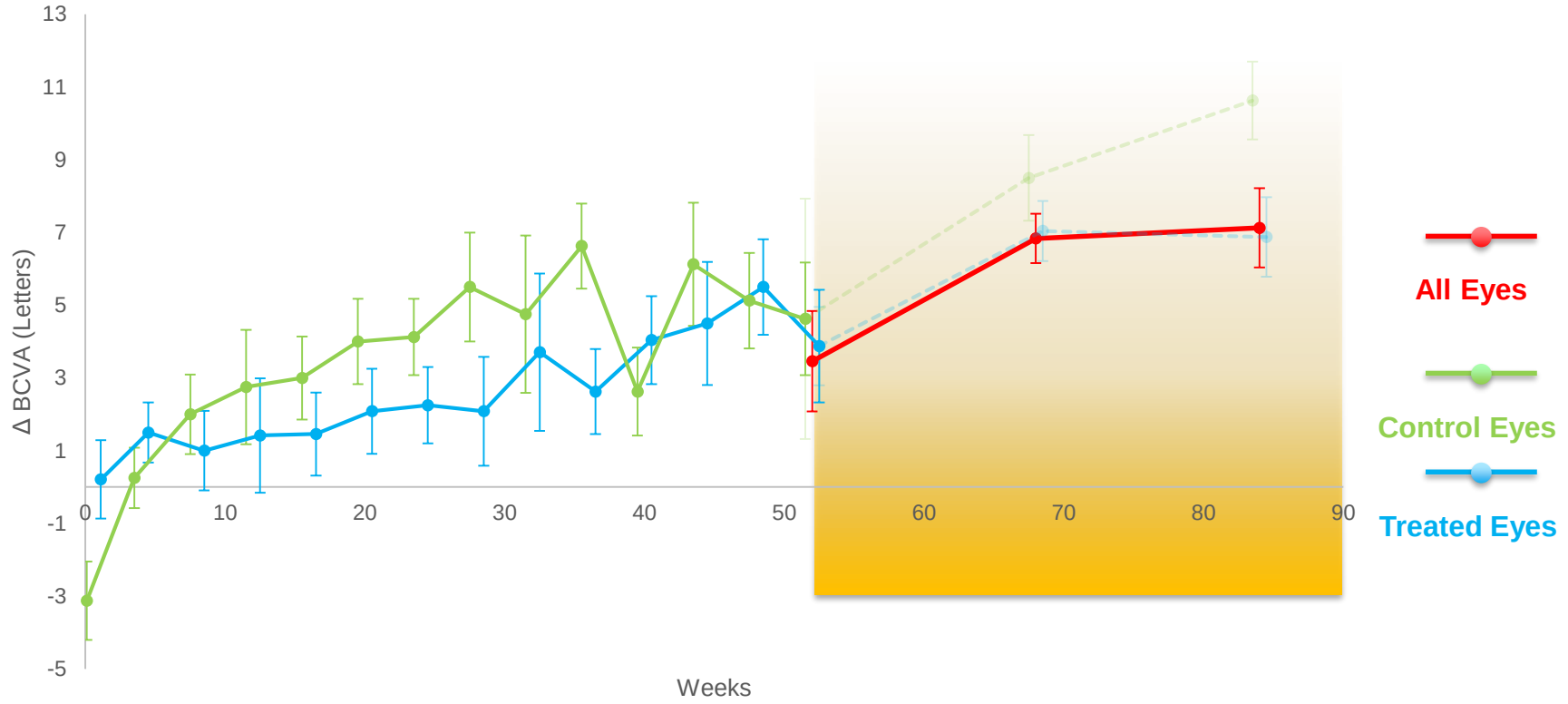

Challenges

- Two Questions – One Study
- Delayed improvement in visual function
  - Not unique to Elamipretide
    - Idebenone
    - EPI-743
- Placebo Effect
- Variability in natural history
- Bilateral improvement

Potential Treatment for LHON

- Small Study
- Larger clinical trial is warranted

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  - Ellen Pascual PhD
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  - Janett Mendez
  - Rosio Mendoza
  - Shellee Rockwell

Stealth BIOTHERAPEUTICS