Results of a phase 1b/2 trial of intravitreal (IVT) sepofarsen (QR-110) antisense oligonucleotide in Leber congenital amaurosis 10 (LCA10) due to p.Cys998X mutation in the *CEP290* gene

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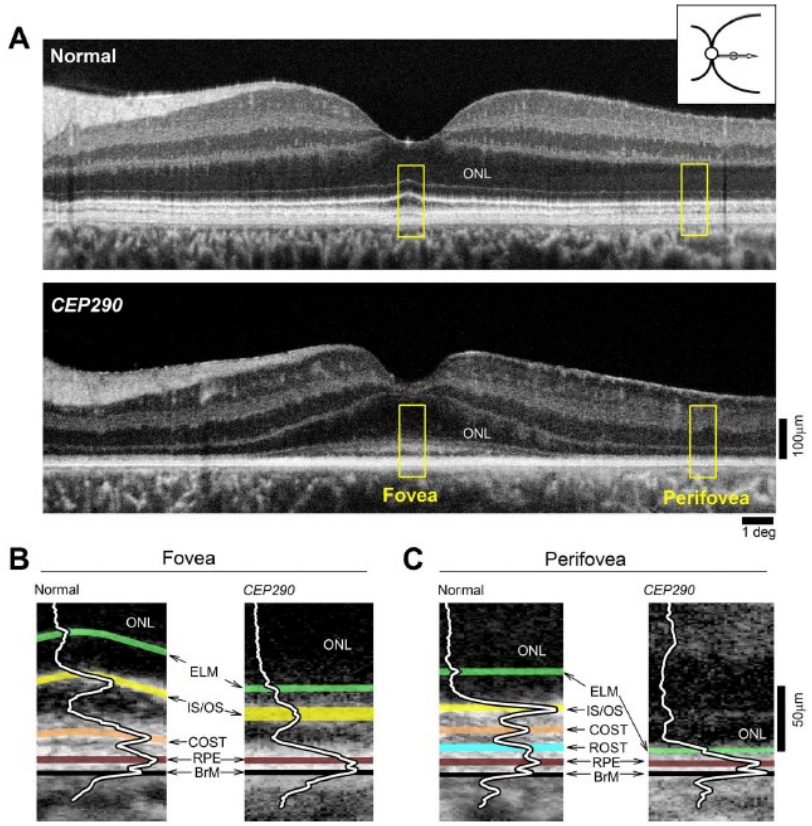
Disclosures

Stephen R. Russell, Arlene V. Drack, Artur V. Cideciyan, Samuel G. Jacobson, Bart P. Leroy, Caroline Van Cauwenbergh, Julie De Zaeytijd, and Allen C. Ho report grant funding from ProQR Therapeutics during the conduct of the study. Michael R. Schwartz, Wil den Hollander, Aniz Girach and David M. Rodman are employees of ProQR. Wanda L. Pfeifer, Alina V. Dumitrescu, Alexandra V. Garafalo have nothing to disclose.

High Unmet Medical Need in LCA10

- Autosomal-recessive mutations in the *CEP290* gene
  - Can be detected as at least one of the two CEP290 mutations in >50% of LCA10 patients[1-3]
  - *CEP290* c.2991+1655A>G mutation accounts for up to 21% of all LCA cases[1-3]
- Lack of CEP290 protein leads to disruption of protein interactions, which induces photoreceptor degeneration[4,5]
- Severe visual impairment manifests in infancy or early childhood[1,6]
  - 60–90% reporting severe vision impairment[4]
  - Usually from legally blind (Snellen< 20/200) to light perception or no light perception
- No approved treatments

Decreased ONL thickness[4]



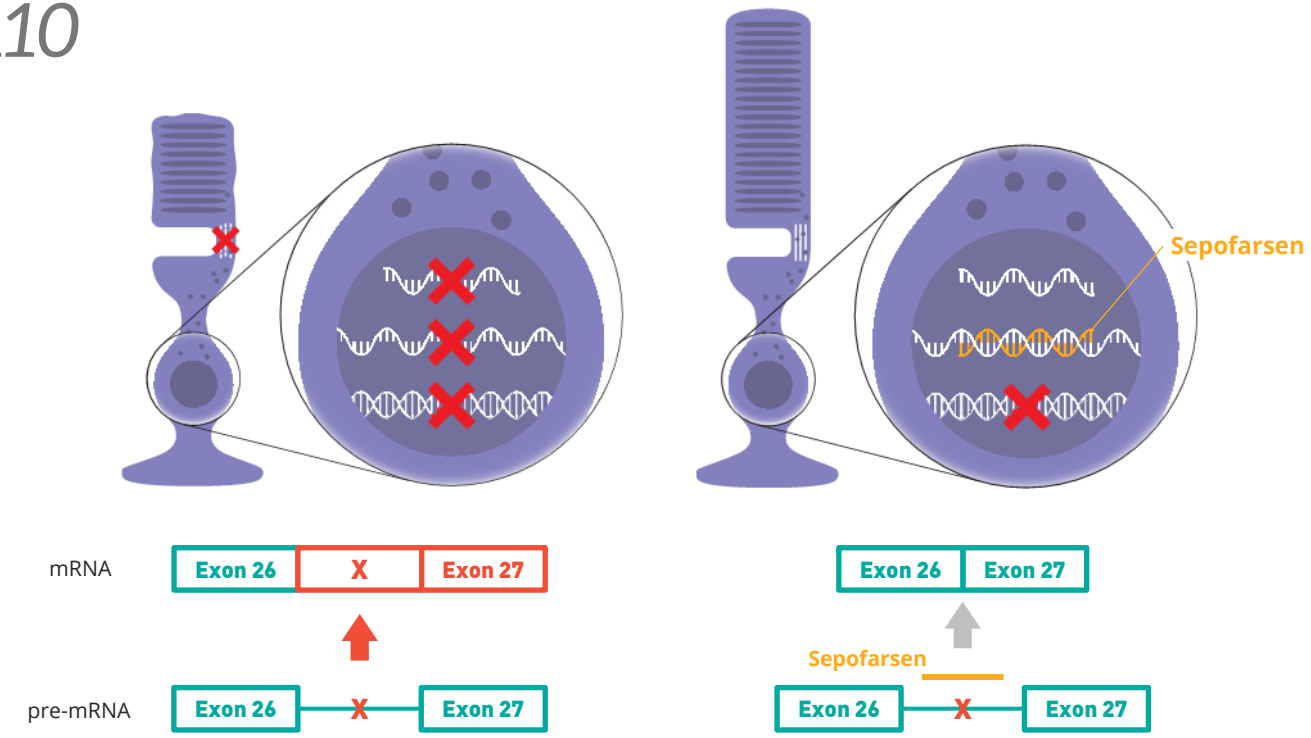
CEP290, centrosomal protein 290 kDa; LCA10, Leber congenital amaurosis 10; ONL, outer nuclear layer.

1. den Hollander AI, et al. *Prog Retin Eye Res*. 2008;27(4):391–419; 2. den Hollander AI, et al. *Am J Hum Genet*. 2006;79(3):556–61; 3. Dulla K, et al. *Mol Ther Nucleic Acids*. 2018;12:730–40; 4.Cideciyan AV, Jacobson SG. *Invest Ophthalmol Vis Sci.* 2019;60(5):1680–95; 5. Shimada H, et al. *Cell Rep*. 2017;20(2):384–96; 6. Nash BM, et al. *Transl Pediatr*. 2015;4(2):139–63.

Splice correction for c.2991+1655A>G CEP290 mRNA (p.Cys998X)

Sepofarsen (QR-110) for LCA10

- A 17-mer 2'-O-methyl modified phosphorothioate antisense RNA oligonucleotide[1]
- **Binds to the target pseudo-exon region and prevents recognition by splice factors**[2-5]
- Normal *CEP290* splicing of the pre-mRNA transcript and production of full-length CEP290 protein[2-5]
- Sepofarsen (QR-110) induces mRNA editing and cilia growth in LCA10 (p.Cys998X) patient-derived retinal organoids[5]



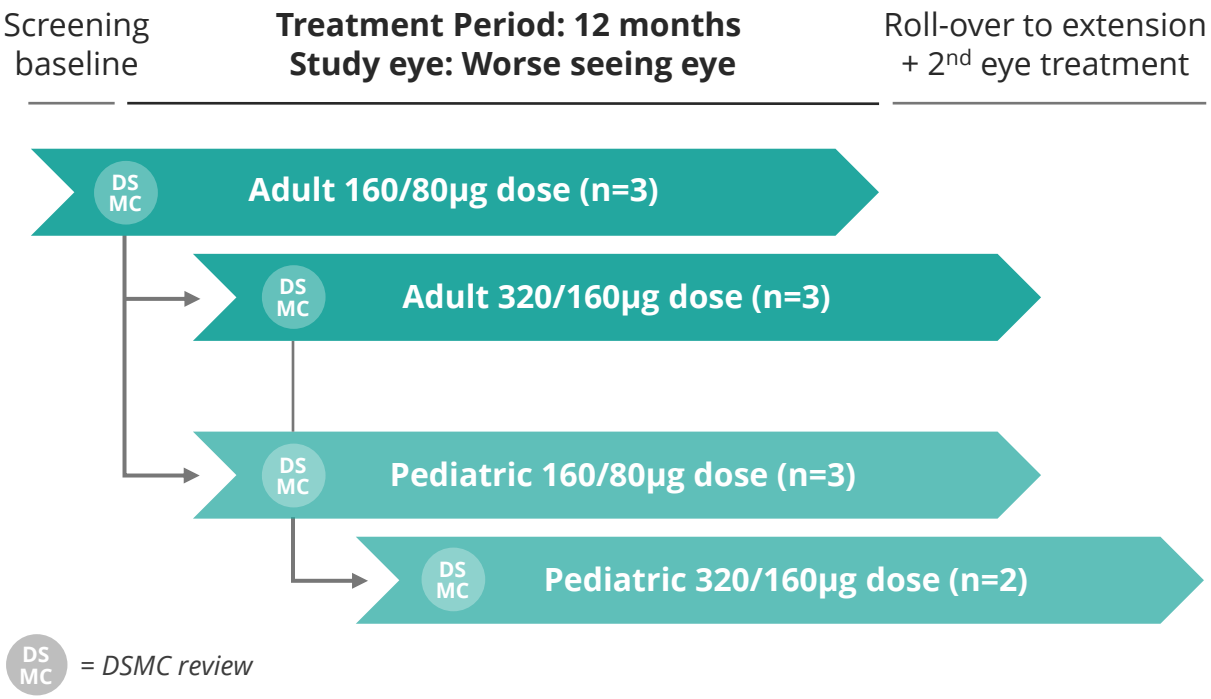
In p.Cys998X-LCA10 cells protein transport is hampered and the outer segment degenerates

Exclusion of the cryptic exon from the mutated mRNA leads to full-length CEP290 protein

1. Dulla K, et al. *Mol Ther Nucleic Acids* 2018;12:730-40; 2 Collin RW, et al. *Mol Ther Nucleic Acids* 2012;1:e14; 3. Gerard X, et al. *Mol Ther Nucleic Acids* 2012;1:e29; 4. Cideciyan AV, et al. *Nat Med* 2019;25:225-28.; 5. Parfitt DA, et al. *Cell Stem Cell* 2016;18:769-81

PQ-110-001 – Phase 1/2 – trial design

First-in-Human, open label, multiple dose, dose escalation trial



- Enrolled 11 LCA10 patients (**age range 8-44**) with 1 or 2 copies of the p.Cys998X mutation
- Up to 4 intravitreal injections to the study eye, defined as the worse-seeing eye
- 3 participating sites: major sites in EU (UGhent) and US (UPenn, UIowa)

Objectives:

- Primary outcomes: Safety/tolerability
- Secondary outcomes: best corrected visual acuity (BCVA), full-field stimulation (FST), Identify target dose, Mobility course feasibility in LCA10

Baseline Demographics and Genotypes

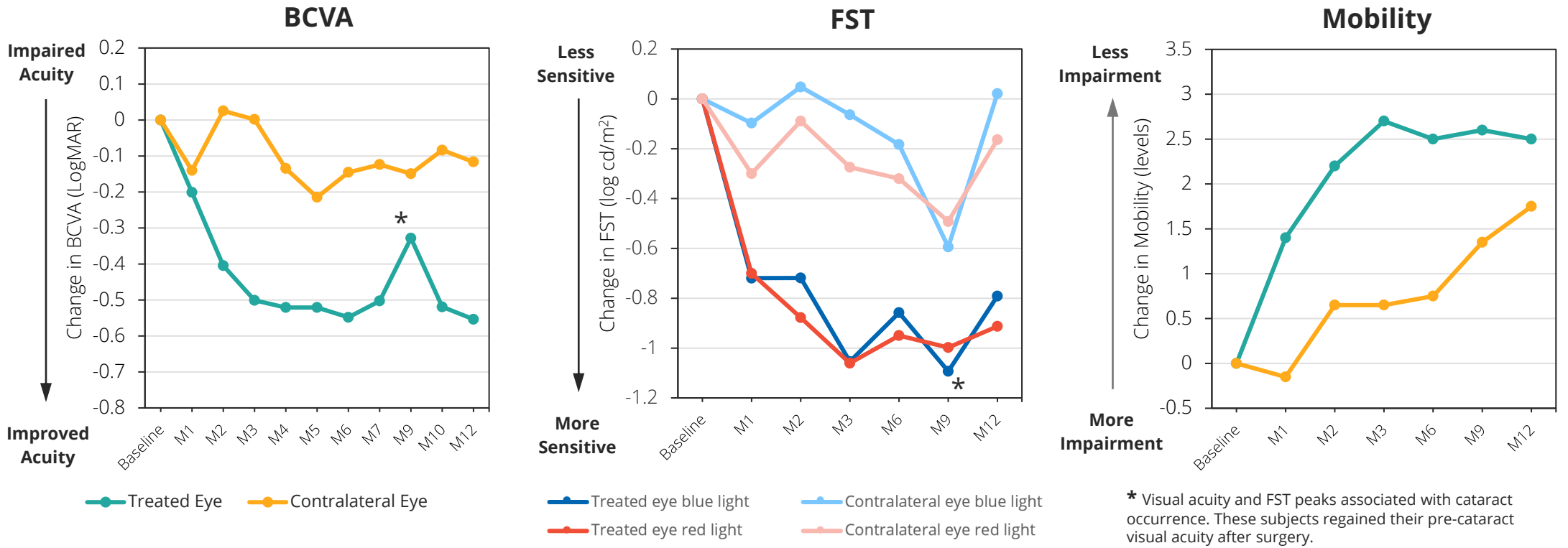
	Sex	2nd *CEP290* Allele	Age/Group	Baseline VA	Treated	Dose
	(M/F)		(Adult/Ped)	[log MAR]	Eye	[µg]
P1	M	c.2506_2507delGA	19 / A	LP / LP	RE	160/80
P2	M	c.4723A>T	41 / A	LP / LP	RE	160/80
P3	M	c.5668G>T	44 / A	2.4 / 2.3	LE	160/80
P4	F	c.4438-3delC	16 / P	2.5 / 2.5	RE	160/80
P5	M	c.6277delG	8 / P	1.9 / 2.1	LE	160/80
P6	F	c.3167_3168insA	21 / A	LP / LP	RE	320/160
P7	F	c.4723A>T	27 / A	1.1 / 0.7	RE	320/160
P8	M	c.6277delG	10 / P	1.9 / 1.4	RE	320/160
P9	F	c.4393C>T	24 / A	LP / LP	RE	320/160
P10	F	c.547_550delTACC	15 / P	LP / LP	RE	320/160
P11	F	c.2991+1655A>G	14 / P	0.63/0.63	LE	160/80

Results - Safety Summary

	Cataracts	Cystoid Macular Edema	Retinal thinning
SAE/AE	6 SAE (surgery)/2 AE	0 SAE / 2 AE	0 SAE / 2 AE
Timing (160µg/80µg cohort)	8-12 months	No cases	No cases
Timing (320µg/160µg cohort)	3-9 months	3-4 months	3-10 months
Treatment-responsive	Yes	Yes	Stabilized

Results – Mean Efficacy

All Treated Subjects (n=11)

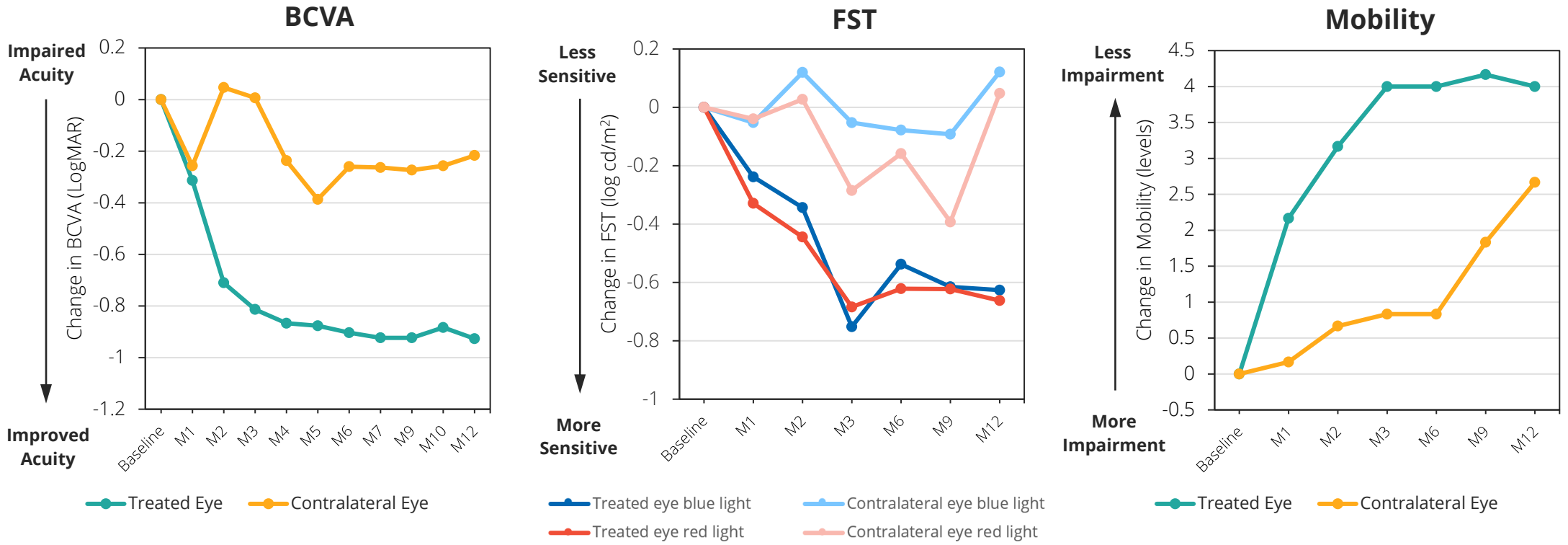


* Visual acuity and FST peaks associated with cataract occurrence. These subjects regained their pre-cataract visual acuity after surgery.

Eye	BCVA – LogMAR (n=11)	Red FST – log cd/m2 (n=10)	Blue FST – log cd/m2 (n=10)	Mobility course – composite score (n=10)
Treated (TE)	**-0.55 (0.26) p<0.05 vs. CE**	**-0.91 (0.18) p<0.01 vs. CE**	**-0.79 (0.23) p<0.02 vs. CE**	**2.5 (0.99) p=0.1 vs. CE**
Untreated (CE)	-0.12 (0.07)	-0.16 (0.16)	0.02 (0.11)	1.75 (0.75)

Key Outcomes – Month 12 - 160µg/80µg Cohort

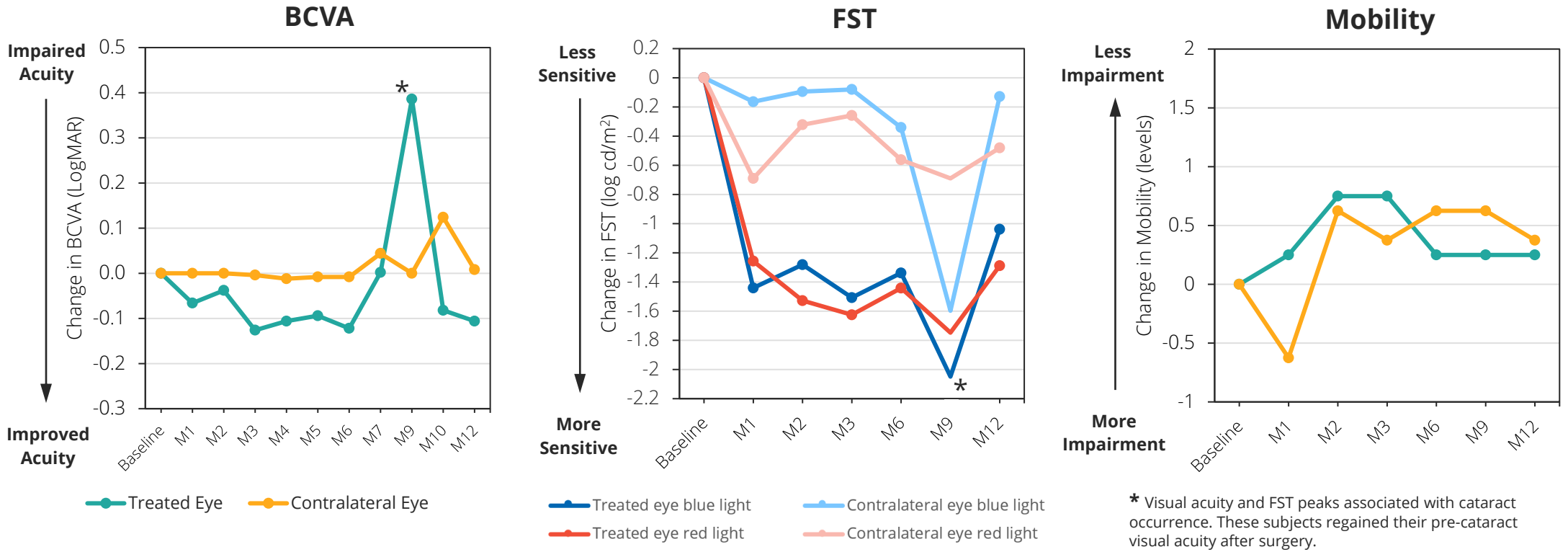
Change in mean BCVA, FST and Mobility Course Level (n=6)



Eye	BCVA – LogMAR (n=11)	Red FST – log cd/m2 (n=10)	Blue FST – log cd/m2 (n=10)	Mobility course – composite score (n=10)
Treated (TE)	**-0.93 (0.43) p=0.13 vs. CE**	**-0.66 (0.14) p<0.05 vs. CE**	**-0.63 (0.31) p=0.09 vs. CE**	**4.0 (1.27) p=0.06 vs. CE**
Untreated (CE)	-0.22 (0.11)	0.05 (0.17)	0.12 (0.16	2.7 (1.11)

Key Outcomes – Month 12 - 320µg/160µg Cohort

Change in mean BCVA, FST and Mobility Course Level (n=5)

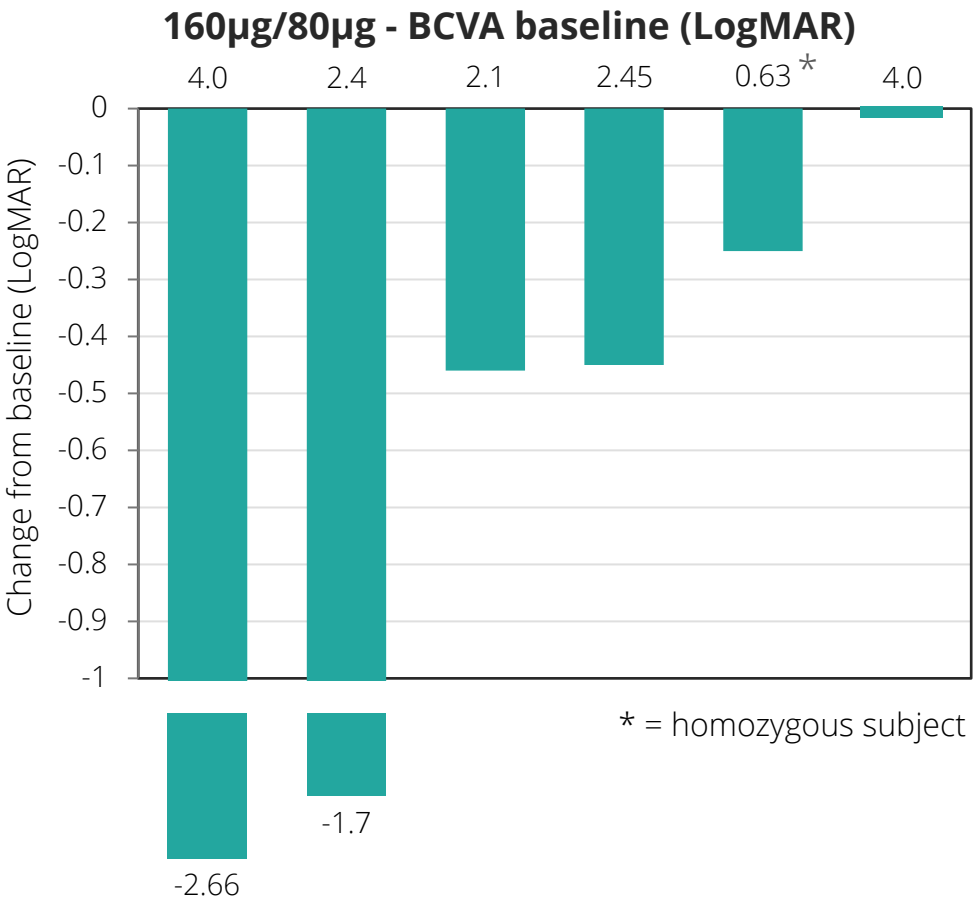


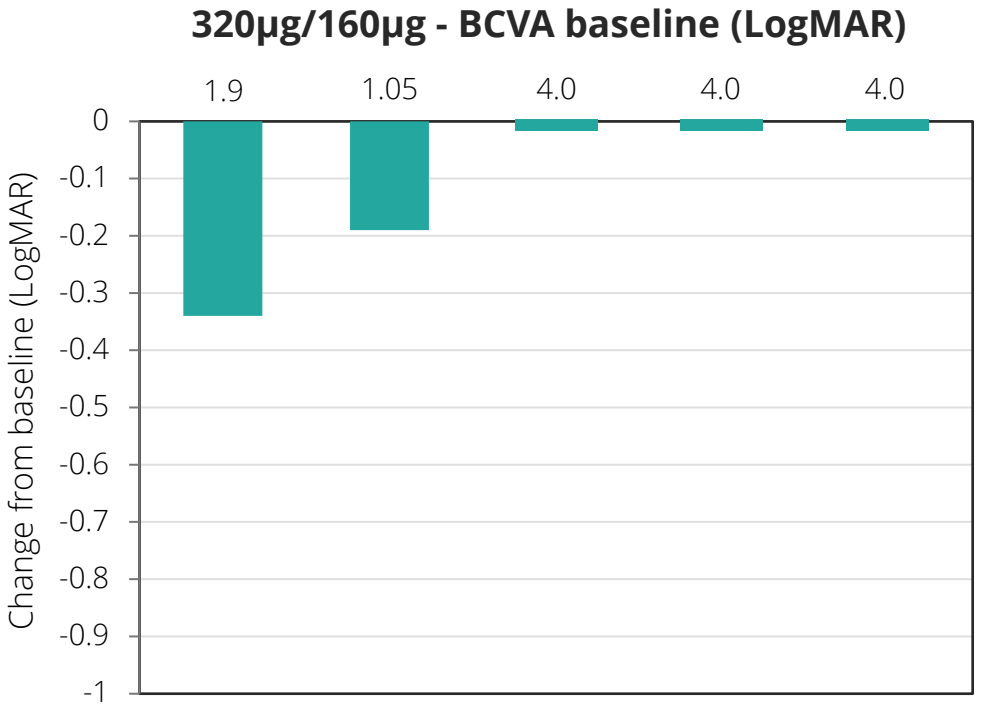
* Visual acuity and FST peaks associated with cataract occurrence. These subjects regained their pre-cataract visual acuity after surgery.

Eye	BCVA – LogMAR (n=11)	Red FST – log cd/m2 (n=10)	Blue FST – log cd/m2 (n=10)	Mobility course – composite score (n=10)
Treated (TE)	**−0.11 (0.07)**	**−1.29 (0.35)**	**−1.04 (0.36)**	**+0.25 (0.66)**
Untreated (CE)	0.01 (0.04)	−0.48 (0.27)	−0.13 (0.12)	+0.38 (0.38)

Comparison of Response / Change in BCVA

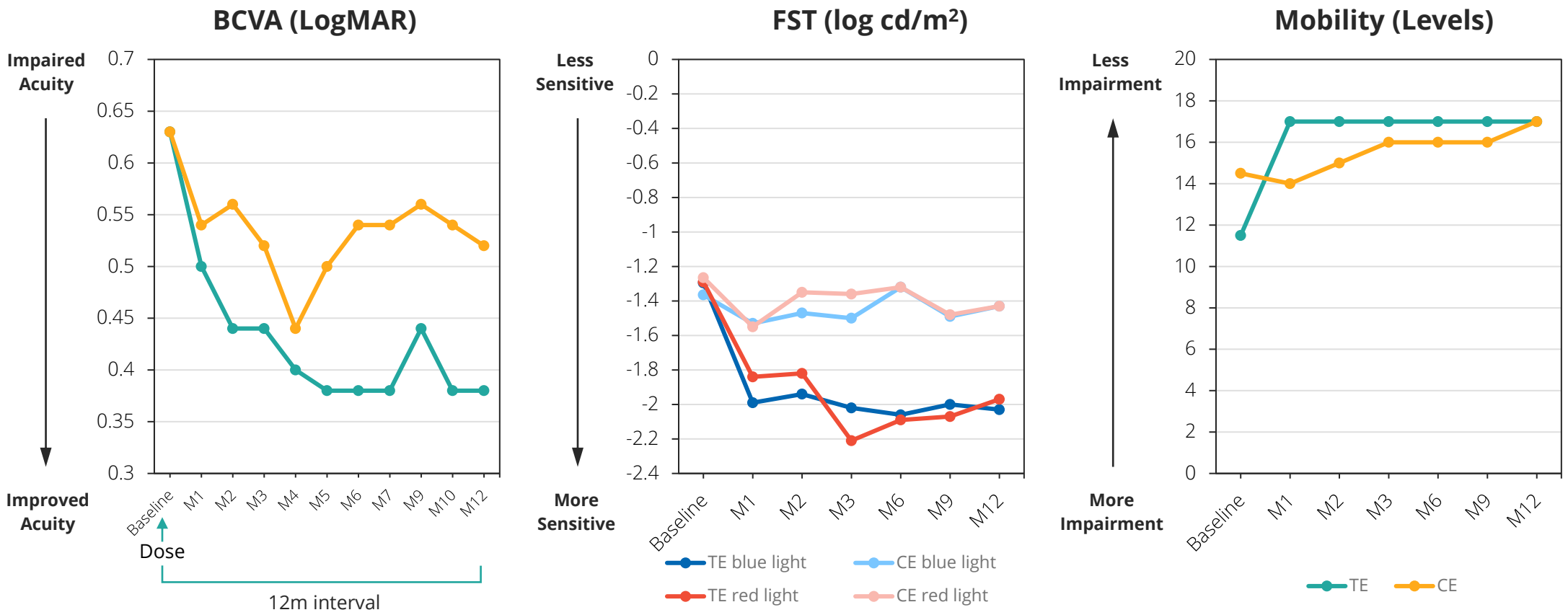
160µg/80µg and 320µg/160µg cohorts at month 12



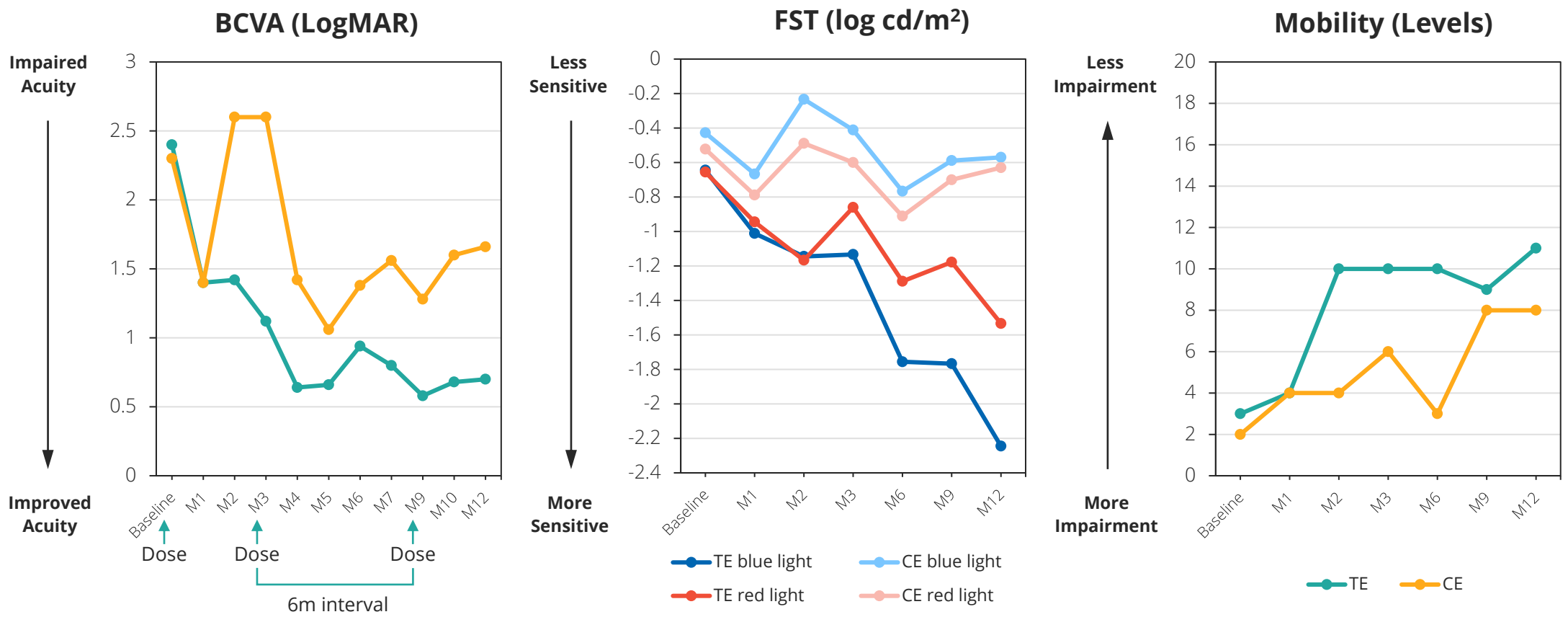


Homozygous p.Cys998X Subject in the 160µg/80µg Cohort

13-letter improvement in BCVA with robust improvement in mobility and FST



Heterozygous p.Cys998X Response in the 160µg/80µg Cohort



Conclusions – Sepofarsen for LCA10

- **Completed 12-month, Phase 1/2 safety and dose-ranging trial**
  - Cataracts are primary safety adverse event (AE; N=8)
    - Onset shorter in 320µg/160µg compared to 160µg/80µg cohort
    - Cataract surgery performed in 6 subjects
  - Cystoid macular edema and retinal thinning seen only in 320µg/160µg dosing cohort
    - Not associated with visual loss
    - CME managed topically
    - Retinal thinning stabilized
  - No systemic AEs, those related to injections self-limited
- **Given progression and severity of LCA10, sepofarsen appears to have positive benefit/risk**
- **Maximum tolerated dose identified**
- **Subjects: Extension trial ongoing and Phase 2b/3 trial recruiting**