AAO 2020
BEST POSTER
AWARD

# Full-field stimulus testing (FST) to assess sepofarsen patient response in Leber congenital amaurosis type 10 (LCA10)

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# Financial Disclosure

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# High Unmet Medical Need in LCA10

| | |
|---|---|
| **LCA is a severe form of IRD[1]** | • Autosomal-recessive mutations in the *CEP290* gene<br>  • Pathogenic *CEP290* mutations identified in >50% of LCA10 patients[3]<br>  • Most frequently occurring mutation is c.2991+1655A>G which accounts for up to 21% of all LCA cases & leads to inclusion of a cryptic exon X[1,2]<br>• Lack of functional CEP290 protein leads to disruption phototransduction & ultimately photoreceptor degeneration[4,5]<br>• Currently no approved treatments available |
| **Characteristic Clinical Features[1,6]** | • Severe visual impairment manifests in infancy or early childhood<br>• >80% patients have off-chart visual acuity<br>• High refractive errors<br>• Sensory nystagmus<br>• Amaurotic pupils<br>• Oculo-digital signs, such as eye-poking<br>• Photophobia<br>• Keratoconus and cataracts |
| **Diagnosis** | • Genetic testing leads to definitive diagnosis in approximately 60-80%[7-9] confirming eligibility for genetic therapies |

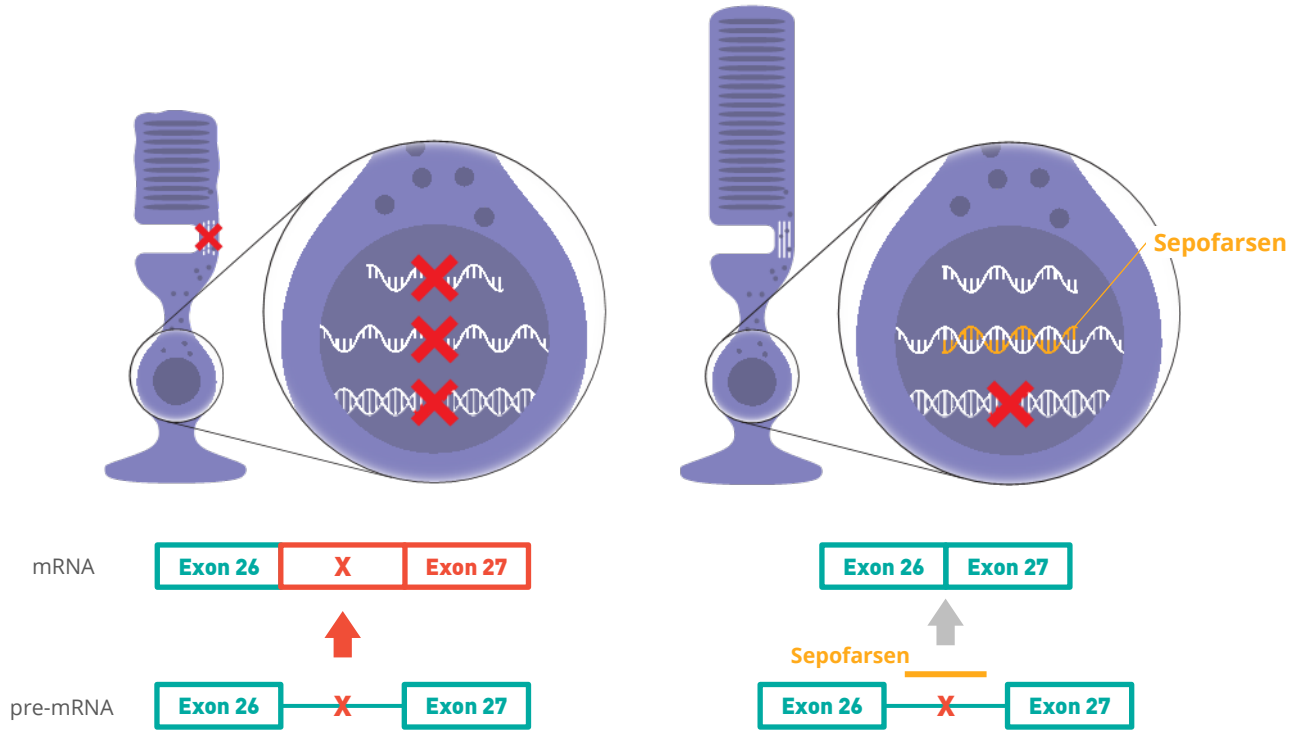
IRD, inherited retinal disease; LCA, Leber congenital amaurosis; CEP290, centrosomal protein 290 kDa

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. Shimada H, et al. *Cell Rep*. 2017;20(2):384–96; 5. Nash BM, et al. *Transl Pediatr*. 2015;4(2):139–63; 6. Chacon-Camacho OF, Zenteno JC. *World J Clin Cases*. 2015;3(2):112–24; 7. Siemiatkowska AM, et al. *Cold Spring Harb Perspect Med*. 2014;4(8):a017137; 8. Stanwyck LK, et al. *Am J Ophthalmol Case Rep*. 2019;15:100461; 9. Ellingford JM, et al. *Ophthalmology*. 2016;123(5):1143–50.

# Sepofarsen (QR-110) for LCA10

## *Splice Correction for c.2991+1655A>G (p.Cys998X) mRNA*

- A 17-mer 2'-O-methyl modified phosphorothioate antisense RNA oligonucleotide[1]
- Alters mRNA splicing & prevents inclusion of the cryptic exon X[2-5]
- Restores normal *CEP290* mRNA splicing & production of full-length CEP290 protein[2-5]
- mRNA splice modulation & cilia growth were demonstrated in c.2991 +1655A>G -LCA10 patient-derived retinal organoids[5]



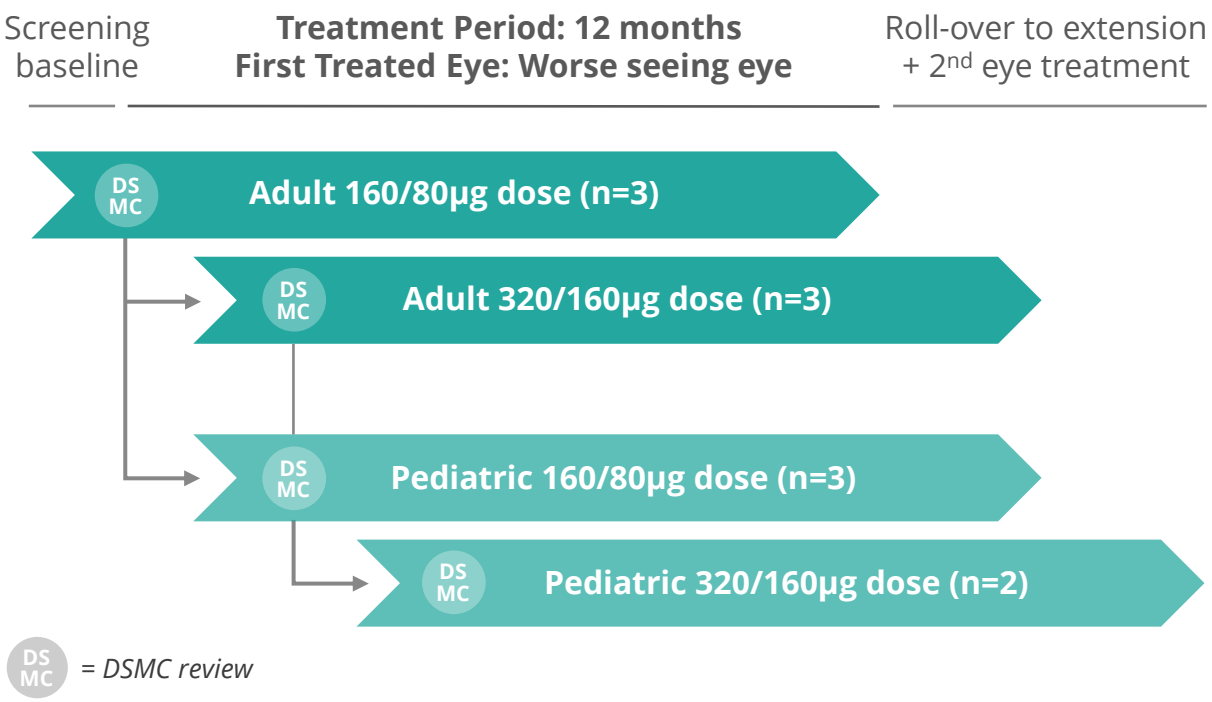

In c.2991+1655A>G LCA10 cells protein transport is hampered & the outer segment degenerates

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

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**) homozygous or compound heterozygous for the c.2991+1655A>G (p.Cys998X) mutation
- Up to 4 intravitreal injections to the treated eye, defined as the worse-seeing eye
- Manageable safety profile and improvements in visual function reported at ARVO 2020[1]
- We assess the change from baseline to Month 12 in Full-field Stimulus Threshold testing (FST) and in Best Corrected Visual Acuity (BCVA)

Pediatric: 6 to 17 years of age as inclusion criterion

1. Russell SR, et al. *Invest Ophthalmol Vis Sci* 2020;61:866; Pediatric = 6-17 yrs of age as inclusion criterion

# Overview of BCVA and FST methods

## BCVA[1-3]

- **Assesses cone function in the fovea at a high contrast, high-luminance conditions**
- Available methods assess VA for patients at least able to identify shaped objects:
  - ETDRS method cover VA range from -0.3 (Snellen 20/10) to +1.6 LogMAR (Snellen 20/800) (on-chart patients)
  - For off-chart patients, BRVT method and FraCT computerized VA test cover range up to +2.6 LogMAR (Snellen 20/8000)
- Patients with VA below 20/2000 are considered as off-chart patients and often classified as CF, HM, LP and NLP due to the lack of reliable method to assess VA of this population.

## FST[4-7]

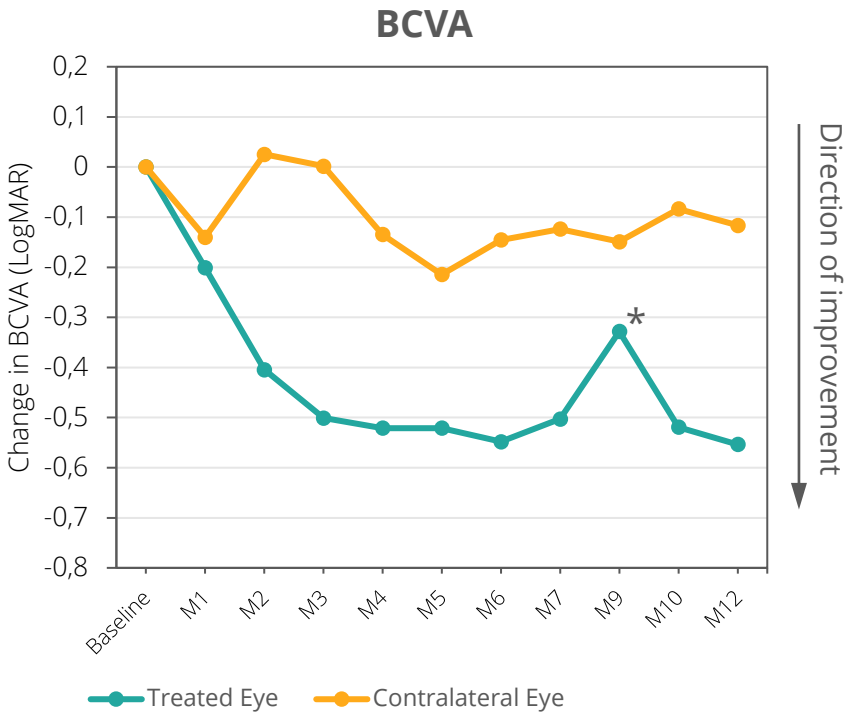
- **Assesses threshold of the most sensitive part of the retina at a dark-adapted state**
- Chromatic (red and blue) stimuli which differentiates the sensitivity threshold derived from cone or rod photoreceptors
- Broad dynamic range of stimulus intensity – low vision patients
- No retinal fixation required
- FST is an applicable method to assess retinal sensitivity changes pre- and post-treatment in severely visually impaired patients

BCVA, Best-Corrected Visual Acuity; BRVT, Berkeley Rudimentary Vision Test; CF, Counting Fingers; ETDRS, Early Treatment of Diabetic Retinopathy; FraCT, Freiburg visual acuity test; FST, Full-Field Stimulus Testing; HM, Hand Motion; LogMAR, Logarithm of the minimum angle of resolution; LP, Light Perception; NLP, Non-Light Perception; VA, Visual Acuity;

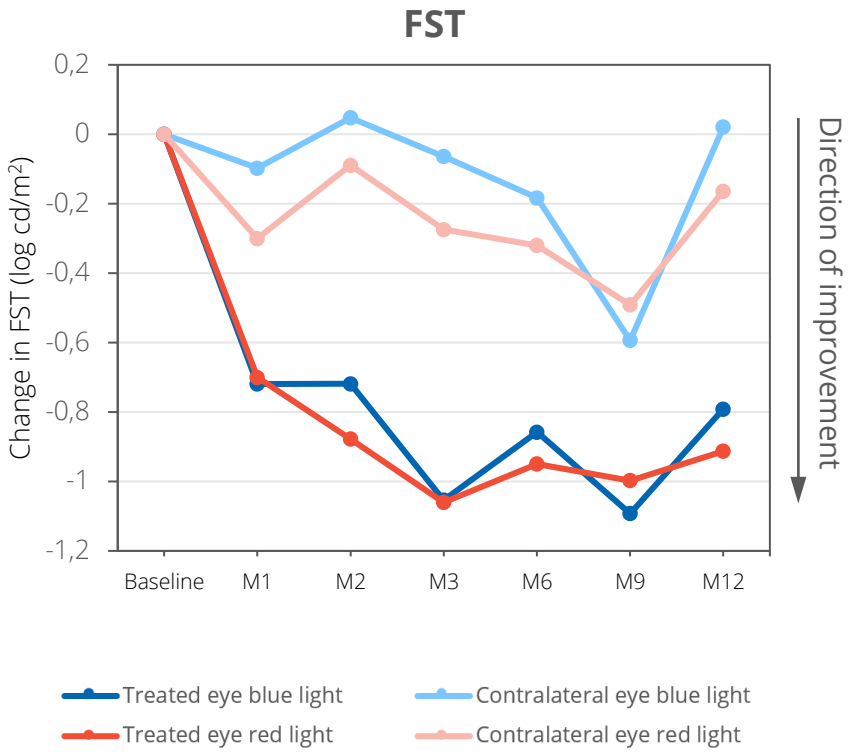
1.Bailey IL et al. *Vision Res.* 2013;90:2-9; 2. Schulze-Bonsel K et al. *Invest Ophthalmol Vis Sci*. 2006;47(3):1236-40; 3. Holladay JT et al. *J Refract Surg*. 1997;13(4):388-91; 4. Roman AJ et al. *Physiol Meas*. 2007;28(8):N51-6; 5. Jacobson SG et al. *Invest Ophthalmol Vis Sci.* 2009;50(5):2368-75; 6. Collison FT et al. *Invest Ophthalmol Vis Sci*. 2015;56(12):7130-6. 7. Klein M et al. *Doc Ophthalmol.* 2009;119(3):217-24.

# Results – Mean Efficacy

*All Treated Subjects (n=11)*



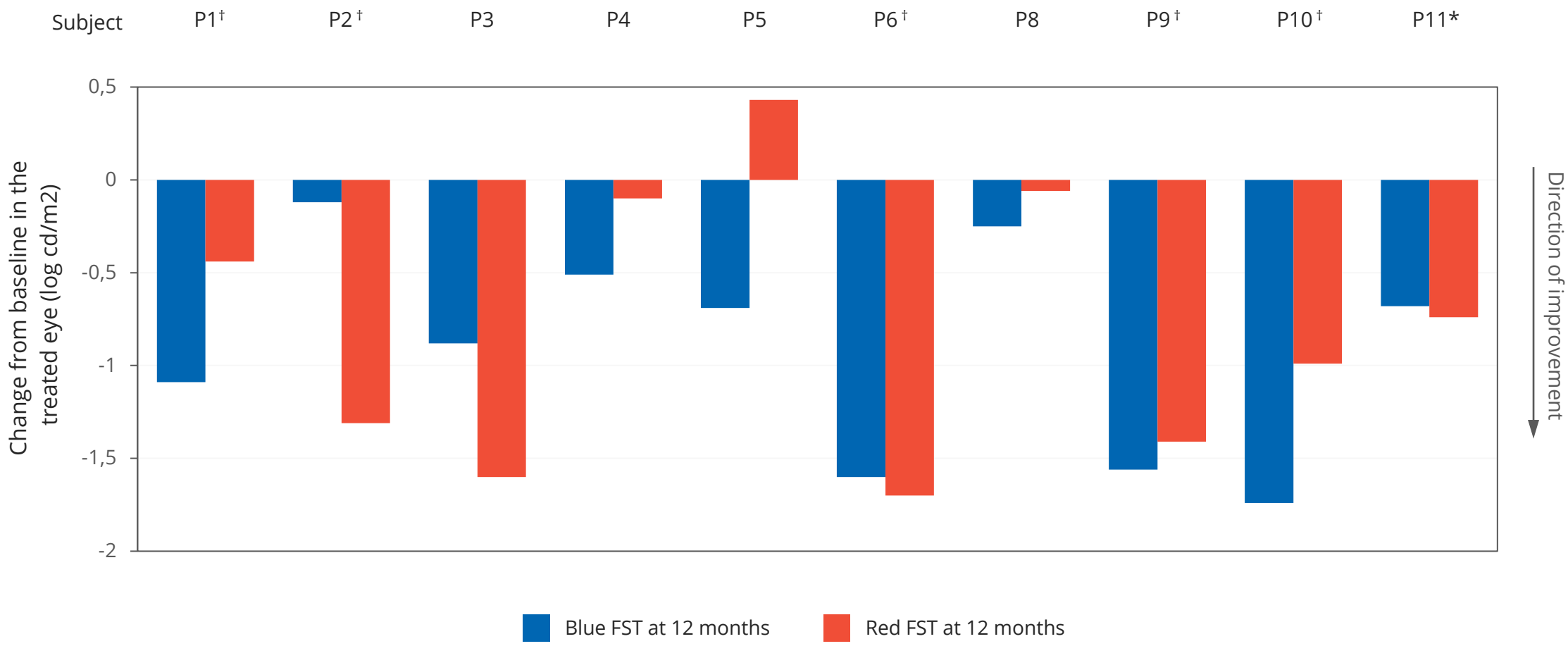

* Visual acuity peak associated with cataract occurrence. These subjects regained their pre-cataract visual acuity after surgery.




| Eye | BCVA – LogMAR (n=11) | Red FST – log cd/m2 (n=10) | Blue FST – log cd/m2 (n=10) |
|---|---|---|---|
| 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** |
| Untreated (CE) | -0.12 (0.07) | -0.16 (0.16) | 0.02 (0.11) |

# FST Changes From Baseline at M12

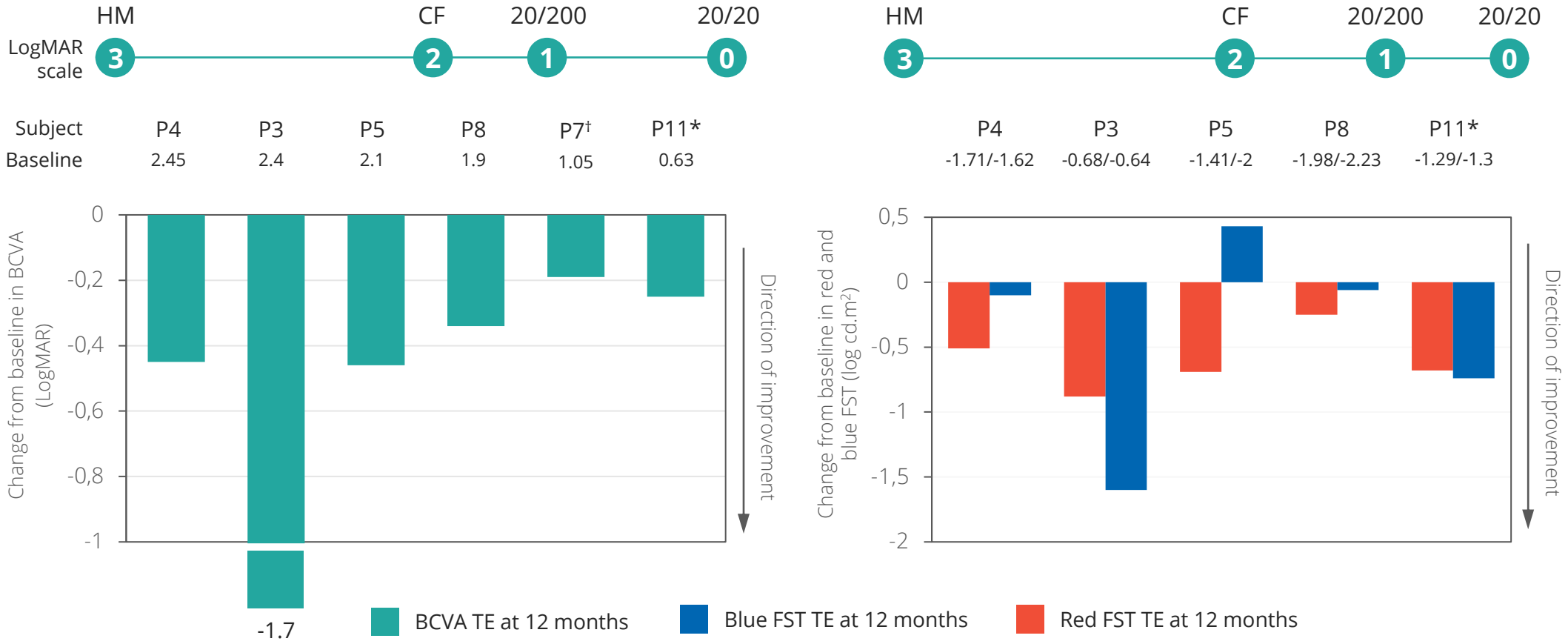
*High response rate in light sensitivity as measured by FST*




FST baseline data with the "pulse" stimulus test were missing for P7, FST data for this subject were excluded from the efficacy analysis.
† P1, P2, P6, P9 and P10 are Light Perception (LP) patients, 1 out of 5 LP patients (P2) also showed a BCVA improvement of -2.66 LogMAR.
*Homozygous subject

# BCVA and FST Changes From Baseline at M12

*All patients with baseline VA of Hand Motion or better responded on BCVA supported by an improvement in light sensitivity*




†FST baseline data with the "pulse" stimulus test were missing for P7, FST data for this subject were excluded from the efficacy analysis.
*Homozygous subject
CF, Counting Fingers; HM, Hand Motion; TE, Treated Eye

# Conclusion

- **Sepofarsen showed meaningful improvement in mean BCVA and FST in the treated eye versus untreated eye**
- **All patients in this trial showed a response to sepofarsen in visual acuity (BCVA) and/or in retinal sensitivity using FST testing**
  - FST is a sensitive method to assess retinal sensitivity improvement in response to sepofarsen for all patients, including LP patients
  - FST improvements are generally in line with BCVA response to sepofarsen for patients with baseline BCVA of HM or better
- **LCA10 patients with severe visual impairment need a sensitive enough method to assess potential improvement upon treatment**
- **Further investigation of the impact of sepofarsen on LCA10 patients is underway in the ongoing Ph2/3 trial (Illuminate; NCT03913143).**

# References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