Safety and efficacy of sepofarsen in the second treated eye in a Ph1b/2 extension trial in Leber Congenital Amaurosis type 10 (LCA10)

Stephen R. Russell[1], Arlene V. Drack[1], Artur V. Cideciyan[2], Samuel G. Jacobson[2], Bart P. Leroy[3,4], Wilhelmina den Hollander[5], Adriana Hollestein-Havelaar[5], Michael R. Schwartz[5], Aniz Girach[5]

[1]Department of Ophthalmology and Visual Sciences, Carver College of Medicine, University of Iowa, Iowa City, IA, USA; [2]Scheie Eye Institute, Department of Ophthalmology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [3]Department of Ophthalmology & Center for Medical Genetics, Ghent University Hospital & Ghent University, Ghent, Belgium; [4]Ophthalmic Genetics & Visual Electrophysiology, Division of Ophthalmology, The Children's Hospital of Philadelphia, PA, USA; [5]ProQR Therapeutics, Leiden, the Netherlands

Disclosures

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WDH, AHH, MRS, and **AG** are employees of ProQR.

High unmet medical need in LCA10

LCA10 is a severe form of IRD[1]

- Autosomal-recessive mutations in the *CEP290* gene cause LCA10
  - Mutations in CEP290 accounts for about 15% to 30% of LCA cases[1-3]
  - Most frequently occurring mutation is c.2991+1655A>G which accounts for >50% of LCA10 cases up to 21% of all LCA cases[1,2,,4]
- c.2991+1655A>G leads to inclusion of a cryptic exon X that results in lack of functional CEP290 protein leads to disruption phototransduction & ultimately photoreceptor degeneration[4]
- Currently no approved treatments available

Characteristic Clinical Features[1,5,6]

- Severe visual impairment manifests in infancy or early childhood
- VA for about 62% to 89% of LCA10 patients is off-chart
- High refractive errors
- Sensory nystagmus
- Amaurotic pupils
- Oculo-digital signs, such as eye-poking
- Photophobia
- Keratoconus and cataracts
- Significant impact on quality of life

Diagnosis[7-10]

- Genetic testing leads to definitive diagnosis in approximately 60-80% of cases and can help patients in gaining access to current treatment options or clinical trials

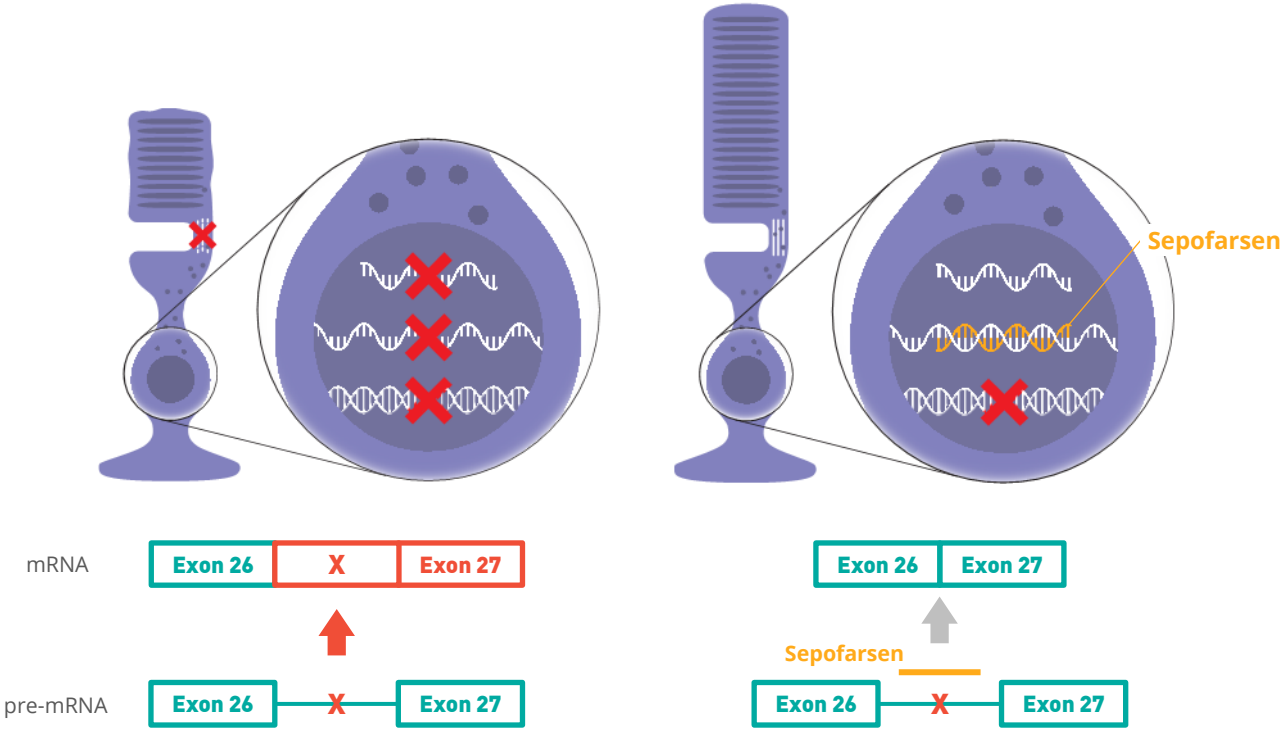
IRD, inherited retinal disease; LCA, Leber congenital amaurosis; CEP290, centrosomal protein 290 kDa; VA, Visual Acuity

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. Coppieters F et al. Hum Mutat. 2010;31(10):E1709-66; 4. Dulla K, et al. *Mol Ther Nucleic Acids*. 2018;12:730–40; 5. Chacon-Camacho OF, Zenteno JC. *World J Clin Cases*. 2015;3(2):112–24; 6. Cideciyan AV et al. *Invest Ophthalmol Vis Sci*. 2019;60(5):1680-95; 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; 10. Neveling K, et al. Methods Mol Biol. 2013;935:3–23

Sepofarsen (QR-110) for LCA10

Splice Correction for c.2991+1655A>G 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]
- Results in an increase of wild-type mRNA transcript, leading to a production of functional full-length CEP290 protein[2-5]
- mRNA splice modulation, increase in CEP290 protein levels & cilia growth were demonstrated following treatment 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

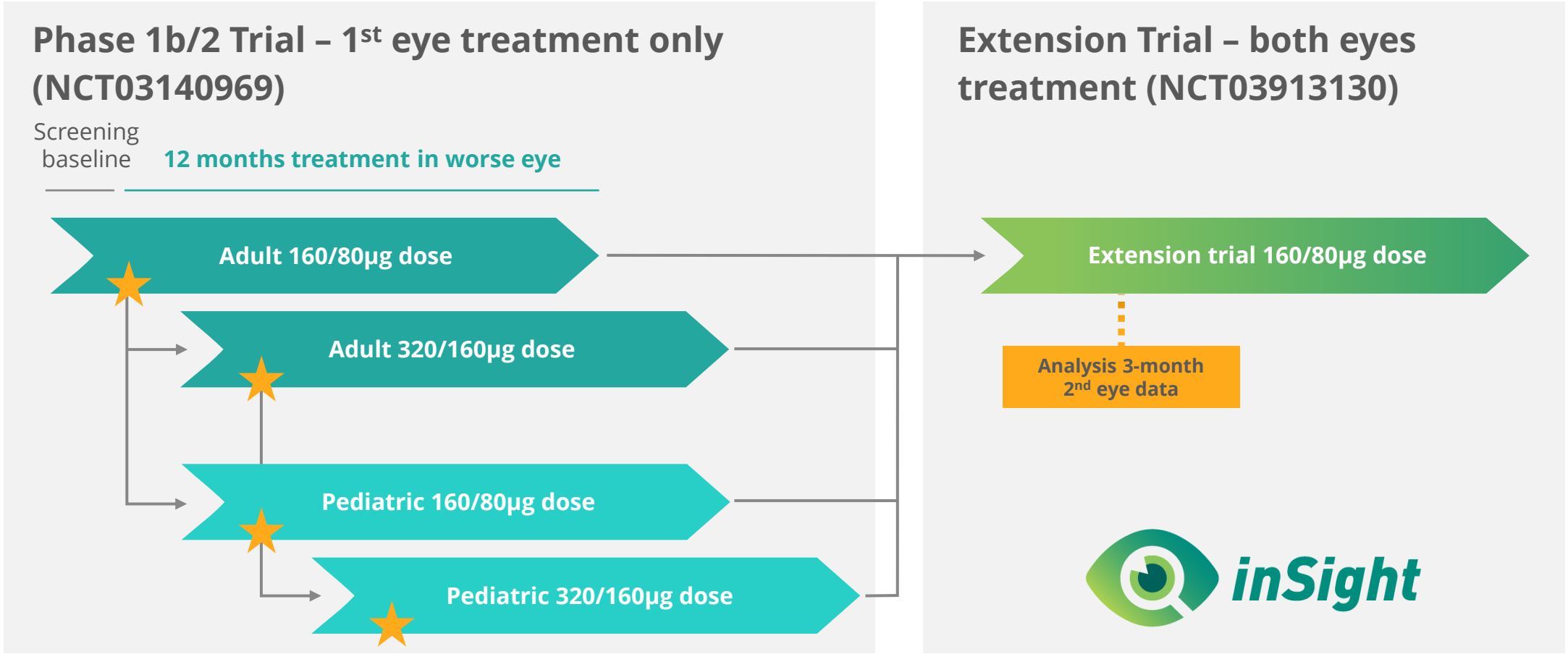
Exclusion of the cryptic exon from the mutated mRNA leads to full-length CEP290 protein production

LCA, Leber congenital amaurosis; mRNA, messenger ribonucleic acid; CEP290, centrosomal protein 290 kDa;

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

Sepofarsen phase 1b/2 + extension trial design

Open label, extension trial, LCA10 patients with 1 or 2 copies of c.2991+1655A>G mutation

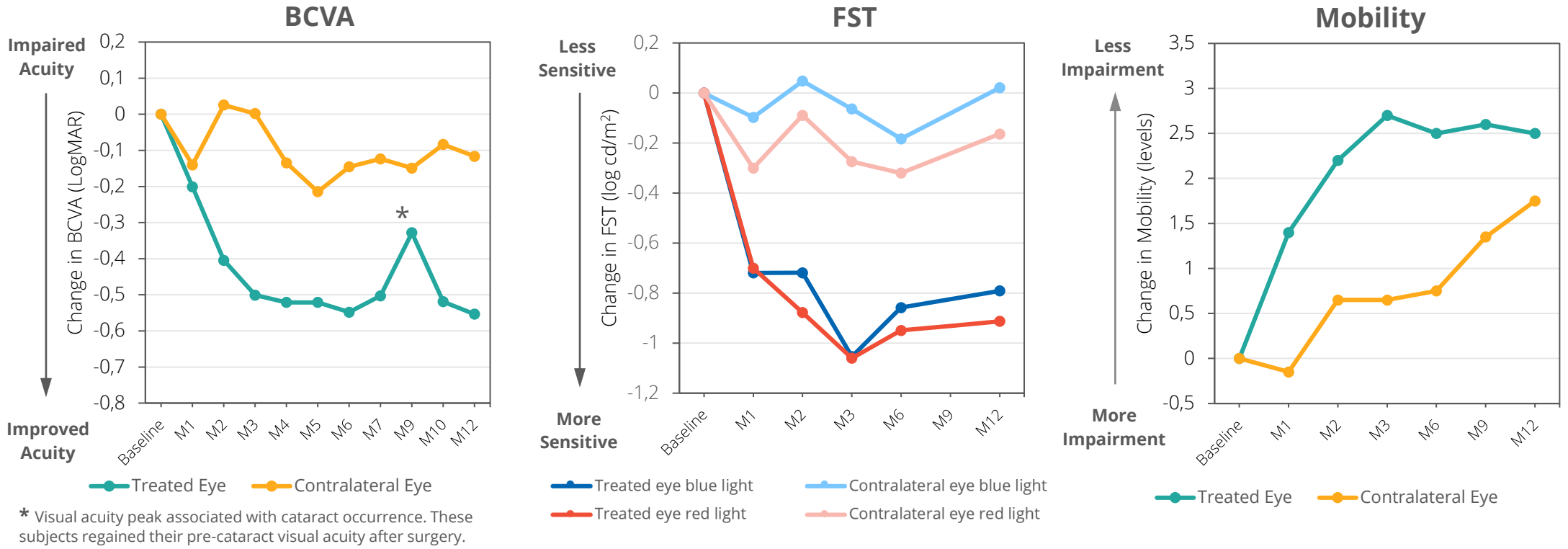


★ = Data and Safety Monitoring Committee (DSMC) review

LCA, Leber congenital amaurosis

Results – Mean efficacy in the Ph1b/2 trial

All Treated Subjects (n=11)

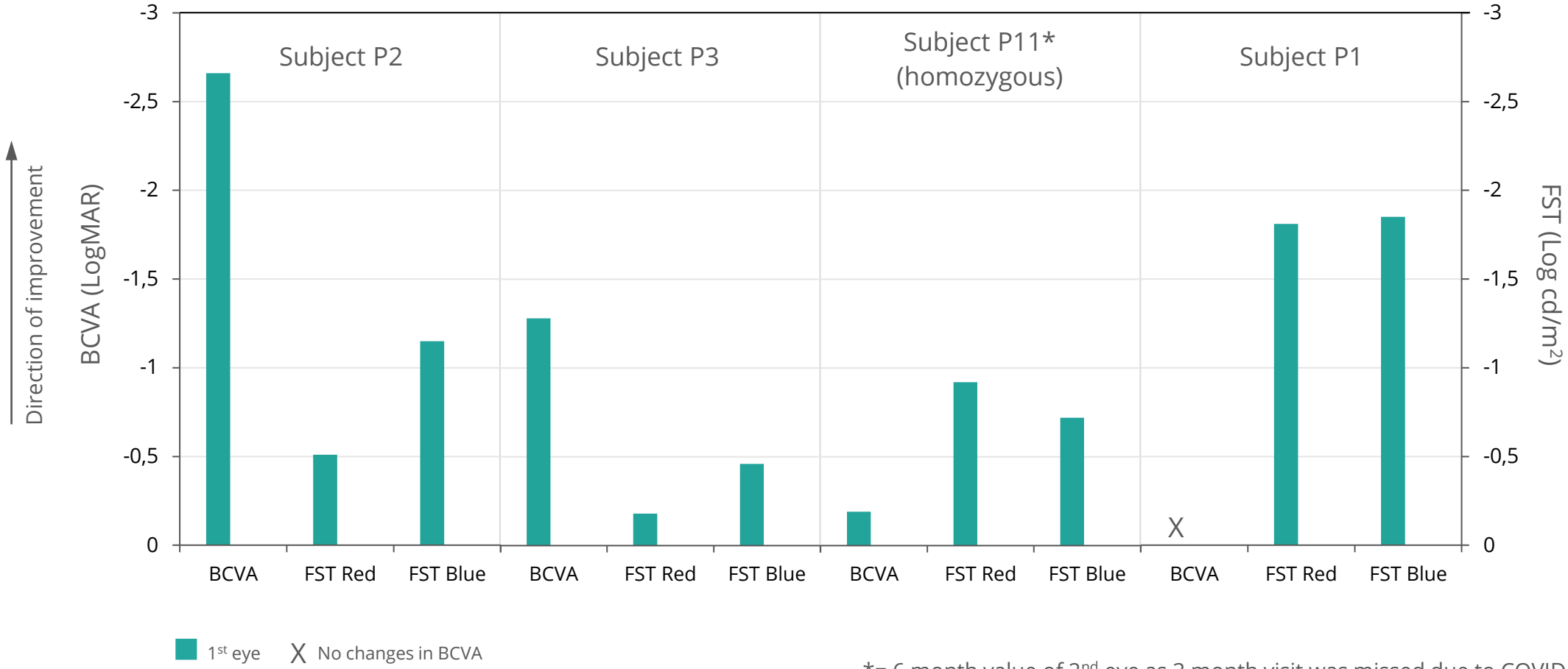


* Visual acuity peak associated with cataract occurrence. These subjects regained their pre-cataract visual acuity after surgery.

Eye	BCVA – LogMAR (n=11)	Red FST – log cd/m2 (n=10)	Blue FST – log cd/m2 (n=10)	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)

Phase 1b/2 sepofarsen trial – PQ-110-001; NCT03140969

Phase 1/2 trial - change from baseline to 3 months post dosing



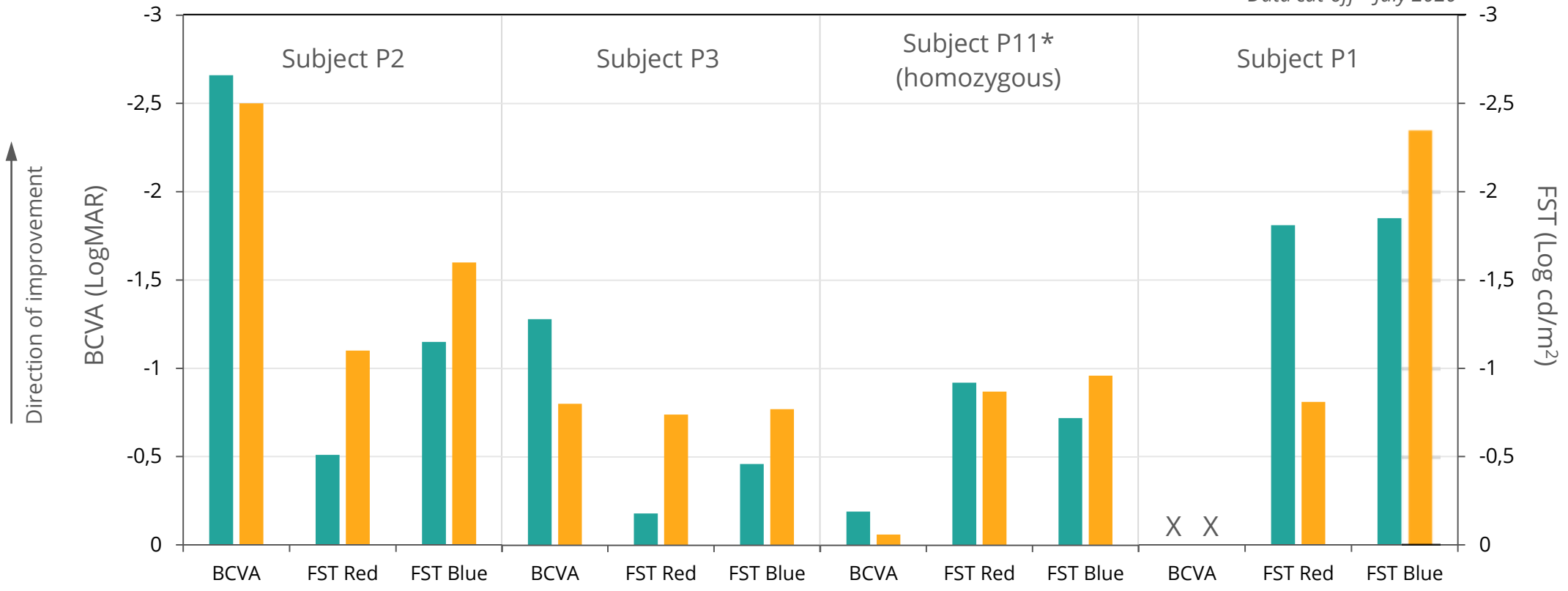
*= 6 month value of 2nd eye as 3 month visit was missed due to COVID-19

Phase 1b/2 sepofarsen trial – PQ-110-001; NCT03140969

Phase 1/2 extension trial – change from baseline to 3 months post dosing

Consistent treatment response in both eyes

Data cut-off – July 2020



*= 6- month value of 2nd eye as 3- month visit was missed due to COVID-19

Baseline BCVA = average pre-treatment value (1st eye), most recent value prior to first dose (2nd eye)

Baseline FST = average of pre-treatment values (1st eye), most recent value prior to first dose (2nd eye)

Conclusions

- **Safety profile of 160/80 ug consistent with Ph1b/2 safety data**
  - Available data confirm the manageable safety profile of IVT sepofarsen
  - Limited observation period of 3 months (earliest timepoint that cataracts, macular edema or retinal thinning was seen in phase 1b/2 was at 3 months).
- **Efficacy data in 2nd eye appears to parallel the magnitude of the unexpected clinically meaningful vision improvements observed in the 1st eye (Ph1b/2 trial)**
  - 4 out of 4 second eyes responded to treatment (in visual acuity or retinal sensitivity) to a similar extent as compared to the initially treated eyes
- **Observations continuing from the ongoing extension trial (INSIGHT; NCT03913130)**
- **Ongoing phase 2/3 trial (ILLUMINATE; NCT03913143)**