LONG-TERM SAFETY AND EFFICACY OF SEPOFARSEN IN A PH1B/2 EXTENSION TRIAL IN *CEP290*-ASSOCIATED INHERITED RETINAL DISEASE (LCA10) (*INSIGHT*)

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Disclosure slide

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- This study was sponsored by ProQR Therapeutics.

High unmet medical need

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 which leads to disruption of phototransduction & ultimately photoreceptor degeneration[4]
	• Currently no approved treatments available

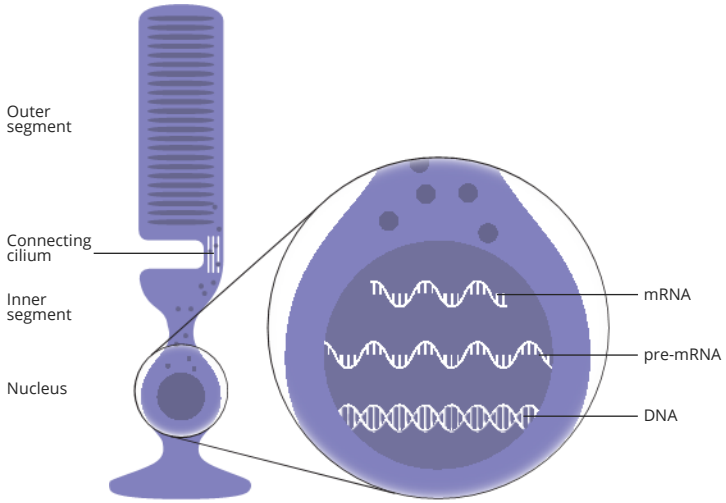
Characteristic Clinical Features[1,5,6]	• Severe visual impairment manifests in infancy or early childhood • VA for about 62% to 89% of LCA10 patients is off-chart • High refractive errors • Sensory nystagmus • Amaurotic pupils • Oculo-digital signs, such as eye-poking • Photophobia • Keratoconus and 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 clinical trials

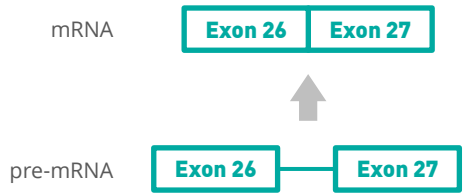
IRD, inherited retinal disease; LCA, Leber congenital amaurosis; CEP290, centrosomal protein 290 kDa; VA, Visual Acuity

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;

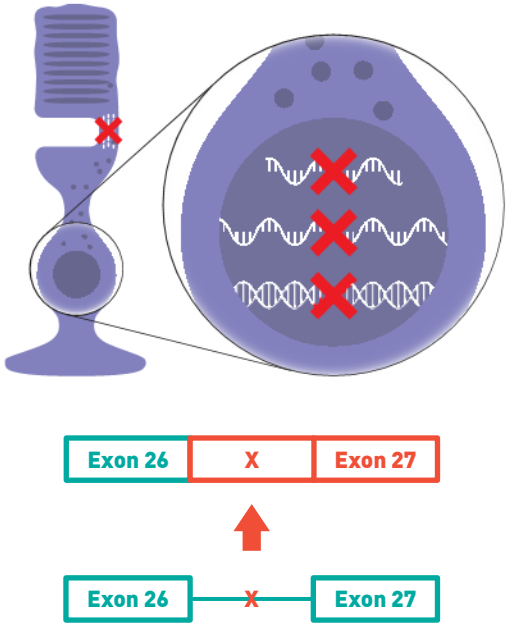
Sepofarsen intravitreal RNA therapy

Splice correction for c.2991+1655A>G CEP290 mRNA

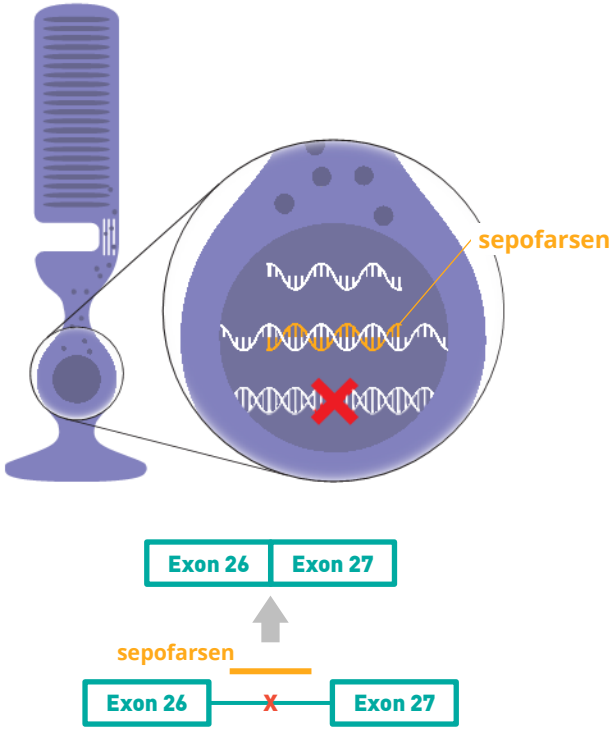




In wild-type cells *CEP290* maintains cilium structure and enables normal protein transport



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



Exclusion of the cryptic exon from the mutated mRNA leads to wild-type CEP290 protein

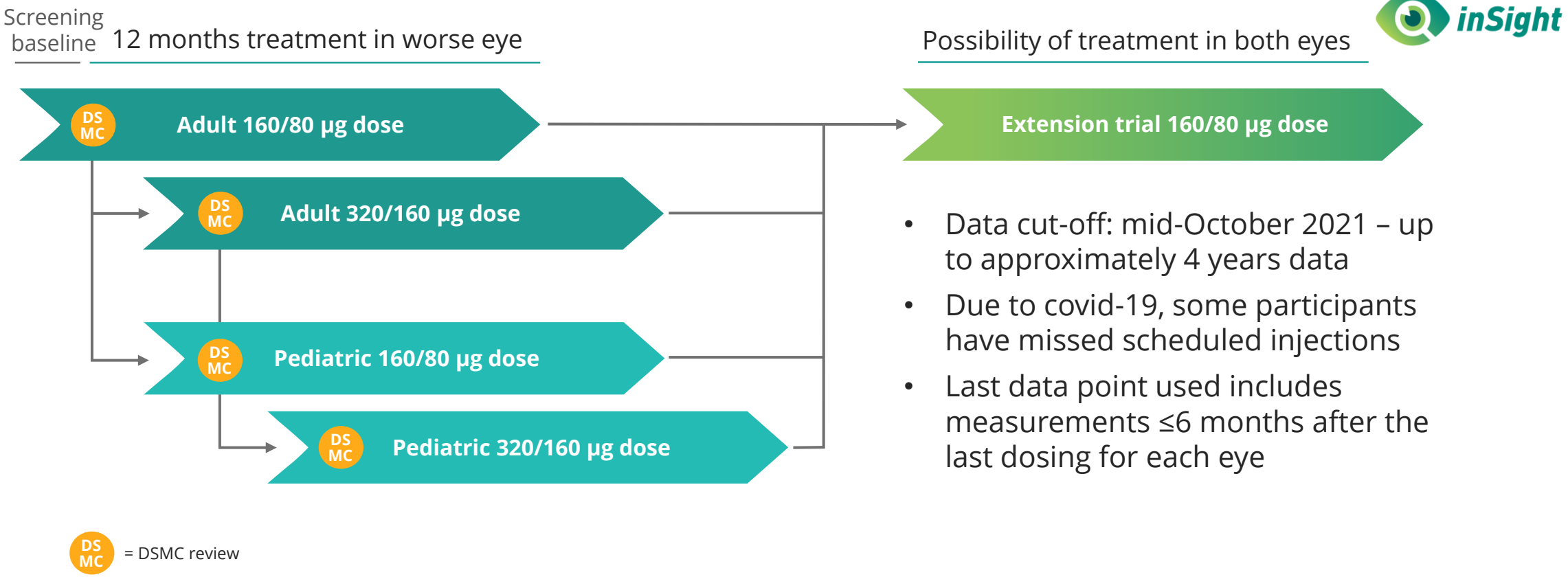
Dulla K et al. Mol Ther Nucleic Acids. 2018;12:730–740

Phase 1/2 + *InSight* extension trial design

Open label, extension trial for Phase 1/2 participants

Phase 1/2 Study (NCT03140969; n=11)

InSight extension study (NCT03913130, n=9)



- Data cut-off: mid-October 2021 – up to approximately 4 years data
- Due to covid-19, some participants have missed scheduled injections
- Last data point used includes measurements ≤6 months after the last dosing for each eye

Long-term safety overview

- Sepofarsen safety profile was consistent with that observed in the Ph1b/2
- No reported inflammation (endophthalmitis, etc..)
- Summary of adverse events of special interest (AESIs):

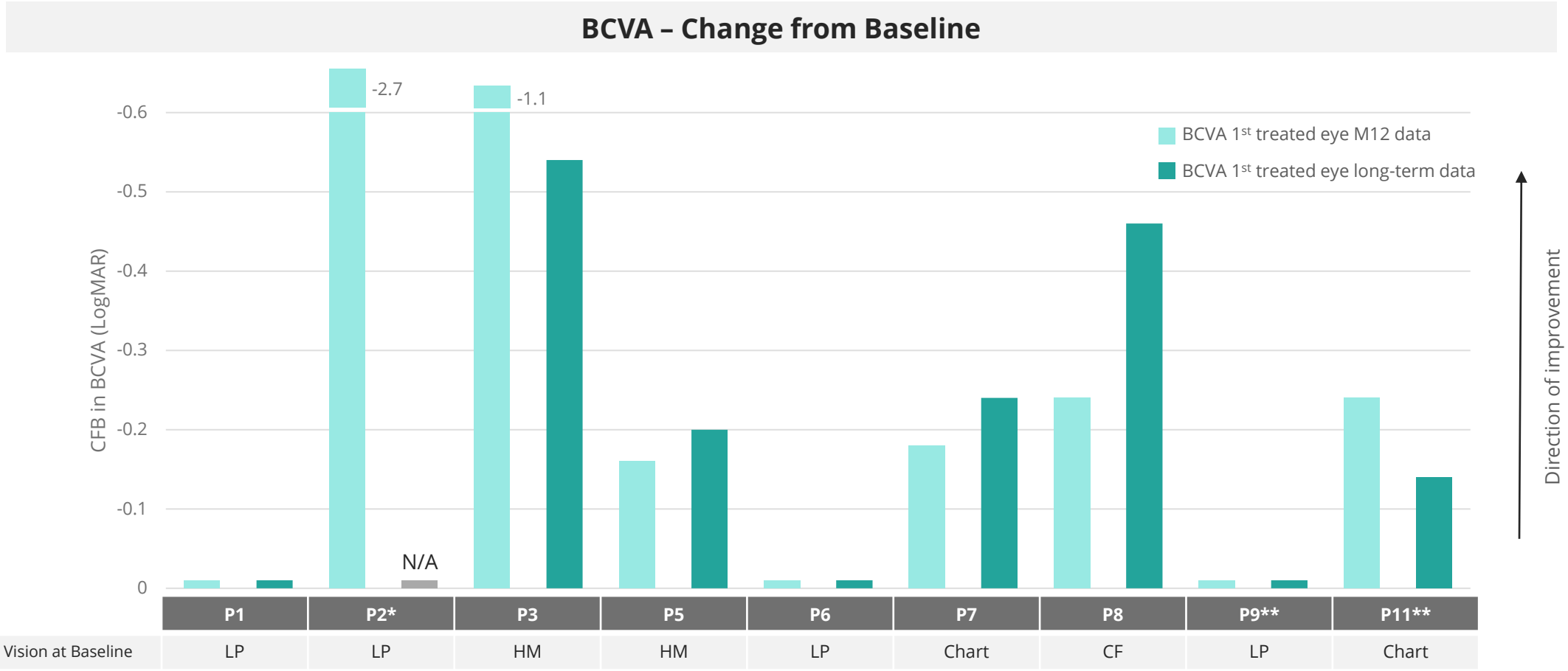
	PQ-110-001 (n=11)		PQ-110-002 (InSight; n=9)	
	First eye	Second eye	First eye	Second eye
Cataracts	8	N/A	3*	2
CME	2	N/A	0	0
Retinal thinning	2	N/A	0**	0

- Cataracts were resolved in 1 participant following lens replacement in both eyes and 1 participant following lens replacement in the first eye treated.

CME, Cystoid Macular Edema
**One of these participants also reported cataract during study PQ-110-001; One retinal thinning was reported post data cut-off*

Best-corrected visual acuity (BCVA)

M12 and long-term data in the first treated eye of patients enrolled in InSight (n=9)



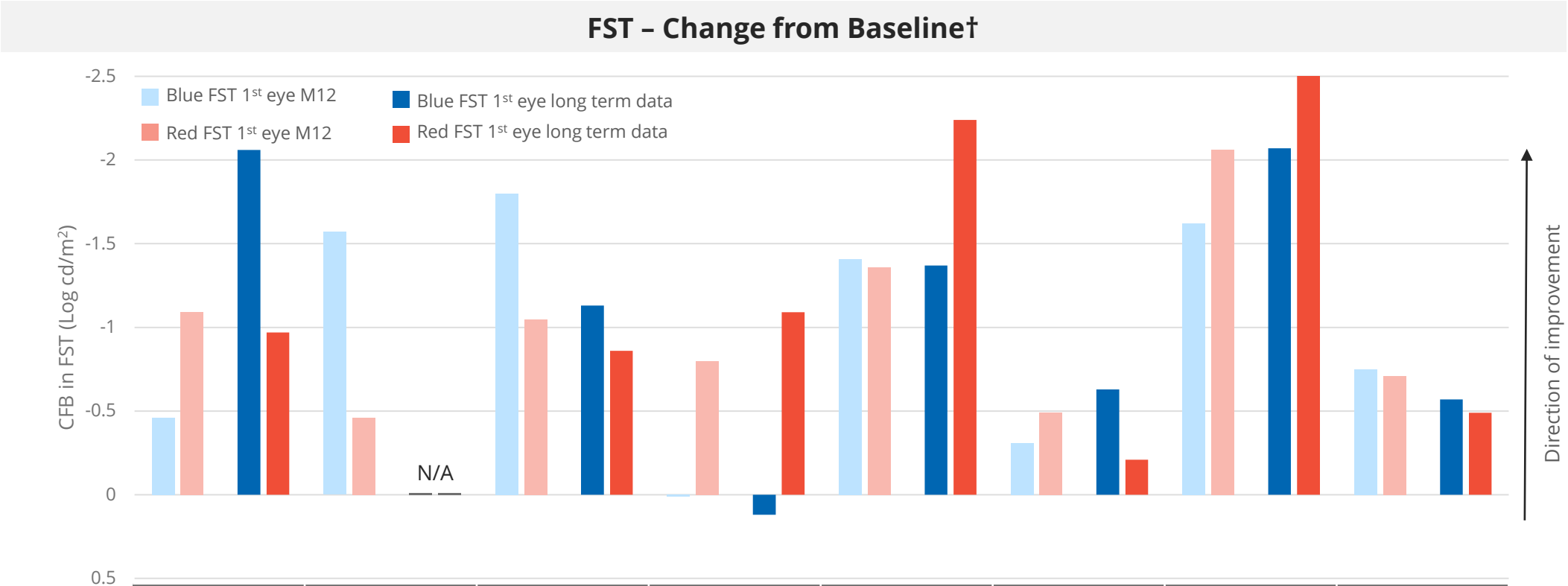
CFB: Change from baseline, baseline for the first eye is defined as the best pre-treatment value; CF: Counting Fingers; HM: Hand Motion; LP: Light Perception

**Due to covid-19, Participant P2 has missed scheduled injections in the first eye*

***Participants P9 and P11 received only injections in PQ-110-001 and no further injection in the InSight extension trial. Data presented here shows assessment at their last visit.*

Full-field stimulus testing (FST)

M12 and long-term data in the first eye treated with sepofarsen - patients enrolled in InSight (n=9)



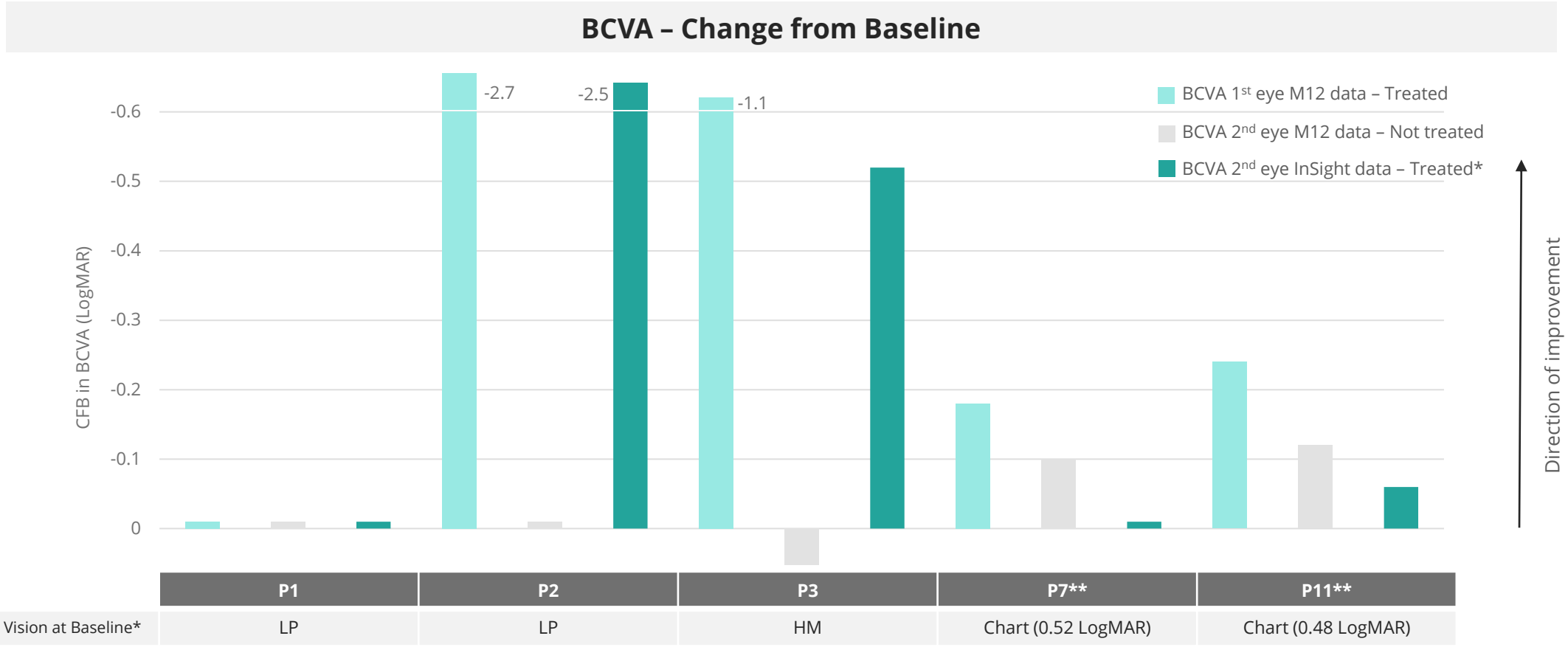
	P1	P2*	P3	P5	P6	P8	P9**	P11**
Vision at Baseline	LP	LP	HM	HM	LP	CF	LP	Chart

CFB: Change from baseline ; CF: Counting Fingers; HM: Hand Motion; LP: Light Perception

*†FST data are missing for participant P7 due to incorrect baseline FST procedure; *Due to covid-19, Participant P2 has missed scheduled injections in the first eye; ** Participants P9 and P11 received only injections in PQ-110-001 and no further injection in the InSight extension trial. Data presented here shows assessment at their last visit.*

Best-corrected visual acuity (BCVA)

CFB without and with sepofarsen in the second eye treated with sepofarsen in InSight (n=5)

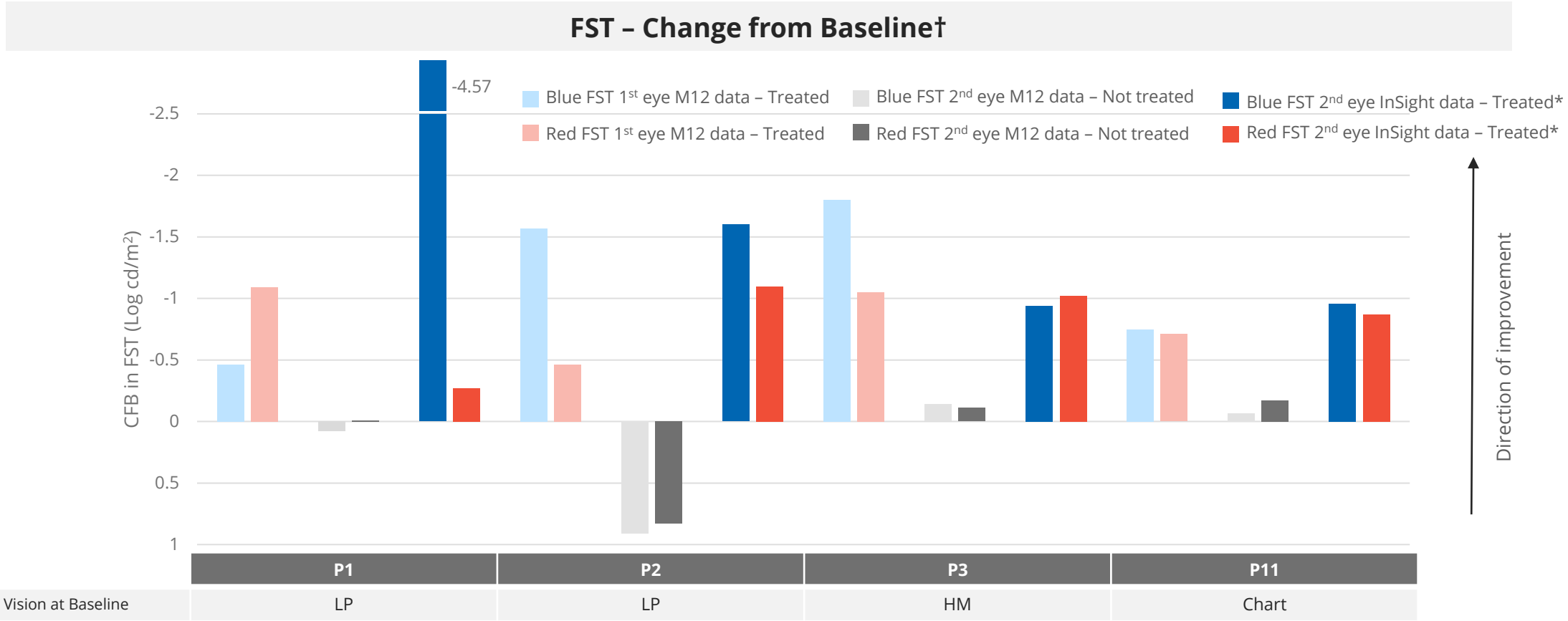


CFB: Change from baseline; CF: Counting Fingers; HM: Hand Motion; LP: Light Perception

**Baseline BCVA for the first eye is defined as the best pre-treatment value, baseline BCVA for the 2nd treated eye in Insight is at time of the first injection; ** Started with high on-chart vision at baseline potential ceiling effect*

Full-field stimulus testing (FST)

CFB without and with sepofarsen in the second eye of patients enrolled in InSight (n=4)



CFB: Change from baseline ; CF: Counting Fingers; HM: Hand Motion; LP: Light Perception

*†FST data are missing for participant P7 due to incorrect baseline FST procedure; *Baseline BCVA for the 2nd treated eye in Insight is at time of the first injection*

InSight sepofarsen extension trial

Summary

- Up to approximately 4 years of follow-up following first injection of sepofarsen reported (n=9)
- Covid-19 crisis has impacted scheduled injections
- Sepofarsen long-term safety profile is consistent with that observed in the Phase 1b/2
- The data analysis confirms the BCVA and FST improvements observed in the Phase 1b/2 and showed a sustained improvement with sepofarsen
- The second treated eye response to sepofarsen generally parallel with the first treated eye response both in visual acuity and retinal sensitivity improvements