AAO 2020
BEST POSTER
AWARD

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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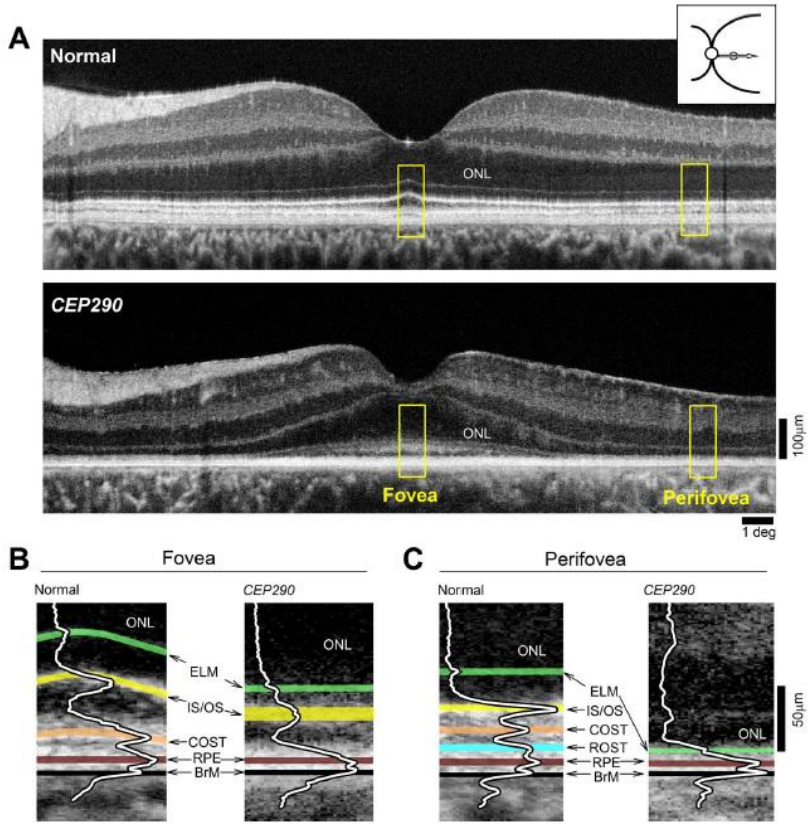
High Unmet Medical Need in LCA10

- 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 (p.Cys998X) mutation accounts for up to 21% of all LCA cases[1-3]
- Lack of functional 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 to light perception or no light perception
- No approved treatments

Decreased ONL thickness[4]



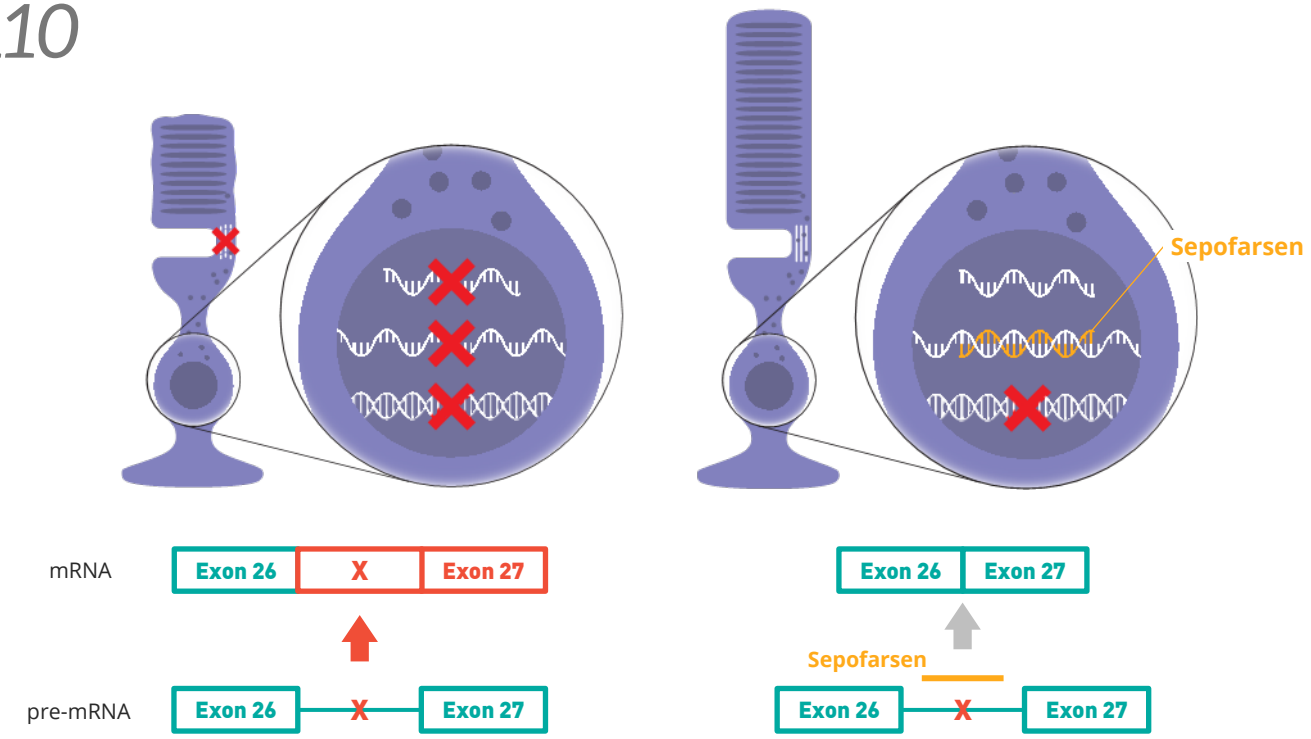
CEP290, centrosomal protein 290 kDa; LCA10, Leber congenital amaurosis 10; ONL, outer nuclear layer.

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 c.2991+1655A>G-LCA10 patient-derived retinal organoids[5]



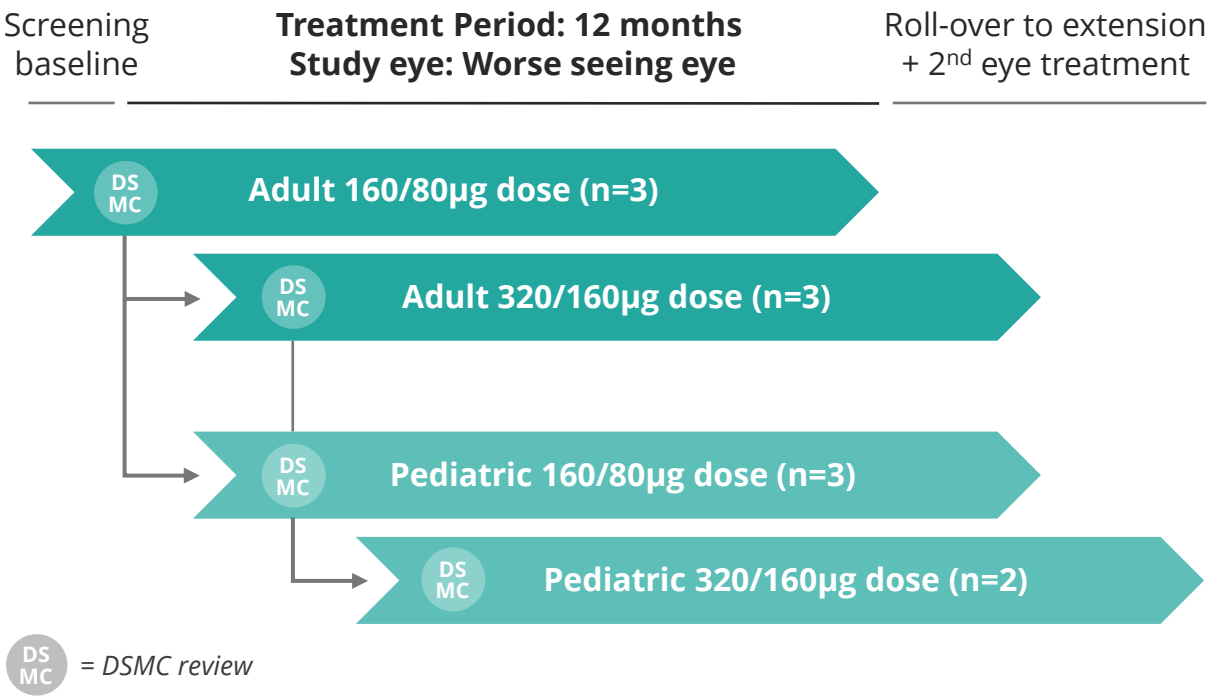
In c.2991+1655A>G-LCA10 cells protein transport is hampered and the outer segment degenerates

Exclusion of the cryptic exon from the mutated mRNA leads to 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



Pediatric: 6 to 17 years of age as inclusion criterion

- 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 study eye, defined as the worse-seeing eye
- 3 participating sites: 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

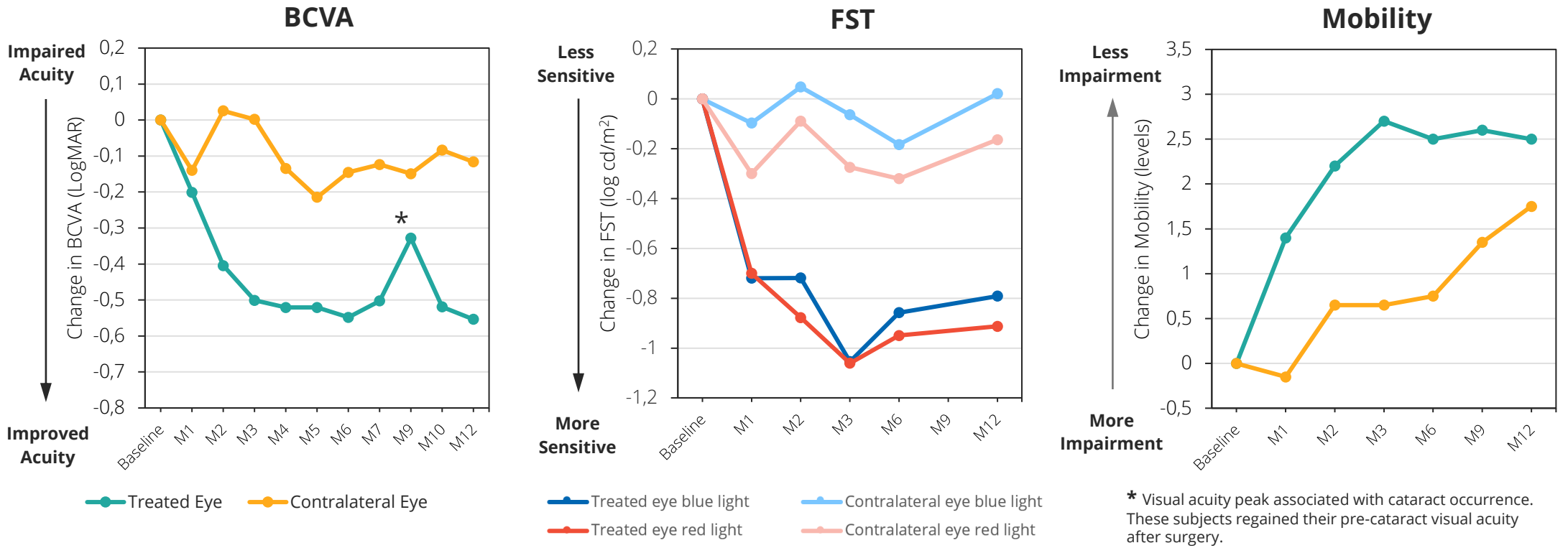
	Sex	2nd *CEP290* Allele	Age/Group	Baseline VA	Treated	Dose
	(M/F)		(Adult/Ped)	[log MAR]	Eye	[µg]
P1	M	c.2506_2507delGA	19 / A	LP / LP	RE	160/80
P2	M	c.4723A>T	41 / A	LP / LP	RE	160/80
P3	M	c.5668G>T	44 / A	2.4 / 2.3	LE	160/80
P4	F	c.4438-3delC	16 / P	2.5 / 2.5	RE	160/80
P5	M	c.6277delG	8 / P	1.9 / 2.1	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	0.6/0.6	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 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)

Conclusions – Sepofarsen for LCA10

- **12-month results from Phase 1/2 safety and dose-ranging trial**
- **The RNA antisense oligonucleotide sepofarsen had a manageable safety profile in adults and children with LCA10 specifically in 160µ/80µg dose cohort**
  - Cataracts are primary adverse event (AE; N=8)
    - Onset earlier in 320µg/160µg compared to 160µg/80µg cohort
    - Standard cataract surgery performed in 6 subjects with restoration of pre-cataract vision
  - Cystoid macular edema and retinal thinning not observed in 160µg/80µg dose cohort
  - No systemic AEs, those related to injections self-limited
- **First treatment to show statistically significant differences for the within-subject improvement in mean visual acuity, and FST, supporting the strength of a potential therapeutic benefit**
- **Subjects: Extension trial ongoing and Phase 2b/3 trial recruiting (Illuminate; NCT03913143).**

References

- Cideciyan AV, Jacobson SG. *Invest Ophthalmol Vis Sci.* 2019;60(5):1680–95
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- den Hollander AI, et al. *Am J Hum Genet*. 2006;79(3):556–61
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