Efficacy and safety of sepofarsen, an intravitreal RNA antisense oligonucleotide, for the treatment of *CEP290*-mediated Inherited Retinal Disease (LCA10): A randomized, double-masked, sham-controlled, Phase 2/3 study (*Illuminate*)

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Introduction

CEP290-mediated Inherited Retinal Disease (IRD) also called Leber congenital amaurosis type 10 (LCA10) is an ultra-orphan non-syndromic autosomal recessive disease of the retina which causes severe visual impairment in infancy or early childhood.[1-3] The most frequently occurring mutation in the *CEP290* gene is c.2991+1655A>G which accounts for >50% of LCA10 cases and up to 21% of all LCA cases.[1,4,5] There are currently no approved treatments available.

Sepofarsen is an investigational RNA-based antisense oligonucleotide targeting the c.2991+1655A>G variant in the *CEP290* gene to correct the aberrant splicing of the pre-mRNA transcript, resulting in an increase of CEP290 protein synthesis.[5]

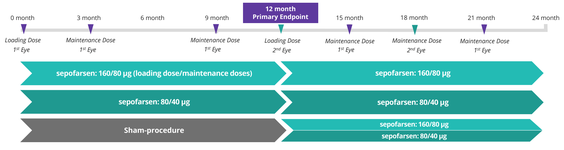
It is administered via intravitreal injections (up to two injections per year). In a Phase 1b/2 trial, sepofarsen showed a manageable safety profile and statistically significant improvements in visual acuity and retinal sensitivity.[6]

Materials & Methods

Illuminate (NCT03913143) is a double-masked, randomized, sham-controlled study performed across 14 sites in Europe, North America and Latin America. Eligible participants were aged ≥ 8 years, carried at least one c.2991+1655A>G in the *CEP290* gene and had best-corrected visual acuity (BCVA) ranging from 0.4 (20/50 Snellen equivalent) to 3.0 logMAR (Hand Motion).

Participants were randomly assigned (1:1:1) to receive intravitreal injection of sepofarsen 160/80 µg (maintenance dose of 80 µg every 6 months, starting 3 months after the loading dose of 160 µg), 80/40 µg (same regimen but doses of 40µg and 80µg respectively), or sham. (Figure 1)

The primary endpoint was mean change from baseline in BCVA, in the treatment eye (worse seeing eye), compared with sham at Month 12. Secondary endpoints included full-field stimulus testing threshold (FST; red, blue, white), a mobility course composite score, and safety.



Key inclusion criteria:
- LCA10 due to the c.2991+1655A>G mutation in the *CEP290* gene
- Age ≥ 8 years
- BCVA = 0.4 to 3.0 logMAR (20/50-HM)

Study design:
- Multicenter, Randomized, Double-Masked, Sham controlled phase 2/3 study

Primary Endpoint:
- Change from baseline in BCVA (logMAR) at Month 12

Secondary Endpoints:
- Mobility course
- Full field stimulus testing (FST)
- Optical coherence tomography (OCT)

Figure 1. Sepofarsen pivotal Phase 2/3 trial design

Baseline Characteristics

Between March 29, 2019 and January 6, 2021, 52 participants were screened, of whom 36 were randomized. Demographic and baseline characteristics were similar across groups. (Table 1)

Data are mean (SD) or n (%)	Sepofarsen 160/80 µg (n = 12)	Sepofarsen 80/40 µg (n = 12)	Pooled sepofarsen (n = 24)	Sham (n = 12)
Age				
Years of age	24.7 (14.4)	28.5 (14.8)	26.6 (14.4)	33.8 (13.8)
Category < 18 y	5 (41.7%)	4 (33.3%)	9 (37.5%)	3 (25.0%)
Category ≥ 18 y	7 (58.3%)	8 (66.7%)	15 (62.5%)	9 (75.0%)
Gender				
Male	7 (58.3%)	5 (41.7%)	12 (50.0%)	7 (58.3%)
Female	5 (41.7%)	7 (58.3%)	12 (50.0%)	5 (41.7%)
Genotype				
Homozygous	7 (58.3%)	5 (41.7%)	12 (50.0%)	4 (33.3%)
Compound Heterozygous	5 (41.7%)	7 (58.3%)	12 (50.0%)	8 (66.7%)
BCVA 1st Treated Eye				
On-chart participants	10 (83.3%)	10 (83.3%)	20 (83.3%)	11 (91.7%)
Off-chart participants	2 (16.7%)	2 (16.7%)	4 (16.7%)	1 (8.3%)
BCVA in TE, logMAR (all participants)*	1.173 (0.539)	1.380 (0.878)	1.277 (0.720)	1.235 (0.633)
BCVA in TE, logMAR (on-chart participants)*	0.998 (0.368)	1.036 (0.390)	1.017 (0.370)	1.084 (0.372)

Table 1. Demographics and baseline characteristics

* 1st treated eye

Results

Key efficacy outcomes – Pooled sepofarsen group

No additional benefit was seen in sepofarsen versus sham groups. *Illuminate* did not meet its primary endpoint at Month 12, the mean change from baseline in BCVA in the pooled sepofarsen groups was -0.16 logMAR and in the sham group -0.11 logMAR. For secondary endpoints full-field stimulus test (FST) and mobility course, there was also no difference between the treated and sham groups. (Figure 2)

In the sepofarsen 80/40µg cohort, one participant was subsequently found to be Light Perception and has been excluded from the analyses. (n=23)

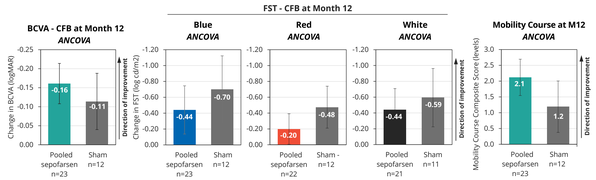
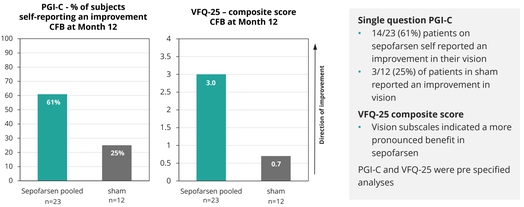


Figure 2. Mean Change form baseline in BCVA, FST (blue, red and white) and Mobility Course in the sepofarsen group vs. sham (*post hoc analysis*)

Sepofarsen treated participants self-reported an improvement in vision on 2 separate Patient Reported Outcomes (PROs), the Patient Global Impression of change (PGI-C) and the Visual Function Questionnaire (VFQ-25) composite score. (Figure 3)



Single question PGI-C
- 14/23 (61%) patients on sepofarsen self reported an improvement in their vision
- 3/12 (25%) of patients in sham reported an improvement in vision

VFQ-25 composite score
- Vision subscales indicated a more pronounced benefit in sepofarsen

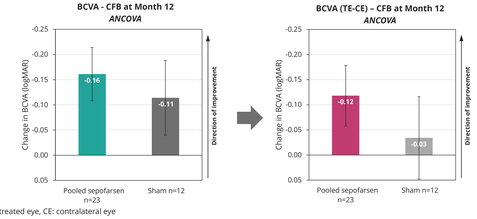
PGI-C and VFQ-25 were pre specified analyses

Figure 3. Summary of Patient Reported Outcomes (*post hoc analysis*)

Illuminate additional analysis

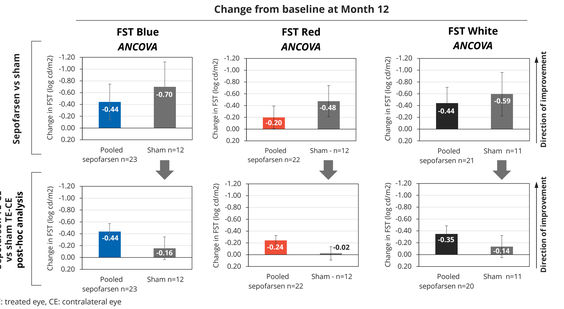
In this heterogenous, rare disease population, the inter-patient variability is greater than the intra-patient variability, therefore, sham comparator is likely not best control. The contralateral eye may be a better comparison, to reduce variability.

Similar to the Phase 1/2 study, further analyses were performed looking at treatment eye (TE) comparison to the untreated (contralateral, CE) eye (TE minus CE), rather than sham. Efficacy was observed with BCVA, but also FST, Mobility and PROs. (Figures 4 to 6)



TE: treated eye, CE: contralateral eye

Figure 4. Mean change from baseline and treated eye minus contralateral eye (TE-CE) in BCVA at Month 12 in pooled sepofarsen group vs. sham (*post hoc analysis*)



TE: treated eye, CE: contralateral eye

Figure 5. Change from baseline and benefit analysis (TE-CE) in blue, red and white FST in the pooled sepofarsen groups vs. sham group - Comparing sham and contralateral eye as control (*post hoc analysis*)

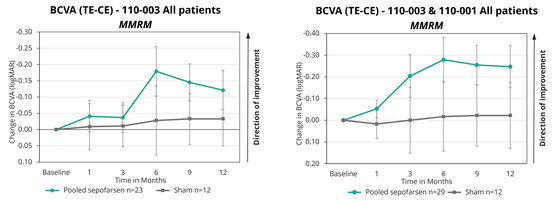


Figure 6. BCVA Benefit analysis (TE-CE) and meta-analysis combining Phase 1/2[6] and Phase 2/3 data (*post hoc analysis*)

Approximately a third of the participants benefited across multiple concordant endpoints in the *Illuminate* trial. Responses were also seen in Year 2 when the second eye/sham was treated.

One example is presented in Figure 7. The participant, a female heterozygous for the c.2991+1655A>G mutation in the *CEP290* gene showed improvements in BCVA, FST, mobility course as well as in PROs (VFQ-25 and PGI-C) after receiving sepofarsen.

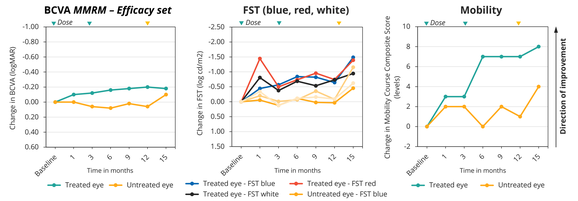


Figure 7. Patient response to sepofarsen in BCVA, FST and mobility course

Safety summary

Sepofarsen was observed to be generally well-tolerated. (Table 2) Reported ocular Treatment Emergent Adverse Events (TEAEs) (Table 3) were consistent with the findings observed in the Phase 1/2 trial.[6]

Three serious adverse events were reported in the sepofarsen groups, one acute angle closure glaucoma in the 80/40µg sepofarsen group (occurred post Month 12; 11 weeks after first dose in CE, and the participant had history of iridotomies); one case of transient epileptic seizure and one case of decrease in foveal thickness (>40 microns from baseline) both in the 160/80µg sepofarsen group. The acute angle closure glaucoma and decrease in foveal thickness have been subject of expedited SUSAR reports.

One serious adverse event was reported in the sham group (Alcohol Induced Mental Confusion).

	Sepofarsen 160/80 µg (n=12)	Sepofarsen 80/40 µg (n=12)	Sham (n=12)
Any Ocular TEAE, n (%)	12 (100.0%)	12 (100.0%)	9 (75.0%)
Mild	7 (58.3%)	10 (83.3%)	7 (58.3%)
Moderate	2 (16.7%)	2 (16.7%)	2 (16.7%)
Severe	2 (16.7%)	0 (0.0%)	0 (0.0%)
Any Ocular AESI	4 (33.3%)	2 (16.7%)	1 (8.3%)
Any Ocular Serious TEAE	1 (8.3%)	0 (0.0%)	0 (0.0%)
Any Ocular TEAE leading to study drug discontinuation	1 (8.3%)	0 (0.0%)	0 (0.0%)
Any Ocular TEAE leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)

Data are n of subjects (%)
AESI: adverse events of special interest; TEAE: treatment emergent adverse events

Table 2. Reported Ocular events – first treated eyes overall study data

	Sepofarsen 160/80 µg (n=12)	Sepofarsen 80/40 µg (n=12)	Sham (n=12)
Cataract Events (11 of 36 past medical history)			
Mild	2 (16.6%)	0 (0.0%)	1 (8.3%)
Moderate	0 (0.0%)	1 (8.3%)	***0 (0.0%)
Severe	1 (0.0%)	0 (0.0%)	0 (0.0%)
Cystoid Macular Edema (CME) Events (4 of 36 past medical history)			
Mild	0 (0.0%)	2 (16.7%)	0 (0.0%)
Moderate	0 (0.0%)	1 (8.3%)	1 (8.3%)
Severe	1 (8.3%)	0 (0.0%)	0 (0.0%)
Retinal Thinning Events (5 of 36 past medical history)			
Mild	**0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	*2 (16.6%)	0 (0.0%)	1 (8.3%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)

** 1 Retinal thinning considered a SUSAR* ***1 additional subject had retinal thinning post Data Lock Point*
**** 1 additional subject posterior capsule opacification at Month 12 in treated CE*

Table 3. Reported Ocular TEAEs

Conclusions

***Illuminate* did not meet its primary endpoint at Month 12**
- **The use of a Sham arm as control introduced variability which masked the treatment effect of sepofarsen**

However, when BCVA, the primary endpoint, in the treatment eye is compared with the contralateral eye, a positive sepofarsen treatment effect can be seen, as well as in secondary endpoints
- **Consistent with what was seen in the Phase 1/2 study**
- **Individual participants demonstrated an improvement from baseline in BCVA**
- **Responses also seen in Year 2 when 2nd eye/sham was treated**

Overall good safety profile – no inflammation
Positive benefit/risk

Next steps: Discussions with regulatory agencies and continue the 2-year study

Literature

1. den Hollander AI, et al. Prog Retin Eye Res. 2008;27(4):391–419; 2. Chacon-Camacho OF, Zenteno JC. World J Clin Cases. 2015;3(2):112–24; 3. Cideciyan AV et al. Invest Ophthalmol Vis Sci. 2019;60(5):1680-95; 4. den Hollander AI, et al. Am J Hum Genet. 2006;79(3):556–61; 5. Dulla K, et al. Mol Ther Nucleic Acids. 2018;12:730–40; 6. Russell SR, et al. Nat Med. 2022 Apr 4. Epub ahead of print.

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