RNA-based therapy in Leber congenital amaurosis type 10 (LCA10): key lessons learned from the randomized, double-masked, sham-controlled, Phase 3 study of sepofarsen

6395 – A0510

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Introduction

- *CEP290*-related inherited retinal disorder (*CEP290*-IRD) manifests mostly as Leber congenital amaurosis type 10 (*CEP290*-LCA10), an ultra-rare disease that causes severe visual impairment in early childhood[1]
- There are no approved treatments, only symptomatic management[1]
- The investigational RNA antisense oligonucleotide sepofarsen targets the frequent c.2991+1655A>G mutation in *CEP290*. It restores normal splicing of the pre-mRNA transcript to result in normal *CEP290* mRNA and increased production of functional CEP290 protein[2]
- The Phase 3 ILLUMINATE study (NCT03913143; **Figure 1**) was a double-masked, randomized, parallel-arm, sham-controlled, Phase 3 study which investigated the efficacy, tolerability, and safety of sepofarsen in 36 participants aged ≥8 years with *CEP290*-LCA10 with at least one allele with the c.2991+1655A>G mutation[3]
- ILLUMINATE did not meet its primary endpoint of change from baseline in best-corrected visual acuity (BCVA) at Month 12 versus sham-procedure (**Figure 2**)[4]
- Treatment effects were difficult to estimate due to large variability in participant responses

Figure 1. ILLUMINATE study design

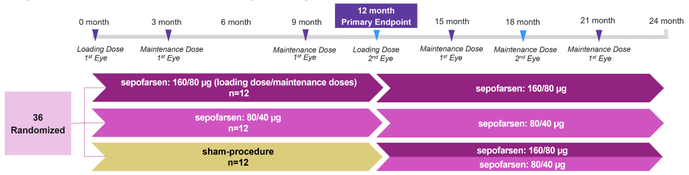
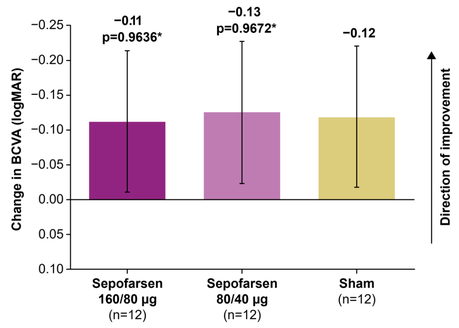


Figure 2. Change from baseline in BCVA at Month 12 versus sham-procedure in ILLUMINATE study (ANCOVA efficacy set)



ANCOVA, analysis of covariance; BCVA, best-corrected visual acuity

- Evidence of clinically meaningful improvements in visual function were observed in individual-level data (data on file)
- In the context of an ultra-rare disease with significant heterogeneity, inter-participant and inter-visit variability in treatment response, a post-hoc analysis of ILLUMINATE was conducted emulating a paired-eye design to estimate treatment effect

Methods

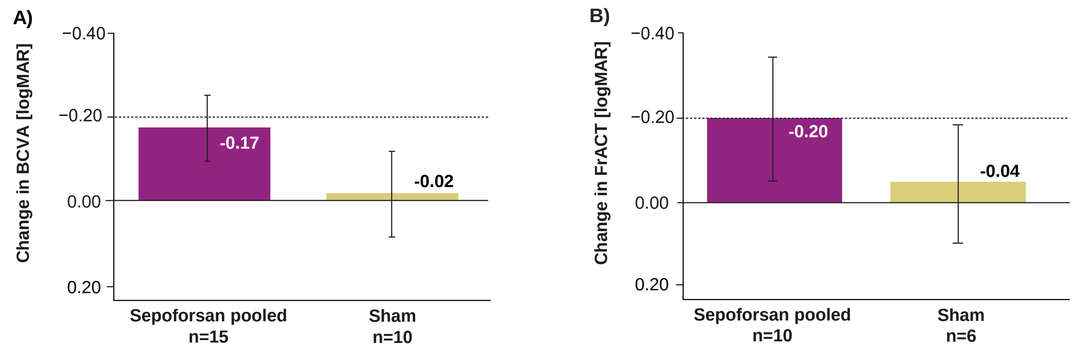
Post-hoc analysis

- This post-hoc analysis compared the paired treated eye (TE) with the untreated contralateral eye (CE) for each individual participant with symmetric disease receiving sepofarsen – referred to as the "paired-eye comparison"
  - The untreated CE served as a surrogate for a randomized placebo control eye
- The same analysis was performed in the sham arm to assess for expectation and selection bias
- For comparison, the original parallel design analysis is repeated on patients with symmetric disease (**Table 1**)
- Mean estimated difference (MED) of the logarithm of the minimum angle of resolution (logMAR) was assessed

Results

- In the paired-eye comparison, BCVA improvement from baseline was observed in the pooled sepofarsen arm at Month 12 but not in the sham arm, as measured by ETDRS/BVRT and FrACT assessments (**Figure 3**)

Figure 3. Estimated mean difference in a) BCVA (logMAR) using ETDRS/BRVT and b) BCVA (logMAR) using FrACT from baseline at Month 12 – paired-eye comparison*



*The primary analysis used an extension of a paired t-test to allow for the inclusion of baseline visual acuity (average BCVA of both eyes) and laterality of the eye as covariates.
BCVA, best-corrected visual acuity; BRVT, berkeley rudimentary vision test; ETDRS, early treatment diabetic retinopathy study; FrACT, freiburg visual acuity and contrast test; LogMAR, logarithm of the minimum angle of resolution.

- BCVA MED variability was reduced by 39%, reflecting an improvement, with the paired-eye comparison providing a more reliable estimate of treatment effect than the parallel design (**Table 1**)

Table 1. Variability by endpoint

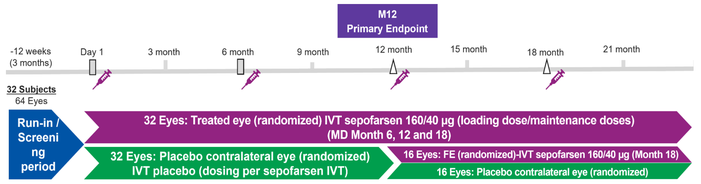
Endpoint	N (participants)		LS mean difference (95% CI)		Equivalent SD		Reduction [%]		
	Parallel Overall (Active, Sham)	Paired	Parallel	Paired	Parallel	Paired	N (subjects)	95% CI Width	Equivalent SD
BCVA [logMAR]	25 (15,10)	15	-0.07 (-0.32,0.18)	-0.17 (-0.33,-0.02)	0.61	0.28	40,0%	38,8%	54,4%
FST.R [log cd_m2]	23 (14, 9)	14	0.18 (-0.40,0.77)	-0.27 (-0.53,-0.01)	1.36	0.45	39,1%	55,9%	66,9%
LogCS [log10(InvPerc)]	17 (11, 6)	11	0.20 (-0.13,0.53)	0.15 (-0.04,0.35)	0.65	0.29	35,3%	41,2%	55,0%
MOBILITY [Score]	24 (14,10)	14	2.34 (0.47,4.21)	1.04 (-0.40,2.48)	4.44	2.50	41,7%	23,1%	43,7%

cd, candela; CI, confidence interval; invPerc, inverted Percent; Log, logarithm; LS, least square; MAR, logarithm of minimum angle of resolution; SD, standard deviation.

Conclusions

- These findings suggest that a paired-eye design:
  - Is effective in controlling for inter-participant and inter-visit variability in efficacy endpoint assessments
  - May be more appropriate in evaluating efficacy in an ultra-rare IRD, such as *CEP290*-LCA10, by providing more reliable estimates of treatment effects across multiple efficacy endpoints
- These learnings from ILLUMINATE have informed the design of HYPERION – an innovative, paired-eye, randomized, Phase 3 study of the efficacy and safety of sepofarsen (**Figure 4**)
  - To reduce inter-participant and inter-visit variability, HYPERION includes changes to the run-in period (additional training and familiarization) and endpoint selection (see poster 6393 - A0508)

Figure 4. HYPERION design – an innovative, paired-eye, Phase 3 study



IVT, intravitreal; LD, loading dose; M, month; MD, maintenance dose.

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Disclosures for first author

Bart P. Leroy has served as a consultant/contractor for Laboratoires THEA.

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