# 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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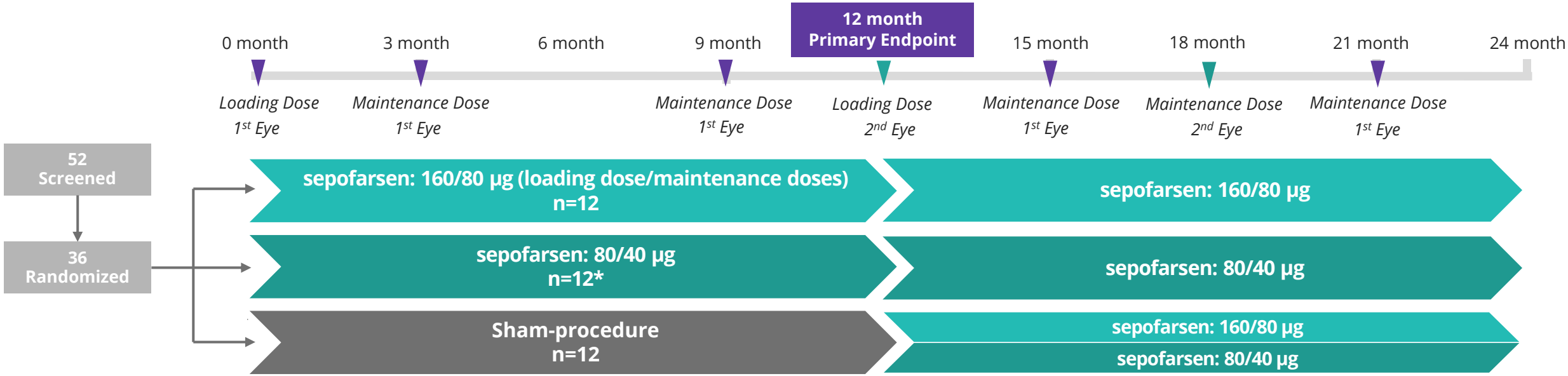
- **4DMT:** consultancy fees
- **AAVantgardeBio:** consultancy fees
- **Akouos:** consultancy fees
- **Asthena Therapeutics:** consultancy fees
- **Bayer:** consultancy fees
- **Biogen:** consultancy fees, trial support
- **GenSight Biologics:** consultancy fees, travel support, trial support
- **IVERIC Bio:** consultancy fees, travel support
- **Johnson & Johnson -Jansen:** consultancy fees, trial support
- **LookoutGTx:** unpaid consultancy
- **MeiraGTx:** trial support
- **Novartis:** consultancy fees, travel support, trial support
- **Opus Genetics:** consultancy fees
- **Oxurion:** consultancy fees
- **ProQR Therapeutics:** consultancy fees, travel support, trial support
- **Santen:** consultancy fees
- **Spark Therapeutics:** consultancy fees, travel support
- **REGENXBIO:** consultancy fees
- **Vedere Bio:** consultancy fees
- **ViGeneron:** consultancy fees

# Sepofarsen pivotal Phase 2/3 trial design

*All 36 participants at 14 sites in 9 countries at the 12M timepoint*




**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)

*One participant was subsequently found to be a Light Perception patient and has been excluded from the analyses

# Demographics and baseline characteristics

*Demographic and baseline characteristics were similar across groups*

| | 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) |

*Data are mean (SD) or n (%)*

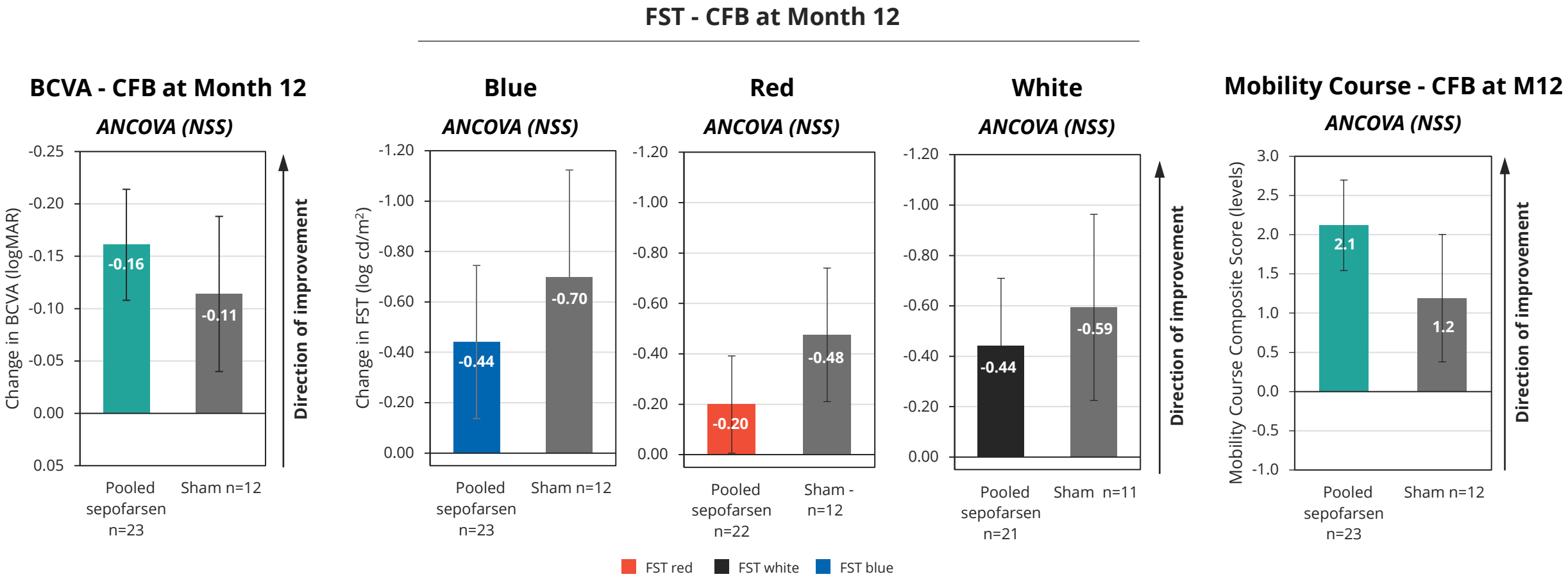
* 1st treated eye

# Efficacy summary

*12-month data*

# Key efficacy outcomes – Pooled sepofarsen group

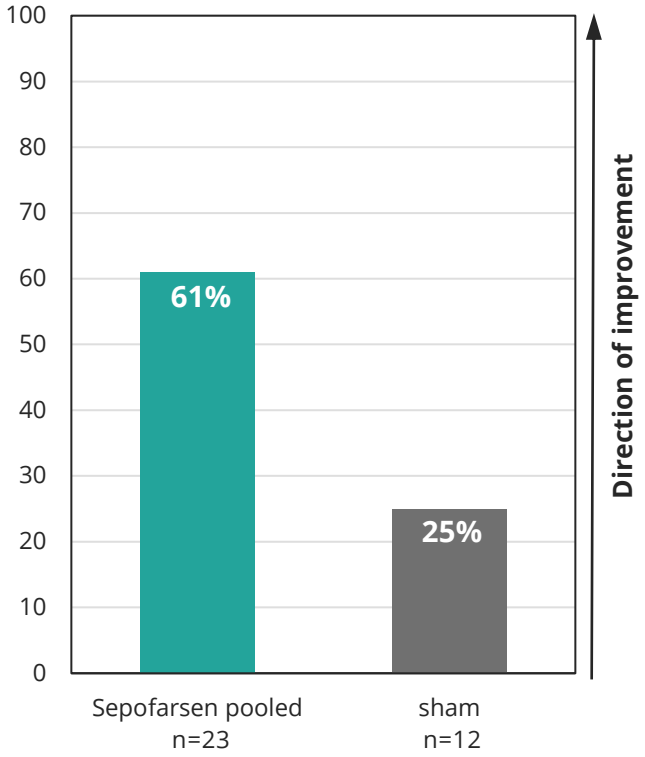
*No additional benefit seen in Sepofarsen vs Sham groups*



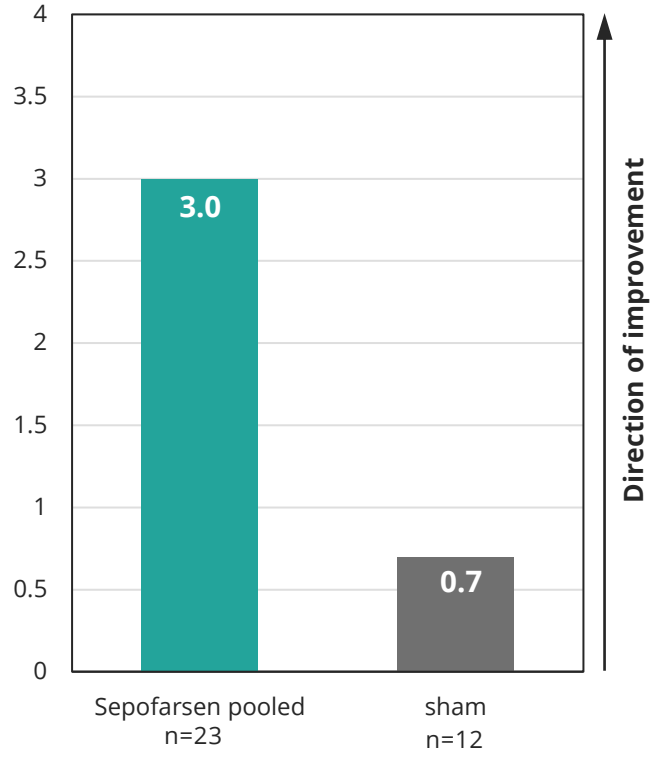

*BCVA, Best corrected visual acuity; CFB, Change from baseline; FST, full-field stimulus test; NSS, Not Statistically Significant*

# Sepofarsen treated patients self-report an improvement in vision on 2 separate PROs

**PGI-C - % of subjects self-reporting an improvement CFB at Month 12**




**VFQ-25 – composite score CFB at Month 12**




**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**

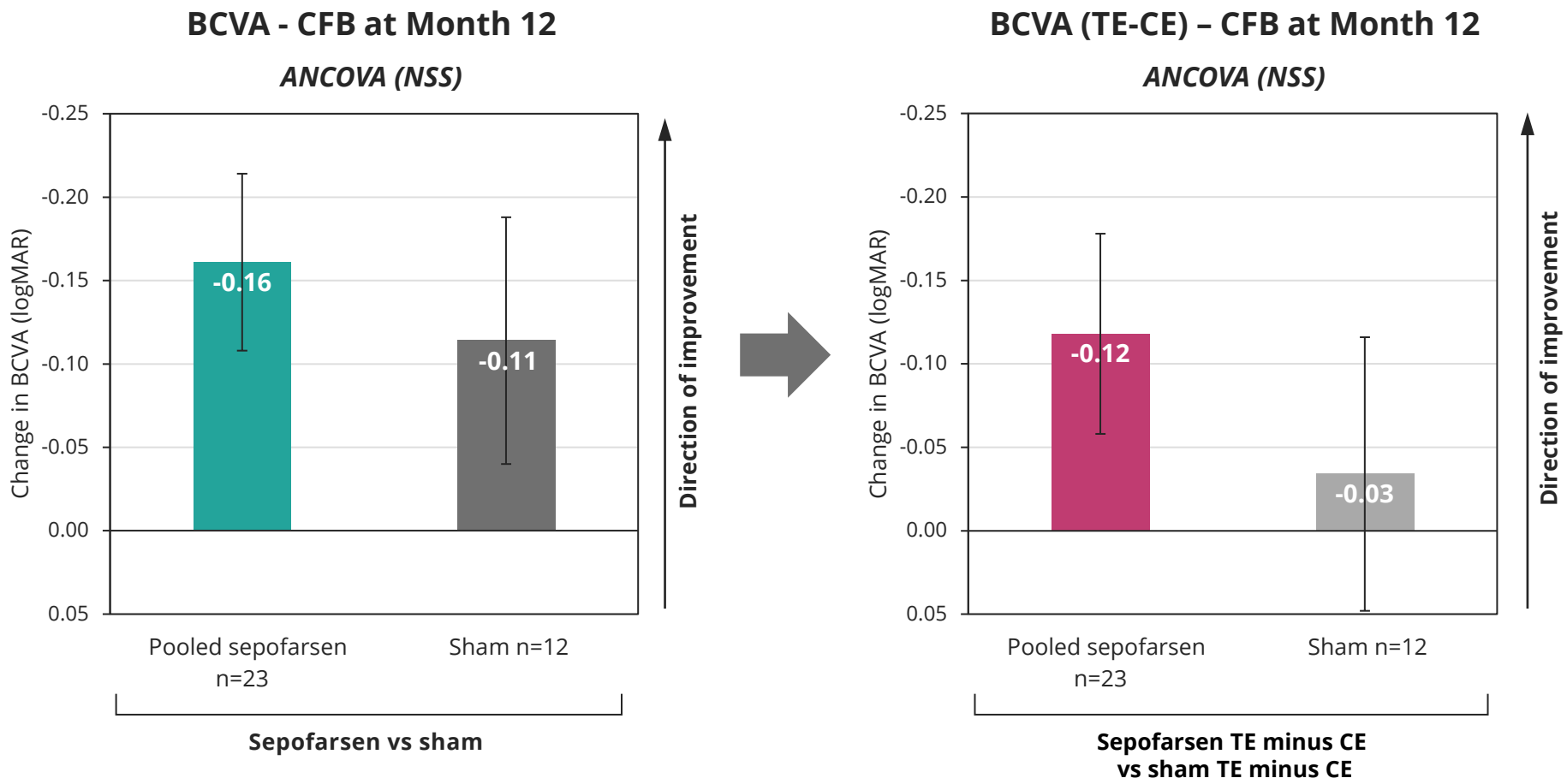
- Vision subscales indicated a more pronounced benefit in sepofarsen

PGI-C and VFQ-25 were pre specified analyses

*CFB, Change from baseline; PGI-C, Patient Global Impression of change; PRO, Patient Reported Outcomes; VFQ, Visual Function Questionnaire*

# BCVA at Month 12

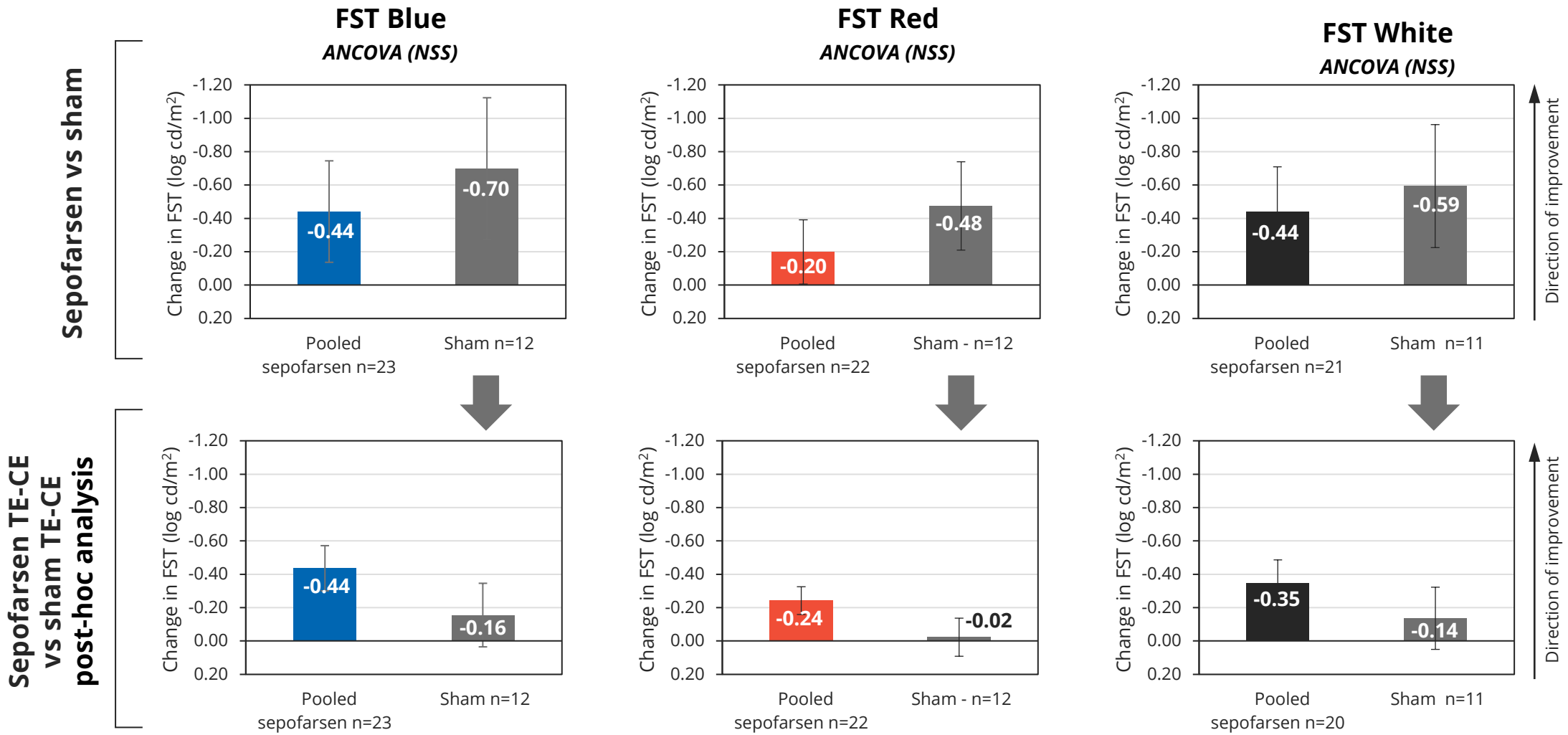
*Sepofarsen vs sham – additional analyses*




*BCVA, Best corrected visual acuity; CE, Contralateral eye; CFB, Change from baseline; NSS, Not Statistically Significant; TE, Treated eye*

# FST - Comparing sham and contralateral eye as control

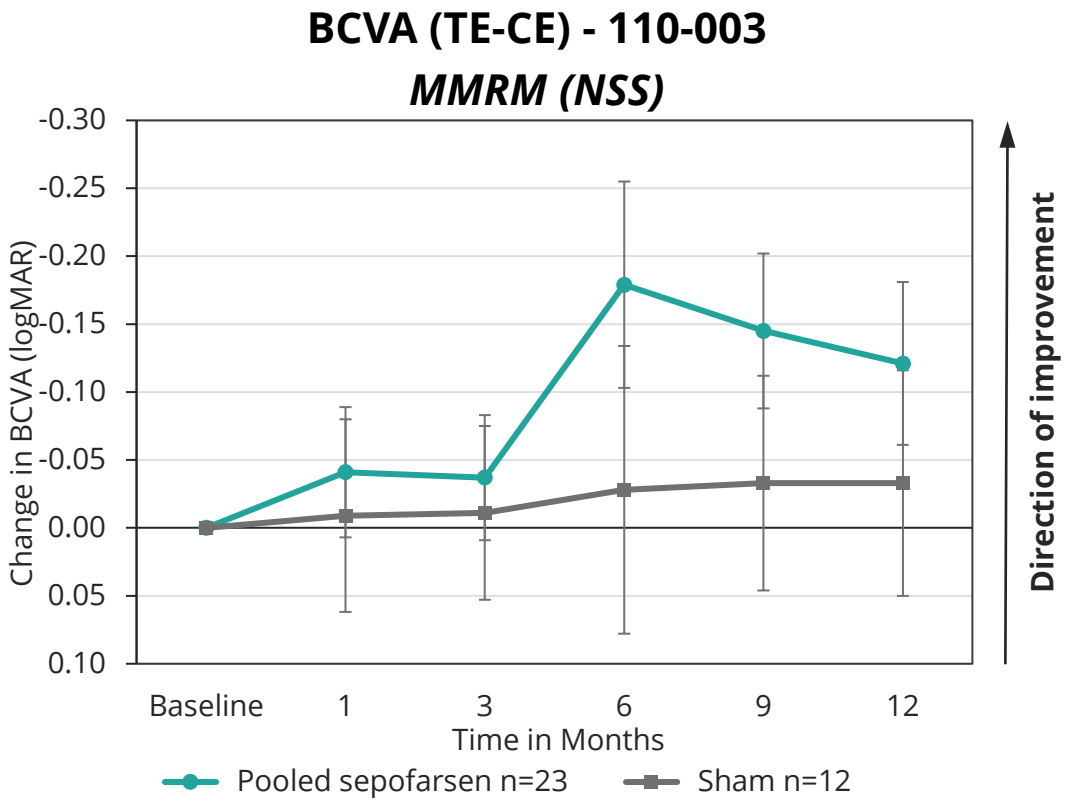
**Change from baseline at Month 12**

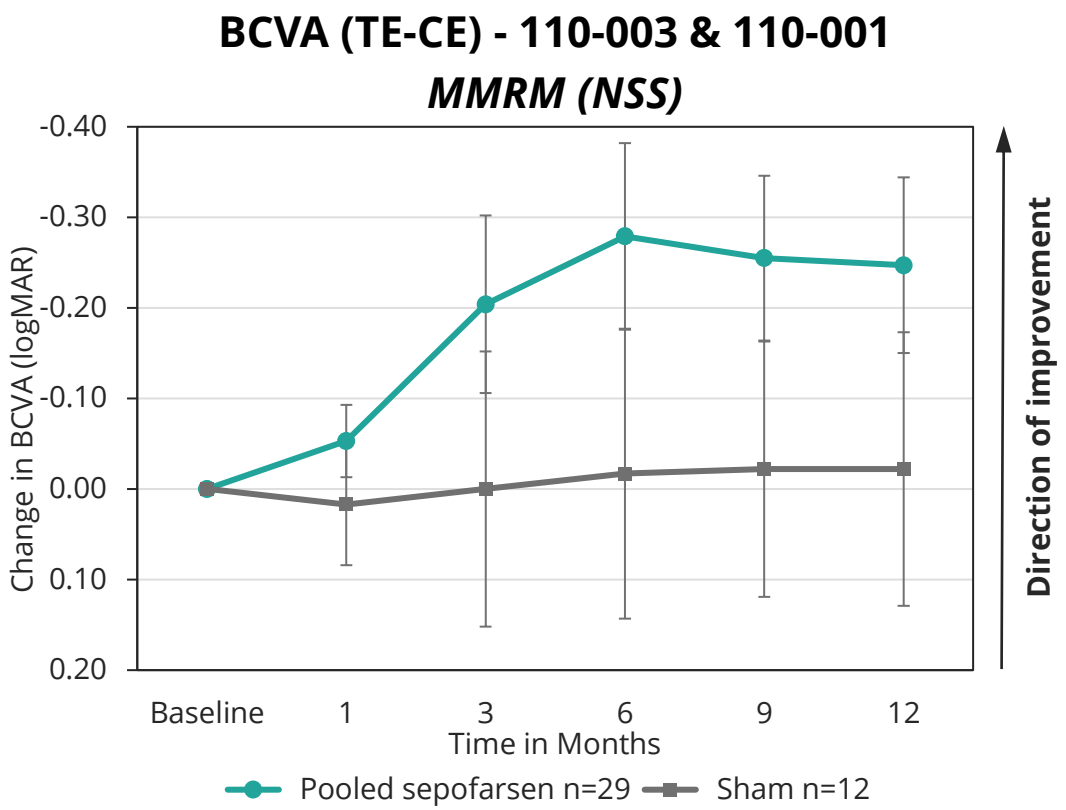



*CE, Contralateral eye; CFB, Change from baseline; FST, full-field stimulus test; NSS, Not Statistically Significant; TE, Treated eye*

# Change in BCVA TE minus CE

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




1. Russell SR, et al. Nat Med. 2022 Apr 4. Epub ahead of print

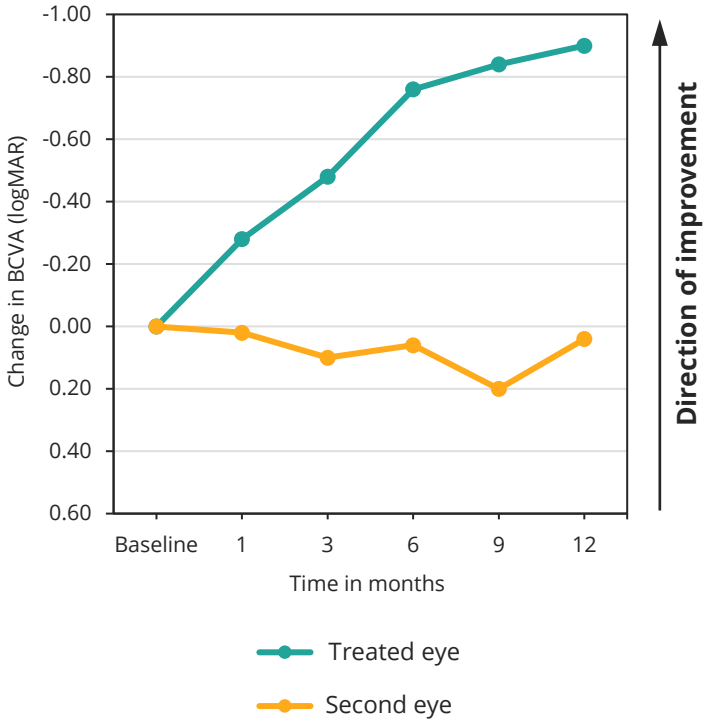
*BCVA, Best corrected visual acuity; CE, Contralateral eye; CFB, Change from baseline; MMRM: Mixed Model Repeated Measures; NSS, Not Statistically Significant; TE, Treated eye*

# Individual patient examples

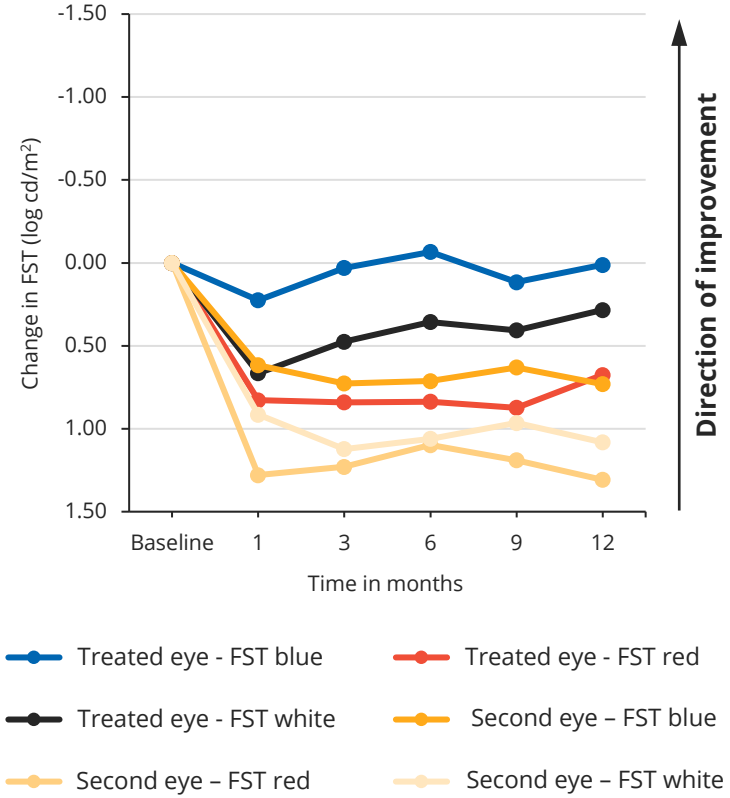
# Patient 1 – group sepofarsen

*Female, heterozygous – first eye treated*

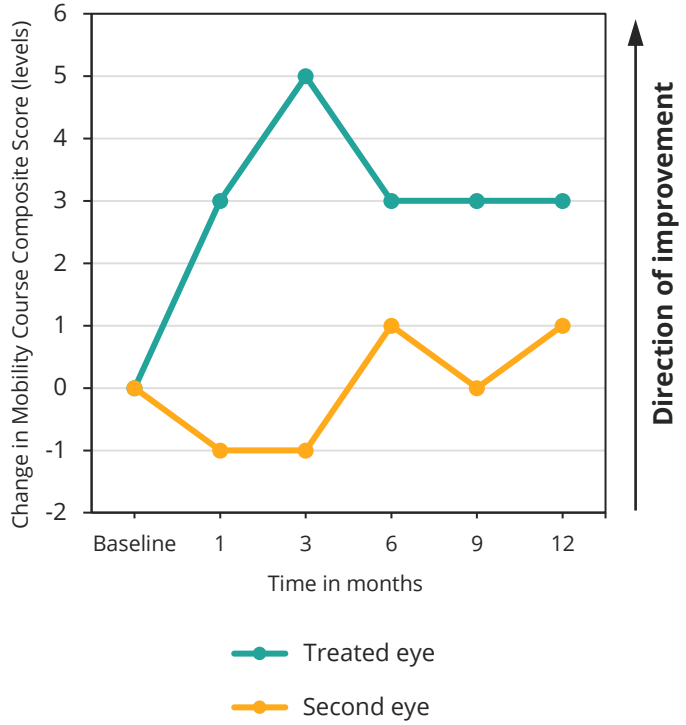
**BCVA**




**FST (blue, red, white)**



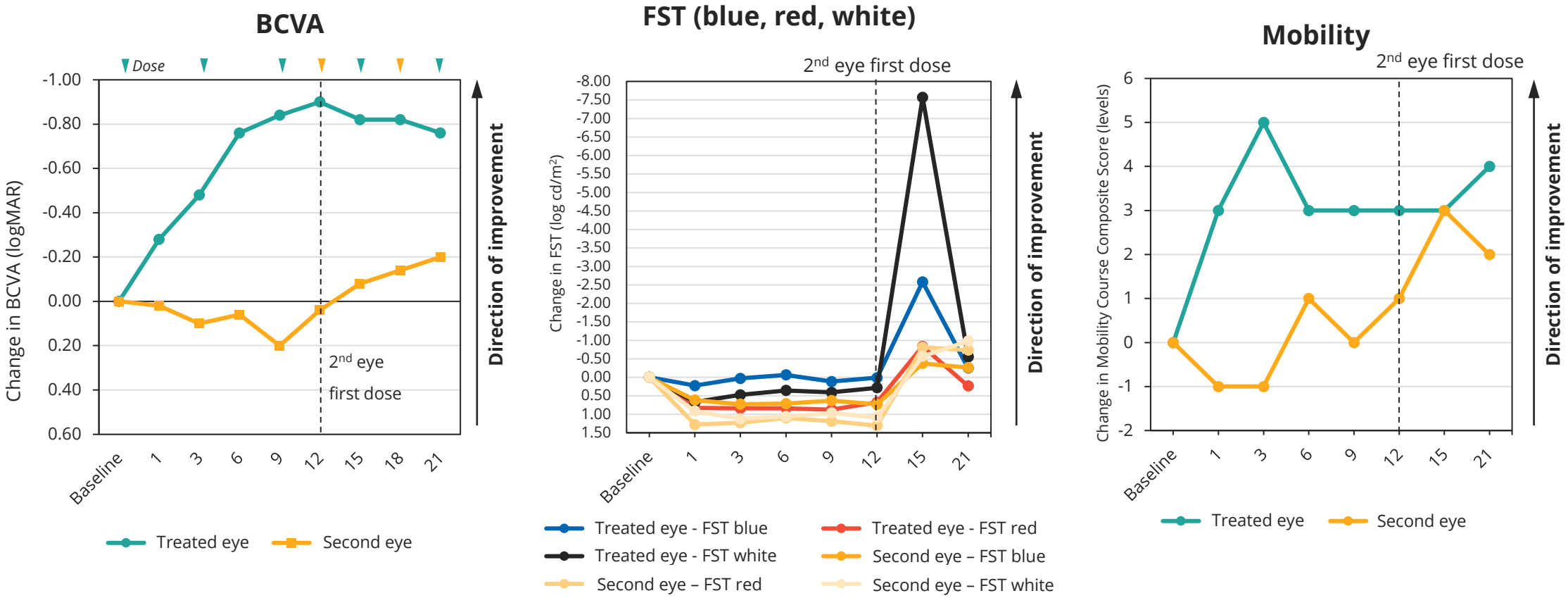

**Mobility**




- At Month 12, Patient 1 improved on BCVA and Mobility
- In addition, the patient also improved in VFQ-25, PGI-Change and contrast sensitivity

# Patient 1 – group sepofarsen

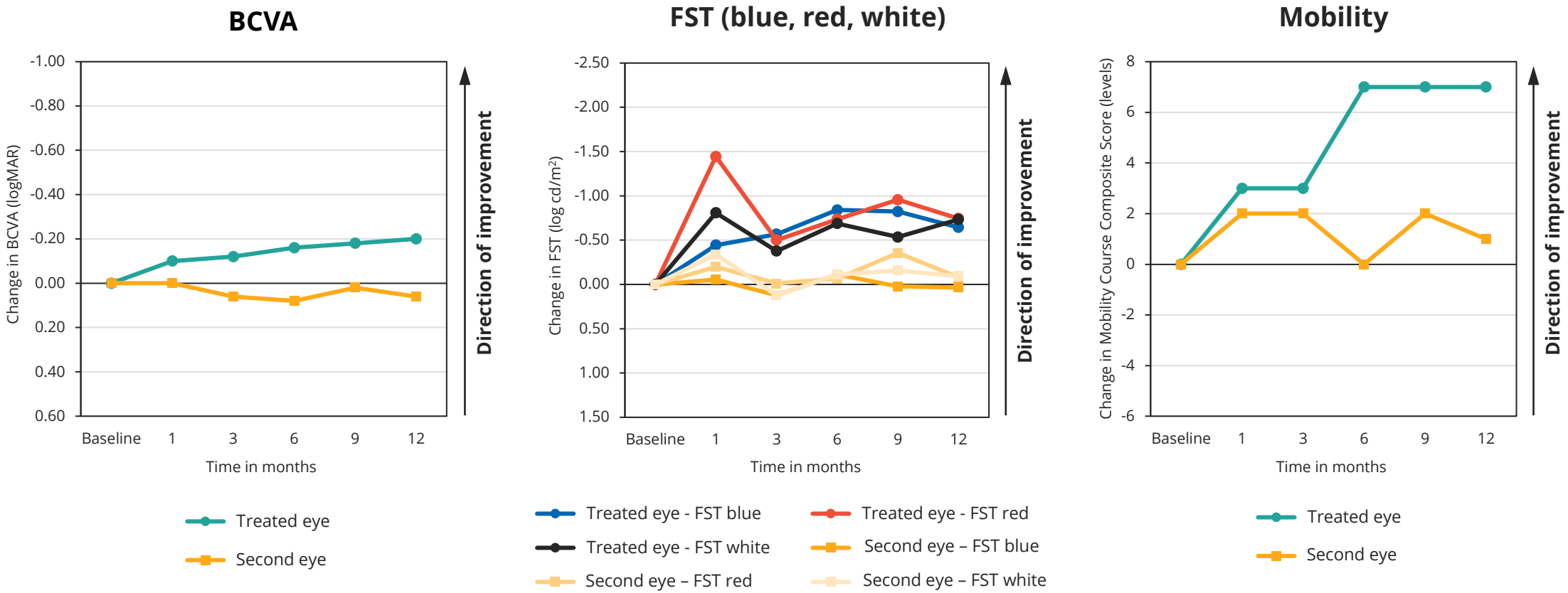
*Female, heterozygous – second eye treated*




- At year 2, once the 2nd eye was treated, Patient 1 showed a greater than a -0.2 logMAR improvement. Improvement was also reported in FST and Mobility

# Patient 2 – group sepofarsen

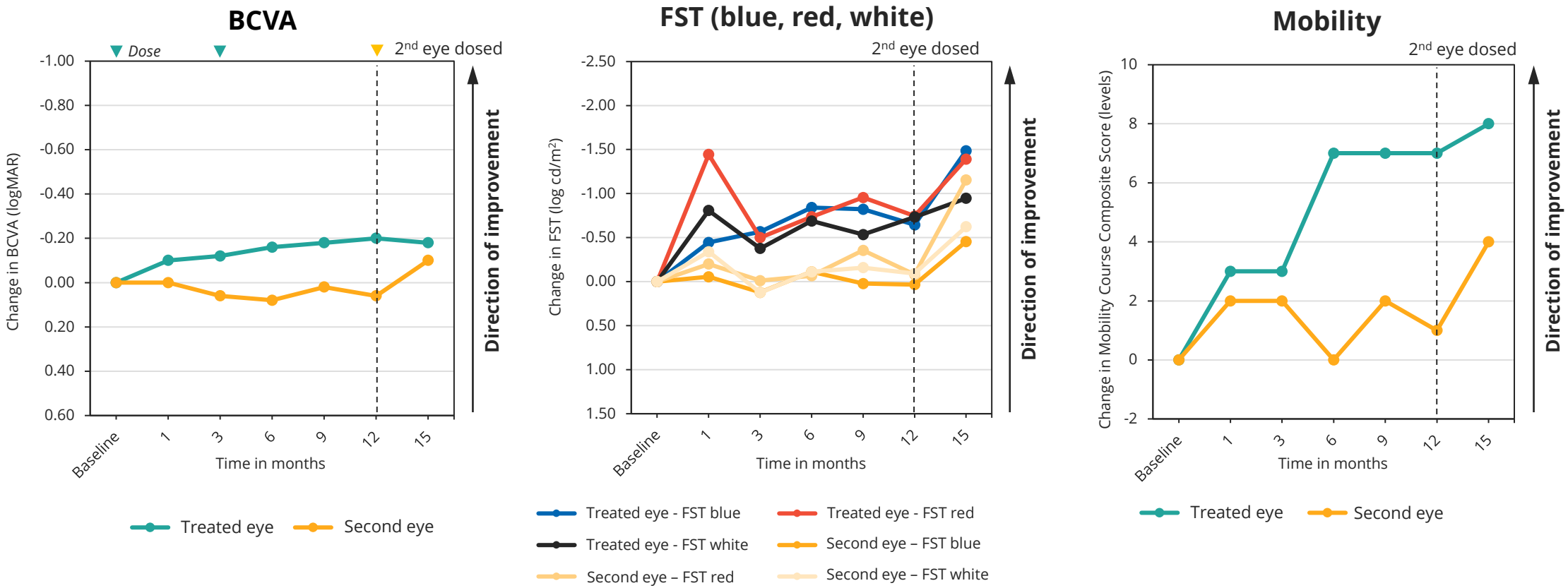
*Female, heterozygous – first eye treated*




- At Month 12, Patient 2 improved on BCVA, FST and Mobility

# Patient 2 – group sepofarsen

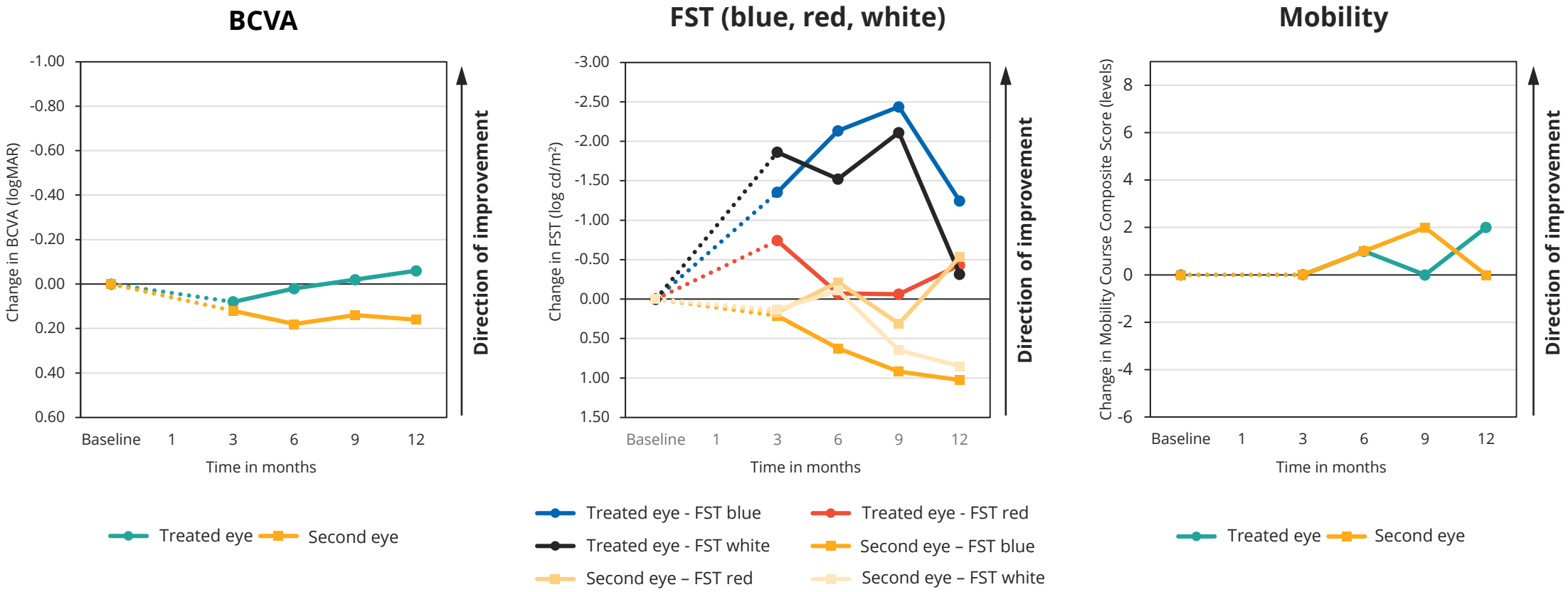
*Female, heterozygous – second eye treated*




- Patient maintained effect in first eye to 15M. When second eye was treated, that eye was improving on BCVA (after being stable for 12M before that eye was treated).

# Patient 3 – group sham

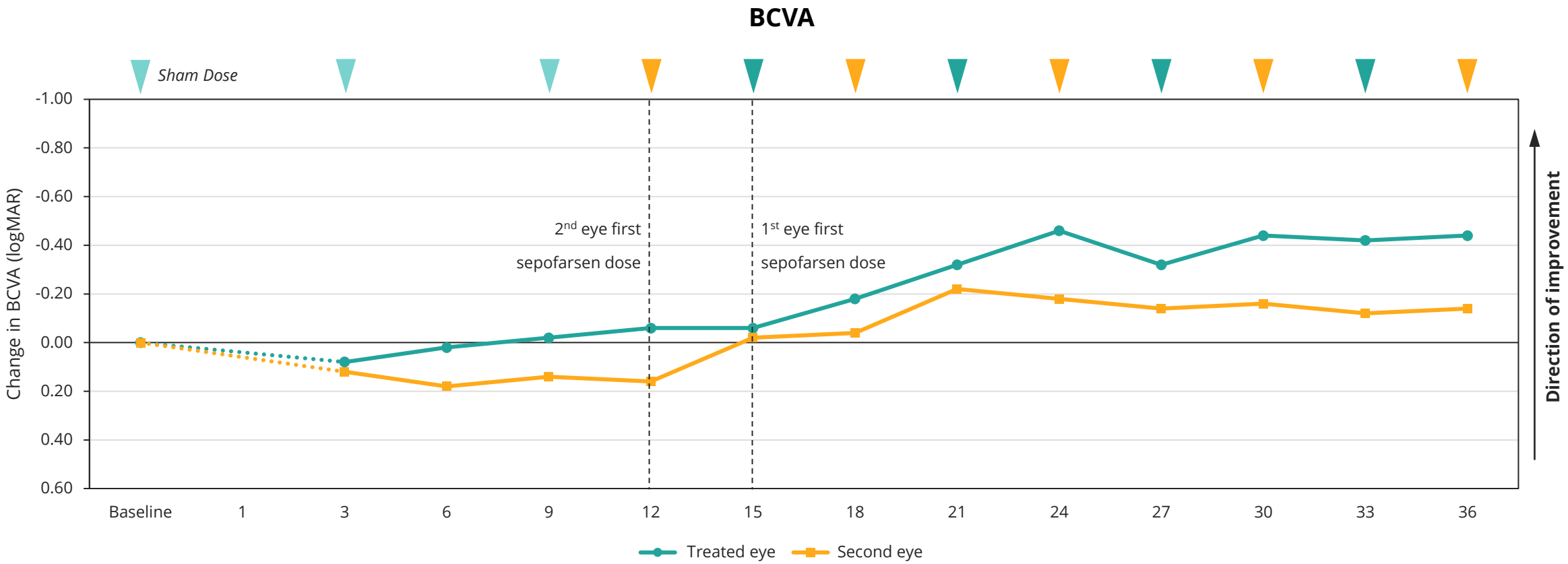
*Male, heterozygous*




- At Month 12, the patient showed no changes in BCVA, high variability with blue and white FST from M3 to M12 and a change of 2 levels in mobility which looks variable from M9 to M12

# Patient 3 – cross-over sham to sepofarsen

*Male, heterozygous*




- Patient was on sham for first 12 months and was relatively stable. When 1st eye treated at M12, patient had an improvement of ~ 0.4 logMAR.
- Following the 2nd eye treatment, a similar response of ~0.4 logMAR was seen.

# Safety summary

*Overall study data*

# Serious adverse events

| | Sepofarsen 160/80 µg (n=12) | Sepofarsen 80/40 µg (n=12) | Sham (n=12) |
|---|---|---|---|
| Acute Angle Closure Glaucoma*¶/ Acute angle closure glaucoma | 0 ( 0.0%) | 1 ( 8.3%) | 0 ( 0.0%) |
| Alcohol Induced Mental Confusion/ Acute alcohol intoxication | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 8.3%) |
| Transient Epileptic Seizure/ Epileptic seizure | 1 ( 8.3%) | 0 ( 0.0%) | 0 ( 0.0%) |
| Decrease in foveal thickness (>40 microns from baseline)*/ Retinal thinning | 1 ( 8.3%) | 0 ( 0.0%) | 0 ( 0.0%) |

* Expedited SUSAR report.

¶ Occurred post Month 12; 11 weeks after first dose in CE, had history of iridotomies.

*CE, Contralateral eye; SUSAR; Suspected unexpected serious adverse reaction*

# Safety overview

## Ocular events
First treated eyes overall study data

| | 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*

## Ocular TEAEs
Key ocular events - treated eyes by worst severity

| | 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*

# Overall summary

- 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