Freiburg Vision Test (FrACT) for assessing visual acuity in Leber congenital amaurosis type 10 (LCA10) patients

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Introduction

Drug development remains a challenge for rare diseases due to low participant numbers and high inter-participant variability

Sepofarsen is an investigational RNA therapy for *CEP290*-associated LCA10, due to the c.2991+1655A>G mutation[3]

The Early Treatment Diabetic Retinopathy Study (ETDRS) charts are limited in patients with very low vision[4]

CEP290-associated Leber Congenital Amaurosis 10 is an ultra-rare genetic disease[1,2]

We compare BCVA measured by FrACT compared to ETDRS/BRVT using data from a Phase 3 trial (ILLUMINATE)

The Freiburg Vision Test (FrACT) is an alternative assessment of BCVA with good reproducibility in individuals with low vision (Table 1)[5,6]

Table 1: The FrACT – key advantages, characteristics, and clinical trial use

Key advantages[7,8]	Characteristics[7]	Clinical trials with FrACT outcome measure[7]*
• Freely available as an open-source computer program • Self-paced • Assesses visual acuity, contrast sensitivity, and Vernier acuity • Recommended by the Harmonization of Outcomes and Vision Endpoints in Vision Restoration Trials Taskforce • Used in laboratories and trials worldwide • Independently validated	• Includes a range of test symbols and optotypes • Thresholds are assessed with a progression of symbols, using a Bayesian approach • Results can be displayed as LogMAR, Snellen fraction, or decimal acuity • Parameters are customizable	• More than 20 registered clinical trials have used, or are using, FrACT as an endpoint • FrACT has been used as an endpoint across a broad age range of patients, including elderly and pediatric populations

*Examples only, this list is not exhaustive

LogMAR, logarithm of the minimum angle of resolution

Methods

Study design and participants

- ILLUMINATE (NCT03913143) was a double-masked, randomized, sham-controlled, Phase 3 trial (**Figure 1**)[9]

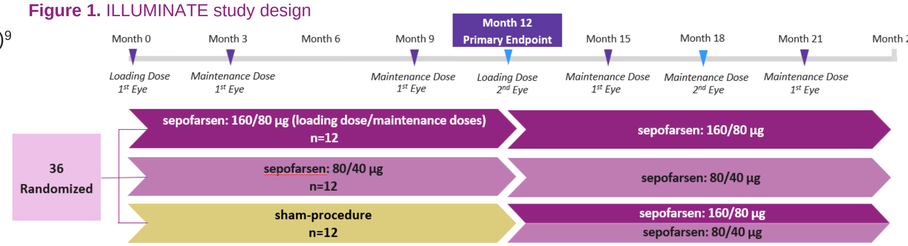
Primary endpoint

- Change from baseline in BCVA [logMAR] at month 12
- Assessed using
  - ETDRS extended by BRVT
  - FrACT

Post-hoc analysis

- 12-month data from the pooled sepofarsen treatment groups were used to assess the alignment of the FrACT and ETDRS/BRVT by:
  A. Comparing the effect sizes in an emulated paired-eye design
  B. Comparing repeatability of FrACT with ETDRS/BRVT utilizing a Bland-Altman analysis

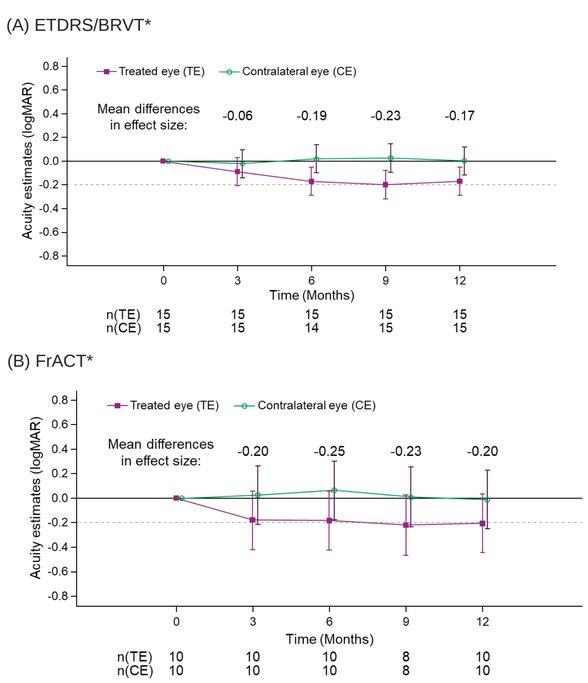
Figure 1. ILLUMINATE study design



Results

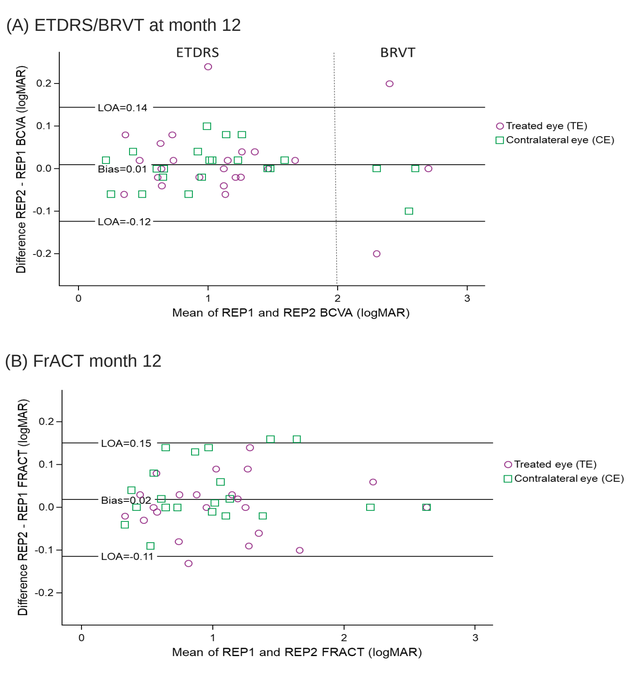
- In the emulated paired-eye design analysis, comparable estimated treatment effect sizes were seen with ETDRS/BRVT and FrACT (**Figure 2**)
- Repeatability of BCVA with ETDRS/BRVT and FrACT at month 12 was 0.13 logMAR for both methods
- Bland-Altman plots showed lower variability with FrACT for participants with very low vision (n=24; **Figure 3**)
- The maximum difference in repeated measurements from ETDRS/BRVT was 0.2 logMAR compared to 0.06 logMAR with FrACT

Figure 2. Estimated means for pooled sepofarsen groups in paired-eye design missing at random (MAR) for ETDRS/BRVT and FrACT



Error bars are 95% CI. *The dashed line indicates a clinically meaningful difference in BCVA.
BCVA, best-corrected visual acuity; BRVT, Berkeley Rudimentary Vision Test; CE, contralateral eye; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; FrACT, Freiburg Vision Test; logMAR, logarithm of the minimum angle of resolution; MAR, missing at random; N, number of eyes; TE, treatment eye.

Figure 3. Bland-Altman plot for ETDRS/BRVT and FrACT at month 12



BCVA, best-corrected visual acuity; BRVT, Berkeley Rudimentary Vision Test; CE, contralateral eye; ETDRS, Early Treatment Diabetic Retinopathy Study; FrACT, Freiburg Vision Test; LOA, limit of agreement; logMAR, logarithm of the minimum angle of resolution; REP, repeated measurement; TE, treatment eye.

Conclusions

- This post-hoc analysis from ILLUMINATE shows consistency between BCVA outcomes when measured by ETDRS/BRVT and FrACT
- Bias was negligible (≤1 letter)
- Variability was lower with FrACT testing compared to ETDRS/BRVT for participants with very low vision
  - FrACT therefore may offer a more suitable BCVA assessment method for participants with low vision
  - A possible explanation is the continuous ETDRS scale used by FrACT, in contrast to BRVT[10]
- These results inform endpoint selection for the Phase 3 HYPERION trial

Acknowledgments

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Disclosures for first author

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