Twelve-month Natural History Study of *CEP290*-associated Retinal Degeneration

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OBJECTIVE

To define the clinical characteristics of *CEP290*-associated IRD caused by the c.2991+1655A>G IVS26 mutation and to determine which assessments may provide reliable endpoints in future interventional trials.

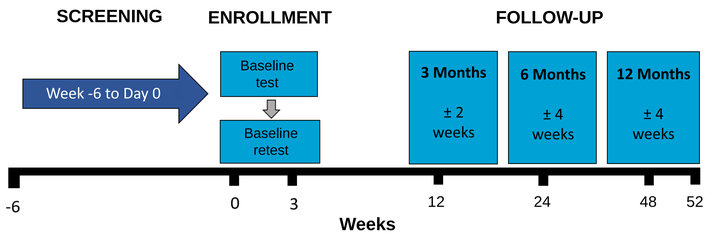
PURPOSE

- Inherited retinal degenerations (IRDs) are a leading cause of blindness, affecting approximately 1 in 2000 people worldwide.[1]
- Centrosomal protein 290 (CEP290) is a 290 kDa protein that localizes to the transition zone between photoreceptor inner and outer segments and plays a key role in photoreceptor function.[2]
- Biallelic mutations to the *CEP290* gene cause *CEP290*-associated IRD,[3] a severe IRD characterized by early photoreceptor death and blindness within the first decade of life.[4]
- There is no available treatment for *CEP290*-associated IRD.
- This 12-month prospective study (NCT03396042) aimed to define the clinical characteristics of *CEP290*-associated IRD and to determine which assessments may provide reliable endpoints in future interventional trials.

METHODS

- Patients with *CEP290*-associated IRD and best-corrected visual acuity (BCVA) from light perception to 0.4 logMAR were recruited in eight cohorts that spanned four age ranges (3–5, 6–11, 12–17, ≥ 18 years) and two BCVA ranges (light perception to > 1.0 logMAR, 1.0 logMAR to 0.4 logMAR).
- Functional outcomes included BCVA, full-field stimulus threshold (FST) sensitivity, and Visual Navigation Challenge (Ora–VNC™) composite score.
- Optical coherence tomography–outer nuclear layer (OCT–ONL) thickness was included as an anatomical outcome.
- BCVA, FST sensitivity, VNC composite score, and OCT–ONL thickness were assessed at screening, baseline test, baseline retest, and months 3, 6 and 12 **(Figure 1)**.

Figure 1. Natural History Study Design



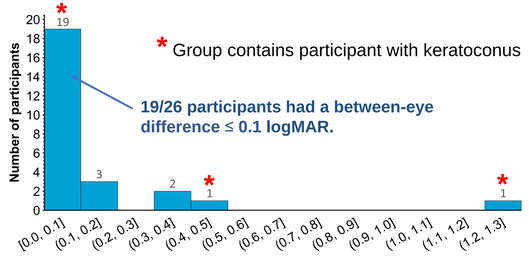
Six-week screening period followed by 2 baseline visits (test-retest) and 3 follow-up visits at 3, 6, and 12 months.

RESULTS

Baseline Characteristics of Participants

- Nineteen of 26 enrolled participants were female.
- At screening, 13/16 adult and 9/10 pediatric participants had BCVA > 1.0 logMAR. At baseline, median (range) BCVA was 2.0 (0.5–3.9) logMAR.
- BCVA was not correlated with age or zygosity.
- BCVA mean (SD) between-eye difference was 0.13 (0.27) logMAR, with ~ 73% of participants having a between-eye difference ≤ 0.1 logMAR **(Figure 2).**
- There were no between-eye differences in FST, VNC score, or OCT-ONL thickness.

Figure 2. Between-eye Differences in BCVA



BCVA, Best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution

Test-retest Variability and Stability at 12 Months

- **Table 1** presents assessment test-retest variability and stability. A greater than expected test-retest variability was observed for OCT–ONL average thickness.

Table 1. Assessment Variability and Stability at 12 Months

Assessment (Worse eye)	N	Mean (95% CI) change from baseline test to retest
BCVA (logMAR)	25	-0.04 (-0.09, 0.01)
VNC composite score	18	0.6 (-0.1, 1.3)
Red FST (log cd/m^2)	14	0.10 (-0.07, 0.27)
OCT–ONL avg thickness (µm)	14	5 (0, 10)
OCT–ONL central thickness (µm)	14	2 (-4, 9)
Assessment (Worse eye)	**N**	**Mean (95% CI) change from baseline to 12 months**
BCVA (logMAR)	23	0.06 (-0.17, 0.29)
VNC composite score	17	0.4 (-0.5,1.2)
Red FST (log cd/m^2)	16	-0.15 (-0.43, 0.14)
OCT–ONL avg thickness (µm)	13	-2 (-10, 6)
OCT–ONL central thickness (µm)	13	-8 (-17, 2)

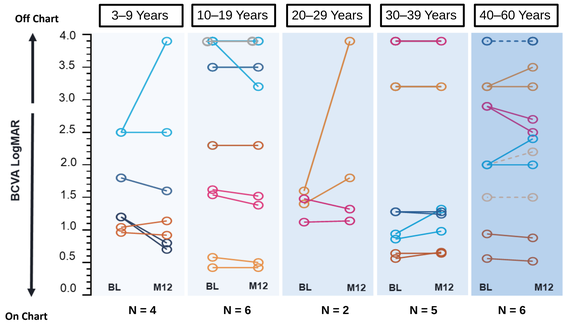
BCVA, Best-corrected visual acuity; BL, Baseline; FST, Full-field stimulus threshold; LogMAR, logarithm of the minimum angle of resolution; OCT, Optical coherence tomography; ONL, Outer nuclear layer.

- BCVA, FST, VNC score, and OCT–ONL thickness did not significantly change from baseline to 12 months.

BCVA Is Stable over 12 Months

- Across age groups, mean (95% CI) change in BCVA from baseline to 12 months was 0.06 (-0.17–0.29) logMAR, indicating good stability **(Figure 3)**.

Figure 3. Change in BCVA from Baseline to 12 Months



Each pair of lines bounded by circles of the same color represents the worse and better eyes at baseline and 12 months in a single participant. Unpaired lines are superimposed and represent participants with a similar change in both eyes from baseline to 12 months. Dashed lines represent participants with keratoconus. BL, Baseline; M12, Month 12.

- A large BCVA decline from baseline to 12 months was noticed for two participants, one of whom was observed to have had intra-retinal cysts across the study visits.

CONCLUSION

- BCVA, FST, and VNC composite score demonstrated good test-retest variability and stability over 12 months.
- BCVA, FST, and VNC composite score are viable endpoints for future clinical studies in patients with *CEP290*-associated IRD.
- Repeatability of OCT measures poses potential challenges for quantifying anatomical changes in this population as nystagmus impacted ability to repeat measures at the same retinal location.
- The mostly stable nature of retinal degeneration and the similarity in disease trajectory between eyes opens the possibility of using the contralateral eye as a within-subject control in future interventional trials in patients with *CEP290*-associated IRD.

REFERENCES

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DISCLOSURES

At the time of abstract submission, BSA, MD, KK, AR, and RM were employees of Editas Medicine. MP is a paid consultant for Editas Medicine.

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