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Preliminary Results from Adult Participants in a Phase 1b/2a Clinical Study of OPGx-BEST1 Gene Therapy for ARB and BVMD due to *BEST1* Mutations

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Purpose

- Best disease is a rare inherited retinal degeneration (IRD) caused by *BEST1* mutations[1]
- Mutations, depending on the impact on *BEST1* function, may lead to serous retinal detachment, vitelliform lesions, macular atrophy, and loss of central vision[1]
- *BEST1* is characterized by retinal lesions, with symptoms including dimness of vision, metamorphopsia, or scotoma[2]
- Autosomal recessive bestrophinopathy (ARB) and Best vitelliform macular dystrophy (BVMD), two main *BEST1* phenotypes, differ in severity, but share similar retinal pigment epithelium (RPE) pathophysiology.[1]
- *BEST1*-related retinopathy represents one of the largest IRD patient populations globally, with approximately 22,050 patients affected.[3]
- OPGx-BEST1 gene therapy leverages an adeno-associated virus 2 (AAV2) capsid to deliver a functional copy of the *BEST1* gene. It contains an RPE-specific promoter.
- OPGx-BEST1 is administered as a one-time subretinal injection and aims to augment the mutated gene and restore normal function of RPE cells.
- An ongoing Phase 1b/2a clinical study is evaluating the safety and tolerability of subretinal injection of OPGx-BEST1 in adult patients with BVMD or ARB.
- Baseline demographics of five enrolled participants from Cohort 1 and three-month data from the sentinel participant in Cohort 1 are presented.

Methods

- Adaptive, open-label, dose-exploration basket study (NCT07185256) to investigate a single unilateral subretinal (SR) injection of OPGx-BEST1 gene therapy in adult participants (≥18 years old).
- Up to two vector doses are being evaluated in a minimum of 5 participants at each dose: 1.5E9 vg/eye (Cohort 1) and 4.5E9 vg/eye (Cohort 2).
- Primary endpoints include dose-limiting toxicities (DLTs), and procedure- and treatment-related adverse events (AEs).
- Secondary endpoints include change from baseline in retinal morphology (spectral domain optical coherence tomography [SD-OCT]), neovascularization (optical coherence tomography angiography), retinal sensitivity (microperimetry), best-corrected visual acuity (best-corrected visual acuity [BCVA]) letter score (Early Treatment of Diabetic Retinopathy Study [ETDRS]; logarithm of the Minimum Angle of Resolution [logMAR]), low luminance visual acuity (ETDRS), and participant-reported outcomes.
- Safety and efficacy will be evaluated over 5 years.

Results

Table 1. Cohort 1 Baseline Demographics (n=5)

Participant #	101-101	101-104	102-101	102-102	101-106
Age	63	59	50	45	31
Sex	Female	Female	Male	Male	Male
BEST phenotype	ARB	ARB	BVMD	BVMD	BVMD
Study eye	OS	OD	OS	OS	OS
Baseline VA (study eye)	1.68	0.7	0.72	0.49	0.77
Baseline VA (fellow eye)	0.84	0.41	0.34	0.27	0.58

Table 2. Preliminary Safety Summary for Sentinel Participant 101-101

Day 14	• Few pigmented cells in vitreous • No anterior chamber inflammation • Steroid taper initiated
Month 1	• No ocular inflammation • No ocular AEs • No treatment-related AEs or DLTs
Month 3	• No ocular inflammation • No ocular AEs • Steroid taper complete

Figure 1. BCVA in Treated Eye Improved Over 3 Months in the Sentinel Participant 101-101

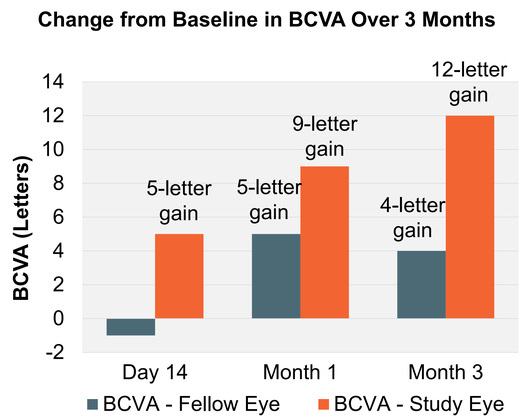


Figure 2. Central Subfield Thickness (CST) in Treated Eye Improved Over 3 Months in the Sentinel Participant 101-101

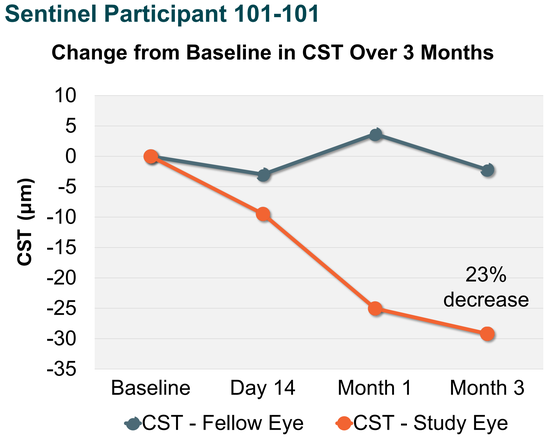
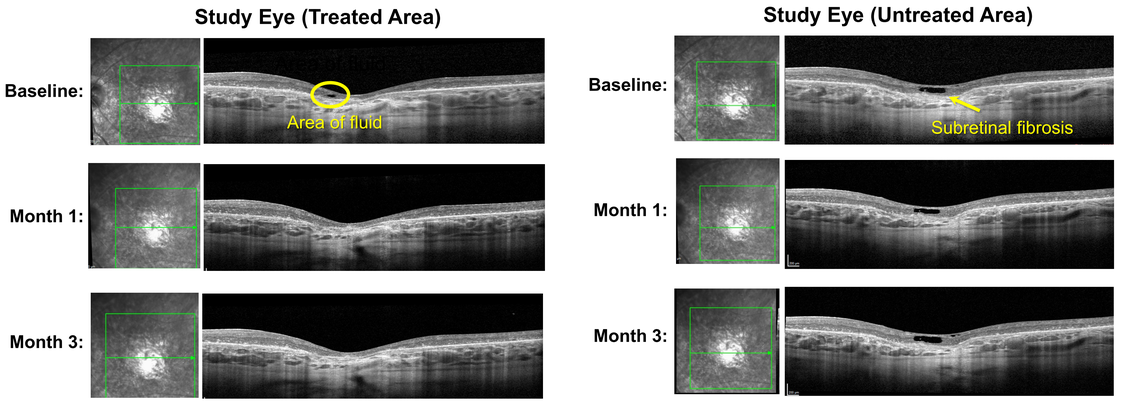


Figure 3. Improvements at 3 Months on SD-OCT in the Sentinel Participant 101-101 with Underlying RPE



Reduction of intraretinal fluid as early as 1 month in areas with less atrophy

In areas of absent RPE and severe atrophy outside the bleb, there was no change over time

Conclusions

- OPGx-BEST1 is a targeted gene augmentation approach designed to restore RPE function and address the underlying cause of *BEST1*-related IRD.
- 3-month results in the sentinel participant show OPGx-BEST1 is well-tolerated with no ocular inflammation, no ocular or treatment-related AEs, and no DLTs.
- Early signal of functional improvement (12 letter gain) observed in the study eye; Participant commented that their vision was no longer "darkening".
- Structural improvement (23% decrease) observed in the study eye.

Early Phase 1/2 study results are encouraging with excellent safety data and early signals showing promise for patients with viable RPE

References: 1. Johnson AA, et al. *Prog Retin Eye Res.* 2017;58:45-69. **2.** Tripathy K, et al. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. **3.** Data on file. Opus Genetics, Inc.

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