Exploratory Immuno-Safety Profile of EDIT-101, a First-in-Human In Vivo CRISPR Gene Editing Therapy for CEP290-Related Retinal Degeneration

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16 May 2022
Disclosures

Brian R. Duke, Saleh El-Husayni, Michael C Jaskolka, Amanda Erlwein, Rene Myers, Mark S. Shearman, Kate Zhang, and Swati Mukherjee are all employees of Editas Medicine
**CEP290-related retinal degeneration: A leading cause of early onset vision loss**

*Currently no approved treatments for CEP290-related retinal degeneration*

- Leber Congenital Amaurosis Type 10 (LCA10) is a rare, autosomal recessive inherited disorder that causes progressive vision loss in children within the first decade of life\(^1,2\)

- Disease is characterized by early loss of rod photoreceptors with cones being structurally intact and viable until the 4\(^{th}\) decade of life

- LCA10 is most commonly caused by the *CEP290-IVS26* mutation, accounting for 15–20% of all cases\(^1\)

- This mutation results in a truncated, non-functional CEP290 protein due to early translational termination

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CEP290: centrosomal protein 290; CEP290-IVS26: c.2991+1655A>G mutation with intron 26; LCA10, Leber Congenital Amaurosis.

EDIT-101 is designed to specifically edit *CEP290* within photoreceptors

AAV5 with DNA encoding two gRNAs and SaCas9 delivered subretinally as a single dose

- **Photoreceptor-tropic** AAV5 vector
- **Highly specific** Guide RNAs
- **Restricted** SaCas9 expression in photoreceptor cells via human G-coupled Receptor Kinase 1 (hGRK1)
- **Local delivery to key subretinal space** targeting the structurally retained cones in the fovea, for functional restoration

**EDIT-101**

AAV5-CRISPR-Cas9 gene editing

Images courtesy of Mark Pennesi, MD
Oregon Health & Science University Casey Eye Institute, Portland, OR

EDIT-101 is designed to specifically edit CEP290 within photoreceptors

AAV5 with DNA encoding two gRNAs and SaCas9 delivered subretinally as a single dose

AAV5: adeno-associated virus type 5; SaCas9: Staphylococcus aureus CRISPR associated protein 9; hGRK1: human G-coupled Receptor Kinase 1.
BRILLIANCE Trial

Phase 1/2, open-label, single ascending dose study for EDIT-101 (NCT03872479)

1. Adult Low Dose (6 x 10^{11} vg/ml) N = 2
2. Adult Mid Dose (1.1 x 10^{12} vg/ml) N ≥ 4
3. Adult High Dose (3.0 x 10^{12} vg/ml) N ≥ 4
4. Pediatric Mid Dose (1.1 x 10^{12} vg/ml) N ≥ 4
5. Pediatric High Dose (3.0 x 10^{12} vg/ml) N ≥ 4

Screening Baseline → 12 Months Following Single Sub-Retinal Treatment in Worse Eye → 2 Year Extension with Option for 12 Years of Follow-up

Primary Objective: Safety
Secondary Objectives: Tolerability & Efficacy
Defining Target Dose (MTD)
Immunogenicity
Viral Shedding

All subjects were placed on a low dose prophylactic oral prednisone regimen for 3 days prior to surgery until approx. 6 weeks following surgery.

Independent Data Monitoring Committee Review
AAV gene therapy based clinical trials require monitoring adaptive immunity
Cell mediated and humoral immune responses are being monitored in the BRILLIANCE trial

A. Cell Mediated Responses

- Subject PBMCs are collected and IFNγ ELISpot is performed
- Cells are stimulated with peptide pools derived from AAV5 capsid protein and SaCas9

B. Humoral Responses

- AAV5 and SaCas9 binding antibodies (BAB) are measured in subject serum using electrochemiluminescence ELISA
- AAV5 neutralizing antibodies (nAb) in subject plasma are measured using a cell-based infectivity assay

AAV5: adeno-associated virus type 5; BAB: binding antibody; CD: cluster of differentiation; DC: dendritic cell; MHC: major histo compatibility complex; nAb: neutralizing antibody; PBMCs: peripheral blood mononuclear cells; SaCas9: Staphylococcus aureus CRISPR associated protein 9; TCR: T-cell receptor.
Profile of subjects with pre-existing immune response to AAV5 and SaCas9

- Pre-existing humoral immunogenicity to AAV5 was seen at screening in 3 of 11 subjects dosed. Only 1 subject’s pre-existing antibodies were neutralizing.
- No pre-existing humoral immunogenicity to SaCas9 was observed.
- 6 of 11 subjects exhibited cell mediated responses to AAV5 at screening.
- 2 subjects had pre-existing cell mediated responses to both AAV5 and SaCas9.
- Pre-existing antibody responses have no clear correlation with cell mediated responses.

AAV5: adeno-associated virus type 5; BAB: binding antibody; SaCas9: Staphylococcus aureus CRISPR associated protein 9.
SaCas9 and AAV5 humoral response: Binding Antibodies

- No subjected treated with EDIT-101 developed BABs against SaCas9
- 9 of 11 subjects produce detectible levels of AAV5 BAB post dosing
- The observed titer of AAV5 BAB is independent of EDIT-101 dose level

BAB: binding antibody; HD: high dose patient; LD: low dose patient; MD: mid dose patient.
Most antibody responses to AAV5 are neutralizing

- AAV5 BAB titer positively correlates with levels of AAV5 neutralizing antibodies
- Not all antibody responses are equally neutralizing
- nAb titers are not correlated with EDIT-101 dose level and remain stable out to month 6 post-dosing

No subject developed post-treatment cell mediated responses to EDIT-101

Cell mediated responses to AAV5 capsid and SaCas9 were assessed via IFNγ ELISpot. A positive response to any peptide pool at ≥2 timepoints post-treatment was considered positive for the corresponding protein.

• Only subjects with pre-existing SaCas9 and AAV5 cell mediated responses respond post dosing
• EDIT-101 treatment does not induce new cell mediated immune responses to AAV5 and SaCas9

<table>
<thead>
<tr>
<th>Subject</th>
<th>Latest Timepoint</th>
<th>AAV5 Pre-Existing/Post-Treatment</th>
<th>SaCas9 Pre-Existing/Post-Treatment</th>
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<td>LD1</td>
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Conclusions

Our data and patient profile indicate EDIT-101 has a favorable immunogenicity profile

Some subjects across all cohorts exhibit pre-existing immunity to AAV5 and/or SaCas9

No subject developed post-treatment cellular or humoral immunogenicity to SaCas9

EDIT-101 treatment resulted in AAV5 BAB and nAB responses in 9 of 11 subjects; antibody titers did not correlate with EDIT-101 dose level

No subject developed new post-treatment cell mediated responses to EDIT-101

AAV5: adeno-associated virus type 5; BAB: binding antibody; nAb: neutralizing antibody; SaCas9: Staphylococcus aureus CRISPR associated protein 9;
Acknowledgements

We would like to acknowledge and thank all patients in the BRILLIANCE clinical trial and their families!

Additional thanks to clinical and translational operations, data management, our external PIs, the clinical sites, our partner CROs, and the Foundation Fighting Blindness
Questions?