Ongoing Progress in the Phase 1/2 BRILLIANCE Clinical Trial for Treatment of CEP-290 Retinal Degeneration

*In vivo* CRISPR gene editing therapies for ocular disease

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Editas Medicine, Chief Scientific Officer
Disclosure

The speaker is an employee and stockholder of Editas Medicine.
Presentation Outline

• Editas Medicine proprietary gene editing technology

• EDIT-101 for treating CEP290 mutation-associated LCA-10

• EDIT-103 for treating rhodopsin mutation-associated autosomal dominant Retinitis Pigmentosa

• EDIT-102 for treating Usherin mutation-associated Usher Syndrome Type 2A
Highly Differentiated Gene Editing and Delivery Technology

Advanced Bioinformatics and Analytics
Mastery in design based on proprietary sequencing tools

Proprietary CRISPR Enzymes and RNA Chemistry
Efficient high precision editing

Multiple Delivery Solutions
AAV, RNP, LNP delivered in vivo, ex vivo, and via engineered cells

Multiplex Gene Editing
In vivo and fully characterized engineered cell knock-ins

iPSC Platform
Off-the-shelf cell therapies

AAV: Adeno-associated virus; iPSC: Induced pluripotent stem cell; LNP: Lipid nanoparticle; RNP: Ribonucleoprotein
# Expansive Pipeline of Gene Editing Medicines for Ocular Diseases

<table>
<thead>
<tr>
<th></th>
<th>EDIT-101: Leber Congenital Amaurosis type 10 (LCA-10)</th>
<th>EDIT-103: Rhodopsin-associated autosomal dominant retinitis pigmentosa (RHO-adRP)</th>
<th>EDIT-102: Usher Syndrome (USH2A)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gene</strong></td>
<td>CEP-290</td>
<td>Rhodopsin</td>
<td>Usherin</td>
</tr>
<tr>
<td><strong>Mutation</strong></td>
<td>c.2991+1655A&gt;G mutation in intron 26</td>
<td>All RHO mutations</td>
<td>Exon 13 mutations</td>
</tr>
<tr>
<td><strong>Target Cells</strong></td>
<td>Photoreceptors</td>
<td>Photoreceptors</td>
<td>Photoreceptors</td>
</tr>
<tr>
<td><strong>Approach</strong></td>
<td>Remove intron region containing mutation</td>
<td>Knockout mutated RHO gene and replace with normal copy</td>
<td>Remove exon 13 containing mutations</td>
</tr>
</tbody>
</table>

There are currently no approved treatments for these diseases

adRP: Autosomal dominant retinitis pigmentosa; CEP-290: Centrosomal protein 290; RHO: Rhodopsin; USH2A: Usher syndrome
CEP290-Related Retinal Degeneration: A Rare Cause of Early Onset Loss of Vision

No Currently Approved Treatments for CEP290-related retinal degeneration

- CEP290-related retinal degeneration causes progressive vision loss/blindness in children within the first decade of life\textsuperscript{1,2}
- Autosomal recessive disease characterized by early loss of photoreceptors
- Focal cone rich area of the retina near the fovea remains intact until adulthood, which provides the opportunity for gene correction

Top: Cross-sectional OCT scan along the horizontal meridian through the fovea in normal subject. Bottom: CEP290-LCA patient. ONL is highlighted in purple

CEP290-Related Rod Photoreceptor Loss with Increasing Retinal Eccentricity

CEP290: Centrosomal protein 290; OCT: Optical coherence tomography; ONL: Outer nuclear layer
CEP290-Related Degeneration: Symptom Burden and Patient Impact

**DISEASE SYMPTOMS**
- Blindness usually diagnosed in infancy or early childhood
- Severely impaired visual acuity
- Loss of peripheral vision
- Night blindness
- Rapid, involuntary eye movements (nystagmus)

**PATIENT IMPACT**
- Inability to adequately navigate enclosed spaces
- Risk of falls and injury
- Inability to be mobile or independently use public transportation
- Constrained social function
- Impaired academic performance
- Challenges with employment

**PATIENT RETINA & VISION**

NORMAL

CEP290

Image source: Kubota Pharmaceutical Holdings
The IVS26 Mutation in CEP290 Is a Clearly Defined Target for Gene Editing

- **DNA**: Exon 26
- **mRNA**: Exon 26
- **Protein**: p.Cys998X prematurely truncated and non-functional CEP290

- **2991+1655A>G mutation in CEP290 corrected**
- **Full-length, functional CEP290**
- **Protein trafficking**
EDIT-101 Allows for Local Delivery of the Editing Complex to Specifically Target the Photoreceptors to Be Corrected

EDIT-101
CRISPR-Cas9 gene editing

AAV5 encoding two gRNAs and SaCas9 delivered subretinally as a single administration

EDIT-101 specifically targets the part of the retina containing viable photoreceptors

- Photoreceptor-tropic AAV5 vector
- Highly specific Guide RNAs
- Restricted Cas9 expression in photoreceptor cells
- Local delivery to subretinal space limits the risk of biodistribution outside of the eye

AAV5: Adeno-associated virus type 5; Cas: CRISPR-associated protein; gRNA: guide ribonucleic acid

Natural History Study (NHS) Assessments Were Executed to Inform the Design of the Phase 1/2 BRILLIANCE Trial

- This study aimed to describe the natural history of an otherwise ill-defined study population and to inform on potential endpoints, trial design, and registrational strategy

Eligibility Criteria
- Patients (n = 40) ≥ 3 years of age with CEP290-related retinal degeneration caused by a compound heterozygous or homozygous IVS26 mutation
- Visual acuity (VA) up to 20/50 in each eye

Stratification
- Recruited five patients in each of eight cohorts
  - Four age ranges
  - Two VA ranges

Follow-Up Timepoints
- 3 Month ± 2 weeks
- 6 Month ± 4 weeks
- 12 Month Or Early Termination ± 4 weeks

Screening: Week -6 to Day 0
Enrollment:
- Baseline BL 1
- Baseline BL 2

Study Duration: 52 Weeks (1 Year)
Natural History Study Identified Feasible, Reliable, and Stable Endpoints for Clinical Studies Including VA and FST Scores

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Endpoints</th>
<th>Category</th>
<th>Feasible</th>
<th>Reliable</th>
<th>Stable over 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optical coherence tomography (OCT)</td>
<td>Thickness of the ONL and integrity of the ellipsoid zone</td>
<td>Anatomical</td>
<td>✔️</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Pupillometry</td>
<td>Pupil size, pupil constriction</td>
<td>Physiological</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Oculomotor control and instability (OCI)</td>
<td>Gaze tracking</td>
<td>Physiological</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>BCVA</td>
<td>LogMAR measurement of best-corrected visual acuity</td>
<td>Functional</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Full field light sensitivity threshold (FST)</td>
<td>Dark adapted visual sensitivity to white, red, and blue light</td>
<td>Functional</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Contrast sensitivity+</td>
<td>LogMAR measurement of contrast sensitivity</td>
<td>Functional</td>
<td>✔️</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Microperimetry+</td>
<td>Macular sensitivity</td>
<td>Functional</td>
<td></td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Kinetic perimetry</td>
<td>Visual field</td>
<td>Functional</td>
<td></td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Color vision+</td>
<td>Farnsworth 15 score</td>
<td>Functional</td>
<td>✔️</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Quality of Life (QoL)</td>
<td>QoL questionnaire (CVFQ; NEI VFQ-25) Global Impressions of Change</td>
<td>Patient Reported</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td></td>
<td>Global Impressions of Severity</td>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BCVA: Best-corrected visual acuity; CVFQ: Children’s visual function questionnaire; FST: Full-field light sensitivity threshold; NEI VFQ: National Eye Institute visual function questionnaire-25; NHS: Natural history study; OCI: Oculomotor control and instability; OCT: Optical coherence tomography; ONL: Outer nuclear layer; Ora-VNC: Ora Visual Navigation Challenge
## BRILLIANCE Phase I/II Dose Escalation Trial

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Patients</th>
<th>Dose</th>
<th>Status/Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adult, n = 2</td>
<td>LOW (6.0 x 10^{11} vg/ml)</td>
<td>Dosing complete  &lt;br&gt; No dose-limiting toxicity (DLTs)  &lt;br&gt; No serious adverse events (SAEs)</td>
</tr>
<tr>
<td>2</td>
<td>Adult, n = 4</td>
<td>MID (1.1 x 10^{12} vg/ml)</td>
<td>Dosing complete  &lt;br&gt; No DLTs  &lt;br&gt; No SAEs</td>
</tr>
<tr>
<td>3</td>
<td>Adult, n = 4</td>
<td>HIGH (3.0 x 10^{12} vg/ml)</td>
<td>Dosing complete  &lt;br&gt; No DLTs  &lt;br&gt; No SAEs</td>
</tr>
<tr>
<td>4*</td>
<td>Pediatric, n = 4</td>
<td>MID (1.1 x 10^{12} vg/ml)</td>
<td>First patient dosed</td>
</tr>
<tr>
<td>5</td>
<td>Pediatric, n = 4</td>
<td>HIGH (3.0 x 10^{12} vg/ml)</td>
<td>Awaiting IDMC endorsement</td>
</tr>
</tbody>
</table>

### Primary outcomes: Safety
- Adverse events (AEs) / DLTs

### Secondary outcomes: efficacy
1. Maximum tolerated dose
2. Visual navigation (△ mobility course score)
3. BCVA (△ Logarithm of the minimum angle of resolution)
4. Change in macula thickness
5. Pupillometry and microperimetry
6. Light and contrast sensitivity
7. Change in color vision score
8. Quality of life

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*Next independent data monitoring committee (IDMC) safety review. BCVA: Best corrected visual acuity; DLT: Dose-limiting toxicity; SAE: Serious adverse effects*

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Single dose administered at Month 0, with 3 follow ups until Month 12
Primary Outcomes: Safety and DLTs

- No DLTs or SAEs observed to date in first two cohorts
- To date, no observed treatment-related cataracts, edema, or retinal thinning
- Most frequently reported AE was eye pain related to surgical procedure
- Only mild cases of treatment-related inflammation reported
  - No subject has developed post-treatment cellular or humoral immunogenicity to SaCas9

### Primary Outcomes: No Reported SAEs or DLTs

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 Adult Low dose (n = 2)</th>
<th>Cohort 2 Adult Mid Dose (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>26 (22 Mild, 4 Moderate)</td>
<td>25 (23 Mild, 2 Moderate)</td>
</tr>
<tr>
<td>Ocular AEs</td>
<td>22 (18 Mild, 4 Moderate)</td>
<td>9 (9 Mild)</td>
</tr>
<tr>
<td>EDIT-101 AEs</td>
<td>8 (6 Mild, 2 Moderate)</td>
<td>3 (3 Mild)</td>
</tr>
<tr>
<td>SAEs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DLTs</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

AE: Adverse event; DLT: Dose-limiting toxicity; FST: Full-field light sensitivity threshold; SAEs: Serious adverse events
BRILLIANCE Secondary Outcomes: Mid-dose Cohort Demonstrates Early Signs of Efficacy

**BRVT**

Berkeley Rudimentary Vision Test

Baseline

![BRVT Test Display]

LogMar 2.7 (20 / 10,000)

**After Six Months**

![BRVT Test Display]

LogMar 2.0 (20 / 2,000)

**Navigation**

ORA Visual Navigation Course™

PASS at 500 lux

![Navigation Course Display]

Commercial Light 500 lux

*E.g., Office*

Straight course, 3 random obstacles

**What the patient can now see**

PASS at 63 lux

![Navigation Course Display]

Low Light 63 lux

*E.g., Dim Hallway*

Multiple turns course, 10 random obstacles

**How the patient can now navigate**

EDIT-101 Summary To Date

EDIT-101 for treatment of CEP290-related retinal degeneration is the first clinically investigated in vivo CRISPR gene editing therapy, including first pediatric patient to be dosed.

To date, no dose-limiting toxicities or serious adverse events have been reported.

Early efficacy signals in the mid-dose cohort suggest positive biological activity and potential early clinical benefits.

Clinical update on BRLLIANCE trial in adult mid- and high-dose cohorts to be provided in 2H 2022.
Rhodopsin-Associated Autosomal Dominant Retinitis Pigmentosa (RHO-adRP)

**Rhodopsin (RHO)**
- Light-sensitive receptor protein, located in outer segments, involved in phototransduction in rod photoreceptors
- Approximately 30% of adRP caused by RHO dominant mutations (US and UK)
- >150 mutations identified in the RHO gene cause RHO-adRP
- Dominant mutations in the RHO gene are toxic for rods: progressive loss of rods followed by loss of cones

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**Rod and Cone Photoreceptor Structure**
- Structure of rods and cones
- Outer segment of rod

**Changes to Retinal Morphology in RP**
- Normal
- RP
- End-stage RP
- Nerve fiber layer (NFL)
- Ganglion cell layer (GCL)
- Inner plexiform layer (IPL)
- Inner nuclear layer (INL)
- Outer plexiform layer (OPL)
- Outer nuclear layer (ONL)
- Inner/outer segments of photoreceptors (IS/OS)
- Retinal pigment epithelium (RPE)
- Choroid

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RHO-adRP: Symptom Burden and Patient Impact

**DISEASE SYMPTOMS**
- Night blindness beginning in childhood and adolescence
- Blind spots in peripheral vision
- Progressive loss of peripheral vision leading to tunnel vision
- Blindness in later life

**PATIENT IMPACT**
- 7,500 patients in US
- 12,100 patients in EU and UK
- Impaired academic performance
- Lower quality of life
- Psychological stress, depression, and anxiety

**PATIENT VISION**
- TUNNEL VISION IN RHO-adRP
- HEALTHY CENTRAL VISION


Image source: Usherkidsuk.com
EDIT-103: Dual AAV-Based “Knockout and Replace” Therapeutic Strategy

- Agnostic to any RHO mutation – thus will knockout any dominant gain-of-function rhodopsin mutant
- **Step 1:** Both mutant and normal endogenous RHO will be **knocked out** in the treated area
- **Step 2:** Exogenous normal RHO (resistant to editing) will **replace** endogenous RHO
- One-time subretinal administration aimed to restore/prevent vision loss

**Details of EDIT-103**

- gRNA is on the vector carrying RHO-replace, thus assuring knockout takes place only in photoreceptor cells that express RHO-replace
- The RHO promoter for Cas9 and RHO-replace restricts therapeutic activity to rod photoreceptors

EDIT-103: Proof-of-Concept in Non-Human Primates

EDIT-103 is a highly specific “knock out & replace” system for treating RHO-adRP with near 100% editing efficiency.

EDIT-103 shows near 100% editing and functional RHO replacement.

EDIT-103 (KO and Replace)

EDIT-103 (KO only)

Vehicle KO 3E12 (vg/ml)
EDIT-103 3E12 (vg/ml)
EDIT-103 6E12 (vg/ml)

Normalized Productive Editing (%)

0 25 50 75 100 125

Vehicle KO EDIT-103 EDIT-103

% of hRHO protein (compared to NHP RHO in Vehicle)

0 10 20 30 40 50

Vehicle KO EDIT-103 EDIT-103

Volume: 100 μl. AAV ratio: 1:1. Time point: 13 wks. *p<0.05, **p<0.01, ***p<0.001

RHO Protein Expression and Retinal Morphology Preserved in EDIT-103-Treated Versus KO-Treated NHP Retinas

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>KO (3E12 vg/ml)</th>
<th>EDIT-103 (3E12 vg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHO protein / Cas9 genome</td>
<td><img src="image1" alt="" /></td>
<td><img src="image2" alt="" /></td>
<td><img src="image3" alt="" /></td>
</tr>
<tr>
<td>H&amp;E staining</td>
<td><img src="image4" alt="" /></td>
<td><img src="image5" alt="" /></td>
<td><img src="image6" alt="" /></td>
</tr>
</tbody>
</table>

- AAV transduction in treated groups reveals positive **Cas9 genome** staining
- Nearly absent **RHO protein** and lack of OS (yellow arrow) in the KO group
- Preservation of **RHO protein**, improved photoreceptor organization, and improved IS/OS morphology in EDIT-103-treated groups
- EDIT-103 at the dose of 3E12 vg/mL appeared superior

AAV: Adeno-associated virus; H&E: Hematoxylin and eosin; IS/OS: Inner/outer segments; KO: knock-out; NHP: Non-human primate; ONL: Outer nuclear layer; RHO: rhodopsin; RPE: Retinal pigment epithelium

AAV ratio: 1:1; Injection volume: 100 μL; Time point: 13 weeks
Retinal Function Preserved in EDIT-103 Treated Versus KO-Treated NHP Eyes

- KO of endogenous RHO significantly reduced a- and b-wave amplitudes
- EDIT-103 dosing preserved a- and b-wave amplitudes
- EDIT-103 at the dose of 3E12 vg/mL appeared superior

AAV: adeno-associated virus; ERG: electroretinogram; GCL: ganglion cell layer; INL: inner nuclear layer; IPL: inner plexiform layer; IS/OS: inner/outer segments of photoreceptors; KO: knockout; NFL: nerve fiber layer; ONL: outer nuclear layer; OPL: outer plexiform layer; RHO: rhodopsin; RPE: retinal pigment epithelium; SD: Standard deviation.
Usher Syndrome (USH2A): Symptom Burden and Patient Impact

**DISEASE SYMPTOMS**

- Most common form of syndromic retinitis pigmentosa
- Severe loss of vision, progressively constricted visual fields (tunnel vision)
- Congenital hearing loss
- Impaired coordination, balance, and vestibular reflexes

**PATIENT IMPACT**

- Affects approximately 4-17 per 100,000 persons
- Accounts for 50% of all hereditary deaf-blindness cases
- Impaired speech ability unless fitted with cochlear implants
- Reliance on sign language, or on tactile signs once vision is lost

**PATIENT RETINA & VISION**

- Narrow visual field (tunnel vision)
- Usher syndrome (L) Normal retina (R)
- Pale optic nerve (arrow), thin blood vessels (stars), retinal pigmentation (double arrows)

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EDIT-102: Gene Editing for USH2A with Optimized AsCas12a Increases Productive Editing

- Development of an AsCas12a in vivo editing platform outperforms prior EDIT-102 construct
- Improved gRNA and AsCas12a activity.
- Co-developed single- and dual-vector platforms

**USH2A productive editing**

<table>
<thead>
<tr>
<th>RNP (µM)</th>
<th>% Frameshift (Productive editing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td>0.1</td>
<td>25</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>75</td>
</tr>
</tbody>
</table>

**Editing with ribonucleoprotein in relevant cell type**

<table>
<thead>
<tr>
<th>RNP (µM)</th>
<th>% Frameshift (Productive editing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td>0.1</td>
<td>25</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>75</td>
</tr>
</tbody>
</table>

**USH2A Exon 13 deletion (%)**

- Single-vector AsCas12a
  - AsCas12a (Original): 13%
  - AsCas12a (Optimized): 30%
  - SaCas9 (EDIT-102): 21%

- Dual-vector AsCas12a
  - AsCas12a (Optimized): 52%
  - SaCas9 (EDIT-102): 24%

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**USH2A: Usher syndrome 2A**

- Large patient population
- Ability to edit gene with either SaCas9 or AsCas12a nucleases and guides
- Exploration of multiple delivery modalities
Summary

- **Editas Medicine** utilizes proprietary technology with an expansive pipeline of gene editing medicines in ophthalmology, hemoglobinopathies and oncology.

- **EDIT-101** achieved *in vivo* proof-of-concept in 2021 for treating CEP290 retinal degeneration
  - BRILLIANCE data provide clinical evidence of successful delivery and editing with meaningful improvements in vision
  - BRILLIANCE Phase 1/2 subjects demonstrate no SAEs or DLTs
  - The single subretinal injection delivery of EDIT-101 is an advantageous treatment solution for LCA10

- **EDIT-103** is a highly specific and efficient “knock out & replace” system for treating RHO-adRP with near 100% editing efficiencies
  - Shows promise for other autosomal dominant disease indications where deleterious mutations need to be corrected

- **EDIT-102** has resulted in the development of enhanced gene cassette constructs that increase editing efficiency and presents opportunities for future targets in other diseases
  - Developed single- and dual-vector platforms
  - Proprietary SaCas9 or AsCas12A nuclease

CEP290: Centrosomal protein 290; DLTs, Dose-limiting toxicity; LCA: Leber congenital amaurosis; RHO-adRP: Rhodopsin-Associated Autosomal Dominant Retinitis Pigmentosa; SAEs, serious adverse events