

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

Mark S. Shearman

Editas Medicine, Chief Scientific Officer

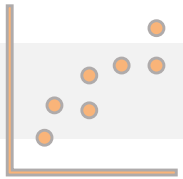
Disclosure

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

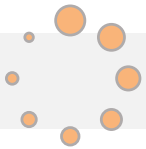


Advanced Bioinformatics and Analytics

Mastery in design based on proprietary sequencing tools

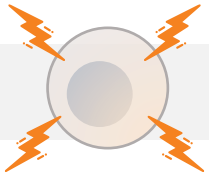
Proprietary CRISPR Enzymes and RNA Chemistry

Efficient high precision editing



Multiple Delivery Solutions

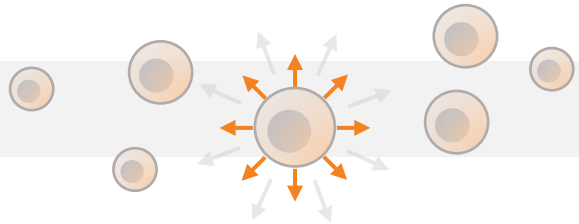
AAV, RNP, LNP
delivered *in vivo*, *ex vivo*, and via engineered cells



Multiplex Gene Editing

In vivo and fully characterized engineered cell knock-ins

SLEEK™ GENE EDITING



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

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

There are currently no approved treatments for these diseases

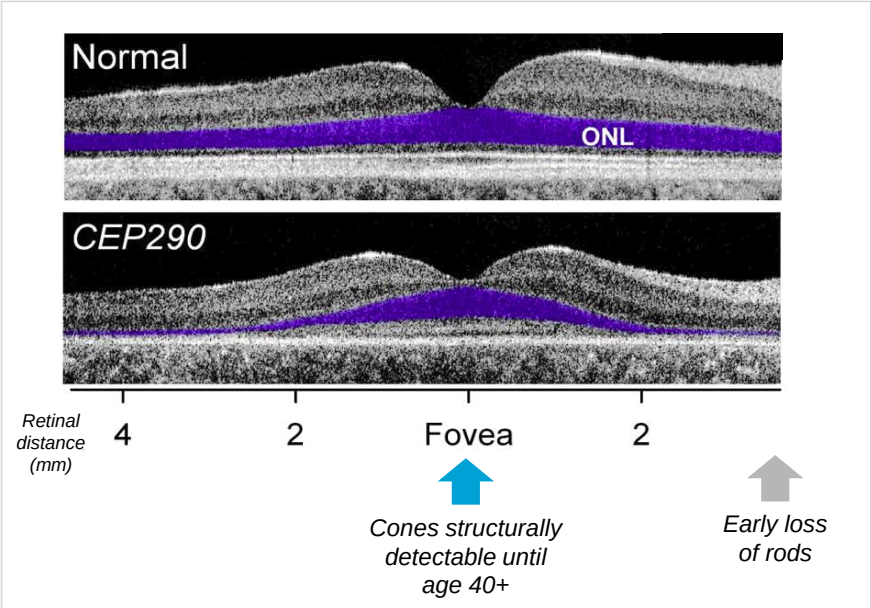
adRP: Autosomal dominant retinitis pigmentosa; CEP-290: Centrosomal protein 290; RHO: Rhodopsin; USH2A: Usher syndrome

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[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

CEP290-Related Rod Photoreceptor Loss with Increasing Retinal Eccentricity



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: Centrosomal protein 290; OCT: Optical coherence tomography; ONL: Outer nuclear layer

1. Kumaran N, et al. *Br J Opthalmol.* 2017; 2. Weleber RG. LCA G*ene Reviews*. 2013

CEP290-Related Degeneration: Symptom Burden and Patient Impact

DISEASE SYMPTOMS

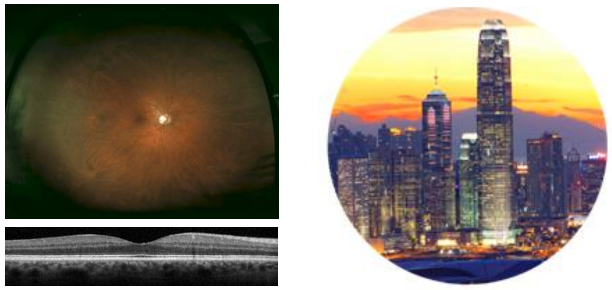
- Blindness usually diagnosed in infancy or early childhood
- Severely impaired visual acuity
- Loss of peripheral vision
- Night blindness
- Rapid, involuntary eye movements (nystagmus)

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

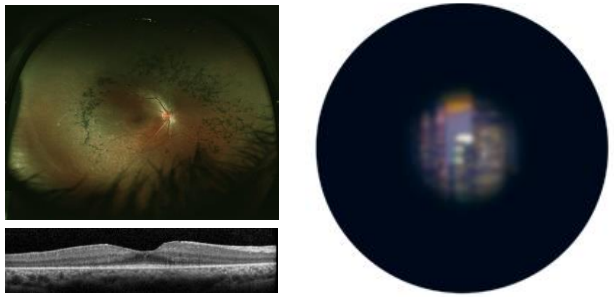
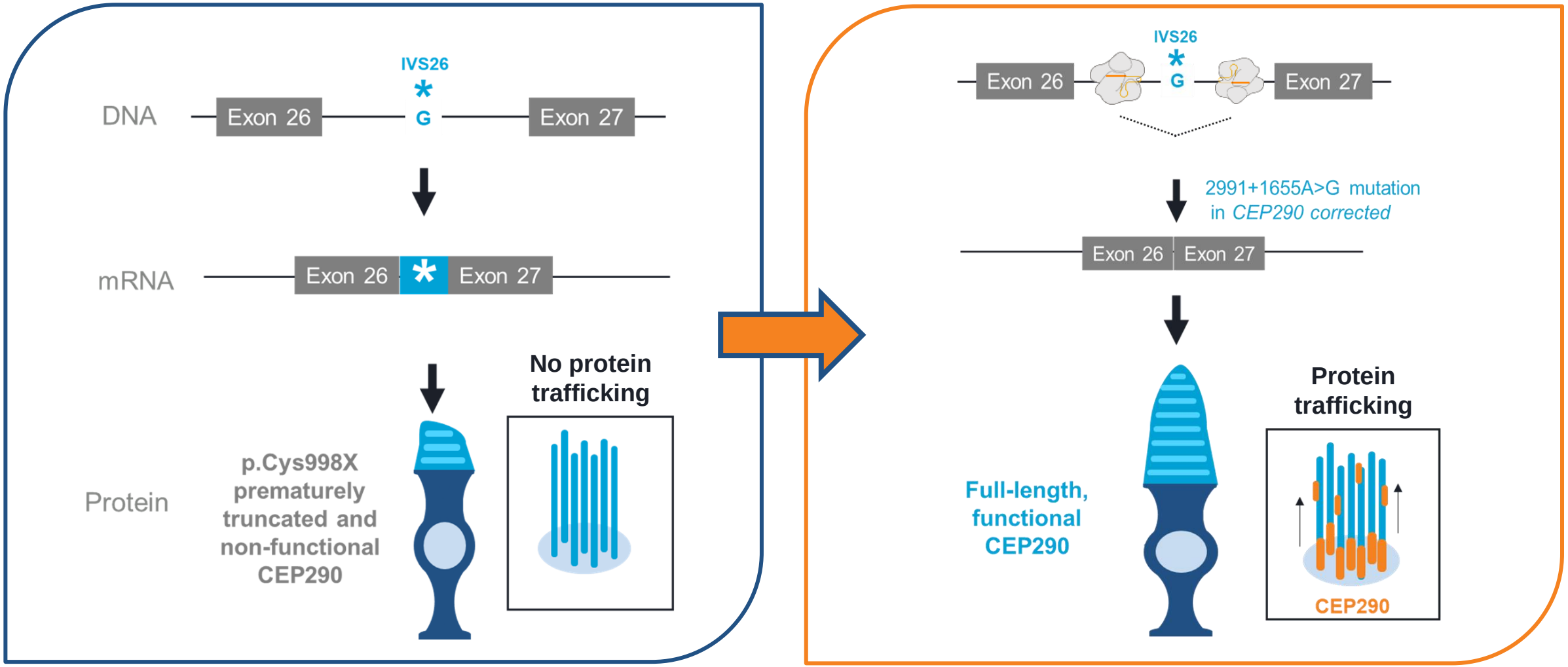


Image source: Kubota Pharmaceutical Holdings

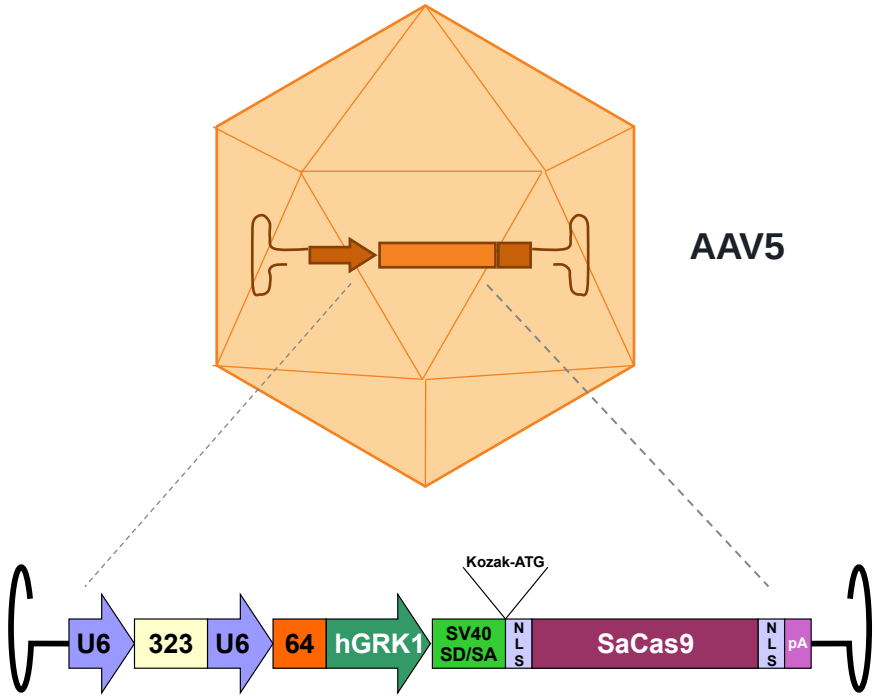
The IVS26 Mutation in CEP290 Is a Clearly Defined Target for Gene Editing



EDIT-101 Allows for Local Delivery of the Editing Complex to Specifically Target the Photoreceptors to Be Corrected

EDIT-101

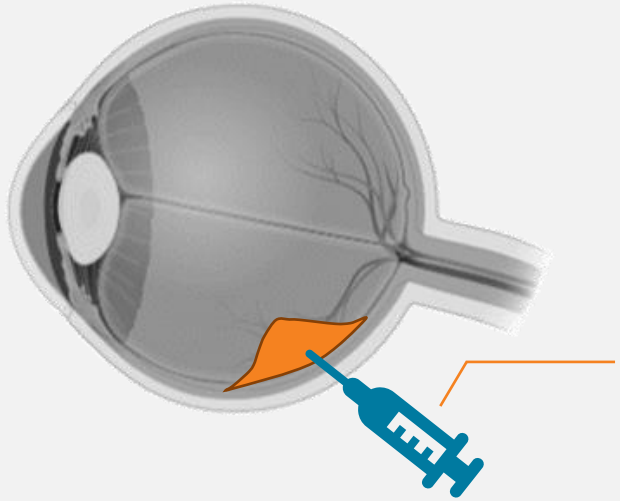
CRISPR-Cas9 gene editing



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



Subretinal injection to parafoveal region

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

Maeder ML, et al. *Nat Med.* 2019

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

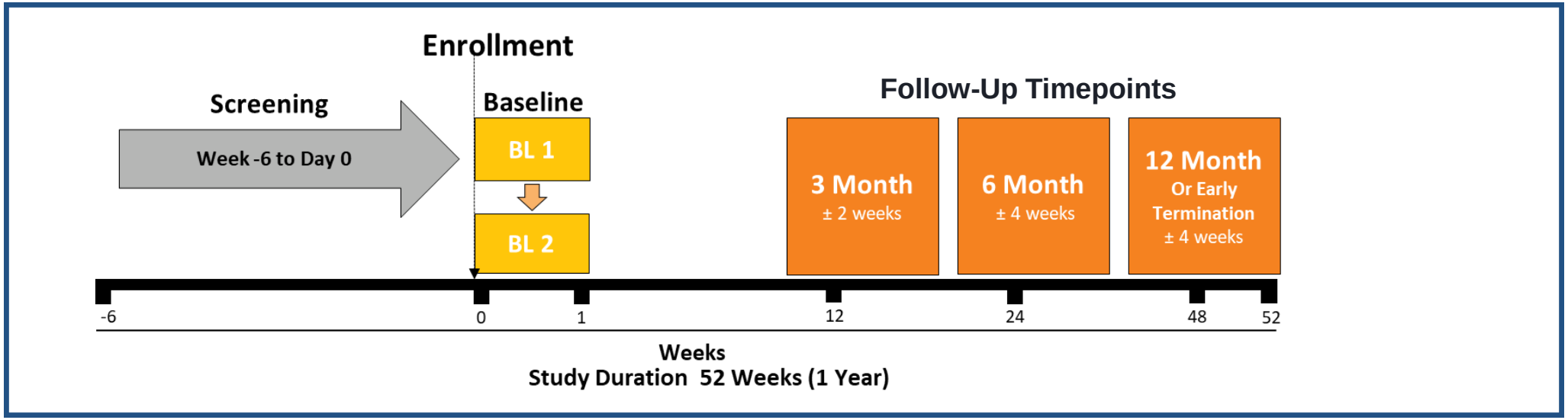
Eligibility Criteria

- 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



VA: Visual acuity

Natural History Study Identified Feasible, Reliable, and Stable Endpoints for Clinical Studies Including VA and FST Scores

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

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

Cohort	Patients	Dose	Status/Safety
1	Adult, n = 2	**LOW** (6.0×10^{11} vg/ml)	**Dosing complete** No dose-limiting toxicity (DLTs) No serious adverse events (SAEs)
2	Adult, n = 4	**MID** (1.1×10^{12} vg/ml)	**Dosing complete** No DLTs No SAEs
3	Adult, n = 4	**HIGH** (3.0×10^{12} vg/ml)	**Dosing complete** No DLTs No SAEs
4*	Pediatric, n = 4	**MID** (1.1×10^{12} vg/ml)	**First patient dosed**
5	Pediatric, n = 4	**HIGH** (3.0×10^{12} vg/ml)	**Awaiting IDMC endorsement**

Single dose administered at Month 0, with 3 follow ups until Month 12

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

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

BRILLIANCE Primary Outcomes: No Reported SAEs or DLTs

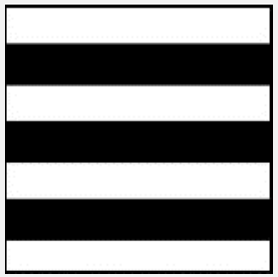
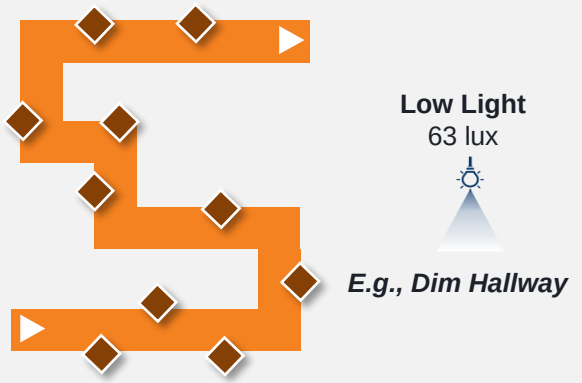
Primary Outcomes: Safety and DLTs

- 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

	Cohort 1 Adult Low dose (n = 2)	Cohort 2 Adult Mid Dose (n = 4)
AEs	26 (22 Mild, 4 Moderate)	25 (23 Mild, 2 Moderate)
Ocular AEs	22 (18 Mild, 4 Moderate)	9 (9 Mild)
EDIT-101 AEs	8 (6 Mild, 2 Moderate)	3 (3 Mild)
SAEs	0	0
DLTs	0	0

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

	Baseline	What the patient can *now* see	After Six Months
BRVT Berkeley Rudimentary Vision Test	 LogMar 2.7 (20 / 10,000)	→	 LogMar2.0 (20 / 2,000)
Navigation ORA Visual Navigation Course™	**PASS at 500 lux**  Straight course, 3 random obstacles	How the patient can *now* navigate →	**PASS at 63 lux**  Multiple turns course, 10 random obstacles

Cohort 2: Patient 1 – patient with longest follow-up assessments from mid-dose cohort. BRVT: Berkeley Rudimentary Vision Test; Ora-VNC: Ora Visual Navigation Challenge

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**

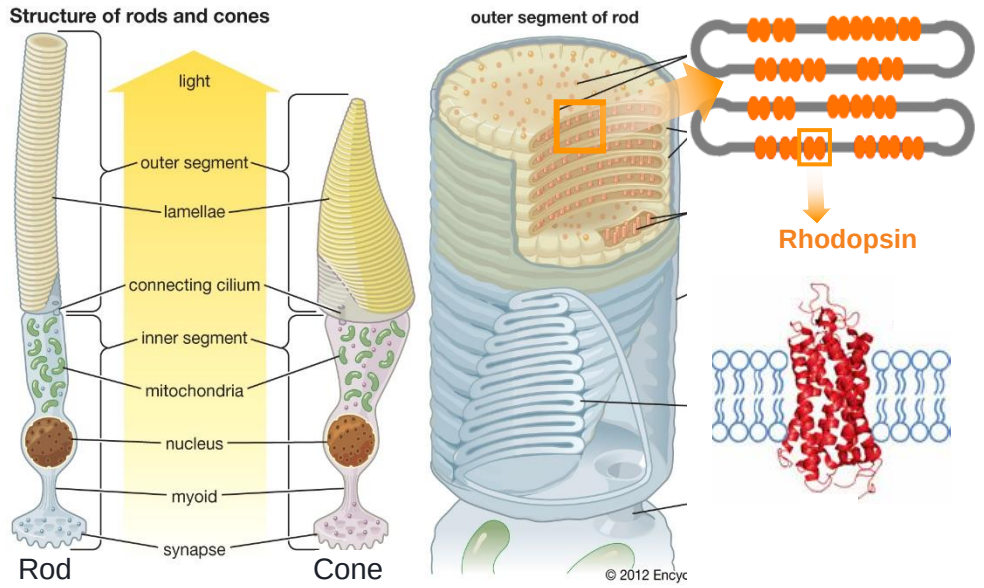
Clinical update on BRLLIANCE trial in adult mid- and high-dose cohorts to be provided in 2H 2022

Rhodopsin-Associated Autosomal Dominant Retinitis Pigmentosa (RHO-adRP)

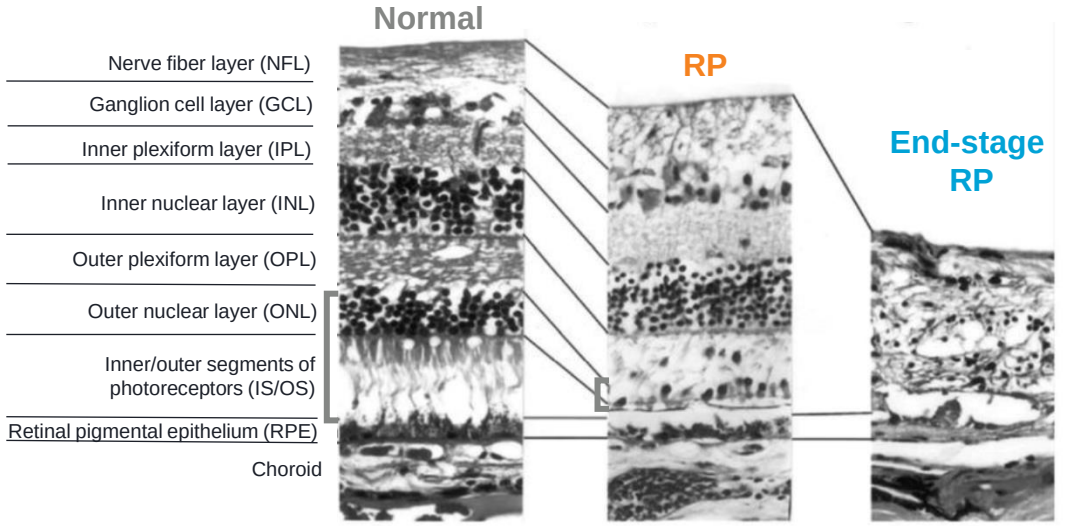
Rhodopsin (RHO)

- 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[1]
- Dominant mutations in the *RHO* gene are toxic for rods: progressive loss of rods followed by loss of cones

Rod and Cone Photoreceptor Structure



Changes to Retinal Morphology in RP



Valle D. *et al. OMMBID* 2014

adRP: Autosomal dominant retinitis pigmentosa RHO: Rhodopsin; RP: Retinitis pigmentosa.

1. Athanasiou, D. *et al*. *Prog Retin Eye Res.* 2018

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[1]

PATIENT IMPACT

- 7,500 patients in US
  12,100 patients in EU and UK[2]
- Impaired academic performance
- Lower quality of life
- Psychological stress, depression, and anxiety[3]

PATIENT VISION

TUNNEL VISION IN RHO-adRP

HEALTHY CENTRAL VISION

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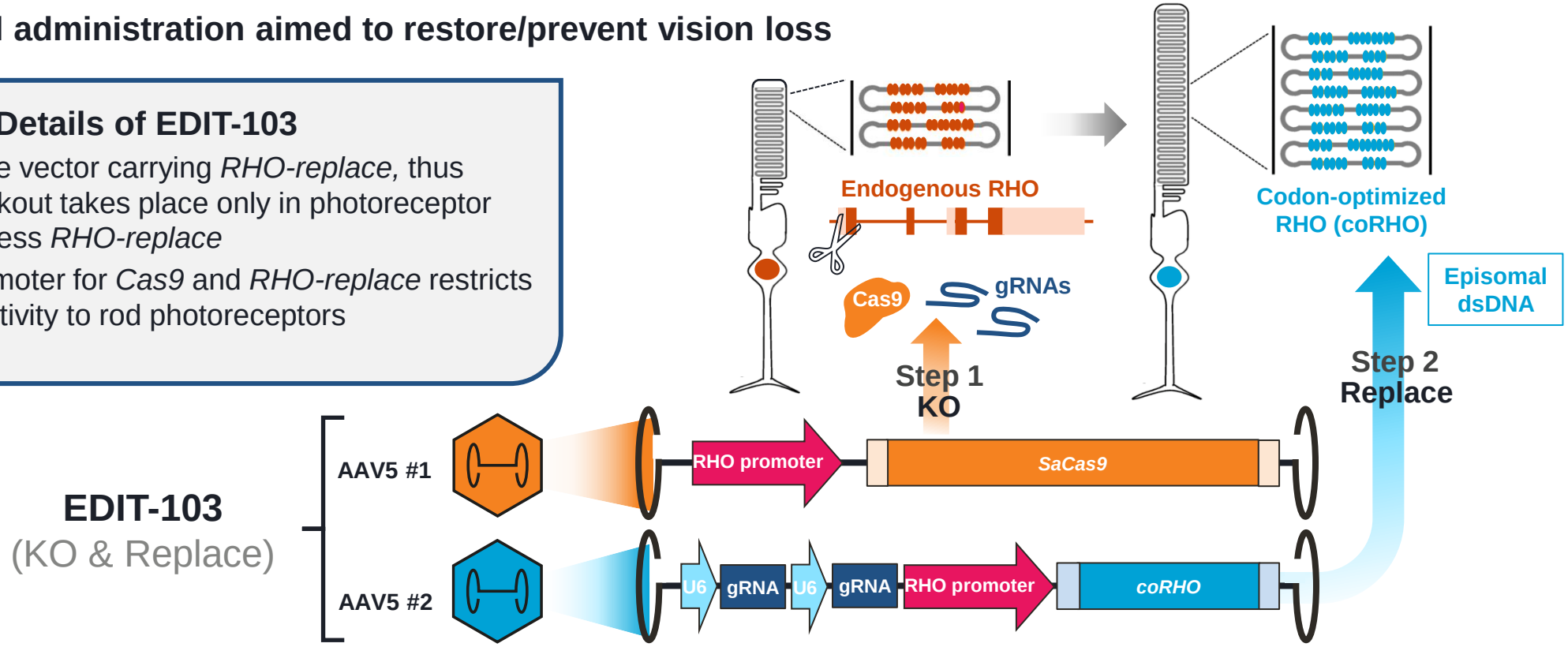
1. Daiger SP, et al. *Cold Spring Harb Perspect Med.* 2015; 2. Athanasiou, D et al. *Prog Retin Eye Res*. 2018; 3. Chaumet-Riffaud AE, et al. *Am J Ophthalmol*. 2017.
Image source: Usherkidsuk.com

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

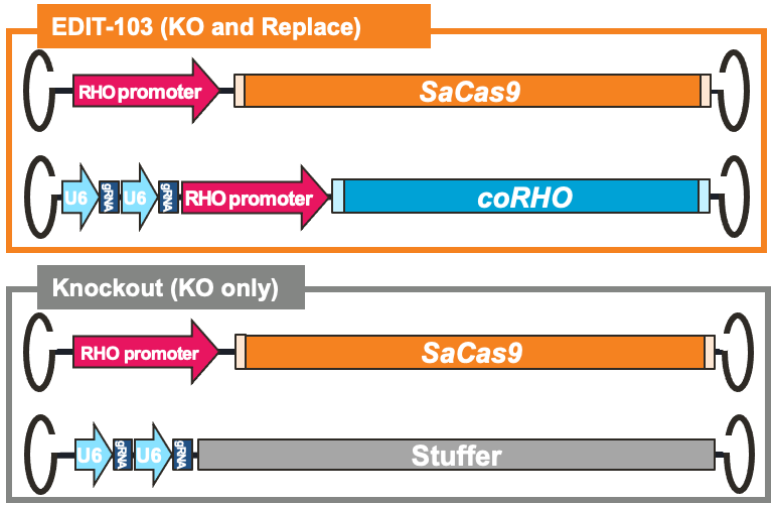
- gRNA is on the vector carrying *RHO-replace,* thus assuring knockout takes place only in photoreceptor cells that express *RHO-replace*
- The *RHO* promoter for *Cas9* and *RHO-replace* restricts therapeutic activity to rod photoreceptors

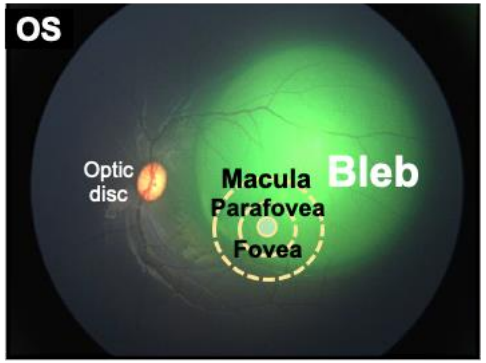


AAV: adeno-associated virus; Cas9: CRISPR-associated protein 9; coRHO: codon-optimized rhodopsin; gRNA: guide ribonucleic acid; KO: knock-out; RHO: rhodopsin; SaCas9: *staphylococcus aureus* CRISPR-associated protein 9.

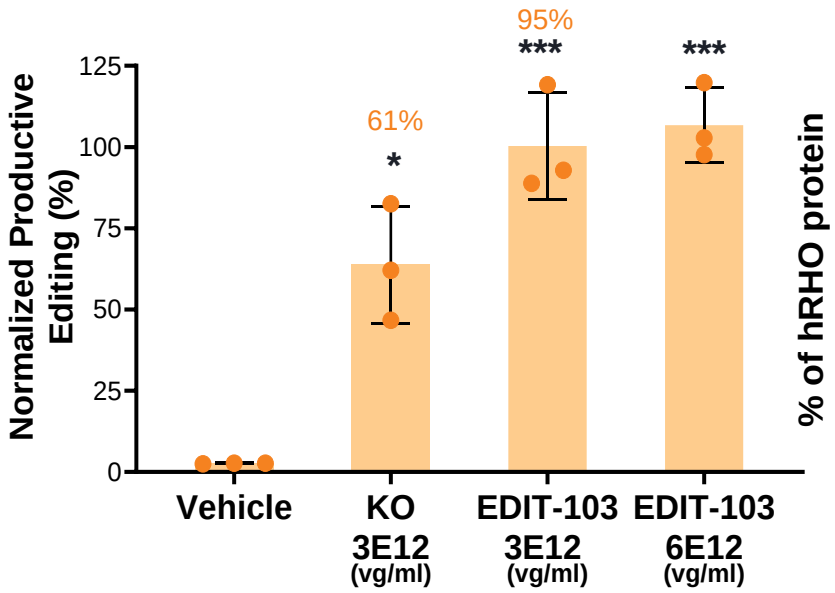
EDIT-103: Proof-of-Concept in Non-Human Primates

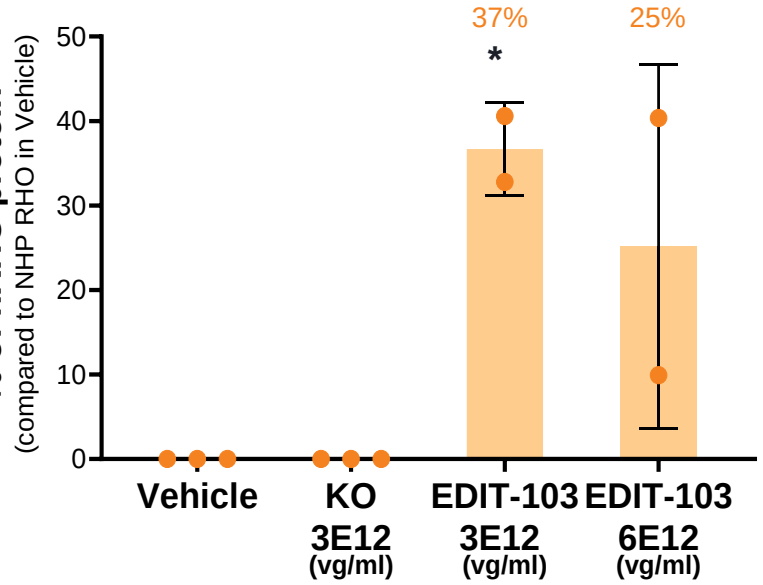
EDIT-103 is a highly specific “knock out & replace” system for treating RHO-adRP with near 100% editing efficiency





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

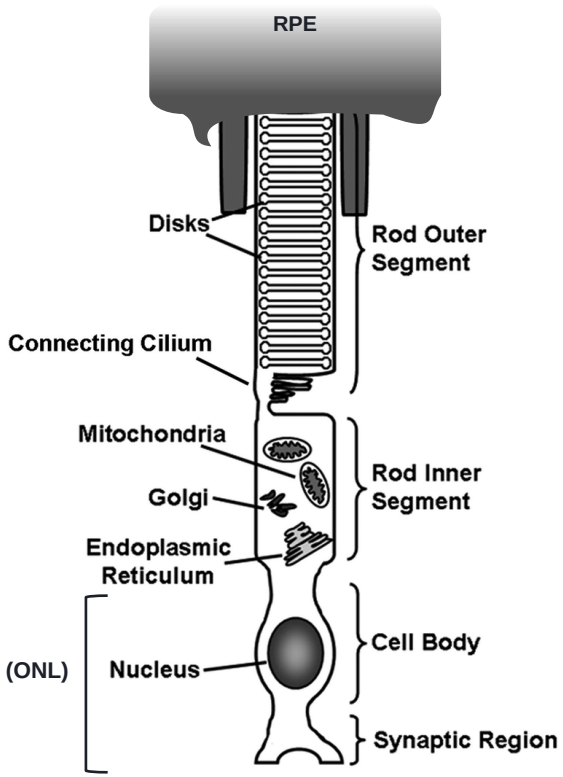




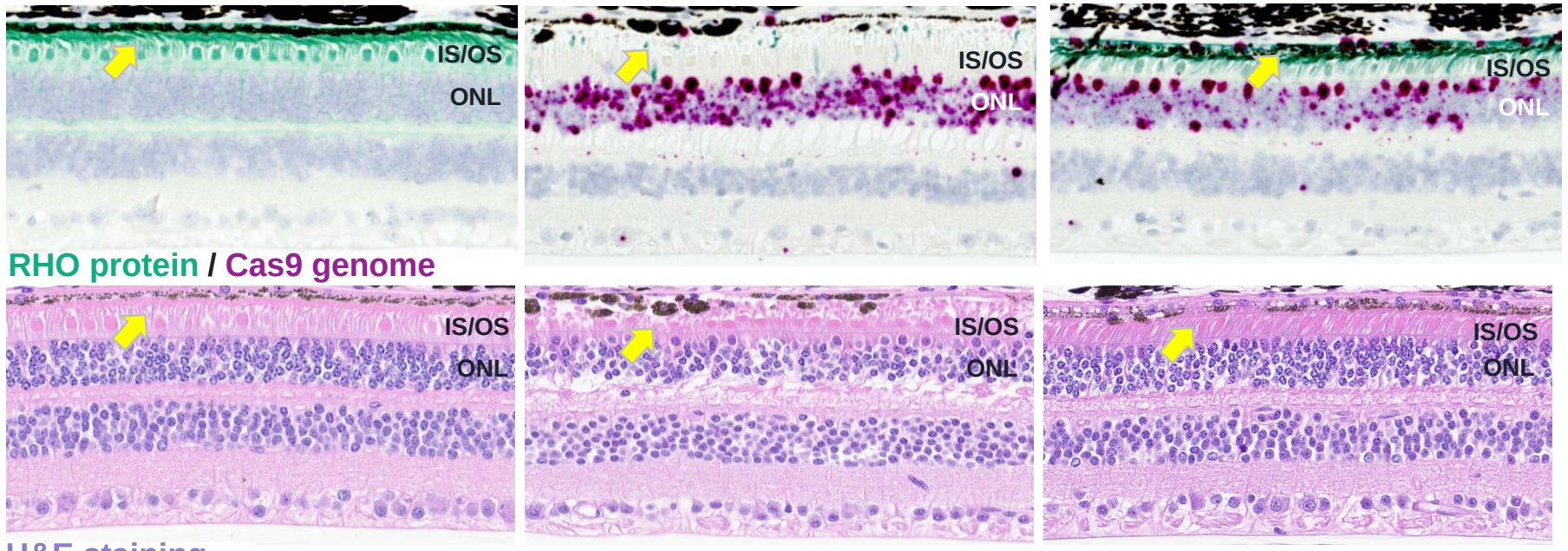
Volume: 100 µl . AAV ratio: 1:1. Time point: 13 wks. *p<0.05, **p<0.01, ***p<0.001

NHP: Non human primate; RHO: Rhodopsin; RHO-adRP: Rhodopsin-associated autosomal dominant retinitis pigmentosa

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



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



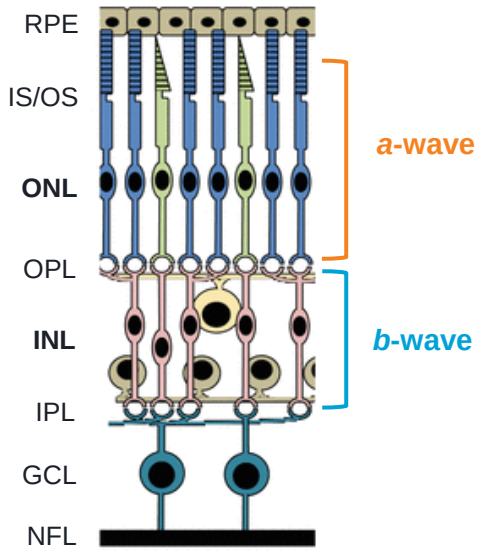
AAV ratio: 1:1; Injection volume: 100 µL; Time point: 13 weeks

- 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

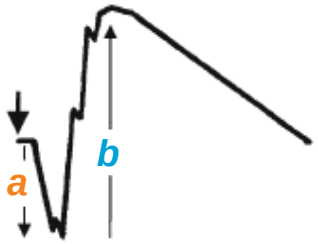
AAV: Adeno-associated virus; H&E: Hematoxylin and eosin; IS/OS: Inner/outer segments; KO: knock-out; NHP: Non-human primate; ONL: Outer nuclear layer; RHO: rhodopsin; RPE: Retinal pigment epithelium

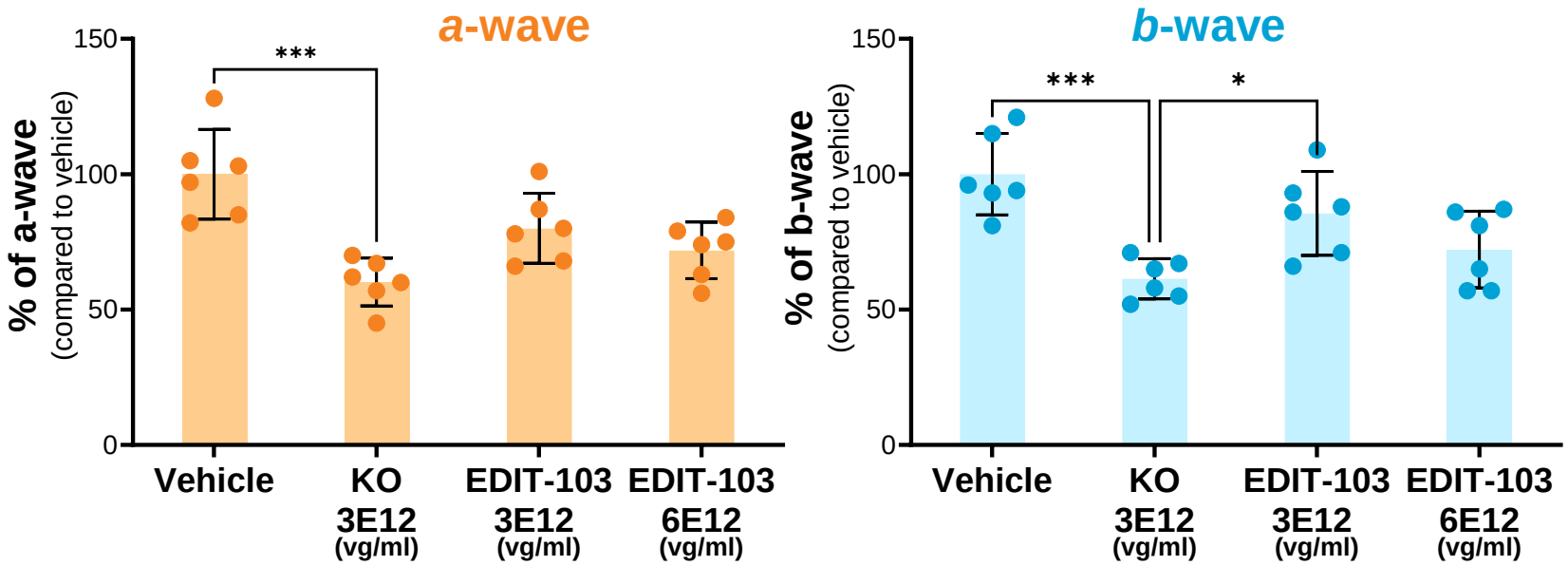
Retinal Function Preserved in EDIT-103 Treated Versus KO-Treated NHP Eyes

Retinal layers



Dark-adapted 3.0 ERG (combined rod-cone response)





AAV ratio: 1:1; Injection volume: 100 µL; Time point: 13 weeks; Mean (±SD) is presented; *p<0.05, ***p<0.001

- 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 pigmental epithelium; SD: Standard deviation.

Usher Syndrome (USH2A): Symptom Burden and Patient Impact

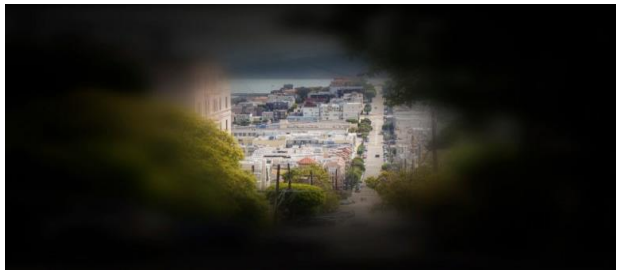
DISEASE SYMPTOMS

- Most common form of syndromic retinitis pigmentosa
- Severe loss of vision, progressively constricted visual fields (tunnel vision)
- Congenital hearing loss
- Impaired balance, coordination, and vestibular reflexes[1]

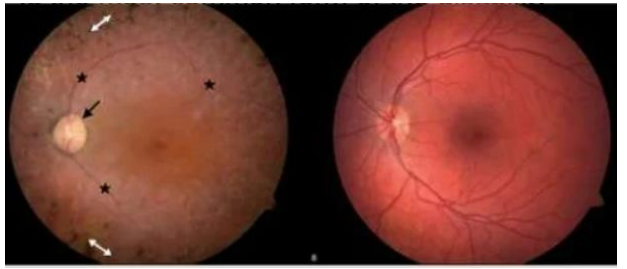
PATIENT IMPACT

- Affects approximately 4 -17 per 100,000 persons
- Accounts for 50% of all hereditary deaf-blindness cases[2]
- Impaired speech ability unless fitted with cochlear implants
- Reliance on sign language, or on tactile signs once vision is lost[3]

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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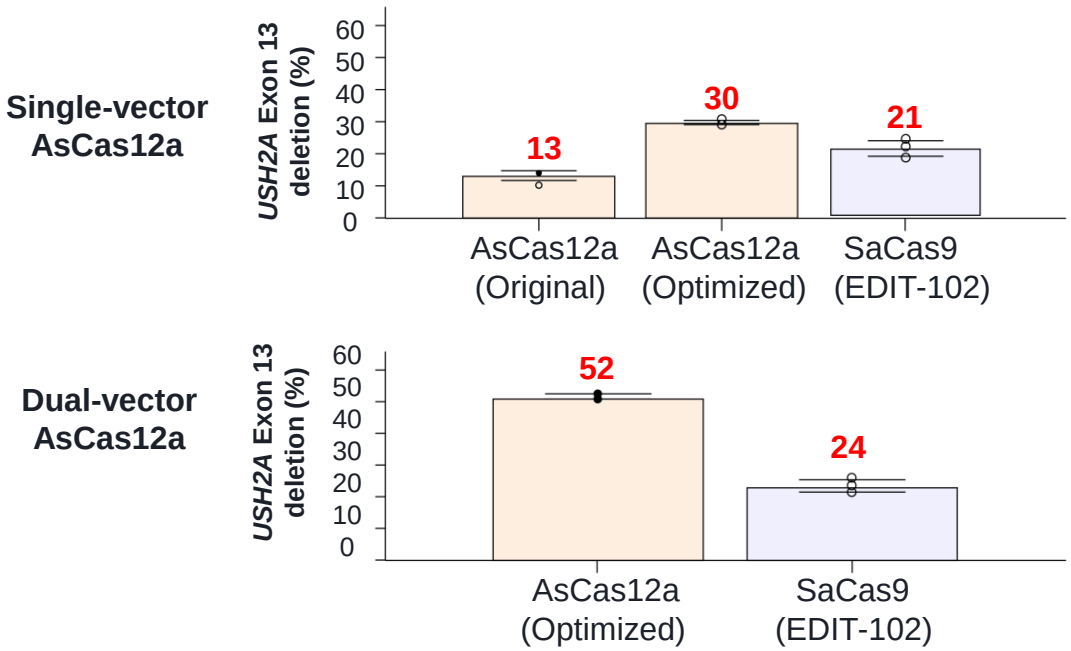
1. Koenekoop RK, et al. *Gene Reviews*. 2020, Seattle, WA. 2. Boughman JA, et al. *J Chronic Dis*. 1983; 3. Ben-Rebeh I, et al. *Mol Vis*. 2016. Image sources: Medicine Net, Gene vision

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

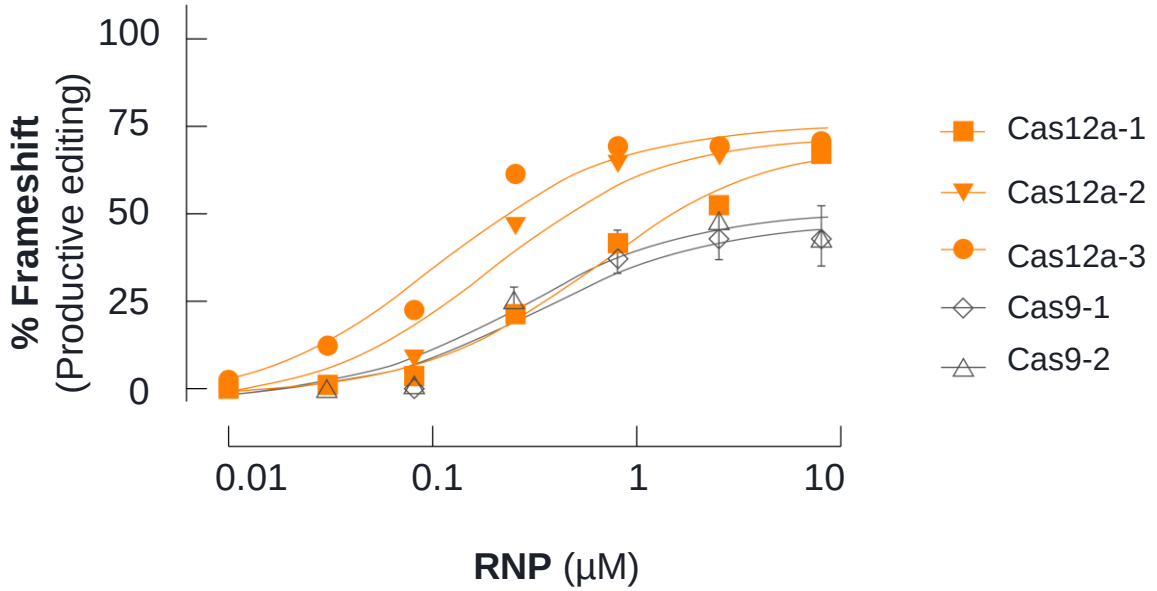
- Development of an AsCas12a *in vivo* editing platform outperforms prior EDIT-102 construct
- Improved gRNA and AsCas12a activity.
- Co-developed single- and dual-vector platforms

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

USH2A productive editing



Editing with ribonucleoprotein in relevant cell type



USH2A: Usher syndrome 2A

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