Open-Label, Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Efficacy of EDIT-101 in Adult and Pediatric Participants with Leber Congenital Amaurosis Type 10 (LCA10), with Centrosomal Protein 290 (CEP290)-Related Retinal Degeneration Caused by a Compound Heterozygous or Homozygous Mutation Involving c.2991+1655A>G in Intron 26 (IVS26) of the CEP290 Gene (*LCA10-IVS26*)

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Primary-To evaluate the safety and tolerability of a single dose of EDIT-101 when administered to participants with LCA10-IVS26 mutationSecondary-To evaluate different doses of EDIT-101 for subsequent clinical evaluation-To evaluate the efficacy of...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Eye disorders congenital
Study type	Interventional

Summary

ID

NL-OMON54872

Source
ToetsingOnline

Brief title
EDIT-101 study in patients with LCA10

Condition

- Eye disorders congenital

Synonym
CEP290-gene mutation and inherited retinal degeneration

Research involving
Human

Sponsors and support

Primary sponsor: Editas Medicine, Inc.
Source(s) of monetary or material Support: Editas Medicine Inc

Intervention

Keyword: EDIT-101, Leber congenital amaurosis, Type 10

Outcome measures

Primary outcome

• Incidence of DLT, as detailed in Section 8.3.8.1 of the protocol

• Frequency of AEs related to EDIT-101

• Number of procedural related AEs

Secondary outcome

Secondary

-Maximum tolerated dose as determined by DLT

-Change from baseline in the following parameters:

* Visual Function Navigation course score of the study eye, contralateral eye,

and both eyes together

* logMAR measurement of BCVA

* Pupil size in dark (maximum diameter), pupil size in light (minimum diameter), mean pupil constriction velocity, maximum pupil constriction velocity, amount of constriction after stimulus, percent of constriction after stimulus

* Gaze tracking

* Dark adapted visual sensitivity to white, red, and blue light

* The thickness of the ONL and integrity of the ellipsoid zone

* LogMAR measurement of contrast sensitivity.

* Macular sensitivity

* Visual field

* Farnsworth 15 score

* QoL questionnaires

* Global Impressions of Change

* Global Impressions of Severity

Exploratory

• Detection of anti-drug antibodies to AAV5 (BAB by ELISA and NAB using a cell-based assay) and Cas9 (BAB by ELISA)

• Detection of T cell response to AAV5 and Cas9 by ELISPOT

• Quantification of vector DNA in blood, nasal mucosa, semen, and tears

• Changes in area of autofluorescence

Study description

Background summary

LCA10-IVS26-related retinal degeneration is an ultra-rare and seriously debilitating disease, usually emerging early in infancy and resulting in significant vision loss. There are currently no approved treatments for LCA10-IVS26. EDIT-101 (chemical name: AAV5-CEP290gRNA323/64-GRK1-SaCas9) is a novel gene editing product designed to eliminate the mutation on the CEP290 gene that results in the retinal degeneration that defines LCA10-IVS26. In vitro studies and preliminary results from a first-in-human study of the investigational product QR-110 (www.clinicaltrials.gov NCT03140969) suggest that the cellular and functional changes induced in Leber congenital amaurosis type 10 (LCA10) patients may be reversible following a treatment that increases levels of the centrosomal protein 290 (CEP290) protein. As such, EDIT-101 has the potential to improve visual function in these patients.

Study objective

Primary
-To evaluate the safety and tolerability of a single dose of EDIT-101 when administered to participants with LCA10-IVS26 mutation

Secondary
-To evaluate different doses of EDIT-101 for subsequent clinical evaluation
-To evaluate the efficacy of a single dose of EDIT-101 on:
* Visual Function Navigation (Ora-VNC)
* Visual acuity
* Pupillometry
* Oculomotor control and instability (OCI)
* Full field light sensitivity threshold (FST)
* OCT
* Contrast sensitivity
* Microperimetry
* Kinetic perimetry
* Color vision
* QoL

Exploratory
-To evaluate an immune response to EDIT-101
-To evaluate viral shedding in blood, nasal mucosa, semen, and tears
-Fundus autofluorescence (FAF and NIRAF)

Study design

This is an open-label, single ascending dose study of EDIT-101 in adult and pediatric (ie, ages 3 to 17) participants with LCA10-IVS26. Approximately 18 participants will be enrolled in up to 5 cohorts to evaluate up to 3 dose levels of EDIT-101 in this study.
Participants will receive a single study intervention treatment (EDIT-101) administered, following vitrectomy via subretinal injection) in one eye (the study eye). The study eye will be determined at Screening: if both eyes meet eligibility criteria, the eye with the worse visual acuity will be chosen as the study eye. Participants will be followed on study for 3 years, after which they will be asked to consent to participate in a long-term follow-up study for an additional 12 years.
Administration (via subretinal injection surgery) of EDIT-101 will occur at study sites that have been selected by the sponsor based on their suitable surgical facilities and their expertise in performing the necessary retinal surgery.
Dose escalation and cohort progression will be determined by the sponsor, the investigators, and an independent data monitoring committee (IDMC).

Intervention

Participants will receive a single study intervention treatment (EDIT-101 administered, following vitrectomy, via subretinal injection) in one eye (the study eye). The study eye will be determined at screening: if both eyes meet eligibility criteria, the eye with the worse visual acuity will be chosen as the study eye.

Study burden and risks

The study will include a total of 20 visits and will be 3 years in duration. Subjects are expected to undergo procedures/assessments as described in the section 1.3 of the study protocol, which include: Physical exam, vital signs, demographic and medical history; ECG; Blood and urine tests (including urine drug screening); Completion of questionnaire and answering questions from the study team; Pregnancy tests in women of childbearing potential; Female patients: no breastfeeding allowed.

Risks of the Study Drug
- There is a theoretical risk that the study drug could spread to other parts of the patient's body. If the study drug were to spread to other parts of your body, it is possible that they could have a systemic reaction (discomfort throughout the body). Animal studies with other AAV investigational treatments showed that the risk of spread was very low and that general discomfort in the body would be mild and only last a short time if it happens.
- There is also a theoretical risk that the study drug can create changes in the patient's genes at places outside of the CEP290 gene. This can cause damage to the genes in their retina or other parts of their body. This type of damage

was not seen in laboratory studies done to prepare for this clinical trial.
In those studies the study drug did not appear to make unwanted changes in the genes of human cells. Since the study drug will stay in the retina permanently, there may be a small risk of unwanted changes in the patient's genes that could occur over time. In the great majority of cases, such unwanted gene changes would not create medical problems in the treated portions of the retina. It is possible such gene changes could change how the retinal cells work.
- The patient may receive either too little or too much of the study drug. If they get too little, there could be a lack of benefit to their visual function, and it may be more difficult to give an effective dose in the future, due to the prior surgery. If too much is given, it is possible that damage to the retina could occur, which could result in worse vision.
- There is a risk that the study drug could be delivered to the vitreous (the center compartment of the eye) instead of going to the location we plan to inject it (under the retina or subretinal). This could happen if tissue in the retina has become scarred as part of the disease process. If this happens during the surgery, the surgeon will remove the study drug from the vitreous and repeat the procedure in another portion of the retina, if possible. If the treatment works, it is possible that the patient may be disturbed and uncomfortable having additional vision. Treatment for such an unlikely outcome will be made available to the patient.

Risks associated with the Vitrectomy Surgery and the Injection Procedure
- Bleeding under the retina
- Cloudiness of the lens of the eye (cataract)
- Blood on the outside of the eye (conjunctival hemorrhage)
- Scratch on the surface of the eye (corneal abrasion)
- Swelling of the surface layer of the eye (corneal edema)
- Loss of sight (decreased visual acuity)
- Droopy eyelid
- Dry eye syndrome
- Increased pressure within the eye (elevated intraocular pressure)
- Eye irritation
- Eye pain
- Fluid accumulation behind the retina
- Fluid accumulation within the macula
- Swelling of the outside of the eye and/or white blood cells inside the eye (inflammation on or within the eye)
- Damage to the center part of the retina (macular injury)
- A hole occurs in the central part of the retina (macular hole)
- Wrinkling on the surface of the center part of the retina (maculopathy)
- Swelling of the interior of the eye (Ocular (eye) infection including endophthalmitis)
- Optic nerve damage
- The retina separates from the back of the eye (retinal detachment)
- Damage to the retina outside the macula (retinal thinning)
- Membranes can distort the macula (traction on the macula)

- Blood in the vitreous cavity (vitreous hemorrhage)

Risks associated with the use of short-term oral prednisone
Prednisone is a drug that decreases inflammation and swelling. Common side effects of prednisone include:
- increased blood pressure
- fluid retention
- increased blood glucose
- weight gain
- increased appetite
- an upset stomach
- nervousness or restlessness.

Allergic Reaction Risks
As with taking any treatment, there is a risk of allergic reaction during this study. Some symptoms of allergic reactions are:
- Rash
- Wheezing and difficulty breathing
- Dizziness and fainting
- Swelling around the mouth, throat or eyes
- A fast pulse
- Sweating

Risks of Local or General Anesthesia
- There are serious but very rare adverse events (negative side effects) related to any type of anesthesia and surgery. These can include:
o seizure
o coma
o death.
- Rare but serious problems connected with general anesthesia include:
o irregular heartbeat
o increases or decreases in blood pressure
o a rapid increase in body temperature
o rare reactions to medications used in the anesthesia
o blockage of breathing passages.

Eye examination risks
- During the study, various eye tests will be performed on the eyes. Some of these tests may require patients to sit in a dark room or have their eyes patched for approximately an hour. The eyes will be exposed to bright lights that may cause some discomfort. The risks of such light exposure are minimal. The devices use safe levels of light. Some patients may experience some neck discomfort from sitting at the chin rest for 15-10 minutes at a time.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

-Adult participants enrolling in Cohorts 1, 2, or 3 must be at least 18 years of age at the time of informed consent. Pediatric participants enrolling in Cohorts 4 or 5 must be 3 to 17 years of age, inclusive, at the time of informed consent.
-CEP290-related retinal degeneration caused by a homozygous or compound heterozygous mutation involving c.2991+1655A>G in IVS26 of the CEP290 gene confirmed by DNA sequencing (ie, 1 or 2 intron 26 c.2991+1655A>G mutations) and 100% match for both gRNA and PAM sequences.
-Male or Female.
-A sexually mature male participant must agree to use contraception as detailed

in Section 10.7 of this protocol from the time of informed consent through at least 12 months after study intervention, and to refrain from donating sperm during this period.
-A female participant is eligible to participate if she is not pregnant (has a negative urine pregnancy result prior to study intervention), not breastfeeding, and at least one of the following conditions applies: Not a WOCBP as defined in Protocol Section 10.7, OR A WOCBP, or who reaches childbearing potential during the study, who agrees to follow the contraceptive guidance in Protocol Section 10.7 from the time of informed consent through at least 12 months after study intervention.
-The participant (or guardian, in the case of a minor) must provide written informed consent prior to any study related procedures. Minors must provide assent in accordance with country and local regulations, as applicable.
-Both eyes must be at least LP. The study eye will be the worse seeing eye and must meet the following BCVA criteria:
Cohort 1: BWD, WFP, or LP
Cohorts 2 - 5: LP to 0.4 logMAR (20/50 Snellen equivalent).). Note: The sentinel participant in each of these cohorts will have severe vision loss with a logMAR BCVA of >=1.6 to 3.9 (20/800 or worse to LP) in the study eye. Subsequent participants in each cohort will have LP to 0.4 logMAR (20/50 Snellen equivalent) best-corrected visual acuity in the study eye. If both eyes have the same BCVA but the worse seeing eye (as determined by the participant and the examiner) does not meet the above criteria, the better seeing eye may be designated as the study eye as long as the participant agrees and the better seeing eye meets all eligibility criteria.
-Photoreceptor ONL identifiable in fovea by spectral domain OCT in the study eye.
-Able, as assessed by the investigator, and willing to complete study assessments and follow study instructions for the duration of the study.
-If currently enrolled in Study EDIT-NHS01 (the Natural History Study of CEP290-Related Retinal Degeneration), the participant must agree to complete the early
termination visit for that study, and be withdrawn from that study, before enrolling in this study.

Exclusion criteria

-Other known disease-causing mutations documented in the participant's medical history or identified through the retinal dystrophy gene panel evaluation performed at screening (including but not limited to bi-allelic mutations in other genes known to cause LCA) that, in the opinion of the investigator, would interfere with the potential therapeutic effect of the investigational product or the quality of the assessments.
-Achieves a passing score for the Visual Function Navigation course at the maximum level of difficulty (ie, passes the most challenging Visual Function

Navigation course under the
dimmest lighting conditions) with either eye independently or both eyes together.
-In either eye, cataract surgery in the last 3 months before the screening visit.
-In either eye, any active ocular/intraocular infection or inflammation (such as blepharitis, infectious conjunctivitis, keratitis, scleritis, endophthalmitis, idiopathic or autoimmune-associated uveitis, or herpetic lesions), assessed at screening.
-In either eye, history of steroid-responsive intraocular pressure increases such that the affected eye had a pressure > 25 mm Hg following corticosteroid exposure despite topical
intraocular-pressure-lowering pharmacologic therapy.
-In either eye, Argus retinal implant.
-In the study eye, absence of clear ocular media and adequate pupil dilation, assessed at screening, to permit good quality OCT images.
-In the study eye, presence of vitreous hemorrhage.
-In the study eye, any history of rhegmatogenous retinal detachment.
-In the study eye, spherical equivalent of the refractive error demonstrating more than -8 diopters of myopia and more than +6 diopters of hyperopia (prior to cataract or refractive surgery), assessed at screening.
-Uncontrolled diabetes mellitus (hemoglobin A1c >=10%) in the last 3 months before the screening visit or at screening.
-Active gastric ulcer at screening.
-Use of systemic immunosuppressive medications for any chronic disease in the last 3 months before the screening visit, or during the screening period.
-Any vaccination/immunization in the last 28 days before screening, or during the screening period.
-An inability or unwillingness to take the course of oral prednisone that is required in this study.
-Current enrollment in an investigational interventional drug or device study (ocular or non-ocular) or participation in such a study within 6 months before the screening visit.
(This does not include observational studies. Prior or current participation in Study EDIT-NHS01 is not an exclusion.)
-Received prior gene therapy or oligonucleotide treatment of any kind.
-The participant has a condition or is in a situation which, in the investigator's or operating surgeon's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Genetic modified organism

Ethics review

Approved WMO Date:	23-07-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-06-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-004981-16-NL
ClinicalTrials.gov	NCT03872479
CCMO	NL73358.000.21