Future Rare Diseases

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Future Rare Diseases

A plain language summary of the phase 1/2 study of AAV5-hRKp.*RPGR* (botaretigene sparoparvovec) in people with *RPGR*-associated X-linked retinitis pigmentosa

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Where can I find the original article on which this summary is based?

The original article, called 'Phase 1/2 AAV5-hRKp.*RPGR* (Botaretigene Sparoparvovec) Gene Therapy: Safety and Efficacy in *RPGR*-Associated X-Linked Retinitis Pigmentosa', was published in November 2024 in the scientific journal, the *American Journal of Ophthalmology* (2024), volume 267, pages 122-134. You can read it for free at: https://www.ajo.com/article/S0002-9394(24)00244-7/fulltext.

Summary

How to say (download PDF and double click sound icon to play sound)…

- **Botaretigene sparoparvovec:** boh-tah-REH-tih-jeen spar-oh-PAR-voh-vek
- **Photoreceptor:** foh-toh-ree-SEP-ter
- **Retina:** RET-uh-nuh
- **Retinitis pigmentosa:** reh-tuh-NIGH-tis pig-men-TOH-suh

What is this summary about?

This plain language summary describes the results of a study published in the *American Journal of Ophthalmology* in 2024. The study looked at a new gene therapy for X-linked retinitis pigmentosa (XLRP), a severe inherited eye disease caused by a change in the retinitis pigmentosa GTPase regulator (*RPGR* for short) gene. Changes in *RPGR* cause the breakdown of cells in the retina of the eye, leading to significant vision problems. AAV5hRKp.*RPGR* (botaretigene sparoparvovec; bota-vec) is an investigational therapy designed to deliver a working copy of the *RPGR* gene. This may help repair the retina and improve vision in XLRP. In this three-part study, researchers evaluated the safety and effectiveness of different doses of bota-vec in participants with XLRP over 52 weeks.

What were the key results?

A total of 45 participants received bota-vec gene therapy. Thirteen participants started treatment at Week 26, which allowed researchers to compare treated and untreated participants. Of the 45 treated participants, 37 experienced at least one side effect before Week 26. Most side effects were considered mild or moderate and related to the surgery required to receive the therapy. Participants who received bota-vec had improvements in vision and function of the retina compared with participants who were untreated until Week 26.

What do the results mean?

Participants generally found that bota-vec had an acceptable safety profile and was well tolerated, and it trended toward visual improvements. These positive results supported investigation of bota-vec in a larger study in participants with XLRP.

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What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you to understand the findings from recent research.

Bota-vec is not approved to treat the condition under study that is discussed in this summary.

Who is this article for?

This summary may help people with XLRP and their caregivers, patient advocates, payers, and health care professionals learn about early data on bota-vec, a gene therapy in development for treating people with XLRP.

Who sponsored this study?

MeiraGTx UK II Ltd in collaboration with Johnson & Johnson **sponsored** the study.

Sponsor: A company or organization that oversees and pays for a clinical research study. The sponsor also collects and analyzes the information from the study.

What is XLRP?

XLRP is a severe form of retinitis pigmentosa, a group of inherited eye diseases that causes serious vision problems. These vision problems start early in life and worsen over time as the retina – the part of the eye that helps us see – breaks down, which often leads to blindness.

One of the common first signs of XLRP is difficulty seeing in low light, also known as night blindness. People with XLRP also have some trouble seeing clearly, known as visual acuity. The loss of visual acuity means they may have difficulty reading or seeing details.

As the disease progresses, people with XLRP may experience 'tunnel vision', where only their central vision remains clear and they lose their ability to see objects to the side.

There are no approved treatments for XLRP. However, care options, such as low-vision rehabilitation and optical aids, are available to help manage symptoms.

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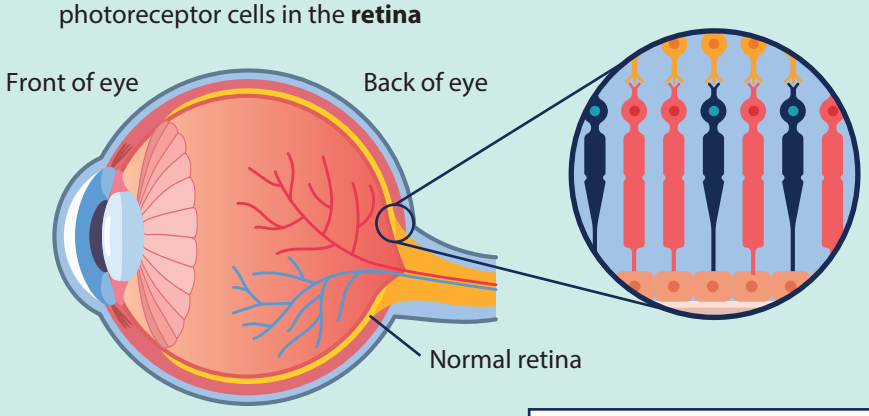
What causes XLRP?

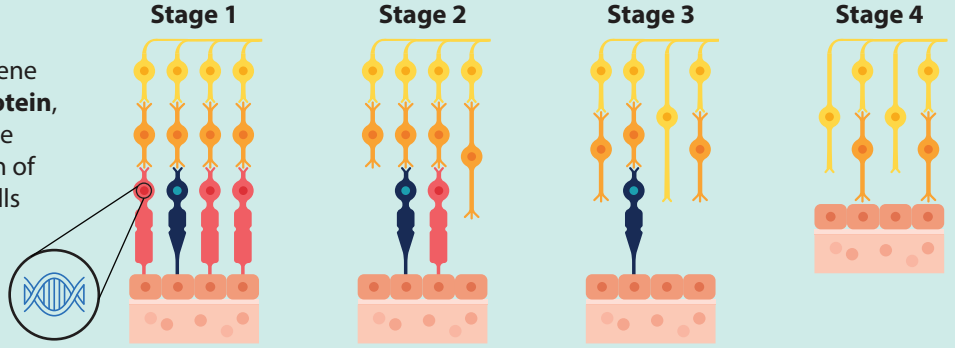
XLRP, an inherited condition, is caused by changes in the *RPGR* gene that disrupt the function of photoreceptor cells in the **retina**



Photoreceptor cells detect light and send signals to the brain to create an image

Variations in *RPGR* lead to loss of photoreceptor cells

The altered *RPGR* gene produces a faulty **protein**, which leads to the gradual breakdown of photoreceptor cells



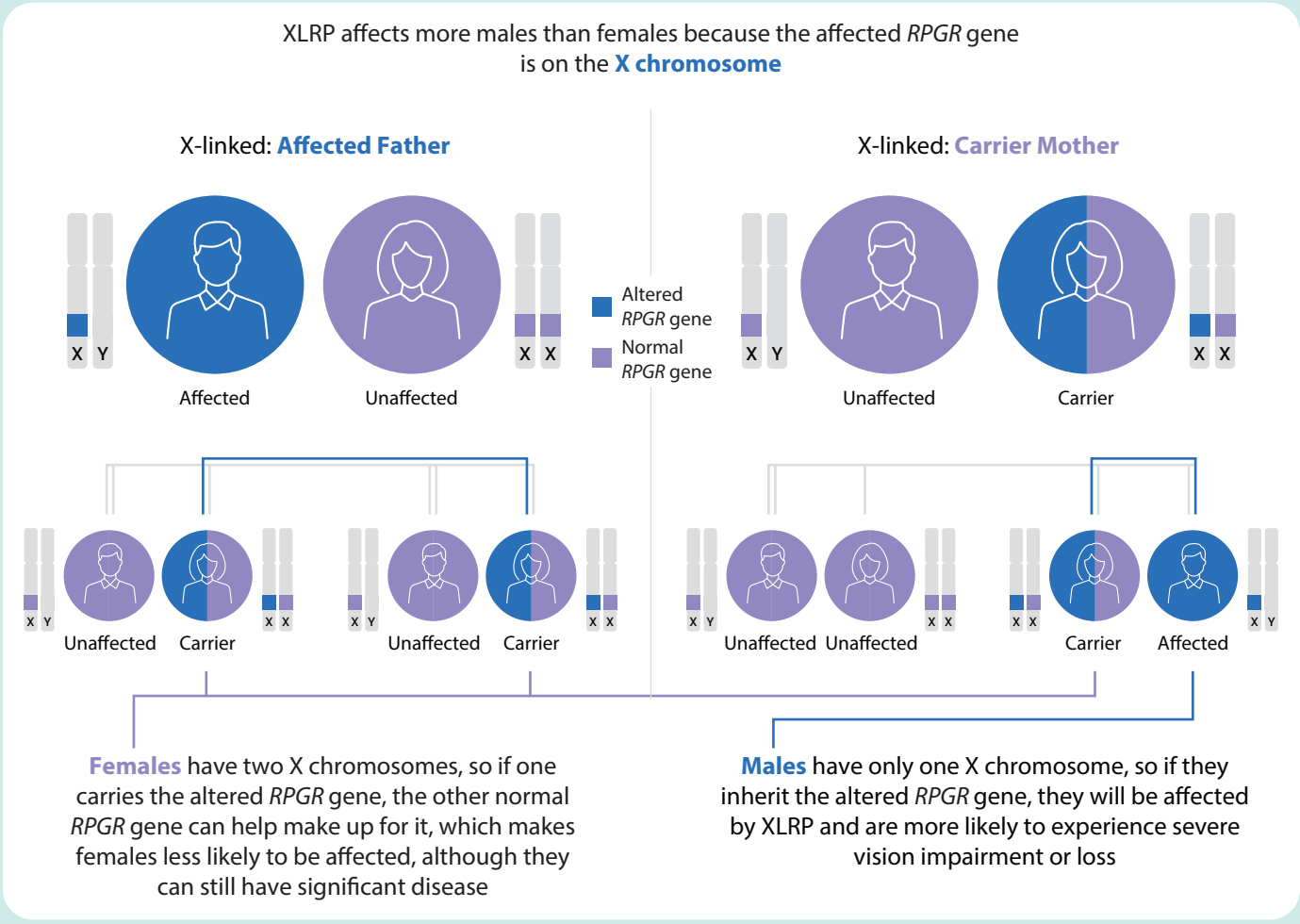
This process often begins with night blindness and tunnel vision and can progress to legal blindness

10 years of age or less

Approximately 30-40 years of age

XLRP is passed down through families

Retina: The layer at the back of your eye that reacts to light and sends signals to your brain, which allows you to see.
Photoreceptors: Specialized cells that line the retina and turn light into electrical signals that your brain can use to help you see in different light levels and colors.
Protein: A large molecule that is responsible for maintaining the structure and function of different cells in the body.



What is gene therapy?

Gene therapy aims to fix the root cause of a genetic disorder. It often does this by adding a working copy of the causative gene into a person's cells or by changing or removing the faulty gene. In this study, researchers administered bota-vec gene therapy to deliver a working copy of the affected *RPGR* gene into participants' retinal cells. This new gene copy, called the therapeutic gene (or sometimes called a healthy, functioning, or working gene), provides instructions to produce a healthy RPGR protein. This helps retinal cells function properly again.

Gene therapies primarily target **somatic cells**, which are not reproductive cells. Therefore, gene therapies do not affect genes that could be passed to future children. Since gene therapies cannot be taken as a pill, doctors must deliver them directly to a person's cells through the blood or tissue using a **vector**. A vector acts like a vehicle to carry the therapeutic gene into cells. Researchers use viruses to create vectors because they are good at entering cells. Vectors remove the virus's harmful genes, leaving only the therapeutic gene. Then, the vector is injected or infused into the patient.

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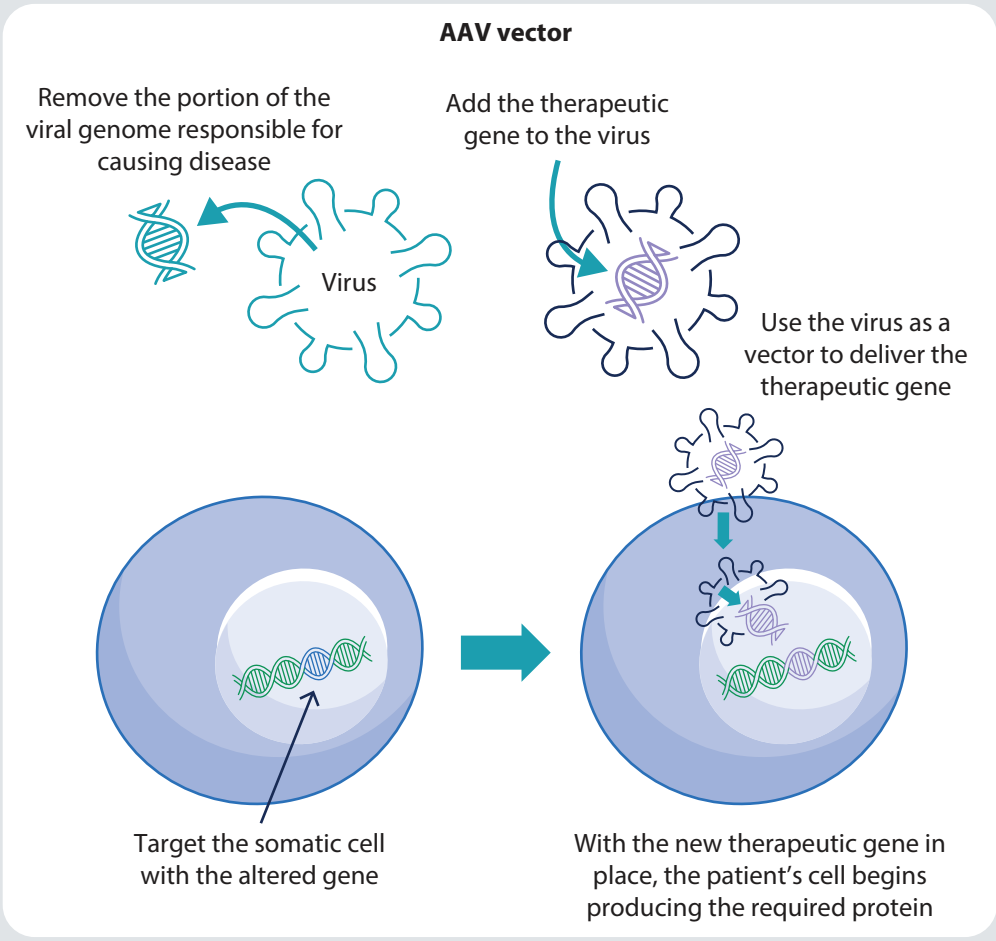
Somatic cell: Any cell in the body, except sperm and egg cells, that contains two sets of chromosomes (one from each parent); DNA changes in somatic cells affect the person but are not passed to their children.
Vector: A tool used in biology to carry and insert a gene into target cells, often made from a virus.
Adeno-associated virus: A type of virus that is commonly used as a vector in gene therapy because it is generally safe and can deliver genes directly into specific cells.

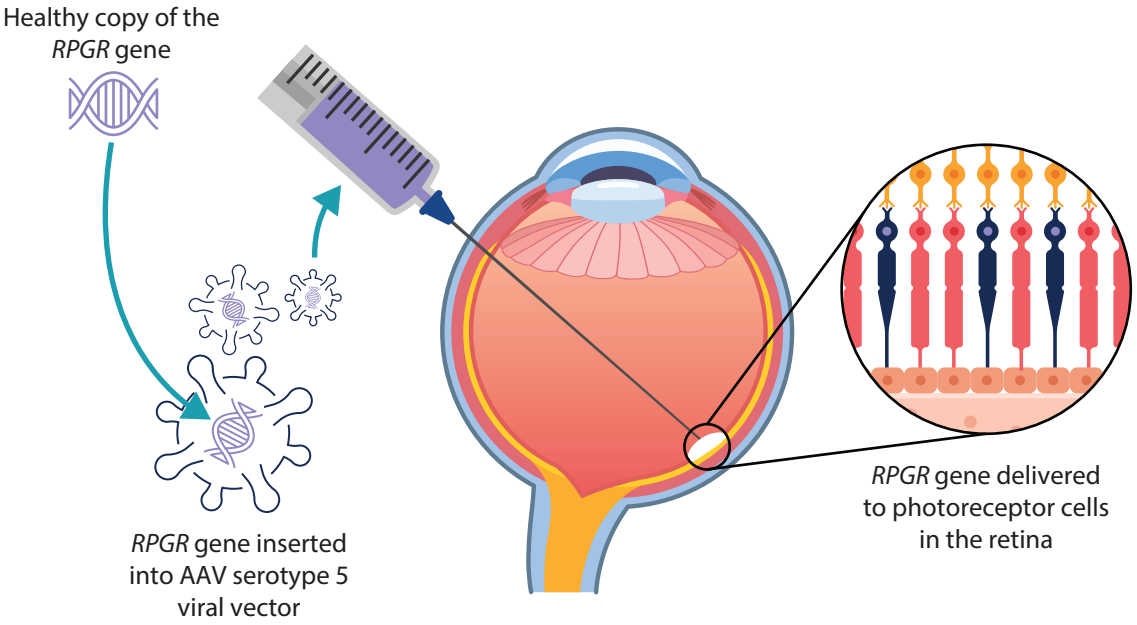
The eye is a good target for gene therapy. It's easy to reach, has special protection from the immune system, and offers different ways to deliver treatment, like injections into the eye, with fewer side effects on the rest of the body. Researchers often use **adeno-associated viruses** (AAVs) as vectors for gene therapy. AAVs are effective at delivering the gene therapy directly to specific areas, like the eye.

Although effective, AAV vectors may present challenges for delivering gene therapy. People can develop antibodies against AAVs after being infected by them in the past. Antibodies are proteins made by the immune system to recognize and bind to foreign substances, like viruses, which allow them to be eliminated from the body. If someone has antibodies against AAV, they may also react to the gene therapy vector – because its exterior looks like the virus – and block the therapy from working well. This can also trigger an immune response, which is the body's way of defending itself from foreign substances. Sometimes, this immune response can cause inflammation or swelling and flu-like symptoms. In rare cases, it may lead to complications like thrombotic microangiopathy, a serious blood clotting condition that can cause low red blood cell levels, kidney injury, or bleeding.



What is bota-vec?

Bota-vec is an investigational gene therapy that uses a virus called **AAV serotype 5** as a vector to deliver a healthy copy of the *RPGR* gene directly to photoreceptor cells in the retina



Bota-vec gene therapy is injected under the retina by a retinal surgeon. The procedure takes place in the operating room and does not require an overnight stay. Each eye only needs one outpatient procedure performed on different days.

Providing a healthy copy of the *RPGR* gene to the retina may repair photoreceptor cell damage, which helps the cells work properly to preserve vision.

Serotype: A group of viruses with the same surface markers (with over 10 types for AAV), each of which is capable of infecting specific cells, making AAV useful for targeted gene delivery; bota-vec uses the type 5 serotype of AAV.

How was this study carried out?

This study was an open-label, multicenter trial. That means it took place at several locations where both doctors and participants knew what treatment was being given. This phase 1/2 clinical study was the first time researchers studied bota-vec in humans. Researchers tested different doses of bota-vec to determine the ideal dose that was effective and had an acceptable safety profile. The main goals aimed to determine if gene therapy had an acceptable safety profile and if it helped improve vision in males with XLRP caused by changes in the *RPGR* gene.

For rare diseases treated with gene therapy, researchers often combine phase 1 and 2 studies and conduct them in patients affected by the disease. This approach enables researchers to gather data quickly with fewer participants.

The study can be broken into three parts – a dose-escalation phase, a dose-confirmation phase, and a controlled dose-expansion phase.

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Dose escalation

Researchers tested **low, intermediate, and high doses** of bota-vec to find the most effective dose with the most acceptable safety profile for adults

Dose confirmation

Researchers used the **dose with the most acceptable safety profile** from the dose escalation to confirm that it worked well and had an acceptable **safety profile for children**

Controlled dose expansion

Researchers gave the **doses with the most acceptable safety profile** to a larger group of children and adults to further assess safety and effectiveness

Participants were randomly assigned in a **1:1:1 ratio** to receive either a low or intermediate dose of bota-vec as part of the **immediate-treatment group**, or as a deferred treatment in the **control group**, where participants did not receive the treatment until after their Week 26 visit

Immediate-treatment group: Participants in the trial who received treatment with bota-vec before Week 26.
Control group: A group in a study that does not receive the tested treatment but instead receives standard treatment or a placebo, allowing researchers to compare results and determine how well the new treatment works. In this study, the control group did not receive bota-vec during the first 26 weeks of the controlled dose-expansion phase.

Who took part in the study?

The study took place at five locations in the United States and the United Kingdom and had several requirements.

To join the study, participants had to meet these criteria:

- Male 5 years of age or more
- Diagnosed with XLRP by a retina specialist
- Had a harmful (disease-causing) change in the *RPGR* gene, confirmed by a special lab test
- Had similar vision in both eyes (measured by best corrected visual acuity, or BCVA, which is an assessment of the best vision a person can achieve, and is measured using an eye chart)
- Had some healthy central retinal cells remaining
- Showed difficulty navigating in low light (for example, moonlit night or a dim room with some light from outside)

In this study, researchers considered adults to be participants who were 16 or more years of age in the United Kingdom and 18 or more years of age in the United States.

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What was evaluated?

The main goal of this study was to check if the gene therapy treatment, bota-vec, had an acceptable safety profile

Researchers looked for serious problems that might occur after bota-vec administration

They focused on five specific concerns:

1. A change in vision (measured by an eye chart)
2. Severe eye inflammation that did not improve
3. Serious eye infection called infective endophthalmitis
4. Cancer in the eye
5. Serious health problems that were not related to the eye

In the dose-escalation phase, experts reviewed safety data from each participant group for at least **9 weeks before** deciding on the next dose

The secondary goals of the study were to see if bota-vec could improve:

Functional vision
How well participants could see and move around in their daily lives

Retinal function
How well the retina was working

Visual function
How clearly participants could see and the sharpness of their vision

How was the treatment administered?

During the dose-escalation and dose-confirmation phases, doctors delivered bota-vec to the eye with poorer vision, as agreed upon by both the participant and the doctor. In the dose-expansion phase, the treatment was given to one eye chosen at random.

Before surgery, participants took:

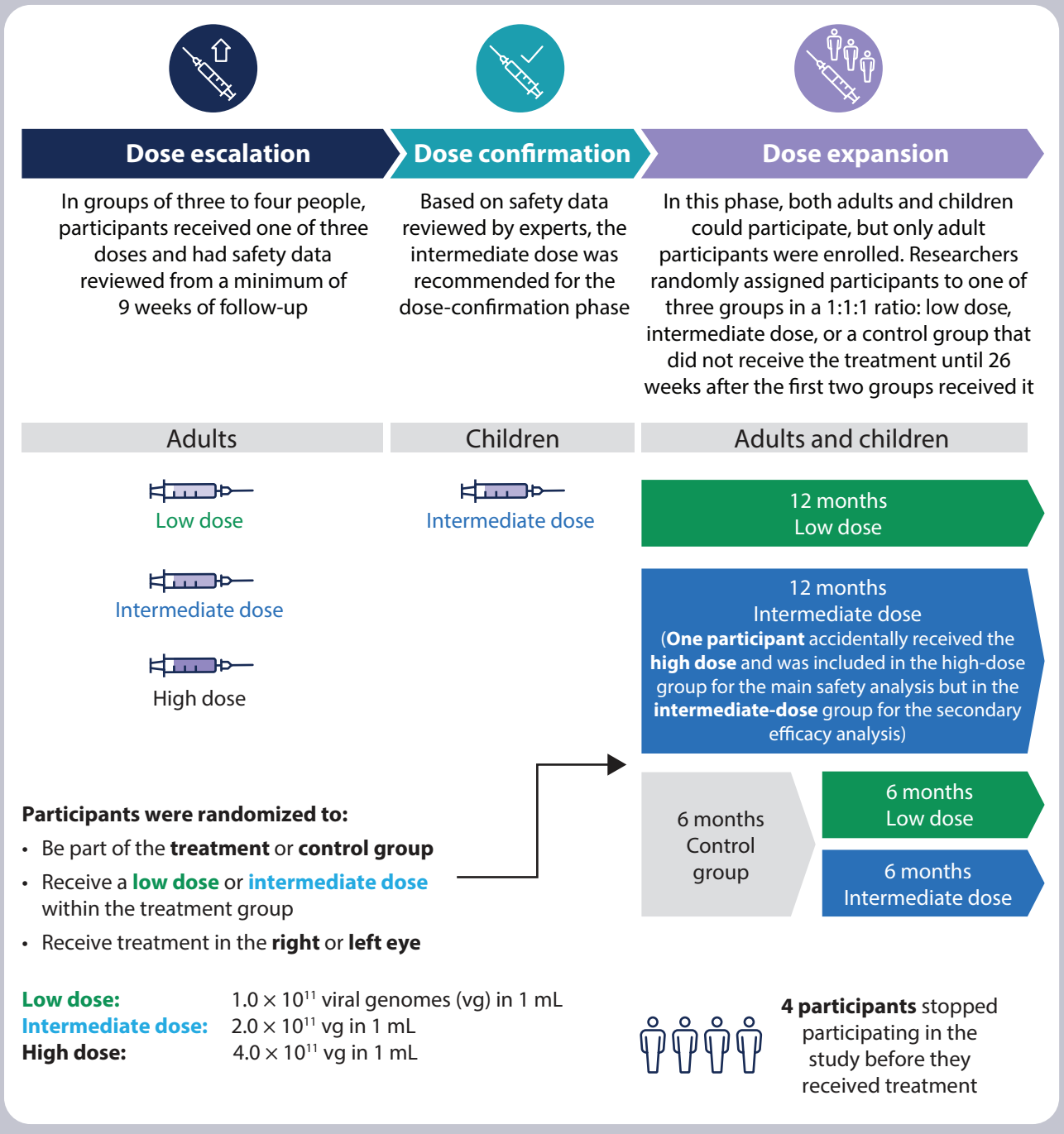
Steroids by mouth, adjusted for their age and weight, to help prevent inflammation

During surgery, local practices were followed and participants received:

- Antibiotics
- Steroids
- Medications to protect the stomach

What happened in the study?

In the dose-escalation phase of this study, small groups of adult participants received different doses of bota-vec to determine the dose that was most effective and had the most acceptable safety profile. The dose-confirmation phase used that same dose to check for safety in children. Finally, in the controlled dose-expansion phase, participants were randomly assigned to treatment with one of the two doses of bota-vec with the most acceptable safety profiles or delayed treatment with those same doses (in the control group).



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Who participated in the study?

49 males with XLRP

Average age

were White

Vision loss was similar across groups in the expansion phase

Of the 49 participants who joined the study, 45 received bota-vec. Four participants in the dose-expansion phase left the study before receiving treatment.

What were the general safety findings?

Bota-vec had a generally good safety profile and was well tolerated. **Treatment-emergent adverse events (TEAEs)** are the side effects that occurred after the participants had received treatment. TEAEs were mostly mild or moderate in severity. The severity of TEAEs was determined using a grading system called the Common Terminology Criteria for Adverse Events, which was developed by the National Institutes of Health. Researchers considered TEAEs that did not require treatment as **mild**, while they considered those that required minor treatment and affected daily tasks as **moderate**. Researchers reported no **serious** problems that affected the dose. No participants left the study early because of an adverse event.

0

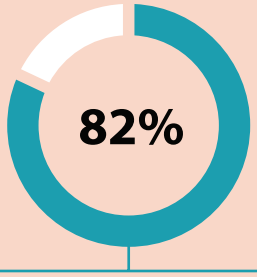
Events or side effects that may prevent a higher dose from being safely given

0

TEAEs that led to participants stopping the clinical study

How many participants had treatment-emergent adverse events?

37 of 45 participants had 1 or more TEAE before Week 26

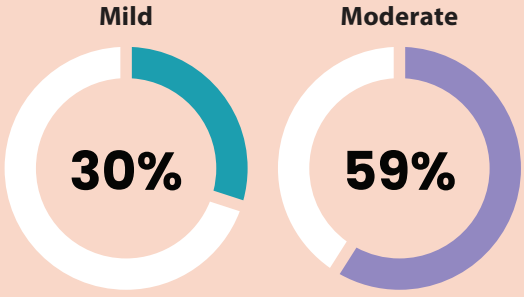


100%
of participants in the immediate-treatment group (32/32)

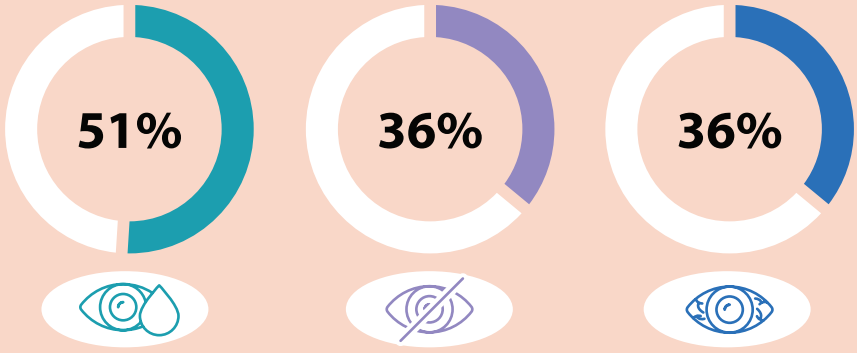
39%
of participants in the control group (5/13)

What were the most common treatment-emergent adverse events?
Across all three parts of the study, events that involved the eye were the most common TEAEs, and the severity of most TEAEs was mild to moderate.

Most TEAEs were considered mild to moderate in severity



Among the **45 participants** who received bota-vec across the dose-escalation, dose-confirmation, and dose-expansion phases, the most common TEAEs were:



Conjunctival hemorrhage **or bleeding on the surface of the eye**

Visual acuity reduction **or worsening vision**

Anterior chamber cell **or inflammation in the eye**

Were there any serious adverse events?
Researchers reported no **dose-limiting events**. Three serious adverse events occurred:

Who	What happened	What caused it	What was done
Treated participant	Retinal detachment	Caused by the surgery	Resolved with another surgery
Treated participant	Had severe eye inflammation (severe uveitis)	Caused by the treatment	Did not go away by the end of the study
Control group participant	High eye pressure	Happened after treatment	Resolved with another surgery

Were treatment-emergent adverse events related to bota-vec therapy or to the surgery?
In the immediate-treatment group, 19 of the 32 participants (59%) had a TEAE related to bota-vec. Almost all participants (31/32; 97%) had TEAEs related to the surgery. These TEAEs were typically temporary and resolved without additional treatment.

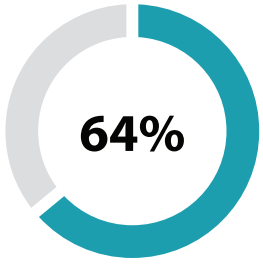
Treatment-emergent adverse event: An unexpected problem or side effect that starts or gets worse after starting treatment, either as a new issue or by making an existing condition worse.
Mild adverse event: A condition with mild or no noticeable symptoms that are only observed during tests or check-ups and do not require any treatment.
Moderate adverse event: A condition with symptoms that may require minor treatment and make it harder to do daily tasks, such as cooking, shopping, or managing money.
Severe adverse event: A condition with serious symptoms that may require hospitalization or an extended hospital stay and makes it difficult to take care of basic needs, such as bathing, dressing, eating, or using the toilet.
Dose-limiting event: A serious side effect of a drug or treatment that is bad enough to stop doctors from increasing the dose or level of that treatment.

How many participants had inflammation in the eye?

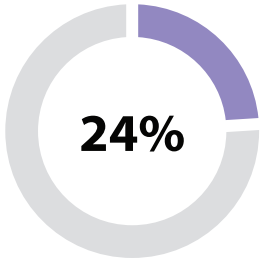
Inflammation-related TEAEs, although typically mild, were relatively common among participants. The use of a specific steroid treatment helped lower how often they occurred and how severe they were.

More than half of the participants **(25/45; 56%)** in the immediate-treatment group had at least one inflammation-related side effect. Most of these side effects were:

Mild



Moderate



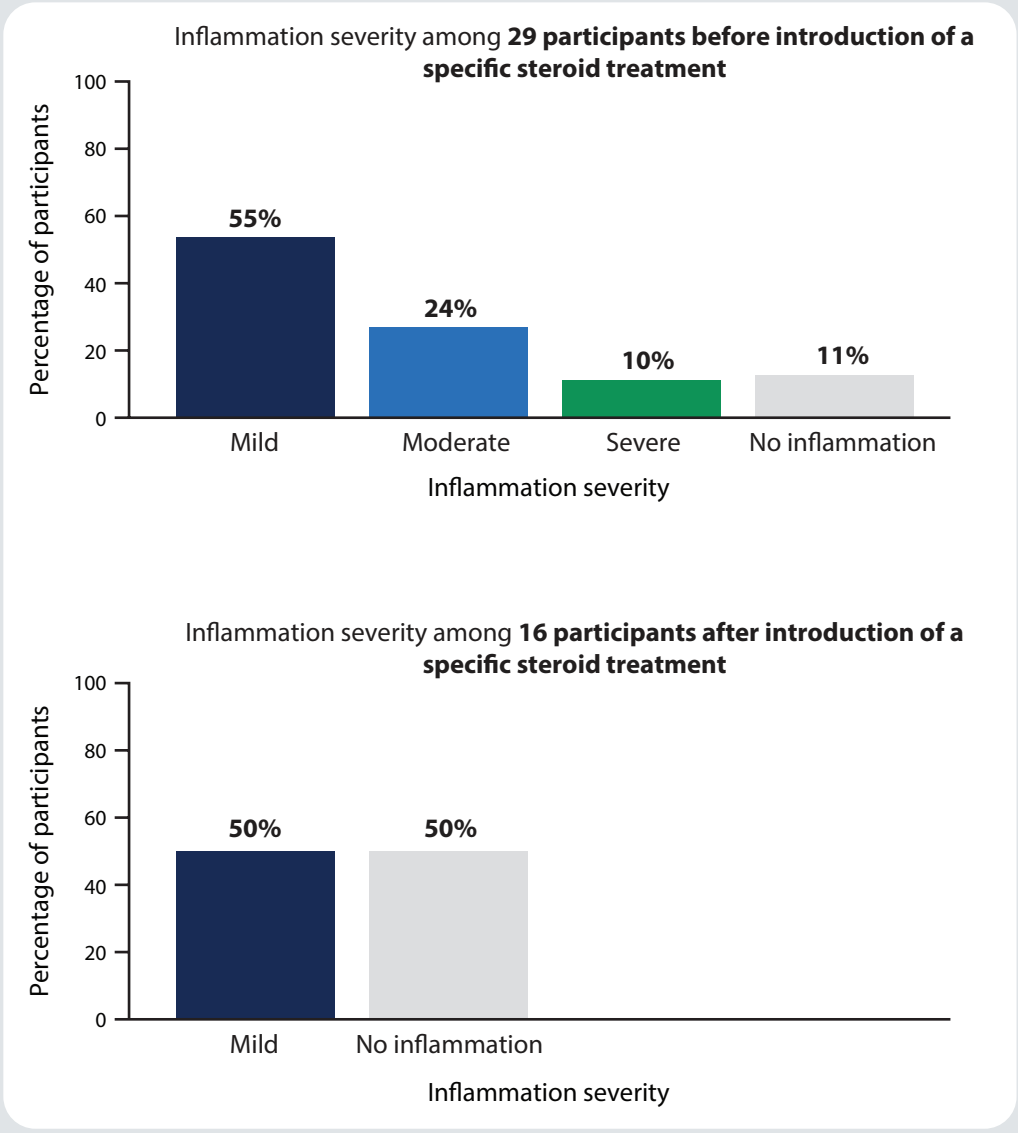
The frequency and severity of these events were lower with a specific steroid treatment used in the dose-expansion phase:

50%
(8/16 participants)

of those who received this steroid treatment had mild inflammation-related TEAEs

90%
(26/29 participants)

of those who did **not** receive this steroid treatment had inflammation-related TEAEs, with some being severe



How many participants had increased pressure in the eye?

More than one-third of participants (16/45; 36%) in the immediate-treatment group reported increased eye pressure. Increased eye pressure was linked to bota-vec in two participants and to surgery in four participants.

All cases of increased eye pressure resolved and were either monitored closely or treated using standard of care.

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Did bota-vec treatment result in improvements in functional vision?

Functional vision

A low-light maze was used to measure the participants' ability to navigate through a course under different lighting conditions. Participants who received low or intermediate doses of bota-vec were able to complete the low-light maze more quickly.

At Week 26, participants who received bota-vec navigated the maze course

37 seconds faster in 1 lux

Very dim light, similar to half moon light

19 seconds faster in 4 lux

Dim light, like residential street lights

6 seconds faster in 16 lux

Low light, similar to twilight

compared with those who did not receive bota-vec

Lux: A way to measure how bright light is in a certain area. The higher the lux number, the brighter the light. The lower the lux number, the dimmer the light.

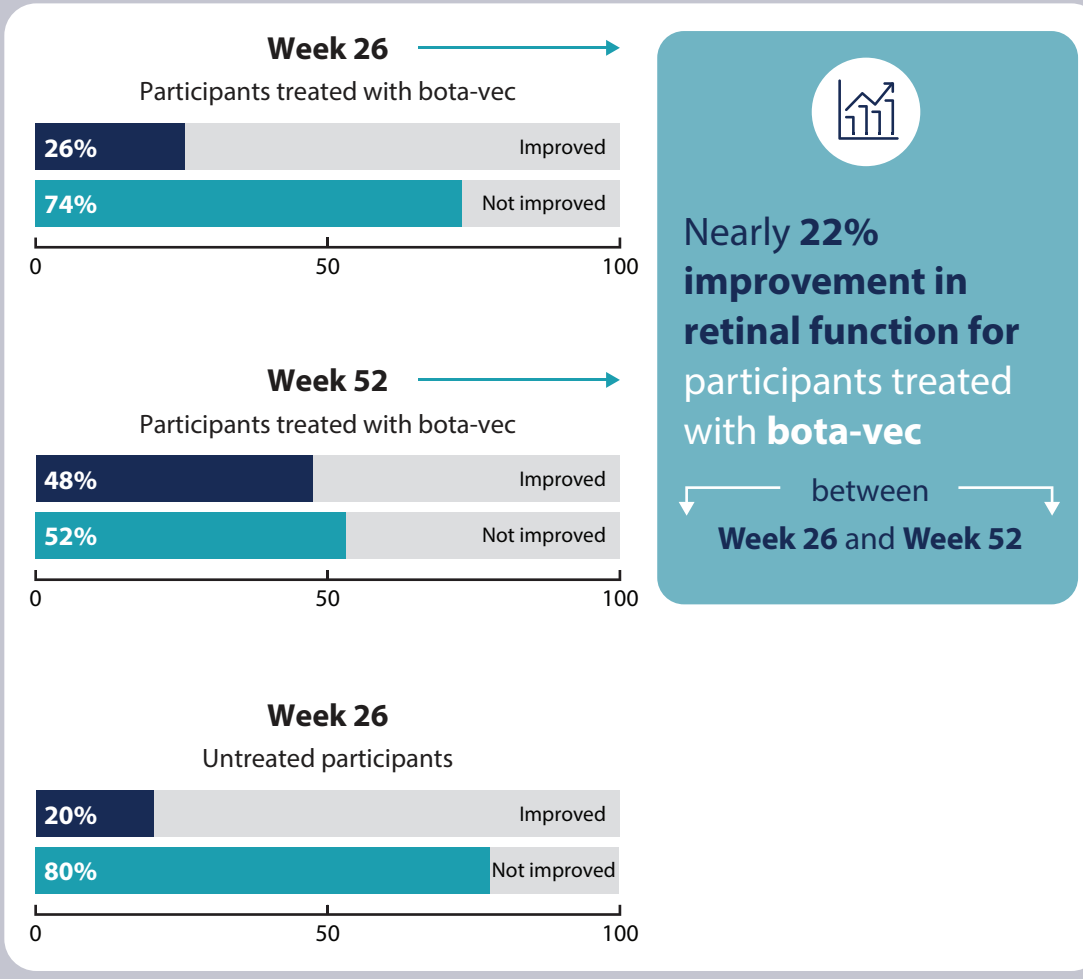
Participants treated with bota-vec also demonstrated improvements in maze-navigation time compared with their performance before treatment. These improvements were maintained through Week 52.

Did bota-vec treatment result in improvements in retinal function?

Retinal function

Participants who received bota-vec had improvements in retinal sensitivity (in other words, how well the retina responded to light). At Week 26, participants who were treated with bota-vec had a better response to light compared with untreated participants, with improvements staying stable through Week 52.

Treated participants also had better vision in the dark at both Week 26 and Week 52.



Did bota-vec treatment result in improvements in visual function?

Visual function

Participants who were treated with bota-vec showed improvements in their ability to see, with a small increase in their visual acuity, or ability to see clearly, compared with untreated participants. These improvements stayed the same through Week 52.

Researchers observed little difference in contrast sensitivity (the ability to tell the difference between shades of gray) between treated and untreated participants at Week 26. Treated participants also showed no change in contrast sensitivity from Week 26 to Week 52 compared with the beginning of the study.

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What do the results of this study mean?

This study tested a new gene therapy for the treatment of XLRP, a genetic disease that often causes legal blindness by the fourth decade of life.

Safety
Bota-vec had a generally acceptable safety profile and was well tolerated, with most side effects related to eye inflammation, which doctors managed with steroids. Three serious eye problems were reported: a detached retina from surgery, lasting eye inflammation from treatment, and high eye pressure from treatment and surgery. Adding a steroid treatment at the end of surgery helped reduce both the severity and number of eye-inflammation side effects.

Effectiveness
Participants who received bota-vec appeared to show improvements in the following areas, which were seen at Week 26 after treatment and continued through Week 52:

- Functional vision: They could better navigate a maze in low-light conditions
- Retinal function: Their retinas responded better to light, both in regular and dark conditions
- Visual function: They could see letters on an eye chart more clearly

Future directions

Based on these positive results, researchers have completed a larger phase 3 study to further test bota-vec. This larger study measured vision and eye function in a similar way, but over a longer period of time.

Important things to keep in mind

- This clinical study was mainly conducted to confirm whether the treatment had a generally good safety profile and to see early signs of how well it might be used as a treatment for XLRP. It was not designed to fully prove that the treatment works.
- This study was designed to evaluate safety and explore potential indicators of efficacy of bota-vec; as such, no formal sample size calculation to find the required number of participants for statistical testing was performed. Due to the study's exploratory nature and limited number of participants, no conclusions regarding statistical significance (to show if efficacy was due to the treatment or random chance alone) could be drawn from the results.
- Some of the tests used in the study were not part of regular eye examinations, so the results might not be the same as what we would see in real life.
- The control group received the treatment after 26 weeks, so there was no comparison made with an untreated group for the full 52 weeks.
- Additionally, COVID-19 caused some participants to miss certain tests.

Where can I find more information about this study?

The original article that reported the results of the phase 1/2 study described here was published in the *American Journal of Ophthalmology*, and you can read it for free at: https://www.ajo.com/article/S0002-9394(24)00244-7/fulltext.

You can find more information on the phase 1/2 study (NCT03252587) on the official ClinicalTrials.gov website: https://www.clinicaltrials.gov/study/NCT03252847.

Acknowledgments

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Author contributions

Michel Michaelides, Cagri G. Besirli, and James Bainbridge all critically reviewed and revised the manuscript and approved the final version for publication.

Disclosure statement

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