CLINICAL TRIAL RESULTS

A Study to Learn About the Safety of the Gene Therapy BIIB111 When Given to Both Eyes in Adults with Choroideremia (GEMINI)

Drug Studied: BIIB111 (Timrepigene emparvovec)
Protocol Number: 273CH203 (NSR-REP-02)
Study Dates:
Start Date: November 29, 2017
Completion Date: June 29, 2022

Biogen®

Thank you!

A clinical study participant belongs to the larger clinical research community around the world.

By participating in a study, they help researchers answer important health questions and learn about new medications.

In this study, researchers learned more about the **investigational drug BIIB111 and its safety in people with choroideremia**. Choroideremia is a rare genetic condition that causes vision problems and eventually leads to blindness.

An investigational drug is one that has not yet been approved for use outside of clinical studies. This is also known as the **study drug**.

Biogen, the sponsor of this study, thanks those who participated and believes it is important to share the overall results of the study. If you have questions, please speak with the doctor or staff at the study research center.

Why was this study done?

Researchers are looking for a treatment to help people with choroideremia.

Choroideremia is a rare eye condition that begins in childhood and eventually leads to blindness by middle age. It mostly affects males. Choroideremia is caused by a defect in the *CHM* gene located on the X-chromosome. This gene gives the body instructions for making a protein that is important for cells in the retina. The retina is the part of the eye that senses light. Without the protein, the cells in the retina slowly die.

People with choroideremia may first have trouble seeing in dim light. They may have a hard time seeing things on the sides of their vision. As the disease gets worse, central vision also becomes affected. Gradual vision loss occurs over many years. Most people with choroideremia become blind by their 40s. There is currently no cure or approved treatment for choroideremia.

Researchers wanted to learn about the **use of BIIB111 as a gene therapy** in male participants with choroideremia. This gene therapy works by replacing a non-working copy of the *CHM* gene with a working copy within the retina.

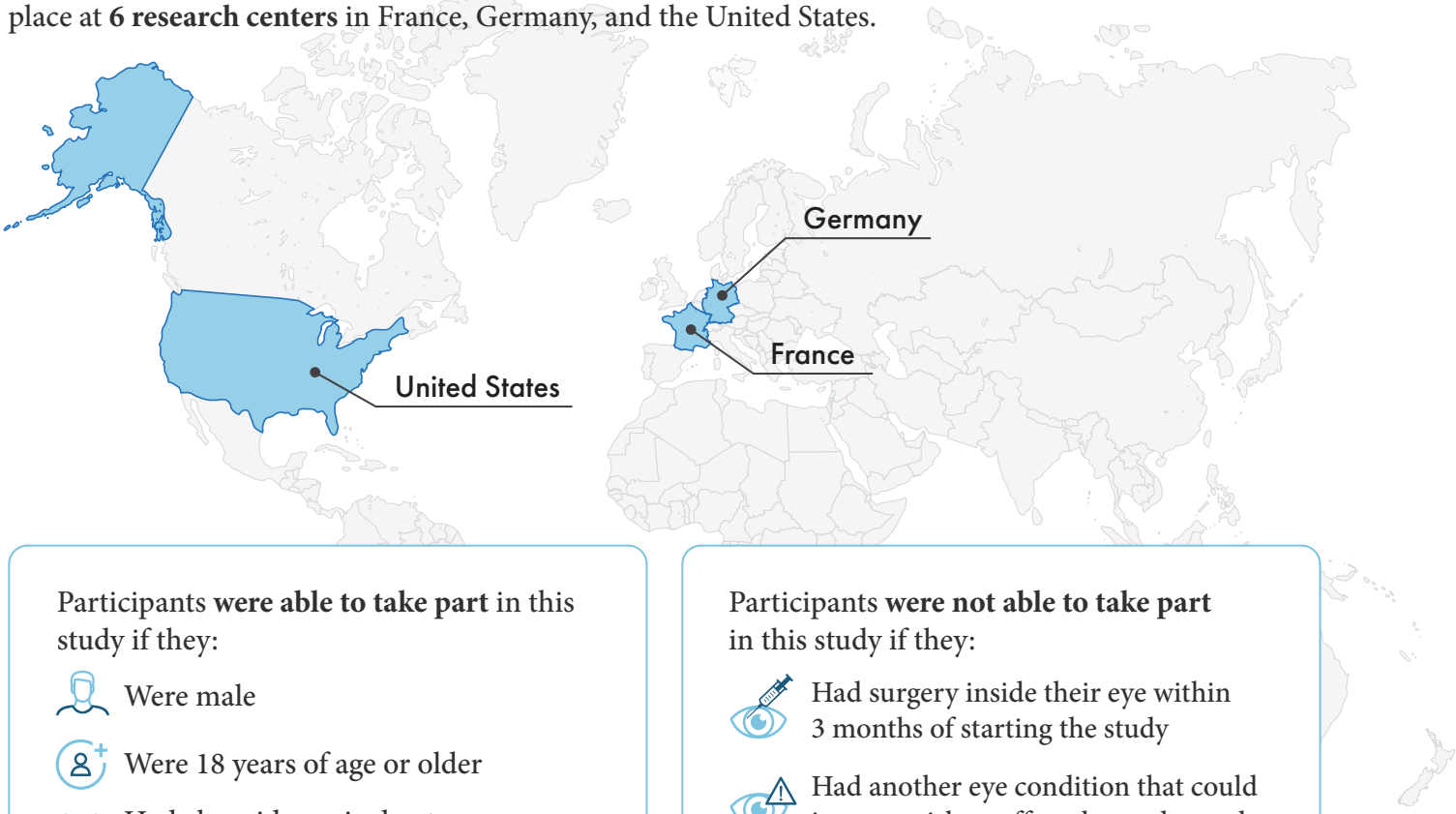
Researchers wanted to find out more about the **safety of BIIB111 injections** and how they may affect the eyes over time.

The main questions that the researchers wanted to answer were:

- Did participants' sharpness of vision decrease after receiving BIIB111?
- Were there any changes in the pressure inside the eye?
- Were any problems found in participants' eyes during examinations of the eyes with a slit lamp microscope?
- Were there any changes in the cloudiness of participants' eye lenses?
- Were any problems found in participants' eyes during exams after their eyes were dilated?
- Were there any changes found in participants' eyes using a retinal scan?
- Were there any changes to the back of the eye when examined with a light that makes certain parts of the eye's pigment glow?
- Were there any changes to the back of the eye when examined by photography?
- Were there any changes in participants' field of vision?
- Was BIIB111 found in participants' tears, urine, saliva, or blood after treatment and how long did it remain?
- Did participants develop an immune reaction to BIIB111?
- Did participants' vital signs change after receiving BIIB111?
- How many participants had adverse events during the study?

Who took part in the study?

The study included 66 participants. All participants were between **18 and 74 years old**. The study took place at **6 research centers** in France, Germany, and the United States.



Participants **were able to take part** in this study if they:

- Were male
- Were 18 years of age or older
- Had choroideremia due to defect in the *CHM* gene

Participants **were not able to take part** in this study if they:

- Had surgery inside their eye within 3 months of starting the study
- Had another eye condition that could increase risk or affect the study results

For more information on who could take part in this study, please refer to the websites listed on the last page of this summary.

What study drug did the participants receive?

Researchers studied the following drug:

- **BIIB111, up to 0.1 mL (milliliters)**, given once in each eye as an injection under the retina.

What happened during the study?

This study was:

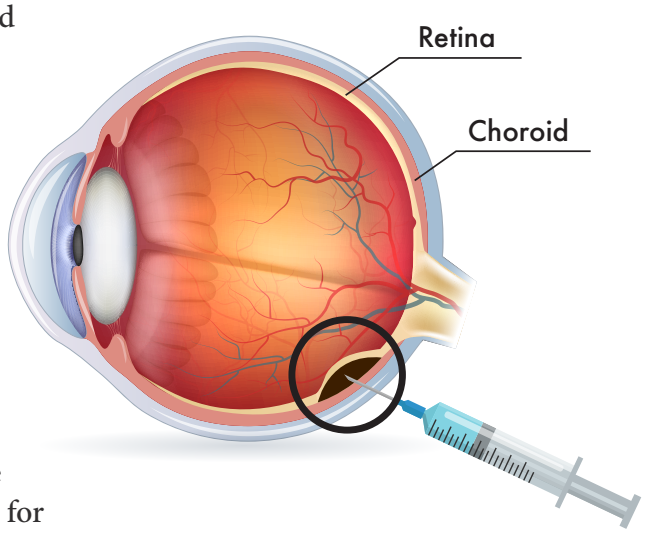
Phase 2: The researchers wanted to learn how well BIIB111 worked in a small number of participants with choroideremia. They also wanted to find out if the participants had any adverse reactions. An adverse reaction is a medical problem that the study doctors report as potentially related to the study drug.

Open label: The study was open label. This means that both the researchers and the participants knew that all participants received BIIB111.

At the beginning of the study, all participants had a screening visit.

- Doctors collected blood, tears, urine, and saliva for testing.
- They measured participants' vital signs such as pulse and blood pressure.
- The visit also included a vision test, a full eye exam, and other eye tests and scans.
- Participants also answered questions about their medical history.

For BIIB111 to be properly administered, participants had to undergo eye surgery. During the surgery, the retina was temporarily detached. Then, BIIB111 was injected under the retina.



During **screening,** researchers evaluated both eyes of each participant. They chose which eye would undergo surgery first. This was called **Study Eye 1** and it was usually the worse eye. The other eye was called **Study Eye 2**.

Study Eye 2 would undergo surgery at a later time. The exact time between surgeries was chosen by the study doctors and was different for each participant. For some participants the time between surgeries was a few months, for other participants, it was over a year later.

During **Period 1,** participants visited the clinic for surgery. Researchers injected BIIB111 into Study Eye 1, and then monitored participants. Participants had up to 9 visits during the period.

Any serious issues that arose in the eye during Period 1 had to be resolved before Period 2 could begin. When participants were ready for their 2nd surgery, they visited the clinic for a check-up. Study doctors did the same tests as they did during the screening visit.

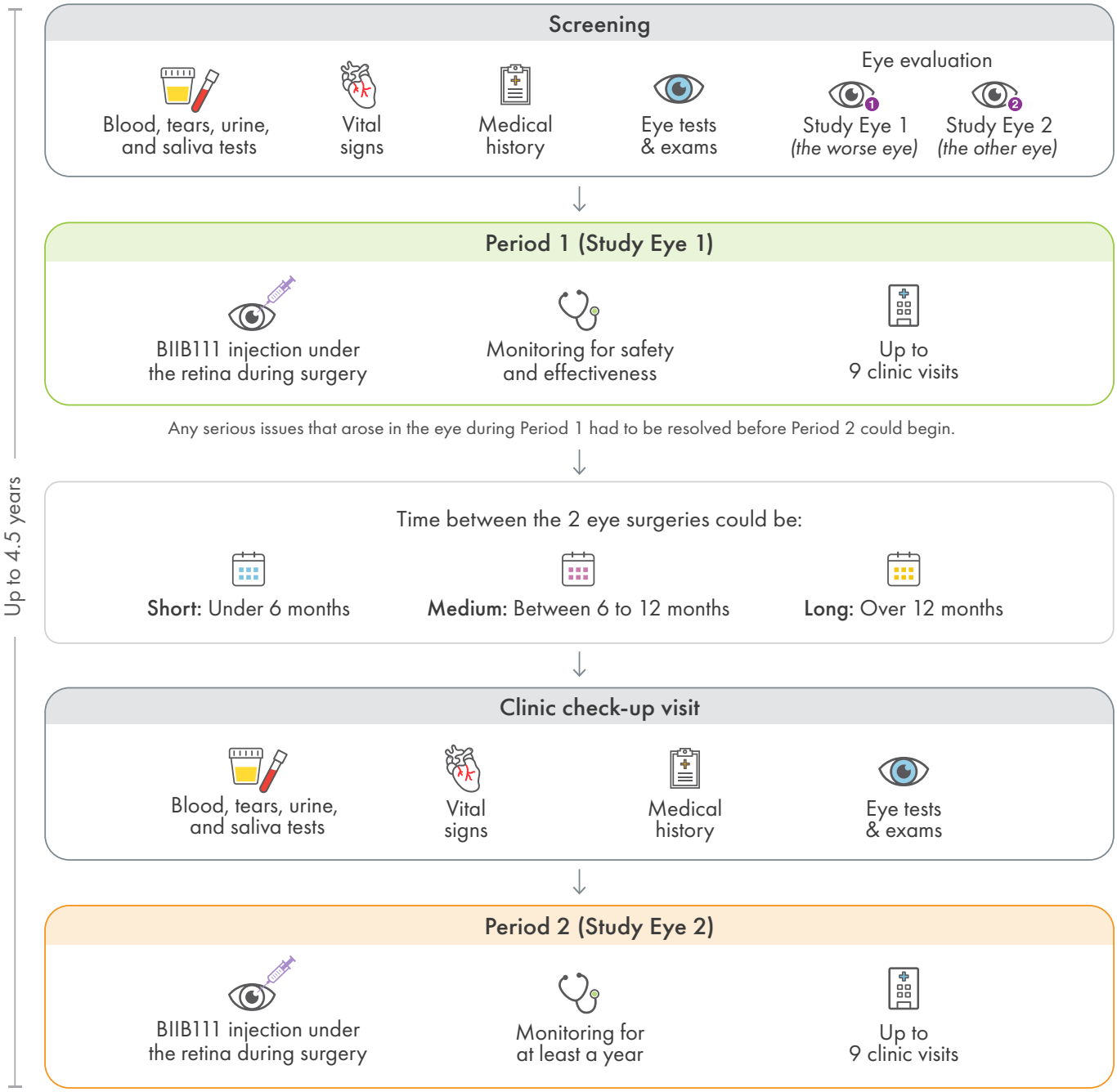
Then, **Period 2** began when participants visited the clinic for the 2nd surgery. Researchers injected BIIB111 into Study Eye 2 and then monitored participants for at least a year. Study Eye 1 continued to be monitored as well. Period 2 also had up to 9 visits.

During the **clinic visits,** researchers collected more blood, tears, urine, and saliva samples and performed vision tests and eye exams. They also checked if participants had any adverse events. **Adverse events** are any medical problems that participants experience during the study.

Some participants took part in another earlier trial for BIIB111 where they received the study drug in only 1 eye (Study Eye 1). If they joined this study, they started directly in Period 2 for the other eye (Study Eye 2).

Participants remained in this study until the 9th visit of Period 2. Some participants left early due to adverse events or other reasons. The total duration of the study was about 4 and a half years.

The graphic below shows how the study was done.



What were the study **results?**

When the study ended, Biogen created a report of the results. This is a summary of that report. The summary of the results is presented for 66 participants who received BIIB111.

The results below are from this study only. Other studies may have different results. If you have questions, please ask your study doctor or study research center staff.

Researchers collected data at each study visit. Not all 66 participants had data available for every test and every visit. The percentages provided below are based on the number of participants with data available.

Did participants' sharpness of vision decrease after receiving BIIB111?

Sharpness of vision is also called visual acuity. **Visual acuity** is a measurement of how clearly participants can see. The vision test used in the study was the **Best-Corrected Visual Acuity Test (BCVA)**.

Researchers had participants read letters at a distance of 4 meters (about 13 feet) from the chart. If participants could not read the chart at this distance, they then tried to read it at 1 meter (about 3 feet). The vision test was done multiple times throughout the study for each eye.

Overall, researchers found that both study eyes of the participants had a decrease in visual acuity after surgery. This decrease in sharpness of vision remained until the end of the study for both study eyes.

Were there any changes in the pressure inside the eye?

Researchers measured the pressure of the fluid inside the eye. Overall, they found that there were no meaningful changes to pressure in either study eye of the participants after surgery.

Were any problems found in participants' eyes during examinations of the eyes with a slit lamp microscope?

A slit lamp is a special microscope that shines a bright light in specific parts of the eye. The parts of the eye include the cornea, conjunctiva, iris, lens, and anterior segment. Study doctors used a slit lamp microscope to closely examine each part of the eye for issues.

For most participants, no issues were found. No abnormal changes were found in the cornea, conjunctiva, iris, or anterior segment at the final Month 12 visit compared to the start of the study. A few participants had temporary changes in other parts of the eye:

Lens – The lens is located near the front of the eye. It helps focus light.

- **1 participant** had a lens issue during Period 1 in Study Eye 1.
- **2 participants** had a lens issue during Period 2 in Study Eye 1.
- **1 participant** had a lens issue during Period 2 in Study Eye 2.

Anterior chamber – The anterior chamber is the fluid-filled clear front part of the eye. Researchers found signs of inflammation in the anterior chamber where cells were detected in a few participants.

- **1 participant** developed anterior chamber cells during Period 1 in Study Eye 1.
- **1 participant** developed anterior chamber cells during Period 2 in Study Eye 2.

Vitreous humor – The vitreous humor is the fluid between the lens and the retina. Researchers found signs of vitreous inflammation in a few participants.

- **1 participant** had an issue during Period 2 in Study Eye 1.
- **1 participant** had an issue during Period 2 in Study Eye 2.

Were there any changes in the cloudiness of participants' eye lenses?

Researchers examined participants' eye lenses to see if they got cloudier over time. Cloudy lenses could lead to a decrease of vision.

Overall, researchers found that most participants did not have cloudier lenses at the last visit of each period. Changes were similar in both study eyes in both periods.

Were any problems found in participants' eyes during exams after their eyes were dilated?

Researchers examined participants' eyes after using eye drops that dilated participants' pupils. This allows doctors to see the back of the eye more clearly.

Overall, researchers found no problems in most of the parts of the eyes. Temporary or minor changes were seen in the vitreous humor, the macula, and the optic nerve. Changes were similar in both study eyes in both periods.

The macula is the central part of the retina. The optic nerve carries information from the eye to the brain.

Were there any changes found in participants' eyes using a retinal scan?

Researchers used an advanced scanning technique called SD-OCT to look at different layers of the retina. No meaningful changes or serious issues were found throughout the study in either study eye or between periods.

At the start of the study, the majority of participants had very reflective spots on their retina. By the end of the study, all participants did. These types of spots are abnormal and could be a sign of eye disease.

Were there any changes to the back of the eye when examined with a light that makes certain parts of the eye's pigment glow?

The retina contains pigments that can glow when looked at with advanced imaging tools. This allows researchers to create images which show different disease processes. These images are based on the level of glowing pigment throughout the retina. That way, abnormalities can be found.

Researchers found that the areas of the retina that glow decreased slowly throughout the study after BIIB111 was given. Changes were similar in both study eyes in both periods.

The foveal center is a small central pit at the center of the retina responsible for sharp central vision. No meaningful changes were found in the foveal center during the study.

Were there any changes to the back of the eye when examined by photography?

Researchers used a special camera to take pictures of the back of the eye.

For most participants, no changes were observed. A few participants had narrowing of the small blood vessels in the retina at the last visit when compared to the start of the study.

Period 1		Period 2	
Study Eye 1 (15 participants)	**Study Eye 2** (15 participants)	**Study Eye 1** (50 participants)	**Study Eye 2** (49 participants)
3 participants (20%)	2 participants (13%)	1 participant (2%)	3 participants (6%)
1 participant had blood vessel narrowing at the start of the study in **Study Eye 1** which was resolved by the end of Period 2			

NOTE: Not all participants had this exam done.

Were there any changes in participants' field of vision?

Researchers measured the sensitivity of the retina to light. They shine a light at different parts of the retina. Participants look at a fixed spot and press a button when they see light. By doing this, doctors can create a map of participants' field of vision.

Overall, researchers found that changes were temporary and minor. The changes were similar between both study eyes at the last visit.

Was BIIB111 found in participants' tears, urine, saliva, or blood after treatment and how long did it remain?

As a gene therapy, BIIB111 uses virus-like particles called vectors to spread modified genes through cells. Researchers wanted to know if these particles could be found in various body fluids after treatment.

The list below shows the results for each bodily fluid:

Tears

- **On Day 1 after surgery,** 4 participants in Period 1 and 5 participants in Period 2 had BIIB111 in their tears.
- **After Day 14,** there was no BIIB111 found in the tears.

Saliva

- **On Day 1 after surgery,** 1 participant in Period 1 and 1 participant in Period 2 had BIIB111 in their saliva.
- **After Day 14,** there was no more BIIB111 found in the saliva.

Blood

- **On Day 1 after surgery,** no participants had a measurable amount of BIIB111 in their blood.
- **After Month 1,** there was no more BIIB111 found in the blood.

Urine

- No samples of urine had BIIB111 detected at any time.

Did participants develop an immune reaction to BIIB111?

Researchers took blood samples to measure how participants' immune systems reacted to BIIB111. The body can produce different types of antibodies and cells in response to foreign substances, including BIIB111. This process is called an immune reaction. Although antibodies are there to protect the body, they may also prevent the study drug from working or may cause an allergic reaction.

Overall, researchers found that no participants had anti-drug antibodies in their blood during the study, both before and after BIIB111 treatment. However, researchers found that some participants did have neutralizing antibodies (NAbs) to BIIB111 in their blood.

About 1/3 of the participants already had NAbs before treatment. During the study, some of these participants maintained their NAb levels, some NAb levels increased, while other NAb levels decreased.

For those participants who did not already have NAbs, a small number developed NAbs during the study, but most did not. Currently, researchers are still not sure of the significance of already having NAbs or developing them after treatment. Either way, researchers did not find an increase in allergic reactions in the participants who had NAbs in their blood.

The body can also activate white blood cells such as T-cells to target foreign substances, including BIIB111. Researchers measured the body's cellular immune response to BIIB111. They found that it was not associated with the following problems:

- Decrease in sharpness of vision
- Eye inflammation
- Allergic reaction

Did participants' vital signs change after receiving BIIB111?

Researchers measured participants' blood pressure and pulse throughout the study.

Overall, researchers found that participants' vital signs did not change over time.

How many participants had adverse events during the study?

An **adverse event** is an unwanted medical problem that may or may not be caused by a study drug. An adverse event is considered **serious** when it results in death, is life-threatening, causes lasting problems, or requires hospital care.

When new drugs are being studied, researchers keep track of all adverse events that participants have during a study. Not everyone experiences the same adverse events.

The table below shows how many participants had adverse events during this study. The number of participants is given in parenthesis.

Summary of adverse events

	Period 1 (60 participants)	Period 2 (56 participants)	Total (66 participants)
How many participants had adverse events?	100% (60)	96% (54)	100% (66)
How many participants had serious adverse events?	20% (12)	14% (8)	29% (19)
How many participants left the study due to adverse events?	7% (4)	0	6% (4)
How many participants died due to adverse events?	0	2% (1)	2% (1)

What **adverse reactions** happened during the study?

This section is a summary of the adverse reactions the participants had during the study.

An **adverse reaction** is an adverse event that the study doctors reported as related to the study drug.

When new drugs are being studied, researchers keep track of all adverse reactions that participants have during a study. Not everyone experiences the same adverse reactions.

How many participants had adverse reactions during the study?

The table below shows how many participants had adverse reactions during this study. The number of participants is given in parenthesis.

Summary of adverse reactions

	Period 1 (60 participants)	Period 2 (56 participants)	Total (66 participants)
How many participants had adverse reactions?	20% (12)	20% (11)	29% (19)
How many participants had serious adverse reactions?	7% (4)	5% (3)	11% (7)
How many participants left the study due to adverse reactions?	3% (2)	0	3% (2)
How many participants died due to adverse reactions?	0	0	0

What serious adverse reactions happened during this study?

The table below shows the most common serious adverse reactions that happened in at least 2 participants. All other serious adverse reactions happened in only 1 participant.

Serious adverse reactions

	Period 1 (60 participants)		Period 2 (56 participants)		Total (66 participants)	
	Study Eye 1	Study Eye 2	Study Eye 1	Study Eye 2	Study Eye 1	Study Eye 2
Decrease in sharpness of vision	5% (3)	0	0	5% (3)	5% (3)	5% (3)
Swelling of the retina (not caused by an infection)	3% (2)	0	0	0	3% (2)	0

What were the most common adverse reactions that happened during this study?

The table below shows the most common adverse reactions that happened in at least 2 participants. There were other adverse reactions, but they did not happen as often and are not included in the table below.

Most common adverse reactions

	Period 1 (60 participants)		Period 2 (56 participants)		Total (66 participants)	
	Study Eye 1	Study Eye 2	Study Eye 1	Study Eye 2	Study Eye 1	Study Eye 2
Decrease in sharpness of vision	5% (3)	0	0	5% (3)	5% (3)	5% (3)
Inflammation in the fluid between the lens and retina	2% (1)	2% (1)	7% (4)	7% (4)	6% (4)	8% (5)
Inflammation of the clear front part of the eye	3% (2)	0	0	2% (1)	3% (2)	2% (1)
Swelling of the retina (not caused by an infection)	3% (2)	0	0	0	3% (2)	0
Vision blurred	2% (1)	0	0	4% (2)	2% (1)	3% (2)

How did this study **help** patients and researchers?

This study helped researchers learn more about the safety of BIIB111 and the potential to help people with choroideremia.

Overall, the researchers in this study found the safety of BIIB111 was acceptable. Results were similar between study eyes and treatment periods. There were also no meaningful trends seen when comparing participants by the times between their 2 eye surgeries.

All participants had adverse events and 19 participants (29%) had at least 1 adverse reaction. Results from the various eye exams and scans showed minimal changes.

It is important to know that the results in this summary are from this study only. Other studies may have different results. A long-term follow-up study investigating BIIB111 is currently ongoing.

Where can I **learn more** about the study?

You can find more information about the study online at the following websites:

ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/NCT03507686
EU Clinical Trials Register	https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-002395-75

Official Study Title: An Open-Label Safety Study of Retinal Gene Therapy for Choroideremia with Bilateral, Sequential Administration of Adeno-Associated Viral Vector (AAV2) Encoding Rab Escort Protein 1 (REP1).

You can find more information about the long-term follow-up study, SOLSTICE, at the following websites:

ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/NCT03584165
EU Clinical Trials Register	https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-003104-42

If you have questions about BIIB111 or the results of this study, please speak with the doctor or staff at the study research center.

The results presented here are for a single study. You should not make changes to your therapy based on these results without first consulting your doctor.

Biogen, the sponsor of this study, has its headquarters in Cambridge, Massachusetts (USA).

Thank you!

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