CLINICAL TRIAL RESULTS

Clinical Trial of an Investigational Gene Therapy for X-linked Retinitis Pigmentosa

- **Drug Studied:** BIIB112
- **Protocol #:** 274RP101 (NSR-RPGR-01)
- **Study Dates:**
  - **Start:** March 16, 2017
  - **End:** November 18, 2020

Biogen

Thank you!

Thank you to the participants who took part in the study for **BIIB112.** All participants helped researchers learn more about BIIB112 in people with a specific form of **X-linked retinitis pigmentosa,** also called **XLRP.** XLRP is one of many forms of retinitis pigmentosa. Retinitis pigmentosa is a group of genetic, or inherited, diseases that cause vision problems and often leads to blindness.

NightstaRx Ltd, a Biogen company, sponsored this study and reviewed the results when this study ended. Biogen thinks it is important to share the results with the participants and the public.

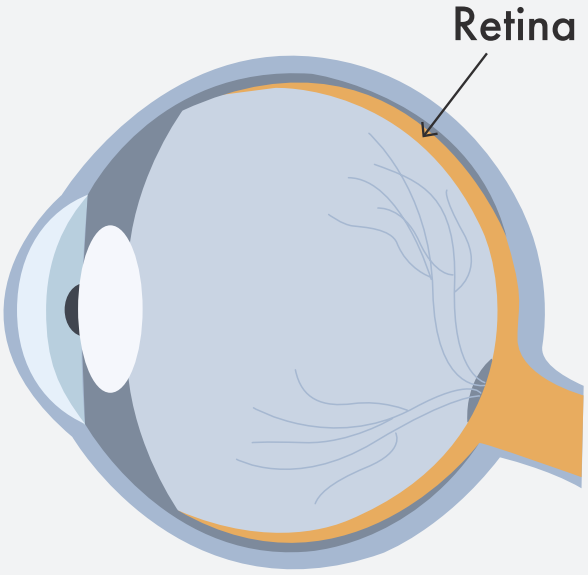
We hope this helps the participants understand and feel proud of their important role in medical research. If you have questions, please speak with the doctor or staff at the study site.

Why was this **study** needed?

Researchers wanted to learn about the use of **BIIB112 as a gene therapy in male participants with XLRP** caused by the RPGR gene. In this study, BIIB112 was intended to replace a gene that was not working with a healthy gene in the retina.

One form of XLRP is caused by a defect in the *RPGR* gene located on the X-chromosome. This is why the disease is called X-linked retinitis pigmentosa. The X-chromosome is inherited from the mother. Females have two X-chromosomes and males have only one X-chromosome. In females, having a working gene on one X-chromosome can provide some protection from the gene that is not working on their second X-chromosome. If a male has a gene that is not working on his only X-chromosome it means he will be impacted by that gene. As a result, it is mostly males that are impacted by XLRP.

Most participants living with XLRP become blind by their 40s after progressive vision loss, which occurs over a period of many decades. There are no current treatments that can cure XLRP.



Researchers wanted to find out if replacing the defective *RPGR* gene that causes XLRP with a healthy copy of the gene can help the vision of participants living with XLRP.

What was the **purpose** of this study?

The main questions that the researchers wanted to answer were:

- How many participants in each group had medical problems that were serious enough to prevent an increase in dose of study drug in Part 1?
- How many participants had a lasting improvement in the visual function of the central retina area in the study eye 1 year after receiving BIIB112 in Part 2 of the study?
- What medical problems happened during the study in Part 1 and Part 2?

In Part 2 of the study, there were other questions that the researchers wanted to answer. They were:

- How many participants had overall improvement in visual function of the study eye 1 year after receiving BIIB112?
- How many participants had an improvement in visual acuity or night vision of the study eye?
- How many participants had an improvement in their vision when tested by the Octopus 900, a type of vision test?

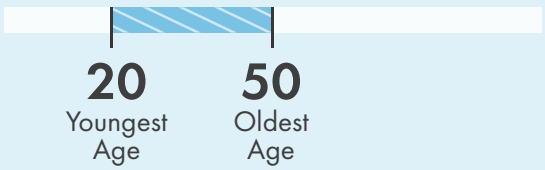
The study included a Part 1 and a Part 2. Part 1 happened before Part 2. Participants from Part 1 did not participate in Part 2.

Who **took part** in the study?

The study included **male participants** living with XLRP who had a mutation (change in the DNA sequence) in the *RPGR* gene.

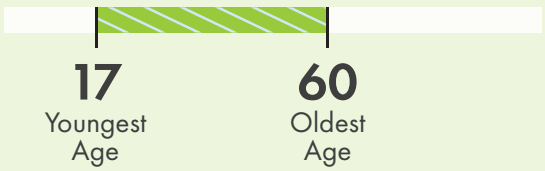
Part 1

The study included
18 participants between
20 to 50 years old.



Part 2

The study included
32 participants between
17 to 60 years old.



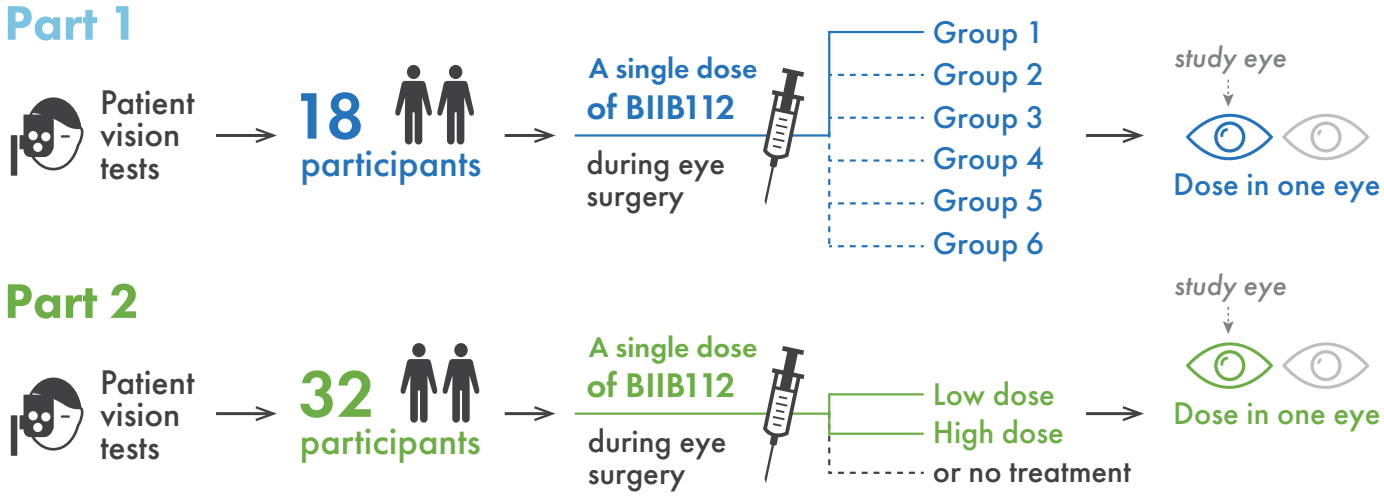
The study took place at 5 research centers in the **United States** and 3 research centers in the **United Kingdom.**

What **happened** during the study?

The study started in March 2017 and ended in November 2020. There were 49 adults and 1 teen who participated in the study. Participants had to have XLRP with a mutation (change in the DNA sequence) in the *RPGR* gene. They answered questions about their medical history before the study began. When the study ended, the sponsor created a report of the results. This is a summary of that report.

The doses and number of participants for each group in Part 1 and Part 2 are shown in the figures below.

How was the study done?



All dosed participants received BIIB112 through an injection into the eye during eye surgery. During the surgery, one dose of BIIB112 was injected under the retina of one eye. **The eye that received BIIB112 is called the study eye.** The other eye did not have surgery and did not receive BIIB112.

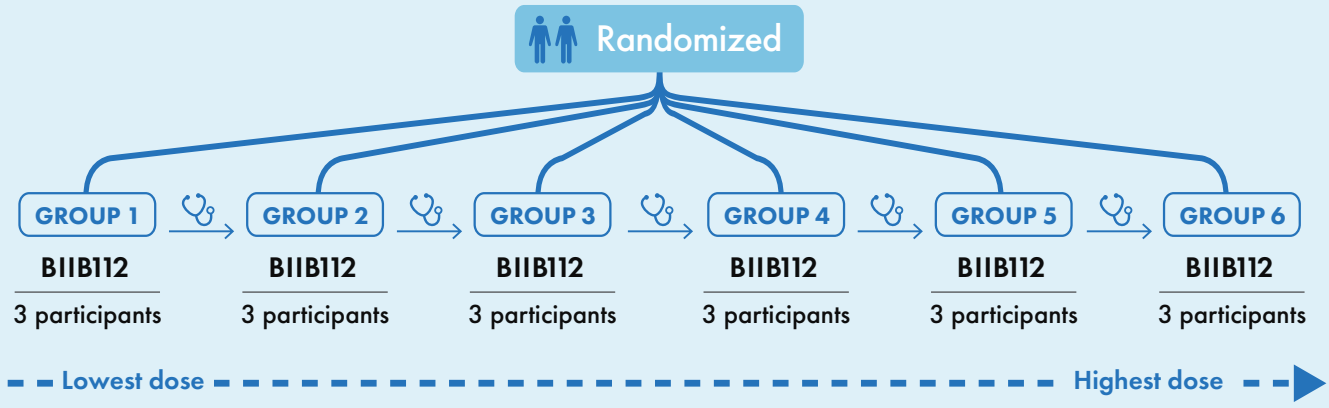
Part 1 Study Design

Participants were put into 1 of 6 different dose groups, with 3 participants in each group. Researchers gave a low dose of BIIB112 to the 3 participants in Group 1, then checked them to see if they had certain medical problems.

The medical problems researchers were interested in included:

- **Worsening vision**
- **Swelling or redness in the eye**
- **Retinal damage (damage to the retina)**
- **Other medical problems other than expected vision loss from XLRP**

If the participants in Part 1 did not have any of these medical problems after receiving BIIB112, the researchers then gave a higher dose to the next 3 participants in Group 2. Researchers repeated this process, giving Group 2 through Group 6 higher doses and checking for medical problems each time.

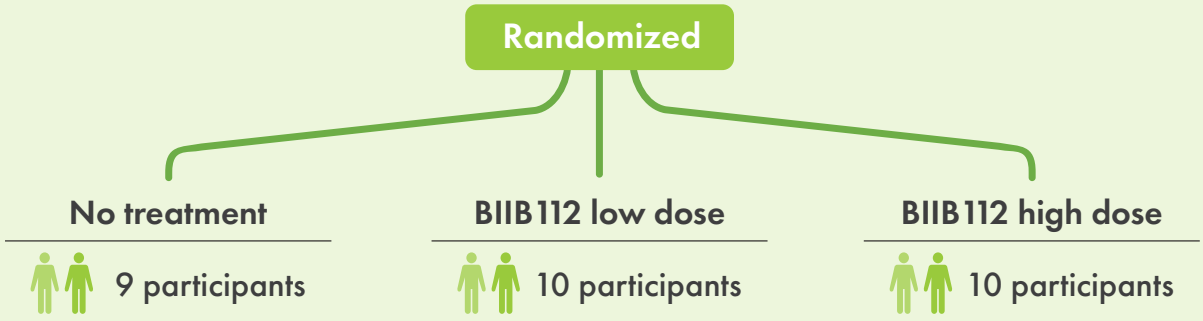


Participants visited the study site 10 times over 24 months after the surgery so that researchers could see if they had any medical problems after receiving BIIB112.

At the end of Part 1, researchers chose two doses to use in Part 2.

Part 2 Study Design

Participants were randomly put into 1 of 3 different dose groups. There were 3 participants that signed up for the study but did not received treatment. They are not included in the study results.



Participants visited the study site 8 times over 12 months after the surgery date or the planned start date for the no treatment group. During these visits, study doctors and staff checked participants for any medical problems. Participants also took part in several vision tests.

What were the study **results?**

Below is an overall summary of the results and the key questions researchers asked during the study.

Part 1

How many participants in each group had medical problems that were serious enough to prevent an increase in dose of study drug in Part 1 of the study?

None of the 18 participants in Part 1 had any of the pre-defined medical problems that would stop researchers from giving BIIB112 to the next group of 3 participants. At the end of Part 1, researchers decided it was safe to start Part 2.

Part 2

How many participants had a lasting improvement in visual function of the central retina of the study eye 1 year after receiving BIIB112 in Part 2 of the study?

Researchers used Macular Integrity Assessment (MAIA) microperimetry to see if the participants had an improvement in visual function after receiving BIIB112. Microperimetry can measure how sensitive the retina is to light at specific points. Participants were asked to look into a machine and click a button when they saw a light while staring at a fixed point. The light moved around their field of vision. This test makes a map of the sensitivity of their vision in many locations. This can measure if a person has lost any of part of their vision.

In this study, participants were considered to have a visual function improvement if their retinas were more sensitive to light.

Participants with visual function improvement in central retina of the study eye 1 year after receiving BIIB112			
	No treatment (9 participants)	**BIIB112 low dose** (10 participants)	**BIIB112 high dose** (10 participants)
Participants with improvement	2 (22%)	4 (38%)	2 (25%)

Researchers found that the differences between the 3 groups were not significant, rather than because of BIIB112.

What other questions did researchers want to answer?

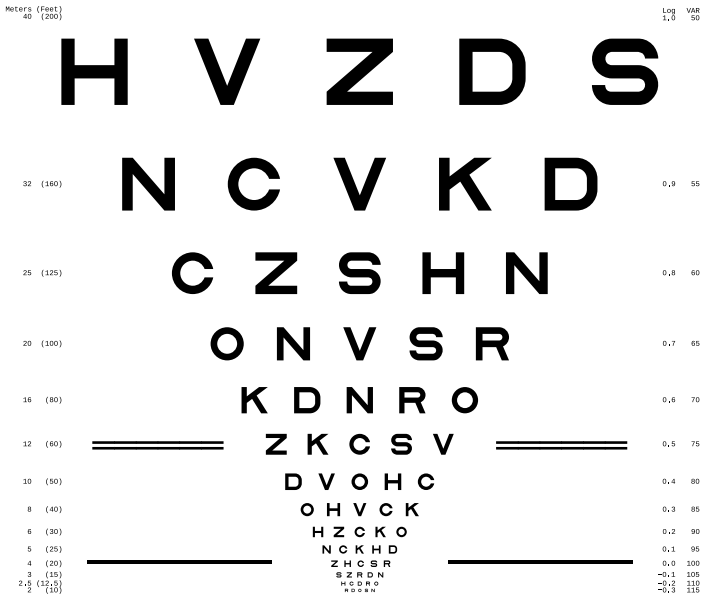
Researchers also had other questions they wanted to answer besides the main question for Part 2.

How many participants had overall improvement in visual function of the study eye 1 year after receiving BIIB112?

When compared to the group that did not receive treatment, participants in the BIIB112 low dose group had improvement in visual function 1 year after treatment. There was no difference in visual function in the high dose group.

How many participants had an improvement in clarity of vision or night vision of the study eye?

Visual acuity tested how clearly a participant can see using the Best-Corrected Visual Acuity Test. To test visual acuity initially 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 a distance of 1 meter (a little over 3 feet). The visual acuity results were reported as number of letters read correctly by the participant. The visual acuity was also tested in low light conditions, also known as night vision. This was done by placing a night vision filter over the front of each eye, then having the participant read the same chart that was used for the best-corrected visual acuity test.



- When compared to the group that did not receive treatment, more participants in the **BIIB112 low dose group** had a **visual acuity increase** of 1 line on the chart 1 year after receiving BIIB112. This means that they could read 1 smaller line than they could before receiving BIIB112.
- When compared to the group that did not receive treatment, more participants in the **BIIB112 low dose group** had a **night vision increase** of three lines on the chart 1 year after receiving BIIB112. This means that they could read 3 smaller lines than they could before receiving BIIB112.
- When compared to the group that did not receive treatment, more participants in the **BIIB112 low and high dose groups** showed a **night vision increase** of 1 line (5 letters) on the chart 1 year after receiving BIIB112.

How many participants had an improvement in their vision when tested by the Octopus 900, a type of vision test?

There was no difference between the groups that received either dose of BIIB112 and the group that received no treatment.

What **medical problems** happened in the study eye during the study?

A lot of research is needed to know whether a drug causes a medical problem, also called an adverse event. An adverse event is considered **serious** when it results in death, is life-threatening, causes lasting problems, or requires hospital care. When drugs are being studied researchers keep track of all adverse events that patients have. This includes during this study and for a while after it ends. Not everyone experiences them, and they may or may not be caused by the study drug.

One goal of this study was to learn more about the adverse events in participants who received BIIB112.

How many participants had adverse events in each group?

Part 1

Summary of Adverse Events in the Study Eye						
	BIIB112 Group 1 (3 participants)	**BIIB112 Group 2** (3 participants)	**BIIB112 Group 3** (3 participants)	**BIIB112 Group 4** (3 participants)	**BIIB112 Group 5** (3 participants)	**BIIB112 Group 6** (3 participants)
How many participants had adverse events?	3 (100%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)
How many participants had serious adverse events?	1 (33%)	1 (33%)	0	0	1 (33%)	2 (67%)

No participants discontinued from the study during Part 1 of the study due to serious adverse events.

Part 2

Summary of Adverse Events in the Study Eye			
	No treatment (9 participants)	**BIIB112 low dose** (11 participants)	**BIIB112 high dose** (12 participants)
How many participants had adverse events?	5 (56%)	11 (100%)	12 (100%)
How many participants had serious adverse events?	1 (11%)	3 (27%)	5 (42%)

No participants discontinued from the study during Part 2 of the study due to serious adverse events.

No participants died in this study from adverse events or any other health problems.

What were the **adverse events** in the study eye?

What were the **most common** adverse events?

Most Common Adverse Events in the Study Eye in Part 1	BIIB112 Group 1 (3 participants)	BIIB112 Group 2 (3 participants)	BIIB112 Group 3 (3 participants)	BIIB112 Group 4 (3 participants)	BIIB112 Group 5 (3 participants)	BIIB112 Group 6 (3 participants)
Inflamed retina	0	0	0	1 (33%)	1 (33%)	3 (100%)
Bleeding in the clear surface of the eye	3 (100%)	0	0	0	0	0
Increased pressure in the eye	0	1 (33%)	1 (33%)	1 (33%)	1 (33%)	2 (67%)
Inflamed and swollen eye	0	0	1 (33%)	1 (33%)	2 (67%)	0
Inflamed front of eye	0	2 (67%)	0	1 (33%)	0	0

Most Common Adverse Events in the Study Eye in Part 2	Untreated (9 participants)	BIIB112 low dose (11 participants)	BIIB112 high dose (12 participants)
Bleeding of the conjunctiva (the clear membrane that covers the whites of the eye)	0	6 (55%)	9 (75%)
Increased pressure in the eye	1 (11%)	6 (55%)	5 (42%)
Presence of cells in the front of the eye	0	5 (45%)	6 (50%)
Reduced vision	0	2 (18%)	5 (42%)
Suture-related complications	0	0	5 (42%)
Inflamed retina	0	0	5 (42%)
High white blood cell count	0	2 (18%)	4 (33%)
Swelled macula	0	2 (18%)	4 (33%)
Straight lines appear wavy	0	1 (9%)	4 (33%)
Vision blurred	1	1 (9%)	4 (33%)
Presence of cells in the back of the eye	0	1 (9%)	4 (33%)

What **serious adverse events** did participants have?

Part 1

Serious Adverse Events in the Study Eye						
	BIIB112 Group 1 (3 participants)	**BIIB112 Group 2** (3 participants)	**BIIB112 Group 3** (3 participants)	**BIIB112 Group 4** (3 participants)	**BIIB112 Group 5** (3 participants)	**BIIB112 Group 6** (3 participants)
Reduction in visual acuity	0	0	0	0	1 (33%)	1 (33%)
Retina detached from the back of the eye	0	1 (33%)	0	0	0	0
Vision loss	1 (33%)	0	0	0	0	0
Noninfective retinitis	0	0	0	0	0	1 (33%)

Part 2

Serious Adverse Events in the Study Eye			
	Untreated (9 participants)	**BIIB112 low dose** (11 participants)	**BIIB112 high dose** (12 participants)
Reduction in visual acuity	0	1 (9%)	2 (17%)
Fluid in sub-retinal space	0	0	3 (25%)

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

You can find more information about the study online at www.clinicaltrials.gov. Once on the site, type **NCT03116113** into the search box and click **Search**.

You can also find more information online at Clinical Trials Register. Once on the site, click **Home & Search**, then type **2016-003852-60** in the search box and click **Search**.

If you have questions about BIIB112 or the results of this study, please speak with the doctor or staff at the study research center.

Official Study Title: A dose escalation (phase 1), and dose expansion (phase 2/3) clinical trial of retinal gene therapy for X-linked retinitis pigmentosa using an adeno-associated viral vector (AAV8) encoding retinitis pigmentosa GTPase Regulator (RPGR)

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

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.

US Clinical Study Database

- **https://www.clinicaltrials.gov/ct2/show/NCT03116113**
- www.clinicaltrials.gov
- Study #: NCT03116113

EU Clinical Study Database

- **https://www.clinicaltrialsregister.eu/ctr-search/search?query=2016-003852-60**
- www.clinicaltrialsregister.eu
- Study #: 2016-003852-60

Thank you.

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