CLINICAL TRIAL RESULTS

A Study to Learn More About the Safety of BIIB078 in Adults with *C9ORF72*-Associated Amyotrophic Lateral Sclerosis

- **Drug Studied:** BIIB078
- **Protocol Number:** 245AS101
- **Study Dates:**
  - **Start Date:** 10 September 2018
  - **Completion Date:** 17 November 2021

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Thank you!

Thank you to the participants who took part in this study for BIIB078. In this study, researchers learned more about the safety of the study drug, BIIB078, to see if it could be used to help people with ***C9ORF72*-associated amyotrophic lateral sclerosis (*C9ORF72*-ALS).**

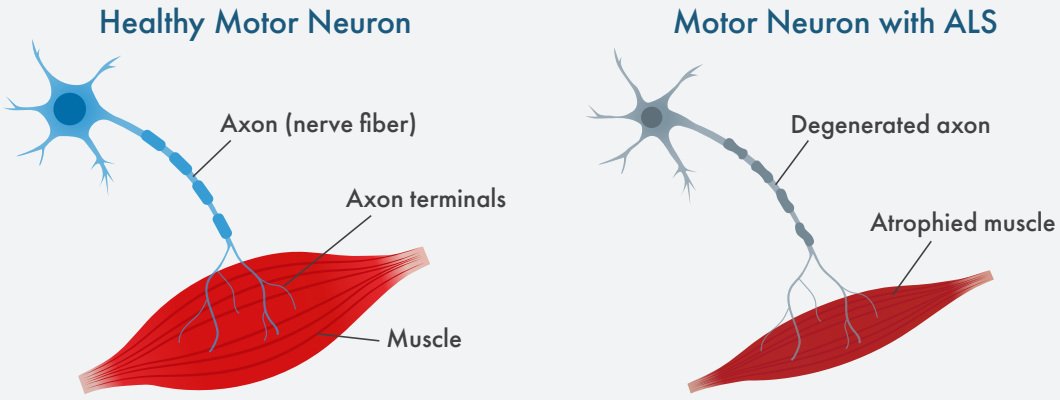
Biogen sponsored this study and reviewed the results when this study ended. Biogen believes it is important to share the results with study participants and the public.

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

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

Researchers are looking for new drugs to help people living with **amyotrophic lateral sclerosis,** also known as **ALS.**

ALS is a rare **neurodegenerative disease** that damages nerve cells in the brain and spinal cord which help control movement. These nerve cells are called **motor neurons**.



Damage to motor neurons in ALS causes weakness in muscles that may lead to difficulty walking, speaking, eating, and breathing. It is a progressive disease, which means that it slowly gets worse with time.

The cause of ALS varies. In certain people, a mutation in a specific gene in their DNA can lead to the development of ALS. The most common genetic cause of ALS is a **mutation in the *C9ORF72* gene**. Researchers think this mutation leads to the production of toxic genetic materials and proteins. The *C9ORF72* genetic form of ALS is referred to as *C9ORF72*-associated ALS, or simply ***C9ORF72*-ALS**.

While there are some approved treatments for ALS, there is no specific treatment for *C9ORF72*-ALS. In this study, researchers studied an investigational drug called BIIB078. This drug was designed to stop the mutated form of the C9ORF72 gene from producing toxic materials.

This study was done to learn about the safety of the study drug, BIIB078, in people with *C9ORF72*-ALS.

The main question that the researchers wanted to answer was:

- How many participants had adverse events during the study while taking BIIB078?

Who took part in the study?

The study included **106 participants** at 22 research centers in **6 countries.** The map below shows how many participants were in each country.

The study included **48 (45%) men** and **58 (55%) women.** Participants were between 30 and 73 years old with an average age of 57 years.

48 (45%) men

58 (55%) women

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

- Were at least 18 years of age
- Had ALS with a documented disease-causing *C9ORF72* mutation
- Had at least 50% of their predicted lung strength
- Met other key study requirements

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

- Were taking certain medications prior to the study or were taking a study drug in another study
- Had certain medical conditions
- Had ongoing infection(s) or irregular screening test results
- Were unable to meet other necessary criteria required to participate in the study

For more information on the requirements needed to take part in this study, please refer to the websites listed at the **end of the summary**.

What **happened** during the study?

The study started in September 2018 and ended in November 2021. There were 106 people who participated in the study.

This was a **Phase 1 study.** In a Phase 1 study, researchers typically look to see how an experimental drug works in the human body and they check for any side effects. In this study, participants received either the study drug (BIIB078) or **placebo.** Who received which drug was decided **randomly.** The study was also **double-blind,** which means that neither the participants nor the researchers knew who received which drug.

A **placebo** looks like the study drug but does not contain any active ingredients. Using a placebo helps researchers learn if the results of the study are due to the study drug or other factors.

The researchers used a computer program to **randomly** choose if a participant received BIIB078 or placebo. This process helps to treat participants fairly and allows treatment effects to be compared in an unbiased way.

A **double-blind** study means that none of the participants, doctors, or other study staff knew if each participant took the study drug (BIIB078) or placebo. This is done to make sure the study results are not influenced in any way.

At the beginning of the study, all participants visited the clinic to make sure they could join the study. This visit included an evaluation of their ALS disease, a physical and neurologic exam, hearts tests, and blood and urine tests. They also answered questions about their medical history. This part of the study lasted 6 weeks.

In this study, participants entered into 6 different dosing groups. Participants were given either BIIB078 or placebo in each group. Participants had a 75% chance of receiving BIIB078 and a 25% chance of receiving placebo. At each dose level, at least 6 participants were given BIIB078 and at least 2 participants were given placebo. Researchers completed testing each group before starting the next one.

Participants receiving BIIB078 in the first group took the lowest dose. Researchers decided whether to start the next group at a higher dose based on the safety results from the first group. This continued for each of the following groups. The dose of BIIB078 was measured in milligrams, which is shortened to mg.

The list below shows the doses of BIIB078 that participants in each group received:

- **Group 1:** 5 mg
- **Group 2:** 10 mg
- **Group 3:** 20 mg
- **Group 4:** 35 mg
- **Group 5:** 60 mg
- **Group 6:** 90 mg

BIIB078 or placebo were injected with a thin needle into the lower back and into the fluid around the spinal cord. This fluid is called the cerebrospinal fluid, also known as CSF. This medical procedure is known as a lumbar puncture.

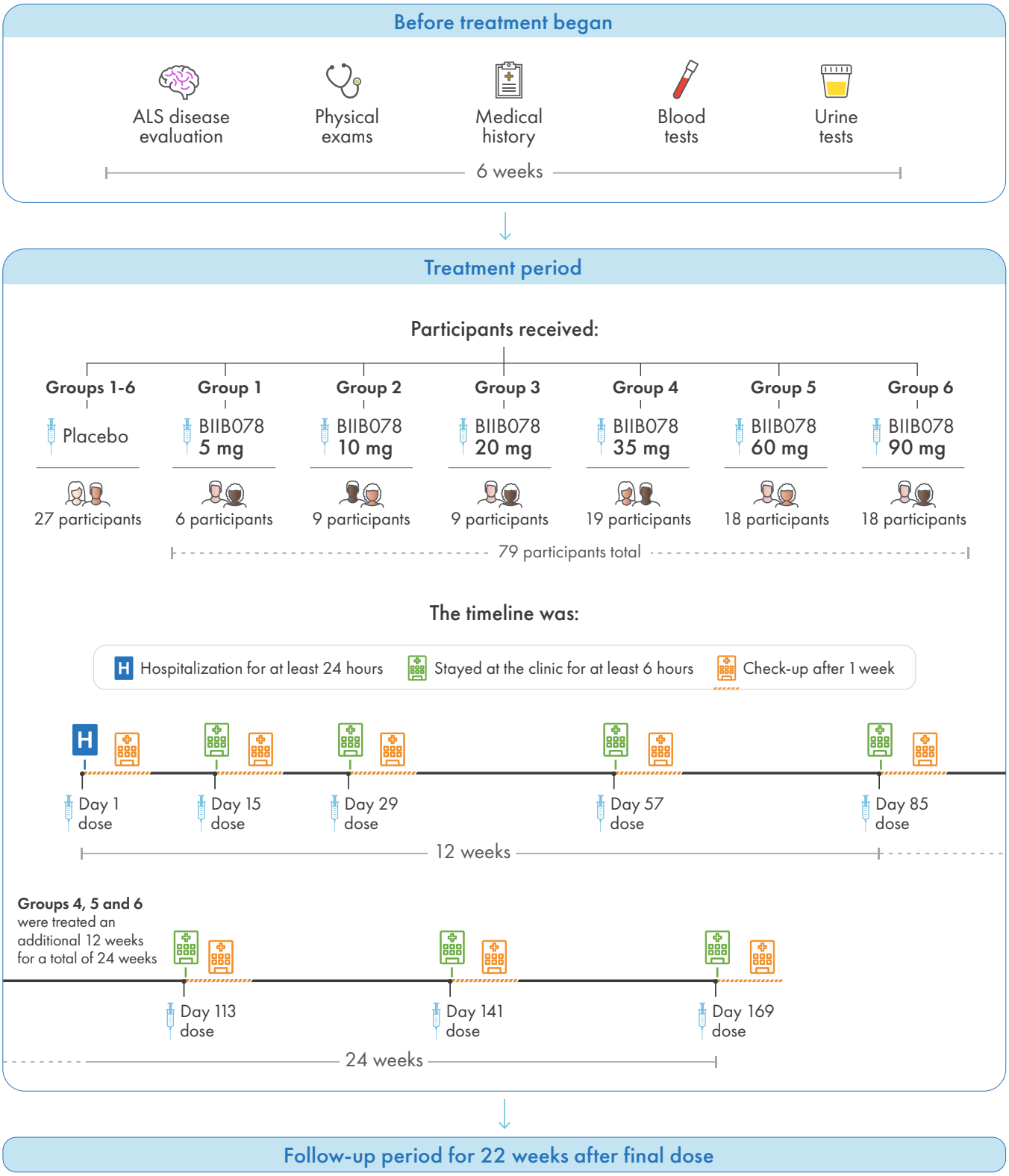
- Participants in Groups 1, 2, and 3 received up to 5 doses of BIIB078 or placebo over about 3 months.
- Participants in Groups 4, 5, and 6 received up to 8 doses of BIIB078 or placebo over about 6 months.

After the first dose, participants were hospitalized for at least 24 hours. After each other dose, they stayed at the clinic for at least 6 hours. During this time, researchers checked participants for any adverse events. An adverse event is a new or worsening medical problem that may or may not be caused by a study drug.

During the study, researchers also regularly collected samples of CSF, blood, urine, and reports of adverse events. They checked these samples to minimize participants' risk, while also tracking levels of BIIB078 as well as other substances that may be related to ALS disease activity.

Participants visited the study clinic again 1 week after receiving each dose for a check-up. Researchers also called participants regularly throughout the study to check on them. Participants returned to the clinic 7 weeks and 13 weeks after the final dose for follow-up visits. Participants stayed in the study for up to about 1 year.

The graphic below shows how the study was done.



What were the study **results?**

When the study ended, Biogen reviewed the data and created a report of the results. This is a summary of that report. Below is an overall summary of the results and the key questions researchers asked during the study.

How many participants had adverse events during the study while taking BIIB078?

This section is a summary of the adverse events the participants had during the study. An **adverse event** is a new or worsening medical problem that may or may not be caused by a study drug. A lot of research is needed to know whether a study drug causes 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 new drugs are being studied, researchers keep track of all adverse events that happen to participants during a study. Not everyone experiences the same adverse events, and they **may or may not** be caused by the study drug.

A summary of all the adverse events that happened during the study are shown in the table below. The number of participants is given in parenthesis.

Summary of adverse events

	Placebo 27 participants	BIIB078						
		5 mg 6 participants	10 mg 9 participants	20 mg 9 participants	35 mg 19 participants	60 mg 18 participants	90 mg 18 participants	Total 79 participants
How many participants had adverse events?	100% (27)	100% (6)	100% (9)	100% (9)	100% (19)	100% (18)	100% (18)	100% (79)
How many participants had serious adverse events?	33% (9)	0	22% (2)	11% (1)	37% (7)	6% (1)	17% (3)	18% (14)
How many participants stopped treatment because of adverse events?	4% (1)	0	0	0	16% (3)	6% (1)	11% (2)	8% (6)
How many participants died due to adverse events?	11% (3)	0	11% (1)	0	16% (3)	6% (1)	0	6% (5)

There were 8 deaths during this study.

- 3 participants in the **placebo group** and 1 participant in the **BIIB078 group** died because they had difficulty breathing.
- 1 participant in the **BIIB078 35 mg group** died due to shortness of breath as a result of disease progression.
- 1 participant in the **BIIB078 35 mg group** died because their heart stopped pumping after continued disease progression.
- 1 participant in the **BIIB078 35 mg group** died due to a head injury after falling.
- 1 participant in the **BIIB078 60 mg group** died due to a blood clot in their lungs.

Study doctors did not think any of these deaths were related to BIIB078 or placebo.

What serious adverse events happened during the study?

During the study, 23 out of 106 total participants (22%) reported having a serious adverse event. Study doctors did not think any of the serious adverse events were related to BIIB078 or placebo. Most events were related to underlying ALS disease or disease progression.

The table below shows the serious adverse events that happened in at least 2% of participants taking BIIB078.

Serious adverse events								
	Placebo 27 participants	BIIB078						
		5 mg 6 participants	10 mg 9 participants	20 mg 9 participants	35 mg 19 participants	60 mg 18 participants	90 mg 18 participants	Total 79 participants
Breathing failure	7% (2)	0	11% (1)	0	16% (3)	0	6% (1)	6% (5)
ALS progression	0	0	0	0	11% (2)	0	0	3% (2)
Difficulty swallowing	4% (1)	0	0	0	5% (1)	0	6% (1)	3% (2)
Fall	0	0	0	0	5% (1)	0	6% (1)	3% (2)
Lung infection caused by breathing in food or fluids	0	0	0	0	11% (2)	0	0	3% (2)
Blood clot in the lungs	0	0	0	0	0	6% (1)	6% (1)	3% (2)

What were the most common adverse events that happened during the study?

During the study, all 106 participants (100%) reported having at least 1 adverse event.

The table below shows the most common adverse events that happened in at least 15% of participants taking BIIB078.

Most common adverse events								
	Placebo 27 participants	BIIB078						
		5 mg 6 participants	10 mg 9 participants	20 mg 9 participants	35 mg 19 participants	60 mg 18 participants	90 mg 18 participants	Total 79 participants
Fall	37% (10)	67% (4)	44% (4)	33% (3)	58% (11)	56% (10)	56% (10)	53% (42)
Pain from study procedure	52% (14)	50% (3)	33% (3)	44% (4)	42% (8)	61% (11)	33% (6)	44% (35)
Headache	52% (14)	67% (4)	22% (2)	22% (2)	32% (6)	33% (6)	11% (2)	28% (22)
Post lumbar puncture syndrome*	30% (8)	17% (1)	22% (2)	11% (1)	37% (7)	28% (5)	22% (4)	25% (20)
Joint pain	22% (6)	33% (2)	22% (2)	22% (2)	5% (1)	17% (3)	28% (5)	19% (15)
Bruising	19% (5)	0	11% (1)	11% (1)	21% (4)	17% (3)	28% (5)	18% (14)
Fatigue	19% (5)	0	22% (2)	11% (1)	16% (3)	0	39% (7)	17% (13)
Constipation	30% (8)	0	22% (2)	22% (2)	11% (2)	17% (3)	17% (3)	15% (12)

*Post lumbar puncture syndrome is a headache along with dizziness, nausea, and vomiting that people may experience after having a sample of their CSF taken.

What related adverse events happened during the study?

A related adverse event is a new or worsening medical problem that a participant experiences during the study that the study doctor thinks is related to the study drug. Only those adverse events that the study doctors believed to be related to treatment with BIIB078 or placebo are included in this section. However, these adverse events are not confirmed to be caused by BIIB078 or placebo.

The table below shows how many participants had related adverse events during the study.

Summary of related adverse events								
	Placebo 27 participants	BIIB078						
		5 mg 6 participants	10 mg 9 participants	20 mg 9 participants	35 mg 19 participants	60 mg 18 participants	90 mg 18 participants	Total 79 participants
How many participants had related adverse events?	19% (5)	0	22% (2)	22% (2)	21% (4)	11% (2)	22% (4)	18% (14)

Overall, 19 out of 106 total participants (18%) experienced an adverse event that was considered related to treatment.

- No participants had any related serious adverse events.
- No participants stopped treatment or died due to a related adverse event.

Most of the related adverse events only happened to 1 participant each. The table below shows the related adverse events that happened to at least 2 participants.

Most common related adverse events								
	Placebo 27 participants	BIIB078						
		5 mg 6 participants	10 mg 9 participants	20 mg 9 participants	35 mg 19 participants	60 mg 18 participants	90 mg 18 participants	Total 79 participants
Fatigue	0	0	0	11% (1)	5% (1)	0	6% (1)	4% (3)
Protein levels in CSF increased	0	0	0	0	5% (1)	6% (1)	0	3% (2)
Dizziness	4% (1)	0	0	0	0	6% (1)	0	1% (1)
Headache	7% (2)	0	0	0	0	0	0	0

How has this study **helped** patients and researchers?

This study helped researchers learn more about the safety of BIIB078 in participants with *C9ORF72*-ALS. The researchers found that most adverse events were non-serious and that they happened at a similar rate across the BIIB078 and placebo groups. The most common adverse events in participants who received BIIB078 were fall, pain from the study procedure, and headache.

Researchers also studied whether BIIB078 was able to provide a clinical benefit to participants. They measured levels of proteins in the CSF that reflect signs of nerve damage and gave participants tests intended to measure the functional symptoms of ALS. In the highest dose groups, BIIB078 was associated with increased levels of proteins in the CSF that reflect signs of nerve damage. At the same time, participants receiving the highest dose of BIIB078 tended to do worse on measures of functional symptoms of ALS. Overall, there was no improvement found in any of the BIIB078 dose groups. As a result, Biogen currently has no studies planned to investigate BIIB078 any further as a potential treatment for ALS.

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 **NCT03626012** into the search box and click **Search.**

You can also find more information online at www.clinicaltrialsregister.eu. Once on the site, click **Home & Search,** then type **2017-000294-36** in the search box and click **Search.**

If you have questions about BIIB078 or the results of this study, please speak with the doctor or staff at the study research center.

Official Study Title: A Phase 1 Multiple-Ascending-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of BIIB078 Administered Intrathecally to Adults with *C9ORF72*-Associated Amyotrophic Lateral Sclerosis

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/NCT03626012**
- www.clinicaltrials.gov
- Study #: NCT03626012

EU Clinical Study Database

- **https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-000294-36**
- www.clinicaltrialsregister.eu
- Study #: 2017-000294-36

Thank you.

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