CLINICAL TRIAL RESULTS

A Study to Learn How Well BIIB033 (Opicinumab) Works as an Add-on Therapy and More About its Safety in People With Relapsing Forms of Multiple Sclerosis

- **Drug Studied:** BIIB033
- **Protocol #:** 215MS202
- **Study Dates:**
  Start: 14 November 2017
  End: 21 October 2020

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Thank you!

Thank you to the participants who took part in the investigational study for BIIB033. All the participants helped the researchers learn more about using BIIB033 to help people with relapsing forms of multiple sclerosis. Biogen 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.

This study did not produce the results that researchers expected. The study was ended early, and Biogen decided to stop further work on BIIB033. This decision was not based on any safety concerns. Biogen remains dedicated in its research to find new ways to treat multiple sclerosis and help repair damaged nerves.

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

Researchers wanted to learn about the use of BIIB033 in people with certain types of multiple sclerosis. **Multiple sclerosis is also known as MS.** In MS, the immune system attacks the nerves in the brain and spinal cord. This causes damage to the **myelin**, a protective covering on the nerves. Myelin also helps send information to and from the brain. The damage to the myelin makes it difficult for the brain to function and send messages throughout the body.

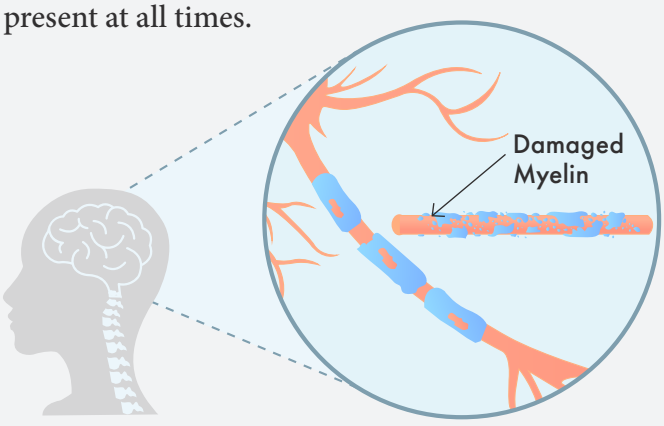
MS is a progressive disease, meaning that it slowly gets worse over time. This also means that patients' disability increases over time. A **disability** is a condition where patients find it more difficult to do certain activities and interact with the world around them.

Symptoms of MS include tiredness, numbness and tingling, muscle weakness as well as problems with vision, walking, thinking, and using the bathroom. In people with **relapsing-remitting MS**, also known as **RRMS**, these symptoms may last a few hours or days, then disappear only to come back again later. When symptoms disappear, it is called **remitting**. The start of different MS symptoms is called **a relapse**. In people living with RRMS, disability can worsen over time with each relapse. Eventually, RRMS could become **secondary progressive MS, also known as SPMS.** For people living with SPMS, their MS symptoms steadily become worse over time.

Current treatments for MS include medications to prevent the immune system from attacking the nerves as often. However, these treatments do not cure MS or repair damaged nerves. In this study, researchers were interested in a study drug called **BIIB033**, also known as **opicinumab**. This study drug was thought to work by blocking LINGO-1, a protein found in the nerves that may prevent myelin formation. Blocking LINGO-1 may help create myelin and repair nerves damaged by MS.

In this study, the researchers wanted to learn about using BIIB033 as an add-on therapy in people with MS. An add-on therapy is a medication that patients take in addition to other treatments for a medical condition. This study included people living with RRMS and SPMS who were already taking other treatments.

Researchers wanted to know if BIIB033 could have an effect on participants' baseline disability. Baseline disability refers to the symptoms that are present at all times.



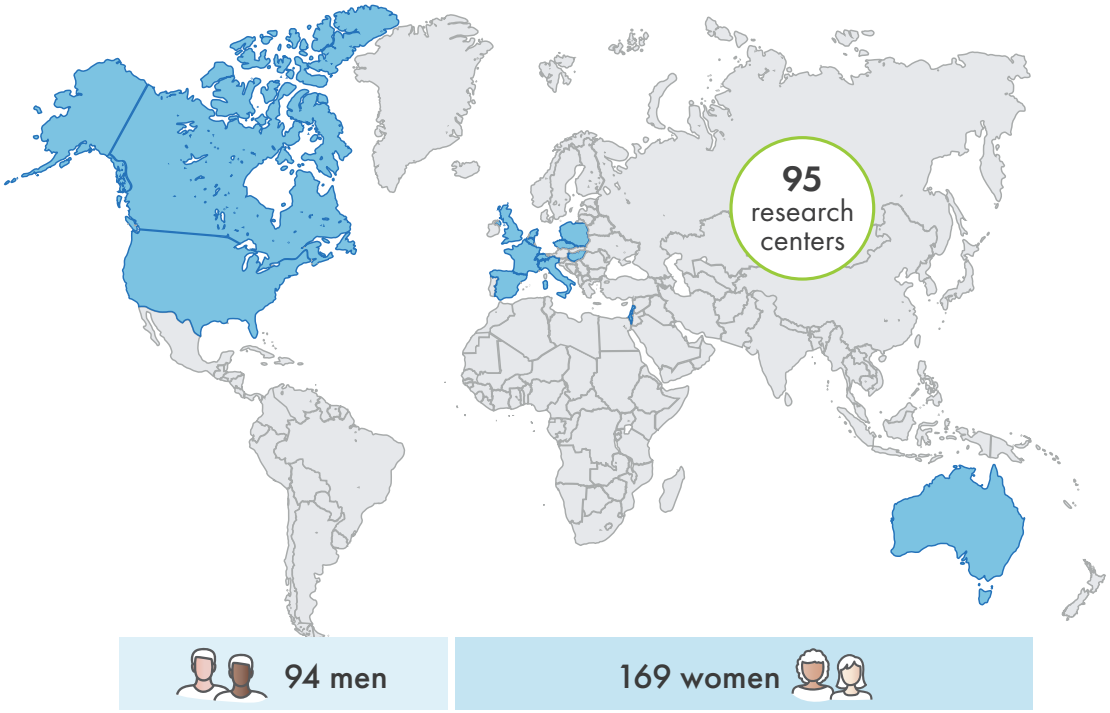
The main questions that the researchers wanted to answer were:

- Did the participants' disability change over 72 weeks due to BIIB033 treatment compared with placebo treatment?
- What medical problems did the participants experience?

Who **took part** in the study?

The study included **263 participants** at **95 research centers** around the world. This was **94 men** and **169 women**. All participants were between **18 to 58 years** old.

The study took place in **Australia, Belgium, Canada, Czech Republic, France, Germany, Hungary, Israel, Italy, Netherlands, Poland, Spain, Switzerland, United Kingdom, and the United States.**



Participants **took part** in this study if they:

Had RRMS or SPMS

Were on a stable dose of their normal MS medication

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 **happened** during the study?

This study had **2 parts**: Part 1 and Part 2. The study started in **November 2017** and ended early on **21 October 2020**. After reviewing the results of Part 1 of the study, Biogen learned that BIIB033 was not helping the participants as they expected. As a result, Biogen decided to end Part 2 early. The study was not ended early due to any safety concerns. When the study ended, Biogen created a report of the results. This is a summary of that report.

This study was a **Phase 2 study**. Phase 2 means that a treatment is tested in a relatively small number of participants:

- **Part 1** was **randomized** and **double-blind.** Randomized means that a computer program randomly chose the treatment for each participant. Double-blind means that none of the participants, doctors, or other study staff knew if each participant received BIIB033 or a placebo. Part 1 was planned to last 72 weeks.
- **Part 2** was **open-label**. This means that the participants, study staff, and researchers knew what treatment each participant was receiving. The participants in Part 2 received BIIB033. Part 2 was planned to last 96 weeks.

A **placebo** looks like a study drug but contains no real medicine. Using a placebo helps researchers learn if the study drug works.

The participants received BIIB033 or the placebo through a needle put into their vein. This is also known as an **infusion**. The dose of BIIB033 was measured in milligrams, also known as mg. In both parts of the study, participants received 750 mg of BIIB033 every 4 weeks.

How was the study done?

At the start of the study, the participants:

- answered questions about their medical history
- had physical exams done
- gave blood and urine samples
- had their disease condition checked using various tests and methods

Part 1

During Part 1, the participants were randomly placed into 1 of 2 groups in equal numbers. The participants received either BIIB033 or the placebo for 72 weeks if they did not leave the study early. Throughout the study, the participants also continued taking their normal medications for MS.

During the study, the study doctors:

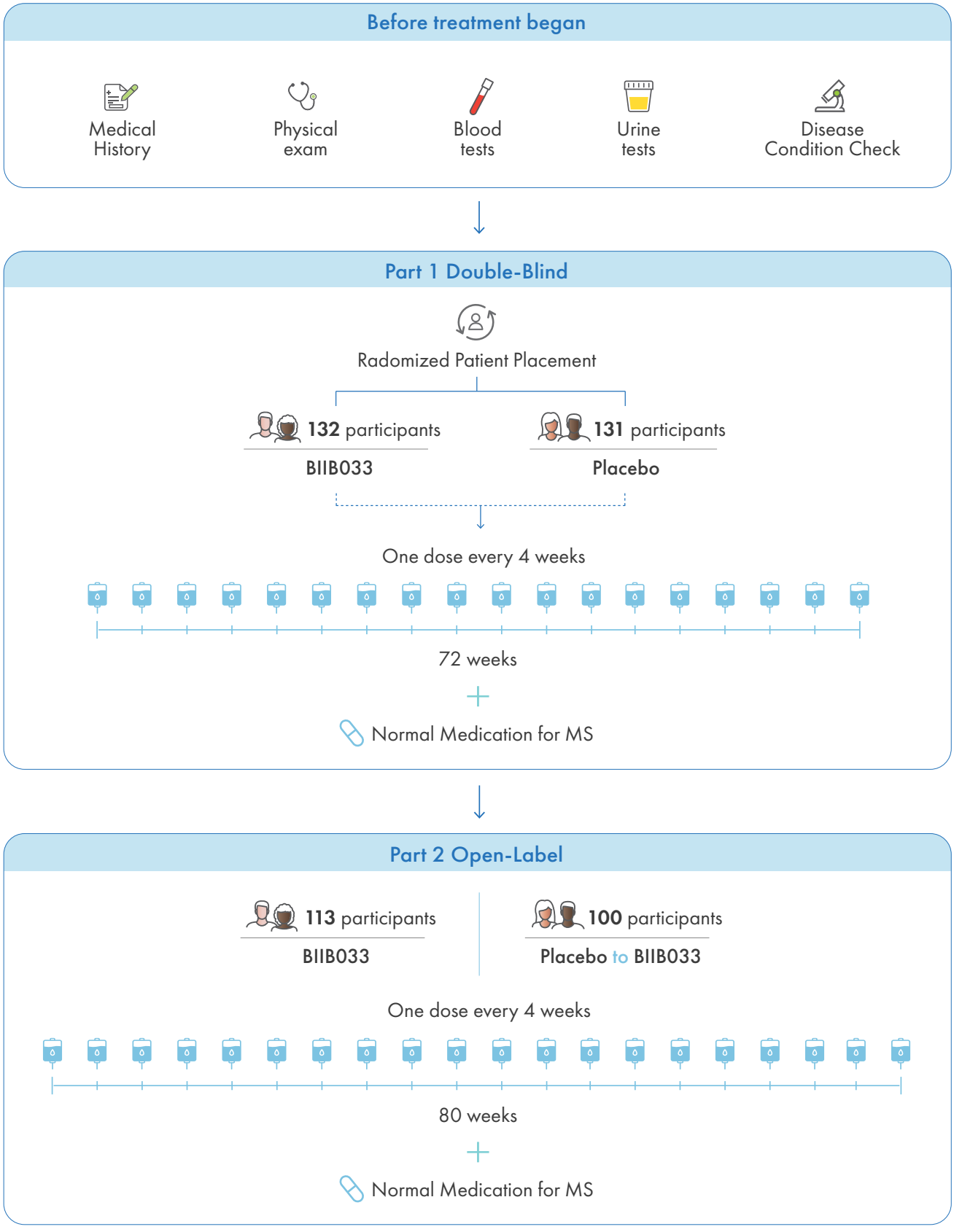
- asked participants about any medical problems they were having
- checked for any change in their level of disability due to MS

Part 2

Part 2 was planned as a longer treatment period. This longer treatment period is called the **long-term extension** part of the study. It was meant to observe participants receiving BIIB033 as an add-on therapy. The main goal of this part of the study was to check if participants had medical problems or changes in their disability after receiving BIIB033 for a longer time.

Out of 263 participants from Part 1, 100 participants from the placebo group and 113 participants from the BIIB033 group chose to enter Part 2. All participants received BIIB033 infusion once every 4 weeks until the study was stopped. Researchers recorded any medical problems that the participants had. The participants received BIIB033 for up to about 80 weeks.

The doses and number of participants for each group in the **double-blind** and **open-label** periods are shown below.



What were the study **results** when the study ended?

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 main results and the key question the researchers asked during the study.

There were other questions the researchers asked during this study. However, those results are not included in this summary. For more information, please refer to the websites at the **end of this summary**.

Did the participants' disability change over 72 weeks due to BIIB033 treatment compared with placebo treatment?

To answer this question, the study doctors gave each participant 4 tests at the start of the study to measure their disability. The study doctors then repeated these tests every 12 weeks and recorded the results.

The 4 tests were:

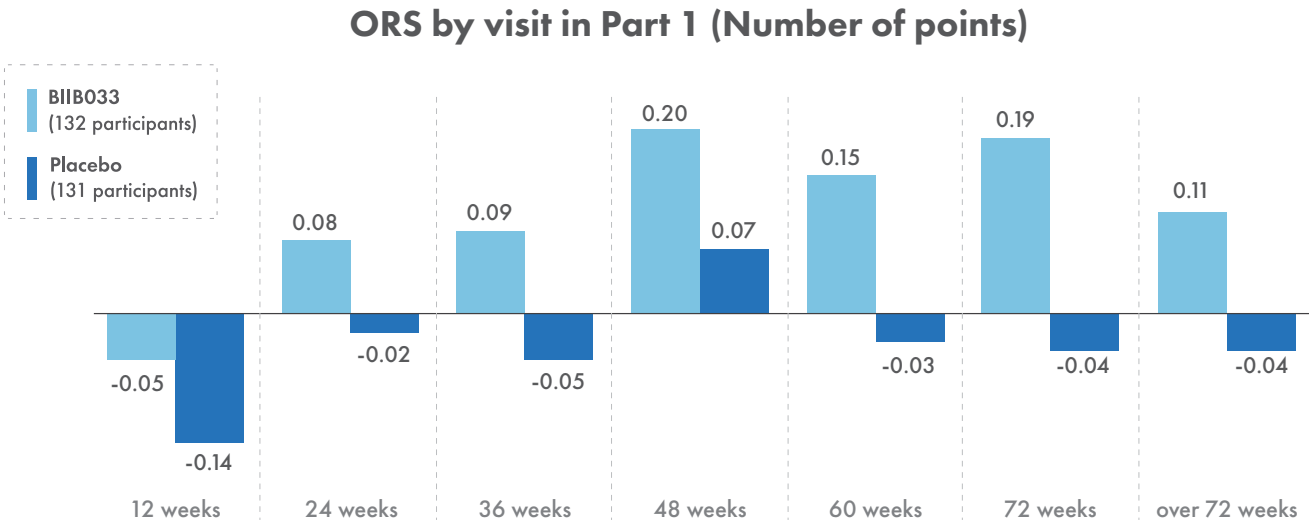
- **Expanded Disability Status Scale**, which measured the overall amount of disability that the participants were experiencing.
- **Timed 25-Foot Walk,** which measured how quickly the participants walked for 25 feet.
- **9-Hole Peg Test, dominant hand,** which measured the participants' control of their dominant hand. The dominant hand is the hand that is used while doing daily tasks, like writing, brushing your teeth, or catching a ball.
- **9-Hole Peg Test, non-dominant hand,** which measured the participants' control of their non-dominant hand. The non-dominant hand is the 'less preferred' hand.

Researchers used these tests to give each participant an **overall response score**, also known as the **ORS**.

- If a participant's score improved on a test in the study, it was scored as a +1.
- If a participant's score worsened on a test in the study, it was scored as a -1.

Researchers then added the results of all 4 tests together to get each participant's ORS. It included the number of points obtained by each participant in the 4 tests. As a result, the **ORS ranged from +4 to -4.**

The diagram below shows the ORS for each group based on each participant's visit, in Part 1. A negative number means an overall worsening in the tests. A positive number means an overall improvement in the tests.



Overall, the researchers found that there was no difference in the participants' disability between the BIIB033 and placebo groups. Biogen learned that BIIB033 was not helping the participants as they expected. As a result, Biogen decided to end Part 2 early.

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

This section is a summary of the medical problems the participants had during the study. A lot of research is needed to know whether a medical problem, also called an **adverse event,** is 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 the study. Not everyone experiences the same adverse events, and they may or may not be related to the study drug.

One goal of this study was to learn more about the potential adverse events of BIIB033.

Did any adverse events happen during this study?

The researchers recorded all adverse events the participants had in Part 1 and Part 2 of the study. A summary of the adverse events in Part 1 is shown in the table below. The number of participants is given in parenthesis.

Summary of adverse events in Part 1		
	BIIB033 (132 participants)	**Placebo** (131 participants)
How many participants had adverse events?	86% (113)	85% (111)
How many participants had serious adverse events?	7% (9)	5% (6)
How many participants stopped treatment because of adverse events?	less than 1% (1)	2% (3)
How many participants died due to events?	less than 1% (1)	0

One participant died during Part 1 in this study due to a motor vehicle accident.

A summary of the adverse events in Part 2 is shown in the table below.

Summary of adverse events in Part 2		
	Placebo to BIIB033 (100 participants)	**BIIB033** (113 participants)
How many participants had adverse events?	71% (71)	67% (76)
How many participants had serious adverse events?	9% (9)	2% (2)
How many participants stopped treatment because of adverse events?	2% (2)	0
How many participants died due to events?	0	0

What most common adverse events happened during the study?

Most common adverse events in Part 1		
	BIIB033 (132 participants)	**Placebo** (131 participants)
Common cold	20% (26)	23% (30)
Infection of the upper airways	23% (31)	15% (20)
MS relapse	17% (23)	15% (20)
Headache	14% (19)	18% (23)
Urinary tract infection	14% (18)	15% (19)
Fall	13% (17)	9% (12)
Tiredness	11% (14)	11% (14)

Most common adverse events in Part 2		
	Placebo to BIIB033 (100 participants)	**BIIB033** (113 participants)
MS relapse	12% (12)	12% (13)
Headache	11% (11)	8% (9)
Urinary tract infection	6% (6)	9% (10)
Infection of the upper airways	5% (5)	8% (9)
Fall	4% (4)	7% (8)
Common cold	4% (4)	6% (7)

What serious adverse events happened during the study?

Part 1

In Part 1, **6%** of the participants had **serious adverse events**. This was 15 out of 263 participants. The table below shows all of the serious adverse events that happened during Part 1.

Serious adverse events in Part 1		
	BIIB033 (132 participants)	**Placebo** (131 participants)
Kidney infection	less than 1% (1)	less than 1% (1)
A collection of infected fluid in the pelvic area	0	less than 1% (1)
Pneumonia	less than 1% (1)	0
Rectal cancer (rectal adenocarcinoma)	0	less than 1% (1)
Alcohol use disorder	0	less than 1% (1)
MS relapse	0	less than 1% (1)
MS worsening due to overheating	0	less than 1% (1)
Stomach pain because of a compressed artery	less than 1% (1)	0
Narrowing of the space of the spine in the neck	0	less than 1% (1)
Tissue thickening in the uterus	less than 1% (1)	0
Uterus tissue growing outside of the uterus	less than 1% (1)	0
Birth defect	less than 1% (1)	0
Chest pain	less than 1% (1)	0
Broken ankle	less than 1% (1)	0
Fall	less than 1% (1)	0
Traffic accident	less than 1% (1)	0

Part 2

In Part 2 of the study, 5% of the participants had **serious adverse events**. This was 11 out of 213 participants. The table below shows all of the serious adverse events that happened during Part 2.

Serious adverse events in Part 2		
	Placebo to BIIB033 (100 participants)	**BIIB033** (113 participants)
Inflammation of the appendix (appendicitis)	1% (1)	0
Urinary tract infection	1% (1)	0
Infection throughout the body	1% (1)	0
Blood and bone marrow cancer	1% (1)	0
Lung cancer	1% (1)	0
Tumor in the parathyroid gland	0	less than 1% (1)
Major depression	0	less than 1% (1)
A type of birth defect in the spinal cord	1% (1)	0
Pregnancy loss	1% (1)	0
Fall	1% (1)	0
Broken bone (thigh bone)	1% (1)	0
Rupture of the tissue that connects one bone to another	1% (1)	0

The number of participants with adverse events was similar in both groups. There were no new adverse events seen during this study.

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 **NCT03222973** 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 **2017-001224-22** in the search box and click **Search.**

If you have questions about BIIB033 or the results of this study, please speak with the doctor or staff at the study research center.

Official Study Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study With Optional Open-Label Extension in Subjects With Relapsing Multiple Sclerosis to Evaluate the Efficacy and Safety of BIIB033 as an Add-On Therapy to Anti-Inflammatory Disease-Modifying Therapies

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/NCT03222973**
- www.clinicaltrials.gov
- Study #: NCT03222973

EU Clinical Study Database

- **https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-001224-22**
- www.clinicaltrialsregister.eu
- Study #: 2017-001224-22

Thank you.

Biogen

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