CLINICAL TRIAL RESULTS

A Phase 2 Efficacy, Safety, and Tolerability Study of Natalizumab in Focal Epilepsy (OPUS)

- **Drug Studied:** Natalizumab (BG00002)
- **Protocol #:** 101EP201
- **Study Dates:**
  - **Start:** March 20, 2018
  - **End:** November 18, 2020

Biogen

Thank you!

A clinical study participant belongs to a large community of clinical research participants around the world.

By participating in a study, they help researchers answer important health questions and evaluate new medical treatments.

The clinical study for the drug **BG00002,** also known as **natalizumab**, helped researchers learn more about natalizumab (BG00002) and its safety when used as an add on therapy in people with **drug-resistant focal epilepsy.**

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 the **research** needed?

Epilepsy is a disorder that affects the normal functioning of the central nervous system. The central nervous system includes the brain and spinal column and controls the functioning of the body. Certain cells in our brain send and receive signals that process information. **When the signals are abnormally interrupted or changed, this can cause seizures.** Seizures are uncontrolled activity in the brain. Symptoms include temporary confusion, uncontrolled jerking movements of the arms and legs, constant staring, and loss of awareness. In severe cases, the patient may even become unconscious. There are different types of epilepsy, depending on the part of the brain that is affected. When only one area of the brain is involved, it is called focal epilepsy. When more than one area of the brain gets affected, it is called generalized epilepsy.

The immune system fights infections and disease. In people with epilepsy, **seizures can cause abnormal activation of the immune system.** Sometimes, this can lead to inflammation, also known as swelling and redness. White blood cells are a part of the body's immune system, that can cause inflammation. Inflammation can cause more seizures and can worsen epilepsy.

Antibodies are made by the body's immune system to fight germs and infections. A **monoclonal antibody** is a type of antibody that is made in a laboratory and is similar to the antibodies made by the immune system. Natalizumab is a monoclonal antibody.

Natalizumab works by preventing white blood cells from causing inflammation. This can potentially help in controlling seizures. Epilepsy is usually treated by antiepileptic drugs (AEDs). Unfortunately, AEDs do not work for some patients. This is called AED resistant epilepsy.

Even with treatment, about 30% of people living with epilepsy still have symptoms. Researchers are looking for new treatments to help people living with epilepsy.

In this study, researchers wanted to learn more about natalizumab. They wanted to see if natalizumab used as an add-on therapy with an AED would help participants with drug-resistant focal epilepsy. An add-on therapy is a medication that patients take in addition to other medications. They also wanted to see if natalizumab would work better than a placebo treatment. A placebo looks like a study drug but contains no real medicine. Using a placebo helps researchers learn if the study drug works.

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

The question that the researchers wanted to answer was:

What was the change in the number of seizures per month before and during Months 2 through 6 of treatment?

Who **could join** this study?

Participants could take part in the study if they

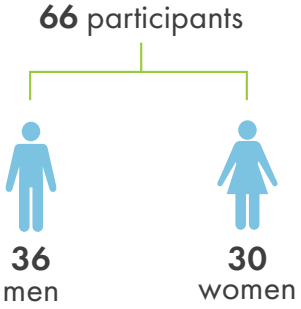
- Were 18 to 75 years of age
- Were diagnosed with drug-resistant, focal epilepsy
- Had 6 or more seizures during the 6 weeks before starting the study treatment

Who **took part** in the study?

The participants in this study were people with focal epilepsy.

The study included **66 participants** which included 36 men and 30 women. All participants were between 19 to 74 years old.

The study took place at 31 research centers in the **United States.**



What **treatments** did the patients receive?

Researchers studied the following treatments.

- **Natalizumab,** 300 milligrams (mg), given as an infusion, which is a slow injection given into the vein using a needle. This medication was given once every 4 weeks, up to Week 48.
- **Placebo,** given as an infusion, once every 4 weeks, up to Week 24.

All participants were taking AED medications during the study in addition to the study medications.

What **type** of study was this?

This study was:

- **Phase 2:** In a Phase 2 study, a treatment is tested in a small number of participants.
- **Randomized:** Who received natalizumab and who received placebo was decided randomly (like tossing a coin).

The study was conducted in **2 parts:**

Part 1

- **Double-blind:** This means that the participants and people involved in the study, including the study doctor or staff, did not know which participants were receiving natalizumab or placebo during the study.
- **Placebo-controlled:** A placebo was used in the study, and only some participants received it.

Part 2

- **Open-label:** This means that the participants, study staff, and researchers knew what treatment each participant was getting. The participants were all given natalizumab.

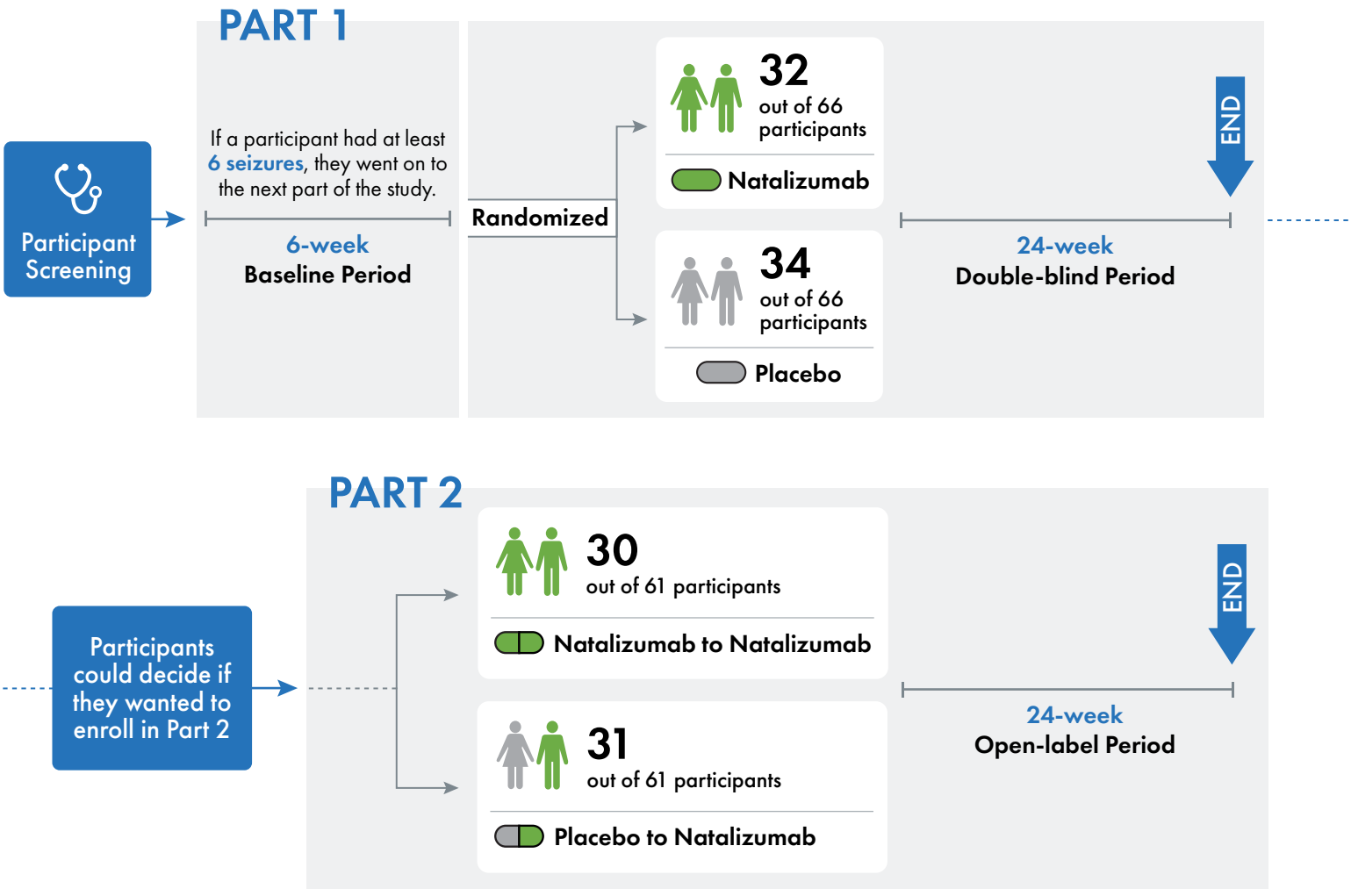
What **happened** during the study?

The study started in March 2018 and ended in November 2020.

All participants were screened to know if they were a good fit for the study. The screening included blood and urine tests, magnetic resonance imaging (MRI) scans, physical exams, pregnancy tests, and other special tests for epilepsy.

After screening, the participants entered Part 1. Participants visited the clinic every 4 weeks to receive the treatment. The participants were provided with a diary to record their seizures during the study.

The graphic below shows what happened during the study. The study was conducted over a period of 74 weeks.



AFTER PARTS 1 AND 2

Researchers followed up with all participants after active treatment ended

12-week Follow-up Period

All participants received a follow-up call from researchers after their last dose of study medication. Researchers wanted to check participant's overall well-being and for side effects

24-week Follow-up Call

What were the study **results?**

Below is an overall summary of the results and the key questions researchers asked during the study. The summary results are presented for 66 participants who received the study medications. The individual results of each participant might be different and are not in this summary.

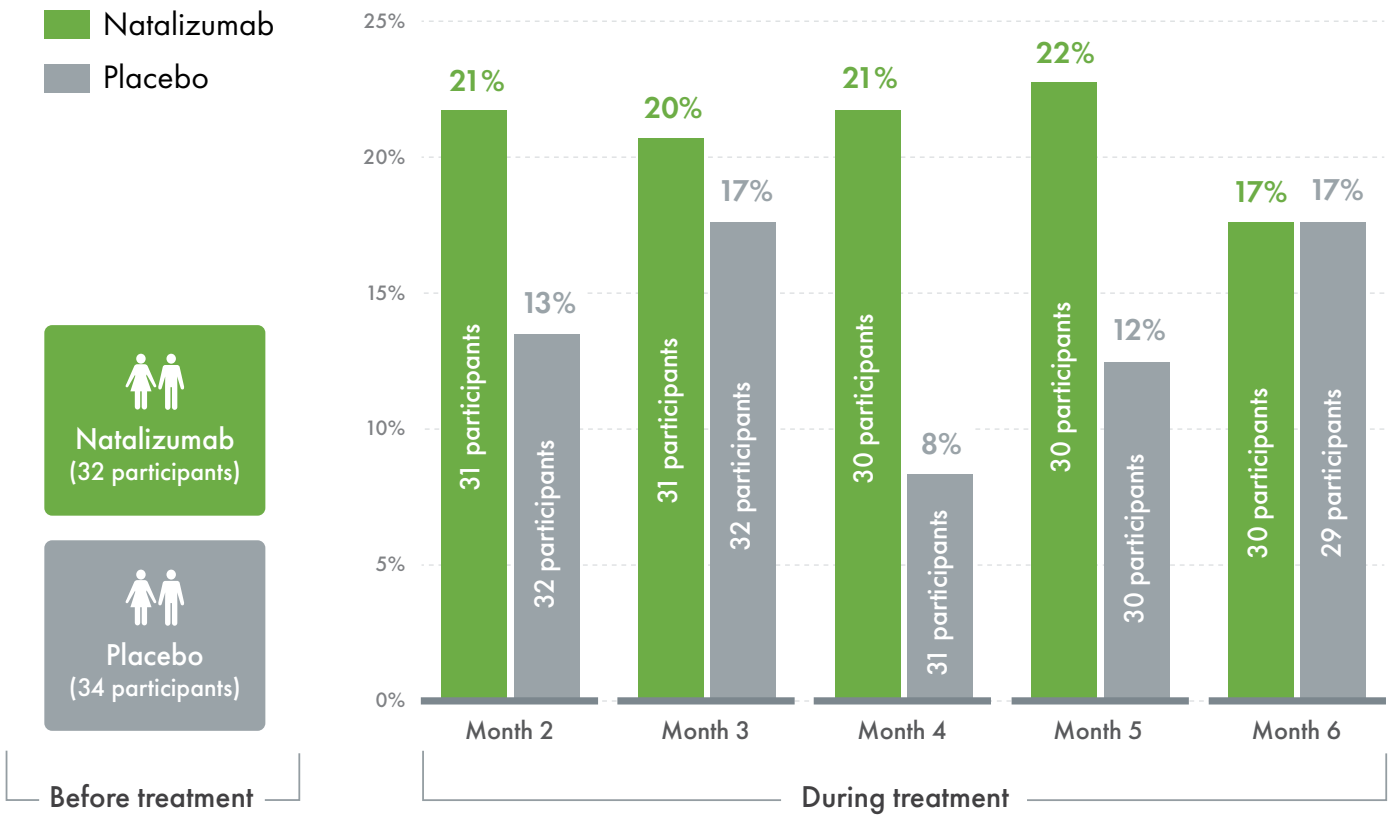
What was the change in the number of seizures per month before and during Months 2 to 6 of treatment?

To answer this question, researchers found out how often each participant had seizures. This was calculated by the entries made by the participants in the seizure diary.

The average change in seizures every month is represented as a percentage.

The chart below shows the average percent change in seizures from before treatment to months 2 to 6 during treatment.

Percent reduction in seizures



There was a slight difference in the number of seizures per month between the natalizumab and placebo groups. However, researchers decided that the difference was not statistically significant.

What **adverse events** did participants have?

A lot of research is needed to know whether a drug causes a medical problem, also called an adverse event. One of the main objectives of this study was to learn more about the adverse events of this treatment. When new drugs are being studied, researchers keep track of all adverse events that participants have both during and after the study is completed. Not everyone experiences them, and they may or may not be related to the study drug.

The results from several studies are needed to decide if an adverse event is related to a treatment. This section is a summary of all the adverse events, whether they might be related to the study treatment or not.

How many participants had adverse events?

The study had 2 parts, and the adverse events are presented separately for both parts.

Part 1

The summary is presented for 66 participants who received at least one dose of the study drug. The table below shows how many participants had adverse events during this part of the study.

Summary of Adverse Events		
	Natalizumab (32 participants)	**Placebo** (34 participants)
How many participants had adverse events?	24 (75%)	22 (65%)
How many participants had serious adverse events?	1 (3%)	1 (3%)
How many participants stopped treatment because of adverse events?	1 (3%)	1 (3%)

Part 2

The summary is presented for 61 participants who received at least one dose of the study drug. The table below shows how many participants had adverse events during this part of the study.

Summary of Adverse Events		
	Natalizumab to Natalizumab (30 participants)	**Placebo to Natalizumab** (31 participants)
How many participants had adverse events?	17 (57%)	20 (65%)
How many participants had serious adverse events?	2 (7%)	3 (10%)
How many participants stopped treatment because of adverse events?	0	2 (6%)

What were the most common adverse events?

Part 1

The most common adverse events were headache, dizziness, and falls.

The table below shows the most common adverse events that happened in at least 5% of participants.

Most Common Adverse Events		
	Natalizumab (32 participants)	**Placebo** (34 participants)
Headache	6 (19%)	5 (15%)
Dizziness	5 (16%)	1 (3%)
Fall	4 (13%)	2 (6%)
Back pain	2 (6%)	3 (9%)
Joint pain (Arthralgia)	2 (6%)	2 (6%)
Nausea	3 (9%)	1 (3%)
Bruising (Contusion)	2 (6%)	1 (3%)
Tiredness with lack of energy (Fatigue)	1 (3%)	2 (6%)
Reddening of skin (Flushing)	0	3 (9%)
Sleepiness (Somnolence)	0	3 (9%)
Blurred vision	2 (6%)	1 (3%)
Vomiting	2 (6%)	1 (3%)
Memory loss (Amnesia)	0	2 (6%)
Low red blood cell count (Anemia)	2 (6%)	0
Flu (Influenza)	0	2 (6%)
Difficulty in sleeping (Insomnia)	0	2 (6%)
Fainting (Syncope)	0	2 (6%)

What were the most common adverse events?

Part 2

The most common adverse events were nausea, tooth decay (dental caries), and chest discomfort.

The table below shows the most common adverse events that happened in at least 5% of participants.

Most Common Adverse Events		
	Natalizumab to Natalizumab (30 participants)	**Placebo to Natalizumab** (31 participants)
Nausea	2 (7%)	0
Tooth decay (Dental caries)	2 (7%)	0
Chest discomfort	0	3 (10%)
Urinary tract infection	2 (7%)	1 (3%)
Common cold (Nasopharyngitis)	0	2 (6%)
Fall	3 (10%)	2 (6%)
Skin cuts (Skin laceration)	1 (3%)	2 (6%)
High blood glucose (Hyperglycemia)	0	2 (6%)
Joint pain (Arthralgia)	2 (7%)	1 (3%)
Muscle cramps (Muscle spasms)	0	2 (6%)
Dizziness	2 (7%)	1 (3%)
Headache	3 (10%)	3 (10%)
Seizure	1(3%)	2 (6%)
High blood pressure (Hypertension)	0	2 (6%)

What serious adverse events did participants have?

An adverse event is considered serious when it results in death, is life-threatening, causes lasting problems, requires hospital care.

Part 1

During this part of the study, 2 of the 66 participants had serious adverse events. There was only 1 participant with a serious adverse event in each treatment group.

The table below shows the serious adverse events in each group.

Serious Adverse Events		
	Natalizumab (32 participants)	**Placebo** (34 participants)
Seizure	1 (3%)	1 (3%)

Part 2

During this part of the study, 5 of the 61 participants had serious adverse events. Punctured or pierced (perforated large intestine), COVID-19, seizure, more than 2 seizure episodes (seizure cluster), and lung infection with fluid (pneumonia aspiration) were the serious adverse events reported during the study.

The table below shows the serious adverse events in each group.

Serious Adverse Events		
	Natalizumab to Natalizumab (30 participants)	**Placebo to Natalizumab** (31 participants)
Punctured or pierced large intestine (perforated large intestine)	1 (3%)	0
COVID-19	0	1 (3%)
Seizure	1 (3%)	1 (3%)
More than 2 seizure episodes (seizure cluster)	0	1 (3%)
Lung infection with fluid (Pneumonia aspiration)	1 (3%)	0

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

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 **NCT03283371** 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 **2017-001995-45** in the search box and click **Search**.

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

Official Study Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Exploring the Efficacy, Safety, and Tolerability of Natalizumab (BG00002) as Adjunctive Therapy in Adult Subjects With Drug-Resistant Focal Epilepsy.

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/NCT03283371**
- www.clinicaltrials.gov
- Study #: NCT03283371

EU Clinical Study Database

- **https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-001995-45**
- www.clinicaltrialsregister.eu
- Study #: 2017-001995-45

Thank you.

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