CLINICAL TRIAL RESULTS

A Study to Learn About the Effect of Natalizumab on Brain Lesions When Given Every 6 Weeks Compared to Every 4 Weeks in Participants with Relapsing-Remitting Multiple Sclerosis and Which Method of Drug Delivery They Prefer

Drug Studied: Natalizumab (Tysabri/BG00002)
Protocol Number: 101MS329
Study Dates:
Start Date: 27 November 2018
Completion Date: 24 July 2023

Biogen

Thank you!

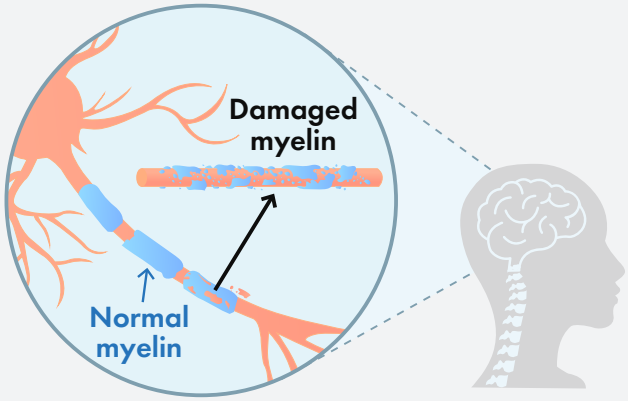
A clinical study participant belongs to the larger research community around the world. By participating in a study, they help researchers answer important health questions and learn about new medications.

In this study, researchers learned more about natalizumab treatment for **people with relapsing forms of multiple sclerosis**.

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?

In **multiple sclerosis (MS)**, the immune system attacks the nerves in the brain and spinal cord. This causes **damage to the myelin** which is a protective covering on the nerves.



This damage can make it difficult for the brain to function and send messages throughout the body. **Symptoms of MS** include numbness, tingling, and 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 for a few days, then disappear only to come back later. When symptoms do not get any worse, lessen, or disappear, the MS is called **remitting**. The start of different or worsening MS symptoms is called a **relapse**.

MS is a progressive disease. This means that it slowly gets worse and, in rare cases, can lead to death. Currently, there are no drugs to cure MS or repair damaged nerves. Treatments for MS include drugs that try to prevent the immune system from attacking the nerves as often.

Natalizumab is a drug that doctors have used to treat RRMS for over a decade. The standard approved dose is to give it once every 4 weeks. Despite its positive impact on quality of life, long term use of natalizumab is linked to a risk of developing a serious viral brain infection. This infection is called **progressive multifocal leukoencephalopathy**, also known as **PML**. Studies have shown that extending the time between doses of natalizumab can help reduce the risk of PML.

In the 1st part of this study, researchers wanted to learn if giving participants natalizumab less frequently would still be effective to help prevent brain lesions. **Lesions** are damaged or abnormal areas in the brain.

In the 2nd part of this study, researchers compared injections of natalizumab under the skin to infusions directly into a vein.

The main questions that the researchers wanted to answer were:

- How many new or growing brain lesions did participants who received natalizumab every 6 weeks have compared to those who received the standard dosing of natalizumab every 4 weeks?
- How many participants preferred receiving natalizumab injections under the skin compared to infusions into a vein?
- What adverse reactions did the participants have?

An **adverse reaction** is a medical problem that study doctors reported as possibly being caused by the study drug. This can happen during a clinical study or within a certain amount of time after the study has ended.

Who took part in the study?

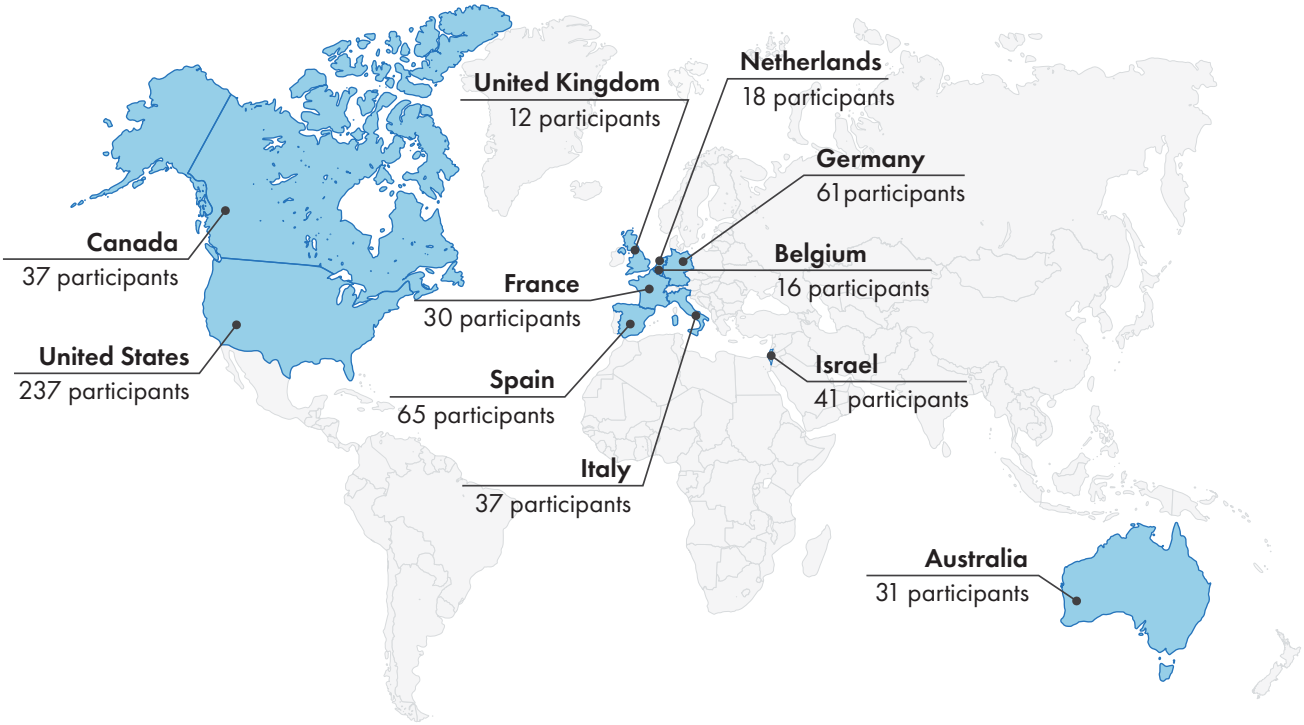
A total of **585 participants** took part in the study, which included 168 men and 417 women.

168 (29%) men	417 (71%) women

Part 1 of the study included 499 participants. **Part 2** included 158 participants.

All participants were between **19 and 60 years old**.

Part 1 took place at 89 research centers around the world.
Part 2 took place at 29 research centers around the world.



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

- Were between 18 and 60 years of age
- Had been diagnosed with RRMS
- Had been taking natalizumab every 4 weeks (standard dosing) for at least 1 year before the study.
  This was required so that all participants were at the same starting point before being treated in this study.
- Did not have any relapses in the past year

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

- Had progressive MS
- Could not receive magnetic resonance imaging (MRI) scans, which is a type of brain imaging scan
- Had cancer or other types of disorders that could interfere with the study

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 in this study:

Natalizumab
300 milligrams (mg)

Part 1

Once every 4 or 6 weeks.
Given as an **intravenous (IV)** infusion, which is an injection into a vein using a needle, lasting about an hour.

Part 2

Once every 6 weeks.
Given as an **IV** infusion or as a **subcutaneous (SC)** injection, which is an injection under the skin.

What **happened** during the study?

How was the study done?

This study was:

Phase 3b: Phase 3 is usually the last phase of clinical study before a new drug is submitted to government authorities for approval for use outside of clinical studies. A Phase 3b study is done after approval. In this study, researchers compared the approved 4-week standard dosing of natalizumab to an extended 6-week dosing. They wanted to learn how effective the extended 6-week dosing was and whether participants had any adverse reactions during the study.

Open label: This means that both the researchers and the participants knew that all participants received natalizumab and how often.

Randomized: This means the researchers used a computer program to randomly choose the dosing schedule for each participant. This helped make sure the groups were chosen fairly.

Crossover: Part 2 of the study was a crossover study. This means that all participants had both IV and SC treatment with natalizumab, but in a different order. Crossover studies allow researchers to compare results in the same group of participants.

The study was split into 2 parts. Participants could complete both **Part 1** and **Part 2**, or only join the study for one of the parts. Participants were screened before they could join the study.

To join the study, participants must have been taking **natalizumab every 4 weeks** for at least a year. Participants had a physical exam, and their medical history was checked.

The screening also included:


MRI scan


Neurological exam to measure MS symptoms


Blood tests


Questions about their life

These tests were also done regularly throughout the study.

Part 1

- Participants were randomly assigned to either continue taking **natalizumab every 4 weeks** or switch to taking **natalizumab every 6 weeks**.

Natalizumab every 4 weeks

248 participants

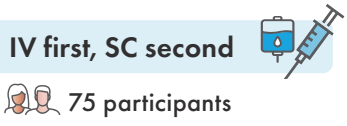
Natalizumab every 6 weeks

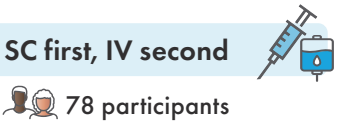
251 participants

- Natalizumab was given as an IV infusion during Part 1.
- All participants were treated for 72 weeks.
- Researchers compared MRI scans from the beginning of the study to the scans taken at Weeks 24, 48, and 72 to check for brain lesions.
- Participants from Part 1 moved directly into Part 2. If they chose not to, they had a follow-up visit after 12 weeks and a final phone call 24 weeks after their last dose.

Part 2

- Both newly joining participants and those who continued from Part 1 were all given **natalizumab every 6 weeks**.
- Participants first received natalizumab as an **IV infusion** for 36 weeks, which was called the **Run-In**. This was done to get all participants on the same stable dose.
- Participants were then randomly assigned to receive natalizumab as an **IV infusion first, then SC injection** or as a **SC injection first, then IV infusion**.
- All participants were treated for 24 weeks, then switched to the other method of drug delivery for another 24 weeks.

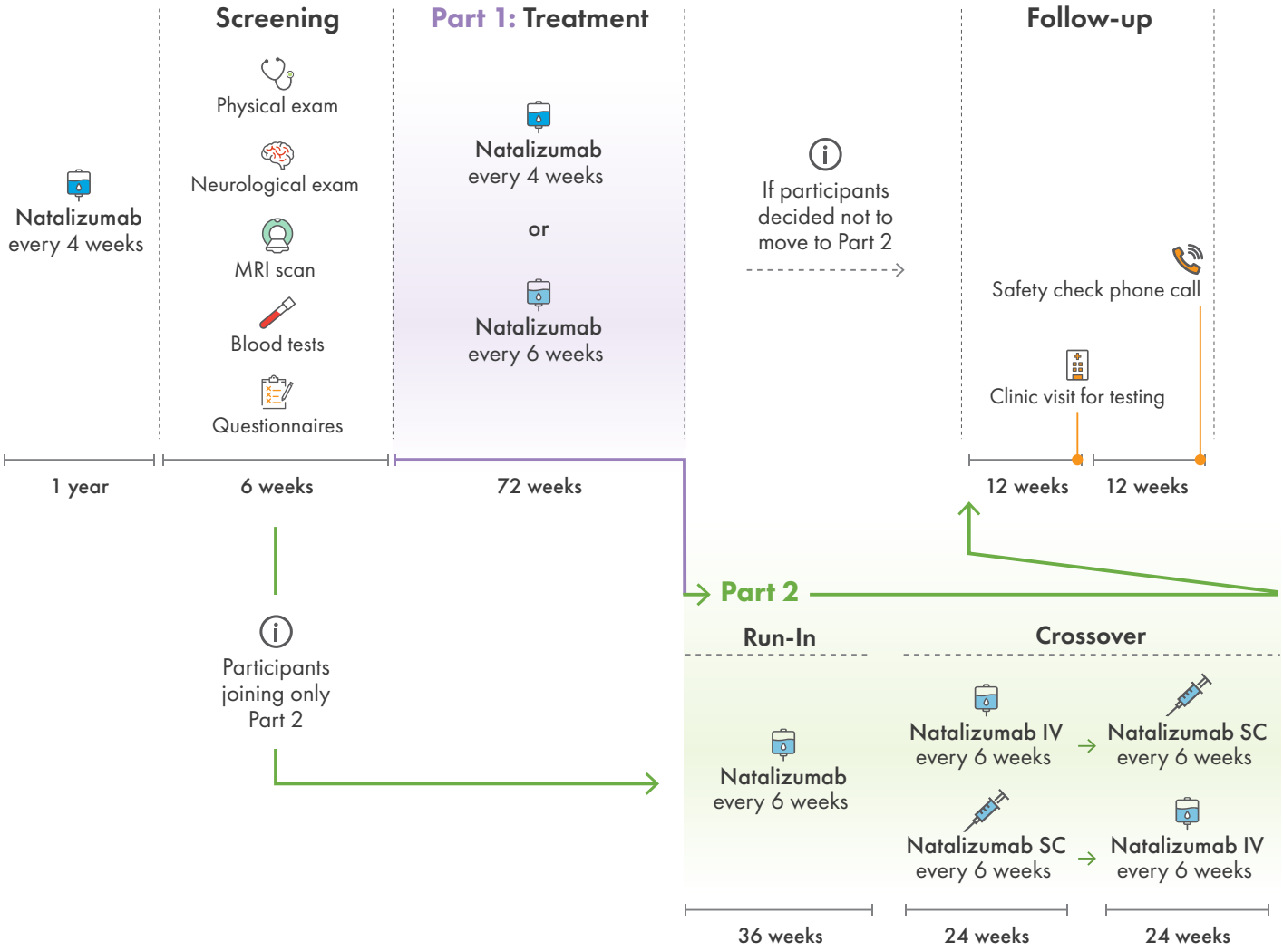
IV first, SC second

75 participants

SC first, IV second

78 participants

- After 48 weeks, participants chose which method of delivery they wanted to receive for their final dose of natalizumab.
- At the end of Part 2, participants had a follow-up visit after 12 weeks and a final phone call 24 weeks after their last dose.

Participants who completed both Part 1 and Part 2 stayed in the study for up to 186 weeks.

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 results are presented for 576 participants who received at least 1 dose of natalizumab. The individual results of each participant might be different and are not in this summary.

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.

The following questions were the **primary endpoints** of the study. Primary endpoints are the main questions that researchers wanted to answer.

Part 1: How many new or growing brain lesions did participants who received natalizumab every 6 weeks have compared to those who received the standard dosing of natalizumab every 4 weeks?

Researchers compared MRI scans taken at the beginning of the study to those taken after 72 weeks of treatment in Part 1. They counted the number of new or growing brain lesions.

Of the 499 participants who were randomized in Part 1, 489 participants received at least 1 dose of natalizumab and had MRI scans that could be compared.

Researchers found that the difference between the group that received **natalizumab every 6 weeks** and the group that received **natalizumab every 4 weeks** was **too small to be *meaningful***.

The table shows the results.

	Natalizumab every 4 weeks (242 participants)	**Natalizumab every 6 weeks** (247 participants)
Average number of new or growing brain lesions	0.05	0.20

Part 2: How many participants preferred receiving natalizumab injections under the skin compared to infusions into a vein?

Researchers gave participants a questionnaire that asked whether they preferred the SC or IV method of drug delivery.

To answer this question, researchers looked at the answers from 123 participants after their last dose in the crossover part of the study.

> Overall, **88% of participants preferred receiving natalizumab injections under the skin**. This was 108 out of 123 participants.

The main reasons for preferring SC injections were:

- It requires **less time** in the clinic.
- Receiving the treatment this way felt **more comfortable**.

What possible **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 a medical problem that the study doctors reported as related to the study drugs. An adverse reaction 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 reactions that participants have during the study. Not everyone experiences the same adverse reactions.

The results below include only the participants who received at least 1 dose of natalizumab during the study.

How many participants had adverse reactions during this study?

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

For **Part 2**, adverse reactions were recorded for the type of treatment the participant was undergoing at the time the reaction happened.

Summary of adverse reactions

	Part 1		Part 2	
	Natalizumab every 4 weeks (247 participants)	Natalizumab every 6 weeks (250 participants)	Natalizumab IV (136 participants)	Natalizumab SC (132 participants)
How many participants had adverse reactions?	8% (19)	12% (29)	9% (12)	14% (19)
How many participants had serious adverse reactions?	0	1% (3)	0	1% (1)
How many participants stopped taking natalizumab due to adverse reactions?	0	0	0	0
How many participants died due to adverse reactions?	0	0	0	0

What serious adverse reactions happened during this study?

There were 4 serious adverse reactions that happened during the study. Of those, 3 reactions were during **Part 1**, and the 4th reaction was during **Part 2**.

The table below shows the serious adverse reactions that happened during the study.

Serious adverse reactions

	Part 1		Part 2	
	Natalizumab every 4 weeks (247 participants)	Natalizumab every 6 weeks (250 participants)	Natalizumab IV (136 participants)	Natalizumab SC (132 participants)
COVID-19 lung infection (COVID-19 pneumonia)	0	Under 1% (1)	0	0
Viral brain infection (progressive multifocal leukoencephalopathy – PML)	0	Under 1% (1)	0	0
Infection of the airways (respiratory tract infection)	0	Under 1% (1)	0	0
Bile duct infection (cholangitis infective)	0	0	0	1% (1)

What common adverse reactions happened during this study?

The most common adverse reaction that happened during the whole study was a bladder or kidney infection (urinary tract infection).

The table below shows the most common adverse reactions that happened in more than 1% of participants in any group. There were other adverse reactions, but they did not happen as often and are not included in the table below.

Most common adverse reactions				
	Part 1		Part 2	
	Natalizumab every 4 weeks (247 participants)	Natalizumab every 6 weeks (250 participants)	Natalizumab IV (136 participants)	Natalizumab SC (132 participants)
Bladder or kidney infection (urinary tract infection)	1% (3)	1% (2)	2% (3)	2% (2)
Feeling tired (fatigue)	0	1% (3)	2% (3)	1% (1)
Injection site pain	0	0	0	5% (6)
Headache	Under 1% (1)	2% (4)	0	1% (1)
Shingles (painful rash) (herpes zoster)	Under 1% (1)	1% (3)	0	0
Levels of white blood cells increased (lymphocyte count increased)	0	0	1% (2)	1% (1)
Too many white blood cells (eosinophilia)	Under 1% (1)	Under 1% (1)	1% (2)	1% (1)
Injection site reaction	0	0	0	2% (2)

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

This study helped researchers learn more about different methods of natalizumab treatment and their potential to help people with RRMS.

Overall, the researchers in this study found that:

- There was no meaningful difference in new brain lesion growth when taking natalizumab every 6 weeks compared to every 4 weeks.
- Most participants preferred receiving natalizumab under the skin (SC injection) rather than directly into a vein (IV infusion).
- The safety of natalizumab given every 6 weeks was similar to the known safety of natalizumab given by standard dosing every 4 weeks.
- Some participants who received natalizumab developed infections, including one who developed PML. However, the study's design did not allow for conclusions about rare events such as PML.

It is important to know that the results in this summary are from this study only. Other studies may have different results. Other studies with natalizumab are ongoing and future studies are planned.

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/study/NCT03689972
EU Clinical Trials Register	https://www.clinicaltrialsregister.eu/ctr-search/search?query=2018-002145-11

Official Study Title: A Randomized, Controlled, Open-Label, Rater-Blinded, Phase 3b Study of the Efficacy, Safety, and Tolerability of 6-Week Extended Interval Dosing (EID) of Natalizumab (BG00002) in Subjects With Relapsing-Remitting Multiple Sclerosis Switching From Treatment With 4-Week Natalizumab Standard Interval Dosing (SID) in Relation to Continued SID Treatment - Followed by an Open-Label Crossover Extension Study Comprising Subcutaneous and Intravenous Natalizumab Administration

If you have **questions about natalizumab** 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!

Biogen

225 Binney Street
Cambridge, MA 02142 (USA)
ClinicalTrials@Biogen.com