Publication Summary

Study Sponsor: Biogen
Drug Studied: Natalizumab
Protocol Number: IMA-06-02
Study Description: A study to learn how safe natalizumab is and how well it is working during routine clinical care in patients with relapsing-remitting multiple sclerosis, also called RRMS

Thank you

Thank you to the patients who are taking part in this clinical study for natalizumab, also called the Tysabri Observational Program (TOP). All the patients help the researchers learn more about using natalizumab to help people with relapsing-remitting multiple sclerosis, also called RRMS.

Biogen sponsored this study and reviewed the results so far. Biogen thinks it is important to share the results with the patients and the public. Biogen has published an article in the Journal of Neurology, Neurosurgery, and Psychiatry about the results of this study so far. The article was first published on March 31, 2020. This is a summary of that article.

We hope this helps the patients understand and feel proud of their important role in medical research. If you participated in the study and have questions about the results so far, please speak with a doctor or staff at a study site.

Why was the research needed?

Researchers want to learn more about long-term natalizumab treatment in patients with relapsing-remitting multiple sclerosis, also called RRMS.

People with multiple sclerosis have increased inflammation in the body that affects their nerves. Their immune system attacks a layer of cells that helps cover and protects nerves in the body. When the layer is damaged, electrical signals between the brain and the rest of the body are slowed down or blocked. People with multiple sclerosis may have problems with vision, thinking and memory skills, muscle movement, and coordination.

In people with RRMS, old symptoms return or new symptoms form after the disease seemed to be gone for some time. When new symptoms happen or there is a worsening of old symptoms, this is called a "relapse". The study drug, natalizumab, is available as a treatment for RRMS.

In this study, the researchers collected information from patients with RRMS as part of their routine care. The patients in this study have been receiving natalizumab as part of their routine care for up to 10 years so far. The researchers want to better understand the safety of natalizumab. They also want to learn how natalizumab is affecting the patients' RRMS.

What is the purpose of this study?

The questions the researchers want to answer in this article are:

- What serious medical problems have happened during this study so far?
- How has natalizumab affected the patients' RRMS relapses?
- How has natalizumab affected the patients' disability?

Who could join this study?

The patients in this study are men and women with RRMS. The researchers are using information from patients who had either never received natalizumab or had 3 or fewer doses of natalizumab before joining this study.

The average age of the patients when they joined this study was 37 years old.

As of November 2017, the study included 6,148 patients in 17 countries:

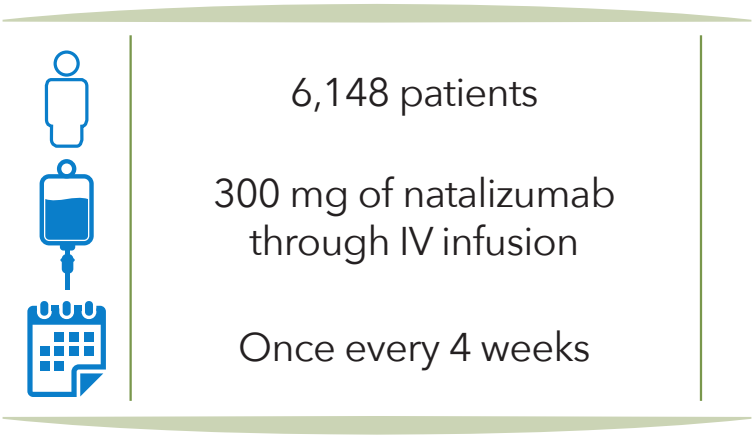
Argentina	France	The Netherlands
Australia	Germany	Norway
Belgium	Great Britain	Slovakia
Canada	Greece	Spain
Czech Republic	Italy	Portugal
Finland	Mexico	

What treatments are the patients receiving?

All of the patients in this study are receiving natalizumab under the care of their own doctors when they join this study. The researchers in this study also checked on these patients after they stopped natalizumab treatment. This is an "open-label" study. This means each patient knows what they are receiving, and their doctors and the researchers also know. The patients in this study are receiving natalizumab through a needle into their vein every 4 weeks. This is called an intravenous infusion, also called an IV infusion. Each dose of natalizumab is 300 milligrams, also called mg.

This is also an "observational" study. This means the patients are not receiving any new treatments or having tests and measurements done for this study. They had either never received natalizumab before or had 3 or fewer doses of natalizumab before joining this study. The researchers are reviewing information collected by the patients' doctors as part of their routine care. This type of study helps researchers learn more about how a treatment works and how safe it is over a long period of time.

The chart below shows the treatment the patients are receiving.



What is happening during this study?

The results in this summary are from November 2017, when the researchers last reviewed the results. At that time, the patients had been in the study for about 10.5 years.

The study started in June 2007 and is planned to end in January 2029.

There are no required tests or measurements for this study. The patients visit their own doctors as part of their routine care about every 6 months. At the patients' visits, their doctors:

- ask the patients about what medicines they are taking, including any new treatments for RRMS
- ask the patients how they are feeling and if they have any medical problems
- check the patients' RRMS symptoms

What are the results of this study so far?

This is a summary of the main results from this publication as of November 2017. The individual results of each patient might be different and are not in this summary.

This study has limitations and may not be as reliable as a controlled clinical trial with a comparison to a placebo. This study took place in many countries, and the results may be affected because of different treatment practices.

The 6,148 patients in this study were at various stages in their natalizumab treatment. Patients had been receiving natalizumab for different amounts of time, and some patients had discontinued treatment.

These results are only from 1 study. Other studies may provide new information or different results. Always talk to a doctor before making any treatment changes.

What serious medical problems have happened during this study so far?

This section is a summary of the serious medical problems the patients had as of November 2017.

A lot of research is needed to know whether a treatment 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 treatments are being studied, researchers keep track of all the adverse events that patients have. Not everyone experiences adverse events. It takes further research 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.

In this study, the researchers mainly want to learn about any serious adverse events that the patients have while receiving natalizumab treatment and up to 6 months after stopping treatment. So, the results below only include information about serious adverse events that happened between June 2007 and November 2017.

Have any serious adverse events happened during this study so far?

Yes, there are patients who have had serious adverse events during this study.

- 13.5% of the patients have had serious adverse events. This is 829 out of 6,148 patients.
- 4.7% of the patients have had serious adverse events related to natalizumab treatment. This is 290 out of 6,148 patients.

What serious adverse events have happened during this study so far?

The most common serious adverse events that have happened during this study so far are:

- A condition called "progressive multifocal leukoencephalopathy", also called PML. This is a rare brain infection that is caused by a virus that usually leads to death or severe disability.
- A condition called "immune reconstitution inflammatory syndrome", also called IRIS. This can make the immune system have an over-reaction and make MS symptoms worse or cause new symptoms. Most of the patients who stopped treatment due to PML also had IRIS. In patients with IRIS, natalizumab treatment must be stopped after PML happens. In this study, there was 1 patient who did have IRIS without having PML.

The table below shows the serious adverse events that happened in more than 10 patients overall. There have been other serious adverse events, but these happened in fewer patients.

Most common serious adverse events in this study between June 2007 and November 2017

	Total (out of 6,148 patients)
IRIS	54 (0.9%)
PML	53 (0.9%)
Miscarriage	37 (0.6%)
Allergic reaction	26 (0.4%)
Pneumonia (a lung infection)	23 (0.4%)
Urinary tract infection	20 (0.3%)
Fall	19 (0.3%)
Depression	18 (0.3%)
Epilepsy (a seizure disorder)	18 (0.3%)
Shingles	17 (0.3%)
Worsening of MS	15 (0.2%)
Breast cancer	12 (0.2%)
Slipped disc (when the soft cushion of tissue between the bones in your spine pushes out)	12 (0.2%)
Urinary tract infection from *E. coli* bacteria	12 (0.2%)
Suicide attempt	11 (0.2%)

There have been 0.5% of the patients who have died due to serious adverse events during this study so far. This is 30 out of 6,148 patients. Out of the 30 deaths, the study doctors thought that 8 of them were related to treatment with natalizumab:

- 4 patients died due to PML.
- 2 patients died due to IRIS.
- 1 patient died due to breast cancer that had spread in the body.
- 1 patient died due to an imbalance in their autonomic nervous system, which controls things like blood pressure and breathing rate.

What serious adverse events of interest have happened during this study?

Other studies with natalizumab showed that the patients in those studies had specific medical problems. These are called "serious adverse events of interest". The researchers want to learn if the patients in this study also have these medical problems. These are:

- **Opportunistic infections,** which are infections that happen more often and are more severe in people with weak immune systems. They can be caused by bacteria, viruses, or living organisms.
- **PML,** which is a rare brain infection caused by a specific virus that usually leads to death or severe disability.
- **Cancer,** which is a disease that happens when the body cannot control the growth of cells.

Overall, the researchers have found that over about 10 years of natalizumab treatment:

- 0.2% of the patients have had opportunistic infections other than PML. This is 11 out of 6,148 patients.
- 0.9% of the patients have had PML. This is 53 out of 6,148 patients.
- 1.0% of the patients have had cancer. This is 63 out of 6,148 patients.

How has natalizumab affected the patients' RRMS relapses?

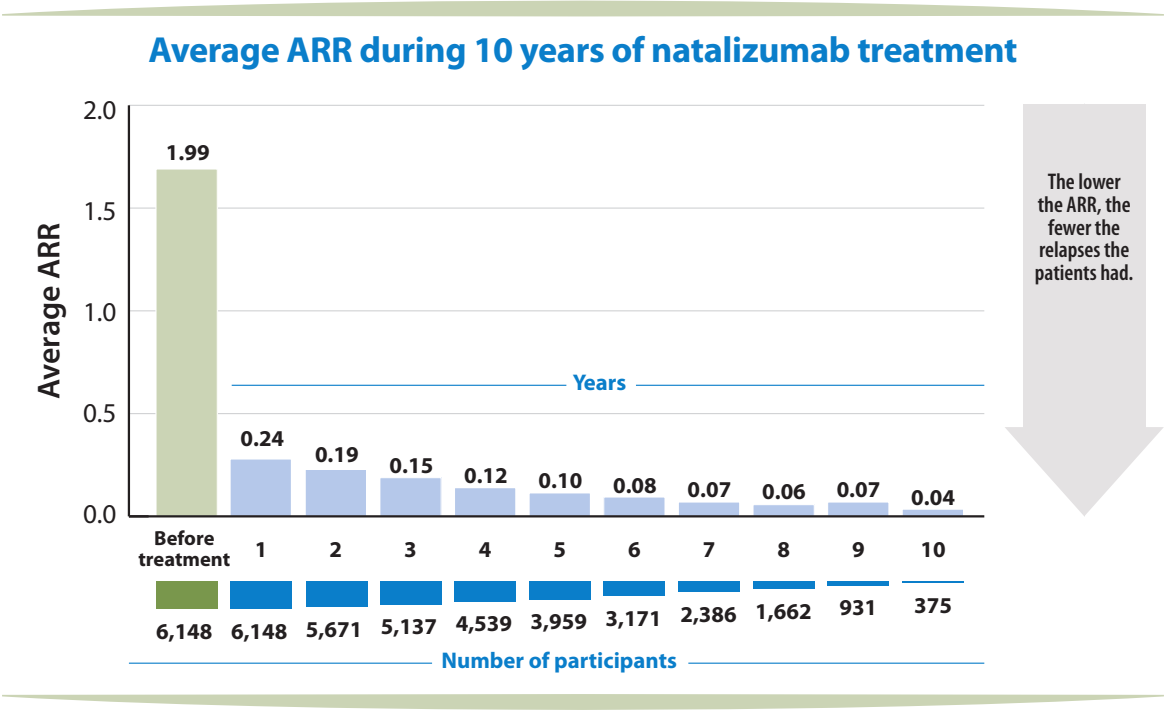
To answer this question, the researchers count how many relapses the patients have each year. In this study, a relapse means that new or returning MS symptoms last for at least 1 day. After that, the symptoms either stay the same or become less severe for 30 days.

The number of relapses each year is called the "annualized relapse rate", also called the ARR. The lower the ARR, the fewer relapses the patients had while receiving natalizumab.

In the year before starting natalizumab treatment, the patients had an average ARR of 1.99. Overall, the researchers found that:

- On average, the patients' average ARR was 0.15 during the 10 years of treatment. This was a 92.5% decrease in the patients' average ARR in the year before treatment.
- Most of the decreases in the average ARR happened during the first year of natalizumab treatment. The average ARR decreased from 1.99 in the year before treatment to 0.24 after the first year of treatment.
- After that, the average ARR stayed less than or equal to 0.20 over the 10 years of the study.

The chart below shows these results.



How has natalizumab affected the patients' disability?

To answer this question, the patients' doctors use a survey called the Expanded Disability Status Score, also called the EDSS. The doctors give each patient an EDSS score based on their level of disability. The scores range from 0 to 10. The higher the score, the higher a patient's level of disability.

There were 85.0% of the patients who had a score of 2 or higher on the EDSS before they started receiving natalizumab. This was 5,179 out of 6,124 patients. The researchers found that over 10 years of natalizumab treatment:

- 23.4% of these 5,179 patients had lower EDSS scores compared to when they started natalizumab treatment. This was 1,210 out of 5,179 patients. This meant that in these patients, there was an improvement in their level of disability.

The researchers also calculated the "cumulative probability" that the 5,179 patients' disability would worsen or improve. Using the results during 10 years of natalizumab treatment, the researchers calculated how likely it was that the 5,179 patients' level of disability would change. Overall, the researchers found that over the 10 years of the study, the 5,179 patients had a:

- 27.8% chance of a worsening of their level of disability
- 33.1% chance of an improvement in their level of disability

How has this study helped patients and researchers?

The results from this study so far have helped researchers learn more about the safety of natalizumab in patients with RRMS. The researchers have also learned how nearly 10 years of natalizumab treatment has affected patients.

Further research with natalizumab is ongoing.

Where can I learn more about the study?

You can find more information about this study on the websites listed below:

- www.clinicaltrials.gov – Enter **"NCT00493298"** in the search bar

The full title of the original publication in the *New England Journal of Medicine* is: Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP)

You can read the abstract of the original article at: https://jnnp.bmj.com/content/91/6/660. To read the full article, you will need to pay a small fee.

Full Study Title: TOP: Tysabri® Observational Program

Biogen sponsored this study and has its headquarters in Cambridge, Massachusetts (USA).

The phone number for general information in the USA is 1-866-633-4636.

Thank you

Patients in clinical studies belong to a large community of people who take part in clinical research around the world. They help researchers answer important health questions to find medical treatments for patients.

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www.ciscrp.org

