NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn about the effects of fingolimod on different types of immune system cells in people with relapsing multiple sclerosis

Protocol number: CFTY720DUS40

Thank You!

Novartis, the sponsor of this clinical trial, would like to thank you for taking part in this trial for the marketed drug fingolimod, also known as FTY720. You helped researchers learn more about how fingolimod affects the different types of immune cells in people with relapsing multiple sclerosis.

As a clinical trial participant, you belong to a large community of people around the world. Your invaluable contribution to medicine and healthcare is greatly appreciated.

This summary only shows the results of a single clinical trial. Other clinical trials may have different findings. Researchers and health authorities, such as the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) in Europe, look at the results of many clinical trials to understand which drugs work and if they are safe. It takes many people in multiple clinical trials around the world to advance medical science and healthcare. If you have any questions about these trial results, please talk to the doctor or staff at your trial site.

How long was this trial?

This trial was designed so that an individual participant could take part for up to 13 months. The trial started in September 2017 and ended in June 2019. The entire duration of the trial, from enrolling the first participant to the last participant completing the trial was 1 year and 9 months.

The researchers completed this trial as planned. When the trial ended, the researchers collected information on the trial treatment, fingolimod (FTY720), and created a report of the trial results. This summary is based on that report.

Why was the research needed?

Multiple sclerosis, also known as MS, is a condition that affects the brain and spinal cord (central nervous system). In people with MS, certain types of immune system cells (lymphocytes) cause damage to the myelin coating that protects the nerves. Damage to the myelin causes a range of symptoms.

Relapsing multiple sclerosis (RMS) is a type of MS in which the disease fluctuates between episodes of relapses (often with symptoms) and periods of no relapses (remittance).

Fingolimod is approved and marketed to treat RMS in adults and pediatrics. It does not cure RMS, but it decreases the frequency of relapses. It is thought to work in MS by redistributing the lymphocytes present in the blood, preventing them from attacking and damaging the myelin that protects the brain and spinal cord.

Researchers were looking to understand how fingolimod, an approved and marketed treatment for MS, affects different types of immune cells. The main types of immune cells studied were:

- Innate (General) immune cells which function as the first line of defense against germs entering the body, AND
- Adaptive (Specialized) immune cells (known as lymphocytes) which function as the second line of body defense.

Trial drug

The drug studied in this trial was:

Fingolimod (FTY720) 0.5 milligram (mg) once daily by mouth, which is approved and was prescribed to the participants for the treatment of RMS.

Throughout the trial, along with fingolimod, the participants could continue to take the other medications prescribed by their physician.

Trial purpose

The main question the researchers wanted to answer in this trial was:

At Month 6, how were the different types of immune cells affected in participants new to treatment with fingolimod and in participants who had been taking fingolimod continuously for at least 2 years?

The other questions researchers wanted to answer in this trial were:

- **At Month 12,** how were the different types of immune cells affected in participants new to treatment with fingolimod and in participants who had been taking fingolimod continuously for at least 2 years?
- How many participants had at least 1 relapse during the study?
- Did the levels of antibodies against the John Cunningham (JC) virus in participants with RMS change over time?

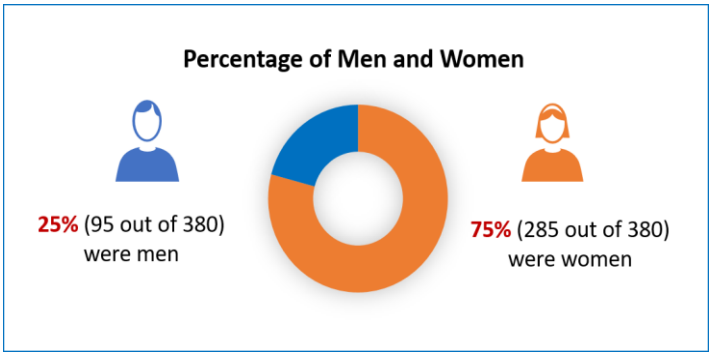
The John Cunningham (JC) virus causes progressive multifocal leukoencephalopathy (PML). PML is a serious infection in the brain that people with weakened immune systems can develop. When a person gets infected with the JC virus, they develop antibodies, a type of protein of the immune system, against this virus.

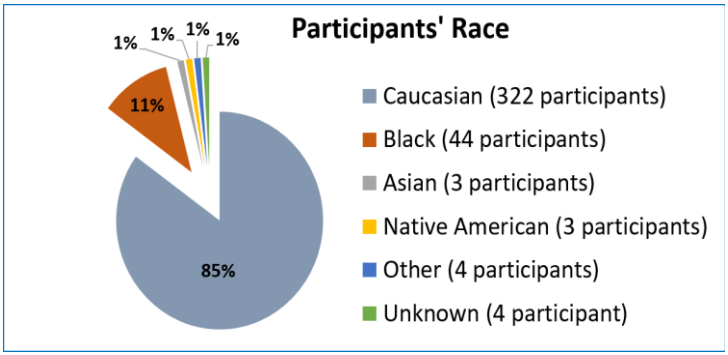
Who was in this trial?

The participants could take part in this trial if they:

- were at least 18 years of age.
- had a diagnosis of RMS.
- were new to treatment with fingolimod OR had been taking fingolimod treatment continuously for at least 2 years.

- had not experienced any heart problems in the 6 months before entering the trial.
- A total of 380 participants from 66 centers in the United States were treated in this trial. The average age of participants was 46 years. Participants' age ranged from 18 to 71 years. 75% of trial participants, or 285 out of 380, were women. 85% of the trial participants, or 322 out of 380, were white (Caucasian).





What kind of trial was this?

This was an open-label trial. This means that the participants, trial doctors, and trial staff knew the participants were receiving marketed fingolimod, as prescribed by their doctors.

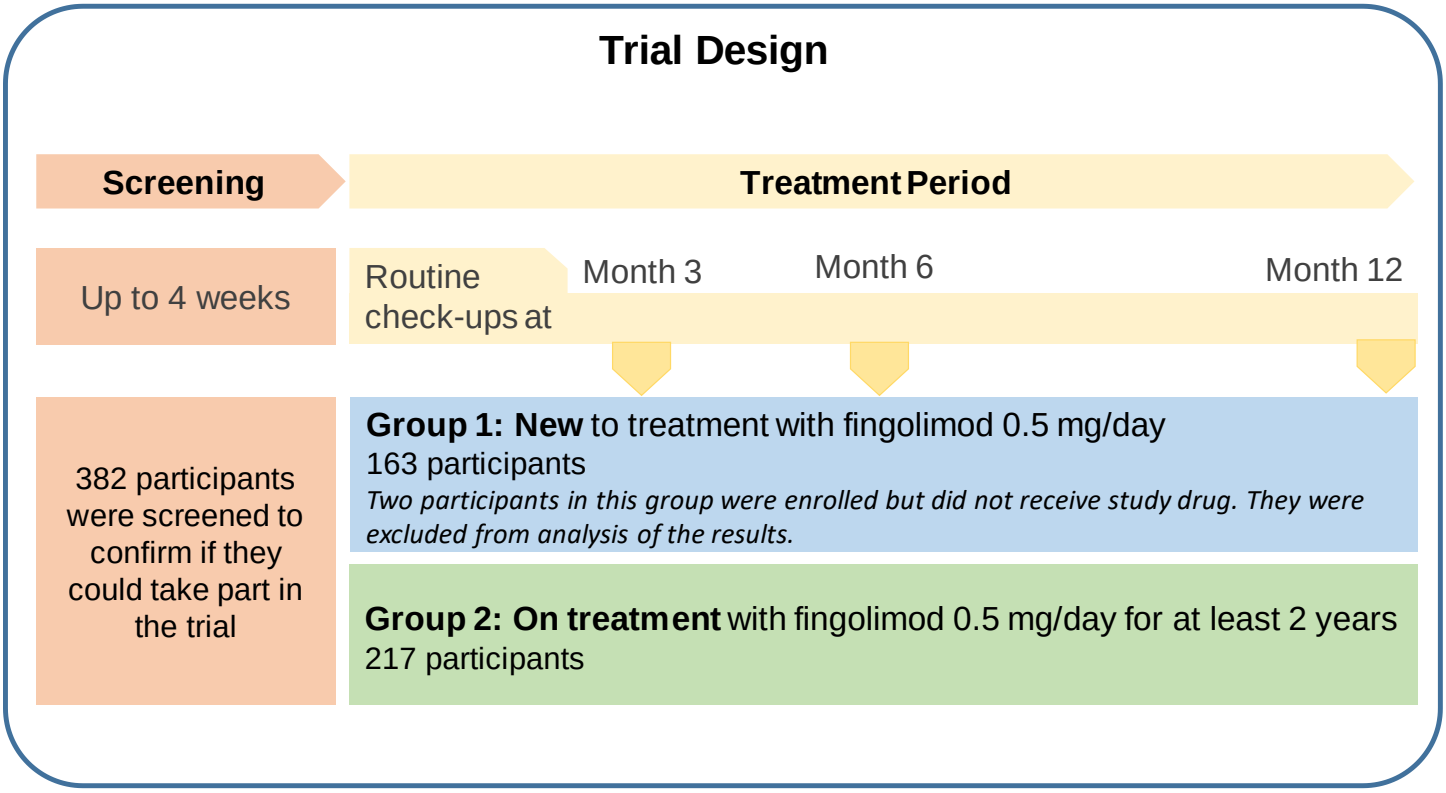
What happened during this trial?

Participants went through a screening period to confirm that they could take part in the trial.

Researchers placed the participants in one of two groups:

- **Group 1** included participants who were new to treatment with fingolimod.
- **Group 2** included participants who had been taking fingolimod treatment continuously for at least 2 years.

Participants received 12 months of treatment in this trial.



At routine visits, researchers collected the participants' blood to check for:

- the amount of the different types of immune cells, and
- the levels of an antibody against the JC virus, known as anti-JCV antibody.

Throughout the trial, researchers recorded the number of MS relapses that each participant had and checked their well-being.

What were the key results of this trial?

This is a summary of the average results for all participants in different groups. It does not show the results of each individual participant. Results of individual participants could be different from the results of the total group of participants. A detailed presentation of the results can be found on the websites listed at the end of this summary.

At Month 6, how were the different types of immune cells affected in participants new to treatment with fingolimod and in participants who had been taking fingolimod continuously for at least 2 years?

Adaptive immune cells (known as lymphocytes)

Group 1: Participants who were new to treatment with fingolimod had a reduction in the average amount of adaptive immune cells after their first 6 months of treatment.

Fingolimod's action was as expected. It reduced the number of adaptive immune cells in the blood of participants from when they first started treatment.

Group 2: Participants who had been taking fingolimod for at least 2 years had no change in the average amount of adaptive immune cells by Month 6.

Continuous use of fingolimod maintained the reduction of adaptive immune cells in blood, as expected in people taking fingolimod for longer periods.

Innate immune cells

In both Groups 1 and 2, the average amount of innate immune cells varied by Month 6, with some increased and some decreased. Further studies may be needed to understand the effect of fingolimod on the innate immune cells.

What were the other results of this trial?

At Month 12, how were the different types of immune cells affected in participants new to treatment with fingolimod and in participants who had been taking fingolimod continuously for at least 2 years?

In **Group 1**, after 12 months of treatment with fingolimod, no additional reduction of adaptive immune cells (known as lymphocytes) was observed.

In **Group 2**, the amount of adaptive immune cells (known as lymphocytes) remained the same throughout the study.

At the Month 12 check, the average amount of innate immune cells varied between participants. Researches could not confirm why this occurred.

How many participants had at least 1 relapse during the study?

During the study, 24 out of 380 (6%) participants had a total of 25 relapses. One relapse in Group 1 was reported as a serious adverse event (please refer to the *'What were the serious adverse events?'* section further ahead in this summary) because the participant required hospitalization.

- In **Group 1**, 11 out of 163 (7%) participants had 12 relapses. 10 participants had 1 relapse each and 1 participant had 2 relapses.
- In **Group 2**, 13 out of 217 (6%) participants had 13 relapses. Each participant had 1 relapse.

Did the levels of antibodies against the JC virus in participants with RMS change over time?

Both Groups 1 and 2 had about the same level of anti-JCV antibodies at the beginning of the study. These levels remained the same throughout the study. This means that fingolimod has no effect on the level of anti-JCV antibodies.

What medical problems did the participants have during the trial?

Medical problems that happen in clinical trials are called "adverse events".

A lot of research is needed to know whether a drug causes an adverse event. During a trial, all adverse events are recorded, whether or not they are thought to be caused by the trial drug. When new drugs are being studied, researchers keep track of all adverse events participants have.

This section is a summary of the adverse events that happened during this trial. The websites listed at the end of this summary may have more information about all the adverse events that happened in this trial.

An adverse event is an unwanted sign, symptom, or disease that participants have during a trial.

An adverse event is considered "serious" when it is life-threatening, causes lasting problems, or the participant needs hospital care. These problems may or may not be caused by the trial drug.

How many participants had adverse events?

189 out of 380 participants (50%) reported 1 or more adverse events. Serious adverse events were reported in 21 out of 380 participants (6%) in the trial. During the trial, 32 out of 380 participants (8%) stopped the drug early because of adverse events. No participants died during this trial.

Number of Participants (%) With Adverse Events

Participants with	**Group 1** (Out of 163 participants)	**Group 2** (Out of 217 participants)
At least 1 adverse event (serious or non-serious event)	92 (56%)	97 (45%)
At least 1 serious adverse event	9 (6%)	12 (6%)
Stopped drug due to adverse event	20 (12%)	12 (6%)

What were the most common non-serious adverse events?

The most common non-serious adverse events that happened in at least 5% (5 out of 100) of participants in any group are presented below.

Number of Participants (%) With Most Common Non-Serious Adverse Events

Participants with	**Group 1** (Out of 163 participants)	**Group 2** (Out of 217 participants)
Common cold	8 (5%)	6 (3%)
Decrease in lymphocytes below the normal range	9 (6%)	1 (<1%)
Fall	5 (3%)	12 (6%)
Feeling very tired (fatigue)	8 (5%)	3 (1%)
Headache	13 (8%)	4 (2%)
Pain in arms and legs	9 (6%)	3 (1%)

What were the serious adverse events?

An adverse event is considered “serious” when it is life-threatening, causes lasting problems, or the participant needs hospital care. These problems may or may not be caused by the trial drug.

Of the 380 participants, 21 (6%) experienced serious adverse events (SAEs). These 21 participants are divided among the treatment groups:

- **In Group 1**, 9 participants (6%) experienced SAEs.
- **In Group 2**, 12 participants (6%) experienced SAEs.

Each SAE occurred once. These SAEs were reported in people with relapsing MS treated with marketed fingolimod. The SAEs included multiple sclerosis relapse, abdominal pain, abnormal uterine bleeding, anxiety, back pain, and bacterial infection on skin and in nose. A full list of these SAEs is available on the websites listed at the end of this document.

How many participants stopped trial drug due to adverse events?

During the trial, 34 out of 380 (9%) participants stopped fingolimod treatment early.

In Group 1, the most common adverse events that led to stopping the trial drug were an increase of the liver proteins* called alanine aminotransferase and aspartate aminotransferase in the blood and/or a decrease in number of lymphocytes below the normal range.

In Group 2, the most common adverse events that led to stopping the trial drug were an increase of the liver proteins* called alanine aminotransferase and aspartate aminotransferase in the blood.

*An increase in the level of alanine aminotransferase and/or aspartate aminotransferase in the blood may indicate that the liver may be inflamed or injured.

How was this trial useful?

This trial helped researchers learn about the effects of treatment with fingolimod on different types of immune cells in people with RMS. It also helped researchers to further understand that the effect of fingolimod on the immune cells was as expected. Researchers observed that participants with RMS treated with fingolimod for 2 years or more did not experience further changes to their adaptive immune cells (known as lymphocytes).

Increases in the level of JC virus antibodies may mean a greater risk of developing serious infections. In this trial, researchers observed that the levels of JC virus antibodies did not increase in participants over time.

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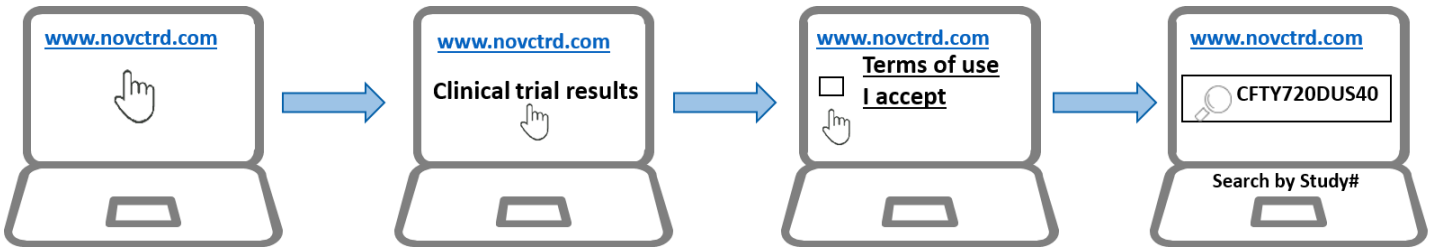
trials around the world to advance medical science and healthcare. If you have any questions about these trial results, please talk to the doctor or staff at your trial site.

Where can I learn more about this trial?

More information about the results and adverse events in this trial can be found in the scientific summary of the results available on the Novartis Clinical Trial Results website (www.novctrd.com).



You can find more information about this trial on the following website:

- www.clinicaltrials.gov Use the NCT identifier NCT03257358 in the search field.

Full clinical trial title: A 12-month, prospective, multicenter, two-cohort, nonrandomized, open-label study in adult patients with Relapsing Multiple Sclerosis (RMS), to investigate changes in immune phenotype biomarkers after treatment with 0.5 mg fingolimod (FTY720) [FLUENT]

Thank you

Thank you for taking part in this trial. As a clinical trial participant, you belong to a large community of people around the world. You helped researchers answer important health questions and test new medical treatments.

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Novartis is a global healthcare company based in Switzerland that provides solutions to address the evolving needs of patients worldwide.

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