NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn more about the effects and safety of BAF312 compared to placebo in people with secondary progressive multiple sclerosis

Protocol number: CBAF312A2304, also known as the EXPAND trial

Thank You!

Novartis, the sponsor of this clinical trial, would like to thank you for taking part in this trial for the drug BAF312, also known as siponimod. You helped researchers learn more about how BAF312 works in people with secondary progressive multiple sclerosis, also known as SPMS.

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.

Important note: This summary only shows the results of a single clinical trial. Other clinical trials may have different findings. Researchers and health authorities 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 to have 2 parts, known as the Core Part and the Extension Part. The Core Part of the trial is complete. The Extension Part is still ongoing and estimated to be completed in 2024.

The trial started in December 2012. The Core Part ended in April 2016 as planned. An individual participant could be in the Core Part of the trial for up to 3 years.

The results of the Core Part of the trial were evaluated and the trial report was created. This is a summary of the report on the Core Part of the trial.

The Extension Part of the trial is still ongoing and when it is completed, a summary of its results will be available.

Why was the research needed?

Multiple sclerosis, also known as MS, is a condition that affects the brain and spinal cord. In MS, the coating that protects the nerves, known as myelin, is damaged. This causes a range of symptoms. Researchers were looking for a better way to treat a type of MS called secondary progressive multiple sclerosis, also known as SPMS. Many people diagnosed with MS transition to having SPMS over time. This means that their MS symptoms worsen steadily over time.

The main purpose of this trial was to find out if BAF312 was safe and had beneficial effects for people who have SPMS.

In people with MS, certain types of white blood cells can cause damage to the nervous system and lead to MS symptoms. BAF312 works to reduce the number of these white blood cells in the nervous system.

Trial drugs

The drugs given in this trial were:

- BAF312, also known as siponimod.
- Placebo, which looks like the trial drug but does not have any medicine in it. Using placebo helps researchers to better understand the effect of a trial drug.

Participants were required to stop taking any other MS medicines at the time of screening, before taking any trial drug. This was to help avoid a mix-up of effects between any medicines they had been taking and the trial drug. If participants had worsening symptoms of SPMS, they were given doses of corticosteroid medicine, as needed, to help treat the symptoms.

Trial purpose

This trial was done to learn more about the effects and safety of BAF312. The main question the researchers wanted to answer in this trial was:

- How many participants showed worsening of SPMS symptoms that lasted for at least 3 months?

Researchers also monitored the health of participants throughout the trial.

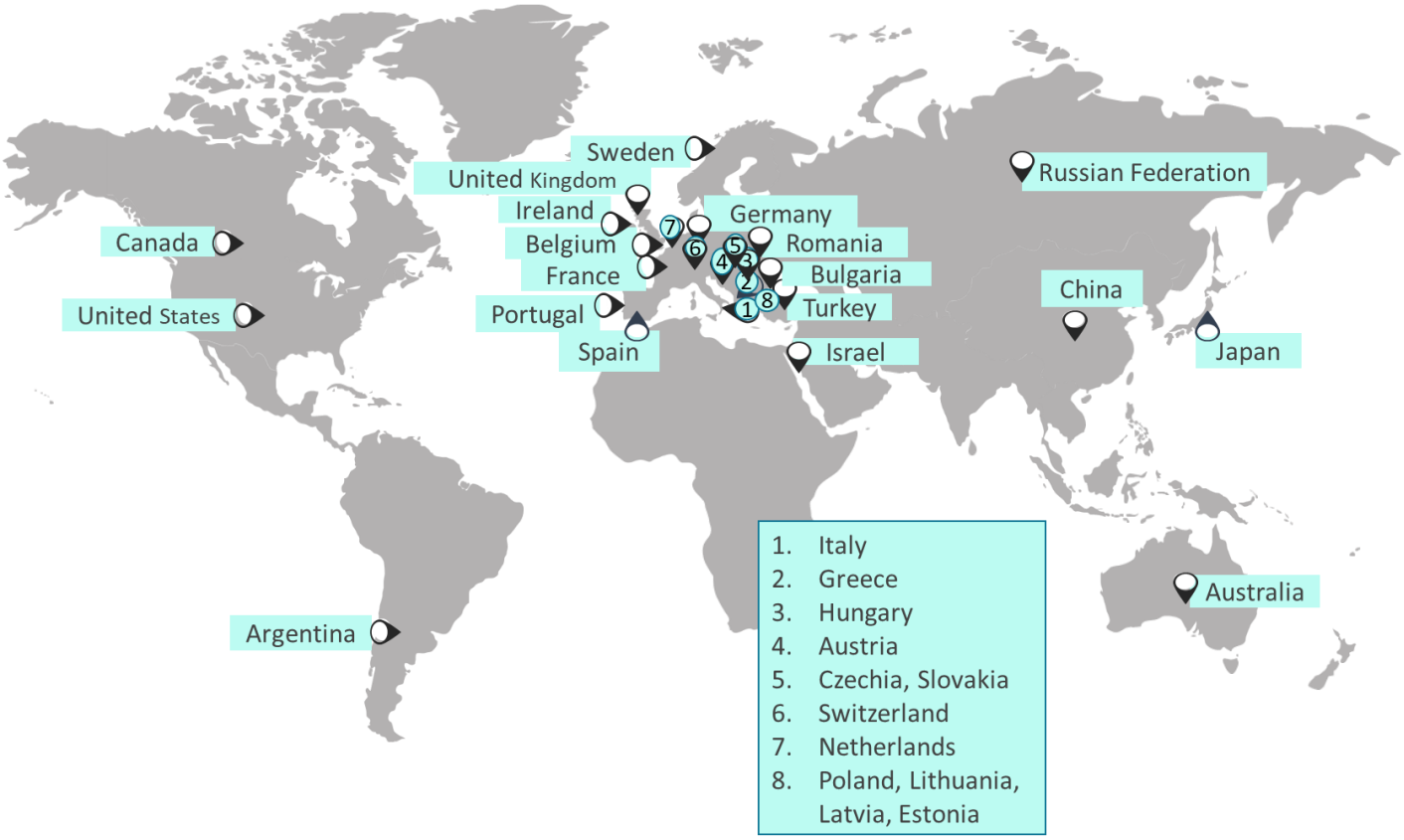
Who was in this trial?

The participants could take part in this trial if they:

- were between the ages of 18 and 60 years,
- had SPMS for at least 6 months before the trial,
- did not have an immune system disease other than SPMS, and
- had not taken corticosteroid treatment or had an MS relapse within 3 months before they started treatment in the trial.

A total of 1651 participants from 31 countries participated in this trial.

Countries of Trial Participants



The average age of participants was 48 years. 60% of trial participants, equal to 992 out of 1651, were female.

What kind of trial was this?

The Core Part of the trial was called double-blind. This means that none of the participants, trial doctors, or trial staff knew what treatment participants were receiving. Some trials are done this way because knowing what treatment each participant is getting can affect the results of the trial. Doing a trial this way helps to make sure that the results are looked at with fairness towards all treatments.

What happened during this trial?

At the start of the trial, the researchers randomly assigned the participants to receive either:

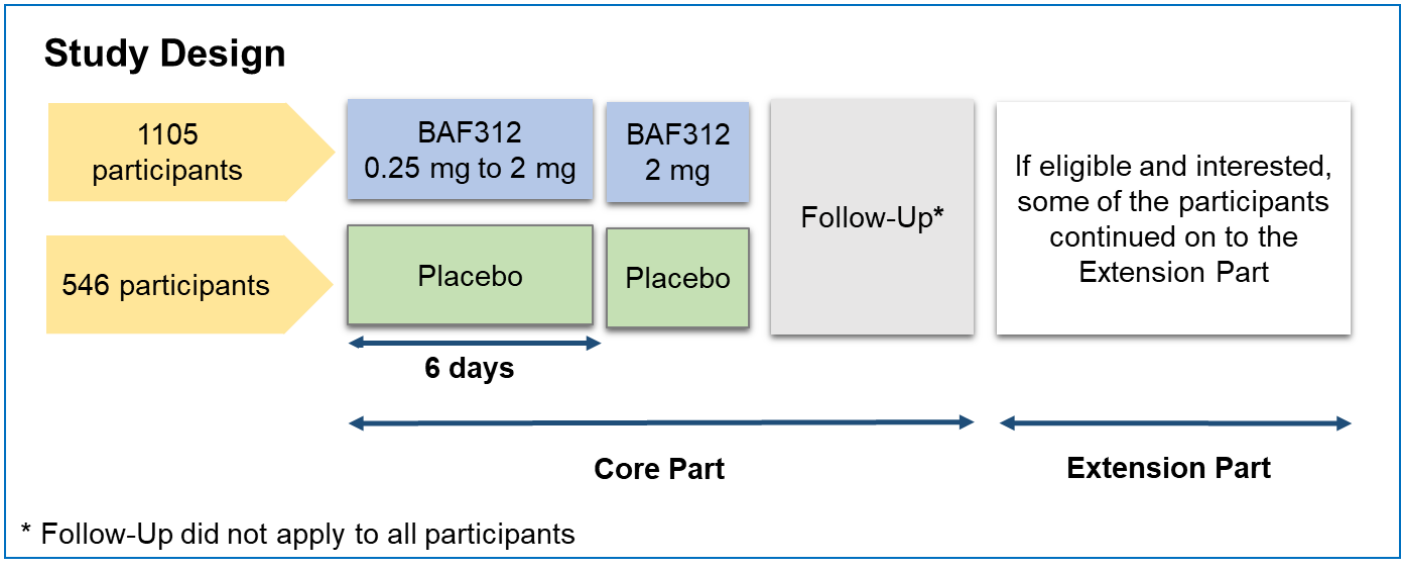
- 2 milligram (mg) BAF312
- placebo

For every 3 participants who took part in the trial, 2 received BAF312 and 1 received placebo.

Over 6 days, the amount of BAF312 the participants were given per day was slowly increased from 0.25 mg on Day 1 to 2 mg on Day 6. The participants then received 2 mg BAF312 per day for the rest of the trial.

Participants who were in the placebo group were given tablets that looked like the BAF312 tablets, but they did not have any medicine in them.

Participants were asked to take the tablets once each day by mouth, preferably at the same time each day prior to lunch.



The Core Part was completed when a specific number of symptoms were recorded in the entire group of participants. At most scheduled visits, blood samples were taken to monitor the number of white blood cells in the blood. The researchers reduced the dose of the trial drug if the number of white blood cells was too low in the participant's blood. Other tests and questionnaires were also used to track participants' health and response to the treatment throughout the trial.

If participants had worsening of MS symptoms that lasted for at least 6 months, they were given the option to make no change to their treatment, switch to 2 mg BAF312, or switch to a different MS treatment. After completing the Core Part/Follow-Up visit, the participants could join the Extension Part of the trial. In the ongoing Extension Part, all participants receive treatment with BAF312.

The researchers monitored the participant's health throughout the trial.

What were the key results of this trial?

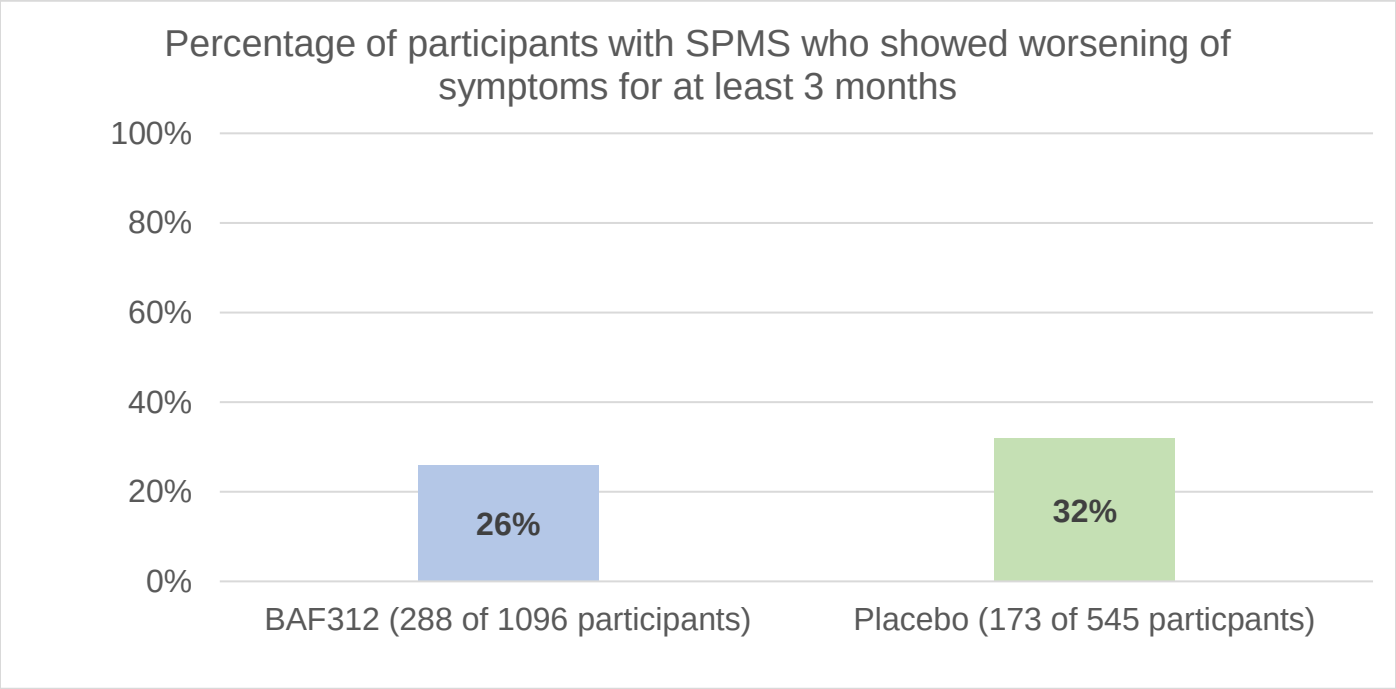
This is a summary of the overall results for all participants for both treatment groups. It does not show the results of each individual participant. Results of individual participants could be different from the results of the total group of participants. More details on the results can be found on the websites listed at the end of this summary.

How many participants showed worsening of SPMS symptoms that lasted for at least 3 months?

Results for this question were available for 1096 participants who took BAF312 and 545 participants who took placebo.

Researchers found that participants who took BAF312 were around 21% less likely to have worsening symptoms than those who took placebo.

During this trial, 26% (288 of 1096) of participants who were given BAF312 had worsening symptoms of SPMS for at least 3 months. In comparison, 32% (173 of 545) of participants who were given placebo had worsening of SPMS symptoms for at least 3 months.



What medical problems did the participants have during the trial?

Medical problems that happen in clinical trials are called “adverse events”. An adverse event is an unwanted sign or symptom 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.

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. So, when new drugs are being studied, researchers keep track of all adverse events.

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 the adverse events that happened in this trial.

How many participants had adverse events?

Adverse event results were available for 1099 participants who took BAF312 and 546 participants who took placebo.

In the BAF312 group, 89% (975 of 1099) of participants had 1 or more adverse events. In the placebo group, 82% (445 of 546) of participants had 1 or more adverse events.

In total, 8% (84 of 1099) of participants who took BAF312 and 5% (28 of 546) of participants who took placebo stopped the drug early because of adverse events.

A total of 8 deaths were reported during the trial. Out of the 8 participants who died during the trial, 4 participants were in the placebo group and 4 participants were in the BAF312 group. The table below shows a summary of adverse events that happened during the trial.

Summary of Adverse Events

	BAF312 Percentage (out of 1099 participants)	**Placebo Percentage (out of 546 participants)**
At least one adverse event	89% (975)	82% (445)
At least one serious adverse event	18% (197)	15% (83)
Stopped drug due to adverse event	8% (84)	5% (28)
Deaths	0.4% (4)	0.7% (4)

What were the most common non-serious adverse events?

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

Most Common Non-Serious Adverse Events		
	BAF312 Percentage (out of 1099 participants)	**Placebo Percentage (out of 546 participants)**
Headache	14% (159)	13% (71)
Nose and throat infection	14% (149)	14% (79)
Urinary tract infection (UTI)	12% (128)	14% (75)
Fall	11% (126)	11% (59)
High blood pressure	10% (114)	8% (41)
Feeling very tired	9% (100)	9% (51)
Common cold	8% (89)	8% (41)
Back pain	6% (66)	8% (43)
Dizziness	7% (74)	5% (26)
Feeling like you want to be sick (nausea)	7% (73)	3% (19)
Flu	7% (72)	7% (40)
Diarrhea	6% (69)	4% (22)
Pain in the arms or legs	5% (60)	4% (21)
Increase of protein called alanine aminotransferase in the blood	5% (58)	1% (8)
Joint pain	4% (49)	6% (35)
Depression	4% (44)	5% (28)

What were the most common serious adverse events?

The table below shows the most common serious adverse events that happened in at least 0.5% (5 of 1000) of participants in any group.

For a full list of the serious adverse events that occurred in this trial, please visit the websites listed at the end of this summary.

Most Common Serious Adverse Events		
	BAF312 Percentage (out of 1099 participants)	**Placebo Percentage (out of 546 participants)**
Urinary tract infection (UTI)	1.4% (15)	1.3% (7)
Skin cancer	1% (11)	1% (7)
Increase of protein called alanine aminotransferase in the blood	0.9% (10)	0.4% (2)
Increase of protein called aspartate aminotransferase in the blood	0.5% (5)	0.2% (1)
Head injury	0.5% (5)	0% (0)
Depression	0.5% (5)	0.4% (2)
Seizure disorder	0.5% (5)	0% (0)
Severe infection that spreads from the urinary tract throughout the body	0.5% (5)	0.2% (1)
Suicide attempt	0.4% (4)	0.6% (3)
Worsening of MS	0.2% (2)	1% (7)
Difficulty maintaining balance	0.1% (1)	0.6% (3)
Partial paralysis of the lower limbs	0% (0)	0.6% (3)

How was this trial useful?

This trial helped researchers learn how well BAF312 works and if it is safe to use in people with SPMS. Results from this trial may be used in other clinical trials for people with SPMS.

BAF312 is approved in the United States of America. It is currently being researched in North and South America, Europe, Asia, and Oceania.

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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). Once on the site, click “Clinical trial results” at the bottom of the page. After agreeing to enter the Novartis website, type CBAF312A2304 into the keyword search box and click “Search”.

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

- www.clinicaltrials.gov. Use the NCT identifier NCT01665144 in the search field.
- www.clinicaltrialsregister.eu. Use the EudraCT identifier 2012-003056-36 in the search field.

Full clinical trial title: A multicenter, randomized, double-blind, parallel-group, placebo-controlled variable treatment duration study evaluating the efficacy and safety of siponimod (BAF312) in patients with secondary progressive multiple sclerosis followed by extended treatment with open-label BAF312.

Thank you

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

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