NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn more about a new way of managing fever in people taking dabrafenib and trametinib to prevent melanoma from coming back

Clinical trial protocol number: CDRB436F2410

Thank you!

Thank you to the participants who took part in the clinical trial for a new way to manage fever when taking the drugs **dabrafenib** and **trametinib**.

All of the participants helped the researchers learn more about managing fevers in people taking dabrafenib and trametinib to prevent **advanced (stage 3) melanoma** from coming back after surgery. Novartis sponsored this clinical trial and believes it is important to share what was learned from the results of this trial with the participants and the public.

We hope this helps the participants understand their important role in medical research.

? **If you were a participant and have any questions about the results, please talk to the doctor or staff at the trial site.**

This summary only shows the results of a single clinical trial. Other clinical trials may have different findings.

Why was the research needed?

Researchers are looking for a better way to lessen severe side effects from treatments to prevent stage 3 melanoma from coming back after surgery. **Stage 3 melanoma** is skin cancer that has spread from where it started to a nearby lymph node. Surgery is the main treatment to remove stage 3 melanoma. Many people have treatment after surgery (**adjuvant treatment**) to lower the chance of melanoma coming back.

Some people who have melanoma have adjuvant treatment with **dabrafenib** (pronounced duh-BRA-feh-nib) and **trametinib** (pronounced truh-MEH-tih-nib). Previous clinical trials found that the most common possible side effect of dabrafenib and trametinib is **fever**, which can lead to **severe fever-related problems**.

The **standard way to manage fever** was to have participants stop taking dabrafenib and continue taking trametinib if their temperature was **38.5°C (101.3 °F) or higher**. In a trial that used the standard way of managing fever, the most common reason people with stage 3 melanoma permanently stopped treatment was fever.

What are fever and severe fever-related problems?

A **fever** (pyrexia) is a body temperature of 38°Celsuis (100.4 °Fahrenheit) or higher. Symptoms of fever may also include chills, shivering, sweating, or flu-like symptoms.

Severe fever-related problems include:

- Hospitalization due to fever
- **Severe fever**, which is higher than 40°C (104°F) or causes low blood pressure, dehydration (not enough fluids in their body), or kidney failure
- Having to permanently stop taking treatment due to fever

Trial purpose

The main purpose of this trial was to learn if a new way of managing fever could lower the number of severe fevers and severe fever-related problems in people taking dabrafenib and trametinib to prevent stage 3 melanoma from coming back after surgery.

The main questions the researchers wanted to answer in this trial were:

- How many participants had one or more severe fever-related problems during treatment?
- What medical problems did the participants have during the trial?

How long was this trial?

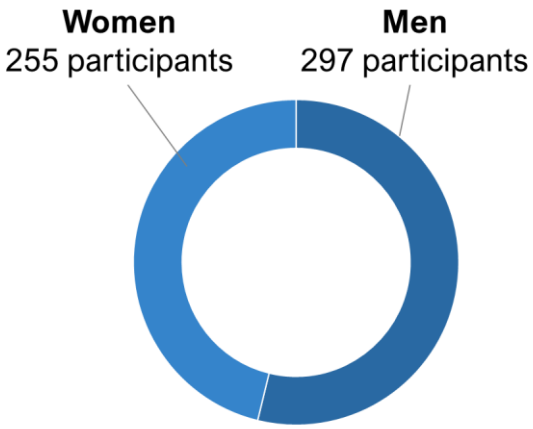
This trial was designed so that each participant could take part for about 2 years. The trial started in August 2018 and ended in September 2021.

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

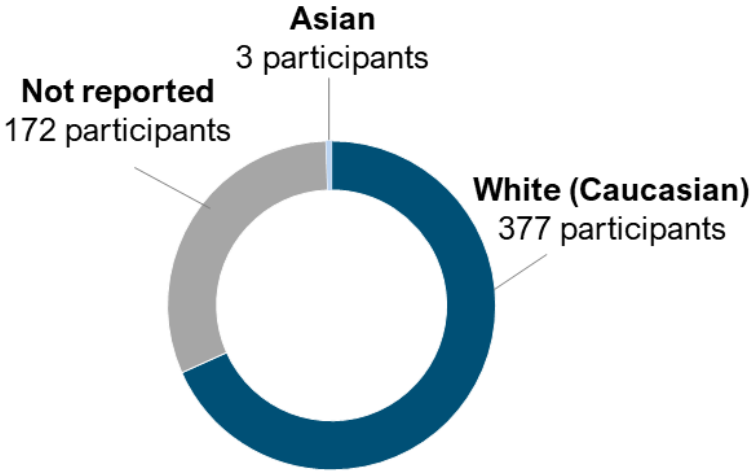
Who was in this trial?

552 participants with melanoma were in this trial. Participants' ages ranged from 18 to 82 years. Their average age was 53 years.

Participants reported their gender as:



Participants reported their race as:



The participants could take part in this trial if they:

- Had stage 3 *BRAF V600*-positive melanoma
    - **BRAF** is a gene inside cells that helps control cell growth. *BRAF* positive means that cancer cells have a mutation (change) in the *BRAF* gene that lets cells grow uncontrolled, which can cause cancer.
- Had surgery that completely removed their melanoma up to 12 weeks before joining the trial
- Had not taken any other adjuvant treatment
- Had no other serious cancer or heart, lung, or blood conditions

Participants took part at trial sites in 23 countries. The map on the next page shows how many participants took part in each country.

What treatments did the participants receive?

The treatments in this trial were:

Dabrafenib and trametinib: Drugs that are approved in some countries to be used together to treat advanced (stages 3 and 4) melanoma with *BRAF* V600E and V600K gene changes. They're approved to be given as adjuvant treatment or to treat melanoma that can't be removed by surgery. Participants in this trial took:

- **Dabrafenib** by mouth as 150 mg capsules 2 times a day
- **Trametinib** by mouth as 2 mg tablets one time a day

Trial doctors could lower or stop each participant's dose of dabrafenib and trametinib if needed.

The new way of managing fever, which had participants **stop taking both dabrafenib and trametinib** if their temperature was **38°C** (100.4 °F) **or higher** or they had other symptoms of fever. They could start taking them again at the same dose 24 hours after their fever or fever symptoms went away.

Along with the treatments above, participants could take anti-inflammatory medicines to reduce their fever symptoms, such as paracetamol or ibuprofen. The trial doctors could also prescribe corticosteroids (medicines to lessen the immune system's response), if needed to manage a participant's fever.

This was an open-label trial, which means that the participants and clinical trial team knew what treatment each participant took. In this trial, all participants took dabrafenib and trametinib.

What happened during this trial?

Up to 28 days before treatment

During screening

Trial doctors checked participants' health and the results from their melanoma surgery to make sure they could be in this clinical trial.

552 participants took part in this trial.

Up to 1 year

During treatment

The participants took both of these treatments:

- **Dabrafenib**, which was taken by mouth as 150 mg capsules 2 times a day
- **Trametinib**, which was taken by mouth as 2 mg tablets one time a day

In addition to these, each participant was instructed to use **the new way of managing fever,** which had participants stop taking both dabrafenib and trametinib if their temperature was 38°C or higher. They could start taking them again 24 hours after their fever went away.

Researchers checked the participants' fever-related problems, melanoma, and general health throughout the trial.

Until the end of the trial

During follow-up

Participants returned to their trial site every 3 to 6 months for up to 2 years after their last treatment dose for follow-up visits.

During survival follow-up

Trial staff called each participant every 3 months after their last trial visit to check their health until the trial ended.

What were the main results of this trial?

How many participants had one or more severe fever-related problems during treatment?

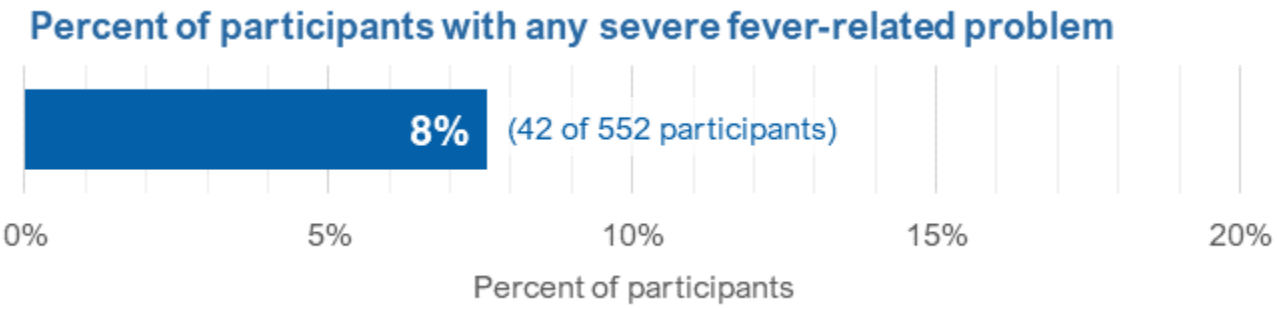
42 of 552 participants (about 8%) had at least one severe fever-related problem during treatment. The most common severe fever-related problem was hospitalization due to fever.

The researchers kept track of how many participants had severe fever-related problems during treatment. **Severe fever-related problems** included:

- Hospitalization due to fever
- Severe fever, which is higher than 40°C (104°F) or causes low blood pressure, dehydration (not enough fluids in their body), or kidney failure
- Having to permanently stop taking treatment due to fever

Severe fever-related problems during treatment

The graph below shows the percent of participants who had one or more severe fever-related problems.



How do these results compare with participants who used the standard way of managing fever in an earlier trial, CDRB436F2301?

A past trial, CDRB436F2301, that took place from 2013 to 2017, also included participants with melanoma who took dabrafenib and trametinib as adjuvant treatment after surgery. In this trial, participants followed a standard way to manage fevers, which was to **stop taking only dabrafenib** and continue taking trametinib if their temperature was **38.5°C (101.3 °F) or higher.**

87 of 435 participants (20%) in CDRB436F2301 had one or more severe fever-related problems.

Compared to the 42 out 552 participants (8%) who had one or more severe fever-related problems in this trial CDRB436F2410, the researchers concluded that these results were meaningfully different.

What were the other results of this trial?

Researchers checked to see how many of the participants were alive and did not have their melanoma come back after starting treatment.

The percent of participants who were alive was:

- 99% at 12 months after starting treatment
- 93% at 24 months after starting treatment

The percent of participants who were alive and did not have their melanoma come back was:

- 92% at 12 months after starting treatment
- 58% at 24 months after starting treatment

The researchers concluded that the new way of managing fever did not change how well the treatments worked to prevent melanoma from coming back.

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. So, when new drugs are being studied, researchers keep track of all adverse events the participants have, whether or not they are thought to be caused by the trial treatment.

This section is a summary of the adverse events that happened during treatment and up to 30 days after treatment. The websites listed at the end of this summary have more information about the adverse events that happened in this trial.

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 treatment.

How many participants had adverse events?

The table below shows the number of participants who had adverse events during the trial:

	Dabrafenib and trametinib Number out of 552 participants Percent
Participants who had at least 1 adverse event	**526** of 552 95%
Participants who had at least 1 serious adverse event	**121** of 552 22%
Participants who stopped taking one or both trial drugs due to an adverse event	**87** of 552 16%
Deaths while taking trial treatment	**1** of 552 Less than 1%

What were the serious adverse events?

One death happened while the participant was taking the trial treatment.

121 participants had serious adverse events. The table below shows the **most common serious adverse events**, which happened in **3** or more of **552** participants (**1**% or more).

	Dabrafenib and trametinib Number out of 552 participants Percent
Fever Pyrexia	**28** participants 5%
The heart doesn't pump out enough blood Ejection fraction decreased	**19** participants 3%
A skin infection that causes redness, swelling, and pain Cellulitis	**5** participants 1%
A type of skin cancer Basal cell carcinoma	**4** participants 1%
Irregular heartbeat Atrial fibrillation	**3** participants 1%
A bacterial skin infection Erysipelas	**3** participants 1%
Flu-like illness Influenza like illness	**3** participants 1%
Blood clot in the lungs Pulmonary embolism	**3** participants 1%

What were the most common non-serious adverse events?

526 participants had adverse events that were not considered serious.

The table on the next page shows the **most common non-serious adverse events**, which happened in **142** or more of **552** participants (**26**% or more).

	Dabrafenib and trametinib Number out of 552 participants Percent
Fever Pyrexia	**374** participants 68%
Headache	**174** participants 32%
A higher level of protein in the blood Blood creatine phosphokinase increased	**168** participants 30%
Frequent, loose, or watery stool Diarrhea	**149** participants 27%
Chills	**146** participants 26%
Feeling tired Fatigue	**142** participants 26%

How has this trial helped?

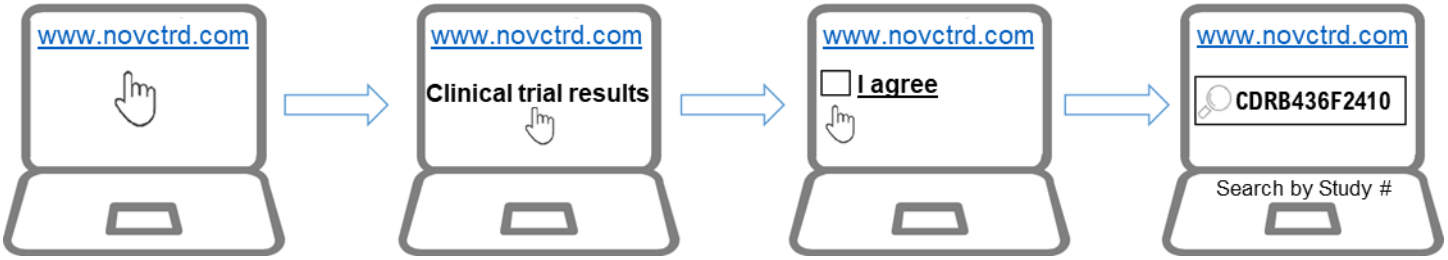
The researchers concluded that the participants in this trial had fewer severe fever-related problems than the participants in the past trial who used the standard way of managing fever. Based on the results of this trial, Novartis informed the health authorities and updated the prescribing information to include the new way of managing fever.

Where can I learn more about this trial?

This is a summary of the overall results for all participants. 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 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).

Follow these steps to find the scientific summary:



You can find more information about this trial on these websites:

- www.clinicaltrials.gov. Use the NCT identifier **NCT03551626** in the search field.
- www.clinicaltrialsregister.eu. Use the EudraCT identifier **2018-000168-27** in the search field.

Full clinical trial title: COMBI-APlus: Open-label, phase IIIb study of dabrafenib in COMBInation with trametinib in the adjuvant treatment of stage III BRAF V600 mutation-positive melanoma after complete resection to evaluate the impact on pyrexia related outcomes of an adapted pyrexia AE-management algorithm

To learn more about the past trial, CDRB436F2301, visit these websites:

- www.clinicaltrials.gov. Use the NCT identifier **NCT01682083** in the search field.
- www.clinicaltrialsregister.eu. Use the EudraCT identifier **2012-001266-15** in the search field.

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.

NOVARTIS

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

1-888-669-6682 (US); +41-61-324 1111 (EU);
www.novartisclinicaltrials.com