Clinical Trial Results – Layperson Summary

Two identical studies to compare the safety and effectiveness of etrolizumab with placebo or adalimumab in people with "ulcerative colitis," a long-term illness where the lower part of the gut is inflamed

See the end of the summary for the full title of the studies.

About this summary

This is a summary of the results of clinical trials (called "study" or "studies" in this document), written for:

- Members of the public, and
- People who took part in the studies.

This summary is based on information known at the time of writing (November 2021). More information may now be known.

The studies (HIBISCUS I and HIBISCUS II) started in November 2014. HIBISCUS I finished in March 2020. HIBISCUS II finished in May 2020. This summary was written after the studies had ended.

No two studies can tell us everything about the risks and benefits of a medicine. It takes lots of people in many studies to find out everything we need to know. The results from these studies may be different from other studies with the same medicine.

- This means that you should not make decisions based on this one summary—always speak to your doctor before making any decisions about your treatment.

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Thank you to the people who took part in these studies

The people who took part have helped researchers to answer important questions about the study medicine, and a long-term illness called "ulcerative colitis," an inflammatory bowel disease where the lower part of the gut is inflamed.

Key information about these studies

Key methods

- These studies were done to compare the study medicine, called "etrolizumab," with a placebo and an existing medicine, called "adalimumab," in people with ulcerative colitis.
    - The placebo looked the same and was given in the same way as the study medicines but did not contain any real medicine.
- In these studies, people received either etrolizumab; an existing medicine, called "adalimumab"; or a placebo. It was decided by chance using a computer which treatment each person received.
- HIBISCUS I included 358 people in 14 countries. HIBISCUS II included 358 people in 18 countries.

Key findings

- The main finding was that in HIBISCUS I, significantly more people with ulcerative colitis who were treated with etrolizumab (19 out of 100) had reduced inflammation and symptoms compared with placebo (7 out of 100). In HIBISCUS II, the number of people who had reduced symptoms was similar between people treated with etrolizumab (18 out of 100) and placebo (11 out of 100).
- In HIBISCUS I, one person who received etrolizumab and one person who received a placebo each had a serious side effect that the study doctor believed was related to treatment. In HIBISCUS II, one person who received etrolizumab and one person who received a placebo each had a serious side effect that the study doctor believed was related to treatment.
- At the time of writing this summary, the studies have concluded. No new information is being collected.

1. General information about these studies

Why were these studies done?

Ulcerative colitis is a long-term illness where the lower part of the gut becomes inflamed, causing ulcers to form. People with ulcerative colitis often experience diarrhea with blood, stomach cramps, and the urgent need to have a bowel movement. These painful and debilitating symptoms can get in the way of sleep, social activities, and other daily activities.

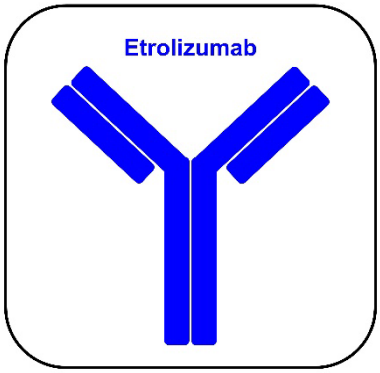
There are different types of medicines available to help treat ulcerative colitis and its symptoms. These medicines often do not work for everyone, or don't work for a long time in some people with ulcerative colitis, so researchers are looking at new medicines that work in other ways.

These studies looked at etrolizumab, which works differently in the body than existing medicines, such as adalimumab. The study doctors wanted to find out if etrolizumab was

more effective at reducing inflammation and symptoms of ulcerative colitis than adalimumab or placebo. They also wanted to find out how safe etrolizumab was.

What was the study medicine?

A medicine called "etrolizumab" was the focus of these studies. It works in a different way than adalimumab.



- You say this as "et – roe – liz – oo – mab."
- Etrolizumab is a type of protein called an "antibody." It works by sticking to and blocking a second protein, called "β7." You say this as "bay-tuh seh-ven."
    - This prevents the movement of inflammatory cells into the gut and decreases inflammatory processes in the gut.
- Etrolizumab is given as an injection under the skin.

"Adalimumab" is an existing medicine given to people with ulcerative colitis.

- You say this as "ah-daa-lee-mu-mab."
- Adalimumab is a type of protein called an "antibody." It works by attaching to a protein in the body called "tumor necrosis factor alpha" (or "TNF-alpha" for short).
    - TNF-alpha helps the body fight infections, but too much TNF-alpha can damage the gut. Some researchers think that people with ulcerative colitis produce too much TNF-alpha in their bodies.
    - Adalimumab attaches to the TNF-alpha and stops TNF-alpha from damaging the gut.
- Adalimumab is given as an injection just under the skin.

Etrolizumab was also compared with a "placebo."

- You say this as "plah – see – bo."
- The placebo looked the same as etrolizumab and adalimumab but did not contain any real medicine. This means it had no medicine-related effect on the body.
- Researchers compared etrolizumab with a placebo so they could show which benefits or side effects were actually caused by the medicine.

What did researchers want to find out?

Researchers did these studies to find out how well etrolizumab worked compared with a placebo and with an existing medicine called "adalimumab" (see section 4, "What were the results of the studies?").

They also wanted to find out how safe etrolizumab was, by checking how many people had side effects when taking each of the medicines during these studies (see section 5, "What were the side effects?").

The main questions that researchers wanted to answer were:

1. Was etrolizumab more effective than placebo in reducing symptoms of ulcerative colitis?
2. Was etrolizumab more effective than adalimumab in reducing symptoms of ulcerative colitis?
3. Did people who received etrolizumab have any side effects, and if so, what were they?

What kinds of studies were these?

These studies were "phase 3" studies. This means that etrolizumab's efficacy and safety had been tested in a smaller number of people with ulcerative colitis before these studies (called a "phase 2" study). In these phase 3 studies, a larger number of people with ulcerative colitis either received etrolizumab, adalimumab (a standard treatment for ulcerative colitis), or a placebo. This was to find out about the side effects of etrolizumab and to see if etrolizumab was more effective in reducing inflammation and symptoms than placebo or adalimumab.

The studies were "randomized." This means that it was decided by chance, like tossing a coin, whether people in the study would receive either etrolizumab, adalimumab, or placebo. This was done by a computer.

These were "double-blind" studies. This means that neither the people taking part in the study, nor the study doctors, knew which of the study medicines people were receiving. "Blinding" of a study is done so that the person does not know which treatment they are receiving and what effect of the treatment to expect.

These were also "double-dummy" studies, which compare treatments that have a different appearance or look different. This is done so that people do not know which treatment they are receiving based on what it looks like or how they receive it. In these studies, each person received two treatments: one had the active medicine and the other had a placebo that was given in the same way as the other active medicine. Some people also received the placebo in both treatments. This was done so people would not be able to tell if they were receiving etrolizumab, adalimumab, or a placebo.

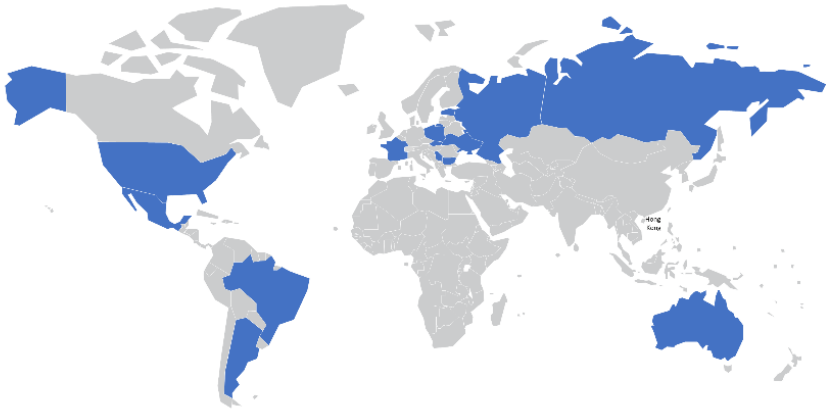
When and where did the studies take place?

HIBISCUS I started in November 2014 and finished in March 2020. HIBISCUS II started in November 2014 and finished in May 2020. This summary was written after the studies had ended.

HIBISCUS I took place at 97 study centers, across 14 countries in Asia, Australia, Europe, North America, and South America. HIBISCUS II took place at 110 study centers, across 18 countries in Asia, Oceania, Europe, North America, and South America. The following maps show the countries where these studies took place.

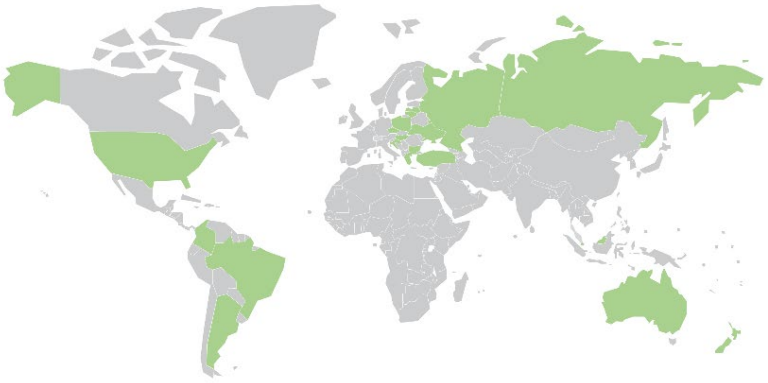
HIBISCUS I

- Argentina
- Australia
- Brazil
- Bulgaria
- Estonia
- France
- Hong Kong
- Mexico
- Poland
- Russia
- Serbia
- Slovakia
- Ukraine
- United States



HIBISCUS II

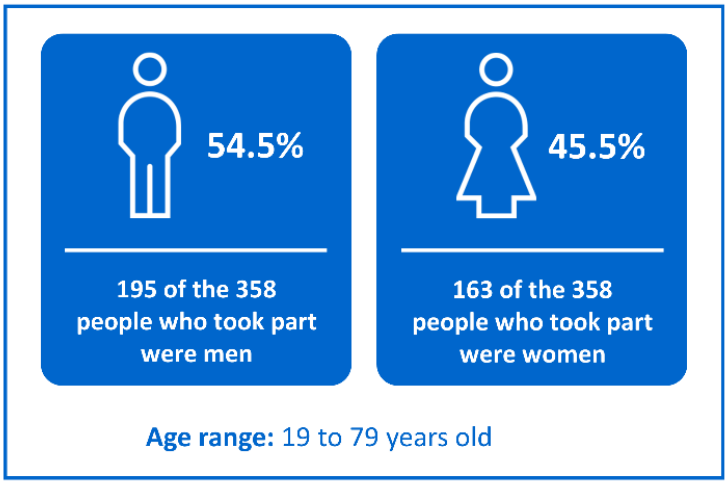
- Argentina
- Australia
- Brazil
- Bulgaria
- Colombia
- Croatia
- Czech Republic
- Greece
- Hungary
- Latvia
- Lithuania
- Malaysia
- New Zealand
- Poland
- Russia
- Turkey
- Ukraine
- United States



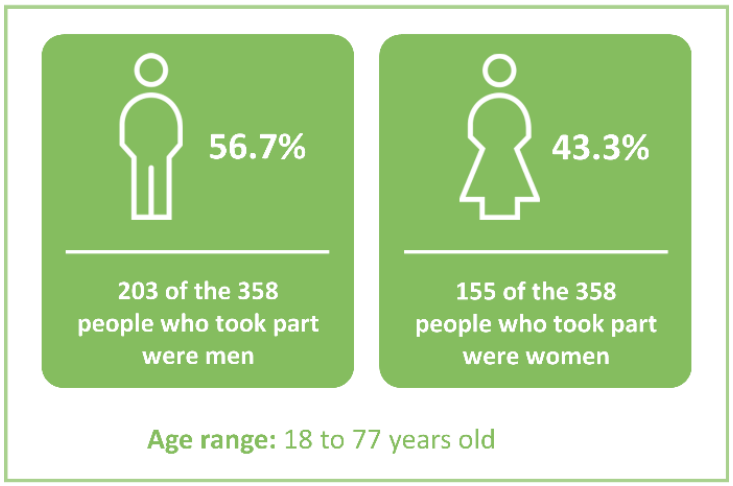
2. Who took part in these studies?

In these studies, 716 people with ulcerative colitis participated (358 people in HIBISCUS I, 358 people in HIBISCUS II). More information on the people who participated is given below.

HIBISCUS I



HIBISCUS II



People **could** take part in the studies if they:

- Were aged 18 to 80 years old
- Had been diagnosed with moderate to severe ulcerative colitis more than 3 months before starting the studies
- Had received treatments for ulcerative colitis that didn't work—or that were not well tolerated
- Had never received a medicine that blocks the protein known as "tumor necrosis factor."

People **could not** take part in the study if they had:

- A history of certain stomach and gut problems, such as a past or present abnormal connection between parts of the gut (called a "fistula") or a painful collection of pus (called an "abscess") in their abdomen, colon polyps that appear to be cancerous (colonic mucosal dysplasia), or a narrowed large intestine, or infections such as HIV or hepatitis B or C, or tuberculosis (to avoid potential safety issues)
- Previously taken certain medicines, such as anti-TNF therapy (including infliximab) or anti-integrin therapy (including vedolizumab or natalizumab)
- Surgery to treat their ulcerative colitis or other stomach or gut problems, including surgery to remove part of the colon to remove cancer (colonic resection or colectomy), or surgery to divert part of the intestine through the abdomen wall (ileostomy or colostomy).

3. What happened during the studies?

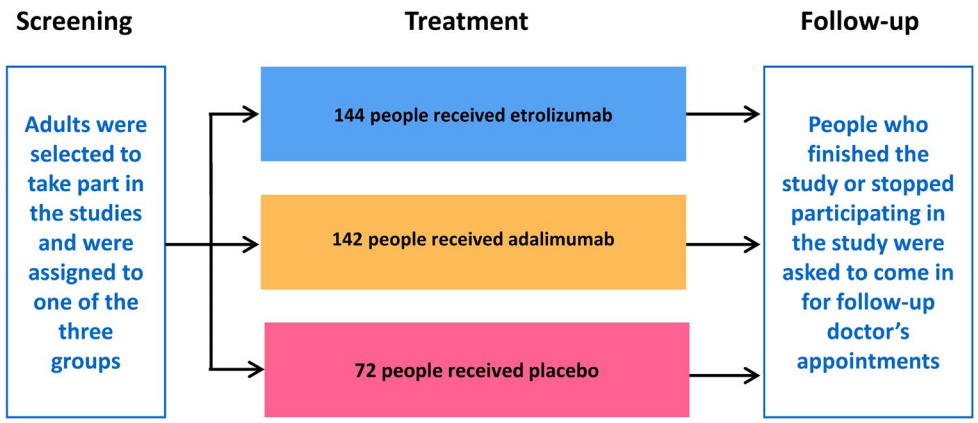
During each study, people were selected to receive either one of two active treatments and a placebo of the other active treatment, or placebo only. The treatments were selected at random by a computer.

The treatment groups were:

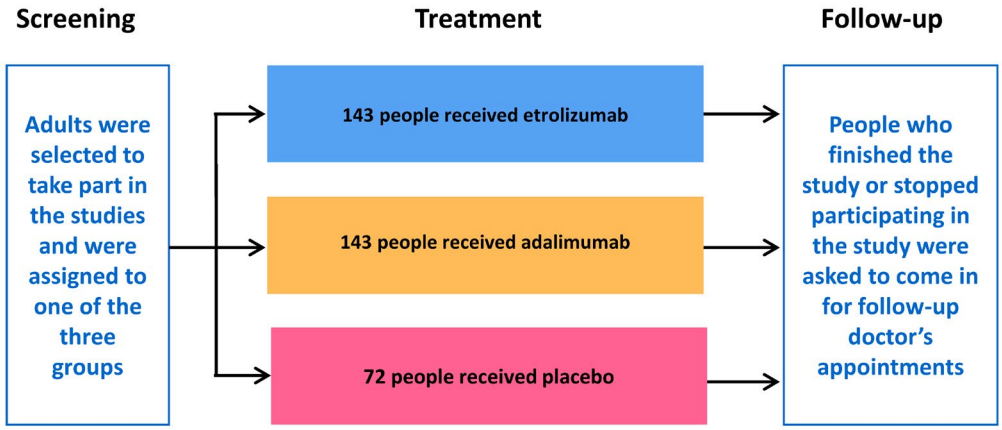
- **Etrolizumab (the study medicine) group:** 105 milligrams of etrolizumab injected just under the skin once every 4 weeks up to week 12 and placebo was injected just under the skin at weeks 0, 2, 4, 6, and 8. People received both treatments so that they would not be able to tell if they received etrolizumab, adalimumab, or a placebo.
  - In HIBISCUS I, 144 people were randomly assigned to this group.
  - In HIBISCUS II, 143 people were randomly assigned to this group.
- **Adalimumab (existing medicine) group:** 160 milligrams of adalimumab injected just under the skin at week 0, 80 milligrams at week 2, and 40 milligrams at weeks 4, 6, and 8, and placebo was injected just under the skin once every 4 weeks up to week 12. People received both treatments so that they would not be able to tell if they received etrolizumab, adalimumab, or a placebo .
  - In HIBISCUS I, 142 people were randomly assigned to this group.
  - In HIBISCUS II, 143 people were randomly assigned to this group.
- **Placebo group:** Injected under the skin in the same way as the two treatments above. This was done so that people in the placebo group would not be able to tell if they were receiving etrolizumab, adalimumab, or a placebo.
  - In HIBISCUS I, 72 people were randomly assigned to this group.
  - In HIBISCUS II, 72 people were randomly assigned to this group.

People in the study attended the study center to receive treatments for up to 14 weeks. When the study finished, the people who took part were asked to go back to their study center for transfer to another study, called an open-label study, where they continued to receive etrolizumab or had follow-up visits to check their overall health. Look below to see more information about what happened in the study.

HIBISCUS I



HIBISCUS II



4. What were the results of the studies?

Question 1: Was etrolizumab more effective than placebo in reducing inflammation and symptoms of ulcerative colitis?

In both studies, researchers looked at whether people who received etrolizumab had reduced inflammation and symptoms at 10 weeks. They compared this with the people who received the placebo, to see if etrolizumab reduced inflammation and symptoms significantly more than placebo.

In HIBISCUS I, about 19 out of 100 people (19%) who received etrolizumab had reduced inflammation and symptoms after 10 weeks. This was compared with fewer than 7 out of 100 people (7%) who received placebo.

In HIBISCUS II, about 18 out of 100 people (18%) who received etrolizumab had reduced inflammation and symptoms of ulcerative colitis after 10 weeks, compared with about 11 out of 100 people (11%) who received placebo. This suggests that etrolizumab significantly reduced inflammation and symptoms more than placebo in HIBISCUS I, but not in HIBISCUS II.

Overall, more people who received etrolizumab had reduced ulcerative colitis symptoms than people who received placebo in HIBISCUS I, but not HIBISCUS II.

Question 2: Was etrolizumab more effective than adalimumab in reducing inflammation and symptoms of ulcerative colitis?

In HIBISCUS I and HIBISCUS II combined, about 19 out of 100 people (19%) who received etrolizumab had reduced symptoms after 10 weeks, compared with about 24 out of 100 people (24%) who received adalimumab.

Overall, a similar number of people who received etrolizumab had reduced symptoms as those who received adalimumab in both HIBISCUS I and HIBISCUS II.

5. What were the side effects?

Side effects (also known as “adverse reactions”) are unwanted medical problems (such as a headache) that happen during a study.

- Only side effects that the study doctor believed were related to the study treatments are described below.

Serious and common side effects are listed in the following sections.

Serious side effects that the study doctor believed were related to the treatment

A side effect is considered “serious” if it is life-threatening, needs hospital care, or causes lasting problems.

During HIBISCUS I, one person who received etrolizumab had a serious side effect. This side effect was an eye infection. One person who received the placebo had a serious side effect. This side effect was pneumonia. No people who received adalimumab had serious side effects.

During HIBISCUS II, one person who received etrolizumab had a serious side effect. This side effect was inflammation in the chest cartilage. One person who received the placebo had a serious side effect. This side effect was a deep vein blood clot. No people who received adalimumab had serious side effects.

During HIBISCUS I, some people decided to stop taking their medicine because of related side effects.

- In the etrolizumab group, less than 1 out of 100 people (less than 1%) stopped taking their medicine because of related side effects.
- In the placebo group, no people stopped taking their medicine because of related side effects.
- In the adalimumab group, less than 1 out of 100 people (less than 1%) stopped taking their medicine because of related side effects.

During HIBISCUS II, there were no people who decided to stop taking their medicine due to related side effects.

Most common side effects that the study doctor believed were related to the treatment

During HIBISCUS I, around 6 out of 100 people (6%) who received etrolizumab had a related side effect, compared with 4 out of 100 people (4%) who received a placebo and 10 out of 100 people (10%) who received adalimumab.

No side effects that the study doctor believed were related to etrolizumab occurred in more than one person, so these side effects are not reported here. The most common side effect that the study doctor believed was related to the placebo was headache, which occurred in two people. The most common side effects that the study doctor believed were related to adalimumab were headache and rash.

During HIBISCUS II, around 8 out of 100 people (8%) who received etrolizumab had a related side effect, compared with 11 out of 100 people (11%) who received a placebo and 11 out of 100 people (11%) who received adalimumab.

No side effects that the study doctor believed were related to etrolizumab or to the placebo occurred in more than one person, so these side effects are not reported here. The most common side effects that the study doctor believed were related to adalimumab were itchy skin, headache, and redness at the injection site.

Other side effects

You can find information about other side effects (not shown in the sections above, such as side effects that doctors did not consider to be related to etrolizumab) on the websites listed at the end of this summary (see section 8, “Where can I find more information?”).

6. How have these studies helped research?

The information presented here is from two studies of 716 people total (358 in HIBISCUS I, 358 in HIBISCUS II) with ulcerative colitis. These results helped researchers learn more about ulcerative colitis and etrolizumab.

No two studies can tell us everything about the risks and benefits of a medicine. It takes lots of people in many studies to find out everything we need to know. The results from these studies may be different from other studies with the same medicine.

This means that you should not make decisions based on this one summary—always speak to your doctor before making any decisions about your treatment.

7. Are there plans for other studies?

At the time of writing this summary (November 2021), the studies have been completed and no more information is being collected. The main finding was that in HIBISCUS I, significantly more people with ulcerative colitis who were treated with etrolizumab (19 out of 100) had reduced inflammation and symptoms of ulcerative colitis compared with placebo (7 out of 100). In HIBISCUS II, the number of people who had reduced symptoms was similar between people treated with etrolizumab (18 out of 100) and placebo (11 out of 100).

Other phase 3 studies looking at the safety and effects of etrolizumab in people with ulcerative colitis who have not received TNF inhibitors (such as infliximab) have taken place.

Currently, researchers are studying etrolizumab in adults with Crohn's disease.

8. Where can I find more information?

You can find more information about these studies on the websites listed below:

- https://clinicaltrials.gov/ct2/show/results/NCT02163759 (HIBISCUS I)
- https://clinicaltrials.gov/ct2/show/results/NCT02171429 (HIBISCUS II)
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-004279-11/results (HIBISCUS I) and https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-004277-27/results (HIBISCUS II)
- https://forpatients.roche.com/

Who can I contact if I have questions about these studies?

If you have any further questions after reading this summary:

- Visit the ForPatients platform and fill out the contact form: https://forpatients.roche.com/
- Contact a representative at your local Roche office.

If you took part in one of these studies and have any questions about the results:

- Speak with the study doctor or staff at the study hospital or clinic.

If you have questions about your own treatment:

- Speak to the doctor in charge of your treatment.

Who organized and paid for these studies?

These studies were organized and paid for by F. Hoffmann-La Roche Ltd., which has its headquarters in Basel, Switzerland.

Full titles of the studies and other identifying information

The full title of each of these studies is: “A study comparing the efficacy and safety of etrolizumab with adalimumab and placebo in participants with moderate to severe ulcerative colitis (UC) in participants naive to tumor necrosis factor (TNF) inhibitors.”

The two studies are known as “HIBISCUS I” and “HIBISCUS II.”

- The protocol numbers for these studies are GA28948 (HIBISCUS I) and GA28949 (HIBISCUS II).
- The ClinicalTrials.gov identifiers for these studies are: NCT02163759 (HIBISCUS I) and NCT02171429 (HIBISCUS II).
- The EudraCT numbers for these studies are: 2013-004279-11 (HIBISCUS I) and 2013-004277-27 (HIBISCUS II).