Summary of Clinical Trial Results

Testing different doses of a new medicine (fenebrutinib) and its effect on heart rhythm (QT interval) in healthy people

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

About this summary

This is a summary of the results of a clinical trial (called a "study" in this document).

This summary is written for:

- Members of the public
- People who took part in the study

This summary is based on information known at the time of writing.

The study started in April 2021 and finished in August 2022. This summary was written after the study had ended.

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

- **This means that you should not make decisions based on this one summary.**
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Contents of the summary

Thank you to the people who took part in this study

The people who took part have helped researchers answer important questions about fenebrutinib.

Key information about this study

- This study was done to test different doses of a new medicine (fenebrutinib) and its effect on QT interval in healthy people.
- People who joined Part A of the study received fenebrutinib. People who joined Part B received fenebrutinib, a placebo (a tablet without any medicine), and moxifloxacin (an approved medicine known to affect heart rhythm).
- This study included 101 people in one country, the USA.
- The main finding was that fenebrutinib did not affect the heart rhythm in any way to cause concern.
- No one in this study had any serious side effects. Fenebrutinib at the low dose and at the high dose caused 4 people each to get side effects (non-serious).

1. General information about this study

Why was this study done?

Multiple Sclerosis (MS) mainly affects the central nervous system (CNS), which includes the brain and spinal cord. Because the CNS coordinates many bodily functions, the effects of MS can impact almost every part of the body.

The disease can cause a wide range of symptoms. Not everyone will have all the symptoms, and they may vary in severity over time.

Recent research has shown that immune cells (B cells, myeloid cells, and microglia) play important roles in this disease.

B cells can become antibody-making cells. In the MS disease state, they create antibodies that damage the protective covering (myelin) of nerves. B cells also act as messengers for other immune cells and can send signals that cause further damage to nerves.

Myeloid cells and microglia add to the ongoing swelling (inflammation) seen in MS. These cells are the main caretakers of our brain and spinal cord in the healthy state. In the MS disease state, myeloid cells and microglia can break down the myelin. They can also release harmful substances and send signals that cause further damage to nerves.

There is no cure for MS. Available approved treatments can delay disease progression and improve quality of life. The treatments come with side effects, some serious, that need to be managed. Researchers are continuing to look for better treatments.

Fenebrutinib is an experimental medicine that researchers are testing. It has shown encouraging results for MS in other studies. Several studies still need to be done to find out more about fenebrutinib

This study was done to find out if fenebrutinib affected the heartbeat – or heart rhythm. To find this out, researchers did a test to measure a part of the heart's electrical signal called the “QT interval” in people treated with fenebrutinib.

Many medicines are known to increase the QT interval. Doctors need to know which medicines fall in this category – so that patients can be monitored for an increased risk for heart-related side effects.

What was the study medicine?

Fenebrutinib: This was the medicine being studied. It is a type of medicine called "Bruton's tyrosine kinase inhibitor" or "BTK inhibitor." It has shown promise in "autoimmune diseases," where the body's own immune system attacks itself. Researchers are currently studying fenebrutinib to see if it can help treat MS.

BTK is a protein that helps activate certain immune cells, including B cells, myeloid cells, and microglia. The incorrect activation of these cells causes MS in some people. By turning off BTK, fenebrutinib might be able to control these immune cells and reduce damage caused by the disease.

Moxifloxacin: This was a medicine used as a "positive control" in this study. It is a type of antibiotic that is known to affect the QT interval. Moxifloxacin was given to people in the study – to confirm that a notable increase in the QT interval could be measured in people in the study.

The QT interval is measured using an electrocardiogram (ECG) test. It is a measure of the time it takes for the heart muscle to contract and then recover. This is the time it takes for an electrical impulse to travel from one section of the heart to another.

Placebo: In this study, some people were treated with a "placebo" instead of the real medicine. The placebo looked like the real medicine, but it did not contain any medicine. Researchers wanted to compare the treatments – to find out the effect of the real medicine.

What did researchers want to find out?

There were two parts to this study: Part A and Part B.

In Part A, the main questions that researchers wanted to answer were:

1. Was it safe, and could people tolerate a single dose of fenebrutinib – based on side effects?
2. What happened to fenebrutinib concentrations in the body – at different time points after taking the medicine?

In Part B, the main question that researchers wanted to answer was:

3. Does fenebrutinib have any effect on the QT interval?

What kind of study was this?

Phase 1 study

This was one of the early studies to test the medicine in people. The aim was to test different doses and look for side effects to see if the doses tested could be tolerated by people.

Randomized study

This was a type of study where it was decided by chance who joined which treatment group. It was like flipping a coin to decide which group to join. This was done to reduce bias in the study results.

Double-blind study
In this study, neither the people in the study nor the researchers knew who was receiving which treatment. This was done to reduce bias in the study results.

Placebo-controlled study
In this study, some people got the actual treatment, while others got a placebo, which looked like the real treatment but did not have any medicinal effect. This was done to be able to see the actual effect of the study medicine – rather than the effect of the belief that you are being treated.

Positive-controlled study
A positive control is a treatment that is already known to produce a certain effect. If the positive control treatment shows the expected effects, it confirms that the effect can be detected in the study. It means the study was correctly set up to measure the effect, even if another medicine (the study medicine) does not generate the effect.

Ascending dose study
In this type of study, the first group of people receive the study treatment at a low dose. Researchers closely monitor them for any side effects or reactions. If the tested dose is found to be safe, the next group gets a higher dose.

Crossover study
In a "crossover study," people receive different treatments in a specific order, over time. After a "washout period" to allow the first treatment to leave the body, each group crosses over (or switches) to another treatment. This type of study allows researchers to compare different treatments in the same person. It is also designed to show that the sequence of getting treatments does not affect the results.

When and where did the study take place?

The study started in April 2021 and finished in August 2022. This summary was written after the study had ended.

The study took place at one study center in one country – the USA.

2. Who took part in this study?

Part A
Sixteen people joined Part A. They were between 24 and 60 years old. Thirteen people (81%) were male and three people (19%) were female.

Part B
Eighty-five people joined Part B. They were between 22 and 60 years old. Sixty-five people (77%) were male and twenty people (24%) were female.

People could take part in the study if they met all of the following conditions:

- Males and females between 18 and 60 years old who could not get pregnant or get their partners pregnant
- Females were not pregnant or breastfeeding
- They met the height to weight ratio (BMI 18-31 kg/m^2)
- In good health (medical history, ECG test, vital signs)
- Blood test results were within the normal range (clinical laboratory tests)
- Negative test results for drug tests

People could not take part in the study if they met any one of the following conditions:

- History or presence of health conditions not allowed in study
- History of surgery or any condition in the stomach and GI that could impact absorption of the study medicine
- History of drug or alcohol addiction within the past year
- Use of any medicine (prescription, over-the-counter, or investigational) during a period when it was not allowed in this study
- Use of tobacco or nicotine-containing products during a restricted period
- Eating or drinking anything with grapefruit, alcohol, or caffeine during a restricted period
- Blood donation, blood loss, or received blood products during a restricted period

3. What happened during the study?

Part A

Screening: Researchers asked questions and did medical tests to see if people interested in joining the study met all the study conditions. This happened up to 28 days before the study started.

Treatment: People who met study conditions checked into the study center one day before treatment (Day -1). The next day (Day 1), people were randomized to get fenebrutinib or placebo. On Day 3, everyone went home.

People in the study received a single dose of treatment (fenebrutinib or placebo) in the morning, after fasting overnight for at least 8 hours. Group 1 received 400 milligrams (mg), and Group 2 received 700 mg. Six people got fenebrutinib and two people got placebo in each group. The treatments were tablets taken by mouth with water.

Follow-up: People in the study received a follow-up phone call from the study center 5 days after the treatment – so that researchers could ask further health-related questions.

Part B

Screening: People were screened just like in Part A.

Treatment: There were four treatments:

- Treatment A: Fenebrutinib 400 mg
- Treatment B: Fenebrutinib 700 mg
- Treatment C: Moxifloxacin 400 mg
- Treatment D: Placebo

Treatment groups: People were randomized to join one of four groups. The treatments were given in the following order to each group:

- Group 1: A, B, C, D
- Group 2: B, C, D, A
- Group 3: C, D, A, B
- Group 4: D, A, B, C

What happened: On Day -1, people checked into the study center. On Day 1, they were randomized into four groups and received their first treatment. On Day 9, they got their second treatment. On Day 11, they went home.

People returned to the study center after at least 8 days had passed since the last treatment. They repeated the above process – and got the third and fourth treatments for their treatment groups.

Each treatment (A, B, C, D) was given at least 8 days apart. This was the "washout" period that allowed for the medicine to become undetectable in the body before the next treatment.

Follow-up: People in the study received a follow-up phone call from the study center 4-6 days after the last treatment – so that researchers could ask further health-related questions.

4. What were the results of the study?

Question 1: Was it safe, and could people tolerate a single dose of fenebrutinib – based on side effects?

There were no serious side effects at the doses tested in this study. There were some non-serious side effects reported for the fenebrutinib doses tested in this study, discussed in detail in Section 5. Based on the nature of side effects and how often they happened, researchers decided that fenebrutinib could be safely tolerated by people up to the highest dose tested in this study.

Question 2: What happened to fenebrutinib concentrations in the body – at different time points after taking the medicine?

Blood samples were collected at different time points and tested for fenebrutinib. The highest concentration found in the body was proportional to the dose (400 or 700 mg) taken. It took about one and a half hours to reach the highest concentration in the body. It took 7-9 hours to fall to half of the highest concentration. These results help researchers decide how often the medicine needs to be taken to be effective.

Question 3: Does fenebrutinib have any effect on the QT interval?

An ECG test to monitor heartbeat was performed at time points between 1 and 4 hours after moxifloxacin dosing. It showed an increase in the QT interval. This meant that if there was an increase in the QT interval in people, it could be measured.
Fenebrutinib treatments did not increase the QT interval in any significant manner.

This section only shows the key results from this study. You can find information about all other results on the websites at the end of this summary (see Section 8).

5. What were the side effects?

Side effects are medical problems (such as feeling dizzy) that happened during the study.

- If they were seen in this study, they will be described in this summary – because the study doctor believed them to be related to the treatments in the study.
- Not everyone in any one study has all the side effects.
- Side effects may be mild to very serious and can be different from person to person.
- It is important to be aware that the side effects reported here are from this single study. Therefore, the side effects shown here may be different from those seen in other studies, or those that appear on the medicine leaflets.
- Serious and common side effects will be listed in the following sections if they happened in this study.

Serious side effects

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

None of the people in this study reported any serious side effects.

No one dropped out of the study because of side effects. There were no deaths in this study related to side effects.

Most common side effects

Some people got side effects that were not serious, but doctors believed they were caused the by the study treatments.

Part A
One out of sixteen people (6%) in Part A experienced a headache following fenebrutinib treatment.

Part B
Four out of eighty-five people (5%) reported side effects after fenebrutinib 400 mg treatments. The side effects were:

- Headache – 2 people (2%)
- Changes in the sense of taste – making food taste strange or causing a strange taste in the mouth (dysgeusia) – 1 person (1%)
- Queasy feeling in the stomach that gives the sensation of wanting to vomit (nausea) – 1 person (1%)

Four out of eighty-five people (5%) reported side effects after fenebrutinib 700 mg treatments. One person reported more than one side effect. The side effects were:

- Nausea – 3 people (4%)
- Diarrhea – 1 person (1%)
- Feeling dizzy – 1 person (1%)

Two people on placebo treatment reported side effects. One person had a feeling that you are about to faint (pre-syncope). Another had back pain.

Nobody reported any non-serious side effects after treatment with moxifloxacin.

Other side effects

You can find information about other side effects (not shown in the sections above) on the websites listed at the end of this summary – see Section 8.

6. How has this study helped research?

The information presented here is from a single study of 101 healthy people. These results helped researchers learn more about fenebrutinib and its side effects – especially its effect on the QT interval.

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

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7. Are there plans for other studies?

At the time of writing this summary, other studies with fenebrutinib were still happening.

8. Where can I find more information?

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

- https://www.isrctn.com/ISRCTN26497758
- https://forpatients.roche.com/en/trials/autoimmune-disorder/multiple-sclerosis/testing-different-doses-of-a-new-medicine--fenebrutinib--and-its.html

Who can I contact if I have questions about this study?

If you have any further questions after reading this summary:

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

If you took part in this study 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 this study?

This study was organized and paid for by Genentech, Inc., South San Francisco, CA, USA. Genentech is part of F. Hoffmann-La Roche Ltd., with headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is:

A two-part, phase 1, randomized, double-blind, single ascending dose study to evaluate the safety, tolerability, and pharmacokinetics of fenebrutinib in healthy subjects (Part A) and a randomized, single-dose, placebo- and positive-controlled, crossover phase 1 study to evaluate the effect of fenebrutinib on the QT/QTC interval in healthy subjects (Part B)

The protocol number for this study is:

GP42654

The International Standard Randomized Controlled Trial Number for this study is:

ISRCTN26497758