# Summary of Clinical Trial Results

## A study to compare two different forms of a study medicine (belvarafenib), and look at the effect of food and stomach acid

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 August 2022 and finished in June 2023. This summary was written after the study had ended.

A single study cannot tell us all there is to know 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 in this study have helped researchers answer important questions about the study medicine.

## Key information about this study

- In this study, people got a study medicine called “belvarafenib.”
- In Part 1, researchers wanted to know if different belvarafenib formulations (MSA and HCl) were absorbed similarly into blood. They also wanted to know if blood concentrations matched the different doses that people took.
- In Part 2, researchers wanted to know what happened when the medicine was taken with food. They also wanted to know the effect of low stomach acid.
- Seventy-four people took part in this study at one study center in the USA.
- Exposure is a measure of the total amount of medicine absorbed into blood over a period. Total exposure was about the same for the two formulations.
- Exposure did not completely correlate to the dose taken – which means that doubling the dose amount did not double the exposure.
- Exposure was higher after eating a high-fat breakfast – in comparison to after an overnight fast.
- Exposure was lower when belvarafenib was taken together with a proton pump inhibitor that reduced the amount of stomach acid.
- There were no serious side effects in this study. Nineteen people (26%) out of 74 – had side effects that were not serious but were due to the study medicine.

## 1. General information about this study

### Why was this study done?

Belvarafenib is a cancer medicine that is being tested in clinical trials. It is a “target therapy” that stops the activity of “RAF dimers” where two RAF proteins come together.

RAF protein is found in different cell types throughout the body. RAF dimers turn on (activate) the MAPK signaling pathway. A "signaling pathway" is a group of molecules in a cell that work together to control (regulate) a cell function.

The MAPK signaling pathway regulates numerous cellular processes, including cell growth (proliferation), changing into a different cell type (differentiation), and cell survival.

In some people, there is a change in the DNA (a mutation) that introduces an error in a protein that regulates a signaling pathway. The “MAPK” signaling pathway stays on without being regulated in cancers where certain mutations are present.

Belvarafenib can disrupt the MAPK pathway, which may stop tumor growth and progression. It has shown activity in cancers with mutations in the *RAS* and *BRAF* genes.

This study was done to learn about the “**bioavailability**” of belvarafenib. When a medicine is taken by mouth, sometimes less than 100% is absorbed into the blood (systemic circulation).

When researchers know how much medicine ends up in systemic circulation, it helps them decide on the proper dose to be taken. Taking belvarafenib with food or certain medicines (proton pump inhibitors) could affect its bioavailability, and these were looked at as well.

There is a need to develop new cancer medicines to open new ways of treating the disease. New medicines that work on different proteins in the cell may be combined with existing treatments to improve outcome. Studying a new cancer medicine can also improve our understanding of cancer biology.

## What was the medicine being studied?

The study medicine was called "**belvarafenib**."

- It is also known by other names (RO7223619, HM95573, GDC-5573, RG6185).
- It is an inhibitor of "RAF dimer" and is known as a "target therapy."
- It is being developed as a treatment for cancers that test positive for mutations in the *RAS* or *RAF* genes.

Some people received the study medicine with another medicine, **rabeprazole**.

- Rabeprazole is a "proton pump inhibitor." It reduces the amount of acid in the stomach.
- Many people take proton pump inhibitors to manage acid-related stomach issues (gastrointestinal disorders). People who take belvarafenib may also take a proton pump inhibitor – its effect on belvarafenib is useful for doctors to be aware of.

## What did researchers want to find out?

Belvarafenib was manufactured as the "HCl formulation." Then, another manufacturing process was adopted and the "MSA formulation" became available.

After taking a medicine, "exposure" refers to how much medicine the body is exposed to over a period. This depends on the amount of medicine that gets absorbed into the blood system, and the length of time it stays in the blood.

**The main questions that researchers wanted to answer were:**

**(Part 1a)** How do the available formulations of belvarafenib (HCl and MSA) compare to each other? What was the exposure from each formulation?

**(Part 1b)** Is exposure from belvarafenib-MSA proportional to the dose taken? When given different doses, will doubling the dose also double the exposure?

**Other questions that researchers wanted to answer included:**

**(Part 2a)** What is the effect of food? How does the exposure from belvarafenib-MSA taken after fasting overnight compare to taking it after eating a high-fat breakfast?

**(Part 2b)** What is the effect of a proton-pump-inhibitor? How does the exposure from belvarafenib-MSA compare to when it is taken with rabeprazole?

## What kind of study was this?

**Phase 1 study**
One or more Phase 1 studies are carried out to find out basic information about a new medicine. This can include safety studies that test different doses and identify side effects caused by the medicine at different doses – so that a safe dose range can be identified. It can include pharmacokinetic studies that measure the medicine concentration in blood. Phase 1 studies enroll a small number of healthy people.

**Crossover study**
People in the study were randomly assigned into Group 1 to receive Treatment A, and Group 2 to receive Treatment B. After a "washout period" to allow the first treatment to leave the body, each group "crossed over" (or switched) to the other treatment. This type of study allowed researchers to compare different treatments in the same person. It was also designed to show that the treatment sequence does not affect the results.

**Food effect**
Food intake can have an impact on absorption, distribution, metabolism, and excretion of a medicine – the "pharmacokinetic" effects of food on a medicine. Understanding food effects is used to determine the best (optimal) conditions under which a medicine should be administered to achieve its desired therapeutic effect. To find out the effect of food, people took their medicine after eating as well as after fasting. The medicine absorbed into blood was measured under both conditions.

**pH effect**
A pH-effect study looks at how stomach acid affects solubility, stability, and absorption of a study medicine – the pharmacokinetic effects of pH. Stomach pH is increased when it becomes less acidic after taking "proton-pump-inhibitors." Such studies provide information about exposure of the study medicine – should a person take the study medicine together with a proton-pump-inhibitor.

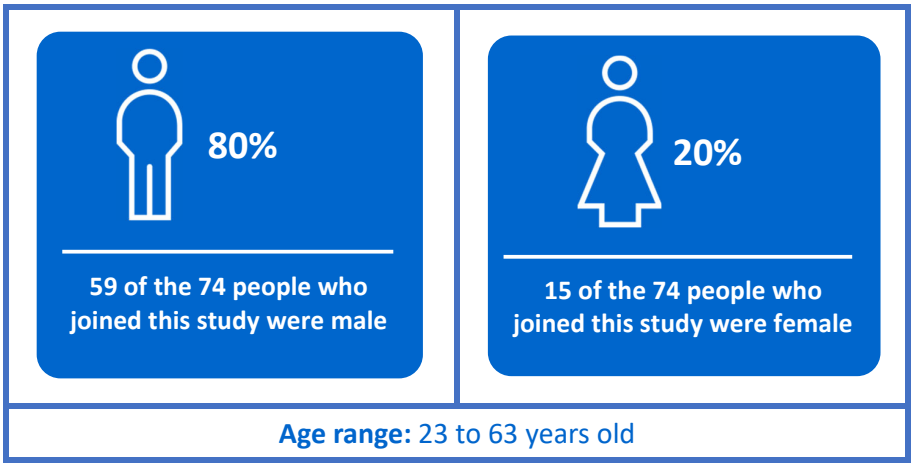
### When and where did the study take place?

The study started in August 2022 and finished in June 2023. This summary was written after the study had ended.

The study took place at a single study center in the USA.

## 2. Who took part in this study?

Seventy-four healthy people took part in this study.




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

- Males or females who could not get pregnant between 18 and 65 years of age
- Met the height to weight requirement (BMI 18 to 32 kg/m$^2$)
- In good health (medical history, ECG test, vital signs, clinical laboratory tests, tests for hepatitis, TB, and HIV)
- Negative test results for drug and alcohol abuse
- Understood and agreed to comply with study requirements, and signed the informed consent form

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

- Past or current health conditions that were not allowed
- Hypersensitivity or allergic reaction to any food or medicine

## 3. What happened during the study?

**Screening:** Researchers asked questions and did medical tests. People interested in joining the study who met all the study conditions could then join the study.

**What happened in the study in Parts 1a, 1b, and 2a**

- First treatment period:
  - People checked into the study center one day before treatment (Day -1).
  - They were assigned to one of two groups at random.
  - On Day 1, the two groups got their first treatment.
  - On Day 10, they went home.
- Washout period:
  - At least 18 days passed between the first and second belvarafenib doses.
- Second treatment period:
  - People checked into the study center on Day -1, got their treatment on Day 1, and went home on Day 10.
- Researchers collected blood samples, did medical tests, and asked questions at several time points before and after dosing during both treatment periods.

**Part 1a treatments:** Comparing two formulations.
A single dose (400 mg) was taken after eating breakfast.

| | **First treatment period** | **Second treatment period** |
|---|---|---|
| **Group 1:** (9 people) | Belvarafenib-MSA | Belvarafenib-HCl |
| **Group 2:** (9 people) | Belvarafenib-HCl | Belvarafenib-MSA |

**Part 1b treatments:** Comparing different doses.
A single dose (belvarafenib-MSA) was taken after eating breakfast.

| | **First treatment** | **Second treatment** |
|---|---|---|
| **Group 1:** (13 people) | 50 mg | 200 mg |
| **Group 2:** (13 people) | 200 mg | 50 mg |

**Part 2a treatments:** The effect of food. A single dose (belvarafenib-MSA, 400 mg) was taken after eating breakfast or after an overnight fast.

| | **First treatment** | **Second treatment** |
|---|---|---|
| **Group 1:** (9 people) | After high-fat breakfast | After overnight fast |
| **Group 2:** (9 people) | After overnight fast | After high-fat breakfast |

**What happened in Part 2b**

- First treatment period:
  - People checked into the study center one day before treatment (Day -1).
  - On Day 1, they got one dose of belvarafenib.
  - On Day 10, they went home.
- Washout period:
  - At least 18 days passed between the first and second belvarafenib treatments.
- Second treatment period:
  - People checked into the study center on Day -1
  - On Day 1 through Day 5, they got one daily dose of rabeprazole.
  - On Day 5, they got a single dose of belvarafenib.
  - They went home on Day 14.
- Researchers collected blood samples, did medical tests, and asked questions at several time points before and after dosing during both treatment periods.

**Part 2b treatments:** A single dose (belvarafenib-MSA, 400 mg) was taken after eating breakfast without or with rabeprazole.

| | First treatment | Second treatment |
|---|---|---|
| 12 people | belvarafenib-MSA | belvarafenib-MSA + rabeprazole |

**End of study, for study Parts 1a, 1b, 2a, 2b**

- People returned to the study center for a day visit at about 21 to 28 days after they took the last dose of belvarafenib.
- Some people got a phone call 28 days after they took the last dose belvarafenib.

## 4. What were the results of the study?

Researchers looked at **exposure**, which is a measure of the total amount of the medicine absorbed into the blood system over the time it is present in blood.

### **Part 1a:** How do the available formulations of belvarafenib (HCl and MSA) compare to each other? What was the exposure from each formulation?

Researchers gave people the same dose of belvarafenib and decided that the two formulations tested had the same clinical impact.

- When taking measurements until the medicine could no longer be detected in blood, exposure was about the same from the MSA and HCl formulations.
- The highest concentration of medicine measured in blood was about the same for the two formulations.

### **Part 1b:** Is exposure from belvarafenib-MSA proportional to the dose taken? When given different doses, will doubling the dose also double the exposure

When given different doses, exposure did not completely correlate to the dose taken – which means that doubling the dose did not double the exposure.

### **Part 2a:** What is the effect of food? How does the exposure from belvarafenib-MSA taken after fasting overnight compare to taking it after eating a high-fat breakfast?

Exposure was higher when belvarafenib was taken after eating a high-fat breakfast – in comparison to taking belvarafenib after an overnight fast.

### **Part 2b:** What is the effect of a proton-pump-inhibitor? How does the exposure from belvarafenib-MSA compare to when it is taken with rabeprazole?

Exposure to belvarafenib was lower when taken together with a proton pump inhibitor, a medicine that reduces stomach acid.

## 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 are described in this summary because the study doctor believes the side effects were related to the treatments in the study.
- Everybody in a study will not have 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 are listed in the following sections if they were seen in this study.

### Serious side effects

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

There were no serious side effects in this study.

There were no deaths due to side effects in this study.

One person in Part 1b stopped the study as a result of a side effect that researchers thought was caused by the study medicine – the side effect was an influenza-like illness.

### Most common side effects

Nineteen (26%) people had 32 side effects that were not serious, but researchers thought they were caused by belvarafenib.
The most common non-serious side effects thought to be related to belvarafenib were:

- Headache, seen in 9 people (12%)
- Muscle pain and tenderness (myalgia), seen in 7 people (10%)

### 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 74 healthy people. These results helped researchers learn more about belvarafenib-MSA, the new formulation.

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## 7. Are there plans for other studies?

At the time of writing this summary, other studies looking at belvarafenib were ongoing.

## 8. Where can I find more information?

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

- https://www.isrctn.com/ISRCTN47564876
- https://forpatients.roche.com/en/trials/healthy-volunteers/a-phase-i--single-dose--randomized--crossover--relative-bioavail.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 Phase I, Single-Dose, Randomized, Crossover, Relative Bioavailability and Food-Effect Study and Phase I, Single-Dose, Fixed-Sequence, Crossover, pH-Effect Study of Belvarafenib (GDC-5573) in Healthy Subjects
- The protocol number for this study is GP44112.
- The "International Standard Randomized Controlled Trial Number" for this study is: ISRCTN47564876.