Summary of Clinical Trial Results

A study to find out what happens to a new medicine (divarasib) inside the human body

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 February 2023 and finished in May 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.**
- **Always speak to your doctor before making any decisions about your treatment.**

Contents of the summary

1. General information about this study
2. Who took part in this study?
3. What happened during the study?
4. What were the results of the study?
5. What were the side effects?
6. How has this study helped research?
7. Are there plans for other studies?
8. Where can I find more information?

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 divarasib, the study medicine.

Key information about this study

- This study was done to find out what happens to a medicine, divarasib, inside the human body. Divarasib was an experimental medicine.
- This study included eight healthy people at one study center in the USA who received a single dose of radioactive divarasib.
- Divarasib was rapidly absorbed into the blood (circulatory system) and reached its highest (peak) concentration in the plasma at about 2 hours after dosing. This concentration fell to half the peak level at about 16 hours after dosing.
- About 94% came out (was recovered) in the first 120 hours after dosing. Within 840 hours after dosing, 98% of the radioactivity was recovered. About 95% was recovered in the feces and about 3% in the urine.
- There were no serious side effects experienced by anyone in this study. One person had a non-serious side effect (nausea) thought to be caused by divarasib.

1. General information about this study

Why was this study done?

"**KRAS**" is a protein found throughout the human body. It acts as a switch in the cell and can be active in the "on" position, or inactive in the "off" position.

When KRAS is in the "on" position, it turns on different signaling pathways. A "signaling pathway" is a group of molecules in a cell that work together to control a cell function.

In healthy cells, KRAS turns on the signaling pathways for cell growth to occur. When cell growth is no longer needed, KRAS becomes inactive.

Once in a while, something goes wrong. There may be an unintended change (mutation) in the DNA, which introduces an error in the KRAS protein. One such mutation in the DNA is called "***KRAS G12C***." This mutation produces a different version of the KRAS protein, called "KRAS G12C," that remains active all the time. KRAS G12C causes uncontrolled cell growth, which results in cancer.

The presence of *KRAS G12C* gene has been found in several types of cancers. Fortunately, researchers have found medicines that can specifically interfere with (inhibit) the KRAS G12C protein and make it inactive.

This study was done to test a medicine, an inhibitor of KRAS G12C, called, "divarasib."

What was the medicine being studied?

Divarasib is a study medicine taken by mouth.

- Divarasib is also known as "**GDC-6036**."
- It binds to the KRAS G12C protein and turns off its cancer-causing signaling by locking the protein into an inactive state.
- It binds irreversibly – it does not fall off KRAS G12C after binding.
- It stops the growth of cancer cells that have this mutation. It also causes the death of cancer cells that have this mutation.
- It is an experimental medicine that may be useful as a treatment for cancer. It is a "targeted therapy" that interferes with a protein that controls the growth of cancer cells. It is also a "small molecule inhibitor" that stops a protein from functioning.

The study medicine was in the form of [^{14}C]-divarasib.

- The [^{14}C] is a radiolabel.
- Radiolabeling is a technique used for tracking (tracing) a medicine.
- Even if the study medicine breaks down or undergoes a chemical change in the body, the radiolabel will still be present in the breakdown products.
- [^{14}C] shows up in tests that detect the radiolabel, "liquid scintillation test."
- [^{14}C]-divarasib was prepared as a 100 milligrams (mg) dose with a known, small amount of the radiolabel.

What did researchers want to find out?

The main questions that researchers wanted to answer were:

1. How much of the medicine went in and out of the body (**mass balance**), and which way (**route**) did the medicine leave the body?
2. How quickly was the medicine absorbed and eliminated?

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 (see below) that measure the medicine concentration in blood. Phase 1 studies enroll a small number of people.

Pharmacokinetic study
This is a type of study that looks at how a medicine moves through the body. It studies how quickly and effectively the medicine is absorbed by the body, distributed within it, broken down, and finally eliminated from the body. It helps in understanding how often and what dose of the study medicine should be given to people to maintain the desired concentration in the body.

When and where did the study take place?

The study started in February 2023 and finished in May 2023. This summary was written after the study had ended.

The study took place at one study in the USA.

2. Who took part in this study?

Eight healthy males took part in this study. They were between 22 and 64 years of age.

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

- Healthy males between the ages of 18 and 65 years
- Met the required height to weight ratio (BMI 18-32)
- In good healthy based upon results of medical history, physical examination, heart test (electrocardiogram), and laboratory tests
- Liver function test results within normal range (AST and ALT)
- Negative test results for drug abuse
- Negative test results for virus infections (Hep B, Hep C, HIV)
- Agreed to take precautions to shield others from contact with sperm – for 3 months after taking divarasib
- Had at least one bowel movement everyday
- Understood and signed the informed consent form

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

- History of medical conditions (including stomach surgery) – not allowed in this study
- History of drug or alcohol abuse within the last year
- Recently took part in another study
- Received COVID-19 vaccine within the past month
- Recent use of prescription or over-the-counter medicines that were not allowed
- Recent use of tobacco- or nicotine-containing products that were not allowed
- Use of alcohol- or caffeine-containing foods or drinks during the 3 days before study start or during the study
- Use of food or drinks that were not allowed during the 7 days before study start or during the study
- Strenuous exercise during the 2 days before study start or during the study
- Donated or received blood or blood products during a period when it was not allowed
- Recent exposure to radiation through another clinical study, any medical procedures, or on the job

3. What happened during the study?

What happened before treatment was given:

- People were examined (screened) up to 28 days before treatment.
- They were admitted to the study center one day before treatment, "Day -1."
- Treatment day was "Day 1."
- Some people agreed to give a bile sample before treatment.

How was the medicine given:

- People had regular meals in the evening. They fasted overnight for about 8 hours and then got their medicine.
- In the morning, a single radioactive capsule was given by mouth with water. They didn't eat for another 4 hours after taking the medicine.
- People in the study were allowed to drink water at all times except one hour before and one hour after taking the divarasib capsule with water.

What happened after getting the medicine:

- People went home sometime between Day 14 and Day 28.
- Some people were asked to return to the clinic for a visit.
- The study staff asked questions and took samples for different tests.
- Blood samples were collected at several time points before and after treatment.
- Urine samples and fecal samples were collected at several time points during the study.

4. What were the results of the study?

Question 1: How much of the medicine went in and out of the body (mass balance), and which way (route) did the medicine leave the body?

Researchers did several different tests on blood, plasma, urine, and feces samples collected at several different time points from people in the study. (Plasma is the liquid part of blood without red blood cells).

Mass balance
After taking the [^{14}C]-divarasib capsule by mouth, most of the radioactivity was removed from the body through passing urine and feces. About 94% came out (was recovered) in the first 120 hours after dosing. About 98% of the radioactivity was recovered over a period of 840 hours after dosing.

Removal routes
Passing urine and feces were the main routes for removal of the radioactive material – about 95% was removed in the feces and 3% in the urine.

Question 2: How quickly was the medicine absorbed and eliminated?

Divarasib was rapidly absorbed into the blood (circulatory system) and reached its highest (peak) plasma concentration at 2 hours after dosing. This concentration fell to half the peak level at about 16 hours after dosing.

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 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 of 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 leaflet.
- 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 seen in this study. There were no deaths due to side effects in this study.

Nobody dropped out (withdrew) from the study because of side effects. One person withdrew from the study before completion, but it was not because of side effects.

Most common side effects

One out of eight people (13%) had a side effect that was not serious, but researchers believed it was caused by divarasib. The person had a queasy feeling in the stomach that gives the sensation of wanting to vomit; wanting to throw up (nausea).

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 eight healthy people. These results helped researchers learn more about how divarasib behaves in the body.

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.**
- **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, other studies looking at divarasib 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/ISRCTN10152571
- https://forpatients.roche.com/en/trials/healthy-volunteers/a-phase-i--open-label-study-of-the-absorption--metabolism--and-e.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 1, open-label study of the absorption, metabolism, and excretion of [^{14}C]-GDC-6036

- The protocol number for this study is GP44415.
- The "International Standard Randomized Controlled Trial Number" for this study is: ISRCTN10152571.