Summary of Clinical Trial Results

What happens to a medicine (entrectinib) when given to people with unhealthy livers

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 January 2020 and finished in September 2021. 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 lots of people in many 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

Thank you to the people who took part in this study

The people who took part have helped researchers answer important questions about liver disease and its effect on entrectinib, the study medicine.

Key information about this study

- This study was done to find out how the health status of the liver affects the amount of the study medicine that gets in the body.
- People with healthy livers and those with different stages of liver disease – were given entrectinib, the study medicine.
- Researchers measured entrectinib and its breakdown product, M5, in blood samples collected at different times after dosing.
- This study included 38 people in three countries.
- All data collected in this study was grouped by severity of liver disease.
- Entrectinib and M5 are both active on cancer. The main finding was that when taken together, entrectinib + M5 levels were similar in people, regardless of liver health.
- In this study, there were no serious side effects – thought to be related to entrectinib. There was one death due to a sudden onset of stomach flu (acute gastroenteritis) – doctors did not think it was caused by the study medicine.

1. General information about this study

Why was this study done?

Entrectinib is a medicine that has been approved for use in several countries. This medicine is prescribed to patients with certain types of cancers if they meet other conditions (criteria).

Researchers know that a protein found in the human liver breaks down entrectinib. This protein is called "cytochrome P450 3A4" or "**CYP3A4**".

CYP3A4 breaks entrectinib down into a molecule called, "**M5**". Both molecules, M5 and entrectinib, are effective on cancer. CYP3A4 further breaks M5 down into other molecules.

Researchers know about the dose of entrectinib and the concentrations of its breakdown products – when entrectinib is given to people with healthy livers and normal levels of CYP3A4.

However, there may be times when entrectinib is given to people who have unhealthy livers. The health status of the liver will affect the levels of CYP3A4 found in people.

Having higher or lower than normal levels of CYP3A4 – will affect the levels of entrectinib and M5.

This study was done to look at entrectinib and M5 levels in people with unhealthy livers – in comparison to people with healthy livers.

What was the medicine being studied?

This study looked at a medicine called "**entrectinib**".

- Entrectinib is also known as: Rozlytrek, RO7102122, and RXDX-101.
- Entrectinib is a medicine known as a "**tyrosine kinase inhibitor**". This medicine interferes with "cell signaling" to disrupt the growth of cancer cells.

What did researchers want to find out?

Researchers wanted to gather information about how peoples' bodies processed entrectinib when they did not have a healthy liver.

The main questions that researchers wanted to answer were:

1. In comparison to a healthy liver, how does an unhealthy liver affect the amount of entrectinib and M5 that becomes available to the body after taking the medicine?
2. Is there a relationship between the amount of entrectinib available to the body and the health status and function of the liver?

What kind of study was this?

This was a "**Phase 1 study**" to gather information about how the study medicine interacts with the human body in people with and without healthy livers. A small number of people were given the study medicine. Information from this study may be used in other studies with more people.

This was an "**open-label study**" because the investigators and people in the study knew which medicine they were getting.

There were four groups in this study. Each group of people had a different level of liver disease. This was a "**parallel group study**" because people in the four groups got the same treatment.

When and where did the study take place?

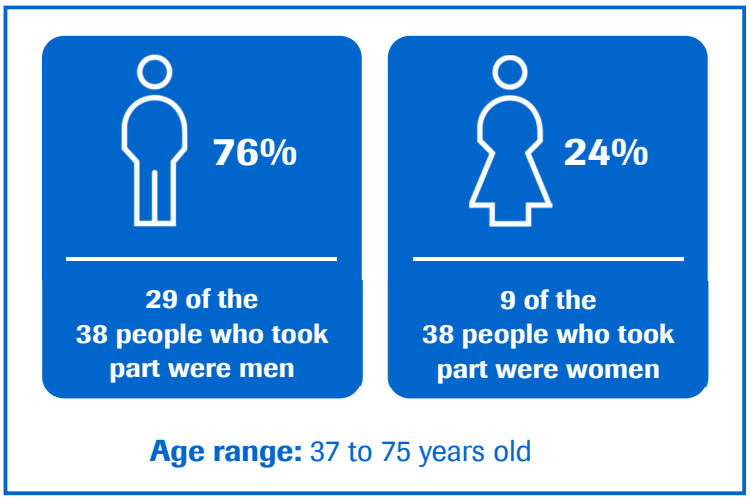
The study started in January 2020 and finished in September 2021. This summary was written after the study had ended.

The study took place at three study centers – in three countries:

- Czech Republic
- Hungary
- Slovakia

2. Who took part in this study?

Thirty-eight people with healthy and unhealthy livers took part in this study.



People could take part in the study if:

- They were men and women between 18 to 75 years old.
- They weighed at least 50 kg and had a certain height to weight ratio (body mass index 18 to 38 kg/m^2).
- They agreed to use birth control methods so they did not get pregnant or get their partners pregnant during the study.
- People who joined the “control group” had healthy liver function.
- People who joined the “mild disease”, “moderate disease”, and “severe disease” groups had disease levels matching the label for their group. They had “cirrhosis” which is scarring (fibrosis) of the liver. Cirrhosis can be caused by many different liver diseases and conditions.

People could not take part in the study if:

- They had any one of a number of liver conditions that did not allow them to join the study.
- They had any one of a number of conditions in the gut (gastrointestinal hemorrhage, gastric bypass surgery, malabsorption syndrome).
- They had signs indicating that the brain was affected (hepatic encephalopathy).
- They had fluid build-up in the stomach area (ascites).
- They had a recent history of other illness or a current condition that made them unsuited for the study.
- They used certain medicines 4 weeks before starting the study.
- They had a history of - or current problems with - drugs or alcohol.
- They donated over 500 mL of blood in the last 3 months.
- Women who were pregnant or nursing were not allowed to join the study.

3. What happened during the study?

The people who volunteered to take part in the study were seen by a doctor to find out the health status of their livers. Based on the results, they were assigned to one of the four study groups:

1. Normal – healthy
2. Mild – unhealthy
3. Moderate – unhealthy
4. Severe – unhealthy

People checked into the study center one day before dosing.

On dosing day, everyone in the study took one dose of entrectinib (100 mg capsule) with a glass of water, They took the medicine within 30 minutes of finishing breakfast.

Blood samples were collected from people on the study – before dosing and at various times after dosing.

Apart from entrectinib, all medicines taken during the study had to be approved for use by the study doctor.

While on the study, the people were asked to refrain from using alcohol and nicotine products. They were not allowed certain foods and drinks. They could not start any new exercise program.

People stayed at the study center until 3 to 7 days after dosing. They were asked to come back to the study center several times, up to 13 days after dosing day.

4. What were the results of the study?

Question 1: In comparison to a healthy liver, how does an unhealthy liver affect the amount of entrectinib that becomes available to the body after taking the medicine?

People with healthy and unhealthy livers joined this study. The data that was collected – was grouped according to the health of the liver.

When data was grouped according to one way of classifying liver disease (Child-Pugh classification), people with liver disease were exposed to higher levels of entrectinib (AUC_{∞}) and similar levels of M5 (AUC_{last}) after dosing – in comparison to people with healthy livers.

When data was grouped according to another way of classifying liver disease (NCI-ODWD classification), people with liver disease were exposed to similar levels of entrectinib (AUC_{∞}) and lower levels of M5 (AUC_{last}) after dosing – in comparison to people with healthy livers.

Question 2: Is there a relationship between the amount of entrectinib that becomes available to the body and the health status and function of the liver?

Entrectinib and M5 are both active on cancer. The main finding was that when entrectinib + M5 levels were analyzed together, they were similar across different groups, regardless of the health of the liver.

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.

- They are described in this summary because the study doctor believes the side effects were related to the treatments in the study.
- Not all of the people in this study had 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.

Serious side effects

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

During this study, nobody had a serious side effect that was thought to be caused by the study medicine.

All 38 people in the study received one dose of the study medicine. One person in the study died due to a sudden onset of stomach flu (acute gastroenteritis) – doctors did not think it was caused by the study medicine.

Most common side effects

One out of the 38 people in this study had a side effect – diarrhea – that was not considered serious – but it was thought to be caused by the study medicine.

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 38 people with different grades of liver disease – from healthy to unhealthy. These results helped researchers learn more about liver health and its effect on entrectinib.

No single study 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 this study may be different from other studies with the same medicine.

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7. Are there plans for other studies?

Studies with entrectinib are still happening and further studies are also planned.

8. Where can I find more information?

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

https://clinicaltrials.gov/ct2/show/NCT04226833

https://forpatients.roche.com/en/trials/metabolic-disorder/hepatic-insufficiency/a-study-to-investigate-the-effect-of-impaired-hepatic-f-07038.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: An open-label, one treatment, four group, parallel group study to investigate the effect of impaired hepatic function on the pharmacokinetics of entrectinib in volunteers with different levels of hepatic function

- The protocol number for this study is GP41174.
- The ClinicalTrials.gov identifier for this study is NCT04226833.
- The EudraCT number for this study is 2019-003065-17.