Summary of Clinical Trial Results

A study of a new medicine for asthma and chronic cough: GDC-6599, a TRPA1 inhibitor

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 September 2021 and finished in January 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.

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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 GDC-6599, a new medicine for asthma and cough.

Key information about this study

- This study was done to test a new medicine called GDC-6599.
- The study checked for side effects at different doses to find out which doses were safe.
- Eighty-one healthy people joined this study. Some were given GDC-6599. Others were given a fake medicine (placebo) that did not have any real medicine in it.
- Researchers wanted to compare side effects of the real medicine with the fake one.
- Results from the study showed no serious side effects. Thirteen people had non-serious side effects that doctors thought were caused by the treatments.

1. General information about this study

Why was this study done?

What is asthma?
Asthma is a condition that affects the lungs and makes it hard to breathe. The airways, the tubes that carry air in and out of your lungs, become inflamed or swollen. The blocked airways can become very sensitive and react strongly to things like dust, pollen, or smoke. Extra mucus is produced. Asthma causes symptoms like coughing, wheezing, shortness of breath, and chest tightness.

Current treatments for asthma
Researchers have developed several treatments to help control asthma. These include:

- Inhaled corticosteroids: Medicines breathed in to reduce inflammation in the airways.
- Long-acting beta agonists: Medicines that help to keep the airways open for longer periods.
- Other controller medications: Other medicines to help manage asthma.

The need for new treatments
New asthma treatments are needed to help people who don't respond well to existing therapies. Better medicines could reduce side effects and improve the quality of life for patients.

GDC-6599, a new medicine
GDC-6599 is a new asthma medicine. It is a "TRPA1 inhibitor," that works by blocking the TRPA1 channel.

TRPA1 channel
The TRPA1 channel is a receptor for pain, cold, itch, and environmental irritants found in some types of nerve cells in the airways and other parts of the body. It can make the airways in the lungs tighten up and become inflamed. This leads to asthma symptoms like coughing and difficulty breathing. By blocking the TRPA1 channel, GDC-6599 may help reduce these asthma symptoms.

Why was this study done
Before GDC-6599 can be used by people with asthma, researchers need to make sure it is safe. This study was designed to test different doses in healthy people – to find a safe dose – by looking at side effects, how serious they were, and how many people got them. Researchers also asked other questions about GDC-6599 in this study.

What was the medicine being studied?

GDC-6599 is a medicine known as a "small molecule inhibitor," that can block the TRPA1 channel in our body.

The **TRPA1 channel** is like a tiny gate in our cells that can open and close to let certain chemicals in and out. In asthma, the TRPA1 channel can play a role in causing inflammation and making the airways in the lungs more sensitive.

When the TRPA1 channel is activated, it can lead to coughing, wheezing, and trouble breathing. By blocking or controlling the TRPA1 channel, researchers hope to reduce these asthma symptoms and help people breathe more easily.

The Sponsor of this study is developing GDC-6599 for use in patients with asthma and cough (refractory chronic cough and unexplained chronic cough).

What did researchers want to find out?

The main question that researchers wanted to answer was:

1. Was GDC-6599 safe for people at the different doses tested in this study?

Researchers answered that question by doing the following:

- Checking for side effects: They looked at how quickly and how often side effects happened. They used special rules (grading scale) to find out how severe the side effects were.
- Doing different tests: They also looked at how often there were problems with important health signs, like blood pressure, lab tests, and heart tests (ECG).

Other questions that researchers wanted to answer were:

2. How did taking different doses affect the amount of GDC-6599 in the body?
3. How did food affect the amount of GDC-6599 in the body?
4. Was there a difference when GDC-6599 was taken as a tablet or as a liquid?
5. Was there any effect of GDC-6599 on the TRPA-1 channel?

What kind of study was this?

This was a placebo-controlled, randomized, double-blind, phase 1 dose escalation safety study. This study was with a small group of healthy volunteers. The main goal was to check if the new medicine was safe – based on side effects. Researchers started with a low dose and gradually increased it.

- **Placebo**: Some volunteers got a fake treatment known as a placebo. It looked like real medicine but did not have any medicine in it. This allowed for a comparison of treatments with and without the real medicine.
- **Randomized**: Volunteers were assigned by chance to either get the placebo or medicine. This way, the assignment was fair and unbiased.
- **Double-blind**: Neither the volunteers nor the researchers knew who got the real medicine and who got the placebo. This helped ensure that results were not influenced by anyone's expectations.
- **Dose escalation**: The first group got the lowest dose and researchers watched for side effects. If the dose was safe, the next group got a slightly higher dose. This process was repeated. It was stopped when a dose became unsafe or if enough doses were tested.
    - **Single ascending dose (SAD)**: Testing a single dose in each group of people, starting small and gradually increasing the dose in new groups.
    - **SAD Food effect (SAD-FE)**: Testing a single dose under two different conditions. Taking the medicine:
        1. After an overnight fast
        2. After a high-fat meal
    - **Multiple ascending dose (MAD)**: Testing multiple doses. Starting with small amounts taken over several days and gradually increasing the dose in new groups.
- **Safety study**: Throughout the study, researchers kept a close watch on everyone to see if anyone has any bad reactions or side effects.

When and where did the study take place?

The study started in September 2021 and finished in January 2023. This summary was written after the study had ended.

The study took place at one study center in the Netherlands.

2. Who took part in this study?

Eighty-one healthy people between 20 and 73 years of age took part in this study. Fifty were female (62%).

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

- Were between 18 and 75 years old
- Understood and could follow instructions
- Met the height-weight ratio (BMI 18-30 kg/m^2)
- Had good veins for blood draw
- Showed a change in blood flow in the skin when an irritating liquid was applied to the area Passed the physical exam in the doctor's office
- Men and women agreed to use birth control
- Men agreed not to donate sperm

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

- Women who were pregnant or breastfeeding
- People who bruised easily
- People who used medicines to stop blood from clotting
- People with health conditions from a list of conditions that were not allowed
- History of drug abuse
- Current or former smoker
- Excessive use of alcohol
- Use of prescription or over the counter medicines that were not allowed
- Recent blood donation that was more than half a liter

3. What happened during the study?

Screening

- Screening happened for about 4 weeks before treatment started.
- Study staff asked people interested in joining the study questions about their health and collected blood and urine samples.
- People could join the study if they met the rules for joining the study.

Study center

- Day −2 or Day −1: People came to stay at the study center one or two days before starting the treatment.
- Day 1: Treatment started on Day 1.
- Day 4: People in the SAD groups went home on Day 4.
- Day 11: People in the SAD-FE and MAD groups went home on Day 11.

Treatment groups

- In each group, people were randomly assigned to receive GDC-6599 or the placebo.
- It was a double-blind study.
- The first group got the lowest dose. If researchers thought it was safe to do so, they increased the dose in the next group. This was repeated until it became unsafe to increase the dose or when enough doses were tested.
- **SAD groups**:
    - There were six groups.
    - Each person got a single treatment.
- **SAD-FE group**:
    - This group tested the effect of food on the medicine in the body.
    - Each person received a single treatment given in two different periods.
    - The periods were at least seven days apart so that one dose cleared from the body before the next dose was taken.
        - In the first period, the dose was given after an overnight fast.
        - In the second period, the dose was given after a high-fat meal.
- **MAD groups**:
    - There were three MAD groups.
    - Each person got multiple treatments.

Treatments

- SAD and SAD-FE groups: A single dose of the treatments was given by mouth.
- MAD groups: Treatments were given by mouth, twice a day, for 8 days.
- Treatments were in tablet or liquid form.

Skin challenge

- People were tested after dosing to find out if GDC-6599 activated the TRPA1 channel.
- The test was called "**Allyl isothiocyanate** (AITC) skin challenge."
- An irritating liquid was applied to skin, and this area was studied. To look for a response to the applied liquid, a special camera was used to look at blood flow in the area and patients were asked to rate their sensation of pain and itch.
- Activation of the TRPA1 receptor would increase blood flow in the area and cause a sensation of pain and itch. But, if GDC-6599 was effective on the TRPA-1 channel, then there would be little or no effect on blood flow, pain, and itch.
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Study follow-up

- People in the SAD groups returned to the clinic for a follow-up visit around Days 6, 8, and 15.
- People in the SAD-FE group received returned to the clinic for follow-up a follow up visit 5, 7, and 14 days after their final dose of GDC-6599 (around Days 13, 15, and 22).
- People in the MAD groups went to the study center for a follow-up visit 4 and 11 days after their final dose of GDC-6599 (around Day 15 and Day 22).
- Study staff collected blood samples, did physical exams, and asked questions about health and side effects.

4. What were the results of the study?

Question 1: Was GDC-6599 safe for people at the different doses tested in this study?

There were no serious side effects and no deaths. There were side effects that were not serious, that were caused by GDC-6599. There were no side effects leading to stopping or interrupting treatment. Based on these results, researchers believed GDC-6599 was safe for humans to use at the doses tested. Side effects are discussed further in the next section.

Question 2: How did taking different doses affect the amount of GDC-6599 in the body?

The amount of medicine in the body went up in relation to the dose, for the lower doses. At higher doses, it increased a bit less than expected in relation to the dose. There was a small buildup of the medicine in the body when taken twice a day for 8 days.

Question 3: How did food affect the amount of GDC-6599 in the body?

When GDC-6599 was taken after eating, the amount of medicine in the body was like when it was taken after an overnight fast. That means food did not have much impact.

Question 4: Was there a difference when GDC-6599 was taken as a tablet or as a liquid?

The way the body handled GDC-6599 was similar whether it was taken as a suspension or as a tablet.

Question 5: Was there any effect of GDC-6599 on the TRPA-1 channel?

When the irritating liquid was applied, there was a change in blood flow in the skin and a sensation of pain and itching reported by participants. Researchers found that taking GDC-6599 decreased this blood flow, pain, and itching. That means GDC-6599 was effective on the TRPA-1 channel.

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 and no deaths. There were no side effects leading to stopping or interrupting treatment.

Most common side effects

During this study, some people had side effects that were not serious, but study doctors believed they were caused by the study treatments.

Some people had more than one side effect. Out of 81 people, 13 people (16%) had a total of 23 side effects.

- SAD groups: Three (8%) people out of 39 had three side effects.
- SAD-FE group: One person (13%) out of 8 had one side effect.
- MAD groups: Nine (27%) people out of 34 had 19 side effects.

All the side effects went away without treatment. The most common side effects – those that happened in two or more people in the entire study – are listed in the table below.

	SAD groups		**SAD-FE group**		**MAD groups**	
Treatment	**GDC-6599**	**Placebo**	**GDC-6599**	**Placebo**	**GDC-6599**	**Placebo**
Number of people in treatment group	29	10	6	2	28	6
Number of people with side effects	2	1	1	0	7	2
Most common side effects:						
Headache	1	0	0	0	2	0
Wanting to throw up (nausea)	0	0	0	0	2	0
Feeling tired or weak (fatigue)	0	0	0	0	1	1
Frequent urination (pollakiuria)	0	0	0	0	1	1

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 81 healthy volunteers. These results helped researchers learn about GDC-6599 that was given to people for the first time.

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7. Are there plans for other studies?

At the time of writing this summary, other studies looking at GDC-6599 were not planned.

8. Where can I find more information?

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

https://forpatients.roche.com/en/trials/respiratory-disorder/asthma/a-study-of-a-new-medicine-for-asthma-and-cough--gdc-6599---a-trp.html#formedicalprofessionals

https://onderzoekmetmensen.nl/en/trial/52277

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, randomized, double-blind, placebo-controlled, single-center study designed to evaluate the safety, pharmacokinetics, and pharmacodynamic effects of single and multiple ascending doses of GDC-6599 and the effect of food on the pharmacokinetics and pharmacodynamics of GDC-6599 in healthy adult subjects

- The protocol number for this study is GA43010.
- The EudraCT number for this study is 2021-002464-48.
- The "Central Committee on Research Involving Human Subjects" in the Netherlands (CCMO) registry trial number is NL-OMON52277.