Summary of Clinical Trial Results

A study in healthy volunteers to look at the side effects of a medicine (GDC-6988) – in comparison to a placebo – and the effects of salbutamol

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 2022 and finished in May 2023. 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.**
- **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 the study medicine – GDC-6988.

Key information about this study

- This study was done to find out if it was safe to give people a new medicine, GDC-6988, using an inhaler.
- People were given either GDC-6988 or a placebo – it was decided by chance which treatment each person was given.
- This study included 41 people in one country, the United Kingdom.
- The main finding was that based on side effects seen in this study, researchers decided the GDC-6988 was safe to give to people at the doses tested.
- Nobody had any serious side effects. Seven people had side effects that were not serious, but the study doctor believed they were caused by the study treatments.
- Some patients had a brief decrease (drop) in their lung function. Taking salbutamol before GDC-6988 largely prevented the drop in lung function from happening.

1. General information about this study

Why was this study done?

Our body has a great method for keeping our airways or breathing tubes clean. This is called "mucociliary clearance" – it is a system that sweeps away dirt and germs from our airways so we can breathe easier.

For this system to work properly, the mucus in our airways needs to be just the right thickness and the right amount. There are special cells that keep the mucus wet.

Sometimes, things go wrong and the mucus can become too thick and sticky. People with cystic fibrosis (CF) have a genetic defect that makes their mucus too thick and sticky. This same problem can also happen in people with other diseases such as asthma, chronic obstructive pulmonary disease (COPD), and non-CF bronchiectasis (NCFB).

Thick and sticky mucus can lead to breathing problems, infections in the lungs, and problems in other parts of the body. Current treatments try to comfort (ease) symptoms, make serious episodes (exacerbations) less frequent, and improve the quality of life of patients.

The available treatments include different types of medication, antibiotics, and techniques to clear the airways. They do not directly tackle the problem of overly thick mucus.

Researchers are working on medicines that provide better treatment options. GDC-6988 is a study medicine – designed to make the airways wet to reverse the mucus thickening and stickiness – so that it can clear away the dirt and germs better. This study was done to test the safety of GDC-6988 in healthy people.

What was the study medicine?

The study medicine was **GDC-6988**. It is a type of medicine called "an inhaled potentiator." You breathe in this medicine through an inhaler. "**Potentiator**" means that this medicine works by boosting (increasing) the activity of another protein in the body.

GDC-6988 boosts the activity of the TMEM16A protein.

TMEM16A is a "channel protein" present on the surface of airway cells and some other cell types. It helps to make the mucus on the airway surface wetter (more hydrated). This control helps keep our airways wet enough so we can easily clear out mucus.

In people with cystic fibrosis, another protein (CFTR) that also makes the surface wetter is missing or does not work well. While GDC-6988 does not replace the needed protein, it makes the TMEM16A protein work better. By boosting the activity of TMEM16A, GDC-6988 makes up for the faulty CFTR protein.

GDC-6988 can help make the mucus in the lungs less sticky and easier to cough up in other diseases such as COPD and NCFB. Scientists do not believe it will increase mucus secretion.

In this study, some people were treated with a "**placebo**" instead of GDC-6988. The placebo looked like GDC-6988 but it did not contain any medicine. Researchers wanted to compare the treatments – to find out the effect of the real medicine.

Sometimes, people were treated with **salbutamol** (also called **albuterol**) before getting GDC-6988 or placebo. Salbutamol is a "**bronchodilator**" – a type of medication that relaxes and dilates (widens) tubes in the lungs (bronchi, bronchioles). This action increases the airflow to the lungs.

What did researchers want to find out?

Researchers have already studied GDC-6988 in people in another Phase 1 study. In the current study, they wanted to use a type of device (Smart DPI), an inhaler to deliver the treatment. They wanted to look at the effect of giving people multiple doses.

"**Smart DPI**" stands for “Smart Dry Powder Inhaler.” It is a device that delivers medication to the lungs in the form of a dry powder. It is a "smart" device with built-in digital technology to monitor how and when the inhaler is used. It is designed to make it easier for people to manage medications for their breathing conditions. This device was not turned on during the study, but might be in future studies.

The main question that researchers wanted to answer was:

1. Was it safe to treat people with GDC-6988 – delivered via a Smart DPI?

What kind of study was this?

Phase 1 study

This was one of the early studies to test the medicine in people. There were only a small number of people in this study. The aim was to test different doses and look for side effects to see if the doses tested were safe and 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. That means, personal preferences of people cannot influence the results – because people do not control who gets which treatment.

Double-blind study

In this study, neither the people in the study nor the researchers knew who was receiving the real treatment and who was receiving the placebo treatment. This was done to prevent people in the study and the researchers from behaving differently based on knowing who was getting GDC-6988 and who was getting placebo.

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 active ingredients and thus didn’t have a 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.

Ascending dose study

In this type of study, the first group of people receive the study treatment at a very 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. This process continues. Gradually, many higher doses are tested in every new group, as long as no serious side effects were seen with the lower doses. The main goal is to identify the highest dose that can be given to people safely – without causing unacceptable side effects.

Bridging study
A "bridging study" is done to compare the same dose of medicine – when given in fewer high strength capsules versus several low strength capsules. In a bridging study, researchers are checking to make sure that different dose capsules add up the way they are supposed to – when you measure the medicine concentration in your body.

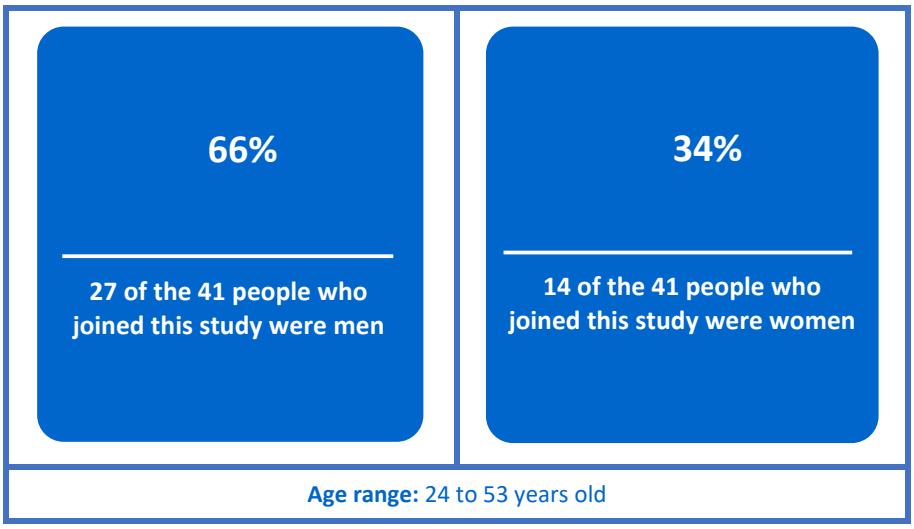
When and where did the study take place?

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

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

2. Who took part in this study?

Forty-one people took part in this study.



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

- Between 18 to 55 years old
- Met a certain height-weight requirement (BMI 18-32 kg/m^2)
- Met health requirements, including lung function
- Were able to use the Smart DPI correctly
- Agreed to use birth control
- Men agreed to not donate sperm during restricted period

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

- Women who were pregnant, breastfeeding, or intended to become pregnant within 28 days after they took their final dose
- Any health condition from a list not allowed in this study
- A history of substance abuse
- A history of illicit drug or hallucinogenic substance use during a restricted period
- A history of tobacco or nicotine use during a restricted period
- Unwilling to abstain from the use of illicit drug, hallucinogenic substance, tobacco, or nicotine – during the study
- Low lung function during a breathing test that was taken during screening

3. What happened during the study?

Screening: People interested in joining the study came for a check-up.

Check-in: Those who met the conditions for taking part in the study checked into the study center 2 days before treatments began and went home 2 days after the last treatment.

Randomization: People were randomly picked to either get GDC-6988 or a placebo.

Double-blind: Neither the people in the study nor the researchers knew who was getting the real medicine.

Treatment: Treatments were delivered through an oral inhaler, the Smart DPI.

Multiple ascending dose (MAD) groups: Thirty-one people joined three study groups. Group 1 received the lowest dose. After reviewing all results – side effects, blood tests, and medical exams – Group 2 got a higher dose when researchers thought it was safe to increase the dose. This was repeated for Group 3, who received the highest dose. People received their dose twice daily, from Day 1 until Day 14.

Bridging group: Another ten people joined a fourth group. Group 4 got the same dose as Group 3, but the dose was delivered using two different capsule strengths. The idea was to compare the two different ways of delivering the same dose.

Group 4 received their dose made of 2.8 milligram (mg) capsules on Day 1. On Day 8, they got the same total dose but it was made of 7 mg capsules.

Salbutamol pre-treatment: People in Groups 1 and 2 were pre-treated with salbutamol about 15 minutes before study treatment, on Days 8-14. Group 3 got the pre-treatment on Days 1-14. Group 4 got pre-treatments on Day 1 and Day 8.

Follow-up: On specified days after the treatments were over, people from all 4 groups returned to the clinic for follow-up visits.

Study procedures: Researchers asked questions, collected blood samples, and did medical tests – at several time points throughout the study.

4. What were the results of the study?

Forty people completed the study.

Question 1: Was it safe to deliver GDC-6988 to people using the Smart DPI at the doses tested?

Researchers thought about safety by looking at what types of side effects occurred, how intense they were, and how frequently were they seen in this study group.

They looked at whether GDC-6988 had any impact on:

- Vital signs – pulse rate, temperature, respiration rate, and blood pressure
- Blood test results
- Spirometry – test for how well your lungs work
- Oscillometry – another lung test

Based on the lack of serious side effects and the presence of few non-serious side effects, researchers thought that people could safely tolerate GDC-6988 at the doses tested. GDC-6988 caused a brief drop in some people's lung function. Taking salbutamol before GDC-6988 largely prevented the drop in lung function from happening.

5. What were the side effects?

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

- If they happened in this study, they will be 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 any one study experience 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 will be 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.

None of the 41 people in this study reported a serious side effect.

There were no deaths in this study resulting from side effects.

One person who received a treatment in the MAD group stopped taking the treatment early because of side effects caused by the study treatment and salbutamol.

Most common side effects

During this study, 7 out of 41 (17%) people had a side effect that was not considered serious, but study doctors thought they were related to the study treatment – GDC-6988 or placebo. Some people had more than one side effect. Here are the side effects:

Side effects	**Seen in people treated with GDC-6988** (32 people received this treatment)	**Seen in people treated with placebo** (9 people received this treatment)
Cough	1 person (3%)	1 person (11%)
Tightness of the throat	2 people (6%)	0
Difficulty breathing (dyspnea)	1 person (3%)	0
Rapid heartbeat that develops when the regular electrical impulses of the heart are disrupted (supraventricular tachycardia)	1 person (3%)	0
Discomfort in the chest	1 person (3%)	0
Abnormal blood test result for liver function (alanine aminotransferase)	1 person (3%)	0
Abnormal blood test result for liver function (aspartate aminotransferase)	1 person (3%)	0

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 41 healthy people. These results helped researchers learn more about GDC-6988.

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.**
- **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, the sponsor was continuing with the development of the study medicine.

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/healthy-volunteers/a-phase-ib--randomized--double-blind--placebo-controlled--single.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 Ib, randomized, double-blind, placebo-controlled, single-center study to evaluate the safety and pharmacokinetics of multiple ascending doses of GDC-6988 with and without albuterol pretreatment in healthy adult subjects

The protocol number for this study is GB43838.

The EudraCT number for this study is 2022-000455-36.