Summary of Clinical Trial Results

Is it safe for people to take a new medicine (GDC-2394) – and how is the medicine is processed by the 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 April 2021 and stopped early – in March 2022 – because two people had serious side effects. 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.**

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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-2394).

Key information about this study

- This study was done to find out if it was safe for people to take a new medicine. Researchers also wanted to find out how the medicine was processed by the body.
- The people who participated in this study did not have a disease or health condition.
- The study medicine was called "GDC-2394". A few people received a placebo instead of GDC-2394. The placebo was a pill without any medicine.
- Apart from taking GDC-2394, some people took another medicine (midazolam). This allowed researchers to study the effect of taking two medicines together.
- This study included 67 people in one country.
- Results showed that the amount of the medicine in the body increased when the dose of the medicine was increased. When taken with food, there was not much difference in the amount of medicine in the body, compared to taking the medicine on an empty stomach.
- The medicine (GDC-2394) did not affect how the second medicine (midazolam) was processed by the body.
- Two out of 67 people (3%) experienced serious side effects that doctors believed to be related to the medicine (GDC-2394). These side effects eventually went away.
- This study was stopped and nobody was allowed any more study medicine (GDC-2394) because of these serious side effects.

1. General information about this study

Why was this study done?

Heart disease is the major cause of death in the world today. Coronary artery disease or "**CAD**" is a type of heart disease.

People with CAD have fatty deposits (plaques) in the arteries, causing narrowing of the arteries. This can lead to heart attacks (acute myocardial infarction) where blood flow to the heart muscle becomes blocked.

Lifestyle changes (diet, exercise, no smoking) and medical treatments make an impact on people's health when they have CAD. However, these are not enough to stop all CAD-related medical events.

Inflammation is believed to be a key mechanism in "atherogenesis", which is the process of plaque formation in arteries.

This study was done to look at a new medicine, "GDC-2394" that could reduce inflammation – and potentially be useful for patients with CAD in the future. This study was done in healthy people.

What were the study medicines?

Two medicines and one placebo were used in this study

GDC-2394

- GDC-2394 is a medicine that stops NLRP3. GDC-2394 is an "**NLRP3 inhibitor**".
- "**NLRP3**" is a "sensor" protein found in cells throughout the body.
- When NLRP3 locates "trigger" molecules in the body, it starts the **inflammation** process. Bacteria and dead cells can trigger NLRP3, and inflammation is a way for the body to rid of infectious agents and cell debris.
- Unfortunately, some diseases generate molecules that can become wrong (**aberrant**) triggers of NLRP3.
- **Cholesterol crystals**, found in people with CAD, are aberrant triggers for NLRP3, leading to inflammation that promotes atherogenesis.
- GDC-2394 may be useful as an anti-inflammatory medicine for patients with CAD.

Midazolam

- When two medicines are taken together, sometimes one medicine can affect the second medicine. That means, the first medicine can increase or decrease the amount of the second medicine in the body.
- In this study, some people took GDC-2394 together with midazolam – to find out if GDC-2394 could change how midazolam is processed by the body.

Placebo

- Some people in the study got a placebo instead of GDC-2394. The placebo looked like the real medicine but it did not contain any medicine.
- People in the study did not know who was getting GDC-2394 and who was getting the placebo.
- Giving people placebo allowed researchers to compare side effects from treatments with and without GDC-2394.

What did researchers want to find out?

The main question that researchers wanted to answer was:

1. Was it safe for people to get single (one day) and multiple treatments (one week) of GDC-2394 at different dose levels?

Other questions that researchers wanted to answer included:

2. Was there a difference when GDC-2394 was taken with or without food?
3. Did GDC-2394 affect the way another medicine was processed by the body?

What kind of study was this?

Phase 1 study

This was a "Phase 1" study, which means that this was one of the first studies for GDC-2394. A small number of healthy people (without CAD) got treatments. Researchers did medical tests on the people to find out more about the treatments.

Placebo-controlled study

Some people got GDC-2394 while others got a placebo. This was done so that all treatments in this study – with and without GDC-2394 – could be compared – to help understand the real effect of GDC-2394.

Double-blind study

The researchers and people in the study did not know who was getting GDC-2394 and who was getting the placebo. That made it a "double-blind" study.

Randomized study

A computer randomly decided who got GDC-2394 and who got placebo. Researchers and people had no control over this.

Dose-escalation study

Each new group of people who joined the study received the next higher dose of the treatment (GDC-2394 or placebo). This type of study is called, "ascending dose study".

The decision to increase the dose level – "dose escalation" – was made after reviewing safety results from people who had already been treated at the lower dose levels.

Some groups only received a single treatment of GDC-2394 or placebo – they were in the "single ascending dose study". Other groups received treatments twice a day for one week – they were in the "multiple ascending dose study".

Food effects study

Most people got their treatments after not eating for several hours. One group got their treatment right after eating a meal to find out the effect of food on how GDC-2394 is processed by the body.

Drug-drug interaction study

When two medicines are taken together and one medicine is able to change the amount of the second medicine in the body, there is "drug-drug interaction" or "DDI". In this study, one group took GDC-2394 and midazolam together – to find out if GDC-2394 caused any DDI. There was no placebo in this (DDI) part of the study.

When and where did the study take place?

The study started in April 2021 and stopped early because two people got serious side effects.

This summary presents the results of the study up until it was stopped in March 2021.

The study took place at one study center – in one country – New Zealand.

2. Who took part in this study?

Sixty-seven healthy people took part in this study, including 28 (42%) men and 39 (58%) women. They were between 18 and 62 years old. They joined 4 different study groups.

	SAD Group Single ascending dose group	**MAD Group** Multiple ascending dose group	**FES Group** Food effects study group	**DDI Group** Drug-drug interaction group
Number of people	32	16	10	9
Number of women	24 (75%)	9 (56%)	3 (30%)	3 (33%)
Number of men	8 (25%)	7 (44%)	7 (70%)	6 (67%)
Age range (years)	20 to 60 years	20 to 50 years	18 to 57 years	21 to 62 years

People could take part in the study if:

- They were 18 to 65 years old.
- Their body temperature and blood pressure measurements were within the specified range for this study.
- Females agreed to use birth control if they could become pregnant, and agreed not to donate eggs for a specified period.
- Men agreed to use birth control with female partners who could become pregnant, and agreed not to donate sperm for a specified period.

People could not take part in the study if:

- They received another study medicine in the last 3 months.
- They were vaccinated or took other medicines within two weeks before the study. The banned medicines included prescriptions, over-the-counter medicines, and herbal remedies (unless the study doctor said it was okay).
- They had major surgery recently, or were going to need surgery during the study.
- They had certain health conditions or infections.
- They recently donated blood beyond what was allowed for this study.
- They tested positive for drugs or alcohol, used tobacco or nicotine products in the last 4 weeks, or used alcohol beyond a certain amount on a regular basis, or had struggled with drug or alcohol abuse in the last one year.
- They had any allergies or conditions that would make it difficult or unsafe to complete the study.
- They were unable or unwilling to follow the rules of the study, which included fasting, or not eating certain foods at times.
- Women who were pregnant, breastfeeding, or intended to become pregnant were not allowed to join this study.

3. What happened during the study?

Healthy volunteers joined the SAD, MAD, FES, and DDI study groups.

Doctors examined all participants and ran tests at times including before, during, and after study treatments.

All side effects were reported.

Blood samples were collected before and at several time points after dosing – from everyone in the study. Urine was also collected.

Randomized double-blind study

- For SAD, MAD, and FES studies, study treatments (GDC-2394 or placebo) were selected for each person at random by a computer.
- Doctors and people in the study did not know which treatment (GDC-2394 or placebo) the people were getting.

Open-label study

- The DDI study was open-label because the doctors and people in the study knew which treatment they were getting.

What were the treatments?

- The people in the SAD, MAD, and FES groups got either GDC-2394 or placebo treatments. People in the FES group took their assigned treatment two times, once after not eating, and once right after eating a meal.
- All people in the DDI group got GDC-2394 and midazolam.

What happened during the study?

- People checked into the clinic 1 or 2 days before dosing (on Day -1 or Day -2).
    - The SAD group got one treatment of either GDC-2394 or placebo. Study center staff did checkups for two weeks after the treatment.
    - The MAD group got their treatments (GDC-2394 or placebo) twice daily from Day 1 until Day 6, and once on Day 7. Study center staff did checkups throughout their treatment and for one month after the final treatment.
    - The FES group got two single treatments of either GDC-2394 or placebo, at least 3 days apart. Study center staff did checkups for two weeks after their final treatment. Checkups were also done between treatments.
    - The DDI group got midazolam on Day 1. They got GDC-2394 twice daily from Day 3 through Day 9. On Day 10, they got one treatment of GDC-2349 and one treatment of midazolam at the same time. Study center staff did checkups throughout their treatment and for one month after the final treatment.
- Treatments (GDC-2394 or placebo) in the SAD and MAD groups were given on an empty stomach.
- In the FES group, people got their first treatment (GDC-2394 or placebo) on an empty stomach, and the second treatment after a high-fat meal.
- Treatments in the DDI group (midazolam and GDC-2493, taken alone or together) were given on an empty stomach

4. What were the results of the study?

Question 1: Was it safe for people to get single (one day) and multiple (one week) treatments of GDC-2394 at different dose levels?

A few people in each of the four study groups had side effects that were thought to be caused by the study medicine (GDC-2394), but were not serious. These included:

- Seven people (22%) in the SAD group.
- Five people (31%) in the MAD group.
- One person (10%) in the FES group.
- Seven people (78%) in the DDI group.

For two people in the DDI group, their side effects became serious. The study was stopped and no persons got GDC-2394 after these serious side effects were seen.

See Section 5 for more details about side effects.

Question 2: Was there a difference when GDC-2394 was taken with or without food?

Researchers compared GDC-2394 concentrations in the body when taken on an empty stomach– and when taken after a high-fat breakfast. They found that the amount of GDC-2394 changed very little when taken after eating a meal.

Question 3: Did GDC-2394 affect the way another medicine was processed by the body?

Researchers wanted to find out if GDC-2394 could affect a second medicine (midazolam) when the two medicines were taken together.

They looked at midazolam concentrations in the same person – when taken alone and when taken with GDC-2394.

They found out that GDC-2394 had no effect on the second medicine – when both medicines were taken together.

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, two people in the DDI group had serious side effects.

- This was at a rate of 2 in 9 people (22%) in the DDI group.
- For the entire study, this was at a rate of 2 in 67 people (3%).

Both people had the same serious side effect of signs of injury to the liver. This was believed to be caused by the study medicine (GDC-2394).

In both people, these side effects were observed after the people had finished all planned dosing with the medicines (GDC-2394 and midazolam).

The two serious side effects happened after 67 people on the study had received their treatments. Nobody received any GDC-2394 after the side effects were reported.

During the study, nobody stopped or delayed their treatments because of any side effect. There were no deaths on this study.

Most common side effects

Some people had side effects that were not considered serious but were thought to be caused by study treatment (GDC-2394). They are included in the table below

- Counts are for **number of people** with that side effect, followed by its percentage for that study group.
- The "total number of side effects" is greater than the number of people who got side effects. That is because some people got more than one side effect.
- People who received placebo treatments did not get any side effects thought to be related to the study treatment but some did have side effects.

	SAD Group	MAD Group	FES Group	DDI Group
All the people in group	32	16	10	9
All the people with side effects thought to be caused by GDC-2394	7 (22%)	5 (31%)	1 (10%)	7 (78%)
Total number of side effects	8	6	1	14
Number of people (and percentage) with each side effect				
Feeling sick to your stomach (nausea)	4 (13%)			1 (11%)
Feeling dizzy	1 (3%)	2 (13%)		1 (11%)
Feeling tired (fatigue)		1 (6%)		2 (22%)
Constipation	2 (6%)			
Liver injury (drug-induced liver injury)				2 (22%)
Feeling bloated (abdominal distension)		1 (6%)		1 (11%)
Headache		1 (6%)		1 (11%)
Stomach ache (abdominal pain)	1 (3%)			
Feeling drowsy (lethargy)		1 (6%)		
Can't sleep (insomnia)			1 (13%)	
Abnormal liver test (alanine aminotransferase increased)				1 (11%)
Disturbance of the senses – taste, smell, vision, or hearing (sensory disturbance)				1 (11%)
Feeling confused (confusional state)				1 (11%)
General discomfort (malaise)				1 (11%)
Rash				1 (11%)

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 67 healthy people. These results helped researchers learn more about GDC-2394.

Researchers learned about the serious side effects from GDC-2394 and decided not to study the medicine any further in this study.

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.**

7. Are there plans for other studies?

At the time of writing this summary, no more studies looking at GDC-2394 were planned.

8. Where can I find more information?

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

https://doi.org/10.1186/ISRCTN15492429

https://forpatients.roche.com/en/trials/cardiovascular-disorder/is-it-safe-for-people-to-take-a-new-medicine-gdc-2394-and-ho.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:

> Phase I, randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety, tolerability, and pharmacokinetics of single and multiple ascending oral doses of GDC-2394, the effect of food on the pharmacokinetics of GDC-2394, and the effects of GDC-2394 on midazolam pharmacokinetics in healthy volunteers.

The protocol number for this study is GC42880.

The clinical trial registry number at ISRCTN is 15492429.