Summary of Clinical Trial Results

A study to look at a new medicine called, “GDC-0134”, for treating patients with amyotrophic lateral sclerosis (ALS)

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, called, “participants”.

This summary is based on information known at the time of writing.

The study started in May 2016, and finished in March 2020. 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 amyotrophic lateral sclerosis (ALS) and a study medicine called “GDC-0134”.

Key information about this study

- This study was done to find out how safe it was for patients with amyotrophic lateral sclerosis (ALS) to be treated with a new study medicine.
- Some patients were given a medicine called "GDC-0134" while others got a placebo that did not have any medicine. It was decided by chance which treatment each patient was given.
- This study included 49 patients with ALS – in 3 countries.
- The main finding was that there is risk from taking this medicine. It is not known whether there is any benefit from this medicine.
- There were 3 parts to this study. The 49 patients could join more than one part of the study:
    - Seventeen patients were treated in Part 1 and received one dose of medicine on up to 4 different occasions. No one had any serious side effects caused by the study medicine.
    - Thirty patients were treated in Part 2 and received up to 4-weeks of medicine.
      No one had any serious side effects caused by the study medicine.
    - Thirty-two patients were treated long-term in Part 3 and received up to 48-weeks of medicine.
      Three patients had serious side effects caused by the study medicine.
- The sponsor decided not to study this medicine any further.

1. General information about this study

Why was this study done?

Amyotrophic lateral sclerosis (**ALS**) is an incurable disease. It affects approximately 3 in every 100,000 adults in the United States. Often times, people are between 40 and 70 years old when they are first diagnosed.

ALS is a disease where there is failure (**degeneration**) of nerves that control movement in the body. This affects the limbs, speech, swallowing, and breathing (respiration).

Patients with ALS may progress to a state where machines may be needed to help with breathing. The majority of patients with ALS die within 3 to 5 years after diagnosis.

There were only two medicines available for patients with ALS at the time this study was started. In some countries, there was only one medicine available. Therefore, there was a need to develop other new medicines that could be better or safer.

GDC-0134 has been tested in animal models. Based on results from such studies, researchers decided that GDC-0134 could be useful as a potential new medicine in patients with ALS.

This study was done to look at whether it was safe for patients with ALS to take GDC-0134. This was the first time that GDC-0134 was given to people.

What was the study medicine?

Researchers have identified a protein in the body involved in the degeneration of nerves. This protein is called, "**DLK**".

- The degeneration of nerves by DLK may be involved in several diseases, including ALS.
- GDC-0134 blocks DLK. It is known as a "**DLK-inhibitor**".
- GDC-0134 could be useful for patients with ALS.
- Researchers wanted to learn about the effects of GDC-0134 in patients with ALS. Therefore, **GDC-0134 was the focus of this study**. The study was designed to look at whether it is safe to give GDC-0134 to humans.

Some patients got GDC-0134 treatment while others got a **placebo** treatment.

- You say this as "plah-see-bo".
- The placebo looked similar to GDC-0134 but did not contain any real medicine. This means it had no effect on the body that was caused by a medicine.
- By comparing effects of the two treatments (GDC-0134 and placebo), researchers wanted to find out the real effect (in this case, safety concerns) of the study medicine.

What did researchers want to find out?

The main question that researchers wanted to answer was:

1. How safe was it for patients with ALS to receive GDC-0134?

Another question that researchers wanted to answer was:

2. What happens to GDC-0134 in the body?

What kind of study was this?

This was a "**phase 1 study**". Being phase 1 means it was one of the early studies. In fact, this was the first time patients were treated with GDC-0134.

In one part of the study, patients received several single doses, each one separated by a few weeks. The dose started from a low dose that kept increasing each time. Each time a patient received a dose, it may have been GDC-0134 or it may have been placebo. This was known as a "**single ascending dose**" (Part 1).

In another part of the study, different groups of patients received multiple doses (once a day dosing for around 28 days in a row). The lowest dose group started their treatment first. After the lower dose was found to be safe, another group of patients received the next higher dose. In each group, a patient may have received GDC-0134 or may have received placebo. This was known as "**multiple ascending doses**" (Part 2).

In the third part of the study, patients received multiple doses for a longer period of time. The longest time patients received doses was about 48-week (just under one year). The doses changed over this period. In this part, every patient received GDC-0134. This was known as "open label safety expansion" (Part 3).

Parts 1 and 2 were "**placebo-controlled** ", which means that researchers could compare results for patients who got the medicine with those who got placebo, which is a pill without any medicine.

The study was "**randomized**". That means it was decided by chance who got the real medicine and who got placebo in Part 2. Randomly choosing makes it more likely that the types of people in both groups (for example, age, race) will be a similar mix. In Part 1, each patient was randomized every time they received a new dose, so the same patient may have received GDC-0134 and placebo on different occasions.

Parts 1 and 2 of the study were "**double-blind**" because patients and their doctors did not know who was getting the medicine and who was getting the placebo. Blinding of treatment is a way to reduce any unfairness (bias) when patients and doctors report what happened after patients got their treatments.

When and where did the study take place?

The study started in May 2016 and finished in March 2020. This summary was written after the study had ended.

The study took place at 10 study centers across 3 countries:

- Canada
- The Netherlands
- United States

2. Who took part in this study?

There were 49 unique patients with ALS who took part in this study. This was a 3-part study. Patients could participate in more than one part of the study. Results are reported for patients in each part of the study:

Part 1 17 patients	**Part 2** 30 patients	**Part 3** 32 patients
Men: 11 (65%) Women: 5 (35%)	Men: 18 (60%) Women: 12 (40%)	Men: 22 (69%) Women: 10 (31%)
Age range: 37 to 74 years	Age range: 37 to 73 years	Age range: 38 to 76 years

People could take part in the study if:

- They were at least 18 years old.
- They were men or women who had ALS. It did not matter whether the diagnosis was possible ALS, probable ALS, or definite ALS.
- They needed to have a certain capacity of muscle strength for breathing – upright forced vital capacity of at least 50%.
- They needed to be able to take pills by swallowing them or eating the contents in applesauce.
- They needed to be able to fast from food for 8 hours prior to dosing and 2 hours after dosing for Parts 1 and 2.

People could not take part in the study if:

- They could not pass a sight test or had other medical conditions of the eye.
- They had certain other diseases caused by the degeneration of nerves.
- They had certain medical conditions.
- They were taking other experimental medicines for ALS. (Patients taking approved medications for ALS were permitted to keep taking these medications as long as the dose was stable for a specified period of time before they started in this study).

3. What happened during the study?

There was a **fasting requirement** for Part 1, and Days 1 and 15 in Part 2. Patients took their treatments in capsule form (GDC-0134 or placebo) after an overnight fast of 8 hours. They were not allowed to eat any food for 2 hours after taking the medicine.

On the other days in Part 2 and throughout Part 3, patients took their treatments without regard to food.

Part 1

Patients joined one of two groups (A and B). Within each group the same patient got a treatment at one dose. After at least 2 weeks had passed, they got another treatment at a higher dose. They may have received GDC-0134 or placebo at each new dose level. This was repeated as follows:

Group A: 20 mg → 40 mg → 80 mg → 160 mg.

Group B: 320 mg → 640 mg.

Placebo – At each dose level, two patients within the group were randomly assigned placebo treatment while the rest of the group got GDC-0134.

Part 2

Patients joined different dose groups and were treated for 28 days. The treatments (placebo or GDC-0134) were assigned to each patient randomly – by a computer. The dose groups are shown in the Table below.

Part 3

Everyone got GDC-0134, and they knew what they were getting – it was "**open-label**". This part of the study was done to find out how safe the study medicine was when given long-term – up to 48 weeks. Treatments were given once daily or twice a day (600 mg x 2). Patients may have received different dose levels at different times.

Other details for different parts of the study:

Part 1 Single ascending dose treatment Total no. patients = 17	Part 2 Multiple ascending dose treatment Total no. patients = 30	Part 3 Open-label safety expansion Total no. patients = 32
Group A – 9 patients. Doses: 20 mg, 40 mg, 80 mg, and 160 mg. (GDC-0134 or placebo) **Group B** – 8 patients. Doses: 320 mg and 640 mg. (GDC-0134 or placebo)	**100 mg** - 8 patients received GDC-0134, 2 received placebo **200 mg** - 4 patients received GDC-0134, 1 received placebo **400 mg** - 4 patients received GDC-0134, 1 received placebo **800 mg** - 4 patients received GDC-0134, 1 received placebo **1200 mg** - 4 patients received GDC-0134, 1 received placebo	Assigned dose levels may have varied for an individual over the 48-week treatment period. There were 4 dose levels. The lowest assigned dose level was 400 mg taken once daily. The highest assigned dose level was 1200 mg taken once daily and 600 mg taken twice daily.

Patients were examined and got medical tests throughout the study. They were treated for side effects when it was needed. Blood samples were collected at several different times before and after treatments. When the study ended, patients were asked to return to their study center for more tests to check their overall health.

4. What were the results of the study?

Question 1: How safe was it for patients with ALS to receive GDC-0134?

Side effects became apparent in Part 3.

The most common side effect was a feeling or sensation that was unusual or painful. This included a burning sensation, or a tingling/numbness sensation in the body. Some patients in Part 3 of the study stopped dosing, paused dosing, or changed (reduced) the dose of GDC-0134 because of side effects.

In Part 3, serious side effects occurred in 3 patients that were believed to be related to GDC-0134. One of these serious side effects - damage to nerve in the eye (ischemic optic neuropathy) – caused permanent blindness. Other serious and non-serious side effects were observed and are described below.

Researchers decided that the side effects from GDC-0134 made it unsafe to continue to investigate this study medicine for patients with ALS.

Question 2: What happened to GDC-0134 in the body?

GDC-0134 was rapidly absorbed into the body after taking it in capsule form. The concentration in the body increased as the dose level of the capsule was increased.

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 patients 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.

Numbers and types of **serious side effects** thought to be caused by the study medicine:

	Part 1	Part 2	Part 3
Patients with serious side effects	None	None	3 patients, 9%
List of serious side effects			Damage to nerve in the eye leading to blindness (optic ischemic neuropathy)
			Uncomfortable sensation in body (dysesthesia)
			Rash and abnormal blood test results (rash erythematosus, proteinuria, and thrombocytopenia)

No one died due to a serious side effect from the study medicine.
Of the 3 patients who had serious side effects, 2 stopped their treatment.

Most common side effects

Some patients had side effects there were not serious but were thought to be caused by the study medicine.

In Part 1, none of the side effects occurred in more than one person – so there were no "most common side effects". In Part 2, 3 of the 11 patients reporting "related" side effects were taking placebo when that side effect occurred.

Most common side effects (seen in 3 or more patients):

	Part 1	Part 2	Part 3
Patients with side effects	4 patients, 24%	11 patients, 37%	20 patients, 63%
No. of side effects	8	25	87
Most common side effects reported overall (occurring in 3 or more patients)		Feeling tired – fatigue (4 patients, 13%)	Constipation (5 patients, 16%) Feeling dizzy (5 patients, 16%) Feeling tired – fatigue (5 patients, 16%) Burning sensation (4 patients, 13%) Eye issue – retinal disorder (3 patients, 9%) Rash (3 patients, 9%) Ringing in the ear – tinnitus (3 patients, 9%) Sleepiness – somnolence (3 patients, 9%) Tingling – paresthesia (3 patients, 9/%)
Patients who stopped treatment due to any side effects	2 patients, (4%)	1 patient, (3%)	9 patients, (28%)

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 49 patients with ALS. These results helped researchers learn more about ALS and GDC-0134.

The researchers decided that the side effects from GDC-0134 made it unsafe to continue to investigate this study medicine in other studies for patients with ALS.

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.

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7. Are there plans for other studies?

At the time of writing this summary, other studies to investigate GDC-0134 were not 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/results/NCT02655614
- https://forpatients.roche.com/en/trials/neurodegenerative-disorder/als/a-study-of-gdc-0134-to-determine-initial-safety--tolerability--a.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, double-blind, randomized, placebo-controlled, multicenter, single- and multiple-ascending-dose study to determine initial safety, tolerability, and pharmacokinetics of GDC-0134 in patients with amyotrophic lateral sclerosis.

- The protocol number for this study is **GN29823**.
- The ClinicalTrials.gov identifier for this study is **NCT02655614**.
- The EudraCT number for this study is **2017-002931-41**.