Summary of Clinical Trial Results

GEN-PEAK: A study that looked at how tominersen was absorbed, distributed and removed in persons with Huntington's disease

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) – written for:

- members of the public and
- people who took part in the study.

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

The study started in September 2019 and finished in January 2022. 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 of 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 to answer important questions about Huntington's disease (HD), an inherited and progressive brain disease that causes problems with thinking, mood and movement. In addition, this study also helped researchers to answer important questions about the investigational medicine studied – tominersen.

Overview of the study and key results

- This study was done to see how tominersen, an investigational medicine, moves through and out of the spinal fluid, blood and urine in adults with manifest HD. The spinal fluid surrounds the spinal cord and brain and is also known as the 'cerebrospinal fluid' or 'CSF'.
- This study looked at what effects tominersen had on people's mutant huntingtin (mHTT) protein levels and how safe tominersen was in adults with manifest HD.
- In this 6-month study, 12 persons with manifest HD from the Netherlands and United Kingdom took part. They were given tominersen twice during this study period: once at the start of the study (Day 1) and again 28 days later (Day 29). People were given one of three doses depending on when they joined:
  - 30 mg of tominersen
  - 60 mg of tominersen
  - 120 mg of tominersen.
- The first dose of tominersen was administered through a catheter (a flexible tube) inserted into the lower back; the second dose was given by an injection into the lower back ('lumbar puncture' or 'intrathecal injection'). The medicine flows up to the brain in the spinal fluid.
- The study found that tominersen could be measured in the spinal fluid, blood and urine, and that it had an effect on mHTT protein levels in all people in all of the dosing groups.
- In each of the groups receiving 60 mg and 120 mg of tominersen, one in four people developed serious side effects of infection/abscess at the spinal-cord level due to the insertion of the catheter and not related to tominersen. No one in the group that was given 30 mg of tominersen had a serious side effect. No one withdrew from the study because of a serious side effect. Side effects or serious side effects might not have been caused by tominersen.

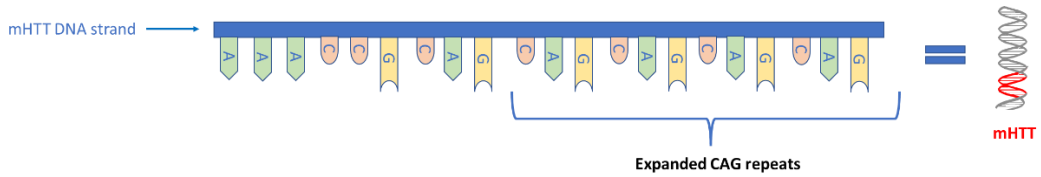
A catheter (in the context of GEN-PEAK) is a flexible tube that is inserted into the lower back by a doctor and can be used to deliver fluids into the body or remove fluids from the body.
An intrathecal injection is a procedure whereby a needle is inserted into the lower back to inject a medicine into the spinal fluid.
Lumbar puncture is a procedure whereby a needle is inserted into the lower back, either to inject a medicine into the spinal fluid (intrathecal injection) or to take out a sample of spinal fluid.
Manifest HD refers to a stage of HD where a person has clear motor (movement) symptoms.
Mutant huntingtin (mHTT) protein is a toxic, unwanted protein that causes brain cells to die, stops the brain from working normally, and causes HD symptoms.

1. General information about this study

Why was this study done?

HD is a rare, inherited disease that causes the breakdown of nerve cells in the brain and causes problems with thinking, mood and movement.

In people who are carriers for HD, even those who do not show any symptoms, a protein called mHTT builds up in the brain, causing HD symptoms. mHTT protein is a toxic version of a naturally occurring protein called huntingtin (HTT). This is caused by a mistake in a person's deoxyribonucleic acid (DNA) – the body's 'protein instruction manual'. This mistake includes an abnormal extension of a segment of DNA known as a 'CAG trinucleotide repeat' (CAG stands for cytosine, adenine and guanine [which are three of the four building blocks that make up DNA]).



mHTT is a toxic, unwanted protein that stops the brain from working normally and can cause loss of brain volume as the disease progresses. This causes problems with thinking, mood and movement. The effects of HD get worse over time, and people may end up having problems with disability and a loss of independence. Persons with HD may need full-time nursing care in the later stages of the disease.

HD is an inherited disease, which means it is passed on from a person's parent. Each child of a parent with HD has a 50/50 chance of getting the disease. HD affects men and women equally and is usually diagnosed by the time a person is between 30 and 50 years old, when they start to have problems with movement, but this can begin much earlier or later. HD typically results in death about 15 years after problems with movement begin; this is an average estimation, but every single case is different.

There is currently no cure for HD or any way to stop it from getting worse. Current approaches aim to reduce the symptoms caused by mHTT protein, rather than target the cause of mHTT protein itself; however, researchers are looking into what causes HD to find possible treatments that can slow the worsening of the disease.

This study was done to look at an investigational medicine called tominersen, which is designed to lower levels of HTT protein and the unwanted mHTT protein in the brain that causes HD. This study also investigated how tominersen moves through and out of the spinal fluid, blood and urine, and how safe tominersen was in adults with manifest HD. This study wanted to learn more about what effects tominersen had on the levels of mHTT protein between injections. It is hoped that tominersen could slow the disease or stop the disease from getting worse, and therefore improve lives.

CAG stands for cytosine, adenine and guanine (which are three of the four building blocks that make up DNA). Persons with HD have a CAG sequence in their DNA that is repeated too many times.

What was the medicine being studied?

A medicine called 'tominersen' was the focus of this study.

- Pronounced as 'tom-ee-ner-sen'.
- Tominersen is designed to work by reducing the production of HTT protein, including unwanted mHTT protein.
- It is being investigated to see if it may slow the worsening of the disease.
- Tominersen was tested at different doses in this study: 30 mg, 60 mg and 120 mg.

What did researchers want to find out?

The main questions that researchers wanted to answer were:

1. How is tominersen absorbed by, distributed in and removed from the spinal fluid and blood?
2. How much tominersen is removed in the urine after the first dose was given?

Other questions that researchers wanted to answer included:

3. How does tominersen change the amount of mHTT protein in the spinal fluid over time in persons with HD?
4. How safe is tominersen in persons with manifest HD?

What kind of study was this?

This was a Phase 1 study that investigated how tominersen is absorbed by, distributed in and removed from the spinal fluid, blood and urine, as well as its effects on the levels of mHTT protein between injections. Twelve persons with manifest HD were given one of three doses of tominersen on Day 1 of the study and again 28 days later (Day 29). The dose people received depended on when they enrolled in the study.

This study was an 'open-label' study, which means that both the people taking part in the study (participants) and the study doctors know which of the study medicines people are taking.

A Phase 1 study takes place in a small number of people to test whether the study medicine is safe.

When and where did the study take place?

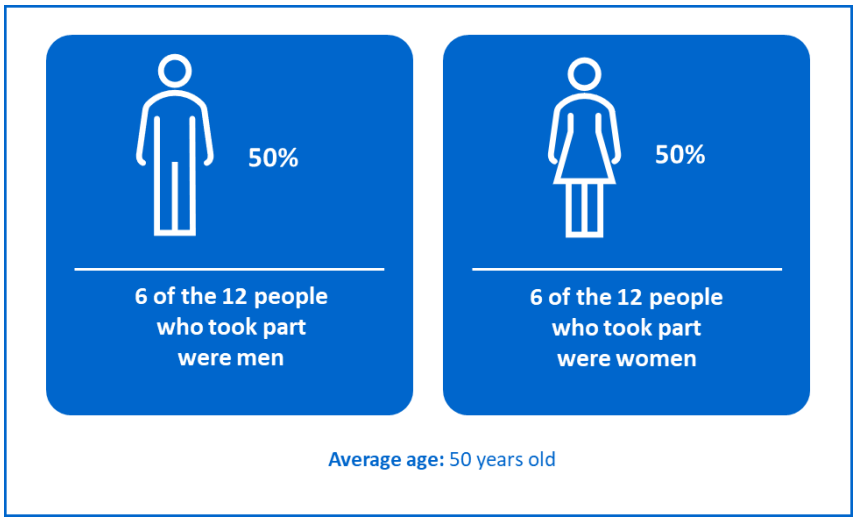
The study started in September 2019 and finished in January 2022. This summary was written after the study had ended. This summary includes the results up until August 2021 (last patient last visit).

The study took place at three clinical research study centres in the Netherlands and the United Kingdom.

2. Who took part in this study?

In this study, 12 persons with manifest HD who were between 30 and 64 years old took part.

More information on the people who participated is provided below.



People could take part in the study if they:	People could not take part in the study if they:
Had manifest HD	Ever had a migraine diagnosis
Were between 25 and 65 years of age	Had any significant cardiovascular disease
Were able to walk and read	Had pre-existing tumours
Were able to tolerate blood draws and lumbar punctures	Had an abnormal spinal structure

3. What happened during the study?

In this study, 12 people received tominersen. People were assigned to a dose level in the order in which they were enrolled in the study.

The dosing groups were:

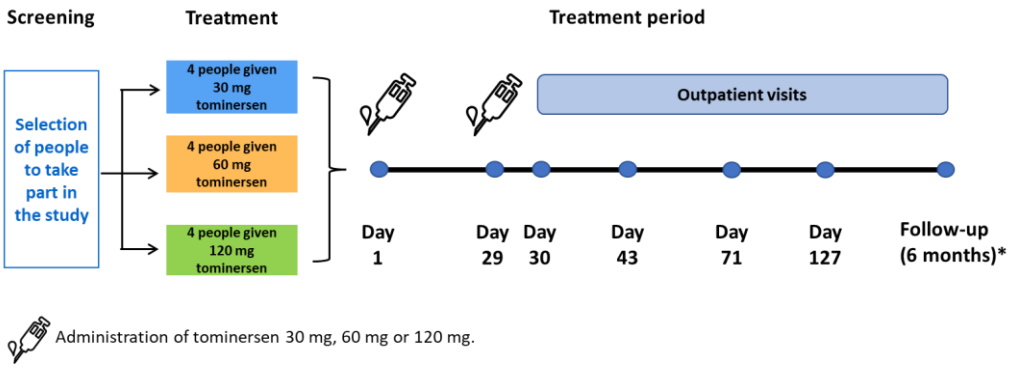
- **tominersen 30 mg**
- **tominersen 60 mg**
- **tominersen 120 mg.**

People were given tominersen on Day 1 and on Day 29 (two doses).

In the first six people, the catheter was inserted into the lower back a day before they received their first dose of tominersen and remained in place for a total of 4 days (96 hours). Blood and spinal fluid samples were taken every few hours over this period. However, due to safety reasons (please see section 4 of this document), in the final six people, the catheter was inserted into the lower back on the day they received their first dose of tominersen and remained in place for a total of 2 days (48 hours). Once all assessments were completed, the catheter was removed. This process required people to stay at the clinical trial site including overnight for the whole 4 days.

The second dose was given by an injection into the lower back ('lumbar puncture' or 'intrathecal injection'), for delivery of the medicine into the spinal fluid on Day 29. People stayed in hospital on Day 28 and Day 29 and then they were discharged on Day 29 after all assessments were completed. The outpatient visits took place on Day 30, Day 43, Day 71 and Day 127.

Below you can find more information about what happened in the study.



* The follow-up visit occurred 6 months after the last dose of tominersen was given.

4. What were the results of the study?

This section only shows the key results from the study. You can find information about all other results on the websites at the end of the study (see "Where can I find more information?").

Question 1: How is tominersen absorbed by, distributed in and removed from the spinal fluid and blood?

Researchers looked at how tominersen is absorbed by, distributed in and removed from the spinal fluid and blood.

Researchers found that tominersen concentration levels were measurable in the spinal fluid and blood samples in all people across the three dosing groups.

- On Day 1, following the first dose of tominersen, the maximum level of tominersen was achieved:
  - within the first 2 hours in the spinal fluid in all three dosing groups
  - between approximately 1 and 5 hours in the blood in all three dosing groups.
- On Day 29, the maximum level of tominersen in the blood occurred between approximately 2 and 4 hours after the second dose of tominersen in all three dosing groups.

Question 2: How much tominersen is removed in the urine after the first dose was given?

One of the most important ways that a drug can leave the body is in urine through the kidneys; researchers wanted to learn about how much tominersen was removed from the body in the urine.

Tominersen levels were measurable in all urine samples across the three dosing groups. The average amount of unchanged tominersen that was removed in the urine through the kidneys over 72 hours after the first dose was given was:

- 0.79% in the 30 mg tominersen group
- 0.35% in the 60 mg tominersen group
- 1.37% in the 120 mg tominersen group.

Question 3: How does tominersen change the amount of mHTT protein in the spinal fluid over time in persons with HD?

Tominersen was designed to reduce the amount of mHTT protein produced in persons with HD. The researchers wanted to investigate how much mHTT protein was present in the spinal fluid of persons with HD treated with 30 mg, 60 mg and 120 mg of tominersen over the course of the study.

Across all three dosing groups, there were no consistent mHTT protein-level changes up to 3 days after the first dose of tominersen was given.

On Day 29 and Day 127, the mHTT protein levels decreased across the three dosing groups.

Question 4: How safe was tominersen in persons with manifest HD?

Side effects are medical problems (such as feeling dizzy) that happen during the study. These may include side effects that might not be caused by the study medicine.

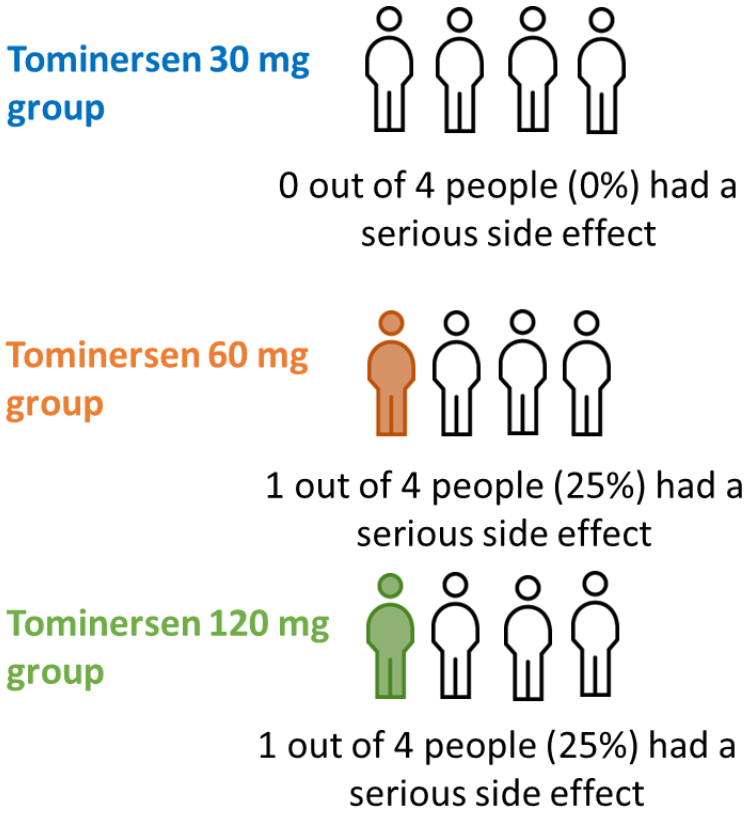
- As the study doctor does not know if the person is taking the placebo or the drug, any possible health issues during the study (e.g. a headache or a fall) are counted as side effects, although in the case of the placebo, these would not have been triggered by the drug. This is standard practice for how side effects are counted.
- Not all people had all of the side effects listed in this summary. Side effects may be mild to very serious and can differ 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.
- Researchers wanted to find out how safe tominersen 30 mg, 60 mg and 120 mg was in persons with manifest HD.
- Every person who took part in this study had a side effect; this includes side effects that might not have been caused by tominersen.
- People may also have more than one side effect.

Placebo is a substance that looks the same as a medicine but does not contain any active ingredient. It is a 'dummy' treatment that has no known physical effect on the body.

What were the serious side effects during the study?

A side effect is considered 'serious' if it is life-threatening, needs hospital care, causes long-lasting problems or death, or is considered medically important. Serious side effects may include side effects that might not be caused by the study medicine.

Researchers found that it is safer to give tominersen to persons with HD by injection rather than via a catheter. During this study, two people had serious side effects related to the catheter that were considered not related to tominersen by the investigator and the sponsor. The number of people in each group who had serious side effects were:



A summary of the serious side effects is shown in the table below.

Serious side effects reported in this study	**Group taking tominersen 30 mg** (4 people total)	**Group taking tominersen 60 mg** (4 people total)	**Group taking tominersen 120 mg** (4 people total)
Pockets of pus that the body cavity has collected (empyema)	0% (0 out of 4)	25% (catheter) (1 out of 4)	0% (0 out of 4)
Spinal canal infection (extradural abscess)	0% (0 out of 4)	0% (0 out of 4)	25% (catheter) (1 out of 4)

There were no deaths reported in this study.

During the study, no study participants refused any additional doses of tominersen because of side effects.

What were the most common side effects during this study?

During this study, the number of most common side effects was greater in the group receiving 30 mg of tominersen than the groups who received 60 mg and 120 mg of tominersen.

The most common side effects reported in more than two people are shown in the table below. Some people had more than one side effect. This means that they are included in more than one row in the table.

Most common side effects reported in this study*	**Group taking tominersen 30 mg** (4 people total)	**Group taking tominersen 60 mg** (4 people total)	**Group taking tominersen 120 mg** (4 people total)
Symptoms after lumbar puncture such as pain, headaches and nausea	75% (3 out of 4)	50% (2 out of 4)	50% (2 out of 4)
Headache	50% (2 out of 4)	50% (2 out of 4)	75% (3 out of 4)
Back pain	25% (1 out of 4)	50% (2 out of 4)	25% (1 out of 4)
Pain in extremity	50% (2 out of 4)	25% (1 out of 4)	25% (1 out of 4)

* If more than two people experienced that side effect in any dosing group.

5. How has this study helped research?

The information presented here is from a single study of 12 persons with manifest HD. These results helped researchers learn more about the pharmacokinetics, pharmacodynamics and safety of tominersen.

This study showed that after the first dose of tominersen, which was given via a catheter on Day 1, and after the second dose of tominersen, which was given via a lumbar puncture or intrathecal injection on Day 29, the concentration of tominersen in the spinal fluid and blood was measurable in all people in the different tominersen dosing groups.

Over 72 hours after the first dose of tominersen was given, tominersen levels were measurable in all urine samples across all three dosing groups.

All doses of tominersen had an effect on people's mHTT protein levels. Across all three dosing groups, there were no consistent mHTT protein-level changes up to 3 days after the first dose of tominersen was given. It was not expected that mHTT protein levels would decrease immediately by Day 3. On Day 29 and Day 127, the mHTT protein levels decreased across the three dosing groups.

Two out of eight people in the 60 mg and 120 mg tominersen groups developed serious side effects consisting of infection/abscess at the spinal cord level. No one in the 30 mg tominersen group had a serious side effect. No one withdrew from this study because of a serious side effect.

Tominersen 30 mg, 60 mg and 120 mg given by lumbar puncture or intrathecal injection showed a better safety profile than tominersen given via a catheter. Two people experienced a catheter-related serious side effect: one was in the tominersen 60 mg group and the other was in the tominersen 120 mg group.

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 to other studies of the same medicine.

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Pharmacokinetics refers to how a drug is absorbed, distributed and removed by the body.
Pharmacodynamics refers to how the body responds to a drug.

6. Are there plans for other studies?

Researchers are investigating tominersen further in a Phase 2 study called GENERATION HD2, which aims to look into lower doses of tominersen in younger adults in an earlier stage of HD.

GENERATION HD2 is an ongoing study (study doctors are still collecting information) which is still recruiting.

7. Where can I find more information?

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

- This study –

  https://clinicaltrials.gov/ct2/show/NCT04000594
  https://forpatients.roche.com/en/trials/neurodegenerative-disorder/hd/a-study-to-investigate-the-pharmacokinetics-and-pharmac-82253.html

- Phase 1/2a study –

  https://www.clinicaltrials.gov/study/NCT02519036?term=NCT02519036&rank=1

- Open-label extension of the Phase 1/2a study – https://www.clinicaltrials.gov/study/NCT03342053?term=NCT03342053&rank=1

- GENERATION HD1 – https://www.clinicaltrials.gov/study/NCT03761849?term=NCT03761849&rank=1

- HD Natural History Study – https://www.clinicaltrials.gov/study/NCT03664804?term=NCT03664804&rank=1

Note: Phase 1 study results submitted are not visible to the public at the following link: https://classic.clinicaltrials.gov/ct2/show/NCT04000594

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/trials/neurodegenerative-disorder/hd/a-study-to-investigate-the-pharmacokinetics-and-pharmac-82253.html%20

- if you have any further questions about the content of this clinical trial summary, please contact Roche Medical Information in your country using the contact form linked above. If you would like more information about Huntington's disease and support that may be available in your community for you and your family, please reach out to your local patient organisation.

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 organised and paid for this study?

This study was organised and paid for by F. Hoffmann-La Roche Ltd who have their headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is: “An Open-Label Adaptive Multiple-Dose Study to Investigate the Pharmacokinetics and Pharmacodynamics of RO7234292 in CSF and Plasma, and Safety and Tolerability Following Intrathecal Administration in Patients With Huntington's Disease”.

- The study is known as ‘GEN-PEAK’.
- The protocol number for this study is: BP40410.
- The ClinicalTrials.gov identifier for this study is: NCT04000594.
- The EudraCT number for this study is: 2018-003010-40.

Glossary

- CAG stands for cytosine, adenine and guanine (which are three of the four building blocks that make up DNA). Persons with HD have a CAG sequence in their DNA that is repeated too many times.
- Catheter (in the context of GEN-PEAK) is a flexible tube that is inserted into the lower back by a doctor and can be used to deliver fluids into the body or remove fluids from the body.
- Huntington's disease (HD) is an inherited and progressive brain disease that causes problems with thinking, mood and movement.
- Intrathecal injection is a procedure whereby a needle is inserted into the lower back to inject a medicine into the spinal fluid.
- Lumbar puncture is a procedure whereby a needle is inserted into the lower back, either to inject a medicine into the spinal fluid (intrathecal injection), or to take out a sample of spinal fluid.
- Manifest HD refers to a stage of HD where a person has clear motor (movement) symptoms.
- Mutant huntingtin (mHTT) protein is a toxic, unwanted protein that causes brain cells to die, stops the brain from working normally, and causes HD symptoms.
- Pharmacodynamics refers to how the body responds to a drug.
- Pharmacokinetics refers to how a drug is absorbed, distributed and removed by the body.
- Phase 1 study takes place in a small number of people to test whether the study medicine is safe.
- Placebo is a substance that looks the same as a medicine but does not contain any active ingredient. It is a 'dummy' treatment that has no known physical effect on the body.
- Side effects are medical problems (such as feeling dizzy) that happen during the study. These may include side effects that might not be caused by the study medicine.