# Summary of Clinical Trial Results

## GEN-EXTEND: A long-term study of tominersen in adults with Huntington's disease (HD) who participated in previous Roche HD studies

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 April 2019 and finished in March 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

- GEN-EXTEND was a study that looked at an investigational medicine called tominersen in people who had participated in previous Roche Huntington's disease (HD) studies. The study aimed to find out about the long-term side effects of tominersen in adults with manifest HD.
- In this study, 234 persons with manifest HD from Austria, Canada, Germany, Italy, the Netherlands, Spain, the United Kingdom and the United States took part. They were given tominersen under a specific treatment schedule, depending on their treatment in a previous study (please see "What was the medicine being studied?"):
  - tominersen 120 mg every month (Part 1 only)
  - tominersen 120 mg every 2 months
  - tominersen 120 mg every 4 months.
- The main finding was that persons with manifest HD who took tominersen less frequently had fewer side effects.
- Some of the most common side effects from the study were falls, bruising and pain from the procedure. These included side effects that might not have been caused by the study medicine.
- No conclusions could be made on how well tominersen worked in this study.
- Following a recommendation in March 2021 from the independent data monitoring committee (iDMC), dosing was paused, and eventually stopped by the study sponsor, Roche. The recommendation was based on an overall assessment that weighed the benefits and risks of tominersen treatment.
- After people finished taking their study medicine, they were asked to go back to their study centre for more visits to check their overall health.

---

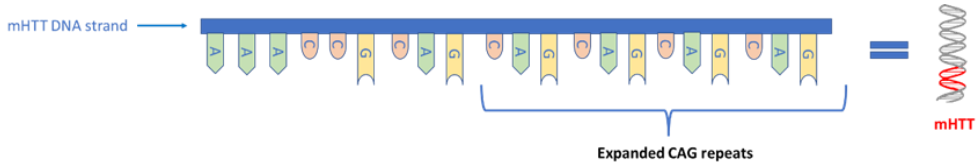
An independent data monitoring committee (iDMC) is a committee of neutral, independent experts who reviewed the study data every 4–6 months to ensure participant safety.
Manifest HD refers to a stage of HD where a person has clear motor (movement) symptoms.
Side effects are medical problems (such as feeling dizzy) that happen during the study. This may include side effects that are not be caused by the study medicine.

# 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 mutant huntingtin (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. It is hoped that tominersen could slow or stop the disease from getting worse, and therefore improve lives. In this current study (GEN-EXTEND), researchers wanted to learn about the safety of tominersen when given over a long period of time.

---

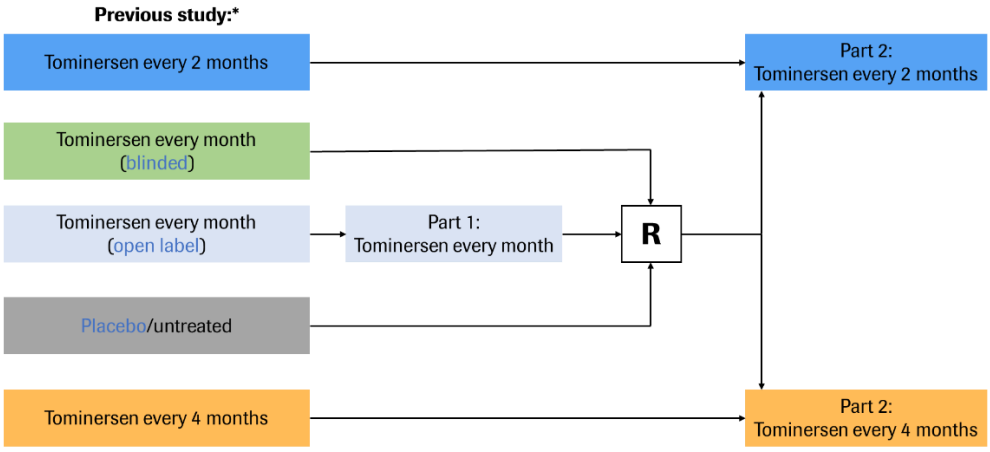
CAG stands for cytosine, adenine and guanine (which are three of the four building blocks that make up DNA). Persons with HD have a CAG sequence in their DNA that is repeated too many times.

## What was the medicine being studied?

- A medicine called ‘tominersen’ was the focus of this studyPronounced 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.

In GEN-EXTEND, some of the people who had taken part in previous Roche HD studies continued taking tominersen and some started taking it for the first time, on a long-term basis.

The safety of 120 mg of tominersen was compared in different groups. These groups are summarised in the figure below.




R, randomised.
* Previous studies include the Phase 1/2a study, the open-label extension of the Phase 1/2a study, GENERATION HD1, and the HD Natural History Study.

Due to a protocol change, the every month dosing frequency was ended and people from Part 1 were randomised to one of the dosing frequencies in Part 2.

---

Blinded means that neither the people taking part in the study nor the study doctors knew which of the study medicines people were taking.
Open label means that both the people taking part in the study and the study doctors knew which of the study medicines people were taking.
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.
Randomised means that it is randomly decided by a computer which participants will receive a placebo or the study medicine.

## What did researchers want to find out?

- Researchers had previously carried out studies to:
  - compare tominersen with a placebo
  - assess the long-term safety of tominersen
  - look at how persons with HD progressed without receiving treatment.

**The main question that researchers wanted to answer was:**

1. How safe is tominersen for persons with manifest HD?

Researchers wanted to assess the long-term safety of tominersen in persons with HD.

**Another question that researchers wanted to answer was:**

2. How effective is tominersen at slowing down the worsening of symptoms in persons with manifest HD?

## What kind of study was this?

This study was a 'Phase 3 open-label extension' study, and there was no placebo group.

Persons with HD took 120 mg of tominersen every 2 months or every 4 months.

People in this study were assigned to a treatment group based on the treatment they received in a previous study (see "What was the medicine being studied?").

---

Phase 3 studies look at how effective and safe a new treatment is in a larger number of individuals and compare the treatment to those that are already available or to a placebo.

## When and where did the study take place?

The study started in April 2019.

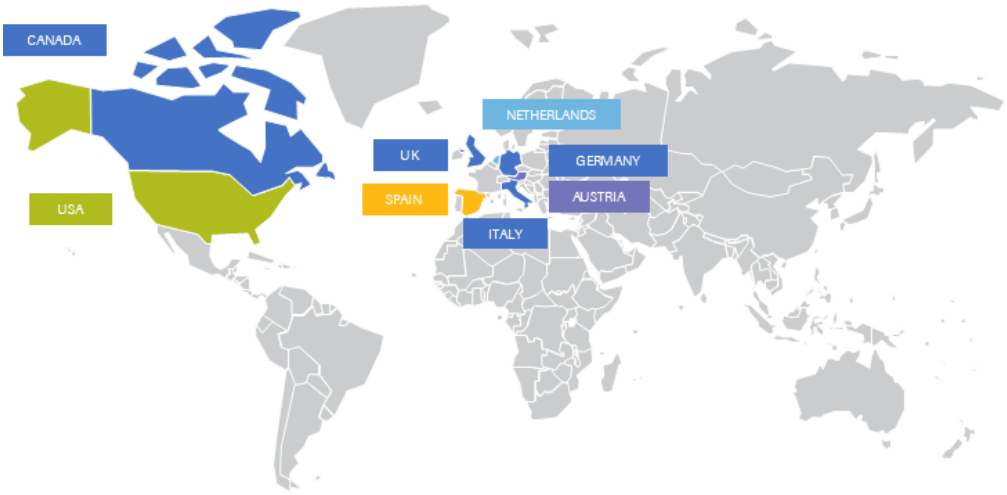
In March 2021, the study stopped early following a recommendation from the iDMC to stop dosing in the Phase 3 GENERATION HD1 study (https://forpatients.roche.com/en/trials/neurodegenerative-disorder/hd/a-study-to-evaluate-the-efficacy-and-safety-of-intrathe-26435.html; https://www.clinicaltrials.gov/study/NCT03761849?term=NCT03761849&rank=1), which weighed the benefits and risks of tominersen treatment.

After people finished taking their study medicine in GEN-EXTEND, they were asked to go back to their study centre for more visits to check their overall health.

GEN-EXTEND was stopped following a decision from the study sponsor, Roche.

This summary was written after the study had ended.

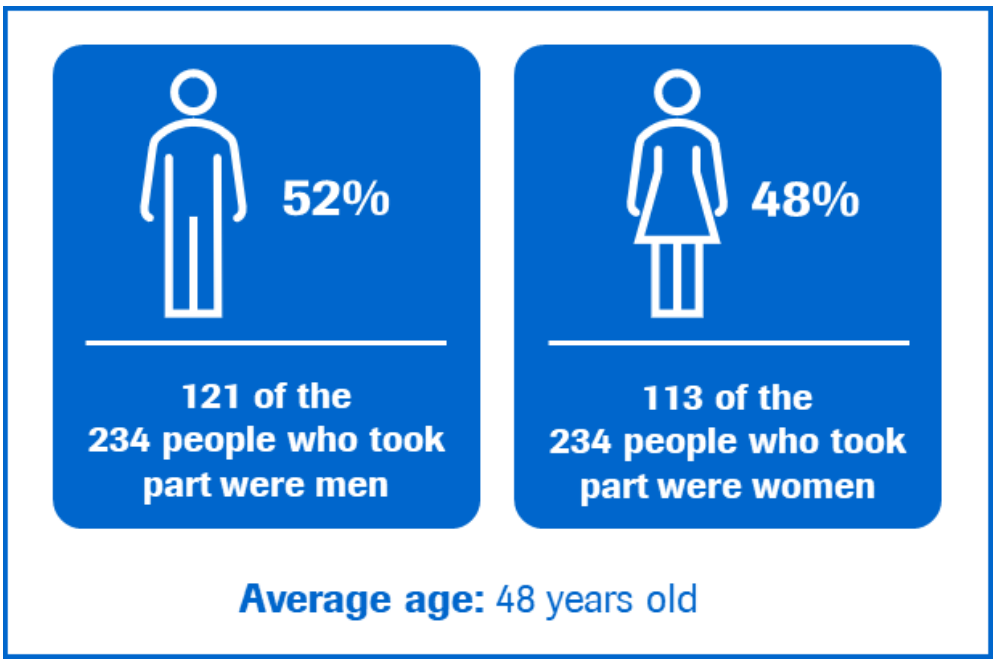
The study took place at 37 study sites in Austria, Canada, Germany, Italy, the Netherlands, Spain, the United Kingdom and the United States. The following map shows the countries where this study took place.

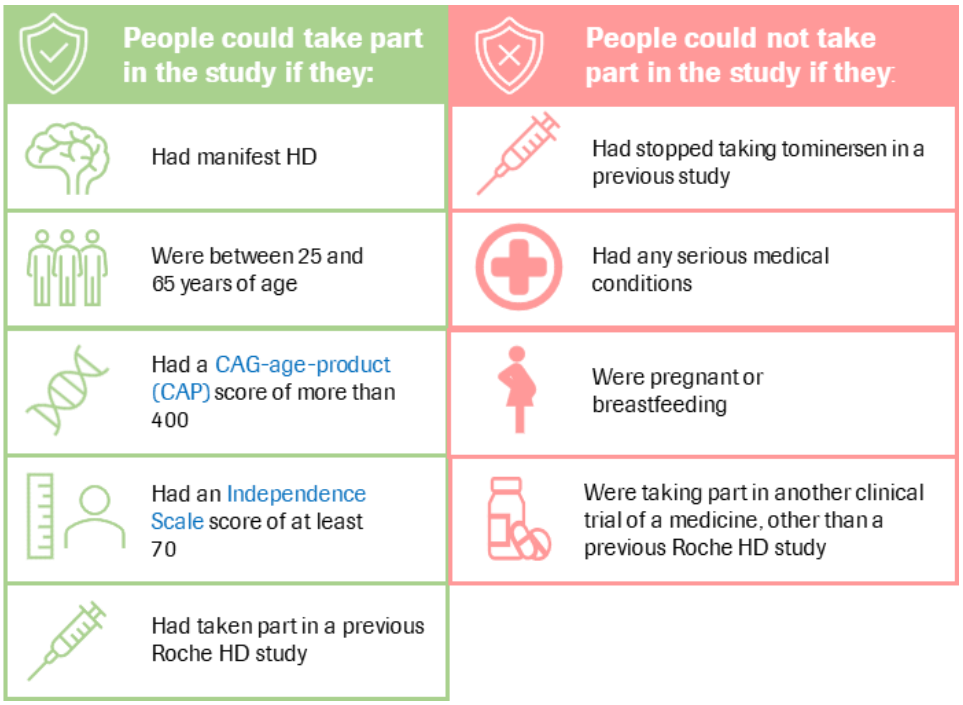



## 2. Who took part in this study?

Seventeen persons with HD took part in Part 1 of GEN-EXTEND and 234 persons with HD took part in Part 2 (including the 17 people from Part 1).

More information on the people who participated is given below.






CAG-age product (CAP) is a measure used by clinicians and scientists which takes into account a person's age and CAG repeat number. It is one way to estimate a person's lifetime exposure to the harmful effects of the mutant huntingtin gene.
Independence Scale is a test that measures how independent a person is. This test determines whether a person may need help performing a task.

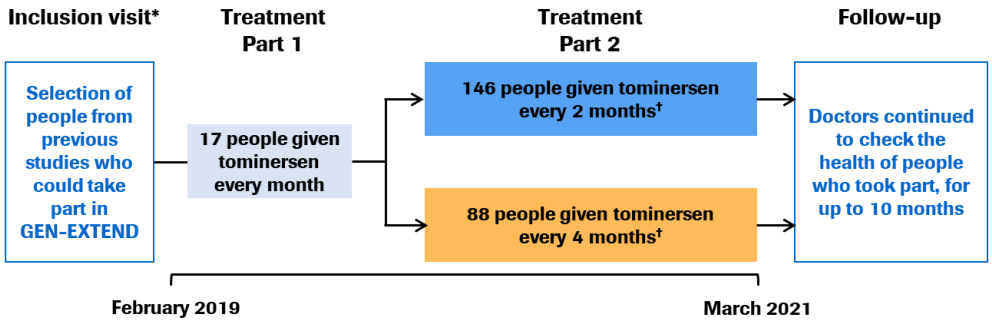
## 3. What happened during the study?

In this study, people were selected to receive tominersen under a specific treatment schedule, depending on their treatment in a previous study (see "What was the medicine being studied?").

The treatment groups were:

- **tominersen 120 mg every month (Part 1 only)**
- **tominersen 120 mg every 2 months**
- **tominersen 120 mg every 4 months.**

The study stopped early following a recommendation from the iDMC to stop dosing in the Phase 3 tominersen study called GENERATION HD1 (https://forpatients.roche.com/en/trials/neurodegenerative-disorder/hd/a-study-to-evaluate-the-efficacy-and-safety-of-intrathe-26435.html; https://www.clinicaltrials.gov/study/NCT03761849?term=NCT03761849&rank=1), (see "When and where did the study take place?").
In all treatment groups, tominersen was given by an injection into the lower back ('lumbar puncture' or 'intrathecal injection'). This was to deliver the medicine into the fluid around the spinal cord and brain called the 'cerebrospinal fluid', 'spinal fluid' or 'CSF'. After it is administered, tominersen flows up to the brain in this fluid. Below you can see more information about what happened in the study.




* Screening was conducted in a small number of people who were eligible for a previous study called GENERATION HD1 but did not take part in that study due to COVID-19.
† Includes people who received tominersen every month before the protocol amendment.

---

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.

## 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 this summary (see "Where can I find more information?").

### **Question 1:** How safe is tominersen for persons with HD?

Researchers looked at the number of side effects in persons with HD (see "What were the side effects?").

**Part 1 of the study included 14 people whose data were analysed to look at the safety of tominersen.**

**Part 2 of the study included 231 people whose data were analysed to look at the safety of tominersen.**

The main finding was that people who took tominersen less frequently had fewer side effects compared with people who took tominersen more frequently. Further information on side effects is presented in the section "What were the side effects?".

### **Question 2:** How effective is tominersen at slowing down the worsening of symptoms in persons with HD?

Researchers wanted to find out what effect tominersen had on the composite Unified Huntington's Disease Rating Scale (cUHDRS), Total Functional Capacity (TFC), Total Motor Score (TMS), Symbol Digit Modalities Test (SDMT), Stroop Word Reading (SWR) and Clinical Global Impression (CGI) scores.

The researchers could not draw any conclusions on effects that tominersen may have had on HD symptoms. This was because of several factors, including the lack of a placebo group, the large differences between people in the study, and the small number of people in the study.

---

Clinical Global Impression (CGI) is a rating scale that measures how much the person's disease has improved or worsened overall.
The composite Unified Huntington's Disease Rating Scale (cUHDRS) is a rating scale that measures three things: movement, ability to process information, and ability to perform daily activities. It can also be used to measure the progression of HD.
Total Functional Capacity (TFC) scale is a rating scale that measures function in HD. It is used to assess a person's capacity to work, handle finances, and perform domestic chores and self-care tasks.
Total Motor Score (TMS) is a test that measures a person's movement.
Stroop Word Reading (SWR) is a test that measures how long a person takes to read a set number of words.
Symbol Digit Modalities Test (SDMT) is a test that measures a person's concentration and decision-making ability.

## 5. What were the side effects?

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.
- They are described in this summary because they were most frequently reported in the study.
- Most people in this study had at least one side effect.
- 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.
- People may also have more than one side effect.

**Note:** The relationship between tominersen and the cause of these side effects has not yet been fully established.

Serious and common side effects that occurred in the study are listed in the following sections.

### Serious side effects

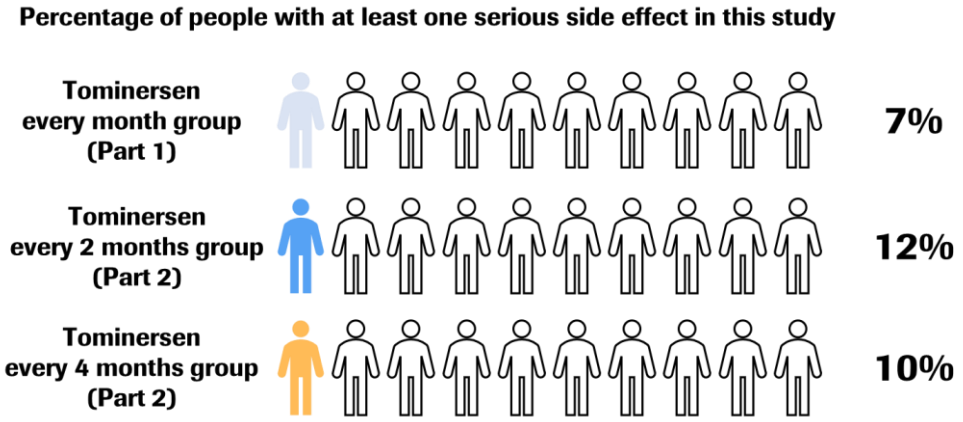
A side effect is considered 'serious' if it is life-threatening, needs hospital care, causes long-lasting problems or death, or is considered medically important. Serious side effects may include side effects that might not be caused by the study medicine.

**Part 1**

- One person (7%) died (assisted suicide). This death was considered unrelated to tominersen by the study investigator.

**Part 2**

- Seventeen people (12%) taking 120 mg tominersen every 2 months had at least one serious side effect.
- Nine people (10%) taking 120 mg tominersen every 4 months had at least one serious side effect.




The most common serious side effects from Part 2 of the study reported in 1% or more of the total population are shown in the following table.

| Serious side effects reported in this study | Group taking tominersen every 2 months (143 people total) | Group taking tominersen every 4 months (88 people total) |
|---|---|---|
| Psychotic disorder | Less than 1% (1 out of 143) | 2% (2 out of 88) |

- Nobody in the 120 mg tominersen every month group stopped taking their medicine because of the side effects (excluding the death of one person, mentioned above).
- Three out of 143 people (2%) in the 120 mg tominersen every 2 months group stopped taking their medicine because of the side effects.
- Nobody in the 120 mg tominersen every 4 months group stopped taking their medicine because of the side effects.

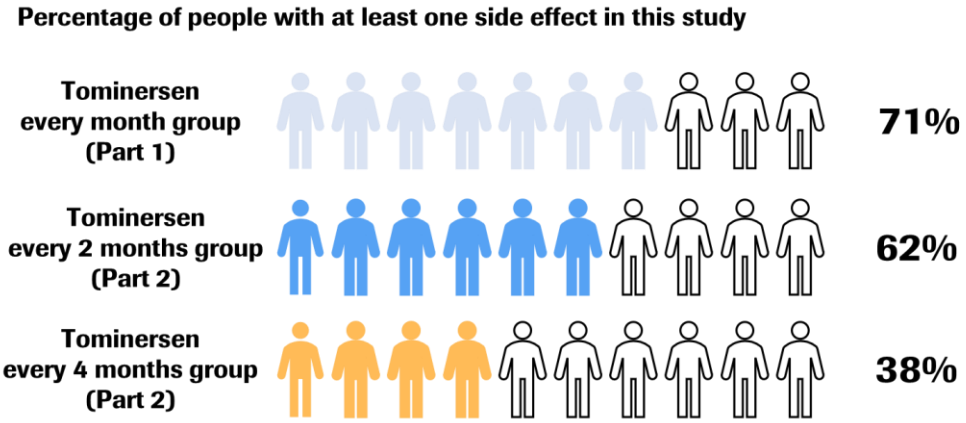
## Most common side effects

During Part 1 of this study, 10 people had at least one side effect that was not considered serious (71%). Of these, three people had a side effect that was considered by the researchers to be related to taking tominersen (21%).

During Part 2 of this study, 192 people had at least one side effect that was not considered serious (83%).

One hundred and twenty people were receiving tominersen every 2 months (62%). Nineteen people in this group had a side effect considered related to receiving tominersen (13%).

Seventy-two people were receiving tominersen every 4 months (38%). Ten people in this group had a side effect considered related to receiving tominersen (11%).



The most common side effects from Part 2 of the study reported in 5% or more of the total population are shown in the following table.

| **Most common side effects reported in this study** | **Group taking tominersen every 2 months** (143 people total) | **Group taking tominersen every 4 months** (88 people total) |
|---|---|---|
| Fall | 29% (42 out of 143) | 19% (17 out of 88) |
| Pain from the procedure | 13% (19 out of 143) | 6% (5 out of 88) |
| Bruising (contusion) | 11% (16 out of 143) | 5% (4 out of 88) |
| Symptoms after lumbar puncture such as pain, headaches and nausea | 8% (11 out of 143) | 2% (2 out of 88) |
| Headache | 9% (13 out of 143) | 7% (6 out of 88) |
| Problems with the stomach and intestines (gastrointestinal disorders) | 19% (27 out of 143) | 18% (16 out of 88) |
| Cold (nasopharyngitis) | 9% (13 out of 143) | 3% (3 out of 88) |
| Back pain | 13% (19 out of 143) | 14% (12 out of 88) |
| Anxiety | 4% (6 out of 143) | 6% (5 out of 88) |

### 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 "Where can I find more information?".

## 6. How has this study helped research?

The information presented here is from a single study of 234 persons with manifest HD. These results helped researchers learn more about the safety of tominersen in HD.

This study showed that tominersen was better tolerated in persons with HD at 120 mg every 4 months compared with 120 mg tominersen every 2 months.

About 12% of people taking tominersen every 2 months had a serious side effect, whereas about 10% of people taking tominersen every 4 months had a serious side effect.

The most common side effects across all treatment groups were: fall; pain from the procedure; bruising; symptoms after lumbar puncture such as pain, headaches and nausea; headache; problems with the stomach and intestines; cold; back pain; and anxiety.

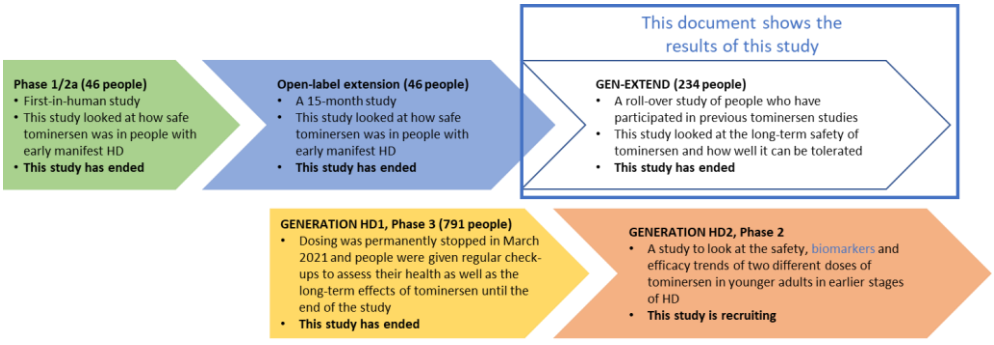
The researchers could not draw any conclusions on effects that tominersen may have had on HD symptoms because of several factors, including the lack of a placebo group, the large differences between people in the study, and the small number of people in the study.

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?

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.



Biomarkers are signs or substances in the body that tell us about a disease process.

## 8. 8. Where can I find more information?

You can find more information about this study and the other Roche HD studies on the websites listed below:

- This study – https://www.clinicaltrials.gov/study/NCT03842969?term=NCT03842969&rank=1 https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-003898-94/results https://forpatients.roche.com/en/trials/neurodegenerative-disorder/hd/an-open-label-extension-study-to-evaluate-the-long-term-82935.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
- GEN-PEAK – https://www.clinicaltrials.gov/study/NCT04000594?term=NCT04000594&rank=1

### 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/an-open-label-extension-study-to-evaluate-the-long-term-82935.html

- 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 Extension Study to Evaluate Long-Term Safety and Tolerability of RO7234292 (RG6042) in Huntington's Disease Participants Who Participated in Prior Roche and Genentech Sponsored Studies”.

- The study is known as ‘GEN-EXTEND’.
- The protocol number for this study is: BN40955.
- The ClinicalTrials.gov identifier for this study is: NCT03842969.
- The EudraCT number for this study is: 2018-003898-94.

## Glossary

- Biomarkers are signs or substances in the body that tell us about a disease process.
- Blinded means that neither the people taking part in the study nor the study doctors knew which of the study medicines people were taking.
- 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.
- CAG-age product (CAP) score is a measure used by clinicians and scientists which takes into account a person's age and CAG repeat number. It is one way to estimate a person's lifetime exposure to the harmful effects of the mutant huntingtin gene.
- Clinical Global Impression (CGI) is a rating scale that measures how much the person's disease has improved or worsened overall.
- composite Unified Huntington's Disease Rating Scale (cUHDRS) is a rating scale that measures three things: movement, ability to process information, and ability to perform daily activities. It can also be used to measure the progression of HD.
- Independent data monitoring committee (iDMC) is a committee of neutral, independent experts who reviewed the study data every 4–6 months to ensure participant safety.
- Independence Scale is a test that measures how independent a person is. This test determines whether a person may need help performing a task.
- 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.
- Open label means that both the people taking part in the study and the study doctors knew which of the study medicines people were taking.
- Phase 3 studies look at how effective and safe a new treatment is in a larger number of individuals and compare the treatment to those that are already available or to a placebo.
- 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.
- Randomised means that it is randomly decided by a computer which participants will receive a placebo or the study medicine.

- Side effects are medical problems (such as feeling dizzy) that happen during the study. These may include side effects that are not be caused by the study medicine.
- Stroop Word Reading (SWR) is a test that measures how long a person takes to read a set number of words.
- Symbol Digit Modalities Test (SDMT) is a test that measures a person's concentration and decision-making.
- Total Functional Capacity (TFC) scale is a rating scale that measures function in HD. It is used to assess a person's capacity to work, handle finances, and perform domestic chores and self-care tasks.
- Total Motor Score (TMS) is a test that measures a person's movements.