Summary of Clinical Trial Results

A study to look at tominersen safety over 15 months in people 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 January 2018 and finished in October 2019. 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 study summary – always speak to your doctor before making any decisions about your treatment.

Contents of the summary

Glossary

- HD = Huntington's disease
- CSF = cerebrospinal fluid

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, an inherited disease that causes the breakdown of nerve cells and affects a person's ability to think, behave and move, as well as their mood.

In addition, this study also helped researchers answer important questions about the investigational medicine studied – 'tominersen'.

Overview of the study design and key results

- This study was done to test the safety of an investigational medicine in adults with Huntington's disease (HD), a disease of the brain that causes problems with a person's ability to think, behave and move.
- In this 15-month study, people were given the medicine being studied (called 'tominersen') either every month or every 2 months.
- The study medicine was given by injection into the lower back ('lumbar puncture' or 'intrathecal injection'), for delivery of the medicine into the fluid that surrounds the spine and brain ('cerebrospinal fluid' or 'CSF'). The study medicine then flows in this fluid up to the brain.
- This study included 46 people with early-manifest HD in 3 countries: Canada, the United Kingdom and Germany.
- The main finding was that people in the group given tominersen every 2 months appeared to tolerate tominersen better than people in the group given tominersen every month.
    - Around 17% of people (4 out of 23 people) in the group given tominersen every month had serious side effects*, compared with around 13% of people (3 out of 23 people) in the group given tominersen every 2 months.
    - No-one in the group given tominersen every 2 months had a serious side effect that study doctors believed was related to the study medicine. In the group given tominersen every month, there were 7 serious side effects in 2 people, which doctors believed were related to the study medicine.

* Including those that might not have been caused by tominersen.

1. General information about this study

Why was this study done?

Huntington's disease (HD) is a rare, inherited disease that causes the breakdown of nerve cells in the brain and affects a person's ability to think, behave and move, and also their mood.

HD happens because of changes in a person's DNA (a mutation). The expanded CAG mutation is in a gene called huntingtin, or *HTT,* and it results in a build-up of an unwanted material called mutant HTT (mHTT) protein.

This unwanted material stops the brain from working normally and can cause a loss of brain volume as the disease progresses. This gives people problems with thinking, memory, planning and judgement, and causes changes in behaviour, personality, mood and emotions, as well as difficulty with movement and balance, including involuntary movements.

The effects of HD get worse over time, and people may end up having problems with disability and functioning on their own, leading to a loss of independence. People with HD may need full-time nursing care in the later stages of the disease.

HD is passed on (inherited) from a person's parents. This means each child of a parent with HD has a 50/50 chance of getting the disease. HD affects men and women equally. People usually find out they have HD in the prime of life, between the ages of 30 to 50 years, when they start to have problems with moving, but this can begin much earlier or later. HD typically results in death about 15 years after problems with moving begin, but it can take more or less time.

There is currently no cure for HD or any way to stop it from getting worse. However, people 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 target the underlying cause of HD. Tominersen reduces the production of HTT protein, including the unwanted mHTT protein, and it is hoped that it could slow or stop the disease getting worse and therefore improve lives.

What was the investigational medicine being studied?

An **investigational** medicine called 'tominersen' was the focus of this study.

- You say this as 'tom-een-er-sen'.
- Tominersen works by reducing the production of HTT protein, including the unwanted mHTT protein, and is being investigated to see if it may slow the progression of the disease.

Investigational
The term 'investigational' means the medicine is not approved by the organisations in charge of regulating medicines for use ('regulatory agencies') and cannot be used except in research studies.

What did researchers want to find out?

- A previous study was done to compare the safety of different doses of tominersen in people with HD. The highest dose was chosen for use in subsequent studies.
- In this study, the people who had taken part in the previous study were given the highest dose of tominersen on a longer-term basis, after the previous study had finished.
- Researchers wanted to gather longer-term information on tominersen:
    - How safe tominersen was over a longer period of time
    - How people's bodies tolerated tominersen in the long term
    - How tominersen changes the amount of mHTT protein.
- Researchers also wanted to find out if there was a difference when people were given tominersen every month or every 2 months.

The main question that researchers wanted to answer was:

1. How many people had side effects after receiving tominersen either every month or every 2 months, throughout the study?

Other questions that researchers wanted to answer included:

2. How much tominersen is left in the fluid around the spine and brain – called the 'cerebrospinal fluid' (CSF) – just before the next injection of tominersen is given?
3. How does tominersen change the amount of unwanted mHTT protein produced in patients who are given the treatment every month versus every 2 months?
4. Was there a change in size of brain structures between the start and end of the study? Using brain images, the researchers measured the change in size of:
    - The whole brain
    - The ventricles, which are the areas of the brain that hold the CSF
    - The caudate, which is an area of the brain involved in movement and behaviour.
5. Was there a change in electrical functioning of the brain (measured using a recording of brain activity called 'electroencephalogram' [EEG]) between the start and end of the study?
6. Was there a change in the 'HD cognitive assessment battery' (HD-CAB) score between the start and end of the study? The 'HD cognitive assessment battery' is a combination of tests used to measure a person's attention and their ability to think, reason, remember or process information.

What kind of study was this?

This was a Phase 2 'open-label extension' study. This means that people who had taken part in a previous study continued participating in this study. This also means that every person knew they were receiving the investigational medicine, tominersen.

Researchers wanted to find out how safe tominersen was in the longer-term and see how people's bodies tolerated tominersen over this time. In this study, people with HD were given tominersen either every month or every 2 months – this was to find out about the number and type of side effects (the 'safety') people had when they were given tominersen at different time intervals.

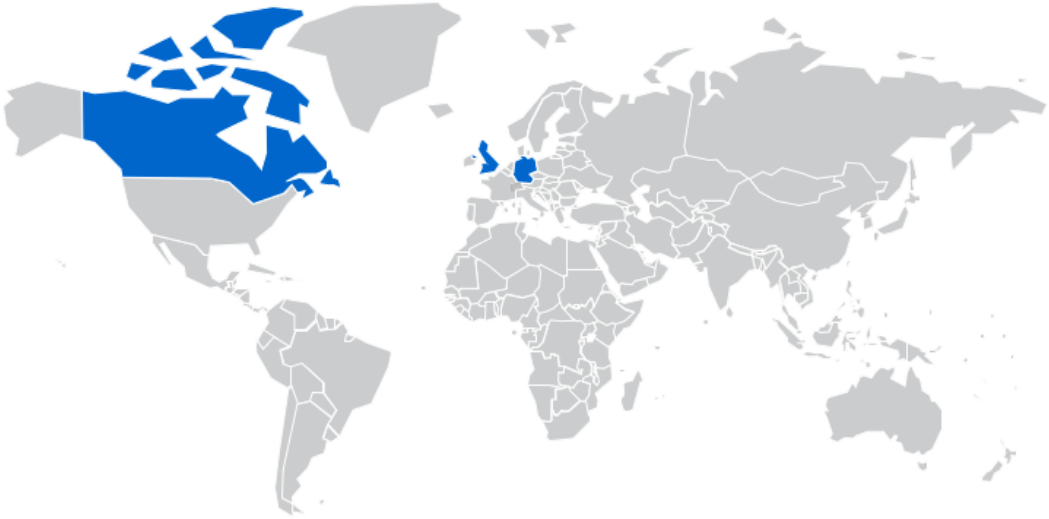
The study was 'randomised'. This means that it was decided by chance whether people were given tominersen every month or every 2 months – like tossing a coin. Randomly choosing how often people would receive the medicine makes it more likely that the types of people in both groups (for example, age, race) will be a similar mix. Once randomly assigned to a group, people

stayed in that group for the duration of the study. Apart from how often the medicine was given, all other aspects of care were the same between the groups.

When and where did the study take place?

The study started in January 2018 and finished in October 2019. This summary was written after the study had ended as part of Roche's commitment to making results of studies available for those involved and the broader community.

The study took place at 9 study sites in 3 countries. The following map shows the countries where this study took place.



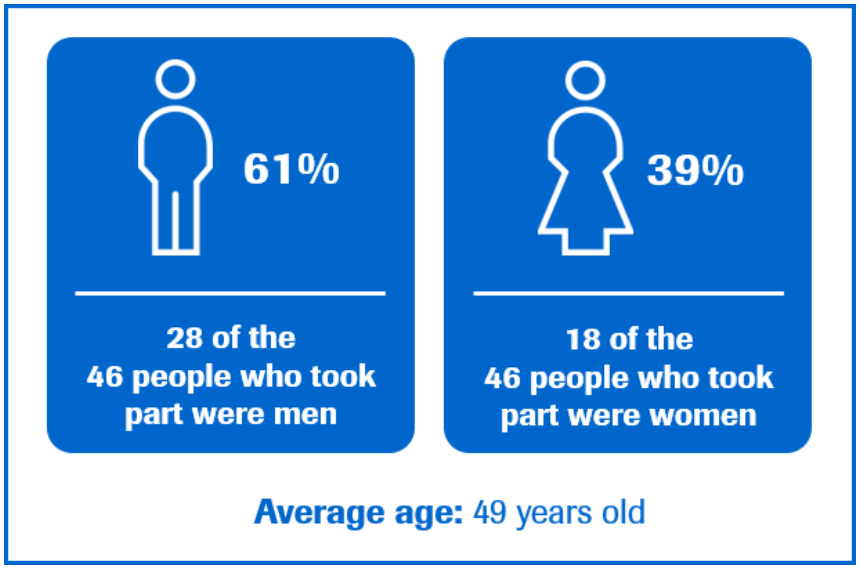
- Canada
- United Kingdom
- Germany

2. Who took part in this study?

The 46 people who took part in the previous study of tominersen all chose to continue into the open-label extension study. All the people included had **early-manifest HD**.

More information on the people who took part is given below.

Early-manifest HD
This term refers to individuals who have been diagnosed with HD based on motor symptoms, and are still able to drive, manage their finances and work independently.



People could take part in the study if:

- They had early-manifest HD
- They were between 25 and 65 years of age
- They had completed the first study of tominersen.

People could not take part in the study if:

- They had a new medical condition, or a medical condition had got worse, that would cause problems with this study

3. What happened during the study?

During the study, everyone received tominersen. People were selected by chance to receive tominersen every month or every 2 months - this was selected at random by a computer.

The treatment groups were:

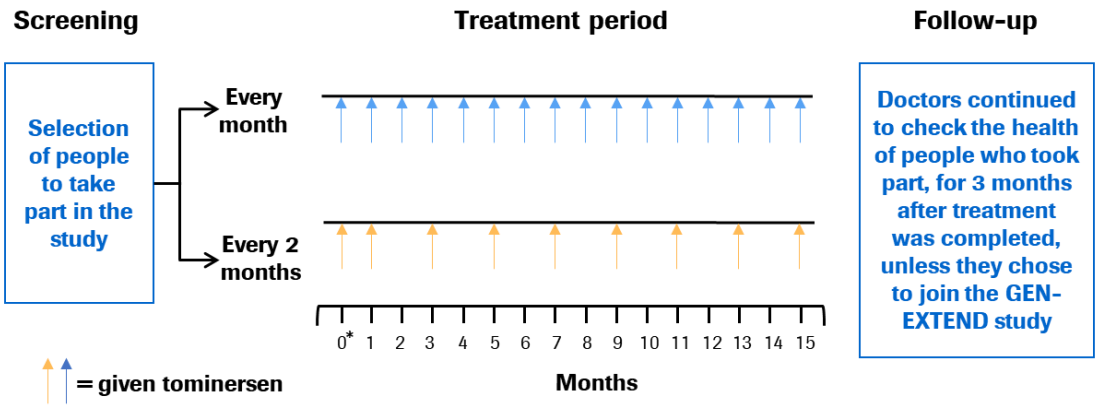
- **Tominersen 120 mg every month**
- **Tominersen 120 mg every 2 months.**

Note: at the start of the study, people in both treatment groups received their first dose of tominersen followed by the second dose after a month.

In both groups, tominersen was given by injection into the lower back ('lumbar puncture' or 'intrathecal injection'), for delivery of the medicine into the fluid around the spine and brain ('cerebrospinal fluid' or 'CSF'). The medicine then flows in this fluid up to the brain.

People in the study received tominersen for 15 months. Once people had received all their doses, they were asked to go back to their study centre for more visits to check their overall health. Alternatively, the people who took part were given the opportunity to join the next study, named '**GEN-EXTEND**'. Look below to see more information about what happened in the study.

GEN-EXTEND is an open-label extension study designed to build on the information gathered in previous research studies, to evaluate what the effects of tominersen are, and how safe it is, over the long term.



*At the start of the study, people in both treatment groups received their first dose of tominersen followed by the second dose after a month

4. What were the results of this study?

Question 1: How many people had side effects after receiving tominersen every month or every 2 months, throughout the study?

Researchers wanted to find out if the number and type of **side effects** was different in the group of people who were given tominersen every month compared with the people in the group given tominersen every 2 months.

Nearly every person had a side effect while receiving tominersen; this included side effects that might not have been caused by tominersen. The numbers of people in each group who had side effects during the study were:

- 23 out of 23 people in the group given tominersen every month
- 22 out of 23 people in the group given tominersen every 2 months.

Side effects are medical problems (such as feeling dizzy) that happen during the study. Side effects include any medical problems that started or got worse after people had their first injection of tominersen. Side effects that might not be caused by the study medicine were also included.

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. People may also have more than one side effect.

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.

Every person (100%) had a side effect* in the group receiving tominersen every month

Nearly every person (96%) had a side effect* in the group receiving tominersen every 2 months

*This included side effects that might not have been caused by tominersen

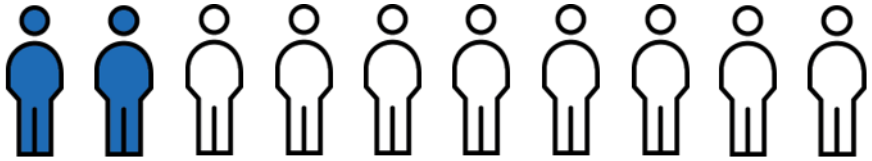
What were the **serious side effects** during the study?

During this study, 7 of the 46 people (15%) had at least one serious side effect; this included serious side effects that might not have been caused by tominersen. The numbers of people in each group who had serious side effects during the study were:

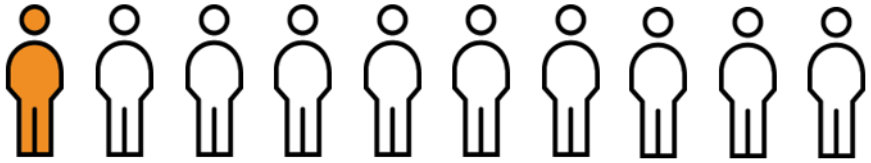
- 4 out of 23 people (17%) in the group given tominersen every month
- 3 out of 23 people (13%) in the group given tominersen every 2 months.

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

People may also have more than one side effect and they may have both serious and non-serious side effects.



Nearly 2 in every 10 people (17%) had a serious side effect* in the group receiving tominersen every month



Around 1 in every 10 people (13%) had a serious side effect* in the group receiving tominersen every 2 months

*This included serious side effects that might not have been caused by tominersen

The numbers of people in each group who had a serious side effect that study doctors thought might have been caused by tominersen were:

- 2 out of 23 people (9%) in the group given tominersen every month
- 0 out of 23 people (0%) in the group given tominersen every 2 months.

The serious side effects that doctors thought might have been caused by tominersen are shown in the following table. Some people had more than one side effect – this means that they are included in more than one row in the table.

Serious side effects believed to be related to study medicine	**Group given tominersen every month** (23 people total)	**Group given tominersen every 2 months** (23 people total)
Inflammation of the protective outer layer that surrounds the brain and spinal cord (chemical meningitis)	4% (1 out of 23)	0% (0 out of 23)
Weakness of one side of the body (hemiparesis)	4% (1 out of 23)	0% (0 out of 23)
Build-up of fluid in the brain (hydrocephalus)	4% (1 out of 23)	0% (0 out of 23)
Under-active tendon reflexes (hyporeflexia)	4% (1 out of 23)	0% (0 out of 23)
Inflammation of a nerve (neuritis)	4% (1 out of 23)	0% (0 out of 23)
Inflammation of the nerve roots in the lower back (radiculopathy)	4% (1 out of 23)	0% (0 out of 23)
Inflammation of the spinal cord (myelitis)	4% (1 out of 23)	0% (0 out of 23)

One person in the group given tominersen every month died due to suicide, but this was not believed to be related to the study medicine by study doctors. No people in the group given tominersen every 2 months died during the study.

During the study, some people stopped taking part in the study because of side effects:

- 2 out of 23 people (9%) in the group given tominersen every month
- 0 out of 23 people (0%) in the group given tominersen every 2 months.

What were the most common side effects during the study?

During this study, 44 out of 46 people (96%) had a side effect that was not considered serious; this included non-serious side effects that might not have been caused by tominersen, and included only non-serious side effects reported in more than 1 person from either treatment group (i.e. 5% or more of each group). The numbers of people in each group who had non-serious side effects during the study were:

- 22 out of 23 people (96%) in the group given tominersen every month
- 22 out of 23 people (96%) in the group given tominersen every 2 months.

The most common side effects are shown in the following table – these are the 13 most common side effects across both groups. 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 given tominersen every month** (23 people total)	**Group given tominersen every 2 months** (23 people total)
Fall	78% (18 out of 23)	52% (12 out of 23)
Pain from the injection procedure	30% (7 out of 23)	52% (12 out of 23)
Swelling in the passages of the nose and throat – commonly known as a 'cold' (nasopharyngitis)	39% (9 out of 23)	43% (10 out of 23)
Abrasion	30% (7 out of 23)	17% (4 out of 23)
Bruising (contusion)	26% (6 out of 23)	22% (5 out of 23)
Headache	26% (6 out of 23)	17% (4 out of 23)
Abnormal walking	26% (6 out of 23)	0% (0 out of 23)
Headache and back pain from the injection procedure (post-lumbar puncture syndrome)	17% (4 out of 23)	22% (5 out of 23)
Diarrhoea	0% (0 out of 23)	22% (5 out of 23)
Localised bleeding outside of blood vessels (haematoma)	17% (4 out of 23)	9% (2 out of 23)
Depression	17% (4 out of 23)	9% (2 out of 23)
Pain where injection happened	9% (2 out of 23)	17% (4 out of 23)
Back pain	9% (2 out of 23)	17% (4 out of 23)

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 7.

Question 2: How much tominersen is left in the fluid around the spine and brain – called the 'cerebrospinal fluid' (CSF) – just before the next injection of tominersen is given?

Another piece of information that researchers collected was how much tominersen is left in the **cerebrospinal fluid** (CSF) – just before the next injection of tominersen is given.

- On average, people in the group given tominersen every month had more tominersen left in their CSF just before the next injection of tominersen was given than those in the group given tominersen every 2 months.

Cerebrospinal fluid (CSF) is the fluid around the spine and brain. The amount of study medicine in the CSF was measured to see how the body processes tominersen, in other words, how the body absorbs, distributes and removes tominersen from the CSF.

This result was expected by researchers as there was less time for the body to remove tominersen from the CSF in people who received tominersen every month compared with every 2 months.

Question 3: How does tominersen change the amount of unwanted mHTT protein produced in patients who are given the treatment every month versus every 2 months?

The unwanted mHTT protein is a by-product of the DNA mutation that causes HD. Tominersen was designed to reduce how much mHTT is produced in people with HD, as it was thought this would be beneficial in slowing or stopping the disease from getting worse. Therefore, the researchers wanted to measure how much mHTT protein was present in the CSF of people with HD treated with tominersen every month, or every 2 months.

- The researchers found that over the long term (over 15 months) tominersen led to a sustained reduction of mHTT protein which was similar in people treated every month or every two months and amounted to a reduction of approximately 40–45% as compared to before treatment.

Question 4: Was there a change in size of brain structures between the start and end of the study?

Another piece of information that researchers collected was the change in size of the whole brain and brain structures (ventricles and caudate) between the start and end of the study.

The size of the brain and brain structures was measured with **magnetic resonance imaging (MRI)**. MRI is used to take detailed images of the inside of the body, including areas like the brain. Taking images of the brain helps researchers understand what might be happening in conditions like HD that affect the brain. However, the importance and meaning of these changes in brain images are not yet understood.

Whole brain

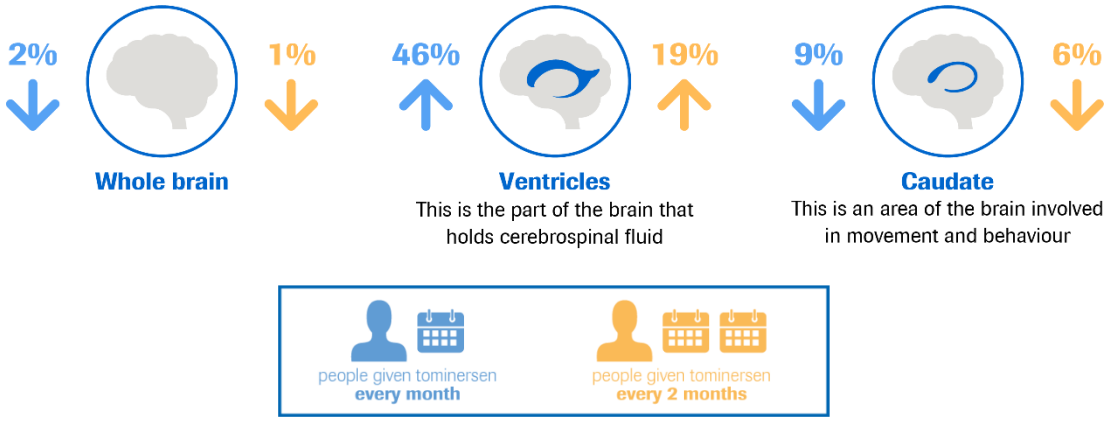
- On average, people in the group given tominersen every month had a 2% decrease in brain size after the 15 months of treatment.
- This compares with a 1% decrease in the group given tominersen every 2 months.

Ventricles

- On average, people in the group given tominersen every month had a 46% increase in the size of their ventricles after the 15 months of treatment.
- This compares with a 19% increase in the group given tominersen every 2 months.

Caudate

- On average, people in the group given tominersen every month had a 9% decrease in the size of their caudate after the 15 months of treatment.
- This compares with a 6% decrease in the group given tominersen every 2 months.



Question 5: Was there a change in electrical functioning of the brain (measured using a recording of brain activity called an 'electroencephalogram' [EEG]) between the start and end of the study?

Researchers looked at electrical recordings of people's brain activity - called an 'electroencephalogram' (EEG) – to see any changes in electrical signals between the start and end of the study.

- After 15 months of treatment, people in the group given tominersen every month appeared to have a bigger increase in brain activity, as measured by electrical signals, compared with people in the group given tominersen every 2 months.

Electrical signals are generated by the nerve cells in our brain, and an **electroencephalogram (ECG)** is a way of measuring brain activity. People with HD have differences in the electrical signals produced in the brain compared with people without HD.

Further research is needed to understand what these results mean for tominersen and people with HD.

Question 6: Was there a change in the 'HD cognitive assessment battery' between the start and end of the study?

Researchers asked each person to complete a questionnaire called the 'HD cognitive assessment battery' (HD-CAB). Researchers compared the score people got when they completed the questionnaire at the start and end of the study.

- There was a small decrease in the score in both groups, but people in the group given tominersen every month had a bigger decrease in the score than people given tominersen every 2 months.

The **HD cognitive assessment battery (HD-CAB)** measures a person's ability to think, reason, remember or process information; a decrease in the score over time indicates a worsening in these areas. More research is needed to understand what changes in HD-CAB score mean over time for people with HD. A larger and longer study is underway to answer these questions.

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 7).

5. How has this study helped research?

The information presented here is from a single study of 46 people with early-manifest HD in 3 countries. These results helped researchers learn more about the safety of tominersen in HD.

In this 15-month study, people were given tominersen either every month or every 2 months – it was decided by chance how often the medicine was given to each person.

The main finding was that people in the group given tominersen every 2 months appeared to tolerate tominersen better than people in the group given tominersen every month. This is in terms of the number and type of side effects and serious side effects experienced in each treatment group.

- Around 17% of people (4 out of 23 people) in the group given tominersen every month had serious side effects, compared with around 13% of people (3 out of 23 people) in the group given tominersen every 2 months.
- No-one in the group given tominersen every 2 months had a serious side effect that study doctors believed was related to the study medicine. In the group given tominersen every month, there were 7 separate serious side effects in 2 people, which doctors believed were related to the study medicine.

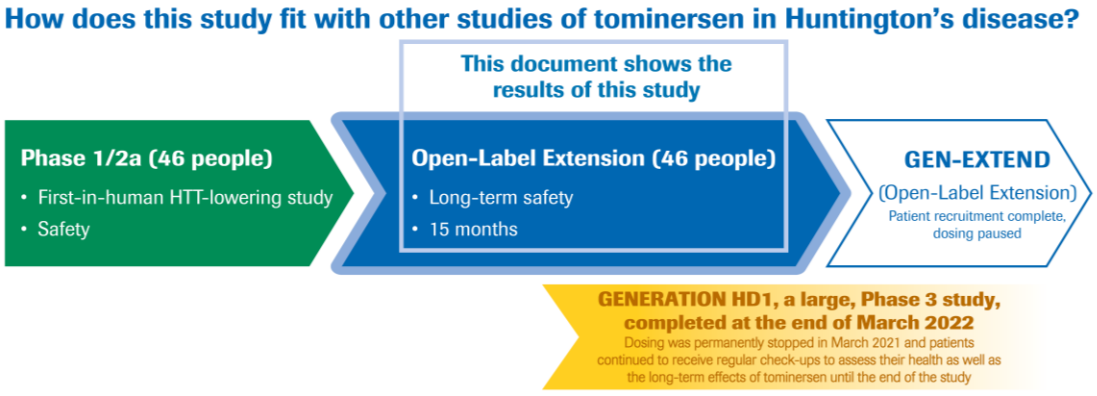
The results from this study have helped inform how often tominersen should be given to people in other studies. Tominersen is being given every 2 months, or less often, in ongoing studies.

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 study summary – always speak to your doctor before making any decisions about your treatment.**

6. Are there plans for other studies?

While this study looked at the safety of tominersen, a larger and longer 'Phase 3' study was subsequently conducted to answer important questions about longer-term effects of tominersen in people with HD. The phase 3 study GENERATION HD1, as well as the open-label extension GEN-EXTEND study, have both completed at the end of March 2022.



For more information on the changes to tominersen clinical trials, please visit https://www.roche.com/media/releases/med-cor-2021-03-22b.htm

7. 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/NCT03342053
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-002471-25/results
- https://forpatients.roche.com/en/trials/neurodegenerative-disorder/hd/study-in-huntington-s-disease-patients-who-participated-34698.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/trials/neurodegenerative-disorder/hd/study-in-huntington-s-disease-patients-who-participated-34698.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 organised and paid for this study?

This study was initially organised and paid for by Ionis Pharmaceuticals, and subsequently the sponsorship was transferred to 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 the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of RO7234292 (ISIS 443139) in Huntington's Disease Patients Who Participated in Prior Investigational Studies of RO7234292 (ISIS 443139)”.

- The protocol number for this study is: BN40697.
- The ClinicalTrials.gov identifier for this study is: NCT03342053.
- The EudraCT number for this study is: 2017-002471-25.