Summary of Clinical Trial Results

GENERATION HD1: A 2-year study of tominersen in adults 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 July 2019, and dosing was stopped early, in March 2021, because the medicine being studied did not work as well as expected. 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 to those from other studies of the same medicine.

This means that no one should 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

- The study was done to test whether tominersen (the investigational medicine being studied) could slow the speed at which HD worsens (efficacy), and to find out about its side effects in adults with HD.
- Tominersen was given by injection into the lower back ('lumbar puncture' or 'intrathecal injection'), for delivery of the medicine into the fluid that surrounds the spinal cord and brain (called 'cerebrospinal fluid', 'spinal fluid' or 'CSF'). The study medicine then flows up to the brain in this fluid.
- This study included 899 persons with manifest HD in 18 countries: Argentina, Australia, Austria, Canada, Chile, Denmark, France, Germany, Italy, Japan, Netherlands, New Zealand, Poland, the Russian Federation, Spain, Switzerland, the United Kingdom and the United States.
- In the original study, 108 people were included and they received tominersen either every month or every 2 months. Based on new information from another study, the tominersen dosing schedule was changed to either every 2 months or every 4 months, and new people were included in the study.
- In the updated study, after the dosing schedule was changed, 791 people were given either tominersen once every 2 months or once every 4 months, or a placebo once every 2 months. It was decided randomly which treatment each person would receive, and how often.
- Following a recommendation in March 2021 from the independent data monitoring committee (iDMC), dosing in GENERATION HD1 was halted. The recommendation was based on an overall assessment that weighed the benefits and risks of tominersen treatment.
- To judge the efficacy of tominersen, changes in composite Unified Huntington's Disease Rating Scale (cUHDRS) and Total Functional Capacity (TFC) scores were measured. The results that have been reported here are up until Week 69 (15 months).
- The researchers found that the people in the group receiving tominersen every 2 months had worse disease outcomes compared with those in the placebo group. The group that received tominersen every 4 months had outcomes comparable to the placebo group.
- Around 1 in 5 people (48 out of 260 people) in the group given tominersen every 2 months had serious side effects, compared with around 1 in 10 people (25 out of 261 people) in the group given tominersen every 4 months and around 1 in 10 people (34 out of 260 people) in the placebo group. This means that side effects or serious side effects might not have been caused by tominersen.

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.
Efficacy means how well a drug works.
An independent data monitoring committee (iDMC) is a committee of neutral, independent experts who review the study data every 4–6 months to ensure participant safety.
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.

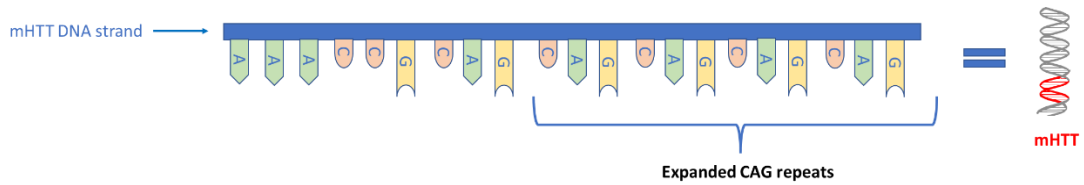
A placebo is a substance that looks the same as a medicine but does not contain any active ingredient. It is a 'dummy' treatment that has no known physical effect on the body.
Side effects are medical problems (such as feeling dizzy) that happen during the study. This may include side effects that are not be caused by the study medicine.
Total Functional Capacity (TFC) 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.

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 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 compared with a 'placebo'.

- The placebo looked the same as tominersen but did not contain any active substance. This means it had no medicine-related effect on the body.
- Researchers compared tominersen with a placebo so they could show which benefits or side effects are actually caused by the medicine.

What did researchers want to find out?

- A previous study showed that tominersen can lower mHTT protein in persons with HD and prompted the launch of this study.
- In this study, researchers wanted to investigate how effective and how safe tominersen was in persons with manifest HD.
- Researchers also wanted to find out if there was a difference between the safety or the effectiveness of tominersen when people were given tominersen every 2 months versus every 4 months.

The main question that researchers wanted to answer was:

1. Can tominersen slow the speed at which symptoms worsen in persons with HD, by measuring their movements, functional abilities and thinking abilities using a common overall HD rating scale (cUHDRS or TFC)?

Other questions that researchers wanted to answer included:

2. Can tominersen slow the speed at which HD worsens in people by looking at separate measurements of movement (Total Motor Score [TMS]), thinking (Symbol Digit Modalities Test [SDMT], Stroop Word Reading [SWR]) and overall symptoms (Clinical Global Impression-Severity [CGI-S])?
3. How does tominersen change the amount of unwanted mHTT protein levels in the spinal fluid?
4. How does tominersen change the amount of neurofilament light protein (NfL) levels in the spinal fluid?

5. Did tominersen cause any changes in the size of the brain's ventricles?

Clinical Global Impression-Severity (CGI-S) is a scale used by clinicians to rate how severe a person's symptoms are overall.
Neurofilament light protein (NfL) is a type of protein that is found in brain cells and neurons that plays a key role in cell structure and sending signals through the nervous system.
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.
Total Motor Score (TMS) is a test that measures a person's movements.
Ventricles are the spaces in the brain that are filled with spinal fluid.

What kind of study was this?

This study was a Phase 3 study. In this Phase 3 study, a larger number of persons with HD either received tominersen or a placebo. This was to find out whether tominersen can slow the speed at which HD worsens, and to find out about the side effects of tominersen. It can then be decided whether the treatment can be approved for persons with HD.

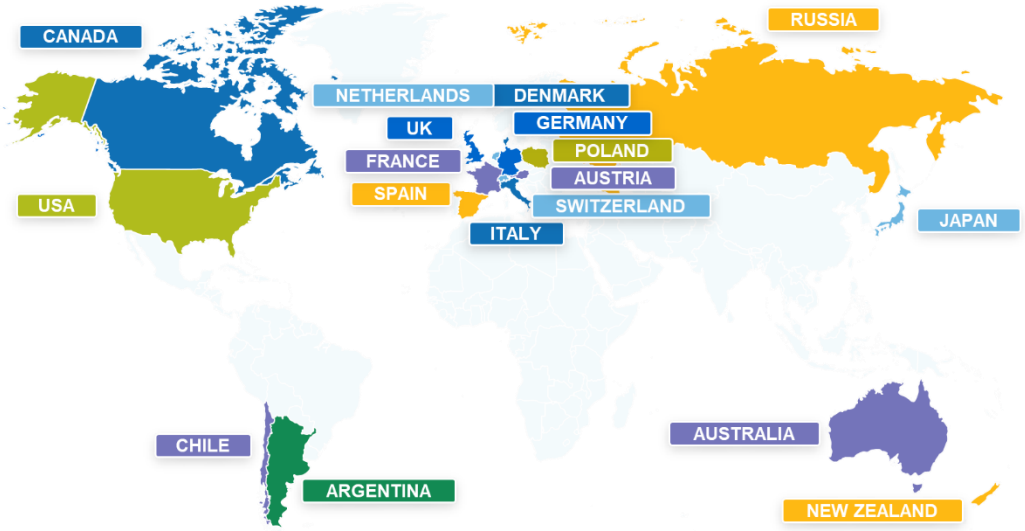
The study was 'randomised'. This means that it was randomly decided by a computer whether people were given tominersen every 2 months or every 4 months. Randomly choosing how often people would receive the medicine makes it more likely that the types of people in both groups (for example, people of different ages or ethnicities) 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.

A Phase 3 study looks at how effective and safe a new treatment is in a larger number of individuals and compares the treatment with those that are already available or with a placebo.

When and where did the study take place?

Under the original protocol, the study started in January 2019, however, due to some results from a different study, the researchers decided to change the protocol and updated the design of the study with a new tominersen dosing schedule. Under the amended protocol, this study started in July 2019 and continued until May 2022 (last patient last visit), even though dosing was stopped early in March 2021. This summary includes the results up until March 2021, when dosing was stopped early following a recommendation from the iDMC. The recommendation was based on an overall assessment that weighed the benefits and risks of tominersen treatment. This summary was written after the study had ended.

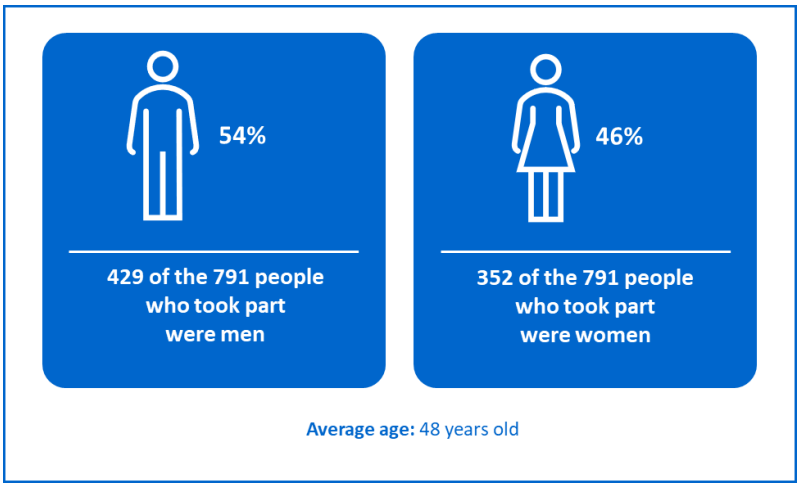
The study took place at 97 study centres across 18 countries. The following map shows the countries where this study took place.



2. Who took part in this study?

Under the original protocol, 108 persons with manifest HD participated in the study, and under the amended protocol, 791 persons with manifest HD participated. In total, 899 persons with manifest HD took part. However, 10 people did not receive any treatment due to various reasons.

More information on the people who participated is given below.



People could take part in the study if they:	People could not take part in the study if they:
Had HD	Had any serious medical conditions (other than HD)
Were between 25 and 65 years of age	Had any infections that required antibiotics
Were able to walk and read	Ever had a migraine diagnosis
	Were pregnant or breastfeeding, or intending to become pregnant during the study or within 5 months after the last dose of the medicine

3. What happened during the study?

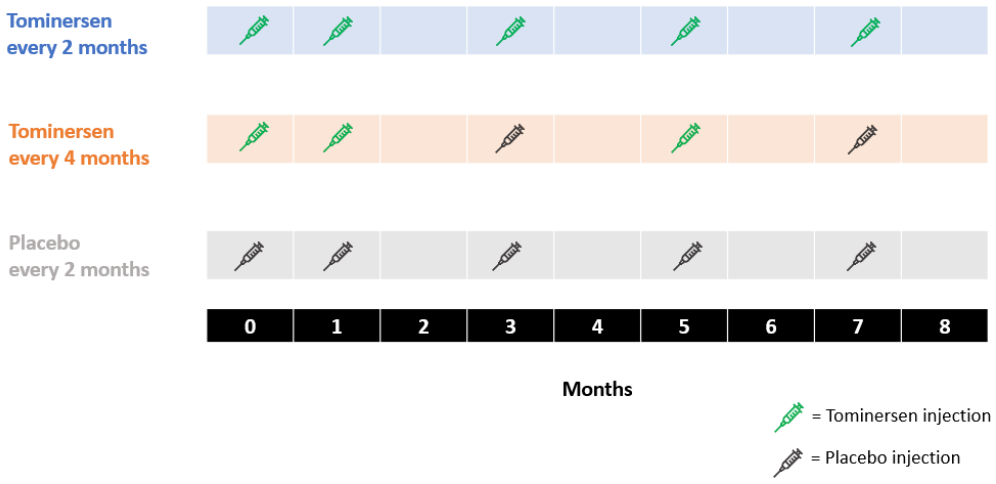
In the original study, 108 people were included and they received tominersen either every month or every 2 months. Based on new information from another study, the tominersen dosing schedule was changed to either every 2 months or every 4 months, and new people were included in the study.

In the updated study, 781 people received tominersen. People were selected by chance to receive tominersen every 2 months or every 4 months.

The treatment groups were:

- **tominersen 120 mg every 2 months**
- **tominersen 120 mg every 4 months**
- **placebo every 2 months.**

Note: At the start of the study, people in both tominersen treatment groups received their first dose of tominersen followed by the second dose after a month. People who received tominersen every 4 months also received a placebo injection every 2 months.

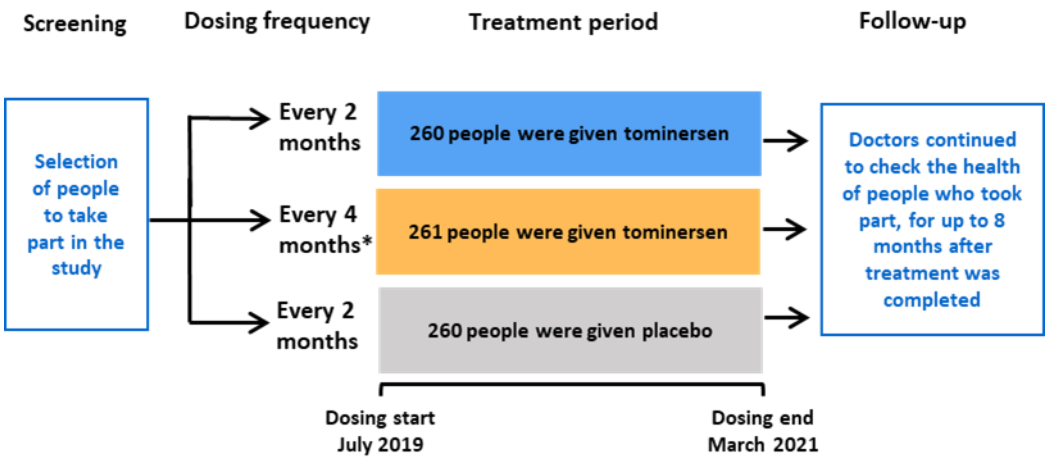


Note: This figure represents the first 8 months of dosing only.

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

It was originally planned that people in this study would receive tominersen or a placebo for approximately 26 months. Due to the study ending early, approximately 70% of people received tominersen or a placebo for an average of 69 weeks (15 months).

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



* This treatment group received a placebo injection every 2 months.

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?").

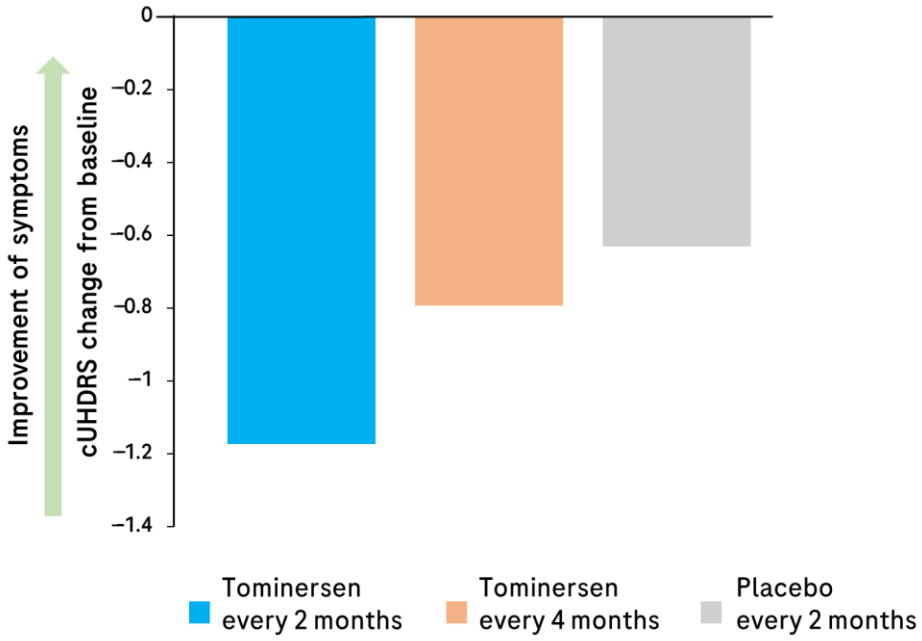
Question 1: Can tominersen slow the speed at which HD worsens in persons with HD, by measuring their movements and thinking abilities using a common overall HD rating scale (cUHDRS or TFC)?

Researchers wanted to find out what effect tominersen had on the cUHDRS or TFC scores.

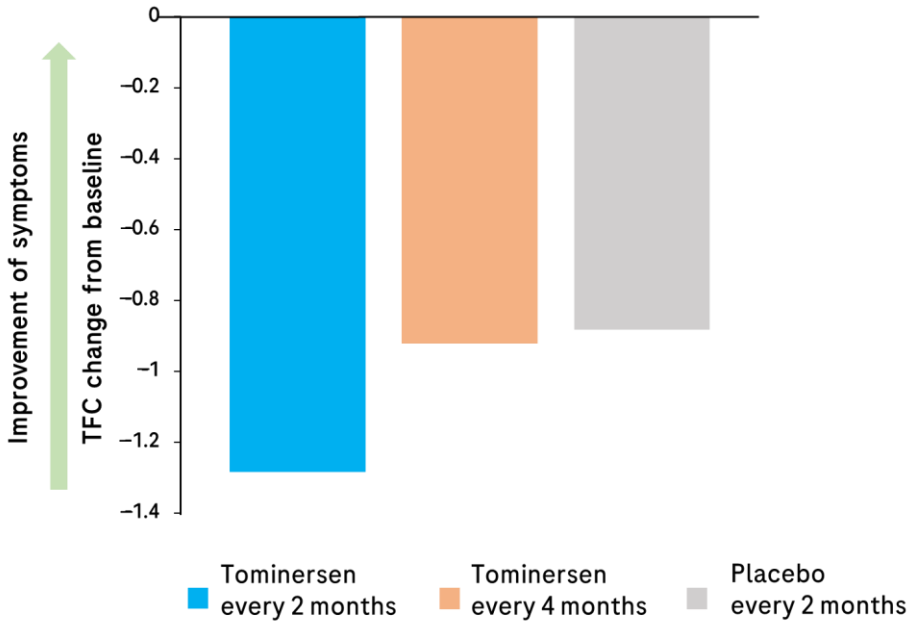
The main finding was that, after 69 weeks, the group receiving tominersen every 2 months did not have any benefits compared with the placebo group. It actually seemed like those people were doing worse than the people in the placebo group. Those receiving tominersen every 4 months had similar results to those who received a placebo.

- The cUHDRS and TFC scores for the group receiving tominersen every 2 months were worse than those in the placebo group after 69 weeks.
- The cUHDRS and TFC scores for the group receiving tominersen every 4 months were similar to those in the placebo group after 69 weeks.

cUHDRS score at Week 69 in all treatment groups



TFC score at Week 69 in all treatment groups



Question 2: Can tominersen slow the speed at which HD worsens by looking at separate measurements of movement (TMS), thinking (SDMT, SWR) and overall symptoms (CGI-S)?

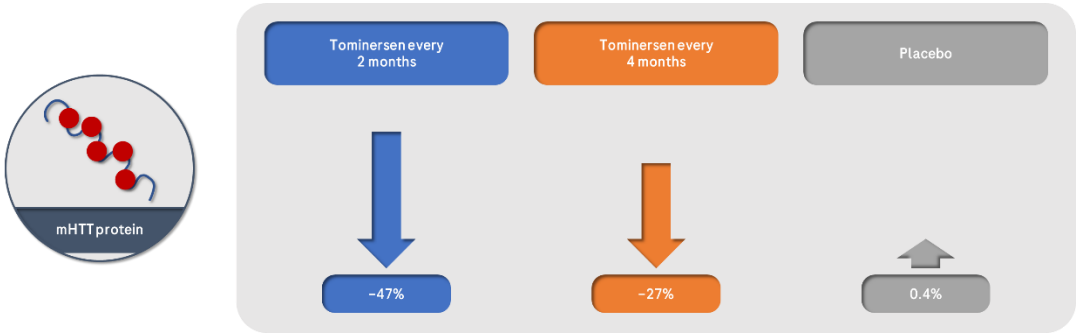
Researchers wanted to find out what effect tominersen had on the TMS, SDMT, SWR and CGI-S scores at Week 69.

- The SDMT and SWR scores for the group receiving tominersen every 2 months were worse than the placebo group. This means that the group who received tominersen every 2 months, on average, performed worse than the placebo group on the measurement scales for their thinking and their ability to process information.
- The TMS scores for the group receiving tominersen every 2 months were similar to the placebo group. This means that the group who received tominersen every 2 months had similar scores to the placebo group on the measurement scale for their ability to move.
- The CGI-S scores for the group receiving tominersen every 2 months were similar to the placebo group. This means that the group who received tominersen every 2 months had similar scores to the placebo group on the overall disease progression measurement scale.
- The TMS, SDMT, SWR and CGI-S scores for the group receiving tominersen every 4 months were similar to the placebo group. This means that the group receiving tominersen every 4 months had similar scores to the placebo group on the measurement scales for their ability to move, think, and process information, and their overall disease progression.

Question 3: How does tominersen change the amount of unwanted mHTT protein levels in the spinal fluid?

Tominersen was designed to reduce how much mHTT protein is 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 tominersen every 2 months or every 4 months, or a placebo after 69 weeks.

- At Week 69, the mHTT protein levels decreased by 47% in the group receiving tominersen every 2 months, 27% in the group receiving tominersen every 4 months and increased by 0.4% in the placebo group.

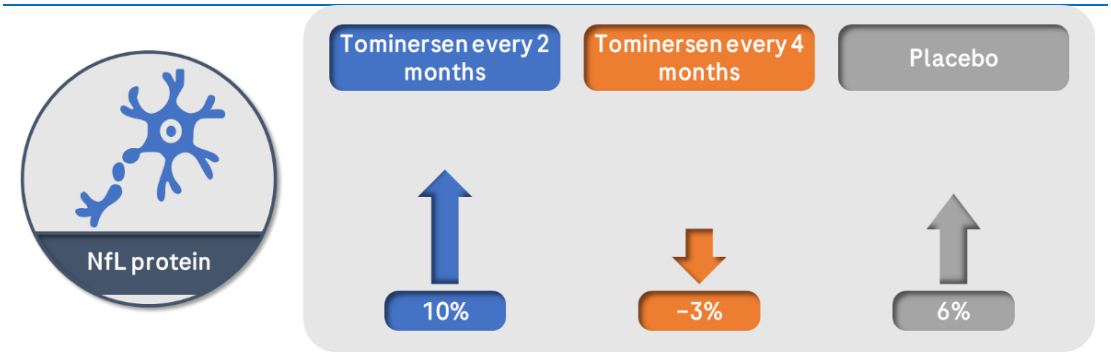


Note: Arrows pointing downwards represent a decrease in mHTT protein levels. The arrow pointing upwards represents an increase in mHTT protein levels.

Question 4: How does tominersen change the amount of NfL protein levels in the spinal fluid?

Increased levels of NfL protein show that there has been an injury to the brain's neurons which may reflect damage to the brain. The researchers wanted to find out what effect tominersen had on the NfL protein at Week 69.

- At Week 69, the NfL protein levels in the spinal fluid increased by 10% in the group receiving tominersen every 2 months, decreased by 3% in the group receiving tominersen every 4 months, and increased by 6% in the placebo group.
- Compared with the placebo group, there was an increase of 4% in the group receiving tominersen every 2 months and a decrease of 9% in the group receiving tominersen every 4 months.
- At Week 21, the NfL protein levels in the group receiving tominersen every 2 months increased but gradually returned to similar levels to the placebo group.

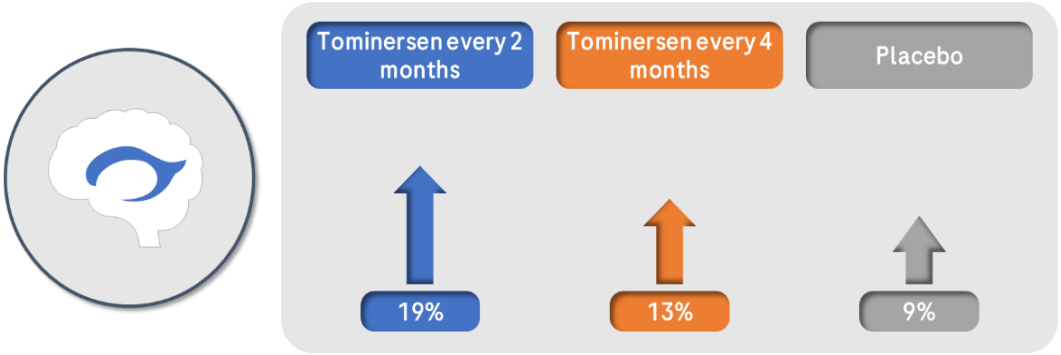


Note: Arrows pointing upwards represent an increase in NfL protein levels in the spinal fluid. The arrow pointing downwards represents a decrease in NfL protein levels.

Question 5: Did tominersen cause any changes in the size of the brain's ventricles?

Researchers wanted to find out if tominersen caused any change in the size of the brain's ventricles between the start of the study and Week 69 of the study.

- At Week 69, the ventricular volume increased by 19% in the group receiving tominersen every 2 months, 13% in the group receiving tominersen every 4 months, and 9% in the placebo group.
- Compared with the placebo group, the ventricular volume increased by 11% in the group receiving tominersen every 2 months and by 5% in the group receiving tominersen every 4 months.
- It is not clear what the cause and meaning of these increases in ventricular volume are.



Note: Arrows pointing upwards represent an increase in ventricular volume.

Ventricular volume refers to the size of the ventricles.

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 the side effects listed in this summary.
- 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.

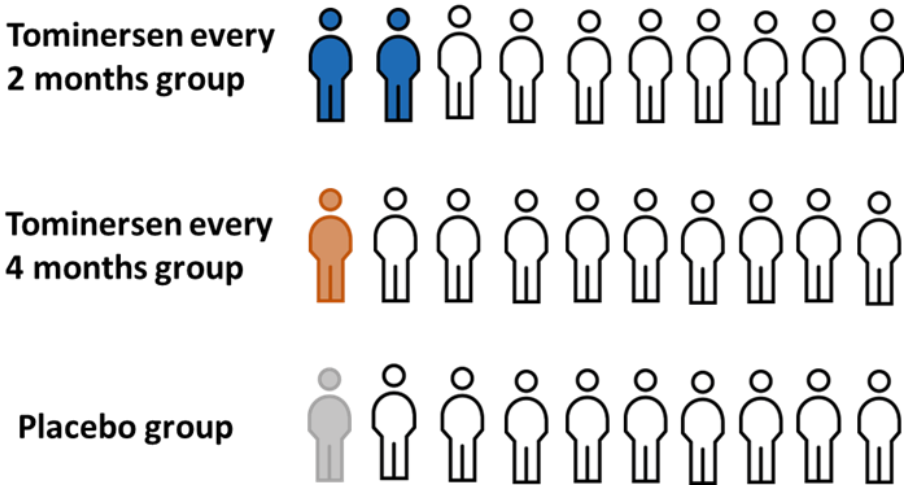
Serious side effects

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.

During this study, the number of serious side effects was greater in the group receiving tominersen every 2 months than the group receiving tominersen every 4 months and the placebo group. This included side effects that might not have been caused by tominersen. The number of people in each group who had serious side effects was:

- 48 out of 260 people (19%) in the group receiving tominersen every 2 months
- 25 out of 261 people (10%) in the group receiving tominersen every 4 months
- 34 out of 260 people (13%) in the placebo group.

Proportion of people with serious side effects



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

Serious side effects reported in this study*	**Group taking tominersen every 2 months** (260 people total)	**Group taking tominersen every 4 months** (261 people total)	**Placebo group** (260 people total)
Suicide attempt	2% (5 out of 260)	0.4% (1 out of 261)	1% (3 out of 260)
Suicidal thoughts	1% (2 out of 260)	0.4% (1 out of 261)	0.4% (1 out of 260)
Symptoms after lumbar puncture such as pain, headaches and nausea	1% (3 out of 260)	0% (0 out of 261)	0.4% (1 out of 260)
Fall	0.4% (1 out of 260)	0% (0 out of 261)	1% (2 out of 260)
Upper arm fracture	0.4% (1 out of 260)	0.4% (1 out of 261)	0.4% (1 out of 260)
Bleeding between the skull and the brain (subdural haematoma)	1% (3 out of 260)	0% (0 out of 261)	0% (0 out of 260)
Shin fracture	0.4% (1 out of 260)	0% (0 out of 261)	1% (2 out of 260)

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

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

There were some people in the study who died due to side effects that may have been related to the study medicine. These were:

- 1 out of 260 people in the group receiving tominersen every 2 months died of asphyxia.
- 2 out of 261 people in the group receiving tominersen every 4 months died due to an unknown cause and a heart attack.
- 3 out of 260 people in the placebo group died of assisted suicide, completed suicide and choking.

During the study, some people decided to stop taking the medicine because of side effects:

- 6 out of 260 people in the group receiving tominersen every 2 months
- 4 out of 261 people in the group receiving tominersen every 4 months
- 3 out of 260 people in the placebo group.

Asphyxia is a condition where the body does not get enough oxygen.

Most common side effects

Around 9 in 10 people in the tominersen and placebo groups had a side effect that was not considered serious.

The most common side effects reported in more than 5% of people are shown in the table below. These are the most common side effects across all treatment 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 taking tominersen every 2 months** (260 people total)	**Group taking tominersen every 4 months** (261 people total)	**Placebo group** (260 people total)
Fall	25% (66 out of 260)	23% (61 out of 261)	30% (77 out of 260)
Headache and feeling unwell after the lumbar puncture	10% (27 out of 260)	7% (18 out of 261)	8% (21 out of 260)
Pain from the procedure	9% (23 out of 260)	8% (21 out of 261)	9% (22 out of 260)
Bruising (contusion)	5% (14 out of 260)	5% (14 out of 261)	7% (18 out of 260)
Headache	24% (61 out of 260)	22% (57 out of 261)	23% (59 out of 260)
Dizziness	8% (20 out of 260)	8% (22 out of 261)	7% (17 out of 260)
Cold (nasopharyngitis)	14% (36 out of 260)	10% (27 out of 261)	17% (44 out of 260)
Back pain	21% (55 out of 260)	22% (57 out of 261)	19% (48 out of 260)
Pain in one or more joints of the body (arthralgia)	7% (18 out of 260)	4% (11 out of 261)	9% (22 out of 260)
Pain in extremity	7% (19 out of 260)	5% (14 out of 261)	6% (15 out of 260)
Puncture-site pain	9% (23 out of 260)	5% (13 out of 261)	9% (24 out of 260)
Diarrhoea	7% (17 out of 260)	6% (15 out of 261)	7% (19 out of 260)
Vomiting	5% (14 out of 260)	6% (16 out of 261)	6% (16 out of 260)
Nausea	5% (12 out of 260)	5% (13 out of 261)	6% (15 out of 260)

* If 5% (1 in 20) or more people experienced that side effect.

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 791 persons with manifest HD. These results helped researchers learn more about the efficacy and safety of tominersen in HD.

This study showed that 120 mg of tominersen given every 2 or 4 months was not effective at slowing disease progression in this group of persons with HD. In this study, people were given tominersen either every 2 months or every 4 months, or a placebo. Overall, the results showed that the people receiving tominersen every 2 months had worse disease outcomes compared with those receiving a placebo. People who received tominersen every 4 months had outcomes comparable to those who received a placebo.

There were no new safety concerns raised. Around 1 in 5 people (48 out of 260 people) in the group given tominersen every 2 months had serious side effects compared with around 1 in 10 people (25 out of 261 people) in the group given tominersen every 4 months, and around 1 in 10 people (34 out of 260 people) in the placebo group.

The most common side effects across all treatment groups were: fall, headache and feeling unwell after the lumbar puncture; pain from the injection procedure; bruising (contusion), headache; dizziness; cold (nasopharyngitis); back pain; pain in one or more joints of the body (arthralgia); pain in extremity; puncture-site pain; diarrhoea; vomiting; and nausea.

Overall, this study did not reach its goal of slowing the worsening of HD. Nevertheless, the researchers wanted to know whether tominersen might have been helpful for any of the people involved in the study. To answer this question, after the study had taken place, the researchers looked at the data further; this is called a *'post hoc'* analysis. The researchers split the data right down the middle, based on the people's age (higher or lower than 48 years) and CAG-age product (CAP) score (high CAP score vs. low CAP score; 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 HD gene). The researchers then divided the data into four different groups known as 'subgroups'. These were: low age/low CAP, low age/high CAP, high age/low CAP, and high age/high CAP.

The results from the *post hoc* analysis showed that of the people receiving tominersen every 4 months, those in the **low-age and low-CAP subgroup might have had some benefit from tominersen.** Their cUHDRS and TFC scores were slightly better compared with the group that received placebo.

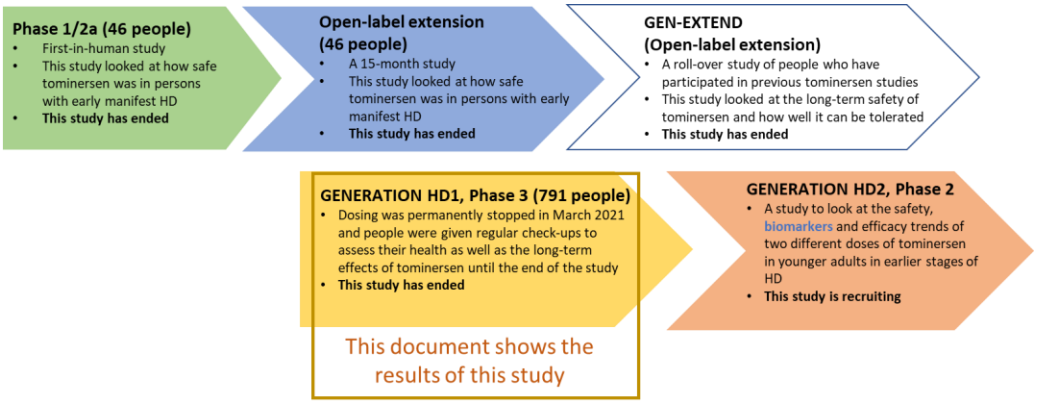
Importantly, *post hoc* analyses are conducted after data have been seen, which means that those findings are not definitive and could just be a chance finding and therefore need to be confirmed. Results from this study have prompted the researchers to look further into the effects of tominersen in younger adults in earlier stages of HD.

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 what 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.

7. Are there plans for other studies?

While this was a Phase 3 study that looked at how effective and how safe tominersen was in persons with manifest HD, **the findings from this study have led the researchers to investigate 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. 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/results/NCT03761849
  https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-002987-14/results
  https://forpatients.roche.com/en/trials/neurodegenerative-disorder/hd/a-study-to-evaluate-the-efficacy-and-safety-of-intrathe-26435.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

- 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/a-study-to-evaluate-the-efficacy-and-safety-of-intrathe-26435.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: “A Study to Evaluate the Efficacy and Safety of Intrathecally Administered RO7234292 (RG6042) in Participants With Manifest Huntington’s Disease”.

- This study is known as ‘GENERATION HD1’.
- The protocol number for this study is: BN40423.
- The ClinicalTrials.gov identifier for this study is: NCT03761849.
- The EudraCT number for this study is: 2018-002987-14.

Glossary

- Asphyxia is a condition where the body does not get enough oxygen.
- Biomarkers are signs or substances in the body that tell us about a disease process.
- 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-Severity (CGI-S) is a scale used by clinicians to rate how severe a person's symptoms are 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.
- Efficacy means how well a drug works.
- Independent data monitoring committee (iDMC) is a committee of neutral, independent experts who review the study data every 4–6 months to ensure participant safety.
- 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.
- Neurofilament light protein (NfL) is a type of protein that is found in brain cells and neurons that plays a key role in cell structure and sending signals through the nervous system.
- Phase 3 study looks at how effective and safe a new treatment is in a larger number of individuals and compares the treatment with those that are already available or with 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 whether 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 ability.

- 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.
- Ventricles are the spaces in the brain that are filled with spinal fluid.
- Ventricular volume refers to the size of the ventricles.