Summary of Clinical Trial Results

A study measuring mutant huntingtin protein in the spinal fluid of persons with Huntington's disease

See the end of the summary for the full title of the study.

About this summary

This is a summary of the results of a clinical trial (called a 'study' in this document) – written for:

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

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

The study started in December 2018 and finished in May 2021. This summary was written after the study ended.

No single study can tell us everything about a particular disease. 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 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.

Overview of the study and key results

- This HD Natural History Study (HD NHS) was done to better understand the role of mutant huntingtin (mHTT) protein in the natural progression of HD, including how levels of mHTT protein change over time without any drug treatment, in persons with early manifest HD.
- A natural history study is a study that follows a group of people with a particular disease over time – in this case, HD. No investigational drug was given.
- In this 15-month study, 95 persons with early manifest HD from Canada, Germany, the United Kingdom and the United States took part.
- Samples of the fluid that surrounds the spinal cord and brain (called 'cerebrospinal fluid', 'spinal fluid' or 'CSF') were taken by inserting a needle into the lower back ('lumbar puncture') at the beginning of the study, and after 3, 9 and 15 months. No intrathecal injections were performed and nothing was inserted back into the spinal fluid.
- Researchers were unable to determine the levels of mHTT protein at the start of the study (called 'baseline levels') and the levels of mHTT protein in some of the samples that were collected during the 15-month period because of sample stability. This meant that the main research question of the study could not be answered.
- The study found changes in the composite Unified Huntington's Disease Rating Scale (cUHDRS) indicating a slight decline in movement, the ability to think or process information and in the ability to perform daily tasks, all indicating disease progression.
- Brain magnetic resonance imaging (MRI) scans showed an increase in the size of the brain's ventricles.
- Two people were excluded from the analysis because they had stopped taking part in the study before spinal fluid samples could be collected.
- Of the 93 people whose data were analysed, 40 people experienced at least one side effect related to the lumbar puncture procedure.
- No one in this study had a serious side effect.

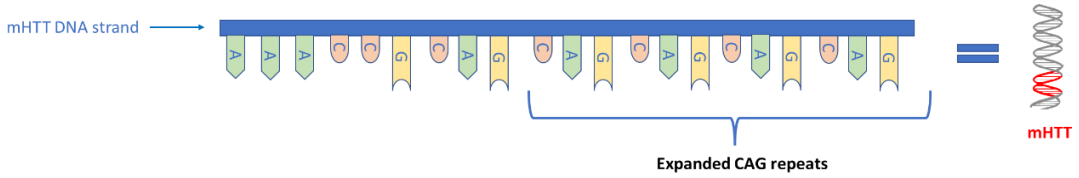
The composite Unified Huntington's Disease Rating Scale (cUHDRS) is a rating scale that measures three things: movement, ability to process information, and ability to perform daily activities. It can also be used to measure the progression of HD.
Early manifest HD refers to an earlier stage of HD, where a person has clear motor (movement) symptoms, but is still able to drive, handle finances and work independently.
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.
Magnetic resonance imaging (MRI) is a method used to scan the brain and spinal cord to see their structures.
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.
Sample stability is when a sample keeps its ability to be used for testing when it is stored.
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.
Ventricles are the spaces in the brain that are filled with spinal fluid.

1. General information about this study

Why was this study done?

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

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



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

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

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

One way of understanding the stage of HD that a person is at is to measure the amount of mHTT protein in the spinal fluid.

This study investigated whether mHTT protein, along with other proteins associated with HD, could be used to predict disease progression in persons with HD. It is hoped that by identifying a change in mHTT protein levels in the spinal fluid of persons with HD, doctors can predict the course of disease and take measures to treat people at an earlier stage of the disease.

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 did researchers want to find out?

The main questions that researchers wanted to answer were:

1. Can the amount of mHTT protein in the spinal fluid at the start of the study predict how much a person's disease will worsen over the course of the study?
2. How much did the disease progress over the course of the study, as measured by people's movements, functional abilities and thinking abilities?
3. How much did the amount of other proteins, such as tau, neurofilament light protein (NfL) and YKL-40, change in the spinal fluid over the 15 months of the study?
4. Was there a change in the size of the brain's ventricles between the start of the study and 3, 9 and 15 months into the study?

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.
Tau is a protein that is mainly found in brain cells and helps stabilise and provide structure to the cells. When tau proteins become mutated, they disrupt the normal function of cells.
YKL-40 is a protein that is found in various cells, such as brain cells and immune cells. It plays a key role in inflammation and cell structure damage. Increased levels of YKL-40 protein may be a sign of certain diseases, including HD.

What kind of study was this?

This study was an 'observational study', meaning researchers observed people in the study who were not taking a study drug.

This study was a 'longitudinal' study. This means the researchers observed and collected data such as cUHDRS scores, MRI scans, and protein measurements over 15 months at specific time points; in this case 3, 9, and 15 months. This type of study allows researchers to see if there is a relationship between two or more different measurable factors, for example protein levels and changes to the brain structure.

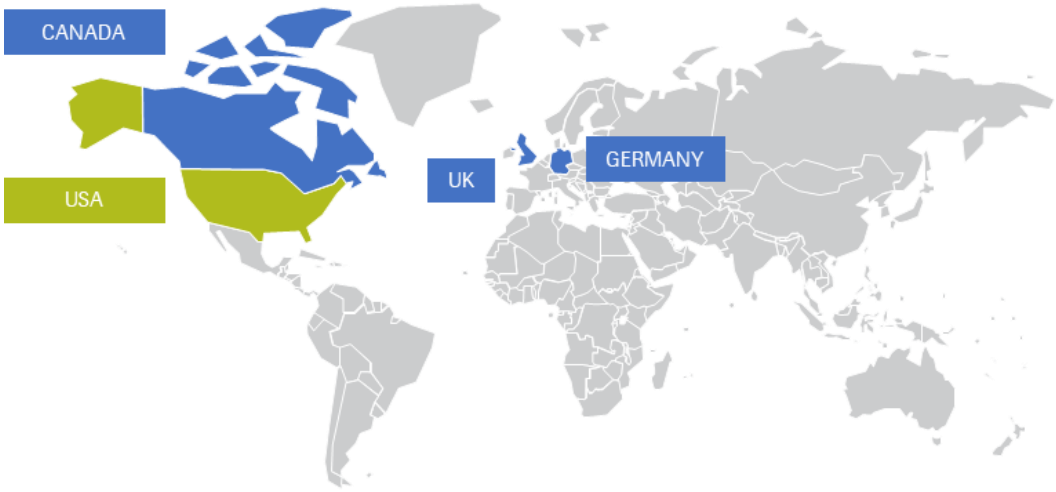
This study was a 'prospective' study. This means that the study population was defined at the beginning of the study, and the population was followed over time.

This was a 'natural history study', which is a study that follows a group of people with a particular disease over time, who are not receiving any treatment.

When and where did the study take place?

The study started in December 2018 and finished in May 2021. This summary was written after the study had ended.

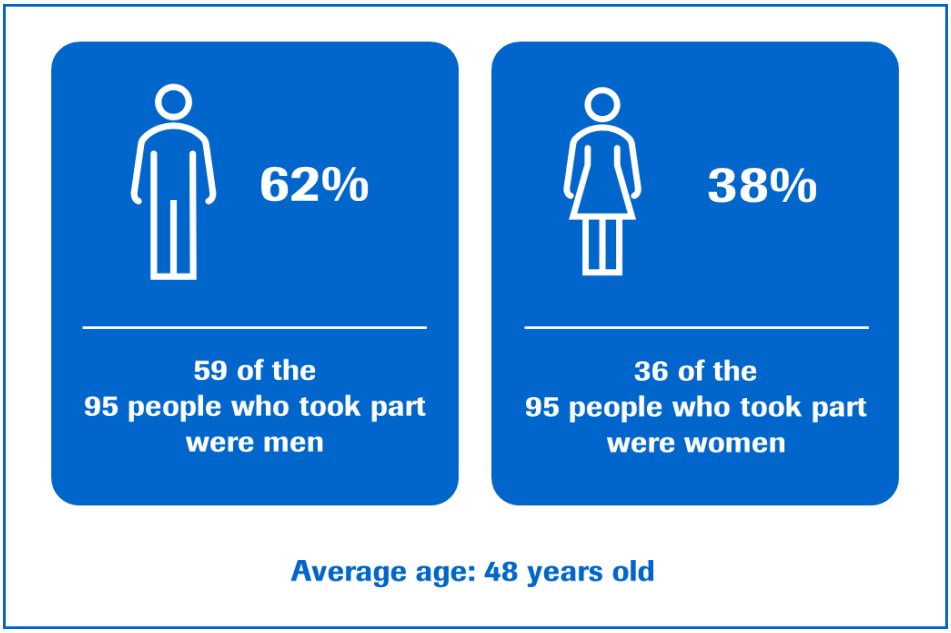
This study took place at 15 sites across four countries: Canada, Germany, the United Kingdom and the United States. The following map shows the countries where this study took place.



2. Who took part in this study?

Ninety-five persons with early manifest HD took part in the study. Two people were excluded from the analysis because they had stopped taking part in the study before spinal fluid samples could be collected.

The youngest person was 27 years old, and the eldest person was 65 years old. 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 early manifest HD (Stage 1 or 2)	Had a history of attempted suicide or suicidal ideation*
Were between 25 and 65 years of age	Had active psychosis, confused state or violent behaviour
Had 36 or more CAG repeats in the huntingtin gene	Had a condition that affected tasks that required pen and paper or a smartphone

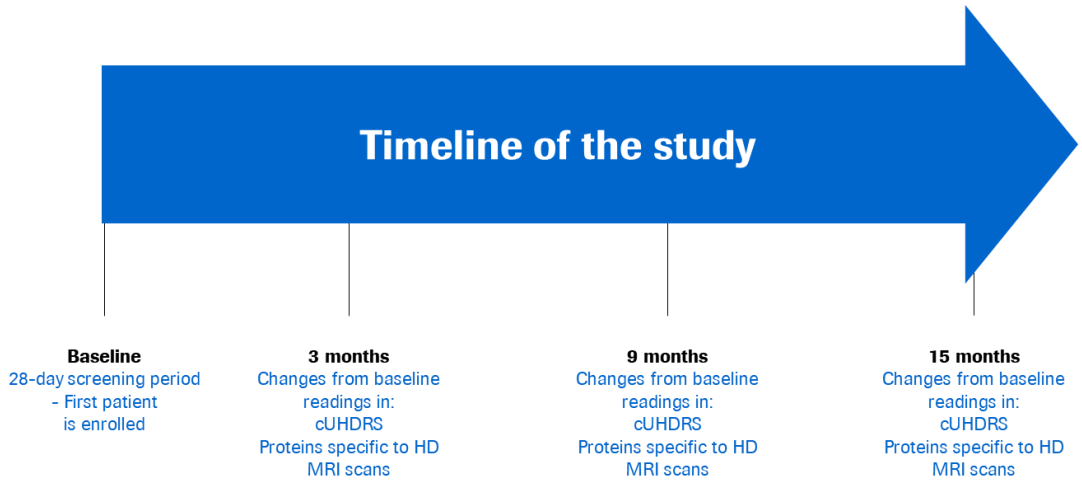
* Was defined as active suicidal ideation that required hospital visit(s) and/or a change in the level of care within 12 months prior to screening for the study.

Psychosis is a mental health condition that causes people to lose touch with reality.

3. What happened during the study?

All people had spinal fluid samples collected by lumbar puncture (no intrathecal injection was performed and nothing was replaced back into the spinal fluid) and MRI scans taken at the start of the study; these were referred to as 'baseline readings'.

People then had additional spinal fluid samples taken at specified time points across 15 months to measure mHTT protein as well as other proteins specific to HD. MRI scans and cUHDRS scores were also assessed over the 15-month period.



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: Can the amount of mHTT protein in the spinal fluid at the start of the study predict how much a person's disease will worsen over the course of the study?

Researchers wanted to measure mHTT protein levels at the start of the study (baseline) and at 3, 9 and 15 months.

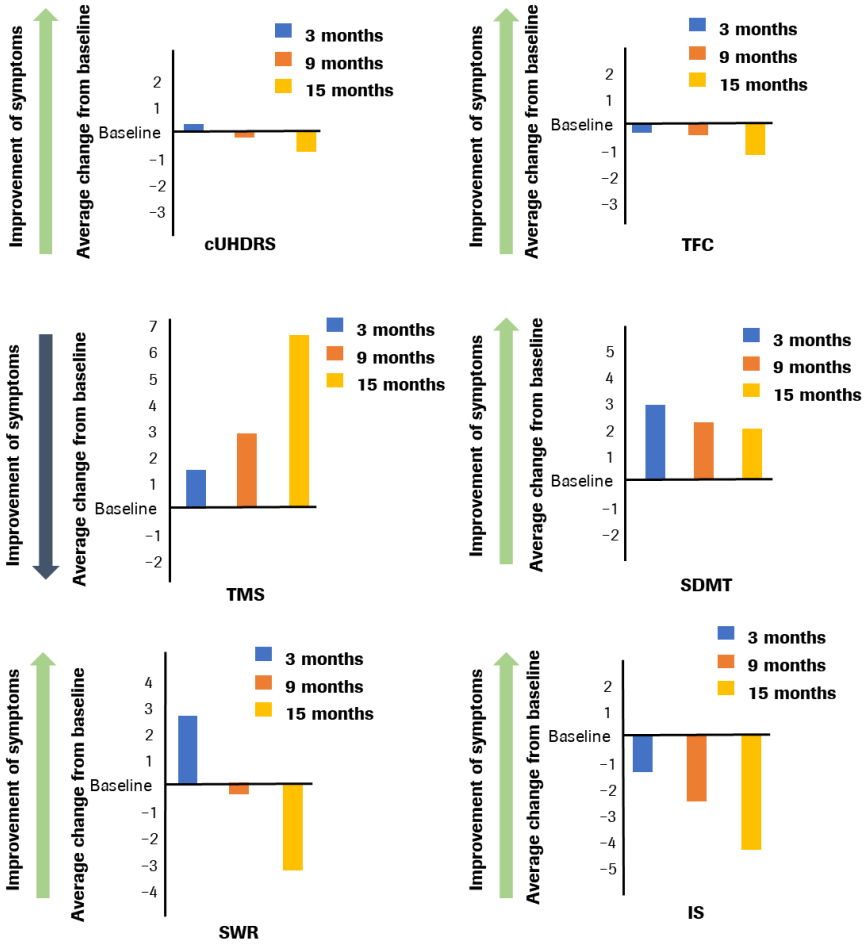
Researchers were unable to determine baseline levels of mHTT protein and the levels of mHTT protein in some of the spinal fluid samples that were collected during the 15-month period because of sample stability. This meant that the samples could not be used to answer this research question.

Question 2: How much did the disease progress over 15 months, as measured by people's movements, functional abilities and thinking abilities?

Researchers looked at cUHDRS, Total Functional Capacity (TFC), Total Motor Score (TMS), Symbol Digit Modalities Test (SDMT), Stroop Word Reading (SWR) and an Independence Scale (IS) at baseline and at 3, 9, and 15 months.

- The average change in cUHDRS score over the 15 months suggests a slight worsening in people's ability to move, think and function, compared with baseline.

Independence Scale (IS) is a test that measures how independent a person is. This test determines whether a person may need help performing a task.
Symbol Digit Modalities Test (SDMT) is a test that measures a person's concentration and decision-making ability.
Stroop Word Reading (SWR) is a test that measures how long a person takes to read a set number of words.
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.
Total Motor Score (TMS) is a test that measures a person's movement.

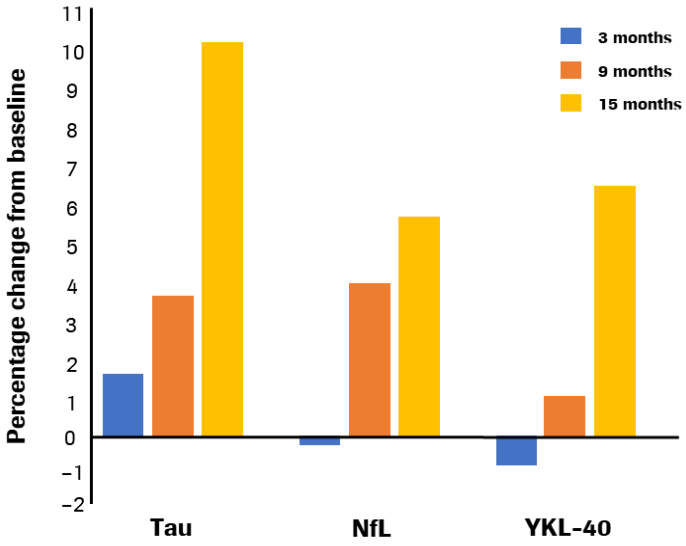


Each of these tests uses a different score to measure change, and each Y-axis represents the average change in the score at 3, 9 and 15 months.

Question 3: How much did the amount of other proteins, such as tau, NfL and YKL-40, change in the spinal fluid over the 15 months of the study?

Researchers looked at baseline levels of tau, NfL and YKL-40 in the spinal fluid, at 3, 9 and 15 months.

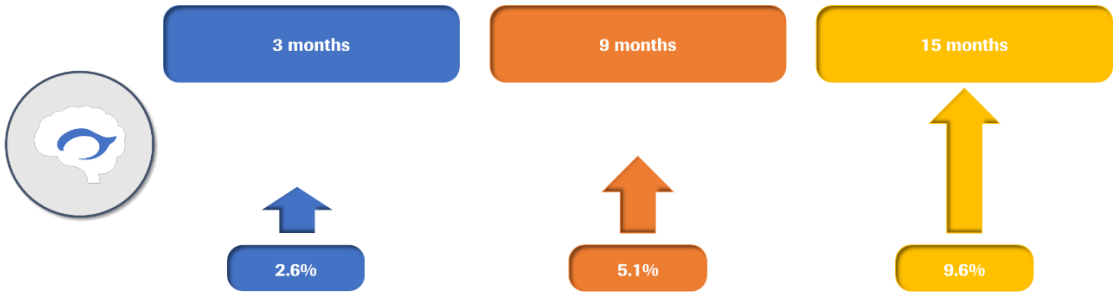
- There was an increase from baseline in spinal fluid tau, spinal fluid NfL and spinal fluid YKL-40, up to 15 months, consistent with the progression of HD.



Question 4: Was there a change in the size of the brain's ventricles between the start of the study and 3, 9 and 15 months into the study?

Researchers looked at changes in the size of the brain's ventricles over 15 months and compared these with the baseline data.

- Researchers found that the ventricular volume increased at each time point compared with baseline.
- There is no correlation between change in ventricular volume and clinical endpoints.



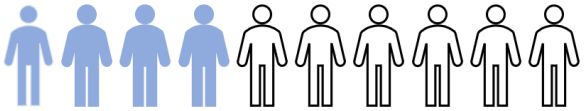
Ventricular volume refers to the size of the ventricles.

5. What were the side effects?

Side effects are medical problems (such as feeling dizzy) that happen during the study. They are described in this summary because the study doctor believes the side effects were related to the lumbar puncture procedure.

- They are described in this summary because they were the most frequently reported in the study.
- Not all the people in this study had all the side effects. 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.
- 40 out of 93 people (43%) experienced at least one side effect related to the lumbar puncture.

Proportion of people with at least one lumbar puncture-related side effect in this study

Persons with HD  **43%**

Lumbar puncture procedure-associated side effect reported in this study*	**Number of people with the side effect** (93 people total)
Post-lumbar puncture syndrome	15.1% (14 out of 93)
Pain from the procedure	7.5% (7 out of 93)
Bruising (contusion) after the lumbar puncture	2.2% (2 out of 93)
Dizziness after the lumbar puncture	2.2% (2 out of 93)
Headache after the lumbar puncture	2.2% (2 out of 93)
Headache	9.7% (9 out of 93)
Tingling feeling (paraesthesia)	3.2% (3 out of 93)
Puncture-site pain	5.4% (5 out of 93)
Injection-site pain	2.2% (2 out of 93)
Back pain	3.2% (3 out of 93)

* A side effect was included if it was reported in more than one person.

- No serious side effects or deaths were reported during the study (a side effect is considered 'serious' if it is life-threatening, needs hospital care, causes long-lasting problems or death, or is considered medically important).

6. How has this study helped research?

This study aimed to investigate how baseline mHTT protein and HD-related protein levels change as HD progresses over 15 months.

Researchers were unable to determine baseline levels of mHTT protein and the levels of mHTT protein in some of the samples that were collected during the 15-month period because of sample stability. This meant that the main research question of the study could not be answered; however, the other mHTT protein samples taken in this study may be used for future research in HD.

This study increases our understanding of the natural disease progression of HD, which could potentially help to design future clinical trials.

This study also showed that repeated lumbar punctures cause few side effects in persons with HD.

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.

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

8. Where can I find more information?

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

- This study – https://www.clinicaltrials.gov/study/NCT03664804?term=NCT03664804&rank=1 https://forpatients.roche.com/en/trials/neurodegenerative-disorder/hd/study-to-measure-cerebrospinal-fluid-mutant-huntingtin--30045.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
- GEN-EXTEND – https://www.clinicaltrials.gov/study/NCT03842969?term=NCT03842969&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/study-to-measure-cerebrospinal-fluid-mutant-huntingtin--30045.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 Multi-Site, Prospective, Longitudinal, Cohort Study measuring Cerebrospinal Fluid-Mutant Huntingtin Protein in Patients with Huntington's Disease”.

- The protocol number for this study is: BN40422.
- The ClinicalTrials.gov identifier for this study is: NCT03664804.

Glossary

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