JOHNS HOPKINS MEDICINE

Approved October 24, 2024

Information for you and your family

GENERATION HD 2

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We are targeting a possible cause of Huntington's disease

In people who are carriers for Huntington's disease (HD), even those who are asymptomatic, a protein called mutant huntingtin (mHTT) builds up in the brain, causing HD symptoms. mHTT is a toxic version of a naturally occurring protein called huntingtin and is caused by a mistake in their 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.'

Current approaches aim to reduce the symptoms caused by mHTT, rather than target the cause of mHTT itself. So we are conducting the GENERATION HD2 study to evaluate an investigational drug (not yet approved by health authorities) called tominersen.

For this study we are looking for approximately 360 participants who:

- Have a formal diagnosis of early manifest HD or who carry the abnormal huntingtin gene and are starting to show very early, subtle signs of HD, which may only be apparent during a detailed examination by a physician
- Are between 25 and 50 years old (inclusive)
- Have a CAP score of 400 to 500, inclusive (this is a research calculation based on your CAG number and age; the study team can tell you more about this measure if you have never come across it before)

Please note, a number of other criteria must also be met for an individual to be able to take part. Your study doctor will be able to discuss these with you.

In addition, participants will be asked to have someone who can act as their 'study companion' throughout the study. This person must be willing to:

- Attend visits at the study center with the participant in-person and be available for consultations over the telephone
- Complete questionnaires throughout the study
- Provide general support to your friend/relative as they participate in the study

Clinical studies help make medicine better

Clinical studies (also known as 'clinical trials') are carefully controlled scientific investigations that help find:

- Potential new medications
- New versions of medications already being used
- New uses for medications already being used

Participant safety is the top priority of every study. In fact, governments have strict rules to protect the safety and privacy of volunteers. Most studies, including the GENERATION HD2 study, have a group of neutral, independent experts, known as an Independent Data Monitoring Committee (iDMC), who regularly review the study data to ensure the safety of participants. By law, participants must be told about all the potential risks and benefits of taking part. This is called the 'informed consent' process, and the study team will tell you more if you would like to join the study.

What is tominersen, and why are we conducting this trial?

Tominersen is an investigational drug designed to reduce the production of all forms of the huntingtin protein (HTT), including mHTT, the possible cause of HD. Tominersen has been studied in five different clinical trials since 2015, including a large Phase III study called GENERATION HD1 that tested two different doses of tominersen in adults with HD.

Unfortunately, the GENERATION HD1 study did not produce the results we hoped for. Overall results showed that participants receiving tominersen every 8 weeks had worse outcomes compared to those who did not get the drug (placebo). And participants receiving tominersen every 16 weeks had outcomes comparable to placebo. Following a recommendation from the iDMC, dosing in GENERATION HD1 was halted. The recommendation was based on an overall assessment that weighed the benefits and risks of tominersen treatment.

But, after the GENERATION HD1 dosing was stopped, exploratory analyses suggested that a subgroup of the younger adult participants who were in earlier stages of HD, and who were receiving less frequent dosing, had favorable outcomes compared with placebo.

Because this analysis was conducted after data had been seen, they are not definitive and could represent a chance finding.

Therefore, GENERATION HD2 is designed to confirm the subgroup findings. The GENERATION HD2 study will evaluate the effectiveness and safety of tominersen in younger adult participants who are in the earlier stages of HD and will investigate lower doses than those used in the previous trial. That is why we are looking for participants – we simply would not be able to answer these important questions without the help of people with HD.

If you want to learn more about GENERATION HD1 and why we are conducting GENERATION HD2, please take a look at the tominersen information brochure that you received along with this one.

What will this study involve?

If you take part in the GENERATION HD2 study, you will be involved for a minimum of 22 months (including screening and follow-up).

Screening period (up to 1 month)

We will carry out some initial assessments to see if you are eligible to take part in the study.

Treatment period (minimum of 16 months)

Participants will randomly (by chance) be assigned to receive either:

- One of two doses of the investigational drug (2 in 3 chance)
- A placebo (1 in 3 chance)

Participants will receive a minimum of five injections via a lumbar puncture (see page 12 for more details), and clinic visits will take place approximately once every 4 months. Participants will receive a telephone call in-between each clinic visit so that we can monitor their health.

Open-label extension period

If the main study is successful, participants who have completed the blinded treatment period may be able to join an extension study to receive the investigational drug.

Follow-up period (approximately 5 months after last dose)

Participants will be asked to attend a final check-up.

Why is the treatment period longer for some participants than others?

This study has what is called a 'common close' design, meaning that everyone finishes the study at the same time. This means that the treatment period will only end when the last person recruited has completed 16 months. So, if you are the first participant, and the last participant starts 8 months later, you will be in the treatment period for 24 months (16-month treatment period plus 8-month extension). This allows us to obtain more information in a shorter time frame – helping us to further understand HD and the effects of tominersen.

What is a placebo?

A placebo looks just like the investigational drug and is given in the same way. However, it contains no active medicine. Many clinical studies (like this one) are 'placebo-controlled.'

Will I know if I am receiving a placebo?

This study is 'double-blind,' meaning you will not know what your injection contains and neither will the study team. This is really important as this knowledge can actually influence your health (a phenomenon known as the 'placebo effect') and give us biased results. But please be reassured that healthcare staff can quickly find out your treatment assignment if needed for safety reasons.

Some health checks during the clinic visits

During each clinic visit, you will have a lumbar puncture injection and several health checks so that we can monitor your health and HD status. These tests can take a few hours, so you should allow around a day for each appointment. In some cases, a visit may take place over more than 1 day. Your study companion will be needed to accompany you to some of your visits, such as the first and last visits.

Here are a few of those health checks and what they involve:

Blood samples

We will take some blood samples to check your general health along with the status of your condition.

Physical examination

We will examine your heart, ears, nose, throat, skin, and muscle function.

Neurological examination

We will check things such as your mental status, how your senses are functioning, motor function, and reflexes.

Vital signs

An examination of your pulse, temperature, blood pressure, and breathing rate.

ECG

An electrocardiogram (ECG) monitors the rhythm of your heart. To do this, small pads (called sensors) are attached to your skin. The pads peel off afterward.

MRI

A magnetic resonance imaging (MRI) scan will be taken to monitor any changes in your brain.

Questionnaires

These help us learn how HD affects your day-to-day life, and your functional and mental state. Some questionnaires will be completed by you, others by the study doctor and your study companion.

Lumbar puncture

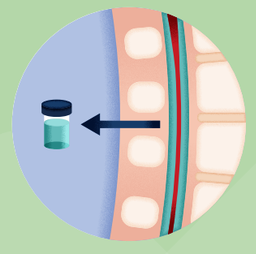
During the study, both the investigational drug and the placebo will be given as injections into the spine. To do this, we will need to carry out lumbar punctures (also known as spinal taps).

We will first give you a local anesthetic to numb the area. We will then carefully place a small hollow needle into your lower spine. A small amount of spinal fluid to measure any changes in mHTT levels will be collected. This typically takes about 15–20 minutes, but it can take longer, which does not mean that anything is wrong. With the needle still in position, the physician will replace the collection syringe with one containing the study drug or placebo. The administration takes about 90 seconds, and you should not feel anything.

Some people experience a headache after a lumbar puncture, which may last a couple of days. But the study team will advise you about how to prevent and reduce possible side effects to lower the chance of discomfort.

Lumbar punctures are routine medical procedures. In Roche tominersen studies to date, more than 10,000 procedures have been conducted.

Needle is inserted into lower spine



Cerebrospinal fluid (CSF) is collected before assigned study drug is inserted

Frequently asked questions

How else would my health be monitored?

During the study, you will receive a telephone call from your physician every 4 months, in between your clinic visits. The physician will ask you about your general health, any changes in your medication, and how you have been feeling.

Will it cost me anything to participate?

No. All study-related drugs and procedures will be provided at no cost to participants. We also offer support for you and your study companion with study-related participation, including transport and accommodation reimbursement. The study team will be more than happy to speak to you if there are financial concerns that may limit your decision to enroll and/or stay in the trial.

Is the study voluntary?

Taking part in a clinical study is a personal decision and no one has to join if they do not want to. It is also important to know that if you join a study and then change your mind, you can leave at any time without any impact on your usual healthcare.

Will I get better if I take part?

Because this study is testing an investigational drug, we cannot promise that your health will improve if you join. You may feel better, you may feel the same or you may feel worse. But please be reassured that your health will be monitored closely throughout the study.

How can I get more information about the tominersen and how the study will be conducted?

Prior to starting the trial, you would be asked to provide your 'informed consent.' To do this, the study team will provide a more in-depth document (informed consent form, ICF) and explain to you what the trial is aiming to show, any benefits and risks involved, and how taking part in the trial may affect you. Once you fully understand the trial, you can decide whether you would like to take part.

Informed consent is an ongoing process. As the trial progresses, if the trial design changes or new benefits, risks, and side effects become known, participants and companions may be required to re-consent to continue the study.

The ICF document will provide additional information on topics such as:

- The purpose, design, and length of the study
- Voluntary participation
- Potential benefits and risks, including the process if there is an unexpected injury
- Special requirements of participants (e.g., participation in other studies, use of other medicines or recreational drugs, contraception)
- Handling and confidentiality of data, medical records, laboratory samples, and genetic information

You will be asked to fully read the ICF document and ask the study team questions if any information is difficult to understand.

How could I get my individual results from GENERATION HD2?

Medical and personal results collected at the study site are included in participants' medical records and can be shared. Study investigators can discuss individual experiences and potential changes that may have been observed since the start of study enrollment, but it is important to remember that individual experiences may or may not be similar to those seen at an overall study population level.

Notes:

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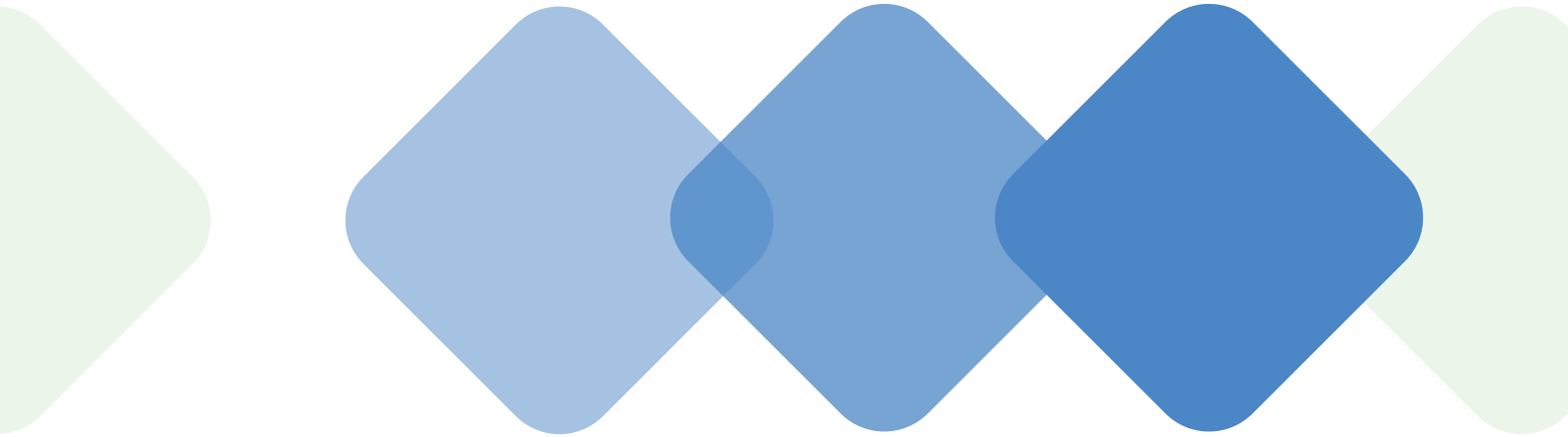
Thank you for taking time to learn about GENERATION HD2

For more information, please contact us for a no-obligation chat. And remember, although we cannot guarantee that your condition will improve, every bit of information we gather will help to improve our understanding of HD both now and in the future.



Study investigator contact details:

Etta Bernard, MPH
Sr. Research Coordinator
Johns Hopkins HD Center
410-614-7671
egoldm17@jhmi.edu

IRB00358575
PI: Jee Bang, MD, MPH