ForPatients
by Roche

Huntington Disease (HD)

A clinical trial to compare different doses of tominersen with a placebo in people with prodromal (very early subtle signs) and early manifest Huntington's disease

GENERATION HD2. A Study to Evaluate the Safety, Biomarkers, and Efficacy of Tominersen Compared With Placebo in Participants With Prodromal and Early Manifest Huntington's Disease.

Trial Status	Trial Runs In	Trial Identifier
Recruiting	15 Countries	NCT05686551 Other BN42489

The source of the below information is the publicly available website ClinicalTrials.gov. It has been summarised and edited into simpler language.

Trial Summary:

This study will evaluate the safety, biomarkers, and efficacy of tominersen compared with placebo in participants with prodromal and early manifest Huntington's Disease

Hoffmann-La Roche Sponsor	**Phase 2** Phase

NCT05686551 Other BN42489
Trial Identifiers

Eligibility Criteria:

Gender	Age	Healthy Volunteers
All	>=25 Years & <= 50 Years	No

1. Why is the GENERATION HD2 clinical trial needed?

Huntington's disease (HD) is a rare, inherited (genetic) disease that affects a person's moving, thinking and behaviour. It is a progressive disease, which means that it gets worse over time, and there is currently no way to prevent, slow or stop disease progression.

Subtle changes in thinking, mood and behaviour are very early symptoms of HD (known as 'prodromal' HD). HD is usually diagnosed when symptoms prevent a person carrying

out daily tasks. Jerky, involuntary movements of the body can make walking and eating difficult (known as ‘early manifest HD’).

A change (mutation) in a single huntingtin gene (HTT) causes HD. People who carry this gene make a toxic (mutant) version of the huntingtin protein called mHTT. mHTT builds up in the brain, which, over time, causes damage to nerves and HD symptoms.

In previous clinical trials, a drug called tominersen was shown to lower levels of toxic mHTT protein by blocking its production. It is hoped that by reducing levels of mHTT, the progression of HD can be slowed or stopped. Tominersen is an experimental drug, which means that health authorities have not approved it for the treatment of HD.

The GENERATION HD2 clinical trial aims to compare the effects, good or bad, of two different doses of tominersen against placebo to find a dose that may benefit people with prodromal (very early subtle signs of HD) or early manifest HD.

2. How does the GENERATION HD2 clinical trial work?

This clinical trial is recruiting people with a health condition called Huntington’s disease (HD). People can take part if they have prodromal (very early subtle signs of HD) or early manifest HD and have a person who can act as a ‘study companion’ throughout the trial.

People with HD who take part in this clinical trial (participants) will be given the clinical trial treatment tominersen OR a placebo every 4 months for at least 16 months and will continue to receive treatment until all clinical trial participants have completed 16 months of treatment. The clinical trial treatment will be given as an injection by lumbar puncture. This involves a needle being placed into the lower back between two lumbar bones (vertebrae), into the space (called the ‘intrathecal space’) where there is fluid that surrounds the spinal cord and brain (cerebrospinal fluid). The clinical trial treatment then flows in this fluid up to the brain. This is a common medical procedure (known as ‘intrathecal injection’) which takes about 15–20 minutes.

The clinical trial doctor will see participants (and their study companion for some visits) approximately every 4 months. These clinic visits will check how the participant responds to the treatment and any side effects (unwanted effects of a drug or medical treatment) they may have. Between clinic visits, participants will receive a telephone call from the trial doctor, who will ask about their general health, any changes in their medication, and if they have not been feeling well. Participants and their study companions will also see the clinical trial doctor 5 months after their last treatment dose at a follow-up visit. The total time of participation will be at least 22 months (including time for initial tests to ensure that participants fit certain criteria, known as ‘screening’, and the follow-up visit). Participants can stop trial treatment and leave the clinical trial at any time. After all participants have

completed at least 16 months of treatment with tominersen or placebo, researchers will check the trial results and decide if participants should have the opportunity to receive tominersen in an extension phase of the trial or not.

3. What are the main endpoints of the GENERATION HD2 clinical trial?

The main clinical trial endpoints (the main results measured in the trial to see if the drug has worked), are:

The number and seriousness of any side effects

Changes in laboratory results from the cerebrospinal fluid, including in the amount of mHTT protein

Changes in results from the brain magnetic resonance imaging (MRI) scan

Changes in function (for example, the ability to move, think and perform daily activities)

The other clinical trial endpoints include changes in the amount of an indicator of nerve damage in cerebrospinal fluid and the effects of tominersen on the immune system.

4. Who can take part in this clinical trial?

People can take part in this trial if they fit certain criteria, including if they:

Are aged 25 to 50 years (at the start of the trial)

Have a CAP score (a research calculation based on age and the number of times the mutated section within the HD gene repeats itself – known as the CAG number) of 400 to 500

Have been diagnosed with early manifest HD or are carriers of the abnormal huntingtin gene who are starting to show very early, subtle signs of HD (known as prodromal HD). This may only be clear during a detailed examination by a physician

Can tolerate giving blood, having lumbar punctures and MRIs

Have a person who can act as a ‘study companion’ throughout the trial

People may not be able to take part in this trial if they:

Are currently receiving or have had certain treatments before, including those for HD that may affect HTT levels

Have a history of gene therapy, cell transplantation, or brain surgery

Have certain other medical conditions, including a build-up of fluid in the brain (hydrocephalus), chronic migraines, certain mental health issues or certain infections or, are pregnant or breastfeeding, or are planning to become pregnant during or soon after the clinical trial.

5. What treatment will participants be given in this clinical trial?

Everyone who joins this clinical trial will be split into 3 groups randomly (by chance) and given:

Group 1: 60mg of tominersen, given as an injection by lumbar puncture (intrathecal injection) once every 4 months for 16 months

OR

Group 2: 100mg of tominersen, given as an injection by lumbar puncture (intrathecal injection) once every 4 months for 16 months

OR

Group 3: an equal amount of placebo, given as an injection by lumbar puncture (intrathecal injection) once every 4 months for 16 months

Participants will have an equal chance of being placed in any group.

This is a ‘placebo-controlled’ clinical trial, which means that one of the groups will be given a substance with no active ingredients (also known as a ‘placebo’); it looks like the drug being tested but does not contain any real medicine. Comparing results from the different groups helps the researchers know whether any changes seen result from the drug or occur by chance.

This is a double-blinded trial, which means that neither the participant nor the clinical trial doctor can choose or know the group the participant is in until the trial is over. This

approach helps to prevent bias. However, the participant's clinical trial doctor can find out which group the participant is in, if their safety is at risk.

If the extension phase of the trial is started, this will be 'open-label', which means everyone involved, including the participant and the clinical trial doctor, will know that the participant has been given tominersen. This will be given at an effective dose that caused limited side effects in the blinded (tominersen or placebo) phase of the trial.

6. Are there any risks or benefits in taking part in this clinical trial?

The safety or effectiveness of the experimental treatment may not be fully known at the time of the trial. Most trials involve some risks to the participant. However, it may not be greater than the risks related to routine medical care or the natural progression of the health condition. People who would like to participate will be told about any risks and benefits of taking part in the clinical trial, as well as any additional procedures, tests, or assessments they will be asked to undergo. All of these will be described in an informed consent document (a document that provides people with the information they need to decide to volunteer for the clinical trial).

Risks associated with the clinical trial drug

Participants may have side effects from the drug used in this clinical trial. Side effects can be mild to severe, even life-threatening, and vary from person to person. Participants will be closely monitored during the clinical trial; safety assessments will be performed regularly. People considering enrolling in the trial will be told about the known side effects of tominersen and possible side effects based on human and laboratory studies or knowledge of similar drugs. They will also be informed of any known side effects of having an intrathecal injection.

Potential benefits associated with the clinical trial

Participants' health may or may not improve from participation in the clinical trial. Still, the information collected may help other people with similar medical conditions in the future.

For more information about this clinical trial see the **For Expert** tab on the specific ForPatients page or follow this link to ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT05686551