17 April 2025

Dear Huntington's patient community leaders,

We appreciate your request for updates on our research efforts. Today we share an update on the Phase II GENERATION HD2 study (NCT05686551), which is testing the investigational drug tominersen in people with early or very subtle signs of Huntington's disease (HD).

As a reminder, GENERATION HD2 was testing two dose levels of tominersen (100mg and 60mg) against placebo, administered every 4 months via a spinal injection. Data from the clinical trial is regularly checked by an independent data monitoring committee (iDMC).

Committee Supports Study Continuation
The iDMC recently reviewed safety data and conducted a pre-planned interim analysis. The iDMC recommended that the GENERATION HD2 study continue. No concerns were raised regarding participant safety or signs of symptom worsening with either tominersen dose. Additionally, the 100mg dose was found to be more likely than the 60mg dose to result in clinical benefit. Therefore for the remainder of the study only the 100mg dose will be tested against placebo, and the 60mg dose will be discontinued. Importantly, the study is ongoing and we cannot draw final conclusions at this time.

Study Remains Blinded and Continues to Collect Data
Roche will now amend the study, and participants will be asked to consent to continue in the modified study. The modification will not change participants' clinic schedules or overall study experience. Participants previously assigned the 60mg dose will be switched to the 100mg dose; participants in the other treatment groups (100mg and placebo) will remain in their assigned groups. Treatment assignments are not known by study doctors, participants nor Roche until after the end of the study.

What Happens Next?
- Investigators have been informed and they are starting to contact study participants about the study modification and next steps.
- The study is fully recruited and expected to complete in 2026.
- The iDMC will continue reviewing study data every 4-6 months to recommend whether to continue, modify or stop the study.

We are incredibly grateful to the 301 participants and their companions enrolled in GENERATION HD2. Each study visit contributes to collecting data that helps the entire HD research community learn more about tominersen, Huntingtin-lowering strategies, and the further understanding of HD.

We thank the HD community for its ongoing support and commitment to research. Below is further information that may assist you. If you have more questions, please do not hesitate to reach out.

Sincerely,

Mai-Lise Nguyen

Global Patient Partnership, on behalf of the Roche/Genentech Huntington's team

Questions & Answers

What did the analysis results show?
The iDMC conducted the interim analysis and Roche does not have access to the data reviewed. We are modifying the GENERATION HD2 study based on the iDMC's recommendations, which were to continue the study and to switch participants on the 60mg dose to the 100mg dose.

Does this mean that the 60mg dose did not work or was not safe?
The iDMC reviewed available trial data and did not raise any concerns regarding participant safety or signs of symptoms worsening with either tominersen dose. Roche is changing the GENERATION HD2 study design to only test the 100mg dose against placebo for the remainder of the study. This change is based on the iDMC's recommendation that the 100mg dose was more likely than the 60mg dose to result in clinical benefit for people with HD.

Does this mean that the 100mg dose works?
The iDMC recommended that the 100mg dose should continue to be tested in the study, based on their review of interim data. The GENERATION HD2 study is ongoing and we cannot draw final conclusions at this time. The study is expected to complete in 2026.

Will study participants know which dose they were receiving? What does "blinding" mean?
From the start of the study, participants, study teams and Roche do not know treatment assignments. This is called "blinding" and it is done to avoid bias in how the study is run and results are obtained. When the study is "unblinded" after the end of the study, it will be possible for participants to learn which treatment group they were assigned - tominersen (including the dose) or placebo.

What happens now for study participants?
All participants will be contacted by their study sites and asked to consent to continue in the modified study. There will be no change to any participants' overall study experience or schedules. After consent, the study pharmacy will switch the dosing of participants previously assigned the 60mg dose to the 100mg dose. There will be no change for participants previously assigned to the 100mg and placebo groups. Treatment assignments remain "blinded" to participants, sites and Roche.

What is an iDMC?
An independent Data Monitoring Committee (iDMC) is a group of experts external to a study, and independent of Roche, who periodically review accumulating data from an ongoing clinical trial. The committee monitors the safety of participants and the balance of benefits and risks of a clinical trial. Based on the reviews of data, an iDMC makes recommendations on how the trial is conducted.

What is an interim analysis and its purpose?
An interim analysis is a planned evaluation of data from an ongoing study before its completion. It allows researchers to make informed decisions about continuing, modifying, or stopping a study. Interim analyses are commonly part of study designs in order to avoid unnecessary study burden and patient exposure to an investigational drug.

Where can people go for more information?
Study participants and family members should contact their study site for questions. Community members can speak with their HD specialist or local patient organisations. Roche Medical Information can be reached at medinfo.roche.com.