



Genentech  
A Member of the Roche Group

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Dear Huntington's patient community leaders,

Following your request to receive timely updates about our Huntington's disease (HD) research efforts, this letter provides information about the opening of the GENERATION HD2 study and a summary of our scientific collaboration efforts in 2022.

### **Phase II GENERATION HD2 study now open**

This study evaluates the safety, biomarkers and efficacy trends of different dose levels of investigational drug tominersen in people aged 25 to 50 with prodromal (very early subtle signs of HD) or early manifest HD.

- The GENERATION HD2 study aims to enroll 360 participants who will each undergo at least 16 months of treatment with either tominersen or placebo. Study details will be on clinical trial directories such as ClinicalTrials.gov and ForPatients.Roche.com.
- This study is planned to run in 15 countries. The study has opened in the United States and potential participants are starting the screening process (eligibility check). Additional locations in North America, Europe, South America and Oceania will be posted on clinical trial directories as sites receive approvals (e.g., from Health Authorities and Ethics Committees) and are ready to accept potential participants.
- Individuals interested in the study should speak to their/their loved one's treating physician or HD specialist about what may be best for their situation. The HD specialist can also contact Roche/Genentech Medical Information for more information.

### **A commitment to advance HD research through continued collaborations**

Also in 2022 we continued our commitment to scientific understanding and HD research, including:

- **Sharing data and learnings** from the Phase III tominersen clinical trial, which occurred at every major HD research forum - including CHDI, Hereditary Disease Foundation, European Huntington Disease Network and Huntington Study Group scientific meetings. Data sharing is part of our commitment to transparency and furthers the research community's collective knowledge about HD and Huntington-lowering therapeutic approaches, including tominersen.
- **Conducting research and partnerships to:**
  - o Explore potential new drug targets and pathways to treat HD
  - o Develop innovative measurement endpoints for clinical trials, with a focus on early stages of HD
  - o Improve understanding and interpretation of HD biomarkers
  - o Understand the true quality of life and burden of people living with HD

We take this opportunity to thank you and the community for the ongoing support. It was one year ago that we announced the tominersen clinical development programme would continue with a more focused research objective. Since then, many community leaders and families have collaborated with us on the design and direction of the new Phase II study. We also thank all past and future HD families who participate in clinical trials. Research progress can only be made through these important partnerships.

Sincerely,

Mai-Lise Nguyen, on behalf of the Roche & Genentech HD team  
Global Patient Partnership, Rare Diseases

*Tominersen is an investigational (not approved) medicine that is being studied for the treatment of people with Huntington's disease.*

## **Questions and answers**

### **What is the Phase II GENERATION HD2 study?**

The GENERATION HD2 study evaluates the safety, biomarkers and efficacy trends of investigational drug tominersen in people with prodromal (very early subtle signs of HD) or early manifest HD. This is a randomized study, where eligible participants will receive one of two doses of tominersen (60mg or 100mg), or placebo, every 4 months via a lumbar puncture. Neither the participant nor study team will know whether the participant is receiving tominersen or placebo. The study will conclude after all participants have completed 16 months of treatment. An independent data monitoring committee (iDMC) will monitor the trial and will review safety, clinical and biomarker data every 4-6 months.

### **What is the basis of the Phase II GENERATION HD2 study?**

Tominersen is an investigational drug that has been studied in several clinical trials since 2015, including in a Phase III study called GENERATION HD1 that tested two different dose regimens of tominersen in adults with manifest HD (120mg every 2 months, and 120mg every 4 months). This was a higher dose than what is used in the new GENERATION HD2 study.

The Phase III GENERATION HD1 study did not meet its main objectives. Dosing of tominersen was stopped in the GENERATION HD1 study in March 2021 after the iDMC evaluated the overall benefits and risks of tominersen in study participants.

However, exploratory analyses conducted after Phase III data were available to Roche suggest that lower exposure to tominersen may benefit younger adults with earlier stages of HD. Findings from these exploratory analyses were not statistically significant (i.e., clearly different) versus placebo and could represent a chance result, so they are not definitive and need to be confirmed. Therefore, the Phase II GENERATION HD2 study aims to assess lower doses of tominersen in an earlier HD population than those involved in the previous study.

### **Where will the study be offered?**

The GENERATION HD2 study is planned to run in 15 countries (Argentina, Austria, Australia, Canada, Denmark, France, Germany, Italy, New Zealand, Poland, Portugal, Spain, Switzerland, UK and USA).

### **Can people relocate to join the study if a study site is not near where they live?**

Enrollment is decided by the study investigator at each site, who takes into account local laws and regulations. Additionally, factors such as institutional site policies, health insurance and travel burden may impact a person's ability to relocate and be accepted into one of the study sites.

### **Will previous tominersen study participants be able to participate in the new study?**

Previous study participants who received placebo and who meet the Phase II GENERATION HD2 study criteria may potentially enroll in the study. However, the new study will not run at all trial sites from previous studies. Interested individuals should speak to their HD specialist.

The new study is testing tominersen in previously untreated adults, therefore individuals who previously received tominersen will not be eligible for the study. This decision was made following extensive consultation with HD experts and community leaders. We recognize that this may be disappointing news for some individuals. As we learn more about tominersen through the GENERATION HD2 study, we will evaluate if additional clinical trial opportunities may be possible.