18 September 2022

Dear Huntington's patient community leaders,

Following your request to receive timely updates about our Huntington's disease (HD) research efforts, we write to share plans for **GENERATION HD2**, a new Phase II clinical study. We expect to start enrolling study participants early next year.

The GENERATION HD2 study will evaluate the safety, biomarkers and efficacy of investigational drug tominersen in people aged 25 to 50 with prodromal (very early subtle signs of HD) or early manifest HD. This global study plans to enroll approximately 360 participants in 15 countries. The study design was presented today at the EHDN Plenary meeting in Bologna, Italy. More study details and site locations will be made available over the next months as information is confirmed.

This will be a randomized, placebo-controlled study, where eligible participants will receive one of two doses of tominersen (60mg or 100mg), or placebo, every 4 months via a lumbar puncture.The study will be double-blinded, meaning 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 new 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 is a higher dose than what will be used in the upcoming GENERATION HD2 study.

The 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 adult patients with earlier stages of HD. It is important to note that 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 new Phase II GENERATION HD2 study aims to assess lower doses of tominersen in an earlier HD population than those involved in the previous study.

HD research is cumulative - thank you to all participants in previous studies
All other tominersen studies closed this summer, and we want to again sincerely thank all study participants, companions and families who supported the previous studies. These studies comprised the first-ever Phase III clinical program to test the huntingtin-lowering hypothesis. Additionally, it was because of the HD community's commitment to research that the trials recruited faster than anticipated, and thus generated data faster than anticipated.

The incredible HD community inspires all researchers to continue pursuing potential options for people impacted by the disease. Regardless of a study's outcome, the journey of tominersen research is an example of how every clinical study adds to the overall body of research knowledge. Every piece of data collected is vital. Even if we learn something may not work, or may work differently than thought, together as a research community we get one step closer to finding out what may work for people with HD. And this research can only be done with the participation of the HD community.

We look forward to providing you with further updates and we thank you for your continued partnership.

Sincerely,

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

Questions and answers

Where can I get more information on the study? Where will the study be offered?
Further study details, including inclusion and exclusion criteria, will soon be posted on ForPatients.Roche.com and clinical trial registries (e.g., ClinicalTrials.gov), as well as shared with HD specialists. 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.

We plan to run the GENERATION HD2 study in approximately 15 countries (Argentina, Austria, Australia, Canada, Denmark, France, Germany, Italy, New Zealand, Poland, Portugal, Spain, Switzerland, UK and USA). Trial sites will be made available on a progressive basis – for example, once a site's infrastructure and approvals (from Health Authorities and Ethics Committees/IRBs) are in place, and sites are nearly ready to enroll patients.

For any clinical study, it is possible that for various reasons an expected study site/country does not proceed to enroll participants. Alternatively, additional locations may be added.

Will previous tominersen study participants be able to participate in the new study?
Phase III GENERATION HD1 study participants who received placebo and who meet the new Phase II GENERATION HD2 study eligibility criteria may potentially enroll in the upcoming tominersen study. However, clinical trial site locations are still being confirmed.

The GENERATION HD2 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, though we recognise that this may still be disappointing news for some individuals.

As we learn more about tominersen through the new Phase II study, we will continue to evaluate if additional clinical trial opportunities may be possible.

Tominersen is an investigational (not approved) medicine that is being studied for the treatment of people with Huntington's Disease. The efficacy and safety of tominersen are currently being studied.

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