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Update on Two Clinical Studies: GENERATION HD2 (tominersen) and POINT-HD (RG6496)

Dear Huntington's patient community leaders,

Following your request to receive timely updates, I am writing to share news about two of our ongoing clinical studies for people with early Huntington's Disease (HD), the GENERATION HD2 study and the POINT-HD study. Consequently, we have made the difficult decision to discontinue both clinical development programmes based on:

- **Phase II GENERATION HD2 top-line results (evaluating investigational drug tominersen)**: While the study met its safety and biomarker objectives, it did not meet its efficacy objective.
- **Phase I POINT-HD (evaluating investigational drug RG6496)** study discontinuation based on new data from a separate non-clinical (animal) study.

These are independent, data-driven events, which have coincided by chance. While this news is deeply disappointing, promptly communicating about the findings is the most responsible way for us to honor the contribution of study participants and allow the HD community to focus efforts on other avenues of research.

GENERATION HD2/tominersen: Study Results

The GENERATION HD2 study was designed to validate a data trend found in adults with early or very subtle symptoms of HD after scientists analysed the results of a prior tominersen study (GENERATION HD1). Recently, the 16-month treatment period for all GENERATION HD2 participants was completed, data collected and initial analyses were conducted. Initial results of the primary analysis show:

- Safety: Tominersen was well tolerated and showed no new safety signals.
- Biomarkers: Tominersen significantly lowered mutant huntingtin protein and Neurofilament Light Chain (NfL) (a protein linked to neuronal damage that is elevated in people with HD), compared to people receiving placebo.
- Efficacy: There was no meaningful impact on clinical efficacy for the study participants receiving tominersen, compared to those on placebo.

POINT-HD/RG6496: New Findings from Non-clinical (Animal) Studies

The POINT-HD study is the first time RG6496 is being tested in people. The study's main aims were evaluating the effects of a single dose of the drug in people with early HD. The study recently opened and has enrolled three participants.

In parallel to the POINT-HD study, Roche was conducting longer-term non-clinical (animal) research to support future plans to give multiple doses of the drug. Based on new data from one of these studies, our team has concluded that RG6496 cannot be given chronically with repeated doses. While there is no safety concern for people to receive one dose, we have chosen to stop the POINT-HD study early, because we can no longer offer participants the possibility of long-term treatment. Enrolled participants will continue to be monitored, per study protocol.

Next Steps

- Communications to Study Participants: Our immediate focus is supporting participants and sites regarding these announcements. Earlier this week, sites were notified so they could contact participants and discuss transition plans and support. Because these studies are running in multiple countries, we acknowledge that families may have received news at different times and in different channels. For further questions, families should contact their sites. Our team can also be reached at medinfo.roche.com.
- Sharing Data & Learnings: Data will continue to be analysed and presented at future medical meetings. We are committed to sharing learnings with the research and family communities to advance the understanding of drug development for HD.
- Further Research: Roche's Phase I/II study of investigational gene therapy RG6662 (formerly from Spark Therapeutics; study SPK-101, NCT06826612) is ongoing as planned. Additionally our interest in exploring multiple HD therapeutic approaches remains, and we will continue to follow promising science.

With profound thanks to the HD community

We have been humbled and inspired by the 1,500+ HD families and broader community who contributed to both programmes - tominersen since clinical studies began in 2015 with our partner Ionis Pharmaceuticals, and RG6496 more recently. These contributions changed the history of HD drug development - proving the protein that causes HD could be lowered in humans, shaping new research and approaches, which will undoubtedly lead to future breakthroughs.

On behalf of all Roche HD team members over the years, we are deeply grateful to this incredible HD community. Progress is only possible together and built over years of partnership. We remain hopeful for the future of HD research.

Sincerely on behalf of the Roche & Genentech HD team,

Mai-Lise Nguyen

Mai-Lise Nguyen

Global Patient Partnership

About the GENERATION HD2 Study

The GENERATION HD2 study (NCT05686551) is a Phase II study that evaluated the safety, biomarker impacts, and clinical efficacy trends of tominersen, compared to placebo over a minimum of 16 months. It investigated whether a 100mg dose of tominersen administered via spinal fluid injection three times a year could offer clinical benefit to adults aged 25-50 years with early HD. In addition to safety and biomarker measures, tominersen was evaluated using composite Unified Huntington's Disease Rating Scale (cUHDRS) or Total Functional Capacity (TFC) scores - scales that are commonly used in HD studies to understand the impact on disease progression. The study enrolled 301 participants across 15 countries (Argentina, Australia, Austria, Canada, Denmark, France, Germany, Italy, New Zealand, Poland, Portugal, Spain, Switzerland, the UK and the USA).

About the POINT-HD Study

The POINT-HD study (NCT07246941) is a Phase I, first-in-human study that evaluated the safety and tolerability of RG6496 in adults aged 25-65 years with early HD. RG6496 was designed to selectively lower mutant huntingtin protein by targeting a specific SNP (a small variation in the DNA sequence) found in the expanded HD gene of some individuals. The study aimed to investigate safety, drug behaviour, and biomarker changes following one dose of RG6496 administered via spinal fluid injection. The study was open in New Zealand, Argentina, and Australia, and had planned to open in Canada and Europe.

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