



20 April 2018

**RG6042 (formerly known as IONIS-HTT<sub>Rx</sub>) development program update  
Presentation of Phase I/IIa study at world's largest neurology conference, thank you to community**

Dear global Huntington's disease community,

Next week will be another milestone for the development program of the investigational medicine RG6042 (formerly known as IONIS-HTT<sub>Rx</sub>). On 24 April 2018 results from the RG6042 Phase I/IIa study in Huntington's disease (HD) will be featured on the main stage of the American Academy of Neurology (AAN) annual meeting, the world's largest forum for neurology research, which is attended by over 12,000 professionals from around the globe.

We wanted you to be aware that news coverage about this study may occur over the next days. Out of more than 3,000 scientific submissions to AAN, the RG6042 Phase I/IIa study results is one of four presentations selected to be part of the meeting's top-featured session. HD will receive a spotlight in the neurology community next week, and we would like to give special acknowledgements to (as Dr. Sarah Tabrizi said during her presentation at the CHDI conference) the "true research heroes"- the 46 participants of the Phase I/IIa study. These incredible individuals and their families had the bravery and commitment to join this first-in-human study and advance scientific progress.

We are honored to work with trial investigators and Ionis Pharmaceuticals to share results of the world's first drug study designed to reduce huntingtin protein at such prominent scientific forums as AAN and last month's CHDI conference, where the data were first debuted. It is a testament to the broad interest in HD and the increasing hope for effective treatments. More importantly, it is a testament to the collaboration and support of the HD community.

**What's happened?**

- The Phase I/IIa study will be presented on 24 April at the AAN annual meeting. Overall results are similar to those previously announced at the CHDI conference.
  - This was a 13-week, first-in-human study evaluating safety and tolerability, where 46 participants received four doses every 28 days.
  - The study showed RG6042 was safe and well-tolerated at all doses.
  - The study was not designed, or expected, to show an effect on clinical symptoms.

- Exploratory analyses showed that RG6042 lowered levels of mutant huntingtin protein, the protein that causes Huntington's disease, in a dose-dependent manner.
- Based on the encouraging signals observed in this study, the development of RG6042 continues. Further research will focus on determining if RG6042 provides a meaningful clinical benefit and if lowering the mutant protein changes the course of HD.

This is an exciting time for HD, but there is still much work to be done. More research and larger studies are needed to determine if RG6042 can slow the relentless progression of HD.

**Important notes/what's happening next:**

- Our team and collaborators continue to analyze the Phase I/IIa data and exploratory signals.
- The Phase I/IIa data will continue to be presented at upcoming scientific and community forums around the world, and they will be submitted for peer-reviewed scientific publication. Ensuring ongoing communications with the scientific community is part of Roche's commitment to data sharing, which enables education, discussion and other researchers to more easily build on insights and expand scientific progress.
- An open-label extension study of RG6042 has started for those who participated in the Phase I/IIa study. This study looks at the safety and tolerability of longer-term dosing of RG6042, as well as the effects on mutant huntingtin protein and other measures tested in the Phase I/IIa study.
- We are in the planning stages of a comprehensive clinical development program for RG6042, including a global study designed to detect clinical benefit and evaluate longer-term safety.
  - We are collaborating with the HD community and engaging global Health Authorities on the design of the clinical development program.
  - We will share details about study information, including eligibility criteria, planned start date, and study sites around the world, as soon as these aspects are finalized.
- At this time, because the benefits and risks of RG6042 are not fully understood, we are not able to grant pre-approval or compassionate access.

Roche's drive to develop treatments for HD is inspired by you - the people whose lives are affected by this disease. We are grateful to the HD community for its ongoing engagement in clinical studies to further the progress in HD research. Please know that we are working with urgency and care, and in partnership with the HD community, to develop a comprehensive clinical development program. We look forward to providing you future updates.

Sincerely,

Your Roche HD Team