28 January 2019

Update on RG6042 Huntington's disease (HD) programme: First patients enrolled in HD Natural History and Phase III GENERATION HD1 clinical studies

Dear Global Huntington's Community,

Just over one year ago, we and our partner Ionis Pharmaceuticals announced the results of the first ever study that tested the huntingtin-lowering scientific hypothesis. Today, we are pleased to announce that the first patient has entered into the GENERATION HD1 clinical study – a pivotal, global Phase III study to investigate the efficacy and safety of RG6042 (formerly known as IONIS-HTT$_{Rx}$). If this clinical study is successful, it is our hope that RG6042 will be approved by health authorities and made available for the treatment of manifest Huntington's disease.

We are grateful to the patients and family members participating in clinical research, as well as everyone supporting them in the broader HD community. Scientific progress is only possible with your collaboration and participation.

Recent updates

- Two global clinical studies have started and first patients are enrolled – an important achievement for the research programme; study status is available on ClinicalTrials.gov
  - *HD Natural History study (NCT03664804)*
    - This observational study for early manifest HD will run in the USA, Canada, Germany and the UK; planned study sites were announced in late 2018.
    - Initial sites have opened and the first patients have enrolled; our team continues to work to open recruitment at all study sites as quickly as possible.
  - *Phase III GENERATION HD1 study (NCT03761849)*
    - We received health authority approvals in the USA and Canada to start this pivotal study for manifest HD. Planned study sites for those countries were announced at the end of 2018 and the first patient has now enrolled.
    - This study will run in approximately 15 countries; we are diligently working to set up study infrastructure and receive approvals in the remaining countries.

- Ongoing open-label extension of the Phase I/IIa study: sponsorship has been transferred from Ionis to Roche
    - Patients who completed the Phase I/IIa study have been participating in an open-label extension study sponsored by Ionis (NCT03342053). Responsibility of this study has now transferred to Roche. Moving forward these patients will roll into a new Roche-sponsored, open-label extension study called GEN-EXTEND. GEN-EXTEND will allow us to continue to study longer-term effects of RG6042 in those participants who have previously completed a clinical trial for the investigational molecule.

Important to note

- At this time, access to RG6042 is only through clinical studies because the benefits and risks of RG6042 are not yet fully understood.
- **Additional countries/sites for the Phase III study:** Information about additional countries/sites will be announced on a progressive basis, once sites are nearly ready to enrol participants; information will be posted on ClinicalTrials.gov
- **Communications about study data:** Roche is committed to transparent and timely communications, as well as ensuring the integrity of ongoing clinical trial operations and data collection. In line with our Global Policy on Sharing of Clinical Study Information, we will share overall programme updates and relevant data from completed and ongoing clinical studies with the scientific community via appropriate channels (e.g., scientific meetings, peer-reviewed journals, etc.).

Our team recognises that the need in HD is greater than the capacity of the RG6042 development programme, and that not every person nor every capable HD centre interested in these clinical studies will be able to participate. We can assure you that the studies are designed to provide health authorities with the required data so that the benefit-risk of RG6042 can be determined as quickly as possible. The ultimate goal is that this investigational medicine can be approved by health authorities and made accessible to the broader HD community.

Our team continues to engage with health authorities and HD communities around the world on the RG6042 research programme. We look forward to providing you with further updates.

Sincerely,

Mai-Lise Nguyen, on behalf of the Roche & Genentech HD team
Patient Partnership Director, Rare Diseases
Roche Pharma Research & Early Development / Roche Innovation Centre Basel, Switzerland

Frequently asked questions and answers

What is the HD Natural History study?
This 15-month observational study aims to further understand the role of mutant huntingtin protein in disease progression, including how levels of mHTT change over time in the absence of any drug treatment. There is no drug treatment in this study. This study will include up to 100 participants with early manifest (Stage I and II) HD. For all patients who complete the HD Natural History study, an open-label extension study with the option of receiving RG6042 (no placebo control) is planned, pending eligibility, approval by Authorities and Ethics Committees/Institutional Review Boards and if data support the continued development of RG6042.

The HD Natural History Study will run at up to 17 sites in Canada, Germany, the United Kingdom and the United States. For more information about the study/trial sites visit ClinicalTrials.gov or contact the local Roche Medical Information team:

- Germany: (+49) 07624-14-2015
- UK: (+44) 0800 3281629 or medinfo.uk@roche.com
- Canada & United States of America: (+1) 888-662-6728

What is the Phase III GENERATION HD1 study?
The GENERATION HD1 study will evaluate the efficacy and safety of RG6042 treatment for manifest HD. The study will run over a period of 25 months (approx. two years). GENERATION HD1 is designed to determine whether RG6042 is safe and effective, and therefore includes a comparison to placebo. Participants will be randomised to one of three treatment study arms: RG6042 monthly, RG6042 once every two months (bi-monthly) or placebo monthly. This means for every two participants randomised to RG6042, one will receive placebo. The study is "double-blinded," meaning neither the participant nor his/her investigator or site staff will know which study arm the participant is assigned.

For all patients who complete the GENERATION HD1 study, an open-label extension study with the option of receiving RG6042 (no placebo control) is planned, pending eligibility, approval by Authorities and Ethics Committees/Institutional Review Boards and if data support the continued development of RG6042.

The GENERATION HD1 study will enrol up to 660 patients with manifest HD at 80-90 sites in approximately 15 countries around the world. Planned sites have been announced for Canada and the United States of America. For more information about the study/trial sites visit ClinicalTrials.gov or contact our Clinical Trial Information Support Line for the USA and Canada at (+1) 888-662-6728. Information about additional countries/sites involved in the study will be announced, as those details are finalised.

How are the clinical study sites selected?
A variety of factors influence site selection, including assessments on experience with HD studies, clinic infrastructure capacity to run the study as well as usual site activities, ability to

operationalise the study as quickly and completely as possible, patient population, and geographic location.

What if there is not a study site near where I live? Can I relocate to participate in a study?
Clinical studies are subject to international, national and local laws and regulations. Additionally, factors such as institutional site policies, health insurance and travel burden may impact your ability to relocate and be accepted into one of the study sites. Eligibility and enrolment are decided by the study investigator at each site, who takes into account all these factors and may also wish to speak to you or your local HD specialist for more information.

Whether your HD centre is selected for participation or not, this is no reflection on the quality of the many outstanding HD clinics and dedicated care providers around the world. The need in HD is greater than the capacity of our development programme. We have designed the programme to provide the required data to health authorities so that the benefits and risks of RG6042 can be determined as quickly as possible. Our ultimate goal is that this investigational medicine can be approved by health authorities, and made accessible to the broader HD community.

Can I access RG6042 outside of clinical studies?
Currently, access to RG6042 is only through clinical study participation because the benefits and risks of RG6042 are not yet fully understood. This means that we are not able to grant pre-approval, compassionate use or “right-to-try” requests at this time. As our understanding of the benefits and risks of RG6042 grows, we will regularly evaluate this position.

Your clinical studies are in early manifest and manifest HD. Will you study RG6042 in other patient populations (e.g., juvenile onset HD or prodromal HD)?
We recognise the critical medical need for a treatment for HD, especially for people living with severe forms like juvenile onset HD. Once there is sufficient scientific and safety rationale, our team will consult with HD community experts and explore the potential use of RG6042 in populations beyond manifest HD.