

21 March 2019

## Amendment to the RG6042 Phase III GENERATION HD1 study design

Dear global HD patient community,

Today we are sharing an important update to the study design of the global Phase III GENERATION HD1 study (NCT03761849) evaluating the efficacy and safety of the investigational medicine RG6042 (formerly known as IONIS-HTT<sub>Rx</sub>) for manifest Huntington's disease (HD).

Preliminary data from the ongoing open-label extension of the Phase I/IIa study (NCT03342053) support continued evaluation of RG6042 as a potential treatment for HD. These data also enable GENERATION HD1 design changes that we believe will make study participation less demanding for patients, their families and healthcare providers.

The 15-month open-label extension of the Phase I/IIa study is evaluating RG6042 treatment in doses every month (every four weeks) and every two months (every eight weeks). Review of nine-month data showed effects on lowering mutant huntingtin protein levels in the cerebral spinal fluid that support the exploration of less frequent dosing. Based on the totality of the data, including safety and tolerability, there appears to be no overall advantage to treatment monthly versus every two months. The open-label extension of the Phase I/IIa study will be completed as planned, and detailed results will be shared at an upcoming scientific meeting.

While it is important to note that these are early data from an open-label study and it is not appropriate to draw conclusions about clinical efficacy or longer-term safety, we are pleased that these data support the GENERATION HD1 study design changes described below.

### Key changes to the GENERATION HD1 study

The study arms involving treatment every two months and placebo will remain, however the study arm that tests monthly treatment will be replaced with one that tests a less frequent dose of once every four months (every 16 weeks).

<b>Original GENERATION HD1 study</b> <i>All patients undergo lumbar puncture procedures monthly and are randomised to one of the study arms below</i>	<b>Future GENERATION HD1 study</b> <i>All patients undergo lumbar puncture procedures every two months and are randomised to one of the study arms below</i>
Study arm 1: RG6042 every two months (placebo during alternating months)	Study arm 1: RG6042 every two months (no placebo)
Study arm 2: RG6042 monthly	Study arm 2: RG6042 every four months (placebo during alternating procedures)
Study arm 3: Placebo monthly	Study arm 3: Placebo every two months

We remain committed to researching the safety and efficacy of RG6042 for people with HD and completing the GENERATION HD1 study as quickly as possible; therefore, the protocol amendment process has already started, and we will be working with study sites and review committees to implement the changes. There will be a temporary pause in enrollment of new patients into the study. Once the protocol amendment is fully approved and in place at a study site, local enrollment will re-open on a site-by-site basis. We understand the community has a keen interest in these research efforts, and our team is working to rapidly activate the updated study protocol around the world.

The GEN-EXTEND open-label extension study (NCT03842969) for patients who complete Roche/Genentech-sponsored HD studies will also evaluate RG6042 treatment every two months and every four months for long-term safety and tolerability, without a placebo control arm. Pending approval by local clinical study review committees, enrollment into the GEN-EXTEND study will be offered to patients from the open-label extension of the Phase I/IIa study, as well as patients in GENERATION HD1 enrolled under the original study design. The contribution of these individuals to the overall RG6042 research programme will continue through their participation in the GEN-EXTEND study.

Patients currently enrolled, or those interested in participating, in a Roche/Genentech-sponsored study should speak to their HD specialist or local clinical study site if they have any questions about these changes or would like further information.

We greatly appreciate the commitment of participants, their families and all those involved in clinical studies that progress HD research every day. We look forward to providing further updates this year.

Sincerely,



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

***About the revised Phase III GENERATION HD1 study design***

*The GENERATION HD1 study will evaluate the efficacy and safety of RG6042 treatment given once every two months (every eight weeks) or every four months (every 16 weeks) over a period of 25 months. This amended global study will enroll up to 660 patients with manifest HD at 80-90 sites in approximately 15 countries around the world.*

*GENERATION HD1 is designed to determine the effectiveness and safety of RG6042, and therefore includes a comparison to placebo. Participants will be randomised to one of three study arms: 120mg RG6042 every eight weeks, 120mg RG6042 every 16 weeks or placebo every eight weeks. This means for every two participants randomised to RG6042 treatment, one will receive only 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, the option of participation in an open-label extension study (GEN-EXTEND) evaluating RG6042 (no placebo control) is planned, pending eligibility, approval by local Authorities and Ethics Committees/Institutional Review Boards and if data support the continued development of RG6042.*