Dear members of the Huntington's community,

On March 1, 2018, Ionis Pharmaceuticals, Inc. and Roche presented initial results from the completed Phase 1/2a study of IONIS-HTT$_{Rx}$ (now known as "RG6042") in people with Huntington's disease (HD) at the 13th Annual CHDI HD Therapeutics conference. The study was a 13-week, randomized, placebo-controlled, dose escalation study in 46 participants with early stage HD. The study evaluated IONIS-HTT$_{Rx}$ (RG6042) at five different doses, given monthly, for a total of four doses. We are excited to provide you with a summary of information from the completed study.

- In the Phase 1/2a study, the mutant huntingtin protein (mHTT), which causes HD, was substantially reduced in a dose-dependent manner in participants treated with IONIS-HTT$_{Rx}$ (RG6042).
- Participants who received either of the two highest doses of IONIS-HTT$_{Rx}$ (RG6042) (90 mg or 120 mg) experienced a reduction of mHTT levels in their cerebral spinal fluid (CSF) that were, on average, approximately 40% lower than at the start of the study, with some individuals experiencing a lowering as high as 60%. At the last measurement, the levels of mHTT were continuing to decline in most IONIS-HTT$_{Rx}$ (RG6042)-treated participants, suggesting that larger reductions may be possible with continued dosing.
- This magnitude of reduction of mHTT in CSF is within the range predicted to provide clinical benefit, based on available evidence of what was needed for improvement in animal models of HD.

The purpose of the Phase 1/2a study was to determine safety and tolerability of IONIS-HTT$_{Rx}$ (RG6042). This study was not designed to detect an effect on clinical symptoms. We are pleased that the study showed IONIS-HTT$_{Rx}$ (RG6042) was safe and well-tolerated at all doses and lowered CSF mHTT levels in a dose-dependent manner, and therefore supports continued development. Since mid-December 2017, Roche is leading the future studies and development of this investigational medicine, which was renamed RG6042.

Recent progress:

- An open-label extension study of IONIS-HTT$_{Rx}$ (RG6042) has started for those who participated in the recently completed Ph1/2a study. This study looks at the safety and tolerability of longer-term dosing of IONIS-HTT$_{Rx}$ (RG6042).
- The next step is to conduct a larger study designed to detect clinical benefit and evaluate longer-term safety. In this study it will determine whether the lowering of mHTT, observed in the first study of IONIS-HTT$_{Rx}$ (RG6042), translates into meaningful benefit for people living with HD.
- Roche is collaborating with the HD community and engaging global health authorities on the design of this larger study. Roche will share details about this planned study, including eligibility criteria, planned start date, and study sites around the world, as soon as these aspects are finalized.

This study will answer critical questions for regulatory approval and broad access. At this time, because the benefits and risks of IONIS-HTT$_{Rx}$ (RG6042) are not fully understood, we are not able to grant pre-approval or compassionate access.

In summary, we are very encouraged by the promise of IONIS-HTT$_{Rx}$ (RG6042) and look forward to continuing to partner with the HD community. We recognize the urgent need to bring effective therapies to individuals affected by HD, and our teams are working to advance IONIS-HTT$_{Rx}$ (RG6042) into the next clinical study as quickly as possible.

Sincerely,
Your Roche & Ionis Team