Status Update on December 19, 2018:

- The observational HD Natural History study (Clinicaltrials.gov ID: NCT03664804) is open and currently recruiting. The planned sites in Canada, US, Germany and UK were announced in November. Information about the study, including individual site status, is posted on ClinicalTrials.gov.

- We are pleased to inform you on progress on the Phase III GENERATION HD1 study (Clinicaltrials.gov ID: NCT03761849). The first countries to open recruitment will be the USA and Canada. Below is a list of planned sites - it is important to note that these sites are not fully activated nor recruiting yet. We hope to complete the final steps as quickly as possible. The GENERATION HD1 study will run in approximately 15 countries; additional countries/sites will be announced on a progressive basis - as we obtain country approvals and when sites are nearly ready to enroll patients. For any clinical study, it is possible that an expected study site does not proceed to enroll participants. This can be for various reasons and we do not want to raise hopes or expectations.

Expected sites for GENERATION HD1 study in the United States of America

Alabama, Birmingham - University of Alabama
Arizona, Phoenix - Barrow Neurological Clinic
California, Davis - University of California, Davis
California, Palo Alto - Stanford University
California, Pasadena - Arcadia Neurology Center
California, San Diego - University of California, San Diego
Colorado, Englewood - Rocky Mountain Movement Disorders Center
District of Columbia, Washington - Georgetown University
Florida, Tampa - University of South Florida
Illinois, Chicago - Northwestern University
Maryland, Baltimore - John Hopkins University
Massachusetts, Boston - Beth Israel Deaconess Medical Center
Missouri, St Louis - Washington University
New York, Amherst - Dent Institute
New York, New York - Columbia University
Pennsylvania, Pittsburgh - University of Pittsburgh Medical Center
Tennessee, Nashville - Vanderbilt University Medical Center
Texas, Houston - University of Texas Health Science Center
Utah, Salt Lake City - University of Utah
Washington, Kirkland - Evergreen Health

Expected sites for GENERATION HD1 study in Canada

Alberta, Edmonton - University of Alberta
British Columbia, Vancouver - University of British Columbia
Ontario, Ottawa - Ottawa Hospital
Ontario, Toronto - Centre for Movement Disorders
Nova Scotia, Halifax - Queen Elizabeth II Health Sciences Centre
Quebec, Montreal - Centre Hospitalier de l'Université de Montréal
Our Clinical Trial Information Support Line for the USA and Canada can be contacted at 1-888-662-6728. Also, information about the GENERATION HD1 study and sites will soon be posted on ClinicalTrials.gov, including individual site status.

Whether your HD clinic or 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 Authorities so that the benefit-risk 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.

The decision to join a clinical trial is personal and involves many factors. We encourage anyone interested in participating in any clinical research to discuss with his/her HD specialist about what may be best for his/her situation.

**About the Phase III GENERATION HD1 Study**
The GENERATION HD1 study will evaluate the efficacy and safety of RG6042 treatment given once per month or once every two months (bi-monthly) over a period of 25 months (approx. two years). This global study will enrol up to 660 patients with manifest HD at 80-90 sites in approximately 15 countries around the world. The study will begin at the end of 2018, with patients starting to enrol by early 2019.

GENERATION HD1 is designed to determine the effectiveness and safety of RG6042, and therefore includes a comparison to placebo. Participants will be randomized to one of three treatment study arms: RG6042 monthly, RG6042 bi-monthly or placebo monthly. This means for every two participants randomized 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.

**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.

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