



HDSA FAQ on the Roche/Genentech RG6042 program

HDSA's frequently asked questions factsheet about the huntingtin-lowering trial ASO program was so good we stole it (with permission)

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On Wednesday, September 26th, HDSA hosted a webinar presented by Genentech/Roche in which representatives from their Huntington's disease team shared details and answered questions about upcoming Genentech/Roche clinical trials for HD. HDSA received hundreds of questions before, during, and after the webinar. Here HDSA's staff scientists, with guidance from Genentech/Roche, have tried to address the most frequently-asked questions.

What Are The Two Upcoming Huntington's Disease Clinical Trials Being Conducted By Genentech/Roche?

Can you tell me the basics about the planned GENERATION-HD1 study that will test huntingtin-lowering drug RG6042?

- The planned GENERATION-HD1 will be a large Phase 3 study to test whether the Genentech/Roche huntingtin-lowering therapy RG6042 (formerly IONIS-Htt-Rx) is safe and effective in HD. It will involve monthly clinic visits for 25 months, with lumbar punctures (spinal tap) and other assessments each time.
- 660 people age 25-65, with manifest HD will be recruited. 220 will receive placebo every month, 220 will receive RG6042 every month, and 220 will receive RG6042 every other month with placebo on alternate months.
- Upon study completion, the plan (if approved by health authorities) is to offer eligible participants in all groups the choice to receive RG6042 monthly or every other month (this is known as an Open-Label Extension Study).

What about the other study that isn't testing a drug – the HD Natural History Study?

- The HD Natural History Study does not involve a drug treatment. It will monitor people with early manifest HD by testing their symptoms and measuring their mutant huntingtin levels over time. It will last for 16 months and includes an initial screening, 4 clinic visits with lumbar punctures and other assessments (at baseline and at months 3, 9, and 15), and 2 phone check-ups (at months 6 and 12).
- Around 100 people age 25-65 will be recruited.
- Upon study completion, the plan (if approved by health authorities) is to offer eligible participants who complete the study the choice to begin receiving RG6042 (this is known as an Open-Label Extension Study).

Where And When Are These Studies Happening?

Where are the clinics? When do you expect to name them?

- Genentech/Roche has devoted many months to identifying clinical sites. As of October 3rd, 2018, none have yet been confirmed, but the first announcements are likely to occur before the end of 2018.

When will the studies begin?

- The first sites to be approved are expected to begin recruiting in late 2018 (for the HD Natural History Study) and early 2019 (for GENERATION-HD1).
- The sites will not begin recruiting all at once, because there are different approval processes for each individual institution. However, HDSA will update the information on www.hdtrialfinder.org as it becomes available.
- The Genentech Trial Information Support Line can also be contacted for more information (888) 662-6728 (Hours: Monday - Friday 5am - 5pm PT)

How many sites will be in the US?

- There are no approved sites yet. For the HD Natural History Study, there will be up to 17 sites in the US, UK, Germany and Canada. For the GENERATION HD1 study there are expected to be up to 80-90 sites worldwide in approximately 15 countries, including the US.

Are all US sites HDSA Centers of Excellence?

- No, but some are likely to be, because participating clinics need to be research centers capable of performing all the procedures involved in the trials. A variety of factors go into site selection, including assessments on experience with HD clinical studies, clinic infrastructure capacity to run the study and usual site activities, ability to operationalize the study as quickly and completely as possible, the patient population, and geographic

location. HDSA does not have any control over site selection for these trials.

Can my clinic apply to be a site?

- Genentech/Roche has informed HDSA that it is not looking for additional sites at this time, but your interest can be provided for future consideration. Contact the Genentech Trial Information Support Line at (888) 662-6728 (Hours: Monday - Friday 5am - 5pm PT).

Will patients be required to live within a certain distance of a site to be able to participate?

- There is no specific distance requirement or catchment area for these trials, but the travel burden will likely be considered during the screening. A major move or a long-distance commitment could create additional stress on a participant and his/her loved ones. Excessive travel may also makes it more likely for someone to drop out of a trial, which could hamper the success of GENERATION-HD1 or the HD Natural History Study. Clinical studies are subject to international, national and local laws and regulations. Additionally, factors such as institutional site policies and health insurance may impact your ability to relocate and be accepted into one of the study sites. Eligibility and enrollment are ultimately 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.

What Are The Commitments And Procedures Involved In These Studies?

How long do visits take and what do they involve? Could someone skip a visit, or leave the study?

- Participants must be able to commit to a full day for every monthly clinic visit, for 25 months in the planned Phase 3 GENERATION-HD1.
- For the HD Natural history study, participants must commit to 4 clinic visits where lumbar punctures and other assessments will be performed (at the start of the study and at months 3, 9 and 15), as well as 2 phone check-ins (at months 6 and 12).
- They must be able to tolerate lumbar punctures and blood draws, undergo MRIs (no claustrophobia or metal in the body), and be able to complete interviews and questionnaires
- To ensure that the study is completed efficiently and provides accurate results, it's very important for anyone considering participation to make a careful decision and to commit fully to every study visit.
- Nevertheless, all research participants have a right to withdraw their consent and to leave the study at any time.

What procedures can I expect during these studies?

- Lumbar punctures (spinal tap): fluid is collected/administered with a needle in the lower spine
- Blood tests to measure health and markers of HD
- Physical exams (heart, ears, nose, throat, skin, muscle function)
- Vital signs (pulse, temp, blood pressure, breathing)
- Questionnaires about day-to-day life, functional and mental states (a study companion may also answer some of these)
- Electrocardiograms (a painless measurement of the heart's electrical activity)
- Neurological exams (mental status, senses, motion, reflexes)
- MRI brain scans
- Wearable technologies (smartphones and wrist devices) to measure signs of HD

What are the potential risks of the study, and how will pain or discomfort be managed?

- Since RG6042 is an investigational drug, the safety of the drug is still being tested
- The study has a big time commitment. Participants will need to allow approximately a day of their time to attend each clinic appointment.
- Lumbar punctures can cause pain from the needle in the back, or side effects such as mild to severe headache afterwards. The long term safety of chronic lumbar punctures is also something that needs to be further investigated.
- Some assessments or exams may be a little uncomfortable, tiring, time-consuming, or stressful. It's a lot of work to get poked, prodded, and examined every month. MRI scans are notoriously loud, and cognitive tests can be a bit taxing or confusing.
- All participants will be closely monitored for any and all side effects, including pain or discomfort. In the previous safety study for this drug, the most common side effect was pain due to the procedure. Lumbar puncture headaches occurred after about 10% of lumbar punctures. There were no serious side effects in people who received RG6042. The safety and tolerability data from the study provided the necessary evidence to support continuing the clinical development program for RG6042.

Questions About Study Eligibility

Are eligibility requirements the same for both studies? Does a person need to have symptoms to be eligible for the studies?

- No, all the eligibility criteria are not the same for both studies.

- For example, the Natural History study will include people with early manifest HD (Stage I or II defined as total functional capacity score of 7-13).
- The Phase 3 GENERATION HD1 study will include people with clinically diagnosed manifest HD. This is defined as people with a CAP score >400, independence scale \geq 70, and who can walk on their own and speak.
- The eligibility criteria for both studies will be available on clinicaltrials.gov or www.hdtrialfinder.org.

For the Phase 3 GENERATION HD1 study inclusion criteria, what is the Independence scale? What does a score of 70 mean?

- The independence scale is a measure of the participants' independence. It ranges from 0-100 where 0 means needing total care, and 100 means that no special care is needed. A score of 70 means: self-care is maintained for bathing, limited household duties (cooking and use of knives), stopped driving, and unable to manage finances.

What age range will be considered for the HD Natural History study and the Phase 3 GENERATION HD1 study?

- For both studies, participants must be age 25 – 65 at the start of the study.

What is a CAP score, and what scores will be considered for the Phase 3 GENERATION HD1 study?

- CAP stands for CAG Age Product, and it is a very basic mathematical formula that can be used in part to estimate a person's age of onset, based on how long they have lived with their mutation.
- CAP score = (length of CAG repeat – 33.66) x age at start of the study
- Participants must have a CAP score of greater than 400.
- **Example.** A person with 44 repeats who is 39 years old, $(44 - 33.66) \times 39 = 403.26$. This person would be eligible
- **Example.** A person with 40 repeats who is 60 years old, $(40 - 33.66) \times 60 = 380.4$. this person would NOT be eligible

Will pre-existing conditions prevent someone from participating in the Phase 3 study?

- In general, participants must have stable medical, psychiatric, and neurological status for at least 12 weeks prior to screening and at the time of enrollment. This means that these types of symptoms must be stable and under control, not requiring emergency visits or major treatment adjustments, and not impairing the person's ability to participate. People with serious medical conditions that may interfere with his/her ability to complete the study will be excluded from study participation. Patients with

any medical conditions that may influence the study results (e.g. chronic migraines) will also be excluded. Additional eligibility criteria are available on clinicaltrials.gov or www.hdtrialfinder.org.

Can a participant stay on current medications during the Phase 3 study (e.g., antidepressants, tetrabenazine)?

- In general, participants will be allowed to continue use of medicines such as tetrabenazine/deutetetrabenazine, antipsychotics, antidepressants and anti-anxiety medications, as long as the dose has been stable for at least 12 weeks prior to the start of the study. There are some exceptions, such as memantine, amantadine, and riluzole, which could affect cognition (ability to process information), and certain heavy-duty blood thinners.
- These criteria around current medications are in place in order to ensure the ability to see the effects of RG6042 without the influence of other drugs. Further information about the study, including detailed inclusion and exclusion criteria, will be posted on www.clinicaltrials.gov and shared with HD healthcare professionals. We encourage you to speak to your/your loved one's HD specialist about what may be best for your situation.

Do I need to be in an observational study like ENROLL-HD to participate?

- It is fine for a participant to be involved in studies like ENROLL-HD, HDClarity, PREDICT-HD, or any other observational research, but this is not required.

What if I participated in a previous research study for an experimental drug?

- Past participation in a clinical trial generally will not prevent someone from participating in the clinical trial, however some exclusions will apply. For example, previous or current treatment with an antisense oligonucleotide will not be allowed. Also, if someone has received past treatment with an investigational therapy that is long-lasting, participation will not be allowed unless enough time has passed to ensure that the drug is completely out of the body. Simultaneous participation in another clinical trial with any intervention, including drug or non-drug intervention, will not be allowed. However, participation in observational trials, such as ENROLL-HD, is acceptable. Further information about the study including detailed inclusion and exclusion criteria, will be posted on www.clinicaltrials.gov and shared with HD healthcare professionals. We encourage you to speak to your/your loved one's HD specialist about what may be best for your situation.

Do I need a companion or partner to participate in all my visits?

- It is encouraged, but not required, that participants know someone (a family member or friend) who can act as their study companion. This would be someone who is able to attend appointments, who they see on a regular basis, and who can sign a consent form

to participate in the study by providing support and filling in questionnaires.

How do I join, or how are participants chosen? Is there a lottery, or can I sign up through HDSA?

- Research studies may recruit through existing doctor-patient relationships, usually at centers that are performing the research, or by referral to a nearby site. Speaking to your current doctor is a great place to start.
- There is no lottery system and no list to sign up. HDSA does not have any control over who participates, and there is no guarantee of participation. There will be many more willing participants than “slots,” but this means that the study is likely to move quickly.

Do I need to be at a Center of Excellence or seeing a doctor who performs research?

- You do not need to be at a Center of Excellence, but generally clinics with a research interest are more likely to participate. Please see the “Where and When” section for more information.

Why is the Phase 3 GENERATION HD1 limited to people who are 25-65 years old with a CAP score of 400?

- Roche/Genentech have chosen to study people in the early stages of HD because they wanted to choose a group that are the mostly likely to show the effects of the therapy. People with HD with high levels of independence (as measured by the Independence Scale) have been selected as they are more likely to be able to complete the 2-year study. They have specified the severity of the disease in the trial population by using CAP, a way to measure the toxicity of mutant huntingtin over time. People with HD with CAP > 400 have been shown to progress faster on key clinical endpoints such as the TFC scale, and therefore they are more likely to show any effect that the drug might have on slowing disease progression.
- Genentech/Roche and those involved in this study of course recognize that these measures vary by individual. However, research studies absolutely require fixed limits like this, and the rules cannot be bent.

Why aren't you including people with the HD gene who don't yet have symptoms (pre-symptomatic gene carriers)? Why aren't you including people who have more advanced symptoms?

- Genentech/Roche is well aware that there is a continuum of HD, involving pre-symptomatic gene carriers, individuals with juvenile onset, later stage symptoms, and onset over 65. They are focusing on the early manifest and manifest stages of the illness because they want to conduct this first important trial in people who have measurable symptoms, but are early enough in disease that they are likely to show the potential effects of the therapy. There was also a previous safety trial in the early

manifest HD population that these new studies will build upon.

I'm older than 65, healthy, and I have a CAP score within range of the study criteria. Would you consider including me in the study?

- Unfortunately, no. The upper limit for the study is age 65. See above for an explanation.

I'm younger than 25, and I have a CAP score within range of the study criteria. Would you consider including me in the study?

- Unfortunately, no. The lower limit for the study is age 25. See above for an explanation.

I don't meet the CAP score requirements but my age is between 25 and 65. Would you consider including me in the study?

- Unfortunately, no. A participant's CAP score must be over 400 when beginning the study. See above for an explanation.

Could I begin the study at 65, even if I would be 67 upon completion?

- Yes, as long as a person is within age range when entering the study, they are eligible.

Could I begin the study at 24, since I would turn 25 during the study?

- Unfortunately, no. The minimum age is 25. If the study is still recruiting when a person turns 25, they would then become eligible.

I am not (or my loved one is not) eligible. What about people who don't fit these criteria?

- At this time, the design and eligibility requirements for these studies are not flexible.
- Genentech/Roche is not ignoring the needs of people that fall outside the age limits or any other eligibility criterion. The team will explore RG6042 in other populations if there is sufficient scientific and safety rationale.

Questions About Drug Approval And Availability

Do you anticipate that RG6042 would be available to a wider population of people in the future, if it becomes approved? For example, presymptomatic individuals, people with late-stage HD, or Juvenile HD patients?

- Genentech/Roche recognize the critical medical need for a treatment for HD, especially for people living with severe forms like juvenile-onset HD. At this time there are no clinical studies planned beyond the three in early manifest and manifest HD (Phase I/IIa OLE, observational HD Natural History and Phase III GENERATION HD1 clinical studies), but the team will explore RG6042 in other populations if there is sufficient scientific and safety rationale.

How is efficacy defined – how will we know if RG6042 worked?

- The primary outcome (the main symptomatic change that will be studied) in the GENERATION-HD1 study in the United States is statistically significant change in Total Functional Capacity of people taking RG6042 compared to placebo. Total functional capacity is a measure of how people function day-to-day. Many other measures will be examined as well, including brain scans, neurological and movement assessments, and levels of huntingtin protein. The study will also investigate whether or not the drug is safe over a longer period of time.

Can the study be stopped early and the drug approved if it is working very well? When will they check?

- It is far too premature to speculate about accelerated regulatory pathways. Roche/Genentech is fully committed to executing and completing the Phase 1 / 2 open-label extension study, the HD Natural History study and the Phase 3 GENERATION HD1 pivotal study.

How long will it take to recruit all 660 people for the study? Will you loosen the eligibility criteria or rethink the study if you can't find that many?

- There's a lot involved in this study for each site and each individual to handle. All sites will not open at once, and all 660 people will not be able to begin at once. It is difficult to predict, but it will likely take time to recruit fully, and the study will officially end when all participants have completed 25 months of clinic visits.
- There are far more willing, eligible participants than will be able to join the study, so recruitment is not expected to be an issue. Months and years of expert discussion shaped the design of this trial, so changes are very unlikely.

When will the Phase 3 study results be released? If this drug works, what happens next?

- It's very difficult to predict the outcome and timing of a large international drug study. We have great hope for the study to be completed as soon as possible, but there is no guarantee on timing.
- If the results are promising, approvals would need to move through regulatory health authorities. Because of the great need of the community and the novelty of a genetic therapy, we hope that this process could move as fast as possible. But again, this is extremely difficult to predict.

Will RG6042 be available through Right to Try or Compassionate Use programs?

- At this time, the safety and efficacy are not fully understood, therefore access is currently only available through a clinical trial. Though Roche/Genentech recognize the community's need, this is a novel experimental therapy and its safety and efficacy need to be ensured through proper clinical research before making it more widely available.

What would be the cost of RG6042?

- This question will be considered carefully by Genentech/Roche, but it's not possible to answer at this time. Whether RG6042 is safe and whether or not it can help people, is what the clinical trials will test. Genentech/Roche is not interested in making a drug that can't be accessed by those in need.

The authors have no conflicts of interest to declare. [For more information about our disclosure policy see our FAQ...](#)

GLOSSARY

Total Functional Capacity A standardized rating scale for function in HD, used to assess capacity to work, handle finances, perform domestic chores and self-care tasks

statistically significant Unlikely to have arisen by chance, according to a statistical test

ASOs A type of gene silencing treatment in which specially designed DNA molecules are used to switch off a gene

huntingtin protein The protein produced by the HD gene.

clinical trial Very carefully planned experiments designed to answer specific questions about how a drug affects human beings

observational A study in which measurements are made in human volunteers but no experimental drug or treatment is given

juvenile HD Huntington's disease where symptoms begin before the age of 20.

CAG repeat The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD

phase III The phase in the development of a new treatment where clinical trials are conducted using many patients, to determine whether the treatment is effective

efficacy A measure of whether a treatment works or not

manifest after HD diagnosis, or when symptoms are already showing

placebo A placebo is a dummy medicine containing no active ingredients. The placebo effect is a psychological effect that causes people to feel better even if they're taking a pill that doesn't work.

magnetic resonance A technique using powerful magnetic fields to produce detailed images of the brain in living humans and animals

HTT one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15

