Roche Ends Two HD Clinical Trials as Other Huntingtin-Lowering Therapies Advance

On July 9, Roche announced it would discontinue two ongoing clinical studies investigating treatments for Huntington's disease (HD) after separate analyses showed the programs would not achieve their intended goals. While the news is a significant disappointment for the HD community, both studies have provided valuable insights that are expected to shape future research.

Understanding Huntington's Disease

Huntington's disease is caused by a mutation in the *huntingtin* (*HTT*) gene, which normally contains a DNA sequence in which the CAG segment is repeated 9–35 times. In people with HD, this sequence is expanded, producing an abnormally long and toxic form of the huntingtin protein known as mutant huntingtin (*mHTT*). Although cells attempt to clear this faulty protein, mHTT gradually accumulates within neurons, forming toxic aggregates that contribute to nerve cell dysfunction and death.

This progressive loss of brain cells leads to the physical, cognitive, and psychiatric symptoms associated with Huntington's disease. Physical symptoms include involuntary movements, lack of coordination, or muscle stiffness; cognitive decline is often seen in mental slowness, memory lapses, trouble focusing, and poor judgment; while psychiatric changes often present in compulsions, irritability, withdrawal, and depression. Symptom severity increases over time, often leading to dementia and an inability to walk, speak, or care for and feed oneself.

GENERATION HD2 Falls Short of Clinical Goals

The Phase II GENERATION HD2 study evaluated tominersen, an antisense oligonucleotide (ASO) originally designed by Ionis and developed by Roche. Tominersen works by targeting *HTT* messenger RNA (mRNA), triggering its degradation via RNase H1 and thereby reducing production of both mutant and wild-type huntingtin protein.

The study enrolled 301 participants across 15 countries with early or very subtle signs of Huntington's disease. Researchers evaluated whether a 100 mg dose of tominersen, administered by spinal injection three times per year, could improve clinical outcomes compared with placebo in adults aged 25–50.

Tominersen has had a long and closely watched development history. In its Phase 1/2a trial, it became the first therapy to demonstrate that huntingtin protein levels could be lowered in people with Huntington's disease. However, the Phase III GENERATION HD1 study was halted in 2021 after an independent data monitoring committee determined that the therapy had an unfavorable benefit/risk profile; while no new major safety signals were identified, there was no clear clinical benefit. A subsequent post hoc analysis suggested that younger individuals with earlier-stage disease might benefit from lower or less frequent dosing, leading to the launch of GENERATION HD2.

After 16 months of treatment, all participants completed the GENERATION HD2 study. Although tominersen was well tolerated and successfully lowered mutant huntingtin protein and neurofilament light chain (NfL), a biomarker of neuronal damage, “there was no meaningful impact on clinical efficacy for the study participants receiving tominersen, compared to those on placebo.” As a result, Roche has decided to discontinue development of the drug. The full dataset for the GENERATION HD2 study, including primary and secondary endpoints, subgroup analyses, and exposure and response, has not been presented as of this article’s writing but is expected to be presented at future meetings.

Despite the disappointing clinical outcome, the study produced important scientific findings. Tominersen demonstrated clear biological activity by lowering expanded huntingtin protein in cerebrospinal fluid (CSF) and reducing NfL levels in both CSF and blood plasma, suggesting the therapy successfully engaged its intended target. The disconnect between biomarker improvements and clinical outcomes raises important questions about whether factors such as treatment timing, dosing, delivery, patient selection, or study duration limited the therapy's effectiveness. Because Huntington's disease progresses slowly, many researchers believe longer follow-up periods or different huntingtin-lowering approaches may still prove beneficial.

Roche has also confirmed that the development of tominersen has been permanently discontinued, meaning there will be no open-label extension or compassionate-use program.

Roche's POINT-HD Study Also Ends Following Non-Clinical Findings

The Phase I POINT-HD study evaluated RG6496, an investigational antisense oligonucleotide designed to selectively lower mutant huntingtin protein while having minimal impact on the normal, or wild-type form of the protein. This distinguishes RG6496 from non-selective huntingtin-lowering approaches, such as tominersen, AMT-130, and RG6662, which lower both mutant and wild-type huntingtin. RG6496 achieves this selectivity by targeting a specific single-nucleotide polymorphism (SNP) — a naturally occurring DNA variation present in some people with Huntington's disease — that allows the treatment to preferentially target the mutant HTT allele.

The first-in-human study began enrolling participants in late 2025 and ultimately dosed only three individuals with early Huntington's disease. Its primary goal was to evaluate the safety and tolerability of a single dose of RG6496 in adults aged 25-65 with early HD.

While the clinical study itself raised no safety concerns, Roche was simultaneously conducting longer-term animal studies to support future multiple-dose treatment. New findings from those non-clinical studies showed that RG6496 could not be administered chronically with repeated doses, prompting Roche to discontinue the trial.

"While there is no safety concern for people to receive one dose, we have chosen to stop the POINT-HD study early, because we can no longer offer participants the possibility of long-term treatment," wrote Mai-Lise Nguyen, Patient Partnership Leader at Roche, in a letter to the Huntington's disease community.

The three participants who received treatment will continue to be monitored. Roche also stated that it will continue analyzing data from both the GENERATION HD2 and POINT-HD studies and share the findings with researchers and the HD community at future medical meetings.

Recognizing the Huntington's Disease Community

The discontinuation of these programs is disappointing for the Huntington's disease community, particularly because tominersen represented one of the first therapies to show that huntingtin protein could be lowered in humans. The program also helped validate biomarkers such as CSF mutant huntingtin (mHTT) and neurofilament light chain (NfL), which will continue to play an important role in future clinical trials.

More than 1,500 Huntington's disease families have participated in Roche's huntingtin-lowering research since the first tominersen studies began over a decade ago.

"These contributions changed the history of HD drug development — proving the protein that causes HD could be lowered in humans, shaping new research and approaches, which will undoubtedly lead to future breakthroughs," the Roche HD team stated.

The company also expressed its gratitude to participants and their families: "On behalf of all Roche HD team members over the years, we are deeply grateful to this incredible HD community. Progress is only possible together and built over years of partnership. We remain hopeful for the future of HD research."

What These Decisions Mean

Although both trial discontinuations were announced simultaneously, Roche emphasized that the decisions were unrelated and based on entirely different datasets. Importantly, neither study was stopped because of safety concerns for participants.

Roche also confirmed that development of its Phase I/II Huntington's disease gene therapy candidate, RG6662, is continuing as planned.

Huntingtin-Lowering Is Still a Viable Strategy

Experts say that encouraging results from other investigational therapies, including uniQure's AMT-130 gene therapy, reinforce the idea that huntingtin-lowering remains a promising strategy rather than one that has been disproven. AMT-130 is a one-time treatment delivered directly into the brain through a surgical procedure. It uses an adeno-associated virus (AAV) to deliver microRNA (miRNA) that can recognize, bind, and non-selectively lower the human huntingtin protein.

Two multicenter, dose-escalating Phase I/II clinical studies are underway to evaluate the safety, tolerability, and exploratory efficacy signals of AMT-130 for the treatment of Huntington's disease. Topline 36-month efficacy results for patients receiving high-dose AMT-130 included: a statistically significant 75% slowing of disease progression as measured by composite Unified Huntington's Disease Rating Scale, which met the primary endpoint of the study, a 60% slowing of disease progression as measured by Total Functional Capacity, which met a key secondary endpoint of the study, an 88% slowing of disease progression as measured by Symbol Digit Modalities Test, a 113% slowing of disease progression as measured by Stroop Word Reading Test, a 59% slowing of disease progression as measured by Total Motor Score, and a mean reduction from baseline in cerebrospinal neurofilament light protein (CSF NfL) of -8.2%.

While the clinical studies for AMT-130 are encouraging, uncertainties remain regarding its long-term durability, the risks associated with surgical delivery, and the need for confirmatory data.

uniQure recently announced that, during a meeting with the FDA, it was communicated that "the FDA has agreed that our current clinical data can support a near-term BLA submission and has committed to work expeditiously with us to align on the design of the required confirmatory study."

RG6662, the Huntington's disease gene therapy candidate that Roche is continuing to develop, is also a microRNA-based therapy that uses an adeno-associated virus (AAV) vector to lower huntingtin protein levels in the brain.

Developed by Spark Therapeutics, which is now part of Roche, RG6662 is still early in its phase 1/2 trial, which will remain ongoing as planned. The therapy is delivered directly to the brain through surgery, and the first patient was dosed in June 2025.

Other huntingtin-lowering approaches remain in development, including allele-selective therapies like Wave Life Sciences' WVE-003, which targets an SNP associated with the mutant HTT gene. It's important to note that setbacks involving non-selective HTT lowering do not necessarily predict how allele-selective approaches will perform.

Looking Ahead

While the discontinuation of both studies represents a significant setback for Roche's Huntington's disease program, it does not mark the end of huntingtin-lowering research. Tominersen showed it's possible to reduce mutant huntingtin protein in people and helped establish important biomarkers that will guide future clinical trials. With other investigational therapies still advancing, including uniQure's AMT-130 and Roche's ongoing RG6662 gene therapy programs, the lessons learned from these studies will help shape more effective treatments. The contributions of the thousands of individuals and families who participated in these trials have advanced Huntington's disease research in ways that will continue to influence the search for disease-modifying therapies for years to come.