EUROPEAN HUNTINGTON'S DISEASE NETWORK

Advancing Research, Conducting Trials, Improving Care

Statement on Roche's Discontinuation of GENERATION HD2 and POINT-HD

On 9 July 2026, Roche shared a community letter announcing the discontinuation of two EHDN-endorsed studies:

- **GENERATION HD2**: A phase 2/open-label extension study of tominersen compared with placebo over a minimum of 16 months.
- **POINT-HD**: A phase 1 single-dose study of RG6496 compared with placebo.

GENERATION HD2 continued the investigation of tominersen, a non-allele-selective antisense oligonucleotide designed to lower huntingtin protein levels – both the regular (wild-type) and expanded (mutant) forms. Roche reports that tominersen significantly reduced mutant huntingtin and neurofilament light chain (NfL), a reliable biomarker of neurodegeneration – but did not show meaningful clinical benefit on the composite Unified Huntington's Disease Rating Scale and Total Functional Capacity scores after 16 months of treatment.

POINT-HD was discontinued for unrelated reasons. This first-in-human, single-dose study evaluated RG6496, designed to selectively lower only the expanded form of huntingtin. Animal data indicated that the drug would not be suitable for repeat dosing, and Roche has confirmed that there are no safety concerns for the trial's participants, who received a single dose.

This is disappointing news. But the contributions of participants and their families to the study of tominersen, since its first phase 1 trial in 2015, have been nothing short of exceptional – and we learn from every trial, regardless of final outcome. Tominersen provided the first proof of concept that huntingtin lowering is achievable in humans, validated by objective biofluid biomarkers of target engagement and neurodegeneration. Roche has shown important dedication to therapeutic development for HD. As more detailed data from GENERATION HD2 become available, critical insights for future clinical trial design are likely to emerge.

Roche has confirmed that data analysis will continue and that learnings will be shared with the research and family communities. EHDN welcomes Roche's commitment to share data from

these trials at the earliest possible time. Roche will present at the upcoming EHDN Clinical Research Congress in Krakow, Poland (22–24 October 2026), and additional plans for communication and dissemination are currently in discussion.

The HD clinical trial landscape is evolving rapidly, with therapeutic strategies and trial designs increasingly prioritising intervention before functional decline begins – when the opportunity to modify disease progression in the brain is likely greatest. However, better tools to measure meaningful clinical benefit – particularly in early HD progression – are needed, and this is something the community, including EHDN, is actively working on.

Importantly, Roche's announcement marks the end of their involvement in developing two specific molecules, not of huntingtin lowering as a strategy. A variety of next-generation methods remain in active development (see all current trials and studies endorsed by EHDN here), and huntingtin lowering remains a viable therapeutic target. The NfL lowering reported in GENERATION HD2 is a biologically relevant signal – achieved without allele specificity or exon 1 targeting. This finding may be informative for other molecules in development.

This progress would not have been possible without the HD community, including the participants, families, clinicians, and researchers who have directly advanced our understanding of HD. EHDN remains committed to keeping the community informed through open and transparent dialogue as further data emerge, and to ensuring participants' contributions continue to inform the design of future trials.

EHDN Executive Committee

14 July 2026