IONIS® InBrief
3 March 2022

Key learnings from GENERATION HD1 study of tominersen highlighted at CHDI 2022

The goal of a late-stage clinical study is to generate safety and efficacy data to support approval of a medicine that provides therapeutic benefit to patients. While the early termination of dosing of the Phase 3 GENERATION HD1 study of tominersen in patients with Huntington's disease (HD) was disappointing for the HD community, findings from a post-hoc analysis suggest a path for further development of tominersen in younger adult HD patients with less disease burden. Based on these findings, Roche plans to initiate a new Phase 2 study in this subset of patients.

Tominersen is a novel investigational antisense medicine designed to reduce the production of all forms of the huntingtin protein (HTT), including its mutated variant, mHTT. Roche licensed tominersen from Ionis in 2017 and has led late-stage development, including the Phase 3 study.

At the CHDI Foundation's 17th Annual HD Therapeutics Conference, held Feb. 28 – March 3, researchers from Roche discussed key learnings from the GENERATION HD1 study, including how the data generated suggest that tominersen should be further evaluated in a new Phase 2 clinical study in younger adult HD patients with less disease burden.

The GENERATION HD1 study is a 25-month, randomized, multicenter, double-blind, placebo-controlled Phase 3 clinical study evaluating the efficacy and safety of treatment with tominersen in people with manifest HD. Study participants were randomized to either 120 mg every two months or 120 mg every four months with intrathecal injections of tominersen, or placebo. The study recruited 791 participants from 18 countries around the world. In March 2021, Roche announced that dosing would be stopped in the study following a recommendation from the independent data monitoring committee (iDMC) based on an overall benefit/risk assessment. The study is ongoing without dosing to allow participants to be followed for safety and clinical outcomes. The study will complete at the last-patient last-visit, as planned in March/April 2022.

KEY TAKEAWAY

"Our findings support the continued development of tominersen in a prospectively designed, randomized, placebo-controlled study in younger patients with less disease burden."

– from abstract, "Understanding the treatment and off-treatment effects of tominersen in the Phase III GENERATION HD1 study" presented at 17th Annual HD Therapeutics Conference

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In a presentation focused on "Understanding the treatment and off-treatment effects of tominersen in the Phase 3 GENERATION HD1 study", researchers highlighted the following:

Key observations in the tominersen program:

- Overall, in the Phase 3 study, the 120 mg Q16W regimen was well tolerated but was not associated with positive clinical outcomes vs placebo
- Safety observations included ventricular expansion, which was most prominent in the 120mg Q8W group and appears to decrease in the post-treatment period
- Post-hoc analyses of GEN-HD1 showed that point estimates of clinical outcomes and NfL (a biomarker associated with neuronal health) in a younger and less disease burdened group who received 120 mg tominersen Q16W were consistently in the favorable direction relative to placebo (this was disclosed in an EHDN webinar on Jan. 20)
- Further post-hoc analyses shared at the CHDI conference show that these findings are associated with lower exposure within the Q16W group

How these key learnings informed next steps

- The identification of a subset of GEN-HD1 participants with point estimates of clinical and biomarker outcomes in the favorable direction is guiding design of the new study
- The observed relationship between tominersen exposure and clinical outcomes suggests there may be a window for exposure and/or HTT lowering and informs dose selection for subsequent trials
- Age and disease burden (how long you've lived with the toxic mutation) may affect your response to HTT lowering and/or to tominersen treatment