Answers to additional questions posed by the HDTC audience

There was insufficient time for Peter McColgan and Lauren Boak to answer all the questions asked after their presentation 'Understanding the treatment and off-treatment effects of tominersen in the Phase III GENERATION HD1 study'; given the exceptional importance of this trial to the wider HD community, they have kindly provided answers to those unanswered questions here:

Have you, or do you plan to, measure total or wtHTT? Is there any difference in subgroups regarding the %mutant vs %wt engagement?

Our clinical-grade, GCP-compliant validated assay specifically quantifies mHTT in human CSF and does not detect wild-type HTT. Tominersen has been demonstrated to lower the levels of HTT irrespective of the allele, suggesting that mHTT and wtHTT levels are expected to be lowered to the same degree. A similar GCP-compliant assay measuring total HTT (mHTT and wild-type) is also being developed.

Can you provide an estimate of the Phase 2 timeline?

The new Phase II study is still in the early planning stages. Details about the study design, including eligibility criteria, planned start date and study sites, will be communicated at an upcoming scientific meeting.

The cUHDRS scores are favourable at week 53 in the low exposure group relative to high exposure group. Is the positive trend a function of where the groups start?

The analyses presented are performed using a mixed model for repeated measures approach, which controls for baseline clinical endpoint, to account for this.

Do you agree that the negative effects of tominersen do not seem to result from excessive lowering of HTT?

Tominersen HTT lowering has been shown to be dose- and exposure-dependent, meaning that the higher the dose or exposure, the higher the extent of HTT lowering. It is therefore difficult to disentangle whether the unfavourable effects seen in the Q8W group are related specifically to non-target-mediated effects (such as the drug itself) or are related to target-mediated effects (HTT lowering).

What is the longest timepoint that you have measured the safety of non-allele specific HTT lowering via tominersen in NHPs?

13-week and 39-week safety studies in non-human primates (NHPs) were conducted.

There is no clinical benefit and there is clearly tox - making patients worse - why should patients sign up for a new trial?

GENERATION HD1 did not meet its primary objectives: tominersen 120 mg Q8W was unfavorable compared to placebo, and 120 mg Q16W showed comparable safety, however there was no apparent benefit, compared to placebo. In hypothesis-driven post hoc exploratory analyses, findings suggest that tominersen may have potential benefit in a subgroup of younger adult patients who received low exposure (less frequent dosing) and who have less disease burden. Tominersen was the first investigational therapy to lower mutant huntingtin, and the post hoc findings are encouraging. These findings, together with safety data of low exposure tominersen, support the continuation of the development program with a new Phase II clinical trial in younger adult patients with lower disease burden. While the findings are encouraging, confirmation in a randomised, placebo-controlled study is important, and the team is utilising the vast amount of data from all tominersen studies to plan a new Phase II study. Safety is the number one priority, and the new study (as with GENERATION HD1) will have rigorous safety monitoring and an iDMC. Clinical trials are necessary to advance research and drug development. Many people agree to take part in a clinical trial to help progress medical science and evaluate investigational therapies. Every clinical trial contributes valuable insights to the broader research community, and clinical trials are not possible without willing participants. Before participating in a new clinical trial, a prospective participant should discuss with their health care professional and site staff to understand and be well informed about the trial.

Can you clarify the changes in ventricular volume for the low target group based on the current data?

Dose regimen-dependent increase in ventricular volume were also observed in the Q16W low-age / low-CAP subgroup. There were no hydrocephalus cases in this subgroup, and change in ventricular volume did not show a linear correlation with clinical endpoints.

For reduction in mHTT - how do you know the reduction is not due to some toxic side effects and actually down to tominersen?

Tominersen is an antisense oligonucleotide designed to reduce levels of the disease-causing mHTT by targeting human HTT mRNA. Tominersen is designed to selectively target HTT mRNA in order to suppress the synthesis of HTT protein. Tominersen has been shown to lower mHTT in a dose- and dose-regimen dependent fashion in the Phase I/IIa study, its open label extension study, and GENERATION HD1.

The "favourable direction" is only presented between weeks 53 and 69. Is the "favourable trend" seen from time 0?

Yes, this is the case, and the full time courses were presented in January at the EHDN-hosted webinar (http://www.ehdn.org/roche-tominersen-programme/).

What about ventricular volume changes in the low age / low CAP group?

Dose regimen-dependent increase in ventricular volume were also observed in the Q16W low-age / low-CAP subgroups. There were no hydrocephalus cases in this subgroup, and change in ventricular volume did not show a linear correlation with clinical endpoints.

Can you share what you would use as a placebo in a possible future phase 2 trial?

The new phase II study will be a placebo-controlled study, in which we will be recruiting participants for a new placebo arm. We will be using the same formulation as in GENERATION HD1, including placebo

What are the AEs in the Q8 treatment group?

The preliminary AE data for the Q8W (datacut 5 February 2021) were presented at the virtual CHDI 2021 conference, available on this website here.

Have you carried out more pre-clinical studies to assess why long-term dosing of tominersen caused worsening of scores as well as ventricular enlargement?

Preclinical work is ongoing to understand the effects of huntingtin lowering. Regarding ventricular enlargement and clinical measures specifically, it is challenging to relate studies in animal models directly to clinical and imaging measures, especially in the case of chronic dosing, due to animal models having much larger CAG repeat lengths and shorter life spans.