COLLABORATING WITH THE COMMUNITY TO CONDUCT CLINICAL TRIALS IN HUNTINGTON'S DISEASE: LESSONS FROM THE TOMINERSEN PHASE III GENERATION HD1 STUDY

Victoria Liddy,[1] David West,[1] Mai-Lise Nguyen,[1] Lauren Boak,[1] Scott A Schobel,[1] Nolwen Olivier,[1] Keir Hodge,[1] HD-COPE, Jenny Townhill[2]

(1) F. Hoffmann-La Roche Ltd, Basel, Switzerland;

(2) Enroll-HD platform.

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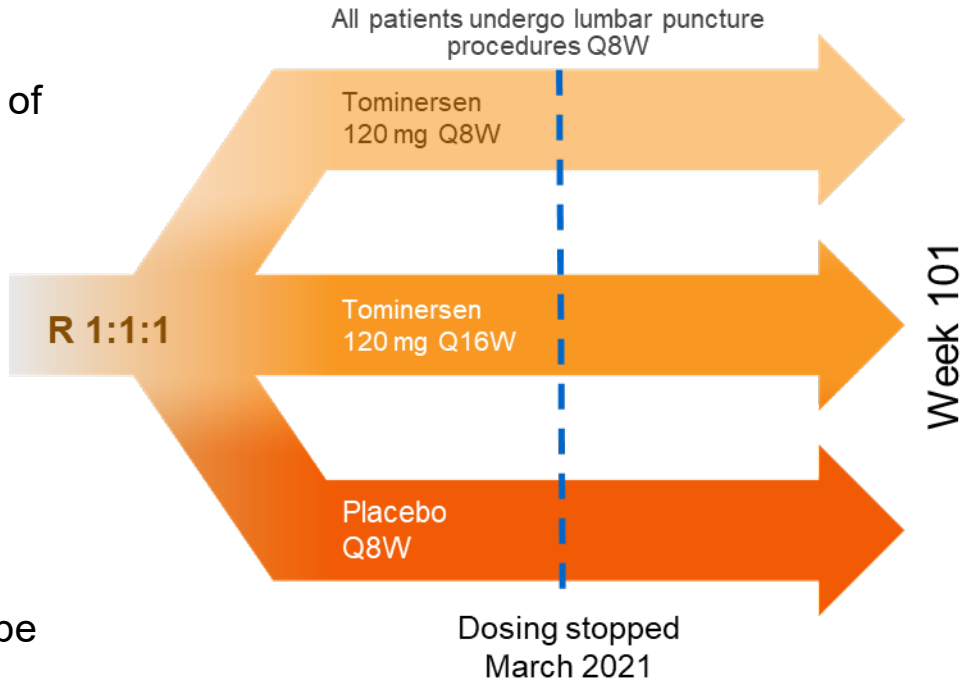
- Many thanks to all the patients who participate in this study and their families

Background

- HD is a rare, genetic, neurodegenerative and ultimately fatal disease that has a **devastating impact on families across generations**.[1,2] There are currently no treatments that can slow or stop the progression of HD
- **Tominersen** is an intrathecally administered ASO that aims to lower mHTT, the underlying cause of HD[3]
- **GENERATION HD1** (NCT03761849), the ongoing, pivotal, Phase III study of tominersen, is being conducted at approximately 100 sites in 18 countries
- Recruitment started in January 2019 and was completed in April 2020. 108 participants were recruited under the original protocol
- The study was amended to include less frequent tominersen dosing. A further 791 participants have been recruited under the new protocol
- On 22 March 2021, Roche announced that dosing would be stopped in GENERATION HD1 following a recommendation from the iDMC based on an overall benefit–risk assessment
  - Participants are encouraged to stay in the study and will continue to be followed per protocol for safety and clinical outcomes until Week 101

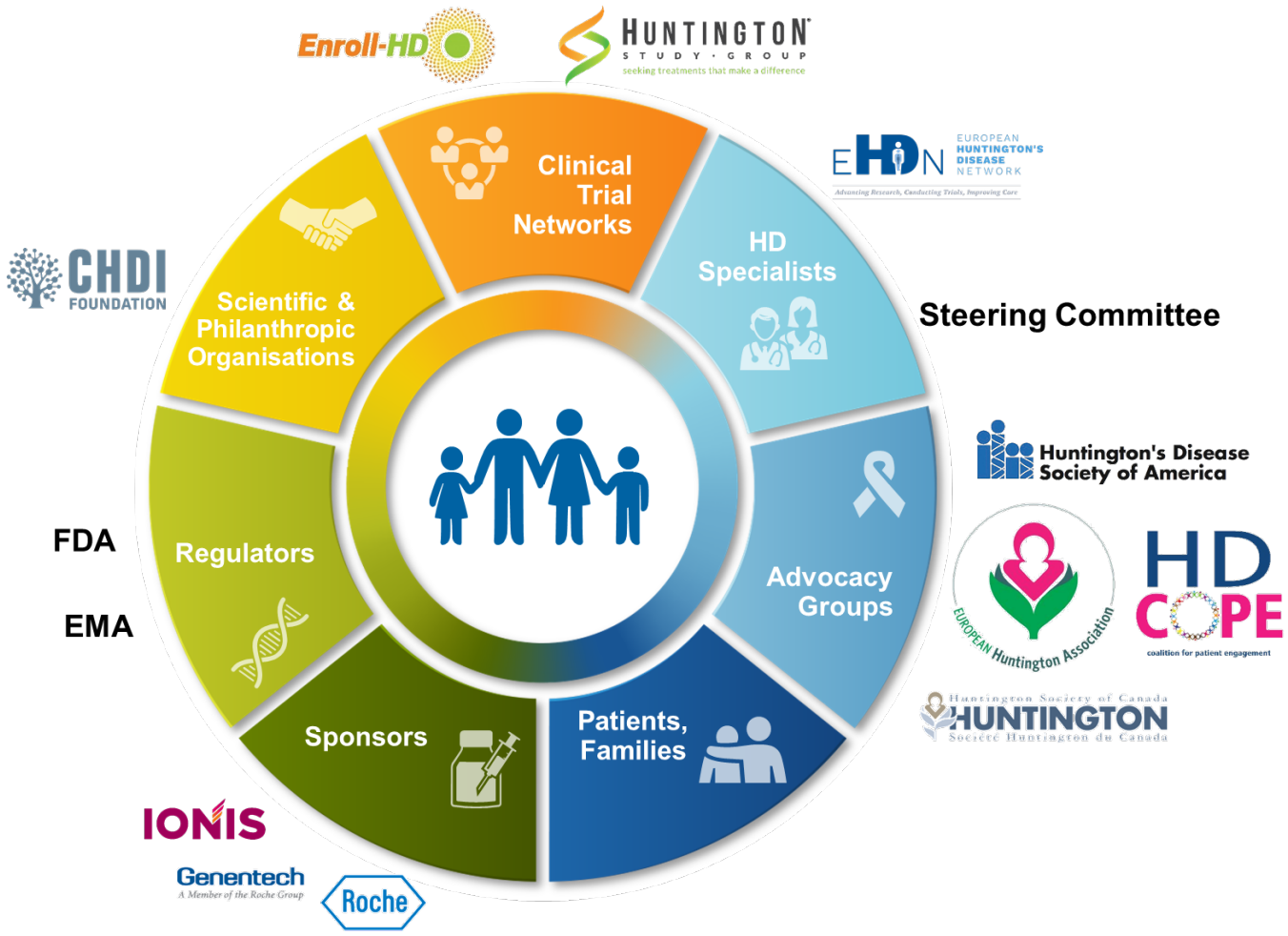
GENERATION HD1 study design



ASO, antisense oligonucleotide; HD, Huntington's disease; iDMC, independent data monitoring committee; mHTT, mutant huntingtin protein; Q8W, every 8 weeks; Q16W, every 16 weeks; R, randomised.

1. Bates GP, et al. *Nat Rev Dis Primers*. 2015; 1:15005; 2. Roos RA. *Orphanet J Rare Dis*. 2010; 5:40; 3. Tabrizi SJ, et al. *N Engl J Med*. 2019; 380:2307–2316.

Partnership with the HD community has been pivotal to the successful initiation of GENERATION HD1



Site selection

- The Enroll-HD team supported site selection activities
- HDSA shared “HDSA Center of Excellence” sites and potential investigators
- Discussions with community leaders
- Final site lists shared with community groups

Protocol development

- Feedback from HD-COPE and global patient representatives
- Reviewed and endorsed by EHDN and HSG
- Endorsement was received from the EHA
- The study site investigators were critical in achieving timely site activation

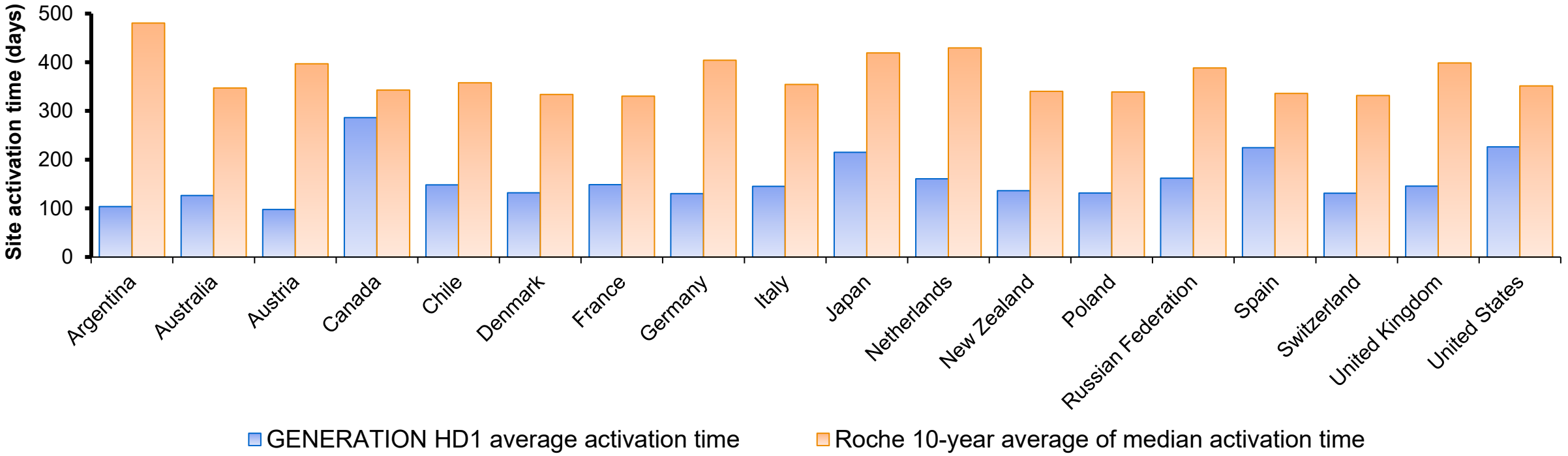
Community partnership

- Family members on the tominersen Steering Committee
- Collaborations supported the development of a more patient-relevant and patient-friendly study design
- Patient Organisation leaders presented at investigator training meetings
- Community letter updates to global Patient Organisations
- Collaboration on educational opportunities

EHA, European Huntington Association; EHDN, European Huntington’s Disease Network; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HD, Huntington’s disease; HD-COPE, HD Coalition for Patient Engagement; HDSA, Huntington’s Disease Society of America; HSG, Huntington Study Group.

Site activation of GENERATION HD1 has been faster than expected

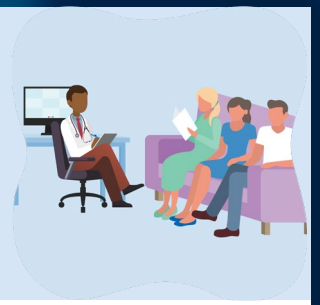
- The start-up performance of countries participating in GENERATION HD1 was assessed by calculating the number of days between the final protocol approval date and the FPI date. This was calculated for each site and the mean was calculated per country
- Metrics were compared with the median estimates calculated for other Roche/Genentech trials conducted at these sites or countries over the past 10 years
- Average site activation times were faster in all countries than for other Roche studies conducted at the same sites in the last 10 years

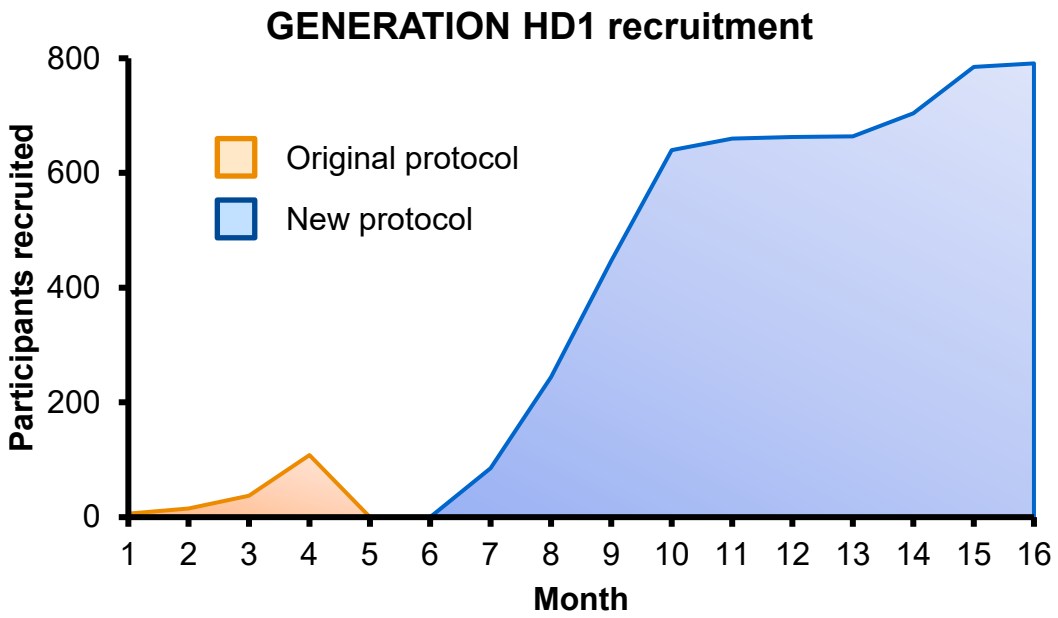


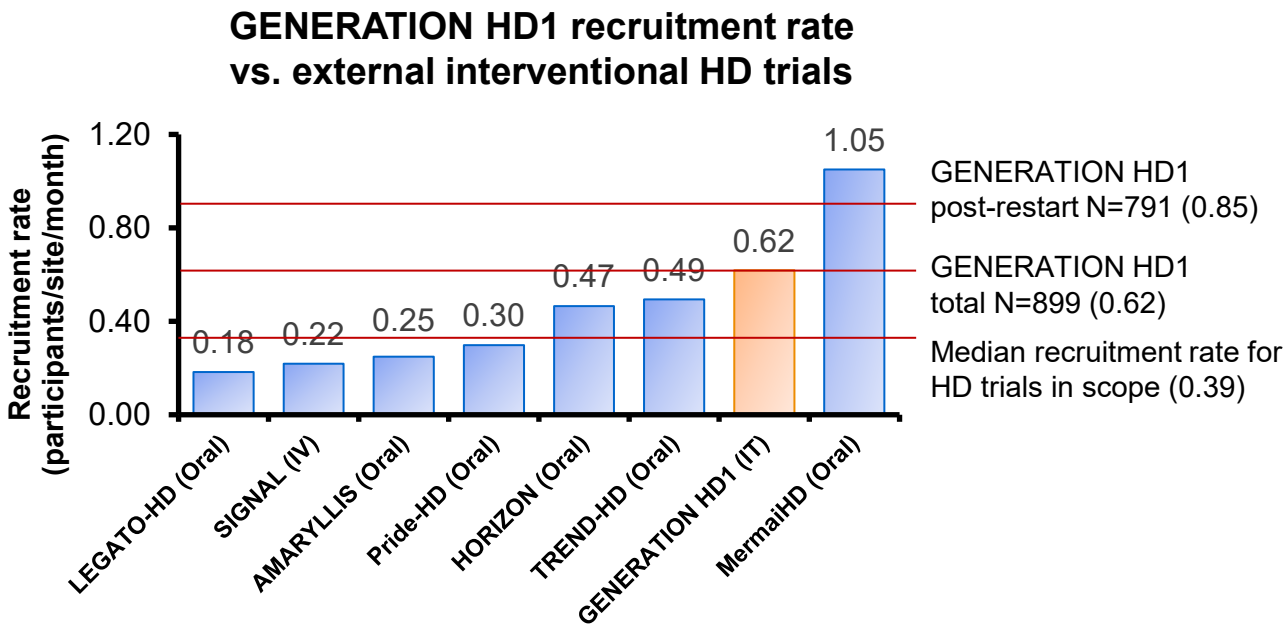
FPI, first patient in.

GENERATION HD1 was among the fastest recruited interventional trials in HD

- Study-level recruitment rate was calculated by dividing the number of participants enrolled by the total number of sites. The study enrolment duration is calculated as the time between the study's first site activation date and the study's last patient in date
- The recruitment rate for GENERATION HD1 was nearly two times faster than the median rate for other non-Roche HD trials conducted over the past 10 years with >250 participants recruited, and was nearly four times faster than the median rate for other Roche trials in rare diseases conducted over the past 10 years





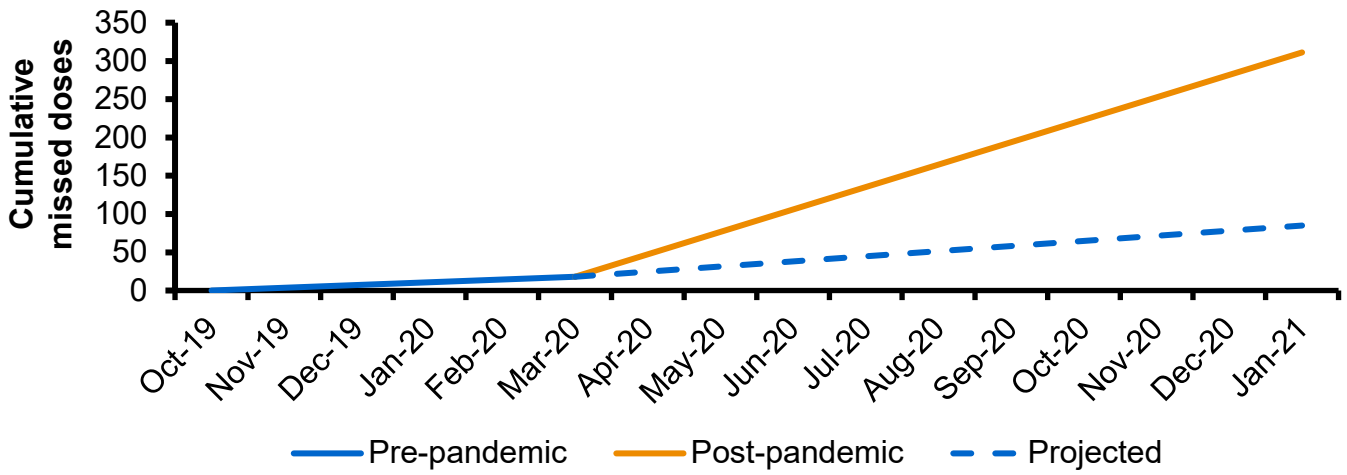


HD, Huntington's disease; IT, intrathecal; IV, intravenous.

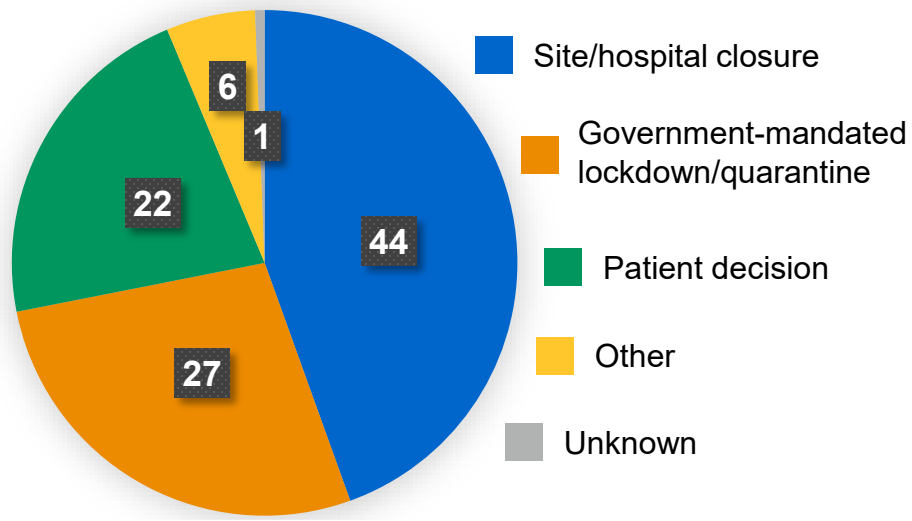
Collaboration with the HD community has been critical to mitigate the effects of the COVID-19 pandemic

- Collaboration with the HD community and knowledge sharing of mitigation measures were critical to mitigate the effects of the COVID-19 pandemic
- Missed doses at the start of the pandemic were primarily due to site/hospital closures, government-mandated lockdowns, and the participant's own decision not to attend their visit
- GENERATION HD1 was almost fully recruited at the start of the pandemic. The statistical power of the study was not impacted by the decision to close recruitment early with 99% of the target recruitment

Effect of the COVID-19 pandemic on missed doses



Reasons for missed doses (%)



HD, Huntington's disease.

Conclusions

- Collaboration with the HD community resulted in a **study design that reflects feedback from HD families**. Close partnership with study sites and an engaged HD community led to accelerated timings and the successful recruitment of the GENERATION HD1 study
- Whilst the experiences and learnings obtained during this process influenced the GENERATION HD1 study design and start-up processes, they have also been **embedded across the tominersen programme** as a whole and are also **contributing to the way Roche works in Rare disease indications** moving forward
- The **effects of the COVID-19 pandemic have been mitigated** due to the support from the HD community, as well as the robust study design
- Support from the community has helped us to **start the study faster than expected**, which has enabled us to learn the outcome of the trial sooner. Whilst the result is not what we hoped for, we have been able to share learnings with the community, ultimately **advancing the understanding of HD and potential treatments**

We would like to thank the patients and families who have participated and who are currently still participating in our research, and the ongoing partnership of the whole HD community

HD, Huntington's disease.