GENERATION HD2 update and further insights from the tominersen programme

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Disclosures

I am an employee of F. Hoffmann-La Roche Ltd

Tominersen is an investigational drug that has not been approved by any health authority. The intent of this presentation is to provide a scientific update on the clinical trial programme of tominersen and the information included should not be interpreted as a recommendation for the use of the product for non-approved uses.

Outline of today's presentation

History of the tominersen programme

GENERATION HD2
Study design and current status

Further insights from GEN-EXTEND
CSF NfL, PK and mHTT lowering

Further insights from GENERATION HD1
Plasma NfL

CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein; NfL, neurofilament light protein; PK, pharmacokinetics.

History of the tominersen programme

10-year tominersen programme history

Building on science and partnerships

2013

Ionis/Roche HD partnership;

investigational compound selected for development

2015–2017

Phase I/IIa study

Roche licenses investigational IONIS-HTT$_{Rx}$ **(tominersen)**

2018–2021

OLE of the Phase I/IIa study;

Natural History Study;

GENERATION HD1 (Phase III);

GEN-PEAK (Phase I);

GEN-EXTEND (OLE)

2021

GENERATION HD1 dosing halted

Data analysis conducted to evaluate path forward

Today/2023

Dose-finding GENERATION HD2 (Phase II) ongoing

HD, Huntington's disease; OLE, open-label extension.

Overview of the tominersen clinical development programme

Phase I/IIa (CS1), N=46[1,2]
- First-in-human study
- Safety, tolerability, PK, PD
- Adults with early manifest HD

OLE (CS2), N=46[3–5]
- 120 mg, Q4W and Q8W
- Long-term safety, tolerability, PK, PD
- Adults with early manifest HD
- 15 months

GEN-EXTEND, N=236[13,14]
- 120 mg Q8W or Q16W
- Roll-over study for participants in previous tominersen studies
- Adults with manifest HD
- Up to 6 years[14]

GENERATION HD2, N=360[15]
- 100 mg or 60 mg Q16W vs placebo, no-loading
- Safety, biomarkers, efficacy
- Adults with prodromal and early manifest HD
- 16+ months

HD Natural History Study, N=95[6,7]
- Prospective, longitudinal study
- Adults with early manifest HD
- 15 months (no treatment)

GENERATION HD1, N=791[8–10]
- 120 mg Q8W and Q16W vs. placebo, loading*
- Long-term safety and clinical outcomes
- Adults with manifest HD
- 25 months (plus follow-up)
- Premature dosing stop as per iDMC recommendation

GEN-PEAK, N≤20[11,12]
- PK/PD in CSF and plasma
- Adults with manifest HD
- 7 months (including follow-up)

* The original protocol included Q4W instead of Q16W. CSF, cerebrospinal fluid; HD, Huntington's disease; iDMC, independent Data Monitoring Committee; OLE, open-label extension; PD, pharmacodynamics; PK, pharmacokinetics; Q4W, every 4 weeks; Q8W, every 8 weeks; Q16W, every 16 weeks.

1. Tabrizi SJ, et al. *N Engl J Med*. 2019; 380:2307–2316; 2. Clinicaltrials.gov/ct2/show/NCT02519036 (Accessed April 2023); 3. Clinicaltrials.gov/ct2/show/NCT03342053 (Accessed April 2023);
4. Tabrizi S, et al. *Mov Disord*. 2019; 34:Suppl S2:S1–S937(A47); 5. Roche study BN40697 protocol; 6. Roche study BN40422 protocol; 7. Clinicaltrials.gov/ct2/show/NCT03664804 (Accessed April 2023);
8. Clinicaltrials.gov/ct2/show/NCT03761849 (Accessed April 2023); 9. Roche Press Release. Available at: https://www.roche.com/media/releases/med-cor-2021-03-22b.htm (Accessed April 2023);
10. Roche study BN40423 protocol; 11. Roche study BP40410 protocol; 12. Clinicaltrials.gov/ct2/show/NCT04000594 (Accessed April 2023);
13. Clinicaltrials.gov/ct2/show/NCT03842969 (Accessed April 2023); 14. Roche study BN40955 protocol; 15. Clinicaltrials.gov/ct2/show/NCT05686551 (Accessed April 2023).

GENERATION HD2

Study design and current status

GENERATION HD2: Testing a refined hypothesis

GENERATION HD1 exploratory *post hoc* findings*

Potential benefit in younger adults with manifest HD with less disease burden and who received lower tominersen exposures

Focused population

GENERATION HD2 will focus on adults with prodromal (very early subtle symptoms) or early manifest HD

Lower and less frequent dosing

GENERATION HD2 will investigate two lower and less frequent doses of tominersen

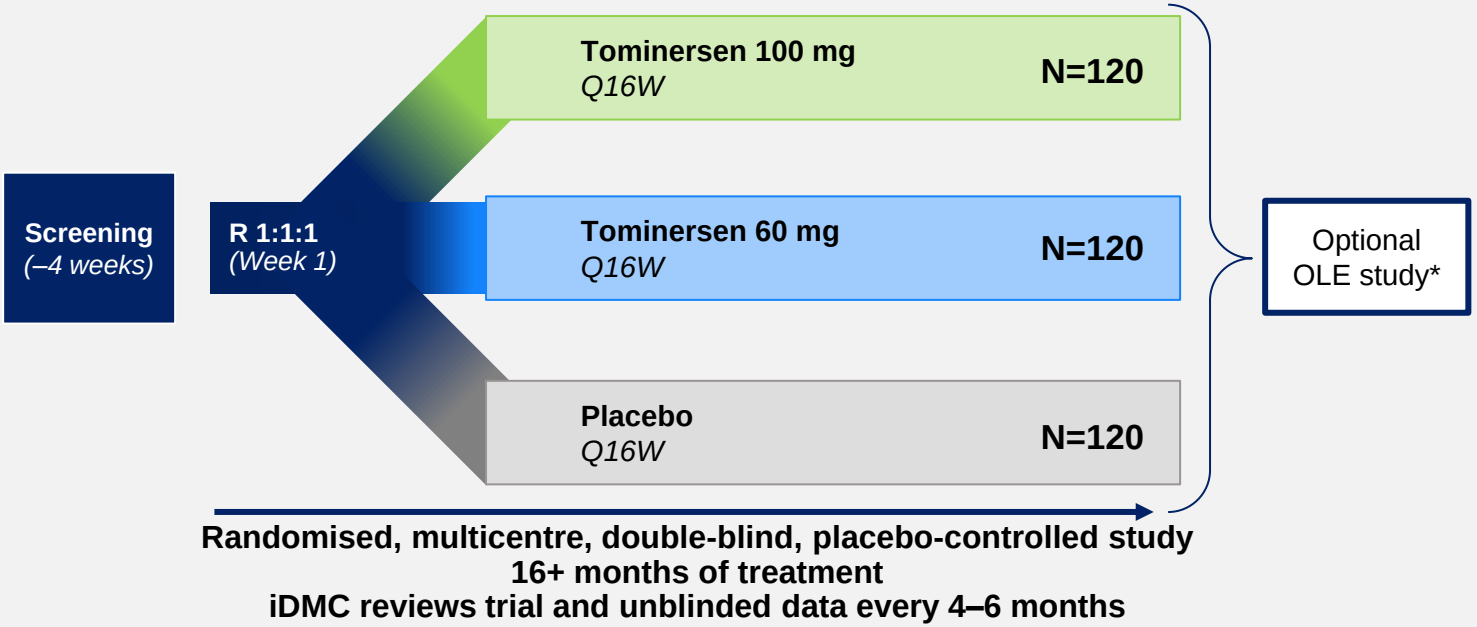
Safety, biomarkers and efficacy trends

GENERATION HD2 will evaluate safety, biomarkers and efficacy trends

* Findings from these exploratory analyses were not statistically significant versus placebo and could represent a chance result, so they are not definitive and need to be confirmed.
HD, Huntington's disease.

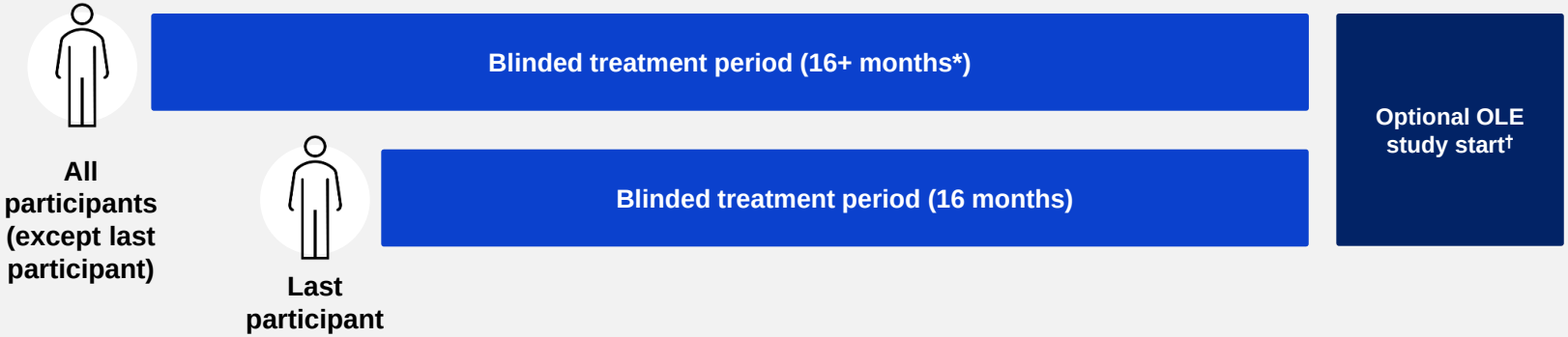
Overview of GENERATION HD2

A study to evaluate the safety, biomarkers and efficacy trends of **two dose levels of tominersen** in participants with **prodromal (~20-/arm) and early manifest (~100-/arm)** HD versus placebo



* Data-dependent planned study; pending approvals from clinical trial authorities.
HD, Huntington's disease; iDMC, independent Data Monitoring Committee; OLE, open-label extension; Q16W, every 16 weeks; R, randomisation.

Key aspect of the GENERATION HD2 study: “Common close” design

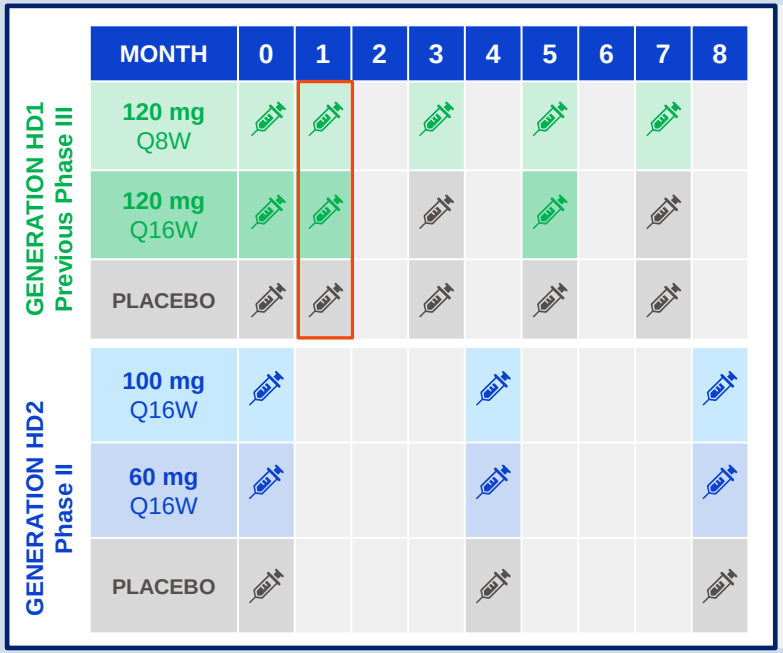


- Minimum 16-month treatment period (seven clinic visits with four interim phone consultations)
- The common close design means that the blinded treatment and study assessments continue for all participants until the last participant completes 16 months of treatment
- Decision about the OLE will be data driven (e.g. appropriate dose and safety determined in study)

* Length of blinded treatment period is dependent on when the participant is randomised. † Data-dependent planned study; pending approvals from clinical trial authorities.
OLE, open-label extension.

Key differences in GENERATION HD2 compared with GENERATION HD1

Loading dose (“load”) = tominersen = placebo injection



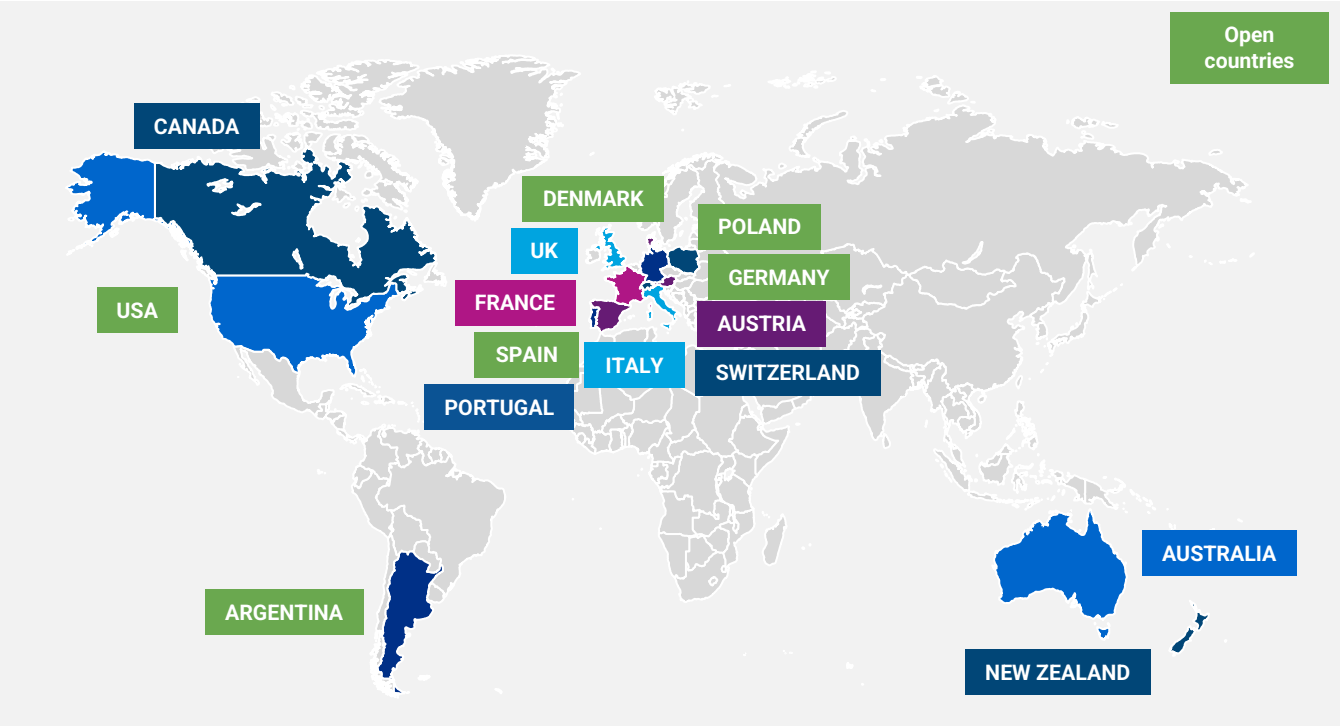
What’s different in GENERATION HD2?

- **Lower doses**: 100 or 60 mg vs 120 mg in previous studies
- **Reduced dosing frequency**: Q16W only
- **No loading dose**
- **CSF sampled between dosing visits at Month 9** to further characterise the CSF mHTT profile

CSF, cerebrospinal fluid; iDMC, independent Data Monitoring Committee; mHTT, mutant huntingtin protein; NfL, neurofilament light protein; Q8W, every 8 weeks; Q16W, every 16 weeks.

GENERATION HD2: Current status

- To date, six countries and 15 sites are open globally
- Study planned to run in 15 countries across 75 sites*
- Specific study sites will be listed on clinical trial registries once they are ready to enrol participants



* Final country participation to be confirmed. For any clinical study, it is possible that for various reasons an expected study site/country does not proceed to enrol participants. Alternatively, additional locations may be added.

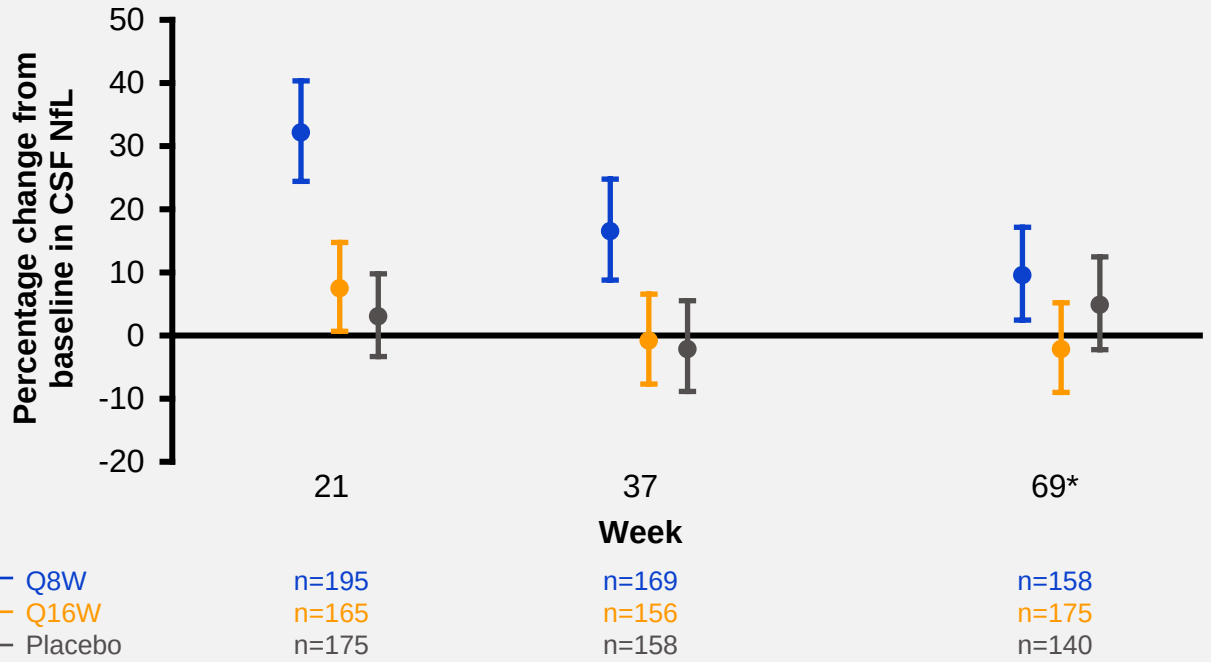
Further insights from GEN-EXTEND

CSF NfL, PK and mHTT lowering

CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein; NfL, neurofilament light protein; PK, pharmacokinetics.

In GENERATION HD1 (with loading dose), transient increases in CSF NfL were observed in the Q8W dosing regimen

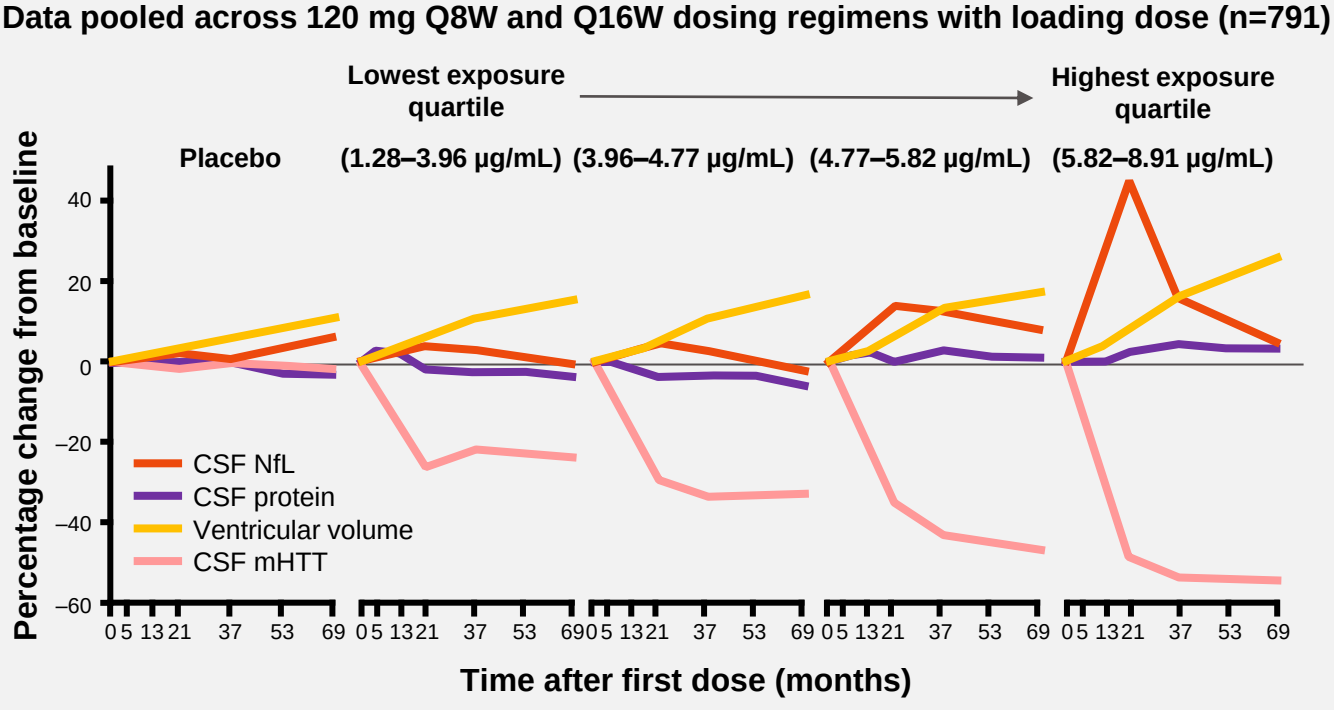
- **Q8W: NfL increases from baseline at all time points, with the greatest increases at Week 21; trending towards baseline by Week 69**
- **Q16W: point estimates greater than baseline at Week 21; in line with baseline levels at Weeks 37 and 69**



* NfL data available for 70% of participants with clinical data at Week 69 (corresponding to 79% of participants with CSF data).
Data points represent geometric mean values and their 95% confidence interval based on the analysis of mixed effect mode for repeated measures.
CSF, cerebrospinal fluid; NfL, neurofilament light protein; Q8W, every 8 weeks; Q16W, every 16 weeks.

Exposure–response relationship of biomarkers in GENERATION HD1 showed that CSF NfL increases can be avoided at lower exposures

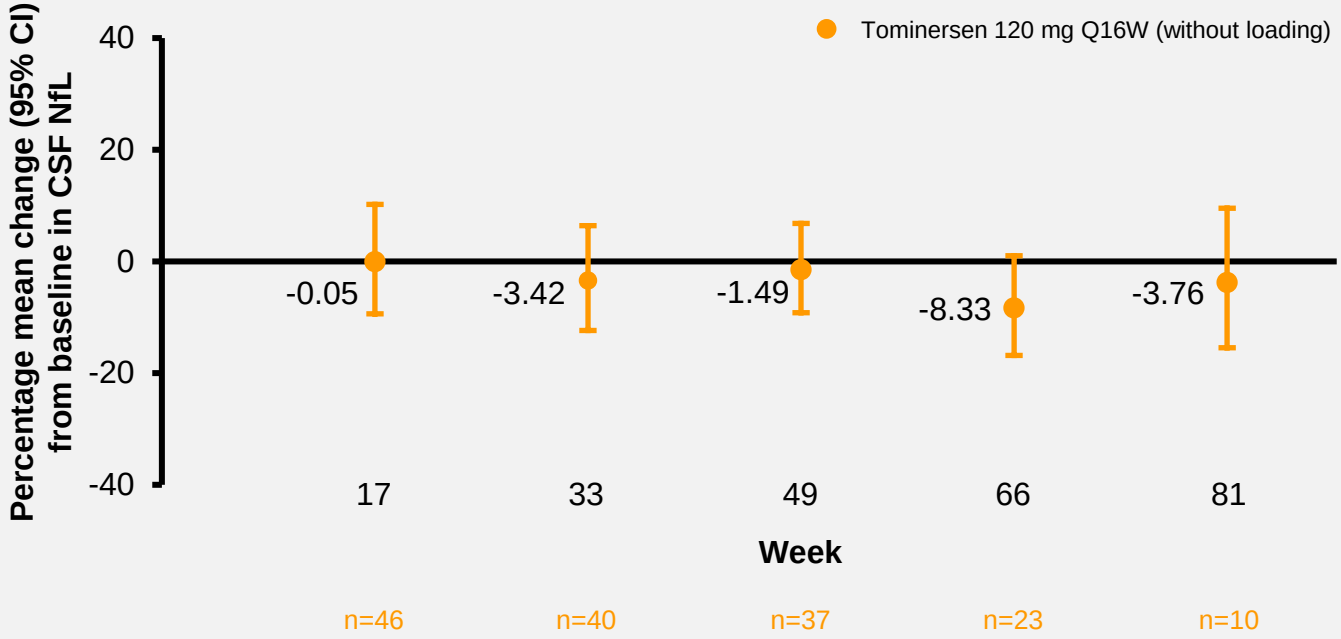
- Increases in CSF NfL and CSF protein were observed in higher exposure quartiles but were not observed in the lowest exposure quartile
- The greatest increases in ventricular volume were observed at the highest exposure with smaller increases at lower exposures



CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein; NfL, neurofilament light protein; Q8W, every 8 weeks; Q16W, every 16 weeks.

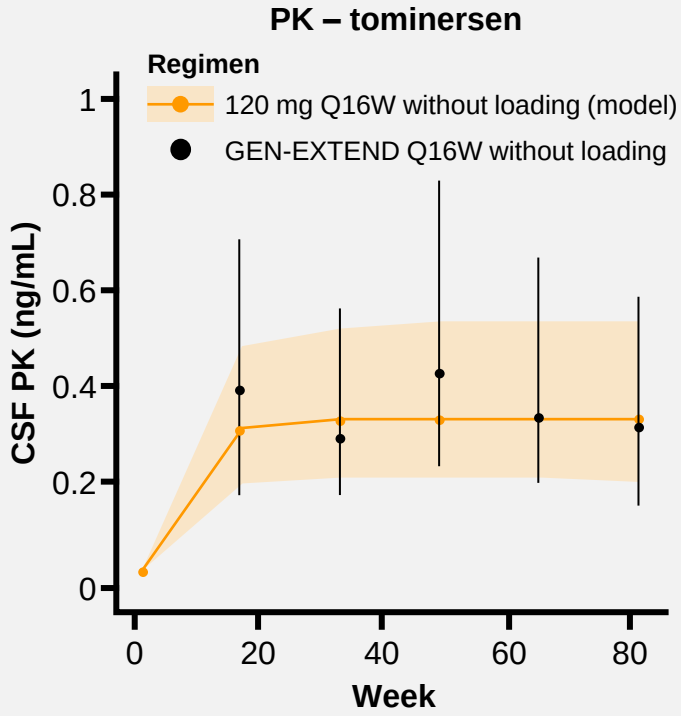
In GEN-EXTEND, CSF NfL levels remained below baseline in the Q16W no-load dosing regimen

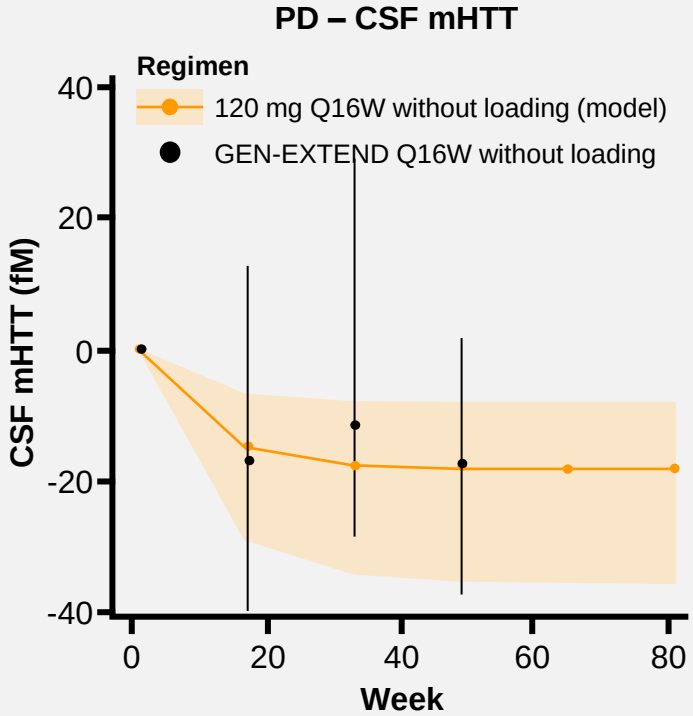
- **No CSF NfL increase above baseline observed in the GEN-EXTEND Q16W no-load group**
- **These data are supportive of the observation that NfL increases can be avoided at lower exposures**



CI, confidence interval; CSF, cerebrospinal fluid; NfL, neurofilament light protein; Q16W, every 16 weeks.

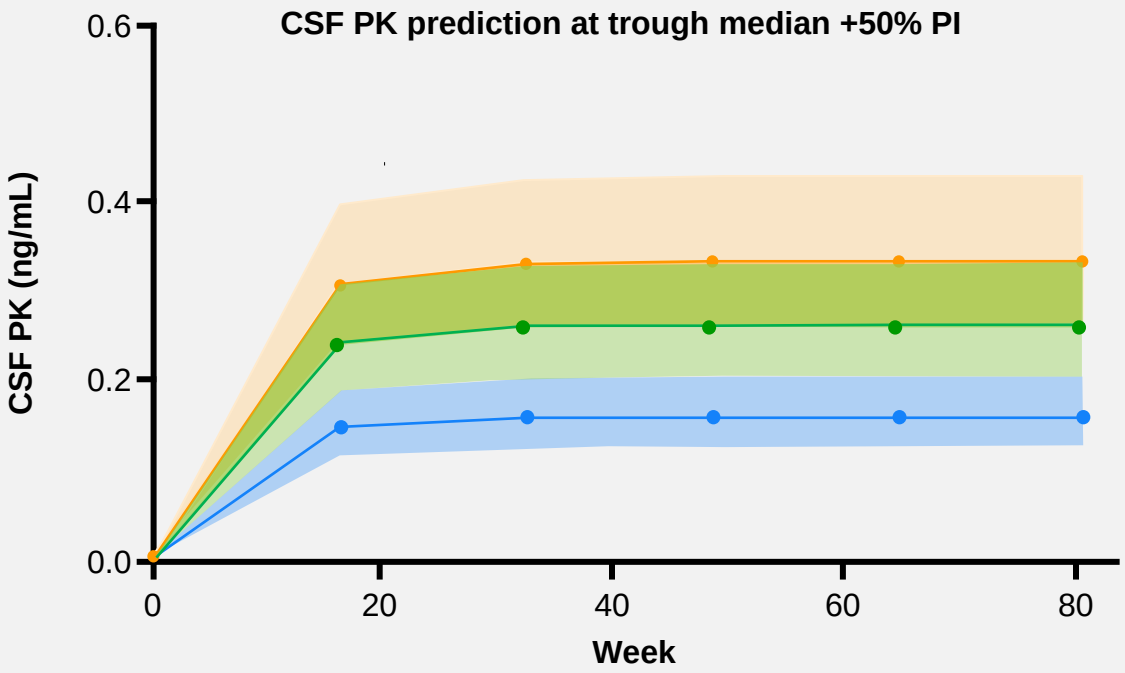
Observed CSF tominersen concentrations and mHTT reductions were within predicted ranges after Q16W no-load dosing in GEN-EXTEND





CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein; PD, pharmacodynamics; PK, pharmacokinetics; Q16W, every 16 weeks.

Simulation of CSF tominersen PK profiles in a typical target GENERATION HD2 population in comparison with simulations in GEN-EXTEND population



Regimen

GEN-EXTEND

120 mg Q16W without loading

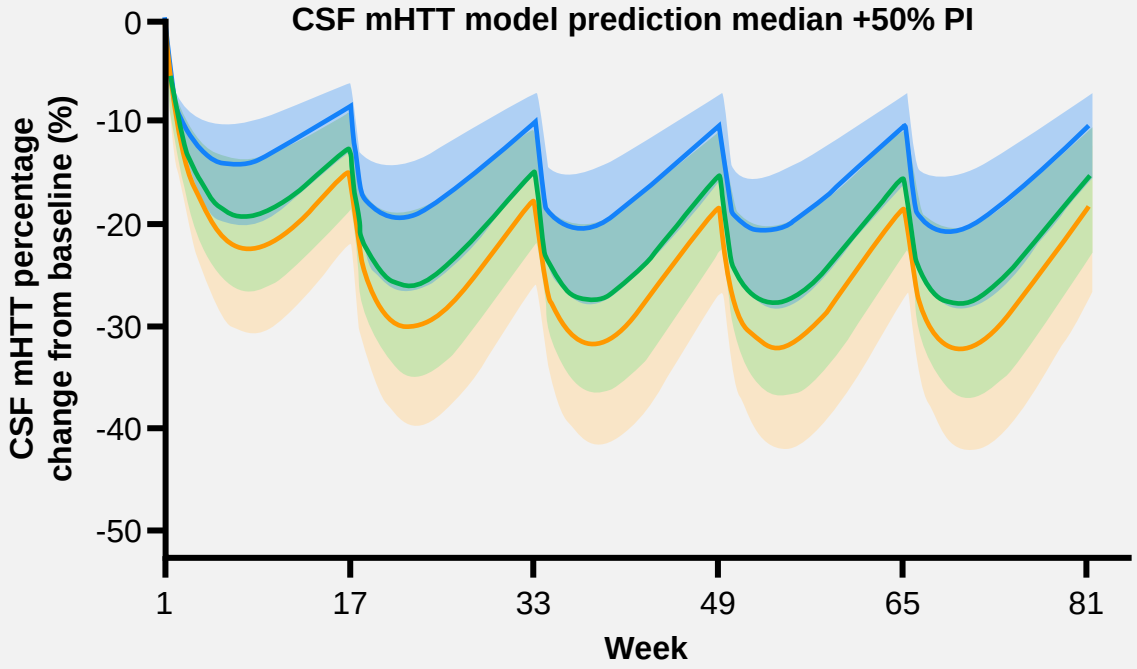
GENERATION HD2

100 mg Q16W without loading

60 mg Q16W without loading

CSF, cerebrospinal fluid; PI, prediction interval; PK, pharmacokinetics; Q16W, every 16 weeks.

Simulation of CSF mHTT profiles in a typical target GENERATION HD2 population in comparison with simulations in GEN-EXTEND population



CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein; PI, prediction interval; Q16W, every 16 weeks.

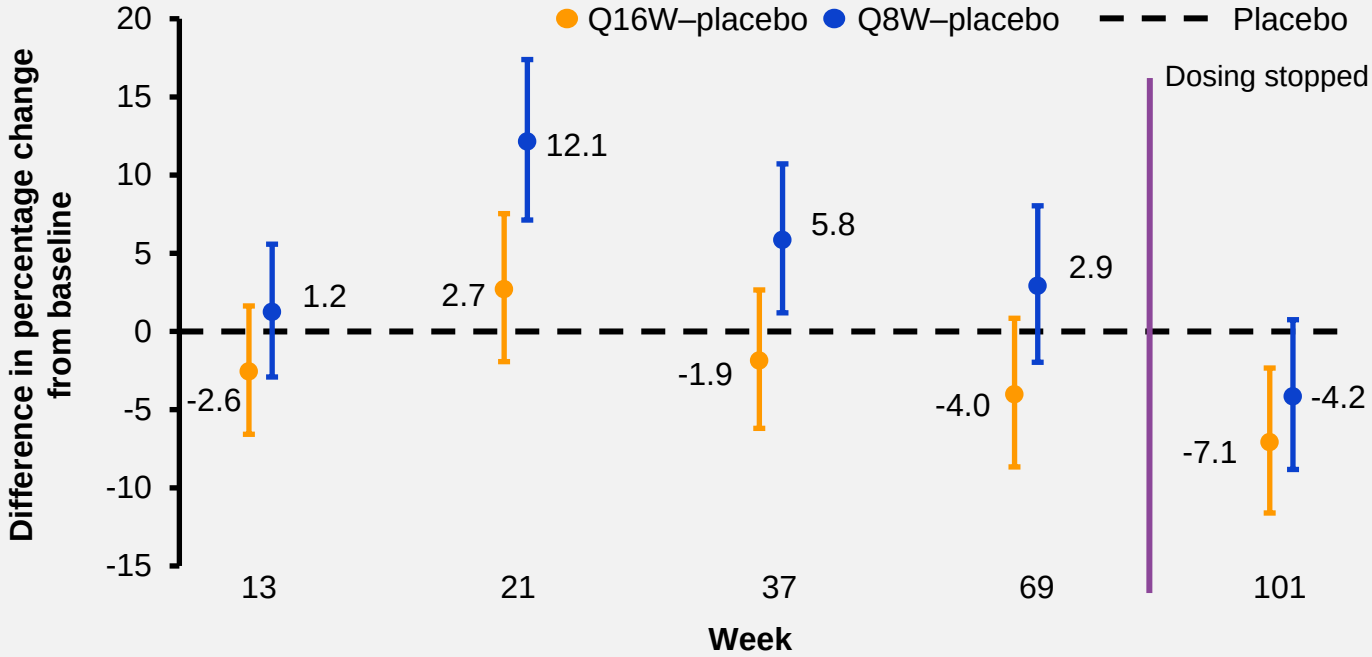
Further insights from GENERATION HD1

Plasma NfL

NfL, neurofilament light protein.

GENERATION HD1: In the Q16W group, plasma NfL showed trends below placebo beyond Week 21

- **Q8W: Plasma NfL greater than placebo at all time points on treatment, below placebo at Week 101 (off treatment)**
- **Q16W: Plasma NfL greater than placebo at Week 21, below placebo at all subsequent timepoints**



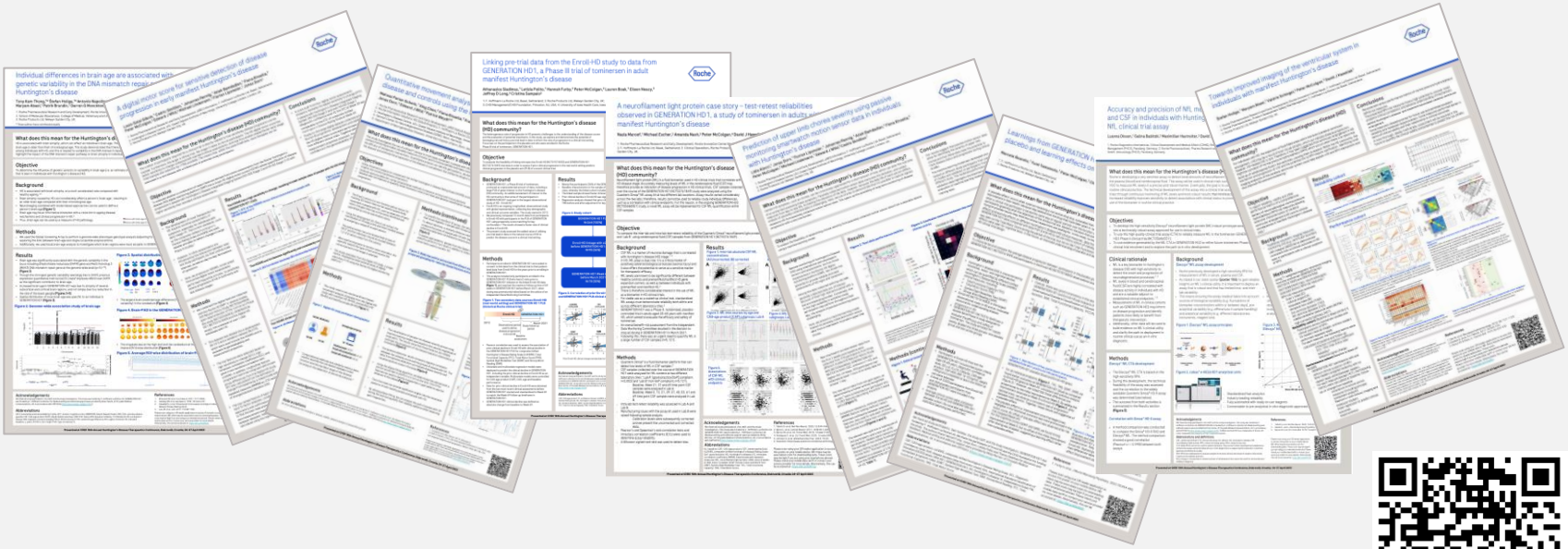
NfL, neurofilament light protein; Q8W, every 8 weeks; Q16W, every 16 weeks.

Summary

- GENERATION HD2 will test two lower dose regimens of tominersen (100 mg and 60 mg Q16W) in prodromal and early manifest HD, evaluating safety, biomarker and efficacy trends
- GENERATION HD2 is planned to run in 15 countries across approximately 75 sites
- New GENERATION HD1 and GEN-EXTEND data suggest that tominersen at lower exposures avoids NfL increases above baseline, while still achieving CSF mHTT lowering, and has the potential for NfL lowering
- These new data provide further support for GENERATION HD2 and the dose regimens selected

CSF, cerebrospinal fluid; HD, Huntington's disease; mHTT, mutant huntingtin protein; NfL, neurofilament light protein; Q16W, every 16 weeks.

More data on tominersen



GENERATION HD1 manuscript under review

Acknowledgements

Ionis discovered tominersen and is partnered with Roche for its development

Special thanks to Frank Bennett, Holly Kordasiewicz, Eric Swayze, Roger Lane and Anne Smith

Special thanks for sharing data and for ongoing collaboration

Deepest gratitude to the investigator network, persons with HD and their families

HD, Huntington's disease.

THANK YOU

A big THANK YOU to the HD community for their ongoing collaboration, especially to all study participants, their families, investigators and site staff, and the tominersen steering committee

Your ongoing contributions to the programme are inspirational

HD, Huntington's disease