Update on GENERATION-HD2

European Huntington Association (EHA) Conference, Clinical Trial updates session
Blankenberge, Belgium - Sunday 22 October 2023

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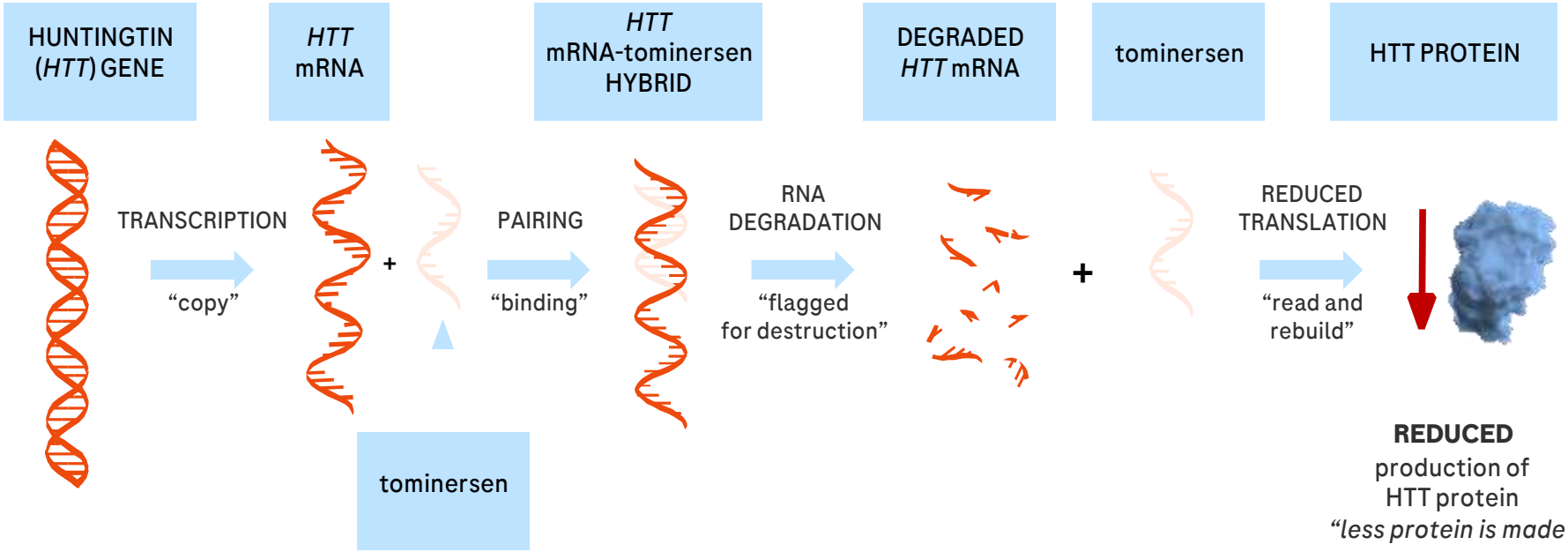
Disclosures

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.

History of the tominersen program

Tominersen is an investigational molecule designed to target the underlying genetic cause of HD



Abbreviations: HTT=huntingtin; mRNA=messenger riboneucleic acid.
Tominersen is an investigational (not approved) medicine that is being studied for the treatment of people with HD.

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

Dose dependent CSF mHTT lowering

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

Well underway globally, with ~30% recruited

HD, Huntingtons disease; OLE, open-label extension.

From GENERATION HD1 to GENERATION HD2

A reminder of GENERATION HD1 results

- **GENERATION HD1** showed a consistent pattern of clinical progression over time in key outcome measures, resulting in interpretable study data to enable recommendations by the Independent Data Monitoring Committee (iDMC)
- **Based on an overall benefit:risk assessment** of data through 17 months, the iDMC recommended to stop dosing in all study arms

 120 mg EVERY 8 WEEKS	In the tominersen 120 mg every-8-weeks dosing arm, tominersen was unfavorable compared with placebo
 120 mg EVERY 16 WEEKS	In the tominersen 120 mg every-16-week dosing arm, the benefit:risk profile was not as clear. The safety profile appeared comparable to placebo; however, there was no apparent benefit observable

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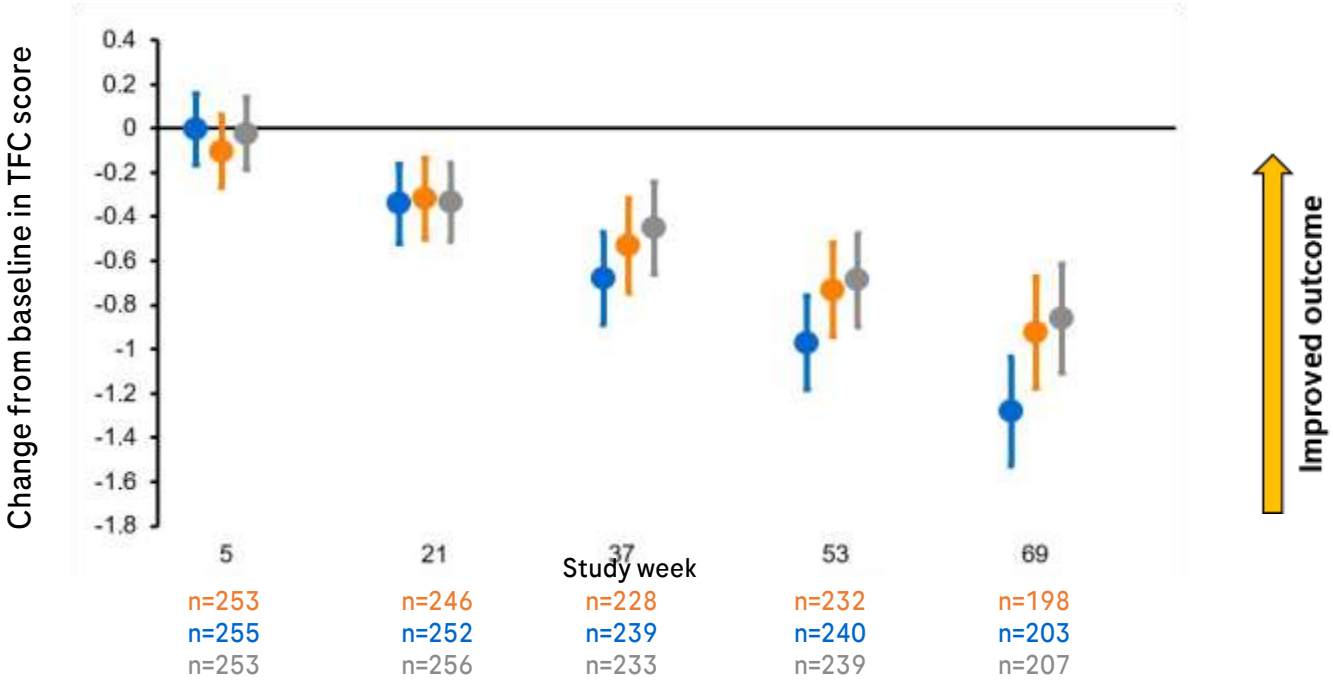
Change from baseline to Week 69 in TFC (total functional capacity) at group level



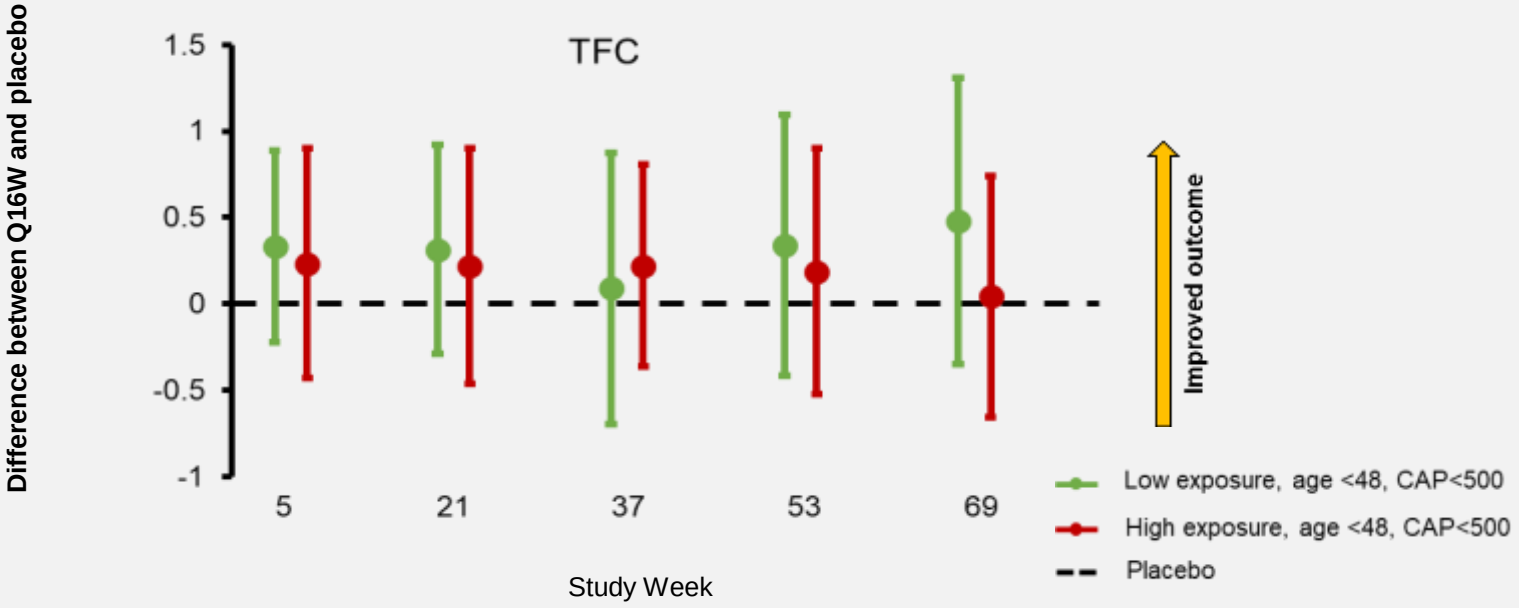
Ref. Boak L. & McColgan P. An update from the tominersen programme, including key findings from the Phase III GENERATION HD1 trial. EHDN webinar January 2022 ehf-epqy-owf

Unfavourable point estimates for 120 mg Q8W compared with placebo, 120 mg Q16W comparable with placebo

Update from what was shown at CHDI in 2021 with all available data following dosing stop in March 2021 (~70% of patients reached Week 69); interpretation not changed.
Data points represent least-squares mean values and their 95% confidence interval based on the analysis of mixed-effect model repeated measure.
TFC, Total Functional Capacity Scale; Q8W, every 8 weeks; Q16W, every 16 weeks.

Potential benefit in younger participants with less advanced disease at lower doses* - GENERATION HD1 subgroup analysis

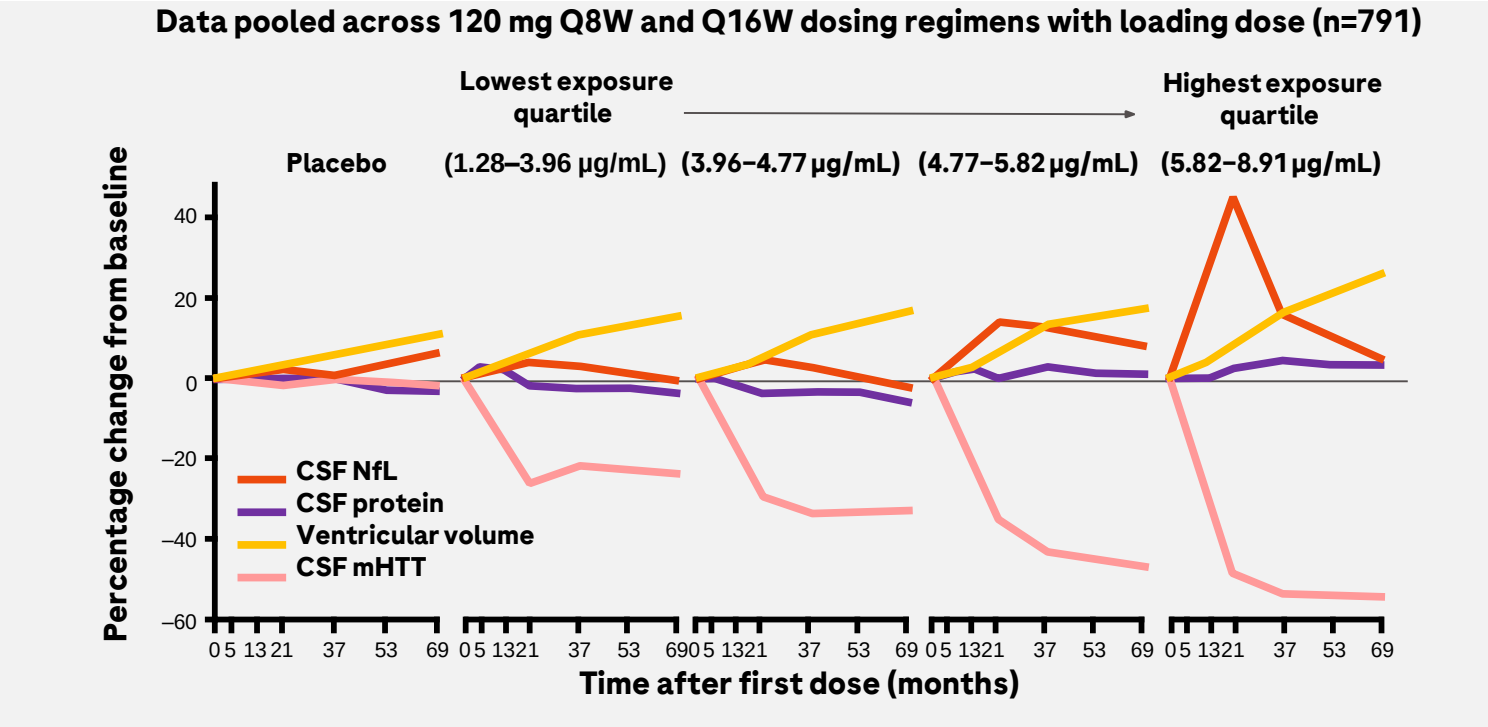
***Median split of the popPK model predicted average CSF tominersen concentration over the 0- to 21-week treatment period for individual GENERATION HD1 patients**



Data points represent least-squares mean values and their 95% confidence interval. Propensity score analysis (PSA) as exposure is a post-randomisation variable.
CAP, CAG-age product; CSF, cerebrospinal fluid; cUHDRS, composite Unified Huntington's Disease Rating Scale; popPK, population pharmacokinetics; Q16W, every 16 weeks; SDMT, Symbol Digit Modalities Test; SWR, Stroop Word Reading; TFC, Total Functional Capacity; TMS, Total Motor Score.

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.

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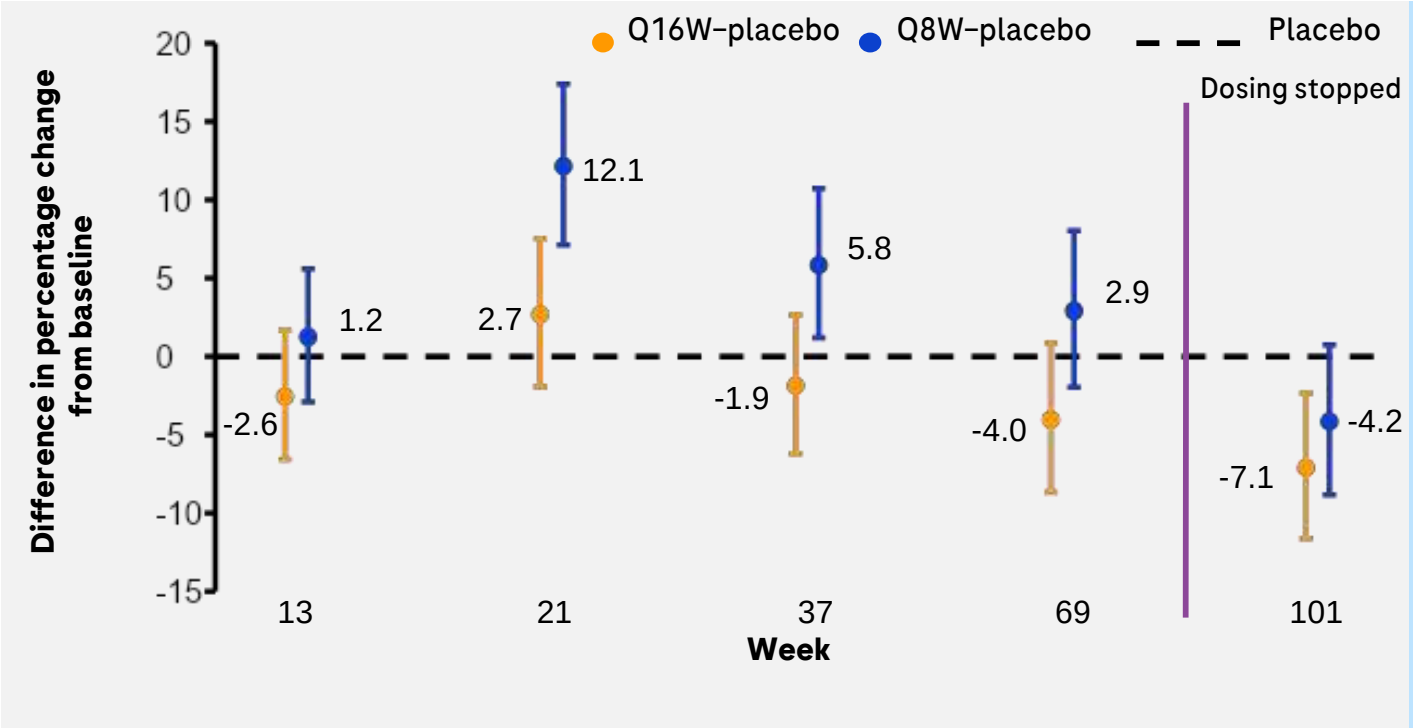
GENERATION HD1: In the 120 mg Q16W group, plasma NfL showed trends below placebo beyond Week 21

- **120 mg Q8W: Plasma NfL greater than placebo at all time points on treatment, below placebo at Week 101 (off treatment)**
- **120mg 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.

GENERATION HD2

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GENERATION HD2: Reasons to Believe

Right Place: tominersen gets into the deep brain regions that are selectively vulnerable in Huntington's disease, including **cortex, striatum and thalamus**

Right Target: tominersen is the only HTT lowering therapy to have conclusively shown dose-dependent **lowering of mHTT protein in CSF**

Safety: safety profile comparable to placebo at Q16W 120mg and the same anticipated at lower doses

Potential Benefit: seen in GENERATION HD1 post-hoc analysis

Supportive Biomarkers: plasma NfL and new digital PSA analysis from GENERATION HD1

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

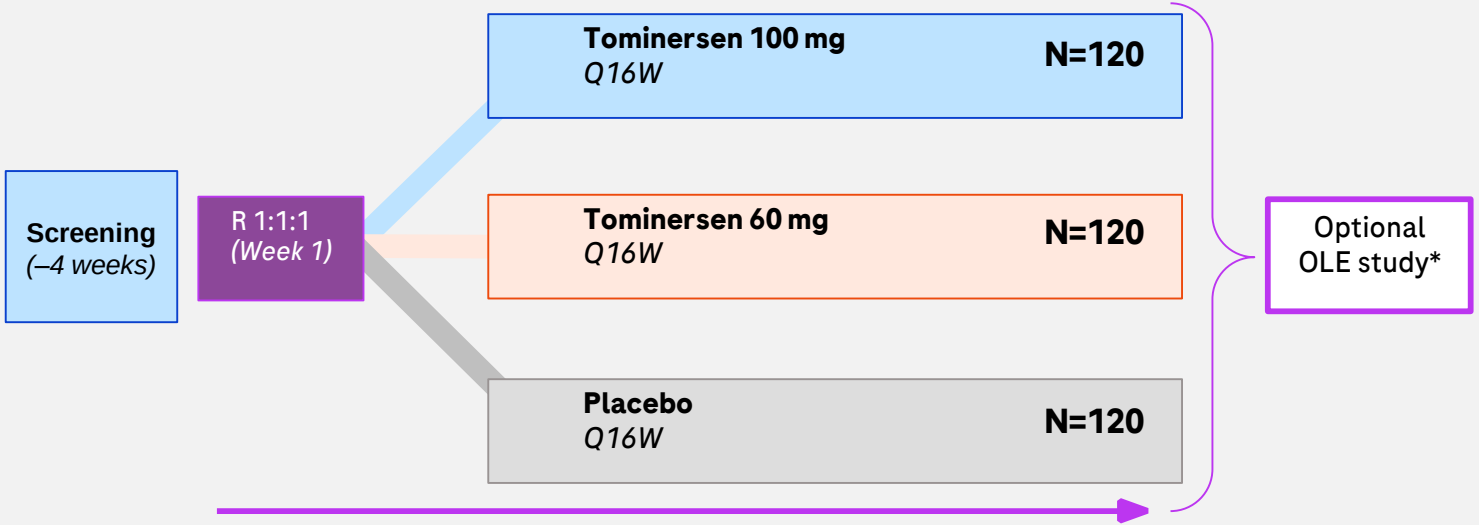
Safety, biomarkers and efficacy trends

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, Huntingtons disease.

Overview of GENERATION HD 2

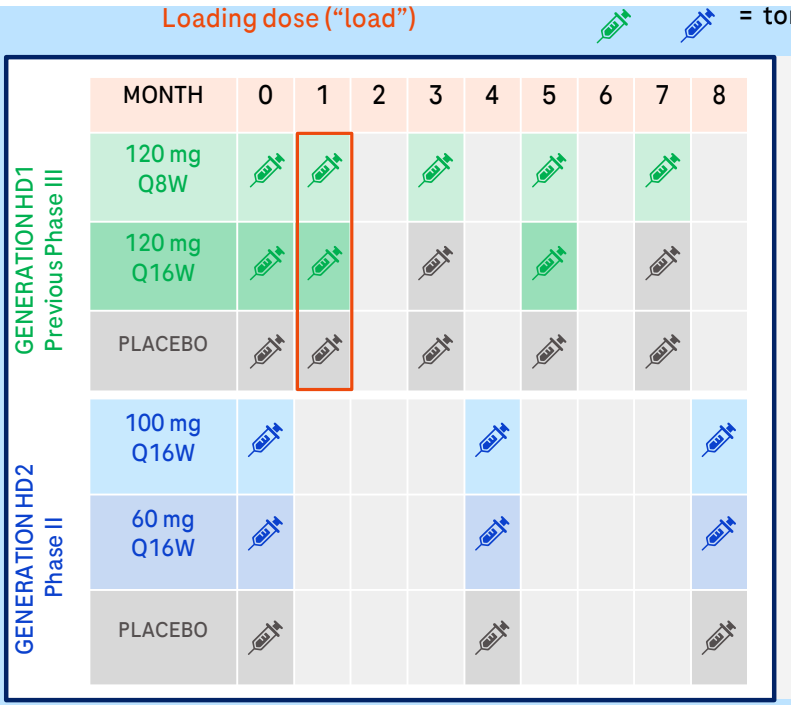
A study to evaluate the safety, biomarkers and efficacy trends of **two dose levels of tominersen** in participants with **prodromal (~20-/arm) and early manifest (~100-/arm)** HD versus placebo



Randomised, multicentre, double-blind, placebo-controlled study
16+ months of treatment; iDMC reviews trial and unblinded data every 4–6 months

* Data-dependent planned study; pending approvals from clinical trial authorities
https://clinicaltrials.gov/study/NCT05686551
HD, Huntingtons disease; iDMC, independent Data Monitoring Committee; OLE, open-label extension; Q16W, every 16 weeks; R, randomisation.

Key differences in GENERATION HD2 compared with GENERATION HD1



What's different in GENERATION HD2?

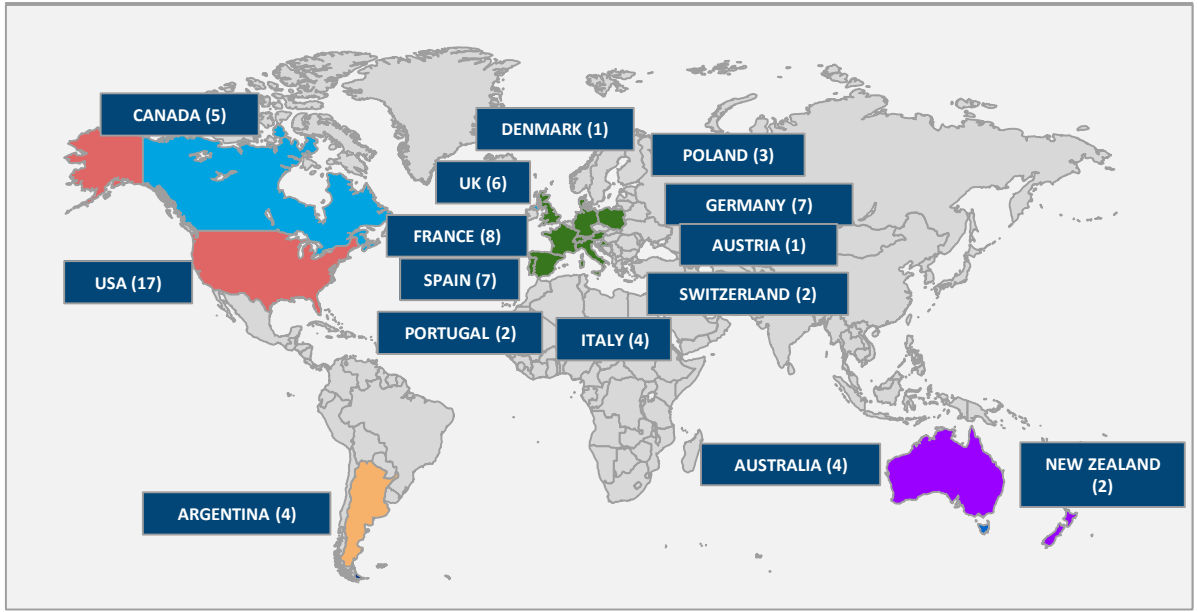
- **Lower doses:** 100 or 60 mg vs 120 mg in previous studies
- **Reduced dosing frequency:** Q16W only
- **No loading dose**
- **CSF sampled** between dosing visits at Month 9 to further characterise the CSF mHTT profile

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

Update on GENERATION HD2, including recruitment and site activation

GENERATION HD2: Global overview

Trial open in 15 countries
Approx. 70 sites activated
Over 30% enrolled



Doing now what patients need next