New fluid biomarker data from GENERATION HD1 and what it means for GENERATION HD2

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Disclosures

I am an employee of and own stoF. 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



What can YKL-40, total Tau and GFAP in CSF tell us?



GENERATION HD1 exposure-response and implications for GENERATION HD2



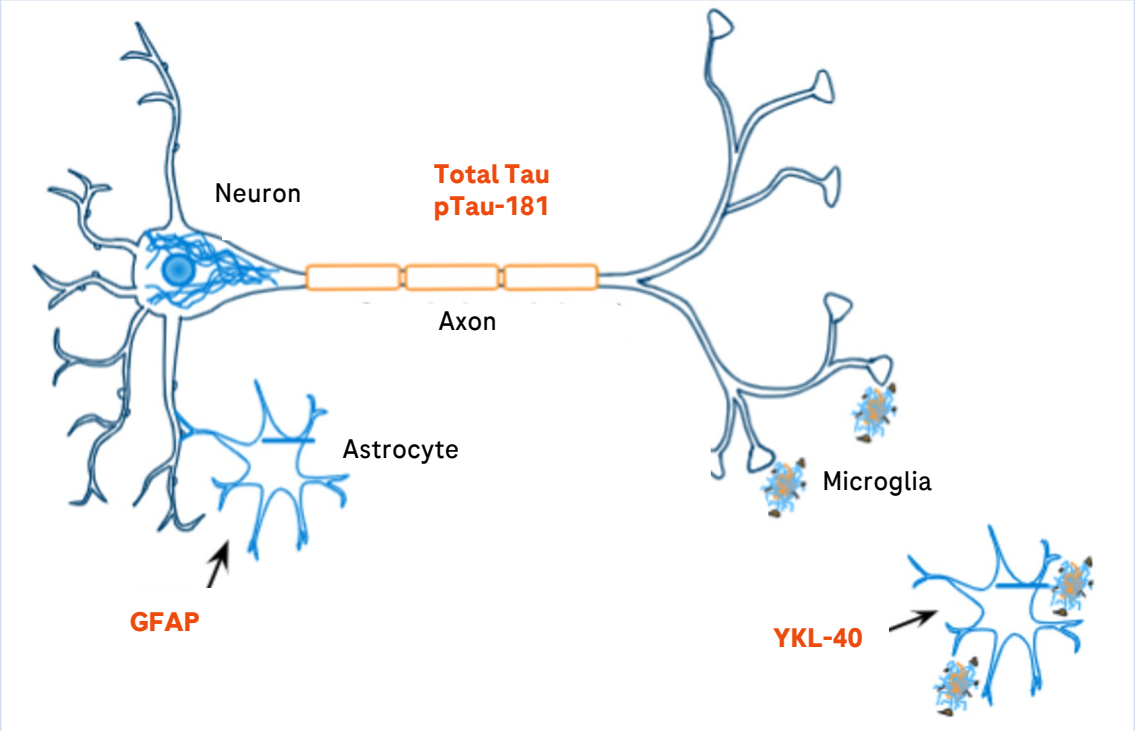
An update on GENERATION HD2: Recruitment and iDMC review

CSF, cerebrospinal fluid; GFAP, Glial fibrillary acidic protein; HD, Huntington's disease.

What can YKL-40, total Tau and GFAP in CSF tell us?

Introducing YKL-40, total Tau, pTau-181 and GFAP

- During neuroinflammation **YKL-40** is expressed and secreted by microglia and is associated with astrocytosis
- **Total Tau** is considered a non-specific marker of neuronal death, while **pTau-181** is specific to aggregated tau
- **GFAP** is a marker of astrocytic reactivity
- **YKL-40, Total tau & GFAP increase in HD relative to healthy controls**[1-4]



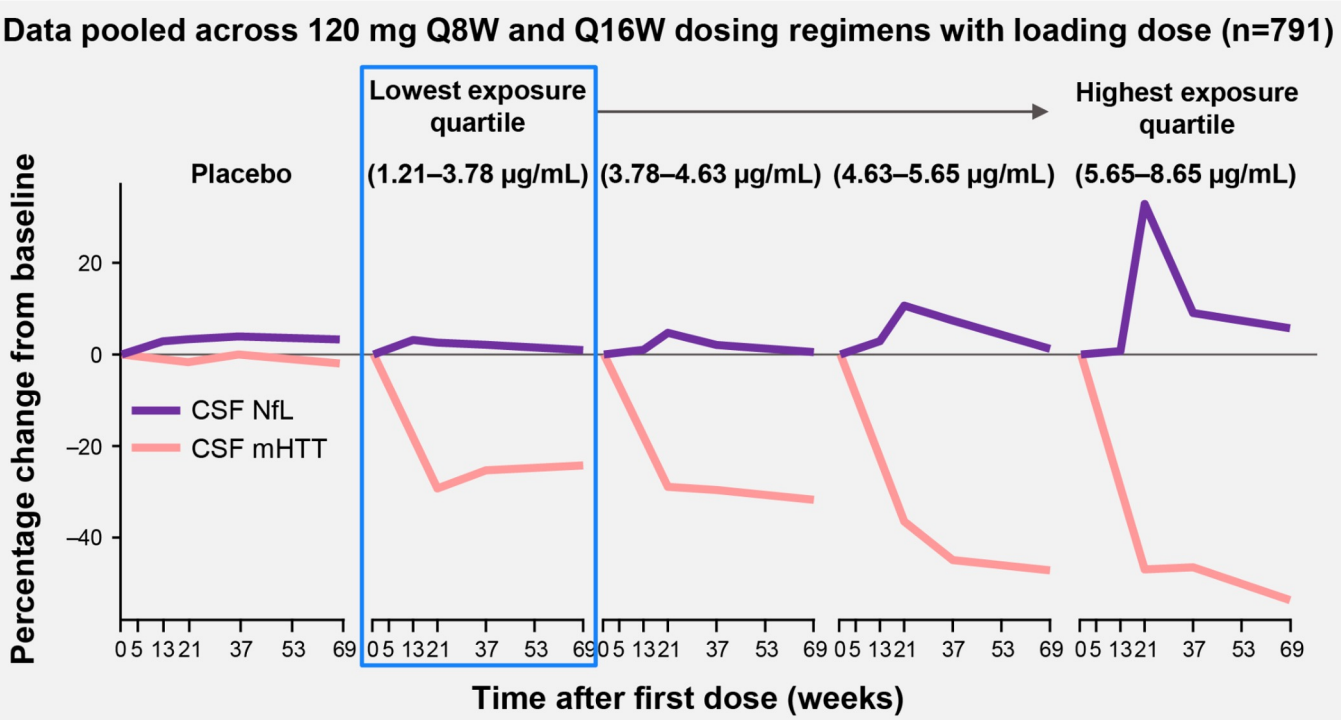
pTau-181 - Phosphorylated Tau 181, GFAP, Glial fibrillary acidic protein.
CSF, cerebrospinal; FDR, false discovery rate multiple comparison correction; HD-YAS, Huntington's disease young adult study; PreHD, Premanifest Huntington's disease.
1 Rodrigues et al., (2016) PLoSONE11(9):e0163479 ; 2 Scahill, Zeun et al., Lancet Neurol 2020; 19: 502–12. 3 Rodrigues et al., J Neurochem 2016 Oct;139(1):22-5. 4 Kinsella, Wild et al. (unpublished data);

Exposure-response in the Phase III GENERATION HD1 study and implications for the Phase II GENERATION HD2 study

See also Poster D009 by *Yamamoto et al.* “Exposure dependent changes in CSF fluid biomarkers following tominersen treatment in GENERATION HD1”

Mitigation of changes in CSF NfL at lower exposures in GENERATION HD1

- Exposure-dependent reduction in CSF mHTT clearly observed
- In the highest exposure quartiles transient CSF NfL increase observed at 21 weeks
- CSF NfL changes in the lowest exposure quartile were comparable to placebo
- **Lowest exposure quartile targeted in GENERATION HD2**

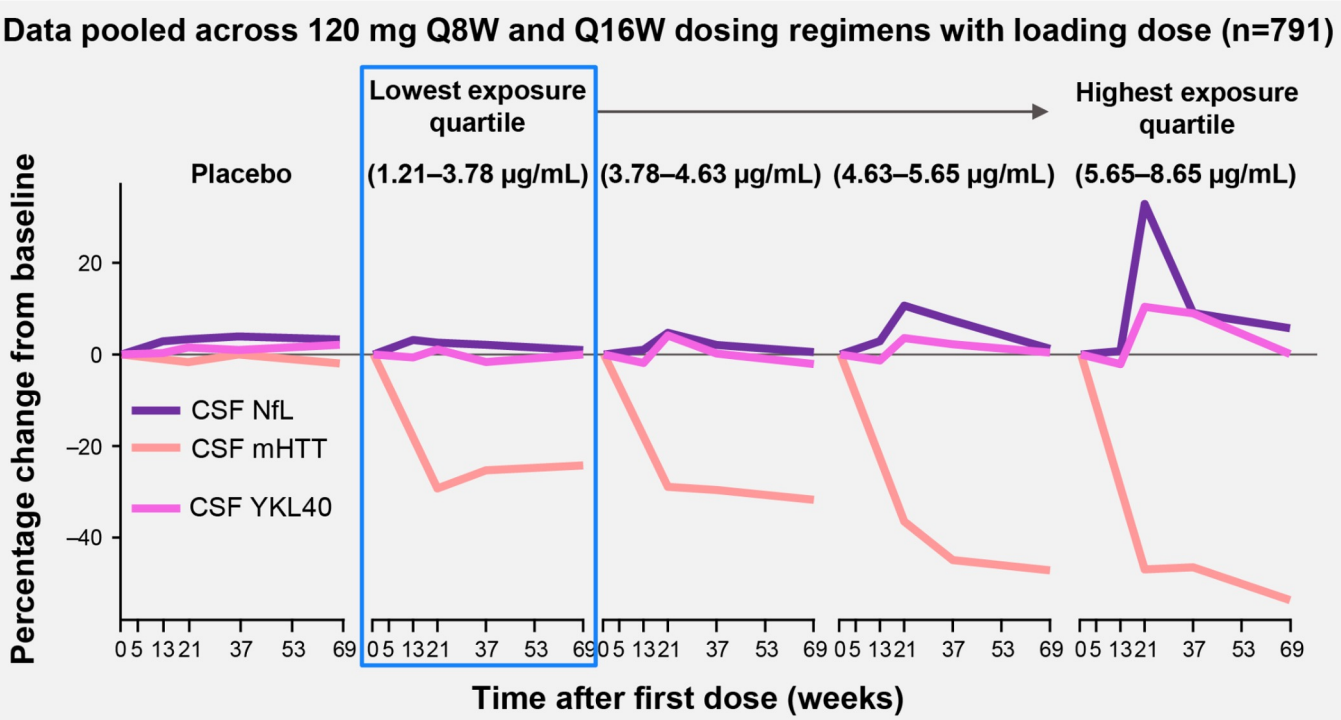


CSF, cerebrospinal fluid; HD, Huntington's disease; mHTT, mutant huntingtin protein; NfL, neurofilament light protein; Q8W, every 8 weeks; Q16W, every 16 weeks; median values displayed

McColgan P. *European Huntington's Disease Network Plenary Meeting*. 2022.

Mitigation of changes in CSF YKL-40 at lower exposures in GENERATION HD1

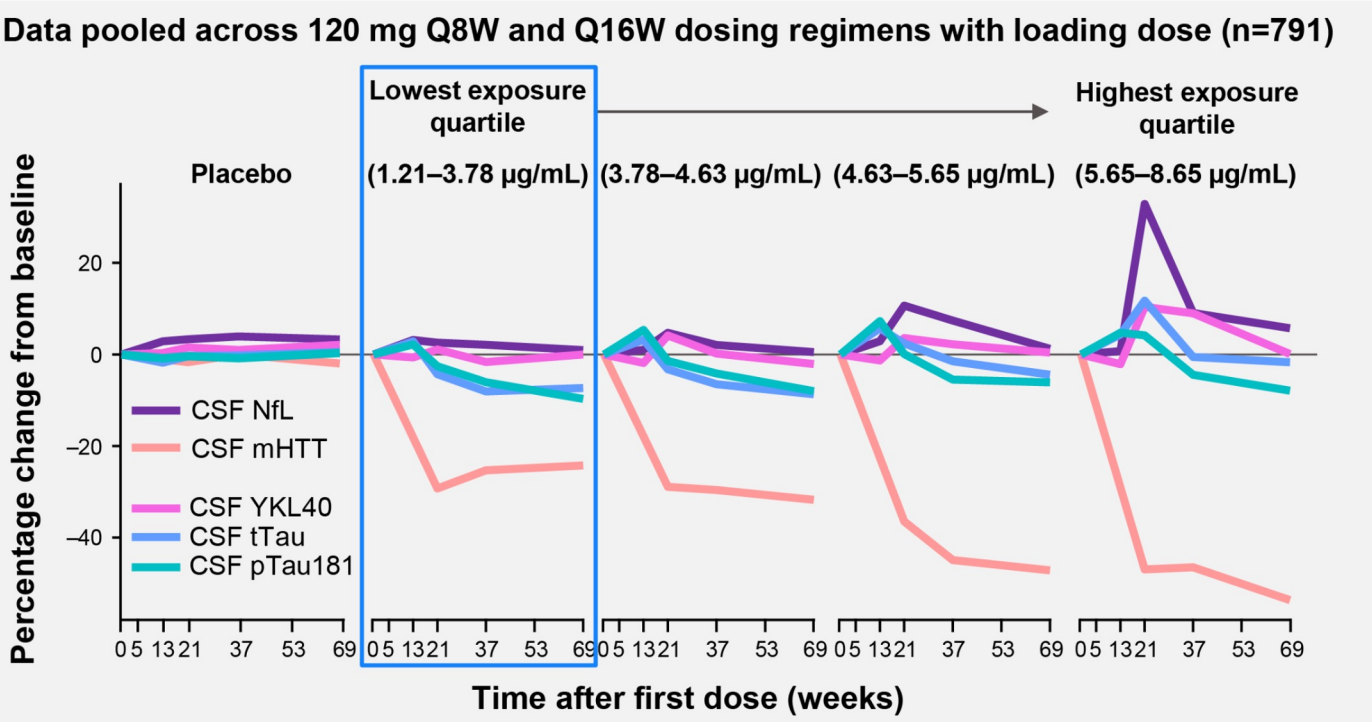
- CSF YKL-40 increases in the highest exposure quartile
- CSF YKL-40 changes in the lowest exposure quartile are trending below placebo
- **Lowest exposure quartile targeted in GENERATION HD2**



CSF, cerebrospinal fluid; HD, Huntington's disease; mHTT, mutant huntingtin protein; NfL, neurofilament light protein; Q8W, every 8 weeks; Q16W, every 16 weeks; median values displayed

Mitigation of changes in CSF total Tau & pTau181 at lower exposures in GENERATION HD1

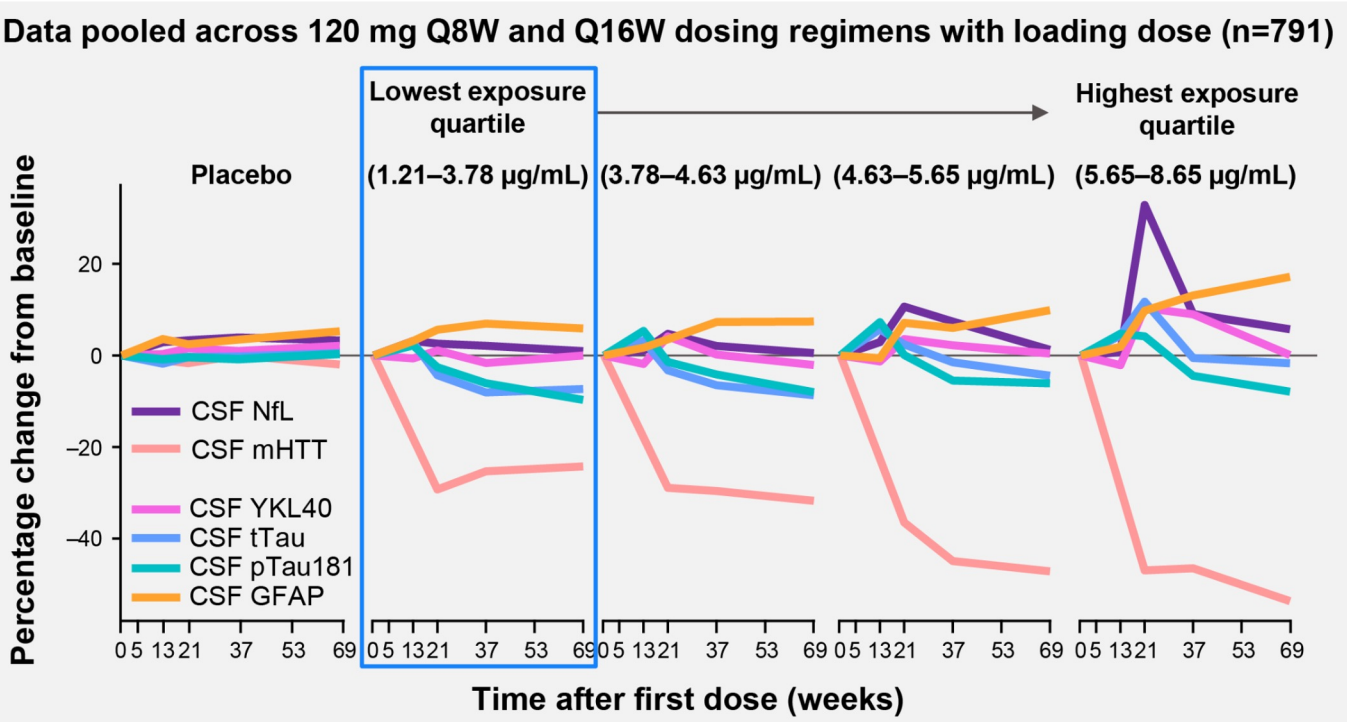
- CSF total Tau increases in the highest exposure quartile
- CSF total Tau changes in the lowest exposure quartile are trending below placebo
- **Lowest exposure quartile targeted in GENERATION HD2**



CSF, cerebrospinal fluid; HD, Huntington's disease; mHTT, mutant huntingtin protein; NfL, neurofilament light protein; tTau, total Tau; Q8W, every 8 weeks; Q16W, every 16 weeks; median values displayed

Mitigation of changes in CSF GFAP at lower exposures in GENERATION HD1

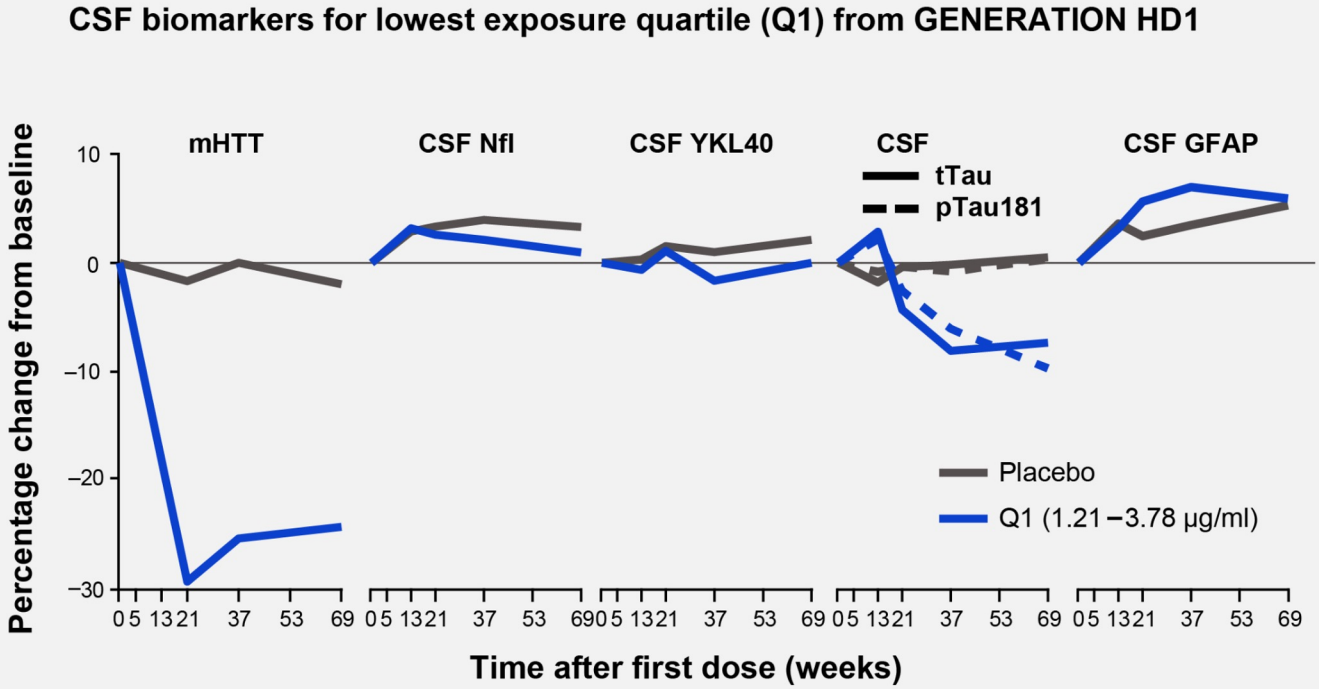
- CSF GFAP increases in the highest exposure quartile
- CSF GFAP changes in the lowest exposure quartile are comparable to placebo
- **Lowest exposure quartile targeted in GENERATION HD2**



CSF, cerebrospinal fluid; GFAP, Glial fibrillary acidic protein; HD, Huntington's disease; mHTT, mutant huntingtin protein; NfL, neurofilament light protein; tTau, total Tau; Q8W, every 8 weeks; Q16W, every 16 weeks; median values displayed

Exposure group targeted in GENERATION HD2 has a favourable biomarker profile

- CSF mHTT lowering 25-30% at trough
- CSF NfL, YKL-40 and total Tau are trending below placebo
- CSF GFAP is comparable to placebo



CSF, cerebrospinal fluid; GFAP, Glial fibrillary acidic protein; HD; mHTT, mutant huntingtin protein; NfL, neurofilament light protein; Q1 - lowest exposure quartile; median values displayed

Summary



CSF YKL-40, total Tau and GFAP provide information about neuroinflammation, neuronal death and astrocytic reactivity, respectively



In GENERATION HD1, no elevations in these biomarkers are observed at the lowest exposures



The exposure group targeted in GENERATION HD2 shows NfL, YKL-40 and total Tau trending below placebo

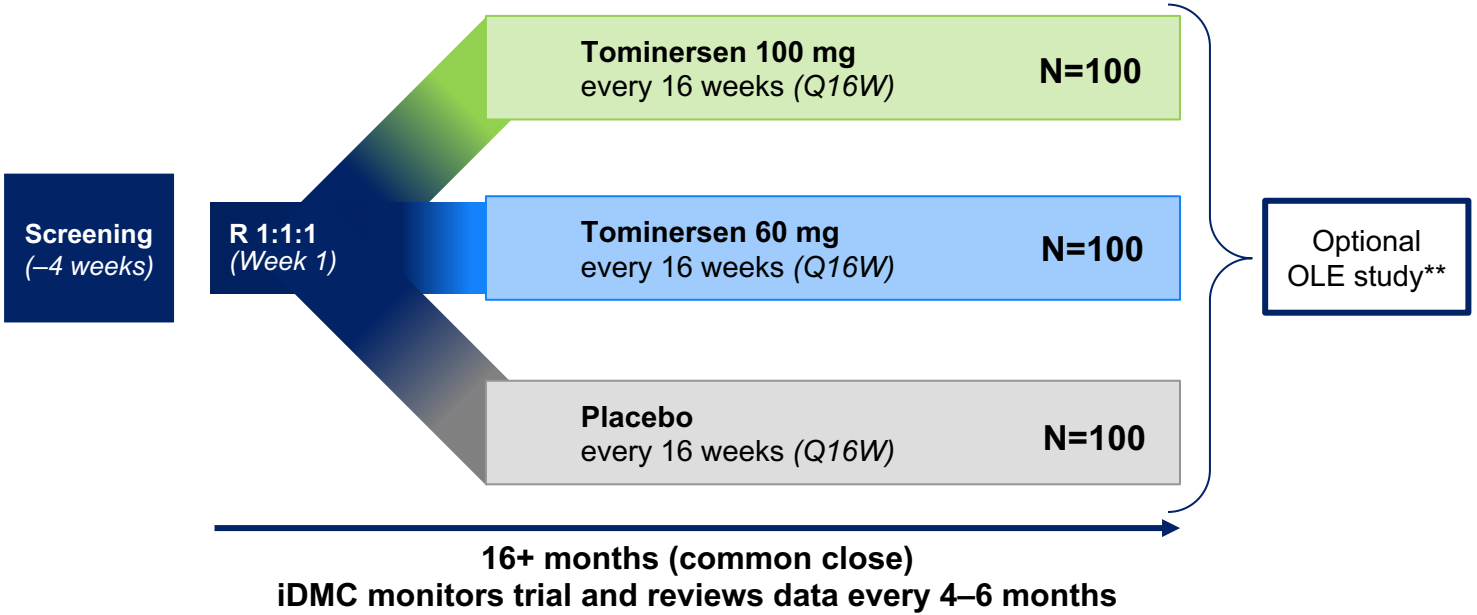
CSF, cerebrospinal fluid; GFAP, Glial fibrillary acidic protein; HD, Huntington's disease; NfL, neurofilament light protein.

An update on the Phase II GENERATION HD2 study:

Recruitment & iDMC review

Overview of GENERATION HD2

A study to evaluate the safety, biomarkers and efficacy of **two dose levels of tominersen** in participants with **prodromal (~17/arm) and early manifest (~83/arm)** HD versus placebo*



*NCT05686551 Clinicaltrials.gov
**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, randomization.

The role of the iDMC in GENERATION HD2

The **Independent Data Monitoring Committee** are a group of people **independent from Roche** with:

- One expert **statistician**
- One expert **brain imaging scientist**
- Three **Huntington's disease expert clinicians**

The **role of the iDMC** is to

- monitor **safety & clinical outcomes** of participants in the study, and
- to regularly review the **balance of risk and benefit**

The iDMC review data on **safety, clinical outcomes, brain imaging MRI & plasma NfL** every **4-6 months** and provide recommendations to continue, modify or stop the study.

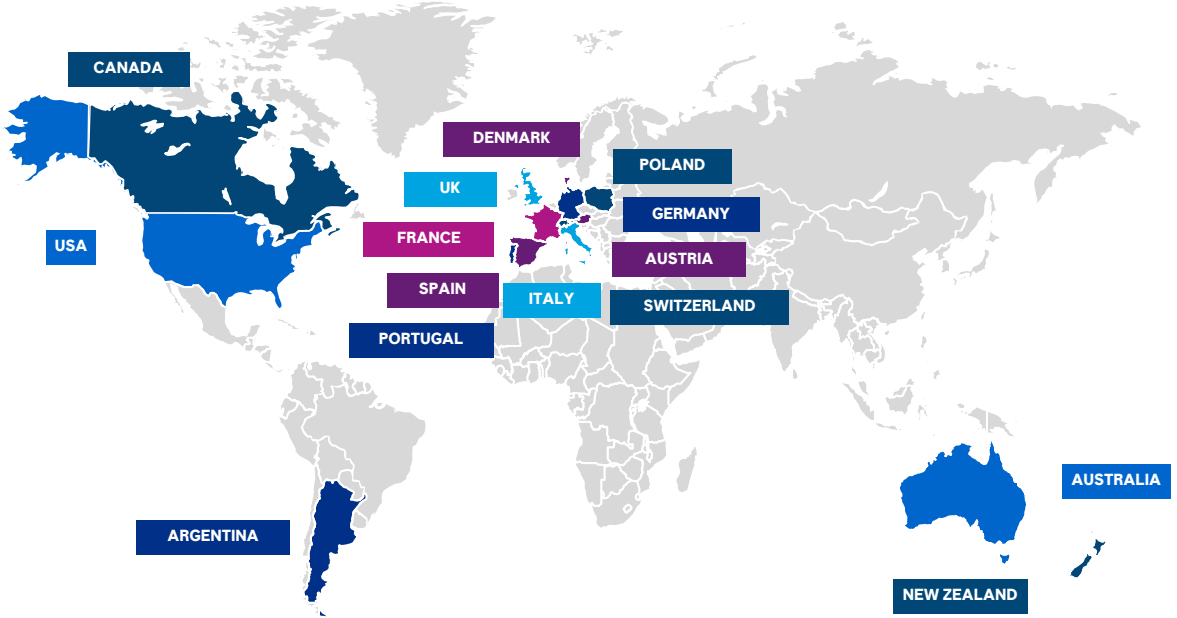
*NCT05686551 Clinicaltrials.gov
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In August 2024, the iDMC recommended continuing the GENERATION HD2 study as planned

GENERATION HD2 is > **80% recruited** and plans to complete recruitment by the end of 2024.

The iDMC recommendation is based on the review of **unblinded safety, clinical, MRI & plasma NfL** data from:

- **219** participants
- **Up to 5 doses** of study treatment
- Average time on treatment of **166 days**



HD, Huntington's disease; iDMC, independent Data Monitoring Committee.

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, study participants and their families

THANK YOU

HD, Huntington's disease