Towards an understanding of the post-treatment and mechanistic aspects of tominersen

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Date of preparation: September 2022 M-XX-00010771

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.

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, HD patients and their families

HD, Huntington's disease.

Outline of today's presentation

GENERATION HD1 post-treatment analysis

- Overview
- Ventricular volume
- cUHDRS/TFC slope analysis

Towards a mechanistic understanding of tominersen

- CSF mHTT lowering
- CSF NfL
- Ventricular volume

CSF, cerebrospinal fluid; cUHDRS, composite Unified Huntington's Disease Rating Scale; mHTT, mutant huntingtin protein; NfL, neurofilament light protein; TFC, total functional capacity.

GENERATION HD1

Post-treatment analysis

Post-treatment analysis overview

Analysis performed at the May 2022 data cut-off (database lock)

Clinical data

80%
of patients remained in GENERATION HD1

of which, approximately
77%
had reached the Week 101 final study visit

Time on treatment
Mean 473 days
Median 527 days (~17 months), range 1–597 days

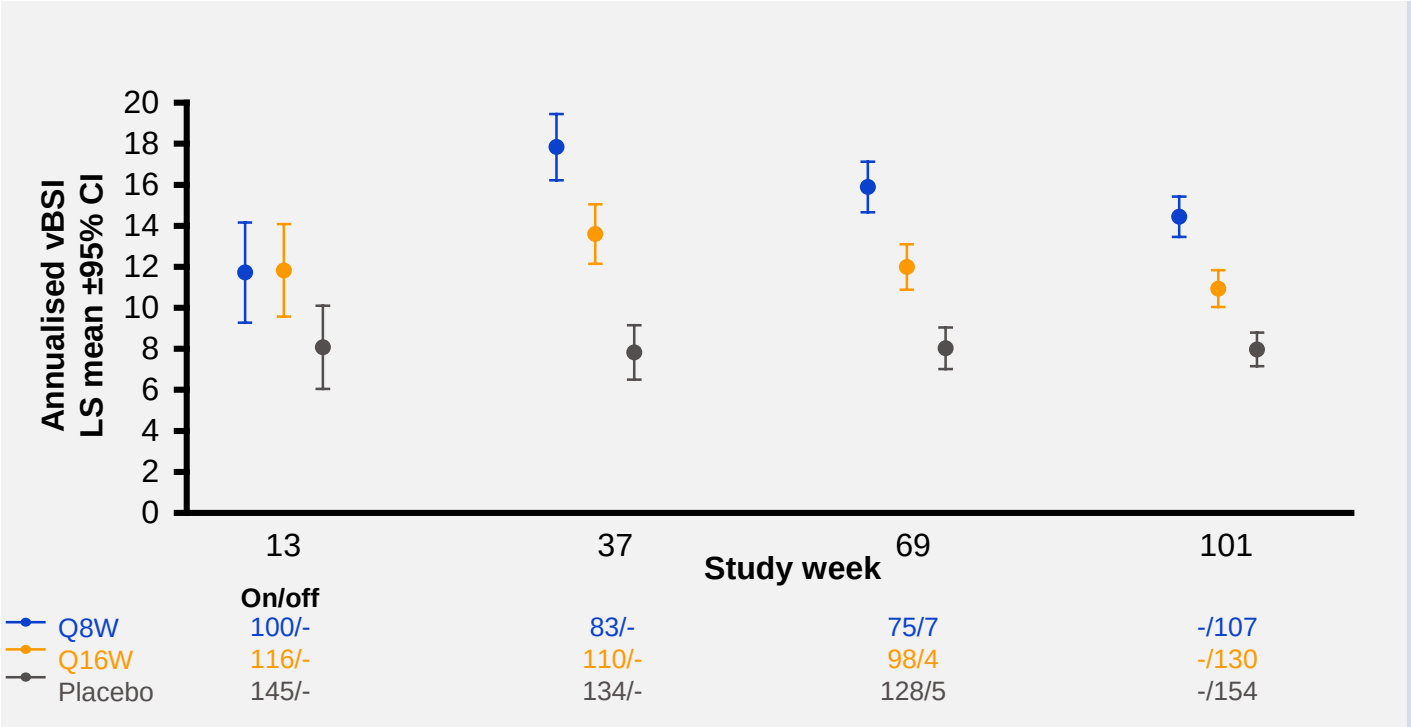
Time post-treatment
Mean 194 days
Median 174 days (~6 months), range 1–672 days

Imaging data

- 50% of data available for Week 101

Annualised vBSI for available subset of participants with Week 101 scan

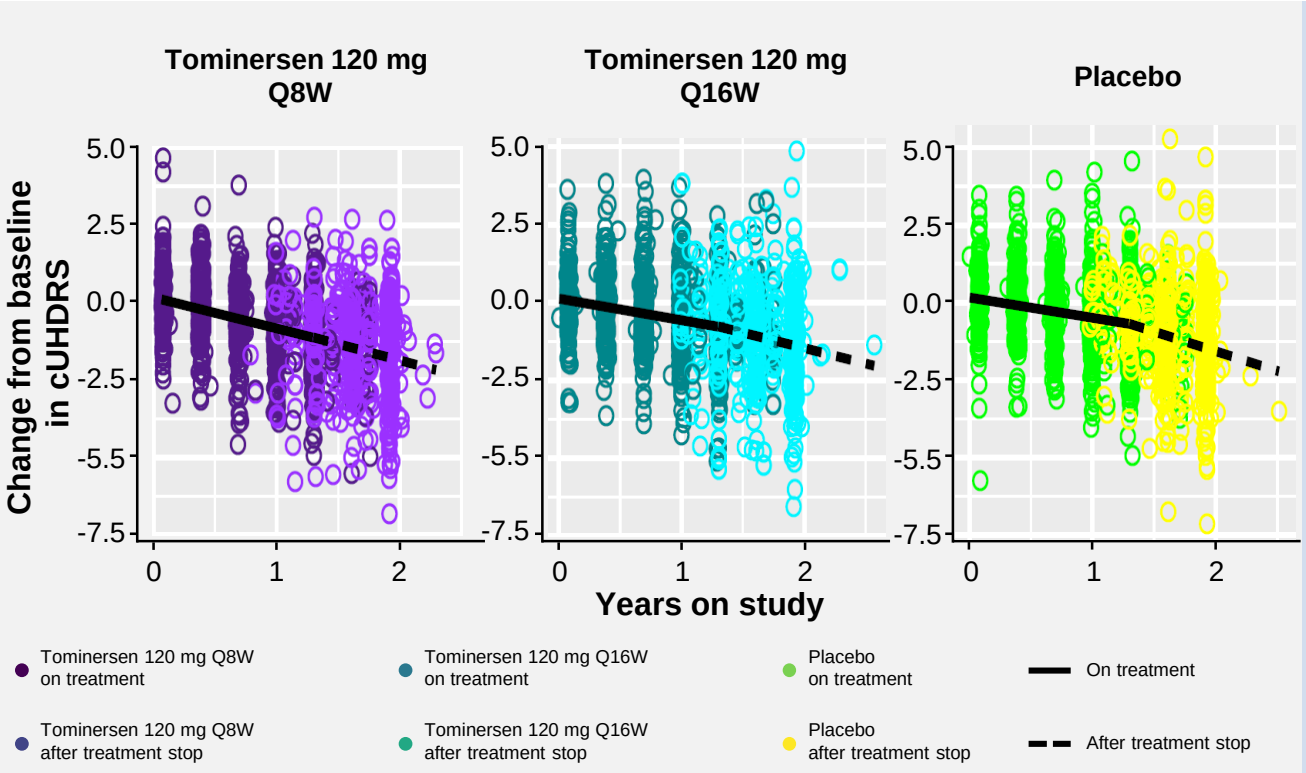
- **Rate of ventricular volume increase (annualised vBSI) is dose-regimen dependent on treatment**
- **Apparent decrease in annualised vBSI after Week 37 in Q8W and Q16W arms**



Data points represent least-squares mean values and their 95% confidence interval based on the analysis of mixed model for repeated measures.
Q8W, every 8 weeks; Q16W, every 16 weeks; vBSI, ventricular boundary shift integral.

cUHDRS on-treatment/post-treatment slope analysis

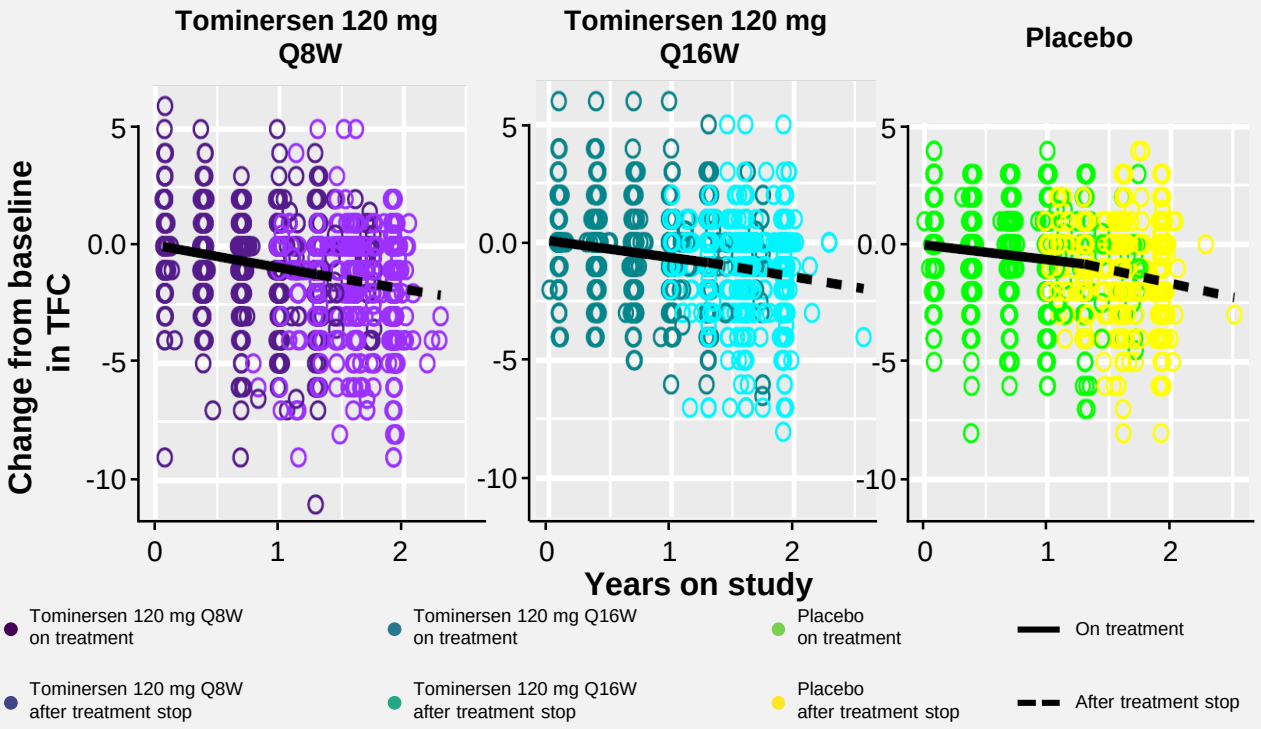
- **On treatment:**
  Statistically significantly greater decline in the Q8W group compared with placebo;
  Q16W group comparable to placebo
- **Post-treatment:**
  Decline in Q8W and Q16W groups comparable to placebo with no statistically significant difference



Analysis of change from baseline is analysed by fitting a linear mixed effect model. The change from baseline is the dependent variable, assuming linear change over time. The model includes random coefficients for intercept and slope and fixed effect terms for treatment group assignment, baseline value for the corresponding endpoint, CAP, CAG and age at baseline, and days of assessment as continuous variables.
CAP, CAG-age product; cUHDRS, composite Unified Huntington's Disease Rating Scale; Q8W, every 8 weeks; Q16W, every 16 weeks.

TFC on-treatment/post-treatment slope analysis

- **On treatment:**
  Statistically significantly greater decline in the Q8W group compared with placebo;
  Q16W group comparable to placebo
- **Post-treatment:**
  Decline in Q8W and Q16W groups comparable to placebo with no statistically significant difference



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CAP, CAG-age product; Q8W, every 8 weeks; Q16W, every 16 weeks; TFC, Total Functional Capacity.

Summary of GENERATION HD1 post-treatment analyses

Rate of ventricular volume increase in the Q8W and Q16W arms appear to decrease after Week 37

Clinical outcomes: no evidence of differential progression rates following treatment cessation

The iDMC has recommended no further follow-up beyond the Week 101 visit in GENERATION HD1

iDMC, independent Data Monitoring Committee; Q8W, every 8 weeks; Q16W, every 16 weeks.

Towards a mechanistic understanding of tominersen

Key mechanistic questions for tominersen

Effects of tominersen and CSF mHTT

- Are they related to target-mediated (i.e. HTT lowering) effects and/or non-target-mediated (i.e. ASO drug) effects?
- Is CSF mHTT lowering associated with clinical outcomes in GENERATION HD1?

Effects of tominersen and CSF NfL

- Are CSF NfL increases in the Q8W group associated with clinical outcomes in GENERATION HD1?
- What mechanistic insights are provided by other fluid biomarkers?
- Can increases in NfL be mitigated?

Effects of tominersen and ventricular volume

- Are ventricular volume increases associated with clinical outcomes in GENERATION HD1?
- What is the relationship between ventricular volume increases and CSF NfL?
- What is the relationship between ventricular volume increases and CSF protein and leukocytes?
- Can increases in ventricular volume be mitigated?

ASO, antisense oligonucleotide; CSF, cerebrospinal fluid; HTT, huntingtin protein; mHTT, mutant HTT; NfL, neurofilament light protein; Q8W, every 8 weeks.

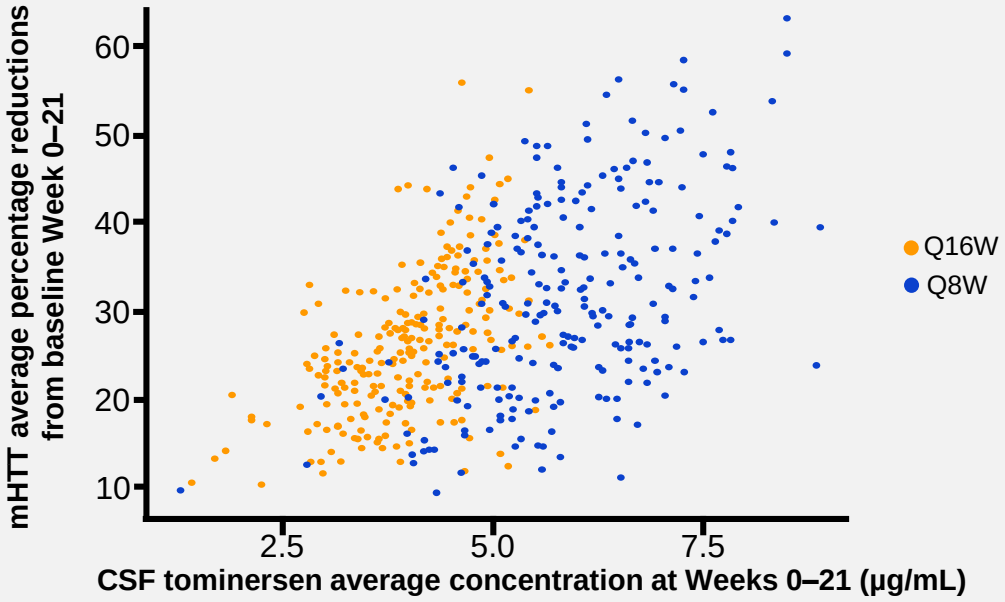
Towards a mechanistic understanding of tominersen

CSF mHTT lowering

CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein.

Are the effects seen with tominersen related to target-mediated (i.e. HTT lowering) and/or non-target-mediated (i.e. ASO drug) effects?

- **Tominersen is a potent drug showing clear target engagement**
- **Average CSF mHTT reduction is related to average CSF tominersen concentration**

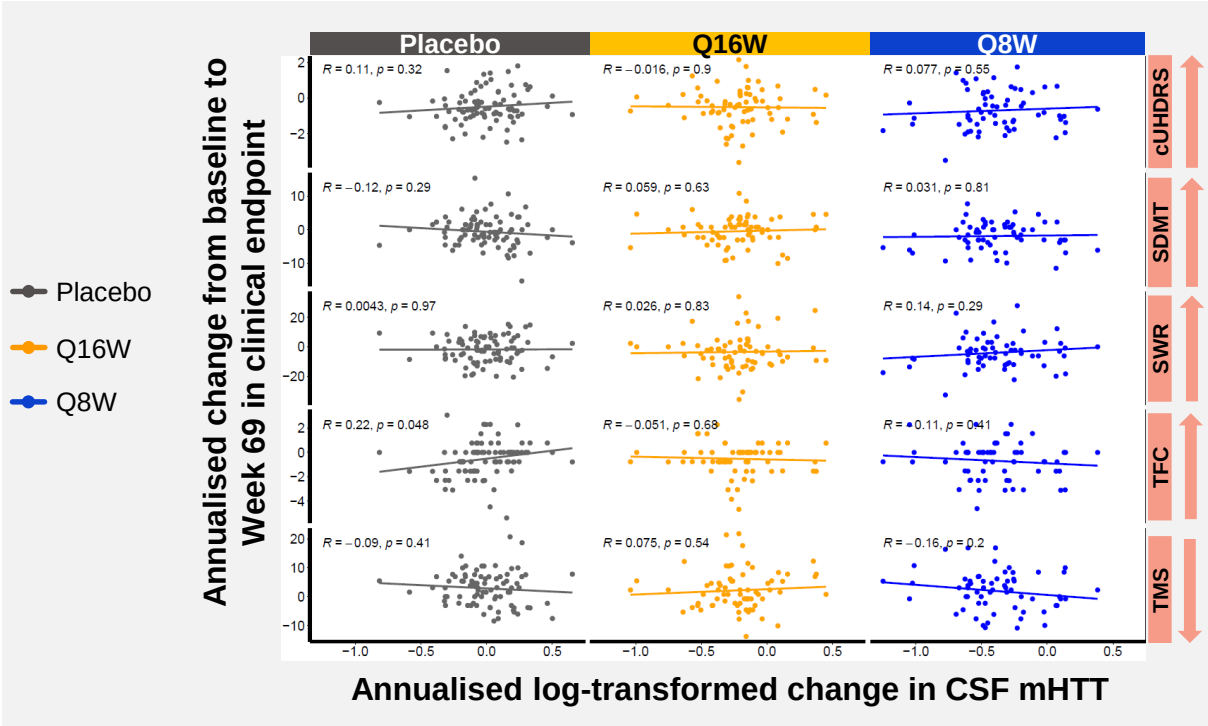


Tominersen CSF exposure and CSF mHTT lowering are correlated, thus it is not possible to disentangle target-mediated effects (i.e. lowering of mHTT and wtHTT) from non-target-mediated effects of tominersen (i.e. ASO drug effects)

Relationship between individual average tominersen concentrations in CSF (Cav, Weeks 1–21) and average mHTT reduction in CSF (mHTTav, Weeks 0–21) over the first 21 weeks post-initial dose. The individual data were predicted using the developed popPK and popPK/PD models, the individual dosing information and sparse CSF PK and mHTT concentration data from GENERATION HD1 patients.
ASO, antisense oligonucleotide; CSF, cerebrospinal fluid; HTT, huntingtin protein; mHTT, mutant HTT; popPK, population pharmacokinetics; popPK/PD, population pharmacokinetics/pharmacodynamics; Q8W, every 8 weeks; Q16W, every 16 weeks; wtHTT, wild-type HTT.

Is CSF mHTT lowering associated with clinical outcomes in GENERATION HD1?

- There is no clear correlation between change in clinical endpoint and change in CSF mHTT at Week 69
- As shown in the GENERATION HD1 *post hoc* analysis, age, CAP and exposure play a role in clinical outcome on tominersen
- The presence of these confounders could explain the absence of correlation between change in clinical endpoint and change in mHTT lowering



Pink arrows indicate direction of improvement.
CAP, CAG-age product; CSF, cerebrospinal fluid; cUHDRS, composite Unified Huntington's Disease Rating Scale; mHTT, mutant huntingtin protein; Q8W, every 8 weeks; Q16W, every 16 weeks; R, Pearson correlation coefficient; SDMT, Symbol Digit Modalities Test; SWR, Stroop Word Reading; TFC, Total Functional Capacity; TMS, Total Motor Score.

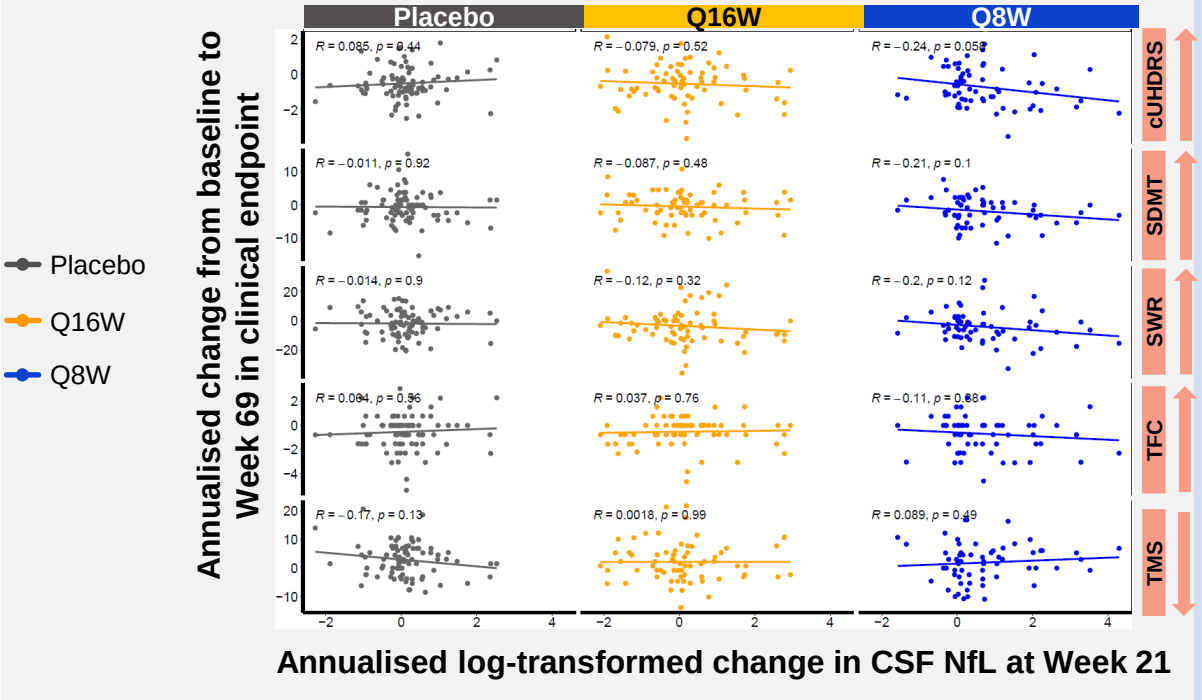
Towards a mechanistic understanding of tominersen

CSF NfL

CSF, cerebrospinal fluid; NfL, neurofilament light protein.

Are CSF NfL increases in the Q8W group associated with clinical outcomes in GENERATION HD1?

- The largest increases in NfL were observed at Week 21 in the Q8W group; Q16W group was comparable to placebo
- There is no clear correlation between change in CSF NfL at Week 21 and change in clinical endpoint at Week 69
- This suggests that NfL increases may not directly explain negative clinical outcomes in the Q8W group
- The absence of relationship may also be related to age, CAP and exposure confounders



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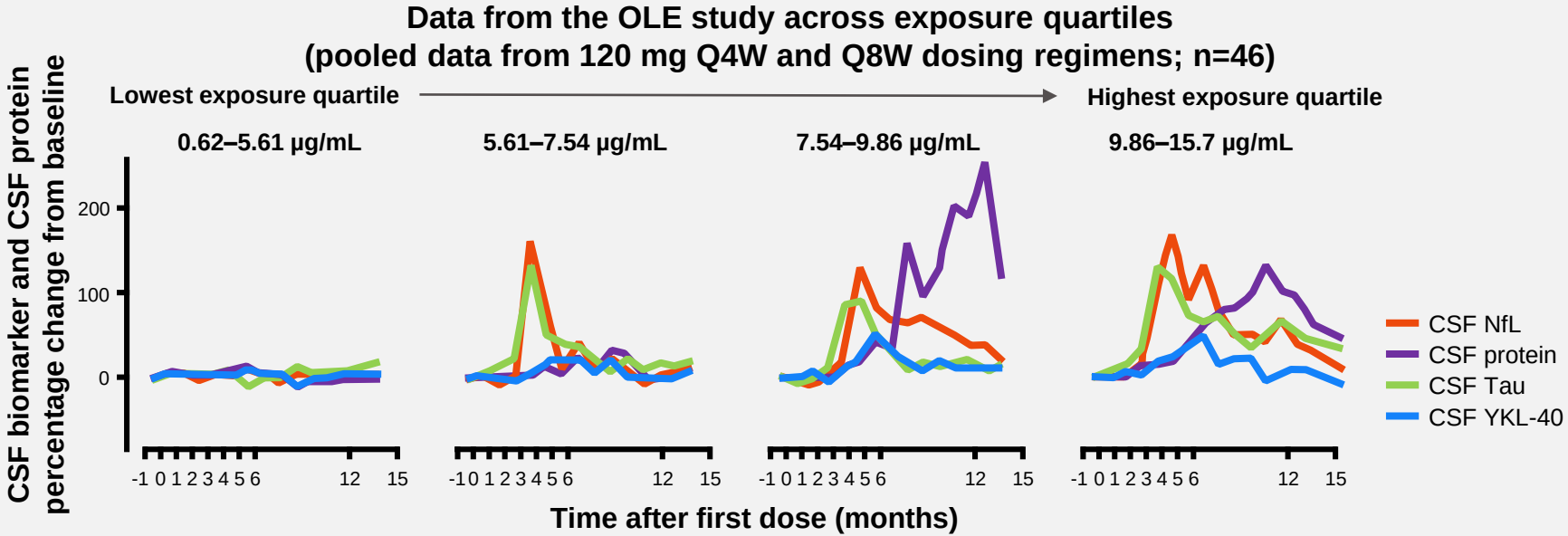
CAP, CAG-age product; CSF, cerebrospinal fluid; cUHDRS, composite Unified Huntington's Disease Rating Scale; NfL, neurofilament light protein; Q8W, every 8 weeks; Q16W, every 16 weeks; R, Pearson correlation coefficient; SDMT, Symbol Digit Modalities Test; SWR, Stroop Word Reading; TFC, Total Functional Capacity; TMS, Total Motor Score.

What is the relationship between the observed CSF NfL increases and other fluid biomarkers in Phase I/IIa OLE?



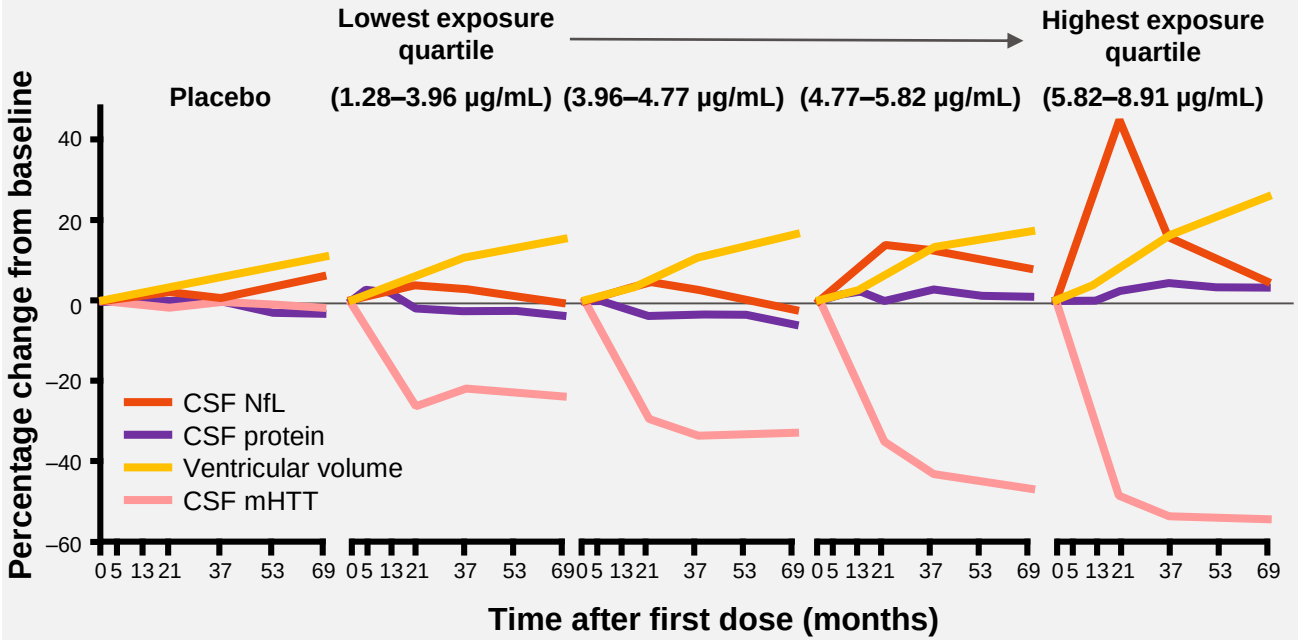
- **Relative concentration time profiles**
- **Increases in CSF NfL, inflammatory markers and other neuronal injury markers were observed in the higher exposure quartile, but were not observed in the lowest exposure quartile**

CSF, cerebrospinal fluid; NfL, neurofilament light protein; OLE, open-label extension; Q4W, every 4 weeks; Q8W, every 8 weeks.

Exposure–response relationship of biomarkers and ventricular volume in the GENERATION HD1 study

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

Data pooled across 120 mg Q8W and Q16W dosing regimens with loading dose (n=791)



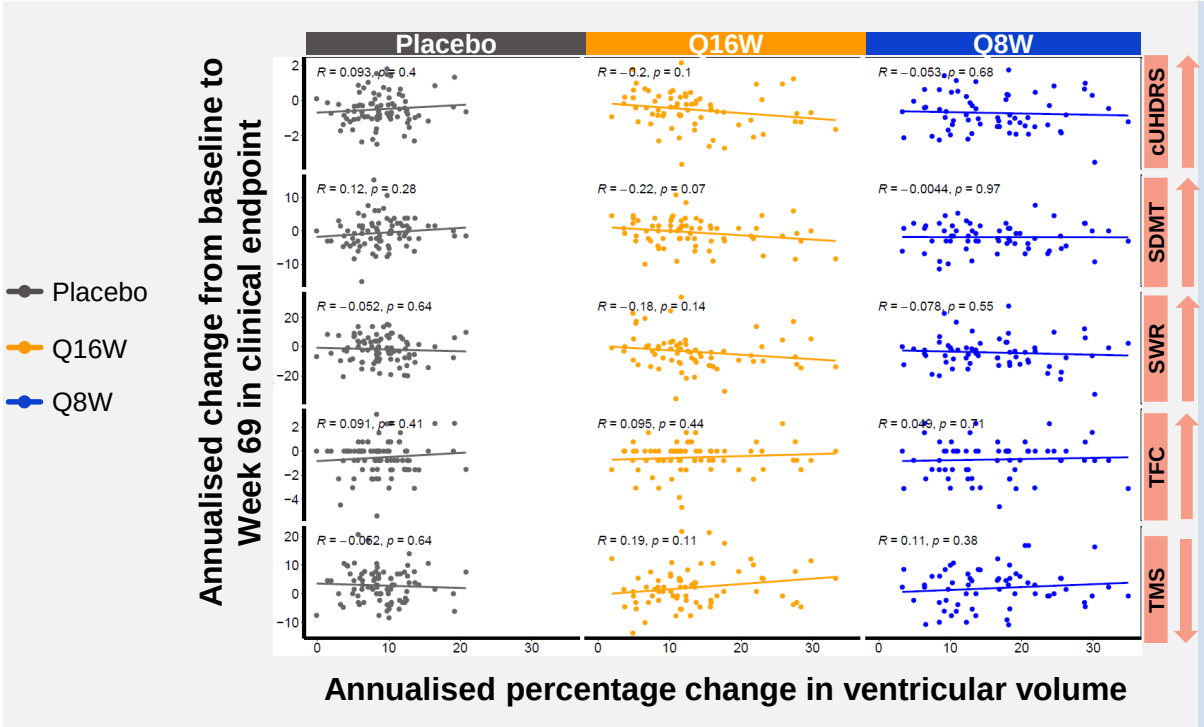
CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein; NfL, neurofilament light protein; Q8W, every 8 weeks; Q16W, every 16 weeks.

Towards a mechanistic understanding of tominersen

Ventricular volume

Are ventricular volume increases associated with clinical outcomes in GENERATION HD1?

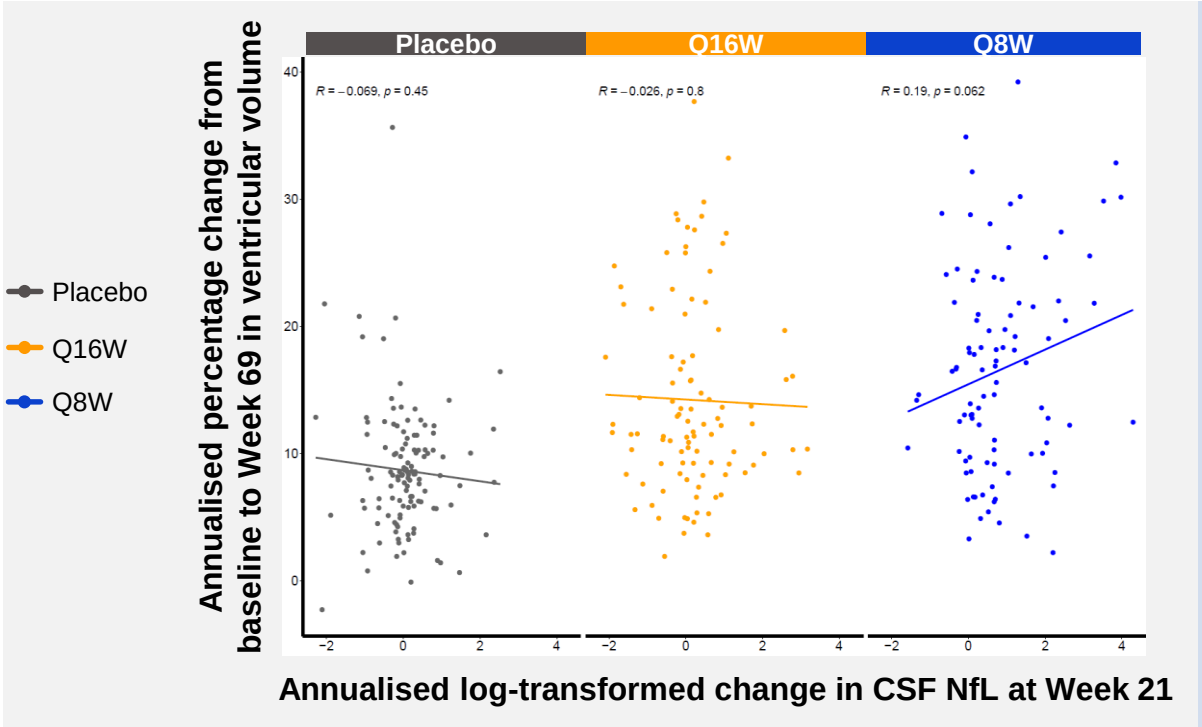
- There is no clear correlation between change in clinical endpoint at Week 69 and change in ventricular volume at Week 69
- This suggests that ventricular volume increases may not directly explain negative clinical outcomes
- The absence of relationship may also be related to age, CAP and exposure confounders



Yellow arrows indicate direction of improvement.
CAP, CAG-age product; cUHDRS, composite Unified Huntington's Disease Rating Scale; Q8W, every 8 weeks; Q16W, every 16 weeks; R, Pearson correlation coefficient; SDMT, Symbol Digit Modalities Test; SWR, Stroop Word Reading; TFC, Total Functional Capacity; TMS, Total Motor Score.

Does the NfL peak at Week 21 in the Q8W group predict future ventricular enlargement?

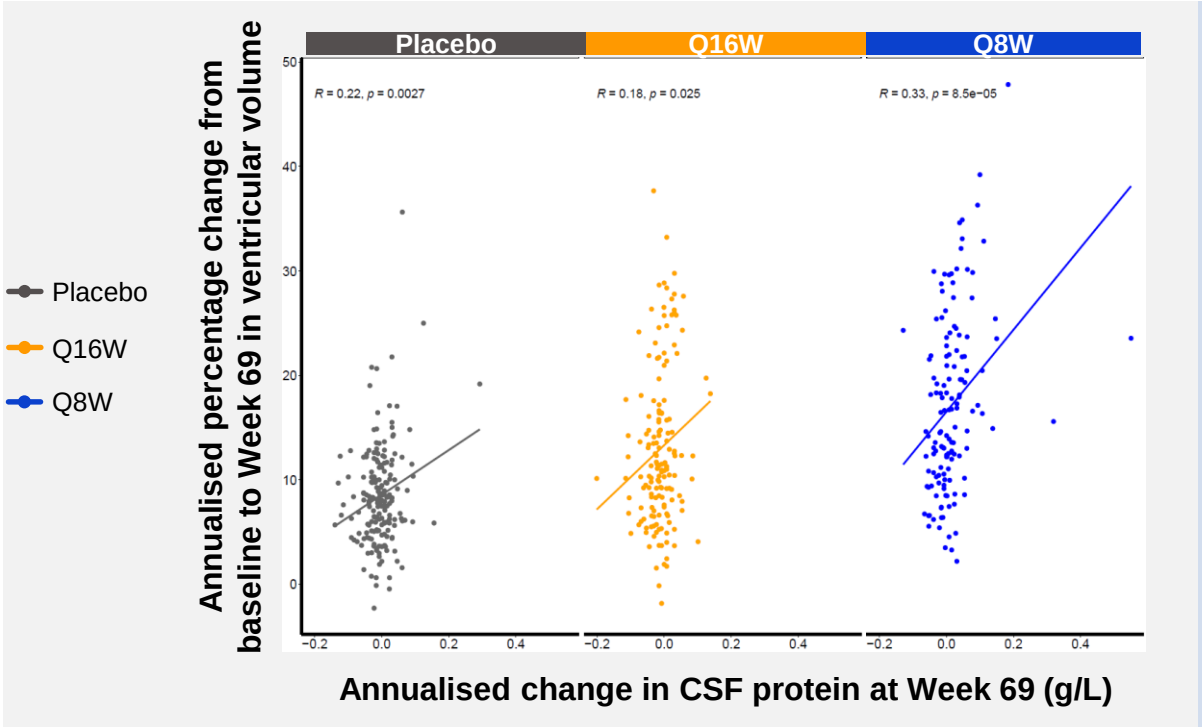
- The largest increases in NfL were observed at Week 21 in the Q8W group; the Q16W was comparable to placebo
- There was a non-significant correlation in the Q8W group but the absence of this relationship in the Q16W group suggests NfL increases and ventricular expansion are not related



CSF, cerebrospinal fluid; NfL, neurofilament light protein; Q8W, every 8 weeks; Q16W, every 16 weeks; R, Pearson correlation coefficient.

What is the relationship between ventricular volume increase and CSF protein?

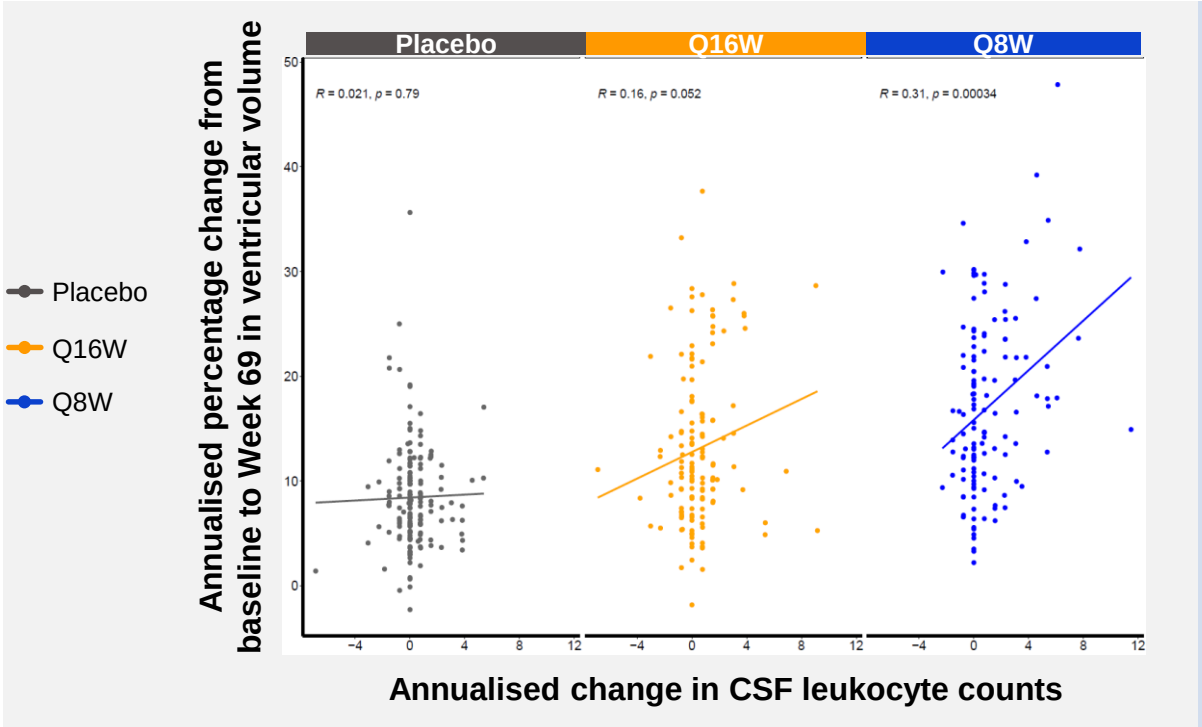
- There was a statistically significant and consistent correlation between annualised change in ventricular volume (Week 69) and annualised change in CSF protein (Week 69)
- Impaired CSF reabsorption could explain increased CSF protein and increased ventricular volume



CSF, cerebrospinal fluid; Q8W, every 8 weeks; Q16W, every 16 weeks; R, Pearson correlation coefficient.

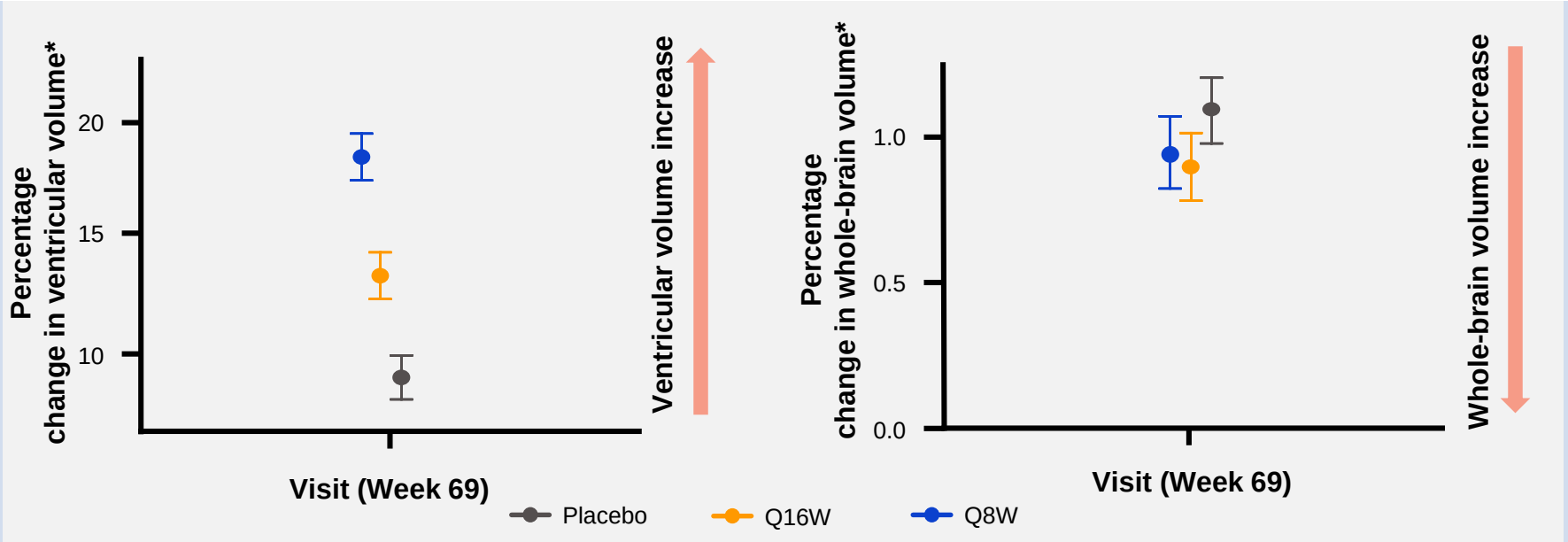
What is the relationship between ventricular volume increase and leukocytes?

- There is a statistically significant linear correlation between annualised change in ventricular volume (Week 69) and annualised change in CSF leukocytes (Week 69) in the Q8W group, with a trend seen in the Q16W group
- Impaired CSF reabsorption could explain increased CSF leukocytes and increased ventricular volume



CSF, cerebrospinal fluid; Q8W, every 8 weeks; Q16W, every 16 weeks; R, Pearson correlation coefficient.

What is the relationship between ventricular volume and whole-brain volume?



Although ventricular volume increases with dose regimen, whole-brain volume does not decrease, which indicates that this effect may not be due to brain atrophy

* Data points represent least-squares mean values and their 95% confidence interval based on the analysis of mixed model for repeated measures.
Q8W, every 8 weeks; Q16W, every 16 weeks.

Mechanistic summary

- **Based on current available data, it is not possible to disentangle on-target- from non-target-mediated effects of HTT lowering due to exposure relationship**
- **Increases in CSF NfL, inflammatory markers and other markers of neuronal injury were observed in the higher exposure quartile in the OLE (pooled data across 120 mg Q4W and Q8W regimens), but were not observed in the lowest exposure quartile**
- **In GENERATION HD1, increases in CSF NfL, CSF protein and ventricular volume were observed in the higher exposure quartile**
- **The increase in ventricular volume was related to CSF protein and leukocytes but not clinical outcomes or changes in whole-brain volume**
  - **One possible explanation for these observations is that ventricular volume expansion may be related to impaired CSF reabsorption, and not atrophy**
- **Ventricular volume and CSF NfL increases can be mitigated at lower exposures**

CSF, cerebrospinal fluid; HTT, huntingtin protein; NfL, neurofilament light protein; OLE, open-label extension; Q4W, every 4 weeks; Q8W, every 8 weeks.

Overall summary

Rates of disease progression in the post-treatment period were not different between individuals receiving tominersen and placebo

Rates of ventricular volume increase initially observed on tominersen treatment decrease at later time points and in the post-treatment period

Lower doses of tominersen may help mitigate the effects on ventricular volume and NfL

NfL, neurofilament light protein.

Announcement of the new Phase II study

Sunday 18 September
11:30–12:30

Plenary Session V:
Update on Planned Clinical Trials

Details of the new tominersen Phase II study to be announced, including:

- **Study design**
- **Inclusion/exclusion criteria**
- **Rationale for dose and patient population**

We look forward to seeing you tomorrow!

THANK YOU

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