Understanding the treatment and post-treatment effects of tominersen in the Phase III GENERATION HD1 study

Lauren Boak, PhD
Peter McColgan, MD, PhD

F. Hoffmann-La Roche Ltd, Basel, Switzerland

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Disclosures

We are both full-time employees of F. Hoffmann-La Roche Ltd

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





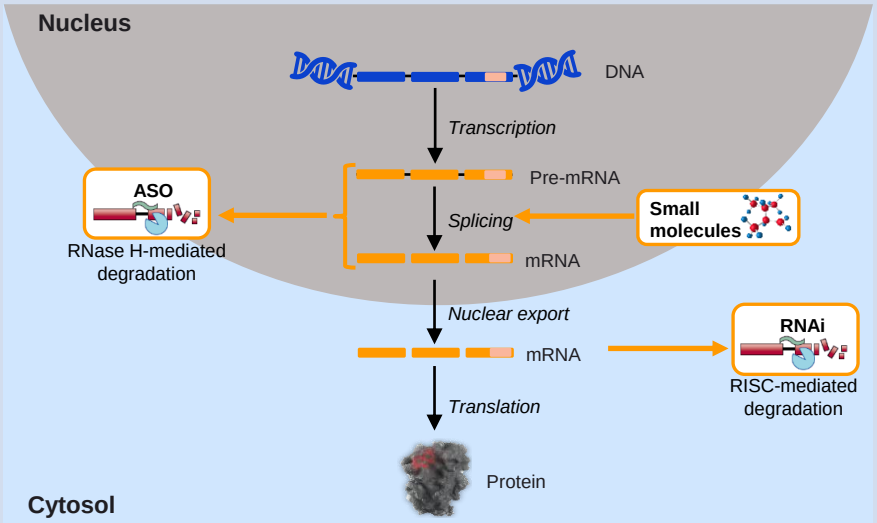




Deepest gratitude to the investigator network, HD patients and their families

HD, Huntington's disease.

Overview of clinical-stage HTT-lowering programmes



HTT-lowering is the most widely pursued therapeutic strategy to slow or stop disease progression in HD

	RoA and relative brain distribution	Advantages	Disadvantages
ASO Non-allele specific (e.g. tominersen)	Intrathecal Cortical>striatal	Possibility to adapt/titrate dosing Suitable for all *HTT* mutation carriers	Unknown risk of wtHTT lowering Repeated dosing Invasiveness
ASO Allele specific	Intrathecal Cortical>striatal	Possibility to adapt/titrate dosing mHTT lowering not limited by wtHTT lowering risk	Multiple drugs required for majority of *HTT* mutation carriers Repeated dosing Invasiveness
RNAi gene therapy Non-allele specific	Intracranial Striatal>cortical	Single treatment Suitable for all *HTT* mutation carriers	Irreversible Unknown risk of wtHTT lowering Invasiveness
Splicer modifier Non-allele specific	Oral Broad, uniform coverage	Possibility to adapt/titrate dosing Convenience Suitable for all *HTT* mutation carriers	Unknown risk of wtHTT lowering Repeated dosing Unknown risk of non-target-mediated effects

ASO, antisense oligonucleotide; HD, Huntington's disease; *HTT*, huntingtin gene; HTT, huntingtin protein; mHTT, mutant HTT; RISC, RNA-induced silencing complex; RNAi, RNA interference; RoA, route of administration; wtHTT, wild-type HTT.
Adapted from: Tabrizi S, et al. *Neuron*. 2019; 101:801–819.

Outline of presentation

What we have learned from the tominersen programme

- Background of the tominersen Clinical Development Programme
- GENERATION HD1 core analyses
- Post-treatment preliminary analysis
- *Post hoc* analysis

Leveraging knowledge for the new Phase II study

- Dose
- Patient population

Where we are today: tominersen programme status

Clinical Development Programme

Phase I/IIa N=46[1,2]
- First-in-human study[3]
- Safety, tolerability, PK and PD[1,2]
- Adults with early manifest HD[2]

OLE N=46[4,5]
- Long-term safety, tolerability, PK and PD[4]
- Adults with early manifest HD[6]
- 15 months[5]

HD Natural History Study N=95[7]
- Prospective, longitudinal study[8]
- Adults with early manifest HD[8]
- 15 months (no treatment)[8]

GENERATION HD1 N=791[9,10]
- Long-term safety and clinical outcomes[9]
- Adults with manifest HD[9]
- 25 months (plus follow-up)[11]

GEN-PEAK N≤20[12]
- PK/PD in CSF and plasma[13]
- Adults with manifest HD[12]
- 7 months (including follow-up)[12]

GEN-EXTEND N=236
- Roll-over study for participants in previous tominersen studies[14]
- Patients with manifest HD[15]
- Up to 6 years[14]

The trial continues without dosing to follow participants for safety and clinical outcomes through March/April 2022

Part 1 of study complete (n=12 patients recruited). Optional Part 2 will not be conducted

- Complete
- Complete, final analysis ongoing
- Ongoing, recruitment complete, **dosing stopped/paused** following a recommendation from the iDMC

CSF, cerebrospinal fluid; HD, Huntington's disease; iDMC, independent Data Monitoring Committee; OLE, open-label extension; PD, pharmacodynamics; PK, pharmacokinetics.

1. Tabrizi SJ, et al. *N Engl J Med*. 2019; 380:2307–2316; 2. Clinicaltrials.gov/ct2/show/NCT02519036 (Accessed March 2022); 3. Tabrizi SJ et al. *J Neurol Neurosurg Psychiatry*. 2018; 89:A97–A98; 4. Clinicaltrials.gov/ct2/show/NCT03342053 (Accessed March 2022); 5. Tabrizi S, et al. *Mov Disord*. 2019; 34:Suppl S2:S1–S937(A47); 6. Roche study BN40697 protocol; 7. Roche study BN40422 protocol; 8. Clinicaltrials.gov/ct2/show/NCT03664804 (Accessed March 2022); 9. Clinicaltrials.gov/ct2/show/NCT03761849 (Accessed March 2022); 10. Roche Press Release. Available at: https://www.roche.com/media/releases/med-cor-2021-03-22b.htm (Accessed March 2022); 11. Roche study BN40423 protocol; 12. Roche study BP40410 protocol; 13. Clinicaltrials.gov/ct2/show/NCT04000594 (Accessed March 2022); 14. Clinicaltrials.gov/ct2/show/NCT03842969 (Accessed March 2022); 15. Roche study BN40955 protocol.

Preclinical data were used to define target mHTT reduction to be achieved in CSF at trough in GENERATION HD1

Roche

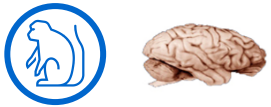
Genentech
A Member of the Roche Group

Tissue lowering to "efficacy"[1,2]
(i.e. improvement in behavioural phenotype)

Transgenic mouse models

Cortex ~30–80%
Caudate ~30%

Tissue to CSF[3]



Cyno tissue/CSF–HTT relationship

% CSF HTT KD	% HTT KD in cortex	% HTT KD in caudate
20–30	**30–55**	5–20
30–40	**40–70**	**15–35**
40–50	**55–80**	**25–45**

CSF[3]

Target trough human CSF mHTT reduction range:

~30–50%

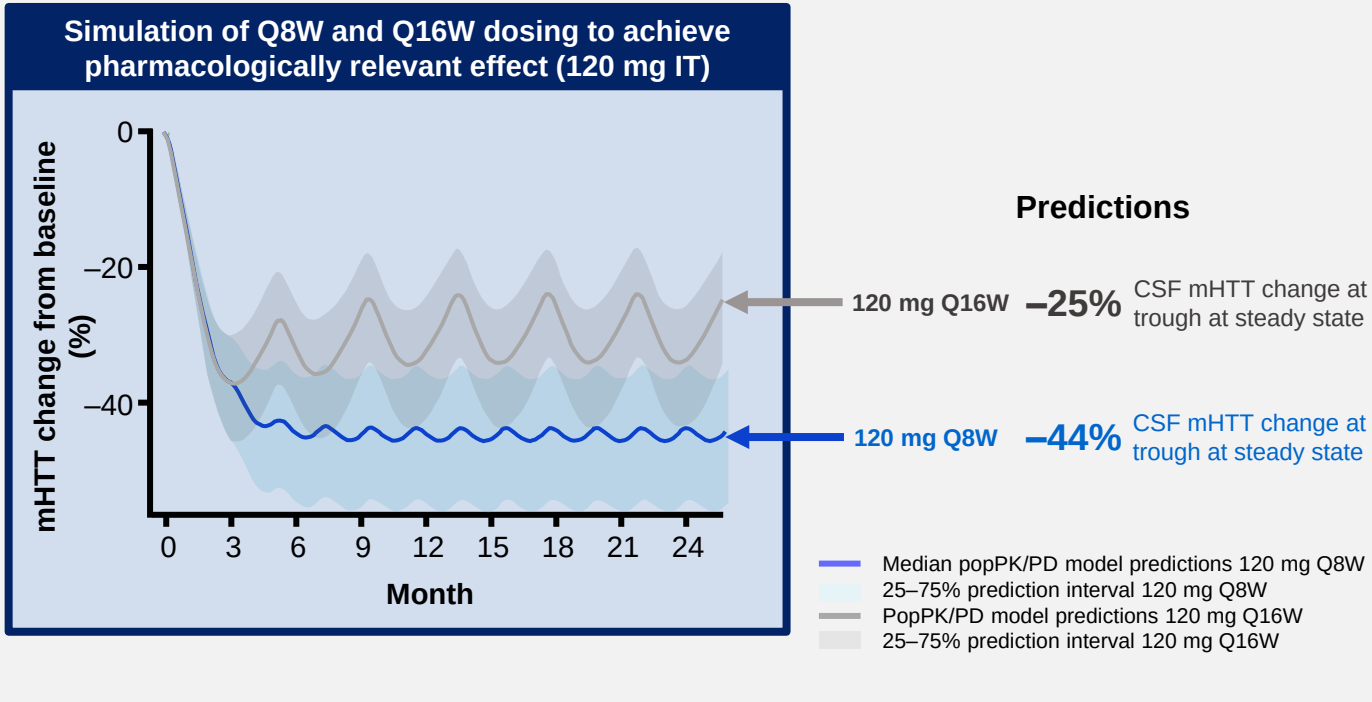
- **CSF mHTT lowering of 30–50% predicted to be associated with therapeutic benefit[2]**
- **GENERATION HD1 targeted 30–50% CSF mHTT reduction at trough to maintain reduction over dosing interval[3]**

CSF, cerebrospinal fluid; HD, Huntington's disease; HTT, huntingtin protein; KD, knockdown; mHTT, mutant HTT.

1. Kordasiewicz HB, et al. *Neuron.* 2012; 74:1031–1044; 2. Stanek LM, et al. *J Huntingtons Dis.* 2013; 2:217–228; 3. Sanwald Ducray P, et al. *Neurology.* 2019; 92(15 Suppl):S16.005.

Clinical popPK/PD model developed based on 9-month OLE data to simulate two 120 mg regimens (Q8W and Q16W)

- **120 mg Q8W dosing exceeds trough CSF mHTT threshold for cortex and caudate; 120 mg Q16W exceeds threshold for cortex**
- **Both 120 mg Q8W and Q16W dosing predicted to achieve maximum CSF mHTT reductions exceeding 30%**



CSF, cerebrospinal fluid; IT, intrathecal; mHTT, mutant huntingtin protein; OLE, open-label extension; PD, pharmacodynamic; PK, pharmacokinetic; popPK/PD, population PK/PD; Q8W, every 8 weeks; Q16W, every 16 weeks.

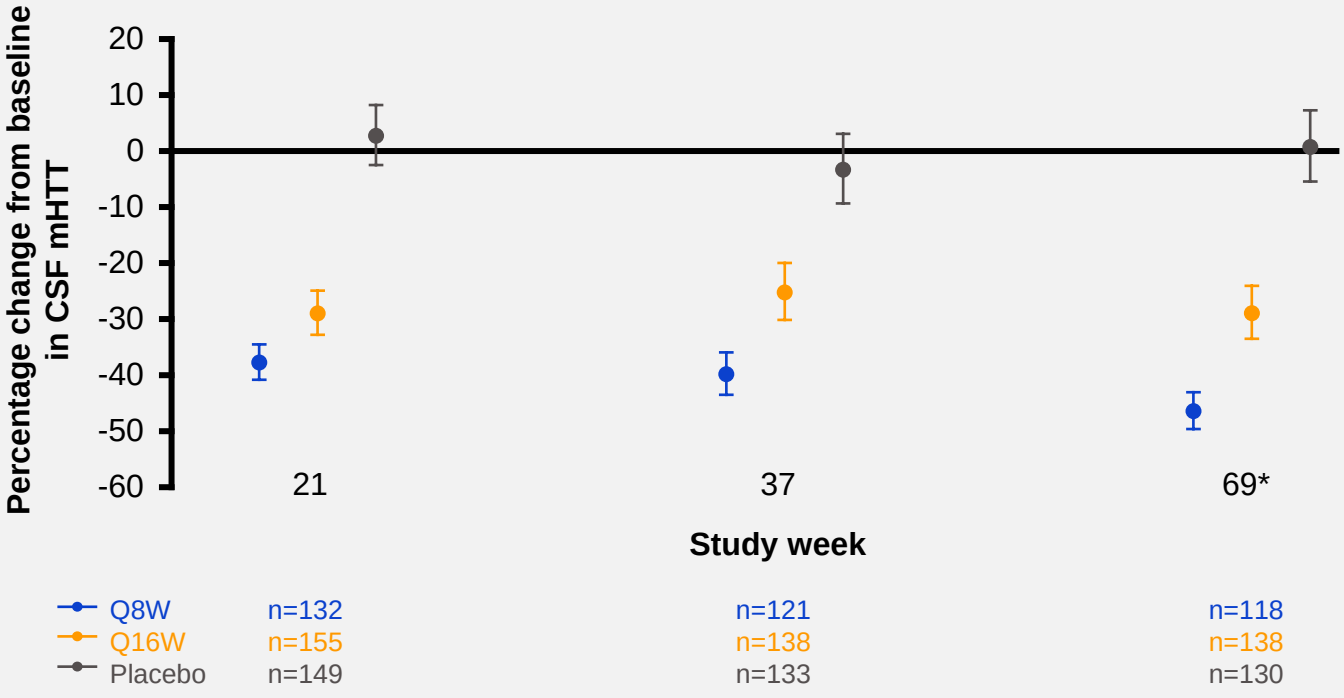
Sanwald Ducray P, et al. *Neurology*. 2019; 92(15 Suppl):S16.005.

GENERATION HD1

Core analysis

Target CSF mHTT lowering was achieved for both the Q8W and Q16W dosing regimens as predicted by the clinical popPK/PD model

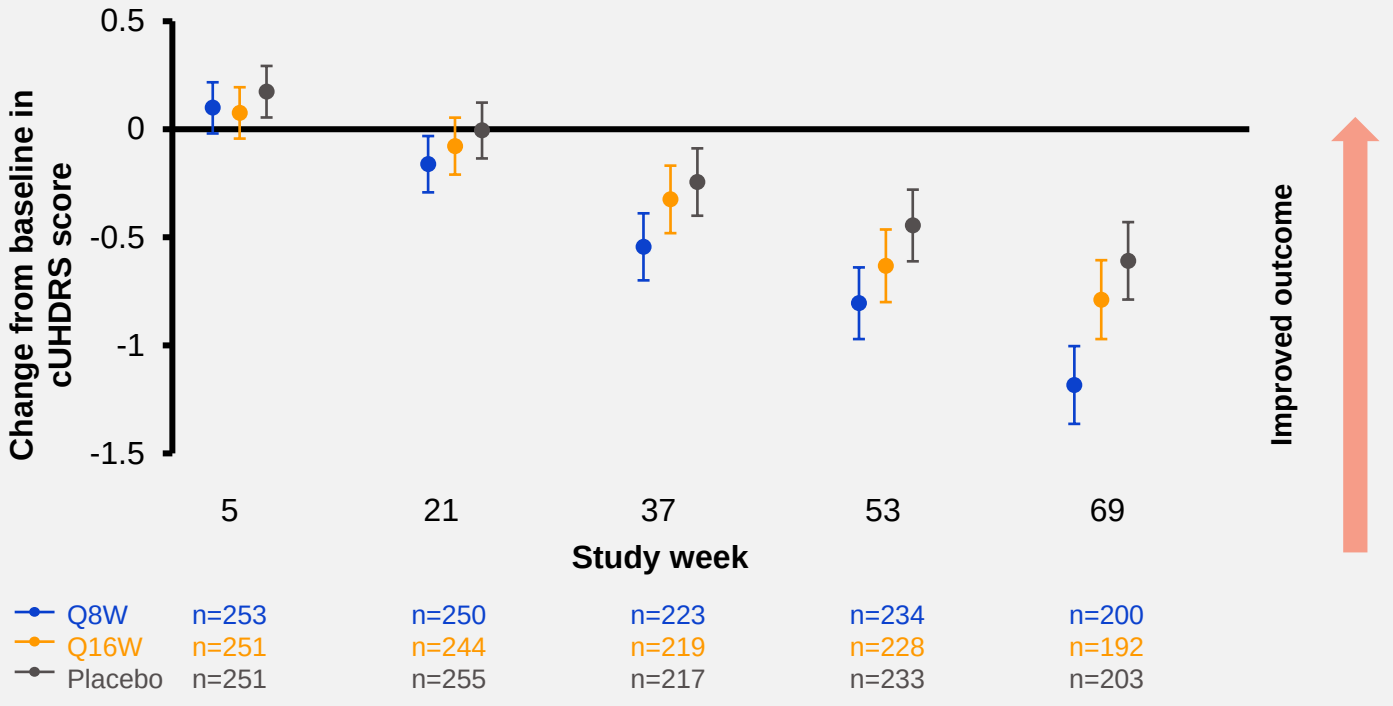
- **Q8W: Observed 46% (predicted 44%) CSF mHTT lowering at trough**
- **Q16W: Observed 29% (predicted 25%) CSF mHTT lowering at trough**



* mHTT data available for 65% of patients with clinical data at Week 69 (corresponding to 73% of patients with CSF).
Data points represent percentage change in geometric mean.
CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein; popPK/PD, population pharmacokinetics/pharmacodynamics; Q8W, every 8 weeks; Q16W, every 16 weeks.

Clinical efficacy not demonstrated: cUHDRS change from baseline to Week 69 similar to or worse than placebo

- In the Q8W group, point estimates were in the unfavourable direction, compared with placebo
- The Q16W group did not show any apparent benefit, compared with placebo



Update from data shown at CHDI 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.
cUHDRS, composite Unified Huntington's Disease Rating Scale; Q8W, every 8 weeks; Q16W, every 16 weeks.

AE profile showed Q16W was similar to placebo and evidence of Q8W being less well tolerated

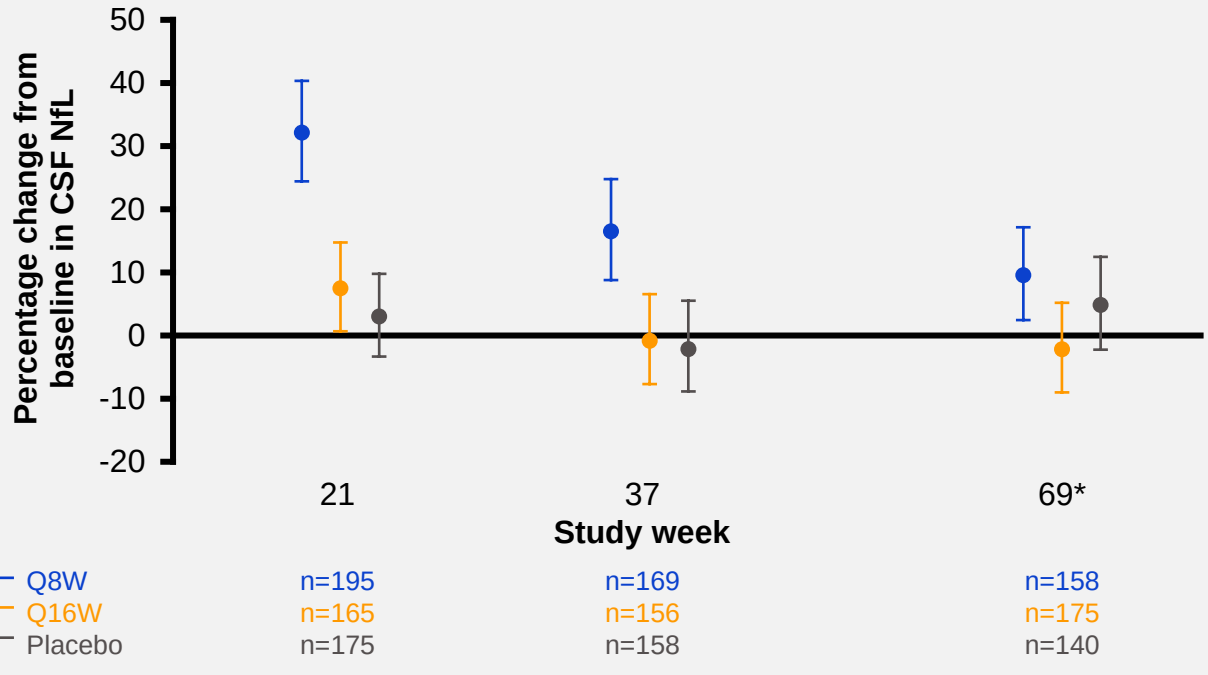
- **No fatal cases were considered related to tominersen**
- **More SAEs observed in the Q8W group compared with the Q16W group and placebo**

	Tominersen 120 mg Q8W (n=260) (n, %)	Tominersen 120 mg Q16W (n=261) (n, %)	Placebo (n=260) (n, %)
Fatal	1 (0.4%) (asphyxia, completed suicide)	2 (0.8%) (unexplained death, myocardial infarction)	2 (0.8%) (assisted suicide, choking)
SUSAR cases (investigator's causality)	5 (1.9%)	1 (0.4%)	2 (0.8%)
SAEs	39 (15.0%)	22 (8.4%)	28 (10.8%)
Severe* AEs	28 (10.8%)	33 (12.6%)	37 (14.2%)
AEs	234 (90.0%)	225 (86.2%)	235 (90.4%)

* Severity rating 3–5.
Preliminary analyses performed on non-final data set. Snapshot date: 5 February 2021.
AE, adverse event; Q8W, every 8 weeks; Q16W, every 16 weeks; SAE, serious AE; SUSAR, Suspected Unexpected Serious Adverse Reaction.

Transient increases in CSF NfL were observed with Q8W dosing

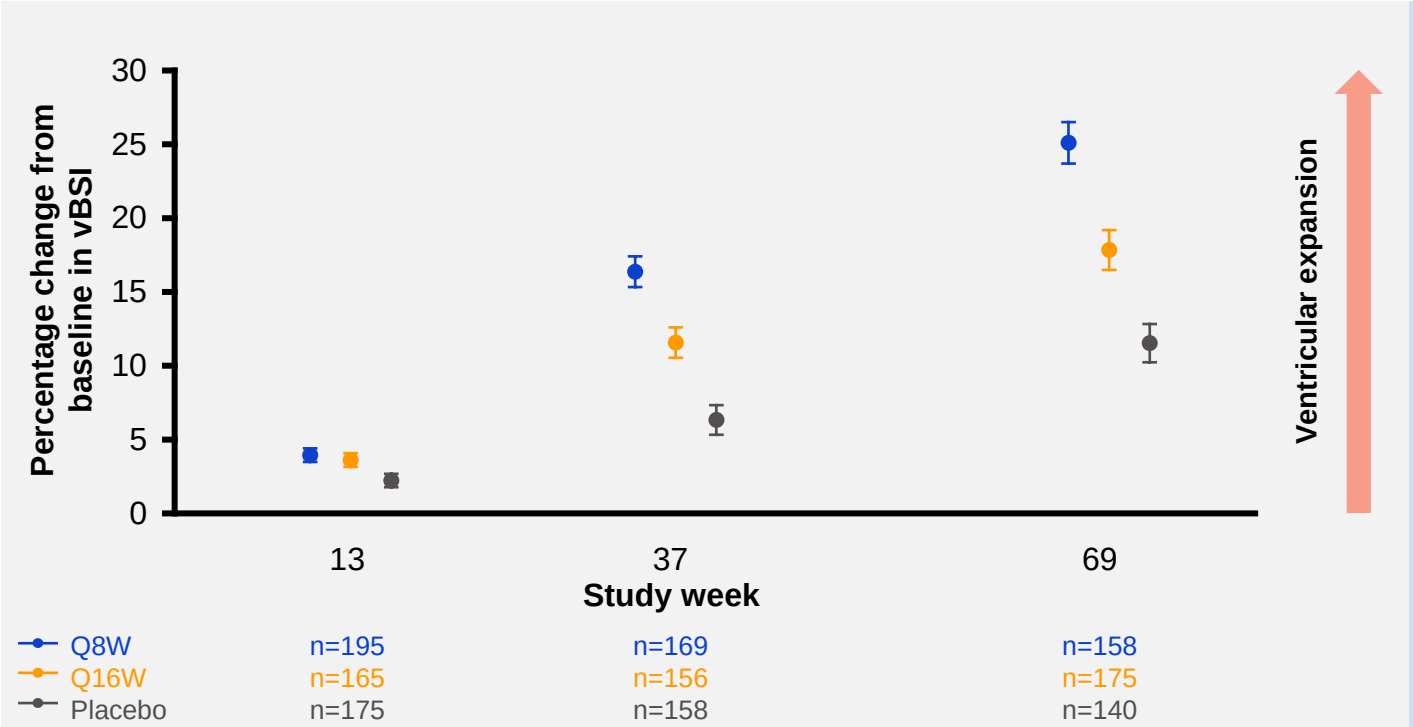
- **Q8W: NfL increases from baseline at all time points, with the greatest increases at Week 21; trending towards baseline by Week 69**
- **Q16W: point estimates greater than baseline at Week 21; in line with baseline levels at Weeks 37 and 69**



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

Dose regimen-dependent increases in ventricular volumes were observed at Weeks 37 and 69

- **Both Q8W and Q16W regimens showed increases in ventricular volume relative to placebo**



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

Key findings from the GENERATION HD1 core analyses

Target CSF mHTT lowering achieved as predicted by clinical popPK/PD model

Efficacy at the group level not demonstrated despite achieving CSF mHTT-lowering targets

Q8W clinical outcomes in general worse than placebo

Q16W well tolerated, whereas Q8W less well tolerated, relative to placebo

Increases in NfL (Q8W) and ventricular volume (Q8W and Q16W) observed

The mechanism behind these observations are not yet understood, although exposure-dependent, on-target and/or non-target related effects may be implicated

ASO, antisense oligonucleotide; CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein; NfL, neurofilament light protein; popPK/PD, population pharmacokinetics/pharmacodynamics; Q8W, every 8 weeks; Q16W, every 16 weeks; wtHTT, wild-type huntingtin protein.

GENERATION HD1

Preliminary post-treatment analysis

Preliminary post-treatment analysis overview

Analysis led by the iDMC performed at the November 2021 data cut-off

Clinical data

84%
of patients remained in GENERATION HD1

Of which, approximately
70%
of patients had reached Week 101 final study visit

Time on treatment
Mean 474 days
Median 527 days (~17 months), range 1–597 days

Time post-treatment
Mean 195 days
Median 175 days (~6 months), range 7–689 days

Imaging data

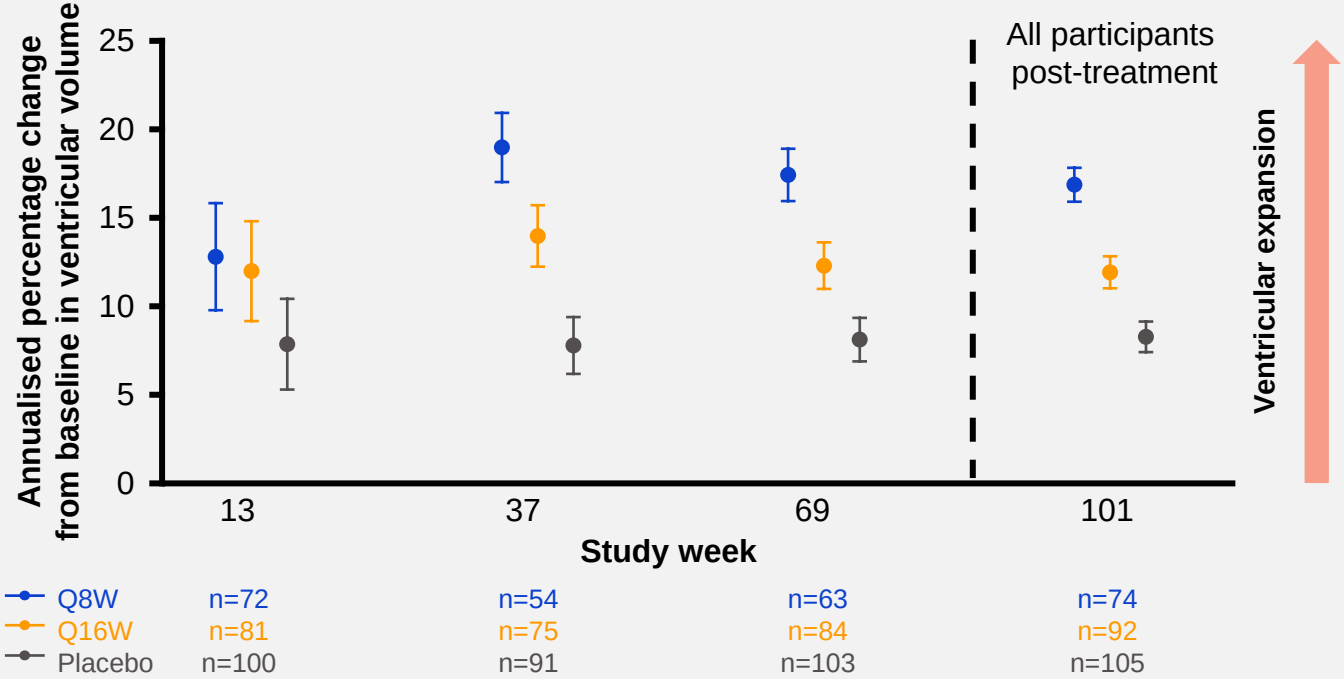
- 40% of data available for Week 101
- Reasons for missing data include QC failures and patients yet to reach Week 101

Following review of these data, the iDMC recommended no further follow-up beyond the Week 101 visit in GENERATION HD1

iDMC, independent Data Monitoring Committee; QC, quality control.

Preliminary analysis: Annualised vBSI for available subset of participants with Week 101 scan

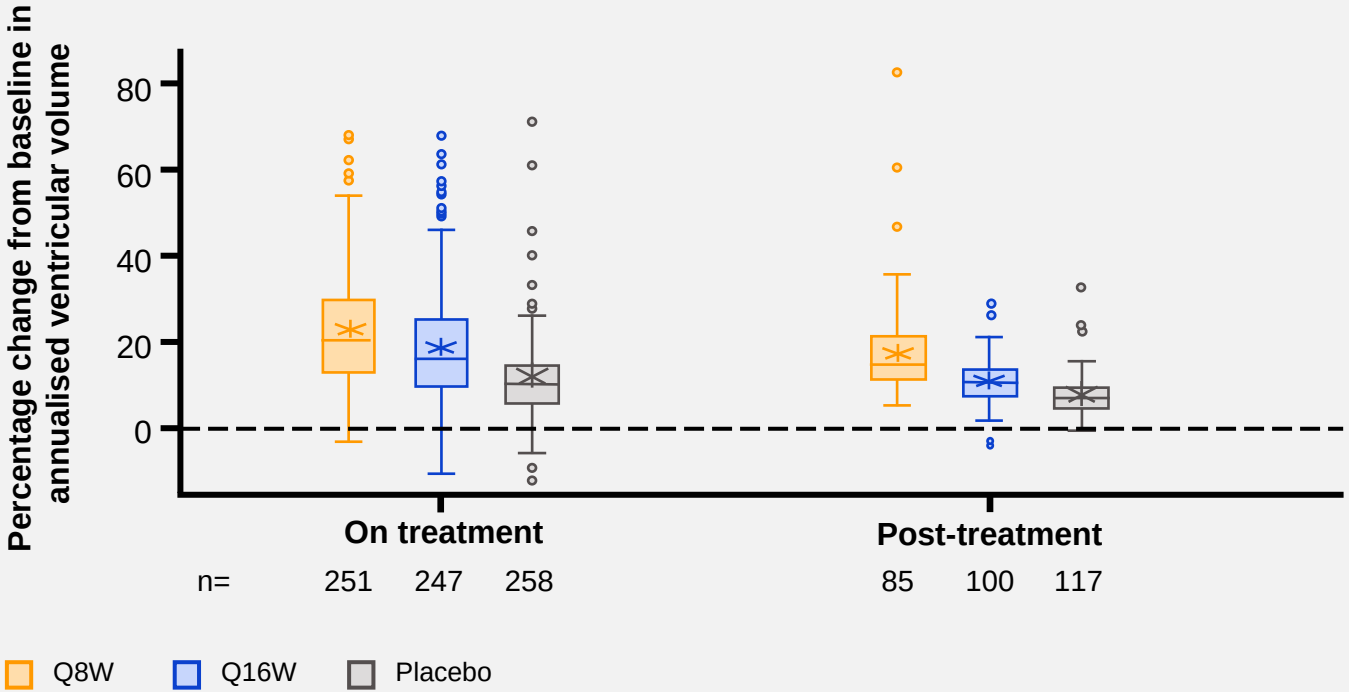
- **Dose regimen-dependent increases in ventricular volume (annualised vBSI) on treatment**
- **Apparent decrease in annualised vBSI after Week 37 in Q8W and Q16W arms**



Snapshot date 18 November 2021. Data points represent least-squares mean values and their 95% confidence interval based on the analysis of mixed-effect model repeated measure.
Q8W, every 8 weeks; Q16W, every 16 weeks; vBSI, ventricular boundary shift integral.

Preliminary analysis: Maximum* annualised vBSI summary statistics for available on- and post-treatment data

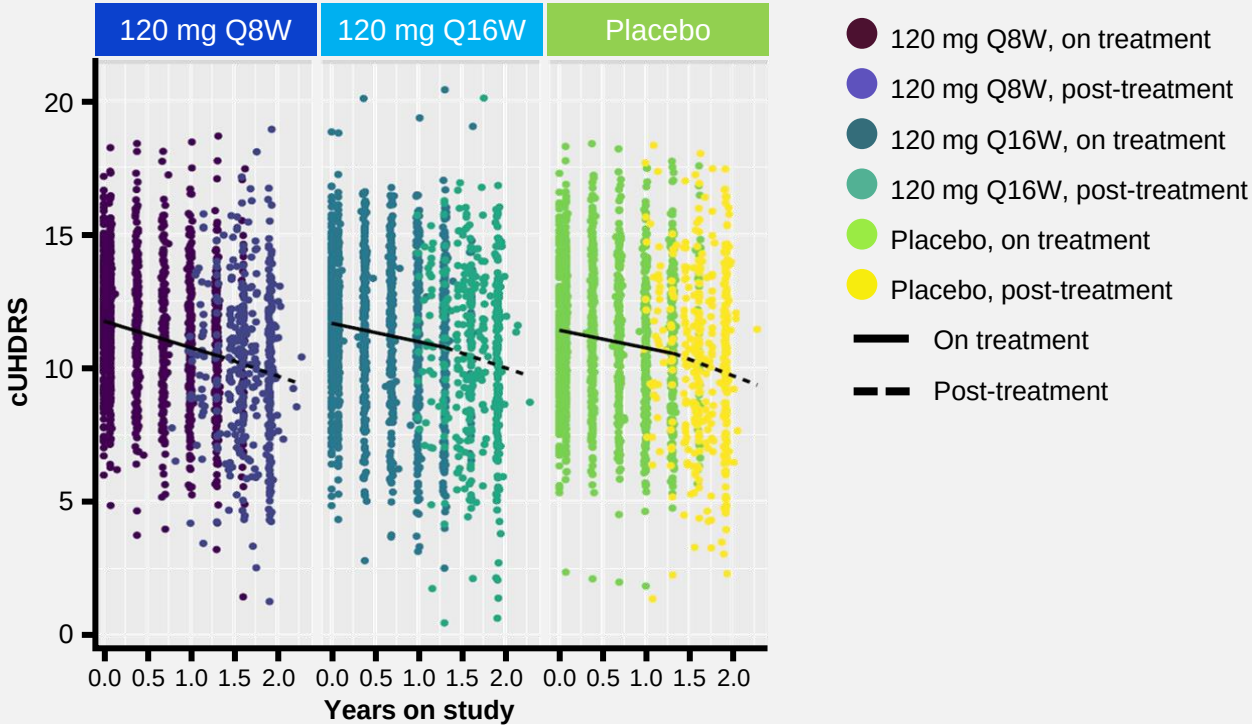
- **Dose regimen-dependent increases in annualised ventricular volume (vBSI) on treatment**
- **Apparent decrease in vBSI in the post-treatment period in all groups**



* Maximum value for each patient at any time point on-/post-treatment.
Snapshot date 18 Nov 2021. Data points represent least-squares mean values and their 95% confidence interval based on the analysis of mixed-effect model repeated measure.
Q8W, every 8 weeks; Q16W, every 16 weeks; vBSI, ventricular boundary shift integral.

Preliminary analysis: cUHDRS on treatment/post-treatment slope analysis

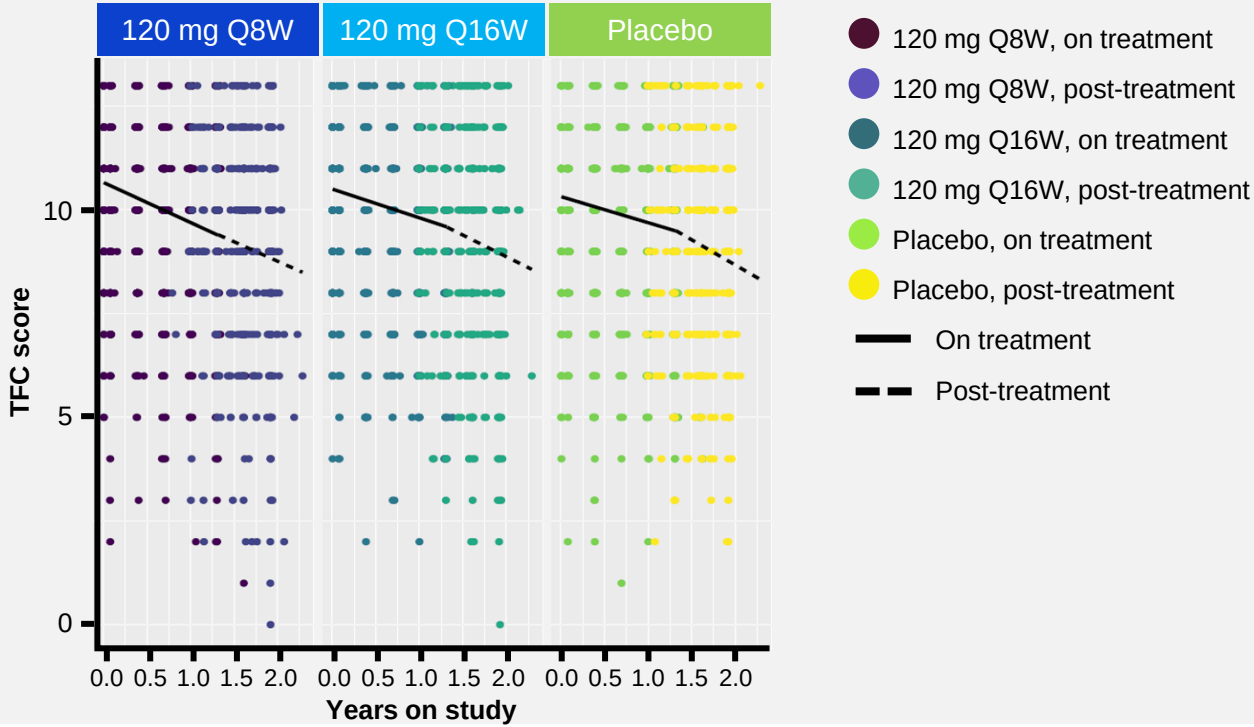
- **On treatment: Statistically significantly greater decline in the Q8W group compared with placebo; Q16W group comparable to placebo**
- **Post-treatment: Decline in Q8W and Q16W groups comparable to placebo with no statistically significant difference**



cUHDRS, composite Unified Huntington's Disease Rating Scale; Q8W, every 8 weeks; Q16W, every 16 weeks.

Preliminary analysis: 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, no statistically significant difference**



Q8W, every 8 weeks; Q16W, every 16 weeks; TFC, Total Functional Capacity.

Summary of GENERATION HD1 preliminary post-treatment analyses

Effects on ventricular volume in the Q8W and Q16W arms appear to decrease after Week 37

Following review of these data, the iDMC recommended no further follow-up beyond the Week 101 visit in GENERATION HD1

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

Final analyses will be conducted once all remaining patients complete the Week 101 visit

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

GENERATION HD1 analysis:

Post hoc analyses

Hypothesis-driven analysis plan built to systematically analyse rich dataset to understand factors determining tominersen response

Patient population

Disease burden

What is the role of disease burden in tominersen's treatment response?

Disease burden + exposure

Exposure

Dose/dosing regimen

What is the role of drug exposure on tominersen's treatment response?

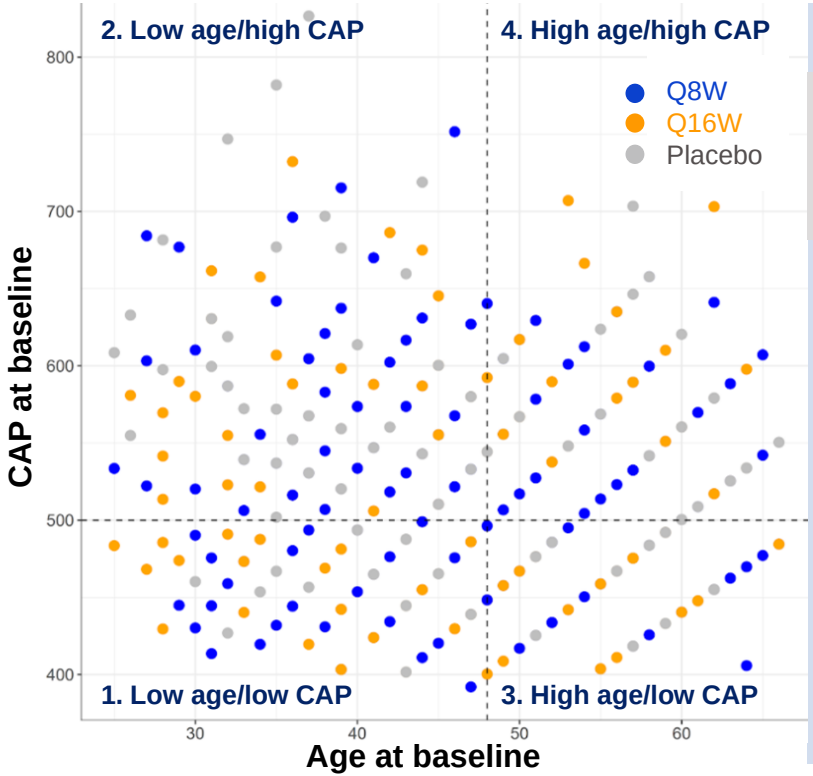
Lower disease burden proxies
- Stage I (~50%)
- CAP <500 (median split)
- Lower brain atrophy

Higher disease burden proxies
- Stage I/II (~50%)
- CAP >500 (median split)
- High brain atrophy

Tominersen CSF concentration average
- Up to Week 21 ($C_{av}21$)
- Up to Week 53 ($C_{av}53$)

CAP = age x (CAG repeat length – 33.66); Stage I: TFC 11–13.
CAP, CAG-age product; C_{av}, average concentration; CSF, cerebrospinal fluid; TFC, Total Functional Capacity.

Subgroups defined based on median* split of baseline age and CAP at baseline avoid the age/CAG confound



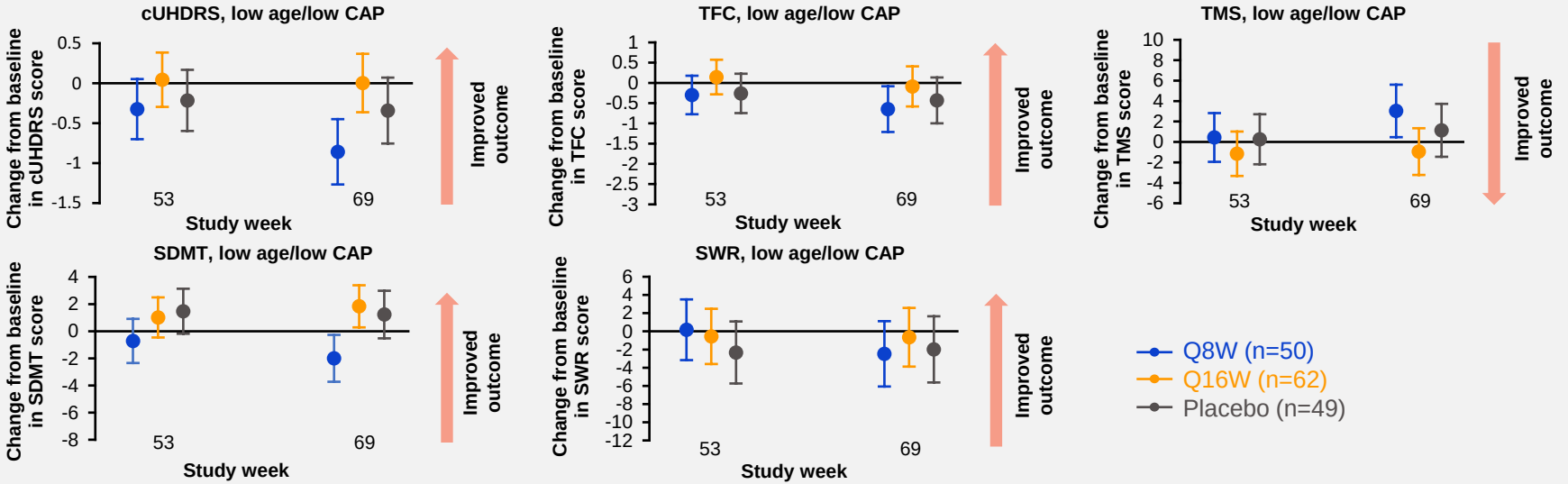
Disease burden and age

- Striatal degeneration at *post mortem* is a function of age x CAG[1]
- CAP = age x (CAG repeat length – 33.66)

Frequency	Low age/ low CAP	Low age/ high CAP	High age/ low CAP	High age/ high CAP	Total
Placebo	50	65	64	85	**264**
Q16W	62	66	69	67	**264**
Q8W	50	74	72	67	**263**
Total	162	205	205	219	**791**

*Median age at baseline: 48; median CAP score at baseline: 508, rounded down to 500 for cut-off.
CAP, CAG-age product; Q8W, every 8 weeks; Q16W, every 16 weeks.
1. Penney Jr JB, et al. *Ann Neurol*. 1997; 41:689–692.

Q16W/low-age/low-CAP subgroup: point estimates consistently in the favourable direction for all UHDRS endpoints at Week 69

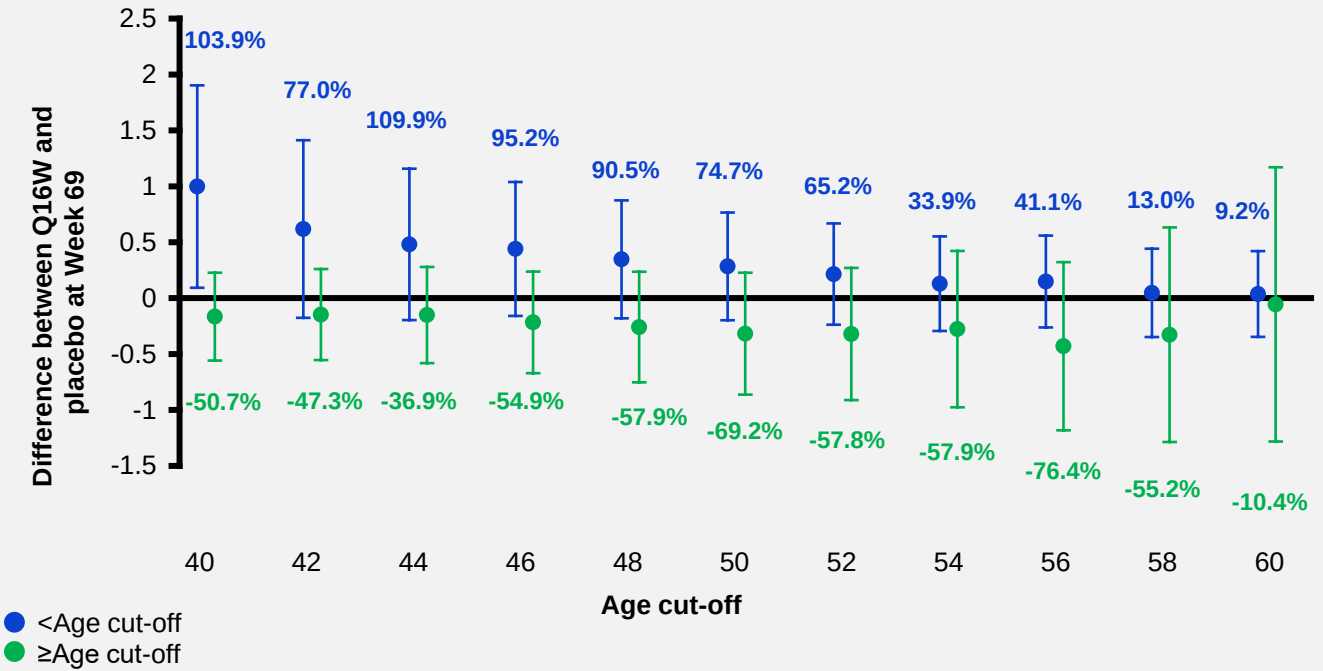


In the Q8W regimen, point estimates were generally unfavourable compared with placebo across subgroups, regardless of age or CAP score

Data points represent least-squares mean values and their 95% confidence interval based on the analysis of mixed-effect model repeated measure.
CAP, CAG-age product; cUHDRS, composite UHDRS; Q8W, every 8 weeks; Q16W, every 16 weeks; SDMT, Symbol Digit Modalities Test; SWR, Stroop Word Reading; TFC, Total Functional Capacity; TMS, Total Motor Score; UHDRS, Unified Huntington's Disease Rating Scale.

Sensitivity analysis across age cut-offs for cUHDRS (CAP<500)

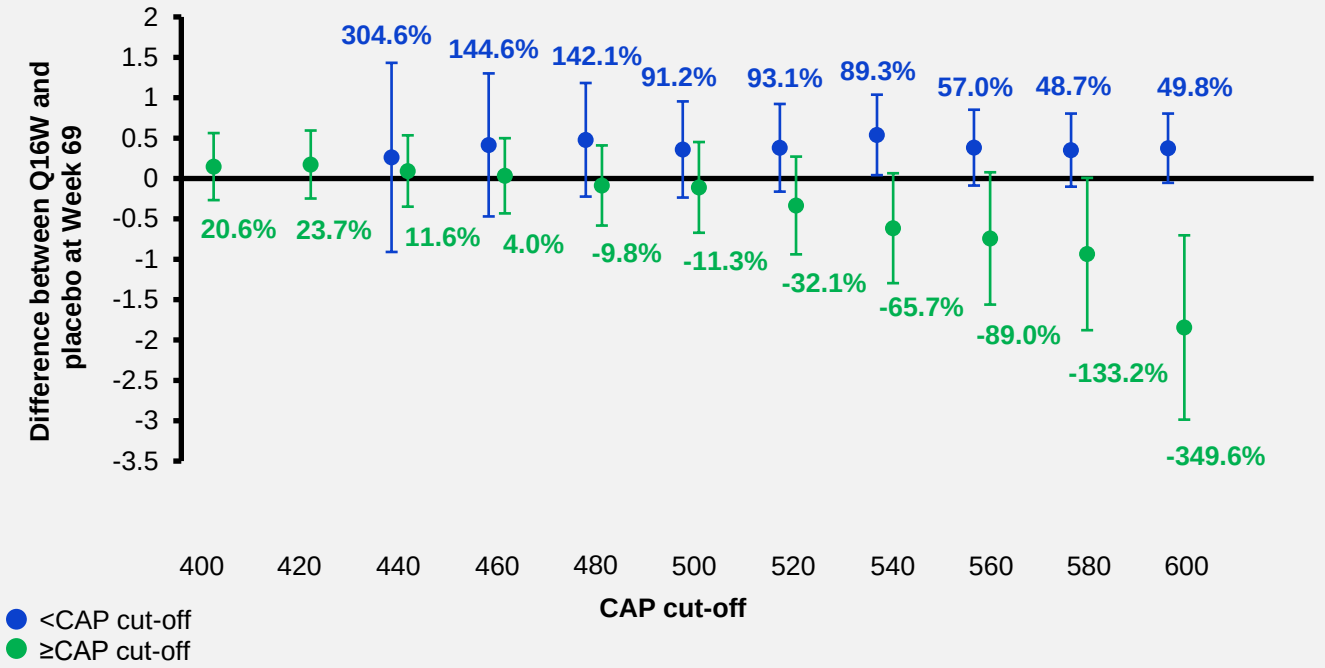
- **Consistent trend of point estimates in the favourable direction for cUHDRS below age cut-offs (blue)**
- **Consistent trend of point estimates in the unfavourable direction for cUHDRS above age cut-offs (green)**



CAP, CAG-age product; cUHDRS, composite Unified Huntington's Disease Rating Scale; Q16W, every 16 weeks.

Sensitivity analysis across CAP cut-offs for cUHDRS (age<48)

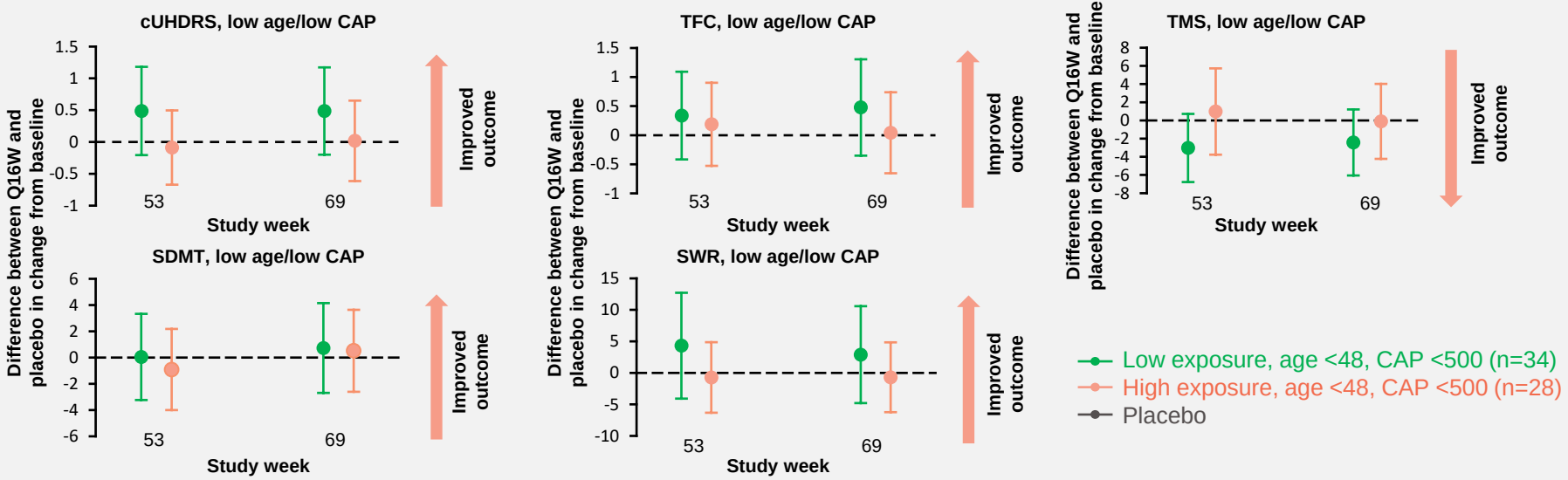
- **Point estimates in the favourable direction for cUHDRS below CAP cut-offs (blue)**
- **Consistent trend of point estimates in the unfavourable direction for cUHDRS above CAP cut-offs (green)**



CAP, CAG-age product; cUHDRS, composite Unified Huntington's Disease Rating Scale; Q16W, every 16 weeks.

Q16W low-age/low-CAP subgroup exposure response analysis: Effects appear to be associated with lower exposure

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



Point estimates in the lower-exposure group were generally in the favourable direction across UHDRS endpoints at Week 69

Data points represent least-squares mean values and their 95% confidence interval.
CAP, CAG-age product; CSF, cerebrospinal fluid; cUHDRS, composite UHDRS; popPK, population pharmacokinetics; Q8W, every 8 weeks; Q16W, every 16 weeks; SDMT, Symbol Digit Modalities Test; SWR, Stroop Word Reading; TFC, Total Functional Capacity; TMS, Total Motor Score; UHDRS, Unified Huntington's Disease Rating Scale.

Summary of GENERATION HD1 *post hoc* analyses

A number of factors may mediate response to tominersen in GENERATION HD1, including:

- Age
- Disease burden (as measured by CAP score)
- Exposure to tominersen (which is related to the extent of mHTT lowering)

For cUHDRS and TFC at Weeks 53 and 69 in the Q16W group, point estimates were in the favourable direction relative to placebo for:

- Age <48
- CAP score <500
- Low exposure (median split CSF PK average at Week 21 Q16W)

CAP, CAG-age product; CSF, cerebrospinal fluid; cUHDRS, composite Unified Huntington's Disease Rating Scale; mHTT, mutant huntingtin protein; PK, pharmacokinetics; Q16W, every 16 weeks.

Leveraging knowledge for the new Phase II study

GENERATION HD1 clinical data inform new hypotheses to be tested in the new Phase II study

Key findings from GENERATION HD1 *post hoc* analyses: In the Q16W low-age/low-CAP (reference) subgroup, point estimates were consistently in the favourable direction on all UHDRS measures at Week 69; effects appear to be associated with lower exposure range within the Q16W group

Dose selection considerations

- **Dose 1 (Q16W):** Target the low exposure range for 120 mg Q16W observed in the GENERATION HD1 reference subgroup
- **Dose 2 (Q16W):** Explore a lower exposure regimen to characterise the lower therapeutic range for tominersen

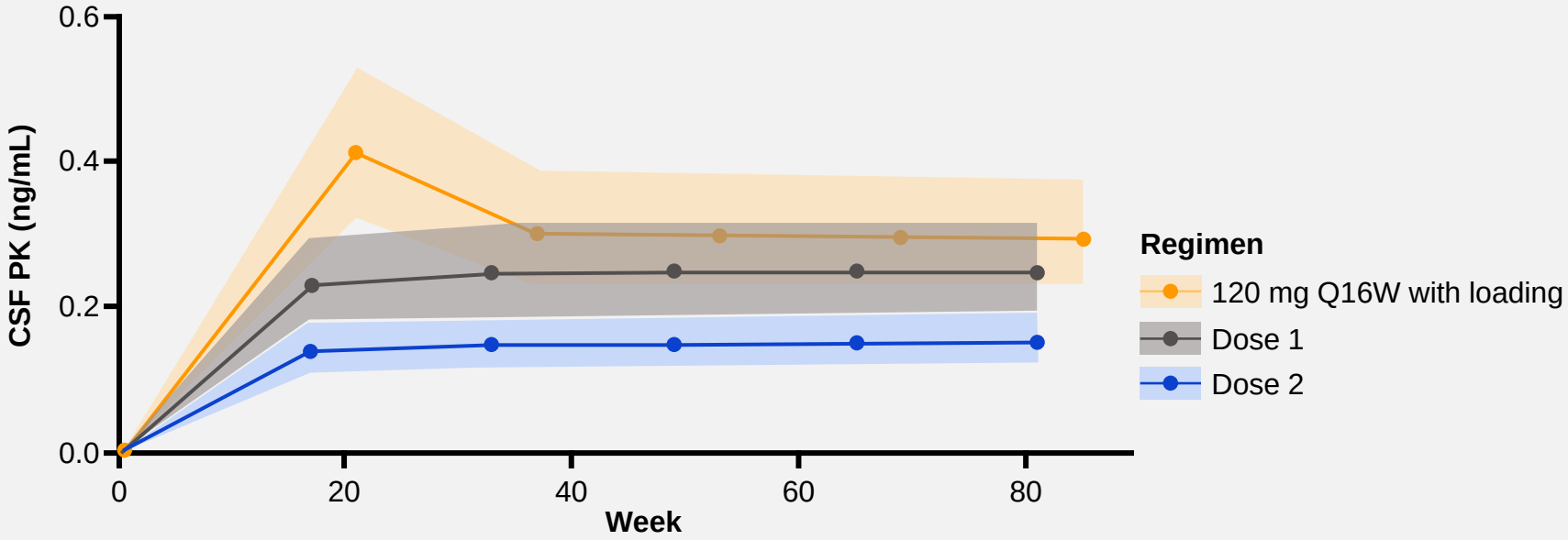
Study population considerations

- Lower age (e.g. age 25–50 years)
- Less disease burden (e.g. CAP <500)
- Application of the new HD-ISS staging system (late Stage 2 and early Stage 3)

CAP, CAG-age product; HD-ISS, Huntington's Disease Integrated Staging System; Q8W, every 8 weeks; Q16W, every 16 weeks; UHDRS, Unified Huntington's Disease Rating Scale.

New Phase II study: Targeting lower CSF exposure

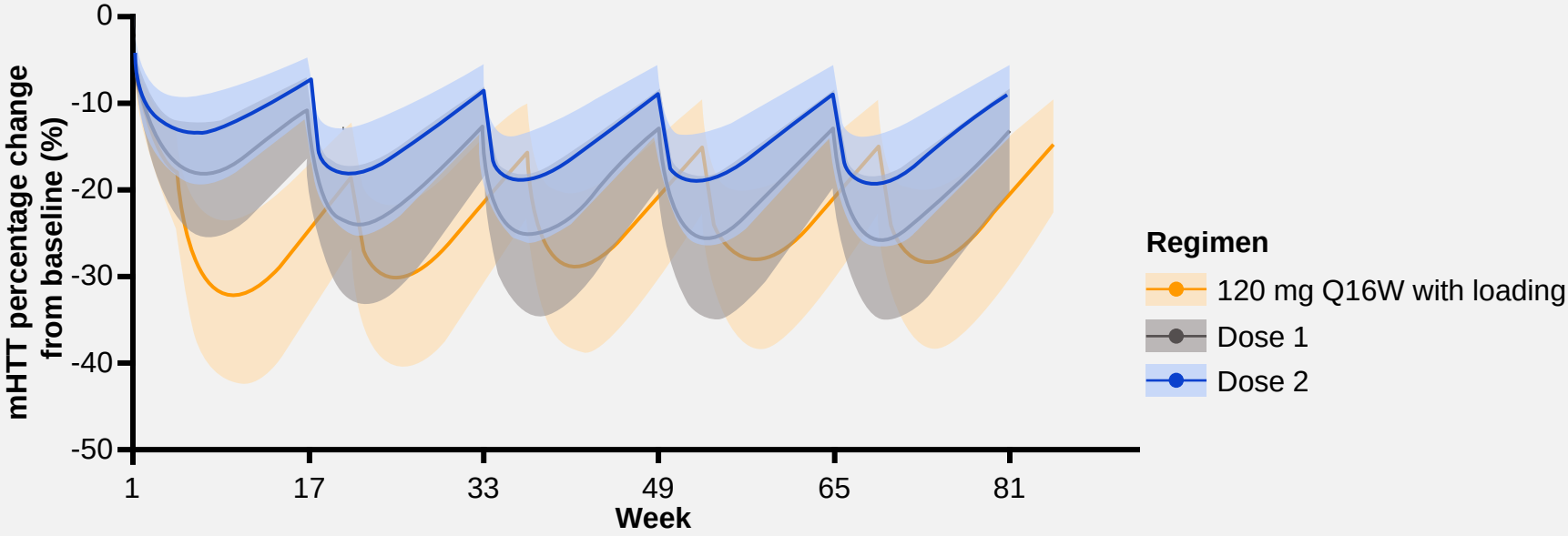
Simulation of CSF PK profiles in typical target population (low age/low CAP)



CAP, CAG-age product; CSF, cerebrospinal fluid; PK, pharmacokinetics; Q16W, every 16 weeks.

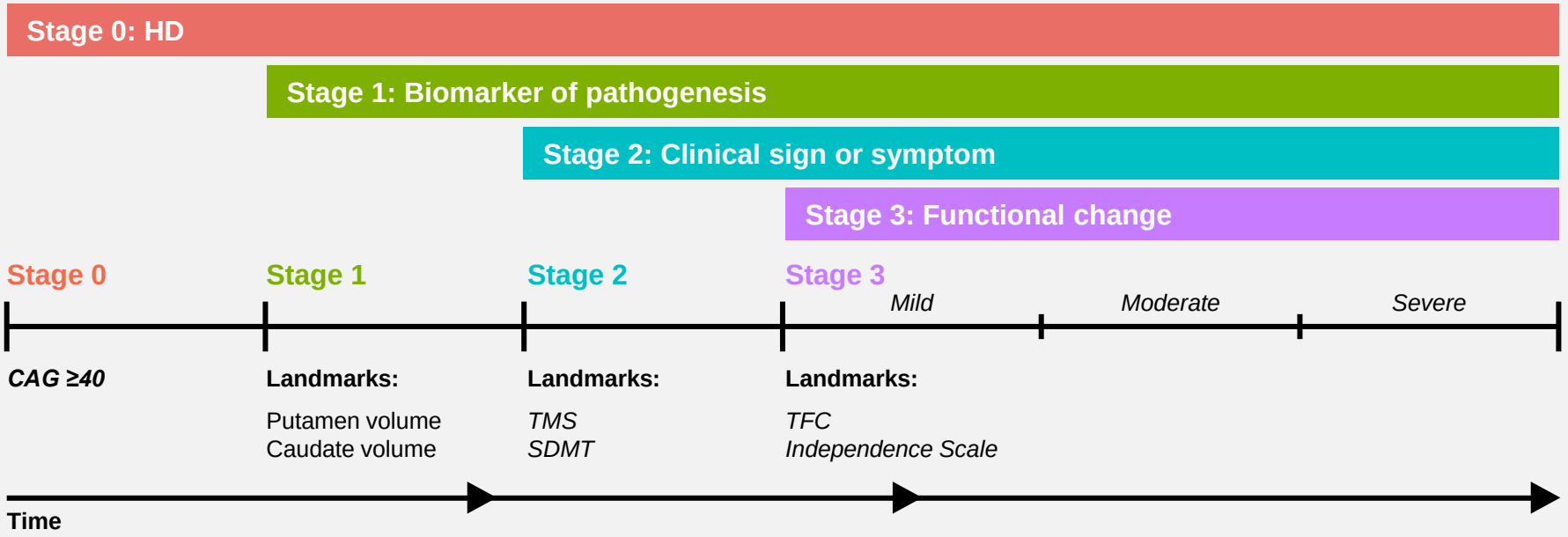
New Phase II study: Targeting less CSF mHTT reduction

Simulation of mHTT profiles in typical target population (low age/low CAP)



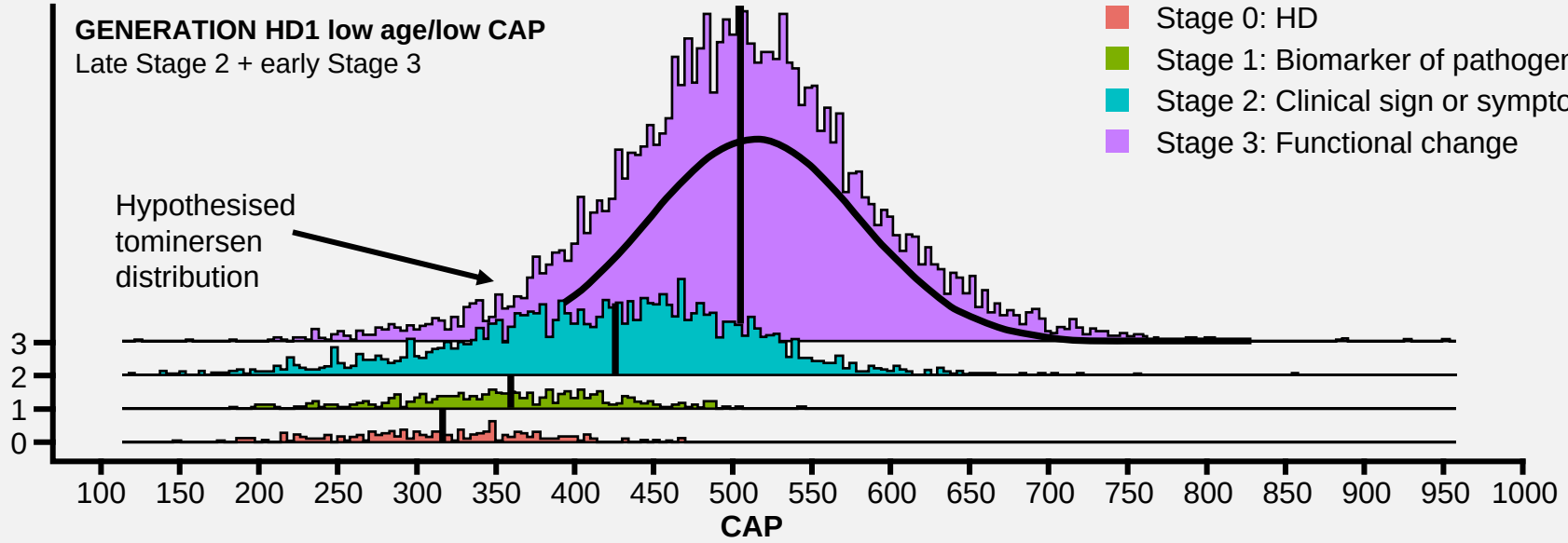
CAP, CAG-age product; CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein; Q16W, every 16 weeks.

HD Integrated Staging System (HD-ISS)



HD, Huntington's disease; HD-ISS, HD Integrated Staging System; SDMT, Symbol Digit Modalities Test; TFC, Total Functional Capacity; TMS, Total Motor Score.
Tabrizi SJ, et al. medRxiv [preprint]. 11 September 2021. https://doi.org/10.1101/2021.09.01.21262503.

Mapping of the GENERATION HD1 reference subgroup to the HD-ISS



CAP, CAG-age product; HD, Huntington's disease; HD-ISS, HD Integrated Staging System.

Summary

Core analysis

- Efficacy at the group level not demonstrated despite achieving CSF mHTT lowering target
- Q8W dosing less tolerated with increases in NfL (Q8W) and ventricular volume (Q8W and Q16W)

Preliminary post-treatment analysis

- Effects on ventricular volume in the Q8W and Q16W arms appear to decrease after Week 37
- Clinical outcomes: no evidence of differential progression rates following treatment cessation

Post hoc analysis

- In the Q16W low-age/low-CAP subgroup, point estimates were consistently in the favourable direction on all UHDRS measures; effects appear to be associated with lower exposure within the Q16W group

New Phase II study: dose and study population guided by clinical data from GENERATION HD1 *post hoc* analysis

- Doses to be selected based on lower tominersen CSF exposure range
- Study to include younger participants with less disease burden and consideration of the new HD-ISS staging system

CAP, CAG-age product; CSF, cerebrospinal fluid; HD-ISS, Huntington's Disease Integrated Staging System; mHTT, mutant huntingtin protein; NfL, neurofilament light protein; Q8W, every 8 weeks; Q16W, every 16 weeks; UHDRS, Unified Huntington's Disease Rating Scale.

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

Roche

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Doing now what patients need next