Placebo response in HD:
Comparing placebo arm in GENERATION HD1 vs Enroll-HD data

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To access this presentation go to:
https://ter.li/n6nhs5

Date of preparation: September 2024 M-XX-00018824

Disclosures

Roche

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I am an employee of and own stock in 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



Quantifying natural history progression: Insights from Enroll-HD



Placebo response in HD: Insights from comparing Enroll-HD with GENERATION HD1



Consequences for trial design and clinical endpoints

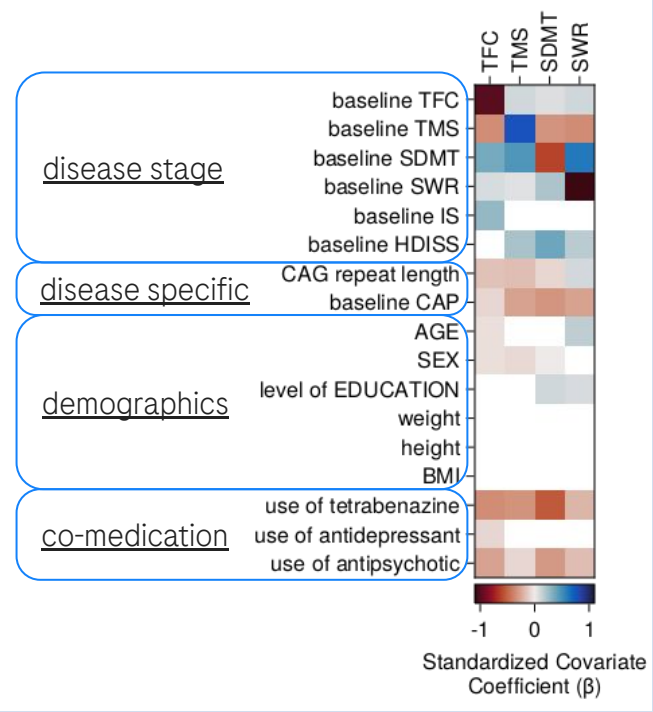
Quantifying natural history progression:
Insights from Enroll-HD

Can we predict clinical progression based on baseline characteristics?

Clinical measurements:
Functional
Total functional capacity (TFC)

Motor
Total motor score (TMS)

Cognitive
Symbol digit modality test (SDMT)
Stroop word reading (SWR)



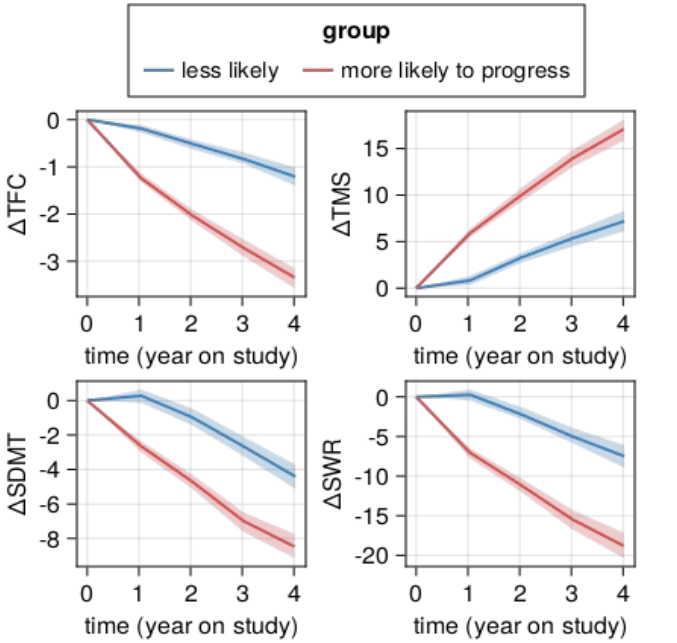
Most relevant characteristics:

- stage of disease
- use of tetrabenazine and antipsychotic
- CAP, CAG

Demographics have minor relevance in predicting progression rate.

BMI, body mass index; CAP, CAG-Age-Product; CI, confidence interval; IS, independent score; HDISS, Huntington's disease integrated staging system;

Quantifying natural history progression:
Insights from Enroll-HD



Cross validation: 70% training, 30% validation. Area: 95% CI

Baseline patient characteristics that can be measured in a clinical visit are good predictors of changes in clinical scores (natural history progression).

Pre-print (MedRxiv)

Modeling disease progression and placebo response in HD: Insights from Enroll-HD and GENERATION HD1 cohorts.

M. Boareto, Y. Yamamoto, J.D. Long, C. Sampaio, P. McColgan, C. Diack, P. Sanwald Ducray

CI, confidence interval; SDMT, symbol digit modality test; SWR, Stroop word reading; TFC, total functional capacity; TMS, total motor score;

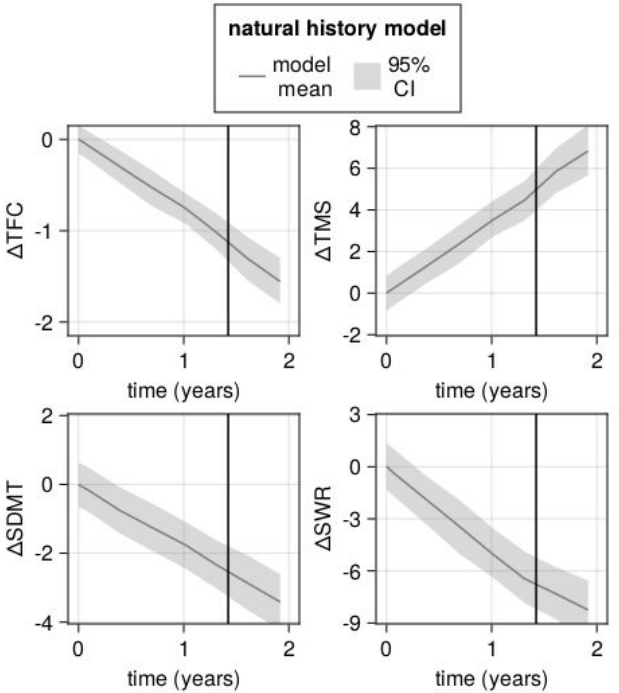
Placebo response in HD:
Insights from comparing Enroll-HD with GENERATION HD1

Baseline characteristics can be used to predict the expected natural history progression.

We applied this model to GENERATION HD1 placebo arm (n=260).

Dosing regimen in GENERATION HD1 stopped at week 69 (vertical line), and participants were followed until week 101.

Differences between progression in the trial and natural history progression can be interpreted as placebo response.



SDMT, symbol digit modality test; SWR, Stroop word reading; TFC, total functional capacity; TMS, total motor score; CI, confidence interval; GEN-HD1, GENERATION HD1.

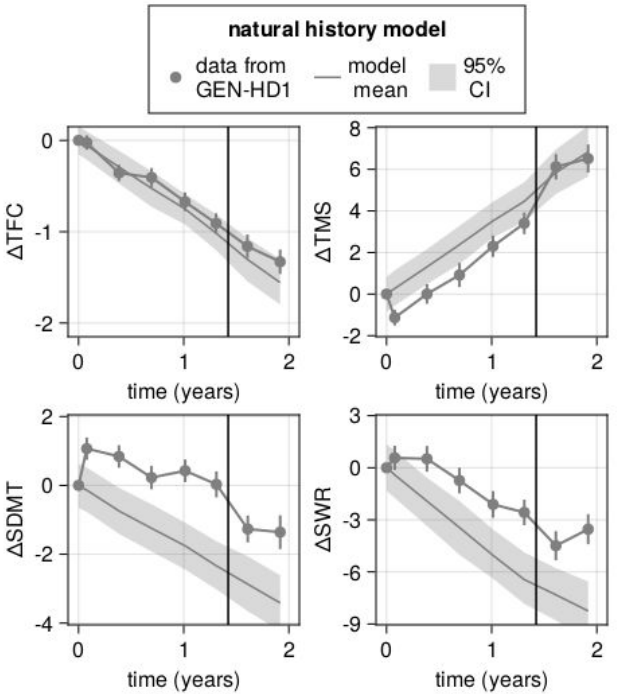
Placebo response in HD:
Insights from comparing Enroll-HD with GENERATION HD1

Functional score (TFC):
no evidence of placebo response

Motor score (TMS):
improvement after baseline with an offset after end of dosing regimen: placebo effect

Cognitive scores (SWR, SDMT):
improvement after baseline, with **no** offset after end of dosing regimen: practice effect

Once placebo response is corrected (as a initial improvement) the rate of progression is consistent with natural history: Enroll-HD is a great source of natural history data



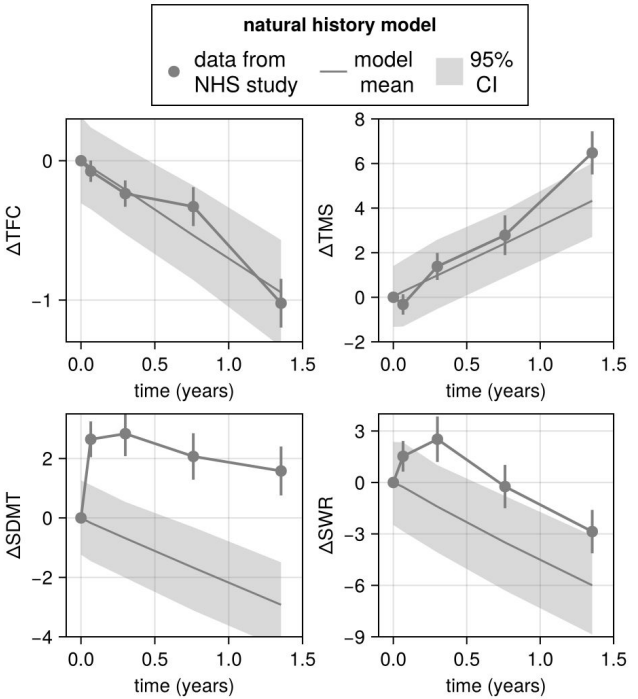
SDMT, symbol digit modality test; SWR, Stroop word reading; TFC, total functional capacity; TMS, total motor score; CI, confidence interval; GEN-HD1, GENERATION HD1;

Placebo response in HD:
Insights from Roche Natural History study

Roche Natural History study: Total of 93 participants. Inclusion criteria similar to GENERATION-HD1

Functional score (TFC) and motor score (TMS):
Progression consistent with natural history predictions. This confirms our interpretation of placebo effect in TMS observed in GENERATION-HD1

Cognitive scores (SWR, SDMT):
Strong improvement after first measurement. This confirms our interpretation of practice effect, strongly dependent on trial design.



SDMT, symbol digit modality test; SWR, Stroop word reading; TFC, total functional capacity; TMS, total motor score; CI, confidence interval; NHS: Natural History Study

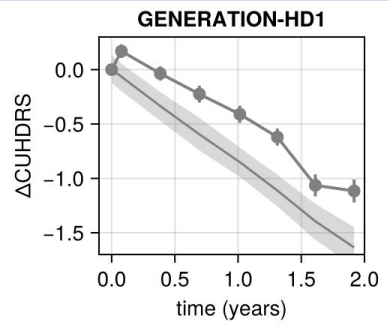
Consequences for trial design and clinical endpoints

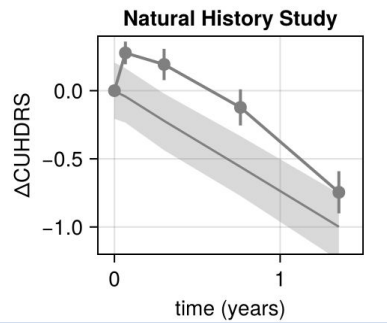
Functional score (TFC): robust against placebo response

Motor score (TMS): susceptible to placebo effect, which might be dependent on expectations regarding the drug effect

Cognitive scores (SWR, SDMT): highly susceptible to practice effect. Frequent testing may lead to improvements due to practice and caution should be taken when comparing with natural history data (annual testing).

cUHDRS (composite of TFC, TMS, SWR, SDMT):
cUHDRS is affected by both placebo effect (TMS) and practice effect (SDMT, SWR). The impact of these effects on sample size estimates should be considered.





SDMT, symbol digit modality test; SWR, Stroop word reading; TFC, total functional capacity; TMS, total motor score; cUHDRS, composite Unified Huntington's Disease Rating Scale; CI, confidence interval; NHS: Natural History Study

Summary

Quantifying natural history progression: Insights from Enroll-HD
Baseline characteristics are strong predictors of natural history progression.

Placebo response in HD: Insights from comparing Enroll-HD with GENERATION HD1
Placebo effect in motor and practice effect in cognitive measurements.

Consequences for trial design and clinical endpoints
Practice effect in cognitive scores seems dependent on frequency of testing. Requires caution when comparing with natural history studies with annual testing.
cUHDRS affected by placebo effect and practice effect, which may affect sample size estimates.

cUHDRS, composite Unified Huntington's Disease Rating Scale

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

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