Roche update on GENERATION HD1, the first Phase III Huntingtin-lowering study

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Rare Conditions Partner, Huntington Disease

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Disclosures

We thank the LIRH Foundation for its request to receive an update on Roche research efforts

This presentation is intended for an international audience. It contains general information about our Huntington's disease programme and i**s not intended as specific medical advice**

Roche is testing an **investigational (not approved by health authorities)** molecule for the treatment of manifest Huntington's disease. The effectiveness and safety of this molecule are currently being studied

You should talk with your healthcare provider for information and advice about your condition, including any current or potential treatments

Thank you to our clinical study volunteers

These volunteers are helping progress HD research every day. Our company and the entire HD community support and thank you for your efforts

To clinical study participants in this audience, we should have limited or no knowledge of your personal treatment experience. **This helps protect the integrity of the study**

We encourage you to **share your experiences, both positive and negative, with your clinical trial investigator**. It is important that they receive this information so that it can be documented as part of the clinical study

Thank you for helping to advance Huntington's disease research

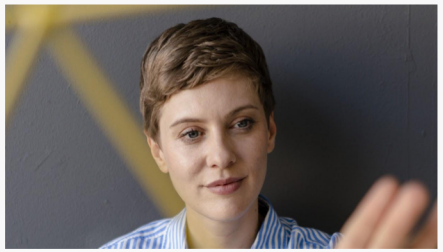
HD, Huntington's disease.

AGENDA

- Roche in Neuroscience: Our mission
- Tominersen Clinical Development Program
- GENERATION HD1 trial Update and the impact of Covid 19 Pandemic
- Q&A

Our Neuroscience Portfolio

One of the most diverse & promising in the industry



NeuroImmunology

Multiple sclerosis

Neuromyelitis optica spectrum disorder

NeuroDegeneration

Alzheimer’s disease

Huntington’s disease

Parkinson’s disease

NeuroMuscular

Spinal muscular atrophy

Duchenne muscular dystrophy

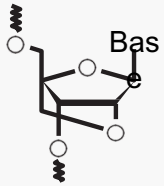
NeuroDevelopment

Autism spectrum disorder

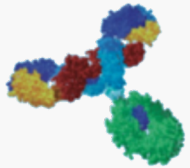
Angelman syndrome

In neuroscience we are pursuing different modalities, and leveraging digital approaches & data to improve research and disease management

Exploring different therapeutic modalities

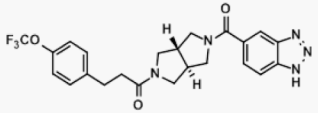


Locked Nucleic Acids (Lna)/Aso

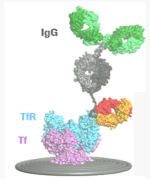


Monoclonal Antibodies

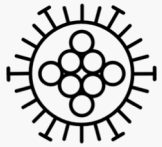
Digital Therapeutics



Small Molecules



Brain Shuttle



Gene Therapy

&

Measuring what matters

Remote Monitoring

Biomarkers, both digital and wet

Genetic Data Analysis to Stratify SMA Patients

ASO, Antisense Oligonucleotide

Tominersen: 7-year HD programme history

Continuing to build on strong science and partnerships

April 2013

Roche/Ionis HD partnership:
Non-allele-selective candidate selected for development

Sep 2015

First patient in Phase I/IIa study[1]

- Safety, tolerability, PK and PD
- Early manifest HD patients
- N=46

2015–2017

mHTT assay clinical and digital endpoint development

End 2017

Completion of the Phase I/IIa study

Roche licenses investigational IONIS-HTT$_{Rx}$ **(tominersen)**

2018

Launch of pivotal GENERATION-HD1 study; initiation of registrational programme activities; deepen partnership with community

2019

Observational natural history study enrolment complete. GEN-PEAK study initiated. Reduced dosing frequency in GEN-HD1

2020

Completed recruitment of Phase III study

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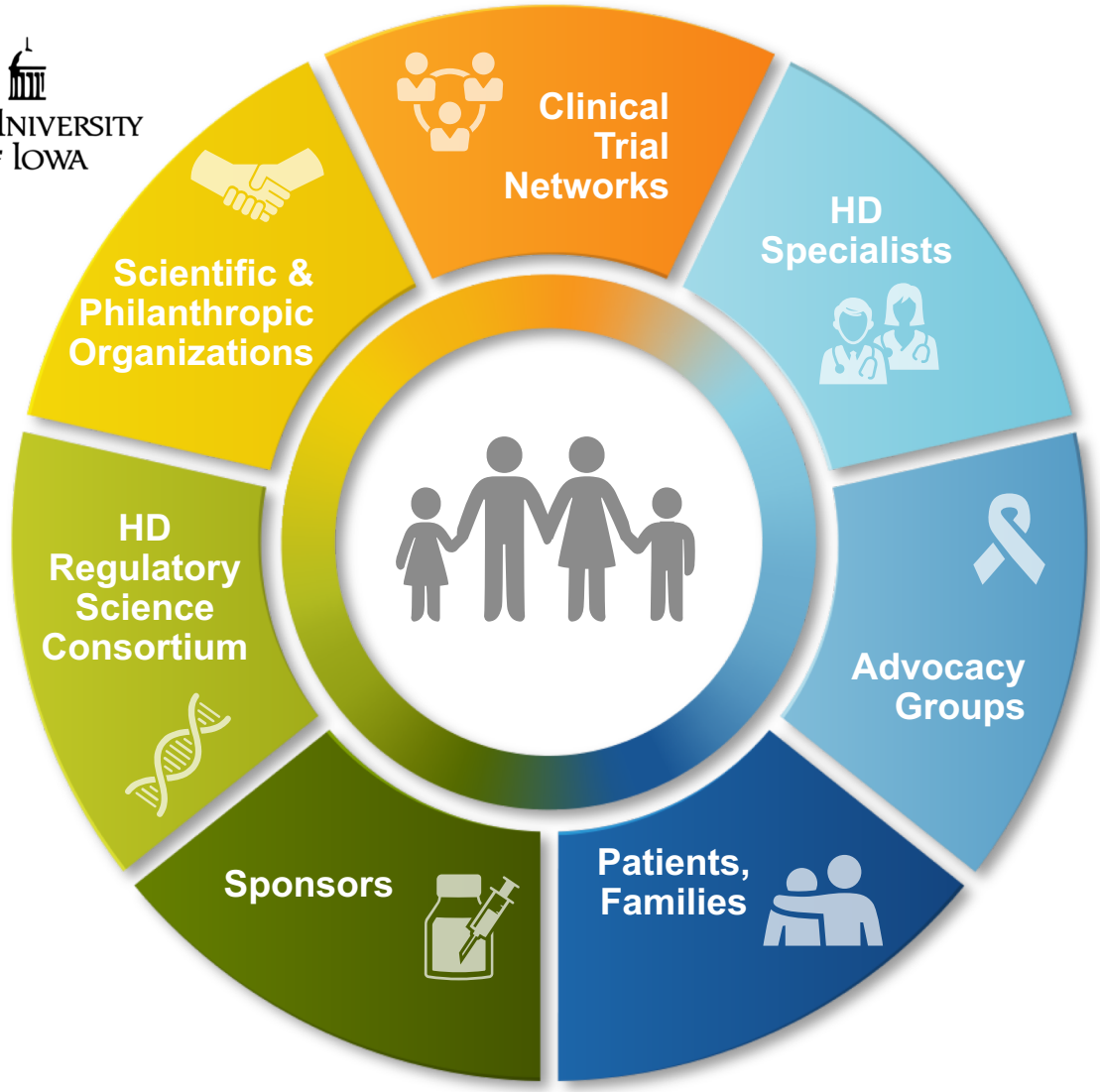
HD, Huntington's disease; mHTT, mutant huntingtin protein; PD, pharmacodynamics; PK, pharmacokinetics.
1. Clinicaltrials.gov/show/NCT02519036 (Accessed May 2020).

Collaboration has been a cornerstone for the programme

Strategic Advisory Committee



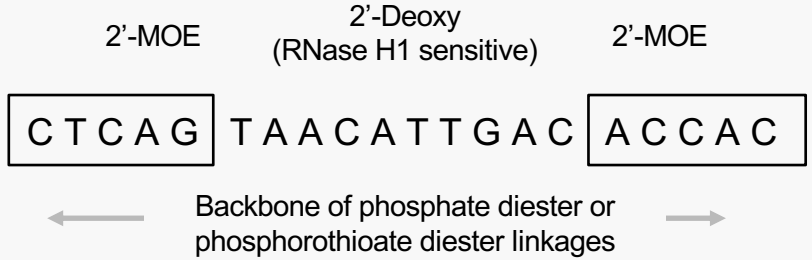
HD, Huntington's disease.

Tominersen

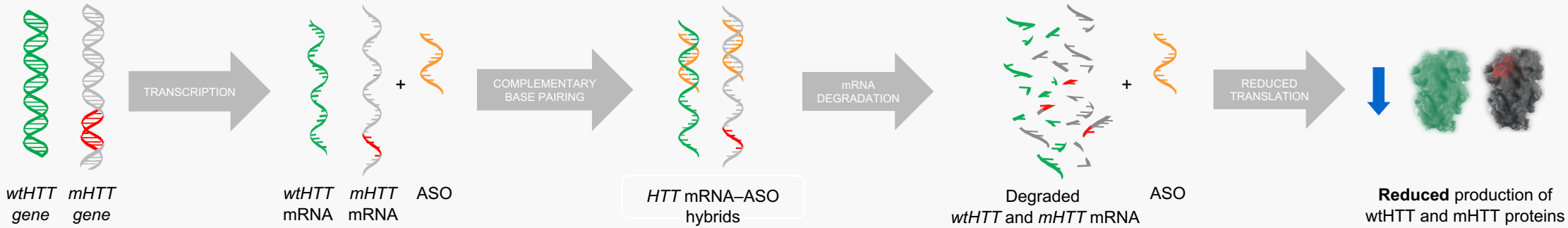
First treatment to target the underlying cause of HD, lowering CSF mutant HTT protein

Tominersen, a 20-mer synthetic DNA strand with sequence complementary to HTT mRNA, binds both HTT pre-mRNA (in the nucleus) and HTT mRNA (in the cytoplasm), resulting in a complex that is recognised as foreign by the cell, thereby recruiting RNase H1 to mediate degradation of the hybrid ASO–HTT mRNA[1–4]

Tominersen sequence[1]



Tominersen MoA



2'-MOE, 2'-O-(2-methoxyethyl); ASO, antisense oligonucleotide; HTT, huntingtin gene; HTT, huntingtin protein; mHTT, mutant HTT; mHTT, mutant HTT; MoA, mechanism of action; wtHTT, wild-type HTT; wtHTT, wild-type HTT.

1. Kordasiewicz HB, et al. *Neuron*. 2012; 74:1031–1044; **2.** Southwell AL, et al. Sci Transl Med. 2018;10 *pii*: eaar3959; **3.** Lane RM, et al. *Methods Mol Biol.* 2018; 1780:497–523; **4.** Liang XH, et al. *Mol Ther.* 2017; 25:2075–2092.

Antisense drugs

Delivery to the central nervous system

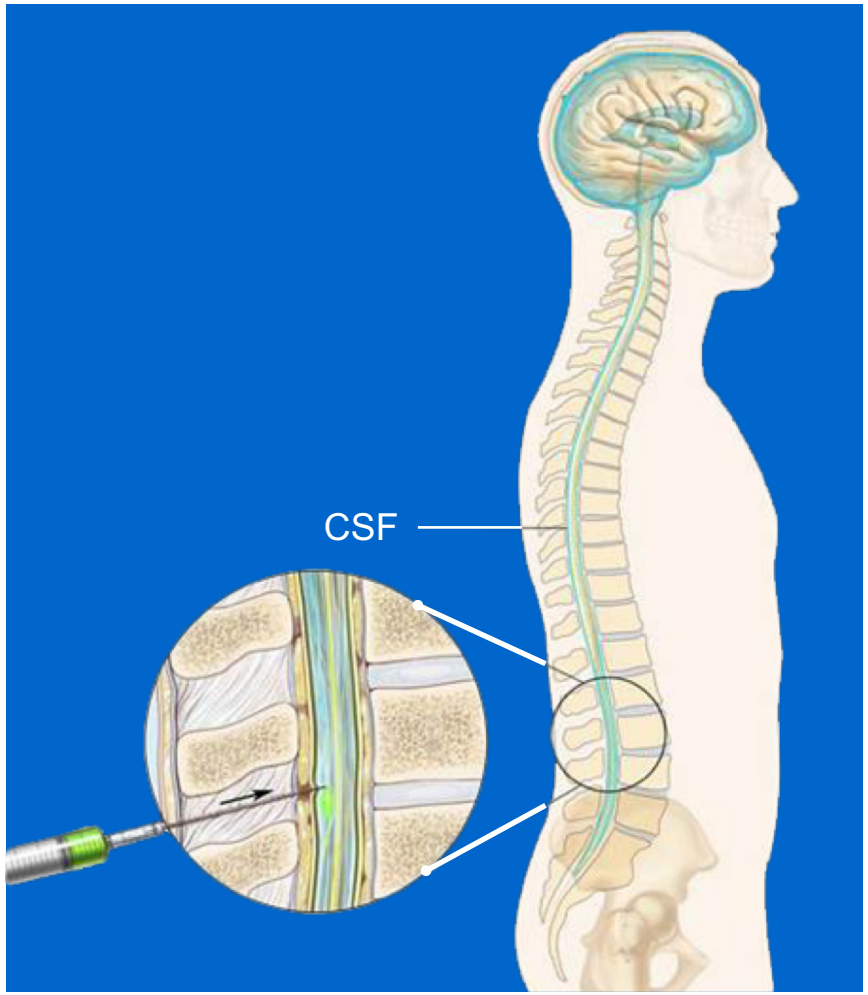


Image adapted from www.cancer.gov

Intrathecal injections

- This procedure is commonly called a lumbar puncture
- The drug is injected into the lower back in the space around the spinal cord (an intrathecal injection) and travels to the brain in the CSF
- CSF is a clear fluid that surrounds the brain and spinal cord

CSF, cerebrospinal fluid, which is the fluid that surrounds your brain and spinal cord.

HTT-lowering therapy approach

ASO design considerations

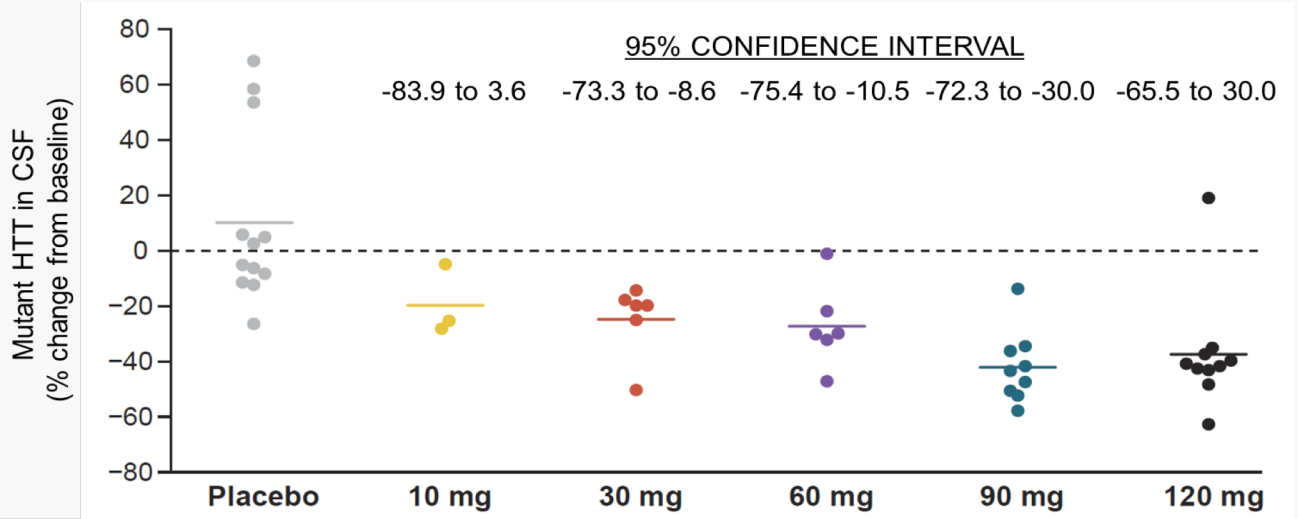
- Ability to broadly screen the entire *HTT* to identify a potent ASO
- Potential to treat all patients with HD regardless of individual genetic background
- Dose-dependent lowering of HTT
- Data to support safety and tolerability in animals and humans

ASO, antisense oligonucleotide; HD, Huntington's disease; *HTT*, huntingtin gene; HTT, huntingtin protein.

Tominersen

Tominersen treatment resulted in a dose-dependent reduction in the concentration of mutant huntingtin in CSF in a phase 1-2a trial

Percentage change in CSF concentration of mutant HTT, according to dose group



MEAN PERCENTAGE CHANGE FROM BASELINE	Placebo	10 mg	30 mg	60 mg	90 mg	120 mg
	10%	-20%	-25%	-28%	-42%	-38%

Dose-dependent reduction in CSF concentration of mutant HTT protein (phase 1-2a trial)[3]

CSF, cerebrospinal fluid; HD, Huntington's disease; HTT, huntingtin.

Tominersen/RG6042 is an investigational medication and has not yet received regulatory approval in any country.

1. Nopoulos PC. *Dialogues Clin Neurosci.* 2016;18:91-98. **2.** Kordasiewicz HB, et al. *Neuron.* 2012;74(6):1031-1044. **3.** Tabrizi SJ, et al. *N Engl J Med.* 2019;380(24):2307-2316.

The tominersen Clinical Development Programme is contributing further data to evaluate the efficacy and safety of tominersen

Clinical Development Programme

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

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

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

GENERATION HD1 N=791*[9]
- Pivotal, long-term efficacy and safety[9]
- Manifest HD patients[9]
- 25 months (plus follow-up)[10]

GEN-PEAK N≤20[12]
- PK/PD in CSF and plasma[11]
- Manifest HD patients[12]
- 7 months (including follow-up)[12]

GEN-EXTEND N~1,050†[14]
- Roll-over study for participants in previous tominersen studies[13]
- Manifest HD patients[14]
- Up to 5 years[13]

Complete

Complete, final analysis ongoing

Ongoing, recruitment complete

Ongoing, recruiting

Includes digital monitoring platform

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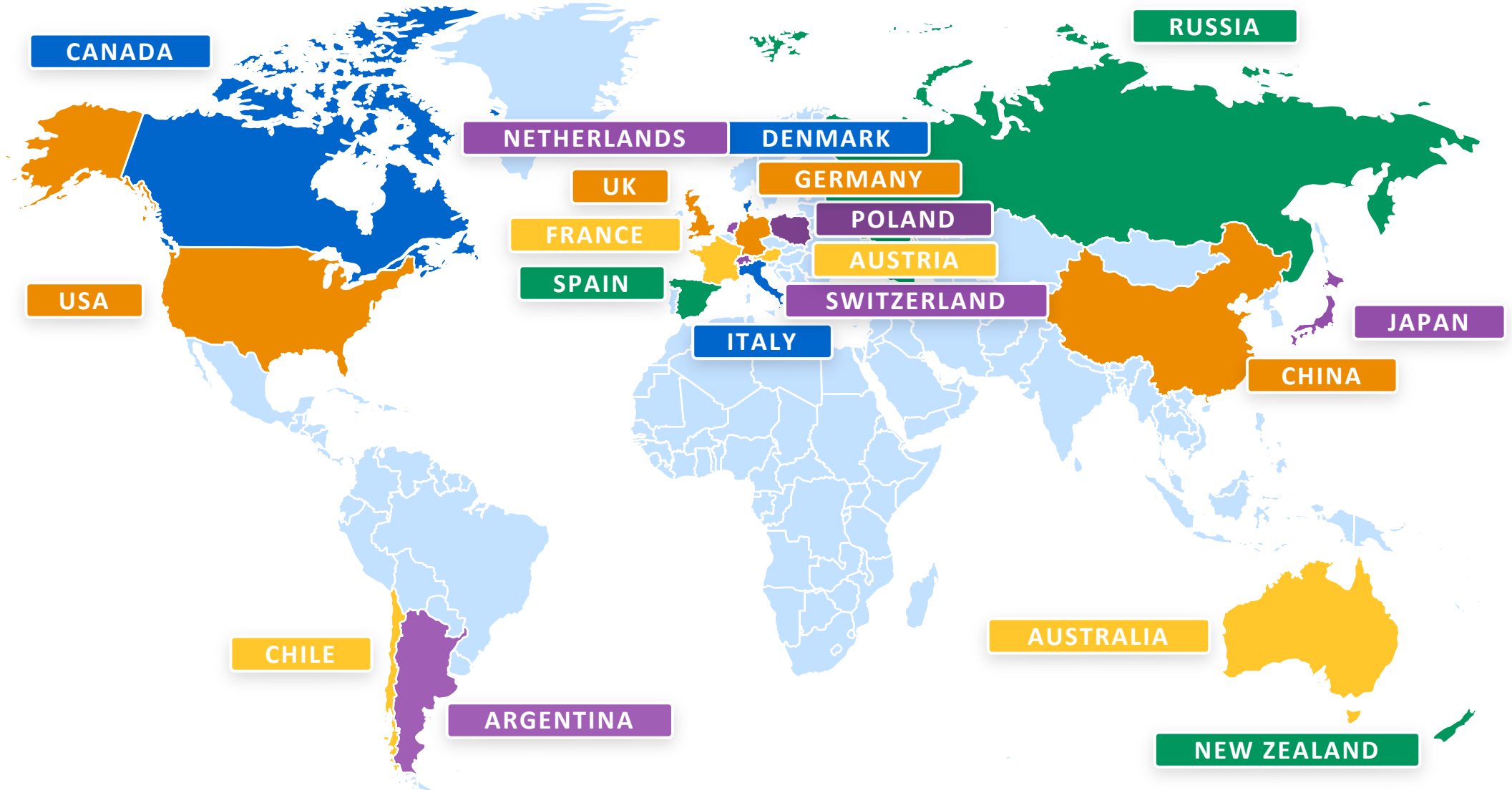
* China extension study still recruiting. † According to projected enrolment.
CSF, cerebrospinal fluid; HD, Huntington's disease; PD, pharmacodynamics; PK, pharmacokinetics; SAE, serious adverse event.
See slide notes for references.

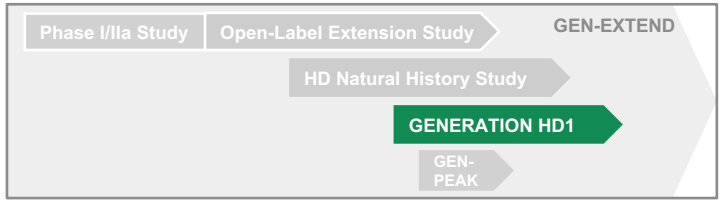
GENERATION HD1: Phase III pivotal Study

A global study at 100+ sites in 19 countries



GENERATION HD1 – Study inclusion criteria

Focus on early stages of HD where patients can plausibly benefit and symptoms are measurable



Premanifest

Presymptomatic | **Prodromal**

Cognitive/behavioural symptoms ~10 years before motor onset

Manifest

Early | **Moderate** | **Advanced**

Individuals are able to live at home, but may also have minor difficulties with activities of daily living

CONTINUUM OF HD

AGE OF ONSET

Juvenile-onset HD
(≤ 20 years)

Paediatric HD (<18 years)

Adult onset
(average age of motor onset is ~30–50 years)

Late-onset
(≤60 years)

Inclusion criteria

- Clinically diagnosed HD (DCL=4)
- Independence scale ≥70
- Age 25–65 years
- CAP score >400*

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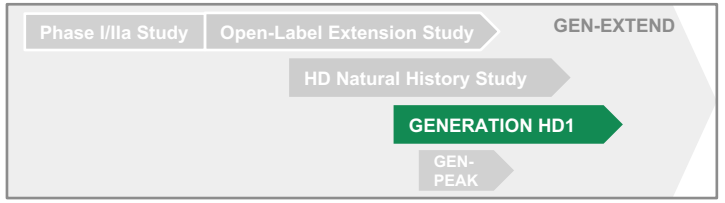
* CAP >400.01. CAP, CAG-age product; DCL, diagnostic confidence level; HD, Huntington's disease.
Clinicaltrials.gov/show/NCT03761849 (Accessed May 2020); Schobel S, et al. *J Neurol Neurosurg Psychiatry.* 2018; 89(Supp 1):A98.

GENERATION HD1 first study protocol revision, March 2019

Protocol changes that make study participation less demanding for participants and HCPs



Data from the ongoing tominersen OLE study supports the continued development of tominersen

In March 2019, the GENERATION HD1 study protocol was revised to be less demanding for patients, their families and HCPs

Original GENERATION HD1 protocol

All patients undergo LP procedures **monthly** and are randomised to one of the study arms below

R 1:1:1

- **Tominersen 120 mg Q4W** (Q4W IT bolus)
- **Tominersen 120 mg Q8W** (Q4W tominersen 120 mg for Doses 1–2, thereafter, tominersen 120 mg alternating with placebo Q4W IT bolus)
- **Placebo Q4W** (Q4W IT bolus)

Revised GENERATION HD1 protocol, March 2019

All patients undergo LP procedures **every two months** and are randomised to one of the study arms below

R 1:1:1

- **Tominersen 120 mg Q8W** (Q4W tominersen 120 mg for Doses 1–2, thereafter, tominersen 120 mg Q8W IT bolus)
- **Tominersen 120 mg Q16W** (Q4W tominersen 120 mg for Doses 1–2, thereafter, tominersen 120 mg alternating with placebo Q8W IT bolus)
- **Placebo Q8W** (Q4W for Doses 1–2, thereafter, Q8W IT placebo bolus)

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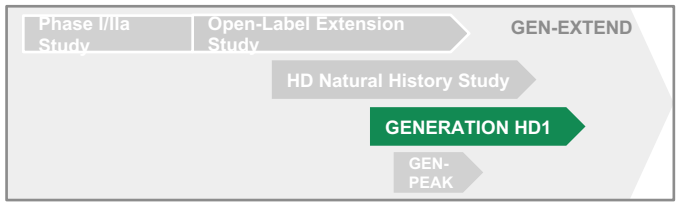
HCP, healthcare practitioners; HD, Huntington's disease; IT, intrathecal; LP, lumbar puncture; OLE, open-label extension; Q4W, once every month; Q8W, every 2 months; Q16W, every 4 months; R, randomised.
Clinicaltrials.gov/show/NCT03761849 (Accessed May 2020).

Recruitment of GENERATION HD1 is now complete, study is currently ongoing



Objective: Evaluate efficacy and safety of intrathecally administered tominersen in adult patients with manifest HD

Ongoing study

Countries: ~100 sites in 19 countries (including China)

Randomised, multicentre, double-blind, placebo-controlled study[1,2]

Key inclusion criteria:

- clinically diagnosed manifest HD (DCL=4)
- aged 25–65 years
- CAP>400*
- Independence Scale ≥70
- ambulatory, verbal

N=791

R 1:1:1

Tominersen 120 mg Q8W
(Q4W tominersen 120 mg for Doses 1–2, thereafter, tominersen 120 mg Q8W IT bolus)

Tominersen 120 mg Q16W
(Q4W tominersen 120 mg for Doses 1–2, thereafter, tominersen 120 mg alternating with placebo Q8W IT bolus)

Placebo Q8W
(Q4W for Doses 1–2, thereafter, Q8W IT placebo bolus)

25 months (plus follow-up)

GEN-EXTEND[3] (OLE)
(optional)†

Tominersen Q8W or Q16W

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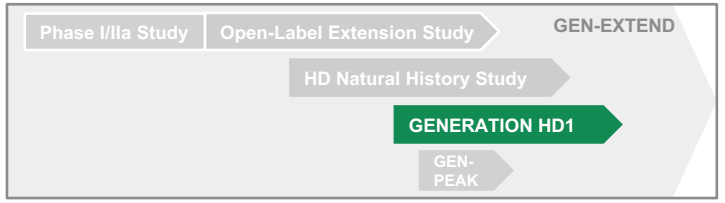
* CAP >400.01. † Provided participants meet eligibility criteria, the data for tominersen support continued development and the study is approved by Authorities and Ethics Committees/Investigational Review Boards.
CAP, CAG-age product; cUHDRS, composite Unified HD Rating Scale; DCL, diagnostic confidence level; HD, Huntington's disease; IT, intrathecal; OLE, open-label extension; Q8W, every 2 months; Q16W, every 4 months; R, randomised; TFC, Total Functional Capacity.

1. Clinicaltrials.gov/show/NCT03761849 (Accessed October 2019); 2. Schobel S, et al. *J Neurol Neurosurg Psychiatry*. 2018; 89(Supp 1):A98; 3. Clinicaltrials.gov/show/NCT03842969 (Accessed May 2020).

GENERATION HD1 second study protocol revision, October 2019

Protocol changes that increase the statistical power and the diversity of the study



In October 2019, the GENERATION HD1 study protocol was revised to include additional patients and study sites

- An additional **141 patients** will be recruited, bringing the total target study population to 801*
  - In order to increase the statistical power of the study to equally evaluate the benefit–risk profile of both Q8W and Q16W dosing regimens
- The increase in the number of study participants was informed by an updated evaluation of the data from the ongoing, OLE of the Phase I/IIa study of tominersen in HD
- Sites in **China** will also be included to add further diversity to the study
- The protocol was revised to support the development of tominersen and the exploration of the Q8W and Q16W dosing regimens in GENERATION HD1

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* The final recruitment number was 791 individuals.
HD, Huntington's disease; OLE, open-label extension; Q8W, every 2 months; Q16W, every 4 months; TFC, Total Functional Capacity.

Impact of COVID-19

COVID-19, coronavirus disease 2019.

Impact of COVID-19 pandemic on the tominersen Clinical Development Programme

- COVID-19 has been an unprecedented challenge for all clinical trial programmes worldwide
- Roche is **actively managing** the situation by:

- Fortunately, GENERATION HD1 is a particularly **robust study** due to its **large** sample size and **geographic diversity;** missed doses do not mean discontinuation from the study

COVID-19, coronavirus disease 2019.

Summary

- In October 2019, the GENERATION HD1 study protocol was revised to include additional patients and study sites
- GENERATION HD1 study is now fully recruited with 791 participants
- Roche is actively managing the COVID-19 situation, formulating strategies to mitigate any effects it may have on their ongoing trials

OLE, open-label extension; Q4W, every month; Q8W, every 2 months.

Thank you

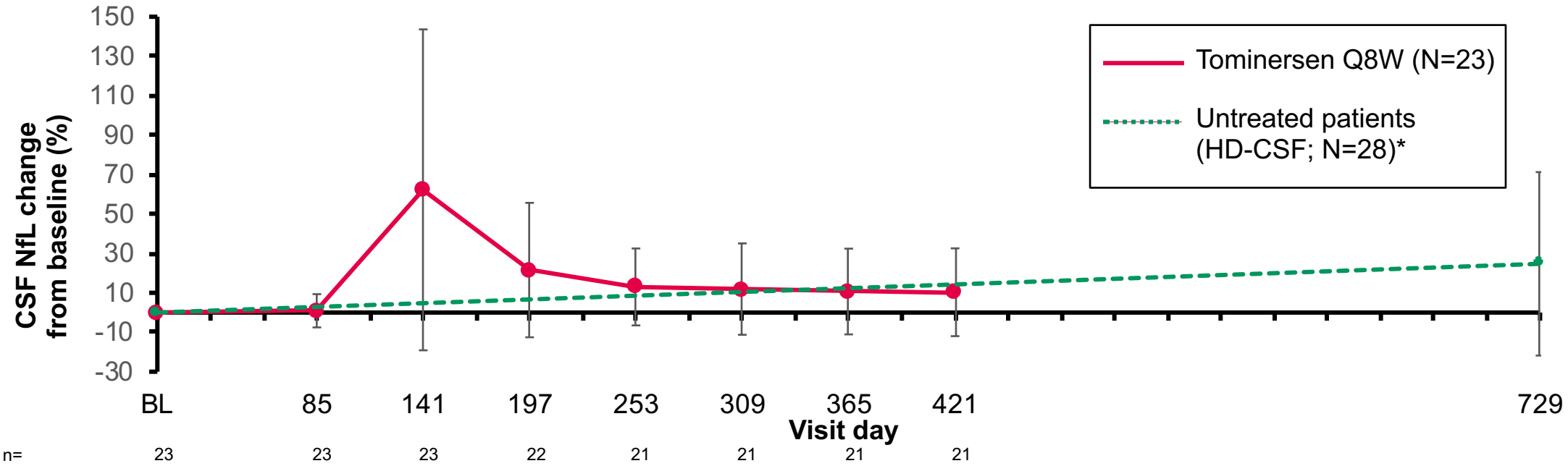
“Our hope is to create a tomorrow where neurological disorders no longer limit human potential – to preserve what makes people who they are”

Roche Neuroscience Community

Q & A

CSF NfL levels in the Q8W arm decrease to within expected natural history range at 15 months

CSF NfL change in the Q8W arm compared with untreated early HD patients in HD-CSF



- NfL increases expected in untreated HD (estimated ~15% median increase at 15 months [HD-CSF])
- Roche HD natural history study data will provide comparator in matched sample with equal follow-up
- The mechanism underlying the NfL increases are currently under further investigation

Data points represent mean values and error bars represent ±1 standard deviation. At the time of the data cut-off (18 July 2019) 43 out of the 46 patients had reached the 15-month visit time point (Q4W: n=22, Q8W: n=21), three patients were enrolled in the study 3 months after all other study participants and the 15-month visit had not been conducted at time of data cut-off. * HD-CSF trendline was interpolated from baseline and 24-month data points from early HD sample of HD-CSF.
BL, baseline; CSF, cerebrospinal fluid; HD, Huntington's disease; NfL, neurofilament light protein; Q4W, every month; Q8W, every 2 months.
Schobel SA. *Presented at the 15th Annual HD Therapeutics Conference 2020*.