A Global Development Program Testing RG6042, an Antisense Oligonucleotide, for the Treatment of Early Manifest Huntington's Disease

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F. Hoffmann-La Roche, Ltd.
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RG6042 (previously known as IONIS-HTTRx) is an investigational medicine and has not yet received regulatory approval in any country.

Disclosures

- I am a full time employee of F. Hoffmann-La Roche, Ltd.
- The views expressed in this talk are my own and not reflective of official company positions

Acknowledgements

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 study participants (present and future) and their families

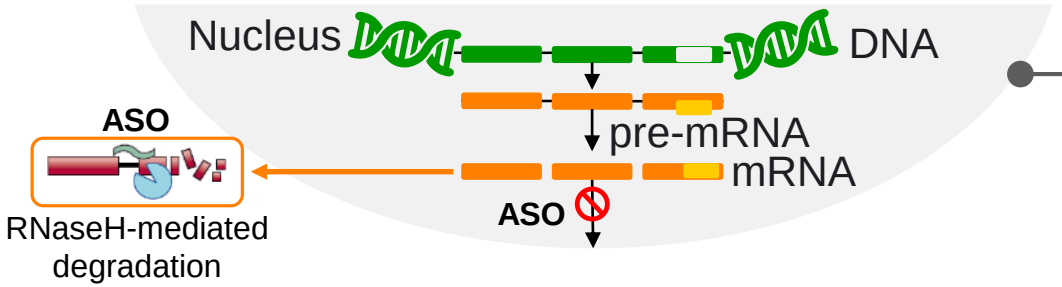
Outline

- Vision for HTT lowering approaches for treatment of HD
- History of Roche/IONIS program development
- Key challenges
  - Dealing with the unknowns of what successful HTT lowering looks like
  - Measuring clinical progression and potential treatment effect in HD
- The Global Development Program: designed to address key challenges
  - Ongoing open-label extension study
  - HD Natural History Study
  - Randomised double-blind placebo-controlled pivotal study in manifest HD
- Conclusions

HD, Huntington's disease; HTT, Huntingtin protein.

HTT lowering therapies may slow or stop clinical progression

MoA schema adapted from Wild and Tabrizi, Lancet Neurology, 2017



HTT lowering therapies generally target upstream pathogenic principles

Roche/IONIS ASO suppresses causal toxic protein (non-allele-selective)

Cause of disease

Toxic mHTT*

Cellular dysfunction

- Impaired axonal transport
- Proteasome inhibition
- Neuronal dysfunction and death
- Excitotoxicity
- Caspase/protease activation
- Synaptic dysfunction
- Transcriptional deregulation
- Mitochondrial dysfunction

Clinical pathological domains

Atrophy
- Brain tissue loss
- Muscle wasting
- Weight loss

Speech and swallowing

Cognitive and functional
- Psychomotor
- Inattention
- Apathy/behavior

Motor
- Coordination
- Balance/gait
- Chorea
- Progressive akinesia

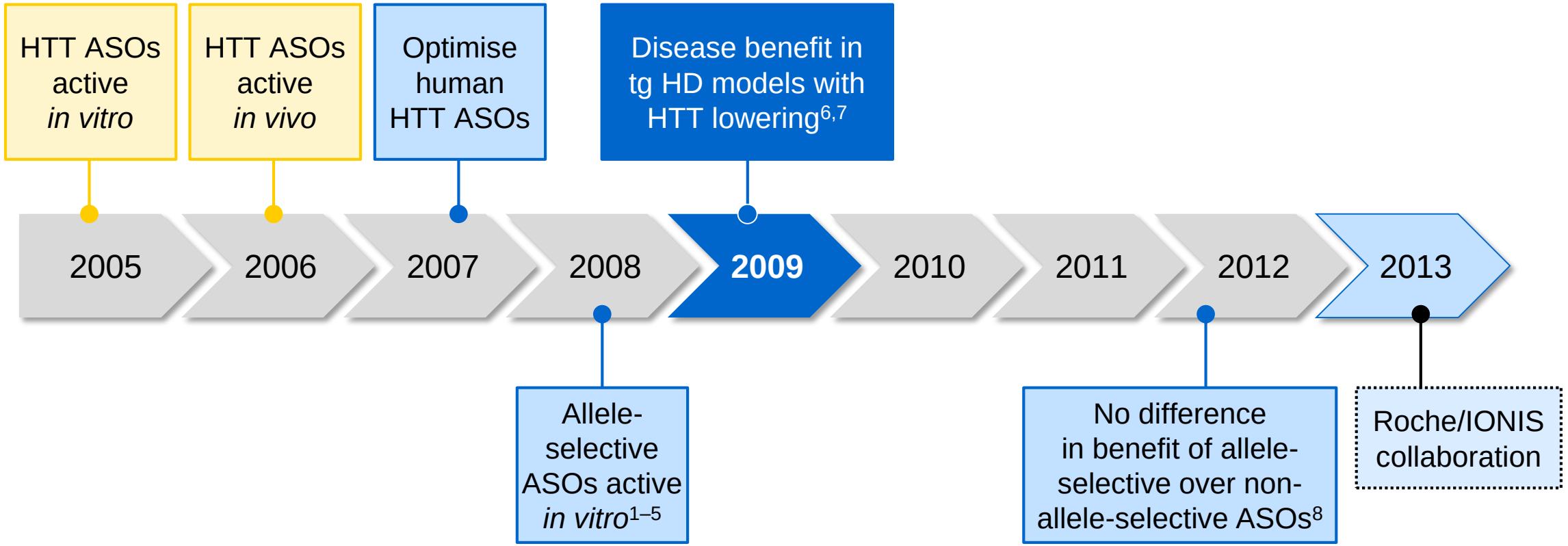
Other current SOC and advanced clinical development candidates target downstream effects likely addressing few or single domains

*Toxic mHTT=*HTT* 36+ CAG repeats.
ASO, antisense oligonucleotide; *HTT*, Huntingtin gene; HTT, Huntingtin protein; mHTT, mutant Huntingtin protein; MoA, mechanism of action; mRNA, messenger RNA; SOC, standard of care.
Wild EJ, Tabrizi SJ. *Lancet Neurol.* 2017; 16:837–847.

Program history

Building on strong science, comprehensive preclinical package and collaborations

IONIS field-leading work with ASOs begins



ASO, antisense oligonucleotide; HD, Huntington's disease; HTT, Huntingtin; tg, transgenic.

1. Ostergaard ME *et al. Nuc Acid Res.* 2013; 41:9634–9650; 2. Southwell AL *et al*. *Mol Ther.* 2014; 22:2093–2106; 3. Skotte NH *et al. PLoS One*. 2014; 9:e107434; 4. Southwell AL *et al. Hum Mol Genet*. 2017; 26:1115–1132; 5. Carroll JB *et al. Neurobiol Dis.* 2011; 43:257–265; 6. Drouet V *et al. Ann Neurol*. 2009; 65:276–285; 7. Boudreau RL *et al. Mol Ther*. 2009; 17:1053–1063; 8. Kordasiewicz HB *et al. Neuron*. 2012; 74:1031–1044.

Non-allele-selective ASO selected for clinical development

Data from RG6042 to date suggest the non-allele-specific approach is well tolerated and has the broadest patient eligibility

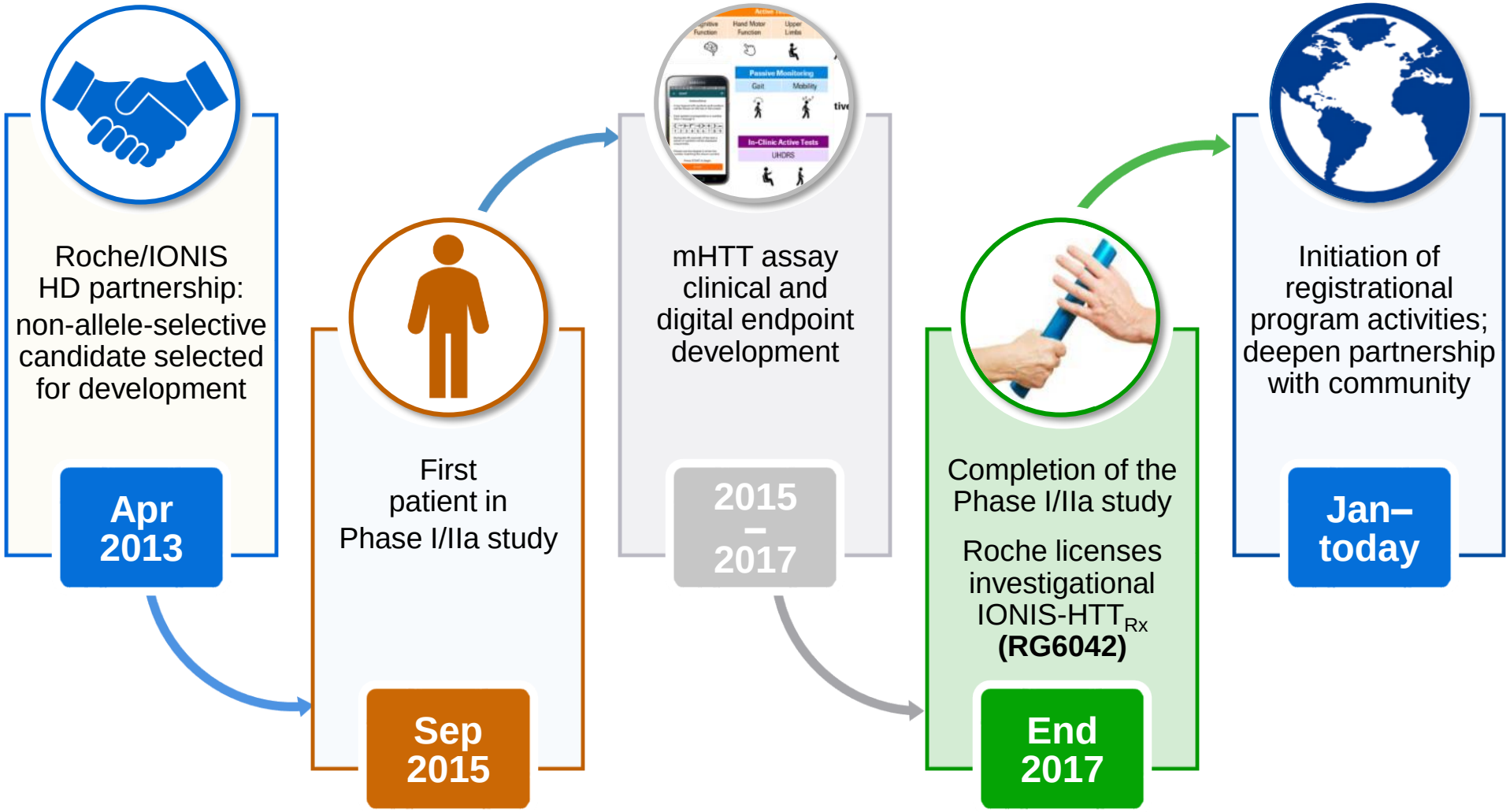
- Non-allele-specific approach preferentially developed due to:
  - broad eligibility for all HD patients irrespective of individual SNP
  - ability to screen the entire *HTT* gene to identify a highly potent ASO with favorable safety profile

Preclinical safety	Preclinical efficacy	Pharmacology
• Lowering of total HTT in the CNS with irreversible (e.g. siRNA) or reversible (e.g. ASO) approaches appear safe in normal animals[1–3]	• Non-allele-specific ASOs have demonstrated efficacy in transgenic animal models, similar to allele selective approaches[1,2,4,5]	• RG6042 results in the dose-titratable, partial and reversible reduction of HTT • Approach appears well tolerated in Phase I/IIa and OLE • >200 doses of RG6042 have been administered in the OLE study to date

RG6042 (previously known as IONIS-HTTRx) is an investigational medicine and has not yet received regulatory approval in any country.
ASO, antisense oligonucleotide; HD, Huntington's disease; *HTT,* Huntingtin gene; HTT, Huntingtin protein; OLE, open-label extension; siRNA, small interfering RNA; SNP, single nucleotide polymorphism.
1. Kordasiewicz HB, *et al. Neuron* 2012; 74:1031–1044; 2. Drouet V, *et al. Ann Neurol.* 2009; 65:276–285; 3. Stiles DK, *et al. Exp Neurol.* 2012; 233:463–471; 4. Stanek LM, *et al. Hum Gene Ther.* 2014; 25:461–474; 5. Boudreau RL, *et al. Mol Ther.* 2009; 17:1053–1063. For further details see poster **J03**: Leavitt B, *et al.* Partial lowering of total huntingtin levels to treat adults with HD: Potential benefits and theoretical risks from human studies and animal models.

Five-year HD program history

Continuing to build on strong science and partnerships



HD, Huntington's disease; mHTT, mutant Huntingtin protein.

Top-line IONIS-HTT$_{Rx}$ (RG6042) Phase I/IIa study results. IONIS Pharmaceuticals website. http://ir.ionispharma.com/static-files/169c61c2-73b4-4f4e-8c03-2d56624a5e8f. Published March 2, 2018. Accessed Sep 12th, 2018.

Big questions need to be answered

Risk/benefit of new approaches needs to be carefully investigated

Drug effect on key mutant protein

Potency

- Is the 40–60% reduction observed in CSF mHTT in Phase I/IIa sufficient?
- How much lowering at steady state?

Duration

- How quickly does protein recover?
- Is sustained suppression necessary for efficacy?

Brain coverage

- Is predominant cortical lowering sufficient?

Measures of clinical efficacy

Measures of progression

- How do we measure meaningful clinical progression?

Population

- In what patients?

Treatment duration

- How long to treat to identify benefit?

What is the optimal administration paradigm for efficacy?

Safety and tolerability

Drug specific

- What is the risk of systemic side effects at the dose required for efficacy?

Target specific

- What magnitude and duration of wild-type HTT protein lowering will be safe/tolerated?

What is the optimal administration paradigm for safety/tolerability?

CSF, cerebrospinal fluid; HTT, Huntingtin protein; mHTT, mutant Huntingtin protein.

RG6042 Global Development Program

Today

Phase I/IIa study[1,2]

- First-in-human study
- Safety, tolerability, PK and PD
- Early manifest HD patients
- N=46

Open-Label Extension Study[3]

- Long-term safety, tolerability, PK and PD
- Early manifest HD patients
- 15 months follow-up
- N=46 *(participants of Phase I/IIa study)*

HD Natural History Study[4]

- Prospective, longitudinal study
- Early manifest HD patients
- 15 months
- N=100

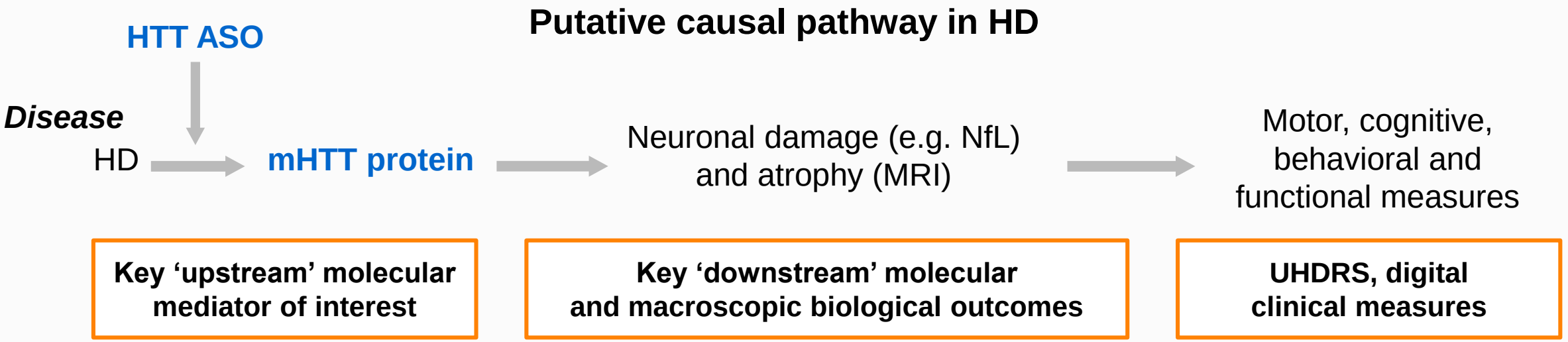
Pivotal Phase III Study

- Long-term efficacy and safety
- Manifest HD patients
- 25 months (plus follow-up)
- N=660

HD, Huntington's disease; PD, pharmacodynamics; PK, pharmacokinetics.
1. ClinicalTrials.gov. NCT03342053; 2. Tabrizi S, *et al. Neurology.* 2018; 90(15 Suppl); Presented at AAN 2018 (Abstract CT.002); 3. ClinicalTrials.gov. NCT02519036;
4. ClinicalTrials.gov. NCT03664804.

First task: To better understand the causal pathway

Bolster the understanding of putative effects of HTT ASO-mediated HTT lowering in a more chronic treatment setting



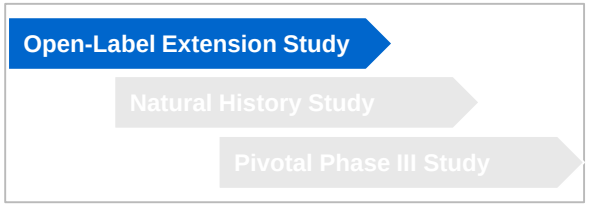
Key studies to inform immediate program goal:

- OLE and linked HD Natural History Study
  - focus on causal pathway and generate further objective evidence of drug effect
  - longitudinal study of biomarkers, clinical outcomes and safety

ASO, antisense oligonucleotide; HD, Huntington's disease; mHTT, mutant Huntingtin; MRI, magnetic resonance imaging; NfL, neurofilament light chain; OLE, open-label extension; UHDRS, Unified Huntington's Disease Rating Scale.

Open-Label Extension (OLE) study of RG6042

Objective: Extend understanding of effects of anticipated therapeutic dose over longer follow-up



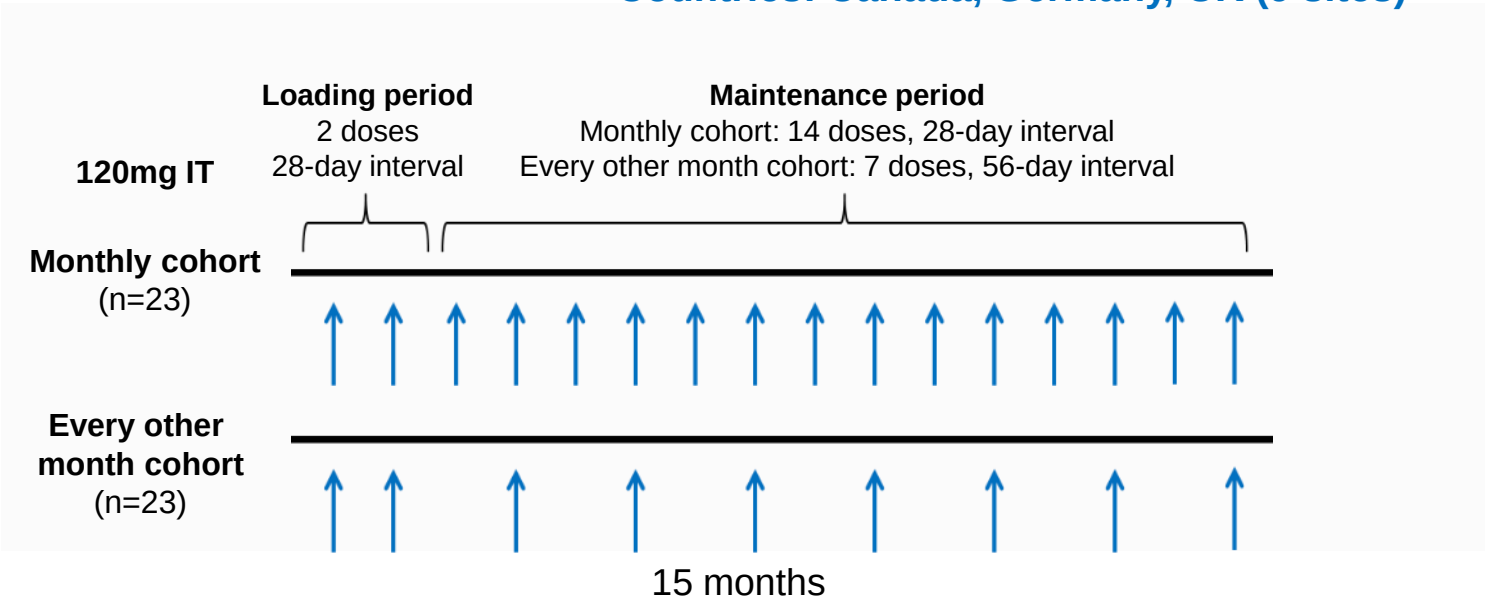
Ongoing study

Countries: Canada, Germany, UK (9 sites)

Key study features

- Early manifest HD patients (Stage I)
- Must have participated in Phase I/IIa study of RG6042
- Participants randomised to more vs. less frequent regimen (all participants to receive active drug in open-label setting)

n=46



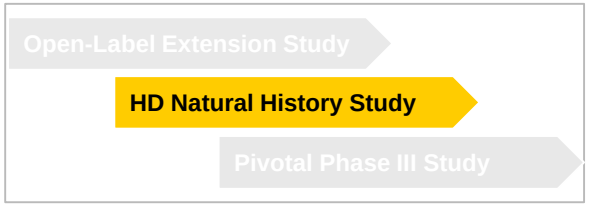
Long-term safety, tolerability, PK and PD of RG6042 120mg in more vs. less frequent regimen

- Explore magnitude and sustainability of PD effect on CSF mHTT
- Explore effects on biomarkers and UHDRS clinical measures and linked digital clinical outcomes

CSF, cerebrospinal fluid; HD, Huntington's disease; IT, intrathecal; mHTT, mutant Huntingtin protein; PD, pharmacodynamics; PK, pharmacokinetics; UHDRS, Unified Huntington's Disease Rating Scale.
ClinicalTrials.gov. NCT03342053

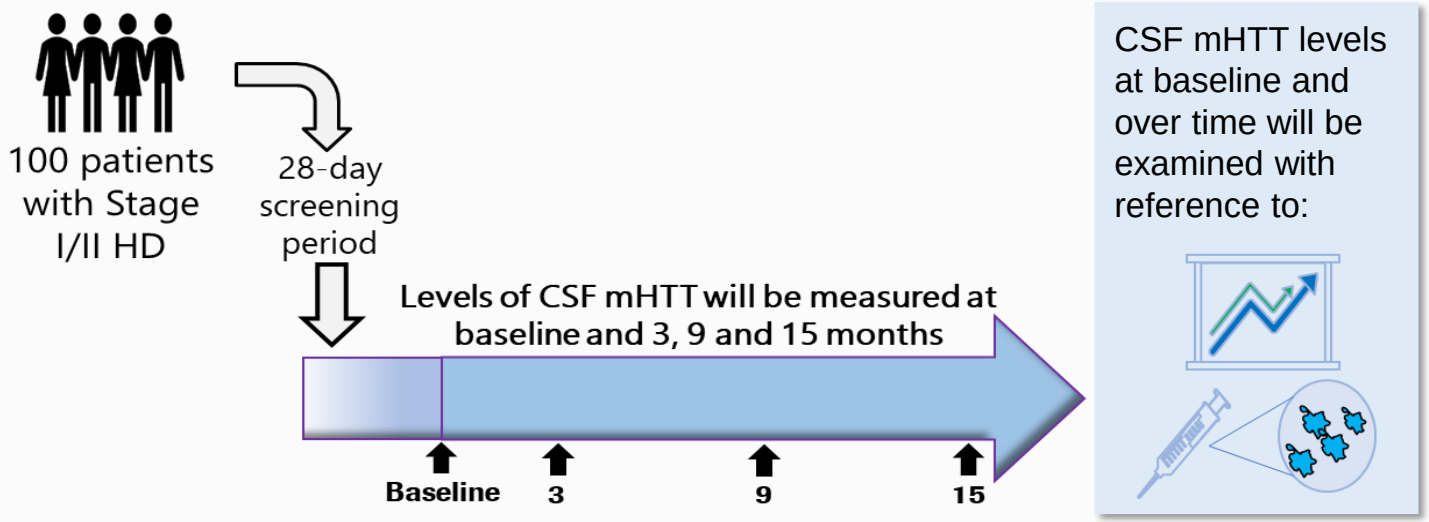
HD Natural History Study

Objective: Enhancing understanding of putative causal pathway through longitudinal evaluation



Study to start in Q4 2018

Countries: US, Canada, Germany and UK (up to 17 sites)



CSF mHTT levels at baseline and over time will be examined with reference to:

Clinical measures (e.g. cUHDRS)

Motor function via phone/watch app

Brain atrophy/volume by MRI

Biomarkers of neuronal injury

Patient-reported outcomes

Investigating causal chain of evidence of HD pathophysiology in early manifest HD population

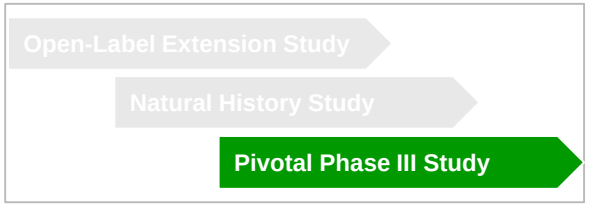
- Prognostic value of biomarkers on UHDRS clinical measures and linked digital clinical outcomes
- Population matched to OLE participants on CAG repeat length and key demographics
- Participants offered open-label access post study completion for within-subject on drug and off drug comparisons*

For further details see poster **F24**: Hooper G, *et al*. Design of a prospective, longitudinal, natural history study in HD.

*Provided participants meet eligibility criteria, the data for RG6042 support continued development and the study is approved by Authorities and Ethics Committees/Investigational Review Boards.
CSF, cerebrospinal fluid; cUHDRS, composite UHDRS; HD, Huntington's disease; mHTT, mutant Huntingtin protein; MRI, magnetic resonance imaging; OLE, open-label extension; UHDRS, Unified Huntington's Disease Rating Scale.
ClinicalTrials.gov. NCT03664804

GENERATION HD1 – RG6042 Pivotal Phase III study design

Objective: Evaluate efficacy and safety of intrathecally-administered RG6042 in adult patients with manifest HD



Study launch planned for end of 2018 with patients enrolling by early 2019

Countries: ~15 countries worldwide (80–90 sites)

Randomised, multicenter, double-blind, placebo-controlled study

Key inclusion criteria

- Clinically diagnosed manifest HD (DCL=4)
- Aged 25–65 years
- CAP >400
- Independence scale >70
- Ambulatory, verbal

n=660

R 1:1:1

RG6042 120mg monthly (Q4W) (n=220)
(Q4W IT bolus)

RG6042 120mg bimonthly (Q8W) (n=220)
(Q4W RG6042 120mg for doses 1–2, thereafter, RG6042 120mg alternating with placebo Q4W IT bolus)

Placebo monthly (Q4W) (n=220)
(Q4W IT bolus)

25 months (plus follow-up)

Open-label extension RG6042 monthly or bimonthly (optional)*

Inclusion criteria for pivotal study are broader than OLE and HD NHS studies†

*Provided participants meet eligibility criteria, the data for RG6042 support continued development and the study is approved by Authorities and Ethics Committees/Investigational Review Boards.
†Pivotal Phase III study protocol is pending approval by Health Authorities, Investigational Review Boards and Ethics Committees.
CAP, CAG-age product; DCL, diagnostic confidence level; GENERATION HD1, Global EvaluatioN of Efficacy and Safety of Roche/Genentech AnTIsense OligoNucletide for Huntington's Disease; HD, Huntington's disease; IT, intrathecal; NHS, Natural History Study, OLE, open-label extension; Q4W, once-a-month.

Decision on primary endpoint for global Phase III study

UHDRS clinical measures are well positioned to demonstrate clinically meaningful efficacy across disease domains

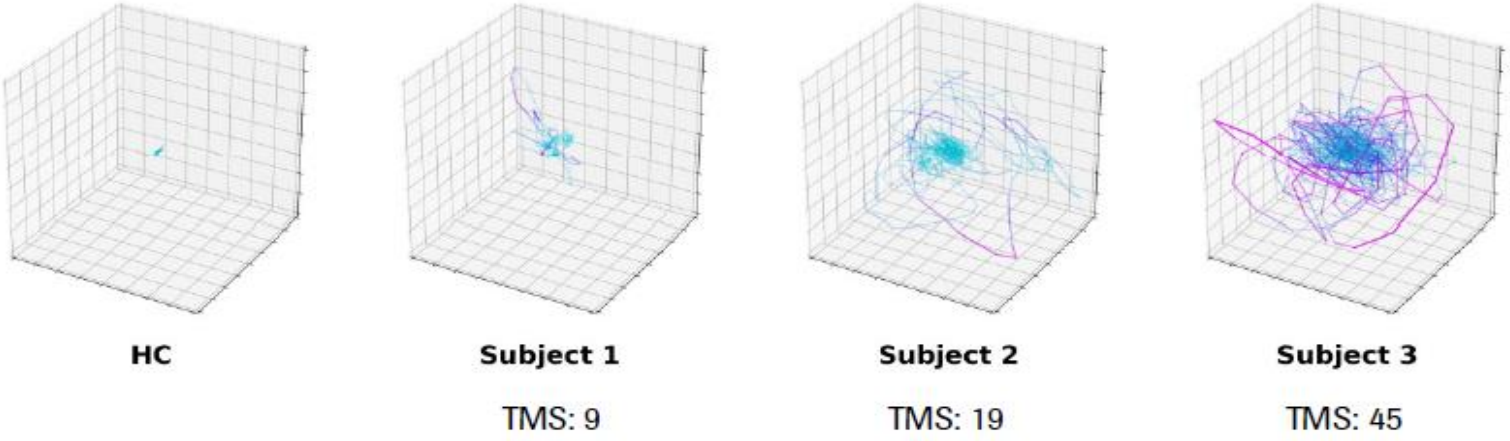
- **cUHDRS** will be the global primary endpoint
  - Best tracks multidomain decline
  - Related to biology and function
  - Supported by EMA
- **The TFC** will be the primary endpoint in US only
  - A component of the cUHDRS
  - Tracks unilateral functional decline well when measured over longer time periods, and consistency of decline is helped by CAP score
  - Required measure of daily function by FDA

Consistency of effect anticipated between cUHDRS and TFC

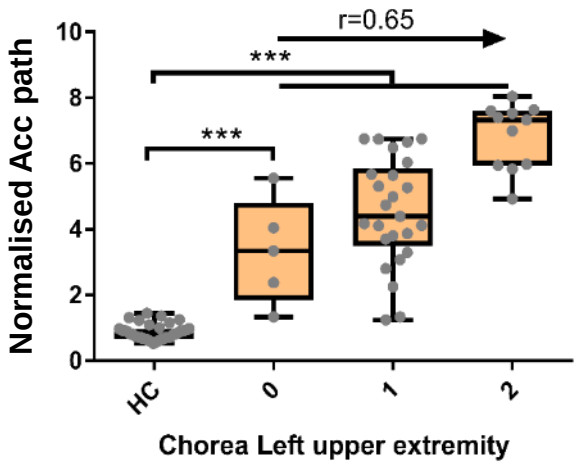
FDA requires the primary endpoint to measure daily functional abilities, so TFC will be primary endpoint in US only
CAP, CAG-age product; cUHDRS, composite UHDRS; EMA, European Medicines Association; FDA, Food and Drug Administration; HD, Huntington's disease; HTT, Huntingtin protein; TFC, Total Functional Capacity; UHDRS, Unified Huntington's Disease Rating Scale.

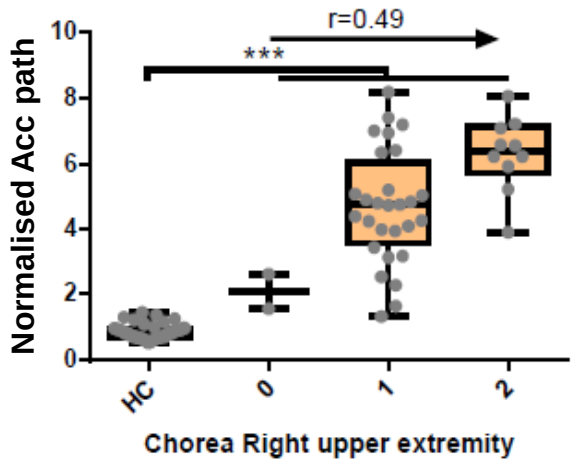
Extending measures of clinical progression through digital technology into the trials

e.g. Digital measurement of chorea appears more sensitive than UHDRS chorea items



Display of illustrative data collected by patients and a control during the Chorea Test. The charts display 5 seconds of the acceleration path mapped to a 3D plane. The stronger the purple hue is, the faster the movement





Digital measurements of progression appear more sensitive than traditional clinical measures

For further details see poster **F23**: Lipsmeier F, *et al*. Digital, high-frequency, long-term monitoring of motor and non-motor symptoms in HD patients.

Acc, acceleration; HC, healthy controls; HD, Huntington's disease; TMS, Total Motor Score; UHDRS, Unified Huntington's Disease Rating Scale.

Conclusions

- mHTT lowering therapies are poised to be transformative
  - RG6042 had a favourable tolerability and safety profile in a first-in-human study in people with HD over 4 monthly doses, building on longer-term data in non-human primates, and OLE data appears safe/tolerated to date
- Multiple challenges exist to translating biological innovation into clinical benefit
- GENERATION HD1 is the first definitive study to test the HTT lowering hypothesis
  - RG6042 has the potential to provide clinically meaningful effects on disease progression in all people with HD
  - The efficacy and safety of RG6042 are being assessed in a global development program

Working together for a new generation in HD

To access an extract of this presentation go to http://bit.ly/2NhPBAz

GENERATION HD1, Global EvaluatioN of Efficacy and Safety of Roche/Genentech AnTIsense OligoNucleotide for Huntington's Disease; HD, Huntington's disease; HTT, Huntingtin protein; mHTT, mutant HTT; OLE, open-label extension.