
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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- 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



Special thanks to Frank Bennett, Holly Kordasiewicz, Eric Swayze, Roger Lane and Anne Smith

Special thanks for sharing data and for ongoing collaboration:

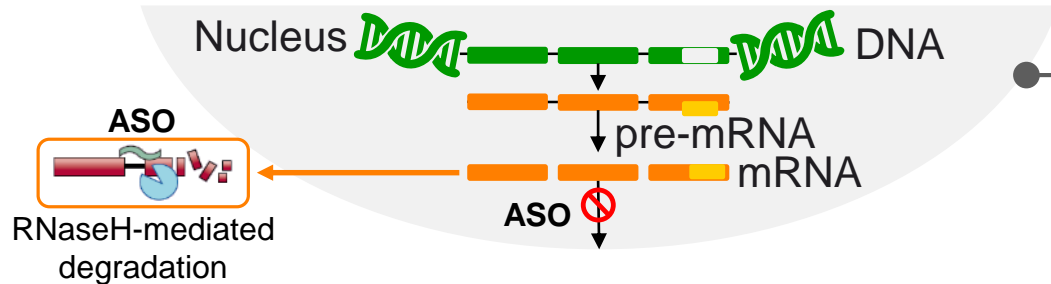


Deepest gratitude to study participants (present and future) and their families

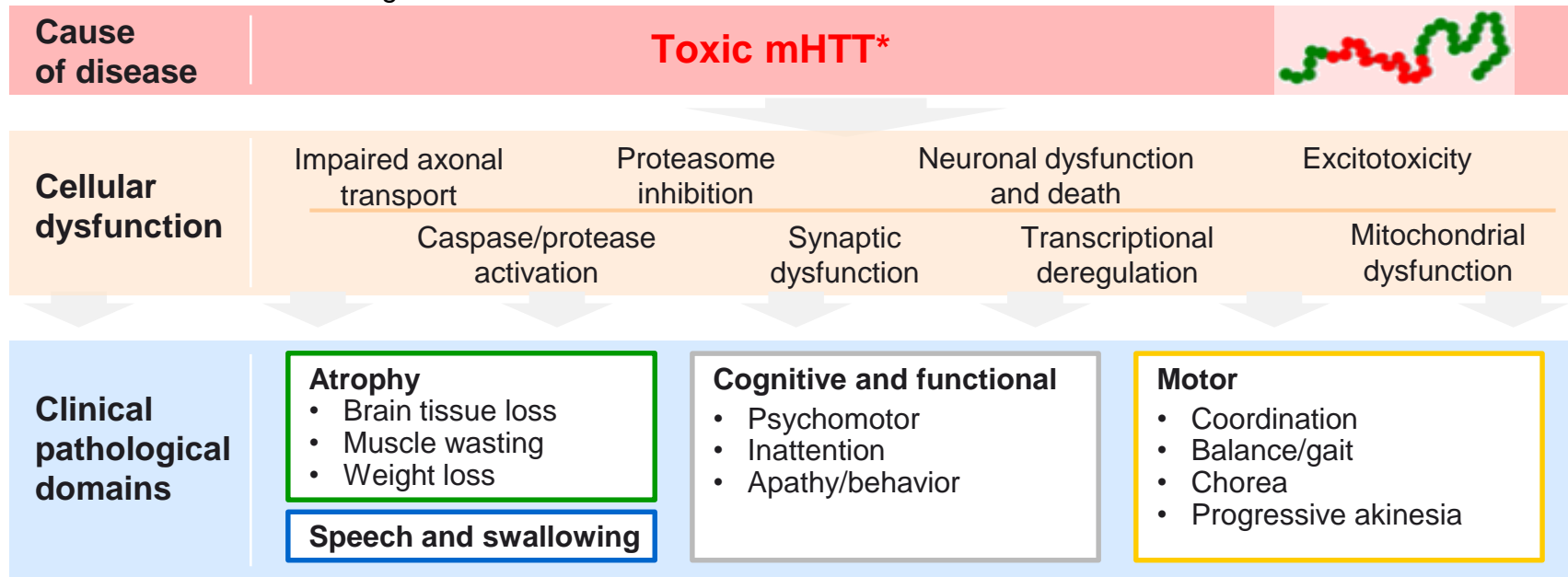
- Vision for HTT lowering approaches for treatment of HD
- History of Roche/IONIS program development
- Key challenges
 - Dealing with the unknowns of what successful HTT lowering looks like
 - Measuring clinical progression and potential treatment effect in HD
- The Global Development Program: designed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

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)



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

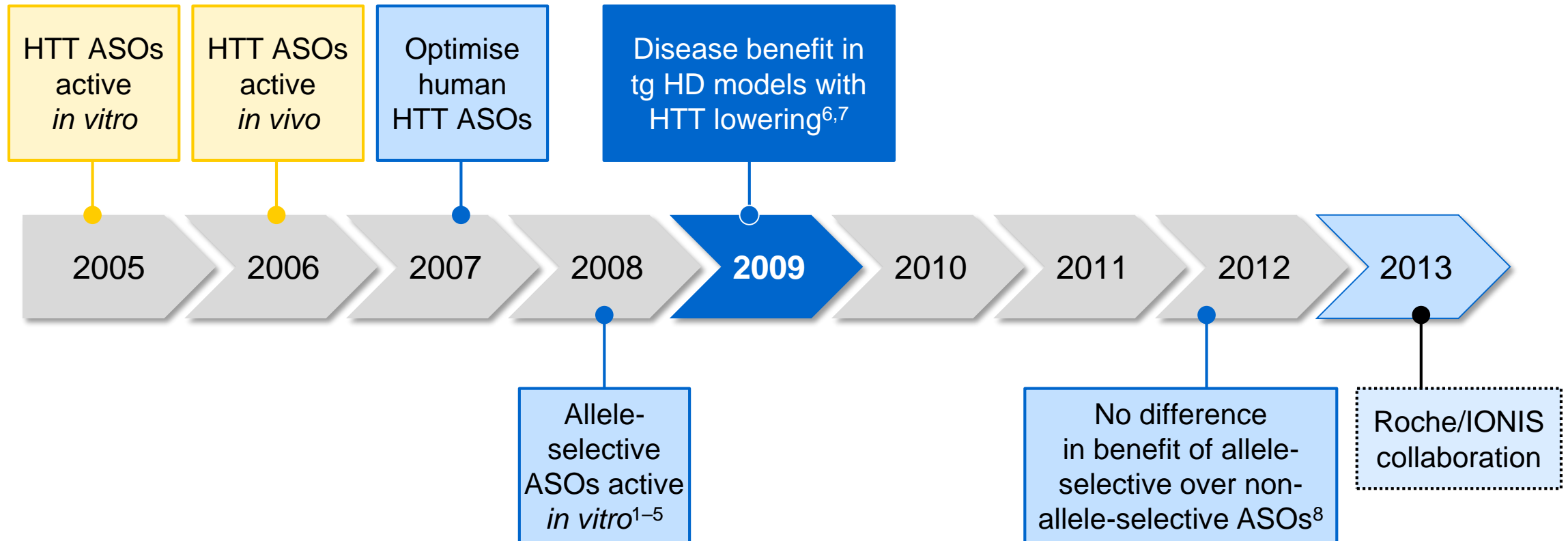
*Toxic mHTT=HTT 36+ CAG repeats.
 ASO, antisense oligonucleotide; HTT, Huntingtin gene; HTT, Huntingtin protein; mHTT, mutant Huntingtin protein; MoA, mechanism of action; mRNA, messenger RNA; SOC, standard of care.
 Wild EJ, Tabrizi SJ. *Lancet Neurol.* 2017; 16:837–847.

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

- Lowering of total HTT in the CNS with irreversible (e.g. siRNA) or reversible (e.g. ASO) approaches appear safe in normal animals¹⁻³

Preclinical efficacy

- Non-allele-specific ASOs have demonstrated efficacy in transgenic animal models, similar to allele selective approaches^{1,2,4,5}

Pharmacology

- 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

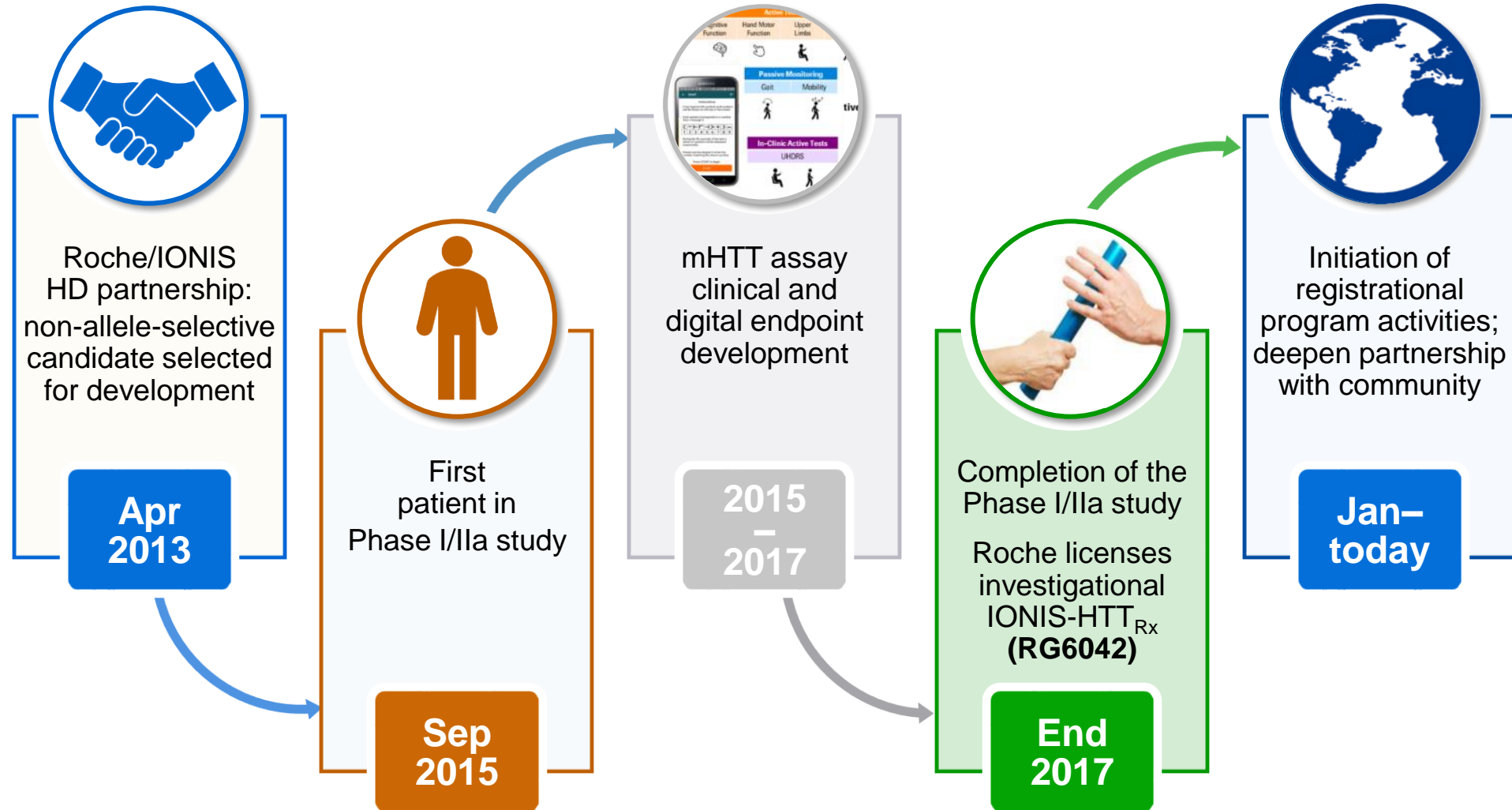
RG6042 (previously known as IONIS-HTTRx) is an investigational medicine and has not yet received regulatory approval in any country.

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

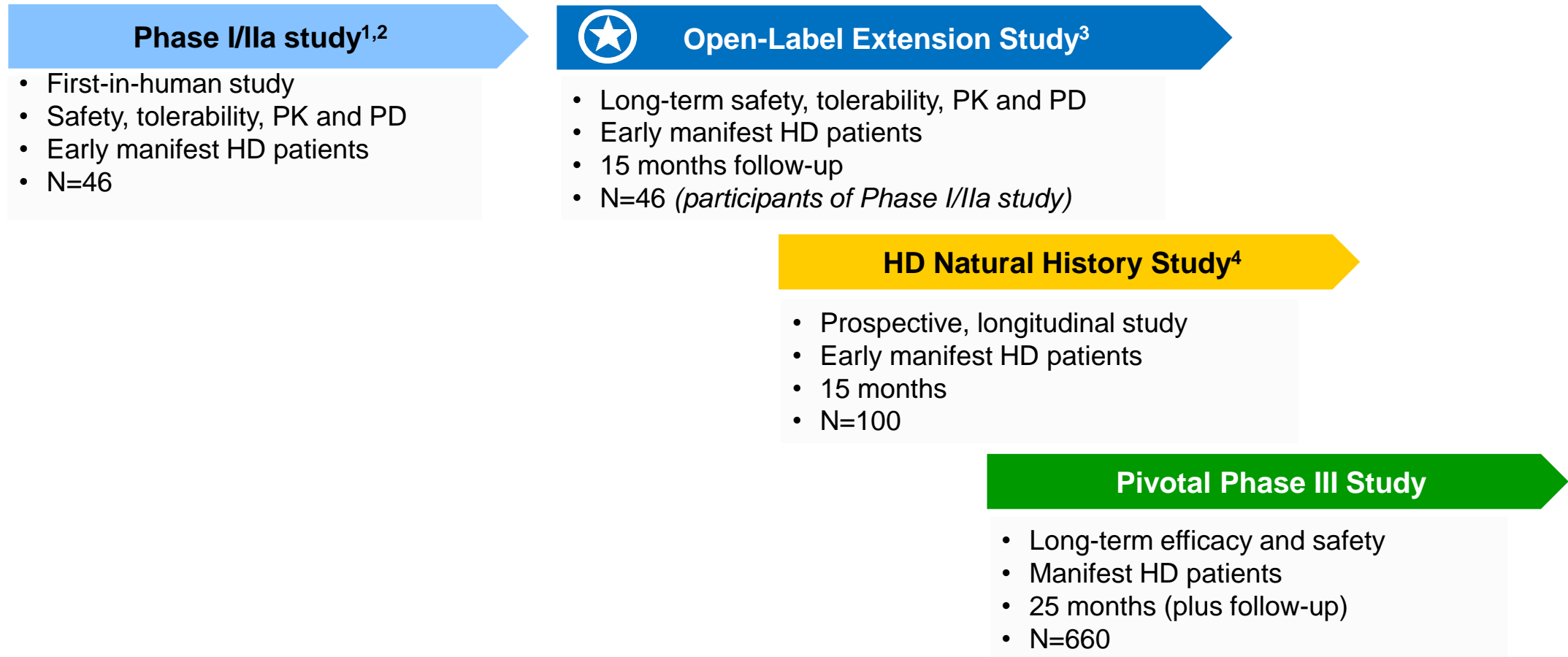
Drug specific

- 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?



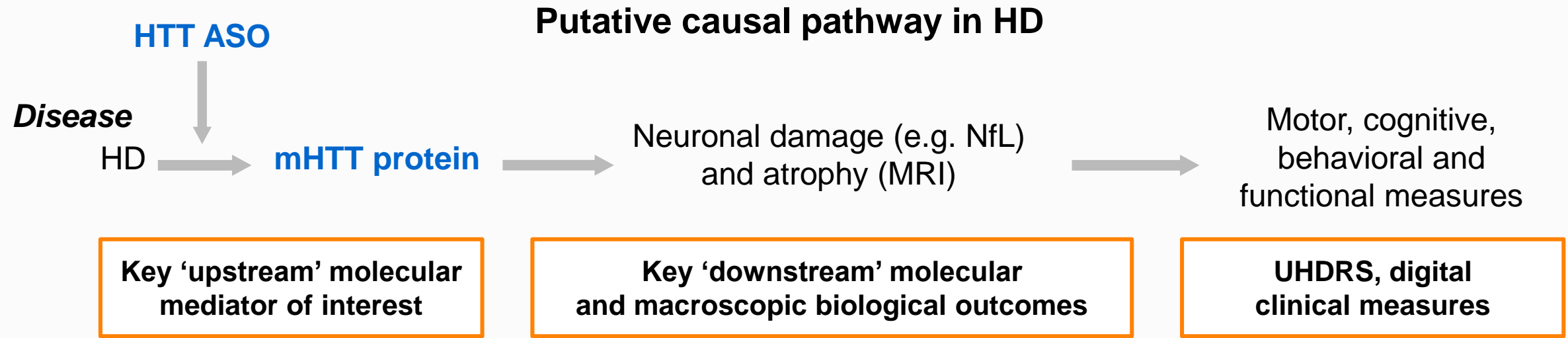
HD, Huntington's disease; PD, pharmacodynamics; PK, pharmacokinetics.

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

Open-Label Extension (OLE) study of RG6042

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

Open-Label Extension Study

Natural History Study

Pivotal Phase III Study

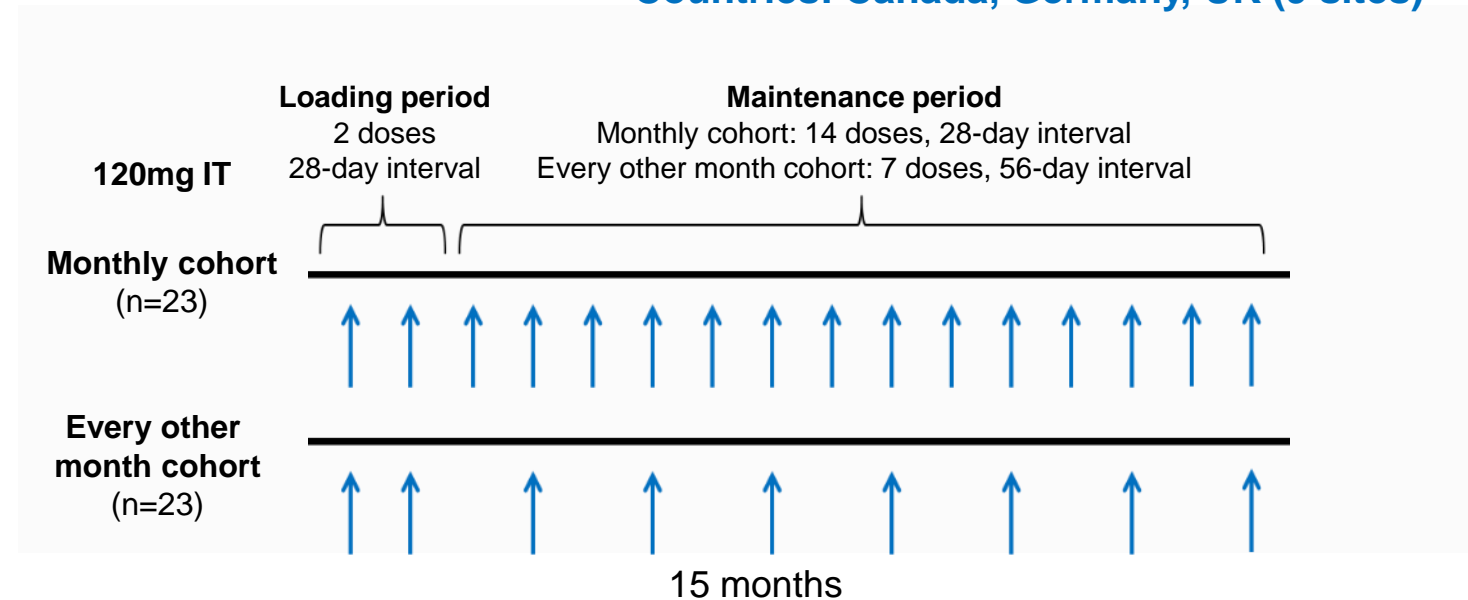
Ongoing study

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

HD Natural History Study

Objective: Enhancing understanding of putative causal pathway through longitudinal evaluation

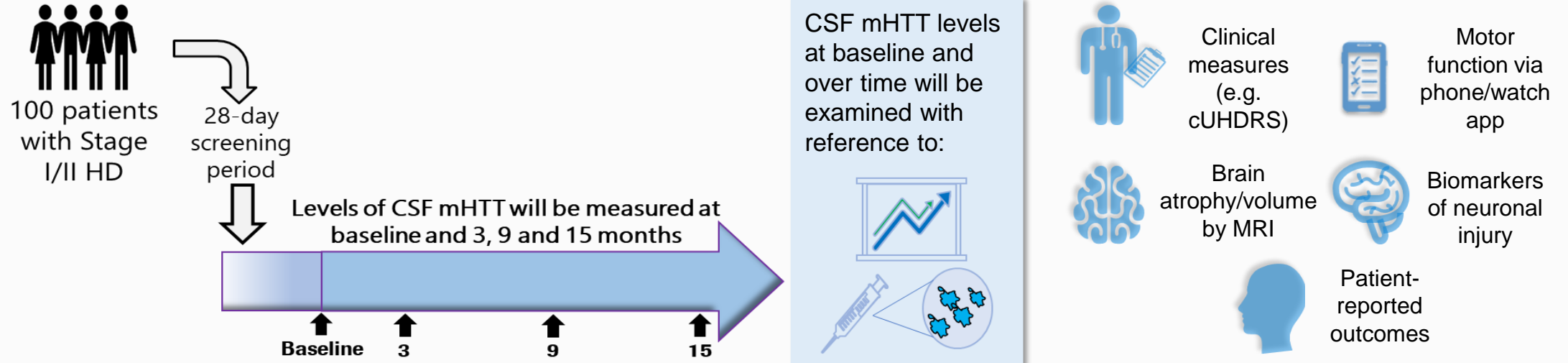
Open-Label Extension Study

HD Natural History Study

Pivotal Phase III Study

Study to start in Q4 2018

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



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

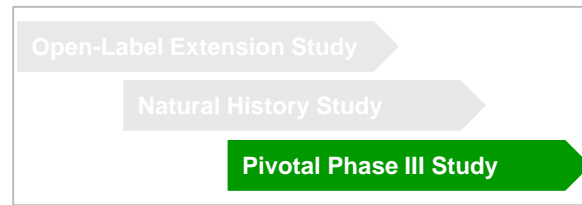
- Prognostic value of biomarkers on UHDRS clinical measures and linked digital clinical outcomes
- Population matched to OLE participants on CAG repeat length and key demographics
- Participants offered open-label access post study completion for within-subject on drug and off drug comparisons*

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)

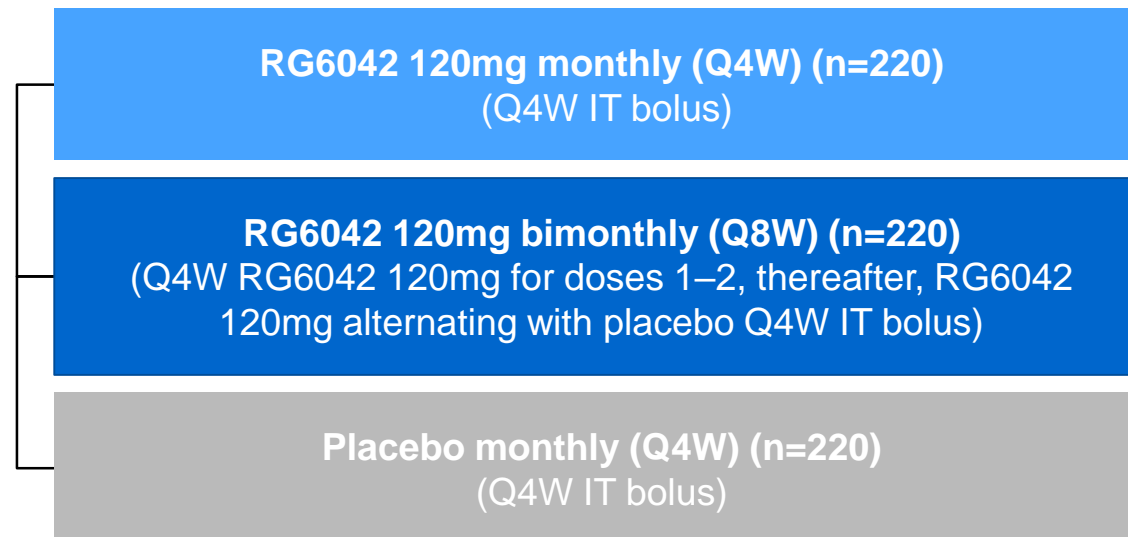
Randomised, multicenter, double-blind, placebo-controlled study

Key inclusion criteria

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

n=660

R 1:1:1



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

25 months (plus follow-up)

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

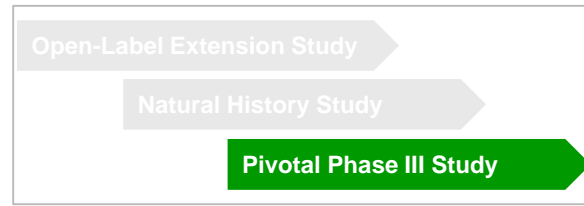
*Provided participants meet eligibility criteria, the data for RG6042 support continued development and the study is approved by Authorities and Ethics Committees/Investigational Review Boards.

†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 OligoNucleotide 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

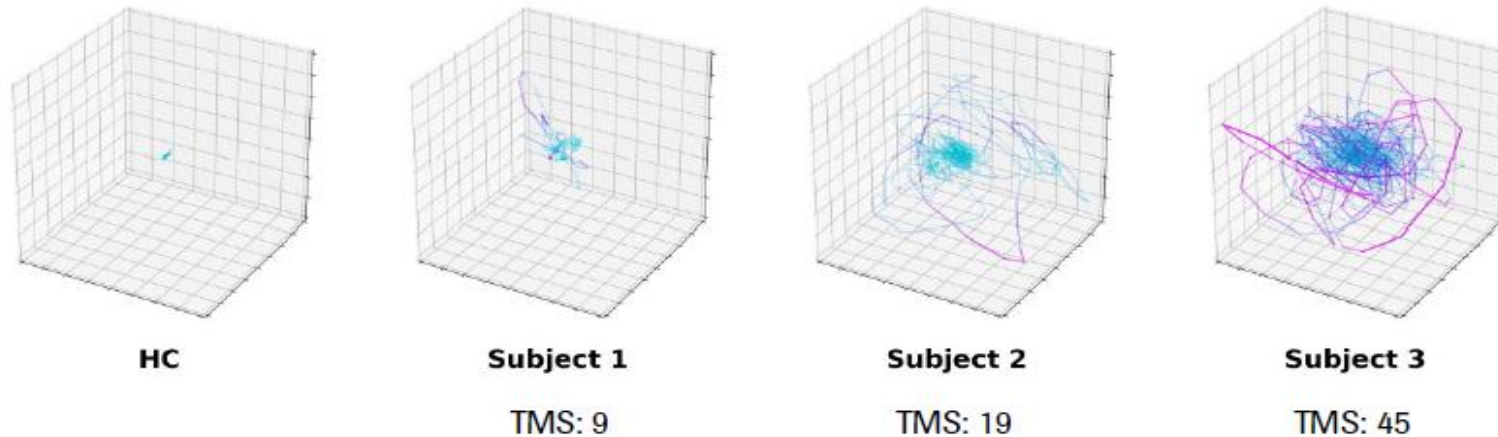
Extending measures of clinical progression through digital technology into the trials

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

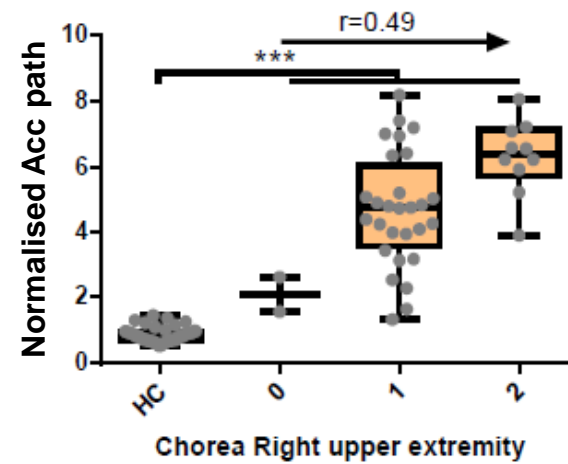
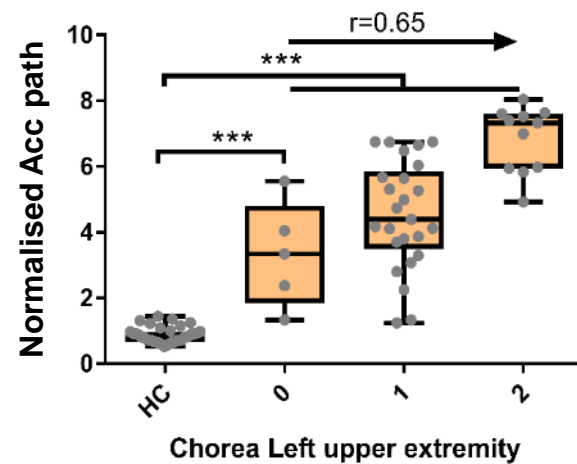
Open-Label Extension Study

Natural History Study

Pivotal Phase III Study



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.

- 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>