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

Scott Schobel, Giuseppe Palermo, Dylan Trundell, Thomas Kremer, Patricia Sanwald-Ducray, Anne Smith, Lauren Boak, Rachelle Doody and the Roche Pivotal Phase Strategic advisory committee

F. Hoffmann-La Roche, Ltd.
September 16, 2018

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. Hoffman-La Roche, Ltd.
- The views expressed in this talk are my own and not reflective of official company positions

Acknowledgments

IONIS PHARMACEUTICALS

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

Special thanks for sharing data and for ongoing collaboration:

CHDI FOUNDATION

EHDN EUROPEAN HUNTINGTON'S DISEASE NETWORK
Advancing Research, Conducting Trials, Improving Care

HUNTINGTON STUDY GROUP
seeking treatments that make a difference

Huntington's Disease Society of America

HD COPE
coalition for patient engagement

Huntington Society of Canada
HUNTINGTON
Société Huntington du Canada

EUROPEAN Huntington Association

THE UNIVERSITY OF IOWA

UCL

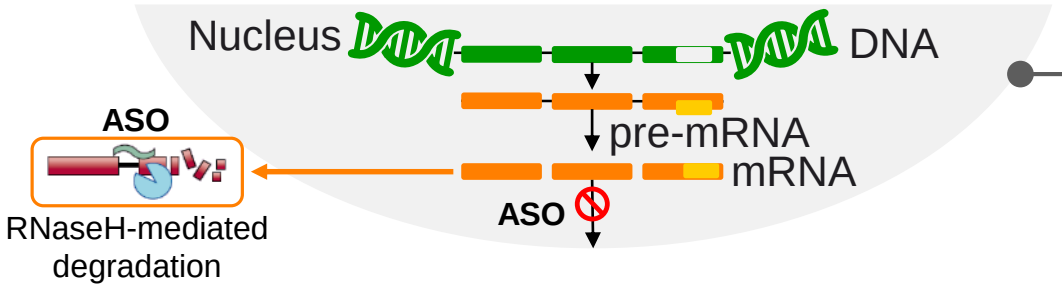
Outline

- 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
  - Natural History Study
  - Randomized double-blind 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

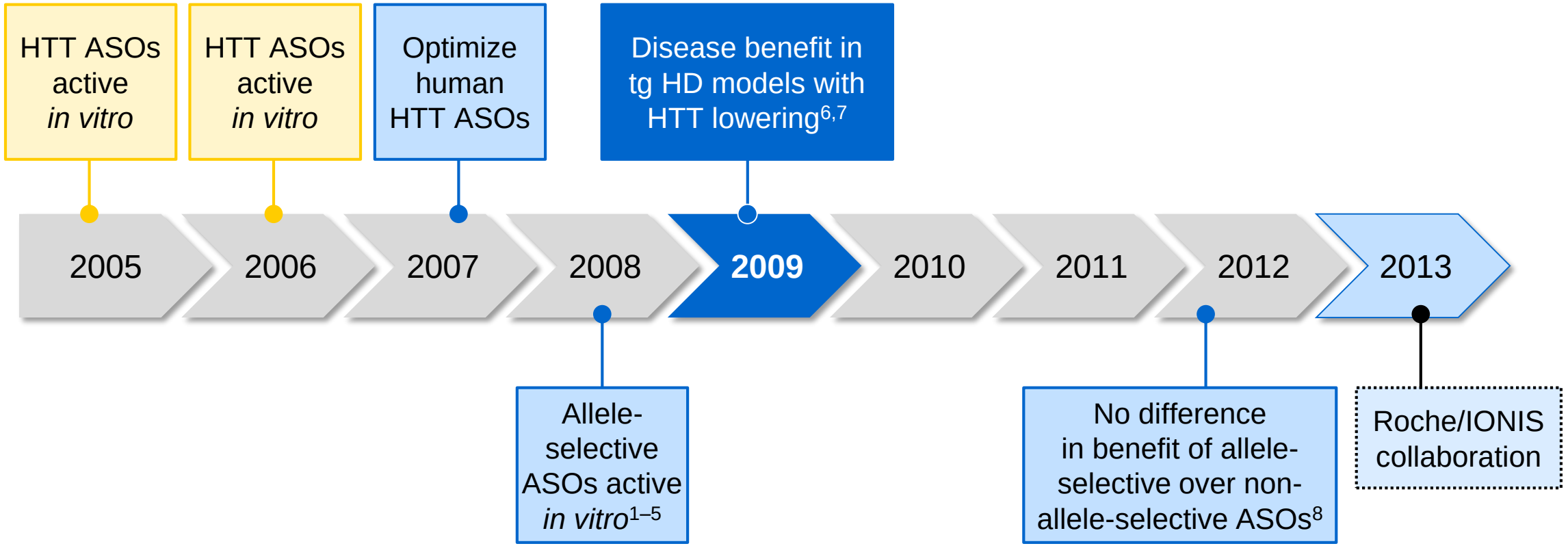
Other current SOC and advanced clinical development candidates target downstream effects likely addressing few or single domains

*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 ASOs 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:
  - broader 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

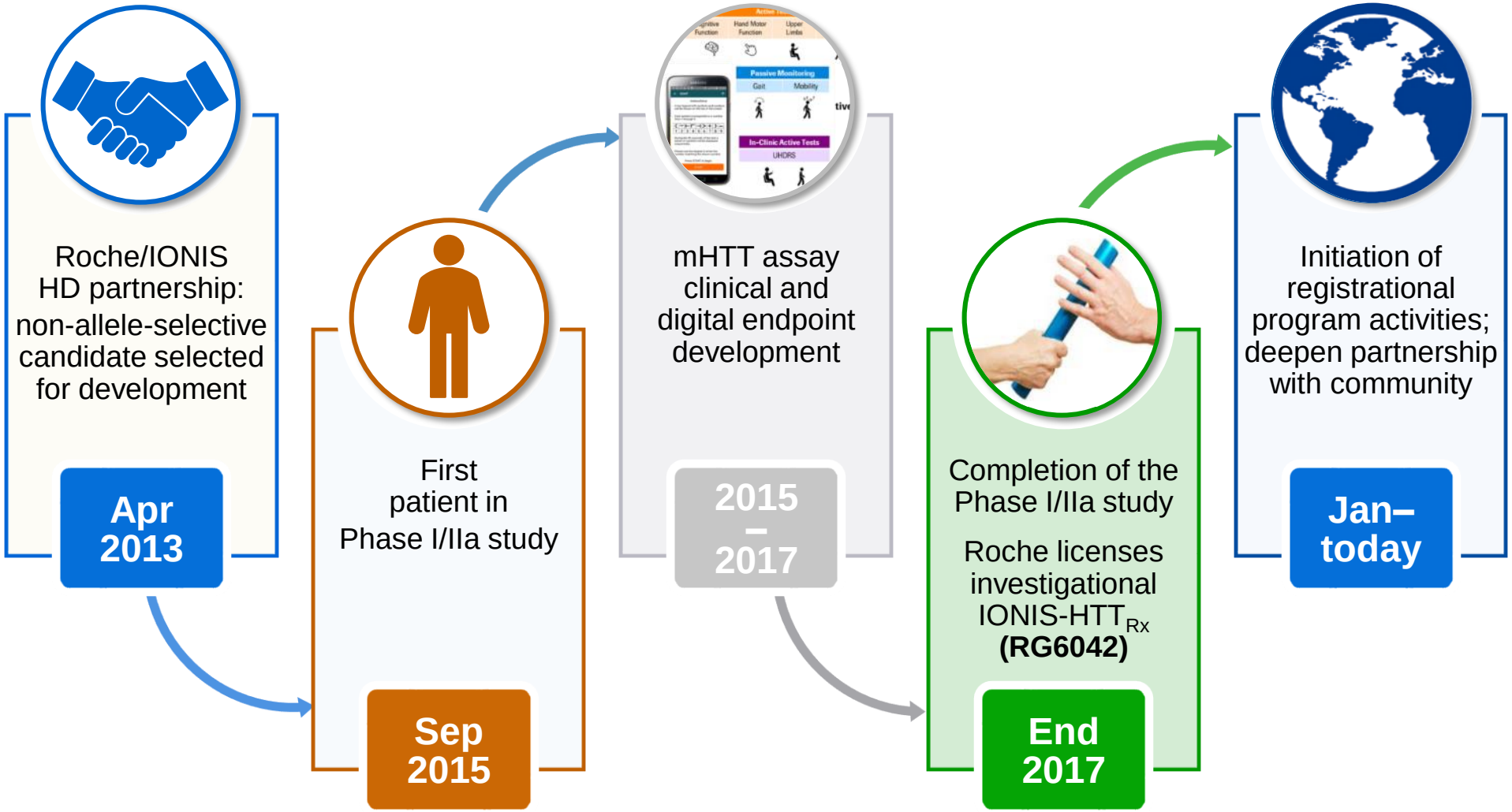
Preclinical safety	Preclinical efficacy	Pharmacology
• Lowering of total HTT in the CNS with irreversible (e.g. siRNA) or reversible (e.g. ASO) approaches appear safe in normal animals[1–3]	• Non-allele-specific ASOs have demonstrated efficacy in transgenic animal models, similar to allele selective 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.

Thank you IONIS team, investigators, and sites – Together forward!

Continuing a historic program in close partnership



Roche full Development Team for the next stage of this journey



(Some of) Your Roche & Genentech HD Team

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?

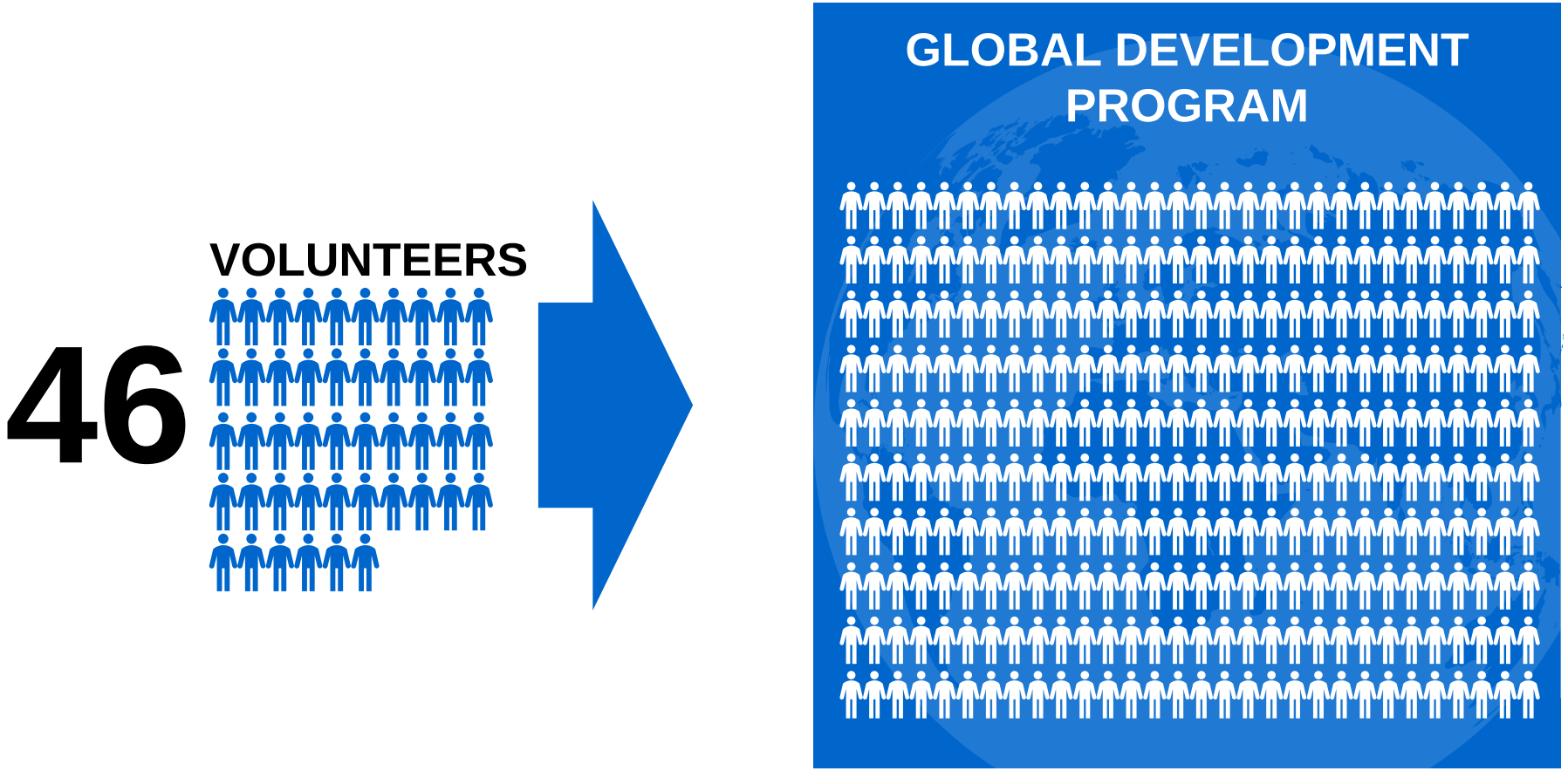
Target specific

- 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.

What is next?



Roche, data on file.

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

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

Pivotal Phase III Study

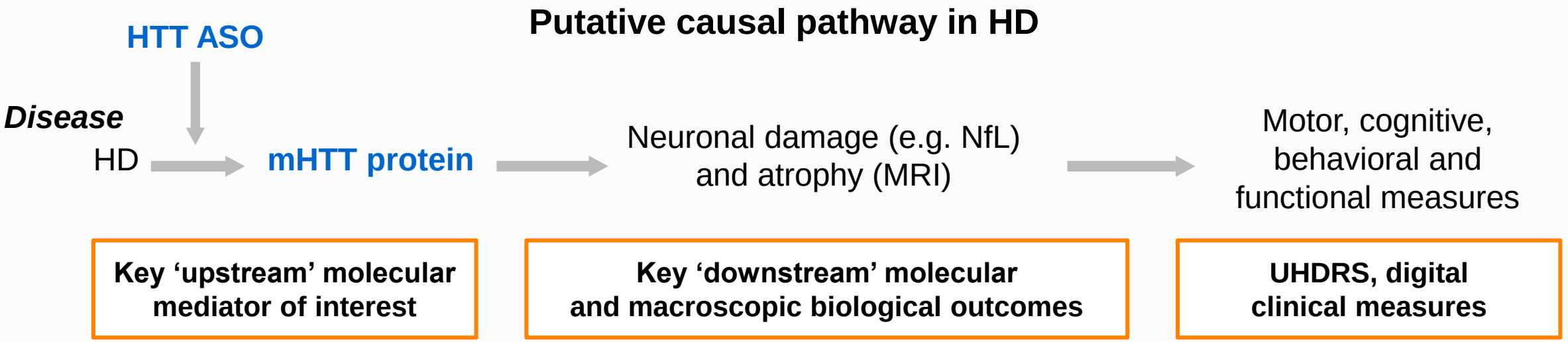
- Long-term efficacy and safety
- Manifest HD patients
- 2 years
- N=660

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.

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 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

Phase II Open-Label Study
Natural History Study
Pivotal Phase III Study

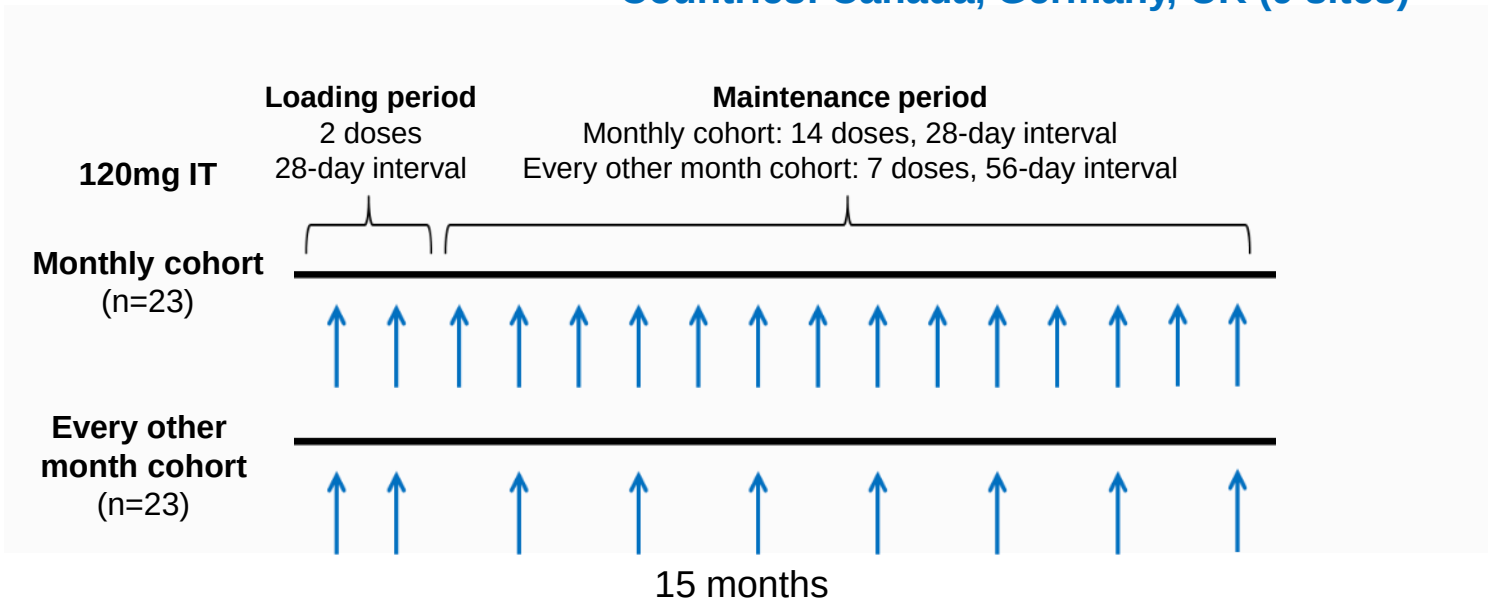
Ongoing study

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 randomized 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

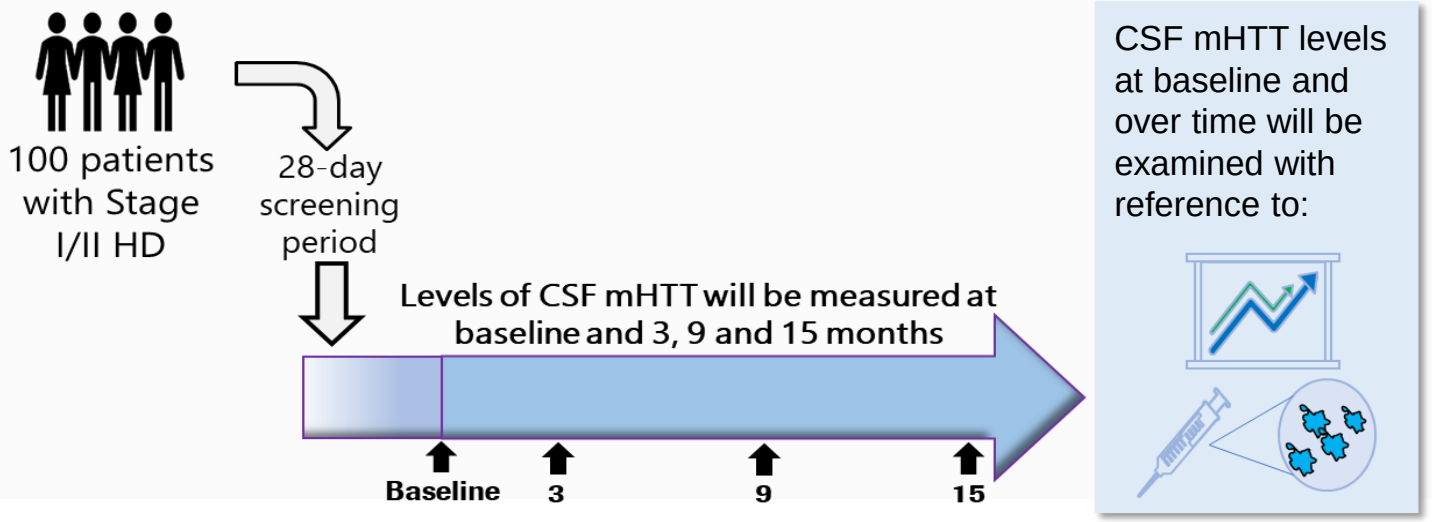
HD Natural History Study

Objective: Enhancing understanding of putative causal pathway through longitudinal evaluation

Phase II Open Label 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.

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.

EHDN 2014, Barcelona

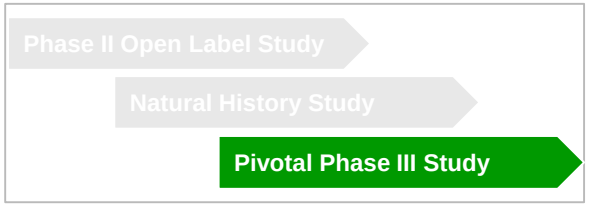
Announcement of the design of the first huntingtin lowering study in the clinic





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)

Randomized, 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 (n=220)
(Q4W IT bolus)

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

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

25 months (2 years)



Open-label extension RG6042 monthly or bimonthly
(optional)

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

*Pivotal Phase III study protocol is currently undergoing review and is awaiting ethical approval.
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.

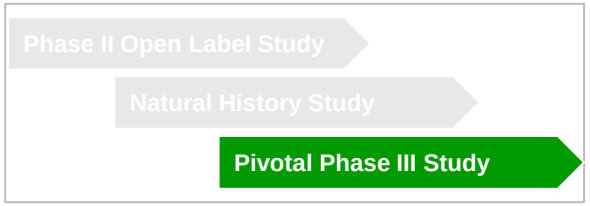
Key challenges of planned study

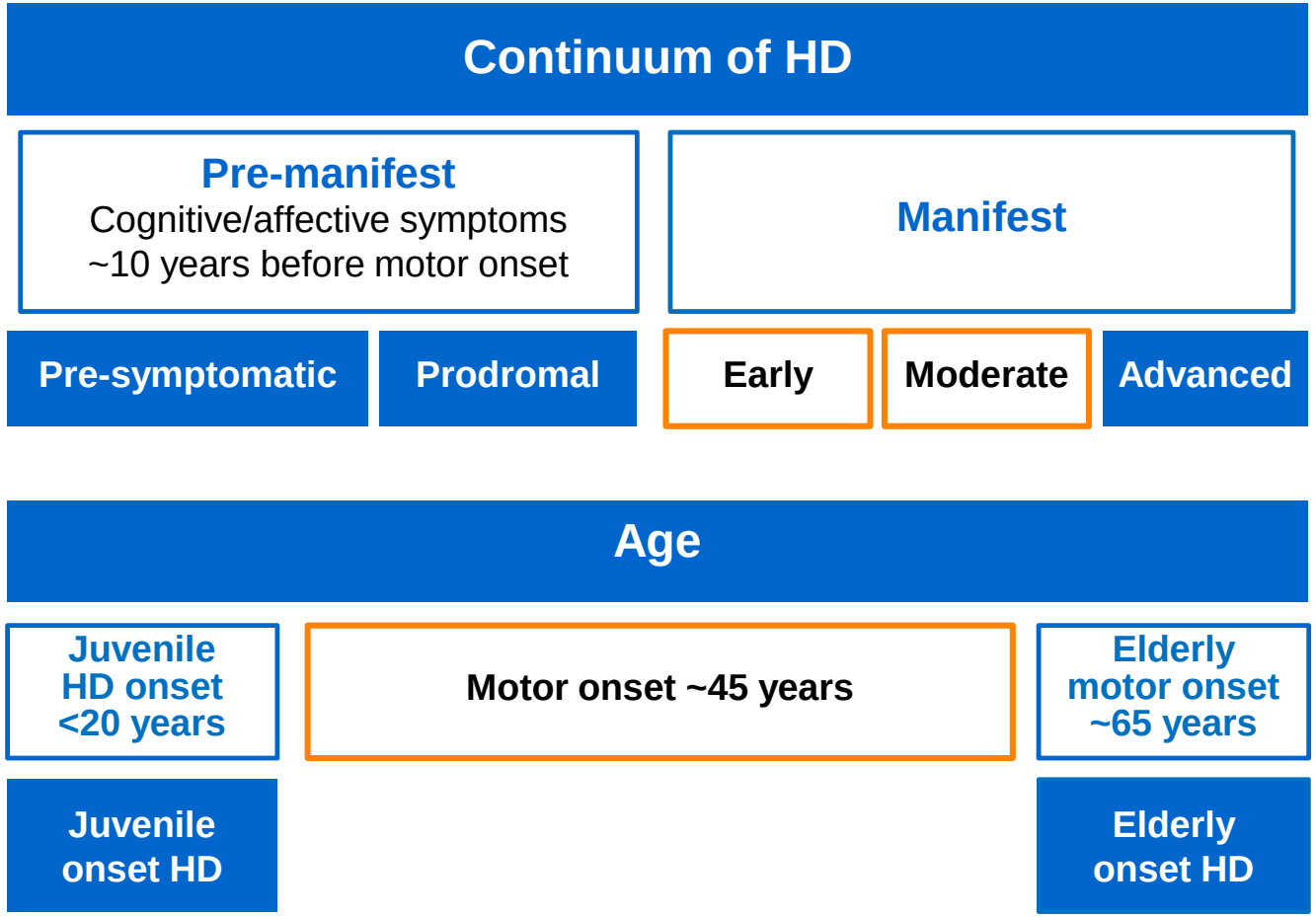
Recruitment and retention	Participants entering the trial stay in the trial for the whole duration
Route of administration	Monthly IT injections will require a commitment from participants (presently no alternatives available to IT route)
Expectancy bias	Objectivity is critical; we need to know if participants are feeling the same, better, or worse

IT, intrathecal.

GENERATION HD1 – Study inclusion criteria

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





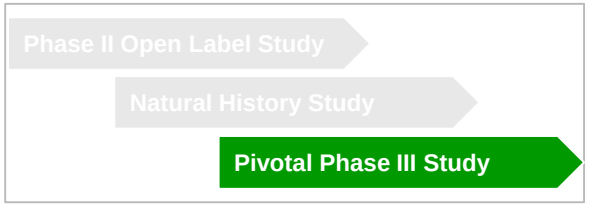
- Clinically diagnosed HD (DCL=4)
- Independence scale >70

- Age 25–65

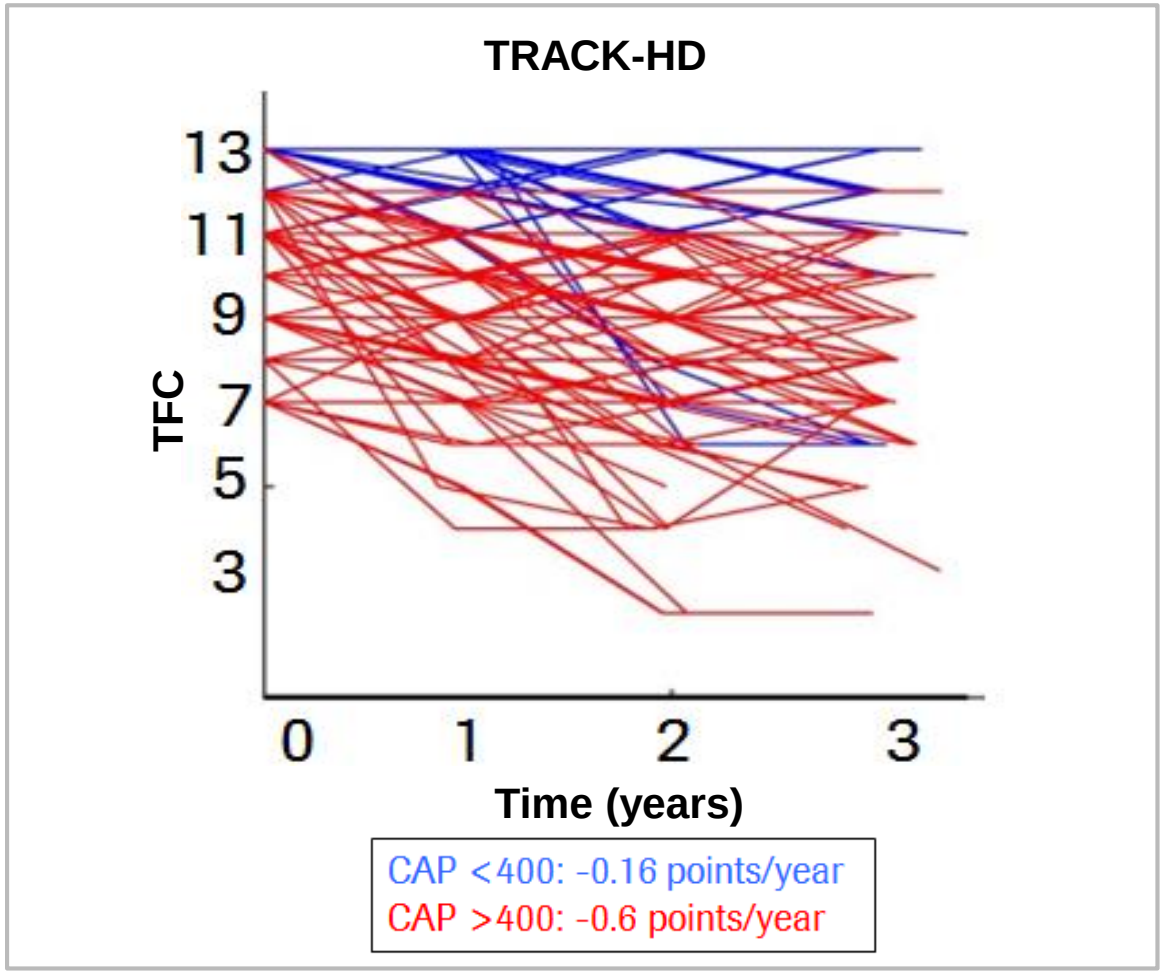
DCL, diagnostic confidence level; GENERATION HD1, Global EvaluatioN of Efficacy and Safety of Roche/Genentech AnTIsense OligoNucleotide for Huntington's Disease; HD, Huntington's disease.
Roche, data on file.

GENERATION HD1 – Study inclusion criteria

CAP criteria allows for more reliable progression rate on key outcomes



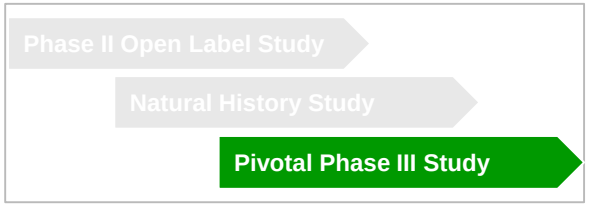
- TFC has variable progression rates in unselected early manifest HD population
- CAP
  - Index of the cumulative toxicity of mHTT at the time of study entry
  - [Age in years at baseline] × [CAG–33.66]
- Modest enrichment of target population with CAP threshold enhances progression rate on the TFC scale



CAP, CAG-age product; GENERATION HD1, Global EvaluatioN of Efficacy and Safety of Roche/Genentech AnTIsense OligoNucletide for Huntington's Disease; HD, Huntington's disease; mHTT, mutant Huntingtin protein; TFC, Total Functional Capacity.
Roche in-house analysis of early manifest HD population from TRACK-HD study.

GENERATION HD1 – Study inclusion criteria

Functional independence threshold established to enhance trial retention



- Clinical assessment to ensure individual has intact functional independence at baseline to maintain self-care and core ADLs
  - Will be used to enhance confidence that patient can complete study
  - Patient with intact functional independence can also plausibly benefit from therapy to maintain independence
- TFC will not be used as inclusion criteria
  - Minimizes the risk of inflation of TFC scores at baseline (since TFC will be a critical outcome variable in trial)
  - Other thresholds in use (e.g. on independence scale, CAP score) allow selection of appropriate target population for trial

INDEPENDENCE SCALE

Please indicate the most accurage current level of subject's independence (only _0 or _5 selections are acceptable)

100: No special care needed
090: No physical care needed if difficult tasks are avoided
080: Pre-disease level of employment changes or ends; cannot perform household chores to pre-disease level, may need help with finances
070: Self-care maintained for bathing, limited household duties (cooking and use of knives), driving terminates; unable to manage finances
060: Needs minor assistance in dressing, toileting, bathing; food must be cut for patient
050: 24-hour supervision appropriate; assistance required for bathing; eating, toileting
040: Chronic care facility needed; limited self feeding, liquified diet
030: Patient provides minimal assistance in own feeding, bathing, toileting
020: No speech, must be fed
010: Tube fed, total bed care

ADLs, activities of daily living; CAP, CAG-age product; GENERATION HD1, Global EvaluatioN of Efficacy and Safety of Roche/Genentech AnTIsense OligoNucleotide for Huntington's Disease; HD, Huntington's disease; TFC, Total Functional Capacity.

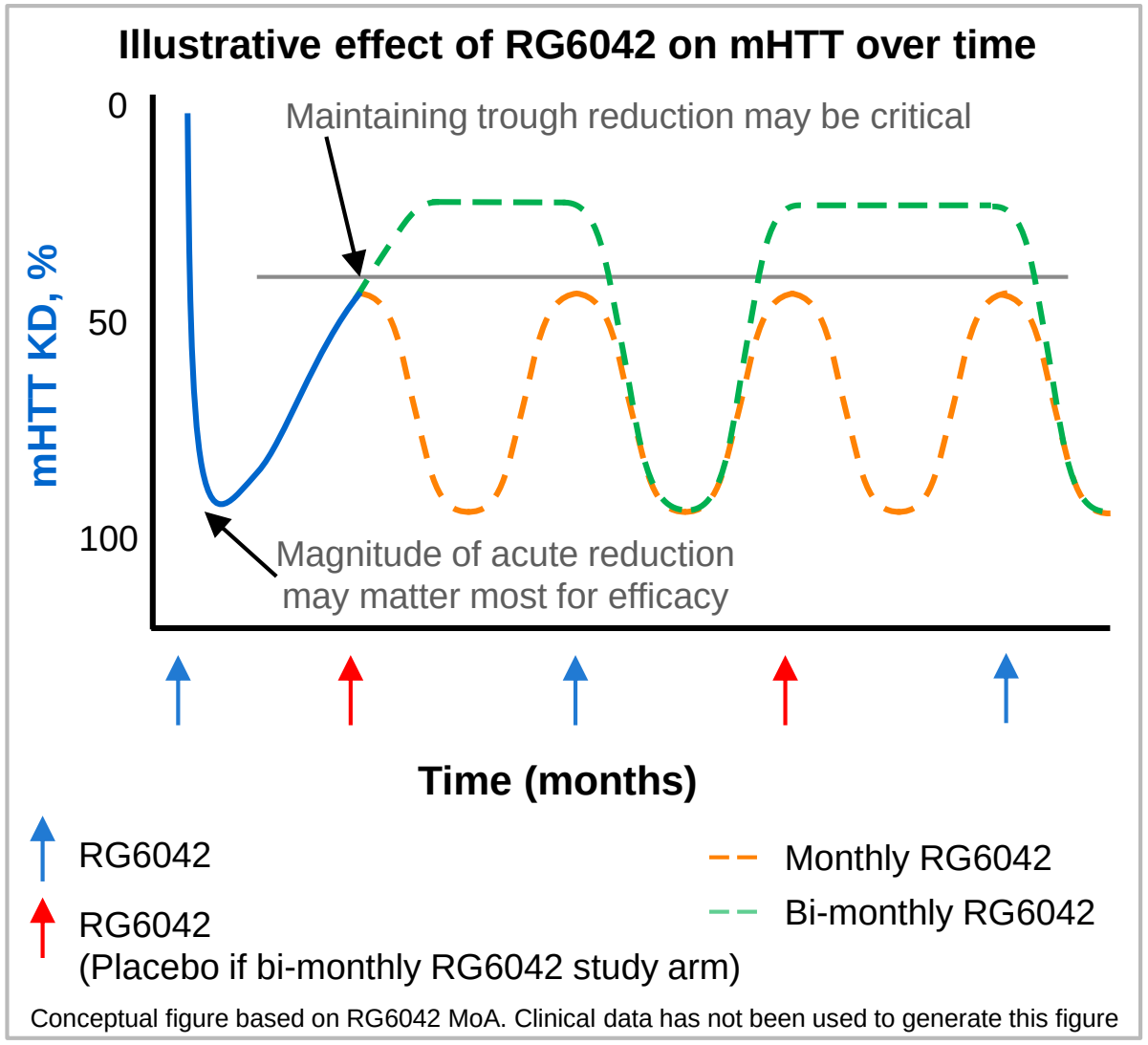
1. Huntington Study Group, *Mov Disord*. 1996;11:136-142.

GENERATION HD1 – Dosing regimen

Testing the more vs. less frequent hypothesis in the randomized setting

Phase II Open Label Study
Natural History Study
Pivotal Phase III Study

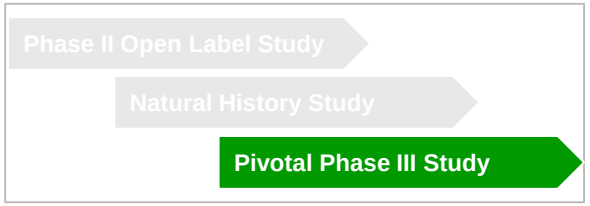
- It is unknown at what dose and how frequently an ASO needs to be given for clinical efficacy
  - Higher dose – more consistent target engagement in Phase I/IIa
  - Less frequent treatment regimen=benefit to patients
- Two high-dose regimens of RG6042 will be tested to compare efficacy, safety, and tolerability
  - Monthly – testing value of maintaining trough reduction
  - Bi-monthly – allowing protein recovery
- Highest safe and tolerated dose from MAD (120mg) chosen to maximize target reduction for pivotal



ASO, antisense oligonucleotide; GENERATION HD1, Global EvaluatioN of Efficacy and Safety of Roche/Genentech AnTIsense OligoNucletide for Huntington's Disease; KD, knockdown; MAD, multiple ascending dose; mHTT, mutant Huntingtin protein; MoA, mechanism of action.

Measuring clinical progression in HD

Ad-hoc working group formed to address endpoint gaps and leverage existing longitudinal data



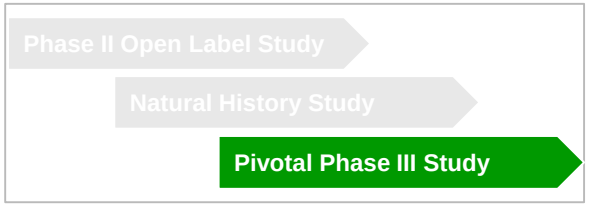
- Primary goal — **better understand clinical progression across domains,** and identify improved measures of clinical progression
- **~4,000 baseline cases, from 6 months–11 years of longitudinal follow-up**
  - Prospective cohort study data:
    - **TRACK-HD, PREDICT-HD; PADDINGTON; COHORT; PHAROS (recent addition of ENROLL-HD through CHDI data sharing)**
  - Placebo group trial data:
    - **CARE-HD, 2-CARE, TREND-HD, HORIZON**



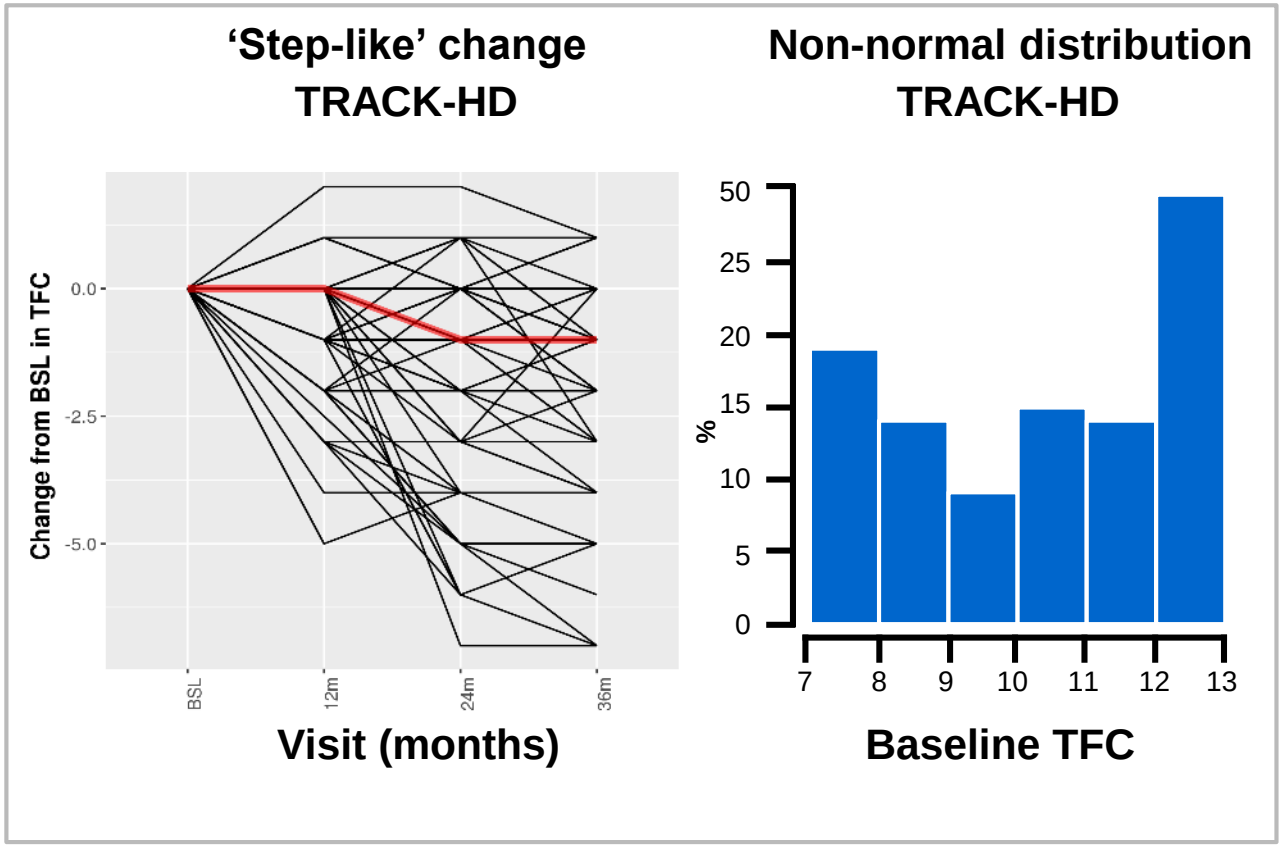
HD, Huntington's disease.

Where we started: TFC scale

Clinically meaningful, but with limited sensitivity, and ability to detect improvements



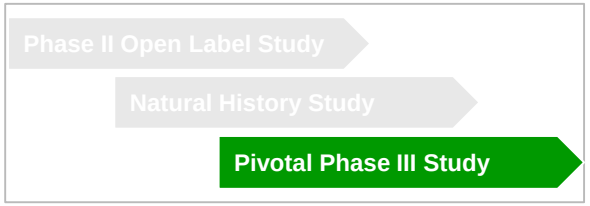
- Measure of daily function in HD
- Changes of >1 point over time are clinically meaningful
- Limited response options
- Loss of points at top of scale can occur due to social factors (e.g. job loss)
- The TFC scale is relatively coarse and has non-normal distribution
  - Cannot easily detect improvements
  - Can detect decline over time in placebo group (and slowing of decline) over longer time period

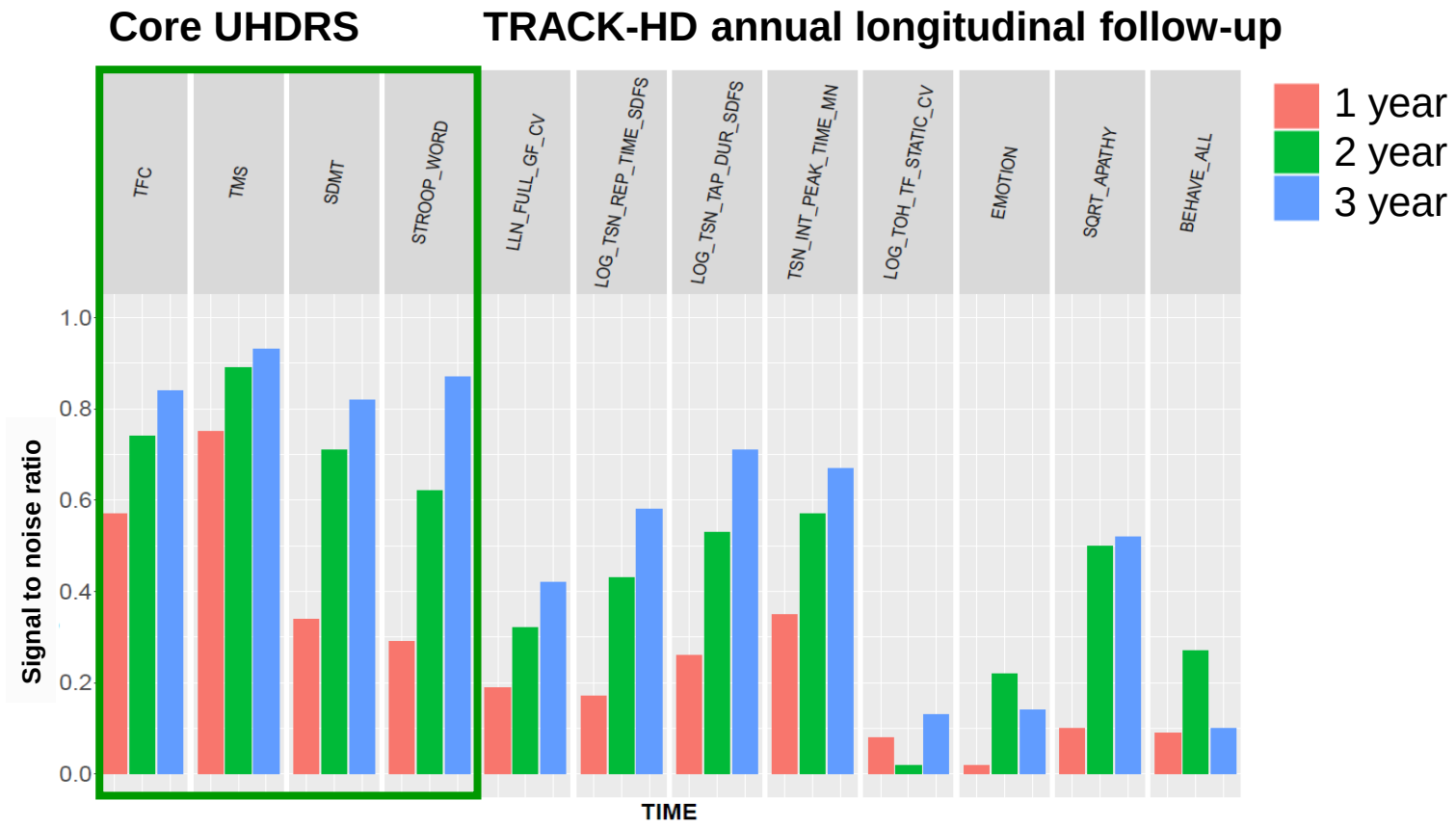


Unmet need: outcome measure to track improvements, as well as slowing of decline

BSL, baseline; HD, Huntington's disease; TFC, Total Functional Capacity.

Working group lesson #1: UHDRS measures performed best relative to behavioral and quantitative motor variables[1,2]





TMS, SDMT, and Stroop Word Reading test highly related to function

Motor, cognitive, and overall functional variables were top performing UHDRS items[1,2]

SDMT, Symbol Digit Modality Test; TFC, Total Functional Capacity; TMS, Total Motor Score; UHDRS, Unified Huntington's Disease Rating Scale.

1. Schobel SA *et al. Neurol*. 2017: 89:2495–2502. 2. Roche analysis on file.

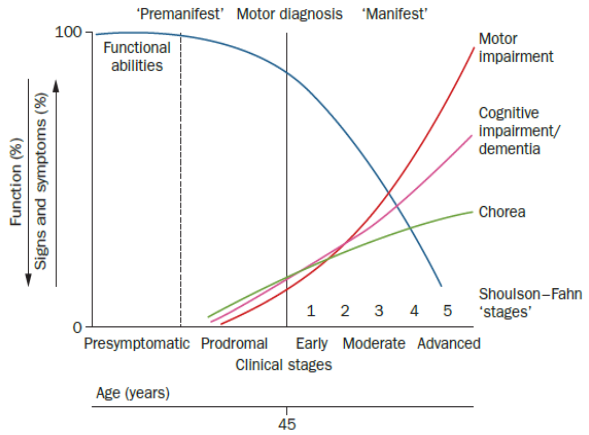
Working group lesson #2: The ‘composite UHDRS’ – A linked pattern of functional, cognitive, and motor decline

Phase II Open Label Study
Natural History Study
Pivotal Phase III Study

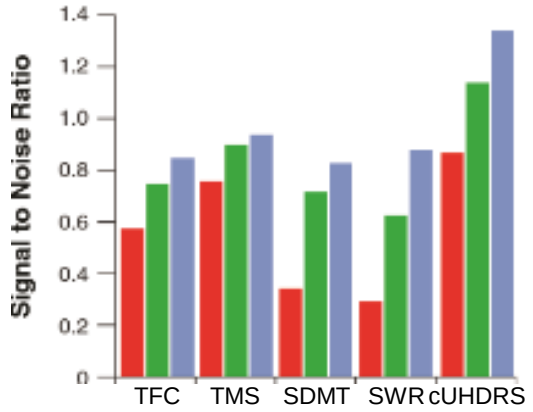
- Motor, cognitive and linked functional decline have a regular pattern of progression[1,2]
  - Inherently meaningful to concept of biological disease progression
  - Allows tracking of clinical disease progression with more sensitivity[2]
- Composite tracks progressive brain atrophy relative to individual measures

cUHDRS tracks clinical and underlying disease progression better than individual measures

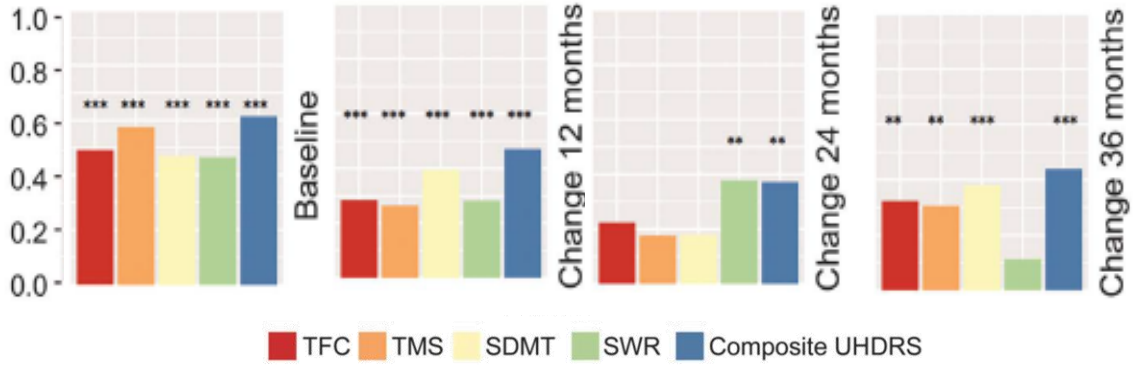
HD disease course[1]



TRACK-HD[2]



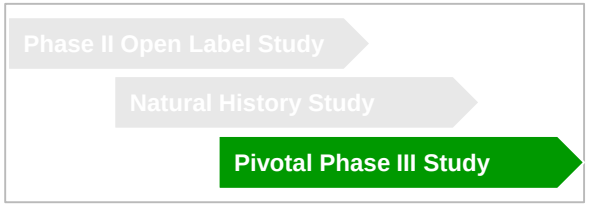
Whole-brain atrophy in early HD[2]



cUHDRS, composite Unified Huntington's Disease Rating Scale; HD, Huntington's disease; SDMT, Symbol Digit Modality Test; TFC, Total Functional Capacity; TMS, Total Motor Score; SWR, Stroop Word Reading (test); UHDRS, Unified Huntington's Disease Rating Scale.

1. Ross CA *et al. Nat Rev Neurol*. 2014; 10:204–216; 2. Schobel SA *et al. Neurol.* 2017; 89:2495–2502.

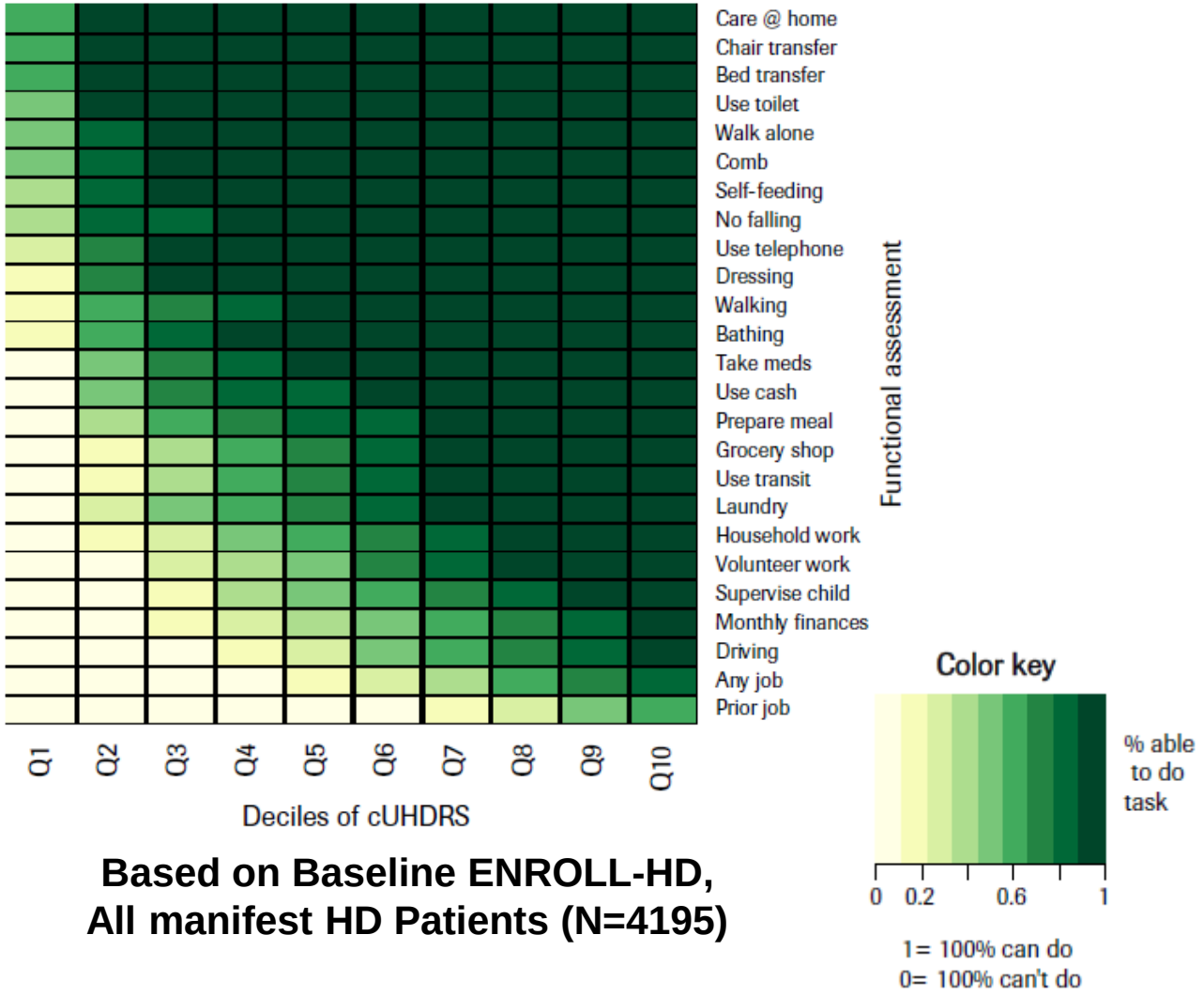
Working group lesson #3: cUHDRS tracks loss of functional ability



- Core symptoms and function measured by cUHDRS are associated with daily function[1]
  - Spearman rank order correlation with UHDRS Functional Assessment: rho=0.82 (P <0.001)
  - As the cUHDRS decile decreases, the proportion of patients unable to perform daily tasks increases
  - Supports use of z-scores

Change in cUHDRS score is a relevant clinical outcome[1]

For further details see poster **F23**: Trundell D, *et al*. Validity, reliability, and ability to detect change and meaningful within-patient change of the cUHDRS.



Based on Baseline ENROLL-HD, All manifest HD Patients (N=4195)

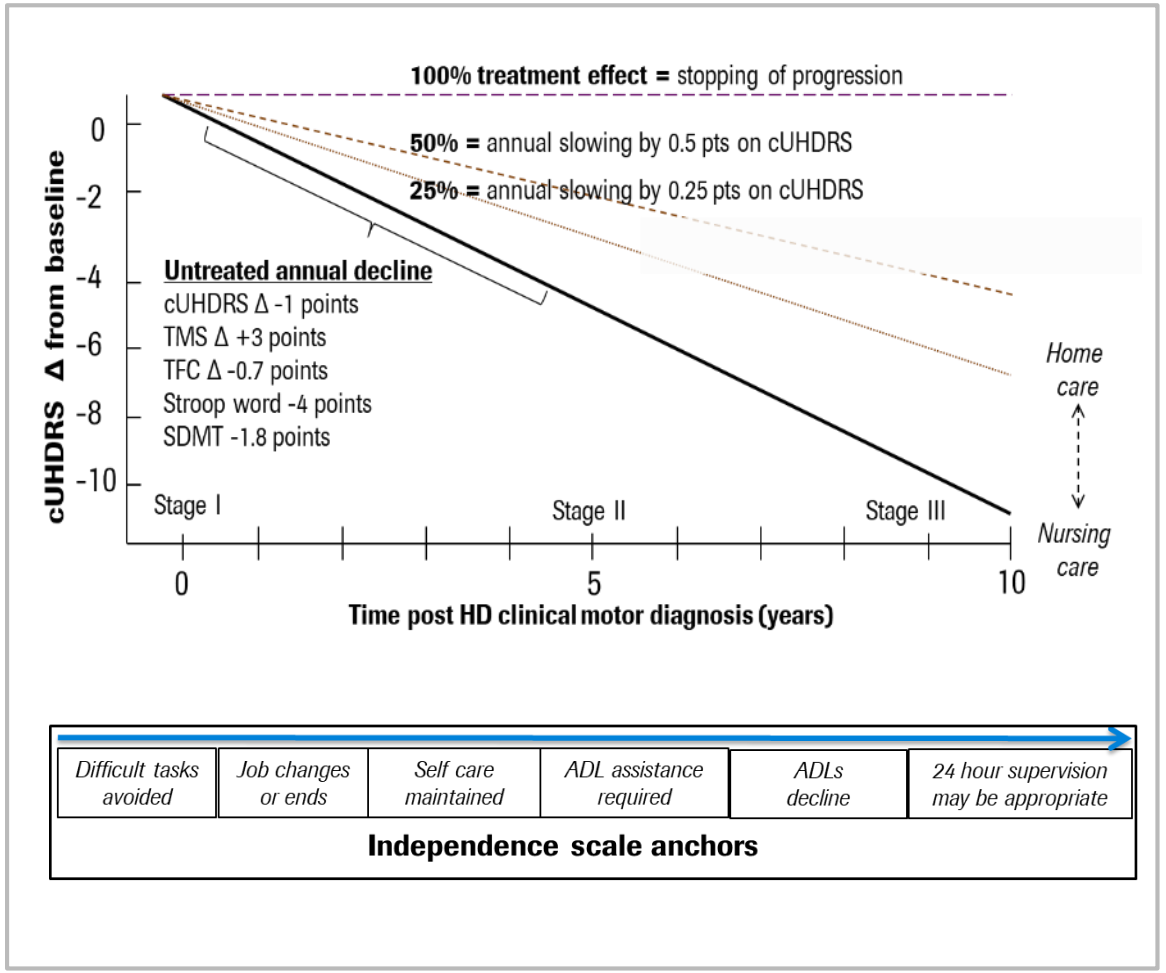
cUHDRS, composite UHDRS; HD, Huntington's disease; UHDRS, Unified Huntington's Disease Rating Scale.

1. EHDN Poster **F23**: Trundell D, *et al*. Validity, reliability, and ability to detect change and meaningful within-patient change of the cUHDRS

Working group lesson #4: cUHDRS tracks loss of functional independence

Phase II Open Label Study
Natural History Study
Pivotal Phase III Study

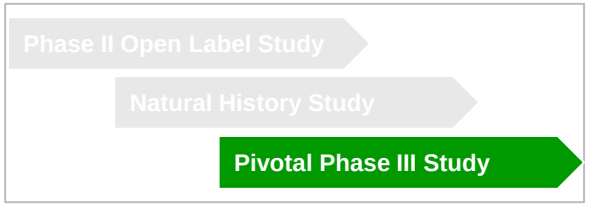
- Independence Scale:
  - (1 point loss on cUHDRS= 10 point loss on Independence Scale), rho=0.77, P <0.001
- Change in the cUHDRS relates to different functionally relevant *anchors*, overcoming the potential *z-score* limitation of obscuring interpretability of the composite score



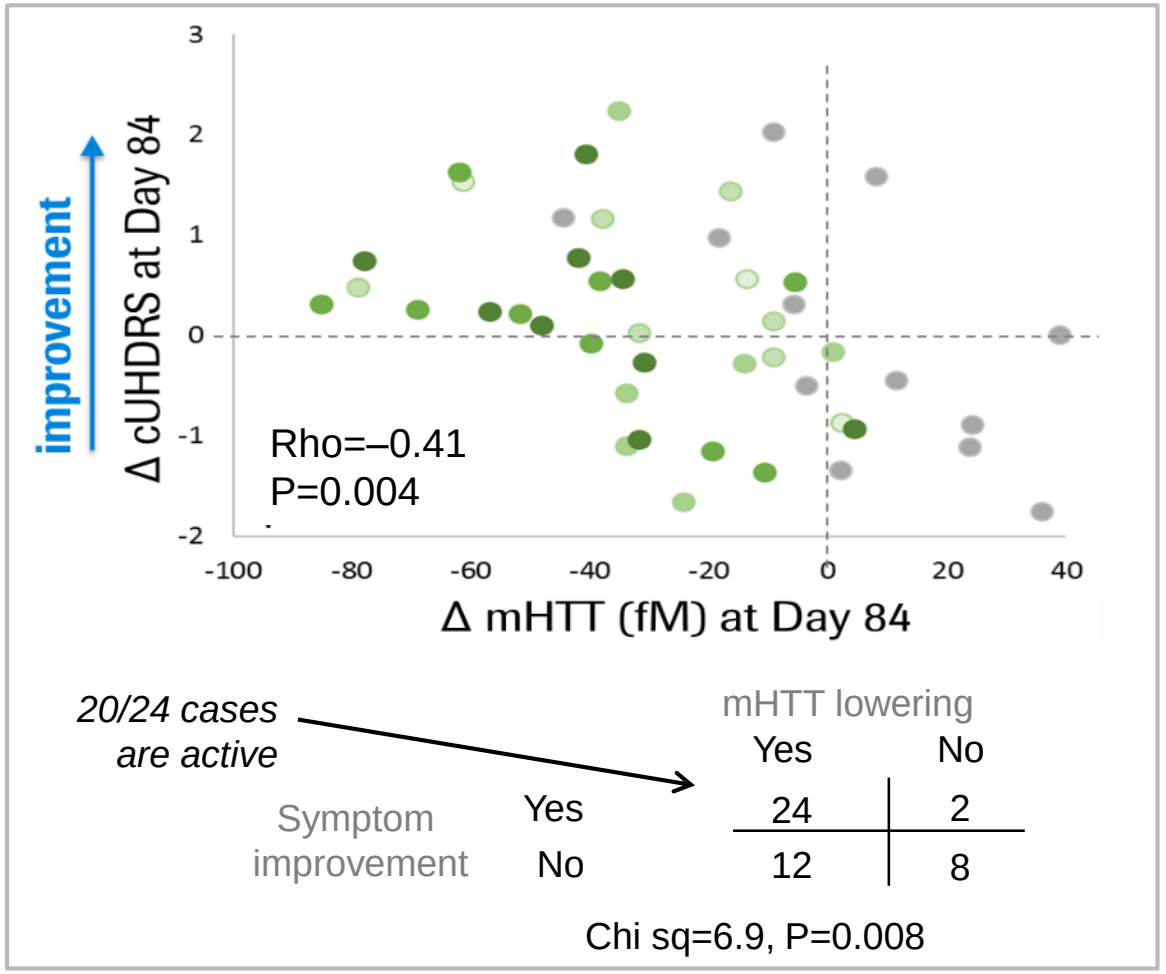
Core symptoms and function measured by cUHDRS are associated with independence

ADL, activities of daily living; cUHDRS, composite Unified Huntington's Disease Rating Scale; pts, patients; SDMT, Symbol Digit Modality Test; SWR, Stroop Word Reading (test); TFC, Total Functional Capacity; TMS, Total Motor Score; UHDRS, Unified Huntington's Disease Rating Scale.
Roche, data on file.

Working group lesson #5: Potential treatment effects of RG6042 may be robust



- In Phase I/IIa exploratory, CSF mHTT lowering was associated with clinical benefit in post hoc analyses
  - Controlling for baseline symptoms; baseline mHTT levels; CAG repeat length and age

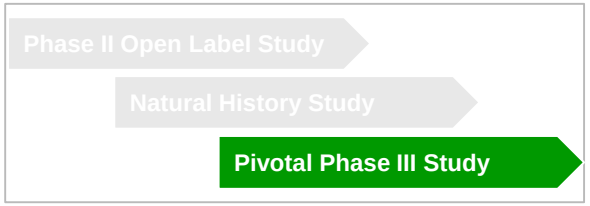


The cUHDRS may have the ability to track improvements, as well as slowing of decline in HD. Preclinical and Phase I/IIa data awaits confirmation in pivotal study

CSF, cerebrospinal fluid; cUHDRS, composite Unified Huntington's Disease Rating Scale; HD, Huntington's disease; mHTT, mutant Huntingtin protein.

Decision on primary endpoints for Pivotal Phase III study

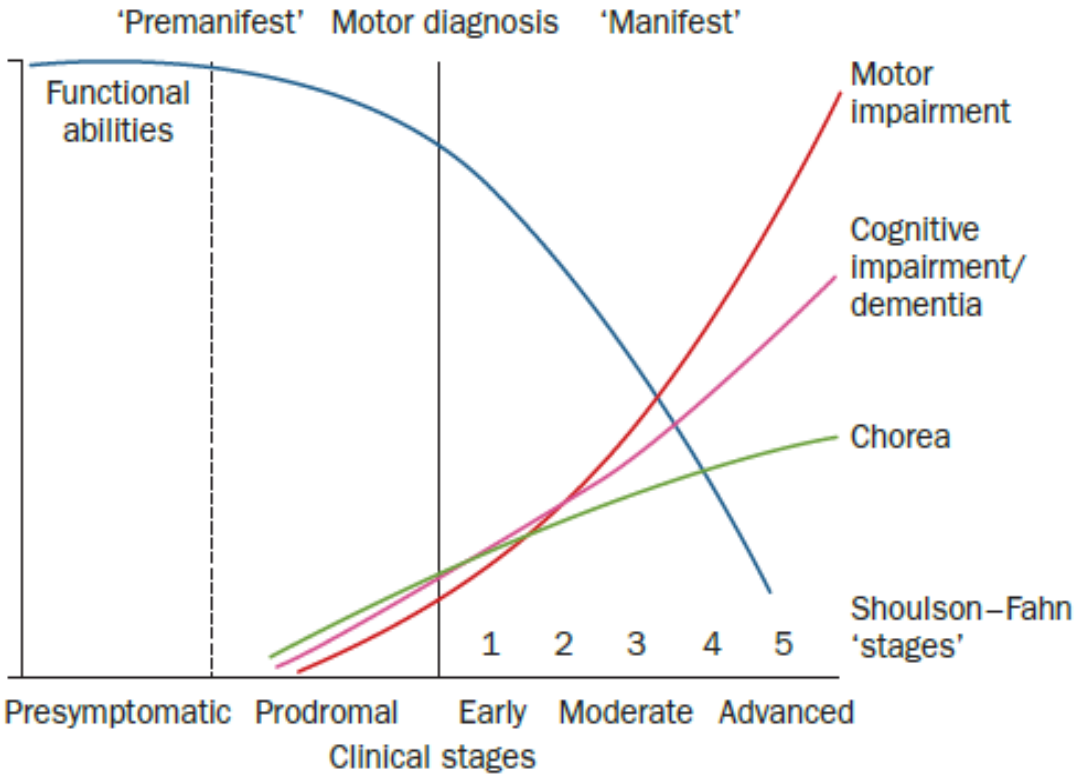
UHDRS clinical measures are well positioned to demonstrate clinically meaningful efficacy across disease domains



- **cUHDRS** will be the global primary endpoint
  - Supported by EMA
  - Best tracks multidomain decline
  - Related to biology and function
- **The TFC** will be the primary endpoint in US only
  - Required measure of daily function by FDA
  - 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

Consistency of effect anticipated between cUHDRS and TFC

HD disease course[1]



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.

1. Ross CA *et al. Nat Rev Neurol*. 2014; 10:204–216.

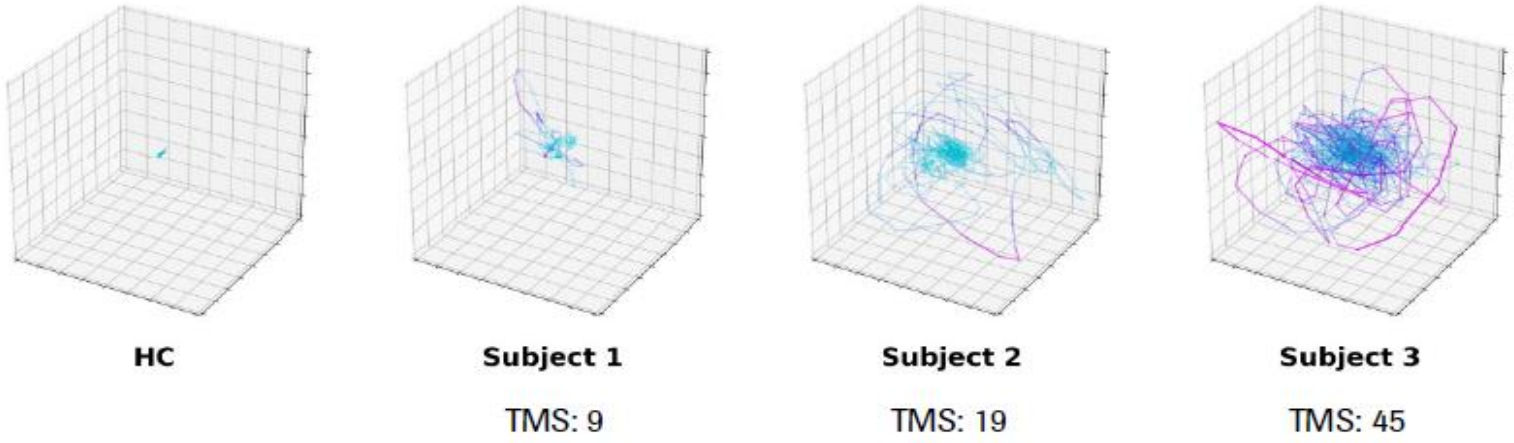
Extending measures of clinical progression through digital technology into the trials

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

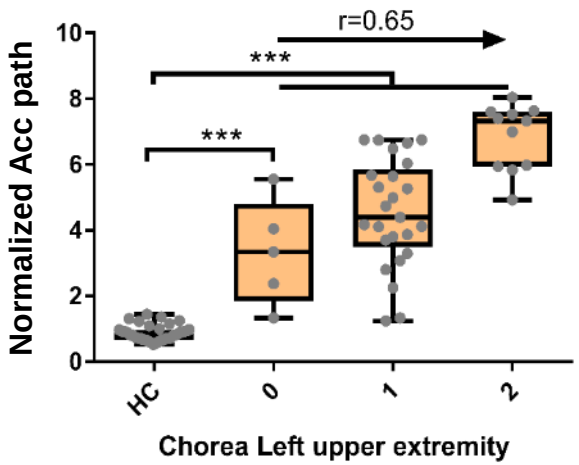
Phase II Open Label Study

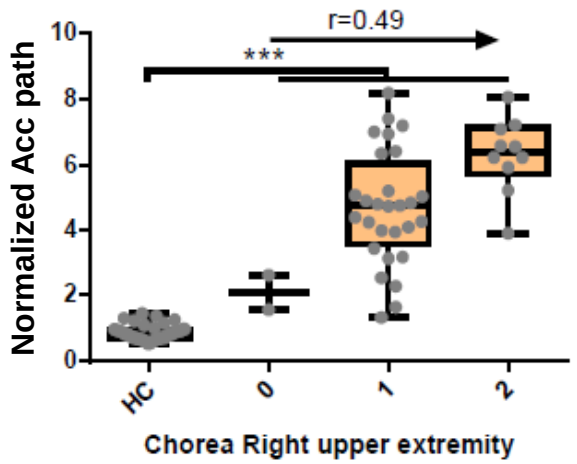
Natural History Study

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

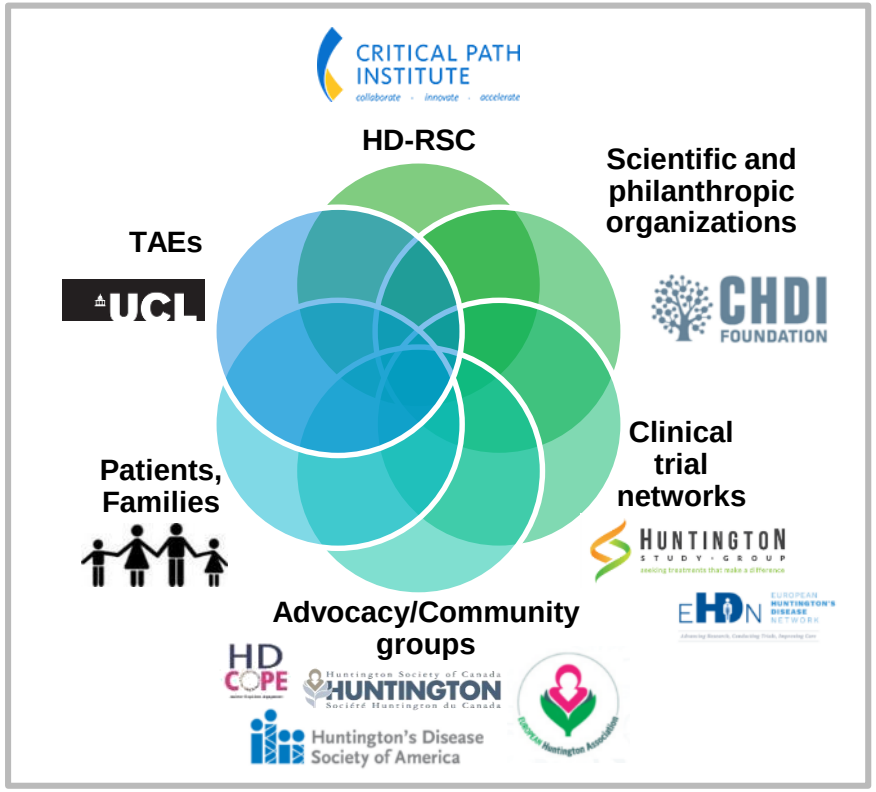
For further details see poster **F23**: Lipsmeier F, *et al*. Digital, high-frequency, long-term monitoring of motor and non-motor symptoms in HD patients.

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

We have already collaborated together well

Now it's time for the definitive test!

- **Clinical trial-ready networks** Huntington Study Group (HSG), European HD Network (EHDN), Enroll-HD Network
- **Highly motivated, well organized and connected** patient organizations
- **Dedicated researchers and research organizations** Roche is a willing collaborator to test this therapy and in so doing push the field forward
- **Huntington's disease regulatory science consortium (HD-RSC)** formed by FDA and CHDI: (Roche is co-founding member)
- **Dedicated pivotal phase strategic advisory committee** comprised of Roche/Ionis and external members including researchers and community members: ***Sarah Tabrizi, Blair Leavitt, Bernhard Landwehrmayer, Jeff Long, Karen Anderson, Rob Haselberg, Cheryl Sullivan Staveley***



Special thanks to EHDN, CHDI/CTCC, HSG and patient group partners for involvement in pivotal protocol review!

CHDI, Cure Huntington's Disease Initiative; CTCC, Clinical Trials Coordination Center; HD-COPE, HD Coalition for Patient Engagement; HSG, Huntington's Study Group; TAEs, therapy area experts; UCL, University College London.

Pivotal Phase III strategic advisory committee kick-off April 2018



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

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.