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

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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
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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

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)

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

<table>
<thead>
<tr>
<th>Cause of disease</th>
<th>Toxic mHTT*</th>
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<tbody>
<tr>
<td>Cellular dysfunction</td>
<td>Impaired axonal transport</td>
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<tr>
<td></td>
<td>Caspase/protease activation</td>
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</tbody>
</table>

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

*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.
Program history
Building on strong science, comprehensive preclinical package and collaborations

IONIS field-leading work with ASOs begins

- **HTT ASOs active *in vitro***
  - 2005

- **HTT ASOs active *in vivo***
  - 2006

- **Optimise human HTT ASOs**
  - 2007

- **Disease benefit in *tg* HD models with HTT lowering**
  - 2008

- **Allele-selective ASOs active *in vitro***
  - 2009

- **No difference in benefit of allele-selective over non-allele-selective ASOs**
  - 2010

- **2011**

- **2012**

- **2013**

- **Roche/IONIS collaboration**

ASO, antisense oligonucleotide; HD, Huntington’s disease; HTT, Huntingtin; *tg*, transgenic.
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 animals

### Preclinical efficacy

- Non-allele-specific ASOs have demonstrated efficacy in transgenic animal models, similar to allele selective approaches

### 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.

Five-year HD program history
Continuing to build on strong science and partnerships

HD, Huntington’s disease; mHTT, mutant Huntingtin protein.
## 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/Ila 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?
RG6042 Global Development Program

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

**Today**

**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

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

**Putative causal pathway in HD**

- **Disease**
  - HD → mHTT protein

- **HTT ASO**

- Neuronal damage (e.g. NfL) and atrophy (MRI)

- Motor, cognitive, behavioral and functional measures

**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

**Key ‘upstream’ molecular mediator of interest**

**Key ‘downstream’ molecular and macroscopic biological outcomes**

**UHDRS, digital clinical measures**

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

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

*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.

Clinical measures (e.g. cUHDRS)

Brain atrophy/volume by MRI

Motor function via phone/watch app

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)

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**Key inclusion criteria**

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

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**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**

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

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