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
• 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**

<table>
<thead>
<tr>
<th>Toxic mHTT*</th>
<th>DNA</th>
<th>pre-mRNA</th>
<th>mRNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNaseH-mediated degradation</td>
<td>ASO</td>
<td></td>
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</tr>
</tbody>
</table>

**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

*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

- **Roche/IONIS collaboration**
  - 2011

- **Optimise human HTT ASOs**
  - 2012

- **Disease benefit in tg HD models with HTT lowering**
  - 2013

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

<table>
<thead>
<tr>
<th>Preclinical safety</th>
<th>Preclinical efficacy</th>
<th>Pharmacology</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lowering of total HTT in the CNS with irreversible (e.g. siRNA) or reversible (e.g. ASO) approaches appear safe in normal animals¹⁻³</td>
<td>• Non-allele-specific ASOs have demonstrated efficacy in transgenic animal models, similar to allele selective approaches¹,²,⁴,⁵</td>
<td>• RG6042 results in the dose-titratable, partial and reversible reduction of HTT</td>
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<tr>
<td></td>
<td></td>
<td>• Approach appears well tolerated in Phase I/IIa and OLE</td>
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<td></td>
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<td>• &gt;200 doses of RG6042 have been administered in the OLE study to date</td>
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</tbody>
</table>

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.

HD, Huntington’s disease; mHTT, mutant Huntingtin protein.
Big questions need to be answered
Risk/benefit of new approaches needs to be carefully investigated

<table>
<thead>
<tr>
<th>Drug effect on key mutant protein</th>
<th>Measures of clinical efficacy</th>
<th>Safety and tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potency</strong></td>
<td></td>
<td><strong>Drug specific</strong></td>
</tr>
<tr>
<td>• Is the 40–60% reduction observed in CSF mHTT in Phase I/IIa sufficient?</td>
<td><strong>Measures of progression</strong></td>
<td>• What is the risk of systemic side effects at the dose required for efficacy?</td>
</tr>
<tr>
<td>• How much lowering at steady state?</td>
<td>• How do we measure meaningful clinical progression?</td>
<td><strong>Target specific</strong></td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td><strong>Population</strong></td>
<td>• What magnitude and duration of wild-type HTT protein lowering will be safe/tolerated?</td>
</tr>
<tr>
<td>• How quickly does protein recover?</td>
<td>• In what patients?</td>
<td><strong>What is the optimal administration paradigm for safety/tolerability?</strong></td>
</tr>
<tr>
<td>• Is sustained suppression necessary for efficacy?</td>
<td><strong>Treatment duration</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Brain coverage</strong></td>
<td>• How long to treat to identify benefit?</td>
<td></td>
</tr>
<tr>
<td>• Is predominant cortical lowering sufficient?</td>
<td><strong>What is the optimal administration paradigm for efficacy?</strong></td>
<td></td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; HTT, Huntingtin protein; mHTT, mutant Huntingtin protein.
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)
- \(N=660\)

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

HTT ASO

Disease
HD → mHTT protein

Key ‘upstream’ molecular mediator of interest

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

Key ‘downstream’ molecular and macroscopic biological outcomes

Motor, cognitive, behavioral and functional measures

UHDRS, digital clinical 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

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.**

**ClinicalTrials.gov. NCT03664804**

**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.*

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*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

*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.

**Key inclusion criteria**

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

**n=660**

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

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

- **RG6042 120mg bimonthly (Q8W) (n=220)**
  - (Q4W IT bolus)

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

**25 months (plus follow-up)**

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

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

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

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

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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