Preliminary results from a 15-month open-label extension (OLE) study investigating RG6042 huntingtin protein (HTT) antisense oligonucleotide (ASO) in adults with manifest Huntington’s disease (HD)

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To access this presentation go to https://bit.ly/2tK3W0D

Corrected on 16 September 2020 to amend Phase I/IIa data on Slides 14 and 15.
Disclosures

- I am a full-time employee of F. Hoffmann-La Roche Ltd
- The data shown in this talk is from preliminary analyses while database lock is ongoing
Acknowledgements

Ionis discovered RG6042 and is partnered with Roche for its development. 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 the Phase I/IIa investigator network, study participants (present and future) and their families
Tominersen is the international non-proprietary name (generic name) for the investigational molecule most recently referred to as RG6042.
Today’s presentation will focus on preliminary 15-month data from the OLE of the tominersen Phase I/IIa study.

**Phase I/IIa**
CHDI 2018

**OLE of the Phase I/IIa study**
*Today:* preliminary 15-month data (N=43 of 46)

**Ongoing studies**
Future

- Completed OLE
- HD Natural History Study
- Phase III GENERATION HD1

**Exploratory fluid biomarkers**

**PK/PD**

**Safety and tolerability**

HD, Huntington's disease; OLE, open-label extension; PD, pharmacodynamics; PK, pharmacokinetics.
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

### 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 behavioural**
  - Psychomotor slowing
  - Executive dysfunction
  - Apathy
  - Irritability

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

*Toxic mHTT*=HTT 36+ CAG repeats.
ASO, antisense oligonucleotide; HTT, huntingtin gene; HTT, huntingtin protein; mHTT, mutant HTT; MoA, mechanism of action; SOC, standard of care.
In vivo preclinical data were used to define target CSF mHTT reduction

Tissue lowering to efficacy\(^1,2\)

Transgenic mouse models
Cortex ~30–80%
Caudate ~30%

See poster 22 “Development of a non-clinical pharmacokinetic/pharmacodynamic model to predict CSF reductions in huntingtin protein in individuals with Huntington’s disease” for more details.

<table>
<thead>
<tr>
<th>% CSF HTT KD</th>
<th>% HTT KD in cortex</th>
<th>% HTT KD in caudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–30</td>
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<td>40–70</td>
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<td>40–50</td>
<td>55–80</td>
<td>25–45</td>
</tr>
</tbody>
</table>

Cyno tissue/CSF–HTT relationship

Target trough human CSF mHTT reduction range:
~30–50%

CSF mHTT lowering of ~20–30% at trough meets observed cortical threshold of efficacy in preclinical models of HD; caudate lowering is only covered at higher levels of CSF reduction (e.g. >30%)\(^1,3\)

-Based on preclinical evidence, a CSF mHTT lowering of 30–50% is expected to be associated with broad therapeutic benefits\(^2\)

7
In 2018, the results of the first-in-human Phase I/IIa study of tominersen (HTT-targeting ASO) were presented at CHDI.
In the Phase I/IIa trial, tominersen treatment produced dose-dependent reductions in CSF mHTT

CSF mHTT lowering of 40–60% was observed after four highest doses in the Phase I/IIa study

CSF mHTT trendline was still decreasing in the Phase I/IIa study

Tominersen was generally well tolerated over 4 monthly doses

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* Nominal p values from prespecified analysis of key exploratory endpoint. † Endpoint is defined as the later of Day 85 or 113.
‡ Day 113 and 141 samples were each performed in randomised subsets of patients, indicated by dotted lines.

CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein; NS, not significant.

Tominersen’s Clinical Development Programme is contributing further data to evaluate the efficacy and safety of the drug. An additional 8 patients may be included to allow investigation of additional dose levels and repeat doses if necessary.

CSF, cerebrospinal fluid; HD, Huntington’s disease; OLE, open-label extension; PD, pharmacodynamics; PK, pharmacokinetics.


**Clinical Development Programme**

**Phase I/IIa**
- N=46
- First-in-human study
- Safety, tolerability, PK and PD
- Early manifest HD patients
  - Complete
  - Complete, final analysis ongoing
  - Ongoing, recruitment complete
  - Ongoing, recruiting
  - Includes digital monitoring platform

**Open-Label Extension**
- N=46
- Long-term safety, tolerability, PK and PD
- Early manifest HD patients
- 15 months

**HD Natural History Study**
- N=95
- Prospective, longitudinal study
- Early manifest HD patients
- 15 months

**GENERATION HD1**
- N=801
- Pivotal, long-term efficacy and safety
- Manifest HD patients
- 25 months (plus follow-up)

**GEN-EXTEND** (OLE)
- Includes digital monitoring platform
- Ongoing, recruitment complete
- Ongoing, recruiting

**GEN-PEAK**
- N=12
- PK/PD in CSF and plasma
- Manifest HD patients
- 7 months including follow-up

* An additional 8 patients may be included to allow investigation of additional dose levels and repeat doses if necessary.
Tominersen’s Clinical Development Programme is contributing further data to evaluate the efficacy and safety of the drug.

Clinical Development Programme

Phase I/IIa¹ N=46
- First-in-human study
- Safety, tolerability, PK and PD
- Early manifest HD patients

Open-Label Extension N=46²
- Long-term safety, tolerability, PK and PD
- Early manifest HD patients
- 15 months

HD Natural History Study N=95³
- Prospective, longitudinal study
- Early manifest HD patients
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GENERATION HD1 N=801⁴
- Pivotal, long-term efficacy and safety
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GEN-PEAK N=12*⁶
- PK/PD in CSF and plasma
- Manifest HD patients
- 7 months including follow-up

GEN-EXTEND⁵ (OLE)
- Includes digital monitoring platform

2. Clinicaltrials.gov/show/NCT03342053 (Accessed February 2020);
3. Clinicaltrials.gov/show/NCT03664804 (Accessed February 2020);
4. Clinicaltrials.gov/show/NCT03761849 (Accessed February 2020);
5. Clinicaltrials.gov/show/NCT03842969 (Accessed February 2020);

* An additional 8 patients may be included to allow investigation of additional dose levels and repeat doses if necessary.

CSF, cerebrospinal fluid; HD, Huntington's disease; OLE, open-label extension; PD, pharmacodynamics; PK, pharmacokinetics.
Design of the open-label extension (OLE) of the Phase I/IIa study

Objective: Replicate and extend understanding of tominersen effects over longer follow-up and gain information earlier than otherwise possible from traditional Phase II study

Key study features
- Early manifest HD patients
- Participated in Phase I/IIa study
- Randomised to more vs less frequent regimen (all participants receive active drug open label)

N=46*

Long-term safety, tolerability, PK and PD of 120 mg tominersen in more vs less frequent regimen to confirm pivotal dose selection and optimise patient convenience
- Well-tolerated dose with sufficient, sustained effect on CSF mHTT within target range
- Exploration of fluid and digital biomarkers and standard clinical outcome measures

* At the time of the data cut-off (18 July 2019) 43 out of the 46 patients had reached the 15-month visit timepoint (Q4W: n=22, Q8W: n=21), three patients were enrolled in the study 3 months after all other study participants and the 15-month visit had not been conducted at time of data cut-off.

CSF, cerebrospinal fluid; HD, Huntington’s disease; IT, intrathecal; mHTT, mutant huntingtin protein; NHS, Natural History Study; PD, pharmacodynamics; PK, pharmacokinetics; Q4W, every month; Q8W, every 2 months.

Baseline characteristics of all 46 patients of the OLE study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>120 mg tominersen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q4W (N=23)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>mean (SD), range</td>
<td>47.7 (9.3), 30–64</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>male/female (n)</td>
<td>15/8</td>
</tr>
<tr>
<td><strong>CAG repeats</strong></td>
<td></td>
</tr>
<tr>
<td>mean (SD), range</td>
<td>44.1 (3.1), 40–55</td>
</tr>
<tr>
<td><strong>CAP score</strong></td>
<td></td>
</tr>
<tr>
<td>mean (SD), range</td>
<td>477 (66.5), 363–640</td>
</tr>
<tr>
<td><strong>HD Stage I/II</strong></td>
<td></td>
</tr>
<tr>
<td>(n)</td>
<td>17/6</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
</tr>
<tr>
<td>mean (SD), range</td>
<td>25.5 (3.0), 18.5–30.8</td>
</tr>
</tbody>
</table>

At the time of the data cut-off (18 July 2019) 43 out of the 46 patients had reached the 15-month visit timepoint (Q4W: n=22, Q8W: n=21), three patients were enrolled in the study 3 months after all other study participants and the 15-month visit had not been conducted at time of data cut-off.

BMI, body mass index; CAP, CAG-age product; HD, Huntington’s disease; OLE, open-label extension; Q4W, every month; Q8W, every 2 months; SD, standard deviation.
Sustained lowering of CSF mHTT was observed in both arms at 15 months (preliminary analysis)

• Pharmacologically relevant CSF mHTT lowering was observed in both treatment arms
• Data show that Q8W dosing is sufficient to reach target CSF mHTT reductions

Data points represent mean values and error bars represent ±1 standard deviations of the full intent-to-treat population.

At the time of the data cut-off (18 July 2019) 43 out of the 46 patients had reached the 15-month visit timepoint (Q4W: n=22, Q8W: n=21), three patients were enrolled in the study 3 months after all other study participants and the 15-month visit had not been conducted at time of data cut-off.

BL, baseline; CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein; Q4W, every month; Q8W, every 2 months.

Sustained lowering of CSF mHTT was observed in both arms at 15 months (preliminary analysis)

Q4W (N=23)
70% mean trough lowering at 15 months

Q8W (N=23)
44% mean trough lowering at 15 months

<table>
<thead>
<tr>
<th>Visit day</th>
<th>% CSF HTT KD*</th>
<th>% HTT KD in cortex</th>
<th>% HTT KD in caudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>20–30</td>
<td>30–55</td>
<td>5–20</td>
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<tr>
<td>23</td>
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</tr>
</tbody>
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Data points represent mean values and error bars represent ±1 standard deviations of the full intent-to-treat population. * Table based on preclinical data.

At the time of the data cut-off (18 July 2019) 43 out of the 46 patients had reached the 15-month visit timepoint (Q4W: n=22, Q8W: n=21); three patients were enrolled in the study 3 months after all other study participants and the 15-month visit had not been conducted at time of data cut-off.

Tominersen OLE of the Phase I/IIa study

SAFETY AND TOLERABILITY
Tominersen 120 mg Q8W appears to be more suitable for chronic dosing than Q4W based upon tolerability and safety

Q4W (N=23)
- 412 AEs in 23 (100%) of patients
  - 86% AEs considered non-drug related
  - 14% AEs considered drug related
- 1 patient (4%) discontinued due to AEs
- 11 patients missed ≥1 dose due to tolerability, patient choice or PI choice associated with programme transition to less-frequent dosing

Severity:
- 78.9% mild
- 18.9% moderate
- 1.7% severe
- 0.2% life threatening
- 0.2% fatal†

SAEs*: 7 events in 3 patients non-drug related†
7 events in 2 patients possibly drug related

SUSAR: 7 events in 2 patients

Q8W (N=23)
- 209 AEs in 22 (95.7%) of patients
  - 98% AEs considered non-drug related
  - 2% AEs considered drug related
- 0 patients discontinued due to AEs
- 1 patient withdrawn due to patient’s decision
- 1 patient missed 1 dose

Severity:
- 80.9% mild
- 14.8% moderate
- 4.3% severe
- 0% life threatening
- 0% fatal

SAEs*: 6 events in 3 patients non-drug related
0 possibly drug related

SUSAR: None

Data cut-off 18 July 2019.
*SAE data cut-off 10 January 2020.
† One non-drug related death (completed suicide in patient with a family history of suicide in two members).
AE, adverse event; PI, principal investigator; Q4W, every month; Q8W, every 2 months; SAE, serious AE; SUSAR, suspected unexpected serious adverse reaction.
No concerning safety laboratory signals with tominersen treatment

<table>
<thead>
<tr>
<th>Potential risk</th>
<th>Q4W (N=23)</th>
<th>Q8W (N=23)</th>
</tr>
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<tbody>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>No AEs reported</td>
<td>No AEs reported</td>
</tr>
<tr>
<td></td>
<td>No trend in lab results</td>
<td>No trend in lab results</td>
</tr>
<tr>
<td><strong>Renal toxicity</strong></td>
<td>1 AE of proteinuria, resolved without any dose interruption</td>
<td>No AEs reported</td>
</tr>
<tr>
<td>(i.e. proteinuria,</td>
<td>No change in mean serum creatinine over time</td>
<td>No change in mean serum creatinine over time</td>
</tr>
<tr>
<td>hyponatremia, low serum</td>
<td></td>
<td></td>
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<tr>
<td>bicarbonate)</td>
<td></td>
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<tr>
<td><strong>Liver</strong></td>
<td>1 AE of hepatic enzyme increase, resolved</td>
<td>No AEs reported</td>
</tr>
<tr>
<td></td>
<td>No patients with persistent lab elevations</td>
<td>No patients with persistent lab elevations</td>
</tr>
<tr>
<td><strong>Immune</strong></td>
<td>8 patients with treatment-induced or boosted anti-drug antibodies (35%)</td>
<td>8 patients with treatment-induced or boosted anti-drug antibodies (35%)</td>
</tr>
</tbody>
</table>

- 120 mg tominersen treatment (Q4W or Q8W) was not associated with ASO class risks
- Incidence of treatment-induced or boosted anti-drug antibodies were in line with known ASO class effects; anti-drug antibodies have been identified for other ASOs, are generally low titre and are not associated with AEs or loss of drug activity

ADA, anti-drug antibody; AE, adverse event; ASO, antisense oligonucleotide; NSAID, non-steroidal anti-inflammatory drug; Q4W, every month; Q8W, every 2 months.
CSF WBC elevations occurred less frequently with tominersen Q8W vs Q4W

- Q8W arm showed fewer elevations in CSF WBCs post-baseline than the Q4W arm
- CSF WBC changes were not associated with AEs and the pattern of CSF changes was generally non-sustained

AE, adverse event; CSF, cerebrospinal fluid; Q4W, every month; Q8W, every 2 months; WBC, white blood cell.
CSF total protein elevation occurred less frequently with tominersen Q8W vs Q4W

- Q8W arm showed fewer elevations in CSF total protein levels post-baseline than the Q4W arm
- CSF total protein changes were not associated with AEs

AE, adverse event; CSF, cerebrospinal fluid; Q4W, every month; Q8W, every 2 months.
Safety and tolerability summary

- The Q8W regimen appears better tolerated than the Q4W regimen in terms of number and nature of AEs and SAEs
- CSF protein and WBCs are less affected in the Q8W regimen
- No evidence for ASO-associated class risks in either regimen
- Overall, these findings suggest that tominersen 120 mg Q8W is more suitable for chronic dosing paradigms
Tominersen OLE of the Phase I/IIa study

CLINICAL PHARMACOLOGY
Tominersen steady state CSF exposure achieved with Q8W dosing

Mean (±SD) trough CSF concentration over time

**Q4W (N=23)**
Exposure ~5.8 ng/mL

**Q8W (N=23)**
Exposure ~1.6 ng/mL (Initial peak at ~3 ng/mL related to loading regimen)

On visual inspection, tominersen CSF PK steady state was achieved for the Q8W regimen at Month 6 (Day 141)

Data points represent mean values and error bars represent ±1 standard deviations.
Patients 1002 (1st dose=90 mg), 1004 and 4304 (Q8W with 4 loading doses) and patients with missed doses are excluded.
CSF, cerebrospinal fluid; PK, pharmacokinetics; Q4W, every month; Q8W, every 2 months; SD, standard deviation.
Similar plasma PK exposure was observed in both Q4W and Q8W.

**Mean (±SD) trough plasma concentration over time**

**Q4W (N=23)**
- Trough exposure ~2.5 ng/mL

**Q8W (N=23)**
- Trough exposure ~2.4 ng/mL

Data points represent mean values and error bars represent ±1 standard deviations. Patients 1002 (1st dose=90 mg), 1004 and 4304 (Q8W with 4 loading doses), Day 57 mean for Q8W (n=4) and patients with missed doses are excluded. PK, pharmacokinetics; Q4W, every month; Q8W, every 2 months; SD, standard deviation.
A clinical population PK/PD model based on Phase I/IIa and OLE data supports programme shift to less frequent dosing.

120 mg Q8W exceeds trough CSF mHTT preclinical efficacy threshold in cortex and caudate; 120 mg Q16W in cortex only.

**GENERATION HD1 pivotal study dose regimen changed from Q4W/Q8W to Q8W/Q16W.**

* Q4W dose was verified with VPC and goodness-of-fit plots before simulating Q8W and Q16W.
† Table based on preclinical data.
CSF, cerebrospinal fluid; IT, intrathecal; KD, knockdown; mHTT, mutant huntingtin protein; OLE, open-label extension; PD, pharmacodynamic; PK, pharmacokinetic; popPK/PD, population PK/PD; Q8W, every 2 months; Q16W, every 4 months; VPC, visual predictive check.
Changes to the dosing regimens have made participation in the Phase III study less demanding.

### Dosing Regimens

| MONTH | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |
|-------|---|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| **Q4W** |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| **Q8W** |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| **PLACEBO** |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| **ORIGIN** |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| **UPDATED** |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| **Q8W** |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| **Q16W** |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| **PLACEBO** |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

- **Q4W**: every month; **Q8W**: every 2 months; **Q16W**: every 4 months.

= Tominersen 120 mg  
= Placebo injection  
= Lumbar puncture only
Tominersen OLE of the Phase I/IIa study

EFFECT ON EXPLORATORY CSF FLUID BIOMARKERS: NfL AND TAU
The plausible role of NfL in HD and other CNS diseases

- NfL increases are associated with disease status and severity, and have prognostic value across a range of diseases
  - HD, AD, ALS, FTD, MS, CJD, stroke, TBI, cardiac arrest, HIV-associated dementia
- NfL lowering with disease-modifying therapies in MS, SMA, HIV-associated dementia and ALS is associated with clinical benefits

- In HD, observational findings require replication
- No data yet on the expected response of NfL in a treatment context

AD, Alzheimer’s disease; ALS, amyotrophic lateral sclerosis; CJD, Creutzfeldt–Jakob disease; CNS, central nervous system; FTD, frontotemporal dementia; HD, Huntington’s disease; HIV, human immunodeficiency virus; MS, multiple sclerosis; NfL, neurofilament light protein; SMA, spinal muscular atrophy; TBI, traumatic brain injury.
CSF NfL increases in both arms at Day 141 and then decreases on continued treatment

Data points represent mean values and error bars represent ±1 standard deviations.
At the time of the data cut-off (18 July 2019) 43 out of the 46 patients had reached the 15-month visit timepoint (Q4W: n=22, Q8W: n=21), three patients were enrolled in the study 3 months after all other study participants and the 15-month visit had not been conducted at time of data cut-off.
BL, baseline; CSF, cerebrospinal fluid; NfL, neurofilament light protein; Q4W, every month; Q8W, every 2 months.

No associations between NfL increases and adverse events were observed.
CSF NfL levels in the Q8W arm decrease to within expected natural history range at 15 months

Data points represent mean values and error bars represent ±1 standard deviations. At the time of the data cut-off (18 July 2019) 43 out of the 46 patients had reached the 15-month visit timepoint (Q4W: n=22, Q8W: n=21), three patients were enrolled in the study 3 months after all other study participants and the 15-month visit had not been conducted at time of data cut-off.

* HD-CSF trendline was interpolated from baseline and 24-month data points from early HD sample of HD-CSF. See poster number 91 for HD-CSF results.

NfL increases expected in untreated HD (estimated ~15% median increase at 15 months [HD-CSF])

Roche HD NHS data will provide comparator in matched sample with equal follow-up

Data points represent mean values and error bars represent ±1 standard deviations.

BL, baseline; CSF, cerebrospinal fluid; HD, Huntington’s disease; NfL, neurofilament light protein; Q4W, every month; Q8W, every 2 months.
CSF NfL and Tau are associated at baseline and over time during tominersen treatment


CSF NfL and Tau are associated at baseline, consistent with literature to date. Changes in CSF NfL and Tau are highly associated during transient peak at Day 141.

CSF, cerebrospinal fluid; NfL, neurofilament light protein; Q4W, every month; Q8W, every 2 months.

CSF Tau levels in the Q8W arm decrease to within expected natural history range at 15 months

Data points represent mean values and error bars represent ±1 standard deviations.

At the time of the data cut-off (18 July 2019) 43 out of the 46 patients had reached the 15-month visit timepoint (Q4W: n=22, Q8W: n=21), three patients were enrolled in the study 3 months after all other study participants and the 15-month visit had not been conducted at time of data cut-off.

* HD-CSF trendline was interpolated from baseline and 24-month data points from early HD sample of HD-CSF. See poster number 91 for HD-CSF results.

BL, baseline; CSF, cerebrospinal fluid; HD, Huntington’s disease; NfL, neurofilament light protein; Q4W, every month; Q8W, every 2 months.

Tau increases expected in untreated HD (estimated ~15% median increase at 15 months [HD-CSF])

Roche HD NHS data will provide comparator in matched sample with equal follow-up
Exploratory fluid biomarker summary

• Based on published literature, NfL appears relevant in HD and NfL and Tau levels are expected to increase in untreated HD\textsuperscript{1,2}

• NfL levels increase then decrease on continued treatment, with Tau following the same trend

• No associations were observed between NfL or Tau increases and adverse events

HD, Huntington’s disease; NfL, neurofilament light protein.
Exploring potential mechanisms underlying the observed NfL changes

- Neurofilaments appear in aggregates in HD and may be mis-localised in HD neurons\(^1,2\)

- Neurofilament is under negative transcriptional regulation by mHTT\(^3\)

**Potential underlying mechanisms**

<table>
<thead>
<tr>
<th>ASO exposure</th>
<th>Non-sustained effects on vulnerable cell populations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reorganisation/remodelling of cells</td>
</tr>
<tr>
<td></td>
<td>Changes in CSF flow dynamics</td>
</tr>
<tr>
<td></td>
<td>Clearance and/or disposition of CNS proteins</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HTT lowering</th>
<th>Non-sustained effects on vulnerable cell populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mHTT and/or wild-type HTT)</td>
<td>Reorganisation/remodelling of cells</td>
</tr>
<tr>
<td></td>
<td>mHTT toxic species sparing in cells</td>
</tr>
<tr>
<td></td>
<td>Aggregate clearing effect in cells</td>
</tr>
</tbody>
</table>

Potential underlying mechanisms*

Progressive loss of neurofilament staining in the human cortex immunostained with SMI-35\(^1\)

Control

Pre-HD

Late-stage HD

The mechanisms underlying observed treatment-induced NfL changes are under investigation

* See poster 110 for ongoing Roche/Genentech/Ionis/academy ongoing preclinical and mechanistic experiments and poster 28 on the role of NfL as a biomarker in HD.

ASO, antisense oligonucleotide; CNS, central nervous system; CSF, cerebrospinal fluid; HD, Huntington’s disease; HTT, huntingtin protein; mHTT, mutant HTT; NfL, neurofilament light protein; SMI-35, mouse anti-phosphorylated neurofilament.

Tominersen’s Clinical Development Programme for HD

* An additional 8 patients may be included to allow investigation of additional dose levels and repeat doses if necessary.

CSF, cerebrospinal fluid; HD, Huntington’s disease; OLE, open-label extension; PD, pharmacodynamics; PK, pharmacokinetics.

2. Clinicaltrials.gov/show/NCT03342053 (Accessed February 2020);
3. Clinicaltrials.gov/show/NCT03664804 (Accessed February 2020);
4. Clinicaltrials.gov/show/NCT03761849 (Accessed February 2020);
5. Clinicaltrials.gov/show/NCT03842969 (Accessed February 2020);

Longer-term follow-up will ultimately inform clinical outcomes of tominersen and the potential prognostic and predictive value of the candidate markers in the context of tominersen treatment of HD.
Overall summary of tominersen clinical development

- Preliminary data from the 15-month OLE study has been used to further inform the tominersen Clinical Development Programme
  - The strength of the 120 mg tominersen effect on CSF mHTT allowed for amendment of GENERATION HD1 for testing less frequent regimens (Q8W and Q16W)
  - Additional collaborative mechanistic studies are ongoing to further understand the observed changes in exploratory fluid biomarkers in the OLE study
- The programme will continue to generate data for tominersen, its effects on biomarkers and, ultimately, on clinical outcomes
  - OLE vs Roche HD NHS comparison; Phase III GENERATION HD1 study

Many thanks to the HD community for the ongoing collaboration as we execute the studies of the Roche/Genentech/Ionis tominersen Clinical Development Programme

To access this presentation go to https://bit.ly/2tK3W0D

CSF, cerebrospinal fluid; HD, Huntington's disease; mHTT, mutant huntingtin protein; NHS, Natural History Study; OLE, open-label extension; Q8W, every 2 months; Q16W, every 4 months.