American Academy of Neurology (AAN) 2019 Congress
Roche Analyst Audio Webcast

Monday, 13 May 2019
Welcome
Karl Mahler, Head of IR

Overview of Roche key data at AAN

Ocrevus benefit on disease progression in multiple sclerosis and long term safety

Satralizumab positive phase III SakuraSky in neuromyelitis optica spectrum disorder

Risdiplam phase III studies in Type 1, 2 & 3 spinal muscular atrophy confirm strong patient benefit

RG6042 bimonthly dose confirmed for phase III program in Huntington's disease

Paulo Fontoura, Global Head Neuroscience and Rare Diseases Clinical Development

Roche Neuroscience and Rare Disease franchise update

Karsten Jung, Therapeutic Area Head Neuroscience and Rare Diseases, Global Product Strategy

Q&A
Roche’s Neuroscience pipeline
Leading the rejuvenation of the pharma business and expanding into new therapeutic areas

Neuroscience NME’s in Phase I-III in clinical development*

<table>
<thead>
<tr>
<th>Company</th>
<th>NMEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biogen</td>
<td>13</td>
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<tr>
<td>Roche</td>
<td>17</td>
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<tr>
<td>Takeda</td>
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<td>Novartis</td>
<td>6</td>
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<tr>
<td>Eli Lilly</td>
<td>4</td>
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<td>Pfizer</td>
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<tr>
<td>AstraZeneca</td>
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<td>Eli Lilly</td>
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<td>Novartis</td>
<td>10</td>
</tr>
<tr>
<td>Roche</td>
<td>17</td>
</tr>
</tbody>
</table>

*Company pipeline websites, accessed May 2019

Roche Neuroscience pipeline

Phase 1 (2 NMEs)
- RD7616
- RD6006

Phase 2 (4 NMEs)
- Prasinezumab
- RD36100
- RD7908
- RD7916

Late Stage (7 NMEs)
- Ocrelizumab
- RG1450
- RG7916
- RG0620
- RG6442

Launched

*Company pipeline websites, accessed May 2019
Overview of Roche key data at AAN
Paulo Fontoura, M.D.
Global Head Neuroscience and Rare Diseases Clinical Development
Ocrevus benefit on disease progression in multiple sclerosis and long term safety

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Neuroscience franchise: Ocrevus in MS

US label covers ~90% of MS patients including “active SPMS”

- The first and only treatment approved for both forms of MS
- OCREVUS offers the first-ever approved treatment for PPMS, a highly disabling form of the disease in which disability accumulates twice as quickly as in RMS

Now approved in over 85 countries, with over 100,000 patients treated globally
Higher exposure to Ocrevus correlated with a reduced risk of disability progression in ORATORIO and OPERA clinical trials

- Highlighting the importance of starting and maintaining approved dosing

IFN=interferon; OCR=ocrelizumab; RMS=relapsing multiple sclerosis; Q=quartile
Kletzl et al, AAN 2019
Importance of B-Cell depletion level in 24W-CDP (RMS)
Lower B cell levels are correlated with delayed CDP

*Higher exposure to Ocrevus correlated with lower B-cell levels and lower rates of disability progression*

IFN=interferon; OCR=ocrelizumab; RMS=relapsing multiple sclerosis; 24W-CDP=24 week-confirmed disability progression
Kletzl et al, AAN 2019
Long term data of over five years show that earlier treatment with Ocrevus significantly reduces risk of permanent disability progression

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RMS Reduction</th>
<th>PPMS Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDP</td>
<td>57% (p&lt;0.001)</td>
<td>29% (p=0.018)</td>
</tr>
<tr>
<td>CDP-T25FW</td>
<td>49% (p&lt;0.01)</td>
<td>27% (p=0.010)</td>
</tr>
<tr>
<td>CDP-9HPT</td>
<td>58% (p=0.07)</td>
<td>50% (p&lt;0.001)</td>
</tr>
<tr>
<td>CCDP3</td>
<td>52% (p&lt;0.001)</td>
<td>29% (p=0.002)</td>
</tr>
</tbody>
</table>

RMS- time to onset of CDP for at least 48 weeks during the DBP and OLE periods

PPMS- time to onset of CDP for at least 48 weeks during the DBP, ECP and OLE (ITT population)

OCR=ocrelizumab; DBP=double-blind period; ECP=extended controlled period; EDSS=Expanded Disability Status Scale; OLE=open-label extension; CDP=confirmed disability progression; 9HPT=9-Hole Peg Test; T25FW=Timed 25-Foot Walk; CCDP=composite confirmed disability progression (defined as increase in EDSS, 20% increase in 9-Hole Peg Test or 20% increase in Timed 25-Foot Walk)

Hauser et al, AAN 2019 and Wolinsky et al, AAN 2019
Ocrevus long term risk/benefit profile in RMS and PPMS confirmed

*Over 100,000 patients treated*

- Safety data presented at AAN from OCREVUS clinical trials remain consistent with the medicine’s favourable benefit-risk profile
- No change in the type or pattern of serious infections identified by year in patients
- Rate of malignancies in Ocrevus-treated patients remained within the range reported in epidemiological data
- Post-marketing data remain consistent with that observed in clinical trials

Hauser et al, AAN 2019
Summary

• Ocrevus effect on reducing the risk of disability progression is associated with higher exposure and lower B-cell levels.

• Long-term data from the Ph III OPERA and ORATORIO trials showed earlier treatment with Ocrevus significantly reduced the risk of permanent disability progression.

• Long term safety data remain consistent with findings from the controlled Ph III trials, supporting Ocrevus favourable benefit-risk profile.
Ocrevus benefit on disease progression in multiple sclerosis and long term safety

**Satralizumab positive phase III SakuraSky in neuromyelitis optica spectrum disorder**

Risdiplam phase III studies in Type 1, 2 & 3 spinal muscular atrophy confirm strong patient benefit

**RG6042 bimonthly dose confirmed for phase III program in Huntington's disease**
Neuromyelitis optica spectrum disorder (NMOSD)  
A rare and debilitating autoimmune CNS disease

**Clinical presentation**

- Most common: optic neuritis and/or longitudinally extensive transverse myelitis
- Symptoms: blindness, severe motor disability, sensory disturbances, neuropathic pain
- Relapsing; disability can accumulate with each subsequent attack
- Pathogenic autoantibodies (AQP4-IgG) detectable in 70 to 80% of patients
- Approximately 40% of patients with NMOSD are first misdiagnosed as having MS

**Approved tx options**

IL-6 is a key driver in the pathogenesis of NMOSD

**Per 100,000**

- Blind within 5 years
- Require wheelchair

**Female : Male prevalence**

- 9:1

**Approved tx options**

- ~5

AQP4-IgG=antibodies against aquaporin; MS=multiple sclerosis
**Satralizumab**

*Recycling antibody designed to sustain consistent inhibition of IL-6 signaling*

**Target:** IL-6 receptor (IL-6R)

**Molecule:** Humanized monoclonal IgG2 antibody; high-affinity binding to soluble and membrane-bound IL-6R

Blocks IL-6 signalling

**SMART-IgG2 antibody**

- Antibody clearance is reduced
- Binds to the antigen multiple times

- Engineered to enable maximal suppression of IL-6 signalling, minimise safety risks in a chronic disease and convenient SC dosing Q4W
Satralizumab Phase III clinical trial program in NMOSD

Two pivotal ph III studies in a clinically relevant population (AQP4+/-) as add-on treatment (SA307) or monotherapy (SA309)

Main inclusion criteria

- Aged from 12 to 74
- NMO (AQP4+/-) or NMOSD (AQP4+) patients
- ≥2 relapses in last 2 years (≥1 relapse in last year)
- **Add-on to baseline immunosuppressive therapy (AZA, MMF, and/or OCs)**

End of double-blind period

- Total number of protocol-defined relapses reaches 26
- **Met primary endpoint**
- Presented at ECTRIMS 2018 and AAN 2019

Study results

- Total number of protocol-defined relapses reaches 44
- **Met primary endpoint**
- To be presented at an upcoming conference

(n=83)  (n=95)

**NMOSD**= Neuromyelitis Optica Spectrum Disorder; **AZA**= azathioprine; **MMF**= mycophenolate mofetil; **OCs**= oral corticosteroids; **AQP4-IgG**= antibodies against aquaporin 4
**SAkuraSky: Study design**

- **Group A:** Satralizumab 120 mg + BL§
- **Group B:** Placebo + BL§

- Primary end point at end of double-blind period: total number of protocol-defined relapses reaches 26

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*Last administration; † Last observation; ‡ Relapse adjudicated by CEC; § Baseline treatment: AZA, MMF, OCs. (For patients aged 12–17y, AZA + OCs, MMF + OCs were permitted); ‖ Defined by Wingerchuk et al. 2006 criteria; ¶ Defined by Wingerchuk et al. 2007 criteria with either longitudinally extensive myelitis or optic neuritis; administration of satralizumab or placebo.
BL=baseline treatment; LA=last administration; LO=last observation; Yamamura et al, AAN 2019
Satralizumab met primary endpoint by significantly reducing the risk of protocol-defined relapse (ITT population) in SAkuraSky

Yamamura et al. presented at ECTRIMS 2018. Analysis based on ITT population; p-value based on log-rank test stratified by geographic region and baseline relapse rate. Protocol-defined relapse as adjudicated by the independent clinical endpoint committee. EDSS/FSS was assessed within 7 days of relapse reporting.

AQP4-IgG=antibodies against aquaporin 4; EDSS=Expanded Disability Status Scale; FSS=functional system scores

Yamamura et al, AAN 2019
Satralizumab treatment benefit was generally consistent and maintained across subgroups in SAKuraSky

<table>
<thead>
<tr>
<th>Baseline risk factors</th>
<th>Placebo (n=42)</th>
<th>Satralizumab (n=41)</th>
<th>Favours satralizumab</th>
<th>Favours Placebo</th>
<th>Hazard ratio (log-rank)</th>
<th>p-Value</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>n (events)</td>
<td>n (events)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;18</td>
<td>42 (18)</td>
<td>41 (8)</td>
<td></td>
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<td>0.378</td>
<td>0.0184</td>
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<td>≥18</td>
<td>39 (17)</td>
<td>37 (7)</td>
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<td>0.362</td>
<td>0.0192</td>
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<td><strong>NMO/NMOSD and AQP4 status</strong></td>
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<td>NMO</td>
<td>28 (12)</td>
<td>33 (6)</td>
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<td>0.314</td>
<td>0.0169</td>
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<td>NMOSD</td>
<td>14 (6)</td>
<td>8 (2)</td>
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<td>0.628</td>
<td>0.5813</td>
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<td>NMO and AQP4 negative</td>
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<td>0.063</td>
<td>0.5947</td>
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<td>NMO and AQP4 positive</td>
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<td>19 (1)</td>
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<td>0.082</td>
<td>0.0118</td>
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<td>NMO/NMCSD and AQP4 positive</td>
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<td><strong>Baseline treatment</strong></td>
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<tr>
<td>Azathioprine</td>
<td>13 (7)</td>
<td>16 (5)</td>
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<td>0.621</td>
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<td>Mycophenolate mofetil</td>
<td>8 (2)</td>
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<td>0.000</td>
<td>0.1025</td>
<td>0.9189</td>
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<td>Oral CSs&lt;sup&gt;^&lt;/sup&gt;</td>
<td>20 (8)</td>
<td>17 (1)</td>
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<td>0.152</td>
<td>0.0462</td>
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<td>Azathioprine + oral CSs&lt;sup&gt;^&lt;/sup&gt;</td>
<td>3 (1)</td>
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<td>NE</td>
<td>NE</td>
<td>NE</td>
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<tr>
<td>Mycophenolate mofetil + oral CSs&lt;sup&gt;^&lt;/sup&gt;</td>
<td>1 (1)</td>
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<td>0.3173</td>
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<td>Asia</td>
<td>18 (7)</td>
<td>18 (1)</td>
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<td>0.150</td>
<td>0.0419</td>
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<td>Europe/Other</td>
<td>24 (11)</td>
<td>25 (7)</td>
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<td>0.485</td>
<td>0.1400</td>
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<td><strong>ARR category</strong></td>
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<tr>
<td>1</td>
<td>20 (8)</td>
<td>20 (3)</td>
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<td>0.354</td>
<td>0.1105</td>
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<td>&gt;1</td>
<td>22 (10)</td>
<td>21 (5)</td>
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<td>0.396</td>
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<td><strong>Race category</strong></td>
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<tr>
<td>Japanese</td>
<td>10 (3)</td>
<td>11</td>
<td></td>
<td></td>
<td>0.000</td>
<td>0.0499</td>
<td>0.9907</td>
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<tr>
<td>Non-Japanese</td>
<td>32 (15)</td>
<td>30 (8)</td>
<td></td>
<td></td>
<td>0.514</td>
<td>0.1337</td>
<td>NE</td>
</tr>
</tbody>
</table>

Model is stratified by baseline ARR (1, >1) and geographical region (Asia, Europe/other). Stratified by geographic region only. ** Stratified by baseline ARR only

AQP4 = aquaporin-4; ARR = annualized relapse rate; ORAL CSs = oral corticosteroids

Yamamura et al, AAN 2019
Satralizumab in SAkuraSky significantly reduced the risk of protocol-defined relapse in AQP4-IgG seropositive patients by 79%
Summary

- Satralizumab in SAKuraSky significantly reduces the risk of relapse in patients with NMOSD as an add on therapy to baseline immunosuppressants
  - 62% risk reduction in protocol-defined relapse overall in the ITT population
  - 79% risk reduction in AQP4-IgG seropositive patients
  - 91.5% of AQP4-IgG seropositive patients were relapse free at 46 and 98 weeks
- Efficacy was generally consistent across pre-specified subgroups
- Satralizumab showed a favourable safety profile
Ocrevus benefit on disease progression in multiple sclerosis and long term safety

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FIREFISH Part 1: a typical SMA Type 1 population who initiated treatment at 6.7 months of age

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cohort A (n = 4)</th>
<th>Cohort B (n = 17)</th>
<th>All infants (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>4 (100)</td>
<td>11 (65)</td>
<td>15 (71)</td>
</tr>
<tr>
<td>Age at onset of symptoms (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.7 (2.0–3.0)</td>
<td>1.5 (0.9–3.0)</td>
<td>2.0 (0.9–3.0)</td>
</tr>
<tr>
<td>Age at diagnosis (months)</td>
<td></td>
<td></td>
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<tr>
<td>Median (range)</td>
<td>3.3 (2.5–5.1)</td>
<td>3.0 (0.9–5.4)</td>
<td>3.0 (0.9–5.4)</td>
</tr>
<tr>
<td>Age at enrolment (months)</td>
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<td></td>
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</tr>
<tr>
<td>Median (range)</td>
<td>6.9 (6.7–6.9)</td>
<td>6.3 (3.3–6.9)</td>
<td>6.7 (3.3–6.9)</td>
</tr>
<tr>
<td>CHOP-INTEND score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>23.5 (10.0–25.0)</td>
<td>24.0 (16.0–34.0)</td>
<td>24.0 (10.0–34.0)</td>
</tr>
</tbody>
</table>

Part 1: Dose-finding period followed by open-label extension
- **Cohort A**: Low dose (n = 4)
- **Cohort B**: High dose (n = 17)
- Endpoints: Safety, tolerability, PK and PD

Part 2: Efficacy & safety at the selected dose (n=41)
- **Primary endpoint**: Proportion of infants sitting without support for 5 seconds after 12 months on treatment as assessed by Gross Motor Scale of the BSID-III

CHOP-INTEND, Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; BSID-III, Bayley Scales of Infant and Toddler development Third Edition; SMA=spinal muscular atrophy
Baranello et al AAN 2019
After 12 months of Risdiplam treatment, 19/21 infants (90.5%) were alive & event-free.

Event free in FIREFISH is defined as alive with no permanent ventilation (i.e. no tracheostomy or BiPAP ≥16 hours per day continuously for >3 weeks or continuous intubation >3 weeks, in the absence of, or following the resolution of, an acute reversible event).

The median age at the combined endpoint for subjects with two SMN2 copies was 10.5 months (IQR 8.1–13.6); event free is defined as alive and no need for permanent ventilation (defined as ≥16 hours per day continuously for ≥2 weeks).

There were 3 deaths (unrelated to treatment) after 1, 8, and 13 months of treatment.

Median exposure to treatment: 14.8 months (range: 0.6–26.0)

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*Event free in FIREFISH is defined as alive with no permanent ventilation (i.e. no tracheostomy or BiPAP ≥16 hours per day continuously for >3 weeks or continuous intubation >3 weeks, in the absence of, or following the resolution of, an acute reversible event).†The median age at the combined endpoint for subjects with two SMN2 copies was 10.5 months (IQR 8.1–13.6); event free is defined as alive and no need for permanent ventilation (defined as ≥16 hours per day continuously for ≥2 weeks). Data cut-off: February 2019. BiPAP, Bilevel Positive Airway Pressure


Baranello et al AAN 2019
Risdiplam treatment for 12 months resulted in strong respiratory and bulbar function

- No infant requiring permanent ventilation
- No infant requiring BiPAP support ≥16 hours per day
- No infant requiring awake-assisted ventilation
- No infant has lost the ability to swallow
- 18/19 (94.7%) infants alive at month 12 are able to feed orally or in combination with a feeding tube*
- 15/19 (78.9%) infants are able to feed exclusively by mouth

*1/19 (5.3%) infants alive at Month 12 fed exclusively via a feeding tube. Data cut-off: 27 February 2019.

BiPAP= Bilevel Positive Airway Pressure
Servais et al AAN 2019
Event free is defined as alive with no permanent ventilation (i.e. no tracheostomy or BiPAP ≥ 16 hours per day continuously for >3 weeks or continuous intubation >3 weeks, in the absence of, or following the resolution of, an acute reversible event).

1 infant was unable to swallow at baseline; Data cut-off: 27 February 2019.

BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination, Module 2; SMA, spinal muscular atrophy;
Baranello et al AAN 2019, Servais et al AAN 2019
SUNFISH Part 1: dose-finding study with broad population

**Part 1:** Dose-finding period followed by open-label extension
- Primary endpoints: Safety, tolerability, PK and PD
- Exploratory: efficacy

**Part 2:** Efficacy & safety at the selected dose (n=180)
- Placebo-controlled (2:1) for 12 months
- Primary endpoint: MFM

### SUNFISH Part 1: Dose-finding study with broad population

<table>
<thead>
<tr>
<th></th>
<th>SUNFISH Part 1 n=51</th>
<th>Natural history(^1,2) n=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at screening, years, median (range)</td>
<td>7 (2–24)</td>
<td>7.1 (2.1–29.8)(^2)</td>
</tr>
<tr>
<td>Gender, female/male, n (%)</td>
<td>27 (52.9) / 24 (47.1)</td>
<td>44 (54.3) / 37 (45.7)(^1)</td>
</tr>
<tr>
<td>Type 2 SMA, n (%)</td>
<td>37 (73)</td>
<td>53 (65)(^1)</td>
</tr>
<tr>
<td>Type 3 SMA, n (%)</td>
<td>14 (27)</td>
<td>28 (35)(^1)</td>
</tr>
<tr>
<td>Motor function at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walkers, n (%)</td>
<td>7 (13.7)</td>
<td>19 (23.5)(^1) Reported for Type 2 only(^1)</td>
</tr>
<tr>
<td>Sitters, n (%)(^*)</td>
<td>33 (64.7)</td>
<td>19 (23.5)(^1)</td>
</tr>
<tr>
<td>Non-sitters, n (%)(^*)</td>
<td>11 (21.6)</td>
<td></td>
</tr>
<tr>
<td>Scoliosis, n (%)</td>
<td>29 (57)</td>
<td>45 (55.6)(^1)</td>
</tr>
<tr>
<td>Baseline MFM32 total score, mean (SD)</td>
<td>42.85 (15.0)</td>
<td>(n=46)(^2) 52.0 (22.3)</td>
</tr>
</tbody>
</table>

Data cut-off for SUNFISH: 9th Jan 2019.
*Non-sitters are defined as scoring 0 on item 9 of the MFM while sitters scored ≥1 on item 9 of the MFM but did not qualify as ambulant. †Excludes seven patients who performed the MFM20 assessment at baseline. IQR, interquartile range; ITT, intent to treat; MFM20, Motor Function Measure (20 items); MFM32, Motor Function Measure (32 items); SMA, spinal muscular atrophy; SD, standard deviation.
Mercuri et al, AAN 2019
Exploratory efficacy: after 12 months of risdiplam Sunfish Part 1 greatly exceeds natural history in younger and older patients

- The MFM32 is a 32 item assessment classified into 3 domains.
- Each item is measured on a 4-point scale with a total score of 0–100 and with higher scores indicating greater motor function.
- The MFM32 has been validated for measuring motor function in patients with neuromuscular diseases including SMA1,2

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>SUNFISH Part 1</th>
<th>NatHis-SMA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2–11 (n=24)†</td>
<td>2–30 (n=39)</td>
</tr>
<tr>
<td>Total MFM32 change from baseline, mean (SD)</td>
<td>3.47 (3.77)</td>
<td>-1.44 (3.68)</td>
</tr>
<tr>
<td>≥3 point change at Month 12, n (95% CI)</td>
<td>17 (71%) (49–87%)</td>
<td>8 (42%) (20–67%)</td>
</tr>
</tbody>
</table>

*Excludes seven patients who performed the MFM20 assessment at baseline and one patient who had dropped out of the study prior to the Month 12 visit; †excludes seven patients who performed the MFM20 assessment at baseline; ‡excludes one patient who had dropped out of the study prior to the Month 12 visit. Based on change from adjusted baseline. SUNFISH data cut-off: 9th Jan 2019.

SUNFISH Part 1 summary

- All patients in SUNFISH Part 1 have been treated for at least 12 months
  - Part 1 of SUNFISH has helped determine the dose for Part 2 of the study

- Risdiplam has been well tolerated at all doses and there have been no drug-related safety findings leading to withdrawal of any patient

- There have been no drug-related ophthalmological findings to date

- Exploratory MFM results showed an improvement over 12 months with risdiplam treatment compared with natural history in a broad age range of patients with broad functional status at baseline

- Enrolment of SUNFISH Part 2 is complete, and follow-up is ongoing

MFM, motor function measure; PK/PD, pharmacokinetics/pharmacodynamics; SMN, survival of motor neuron.
Ocrevus benefit on disease progression in multiple sclerosis and long term safety

Satralizumab positive phase III SakuraSky in neuromyelitis optica spectrum disorder

Risdiplam phase III studies in Type 1, 2 & 3 spinal muscular atrophy confirm strong patient benefit

RG6042 bimonthly dose confirmed for phase III program in Huntington's disease
RG6042 PK/PD modelling strategy

Build models to:
- characterise PD drug effect – reduction of HTT protein – throughout CNS (brain tissues and CSF)
- determine RG6042 doses and regimens expected to be pharmacologically active

Build/refine preclinical PK/PD model

Collect preclinical data

Collect clinical data

Build/refine clinical population PK/PD model

Select doses & regimens for future clinical trials

- Rodent and NHP PK/PD data
- Scaling to human
- Select doses for clinical studies
- Phase I/IIa study
- Phase II OLE study
- Pool totality of data

ASO=antisense oligonucleotide; CNS=central nervous system; CSF=cerebrospinal fluid; HTT=huntingtin protein; mHTT=mutant HTT; NHP=nonhuman primate; OLE=open-label extension; PD=pharmacodynamic; PK=pharmacokinetic.
Sanwald Ducray et al, AAN 2019
Nine-month OLE data show sustained lowering of mHTT in both dosing regimens

- 120 mg Q8W exceeds trough CSF mHTT threshold for cortex and caudate; 120 mg Q16W for cortex
- Both 120 mg Q8W and Q16W achieve acute CSF mHTT reductions exceeding thresholds

CSF, cerebrospinal fluid; IT, intrathecal; 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.

Sanwald Ducray et al, AAN 2019
Empirical data and model prediction led to amendment of GENERATION HD1 pivotal study to allow less frequent dosing

**Original Protocol**

- LP procedures *every month*
- RG6042 120 mg Q4W
- RG6042 120 mg Q8W
- Placebo Q4W

25 months of dosing

**Revised Protocol**

- LP procedures *every 2 months*
- RG6042 120 mg Q8W
- RG6042 120 mg Q16W
- Placebo Q8W

25 months of dosing
Roche Neuroscience and Rare Disease franchise update
Karsten Jung
Therapeutic Area Head Neuroscience and Rare Diseases, Global Product Strategy
Roche is leading the next wave of innovation in neuroscience

**Neuroimmunology**
- Multiple Sclerosis
- Neuromyelitis Optica Spectrum Disorder

**Neurodegeneration**
- Alzheimer’s Disease
- Huntington’s Disease

**Neuromuscular**
- Spinal Muscular Atrophy
- Duchenne Muscular Dystrophy

**Neurodevelopment**
- Autism Spectrum Disorder

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**Strategic building blocks**

**Pipeline**
- Industry-leading portfolio, diverse modalities, significant R&D investment

**Technology**
- Early adoption of disruptive technology and ‘beyond-the-pill’ offerings

**People & operating model**
- Entrepreneurial mindset, world-class expertise, seamless early–late stage collaboration
Neuroscience and rare diseases portfolio

**Strongly differentiated pipeline**

<table>
<thead>
<tr>
<th>Phase 1 (2 NMEs)</th>
<th>Phase 2 (4 NMEs)</th>
<th>Late Stage (7 NMEs)</th>
<th>Launched</th>
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<tbody>
<tr>
<td><strong>RG7816</strong></td>
<td><strong>RG7935</strong></td>
<td><strong>RG7412</strong></td>
<td><strong>RG1594</strong></td>
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<td>GABA&lt;sub&gt;A&lt;/sub&gt; α&lt;sub&gt;5&lt;/sub&gt; PAM</td>
<td>Prasinezumab</td>
<td>Crenezumab</td>
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<td><strong>RG1450</strong></td>
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<td>ALS</td>
<td>aTau</td>
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<td>CIAS</td>
<td>Satralizumab</td>
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<td>Risdiplam</td>
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<td>Spinal muscular atrophy</td>
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<tr>
<td><strong>Phase 2 (4 NMEs)</strong></td>
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<td><strong>RG1450</strong></td>
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<td><strong>RG6042</strong></td>
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<td>Satralizumab</td>
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<td>Neuro-myelitis optica</td>
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<td>Spinal muscular atrophy</td>
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<td>dystrophy</td>
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*Risdiplam is developed in collaboration with PTC therapeutics and the SMA Foundation; RG6042 (ASO HTT) is developed in collaboration with Ionis Pharmaceuticals CIAS=Cognitive impairment associated with schizophrenia; ALS=Amyotrophic lateral sclerosis; Ms=Multiple sclerosis*
Digital Technology at Roche

<table>
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<tr>
<th>Neuroimmunology</th>
<th>Neurodegeneration</th>
<th>Neuromuscular</th>
<th>Neurodevelopmental</th>
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<tr>
<td><strong>Multiple sclerosis</strong>&lt;br&gt;Floodlight app</td>
<td><strong>Parkinson’s disease</strong>&lt;br&gt;Active &amp; passive assessment</td>
<td><strong>Spinal muscular atrophy</strong>&lt;br&gt;Motor assessment</td>
<td><strong>Autism</strong>&lt;br&gt;Digital therapy development</td>
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<td><strong>Huntington’s disease</strong>&lt;br&gt;Remote sensor device</td>
<td><strong>Duchenne muscular dystrophy</strong>&lt;br&gt;Actimyo – ambulation phenotyping</td>
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**Floodlight* app** – the “neurologist in your pocket

**Gait & posture**
- Balance
- U-Turn
- 2MWT

**In-clinic tests**
- BBS, T25FW, 9HPT

**Cognition**
- SDMT

**Hand & arm**
- Pinching
- Draw a Shape

**Experience**
- Mood
- Symptom
- MSIS-29

**Passive Monitoring**
- Gait
- Mobility

*Montalban et al, AAN 2019*
Multiple Sclerosis
Goal to be market leader in MS

- Ocrevus uniquely differentiated in RMS and PPMS now with over 100,000 patients treated

**Efficacy**
- RMS: Superior to SOC DMT
- PPMS: First therapy to show efficacy in setting

**Safety**
- 100,000+ patients; 5.5-year long term safety data presented; consistent and favourable benefit-risk profile

**Convenience**
- IV – twice yearly

**Access**
- Priced below or similar to high efficacy therapies; broad payer coverage in US, reimbursement ongoing in EU

**US: Total Patient Market Share**
- 16%
  - As of Jan 2019

**#1 New MS prescription in US**
- Since July 2017

**Sales split: RMS/PPMS**
- 70/30
  - As of Feb 2019

**Total MS market USD ~23bn in 2017**

SOC=Standard of Care; RMS=Relapsing Multiple Sclerosis; PPMS=Primary Progressive Multiple Sclerosis; DMT=disease modifying therapy

1 Source: Evaluate Pharma 2. US Symphony claims data Jan’19; *for patients starting a new MS treatment (naive or switch)
Satralizumab: a clearly differentiated novel anti IL-6 antibody for the treatment of NMOSD

- NMOSD is a rare, lifelong, and debilitating autoimmune CNS disorder without an approved DMT
- High levels of IL-6 have been shown in patients with active NMOSD, suggesting a pivotal role for IL-6 in driving the disease

- Robust, durable efficacy demonstrated in ITT population, and especially the AQP4-IgG seropositive patient sub-group
- Evidence as monotherapy as well as add-on to SOC in separate Phase III studies
- Safety profile suitable for long-term use
- A self-administered subcutaneous administration at home every four weeks

Satralizumab was engineered to maximize suppression of IL-6 signalling, minimize safety risks, and enable convenient dosing for patients with NMOSD

- Antibody clearance is reduced
- Binds to the antigen multiple times

NMOSD=neuromyelitis optica spectrum disorder; CNS=central nervous system; DMT=disease-modifying treatment; IL-6=interleukin-6; SOC=standard of care; AQP4-IgG=antibodies against aquaporin
Risdiplam: a novel oral SMN2 modifier in Type 1, 2 and 3 SMA

- SMA is the second most common fatal autosomal recessive disorder after cystic fibrosis and the number one genetic cause of death in infants
- SMA is a severe, progressive, inherited neuromuscular disease leading to loss of motor function and reduced life expectancy
- Spectrum of disease severity/classification (Type 1, 2 and 3)

- Durably increases and sustains SMN protein both in the CNS and in the periphery
- Broad clinical program including FIREFISH (type 1), SUNFISH (type 2 & 3) and RAINBOWFISH (pre symptomatic) Ph II/III studies
- Potentially best in class efficacy profile
- To date well tolerated at all doses assessed

SMA=spinal muscular atrophy; SMN=survival of motor neuron; CNS=central nervous system

Risdiplam is developed in collaboration with PTC therapeutics and the SMA Foundation
Doing now what patients need next