Roche Pharma Day 2019

Late Stage Pipeline Neuroscience

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Clinical Development
# Neuroscience and rare diseases portfolio

## Strongly differentiated pipeline

### Phase 1 (3 NMEs)
- **RG7816**
  - **GABA\(_\alpha_5\) PAM**
  - Autism spectrum disorder
- **RG6000**
  - ALS
- **RG6237**
  - undisclosed

### Phase 2 (4 NMEs)
- **RG7935**
  - prasinezumab
  - Parkinson's
- **RG6100**
  - aTau
  - Alzheimer's
- **RG1662**
  - basmisanil
  - CIAS
- **RG7906**
  - Schizophrenia

### Late Stage (6 NMEs)
- **RG1450**
  - gantenerumab
  - Alzheimer's
- **RG7916**
  - satralizumab
  - NMOSD
- **RG7314**
  - balovaptan
  - Autism spectrum disorder
- **RG7916**
  - risdiplam
  - Spinal muscular atrophy
- **RG6206**
  - anti-myostatin adnectin FP
  - DMD
- **RG6042**
  - ASO HTT
  - Huntington's

### Launched
- **RG1594**
  - Ocrevus
  - MS

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- **2019**
  - FDA filing
  - RD = Rare Diseases

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; NMOSD = Neuromyelitis optica spectrum disorders; DMD = Duchenne muscular dystrophy; MS = Multiple sclerosis; FP = Fusion protein.
Late stage pipeline update

Topics covered in presentations and break-out sessions

1. Hematology franchise
   - CLL: Venclexta Gazyva
   - DLBCL: Polivy, Venclexta
   - NHL, DLBCL: mosunetuzumab, CD20xCD3
   - AML: Venclexta, idasanutlin
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2. Breast Cancer franchise
   - HER2+: Kadcyla, Perjeta, FDC SC, Tecentriq
   - TNBC: Tecentriq, ipatasertib
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   - Melanoma: Tecentriq, Cotellix, Zelboraf
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    - DME, nAMD: faricimab
    - AMD: Port Delivery System ranibizumab
    - GA: ASO factor B
    - Choroideremia: Gene therapy

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    - HCC: Tecentriq, Avastin

12. Other oncology
    - GU: Tecentriq

* For further information on target patient populations please consult the appendix; For further details on the late stage pipeline please consult the HY 18 results presentation appendix or visit the IR homepage
Neuroscience franchise: Ocrevus in MS

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

- The first and only treatment approved for both RMS and PPMS
- 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

Source: 1 Roche analysis of MS prevalence epidemiological studies; RMS=relapsing multiple sclerosis; PPMS=primary progressive MS; SPMS=secondary progressive MS; CIS=clinically isolated syndrome
Long term data of >6 years show: Earlier treatment with Ocrevus significantly reduces risk of permanent disability progression

RMS: time to onset of CDP for at least 24 weeks during the DBP and OLE period of OPERA

PPMS: time to onset of CDP for at least 24 weeks during the DBP and OLE period of ORATORIO

- Earlier treatment with Ocrevus significantly reduced the risk of disability progression and this effect was sustained over time

Giovannoni G. et al, ECTRIMS 2019; Wolinsky J.S. et al, ECTRIMS 2019; IFN=interferon; OCR=Ocrevus; RMS=relapsing multiple sclerosis; 24W-CDP=24 week-confirmed disability progression
Long term data of >6 years show: Earlier treatment with Ocrevus significantly reduces risk of patients needing a wheelchair (EDSS ≥7.0)

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

- Earlier initiation of Ocrevus therapy significantly reduced the risk of becoming wheelchair confined by 42% vs those who switched from placebo

Wolinsky J.S. et al, ECTRIMS 2019; CDP=confirmed disability progression; DBP=double-blind period; ECP=extended controlled period; EDSS=Expanded Disability Status Scale; FU=follow-up; HR=hazard ratio; ITT=intention-to-treat; OCR=ocrelizumab; OLE=open-label extension; PBO=placebo
Higher Ocrevus exposure reduces risk of disability progression

Importance of starting and maintaining approved dosing

Hauser S.L. et al, AAN 2019; IFN=interferon; OCR=Ocrevus; RMS=relapsing multiple sclerosis; PPMS=primary progressive MS; Q=quartile
Importance of B-Cell depletion on disability progression

RMS (OPERA): B cell–stratified 24–week confirmed disability progression (CDP)

• Lower rates of disability progression associated with higher Ocrevus exposure and lower median B cell levels prior to the next infusion

Hauser S.L. et al, AAN 2019; IFN=interferon; OCR=Ocrevus; RMS=relapsing multiple sclerosis; 24W-CDP=24 week-confirmed disability progression
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Risdiplam in type 1/2/3 spinal muscular atrophy (SMA)
Broadest Ph III program with potentially best in class efficacy/safety profile

**SMN2 splicing modifier**

- Oral and systemically available SMN2 splicing modifier
- Durably increases SMN throughout CNS and periphery
- Potentially best in class efficacy profile
- To date well tolerated at all doses assessed

**Broadest Ph III clinical program:**

- Enrolment of SUNFISH and FIREFISH Part 2 is complete, and follow-up is ongoing
- First patients recruited into presymptomatic study (RAINBOWFISH)
- 30 Spinraza-treated patients btw age 1 and 60 recruited into non-naive study (JEWELFISH)
- Filing expected in 2019

Risdiplam in collaboration with PTC Therapeutics and the SMA Foundation
Risdiplam in type 1 SMA (FIREFISH Part 1)

Typical type 1 population starting treatment at 6.7 months of age

**Ph III FIREFISH**

- Type 1 SMA
- 1-7 months old
- Two SMN2 gene copies

**Part 1**: Dose-finding period followed by open-label extension

- **Cohort A**: Low dose (n = 4)
- **Cohort B**: High dose (n = 17)
- EP: 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

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19/21 infants (90.5%) were alive & event-free* after 12m treatment

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**PNCR (Finkel) Natural History Study, 2014**:

- 50% event free
- 25% event free
- 8% event free

- Median exposure to treatment: 14.8 months (range: 0.6-26.0)
- There were 3 deaths (unrelated to treatment) after 1, 8, and 13 months of treatment

- Symptom onset
- Age at enrollment
- Prior to treatment
- Cohort A: high dose
- Cohort B: low dose
- Death

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Baranello et al AAN 2019; Data cut-off: 27 February 2019; # Finkel R, et al. Neurology. 2014; 83:810–817. 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); * 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)
Risdiplam in type 1 SMA (FIREFISH Part 1)
Summary of 12 months of treatment

Cohort A+B (all infants)

- **90.5% (19/21)** of infants are alive and event free* after 12 months of treatment
- **0** infants lost the ability to swallow†
- **0** infants reached permanent ventilation/required tracheostomy
- No drug-related safety findings leading to withdrawal to date

Cohort B (high dose)

- **41% (7/17)** infants were able to sit without support for at least 5 seconds (as assessed by BSID-III)
- **1/17 (6%)** infants were able to stand supporting their weight (as assessed by HINE-2)
- **59% (10/17 infants)** had a CHOP-INTEND score ≥40

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*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. 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.
Risdiplam in type 2/3 SMA (SUNFISH Part 1)
Dose-finding in broad population starting at median of 7 years

Ph III SUNFISH

- Type 2 or 3 SMA
- 2–25 years old

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

12 months after treatment start exploratory efficacy 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 is validated measuring motor function in patients with neuromuscular diseases incl. SMA1,2

<table>
<thead>
<tr>
<th>Domain 1: standing, transfers and ambulation</th>
<th>12 months change from baseline</th>
<th>SUNFISH Part 1</th>
<th>Natural history SMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range (years)</td>
<td>2–11 (n=24)†</td>
<td>12–25 (n=19)‡</td>
<td>2–25 (n=43)*</td>
</tr>
<tr>
<td>MFM32 change from baseline, mean (SD)</td>
<td>3.47 (3.77)</td>
<td>1.64 (3.43)</td>
<td>2.66 (3.70)</td>
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<td>≥3 point change at month 12, n (95% CI)</td>
<td>17 (71%) (48–87%)</td>
<td>8 (42%) (20–67%)</td>
<td>25 (58%) (42%–73%)</td>
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**Notes:**
- 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; MFM=Motor Function Measure. 1. Béillard C, et al. Neuromuscul Disord. 2005; 15:463–470; 2. Vuillerot C, et al. Ann Phys Rehabil Med. 2013; 56:673–686
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Satralizumab in NMOSD

Recycling Ab for maximal inhibition of IL-6 signaling

- Recycling mAb with high-affinity to soluble and membrane-bound IL-6 receptor
- Engineered to enable maximal inhibition of IL-6 signalling
- Convenient SC Q4W dosing at home

- NMOSD is a debilitating, chronic, autoimmune CNS disease with lesions in the optic nerves and spinal cord
- IL-6 is thought to impact B-cell mediated pathogenesis incl. AQP4 auto-antibody production
- Robust, durable efficacy demonstrated in AQP4+/- patients either as add-on therapy to SOC (Ph III SAKuraSky) or as monotherapy (Ph III SAKuraStar)

NMOSD=neuromyelitis optica spectrum disorder; CNS=central nervous system; AQP4=aquaporin; SOC=standard of care
**Neuromyelitis optica spectrum disorder (NMOSD)**

*A rare and debilitating autoimmune CNS disease*

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<th>IL-6 is a key driver in the pathogenesis of NMOSD</th>
<th>Satoralizumab efficacy/safety profile</th>
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<td><img src="image" alt="Clinical manifestation" /></td>
<td><img src="image" alt="Highly effective" /></td>
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**Clinical manifestation**
- Optic neuritis and/or longitudinally extensive transverse myelitis
- Blindness, severe motor disability, sensory disturbances, neuropathic pain
- Relapsing: Disability can accumulate with each subsequent attack
- Anti-AQP4 autoantibodies in 70 to 80% of patients
- ~40% of patients with NMOSD are first misdiagnosed as having MS

**Satralizumab efficacy/safety profile**
- **Highly effective**
  - Comparable efficacy to best in disease treatments
- **Flexible and convenient**
  - Only treatment studied as monotherapy and in combination with immunosuppressants
  - Convenient Q4w SC dosing
  - Broadest flexibility on patient profile (AQP4+/−, only treatment for adolescent)
  - Unique mechanism of action
- **Favourable safety profile**
  - Lower rate of infections incl. serious infections

**Per 100,000**

- 1/2 Blind within 5 years
- 5/1 Female/male

| ~5 Blind within 5 years Require wheelchair | Per 100,000 |

AQP4=aquaporin 4; MOA=mechanism of action; Q4W=every 4 weeks; SC=subcutaneous
Satralizumab as add-on therapy in NMOSD
79% relapse risk reduction in AQP4+ patients

Ph III results add-on therapy (SAkuraSky):

- As add-on therapy to baseline immunosuppressive therapy risk of relapse in the ITT population was reduced by 62%, in the AQP4+ patients by 79% with 91.5% of AQP4+ patients being relapse free at 48 and 96 weeks
- Efficacy was generally consistent across pre-specified subgroups

Yamamura et al. 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. CI=confidence interval; EDSS=Expanded Disability Status Scale; FSS=functional system scores; ITT=intent to treat
Satralizumab as monotherapy in NMOSD
74% relapse risk reduction in AQP4+ patients

Ph III results monotherapy (SAkuraStar):

- Relapse risk was reduced by 55% in the ITT population with 76% and 72% of patients being relapse-free at week 48 and 96, respectively.
- Relapse risk was reduced by 74% in AQP4+ patients (not affected by prior therapy or most recent attack type) with 83% and 77% being relapse-free at week 48 and 96, respectively.

Bennett J.L. et al., ECTRIMS 2019; Analysis based on ITT population; p-value (based on log-rank test) and hazard ratio (using Cox proportional-hazards model) stratified by prior therapy for prevention of NMOSD attack (B-cell-depleting or immunosuppressants/other) and by most recent attack in the year prior to screening (first attack vs relapse); CI=confidence interval; HR=hazard ratio; ITT=intention to treat
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HTT-ASO in Huntington’s disease

First drug to reduce toxic mHTT

Antisense RNA targeting total HTT

- Antisense drug binds to wtHTT and mHTT sequence leading to RNase H1 mediated degradation of wild-type and mutant HTT mRNA
- Addresses all patients

Phase II update:

mHTT CSF levels from 9 month OLE cut

- 9 month OLE data show sustained lowering of CSF mHTT in both dosing regimens (Q4W; Q8W) achieving the target reduction range of 30-50%
- Safe and well tolerated with no dose-limiting toxicities identified

Sanwald Ducray P. et al, AAN 2019; mHTT=mutant huntingtin; wtHTT= wild-type huntingtin; CSF=cerebrospinal fluid; OLE=open-label extension; Q4W=every 4 weeks; Q8W=every 2 months; IT=intrathecal; HTT-ASO licensed from IONIS Pharmaceuticals
HTT-ASO in Huntington’s disease

Ph III development program underway

Simulation of Q8W and Q16W dosing to achieve pharmacologically relevant effect (120 mg IT)

- Ph II OLE data and PK/PD modelling led to amendment of Ph III (GENERATION HD1) study to allow less frequent dosing (Q8W; Q16W)
- First patients recruited for new Ph III protocol in Q3
- Ph II OLE and HD Natural history study continue to provide data to inform the development program
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Balovaptan in autism spectrum disorder (ASD)

Early positive data from first Ph II study in adults

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- Oral, selective V1a receptor antagonist
- Vasopressin V1a receptor modulates social behavior and is implicated in ASD
- Good pharmacokinetic profile and well tolerated in Ph I and II studies

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<th>2020</th>
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- Ph II (VANILLA) in adult men: Primary endpoint (SRS-2) not met; however dose dependent treatment effect on the Vineland™-II composite score shows significant improvement in socialization and communication; Published in *Science Translational Medicine*
- Digital biomarkers development for autism to quantify change in core ASD symptoms
- Ph II study (aV1ation) in children and adolescents with ASD ongoing, with Vineland™-II being the primary endpoints; Results expected in 2020
- Ph III trial (V1aduct) in adults with ASD on-going; results expected in 2020

ASD=autism spectrum disorder; SRS-2=social responsiveness scale-2; Vineland™-II=Vineland Adaptive Behavior Scale 2nd Edition
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   - CLL: Venclexta, Gazyva
   - DLBCL: Polivy, Venclexta
   - NHL, DLBCL: mosunetuzumab, CD20xCD3
   - AML: Venclexta, idasanutlin
   - MM: Venclexta

2. **Breast Cancer franchise**
   - HER2+: Kadcyla, Perjeta, FDC SC, Tecentriq
   - TNBC: Tecentriq, ipatasertib
   - HR+: ipatasertib; PI3Kα inhibitor

3. **Lung Cancer franchise**
   - NSCLC: Tecentriq
   - ALK+: Alecensa
   - ROS1+/NTRK+: Rozlytrek

4. **GU franchise**
   - mUC: Tecentriq
   - CRPC: ipatasertib

5. **Pan tumor**
   - NTRK+ tumors: Rozlytrek

6. **Other oncology**
   - Melanoma: Tecentriq, Cotelpic, Zelboraf
   - OC: Tecentriq, Avastin
   - HCC: Tecentriq, Avastin

7. **Hemophilia A**
   - Hemlibra

8. **Infectious diseases**
   - Influenza A/B: baloxavir marboxil

9. **Immunology**
   - Lupus nephritis: Gazyva
   - Ulcerative colitis: etrolizumab
   - Crohn’s disease: etrolizumab
   - Food allergy: Xolair
   - Nasal polyps: Xolair

10. **Neuroscience**
    - MS: Ocrevus update
    - SMA: risdiplam
    - NMOSD: satralizumab
    - Huntington’s disease: HTT-ASO
    - Autism: balovaptan
    - Parkinson’s disease: prasinezumab

11. **Ophthalmology**
    - DME, nAMD: faricimab
    - AMD: Port Delivery System ranibizumab
    - GA: ASO factor B
    - Choroideremia: Gene therapy

*For further information on target patient populations please consult the appendix; For further details on the late stage pipeline please consult the HY 18 results presentation appendix or visit the IR homepage*
Prasinezumab in Parkinson’s disease

First drug to reduce toxic forms of α-synuclein

**Anti-α-synuclein mAb**

- Humanized mAb designed to target aggregated forms of α-synuclein
- Potentially inhibiting neuron-to-neuron transfer of presumed pathogenic forms of α-synuclein, resulting in neuronal protection and slowing progression

**Ph I results:**

- 97% reduction of free α-synuclein serum level after single infusion at highest dose
- Prasinezumab reaches CSF concentrations expected to engage extracellular aggregated α-synuclein in the brain
- Digital endpoints in development for remote and frequent monitoring of symptoms
- Ph II data from Part 1 of the study expected in 2020

**Digital endpoint development:**

- Provided smart phone
- Automatic Wi-Fi data transfer

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Jankovic J. et al, JAMA Neurol. 2018 Jun 18; Lipsmeier et al, Mov.Dis. April 2018; CSF=cerebrospinal fluid; Prasinezumab partnered with Prothena
Developing digital biomarkers in Neuroscience

Digital endpoints for drug development, improved diagnosis & treatment
Developing digital biomarkers in Neuroscience
Collect, process, analyse data to gain clinical knowledge

Develop behavioural tests
Data processing & analysis
Clinical knowledge
Digital biomarkers allow remote patient monitoring
Longitudinal resolution of symptom dynamics & real-world performance

Day in the life of a patient with weak symptoms
Digital biomarkers allow remote patient monitoring

Longitudinal resolution of symptom dynamics & real-world performance

Day in the life of a patient with weak symptoms

Day with a visit to the clinic or physician
Digital biomarkers allow remote patient monitoring

*Longitudinal resolution of symptom dynamics & real-world performance*
Digital biomarkers allow remote patient monitoring

*Longitudinal resolution of symptom dynamics & real-world performance*
Digital biomarkers in Multiple sclerosis

Floodlight: A neurologist in your pocket

Defining new endpoints and improving standard of care

Validating digital outcomes with traditional clinical endpoints for measuring disease progression

- Ph IIIb (ORATORIO-HAND), placebo-controlled: Ocrevus in PPMS including patients in wheelchairs and using upper limb function as 1EP
- Ph IIIb (CONSONANCE and ENSEMBLE) studies with Ocrevus across progressive MS spectrum
- FLOODLIGHT OPEN: Large (N=~10,000) non-interventional global study detecting and measuring progression initiated in Q2 2018

Midaglia L. et al., J Med Internet Res. 2019 Aug 30;21(8):e14863. doi: 10.2196/14863; MS=multiple sclerosis; PPMS=primary progressive MS; 1EP=primary end point
Digital biomarkers in Parkinson’s disease
Continuous monitoring during Ph II development (PASADENA)

High adherence: Active tests performed on 5-6 days/week

Excellent test-retest reliability

Strong clinical relationship: All active tests significant (p ≤ 0.001)

Taylor et al., Oral Presentation at ADPD 2019
# Digital biomarker development in Neuroscience

*Describing abnormalities across diseases*

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Cognition</th>
<th>Hand Motor Function</th>
<th>Gait &amp; balance</th>
<th>Vocalization</th>
<th>Activity &amp; sociability</th>
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Doing now what patients need next