Roche Pharma Research and Early Development (pRED)
Early Drug Development Investor Relations Event 2019
This presentation contains certain forward-looking statements. These forward-looking statements may be identified by words such as ‘believes’, ‘expects’, ‘anticipates’, ‘projects’, ‘intends’, ‘should’, ‘seeks’, ‘estimates’, ‘future’ or similar expressions or by discussion of, among other things, strategy, goals, plans or intentions. Various factors may cause actual results to differ materially in the future from those reflected in forward-looking statements contained in this presentation, among others:

1. pricing and product initiatives of competitors;
2. legislative and regulatory developments and economic conditions;
3. delay or inability in obtaining regulatory approvals or bringing products to market;
4. fluctuations in currency exchange rates and general financial market conditions;
5. uncertainties in the discovery, development or marketing of new products or new uses of existing products, including without limitation negative results of clinical trials or research projects, unexpected side-effects of pipeline or marketed products;
6. increased government pricing pressures;
7. interruptions in production;
8. loss of or inability to obtain adequate protection for intellectual property rights;
9. litigation;
10. loss of key executives or other employees; and
11. adverse publicity and news coverage.

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Agenda

Welcome
• Karl Mahler, Head of Investor Relations

Overview and introduction to Roche pRED
• William Pao, Head of Roche Pharma Research and Early Development

Oncology
• Christian Rommel, Global Head of pRED Oncology

Neuroscience
• Azad Bonni, Global Head of pRED Neuroscience and Rare Diseases

Ophthalmology
• Sascha Fauser, Global Head of pRED Ophthalmology

Closing and Q&A
Roche transitioning: Replace and extend the business

<table>
<thead>
<tr>
<th>Replace/extend existing businesses</th>
<th>Entering new franchises</th>
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<tr>
<td>MabThera/Rituxan</td>
<td><strong>MS:</strong> Ocrevus</td>
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<td><strong>Hemophilia A:</strong> Hemlibra</td>
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<td>Herceptin</td>
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<td><strong>CNS:</strong> NMOSD, SMA, Huntington’s, Autism, Alzheimer’s</td>
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<tr>
<td>Avastin</td>
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<td>Lucentis</td>
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<td>Tamiflu</td>
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<tr>
<th>Significant near term contribution from pRED to Roche pipeline</th>
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<tbody>
<tr>
<td><strong>risdiplam:</strong> Positive update on longer follow up for FIRE- and SUNFISH (Type 1,2,3 data at WMS). Filing on track for H2 2019</td>
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<tr>
<td><strong>satralizumab:</strong> Filed in EU/US</td>
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<tr>
<td><strong>Xofluza:</strong> Ph III positive data in children (miniSTONE2) in Q3. Worldwide filing continuing and transmission studies ongoing.</td>
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<tr>
<td><strong>idasanutlin:</strong> Ph III MIRROS In r/r AML expected in 2020</td>
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<tr>
<td><strong>faricimab:</strong> PH III program in DME and nAMD. DME data expected in 2020</td>
</tr>
<tr>
<td><strong>HTT ASO:</strong> Phase III ongoing and recruiting quickly</td>
</tr>
<tr>
<td><strong>gantenerumab:</strong> Phase III program fully recruited</td>
</tr>
<tr>
<td><strong>balovaptan:</strong> Phase III adult program ongoing. Data from Ph II in children 2020</td>
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<tr>
<td><strong>prasinezumab:</strong> Phase II data in Parkinson’s expected 2020</td>
</tr>
<tr>
<td><strong>basmisanil:</strong> Phase II data in schizophrenia expected 2020</td>
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</table>

FDC=fixed dose combination; NMOSD=neuromyelitis optica spectrum disorder; SMA=spinal muscular atrophy
Introduction to Roche Pharma Research and Early Development (pRED)

William Pao | Head of Roche Pharma Research and Early Development
The Roche Group organisational structure
Roche pRED is one of three independent research & development units

Academia and industry

>150 partners

Partnering

Roche Group

Independent R&D units

pRED

gRED

Chugai

Diagnostics

Worldwide execution

Product Development

Technical Operations

Product Strategy
Roche pRED leaders

Scientific experts who have the ability to inspire, collaborate and drive for results

Head of Roche pRED
William Pao

Operations
Bryn Roberts

I2O
Gijs van den Brink

NRD
Azad Bonni

Oncology
Christian Rommel

Chief of Staff
Yvette Miata Petersen

Business Partners

Communications
Vivienne Schneider

Finance
Carmen Kerschbaum

Human Resources
Claire Bennett

Pharmaceutical Sciences
Thomas Singer

Strategy, Portfolio & Clinical Operations
Stefan Frings

Therapeutic Modalities
Sylke Poehling
The Roche pRED innovation centres
Global reach and diversity with 2,400 employees at seven sites
The Roche Group is investing in Roche pRED’s long-term future 1.63 bCHF to support breakthrough discovery and early drug development.
Foundation for Roche pRED early drug development

Core scientific principles anchoring successful drug discovery

Deep understanding of disease biology

- Identify the right target in the right disease

Fit for purpose molecules

- Develop the right drug with the right format

Personalised healthcare

- Evaluate in the right patient at the right time
Roche pRED’s contributions to launching new medicines
Science and innovation have been keys to success

Newly launched medicines since 2012

Roche pRED supported development

pRED molecules under full development

- CD20XCD3 TCB - NHL
- idasanutlin – AML
- cibisatamab – MSS CRC
- gantenerumab – AD
- balovaptan – autism
- HTT ASO – HD
- faricimab – DME/AMD
- crovalimab – PNH

AML=acute myelogenous leukemia; MSS CRC=microsatellite stable colorectal cancer; AD=Alzheimer’s Disease; SMA=spinal muscular atrophy; HD=Huntington’s Disease; DME=diabetic macular edema; AMD=age-related macular degeneration; PNH=paroxysmal nocturnal hemoglobinuria; TCB=T-cell bispecific; NHL=Non-Hodgkin Lymphoma
Roche pRED delivering “firsts” for Roche
Creating new opportunities across all therapeutic areas and modalities

CEA CD3 TCB (cibisatamab)
First T cell engager in solid tumors

risdipram
First oral small molecule treatment for spinal muscular atrophy

VEGF-ANG2 BsAb (faricimab)
First bi-specific antibody for the eye

idasanutlin
First in class small molecule mdm2/p53 inhibitor

ASO HTT
First disease-modifying therapy for Huntington’s disease

Xofluza
First “one & done” treatment for influenza infection
2019 Roche pRED portfolio

Pre-LIP NME development across multiple disease areas

**I2O**

**Neuroscience & Rare Disease**

**Oncology**

- **Immunology:**
  - Inflammatory bowel disease
  - Obstructive lung disease
- **Infectious Diseases:**
  - Hepatitis B virus
  - Multi-drug resistance antibiotics
- **Ophthalmology:**
  - AMD
  - DME
  - GA

- **Neuroscience:**
  - Parkinson’s disease
  - Autism
  - Multiple sclerosis
  - Alzheimer’s disease
  - Schizophrenia
- **Rare Diseases:**
  - Huntington’s disease
  - Angelman’s syndrome
  - Progressive supranuclear palsy
  - SCA-spinocerebellar ataxia

- **Cancer Immunotherapy:**
  - 1st generation immune cell generators
  - T-cell engagers, immune cell modulators
  - Immunokinases
- **Molecular Targeted Therapy**
- **Pretargeted radiotherapy**
- **Cellular antigen presenting cell based vaccine**
- **Synthetic biology**
- **Cell therapy (ACT)**

LIP=Life Cycle investment point; NME=New molecular entity; DME=diabetic macular edema; AMD=age-related macular degeneration; GA=geographic atrophy
Roche pRED’s contribution to Roche’s future pipeline
NME submissions and additional indications 2019-2021

2019

2020

2021

2022 and beyond

✓ Indicates submission to health authorities has occurred
Unless stated otherwise submissions are planned to occur in US and EU

New Molecular Entity (NME)
Additional Indication (AI)
CardioMetabolism
Oncology / Hematology
Immunology
Infectious Diseases
Neuroscience
Ophtalmology
Other
FDC = fixed-dose combination
*Individualized NeoAntigen Specific Immunotherapy
Expanding our range of modalities to make drugs against new targets

*Seeking the next wave of technologies*

<table>
<thead>
<tr>
<th>Small molecules</th>
<th>Large molecules</th>
<th>RNA therapeutics</th>
<th>DNA therapeutics</th>
<th>Cellular therapies</th>
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<tbody>
<tr>
<td>![Image](Small molecules)</td>
<td>![Image](Large molecules)</td>
<td>![Image](RNA therapeutics)</td>
<td>![Image](DNA therapeutics)</td>
<td>![Image](Cellular therapies)</td>
</tr>
<tr>
<td>Small molecules to drug ‘undruggable’ targets</td>
<td>Tumor activated TCBs to maximise specificity</td>
<td>Delivery of LNAs to new tissues</td>
<td>Gene therapy for rare diseases &amp; future indications with higher patient numbers</td>
<td>Exploring next generation cellular therapy approaches</td>
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</table>
Organs on a chip: a more human-relevant safety assessment

Striving to improve predictive safety testing

Recapitulate human physiology in vitro

- Patient-derived primary human cells used to recreate organ-like cell systems in vitro
- Mimic organ cross-talk and disease aspects

Application across a number of organs and indications

**Blood-brain barrier**
- Multicellular human model to screen for large molecule transport to the brain supporting new **Brain Shuttle** binder selection and optimization

**Choroid**
- Choroid-on-a-chip model mimicking human vs. monkey tissue architecture enables human risk mitigation for clinical development

**Vascular**
- Perfused blood vessels and circulating immune cells recapitulate vascular injury observed in vivo which enables the derisking of antibody options (e.g. for affinity)
Roche pRED Digital Strategy – enhancing data-driven R&D
Leveraging big data, technology and computational paradigms

Data

- Scale, variety, complexity
- Real world (RWD), real time
- FAIR-ification

Technology

- Sensors, wearables, mobile
- Connected app ecosystem
- IOT, blockchain, cloud

Compute

- High performance compute
- Machine learning (ML)
- Deep learning (DL)

FAIR=Findable, Accessible, Interoperable, Re-usable; IOT=Internet of things
pRED Partnerships
Licenses, collaborations and acquisitions
Oncology at pRED

Christian Rommel | Global Head of pRED Oncology
pRED oncology strategy and focus areas
A balanced portfolio focusing on our strengths and in line with the current state of cancer biology

Invest in game-changing innovation

Diversify with molecular targeted therapy
small molecules

Cancer immunotherapy
small molecules

Win in cancer immunotherapy
small and large molecules

Cancer immunotherapy
large molecules
## pRED Oncology Portfolio - 2019/20

### Molecular targeted therapy
**[Small Molecules (SM)]**
- **Preclinical**:
  - Degrader
  - Cancer Genetics
  - Resistance
  - ~ 10 projects

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Phase 0</th>
<th>Phase I</th>
<th>Phase II</th>
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<tbody>
<tr>
<td>Cancer Gen [SM]</td>
<td>Cancer Gen [SM]</td>
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### Cancer immunotherapy
**[Large Molecules (LM) & Small Molecule]**
- **Preclinical**:
  - Targeted
  - Immune-Generators
  - Immune-Engagers
  - Immune-Modulators
  - ~ 30 projects

<table>
<thead>
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<th>Preclinical</th>
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<th>Phase I</th>
<th>Phase II</th>
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<tbody>
<tr>
<td>MEL-TCB [LM]</td>
<td>aPD1-TIM3 [LM]</td>
<td></td>
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<tr>
<td>OVC-TCB [LM]</td>
<td>aPD1-IL2v [LM]</td>
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<td>GBM-TCB [LM]</td>
<td>aCD25 [LM]</td>
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<tr>
<td>Targ CD19 [LM]</td>
<td>FAP-41BBL [LM]</td>
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<tr>
<td>Targ CD40 [LM]</td>
<td>CD19-41BBL [LM]</td>
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<tr>
<td>CIT [SM]</td>
<td>HCC-TLRa [SM]</td>
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<tr>
<td>CIT [SM]</td>
<td>AML-TCB [LM]</td>
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### Novel approaches
**[Novel Modalities]**
- **Preclinical**:
  - Novel MoA
  - Next Gen Engager
  - Antibody formats
  - ~ 5 projects

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Phase 0</th>
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<tbody>
<tr>
<td>Targ Radiotherapy</td>
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<tr>
<td>Novel modalities ('undruggable')</td>
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</table>

### Novel approaches [Novel Modalities]
- **Preclinical**:
  - Cell Therapy
  - Targeted Radiotherapy
  - Novel modalities
  - ~ 5 projects

<table>
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<td>Novel modalities</td>
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**MM**=multiple myeloma; **MEL**=melanoma; **OVC**=ovarian cancer; **GBM**=glioblastoma

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<table>
<thead>
<tr>
<th>CIT</th>
<th>Generators</th>
<th>Engagers</th>
<th>Modulators</th>
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<tbody>
<tr>
<td></td>
<td>Prime / activate</td>
<td>Inhibit / recognize</td>
<td>Accelerate / remove brake</td>
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</table>
Leveraging our competitive antibody engineering expertise

- Bispecific antigens e.g. PD1-TIM3
- Bispecific antigens e.g. Hemlibra (IXa + X)
- Bivalent antigen binding (2+1) e.g. CD20-CD3 bispecific (next gen: TAC, TCR-like etc.)
- Fab ligand fusion e.g. CD19-41BBL
- Ab-small molecule conjugates e.g. toxin or immune agonists
- Fc engineering e.g. PGLALA, e.g. ADCC
- Fc ligand fusion e.g. FAP-IL2v
CD20 CD3 T-cell bispecific antibody
Developing next-gen therapy for haematologic malignancies

**Mechanism of action**

- Bispecific antibody binds to CD20 on B-cells and CD3 on T-cells, recruiting T-cells to target and destroy B-cells

**Differentiation**

- Novel 2:1 format provides avidity (potential for combinations)
- Greater in vitro potency vs. other formats (10-1000x)
- Undiminished activity in presence of residual aCD20 from previous lines of therapy or with Gazyva pre-treatment
- Ability to combine with other aCD20s, including Gazyva

**Status**

- Late stage development decision May 2019
- Phase I study as monotherapy ongoing
- Phase Ib combinations initiated with:
  - G/R-CHOP - Mar 2018
  - Tecentriq - May 2018
  - Continuous Gazyva - Apr 2018
CD20-TCB induces durable CRs in late-line r/r DLBCL patients
58% OR and 39% CR rates in an aggressive NHL population

Best percentage change in SPD for patients who had on-treatment imaging scans (10mg and 16mg cohorts, n=33)

64 year-old male with complete response after 2nd dose of CD20-TCB (primary refractory transformed lymphoma)

+50% from baseline
CD20-TCB + TECENTRIQ in r/r DLBCL
A large effect size with favourable risk-benefit profile
FAP-4-1BBL
Targeted co-stimulatory T-cell agonist

Mechanism of action
- Binds to tumour stroma via fibroblast activated protein (FAP) and activates T-cells by 4-1BB ligand
- Tumour-dependent cross-linking delivers strong, FcgR-independent signalling

Differentiation
- Best-in-class potential 4-1BB agonist with tumour-targeted activation of T-cells
- Greater agonistic activity
- Less toxicity

Status
- EiH occurred April 2018
- Testing as monotherapy and in combination with Tecentriq, chemotherapy and solid tumour TCBs

uPR in patient with thymic carcinoma, upon 2nd dose (45 mg qw)*

EiH=entry into human
CD25
Depletes Tregs without blocking IL-2

**CD25 binder, does not block IL-2 signalling**

- Binds to CD25 (IL-2Rα). CD25 is most strongly expressed on regulatory T-cells (Tregs) and lower on effector T-cells (Teff).
- Does not block IL-2 binding
- Afucosylation enhances ADCC and optimises depletion of Tregs
- Increasing the Teff:Treg ratio lowers the threshold for immune response in the tumour
- Broadly combinable across immunotherapy treatment modalities

**Mechanism of action**

**Differentiation**

- First and only anti-CD25 that does not block IL-2 signalling
- May result in higher efficacy and superior safety profile
- Afucosylated Fc region for more efficient Treg depletion

**Status**

- EiH January 2020

**High Teff/Treg ratio predicts better outcome in NSCLC & other cancers**

- Low T\text{\textsubscript{reg}} FOXP3\text{\textsubscript{low}}
- High T\text{\textsubscript{reg}} FOXP3\text{\textsubscript{high}}

Cumulative survival

Survival months

CD8\text{\textsuperscript{high}}

CD8\text{\textsuperscript{low}}

p<0.001

EiH=entry into human
Targeted IL2v cytokines
Delivering an immunomodulatory cytokine to tumour stroma or TILs

High avidity binding to FAP on tumour stroma

Mechanism of action
- Binds to fibroblast activation protein (FAP) in tumour stroma to deliver IL-2 (IL2v)
- Lacks preferential induction of regulatory T-cells due to abolished IL-2α receptor (CD25) binding. This enables improved activity and reduced toxicity vs standard IL-2 therapy
- Increases immune infiltration and activates NK and T-cells

Differentiation
- Superior activation of effector cells with less activation of suppressive T-cells
- Better tolerability and better tumour targeting
- Maintained exposure after multiple cycles

Status
- Ph I study as monotherapy ongoing
- Ph Ib with cetuximab in HNSCC ongoing
- Ph II combination studies with Tecentriq in HNSCC, cervical, oesophageal and Keytruda in melanoma ongoing

High avidity binding to PD1+ T cells

Mechanism of action
- Binds to PD1+ T-cells to deliver IL-2 (IL2v) to antigen-experienced TILs
- Enhance expansion, activity & durability of neoantigen-specific T-cells

Differentiation
- Replacing CD25 (IL-2Ra) binding with PD-1
- Reduce toxicity while increasing efficacy

Status
- EiH projected to 1H 2020

EiH=entry into human
FAP-interleukin (IL)-2 variant
Delivering an immunomodulatory cytokine to tumour stroma

Status

• Phase I study as monotherapy ongoing
• Ph1b with cetuximab in HNSCC ongoing
• Phase II combination studies with Tecentriq in HNSCC, cervical, oesophageal and Keytruda in melanoma ongoing

High avidity binding to FAP on tumour stroma

Ph I activity in hard to treat tumours

Data cut-off: 27-July-2018, 43/50 patients were response evaluable
Superior anti-tumour efficacy of PD1-IL2v in s.c. PancO2 model

Increased in-vivo Ag-specific T-cells

muPD1-IL2v is superior to aPD-1 in combination with FAP-IL2v in eradicating the tumour and providing long term survival

Significant increase in tumour infiltration by T-cells in mice treated with muPD-1-IL2v
Pushing towards new frontiers in oncology

**Targeted protein degradation**
- Hijacking cells natural recycling system to target undruggable proteins

**Pre-targeted radiotherapy**
- Pre-targeted delivery of alpha particles to solid tumour (mono- and CIT combination)

**Squeeze APC technology**
- Microfluidic squeezing technology for engineering immune cells as a cancer immunotherapy

APC=antigen-presenting cells; CIT=cancer immunotherapy
## pRED Oncology commitment

<table>
<thead>
<tr>
<th>Committed to enabling Roche to be a CIT leader</th>
<th>Building a pipeline for the future</th>
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<tbody>
<tr>
<td>• &gt;12 CIT assets in phase 0+</td>
<td>• CIT – fit for purpose molecules with superior antibody engineering</td>
</tr>
<tr>
<td>• 13 CIT combinations under investigation</td>
<td>• MTT – novel cancer genetics directed small molecules</td>
</tr>
<tr>
<td>• Active/FiC or BiC assets including a novel TCB platform</td>
<td>• Focus on NMEs with transformative benefit</td>
</tr>
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</table>

CIT=cancer immunotherapy; BiC=best in class; FiC=first in class; NME=new molecular entity; TCB=T-cell bispecific
Neuroscience at pRED

Azad Bonni | Global Head of pRED Neuroscience and Rare Diseases
Neuroscience at pRED
*Disease focus on AD, PD, and MS; pioneering in autism*

**Neurodegenerative disorders**
- Alzheimer’s disease (AD)
- Parkinson’s disease (PD)

**Neuroimmunology**
- Multiple sclerosis (MS)
- Alzheimer’s disease
- Parkinson’s disease

**Neurodevelopmental disorders**
- Autism spectrum disorders (ASD)

**Neurosymptomatic domains**
- CIAS
- Negative symptoms schizophrenia
- Pain, psychiatric manifestations of dementia

*Core:*
- proteinopathies
- compartmentalised CNS pathology and innate immune system biology
- circuit level and synapse dysfunction
- circuit level dysfunction

*Technology and modality enablers:*
- optogenetics, chemogenomics, in vivo electrophysiology, live animal 2 photon imaging, neuroinformatics, LNAs, shuttle
Roche neuroscience and rare diseases portfolio

**Strongly differentiated pipeline**

### Phase 1 (4 NMEs)
- **RG7816**
  - GABA$_A$ α5 PAM
  - Autism spectrum disorder
- **RG6000**
  - DLK inhibitor
  - ALS
- **RG6102**
  - Brain shuttle gantenerumab
  - Alzheimer's
- **RG6237**
  - Neuromuscular disorders

### Phase 2 (4 NMEs)
- **RG7935**
  - Prasinezumab
  - Parkinson’s
- **RG6100**
  - Semorinemab
  - Alzheimer’s
- **RG1662**
  - Basmisanil
  - CIAS
- **RG7906**
  - Schizophrenia

### Late Stage (6 NMEs)
- **RG7412**
  - Crenezumab
  - Familial Alzheimer’s
- **RG1450**
  - Gantenerumab
  - Alzheimer’s
- **RG7916**
  - Satralizumab
  - Neuromyelitis optica
- **RG7916**
  - Balovaptan
  - Autism spectrum disorder
- **RG7915**
  - Risdiplam
  - Spinal muscular atrophy
- **RG6042**
  - ASO HTT
  - Huntington’s

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

---

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.
Parkinson’s Disease: severe motor and non-motor related disability

PD progression cannot be slowed or halted as of today
Prasinezumab

First potential disease-modifier in Parkinson’s Disease (PD)

Mechanism of action

- Humanised monoclonal antibody designed specifically to target soluble and insoluble neurotoxic forms of α-synuclein (α-Syn)
- Potential to slow the progression of the disease by preventing cell-to-cell spreading of pathogenic aSyn aggregates thereby preventing the further loss of neurons

Differentiation vs SOC

- Current treatments have only limited effect on PD motor-and non-motor symptoms
- As a first disease modifier, Prasinezumab is designed to go beyond the management of PD symptoms by slowing disease progression
- Symptomatics are expected to be continued to be used as add-on to prasinezumab

Status

- Ph II trial ongoing – Part 1 data in 2020
- Leveraging digital applications with smartphones and wearables to derive new clinical endpoints
- Investigating a novel, minimally invasive skin biopsy, that has the potential to diagnose PD as early as possible
Prasinezumab: PASADENA study

Fully recruited and expect data in 2020

Double-blind, placebo-controlled Ph II study in patients with early Parkinson’s Disease

- Males and females with recently diagnosed (≤2 years) idiopathic PD
- Hoehn and Yahr stage 1 or 2
- Untreated or treated with MAO-B inhibitors
- Age 40-80 years

Primary endpoint: Change from baseline in MDS-UPDRS total score at Wk 52

N=316
Randomise 1:1:1

Part 1
52 wks double-blind treatment (placebo-controlled)

Part 2
52 wks extension (active treatment, blinded to dose)

Follow-up
12 wks

Treatmen-
free
follow-up

Placebo IV Q4W

prasinezumab IV Q4W (1500 mg)

prasinezumab IV Q4W (4500 mg; BW ≥65 kg; 3500 mg; BW <65 kg)

prasinezumab IV Q4W (4500 mg; BW ≥65 kg; 3500 mg; BW <65 kg)

prasinezumab IV Q4W (1500 mg)

prasinezumab IV Q4W (1500 mg)

prasinezumab IV Q4W (4500 mg; BW ≥65 kg; 3500 mg; BW <65 kg)

prasinezumab IV Q4W (4500 mg; BW ≥65 kg; 3500 mg; BW <65 kg)

Placebo IV Q4W

prasinezumab IV Q4W (1500 mg)

prasinezumab IV Q4W (4500 mg; BW ≥65 kg; 3500 mg; BW <65 kg)

prasinezumab IV Q4W (4500 mg; BW ≥65 kg; 3500 mg; BW <65 kg)

prasinezumab IV Q4W (1500 mg)

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prasinezumab IV Q4W (4500 mg; BW ≥65 kg; 3500 mg; BW <65 kg)

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prasinezumab IV Q4W (1500 mg)

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prasinezumab IV Q4W (1500 mg)

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prasinezumab IV Q4W (1500 mg)

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prasinezumab IV Q4W (1500 mg)
Innovating biomarkers and diagnostic tools for Parkinson’s disease

**Skin immunohistochemistry assay for diagnosis of synucleinopathy in living individuals**

- Clinical diagnostic accuracy of Parkinson’s disease is only ca. 85%, and even lower in early stages of disease
- Novel Roche-Ventana IHC assay
- **Preliminary validation** established in academic sample cohort
  - multiple academic datasets available for further validation

<table>
<thead>
<tr>
<th></th>
<th>Control (n=21)</th>
<th>Idiopathic RBD (n=20)</th>
<th>PD (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63.0+/−12</td>
<td>68.0+/−9</td>
<td>70.5+/−15</td>
</tr>
<tr>
<td>Male Sex: n (%)</td>
<td>10 (47.6%)</td>
<td>20 (71.4%)</td>
<td>13 (65.0%)</td>
</tr>
<tr>
<td>Duration Of Disease (yr)</td>
<td>n/a</td>
<td>n/a</td>
<td>7.0(8)</td>
</tr>
<tr>
<td>Total UPDRS III</td>
<td>0.0 (3)</td>
<td>5.5 (9.5)</td>
<td>22.0 (14.5)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr stage</td>
<td>n/a</td>
<td>n/a</td>
<td>2.0(1)</td>
</tr>
<tr>
<td>aSyn positive skin biopsies*</td>
<td>0 (0%)</td>
<td>23 (82.1%)</td>
<td>14 (70%)</td>
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</tbody>
</table>

Data part of a collaboration with Professor R Postuma at the Montreal Neurological Institute (funded by the Michael J. Fox Foundation)
Innovating biomarkers and diagnostic tools for Parkinson’s disease
Digital biomarkers for remote, objective and frequent assessment of motor signs

Second generation Roche PD Mobile Application deployed in Pasedena Study
Digital biomarkers across Neuroscience at Roche
Providing enhanced patient insights and novel endpoints

- Clinical trials utilizing **mobiles, wearables** and **gaming** devices
- More **sensitive, precise** and **objective**
- **Continuous** and **longitudinal** measurement captures episodic and rare events
- Reduced **assessment burden** and greater **real-world relevance**

Multiple Sclerosis
Parkinson’s Disease
Huntington’s Disease
Spinal Muscular Atrophy
Autism Spectrum Disorders
Angelman’s Syndrome…
Roche’s Brain Shuttle technology concept

*Increasing antibody concentrations in the brain*

Brain Shuttle IgG binds to TfR at blood brain barrier

Any mAb with established functionality can be fused to the Brain Shuttle module

The Brain Shuttle module is fused in the back of a complete IgG to conserve its natural functions

"Free" epitope on TfR

Transferrin receptor (TfR)

Transferrin (Tf)

Cell surface

Cargo is actively transported into the brain

Potential to transport various cargos to the brain

Brain Shuttle gantenerumab in Alzheimer’s Disease
First Roche mAb with transporter across the blood brain barrier

**Mechanism of action**
- Microglia-mediated clearance of amyloid beta plaques in the brain
- Brain penetration is greatly enhanced through transferrin receptor-mediated transport across the blood brain barrier

**Differentiation**
- Direct brain access has potential for:
  - faster and wider access to the target. We could therefore see faster amyloid beta removal throughout brain tissue

**Status**
- Currently being tested in a Ph1 trial
Ophthalmology at pRED

Sascha Fauser | Global Head of pRED Ophthalmology
### pRED Ophthalmology focus areas

<table>
<thead>
<tr>
<th>AMD (dry and wet)</th>
<th>DME/DR</th>
<th>Personalised Healthcare</th>
<th>Monogenic Retinal Diseases</th>
<th>Glaucoma</th>
<th>Severe Dry Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination therapy/novel modes of action</td>
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<td>Early disease/prevention</td>
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<tr>
<td>Long-acting delivery (port delivery system)</td>
<td>Combination therapy/novel modes of action</td>
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<tr>
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<td>Long-acting delivery (port delivery system)</td>
<td>Biobanks</td>
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<tr>
<td>Advanced analytics</td>
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<td>Study design</td>
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<td>Diagnostic tools</td>
<td>Gene therapy</td>
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<tr>
<td>IVT approach, platform for retinal disease</td>
<td>Neuroprotection plus IOP reduction</td>
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<tr>
<td>Long-acting treatment (IVT)</td>
<td>Anti-inflammatory / anti-pain treatment</td>
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</table>
Real world outcomes have significant room for improvement

nAMD treatment frequency in real world¹

![Bar chart showing the number of VEGF injections in the first year.](chart)

- Number of eyes (% of eyes)
- Number of VEGF injections in 1st Year

Number of injections correlates with vision improvement¹

![Scatter plot showing the correlation between the number of VEGF injections and vision change.](chart)

- Vision Change (letters)
- Number of VEGF injections in 1st Year

¹ Courtesy of T. Brogan/Vestrum Health, presented by Dr. D. Williams at ASRS 2018; Article in press. Ophthalmology Retina; nAMD=neovascular age-related macular degeneration
pRED Ophthalmology

Personalised healthcare driven by individual patient needs, will lead to improved visual outcomes

New anti-VEGF strategy

- Efficacy
  - High
  - Moderate

- Combination therapy
- Novel targets

- Today's SoC
e.g. Lucentis

- High load
- Long acting

- Personalised healthcare
- PDS

SOC=standard of care; PHC=personalized health care; Q6M=every six months dosing; MOA=mechanism of action
Port Delivery System (PDS) with ranibizumab
Reduces treatment burden, addresses key unmet need in wAMD

<table>
<thead>
<tr>
<th>Port Delivery System (PDS)</th>
<th>Phase II (LADDER) results in nAMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Refillable intraocular implant using proprietary needle assembly</td>
<td>• Median Time to First Refill at 15 months, 80% patients ≥ 6m time to first refill</td>
</tr>
<tr>
<td>• In-office refills</td>
<td>• Ph III (ARCHWAY) in nAMD at fixed Q6M dosing fully recruited, data expected in 2020</td>
</tr>
<tr>
<td>• Customized formulation of ranibizumab</td>
<td>• Ex-US rights to PDS with ranibizumab acquired from Novartis</td>
</tr>
<tr>
<td></td>
<td>• New indications, new MOAs in PDS planned to leverage platform technology</td>
</tr>
</tbody>
</table>

Campochiaro, Peter A. et al. Ophthalmology, Volume 126, Issue 8, 1141–1154; nAMD = neovascular age-related macular degeneration; Q6M = once every six months dosing; MOA = mechanism of action
Faricimab in DME and nAMD
Potential to become the new standard of intra-vitreal therapy

- First bispecific antibody (biMAb) in ophthalmology binding simultaneously to VEGF and Angiopoietin2 (Ang2)
- Ang2 inhibition could improve vascular stability and reduce retinal inflammation

Anti-VEGF/Ang2
Bispecific mAb

• Robust BCVA gains at 6m with a mean of +13.9 letters gained from baseline and a statistically significant gain of +3.6 letters over Lucentis
• Rapid enrollment ongoing in Ph III studies in DME and nAMD
• Additional indications being explored

Sahni et al, Ophthalmology 2019;126:1155-1170; DME=diabetic macular edema; nAMD=neovascular age-related macular degeneration; BCVA= best-corrected visual acuity; *Linear model adjusted for baseline BCVA, previous macular laser treatment status, BCVA category (≥ 64 letters vs ≤ 63 letters)
Port Delivery System with DutaFabs

*Next generation bispecifics designed for increased efficacy & durability*

- DutaFabs are a novel bispecific Fab format significantly smaller than bispecific antibodies
- DutaFabs are compatible with the Port Delivery System enabling increased durability beyond Q6M
- 3 DutaFabs are in pre-clinical and 1 in clinical development targeting different MOAs

**New bispecific format (DutaFabs)**

<table>
<thead>
<tr>
<th>Monospecific Fab fragment</th>
<th>Bispecific mAb (Crossmab)</th>
<th>Bispecific Fab fragment (DutaFab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. Lucentis</td>
<td>e.g. faricimab</td>
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</tbody>
</table>

**Further improving the SOC**

- PHC = personalized health care
- Q6M = every six months dosing
- MOA = mechanism of action

SOC = standard of care
Complement Factor B-ASO (IONIS-FB-L\textsubscript{Rx}) in GA

**Blocking the alternative complement pathway in AMD and GA**

- Antisense drug binds to factor B mRNA and leads to degradation
- Strong genetic link of alternative complement pathway genes for risk of AMD and GA
- Tri-GalNAc conjugated ASOs are selectively taken up into hepatocytes

- Demonstrated target engagement by reduction of plasma factor B levels
- Demonstrated robust pharmacodynamics effect through AH50 level reduction
- No change of CH50 levels indicate overall complement pathway intact to mitigate risks

**Antisense RNA targeting factor B**

**Phase I results in healthy volunteers**

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Grossman et al., Mol Vis 2017; GA=geographic atrophy; ASO=antisense oligonucleotide; Factor B-ASO in collaboration with IONIS Pharmaceuticals

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Next generation Retinal Gene Therapy

Safe procedure for transducing across the entire retina

First-Gen Gene Therapy

- Subretinal injection
- Challenging procedure
- Complications include retinal detachment and scarring
- Limited area of transduction

Next-Gen Gene Therapy

- Intravitreal injection is standard for retinal specialists
- Safe procedure
- Transduction across entire retina
- Potential to treat early stage patients

In collaboration with 4D Molecular Therapeutics
Gene therapy (4D-110) for Choroideremia

Innovative potential of intravitreal (IVT) AAV delivery

Innovation
- Minimal invasive, simple and safe procedure
- Improved transduction across the whole retina
- Potential to treat early stage patients

Recent advancements
- >240 patient eyes injected with rAAV or lentiviral vectors in clinical trials within the past decade
- No “adverse events” reported to US FDA
- First US/EU approval for AAV gene therapy (Spark’s Luxturna) in 2018
- To date, clinical gene therapy trials listed to recruit over 581 subjects

Clinical development 4D-110
- Ph1 study to be initiated in 2020
- Additional monogenetic diseases targeted

Transfecting large retinal area

AAV=adeno associated virus; Source: Modified from http://webvision.med.utah.edu
In collaboration with 4D Molecular Therapeutics (4DMT)
pRED Ophthalmology PHC

Treatment options based on individual disease characteristics

- Curate large biobank of images, liquid and genetic samples
- Advanced analytics to generate predictive algorithms
- Clinical study designs to segment patients for novel treatments
- Develop diagnostic tools for the clinic
Personalised healthcare vision
The right treatment for the right patient at the right time

Current SOC

Future treatments

Analysis

Aqueous humour sample

Aqueous humour profiling

Imaging

Clinical data

Genotyping

Machine learning algorithm

Personalised treatment options

Clinical diagnosis support

Prognosis

Drug choice

Dosing regimen

New combination therapies

Treatment A

Treatment B

Treatment C

SOC=standard of care
Roche Ophthalmology clinical pipeline

<table>
<thead>
<tr>
<th>Core</th>
<th>Phase 0</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>wAMD</td>
<td></td>
<td>Dutafab NME</td>
<td>NME</td>
<td>Faricimab</td>
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<tr>
<td>wAMD and/or DME</td>
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<tr>
<td>DME / DR</td>
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<tr>
<td>Dry AMD/GA</td>
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<td>Explore</td>
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<td>4D-R100 CHM</td>
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<td>Dry Eye / Rare Diseases</td>
<td>4D-R125 XLRP</td>
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<td>Core</td>
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<td>Large molecule</td>
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<td>Gene Therapy</td>
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<td>partnered</td>
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</tbody>
</table>

AMD = age-related macular degeneration; GA: Geographic Atrophy; DR = diabetic retinopathy; DME = diabetic macular edema
Doing now what patients need next