Roche Pharma Day 2019

Late Stage Ophthalmology

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Sascha Fauser | Global Head of Ophthalmology pRED
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
   - MM: Venclexta

2. Breast Cancer franchise
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   - TNBC: Tecentriq, ipatasertib
   - HR+: ipatasertib; PI3Kα inhibitor

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   - ALK+: Alecensa
   - ROS1+/NTRK+: Rozlytrek

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   - OC: Tecentriq, Avastin
   - HCC: Tecentriq, Avastin

7. Neuroscience
   - MS: Ocrevus update
   - SMA: risdiplam
   - NMOSD: satralizumab
   - Huntington’s disease: HTT-ASO
   - Autism: balovaptan
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6. 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
Real world outcomes have significant room for improvement

nAMD treatment frequency in real world

Number of VEGF injections in 1st Year

Number of VEGF injections correlates with vision improvement

N=49,485

<25% received 10+ injections

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
Ophthalmology franchise strategic levers

1. Improved Efficacy via novel MOAs
   - anti-VEGF/Ang-2
   - New MOAs utilizing Dutag Fab platform

2. Long-Acting Delivery technologies
   - Port Delivery System
   - Injectable LADs
   - Gene therapy

3. Internal innovation complemented by external partnering
   - pRED
   - gRED

4. Personalized Healthcare
   - Vision loss prevention and treatment algorithms leveraging AI and machine learning
   - Biomarkers

MOA=mechanism of action; AI=artificial intelligence
## Roche Ophthalmology pipeline

### New MOAs and new technologies

<table>
<thead>
<tr>
<th>MOA</th>
<th>Pre-clinic</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Launched</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>nAMD</strong></td>
<td>Lucentis</td>
<td>faricimab</td>
<td>PDS ranibizumab</td>
<td>RG7921</td>
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<tr>
<td><strong>DME</strong></td>
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<td>NME undisclosed</td>
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<tr>
<td><strong>Diabetic retinopathy</strong></td>
<td>Lucentis</td>
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<tr>
<td><strong>Retinal vein occlusion</strong></td>
<td>Lucentis</td>
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<tr>
<td><strong>Myopic CNV</strong></td>
<td>Lucentis</td>
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<tr>
<td><strong>GA</strong></td>
<td>ASO Factor B inhibitor</td>
<td>RG6147</td>
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<td><strong>Choroideremia</strong></td>
<td>Gene therapy</td>
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Status as of September 2019; Lucentis indications are US only, Lucentis marketed by Novartis ex-US; Factor B-ASO in collaboration with IONIS Pharmaceuticals; MOA=mechanism of action; nAMD=neovascular age-related macular degeneration; DME=diabetic macular edema; GA=geographic atrophy; NME=new molecular entity
Faricimab and PDS address key unmet needs

Opportunity to differentiate on durability of response and efficacy

- Faricimab potential to improve on efficacy
- Anti-VEGF monotherapies
- Faricimab potential to improve on durability of response
- Port Delivery System with ranibizumab reduces real world Tx burden

Efficacy (BCVA change, letters)

1 mo to 6 mos

For illustrative purposes only
Preservation of vision with Personalized Healthcare (PHC)

*Meaningful data at scale and advanced analytics to enhance the pipeline*

<table>
<thead>
<tr>
<th>MDAS</th>
<th>Advanced analytics</th>
<th>Insights on key drivers of unmet need</th>
<th>Impact on personalized treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Deep Learning</td>
<td>ranibizumab</td>
<td>Treat intermediate disease <em>early</em>…</td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
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<td>...to avoid irreversible vision loss</td>
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<td>Remote Monitoring</td>
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</table>

Ultimate goal to treat vision loss and preserve vision
Preservation of vision with Personalized Healthcare (PHC)

Deep learning algorithm to predict progression of AMD and DR

Proof of concept: Performance of deep learning model predicting ≥ 2-Step ETDRS-DRSS worsening

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<tr>
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<th>AUC ± SD</th>
<th>Sensitivity ± SD</th>
<th>Specificity ± SD</th>
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<tr>
<td>Month 24</td>
<td>0.77 ± 0.04</td>
<td>79% ± 12%</td>
<td>72% ± 14%</td>
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Schmidt-Erfurth U. et al, Invest Ophthalmol Vis Sci 2018; 2018 Jul 2;59(8):3199-3208. doi: 10.1167/iovs.18-24106; Arcadu, F. et al. “Deep Learning Algorithm to Predict Diabetic Retinopathy Progression on the Individual Patient Level” (ARVO PB093, Vancouver, Canada 2019; accepted for publication in Nature Digital Medicine); AMD=age-related macular degeneration; DR=diabetic retinopathy; ETDRS=Early Treatment Diabetic Retinopathy Study; DRSS=Diabetic Retinopathy Severity Score
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   - Hemlibra

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* 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
Faricimab in DME and nAMD
Potential to become the new standard of intra-vitreal therapy

Anti-VEGF/Ang2 Bispecific mAb

- First bispecific antibody (biMAb) in ophthalmology binding simultaneously to VEGF and Angiopoetin2 (Ang2)
- Ang2 inhibition could improve vascular stability and reduce retinal inflammation

Phase II (BOULEVARD) results in DME:

Adjusted mean BCVA gains from baseline*

Sahni et al, Ophthalmology 2019;126:1155-1170

- 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)
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Port Delivery System (PDS) with ranibizumab
Reduces treatment burden, addresses key unmet need in nAMD

Port Delivery System (PDS)
- Refillable intraocular implant using proprietary needle assembly
- In-office refills
- Customized formulation of ranibizumab

Phase II (LADDER) results in nAMD:
- Median Time to First Refill at 15months, 80% patients ≥ 6m time to first refill
- Ph III (ARCHWAY) in nAMD at fixed Q6M dosing fully recruited, data expected in 2020
- Ex-US rights to PDS with ranibizumab acquired from Novartis
- New indications, new MOAs in PDS planned to leverage platform technology

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
Port Delivery System

Virtual reality training of the surgeons

- PDS University enables procedural standardization to ensure consistency in outcomes and enhance patient experience
- Virtual reality (VR) technology enables preoperative training of surgeons on PDS procedures (implant insertion and refill)
- Ph III trial (ARCHWAY) represents the first use of VR surgical training in an ophthalmic clinical trial
Port Delivery System with DutaFabs

Next generation bispecifics designed for increased efficacy & durability

New bispecific format (DutaFabs)

- 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 development targeting different MOAs

Further improving the SOC:

SOC=standard of care; PHC=personalized health care; Q6M=every six months dosing; MOA=mechanism of action; PHC=personalized healthcare
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Complement Factor B-ASO (IONIS-FB-L_Rx) in GA

Blocking the alternative complement pathway in AMD and GA

- Strong genetic link of alternative complement pathway genes for risk of AMD and GA
- Monthly subcutaneous route of administration ideal for chronic treatment vs. injection in the eye
- At-home administration possible
- Potential to expand into other indications and earlier stages of AMD

Complement Factor B-ASO (IONIS-FB-LRx) in GA
First drug to reduce factor B in the alternative pathway

Antisense RNA targeting factor B

- Antisense drug binds to factor B mRNA and leads to degradation
- Tri-GalNAc conjugated ASOs are selectively taken up into hepatocytes

Pre-clinical results in monkeys:

- Systemic ASO Factor B knockdown in the liver is sufficient to achieve both systemic as well as ocular FB protein knockdown in monkeys

Grossman et al., Mol Vis 2017; GA=geographic atrophy; ASO=antisense oligonucleotide; Factor B-ASO in collaboration with IONIS Pharmaceuticals
Complement Factor B-ASO (IONIS-FB-L_{Rx}) in GA
Significant factor B reduction achieved in humans

Phase I results in healthy volunteers:

Factor B and downstream product levels:

- 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
Complement Factor B-ASO (IONIS-FB-L_{Rx}) in GA

*Ph II study in GA initiated*

**Phase II trial design (NCT03815825):**

- **Stage 1**
  - Dose Ranging (N=60)
  - Screening & Run-in

- **Stage 2**
  - Dose Expansion (N=270)
  - Screening & Run-in

- **Treatment**

- **Week 49**
  - Dose 1
  - Dose 2
  - Dose 3
  - Placebo

- **IA**

- **IA**

- **IA**

- **IA**

**Objective:**
- Evaluate effect of IONIS-FB-LRx on change of Geographic Atrophy area at week 49, by retinal imaging
- Adaptive trial design; randomized; placebo controlled; double-masked
- First patient dosed in June 2019; overall 330 patients to be randomized
- Sites in the US, AU, NZ

Factor B-ASO in collaboration IONIS Pharmaceuticals; GA=geographic atrophy
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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
**Tissue targeted gene therapy in Ophthalmology**

**Optimized AAV technology for targeted delivery to the retina**

- **4DMT vector tissue optimization screen**
- **Transduction kinetics after single IVT in NHP**

- 4DMT technology optimized AAV vectors for retinal transfection after intravitreal injection
- 4D-R100 efficiently reverts the cells phenotype showing significant restitution of intracellular trafficking
- Widespread and robust transduction of 4D-R100 with rapid onset & durable expression in non-human primates

**AAV=adeno associated virus; IVT=intravitreal injection; NHP=non-human primates; In collaboration with 4D Molecular Therapeutics (4DMT)**
### Gene therapy (4D-110) for Choroideremia

**A rare inherited disorder ultimately leading to complete blindness**

<table>
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<th>Retina damage by Choroideremia</th>
<th>Disease progression</th>
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<td>Healthy Retina</td>
<td>Vision at birth</td>
</tr>
<tr>
<td>Retina damaged by Choroideremia</td>
<td>Vision at age 25</td>
</tr>
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- X-linked recessive disease (incidence rate: 1:50,000 males)
- Loss of function mutation in *CHM* gene which encodes REP1 involved in lipid modification of Rab GTPases
- Cell death & gradual deterioration of retinal pigment epithelium, photoreceptors and choroid
- Loss of peripheral vision precedes central vision loss

Source: Choroideremia Research Foundation; In collaboration with 4D Molecular Therapeutics (4DMT)
Gene therapy (4D-110) for Choroideremia

Innovative potential of intravitreal (IVT) AAV delivery

**Transfecting large retinal area**

**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

AAV=adeno associated virus; Source: Modified from [http://webvision.med.utah.edu](http://webvision.med.utah.edu); In collaboration with 4D Molecular Therapeutics (4DMT)
Potential for gene therapy in ophthalmology

To date 269 genes causing retinal disease have been identified

- To date, there are 269 identified genes that cause retinal disease
- Over 95% of the identified gene mutations initially result in death of rod photoreceptors

Source: [http://webvision.med.utah.edu](http://webvision.med.utah.edu)
Doing now what patients need next