15th Angiogenesis meeting 2018, Miami

Roche virtual pipeline event
Tuesday, 13 February 2018
Agenda

Welcome
Karl Mahler, Head of Investor Relations

Roche in ophthalmology - overview
Jason S. Ehrlich, M.D. Ph.D., Global Head, Clinical Ophthalmology – Product Development

BOULEVARD: Phase 2 results of the bispecific VEGF/Ang2 antibody in diabetic macula edema
Sascha Fauser, M.D., Head pRED Ophthalmology

Q&A
Karl Mahler, Head of Investor Relations
Introduction

Karl Mahler
Head of Investor Relations
2018: Roche off to a good start
Record number of pipeline assets at pivotal stage in multiple disease areas

<table>
<thead>
<tr>
<th>Year</th>
<th>Oncology</th>
<th>Ophthalmology</th>
<th>Neuroscience</th>
<th>Immunology</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>2</td>
<td>1</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>5</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>5</td>
<td>1</td>
<td>33</td>
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</tr>
<tr>
<td>2017</td>
<td>4</td>
<td>1</td>
<td>31</td>
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</tr>
</tbody>
</table>

NMEs: Venclexta, Alecensa, Tecentriq, Hemlibra, idasanutlin, taselisib, lampalizumab, gantenerumab, Ocrevus, satralizumab, lebrikizumab, etrolizumab

2014: Hemlibra, polatuzumab vedotin, idasanutlin, ipatasertib, taselisib
2015: VEGF-ANG2 biMAb, SMN2 splicer, V1a receptor ant. - autism, anti-myostatin adnectin, gantenerumab, crenezumab, Ocrevus, CapEndo, etrolizumab
2016: Hemlibra, idasanutlin, taselisib, VEGF-ANG2 biMAb, SMN2 splicer, V1a receptor ant. - autism, anti-myostatin adnectin, gantenerumab, crenezumab, Ocrevus, CapEndo, etrolizumab
2017: Hemlibra, idasanutlin, taselisib, VEGF-ANG2 biMAb, SMN2 splicer, V1a receptor ant. - autism, anti-myostatin adnectin, gantenerumab, crenezumab, Ocrevus, CapEndo, etrolizumab
Diabetic macular edema (DME): High unmet medical need

Significant global burden due to vision loss

- Rate of T2D continues to grow; 40-45% will develop diabetic retinopathy (DR)\(^1\)
- DME – is the most common diabetic eye disease and the leading cause of irreversible blindness in working age Americans\(^1\)

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Roche in ophthalmology - overview

Jason S. Ehrlich, M.D., Ph.D.
Global Head, Clinical Ophthalmology - Product Development
Roche in ophthalmology

Taking on the leading causes of vision loss through pioneering therapies

Unmet Need

Innovative treatment options are needed to address the leading causes of vision loss affecting 253 million people worldwide\(^1\)

Breakthrough Science

We are pioneers striving for transformative therapies that leverage cutting edge science for diseases with high unmet medical need

Patient-Focused Innovation

Through our smart innovations in molecular engineering, biomarkers and sustained drug delivery, we strive to design the right therapies for the right patients

People and Partnerships

We hire the best people to advance science and improve people's lives. We foster extensive collaborative partnerships with researchers, clinicians and patient groups

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## Ophthalmology pipeline

<table>
<thead>
<tr>
<th>Indication</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>In Submission</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neovascular AMD</td>
<td></td>
<td>ranibizumab Port Delivery System</td>
<td></td>
<td>Lucentis 0.5 mg</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>anti-VEGF/ANG2 biMab (RG7716)</td>
<td></td>
<td>Lucentis 0.3 mg PFS (DME, DR)</td>
<td></td>
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<tr>
<td>Diabetic Eye Disease</td>
<td></td>
<td></td>
<td>anti-VEGF/ANG2 biMab (RG7716)</td>
<td>Lucentis 0.3 mg (DME, DR)</td>
<td>Lucentis 0.5 mg PFS</td>
</tr>
<tr>
<td>Retinal Vein Occlusion</td>
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<tr>
<td>Geographic Atrophy</td>
<td>NME (RG6417)</td>
<td></td>
<td></td>
<td>Lucentis 0.5 mg PFS</td>
<td></td>
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<tr>
<td>Myopic CNV</td>
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<tr>
<td>Giant Cell Arteritis</td>
<td></td>
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<td>Actemra/RoActemra</td>
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<tr>
<td>Multiple Sclerosis</td>
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<tr>
<td>Neuromyelitis Optica</td>
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<td></td>
<td></td>
<td>Ocrevus</td>
<td></td>
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<tr>
<td>Glaucoma</td>
<td>NME (RG7945)</td>
<td></td>
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</tbody>
</table>

Status as of February 1, 2018. Lucentis in collaboration with Forsight and Novartis

DME = diabetic macular edema; DR = diabetic retinopathy; PFS = prefilled syringe; biMab = bispecific monoclonal antibody; NME = new molecular entity
Retinal vascular diseases remain leading causes of vision loss

- **Leading causes of vision loss in…**
  - working-age people in US, Europe: **Diabetic eye disease (DME, PDR)**
  - elderly people in US, Europe: **Neovascular AMD**

### 2017 Ophthalmology market

- nAMD, DME, RVO
- Glaucoma
- Dry Eye
- Ocular inflammation/infections
- Others

**Market size: CHF 18.6bn**

*Source: Evaluate Pharma (January 2018)*

### Neovascular AMD & DME market outlook

<table>
<thead>
<tr>
<th></th>
<th>AMD</th>
<th>DME</th>
</tr>
</thead>
<tbody>
<tr>
<td>USD bn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>4.2</td>
<td>2.8</td>
</tr>
<tr>
<td>2026</td>
<td>5.7</td>
<td>5.3</td>
</tr>
</tbody>
</table>

*US*  
*EU5*  
*Japan*

*Source: Decision Resources (January 2018)*

Note: Figures for 2017 involve forecast values for Q4 2017 as investor reports of all companies are not yet released

DME=diabetic macular edema; PDR=proliferative diabetic retinopathy; AMD=age-related macular degeneration
Vision can be recovered in neovascular AMD and DME
Anti-VEGF therapy can improve outcomes and has become SOC

DME phase III studies: Aflibercept vs laser; mean change from baseline in VA during 52-wks

DME phase III studies: Lucentis vs sham; mean change from baseline in VA during 24-months

*with censoring of values after additional treatment was given (LOCF)

AMD=age-related macular degeneration; DME=diabetic macular edema; VA=visual acuity
Still, many patients remain visually impaired

Improved efficacy is a major unmet need in retinal vascular disease

Despite significant improvements, many people do not achieve a visual acuity score of 20/40 or better

1 RIDE/RISE: Ophthalmology 2011;118:1594–1602; DME=diabetic macular edema
Snellen (eye chart to measure visual acuity) equivalent of 20/40: a person needs to approach to a distance of 6 metres (20 ft) to read letters that a person with normal acuity could read at 12m (40 feet). In an even more approximate manner, this person could be said to have “half” the normal acuity of 6/6 or 20/20.
DME is underdiagnosed and undertreated today

- Rate of type 2 diabetes continues to grow
- 40-45% of people with diabetes will develop diabetic retinopathy¹,²
- DME is a type of DR that is a leading cause of vision loss for people with diabetes³

5.4 mn DME prevalent cases (major markets) in 2015*

~Only 50% of people diagnosed today⁴

Treatment received during the first year following diagnosis

- 75% of all patients receive no treatment in first 28 days

*Source: Decision Resources (January 2018)

DME is underdiagnosed and undertreated today

- Rate of type 2 diabetes continues to grow
- 40-45% of people with diabetes will develop diabetic retinopathy\(^1\,2\)
- DME is a type of DR that is a leading cause of vision loss for people with diabetes\(^3\)

\(^5.4\) mn DME prevalent cases (major markets) in 2015\(^*\)

\(~\text{Only 50\% of people diagnosed today}\)\(^4\)

\begin{equation}
\begin{aligned}
\text{Diagnosed} & : 52\% \\
\text{Drug-Treated} & : 39\%
\end{aligned}
\end{equation}

Treatment received during the first year following diagnosis

\begin{itemize}
\item 60\% of all patients receive no treatment in 1st year
\end{itemize}

\[\text{Patient number} \begin{array}{|c|c|c|c|c|c|c|c|}
\hline
\text{Days} & 28 & 365 & 28 & 365 & 28 & 365 & 28 & 365 \\
\hline
\text{Observation} & \text{Ranibizumab} & \text{Aflibercept} & \text{Bevacizumab} & \text{Laser} & \text{Corticosteroid} & \text{Combination} \\
\hline
\end{array}\]

\(^*\text{Source: Decision Resources (January 2018)\}

Real world outcomes in nAMD, DME limited by treatment burden
Potentially addressed by extending durability of anti-VEGF, targeting additional MOAs, or both

• Patients received a mean of 5.0 and 2.2 injections in the first and second year, respectively.

• There were substantial differences in visual outcomes and injection frequency between countries. More frequent visits and injections were associated with greater improvements in visual acuity.

• Almost 50% of patients receiving anti-VEGF treatment within 28 days of initial DME diagnosis received ≤3 injections in the first year of treatment.

1 F.G. Holz et al., Br J Ophthalmol 2015; 2 J.R. Willis et al., AAO 2017

AMD=age-related macular degeneration; DME=diabetic macular edema; MOA=mechanism of action; VA=visual acuity
Approaches to potentially achieve better outcomes

1. Sustained delivery of intravitreal therapies for months at a time

- **Solid-state reservoir implant**
  - Slowly elutes ranibizumab
  - Implanted in OR by vitreoretinal surgeon
  - Refillable in the office using proprietary needle assembly

**LADDER: Phase 2 multicenter, randomized, interventional, active treatment-controlled study** (NCT02510794)

Wet AMD population (N = 220)

- RPDS Implant RBZ formulation 1
  - N=60
- RPDS Implant RBZ formulation 2
  - N=60
- RPDS Implant RBZ formulation 3
  - N=60
- ITV SOC RBZ 0.5 mg/mL Monthly
  - N=40

Primary endpoint: Time to first refill
Study fully enrolled, data expected 2H2018

ForSIGHT VISION4 acquired by Roche, January 2017

AMD=age-related macular degeneration; RPDS=ranibizumab port delivery system; RBZ=ranibizumab; ITV=intravitreal; SOC=standard of care
Approaches to potentially achieve better outcomes

2. Address vascular homeostasis by targeting Ang-2 along with VEGF

Dual Ang-2/VEGF inhibition in DME may improve both efficacy and durability

- First bispecific antibody in ophthalmology binding to VEGF and Angiopoetin-2 (Ang2)
- Optimized Fc for faster systemic clearance (FcRn), no effector function (FcγR)
- Levels of Ang-2 elevated in retinal vascular diseases
- Ang2 and VEGF are key drivers of angiogenesis
- Angiopoietin/Tie2 axis modulates endothelial cell stabilization

Anti-VEGF/Ang2 biMAb

DME=diabetic macular edema; biMAb=bispecific monoclonal antibody
VA2 RG7716 phase 2 program in both DME and nAMD

BOULEVARD

Diabetic macular edema
N=150 anti-VEGF naïve, 60 anti-VEGF previously-treated
NCT02699450

Primary outcome: Mean change from baseline in BCVA letter score at week 24

Ranibizumab 0.3 mg
RG7716 1.5 mg
RG7716 6 mg

Observational period up to week 36
Every fourth week up to week 20, for a total of 6 administrations

Data at Angiogenesis 2018

AVENUE

nAMD, Treatment naïve
N=273
NCT02484690

Primary outcome: Mean change from baseline in BCVA letter score at week 36

Ranibizumab 0.5 mg Q4 weeks (9 months)
RG7716 D1 Q4 weeks (9 months)
RG7716 D2 Q4 weeks (9 months)
RG7716 D2 Q4 X 4 mo
RBZ Q4 X 3 mo
VA2 D2 Q4 x 6 months

9 month primary efficacy readout
Dose response H2H
Q8 weekly durability
Sub group analysis incomplete responders

Data expected in 2018

STAIRWAY

nAMD, Treatment naïve
N=75
NCT03038880

Primary outcome: Mean change from Baseline in BCVA letter score at week 40

Ranibizumab 0.5 mg q4w
RG7716 short interval duration
RG7716 long interval duration

Data expected in 2018

AMD=age-related macular degeneration; DME=diabetic macular edema; BCVA=best corrected visual acuity
BOULEVARD: Phase 2 results of the bispecific VEGF/Ang2 antibody in diabetic macula edema
Sascha Fauser, M.D.,
Head pRED Ophthalmology
Antigen VEGR/Anti–Angiopoietin-2 Bispecific Antibody RG7716 in Diabetic Macular Edema

Results From the Phase 2 BOULEVARD Clinical Trial

Pravin U. Dugel, MD

Jayashree Sahni, MBBS, FRCOphth, MD; Shamil Sadikhov, MSc; Meike Pauly-Evers, PhD; Piotr Szczesny, MD, PhD; Robert Weikert, MSc

on behalf of the BOULEVARD Study Investigators

1 Retina Consultants of Arizona, Phoenix, AZ, USC Eye Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA
2 Roche Pharma Research and Early Development, Roche Innovation Center, Basel, Switzerland

Presented at Angiogenesis, Exudation, and Degeneration 2018, February 10, 2018
Disclosures

• Relevant financial disclosures
  – Dr. Dugel is a consultant for Genentech/Roche and Novartis
  – Dr. Dugel sits on the Aerpio board of directors

• Study disclosures
  – This study includes research conducted on human subjects
  – Institutional Review Board approval was obtained prior to study initiation
  – Funding was provided by F. Hoffmann-La Roche Ltd. for the study and third-party writing assistance, which was provided by Betsy C. Taylor, PhD, CMPP, of Envision Pharma Group
Take-Home Points

*RG7716 met its primary endpoint in the BOULEVARD phase 2 DME trial*

- RG7716 is the first bispecific antibody designed for intravitreal use that simultaneously binds and neutralizes both Ang-2 and VEGF-A
- RG7716 demonstrated statistically significant BCVA gains over ranibizumab at week 24 in anti-VEGF treatment-naïve patients with DME
- Secondary functional and anatomical endpoints (OCT, DRSS) support BCVA primary outcome
- RG7716 was well tolerated and showed no new or unexpected safety signals
Significant Unmet Need Remains for Patients With DME

There is a need for therapies that improve efficacy and/or reduce treatment burden

DME is an increasing global burden

- Global rate of diabetes is growing and is expected to increase to affect 592 million by 2035\(^1\)
- DR, including associated DME, is a leading cause of vision loss in working-age adults\(^2\)

Anti–VEGF-A monotherapies have hit a ceiling for efficacy

- In RCT, only ~30%–45% of anti–VEGF-treated patients with DME gained ≥ 15 letters*,3-8
- Real-world data show that patients are not receiving the optimal number of injections, highlighting the need for therapies that can reduce treatment burden\(^3-12\)
- DR/DME is a multifactorial disease involving multiple pathways beyond VEGF\(^13,14\)
- Current anti–VEGF treatments only target 1 pathway, primarily addressing vessel leakage and proliferation\(^15\)
- Targeting additional pathways beyond VEGF could improve BCVA outcomes and decrease treatment burden

* Results for years 1 and 2 of treatment.


BCVA, best-corrected visual acuity; DME, diabetic macular edema; DR, diabetic retinopathy; RCT, randomized clinical trial; VEGF, vascular endothelial growth factor.
Ang-2 Signaling Implicated in the Pathology of DR and DME

Evidence supports rationale for Ang-2 inhibition

<table>
<thead>
<tr>
<th>Ocular Characteristics of DR and DME</th>
<th>Associated With Ang-2 Signaling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated vitreous levels of Ang-2(^1)-(^4)</td>
<td>✔ 2,5</td>
</tr>
<tr>
<td>Retinal microvascular inflammation(^5),(^6)</td>
<td>✔ 2,7,8</td>
</tr>
</tbody>
</table>
| Blood-retinal-barrier breakdown\(^5\)  
  • Pericyte dropout\(^2\),\(^5\)  
  • Endothelial cell destabilization\(^5\)  
  • Retinal vessel leukostasis\(^5\),\(^6\) | ✔ 2,5,7,8 |
| Capillary sprouting and remodeling\(^9\) | ✔ 9,10 |


Ang-2, angiopoietin-2; DME, diabetic macular edema; DR, diabetic retinopathy.
RG7716: the First Bispecific Antibody Designed for Intravitreal Use

Engineered for efficacy, duration within the eye, and fast systemic clearance

1 molecule – 2 targets

- **Anti–Ang-2 Fab**
  - Enhanced activity through Ang-2 inhibition

- **Anti–VEGF-A Fab**
  - Proven efficacy through VEGF-A inhibition

- **Optimized Fc**
  - Faster systemic clearance (FcRn)
  - No effector function (FcγR)
RG7716 Simultaneously Binds Both Ang-2 and VEGF-A

Dual inhibition independent of binding order


Ang-2, angiopoietin-2; RU, response units; VEGF-A, vascular endothelial growth factor A.
The BOULEVARD Study:
RG7716 in DME
Study Design

Randomized, active comparator-controlled, double-masked, phase 2 clinical trial

229 patients with center-involving DME*

- 168 anti-VEGF treatment-naïve patients†
- 61 previously anti-VEGF-treated patients‡

Safety data set consists of 224 patients; 2 patients removed due to GCP non-compliance at a single site; 3 patients were randomized but did not receive treatment.

† Patients randomized 1:1:1 into the 3 treatment arms; 2 patients removed from analysis due to GCP non-compliance at a single site.
‡ Patients randomized 1:1 into 0.3 mg ranibizumab and 6.0 mg RG7717 treatment arms.
§ Ranibizumab treatment given and patient exited study if both CST increased by ≥ 50 μm from week 24 and BCVA decreased by ≥ 5 ETDRS letters from week 24 due to DME.

BOULEVARD clinical trial (NCT02699450).

BCVA, best-corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; GCP, Good Clinical Practice; R, randomized; VEGF-A, vascular endothelial growth factor A.
### Key Inclusion and Exclusion Criteria

#### Key inclusion criteria

- Age ≥ 18 years
- Center-involving DME
- CST ≥ 325 μm
- BCVA 73–24 ETDRS letters (20/40–20/320 Snellen equivalent)

#### Key exclusion criteria

- All patients
  - Any signs of high-risk PDR
  - Any prior PRP
  - Any macular laser photocoagulation within 3 months prior to study start
- Previously anti-VEGF-treated patients only
  - Anti-VEGF treatment within 3 months prior to study start

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* CST as measured by Spectralis (Heidelberg) at screening; ≥ 315 μm for Cirrus and Topcon and ≥ 295 μm for Optovue. BOULEVARD clinical trial (NCT02699450). BCVA, best-corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor.
Key Study Objectives

• **Primary objective**
  – Efficacy of RG7716 compared with ranibizumab in anti-VEGF treatment-naïve patients at week 24
    • Mean BCVA change from baseline using a linear model adjusting for baseline BCVA and randomization stratification factors*

• **Key secondary and exploratory objectives**
  – Ocular and systemic safety
  – Anatomical outcomes
  – DR severity outcomes
  – Duration of effect
  – Outcomes in previously anti–VEGF-treated patients
  – Systemic and ocular pharmacokinetics
  – Analysis of plasma, aqueous humor, and vitreous biomarkers

* Linear model adjusted for baseline BCVA, previous macular laser treatment status at randomization, and BCVA category (≥ 64 letters vs ≤ 63 letters) at baseline.

BOULEVARD clinical trial (NCT02699450).
BCVA, best-corrected visual acuity; DR, diabetic retinopathy; VEGF, vascular endothelial growth factor.
Study Results: Week 24 Data for Anti-VEGF Treatment-Naïve Patients
Baseline Demographics

*Well balanced across treatment arms*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0.3 mg Ranibizumab n = 59</th>
<th>1.5 mg RG7716 n = 54</th>
<th>6.0 mg RG7716 n = 53</th>
<th>All Patients N = 166</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>61.6 (9.5)</td>
<td>61.4 (7.7)</td>
<td>60.5 (9.1)</td>
<td>61.2 (8.8)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>37 (62.7%)</td>
<td>19 (35.2%)</td>
<td>33 (62.3%)</td>
<td>89 (53.6%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaska native</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (3.8%)</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (1.9%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>9 (15.3%)</td>
<td>11 (20.4%)</td>
<td>10 (18.9%)</td>
<td>30 (18.1%)</td>
</tr>
<tr>
<td>White</td>
<td>49 (83.1%)</td>
<td>42 (77.8%)</td>
<td>39 (73.6%)</td>
<td>130 (78.3%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1.7%)</td>
<td>1 (1.9%)</td>
<td>1 (1.9%)</td>
<td>3 (1.8%)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hispanic or Latino</td>
<td>11 (18.6%)</td>
<td>8 (14.8%)</td>
<td>9 (17.0%)</td>
<td>28 (16.9%)</td>
</tr>
<tr>
<td>Mean duration of diabetes at randomization, years (SD)</td>
<td>14.0 (10.5)</td>
<td>15.6 (10.0)</td>
<td>14.5 (9.3)</td>
<td>14.7 (10.0)</td>
</tr>
<tr>
<td>Mean HbA1c, % (SD)</td>
<td>7.8% (1.6)</td>
<td>8.2% (1.6)</td>
<td>7.7% (1.8)</td>
<td>7.9% (1.7)</td>
</tr>
</tbody>
</table>

Observed data; anti-VEGF treatment-naïve patients only. BOULEVARD clinical trial (NCT02699450). HbA1c, glycated hemoglobin.
Baseline Ocular Characteristics

Generally well balanced across treatment arms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0.3 mg Ranibizumab n = 58</th>
<th>1.5 mg RG7716 n = 54</th>
<th>6.0 mg RG7716 n = 51</th>
<th>All Patients N = 163</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vision</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean BCVA, ETDRS letters (SD)</td>
<td>61.2 (9.9)</td>
<td>60.9 (11.1)</td>
<td>60.0 (11.0)</td>
<td>60.8 (10.6)</td>
</tr>
<tr>
<td>20/40 or better vision, n (%)</td>
<td>13 (22.4%)</td>
<td>15 (27.8%)</td>
<td>11 (21.6%)</td>
<td>39 (23.9%)</td>
</tr>
<tr>
<td>Worse than 20/40 vision, n (%)</td>
<td>45 (77.6%)</td>
<td>39 (72.2%)</td>
<td>40 (78.4%)</td>
<td>124 (76.1%)</td>
</tr>
<tr>
<td><strong>Anatomic</strong></td>
<td></td>
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<tr>
<td>Mean CST, μm (SD)</td>
<td>490.9 (139.0)</td>
<td>535.4 (163.1)</td>
<td>496.5 (135.0)</td>
<td>507.4 (146.7)</td>
</tr>
<tr>
<td>Diabetic retinopathy status, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>DR questionable</td>
<td>n = 59</td>
<td>n = 54</td>
<td>n = 53</td>
<td>N = 166</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>0 (0.0%)</td>
<td>1 (1.9%)</td>
<td>0 (0.0%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>14 (23.7%)</td>
<td>8 (14.8%)</td>
<td>10 (18.9%)</td>
<td>32 (19.3%)</td>
</tr>
<tr>
<td>Moderately severe NPDR</td>
<td>23 (39.0%)</td>
<td>21 (38.9%)</td>
<td>25 (47.2%)</td>
<td>69 (41.6%)</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>15 (25.4%)</td>
<td>16 (29.6%)</td>
<td>9 (17.0%)</td>
<td>40 (24.1%)</td>
</tr>
<tr>
<td>Prior PRP</td>
<td>1 (1.7%)</td>
<td>1 (1.9%)</td>
<td>1 (1.9%)</td>
<td>3 (1.8%)</td>
</tr>
<tr>
<td>Moderate PDR</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (1.9%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Missing/cannot grade</td>
<td>1 (1.7%)</td>
<td>2 (3.7%)</td>
<td>2 (3.8%)</td>
<td>5 (3.0%)</td>
</tr>
</tbody>
</table>

Observed data; anti-VEGF treatment-naïve patients only. BOULEVARD clinical trial (NCT02699450).

BCVA, best-corrected visual acuity; CST, central subfield thickness; DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, non-proliferative DR; PDR, proliferative DR; PRP, panretinal photocoagulation.
Mean BCVA Gains From Baseline (Observed Values)

RG7716 treatment provided dose-dependent improvements in vision

(Time, Weeks)

Mean BCVA Change From Baseline, ETDRS Letters

- 0.3 mg ranibizumab (n = 59)
- 1.5 mg RG7716 (n = 54)
- 6.0 mg RG7716 (n = 53)

Observed data; anti-VEGF treatment-naïve patients only. Error bars represent 80% CI.

BOULEVARD clinical trial (NCT02699450). BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.
Adjusted Mean BCVA Gains From Baseline

*RG7716 met its prespecified primary endpoint of efficacy*

Linear model adjusted for baseline BCVA and randomization stratification factors*

Observed data; anti-VEGF treatment-naive patients only. Error bars represent 80% CI.

* Linear model adjusted for baseline BCVA, previous macular laser treatment status at randomization, and BCVA category (≥ 64 letters vs ≤ 63 letters) at baseline. † Protocol prespecified significance level, \( P < 0.2 \). BOULEVARD clinical trial (NCT02699450). BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.
Observed data; treatment-naive patients only. Error bars represent 80% CI. BOULEVARD clinical trial (NCT02699450). BCVA, best-corrected visual acuity; CST, central subfield thickness.
Adjusted Mean CST Change From Baseline

CST reduction directionally supports BCVA primary outcome in a dose-dependent manner

Linear model adjusted for baseline CST and randomization stratification factors*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Group Size</th>
<th>CST Reduction (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg ranibizumab</td>
<td>59</td>
<td>-204.7 μm</td>
</tr>
<tr>
<td>1.5 mg RG7716</td>
<td>54</td>
<td>-217.1 μm</td>
</tr>
<tr>
<td>6.0 mg RG7716</td>
<td>53</td>
<td>-225.8 μm</td>
</tr>
</tbody>
</table>

*Observed data; anti-VEGF treatment-naïve patients only. Error bars represent 80% CI.

* Linear model adjusted for baseline CST, previous macular laser treatment status at randomization, and BCVA category (≥ 64 letters vs ≤ 63 letters) at baseline; protocol prespecified significance level, $P < 0.2$. BOULEVARD clinical trial (NCT02699450). BCVA, best-corrected visual acuity; CST, central subfield thickness.
RG7716 Resulted in Improved Proportions of 2- and 3-Line Gainers

Supporting BCVA primary outcome in a dose-dependent manner

** ≥ 2-Line Gainers* at Week 24

<table>
<thead>
<tr>
<th>Dose</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg ranibizumab (n=49)</td>
<td>57.1%</td>
</tr>
<tr>
<td>1.5 mg RG7716 (n=49)</td>
<td>61.2%</td>
</tr>
<tr>
<td>6.0 mg RG7716 (n=44)</td>
<td>70.5%</td>
</tr>
</tbody>
</table>

** ≥ 3-Line Gainers† at Week 24

<table>
<thead>
<tr>
<th>Dose</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg ranibizumab (n=49)</td>
<td>32.7%</td>
</tr>
<tr>
<td>1.5 mg RG7716 (n=49)</td>
<td>36.7%</td>
</tr>
<tr>
<td>6.0 mg RG7716 (n=44)</td>
<td>43.2%</td>
</tr>
</tbody>
</table>

* ≥ 10 ETDRS letters from baseline. † ≥ 15 ETDRS letters from baseline.

Observed data, week 24; anti-VEGF treatment-naïve patients only. BOULEVARD clinical trial (NCT02699450). BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.
RG7716 Resulted in Improved DR Severity Scores

≥ 2-step DRSS improvement data support BCVA primary outcome in a dose-dependent manner

≥ 2-Step DR Improvement at Week 24

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg ranibizumab</td>
<td>12.2</td>
</tr>
<tr>
<td>1.5 mg RG7716</td>
<td>27.7</td>
</tr>
<tr>
<td>6.0 mg RG7716</td>
<td>38.6</td>
</tr>
</tbody>
</table>

Observed data, week 24; anti-VEGF treatment-naïve patients only. BOULEVARD clinical trial (NCT02699450). BCVA, best corrected visual acuity; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Score.
Safety: All Patients
# Safety – All Patients (Anti-VEGF Treatment-Naïve and Previously Treated)

**No new safety signals or unexpected findings**

<table>
<thead>
<tr>
<th>Selected Adverse Events, Study Eye or Systemic, n (%)</th>
<th>0.3 mg Ranibizumab n = 89</th>
<th>1.5 mg RG7716 n = 55</th>
<th>6.0 mg RG7716 n = 80</th>
<th>All Patients N = 224</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraocular inflammation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>3 (3.4%)</td>
<td>0</td>
<td>1 (1.3%)</td>
<td>4 (1.8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (7.9%)</td>
<td>5 (9.1%)</td>
<td>6 (7.5%)</td>
<td>18 (8.0%)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>1 (1.1%)</td>
<td>0</td>
<td>0</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular death</td>
<td>1 (1.1%)</td>
<td>0</td>
<td>1 (1.3%)</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td>All deaths attributed to cardiac, cerebral, hemorrhagic, embolic, other vascular, or unknown causes</td>
<td>1 (1.1%)</td>
<td>0</td>
<td>2 (2.5%)</td>
<td>3 (1.3%)</td>
</tr>
<tr>
<td>Any other death</td>
<td>1 (1.1%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (1.8%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>2 (0.9%)</td>
</tr>
</tbody>
</table>

**IOP, mmHg**

- Baseline; week 24 (pre-dose); (change from baseline)

<table>
<thead>
<tr>
<th></th>
<th>0.3 mg Ranibizumab n = 89</th>
<th>1.5 mg RG7716 n = 55</th>
<th>6.0 mg RG7716 n = 80</th>
<th>All Patients N = 224</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline; week 24</td>
<td>15.1; 15.4 (0.1)</td>
<td>16.0; 16.6 (0.6)</td>
<td>15.3; 15.3 (-0.1)</td>
<td>NA</td>
</tr>
</tbody>
</table>

<sup>a</sup> Kidney failure. <sup>b</sup> Gangrene.

Observed data; safety population includes both anti-VEGF treatment-naïve and previously anti–VEGF-treated patients. BOULEVARD clinical trial (NCT02699450). IOP, intraocular pressure; NA, not applicable.
Safety – All Patients (Anti-VEGF Treatment-Naïve and Previously Treated)

No new safety signals or unexpected findings

- Ocular and systemic safety profile of RG7716 was consistent with the safety profile observed in patients with DME treated with intravitreal anti-VEGF drugs, with no new safety signals observed
- No adverse events of intraocular inflammation or endophthalmitis
- No increase in mean intraocular pressure
- No increase in mean blood pressure

Observed data; safety population includes both anti-VEGF treatment-naïve and previously anti-VEGF-treated patients. BOULEVARD clinical trial (NCT02699450). DME, diabetic macular edema; VEGF, vascular endothelial growth factor.
Outlook

Presentation of additional data and analyses at future meetings

• Efficacy in previously anti–VEGF-treated patients
• Additional anatomical outcomes
• Duration of effect
Conclusions

RG7716 met its primary endpoint in the BOULEVARD phase 2 DME trial

**RG7716**

- The first bispecific antibody specifically designed for intravitreal use that simultaneously binds and neutralizes both Ang-2 and VEGF-A

**BOULEVARD phase 2 study in DME***

- RG7716 demonstrated robust visual acuity gains in patients with DME at 6 months, with a mean of + 13.9 letters gained from baseline
- RG7716 demonstrated statistically significant BCVA gains over ranibizumab at 6 months (mean gain of + 3.6 letters over ranibizumab, \( P = 0.03 \))
- \( \geq 2 \)- and \( \geq 3 \)-line gainers, CST reduction, and DRSS improvement data support BCVA primary outcome
- Both primary and secondary outcomes showed a dose-dependent response
- RG7716 was well tolerated and showed no new or unexpected safety signals

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*Results for anti-VEGF treatment-naïve patients.
Thank You to the More Than 70 Participating Study Sites
Thank You to All Involved in the BOULEVARD Trial

- The authors would like to thank all those involved in the BOULEVARD trial, in particular all of the patients and their families, and all of the investigators

- Principal investigators (all US):
