Financial Disclosures

Adverum (C, R); Alimera Sciences (C); Allegro (C); Allergan (C, R); Alnylam (C); Apellis (C, R); Bayer (C); Clearside Biomedical (C, R); DORC (C); EyePoint (C, R); Genentech/Roche (C, R); Kodiak (C); Neurotech (R); Notal Vision (C); Novartis (C, R); ONL Therapeutics (C); Opthea (R); PolyPhotonix (C); Recens Medical (C); Regeneron (C, R, S); Regenxbio (C, R); Samsung (R), Santen (C, R)
Global Report on Diabetes (2016)

World Health Organization

- 1990s: 2.8%
- 2010: 5.0%
- 2016: 8.0%

79% increase from 1990s to 2010, 60% increase from 2010 to 2016.
Is the Threshold for Treating DR Changing?

Yes, Slowly
Threshold of Treating Diabetic Retinopathy

CI-DME

PDR
Threshold of Treating Diabetic Retinopathy

Non-CI-DME

CI-DME s VA Loss

Non-high Risk PDR
ETDRS Diabetic Retinopathy Severity Scale

**Mild NPDR**
- 35

**Moderate NPDR**
- 43

**Moderately Severe NPDR**
- 47

**Severe NPDR**
- 53

**PDR (PRP)**
- 60

**Absent or Questionable**
- 10-20

**Mild PDR**
- 61

**Moderate PDR**
- 65

**High-Risk PDR**
- 71

**Advanced PDR**
- 81

**Advanced PDR**
- 85
DRSS = Highly Predictive of PDR Development

N at 1 year = 1958; 3 years = 1746; 5 years = 1417.
Health-Related Quality of Life

NEI-VFQ-25 Scores

Driving Difficulty Score

NEI-VFQ-25 Composity Score

Vision-Related Functional Burden of Diabetic Retinopathy Across Severity Levels in the United States

1004 patients NHANES

- Vision Related Functional Burden
  - Mild & Moderate NPDR ≈ 20%
  - Severe NPDR / PDR ≈ 48.5%

Association Between the Severity of Diabetic Retinopathy and Falls in an Asian Population With Diabetes

- 9481 patients Singapore
- Self-reported falls
- Significantly increased fall risk with DR
Neutralization of Vascular Endothelial Growth Factor Slows Progression of Retinal Nonperfusion in Patients with Diabetic Macular Edema

Ophthalmology 2014

Development of RNP

Eyes with no RNP at Baseline

Non-Perfusion, %

Months

Sham / Crossover

Ranibizumab 0.3 mg

Ranibizumab 0.5 mg

Peter A. Campochiaro, MD,1 Charles C. Wykoff, MD, PhD,2 Howard Shapiro, PhD,2 Roman G. Rubio, MD,3 Jason S. Ehrlich, MD, PhD4
DRSS Improvements with Anti-VEGF Dosing

≈1/3rd Improve ≥2 Steps

<table>
<thead>
<tr>
<th>Protocol T</th>
<th>RIDE/RISE</th>
<th>VISTA/VIVID</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Aflibercept)</td>
<td>B (Bevacizumab)</td>
<td>R (Ranibizumab)</td>
</tr>
<tr>
<td>Sham</td>
<td>R 0.3 mg</td>
<td>R 0.5 mg</td>
</tr>
<tr>
<td>N = 170</td>
<td>N = 255</td>
<td>N = 234</td>
</tr>
<tr>
<td>N = 166</td>
<td>N = 234</td>
<td>N = 234</td>
</tr>
<tr>
<td>N = 180</td>
<td>N = 234</td>
<td>N = 234</td>
</tr>
</tbody>
</table>

% Patients achieving ≥ 2 DRSS Step Score Improvement Through 2 Years of Dosing

A = aflibercept
B = bevacizumab
R = ranibizumab
DR Improvements by Baseline DR Severity

- **Sham**
- **Ranibizumab 0.3 mg**
- **Ranibizumab 0.5 mg**

<table>
<thead>
<tr>
<th>Baseline DR Severity Level</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>35/43</td>
</tr>
<tr>
<td>10%</td>
<td>47/53</td>
</tr>
<tr>
<td>16%</td>
<td>74</td>
</tr>
<tr>
<td>12%</td>
<td>86</td>
</tr>
<tr>
<td>78%</td>
<td>88</td>
</tr>
<tr>
<td>81%</td>
<td>74</td>
</tr>
<tr>
<td>7%</td>
<td>30</td>
</tr>
<tr>
<td>31%</td>
<td>29</td>
</tr>
<tr>
<td>36%</td>
<td>33</td>
</tr>
</tbody>
</table>

Phase 3, Double-masked, Randomized, Study of Efficacy & Safety of IAI in Patients with Moderately Severe to Severe NPDR (DRSS Level 47 and 53) N=402**

- Sham N=133
- 2q16 IAI 2 mg Q16 weeks* N=135
- 2q8 IAI 2 mg Q8 weeks* N=134

**Patients were stratified by baseline DRSS level
2q8, 2 mg every 8 weeks; 2q16, 2 mg every 16 weeks; ASNV, anterior segment neovascularization; CI-DME, center-involved diabetic macular edema; DRSS, Diabetic Retinopathy Severity Score; IAI, intravitreal aflibercept injection; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

*After 3 initial monthly doses and 1 q8 interval; *After 5 initial monthly doses, flexible treatment schedule after week 52

Week 24
Primary Endpoint: Proportion of patients improving ≥ 2 steps on DRSS
All IAI Combined versus Sham

Week 52
Primary Endpoint: Proportion of patients improving ≥ 2 steps on DRSS
2q16 and 2q8 individually versus Sham

Follow up through Week 100

Key Secondary Endpoints
% developing PDR/ASNV
% developing CI-DME
Dosing Schedule

Patients progressing to PDR/ASNV or CI-DME were eligible for rescue treatment (IAI or laser) at investigator discretion. Data for patients receiving rescue treatment was censored from the time of rescue.

<table>
<thead>
<tr>
<th>Week:</th>
<th>BL</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
<th>32</th>
<th>36</th>
<th>40</th>
<th>44</th>
<th>48</th>
<th>52</th>
<th>56</th>
<th>...100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>2q16</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>O</td>
<td>X</td>
<td>O</td>
<td>X</td>
<td>O</td>
<td>X</td>
<td>O</td>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2q8</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>+</td>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

= primary endpoints at weeks 24 and 52. X=active injection, O=sham injection
### Baseline Disease Characteristics and Disposition

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Group 1</th>
<th>Group 2</th>
<th>All IAI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (FAS/SAF)</td>
<td>133</td>
<td>135</td>
<td>134</td>
<td>269</td>
<td>402</td>
</tr>
<tr>
<td>ETDRS BCVA (letters)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snellen Equivalent</td>
<td>82.7 (6.03)</td>
<td>82.2 (6.63)</td>
<td>82.3 (5.15)</td>
<td>82.4 (5.96)</td>
<td>82.3 (5.93)</td>
</tr>
<tr>
<td>CRT(microns)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>249.4 (38.41)</td>
<td>246.0 (34.34)</td>
<td>246.8 (31.59)</td>
<td>246.4 (32.94)</td>
<td>247.4 (34.82)</td>
</tr>
<tr>
<td>Diabetic Retinopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity Score (DRSS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 47</td>
<td>99 (74.4%)</td>
<td>102 (75.6%)</td>
<td>101 (75.4%)</td>
<td>203 (75.5%)</td>
<td>302 (75.1%)</td>
</tr>
<tr>
<td>Level 53</td>
<td>34 (25.6%)</td>
<td>33 (24.4%)</td>
<td>33 (24.6%)</td>
<td>66 (24.5%)</td>
<td>100 (24.9%)</td>
</tr>
<tr>
<td>Number of Patients who Completed at Week 24</td>
<td>119 (89.5%)</td>
<td>129 (95.6%)</td>
<td>132 (98.5%)</td>
<td>261 (97.0%)</td>
<td>380 (94.5%)</td>
</tr>
</tbody>
</table>

Group 1: 3 monthly doses followed by 1 Q8 interval then Q16, Group 2: 5 monthly doses then Q8
Treatment Experience through Week 52

# Active Injections
(out of 6 for 2q16 and 9 for 2q8)

Sham n=133, 2q16 n=135, 2q8 n=134
Proportion of Patients with ≥2-Step Improvement from Baseline in DRSS at Week 52

LOCF; Sham n=133, 2q16 n=135, 2q8 n=134

*p < 0.0001 vs. sham
Proportion of Patients with ≥2-Step Improvement from Baseline in DRSS at Week 52

LOCF; Sham n=133, 2q16 n=135, 2q8 n=134
Proportion of Patients Developing a Vision Threatening Complication (VTC) or Center Involved (CI)-DME through Week 52

Proportion of Patients Developing a Vision Threatening Complication (VTC) or Center Involved (CI)-DME through Week 52

VTC (PDR/ASNV) or CI-DME

Proportion of Patients

Reduction vs Sham

76.3% 72.4%

9.6%* 11.2%*

54/133 13/135 15/134

Number needed to treat = 3 patients in order to prevent 1 prespecified VTC or CI-DME event

*p < 0.0003 vs. sham

VTC = Vision threatening complication, PDR/ASNV; FAS; Sham n=133, 2q16 n=135, 2q8 n=134

Number needed to treat = 3 patients in order to prevent 1 prespecified VTC or CI-DME event

*p < 0.0003 vs. sham
Paradigm Shifting
We Should Treat Earlier

VS

Incomplete
Should Not Shift Threshold
Paradigm Shifting
We Should Treat Earlier

• Treating earlier significantly decreases the probability of developing PDR & DME, thresholds traditionally used to initiate treatment

• For many exudative diseases, including nAMD & CI-DME with VA loss, the earlier one intervenes, overall better outcomes can be achieved

• Anti-VEGF treatment can significantly slow the development & progression of RNP, the core vascular pathology of DR

• NPDR is associated with reduced visual function & QOL measures
Interesting But Incomplete
Should Not Shift Current Thresholds for Treatment

• Through 1 year, 59% of control eyes did not develop PDR or DME
  • Therefore a lot of patients will be treated who may not need it

• While rare, intravitreal injections do carry risks

• No data to show that waiting until these eyes develop DME or early PDR & then treating achieves worse outcomes

• Longer-term data is needed as indefinite frequent re-treatments is not realistic
**Ongoing Trials**

**PANORAMA**

Phase 3 RCT: aflibercept vs sham
Moderately severe to severe NPDR Without DME (DRSS Level 47 & 53)

- Aflibercept Regimen 1
- Aflibercept Regimen 2
- Sham

- Week 24 & Week 52 (primary endpoint: Proportion of patients improving ≥2 steps on DRSS)
- Week 100 (secondary endpoints)

**DRCR.Net Protocol W**

Phase 3 RCT: aflibercept vs sham
Moderately severe to severe NPDR Without DME (DRSS Level 47 & 53)

- Sham
- Aflibercept

- Primary outcome: % eyes that develop PDR/PDR-related outcomes or CI DME causing VA loss at 2 years
### TABLE 6 MANAGEMENT RECOMMENDATIONS FOR PATIENTS WITH DIABETES

<table>
<thead>
<tr>
<th>Severity of Retinopathy</th>
<th>Presence of Macular Edema</th>
<th>Follow-up (Months)</th>
<th>Panretinal Photocoagulation (Scatter) Laser</th>
<th>Focal and/or Grid Laser*</th>
<th>Intravitreal Anti-VEGF Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or minimal NPDR</td>
<td>No</td>
<td>12</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>No</td>
<td>12</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>ME</td>
<td>4-6</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>CSME(^1)</td>
<td>1(^*)</td>
<td>No</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>No</td>
<td>12(^2)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>ME</td>
<td>3-6</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>CSME(^1)</td>
<td>1(^*)</td>
<td>No</td>
<td>Sometimes</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>No</td>
<td>4</td>
<td>Sometimes</td>
<td>No</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>ME</td>
<td>2-4</td>
<td>Sometimes</td>
<td>No</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>CSME(^1)</td>
<td>1(^*)</td>
<td>Sometimes</td>
<td>No</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Non-high-risk PDR</td>
<td>No</td>
<td>4</td>
<td>Sometimes</td>
<td>No</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>ME</td>
<td>2-4</td>
<td>Sometimes</td>
<td>No</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>CSME(^1)</td>
<td>1(^*)</td>
<td>Sometimes</td>
<td>No</td>
<td>Sometimes</td>
</tr>
<tr>
<td>High-risk PDR</td>
<td>No</td>
<td>4</td>
<td>Recommended</td>
<td>No</td>
<td>Alternative(^129, 130)</td>
</tr>
<tr>
<td></td>
<td>ME</td>
<td>4</td>
<td>Recommended</td>
<td>No</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>CSME(^1)</td>
<td>1(^*)</td>
<td>Recommended</td>
<td>No</td>
<td>Usually</td>
</tr>
</tbody>
</table>

\(^1\) CSME = Central and/or Superior Macular Edema

\(^*\) Indicates the need for immediate referral to an ophthalmologist.

\(^1\) PDR = Proliferative Diabetic Retinopathy
What is Coming that Will Improve Outcomes?

*It Depends on Your Horizon*
**Additional Anti-VEGFs**
Brolucizumab, Abicipar, Conbercept, KSI-301 & TKi (Sunitinib, DE-120)

**Alternative Targets**
- Ang/Tie-2
- Integrins
- VEGF-C & D
- Tissue Factor
- Endoglin

**MoonShots**
- Subcutaneous
- Gene Therapy
- Stem Cells
- Drops
- Pills

**Drug Delivery Approaches**
Angiopoietin / Tie-2 Pathway

- Key regulator of vascular stability
- Initially identified as a vascular-specific receptor tyrosine kinase pathway essential for vessel development
  - Tie 2: cloned in 1992
  - ANG-1: cloned in 1996
  - ANG-2: cloned in 1997
ANG-2 & VEGF-A = Key Drivers of Angiogenesis

Angiopoietin / Tie-2 axis modulates endothelial cell stabilization

**ANG-1** = Strong activation of downstream signaling, stabilizing normal vasculature & integrity of blood-retinal-barrier

**Tie-2**

**ANG-2** = Partial Tie-2 agonist, competitively inhibiting ANG-1, endothelial destabilization and vascular leakage when overexpressed

**VEGF-A**

Drives vascular permeability, leukostasis and angiogenesis
ANG-2 Can Contribute to Inflammatory Signaling Independent of Tie-2
ANG-2 can drive pericyte apoptosis under hyperglycemic conditions

Angiopoietin-2 Implicated in Exudative Retinal Diseases

**VEGF**

Aiello LP, et al. VEGF in Ocular Fluid of Patients with Diabetic Retinopathy and Other Retinal Disorders *NEJM* 1994

**ANG-2**

Angiopoietin-1 compared to Angiopoietin-2 Levels

Interfering with ANG-2 Cascade

Endothelial cell

Pericyte

Angiogenic switch

ANG-

Tie-2

Stabilizes endothelium & maintains pericytes

Reduces exudation & NV

Reduces influx of inflammatory cytokines

ANG-2

VEGF-A

Tyrosine kinase

Tyrosine kinase
**RG7716 Bispecific**

**N=229**

---

**Adjusted Mean BCVA Gains From Baseline**

RG7716 met its prespecified primary endpoint of efficacy

- Linear model adjusted for baseline BCVA and randomization stratification factors.
  - $P = 0.031$
  - 80% CI 1.03, 5.61

### Adjusted Mean CST Change From Baseline

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

### Week 24

- 35% increase over ranibizumab

### ≥ 2-Step DR Improvement at Week 24

- Patients, %
  - 0% 40% 60% 80%
  - 49 57 66

---

**Nesvacumab + Aflibercept Coformulation**

**N=302**

---

**Mean Change in Best-Corrected Visual Acuity**

*Baseline - Week 12*

- Mean change in logMAR ETDRS letters
  - p = 0.1246 (95% CI: -0.04, 0.07)
  - p = 0.3716 (95% CI: -0.10, 0.18)

**Mean Central Retinal Thickness**

*Baseline - Week 12*

- Proportion of patients with normalization of macular thickness (CRT ≤ 300 μm)
  - LD (n=47)
  - HD (n=49)
  - MI (n=102)

- % with ≥ 2 step DRSS Improvement at Week 12
  - LD (21.3%)
  - HD (17.3%)
  - MI (15.2%)

- $P = 0.51$
**AKB-9778**
Small molecule activator of Tie-2
(Inhibitor of VE-PTP: vascular endothelial protein tyrosine phosphatase)

**Angiogenic switch**

**ANG-2**
Stabilizes endothelium & maintains pericytes
Reduces exudation & NV
Reduces influx of inflammatory cytokines

**Endothelial cell**
**Pericyte**

**Tyrosine Kinase**

**VEGF-A**
**VEGFR2**

**Enhanced Benefit in Diabetic Macular Edema from AKB-9778 Tie2 Activation Combined with Vascular Endothelial Growth Factor Suppression**
Campochiaro et al. Ophthalmology 2016
Subcutaneous Injection

AKB-9778: Small molecule activator of Tie-2

Enhanced Benefit in Diabetic Macular Edema from AKB-9778 Tie2 Activation Combined with Vascular Endothelial Growth Factor Suppression

TIME-2 Trial

% Demonstrating ≥2 Step DRSS Improvement at Month 3 (N=144, secondary endpoint)

Study Eye *

<table>
<thead>
<tr>
<th></th>
<th>AKB-9778</th>
<th>Ranibizumab</th>
<th>AKB-9778 + Ranibizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>46</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>10</td>
<td>11.4</td>
<td>10</td>
<td>8.8</td>
</tr>
</tbody>
</table>

Fellow Eye *

<table>
<thead>
<tr>
<th></th>
<th>Ranibizumab</th>
<th>AKB-9778</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2</td>
<td>11.4</td>
<td></td>
</tr>
</tbody>
</table>

* Not statistically significant differences

Campochiaro et al. Ophthalmology 2016
New drugs & devices are interesting but what else is brewing?

Artificial Intelligence + Deep Learning
Deep Learning Model: trained from 284,335 patients’ retinal images
Predict CV risk factors not previously thought to be quantifiable in retinal images

- Age
- Gender
- Smoking status
- BMI

- HbA1c
- Systolic BP
- Diastolic BP
Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs

Vanun Gulshan, PhD; Lily Peng, MD, PhD; Marc Coram, PhD; Martin C. Stumpe, PhD; Derek Wu, BS; Anuradharam Narayanaswamy, PhD; Subhashini Venugopalan, MSc; Katsumi Wilder, MS; Tom MacGill, ML; Jorge Cuadros, OD, PhD; Ramasamy Kiem, OD, DNB; Rajiv Ramani, MS, DNB; Philip C. Nelson, BS; Jessica L. Megel, MD, MPH; Dale R. Webster, PhD

Author Affiliations: Google Inc.

Translating Artificial Intelligence Into Clinical Care
Andrew L. Beam, PhD; Isaac S. Kohane, MD, PhD

THE NEW YORKER

ANNALS OF MEDICINE. APRIL 3, 2017 ISSUE

AI. VERSUS M.D.
What happens when diagnosis is automated?
By Siddhartha Mukherjee

Geoffrey Hinton
father of deep learning
“They should stop training radiologists now”
Management of Retinal Vascular Diseases
Today & Tomorrow

Thank You

Charles C. Wykoff MD PhD