Intravitreal Afibercept for Moderately Severe to Severe Non-Proliferative Diabetic Retinopathy (NPDR)
The Phase 3 PANORAMA Study

Charles C. Wykoff MD PhD
On Behalf of the PANORAMA Investigators
Disclosures

• Financial Disclosures
  • Adverum (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)

• Study Disclosures
  - This study includes research conducted on human subjects. Institutional Review Board approval was obtained prior to study initiation.
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.

Follow up through Week 100

* 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

Key Secondary Endpoints

% developing PDR/ASNV  
% developing CI-DME

PANORAMA Study Design
Inclusion & Exclusion Criteria

**Inclusion**
- Anti-VEGF treatment naïve with moderately severe to severe NPDR (DRSS levels 47 or 53), confirmed by the central reading center, in whom PRP could be safely deferred for ≥6 months
- BCVA ETDRS letter score of ≥69 letters (~ Snellen equivalent of ≥20/40)

**Exclusion**
- DME threatening the center of the macula
- Evidence of retinal neovascularization
- Any prior treatment with:
  - Focal or grid laser photocoagulation or PRP
  - Systemic or intravitreal anti-VEGF agents
  - Intraocular steroids
- Current ASNV, vitreous hemorrhage, or traction retinal detachment
- HbA1c >12% or HbA1c ≤12% with uncontrolled diabetes mellitus
- Uncontrolled blood pressure
- History of cerebrovascular accident or myocardial infarction within 6 months of study start
### Dosing Schedule

<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>
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<tr>
<td>2q16</td>
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<td>X</td>
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<td>2q8</td>
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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.

= primary endpoints at weeks 24 and 52. X=active injection, O=sham injection
<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>2q16</th>
<th>2q8</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (FAS/SAF)</td>
<td>133</td>
<td>135</td>
<td>134</td>
<td>402</td>
</tr>
<tr>
<td>Age (years (SD))</td>
<td>55.8 (10.31)</td>
<td>55.4 (11.13)</td>
<td>55.8 (10.19)</td>
<td>55.7 (10.53)</td>
</tr>
<tr>
<td>Women # (%)</td>
<td>64 (48.1%)</td>
<td>60 (44.4%)</td>
<td>53 (39.6%)</td>
<td>177 (44.0%)</td>
</tr>
<tr>
<td>Race # (%)</td>
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</tr>
<tr>
<td>White</td>
<td>107 (80.5%)</td>
<td>99 (73.3%)</td>
<td>104 (77.6%)</td>
<td>310 (77.1%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>13 (9.8%)</td>
<td>16 (11.9%)</td>
<td>12 (9.0%)</td>
<td>41 (10.2%)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (3.0%)</td>
<td>12 (8.9%)</td>
<td>7 (5.2%)</td>
<td>23 (5.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (6.8%)</td>
<td>8 (5.9%)</td>
<td>11 (8.2%)</td>
<td>28 (7.0%)</td>
</tr>
<tr>
<td>Hemoglobin A1C (%)</td>
<td>8.5 (1.54)</td>
<td>8.6 (1.69)</td>
<td>8.4 (1.64)</td>
<td>8.5 (1.62)</td>
</tr>
<tr>
<td>Duration of Diabetes (years (SD))</td>
<td>15.5 (9.34)</td>
<td>13.7 (8.61)</td>
<td>14.0 (9.69)</td>
<td>14.4 (9.24)</td>
</tr>
<tr>
<td>Diabetes Type 2</td>
<td>123 (92.5%)</td>
<td>121 (89.6%)</td>
<td>124 (92.5%)</td>
<td>368 (91.5%)</td>
</tr>
</tbody>
</table>
### Baseline Disease Characteristics and Disposition

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>2q16</th>
<th>2q8</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (FAS/SAF)</td>
<td>133</td>
<td>135</td>
<td>134</td>
<td>402</td>
</tr>
<tr>
<td>ETDRS BCVA (mean letters (SD))</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>
</tr>
<tr>
<td>Snellen Equivalent</td>
<td>20/25</td>
<td>20/25</td>
<td>20/25</td>
<td>20/25</td>
</tr>
<tr>
<td>CRT (microns)</td>
<td>249.4 (38.41)</td>
<td>246.0 (34.34)</td>
<td>246.8 (31.59)</td>
<td>247.4 (34.82)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic Retinopathy Severity Score (DRSS)</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>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>100 (24.9%)</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td># of Patients Completing Week 24</td>
<td>119 (89.5%)</td>
<td>129 (95.6%)</td>
<td>132 (98.5%)</td>
<td>380 (94.5%)</td>
</tr>
<tr>
<td># of Patients Completing Week 52</td>
<td>109 (82.0%)</td>
<td>122 (90.4%)</td>
<td>124 (92.5%)</td>
<td>355 (88.3%)</td>
</tr>
</tbody>
</table>
# Active Injections

- Sham: 0.0
- 2q16: 5.5 (6 planned injections)
- 2q8: 8.6 (9 planned injections)

Treatment Experience through Week 52

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 with ≥2-Step Improvement in DRSS by Baseline DRSS Score at Week 52

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

*nominal p < 0.001 vs. sham

Level 47
Level 53
Proportion of Patients with ≥3-Step Improvement from Baseline in DRSS at Week 52

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

*nominal p < 0.001 vs. sham
Proportion of Patients with ≥2-Step Worsening from Baseline in DRSS at Week 52

- **Sham**: 8.3% (11/133)
- **2q16**: 0.7% (1/135)
- **2q8**: 0.0% (0/134)

LOCF; Sham n=133, 2q16 n=135, 2q8 n=134
Mean Change in Best Corrected Visual Acuity

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

nominal p = 0.0494 2q16 vs. sham
0.0895 2q8 vs. sham
Mean Change in Central Retinal Thickness

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

nominal p < 0.0001
2q16 and 2q8 vs. sham
Proportion of Patients Developing a Vision Threatening Complication (VTC) or Center Involved (CI)-DME through Week 52

- **VTC (PDR/ASNV) or CI-DME**
  - 40.6% (54/133)
  - Reduction vs Sham: 76.3% vs 72.4%
  - 9.6%* vs 11.2%* (13/135 vs 15/134)

- **VTC (PDR/ASNV)**
  - 20.3% (27/133)
  - 81.8% vs 85.3%
  - 3.7%* vs 3.0%* (5/135 vs 4/134)

- **CI-DME**
  - 25.6% (34/133)
  - 73.9% vs 67.9%
  - 6.7%* vs 8.2%* (9/135 vs 11/134)

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

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

*p < 0.0003 vs. sham
Proportion of Patients Developing a VTC or CI-DME through Week 52 by Baseline DRSS

VTC or CI-DME

VTC

CI-DME

Proportion of Patients

Level 47
Level 53

Sham 2q16 2q8
Sham 2q16 2q8
Sham 2q16 2q8

VTC = Vision threatening complication defined as PDR/ASNV; FAS; Sham n=133, 2q16 n=135, 2q8 n=134
# Ocular TEAEs in Study Eye through Week 52 (≥3%)

<table>
<thead>
<tr>
<th></th>
<th>Sham (N = 133)</th>
<th>2q16 (N = 135)</th>
<th>2q8 (N = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Patients ≥ 1 AE, n (%)</strong></td>
<td>67 (50.4%)</td>
<td>58 (43.0%)</td>
<td>60 (44.8%)</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctival haemorrhage</td>
<td>7 (5.3%)</td>
<td>16 (11.9%)</td>
<td>23 (17.2%)</td>
</tr>
<tr>
<td>Diabetic retinal oedema</td>
<td>32 (24.1%)</td>
<td>8 (5.9%)</td>
<td>12 (9.0%)</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>3 (2.3%)</td>
<td>6 (4.4%)</td>
<td>12 (9.0%)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>4 (3.0%)</td>
<td>10 (7.4%)</td>
<td>5 (3.7%)</td>
</tr>
<tr>
<td>Retinal exudates</td>
<td>5 (3.8%)</td>
<td>5 (3.7%)</td>
<td>7 (5.2%)</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>1 (0.8%)</td>
<td>2 (1.5%)</td>
<td>6 (4.5%)</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>1 (0.8%)</td>
<td>4 (3.0%)</td>
<td>4 (3.0%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>1 (0.8%)</td>
<td>3 (2.2%)</td>
<td>4 (3.0%)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>4 (3.0%)</td>
<td>3 (2.2%)</td>
<td>4 (3.0%)</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>13 (9.8%)</td>
<td>2 (1.5%)</td>
<td>3 (2.2%)</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>0</td>
<td>1 (0.7%)</td>
<td>4 (3.0%)</td>
</tr>
</tbody>
</table>
### Serious Ocular Events, APTC Events and Deaths through Week 52

#### Serious Ocular AEs

One patient had an SAE of Iris neovascularization, and one patient had 2 SAEs of vitreous hemorrhage and visual acuity reduced.

#### APTC EVENTS

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>2q16</th>
<th>2q8</th>
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<tbody>
<tr>
<td>N (FAS/SAF)</td>
<td>133</td>
<td>135</td>
<td>134</td>
</tr>
<tr>
<td>Number of Patients with at Least One Such AE, n (%)</td>
<td>5 (3.8%)</td>
<td>4 (3.0%)</td>
<td>2 (1.5%)</td>
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</table>

#### Deaths

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<tbody>
<tr>
<td>Deaths</td>
<td>6 (4.5%)</td>
<td>0</td>
<td>1 (0.75%)</td>
</tr>
</tbody>
</table>
• First large, prospective trial of high-risk NPDR eyes (moderately severe & severe NPDR) without DME since the ETDRS

• The proportion of patients with ≥ 2-step improvements in DRSS significantly greater with aflibercept

• PDR/ASNV & CI-DME occurred in a substantially greater proportion of sham patients

• No new safety signals identified
PANORAMA provides high-quality data to inform management of eyes with moderately severe and severe NPDR without DME

PANORAMA is a 100-week study
Thank You

PANORAMA Study Sites

USA (71 sites)

Europe
- Germany (3 sites)
- Hungary (5 sites)
- United Kingdom (2 sites)

Japan (6 sites)