A Phase 3, Double-Masked, Randomized Study Of The Efficacy And Safety Of Aflibercept In Patients With Moderately Severe To Severe NPDR

Week 100 Results

Charles C. Wykoff MD PhD
Disclosures

• This study was funded by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY). The sponsors participated in the design and conduct of the study and analysis of the data.

• CCW: Adverum (C, R); Bayer (C); Genentech/Roche (C, R); Novartis (C, R); Regeneron (C, R); Regenxbio (C, R); Takeda (C)

• Study Disclosures: This study includes research conducted on human patients. 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 PRN IAI 2 mg Q8 weeks* N=134

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
- Time to development of PDR/ASNV or CI-DME

*After 3 initial monthly doses and 1 q8 interval  
*After 5 initial monthly doses, flexible treatment schedule after week 52  
**Patients were stratified by baseline DRSS level

ASNV, anterior segment neovascularization; CI-DME, center-involved diabetic macular edema; DRSS, Diabetic Retinopathy Severity Score; NPDR, nonproliferative diabetic retinopathy;
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

**Notes:**
- BCVA, best-corrected visual acuity; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; HbA1c, glycated hemoglobin; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor.
## Patients progressing to PDR/ASNV or CI-DME were eligible for rescue treatment (IAI or laser) at the discretion of the investigator. 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>60</th>
<th>64</th>
<th>68</th>
<th>72</th>
<th>76</th>
<th>80</th>
<th>84</th>
<th>88</th>
<th>92</th>
<th>96</th>
<th>100</th>
</tr>
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<tbody>
<tr>
<td>Sham</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
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</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>
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<td></td>
</tr>
<tr>
<td>2q8 PRN</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>
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<td></td>
</tr>
</tbody>
</table>

+ = Aflibercept PRN: Injection given unless DRSS is Level 35 or better (mild NPDR) as determined by the investigator.

X=active injection, O=sham injection
## Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>2q16</th>
<th>2q8-PRN</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N (FAS/SAF)</strong></td>
<td>133</td>
<td>135</td>
<td>134</td>
<td>402</td>
</tr>
<tr>
<td><strong>Age (years (SD))</strong></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><strong>Women # (%)</strong></td>
<td>64 (48.1%)</td>
<td>60 (44.4%)</td>
<td>53 (39.6%)</td>
<td>177 (44.0%)</td>
</tr>
<tr>
<td><strong>Race # (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</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><strong>Hemoglobin A1C (%)</strong></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><strong>Duration of Diabetes (years (SD))</strong></td>
<td>15.5 (9.34)</td>
<td>13.7 (8.61)</td>
<td>14.0 (9.67)</td>
<td>14.4 (9.23)</td>
</tr>
<tr>
<td><strong>Diabetes Type 2</strong></td>
<td>123 (92.5%)</td>
<td>121 (89.6%)</td>
<td>124 (92.5%)</td>
<td>368 (91.5%)</td>
</tr>
</tbody>
</table>

FAS, Full analysis set; SAF, Safety analysis set; SD, standard deviation
## Baseline Disease Characteristics and Disposition

<table>
<thead>
<tr>
<th>N (FAS/SAF)</th>
<th>Sham</th>
<th>2q16</th>
<th>2q8•PRN</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>133</td>
<td>135</td>
<td>134</td>
<td>402</td>
</tr>
<tr>
<td>ETDRS BCVA (letters)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (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></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>247.4 (34.82)</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># of Patients Completing Week 100</td>
<td>97 (72.9%)</td>
<td>111 (82.2%)</td>
<td>112 (83.6%)</td>
<td>320 (79.6%)</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>

CRT, central retinal thickness.
Treatment Experience through Week 100

# Active Injections

Sham n=133, 2q16 n=135, 2q8 n=134
Treatment Experience* from Week 56 to 100

- **Fixed Dosing**: 2.6 doses
  - 3 prescribed doses
- **PRN Dosing**: 1.8 doses
  - 6 potential maximum

*Not including IAI rescue treatment.

Patients entering the 2nd year: Sham n=106, 2q16 n=121, 2q8 n=122 (41 patients in 2q8 group did not receive any injections in year 2)
% of Patients by Number of Injections in 2q8 PRN Group in Year 2

≈30% of eyes at each PRN dosing visit did not receive IAI despite a DRSS score worse than Level 35 as determined by the reading center*

*At any visit, twice as many patients did not receive an injection that should have (based on analysis of reading center evaluations) compared to the reverse

Patients in 2q8 group who entered the 2nd year; 2q8 n=122.
Efficacy
Proportion of Patients with ≥2-step Improvement from Baseline in DRSS

**Sham**

**2q16**

**2q8 PRN**

<table>
<thead>
<tr>
<th>Week</th>
<th>Sham</th>
<th>2q16</th>
<th>2q8 PRN</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>6.0%</td>
<td>62.7%</td>
<td>55.2%</td>
</tr>
<tr>
<td>52</td>
<td>15.0%</td>
<td>65.2%</td>
<td>79.9%</td>
</tr>
<tr>
<td>100</td>
<td>12.8%</td>
<td>62.2%*</td>
<td>50.0%*</td>
</tr>
</tbody>
</table>

*Nominal p < 0.0001 vs. sham*

Last observation carried forward (LOCF); Sham n=133, 2q16 n=135, 2q8 n=134

+Independent reading center review of investigator PRN decisions suggests under treatment during Year 2
% of Patients with DRSS Improvement at Week 100 with ≥2-step Improvement in DRSS at Week 52

Of patients who had ≥2-step improvement in DRSS at week 52, >90% had ≥1-step improvement at week 100

Patients in 2q16 and 2q8 group who entered the 2nd year; 2q16 n=121; 2q8 PRN n=122
Proportion of Patients with ≥2-Step Worsening from Baseline in DRSS through Week 100

Kaplan-Meier Analysis

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>2q16</th>
<th>2q8</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAS</td>
<td>133</td>
<td>135</td>
<td>134</td>
</tr>
<tr>
<td>Development of PDR (≥2 step worsening in DRSS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event Rate</td>
<td>20.2%</td>
<td>4.5%*</td>
<td>2.4%*</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.186</td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>

*nominal p<0.001 vs sham

PDR, proliferative diabetic retinopathy
Sham n=133, 2q16 n=135, 2q8 n=134
Proportion of Patients Developing a VTC or CI-DME through Week 52\textsuperscript{\textdagger} and 100

VTC = Vision threatening complication defined as PDR/ASNV; CI-DME = center-involved DME
FAS; Sham \(n=133\), 2q16 \(n=135\), 2q8 \(n=134\).

\textsuperscript{\textdagger}Week 52 represented by shaded portion of columns and black font

\*Nominal \(p < 0.001\) vs. sham
Proportion of Patients Developing a VTC or CI-DME through Week 100
Kaplan-Meier Analysis

VTC (PDR/ASNV) or CI-DME

- Sham: 57.7%
- 2q16: 17.9%
- 2q8: 20.5%
- PRN: 79%

VTC

- Sham: 30.6%
- 2q16: 9.1%
- 2q8: 6.9%
- PRN: 77%

CI-DME

- Sham: 38.4%
- 2q16: 11.3%
- 2q8: 14.4%
- PRN: 76%

% reduction in likelihood of developing the event over time

Proportion of Patients

- VTC = Vision threatening complication defined as PDR/ASNV
- CI-DME = center involved DME
- FAS; At baseline: Sham n=133, 2q16 n=135, 2q8 n=134

*Nominal p < 0.001 vs. sham

^Percentage reductions in risk derived from hazard ratios from Kaplan-Meier estimates.
Proportion of Patients Developing a VTC or CI-DME through Week 100 by Baseline DRSS

VTC = Vision threatening complication defined as PDR/ASNV
CI-DME = center involved DME
FAS; Sham n=133, 2q16 n=135, 2q8 n=134
% of Patients with Events in Year 2 in 2q8 PRN Group by Number of Injections

% of Patients with VTC (PDR/ASNV)

- 0% of Patients with VTC (PDR/ASNV)
- 0% of Patients with VTC (PDR/ASNV)
- 0% of Patients with VTC (PDR/ASNV)
- 0% of Patients with VTC (PDR/ASNV)

% of Patients with CI-DME

- 9.8% of Patients with 0 injections
- 7.1% of Patients with 1-2 injections
- 0.0% of Patients with 3-4 injections
- 0.0% of Patients with 5-6 injections

Patients in 2q8 group who entered the 2nd year; 2q8 n=122
Proportion of Patients Receiving PRP or Vitrectomy through Week 100

Proportion of Patients

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

14/133 (10.5%) for Sham
2/135 (1.5%) for 2q16
2/134 (1.5%) for 2q8 PRN

*Nominal p < 0.002 vs. sham
Mean Change in Best Corrected Visual Acuity

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

Nominal p = NS 2q16 vs. sham
Nominal p = NS 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
Absolute Leakage Area by Visit on Fluorescein Angiography

LOCF; Sham n=133, 2q16 n=135, 2q8 n=134
## Ocular TEAEs in Study Eye through Week 100

(≥3%)

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Sham N (%: 133)</th>
<th>2q16 N (%: 135)</th>
<th>2q8–PRN N (%: 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (FAS/SAF)</td>
<td>133</td>
<td>135</td>
<td>134</td>
</tr>
<tr>
<td>Number of patients ≥ 1 AE, n (%)</td>
<td>76 (57.1%)</td>
<td>77 (57.0%)</td>
<td>81 (60.4%)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>8 (6.0%)</td>
<td>18 (13.3%)</td>
<td>25 (18.7%)</td>
</tr>
<tr>
<td>Diabetic retinal edema</td>
<td>43 (32.3%)</td>
<td>14 (10.4%)</td>
<td>19 (14.2%)</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>3 (2.3%)</td>
<td>7 (5.2%)</td>
<td>13 (9.7%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>5 (3.8%)</td>
<td>8 (5.9%)</td>
<td>8 (6.0%)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>1 (0.8%)</td>
<td>1 (0.7%)</td>
<td>5 (3.7%)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>6 (4.5%)</td>
<td>11 (8.1%)</td>
<td>5 (3.7%)</td>
</tr>
<tr>
<td>Retinal exudates</td>
<td>6 (4.5%)</td>
<td>5 (3.7%)</td>
<td>9 (6.7%)</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>4 (3.0%)</td>
<td>7 (5.2%)</td>
<td>7 (5.2%)</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>1 (0.8%)</td>
<td>2 (1.5%)</td>
<td>7 (5.2%)</td>
</tr>
<tr>
<td>Cataract subcapsular</td>
<td>1 (0.8%)</td>
<td>5 (3.7%)</td>
<td>4 (3.0%)</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>22 (16.5%)</td>
<td>3 (2.2%)</td>
<td>5 (3.7%)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>6 (4.5%)</td>
<td>3 (2.2%)</td>
<td>5 (3.7%)</td>
</tr>
<tr>
<td>Cataract nuclear</td>
<td>0</td>
<td>0</td>
<td>6 (4.5%)</td>
</tr>
</tbody>
</table>

AE, adverse event; TEAE, treatment-emergent AE
### APTC Events and Deaths through Week 100

<table>
<thead>
<tr>
<th>Event</th>
<th>Sham</th>
<th>2q16</th>
<th>2q8-PRN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N (FAS/SAF)</strong></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>7 (5.3%)</td>
<td>8 (5.9%)</td>
<td>4 (3.0%)</td>
</tr>
<tr>
<td>Non Fatal Stroke</td>
<td>3 (2.3%)</td>
<td>5 (3.7%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Non Fatal MI</td>
<td>0</td>
<td>3 (2.2%)</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Vascular Death</td>
<td>4 (3.0%)</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>All Deaths</td>
<td>8 (6.0%)</td>
<td>1 (0.7%)</td>
<td>3 (2.2%)</td>
</tr>
</tbody>
</table>

APTC, Antiplatelet Trialists’ Collaboration; MI, myocardial infarction.
PANORAMA 100 Week Conclusions

- Proportion of patients with a ≥2-step DRSS improvement remained significantly greater with aflibercept vs sham
- Vision threatening complications (PDR/ASNV) and CI-DME occurred in a substantially greater proportion of sham patients

% Patients with ≥2-Step Improvement from BL in DRSS

% Patients Developing^

^Derived from hazard ratios from Kaplan-Meier estimates.

VTC or CI-DME

% reduction in likelihood of developing the event over time:

Nominal *p < 0.001 vs. sham for all comparisons

LOCF; Sham n=133, 2q16 n=135, 2q8 n=134
PANORAMA 100 Week Conclusions

• >92% of eyes that achieved ≥ 2-step DRSS improvement at year 1 maintained DRSS improvements from baseline with decreased dosing through Week 100

• DR is a progressive disease and despite aflibercept therapy, some eyes still developed PDR or CI-DME

• Less frequent dosing in year 2 appeared to be associated with a higher rate of PDR+CI-DME development (although n’s are small)
  – Physician assessment of DRSS scores was suboptimal; Independent reading center review of investigator PRN decisions suggests under treatment during the 2nd year

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

% Patients with ≥2-Step Improvement from BL in DRSS

% Patients Developing

- Derived from hazard ratios from Kaplan-Meier estimates.
- Nominal *p < 0.0001 vs. sham for all comparisons
- Nominal *p < 0.001 vs. sham

Week 100

+ nominal p < 0.0001 vs. sham for all comparisons

% reduction in likelihood of developing the event over time:

- Derived from hazard ratios from Kaplan-Meier estimates.
Thank You

PANORAMA Study Sites

USA (71 sites)

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

Japan (6 sites)