Treatment Effect of Intravitreal Afibercept Injection by Baseline Factors in Moderately Severe to Severe NPDR in PANORAMA

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on behalf of the PANORAMA study investigators

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Disclosures

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- Study disclosures: This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation.

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PANORAMA Study Design

Phase 3, double-masked, randomized, study of efficacy and 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 vs sham

Week 52
Primary endpoint: proportion of patients improving ≥2-steps on DRSS
2q8►PRN individually vs sham

Follow-up through week 100

Key secondary endpoints
• % developing PDR/ASNV
• % developing CI-DME

*Patients were stratified by baseline DRSS level; **After 3 initial monthly doses and 1 q8 interval; *After 5 initial monthly doses, flexible treatment schedule after week 52.
2q8, 2 mg every 8 weeks; 2q16, 2 mg every 16 weeks; AE, adverse event; ASNV, anterior segment neovascularization; CI-DME, center-involved diabetic macular edema; DME, diabetic macular edema; DRSS, Diabetic Retinopathy Severity Score; IAI, intravitreal aflibercept injection; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRN, pro re nata.
Proportion of Patients with ≥2-step Improvement in DRSS from Baseline

Graph showing the proportion of patients (%) for different treatment groups (Sham, 2q16, 2q8 PRN) across weeks 24, 52, and 100.

- Sham: 6% at 24 weeks, 15% at 52 weeks, 12.8% at 100 weeks.
- 2q16: 62.7% at 24 weeks, 65.2% at 52 weeks, 62.2% at 100 weeks (marked with an asterisk).
- 2q8 PRN: 55.2% at 24 weeks, 79.9% at 52 weeks, 50% at 100 weeks (marked with an asterisk).

*Nominal p < 0.0001 vs sham

Through week 52 in PANORAMA, ocular AEs occurring in >10% of eyes treated with sham, 2q16, and 2q8 were conjunctival hemorrhage (5.3%, 11.9%, and 17.2%, respectively) and DME (24.1%, 5.9%, and 9.0%, respectively).

Sham n = 133, 2q16 n = 135, 2q8 n = 134. *Independent reading center review of investigator PRN decisions suggests under-treatment during year 2.
Post Hoc Analysis

• **Objective**
  – To evaluate the difference in treatment effect between IAI and sham by baseline factors for the primary endpoint at weeks 52 and 100

• **Methods**
  – Difference in treatment effect across baseline factors was evaluated by Mantel-Haenszel weighting scheme adjusted by baseline DRSS stratification variable
  – Between-treatment group comparisons were evaluated by 2-sided Cochran-Mantel-Haenszel test adjusted by baseline DRSS stratification variable
  – Treatment-by-subgroup interactions were evaluated by logistic regression model using treatment, subgroup, treatment-by-subgroup interaction, and stratification variable as covariates
  – Last observation carried forward method was used to impute missing or non-gradable post-baseline data
  – For patients who received rescue treatment, data from the time rescue was given were censored
Proportion of Patients with ≥2-Step Improvement in DRSS From Baseline at Week 52

**By Age Tertiles**
- T1: ≤52 years
- T2: >52 – ≤61 years
- T3: >61 years

**By Ethnicity**
- Hispanic or Latino
- Not Hispanic or Latino

**By BMI Subgroups**
- ≤30 kg/m²
- >30 – ≤35 kg/m²
- >35 kg/m²

**By HbA1c Tertiles**
- T1: ≤7.6%
- T2: >7.6 – ≤9.1%
- T3: >9.1%

**By Duration of Diabetes Tertiles**
- T1: ≤10.3 years
- T2: >10.3 – ≤17.6 years
- T3: >17.6 years

**By Baseline DRSS Levels**
- Level 47
- Level 53

n = 133 for sham except for n = 132 in ethnicity, n = 135 for 2q16 except for n = 133 in HbA1c and n = 134 in ethnicity, n = 134 in 2q8 except n = 131 in the ethnicity analysis. BMI, body mass index; T, tertile; HbA1c, glycated hemoglobin.
Treatment Difference for Proportions with ≥2-Step DRSS Improvement at Week 52: **By Demographics**

### Age (years)
- **≤52**
- **52 – ≤61**  \( P = 0.6727 \)
- **>61**

### Hispanic or Latino
- **Yes**  \( P = 0.2540 \)
- **No**

### BMI (kg/m²)
- **≤30**
- **>30 – ≤35**  \( P = 0.8310 \)
- **>35**

**Nominal P vs sham**
- < 0.0001  \((n = 52)\)
- < 0.0001  \((n = 51)\)
- < 0.0001  \((n = 40)\)
- < 0.0001  \((n = 37)\)
- < 0.0001  \((n = 43)\)
- < 0.0001  \((n = 46)\)
- < 0.0001  \((n = 37)\)
- < 0.0001  \((n = 41)\)
- < 0.0001  \((n = 97)\)
- < 0.0001  \((n = 93)\)
- < 0.0001  \((n = 48)\)
- < 0.0001  \((n = 46)\)
- 0.0002  \((n = 48)\)
- < 0.0001  \((n = 47)\)
- < 0.0001  \((n = 39)\)
- < 0.0001  \((n = 41)\)

CI, confidence interval.
Treatment Difference for Proportions with ≥2-Step DRSS Improvement at Week 52: By Disease Characteristics

- **HbA1c (%)**
  - ≤7.6
  - >7.6 – ≤9.1: $P = 0.2482$
  - >9.1

- **Duration of diabetes (years)**
  - ≥10.3
  - >10.3 – ≤17.6: $P = 0.2809$
  - >17.6

- **DRSS score**
  - 47
  - 53

The nominal $P$ values vs sham are as follows:

- 2q16: $0.0004, < 0.0001, < 0.0001, < 0.0001, < 0.0001, < 0.0001, < 0.0001, < 0.0001, < 0.0001
- 2q8: $0.003, < 0.0001, < 0.0001, < 0.0001, < 0.0001, < 0.0001, < 0.0001, < 0.0001, < 0.0001

(n = 47, 50, 40, 38, 46, 46, 51, 46, 38, 48, 46, 40, 102, 101, 33, 33)
Proportion of Patients with ≥2-Step Improvement in DRSS From Baseline at Week 100

By Age Tertiles
- T1: ≤52 years
- T2: >52 – ≤61 years
- T3: >61 years

By Ethnicity
- Hispanic or Latino
- Not Hispanic or Latino

By BMI Subgroups
- ≤30 kg/m²
- >30 – ≤35 kg/m²
- >35 kg/m²

By HbA1c Tertiles
- T1: ≤7.6%
- T2: >7.6 – ≤9.1%
- T3: >9.1%

By Duration of Diabetes Tertiles
- T1: ≤10.3 years
- T2: >10.3 – ≤17.6 years
- T3: >17.6 years

By Baseline DRSS Levels
- Level 47
- Level 53

n = 133 for sham except for n=132 in ethnicity, n = 135 for 2q16 except for n = 133 in HbA1c and n = 134 in ethnicity, n = 134 2q8►PRN except for n = 131 in ethnicity analysis.
Treatment Difference for Proportions with ≥2-Step DRSS Improvement at Week 100: **By Demographics**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Treatment Difference at Week 100, (%)</th>
<th>Nominal P vs sham</th>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
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<td><strong>BMI (kg/m²)</strong></td>
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<td>≤30</td>
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<td>&gt;30 – ≤35</td>
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<td>&gt;35</td>
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</tbody>
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*Nominal P values and sample sizes are provided for each subgroup interaction.*
Treatment Difference for Proportions with ≥2-Step DRSS Improvement at Week 100: **By Disease Characteristics**

- **HbA1c (%)**
  - ≤7.6
  - >7.6 – ≤9.1 \( P = 0.5665 \)
  - >9.1

- **Duration of diabetes (years)**
  - ≥10.3
  - >10.3 – ≤17.6 \( P = 0.9369 \)
  - >17.6

- **DRSS score**
  - 47
  - 53

**Nominal P vs sham**
- ≤7.6: < 0.0001 (n = 47), 0.0039 (n = 50)
- >7.6 – ≤9.1: < 0.0001 (n = 40), < 0.0001 (n = 38)
- >9.1: < 0.0001 (n = 46), < 0.0001 (n = 46)
- ≥10.3: < 0.0001 (n = 51)
- >10.3 – ≤17.6: < 0.0001 (n = 38)
- >17.6: < 0.0001 (n = 46)
- 47: < 0.0001 (n = 102)
- 53: < 0.0001 (n = 101), < 0.0001 (n = 33), < 0.0001 (n = 33)
Conclusions

• This post hoc analysis found no treatment-by-subgroup interactions across selected baseline factors in patients with moderately severe to severe NPDR at both weeks 52 and 100.

• Greater proportions of eyes treated with IAI had a ≥2-step DRSS improvement from baseline compared with sham across all selected demographics and disease characteristics, in eyes with moderately severe to severe NPDR.