Retinal Nonperfusion Extent and Its Relationship with Visual, Anatomic, and Disease State Outcomes Among Eyes Treated for DME

Chirag Shah MD, MPH
_on behalf of the VISTA study investigators_

Ophthalmic Consultants of Boston

Presented at the Retina Society 2020 VR, 53rd Annual Scientific Meeting, September 21-22, 2020
Disclosures

• This study was funded by Regeneron Pharmaceuticals, Inc., and Bayer HealthCare. The sponsor participated in the design and conduct of the study, analysis of the data, and preparation of this abstract.

• Dr Shah is a sub-investigator on clinical trials sponsored by Regeneron, Genentech, NIH, Apellis, Allergan, Novartis, Ellex, Alcon.

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

• Medical writing support was provided by Lisa Heaney, PhD of Prime, Knutsford, UK according to Good Publication Practice guidelines and was funded by Regeneron Pharmaceuticals, Inc.
Progressive Retinal Non-Perfusion

>4 Years Continuous Q 4-10 Week Anti-VEGF Dosing
Neutralization of Vascular Endothelial Growth Factor Slows Progression of Retinal Nonperfusion in Patients with Diabetic Macular Edema

Improvement of RNP in >1 Quadrant

Worsening of RNP in >1 Quadrant

Observed cases. Compared with baseline
For inclusion at each time point, patients must have FA with 4/4 graded quadrants at that time point and at baseline
Digital Angiography Reading Center (Great Neck, NY)
Randomized, multicenter, double-masked trials in patients with clinically significant DME with central involvement and ETDRS BCVA 20/40 to 20/320
Randomized and treated: N = 406 (VIVID) and N = 466 (VISTA)

Patients randomized 1:1:1

IAI 2 mg q4 wks
IAI 2 mg q8 wks*
Laser photocoagulation

Primary endpoint: mean change in BCVA
Primary endpoint: week 52
Continued treatment through year 3

Key secondary endpoints: mean change in OCT % with ≥2-step DRSS improvement

- IAI given q4 weeks or q8 weeks (following 5 monthly doses) significantly improved visual and anatomic outcomes over laser at week 52. These improvements were sustained through week 100 with both IAI regimens
- In an integrated safety analysis, the most frequent serious ocular adverse event at week 100 was cataract (2.4%, 1.0%, and 0.3% for 2q4, 2q8, and control)

*After 5 initial monthly doses. 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; BCVA, best-corrected visual acuity; DME, diabetic macular edema; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; IAI, intravitreal aflibercept injection; OCT, optical coherence tomography.
Objectives

• To quantify macular RNP area in mm$^2$ at baseline and through week 100

• To assess the relationship between changes from baseline in macular RNP area and the following outcomes at week 100:
  – BCVA
  – CST
  – DRSS score

• To evaluate the impact of baseline macular RNP area on the incidence of PDR events

CST, central subfield thickness; PDR, proliferative diabetic retinopathy; RNP, retinal non-perfusion.
• Patients with macular RNP at baseline were included
• Macular RNP area was quantified at baseline, weeks 24, 52, and 100 by a reading center (Digital Angiography Reading Center [DARC], New York, NY)
• PDR events included PDR (graded by reading center), PRP, or vitrectomy
• Full analysis set and observed cases were used; data were censored after rescue treatment was given
• Statistical analyses included MMRM, Mantel-Haenszel weighting scheme, Pearson/Spearman correlation, Kaplan–Meier, Cox PH model
• *P*-values are considered nominal

*FAZ was included when it could be measured. Standard grid size of 7.2 mm for camera systems was used.

FAZ = foveal avascular zone; MMRM = mixed-effects models for repeated measures

Patient Disposition

VISTA (N = 466)

Patients randomized 1:1:1

IAI 2q4
N = 156

IAI 2q8
N = 154

Laser
N = 156

Patients included in the full analysis set (N = 459)

N = 156

N = 154

N = 151

N = 63

Missing images at BL, wk52, or wk100 (n = 50)
Non-gradable images at BL (n = 46)
No RNP at BL (n = 0)

Missing images at BL, wk52, or wk100 (n = 44)
Non-gradable images at BL (n = 47)
No RNP at BL (n = 0)

Missing images at BL, wk52, or wk100 (n = 54)
Non-gradable images at BL (n = 38)
No RNP at BL (n = 2)

Missing images at BL, wk52, or wk100 (n = 54)
Non-gradable images at BL (n = 38)
No RNP at BL (n = 2)

BL, baseline.
## Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Laser</th>
<th>IAI 2q4</th>
<th>IAI 2q8</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>63</td>
<td>60</td>
<td>55</td>
<td>178</td>
</tr>
<tr>
<td><strong>Mean age, years (SE)</strong></td>
<td>60 (1.0)</td>
<td>59 (1.5)</td>
<td>62 (1.4)</td>
<td>60 (0.8)</td>
</tr>
<tr>
<td><strong>Female, n %</strong></td>
<td>29 (46)</td>
<td>24 (40)</td>
<td>26 (47)</td>
<td>79 (44)</td>
</tr>
<tr>
<td><strong>Mean BMI (SE)</strong></td>
<td>31 (0.9)</td>
<td>33 (0.9)</td>
<td>31 (0.8)</td>
<td>32 (0.5)</td>
</tr>
<tr>
<td><strong>Mean HbA1c, % (SE)</strong></td>
<td>7.5 (0.2)</td>
<td>7.8 (0.2)</td>
<td>7.9 (0.2)</td>
<td>7.7 (0.1)</td>
</tr>
<tr>
<td>&gt;8%, n (%)</td>
<td>19 (30)</td>
<td>21 (35)</td>
<td>22 (40)</td>
<td>62 (35)</td>
</tr>
<tr>
<td>&lt;=8%, n (%)</td>
<td>44 (70)</td>
<td>39 (65)</td>
<td>33 (60)</td>
<td>116 (65)</td>
</tr>
</tbody>
</table>

BMI, body mass index; SE, standard error.
## Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographic/Characteristics</th>
<th>Laser</th>
<th>IAI 2q4</th>
<th>IAI 2q8</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>63</td>
<td>60</td>
<td>55</td>
<td>178</td>
</tr>
<tr>
<td>Mean BCVA, letters (SE)</td>
<td>61 (1.4)</td>
<td>61 (1.3)</td>
<td>59 (1.5)</td>
<td>60 (0.8)</td>
</tr>
<tr>
<td>Mean CRT, µm (SE)</td>
<td>496 (17)</td>
<td>486 (16)</td>
<td>502 (23)</td>
<td>495 (11)</td>
</tr>
<tr>
<td>Mean duration of DM, years (SE)</td>
<td>15 (1.2)</td>
<td>15 (1.1)</td>
<td>19 (1.3)</td>
<td>16 (0.7)</td>
</tr>
<tr>
<td>DRSS level, n (%)</td>
<td>0</td>
<td>2 (3.3)</td>
<td>1 (1.8)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td></td>
<td>2 (3.2)</td>
<td>2 (3.3)</td>
<td>1 (1.8)</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td></td>
<td>1 (1.6)</td>
<td>1 (1.7)</td>
<td>3 (5.5)</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td></td>
<td>21 (33.3)</td>
<td>17 (28.3)</td>
<td>21 (38.2)</td>
<td>59 (33.1)</td>
</tr>
<tr>
<td></td>
<td>13 (20.6)</td>
<td>10 (16.7)</td>
<td>12 (21.8)</td>
<td>35 (19.7)</td>
</tr>
<tr>
<td></td>
<td>20 (31.7)</td>
<td>23 (38.3)</td>
<td>15 (27.3)</td>
<td>58 (32.6)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1 (1.7)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td></td>
<td>6 (9.5)</td>
<td>2 (3.3)</td>
<td>1 (1.8)</td>
<td>9 (5.1)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>2 (3.3)</td>
<td>1 (1.8)</td>
<td>3 (1.7)</td>
</tr>
</tbody>
</table>

CRT, central retinal thickness; DM, diabetes mellitus.
## Baseline Macular RNP Area

<table>
<thead>
<tr>
<th></th>
<th>Laser</th>
<th>IAI 2q4</th>
<th>IAI 2q8</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>63</td>
<td>60</td>
<td>55</td>
<td>178</td>
</tr>
<tr>
<td>Mean baseline RNP, mm² (SD)</td>
<td>1.5 (1.7)</td>
<td>1.7 (2.5)</td>
<td>1.5 (1.5)</td>
<td>1.6 (1.9)</td>
</tr>
<tr>
<td>Median</td>
<td>0.9</td>
<td>0.8</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0.1, 7.7</td>
<td>0.1, 13.8</td>
<td>0.2, 6.5</td>
<td>0.1, 13.8</td>
</tr>
</tbody>
</table>

Red tracing outlines area of 1.495 mm² of RNP
Macular RNP Area Change Through Week 100

LS Mean Change From Baseline (±SE)

**Laser**
- Weeks 0: BL, n = 63
- Weeks 24: IAI 2q4, n = 40
- Weeks 52: IAI 2q8, n = 29
- Weeks 100: BL, n = 26

**2q4, n**
- Weeks 0: BL, n = 60
- Weeks 24: IAI 2q4, n = 31
- Weeks 52: IAI 2q8, n = 33
- Weeks 100: BL, n = 23

**2q8, n**
- Weeks 0: BL, n = 55
- Weeks 24: IAI 2q4, n = 33
- Weeks 52: IAI 2q8, n = 31
- Weeks 100: BL, n = 25

*Nominal Full analysis set, VISTA (censor after rescue, OC); error bars represent standard error BL = baseline; CI = confidence interval; LS = Least Square; SE = standard error
Correlations Between RNP and Visual and Anatomic Changes from Baseline at Week 100

<table>
<thead>
<tr>
<th></th>
<th>Laser</th>
<th>IAI 2q4</th>
<th>IAI 2q8</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>26</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>BCVA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation coefficient (95% CI)</td>
<td>0.1 (–0.3, 0.5)</td>
<td>–0.6 (–0.8, –0.2)</td>
<td>–0.5 (–0.7, –0.1)</td>
</tr>
<tr>
<td>$P$ value</td>
<td>0.5084</td>
<td>0.0045</td>
<td>0.0230</td>
</tr>
<tr>
<td>CST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation coefficient (95% CI)</td>
<td>–0.1 (–0.5, 0.3)</td>
<td>0.7 (0.4, 0.9)</td>
<td>0.4 (0.04, 0.7)</td>
</tr>
<tr>
<td>$P$ value</td>
<td>0.5656</td>
<td>0.0002</td>
<td>0.0288</td>
</tr>
<tr>
<td>DRSS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation coefficient (95% CI)</td>
<td>–0.1 (–0.5, 0.3)</td>
<td>0.4 (–0.04, 0.7)</td>
<td>0.1 (–0.32, 0.5)</td>
</tr>
<tr>
<td>$P$ value</td>
<td>0.6670</td>
<td>0.0680</td>
<td>0.6840</td>
</tr>
</tbody>
</table>

CI, confidence interval.
Development of PDR Events By the Extent of Baseline RNP
Proportion of Patients who Developed PDR Events Through Week 100

PDR events = PDR, PRP, or vitrectomy
Patients with baseline macular RNP and NPDR included.
NPDR, nonproliferative diabetic retinopathy.
Time to Development of PDR Events Through Week 100 by the Extent of Baseline Macular RNP

<table>
<thead>
<tr>
<th>T1 (≤0.615 mm²)</th>
<th>T2 (0.615–1.255 mm²)</th>
<th>T3 (&gt;1.255) mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate per 100 PYR</td>
<td>Time to event (days)</td>
<td>Cox Regression</td>
</tr>
<tr>
<td>1.1 NE</td>
<td>25% percentile</td>
<td>P value</td>
</tr>
<tr>
<td>T1</td>
<td>NE</td>
<td>–</td>
</tr>
<tr>
<td>T2</td>
<td>NE</td>
<td>0.6870</td>
</tr>
<tr>
<td>T3</td>
<td>NE</td>
<td>0.0052</td>
</tr>
</tbody>
</table>

Cumulative Incidence (%)

Time to First PDR Event (days)

0 168 364 700
T1 (n = 55) 0 0 0 1
T2 (n = 55) 0 1 2 2
T3 (n = 55) 0 1 6 8

Full analysis set, VISTA (censor after rescue, OC).
PDR events = PDR, PRP or Vitrectomy. NE = not estimable; PYR = person-years at risk; T = tertile.
Hazard Ratio of PDR Event Incidence by Extent of Baseline Macular RNP Area Through Week 100

Patients with NPDR at baseline were included. PDR events = PDR, PRP, or Vitrectomy.
Limitations

- Post hoc analysis
- High missing number of FA images primarily due to the inclusion requirement for having complete set of assessments at baseline and weeks 52 and 100
- Absence of peripheral nonperfusion assessment
• Mean area of RNP at baseline was small, approximately 1.6 mm$^2$
• There were small decreases in RNP from baseline through week 100 across all arms:
  – Decreases in RNP from baseline with IAI was statistically significant at week 100
  – These changes were not statistically different between arms
• Moderate correlations identified between RNP reduction and BCVA increase and CST decrease from baseline at week 100 among IAI-treated patients
• Similar to PANORAMA, lower proportion of patients treated with IAI developed PDR compared to laser
• Extent of baseline RNP associated with increased risk of development of a PDR event, particularly among laser-treated patients.