Incidence of New Diabetic Macular Edema in Fellow Eyes of Patients in the VISTA and VIVID studies

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on behalf of the VISTA and VIVID study investigators

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Disclosures

• Dr Dhoot is a consultant for Regeneron Pharmaceuticals, Inc., Genentech, Allergan, Alimera, Santen, Allegro, and Notal Vision

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

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VIVID and VISTA are 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 = 404 (VIVID) & N = 461 (VISTA).

Patients randomized 1:1:1

Primary endpoint: mean change in BCVA

Primary endpoint: week 52

Continued treatment through year 3

IAI 2 mg q4 wks

IAI 2 mg q8 wks*

Laser photocoagulation

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

• IAI given q4 weeks or q8 weeks (following 5 initial 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).

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 characterize occurrence of DME in fellow eye of patients treated for DME in study eye in the VISTA and VIVID studies through year 2

• Following parameters were evaluated:
  – Incidence of DME in fellow eye
  – Time to development of DME in fellow eye
  – Baseline factors predicting DME occurrence in fellow eye
  – Cumulative rates of DME occurrence in fellow eye by various baseline risk factors
Methods

- **Inclusion criteria**
  - No DME in fellow eye at baseline (from 6 weeks before baseline through 4 weeks after first study eye treatment)
- **Presence of DME in fellow eye** was evaluated based on related AEs and reported medications (anti-VEGF agents) or procedures (laser) for treatment of DME
- **Safety analysis set, observed case**
- **Statistical analyses** included t-test, Kaplan–Meier, Cox proportional hazards model
- **Post hoc analysis**, $P$ value < 0.05 was considered nominally significant

AEs, adverse events; VEGF, vascular endothelial growth factor.
VISTA (N = 466); VIVID (N = 406); Total N = 872

Patients randomized 1:1:1

IAI 2q4 n = 292

IAI 2q8 n = 289

Laser n = 291

Patients included in the safety analysis set (n = 865)

Fellow eyes with DME at baseline n = 46

Fellow eyes with DME at baseline n = 29

Fellow eyes with DME at baseline n = 35

n = 291

n = 287

n = 287

n = 245

n = 287

n = 258

n = 258

n = 252

Fq4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks.
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Laser (n = 252)</th>
<th>IAI 2q4 (n = 245)</th>
<th>IAI 2q8 (n = 258)</th>
<th>Total (n = 755)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SE), years</strong></td>
<td>62.9 (0.5)</td>
<td>62.8 (0.6)</td>
<td>63.6 (0.5)</td>
<td>63.1 (0.3)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>145 (57.5)</td>
<td>141 (57.6)</td>
<td>151 (58.5)</td>
<td>437 (57.9)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>19 (7.5)</td>
<td>30 (12.2)</td>
<td>28 (10.9)</td>
<td>77 (10.2)</td>
</tr>
<tr>
<td>Not Hispanic or Latino, n (%)</td>
<td>230 (91.3)</td>
<td>215 (87.8)</td>
<td>230 (89.2)</td>
<td>675 (89.4)</td>
</tr>
<tr>
<td><strong>Mean duration of diabetes, years (SE)a</strong></td>
<td>16.6 (0.64)</td>
<td>16.0 (0.62)</td>
<td>16.1 (0.64)</td>
<td>16.2 (0.36)</td>
</tr>
<tr>
<td><strong>Hemoglobin A1c, Mean (SE), %b</strong></td>
<td>7.7 (0.1)</td>
<td>7.9 (0.1)</td>
<td>7.8 (0.1)</td>
<td>7.8 (0.1)</td>
</tr>
<tr>
<td>&gt;8%, n (%)</td>
<td>83 (32.9)</td>
<td>95 (38.8)</td>
<td>91 (35.3)</td>
<td>269 (35.6)</td>
</tr>
<tr>
<td><strong>Mean study eye BCVA, lettersa (SE)</strong></td>
<td>60.4 (0.7)</td>
<td>60.0 (0.7)</td>
<td>59.5 (0.7)</td>
<td>59.9 (0.4)</td>
</tr>
<tr>
<td><strong>Study eye DRSS score, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤35</td>
<td>11 (4.4)</td>
<td>15 (6.1)</td>
<td>14 (5.4)</td>
<td>40 (5.3)</td>
</tr>
<tr>
<td>43</td>
<td>87 (34.5)</td>
<td>71 (29.0)</td>
<td>75 (29.1)</td>
<td>233 (30.9)</td>
</tr>
<tr>
<td>47</td>
<td>42 (16.7)</td>
<td>35 (14.3)</td>
<td>50 (19.4)</td>
<td>127 (16.8)</td>
</tr>
<tr>
<td>53</td>
<td>68 (27.0)</td>
<td>75 (30.6)</td>
<td>76 (29.5)</td>
<td>219 (29.0)</td>
</tr>
<tr>
<td>≥61</td>
<td>11 (4.4)</td>
<td>11 (4.5)</td>
<td>12 (4.7)</td>
<td>34 (4.5)</td>
</tr>
<tr>
<td>Missing</td>
<td>33 (13.1)</td>
<td>38 (15.5)</td>
<td>31 (12.0)</td>
<td>102 (13.5)</td>
</tr>
</tbody>
</table>

Data for patients without DME in fellow eye at baseline.  

*Laser (n = 251), IAI 2q4 (n = 244), IAI 2q8 (n = 257), Total (N = 752);  
*bLaser (n = 250), IAI 2q4 (n = 241), IAI 2q8 (n = 258), Total (N = 749).  
SE, standard error.
## Medical History

<table>
<thead>
<tr>
<th>Condition</th>
<th>Laser (n = 252)</th>
<th>IAI 2q4 (n = 245)</th>
<th>IAI 2q8 (n = 258)</th>
<th>Total (n = 755)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>54 (21.4)</td>
<td>53 (21.6)</td>
<td>46 (17.8)</td>
<td>153 (20.3)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>10 (4.0)</td>
<td>8 (3.3)</td>
<td>9 (3.5)</td>
<td>27 (3.6)</td>
</tr>
<tr>
<td>Depression, n (%)</td>
<td>36 (14.3)</td>
<td>23 (9.4)</td>
<td>37 (14.3)</td>
<td>96 (12.7)</td>
</tr>
<tr>
<td>Anxiety, n (%)</td>
<td>22 (8.7)</td>
<td>10 (4.1)</td>
<td>14 (5.4)</td>
<td>46 (6.1)</td>
</tr>
<tr>
<td>Any antidepressants, n (%)</td>
<td>43 (17.1)</td>
<td>41 (16.7)</td>
<td>30 (11.6)</td>
<td>114 (15.1)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>196 (77.8)</td>
<td>189 (77.1)</td>
<td>211 (81.8)</td>
<td>596 (78.9)</td>
</tr>
<tr>
<td>Insulin use, n (%)</td>
<td>173 (68.7)</td>
<td>168 (68.6)</td>
<td>161 (62.4)</td>
<td>502 (66.5)</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>133 (52.8)</td>
<td>142 (58.0)</td>
<td>151 (58.5)</td>
<td>426 (56.4)</td>
</tr>
<tr>
<td>Former</td>
<td>95 (37.7)</td>
<td>71 (29.0)</td>
<td>91 (35.3)</td>
<td>257 (34.0)</td>
</tr>
<tr>
<td>Current</td>
<td>24 (9.5)</td>
<td>32 (13.1)</td>
<td>16 (6.2)</td>
<td>72 (9.5)</td>
</tr>
</tbody>
</table>

Data for patients without DME in fellow eye at baseline.
Proportion of Fellow Eyes That Developed DME Through Week 100

<table>
<thead>
<tr>
<th>Group</th>
<th>Laser n = 252</th>
<th>IAI 2q4 n = 245</th>
<th>IAI 2q8 n = 258</th>
<th>Total N = 755</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion (%)</td>
<td>42.9</td>
<td>44.9</td>
<td>44.2</td>
<td>44.0</td>
</tr>
</tbody>
</table>

Proportion of Patients (%)

*IAI per protocol when available.*
## Cumulative Incidence of DME in Fellow Eye

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate per 100 PYR</th>
<th>Time to event (days)</th>
<th>Cox regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>25th percentile (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Laser</td>
<td>35.4</td>
<td>148 (118, 224)</td>
<td>–</td>
</tr>
<tr>
<td>IAI 2q4</td>
<td>36.7</td>
<td>202 (144, 261)</td>
<td>0.8403</td>
</tr>
<tr>
<td>IAI 2q8</td>
<td>38.4</td>
<td>130 (96, 156)</td>
<td>0.6270</td>
</tr>
</tbody>
</table>

**Cumulative Incidence (%)**

**Time to Development of DME in Fellow Eye (days)**

<table>
<thead>
<tr>
<th>Laser (n = 252)</th>
<th>0</th>
<th>17</th>
<th>47</th>
<th>66</th>
<th>75</th>
<th>81</th>
<th>85</th>
<th>92</th>
<th>95</th>
<th>97</th>
<th>100</th>
<th>101</th>
<th>101</th>
<th>107</th>
<th>108</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAI 2q4 (n = 245)</td>
<td>0</td>
<td>9</td>
<td>40</td>
<td>54</td>
<td>65</td>
<td>75</td>
<td>80</td>
<td>88</td>
<td>91</td>
<td>94</td>
<td>101</td>
<td>105</td>
<td>108</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>IAI 2q8 (n = 258)</td>
<td>0</td>
<td>19</td>
<td>61</td>
<td>81</td>
<td>84</td>
<td>94</td>
<td>101</td>
<td>105</td>
<td>108</td>
<td>108</td>
<td>112</td>
<td>114</td>
<td>114</td>
<td>114</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; PYR, person-years at risk.
## Time to Development of DME in Fellow Eye Through Week 100

<table>
<thead>
<tr>
<th>Patients developed DME</th>
<th>Laser</th>
<th>IAI 2q4</th>
<th>IAI 2q8</th>
<th>IAI 2q4+2q8</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>108</td>
<td>110</td>
<td>114</td>
<td>224</td>
<td>332</td>
</tr>
<tr>
<td>Mean time to DME development, days (SE)</td>
<td>201 (17)</td>
<td>236 (17)</td>
<td>161 (13)</td>
<td>198 (11)</td>
<td>199 (9)</td>
</tr>
<tr>
<td>Min, max (days)</td>
<td>30, 687</td>
<td>31, 687</td>
<td>30, 613</td>
<td>30, 687</td>
<td>30, 687</td>
</tr>
<tr>
<td>Mean difference vs laser, days (95% CI)</td>
<td>–</td>
<td>35.0 (−13.1, 83.2)</td>
<td>−40.6 (−82.6, 1.4)</td>
<td>−3.5 (−42.4, 35.5)</td>
<td>–</td>
</tr>
<tr>
<td>$P$ value</td>
<td>–</td>
<td>0.1530</td>
<td>0.0581</td>
<td>0.8613</td>
<td>–</td>
</tr>
</tbody>
</table>

Difference, CI and $P$ value were calculated using t-test.
Baseline Factors Predicting Development of DME in Fellow Eyes
Univariate Analysis of Baseline Characteristics

Baseline Variables Included in Cox Regression Model

Demographics & Characteristics
- Age
- Gender
- Ethnicity
- BMI
- Smoking history

Disease Characteristics
- Diabetes duration
- BCVA in study eye
- DRSS score in study eye
- CST in study eye

Comorbidities
- Hypertension
- Anxiety
- Depression
- Dyslipidemia
- Hyperlipidemia

Concomitant Medications
- Antidepressants
- Insulin

BMI, body mass index; CST, central subfield thickness.
## Univariate Analysis of Baseline Characteristics

Baseline Variables Identified as Risk Factors in Cox Regression Model

### Demographics & Characteristics
- Age
- Gender
- Ethnicity
- BMI
- Smoking history

### Disease Characteristics
- Diabetes duration
- BCVA in study eye
- DRSS score in study eye
- CST in study eye

### Comorbidities
- Hypertension
- Anxiety
- Depression
- Dyslipidemia
- Hyperlipidemia

### Concomitant medications
- Antidepressants
- Insulin
Univariate Analysis: Hazard Ratio of DME Development in Fellow Eyes

Baseline variables

- CST study eye (per 10 µm increase)  $< 0.0001$
- Duration of diabetes (per 10 yrs decrease)  $0.0046$
- BCVA study eye (per 10 letters increase)  $0.0004$
- Insulin (yes vs no)  $0.0110$
- Study eye DRSS score: 43 vs ≤35  $0.5563$
- 47 vs ≤35  $0.1160$
- 53 vs ≤35  $0.0492$
- ≥61 vs ≤35  $0.0038$
Multivariante Analysis: Hazard Ratio of DME Development in Fellow Eyes

Baseline variables

Duration of diabetes (per 10 yrs decrease)

CST study eye (per 10 µm increase)

Hazard ratio was estimated using Cox regression model and stepwise selection with baseline CST study eye, baseline duration of diabetes diagnosis, baseline study eye BCVA, baseline insulin use, and baseline DRSS score category as the covariates. Model was decided by stepwise selection.

Hazard ratio was estimated using Cox regression model and stepwise selection with baseline CST study eye, baseline duration of diabetes diagnosis, baseline study eye BCVA, baseline insulin use, and baseline DRSS score category as the covariates.

Model was decided by stepwise selection.
Cumulative Incidence of DME Development in Fellow Eye
By Baseline Duration of Diabetes

Cumulative Incidence (%)

Time to Development of DME in Fellow Eye (days)

Data for all groups combined. T, tertile.
Cumulative Incidence of DME Development in Fellow Eye
By Baseline CST in Study Eye

<table>
<thead>
<tr>
<th>Time to Development of DME in Fellow Eye (days)</th>
<th>Rate per 100 PYR</th>
<th>Time to event (days) 25th percentile (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1: ≤412 µm</td>
<td>25.0</td>
<td>302 (159, 454)</td>
<td>–</td>
</tr>
<tr>
<td>T2: 412–534 µm</td>
<td>35.8</td>
<td>141 (106, 202)</td>
<td>0.0226</td>
</tr>
<tr>
<td>T3: &gt;534 µm</td>
<td>53.1</td>
<td>102 (90, 148)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data for all groups combined.
Rates of Fellow Eye DME by Number of Initially Identified Baseline Risk Factors

Number of baseline risk factor = any combination of (no insulin usage), (study eye DRSS score ≥61), (BCVA in study eye ≤67 letters), (CST in study eye >534 µm), (duration of diabetes ≤20 years).

Rate Per 100 PYR

<table>
<thead>
<tr>
<th>Number of Risk Factors</th>
<th>Rate Per 100 PYR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16.8</td>
</tr>
<tr>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>40.3</td>
</tr>
<tr>
<td>3</td>
<td>42.4</td>
</tr>
<tr>
<td>4</td>
<td>77.7</td>
</tr>
<tr>
<td>5</td>
<td>90.9</td>
</tr>
</tbody>
</table>
Limitations

• Post hoc analysis
• DME identified based on AEs and concomitant medications and procedures
• BCVA data was not available for analysis
• No CST data collected for fellow eye
Conclusions

- Almost half of patients with DME in one eye developed DME in fellow eye over 2 years of follow-up
  - Time to development of DME in fellow eye was approximately 6 months
- Shorter duration of diabetes and thicker baseline CST in the study eye were identified as key risk factors for DME development in fellow eye
- Rate of DME development in fellow eye increased with the increasing numbers of risk factors
- These findings suggest that patients with DME in one eye should be closely monitored for DME development in fellow eye