Aflibercept Overview:
Mode of Action and Clinical Evidence in DME management
Outline:

- Mechanism of action of Aflibercept.
- Differences from other anti VEGFs.
- Summary of VIVID and VISTA clinical data.
- How is Aflibercept used in DME?
- Summary of Protocol T clinical data.
Aflibercept was specifically designed for strong, broad and sustained activity

- Recombinant fusion protein consisting of portions of human VEGFR-1 and VEGFR-2 extracellular domains fused to the Fc portion of human IgG1
- Binds VEGF-A and PGF (placental growth factor, also known as PI GF) with higher affinity than their native receptors
- Forms a stable, inert 1:1 complex with VEGF-A, binding both sides of the dimer and preventing interaction with other molecules.
- Aflibercept also binds Galectin-1, which is a growth factor that is found in elevated levels in PDR independent of VEGF level.

Fc, fragment, crystallizable; IgG, immunoglobulin G; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Aflibercept binds or ‘traps’ both sides of the VEGF dimer\textsuperscript{1,2}

- Aflibercept binds or ‘traps’ both sides of the VEGF dimer. Aflibercept–VEGF complexes
- Bevacizumab can ‘daisy-chain’ or ‘paper-doll’ with VEGF, which can lead to large, multimeric conglomerates. Bevacizumab–VEGF dimers
- Ranibizumab–VEGF dimers

\textbullet\ Ab, antibody; Fc, fragment, crystallizable; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Afiblercept strongly inhibits VEGF-A and PGF, both potent promoters of angiogenesis

- All commonly used anti-VEGF agents inhibit all VEGF-A isoforms
  - In a preclinical study, afiblercept blocks VEGF-induced activation of VEGFR-1/-2 with up to 92 times greater potency than ranibizumab and bevacizumab
  - Afiblercept also inhibits the activity of PGF, unlike ranibizumab and bevacizumab

<table>
<thead>
<tr>
<th></th>
<th>VEGFR-1 cell line</th>
<th>VEGFR-2 cell line</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IC(<em>{50}) at 20 pM VEGF-A(</em>{121})</td>
<td>IC(<em>{50}) at 20 pM VEGF-A(</em>{165})</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>854 pM</td>
<td>1,476 pM</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>675 pM</td>
<td>1,140 pM</td>
</tr>
<tr>
<td>Afiblercept</td>
<td><strong>15 pM</strong></td>
<td><strong>16 pM</strong></td>
</tr>
</tbody>
</table>

- IC\(_{50}\), 50% inhibitory concentration; NB, no detectable blocking under the assay conditions used; PGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGF-A\(_{121}\), VEGF-A 121 amino acid splice variant; VEGF-A\(_{165}\), VEGF-A 165 amino acid splice variant; VEGFR, vascular endothelial growth factor receptor.
VEGF-A and PGF are upregulated in mouse retinas with experimentally-induced CNV

- In mouse models, laser-burn induced CNV was associated with significantly elevated levels of VEGF-A and PGF, compared with sham\(^1\)

- Mice lacking PGF developed significantly reduced laser-induced CNV compared to wild-type controls\(^2\)

---

Expression of VEGF-A and PGF

<table>
<thead>
<tr>
<th></th>
<th>Relative protein expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGF</td>
<td>4</td>
</tr>
<tr>
<td>VEGF-A</td>
<td>3</td>
</tr>
</tbody>
</table>

Laser-induced neovascularization in mouse retinas

- *P*<0.05. ***P*<0.001.

- CNV, choroidal neovascularization; PGF, placental growth factor; VEGF, vascular endothelial growth factor.

In Muether et al., ranibizumab was reported to suppress VEGF-A levels for a mean of 36 days

- Prospective study
- 83 eyes of 83 patients; mean 10.3 samples per patient
- Sub- or juxtafoveal CNV attributable to neovascular AMD
- Aqueous samples obtained immediately prior to 0.5 mg ranibizumab injection
- LLD 4 pg/mL VEGF-A
- Mean duration of VEGF-A suppression: **36.4** days (standard deviation ± 6.7 days; range: 26–69 days)

AMD, age-related macular degeneration; CNV, choroidal neovascularization; LLD, lower limit of detection; VEGF, vascular endothelial growth factor.

In a clinical study, aflibercept was reported to suppress VEGF-A levels for a mean of 71 days

- VEGF suppression of individual patients
- Mean suppression time in aqueous humor: 71 days ± 18 days

LLQ, lower limit of quantification; VEGF, vascular endothelial growth factor.

Aflibercept was shown to have a VEGF suppression time twice as long as ranibizumab in neovascular AMD

- **Fauser et al. (2016)** prospectively studied 7 eyes of 7 patients with long-standing persistent activity under ranibizumab therapy who were switched to aflibercept*

- Mean duration of VEGF-A suppression: 34 ± 5 days for ranibizumab and 67 ± 14 days for aflibercept (P<0.001)

![Graph showing the duration of VEGF suppression for each patient](https://example.com/graph.png)

- Aqueous samples obtained immediately prior to injection; LLD 4 pg/mL VEGF-A.
- LLD, lower limit of detection; VEGF, vascular endothelial growth factor; AMD, age-related macular degeneration.
The mean period of clinical CNV inactivity was twice as long with aflibercept as with ranibizumab.

<table>
<thead>
<tr>
<th>Clinical inactivity period (days)</th>
<th>Recurrence of clinical activity (days)</th>
<th>VEGF suppression time (days)</th>
<th>Clinical inactivity as a percentage of VEGF suppression time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab</td>
<td>14 ± 12</td>
<td>20 ± 9</td>
<td>34 ± 5</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>33 ± 6</td>
<td>36 ± 7</td>
<td>67 ± 14</td>
</tr>
</tbody>
</table>

Ratio: aflibercept/ranibizumab: 2.3/1.8/2.0

Aflibercept: VEGF suppression for a mean of ~10 weeks, 2x as long as ranibizumab.

- CNV, choroidal neovascularization; VEGF, vascular endothelial growth factor.
The efficacy of aflibercept is supported by robust Phase III clinical trials

**Neovascular age-related macular degeneration (AMD):**
- VIEW 1 and VIEW 2; SIGHT

**Central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO):**
- GALILEO and COPERNICUS; VIBRANT

**Diabetic macular edema (DME):**
- VIVID (including VIVID-EAST and VIVID-Japan) and VISTA; DRCR.net Protocol T

**Myopic choroidal neovascularization (mCNV):**
- MYRROR

DRCR.net, Diabetic Retinopathy Clinical Research Network.
VIVID and VISTA studies
Afibercept in DME
Study sites across continents

- **Europe**
  - Austria, Czech Republic, Denmark, France, Germany, Hungary, Italy, Poland, Spain

- **Japan**

- **USA**

- **VISTA**
  - 54 centres
  - 466 patients

- **VIVID**
  - 73 centres
  - 406 patients
Study design

Randomised, multicentre, double-masked trials in patients with clinically significant DME with central involvement and ETDRS BCVA 20/40 to 20/320

N=406 (VIVID)  N=466 (VISTA)

Patients randomised 1:1:1

Laser photocoagulation*

Aflibercept 2 mg q4 weeks

Aflibercept 2 mg q8 weeks†

Primary endpoint:
Mean change in BCVA from baseline

Primary endpoint:
Week 52

Secondary endpoints included:
Proportion of eyes that:
Gained ≥15 letters
≥2-step improvement in DRSS

Continued treatment through year 3

*Focal or grid laser; †After 5 initial monthly doses.
BCVA, best corrected visual acuity; DME, diabetic macular edema; DRSS, diabetic retinopathy severity scale; ETDRS, Early Treatment Diabetic Retinopathy Study.
Number of treatments are markedly lower in 2q8 arms than 2q4 arms

- Week 52: 13 or 9 injections possible in 2q4 and 2q8 groups, respectively; # of lasers, minimum = 1, maximum = 5.
- Week 100: 25 or 15 injections possible in 2q4 and 2q8 groups, respectively; # of lasers, minimum = 1, maximum = 9. *Not considering additional treatment.
- VIVID: Laser: n=133; 2q4: n=136; 2q8: n=135; VISTA: Laser: n=154; 2q4: n=155; 2q8: n=152. 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks.
Initial rapid gains in visual acuity are maintained over 100 weeks

**VIVID week 100**
- 10.7 2q8*
- 10.5 2q4*
- 1.2 Laser

**VISTA week 100**
- 12.5 2q4*
- 10.7 2q8*
- 0.2 Laser

- `*P<0.0001 vs. laser.` VIVID: Laser: n=132; 2q4: n=136; 2q8: n=135; VISTA: Laser: n=154; 2q4: n=154; 2q8: n=151.

- Full analysis set. 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

Diabetic Retinopathy Clinical Research Network

Aflibercept, Bevacizumab, or Ranibizumab for DME: Two-year Results

Supported through a cooperative agreement from the National Eye Institute; National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health, Department of Health and Human Services EY14231, EY14229, EY018817
Randomization

Randomly Assigned Eyes (one per participant):
N = 660

Baseline

- Aflibercept (2.0 mg)
  N = 224

One Year

- N = 208 (93%)

One Year Excluding Deaths

- 94%

- Bevacizumab (1.25 mg)
  N = 218

- N = 206 (94%)

- Ranibizumab (0.3 mg)
  N = 218

- N = 206 (94%)

- 96%

- 97%
Main Outcome

Change in visual acuity at 1 Yr (primary outcome) and 2 Yrs
- Adjusted for baseline visual acuity and multiple comparisons
- Multiple imputation for missing values, intent-to-treat principle
- Truncated to 3 SD from the mean

Aflibercept vs. Bevacizumab
Aflibercept vs. Ranibizumab
Bevacizumab vs. Ranibizumab

- Visits were every 4 weeks during year-1 and 4 to 16 weeks during year-2, depending on treatment course
- Starting at the 6-month visit, focal/grid laser treatment was administered if DME persisted and was not improving
- Participants unmasked to treatment group following the publication of the 1yr primary results: though discouraged, decision could be made at that time to switch to a non-study anti-VEGF agent.
- Doses: aflibercept 2.0-mg; bevacizumab 1.25-mg; ranibizumab 0.3-mg
# DME Treatment Through 1 Year: anti-VEGF and Laser

## # of Injections (Max = 13)

|                | Afiblercept N = 208 | Bevacizumab N = 206 | Ranibizumab N = 206 | P-Value
|----------------|---------------------|---------------------|---------------------|---------
| **Mean**       | 9.2                 | 9.7                 | 9.4                 |
| **Median**     | 9 (8, 11)           | 10 (8, 12)          | 10 (8, 11)          |
| **(25th, 75th percentile)** |                   |                     |                     |
| **At least one focal/grid laser** | 37%              | 56%                 | 46%                 |

†Global (overall 3 group comparison) P-value. Pairwise comparisons (adjusted for multiple comparisons): aflibercept-bevacizumab: *P* = 0.045, aflibercept-ranibizumab: *P* = 0.19, bevacizumab-ranibizumab: *P* = 0.22.

‡Global (overall 3 group comparison) P-value. Pairwise comparisons (adjusted for multiple comparisons): aflibercept-bevacizumab: *P*<0.001, aflibercept-ranibizumab: *P* = 0.058, bevacizumab-ranibizumab: *P* = 0.061.
Mean Change in Visual Acuity Letter Score, Full Cohort

52 Week Treatment Group Comparison*:
- Aflibercept vs. Bevacizumab $P < 0.001$
- Aflibercept vs. Ranibizumab $P = 0.034$
- Ranibizumab vs. Bevacizumab $P = 0.12$

* $P$-values adjusted for baseline visual acuity and multiple comparisons
Mean Change in Visual Acuity Letter Score

Baseline Visual Acuity 20/32 to 20/40

Mean Change in Visual Acuity Letter Score

Weeks

Aflibercept
Bevacizumab
Ranibizumab

~+8

~50% of Cohort
Mean Change in Visual Acuity Letter Score

Baseline Visual Acuity 20/50 or Worse

~ 50% of Cohort

1-Year Treatment Group Comparison*:
- Aflibercept vs. Bevacizumab $P < 0.001$
- Aflibercept vs. Ranibizumab $P = 0.0031$
- Ranibizumab vs. Bevacizumab $P = 0.21$

* $P$-values adjusted for baseline visual acuity and multiple comparisons
### # of Visits in Year 2*
(Completers Only)

<table>
<thead>
<tr>
<th></th>
<th>Aflibercept N = 201</th>
<th>Bevacizumab N = 185</th>
<th>Ranibizumab N = 192</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>9.4</td>
<td>9.3</td>
<td>9.3</td>
</tr>
<tr>
<td><strong>Median</strong> (25th, 75th percentile)</td>
<td>10 (8, 12)</td>
<td>10 (7, 12)</td>
<td>10 (7, 12)</td>
</tr>
</tbody>
</table>

* Protocol required monthly visits in year 1 for all 3 groups
### DME Treatment: anti-VEGF
(Completers of the given visit only)

<table>
<thead>
<tr>
<th></th>
<th>Aflibercept</th>
<th>Bevacizumab</th>
<th>Ranibizumab‡</th>
<th>Global P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># of Injections:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>9 (8, 11)</td>
<td>10 (8, 12)</td>
<td>10 (8, 11)</td>
<td>0.045‡</td>
</tr>
<tr>
<td>Year 2</td>
<td>5 (2, 7)</td>
<td>6 (2, 9)</td>
<td>6 (2, 9)</td>
<td>0.32</td>
</tr>
<tr>
<td>Over 2 Years</td>
<td>15 (11, 17)</td>
<td>16 (12, 20)</td>
<td>15 (11, 19)</td>
<td>0.078</td>
</tr>
</tbody>
</table>

**NOTE:** 98% of protocol required re-injections were given over 2 years

† Pairwise comparisons (adjusted for multiple comparisons):  A-B: $P = 0.045$, A-R: $P = 0.19$, B-R: $P = 0.22$.
‡Seven study eyes received 1 injection and 2 eyes received 2 injections of 0.5-mg of ranibizumab prior to the FDA approving a 0.3-mg dosage of ranibizumab for DME treatment and protocol revision to use 0.3-mg dose.
## DME Treatment: Laser
(Completers of the given visit only)

<table>
<thead>
<tr>
<th></th>
<th>Aflibercept</th>
<th>Bevacizumab</th>
<th>Ranibizumab</th>
<th>Global P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one focal/grid laser</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>37%</td>
<td>56%</td>
<td>46%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Year 2</td>
<td>20%</td>
<td>31%</td>
<td>27%</td>
<td>0.046‡</td>
</tr>
<tr>
<td>Over 2 Years</td>
<td>41%</td>
<td>64%</td>
<td>52%</td>
<td>&lt;0.001†</td>
</tr>
</tbody>
</table>

*Pairwise comparisons (adjusted for multiple comparisons): A-B: P<0.001, A-R: P=0.058, B-R: P=0.061
‡ Pairwise comparisons (adjusted for multiple comparisons): A-B: P=0.046, A-R: P=0.12, B-R: P=0.37.
†Pairwise comparisons (adjusted for multiple comparisons): A-B: P<0.001, A-R: P=0.043, B-R: P=0.013.
Efficacy
Mean Change in Visual Acuity Over 2 Years

Full Cohort

Weeks

0 4 8 12 16 20 24 28 32 36 40 44 48 52 68 84 104

Mean Change in Visual Acuity Letter Score

0 2 4 6 8 10 12 14 16 18 20

Aflibercept

Bevacizumab

Ranibizumab

+13.3

+11.2

+9.7

+12.8

+12.3

+10.0

104-Week Treatment Group Comparison*:
- Aflibercept vs. Bevacizumab $P = 0.024$
- Aflibercept vs. Ranibizumab $P = 0.47$
- Ranibizumab vs. Bevacizumab $P = 0.11$

* $P$-values adjusted for baseline visual acuity and multiple comparisons
Mean Change in Visual Acuity Over 2 Years

Baseline Visual Acuity 20/32 to 20/40

~50% of Cohort

104-Week Treatment Group Comparison*:
- Aflibercept vs. Bevacizumab $P = 0.51$
- Aflibercept vs. Ranibizumab $P = 0.51$
- Ranibizumab vs. Bevacizumab $P = 0.31$

* $P$-values adjusted for baseline visual acuity and multiple comparisons
Mean Change in Visual Acuity Over 2 Years

Baseline Visual Acuity 20/50 or Worse

104-Week Treatment Group Comparison*:
- Aflibercept vs. Bevacizumab $P = 0.020$
- Aflibercept vs. Ranibizumab $P = 0.18$
- Ranibizumab vs. Bevacizumab $P = 0.18$

[52-Week: A vs. B $P < 0.001$ / A vs. R $P = 0.003$ / R vs. B $P = 0.21$]

* $P$-values adjusted for baseline visual acuity and multiple comparisons
Mean Change in OCT CST Over 2 Years

Baseline Visual Acuity 20/32 to 20/40

2-Year Treatment Group Comparison*:
- Aflibercept vs. Bevacizumab $P<0.001$
- Aflibercept vs. Ranibizumab $P=0.26$
- Ranibizumab vs. Bevacizumab $P<0.001$

* $P$-values adjusted for baseline visual acuity, OCT central subfield thickness, and multiple comparisons
Mean Change in OCT CST Over 2 Years

Baseline Visual Acuity 20/50 or Worse

2-Year Treatment Group Comparison*:
- Aflibercept vs. Bevacizumab $P = 0.012$
- Aflibercept vs. Ranibizumab $P = 0.18$
- Ranibizumab vs. Bevacizumab $P = 0.18$

* $P$-values adjusted for baseline visual acuity, OCT central subfield thickness, and multiple comparisons
Safety
## Pre-Specified Ocular Adverse Events through 2 Years (Study Eyes)

<table>
<thead>
<tr>
<th>% of eyes with at least 1 event</th>
<th>Aflibercept (N = 224)</th>
<th>Bevacizumab (N = 218)</th>
<th>Ranibizumab (N = 218)</th>
<th>Global P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of injections</td>
<td>2998</td>
<td>3115</td>
<td>3066</td>
<td></td>
</tr>
<tr>
<td>Endophthalmitis*</td>
<td>0</td>
<td>&lt;1%</td>
<td>0</td>
<td>0.66</td>
</tr>
<tr>
<td>Inflammation†</td>
<td>3%</td>
<td>1%</td>
<td>2%</td>
<td>0.69</td>
</tr>
<tr>
<td>Retinal detachment/tear</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1.0</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>7%</td>
<td>8%</td>
<td>5%</td>
<td>0.37</td>
</tr>
<tr>
<td>Injection-related cataract</td>
<td>1%</td>
<td>&lt;1%</td>
<td>0</td>
<td>0.38</td>
</tr>
<tr>
<td>IOP elevation‡</td>
<td>17%</td>
<td>12%</td>
<td>16%</td>
<td>0.31</td>
</tr>
</tbody>
</table>

†Includes anterior chamber cell/flare, choroiditis, episcleritis, iritis, vitreous cells.
‡Includes intraocular pressure increase ≥10mmHg from baseline at any visit, intraocular pressure ≥30 mmHg at any visit, or initiation of intraocular pressure-lowering medications not in use at baseline, or glaucoma surgery.
*Non-study eyes: endophthalmitis in <1% in aflibercept and ranibizumab groups; 0 in bevacizumab group.
# Pre-specified APTC* Adverse Events through 2 Years

<table>
<thead>
<tr>
<th>% of pts with at least one event</th>
<th>Aflibercept (N = 224)</th>
<th>Bevacizumab (N = 218)</th>
<th>Ranibizumab (N = 218)</th>
<th>Global P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal MI</td>
<td>3%</td>
<td>1%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>&lt;1%</td>
<td>3%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Vascular death</td>
<td>1%</td>
<td>4%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Any APTC Event</td>
<td>5%</td>
<td>8%</td>
<td>12%</td>
<td>0.047†</td>
</tr>
</tbody>
</table>

†Pairwise comparisons (adjusted for multiple comparisons): aflibercept-bevacizumab: P = 0.34, aflibercept-ranibizumab: P = 0.047, bevacizumab-ranibizumab: P = 0.20.

Global P-value adjusting for gender, age at baseline, Hemoglobin A1c at baseline, diabetes type, diabetes duration at baseline, insulin use, prior coronary artery disease, prior myocardial infarction, prior stroke, prior transient ischemic attack, prior hypertension, smoking status: P = 0.089.

## Other Pre-Specified Systemic Adverse Events through 2 Years

<table>
<thead>
<tr>
<th>% of pts with at least one event</th>
<th>Aflibercept (N = 224)</th>
<th>Bevacizumab (N = 218)</th>
<th>Ranibizumab (N = 218)</th>
<th>Global P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (any cause)</td>
<td>2%</td>
<td>6%</td>
<td>5%</td>
<td>0.12</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>34%</td>
<td>33%</td>
<td>33%</td>
<td>0.93</td>
</tr>
<tr>
<td>SAEs*</td>
<td>39%</td>
<td>37%</td>
<td>38%</td>
<td>0.90</td>
</tr>
<tr>
<td>Gastrointestinal†</td>
<td>30%</td>
<td>29%</td>
<td>28%</td>
<td>0.85</td>
</tr>
<tr>
<td>Kidney Events‡</td>
<td>22%</td>
<td>21%</td>
<td>16%</td>
<td>0.22</td>
</tr>
<tr>
<td>Hypertension Events</td>
<td>17%</td>
<td>12%</td>
<td>20%</td>
<td>0.080</td>
</tr>
</tbody>
</table>

†Includes events with a Medical Dictionary for Regulatory Activities system organ class of gastrointestinal disorders
‡Includes a subset of Medical Dictionary for Regulatory Activities system organ class of renal and urinary disorders events indicative of intrinsic kidney disease, plus increased/abnormal blood creatinine or renal transplant from other system organ classes
*SAEs = Serious adverse events
### Post Hoc Analysis: Cardiovascular Events* through 2 Years

<table>
<thead>
<tr>
<th>% of pts with at least one event</th>
<th>Afibercept (N = 224)</th>
<th>Bevacizumab (N = 218)</th>
<th>Ranibizumab (N = 218)</th>
<th>Global P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Cardiovascular Event, excluding Hypertension</td>
<td>20%</td>
<td>22%</td>
<td>27%</td>
<td>0.18</td>
</tr>
<tr>
<td>Any Cardiovascular Event</td>
<td>31%</td>
<td>32%</td>
<td>38%</td>
<td>0.26</td>
</tr>
</tbody>
</table>

* Events with a MedDRA system organ class of cardiac disorder or vascular disorder OR considered by the medical monitor as related to a cardiac or vascular event (cardiac murmur, cardiac pacemaker insertion/replacement, coronary arterial stent insertion, heart rate irregular, heart transplant, implantable defibrillator insertion, stent placement, and troponin increased.)
DRCR.net Protocol T: In patients with worse baseline VA (<20/40, <69 ETDRS letters), the AUC was significantly greater with aflibercept than with either comparators over 2 years\(^1\)–\(^3\)

- The area under the curve (AUC) represents the average change in VA

**Worse than 20/40**

**Primary endpoint**

**Comparison over 2 years:**
- **Aflibercept** vs. **bevacizumab** \(P=0.12\)
- **Aflibercept** vs. **ranibizumab** \(P=0.96\)
- **Ranibizumab** vs. **bevacizumab** \(P=0.12\)

- AUC over 2 years:
  - **Aflibercept 17.1**
  - **Ranibizumab 13.6**
  - **Bevacizumab 12.1**

**20/32 to 20/40**

**Comparison over 2 years:**
- **Aflibercept** vs. **bevacizumab** \(P<0.001\)
- **Aflibercept** vs. **ranibizumab** \(P=0.009\)
- **Ranibizumab** vs. **bevacizumab** \(P=0.35\)

- AUC over 2 years:
  - **Ranibizumab 7.5**
  - **Aflibercept 7.5**
  - **Bevacizumab 6.5**

AUC, area under the curve; BCVA, best corrected visual acuity; VA, visual acuity.

Kaiser et al performed a systematic review of selected ocular and systemic adverse events pooled from randomized controlled clinical trials of IAI across 4 indications: wAMD, CRVO, BRVO, DME

4103 patients from 9 clinical trials were included; range of follow-up 4 to 24 months

Analyses based on rates: number of events/person-years at risk (PYR)

PYR account for both the number of patients at risk and the time at risk

---

<table>
<thead>
<tr>
<th>Indication</th>
<th>Clinical Trials</th>
<th>Duration (weeks)</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMD</td>
<td>CLEAR-IT 2</td>
<td>52</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>VIEW 1</td>
<td>104</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>VIEW 2</td>
<td>104</td>
<td>3</td>
</tr>
<tr>
<td>CRVO</td>
<td>COPERNICUS</td>
<td>104</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>GALILEO</td>
<td>76</td>
<td>3</td>
</tr>
<tr>
<td>BRVO</td>
<td>VIBRANT</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>DME</td>
<td>DA-VINCI</td>
<td>52</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>VIVID</td>
<td>52</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>VISTA</td>
<td>52</td>
<td>3</td>
</tr>
</tbody>
</table>

Safety Review across Phase II and III Clinical Trials

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>IAI Rate</th>
<th>Comparator Rate</th>
<th>Indication</th>
<th>Overall Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound Healing</td>
<td>0.03</td>
<td>0.2 (RBZ)</td>
<td>wAMD</td>
<td>IAI: 0.1</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>0.0 (sham)</td>
<td>CRVO</td>
<td>Control: 0.2</td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>0.0 (laser)</td>
<td>BRVO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>0.3 (laser)</td>
<td>DME</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>9.9</td>
<td>10.6 (RBZ)</td>
<td>wAMD</td>
<td>IAI: 12.7</td>
</tr>
<tr>
<td></td>
<td>13.4</td>
<td>13.7 (sham)</td>
<td>CRVO</td>
<td>Control: 14.5</td>
</tr>
<tr>
<td></td>
<td>28.2</td>
<td>47.8 (laser)</td>
<td>BRVO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25.5</td>
<td>24.1 (laser)</td>
<td>DME</td>
<td></td>
</tr>
<tr>
<td>All Deaths</td>
<td>0.8</td>
<td>0.9 (RBZ)</td>
<td>wAMD</td>
<td>IAI: 0.8</td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>0.9 (sham)</td>
<td>CRVO</td>
<td>Control: 0.9</td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>2.5 (laser)</td>
<td>BRVO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.4</td>
<td>0.6 (laser)</td>
<td>DME</td>
<td></td>
</tr>
</tbody>
</table>

Data from phase II/III clinical trials of IAI demonstrate that rates of selected systemic adverse events were low for both fixed and alternative IAI dosing regimens.

Kaiser P. Systematic Review of Safety across the Phase II and Phase III Clinical Trials of Intravitreal Aflibercept Injection in Wet AMD, BRVO, CRVO, and DME [Oral Presentation]. Presented at Macula Society 2014; Key Largo, FL.; Do DV. Systematic Review of Safety across the Phase II and Phase III Clinical Trials of Intravitreal Aflibercept Injection [poster]. Presented at ARVO 2014; Orlando, FL.
## Safety Review across Phase II and III Clinical Trials

<table>
<thead>
<tr>
<th>Adjudicated APTC events</th>
<th>IAI Rate</th>
<th>Comparator Rate</th>
<th>Indication</th>
<th>Overall Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-fatal MI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.79</td>
<td>1.10 (RBZ)</td>
<td>wAMD</td>
<td>IAI: 0.8</td>
</tr>
<tr>
<td></td>
<td>0.38</td>
<td>0.0 (sham)</td>
<td>CRVO</td>
<td>Control: 1.1</td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>0.0 (laser)</td>
<td>BRVO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.27</td>
<td>1.85 (laser)</td>
<td>DME</td>
<td></td>
</tr>
<tr>
<td><strong>Non-fatal Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.40</td>
<td>0.40 (RBZ)</td>
<td>wAMD</td>
<td>IAI: 0.5</td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>0.0 (sham)</td>
<td>CRVO</td>
<td>Control: 0.5</td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>2.5 (laser)</td>
<td>BRVO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.45</td>
<td>0.74 (laser)</td>
<td>DME</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.63</td>
<td>0.30 (RBZ)</td>
<td>wAMD</td>
<td>IAI: 0.6</td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>0.92 (sham)</td>
<td>CRVO</td>
<td>Control: 0.4</td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>0.0 (sham)</td>
<td>BRVO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.72</td>
<td>0.74 (laser)</td>
<td>DME</td>
<td></td>
</tr>
</tbody>
</table>

- The overall rates for adjudicated APTC events were 1.9 for IAI and 1.9 for the control.
- IAI was generally safe and well tolerated in patients in these AMD, CRVO, BRVO, and DME trials.
THANK YOU...