Treatment for Macular Edema from Retinal Vein Occlusion Disease

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Clinical Studies for RVO

BVOS¹
Laser as SOC
(n=139)

CVOS²
Observation as SOC
(n=155)

SCORE³,⁴
BRVO (n=411)
CRVO (n=271)

BRAVO⁵ (n=397)
CRUISE⁶ (n=392)

Ozurdex™
(dexamethasone intravitreal implant)
approved⁷
(n=853)

1980s
1990s
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011-13

Vitrectomy⁸ for RVO and hemorrhage

Optic nerve sheath decompression¹⁰

Intravitreal/intravenous thrombolysis¹¹

Artery thrombolysis¹¹

Radial optic neurotomy¹¹

SOC = standard of care.™ marks owned by Allergan, Inc.

Clinical Trials and Venous Occlusive Diseases

• Laser Studies
  – Branch Vein Occlusion Study (BVOS)
  – Central Vein Occlusion Study (CVOS)

• Steroid Studies
  – SCORE Study
  – Ozurdex® (dexamethasone intravitreal implant) Trials

• Anti-VEGF Studies
BVOS Results

- Laser superior to observation for eyes with macular edema secondary to BRVO
- 20/50 or worse and no improvement after 4 months up to 18 months → laser treatment

CVOS Macular Edema Results

• Does grid treatment preserve or improve VA in eyes (VA ≤ 20/50) with macular edema and CRVO? (20/50 to 5/200)

• NO (No VA benefit although edema resolved)

<table>
<thead>
<tr>
<th></th>
<th>Grid Rx</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>77</td>
<td>78</td>
</tr>
<tr>
<td>Initial VA</td>
<td>20/160</td>
<td>20/125</td>
</tr>
<tr>
<td>Final</td>
<td>20/200</td>
<td>20/160</td>
</tr>
</tbody>
</table>


J Lim
Macular Edema in Retinal Vein Occlusion

- Exact pathogenesis unknown
- Occlusion leads to vascular leakage, fluid results in macular edema
- Low-grade, chronic inflammation is believed to exacerbate the process
- Hypoxia-induced VEGF upregulation occurs in RVO
- Steroids attenuate effects of VEGF

Steroids and Macular Edema

- **SCORE BRVO:**
  - Laser = standard of care
  - Steroid no better than laser and has complications

- **SCORE CRVO:**
  - Steroid better than observation

OZURDEX™ (dexamethasone intravitreal implant) in the Treatment of Macular Edema Following Branch or Central Retinal Vein Occlusion

- Injectable, biodegradable intravitreal implant
- 350 or 700 μg dexamethasone in the NOVADUR™ solid polymer drug delivery system
- Preservative-free

Data on file, Allergan, Inc.
## Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>OZURDEX™ n = 427</th>
<th>Sham n = 426</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>49.2%</td>
<td>43.7%</td>
</tr>
<tr>
<td>Race (white)</td>
<td>75.2%</td>
<td>74.6%</td>
</tr>
<tr>
<td>Age (years) (range)</td>
<td>64.7 (33-90)</td>
<td>63.9 (31-91)</td>
</tr>
<tr>
<td>Diagnosis in study eye</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRVO</td>
<td>31.9%</td>
<td>34.5%</td>
</tr>
<tr>
<td>BRVO</td>
<td>68.1%</td>
<td>65.5%</td>
</tr>
<tr>
<td>Duration of ME (Days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 90</td>
<td>16.4%</td>
<td>15.3%</td>
</tr>
<tr>
<td>90-179</td>
<td>51.3%</td>
<td>51.6%</td>
</tr>
<tr>
<td>&gt; 180</td>
<td>32.3%</td>
<td>33.1%</td>
</tr>
<tr>
<td>Mean VA (range)</td>
<td>54.3 (20/80)</td>
<td>54.8 (20/80)</td>
</tr>
<tr>
<td>Mean OCT (range)</td>
<td>562.0 (127-1320)</td>
<td>538.6 (94-1218)</td>
</tr>
</tbody>
</table>

Data on file, Allergan, Inc.

Please see OZURDEX™ Important Safety Information
Primary Outcome (Gain of ≥ 3 Lines)

Time to Achieve ≥15 Letters Improvement From Baseline BCVA

Log–Rank Test P–value

OZURDEX™ vs Sham: P < .001

No. at Risk

Days from the First Dose

Cumulative Response Rate (%)

Sham (n = 426)

OZURDEX™ (n = 427)

Data on file, Allergan, Inc.
Dexamethasone DDS and Macular Edema in RVO

Patients With Improvement of ≥ 15 Letters From Baseline BCVA*

- **OZURDEX™** (n = 427)
- **Sham** (n = 426)

- **P < .001** at Day 30
  - OZURDEX™: 21.3%
  - Sham: 7.5%

- **P < .001** at Day 60
  - OZURDEX™: 29.3%
  - Sham: 11.3%

- **P < .001** at Day 90
  - OZURDEX™: 21.8%
  - Sham: 13.1%

- **P = .147** at Day 180
  - OZURDEX™: 21.5%
  - Sham: 17.6%

*NS at day 180

*P values are for OZURDEX™ vs sham.

Data on file, Allergan, Inc.
Mean Change in BCVA From Baseline
BRVO Sub-Analysis

![Graph showing mean BCVA improvement over study days for OZURDEX™ (n = 291) and Sham (n = 279).]

- **OZURDEX™ (n = 291)**
  - Baseline: 0
  - Day 30: 8.5
  - Day 60: 10.3
  - Day 90: 8.7
  - Day 120: 7.4
  - Day 150: 0
  - Day 180: 3.8
- **Sham (n = 279)**
  - Baseline: 0
  - Day 30: 5.1
  - Day 60: 5
  - Day 90: 5
  - Day 120: 4.9
  - Day 150: 4.9
  - Day 180: 4.9

*P* values are for OZURDEX™ vs sham.
Data on file, Allergan, Inc.
Mean Change in BCVA From Baseline
CRVO Sub-Analysis

Mean BCVA Improvement Letters

Baseline Day 30 Day 60 Day 90 Day 120 Day 150 Day 180

Mean Change in BCVA From Baseline

CRVO Sub-

P values are for OZURDEX™ vs sham.
Data on file, Allergan, Inc.

Please see OZURDEX™ Important Safety Information

*NS at day 180
### Key Adverse Events

#### Ocular

<table>
<thead>
<tr>
<th>Event</th>
<th>OZURDEX™ (n = 421)</th>
<th>Sham (n = 423)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP increased</td>
<td>106 (25%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>85 (20%)</td>
<td>63 (15%)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>31 (7%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>28 (7%)</td>
<td>20 (5%)</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>17 (4%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td><strong>Cataract</strong></td>
<td>15 (4%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>12 (3%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Sterile or infectious endophthalmitis*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

#### Nonocular

<table>
<thead>
<tr>
<th>Event</th>
<th>OZURDEX™ (n = 421)</th>
<th>Sham (n = 423)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>14 (3%)</td>
<td>7 (2%)</td>
</tr>
</tbody>
</table>

*Intravitreal injections have been associated with endophthalmitis*

Data on file, Allergan, Inc.
Anti-VEGF and Macular Edema

- Ranibizumab (Lucentis®, Genentech)
  - BRAVO
  - CRUISE
- Aflibercept (VEGF Trap-Eye/Eylea™, Regeneron)
  - GALILEO
  - COPERNICUS
BRAVO Study Design

Macular Edema Secondary to Branch Retinal Vein Occlusion (BRVO)

28-Day Screening Period

1:1:1 Randomization

Sham (n=132)
Ranibizumab 0.3 mg (n=134)
Ranibizumab 0.5 mg (n=131)

6-Month Treatment Period
(monthly injections and rescue laser if eligible beginning Month 3)

Laser allowed beginning month 3

Month 6 Primary Endpoint

6-Month Observation Period
(monthly PRN treatment and rescue laser if eligible beginning Month 9)

Ranibizumab 0.5 mg
Ranibizumab 0.3 mg
Ranibizumab 0.5 mg

20/ 40 to 20/ 400
CST ≥ 250 microns
Foveal center ME within 12 months
BRVO or HRVO
**Mean Change From Baseline BCVA to Month 12 Over Time**

- **Sham/0.5 mg (n=132)**
- **Ranibizumab 0.5 mg (n=131)**

*Secondary endpoint. †P<0.01 vs sham. Earliest statistically significant group difference (P<0.01 vs sham) was at Day 7. Vertical bars are ±1 standard error of the mean. The last-observation-carried-forward method was used to impute missing data. BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study.*
Proportion of Subjects Who Gained ≥15 ETDRS Letters From Baseline BCVA at Month 6

*P<0.01 vs sham.
ETDRS = Early Treatment Diabetic Retinopathy Study; BCVA = best-corrected visual acuity.
Mean Change From Baseline CFT Over Time to Month 12*

Sham/0.5 mg (n=132)

Ranibizumab 0.5 mg (n=131)

Mean change from baseline CFT (µm)

Month 0 to Month 6
Monthly Treatment

Month 6 to 12
PRN Treatment

Day 0 to Month 6

Month

*Secondary endpoint

*P<0.01 vs sham. Earliest statistically significant difference at Day 7. Vertical bars are ±1 standard error of the mean.

CFT=central foveal thickness.

Please see the LUCENTIS full prescribing information.
Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)

28-Day Screening Period

1:1:1 Randomization

Sham (n=130)
Ranibizumab 0.3 mg (n=132)
Ranibizumab 0.5 mg (n=130)

6-Month Treatment Period
(monthly ranibizumab or sham injections)

6-Month Observation Period
(monthly PRN treatment)

Ranibizumab 0.5 mg
Ranibizumab 0.3 mg
Ranibizumab 0.5 mg

Month 6 Primary Endpoint
Mean Change From Baseline BCVA Over Time to Month 12*

Mean change from baseline BCVA (ETDRS letters)

- Sham/0.5 mg (n=130)
- Ranibizumab 0.5 mg (n=130)

*Secondary endpoint.
†P<0.01 vs sham. Earliest statistically significant group difference (P<0.01 vs sham) was at Day 7. Vertical bars are ±1 standard error of the mean. The last-observation-carried-forward method was used to impute missing data.

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study.

Please see the LUCENTIS full prescribing information.
Proportion of Subjects Who Gained ≥15 ETDRS Letters From Baseline BCVA to Month 12*

- **Sham/0.5 mg (n=130)**
- **Ranibizumab 0.5 mg (n=130)**

<table>
<thead>
<tr>
<th>Month</th>
<th>Sham/0.5 mg</th>
<th>Ranibizumab 0.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 to Month 6</td>
<td>8.5%</td>
<td>36.9%</td>
</tr>
<tr>
<td>Monthly Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 6 to 12</td>
<td>16.9%</td>
<td>47.7%*</td>
</tr>
<tr>
<td>PRN Treatment</td>
<td>33.1%</td>
<td>50.8%</td>
</tr>
</tbody>
</table>

*Secondary endpoint.

*P<0.01 vs sham (prespecified secondary endpoint). LUCENTIS vs sham P<0.01 at Day 7 and Months 1–5 (post hoc analyses). BCVA=best-corrected visual acuity, ETDRS=Early Treatment Diabetic Retinopathy Study.

Please see the LUCENTIS full prescribing information.
Mean Change From Baseline CFT
Over Time to Month 12*

- Sham/0.5 mg (n=130)
- Ranibizumab 0.5 mg (n=130)

* Secondary endpoint
*P<0.01 vs sham. Earliest statistically significant difference at Day 7. Vertical bars are ±1 standard error of the mean. CFT=central foveal thickness.

Please see the LUCENTIS full prescribing information.
GALILEO and COPERNICUS CRVO Phase 3 Study Design

Randomized, multicenter, double-masked trial
N=165 (per study)

Subjects randomized 3:2

Primary endpoint: Proportion of 3-line gainers

Secondary endpoint: Change in central retinal thickness (OCT)

Treatment to Week 24*
(primary endpoint)

Continued treatment to 1 year

*Beginning at Wk 24, all patients in COPERNICUS will be eligible for PRN VEGF Trap-Eye
PRP rescue available for all subjects

VEGF Trap-Eye 2 mg q4 wks* n=99

Sham N=66
# COPERNICUS
## Baseline Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>VTE 2q4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (full analysis set)</strong></td>
<td>73</td>
<td>114</td>
<td>187</td>
</tr>
<tr>
<td><strong>ETDRS BCVA letter score (SD)</strong></td>
<td>48.9 (14.4)</td>
<td>50.7 (13.9)</td>
<td>50.0 (14.1)</td>
</tr>
<tr>
<td>Snellen Equivalent</td>
<td>20/126</td>
<td>20/100</td>
<td>20/100</td>
</tr>
<tr>
<td><strong>Central Retinal Thickness μm (SD)</strong></td>
<td>672.4 (245.3)</td>
<td>661.7 (237.4)</td>
<td>665.8 (239.8)</td>
</tr>
<tr>
<td><strong>Baseline perfusion status n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfused*</td>
<td>50 (68.5%)</td>
<td>80 (70.2%)</td>
<td>130 (69.5%)</td>
</tr>
<tr>
<td>Non-perfused</td>
<td>12 (16.4%)</td>
<td>14 (12.3%)</td>
<td>26 (13.9%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>10 (13.7%)</td>
<td>18 (15.8%)</td>
<td>28 (15.0%)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (1.4%)</td>
<td>2 (1.8%)</td>
<td>3 (1.6%)</td>
</tr>
</tbody>
</table>

*Less than 10 DA of non perfusion

COPERNICUS Primary Endpoint

% Patients Who Gained ≥ 15 letters at Week 24

% Patients

0% 20% 40% 60% 80% 100%

≥ 15 letter gain^ 12.3% 56.1%*

<table>
<thead>
<tr>
<th>Sham</th>
<th>2q4</th>
</tr>
</thead>
</table>

*P < 0.0001 vs. Sham

^Compared to baseline; LOCF; full analysis set; sham n=73; 2q4 n=114;

COPERNICUSUS Primary Endpoint
% Patients Who Gained ≥ 15 letters at Week 24

22% vs. 60% for GALILEO Study

^Compared to baseline; LOCF; full analysis set; sham n=73; 2q4 n=114;
COPERNICUS
Mean Change in Visual Acuity

LOCF; full analysis set; sham n=73; 2q4 n=114;


+18 vs. +3 letters for GALILEO
Anti-VEGF for Macular Edema in Retinal Vein Occlusion

- Anti-VEGF therapy is the most efficacious Rx
  - Greater improvement in VA than prior std of care
- Anti-VEGF therapy is safe
- Ranibizumab (Lucentis®, Genentech)
  - BRAVO and CRUISE
- Aflibercept (VEGF-Trap Eye/Eylea™, Regeneron)
  - Galileo and Copernicus
- Bevacizumab (Avastin®, Genentech)
## Comparison of Outcomes – CVO and ME: Absolute Difference and Number Needed to Treat

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triamcinolone (SCORE)</strong></td>
<td></td>
</tr>
<tr>
<td>≥15 letter gain with intravitreal triamcinolone vs observation (27%–7%)</td>
<td>+20%</td>
</tr>
<tr>
<td>Number needed to treat (inverse of absolute difference) to get 1 additional patient to improve by 15 or more letters vs control</td>
<td>5</td>
</tr>
<tr>
<td><strong>Ranibizumab (CRUISE)</strong></td>
<td></td>
</tr>
<tr>
<td>≥15 letter gain with intravitreal ranibizumab vs sham treatment (46%–17%)</td>
<td>+29%</td>
</tr>
<tr>
<td>Number needed to treat (inverse of absolute difference) to get 1 additional patient to improve by 15 or more letters vs control</td>
<td>3</td>
</tr>
<tr>
<td><strong>VEGF Trap (Copernicus)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+44%</td>
</tr>
<tr>
<td>Number needed to treat (inverse of absolute difference) to get 1 additional patient to improve by 15 or more letters vs control</td>
<td>2</td>
</tr>
</tbody>
</table>
Anti-VEGF and Macular Edema

• Ranibizumab (Lucentis®, Genentech)
  – BRAVO
  – CRUISE

• Afibercept (VEGF Trap-Eye/Eylea™, Regeneron)
  – GALILEO
  – COPERNICUS
Thank you!
Question

Which one of the following therapies yields the best visual acuity outcomes in the treatment of macular edema from RVO?

1. Laser photocoagulation
2. Intravitreal triamcinolone
3. Extended release dexamethasone
4. Intravitreal anti-VEGF