Treatment Options for VMT and Macular Holes – Observation, Surgery, and Pharmacotherapy

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Financial Disclosures

- Salary/Honoraria: Alcon, Allergan, Bausch + Lomb, Genentech, Regeneron, ThromboGenics, Valeant

- Consulting Fees: Alcon, Allergan, Bausch + Lomb, Genentech, Regeneron, ThromboGenics, Valeant, Bayer

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- Ownership Interest: OptiSTENT, Inc.
Pharmacologic Vitreolysis

- Two broad categories of vitreolytic agents:
  - Those that liquefy the vitreous = liquefactants
  - Those that cleave the VRI = interfactants

Traditional Treatment Paradigm for VMT & MH

- **Full-thickness Macular Hole**
  - Vitrectomy

- **Symptomatic VMA**
  - Watchful Waiting
  - Vitrectomy
# Vitreolytic Agents

Vitreolytic agents under development\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Agent</th>
<th>Classification</th>
<th>Mechanism of action</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondroitinase</td>
<td>Liquefactant and interfactant</td>
<td>Depolymerization of glycosaminoglycans including chondroitin sulfate</td>
<td>No evidence of further development</td>
</tr>
<tr>
<td>Bacterial collagenase (clostridiopeptidase A)</td>
<td>Liquefactant</td>
<td>Cleavage of type II collagen</td>
<td>No evidence of further development</td>
</tr>
<tr>
<td>Dispase</td>
<td>Interfactant</td>
<td>Cleavage of type IV collagen and fibronectin</td>
<td>No evidence of further development</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>Liquefactant</td>
<td>Cleavage of large hyaluronan molecules and other glycosaminoglycans</td>
<td>Despite good liquefactive capacity, evidence suggests it may worsen VMA-related pathologies. No evidence of further development</td>
</tr>
</tbody>
</table>

Interfactant: ability to weaken vitreoretinal adhesion

## Vitreolytic Agents

### Vitreolytic agents under development

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<tbody>
<tr>
<td>Nattokinase</td>
<td>Liquefactant and interfactant</td>
<td>Fibrinolytic effects by enhancing plasminogen activators and inactivating plasmin activator inhibitors</td>
<td>No evidence of further development</td>
</tr>
<tr>
<td>Endogenous plasmin</td>
<td>Liquefactant and interfactant</td>
<td>Mediates fibrinolysis by targeting vitreoretinal interface glycoproteins, including laminin and fibronectin</td>
<td>Independent studies with autologous plasmin enzyme are ongoing</td>
</tr>
<tr>
<td>Plasminogen activator</td>
<td>Liquefactant and interfactant</td>
<td>Indirect activation of plasmin</td>
<td>Therapeutic potential limited by need for adequate concentrations of intraocular plasminogen substrate</td>
</tr>
<tr>
<td>Ocriplasmin</td>
<td>Liquefactant and interfactant</td>
<td>Cleavage of laminin, fibronectin, and collagen at the vitreoretinal interface</td>
<td>Approved for treatment of symptomatic VMA in the US and positive CHMP opinion received for VMT including when associated with MH of diameter ≤400 µm in the EU</td>
</tr>
</tbody>
</table>

Ocriplasmin is a truncated form of human plasmin produced by recombinant DNA technology.

- Ocriplasmin is produced in a *Pichia pastoris* expression system and has a molecular weight of 27.2 kDa.
- Retains the catalytic domain of plasmin and shares the same catalytic properties as human plasmin.

Mechanism of Action

Ocriplasmin exerts proteolytic effects on fibrinogen, fibronectin and, to a lesser extent, laminin and collagen fibrils.\(^1-3\)

Ocriplasmin induces PVD via a two-step mechanism\(^1\)

Vitreous liquefaction \& Vitreoretinal separation

The Vitreolytic Effect of Ocriplasmin on Porcine Vitreous

Histological Studies: Normal Mouse Eye

Blue: Nuclear stainings
Green: Collagen IV
Red: Fibronectin
PVD After Ocriplasmin Injection in Mouse Eye

Blue: Nuclear stainings
Green: Collagen IV (Coll)
Red: Fibronectin (FN)

Ocriplasmin caused both vitreous liquefaction and vitreous separation

PVD = posterior vitreous detachment.
Pharmacokinetics of Ocriplasmin

- At 24 hours post-injection, the concentration of ocriplasmin was below the lower limit of detection (0.27 µg/mL) in half of the vitreous samples\(^1\)
- Because of the small dose administered (0.125 mg) and the rapid intravascular inactivation, detectable levels of ocriplasmin in systemic circulation are not expected after intravitreal injection\(^1,2\)

*Mean concentration is below the lower limit of detection (0.27 µg/mL).
Ocriplasmin Clinical Development Timeline

- **MIVI-001 (Phase 1)**: Dec 2004
- **MIVI-002 (Phase 2)**: Dec 2006
- **MIVI-004 (Phase 2)**: Feb 2007
- **MIVI-005 (Peds)**: Jan 2010
- **MIVI-006**: Nov 2008
- **MIVI-007**: Nov 2008
- **MIVI-008**: Jan 2010
- **MIVI-009**: Oct 2011
- **MIVI-010 (PK)**: Jul 2010
- **MIVI-012**: Q2 2011
- **MIVI-014 (OASIS)**: Oct 2011

- **Completed trials**: Blue
- **Ongoing trials**: Gray
Ocriplasmin Phase III Clinical Trial Program

Phase III MIVI-TRUST: Ocriplasmin for the Treatment of Symptomatic VMA Including Macular Hole
†Patients could proceed to vitrectomy after Day 28 if deemed necessary by the investigator.

Key Inclusion Criteria

- Symptomatic VMA
  - Presence of vitreomacular adhesion on OCT
    - Central vitreal adhesion within 6 mm OCT field surrounded by elevation of the posterior vitreous cortex
  - Symptoms considered by investigator as due to VMA such as
    - Metamorphopsia
    - Decreased visual acuity
    - Other visual complaints

- BCVA ≤20/25 in study eye
Key Exclusion Criteria

- High myopia (more than –8 D)
- History of prior vitrectomy or prior laser photocoagulation to the macula
- Macular hole diameter ≥400 μm
- Other retinal diseases that could affect visual function
Study Endpoints

• **Primary endpoint**
  – Proportion of patients with non-surgical resolution of VMA at Day 28 post-injection, as determined by masked CRC OCT evaluation

• **Key secondary endpoint (alpha protected)**
  – Proportion of patients with total PVD at day 28, as determined by masked investigator assessment of B-scan ultrasound

• **Pre-specified exploratory secondary endpoints**
  – Proportion of patients not requiring vitrectomy
  – Proportion of macular holes that close without vitrectomy as determined by CRC
  – Achievement of $\geq 2$ and $\geq 3$ lines improvement in BCVA without need for vitrectomy
  – Improvement in mean BCVA
  – Improvement in VFQ-25

BCVA = best corrected visual acuity; CRC = Central Reading Centre; OCT = Optical coherence tomography; VMA = vitreomacular adhesion
Select Baseline Characteristics

Baseline Characteristics Were Comparable Across Most Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Vehicle (N=188)</th>
<th>Ocriplasmin (N=464)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr (range)</td>
<td>70.7 (24-97)</td>
<td>72.1 (18–93)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>115 (61.2)</td>
<td>314 (67.7)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>174 (92.6)</td>
<td>428 (92.2)</td>
</tr>
<tr>
<td>Mean baseline BCVA, ETDRS letters (Snellen equivalent)</td>
<td>65.1 (20/50)</td>
<td>63.9 (20/50)</td>
</tr>
</tbody>
</table>

BCVA = best corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study.
Baseline Characteristics Were Comparable Across Most Groups

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<th>Vehicle (N=188)</th>
<th>Ocriplasmin (N=464)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Diagnosis, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VMA</td>
<td>188 (100.0)</td>
<td>464 (100.0)</td>
</tr>
<tr>
<td>VMT</td>
<td>141 (75.0)</td>
<td>358 (77.2)</td>
</tr>
<tr>
<td>FTMH†</td>
<td>47 (25.0)</td>
<td>106 (22.8)</td>
</tr>
<tr>
<td><strong>Baseline Study Eye Ocular Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epiretinal Membrane (ERM), n (%)</td>
<td>68 (36.2)</td>
<td>184 (39.7)</td>
</tr>
<tr>
<td>Pseudophakic, n (%)</td>
<td>53 (28.2)</td>
<td>172 (37.1)</td>
</tr>
<tr>
<td>Non-proliferative Diabetic Retinopathy (NPDR), n (%)</td>
<td>15 (8.0)</td>
<td>30 (6.5)</td>
</tr>
<tr>
<td>Focal VMA diameter &gt;1500 μm, n/N (%)</td>
<td>41/176 (23.3)</td>
<td>102/440 (23.2)</td>
</tr>
</tbody>
</table>

*Percentages are based on total patients in Modified Full Analysis Set.
†The FTMH width of one patient in the ocriplasmin treatment group could not be measured and was not included in the groupings by size.

Primary Outcome: VMA Resolution at Day 28

Time to Response in Patients With Pharmacologic VMA Resolution

VMA = vitreomacular adhesion.

*Proportion of patients with VMA resolution relative to Day 28.

VMT Resolution
Proportion of Patients With Total PVD* at Day 28 (Without Vitrectomy)¹

<table>
<thead>
<tr>
<th>% of Patients Achieving Total PVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle (N=188)</td>
</tr>
<tr>
<td>Placebo (n=47)</td>
</tr>
<tr>
<td>Ocriplasmin (n=106)</td>
</tr>
</tbody>
</table>

OR = 4.27 (95% CI: 1.89–11.32; P<0.001)

OR = odds ratio; PVD = posterior vitreous detachment.

*PVD was investigator determined by B-scan ultrasound.

Proportion of Patients With FTMH Closure at Day 28
By Treatment Group (without vitrectomy)

10.6

10.6

40.6

P < 0.001

<table>
<thead>
<tr>
<th>Baseline Macular Hole, n (%)</th>
<th>Placebo (n=188)</th>
<th>Ocriplasmin (n=464)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Macular Hole, n (%)</td>
<td>47 (25.0)</td>
<td>106 (22.8)</td>
</tr>
<tr>
<td>≤ 250 µm</td>
<td>25 (53.2)</td>
<td>48 (45.3)</td>
</tr>
<tr>
<td>&gt; 250 µm to ≤ 400 µm</td>
<td>19 (40.4)</td>
<td>38 (35.8)</td>
</tr>
<tr>
<td>&gt; 400 µm</td>
<td>3 (6.4)</td>
<td>19 (17.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>–</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

Proportion of Patients With FTMH Closure at Day 28
By Treatment Group (without vitrectomy)

<table>
<thead>
<tr>
<th>Group</th>
<th>≤ 250 µm</th>
<th>&gt; 250 µm to ≤ 400 µm</th>
<th>&gt; 400 µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>16.0</td>
<td>5.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Ocriplasmin</td>
<td>58.3</td>
<td>36.8</td>
<td>0.0</td>
</tr>
</tbody>
</table>

P < 0.001

N= 25 48 19 38 3 19

FTMH Closure With Vitrectomy in Nonresponders

92.3%*  
93.1%*

Proportion of Patients (%)

After Vitrectomy

Vehicle

N= 26

Ocriplasmin

N= 44

*Excludes those patients without evaluable postvitrectomy OCT for macular hole status (n=3 for ocriplasmin and n=1 for placebo).

Does Patient Selection Matter?
**Independent Baseline Features Analyzed for Association with VMA Resolution at Day 28**

### Non-ocular Characteristics
- Treatment group
- Study (MIVI-006 or MIVI-007)
- Age
- Gender
- Race
- Region
- Body mass index
- Expected need for vitrectomy

### Ocular Characteristics
- Full-thickness macular hole (FTMH), equivalent to stage II
- VMA diameter
- Lens status
- Epiretinal membrane (ERM)
- Diabetic retinopathy
- Best-corrected visual acuity (BCVA)

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;65 years</td>
</tr>
<tr>
<td>FTMH(^a) present</td>
</tr>
<tr>
<td>VMA diameter (\leq 1500 \mu m(^b))</td>
</tr>
<tr>
<td>ERM absent</td>
</tr>
<tr>
<td>Phakic</td>
</tr>
</tbody>
</table>

\(^a\) Equivalent to stage II
\(^b\) VMA diameter percentages based on total patients in Modified Full Analysis Set.

What if a patient has more than one predictor at presentation?

(post hoc exploratory analysis)
### Effect of Baseline Predictor Number and Combination on Rate of Pharmacologic VMA Resolution at Day 28*

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Placebo</th>
<th>Ocriplasmin</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic VMA</td>
<td>10.1</td>
<td>26.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ FTMH</td>
<td>25.5</td>
<td>50.0</td>
<td>0.006</td>
</tr>
<tr>
<td>+ age &lt;65 years</td>
<td>46.2</td>
<td>80.0</td>
<td>0.026</td>
</tr>
<tr>
<td>+ diameter ≤1500 μm</td>
<td>50.0</td>
<td>86.4</td>
<td>0.017</td>
</tr>
<tr>
<td>+ no ERM</td>
<td>50.0</td>
<td>86.4</td>
<td>0.017</td>
</tr>
<tr>
<td>+ phakic status</td>
<td>60.0</td>
<td>90.5</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Safety
Exposure to Ocriplasmin

7 Completed Studies
n = 741

Total (any dose)
n = 976

125 µg Dose
n = 582

Phase 3
n = 465

Ongoing Studies
(as of May 31, 2012)
n = 235

Phase 2
n = 276
Suspected Adverse Drug Reactions (ADRs) in Study Eye
By Postinjection Time to Onset: Day 0–7

Suspected ADRs in Study Eye
By Postinjection Time to Onset: Day 8 to End of Study


![Graph showing suspected adverse drug reactions (ADRs) in study eye.](https://via.placeholder.com/150)

- Vitreous floaters
  - Placebo (n=187): 4.8%
  - Ocriplasmin (n=465): 3.9%
- Eye pain
  - Placebo (n=187): 2.7%
  - Ocriplasmin (n=465): 2.6%
- Photopsia
  - Placebo (n=187): 1.6%
  - Ocriplasmin (n=465): 1.7%
- Vision blurred
  - Placebo (n=187): 2.7%
  - Ocriplasmin (n=465): 1.9%
- VA reduced
  - Placebo (n=187): 4.3%
  - Ocriplasmin (n=465): 2.2%
- Visual impairment
  - Placebo (n=187): 1.1%
  - Ocriplasmin (n=465): 2.2%
- Retinal edema
  - Placebo (n=187): 1.1%
  - Ocriplasmin (n=465): 1.7%
- Macular edema
  - Placebo (n=187): 1.6%
  - Ocriplasmin (n=465): 3.4%
- Anterior chamber cell
  - Placebo (n=187): 2.1%
  - Ocriplasmin (n=465): 1.1%
- Photophobia
  - Placebo (n=187): 0.0%
  - Ocriplasmin (n=465): 0.4%
The majority of suspected adverse drug reactions had a median time to resolution of ≤18 days in the ocriplasmin group; most of these events had similar or shorter resolution time compared with placebo.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (N=187)</th>
<th>Ocriplasmin (N=465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitreous floaters</td>
<td>35.0</td>
<td>18.0</td>
</tr>
<tr>
<td>Photopsia</td>
<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>78.0</td>
<td>10.0</td>
</tr>
</tbody>
</table>

## Adverse Events of Special Interest by Category

### Placebo-controlled Studies (TG-MV-006, TG-MV-007)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N=187)</th>
<th>Ocriplasmin 125 µg (N=465)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
</tr>
<tr>
<td><strong>Vision alteration</strong></td>
<td>16</td>
<td>(8.6%)</td>
</tr>
<tr>
<td><strong>Intraocular inflammation</strong></td>
<td>8</td>
<td>(4.3%)</td>
</tr>
<tr>
<td><strong>Cataract</strong></td>
<td>18</td>
<td>(9.6%)</td>
</tr>
<tr>
<td><strong>IOP increase</strong></td>
<td>10</td>
<td>(5.3%)</td>
</tr>
<tr>
<td><strong>Intraocular hemorrhage</strong></td>
<td>8</td>
<td>(4.3%)</td>
</tr>
<tr>
<td><strong>Retinal breaks</strong></td>
<td>8</td>
<td>(4.3%)</td>
</tr>
<tr>
<td><strong>Glaucoma</strong></td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td><strong>Color vision alteration</strong></td>
<td>0</td>
<td>–</td>
</tr>
</tbody>
</table>

*Adverse event terms which were medically similar, eg, “visual acuity reduced,” “visual impairment,” etc, were grouped into relevant categories so as not to underestimate incidence. Data on file. ThromboGenics, Inc. 2012.

### Intravitreal injection-related events
- IOP increase
- Glaucoma
- Intraocular hemorrhage
- Intraocular inflammation
### Adverse Events of Special Interest by Category

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<td>16 (8.6%)</td>
<td>101 (21.7%)</td>
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<tr>
<td>Intraocular inflammation</td>
<td>8 (4.3%)</td>
<td>35 (7.5%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>18 (9.6%)</td>
<td>27 (5.8%)</td>
</tr>
<tr>
<td>IOP increase</td>
<td>10 (5.3%)</td>
<td>19 (4.1%)</td>
</tr>
<tr>
<td>Intraocular hemorrhage</td>
<td>8 (4.3%)</td>
<td>12 (2.6%)</td>
</tr>
<tr>
<td>Retinal breaks</td>
<td>8 (4.3%)</td>
<td>9 (1.9%)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>0 –</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td>Color vision alteration</td>
<td>0 –</td>
<td>4 (0.9%)</td>
</tr>
</tbody>
</table>

*Adverse event terms which were medically similar, eg, “visual acuity reduced,” “visual impairment,” etc, were grouped into relevant categories so as not to underestimate incidence.


**Retinal breaks**
- Retinal tears
- Retinal detachments
Adverse Events of Special Interest by Category

Visual function changes
- Reduced visual acuity
- Dyschromatopsia
- ERG changes

<table>
<thead>
<tr>
<th>Placebo-controlled Studies (TG-MV-006, TG-MV-007)</th>
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</tr>
<tr>
<td>Glaucoma</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Color vision alteration</td>
<td>0</td>
<td>–</td>
</tr>
</tbody>
</table>

*Adverse event terms which were medically similar, eg, “visual acuity reduced,” “visual impairment,” etc, were grouped into relevant categories so as not to underestimate incidence.
Patients With ≥2 Lines Vision Decrease: Day 0 – 7

Placebo
N=187
3 (1.6%)

Ocriplasmin
N=465
36 (7.7%)
Acute $\geq 2$ Line VA Loss

Baseline (53 letters) | 7 days post (42 letters)
14 days post (34 letters) | 3 months post (61 letters)
6 months post (68 letters)
Acute $\geq 2$ Line VA Loss

Baseline (66 letters)  14 days post (50 letters)  7 days post (53 letters)  6 months post (72 letters [+6])
Visual Acuity Recovery in Patients With $\geq 2$ Lines of Acute Vision Loss Between Days 0-7

No 6 mo visual acuity

(LOCF used)
Patients With ≥2 Lines Vision Decrease:
Day 0 – 7

Placebo
N=187

3 (1.6%)

2 (1.1%)

Ocriplasmin
N=465

Day 7

36 (7.7%)

Month 6

6 (1.3%)
### Patients With ≥ 2 Line Loss at D7 and M6

<table>
<thead>
<tr>
<th>Pt #</th>
<th>BL</th>
<th>D7</th>
<th>D28</th>
<th>M6</th>
<th>PPV?</th>
<th>Reason for initial loss</th>
<th>Reason for persistent loss</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocriplasmin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>618-005</td>
<td>76</td>
<td>61</td>
<td>62</td>
<td>66</td>
<td>PPV</td>
<td>VMT progression</td>
<td>PPV complication cataract</td>
</tr>
<tr>
<td>639-001</td>
<td>70</td>
<td>58</td>
<td>-</td>
<td>42</td>
<td>PPV x 2</td>
<td>MH progression</td>
<td>PPV complication foveal atrophy</td>
</tr>
<tr>
<td>730-007</td>
<td>75</td>
<td>46</td>
<td>55</td>
<td>39</td>
<td>PPV x 2</td>
<td>VMT to MH</td>
<td>PPV complication failed MH closure</td>
</tr>
<tr>
<td>781-001</td>
<td>53</td>
<td>33</td>
<td>46</td>
<td>42</td>
<td>-</td>
<td>Unknown</td>
<td>VMA resolution but loss persisted</td>
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<tr>
<td>719-003</td>
<td>77</td>
<td>66</td>
<td>73</td>
<td>66</td>
<td>-</td>
<td>VMT Progression</td>
<td>Needs PPV</td>
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<tr>
<td>622-017</td>
<td>60</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>PPV</td>
<td>MH progression</td>
<td>Not evaluable, consent withdrawn</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>728-003</td>
<td>69</td>
<td>55</td>
<td>56</td>
<td>-</td>
<td>?</td>
<td>MH progression</td>
<td>Not evaluable, consent withdrawn</td>
</tr>
<tr>
<td>635-003</td>
<td>53</td>
<td>28</td>
<td>29</td>
<td>42</td>
<td>-</td>
<td>ION/edema</td>
<td>ION/edema</td>
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</table>
≥ 2 Line Loss in VA (Unknown Etiology)

Baseline

Month 6

53 letters (~20/100)

42 letters (-11 letters) (~20/160)
Dyschromatopsia

- Sixteen events considered clinically significant in 820 subjects (2%)
- Generally described as yellowish vision
- 0.1% of cases not resolved†
- The majority were reported from the same center during 2 clinical trials
- All rated as mild and none were serious

*Includes events in subjects from larger clinical trial program.
†Excludes patients lost to follow up or death.
ERG Changes
(10 of 820 patients)

- a- and b-wave amplitude decreases
- Median time to resolution: 3 to 6 months
- No unresolved cases currently†
- The majority were reported from the same center during 2 clinical trials
- In ongoing OASIS trial subset of 75 patients being followed with ERG

Occurred in 10 of 820 patients (1.2%)*
(8 of 10 had dyschromatopsia)

3 patients lost to follow-up
(VA returned and so patient didn’t return)

7 of 10 cases resolved

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*Includes events in subjects from larger clinical trial program.
†Excludes patients lost to follow up or death.
Potential for Lens Subluxation

- One case of lens subluxation out of 976 patients treated with ocriplasmin at a 40% higher dose
  - The patient also received 0.175-mg ocriplasmin dose in the fellow eye 1 week later and lens subluxation did not occur
Potential for Lens Subluxation

- Lens subluxation was observed in monkeys, rabbits, and minipigs
  - ocriplasmin concentrations 1.4-fold above the intended clinical concentration in the vitreous (41 mg/ml)

- Two doses of ocriplasmin (28 days apart) in monkeys (N=18) at doses of 75 μg/eye (41 mg/mL vitreous) or 125 μg/eye (68 mg/mL vitreous) was associated with lens subluxation in all ocriplasmin-treated eyes
  - These doses are 1.4-fold and 2.3-fold the intended clinical concentration in the vitreous of 29 μg/mL, respectively
Ocriplasmin is the first and only FDA-approved pharmacologic treatment for symptomatic VMA, that dissolves the protein matrix responsible for VMA.

In two Phase 3 pivotal studies, a significantly higher proportion of ocriplasmin-treated patients achieved the following at Day 28 compared with vehicle-treated patients:

- VMA resolution (primary endpoint)
- Total PVD (key secondary endpoint)
Summary and Conclusions

The majority of adverse drug reactions observed in the pivotal studies occurred within the first week and were classified as **non-serious**, **transient**, and **mild in severity**.

Most Common:

1) Vitreous floaters
2) Conjunctival hemorrhage
3) And eye pain