Contemporary Management of Diseases of the Vitreomacular Interface

Course Chair
Szilárd Kiss, MD
Director of Clinical Research
Assistant Professor of Ophthalmology
Weill Cornell Medical College
New York, New York
Contemporary Management of Diseases of the Vitreomacular Interface

Welcome
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Pathogenesis, Staging, and Classification of VMT and Macular Holes

Charles C. Barr, MD
Arthur and Virginia Keeney Professor
Department of Ophthalmology
University of Louisville School of Medicine
Louisville, KY
Disclosures

- Consulting Fees: ThromboGenics
- Speaker: ThromboGenics
VMI Disease

Background – Why The Interest in 2013?

- New findings based on SD OCT
- Better understanding of pathogenesis
- Surgical outcomes linked to OCT findings
- Need to speak a common language – new Classification system
- New therapies – ocriplasmin (Jetrea)
VMI Diseases

Outline of the Talk

• Pathophysiology of diseases of the vitreomacular interface (VMI)
• OCT-based definition, diagnosis, and classification of:
  – Vitreomacular adhesion (VMA)
  – Vitreomacular traction (VMT)
  – Full-thickness macular hole (FTMH)
**VMI Diseases**

**The Importance of the Vitreo-Retinal Relationship:**

- Ophthalmologists must now be able to identify vitreomacular pathology at early stages when treatment may be most effective.

- This is based on optical coherence tomography.
Almost All Acquired Vitreomacular Interface Pathology is the Result of Anomaly in the Normal Vitreous Aging

Two processes occur with age:

1) progressive vitreous liquefaction
2) progressive weakening of the vitreoretinal adhesion

collagen, fibronectin, laminin
Liquefaction

- Liquid vitreous seen in eyes by 4 yrs old
- By late teens, approximately 20% of the vitreous volume is liquid
- Liquefied lacunae increase with age in number, size, and coalescence
- By 70 years, > 50% of vitreous is liquefied
- Despite liquefaction, no PVD in most autopsy eyes < 60 years
VMI Diseases

Weakening of Vitreoretinal Adhesion

• Progressive age-related weakening of adhesion between posterior vitreous cortex (posterior hyaloid) and internal limiting membrane (ILM)

• > 60 yrs, significant correlation between liquefaction and PVD, because at that point, the vitreoretinal adhesion becomes sufficiently weakened to allow separation
• Posterior vitreous detachment
  Prevalence = age
Posterior Vitreous Detachment (PVD)

- Contrary to popular thought, PVD is not an acute process culmination in the formation of a Weiss ring with associated symptoms.
- Rather, it is a long-term, chronic process typically occurring over decades that sometimes culminates in the clinical manifestations of acute PVD.
Evolution of PVD = Johnson Classification Scheme

- PVD begins in perifoveal macula (Stage 1)
- Extends next into superior and temporal midperiphery then into fovea (Stage 2)
- Then inferior midperiphery (Stage 3)
- Finally the optic disc margin resulting in complete PVD – often with Weiss Ring (Stage 4)

Vitreomacular Pathology: Anomalous PVD

- Persistent vitreous traction on fovea and/or disc
- Epiretinal avascular proliferation
- Results in anatomic retinal changes
  - Retinal distortion
  - Retinal thickening
  - Intraretinal cyst formation
  - Subretinal fluid
  - “Schisis” - splitting of inner/outer retinal layers
  - Macular hole formation – full and/or lamellar
Most Vitreomacular Pathology: Anomalous PVD

- Retinal pathology typically develops where vitreous attached to retina most firmly
- Four areas:
  - Vitreous base
  - Along large retinal vessels
  - Optic disc margin
  - Two macular locations
    1) A 500-micron radius “foveolar attachment”
    2) A 1500-micron radius “foveal attachment”
• Vitreous gel: Collagen & HA – 99% water

Vitreous base: firmly adherent
• When vitreous gel detaches, the retina tears in 5%
• This can lead to retinal detachment
4.4 (Malghero and Schepens). Sketches of vertical optical sections through macular breaks with the slit lamp and three-mirror contact lens. Each sketch depicts an incomplete posterior vitreous detachment with various types of residual attachment to the posterior pole. Vitreous body is partly detached and shows multiple syneresis cavities.
Macular Complications of Anomalous PVD

- **Focal**, small (< 500 microns) vitreous adhesions → traction on foveola
- Results in focal macular pathology:
  - Vitreomacular traction (VMT)
  - Cystoid spaces
  - Subretinal fluid
  - Macular hole (FTMH)
  - Lamellar macular hole (LMH)
Broad, large adhesions result in lower tractional forces.

>1500 micron vitreomacular adhesions are less likely to cause macular dehiscence.

More likely to cause diffuse disease:
- Epiretinal membrane
- Traction macular detachment
- Myopic macular schisis
- Hyaloidal thickening in diabetes
- May be related to DME, AMD, RVO
International Classification of Diseases of the Vitreomacular Interface (VMI)

- International panel convened in 2012 to devise a new classification system for VMI disease
- Strictly Anatomic – OCT-based
  - Objective
  - Not based on clinical findings
  - Not based on symptoms
- Simple, easy to use, predictive of surgical and pharmacological outcomes
VMI Diseases

International Classification of Diseases of the Vitreomacular Interface (VMI)

USA
- Jay Duker
- Peter Kaiser
- Elias Reichel
- Vas Sadda
- Jerry Sebag
- Richard Spaide

Europe
- Sussane Binder
- Marc deSmet
- Alain Gaudric
- Peter Stalmans
VMI Classification System: One Finding, Five Diseases

- **“Finding”:**
  - Vitreomacular Adhesion (VMA)

- **Diseases:**
  - Vitreomacular Traction (VMT)
  - Full Thickness Macular Hole (FTMH)
  - Lamellar Macular Hole (LMH)
  - Epiretinal Membrane (ERM)
  - Myopic Macular Schisis
VMI Diseases

Vitreomacular Adhesion (VMA)
VMI Diseases

VMA - Intl Classification Definition

- Posterior vitreous cortex (posterior hyaloid) visible on or above retinal surface
- Posterior vitreous cortex detached from inner retina at some point in the perifoveal area
- Persistent macular attachment, some part of which is attached within a 3-mm radius of fovea
- No anatomic retinal changes on OCT
VMI Diseases

VMA Definition

- VMA is essentially a perifoveolar PVD
- VMA would be considered a stage 1 PVD by Johnson’s classification
VMI Diseases

Vitreomacular Adhesion (VMA)

• Exclusively an OCT finding
  – No: symptoms
  – No: clinical findings
  – Must be present on at least one OCT B scan (line scan) through the fovea
  – Perifoveolar PVD

• Due to age-related changes of the vitreous
• Rarely pathologic
• Common
VMI Diseases

Two VMA Subclassifications

1) **Focal** versus **broad**
   - Focal attachment < 1500 microns
   - Broad attachment > 1500 microns

2) **Isolated** versus **Concurrent** with other macular disease
   - Note: symptoms are NOT a part of the definition
   - Note: VMA may resolve, persist, or go on to VMT
**VMI Diseases**

**Focal versus Broad**

- **Why 1500 microns?**
  - Known site of strong VM adhesion by histology
  - Pre-existing cut-off employed by reading centers
VMI Diseases

Focal VMA

Broad VMA
VMI Diseases

VMA Usually Spontaneously Resolves...But When It Doesn’t....

Vitreomacular Traction (VMT)
Vitreomacular Traction (VMT) – International Classification

- Definition = VMT is VMA with ANY abnormal macular retinal architecture
- OCT diagnosis
- “Symptomatic VMA” = VMT
VMI Diseases

VMT Definition

- Posterior vitreous cortex (posterior hyaloid) visible on or above retinal surface. May be thickened.
- Posterior hyaloid detached from inner retina at some point in the perifoveal area
- Persistent macular attachment within a 3-mm radius of fovea
- Anatomic retinal changes on OCT
- ALWAYS pathological
- May or may not be symptomatic
VMI Diseases

Two VMT Subclassifications

1) *Focal* versus *broad*
   - Focal attachment < 1500 microns
   - Broad attachment > 1500 microns
   - Broad VMA roughly parallel to the RPE and may include focal areas of cortex dehiscence

2) *Isolated* versus *Concurrent* (with other macular disease)
VMI Diseases

Vitreomacular Traction (VMT)

- VMT = VMA with retinal architectural changes
VMI Diseases

Clinical Course of VMT

- **Spontaneous PVD**
  - Usually with regression of symptoms
  - Cystoid spaces may persist
  - Vitreoschisis may still lead to ERM formation

- **Stability**

- **Progression**
  - Severe retinal anatomic distortion
  - FTMH
  - LMH

3 weeks later
VMI Diseases

VMT Course – Spontaneous PVD

- 62 yo female, c/o distortion x 1 month
- VA = 20/40

Courtesy of Carl Regillo, MD
VMI Diseases

2 months later

OS
20/40

Courtesy of Carl Regillo, MD
VMI Diseases

3 months later

VA = 20/25

Persistent cystoid space

Courtesy of Carl Regillo, MD
VMI Diseases

6 months later

VA = 20/20

Courtesy of Carl Regillo, MD
VMI Diseases

Full Thickness Macular Hole (FTMH) - International Classification System
VMI Diseases

FTMH Anatomy and Outcome-Based Intl. Classification System: 3 Factors

1) **Size** of defect
2) **VMT** = present or absent
3) **Primary** versus **secondary**

• Note:
  - Not a “staging” system
  - No longer an “idiopathic” condition = Now referred to as Primary. Due to VMA → VMT

VMI Diseases

FTMHH Classification – Aperture Size

- **Small** = full-thickness retinal defect \( \leq 250 \, \mu m \)
- **Medium** = full-thickness retinal defect \( > 250 \, \mu m \) and \( \leq 400 \, \mu m \)
- **Large** = full-thickness retinal defect \( > 400 \, \mu m \)
VMI Diseases

Size Not Stage Critical for Surgical Outcome

- “Aperture Size”
- Based on OCT measurement
- Horizontal line roughly parallel to RPE measuring the smallest hole diameter in a foveal B scan
- Don’t measure at inner retina – mid retina or outer retina

- OCT caliper function used to measure hole at narrowest width
  192 microns
VMI Diseases

FTMH Subclassification – Small (< 250 microns)

80 microns
VMI Diseases

FTMH Subclassification – Medium (251 – 400 microns)

390 microns
VMI Diseases

FTMH Subclassification – Large (> 400 microns)

516 microns
VMI Diseases

Measure Here

Not Here
VMI Diseases

Why 250 micron and 400 micron Cut-Offs for Aperture Size?

• Ocriplasmin data suggest that best results are for small macular holes < 250 microns

• Clinical studies show surgical success rate for hole closure has a “pivot point” at 400 microns
VMI Diseases

FTMH Subclassifications - VMT

- FTMH with VMT present
- FTMH with VMT released
  - Under Gass classification – this would have been a stage 4 macular hole regardless of size

90 microns

Small FTMH – VMT released
VMI Diseases

FTMH – VMT Present or Absent

Small FTMH
– VMT present

Small FTMH
– VMT released
VMI Diseases

Secondary FTMH

- Pre-existing or concurrent condition or disease without evidence of VMT
  - Trauma
    - Blunt trauma
    - Lightning strike
    - Surgical procedure
  - Myopia
  - Macular schisis
  - MacTel Type 2
  - Choroidal neovascularization (CNV) treated with anti-VEGF
## VMI Diseases

### Macular Hole - Old Versus New

**Old (Based on Gass)**
- Stage 0 macular hole
- Stage 1 macular hole
- Stage 2 macular hole
- Stage 3 macular hole
- Stage 4 macular hole

**New (Intl Classification)**
- VMA in contralateral eye
- VMT
- FTMH – small or medium
- FTMH – medium or large
- FTMH – VMA release, small, medium, large
Vitreomacular Adhesion (VMA) Associated with VMI Disease

Epiretinal Membrane (ERM) (rarely pathologic)

Macular Schisis

Lamellar Macular Hole

VMT (ALWAYS pathologic)

Macular Hole

Epiretinal Membrane (ERM)

25% incidence

33% incidence

= Rare Secondary Paths to Macular Hole
VMI Diseases

Summary

- **VMA** = stage of PVD progression
  - Focal vs broad
  - Isolated vs concurrent
- Abnormalities result in persistence of adhesion with traction = **VMT**
  - Focal vs broad
  - Isolated vs concurrent
VMI Diseases

Summary

- **VMT** can lead to:
  - Severe retinal anatomic abnormalities
  - FTMH
    - Small, medium, large
    - VMA - present or absent
    - Primary vs secondary
  - ERM
  - LMH
  - Macular Schisis
Contemporary Management of Diseases of the Vitreomacular Interface

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

Andrew Moshfeghi, MD, MBA
Bascom Palmer Eye Institute
Palm Beach Gardens, FL
Financial Disclosures

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

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- Fees for Non-CME Services: ThromboGenics, Bayer

- 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>Dispass</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 development¹-⁴

<table>
<thead>
<tr>
<th>Agent</th>
<th>Classification</th>
<th>Mechanism of action</th>
<th>Status</th>
</tr>
</thead>
<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>

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⁴ ThromboGenics NV. Jetrea(ocriplasmin) Summary of product characteristics 2013.
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.

Ocriplasmin at the VRI

- Fibronectin
- Collagen
- Laminin
- ILM

Mechanism of Action

Ocriplasmin exerts proteolytic effects on fibrinogen, fibronectin and, to a lesser extent, laminin and collagen fibrils\textsuperscript{1-3}

Ocriplasmin induces PVD via a two-step mechanism\textsuperscript{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

**Layers and Structures**
- Vitreous Body
- Vitreoretinal interface
- Inner limiting membrane
- Inner plexiform
- Inner nuclear layer
- Outer plexiform
- Outer nuclear layer
- Inner/outer segment and pigmented epithelium
- Bruch’s membrane
- Sclera
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 Dec 2009
MIVI-009 (Peds) Jan 2010
MIVI-014 (OASIS) Oct 2011


MIVI-003 (Phase 3) Dec 2006
MIVI-007 Nov 2008
MIVI-008 Jan 2010
MIVI-010 (PK) Jul 2010
MIVI-006 Nov 2008
MIVI-008 Q2 2011

Completed trials  Ongoing trials
Ocriplasmin Phase III Clinical Trial Program

Phase III MIVI-TRUST: Ocriplasmin for the Treatment of Symptomatic VMA Including Macular Hole
MIVI-006 and 007 Study Design

VMA confirmed by OCT

Investigator determines eligibility

Randomized (N=652)

Ocriplasmin†
125 µg†
(n=464)

Placebo†
(n=188)

Primary end point
- Pharmacologic resolution of VMA at Day 28

Secondary end points
- Total PVD at Day 28
- Nonsurgical closure of FTMH
- VA change
- Need for vitrectomy
- VFQ assessment

MIVI-006 (US only)
MIVI-007 (EU and US)

†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

<table>
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<tr>
<th>Characteristics</th>
<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

Placebo

- 19/188
- 10.1%

Ocriplasmin

- 123/464
- 26.5%

P < 0.01

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>
<th>Placebo (n=47)</th>
<th>Ocriplasmin (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle (N=188)</td>
<td>3.7%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Ocriplasmin (N=464)</td>
<td>n=7</td>
<td>n=62</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)

### Full Thickness Macular Hole Characteristics

<table>
<thead>
<tr>
<th>Baseline Macular Hole, n (%)</th>
<th>Placebo (n=188)</th>
<th>Ocriplasmin (n=464)</th>
</tr>
</thead>
<tbody>
<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)

FTMH Closure With Vitrectomy in Nonresponders

*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)

## Positive Independent Baseline Features

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;65 years</td>
</tr>
<tr>
<td>FTMH&lt;sup&gt;a&lt;/sup&gt; present</td>
</tr>
<tr>
<td>VMA diameter ≤1500 μm&lt;sup&gt;b&lt;/sup&gt;</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 + diameter ≤1500 μm</td>
<td>46.2</td>
<td>80.0</td>
<td>0.026</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>

Exposure to Ocriplasmin

Total (any dose)  
\( n = 976 \)

7 Completed Studies  
\( n = 741 \)

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

125 µg Dose  
\( n = 582 \)

Phase 3  
\( n = 465 \)

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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Placebo (n=187)</th>
<th>Ocriplasmin (n=465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitreous floaters</td>
<td>2.7%</td>
<td>12.9%</td>
</tr>
<tr>
<td>Eye pain</td>
<td>3.2%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Photopsia</td>
<td>1.1%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>0.5%</td>
<td>6.5%</td>
</tr>
<tr>
<td>VA reduced</td>
<td>0.0%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>0.0%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Retinal edema</td>
<td>0.0%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Macular edema</td>
<td>0.0%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Anterior chamber cell</td>
<td>0.5%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Photophobia</td>
<td>0.0%</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

### Suspected ADRs in Study Eye

**By Postinjection Time to Onset: Day 8 to End of Study**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n=187)</th>
<th>Ocriplasmin (n=465)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitreous floaters</td>
<td></td>
<td></td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.9</td>
</tr>
<tr>
<td>Eye pain</td>
<td></td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.6</td>
</tr>
<tr>
<td>Photopsia</td>
<td></td>
<td></td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.7</td>
</tr>
<tr>
<td>Vision blurred</td>
<td></td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.9</td>
</tr>
<tr>
<td>VA reduced</td>
<td></td>
<td></td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.2</td>
</tr>
<tr>
<td>Visual impairment</td>
<td></td>
<td></td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.2</td>
</tr>
<tr>
<td>Retinal edema</td>
<td></td>
<td></td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.7</td>
</tr>
<tr>
<td>Macular edema</td>
<td></td>
<td></td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.4</td>
</tr>
<tr>
<td>Anterior chamber cell</td>
<td></td>
<td></td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.1</td>
</tr>
<tr>
<td>Photophobia</td>
<td></td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
</tbody>
</table>

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>Median Time to Resolution (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=187)</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>35.0</td>
</tr>
<tr>
<td>Photopsia</td>
<td>3.0</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>78.0</td>
</tr>
</tbody>
</table>

## Adverse Events of Special Interest by Category

<table>
<thead>
<tr>
<th>Placebo-controlled Studies (TG-MV-006, TG-MV-007)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Vision alteration</td>
</tr>
<tr>
<td>Intraocular inflammation</td>
</tr>
<tr>
<td>Cataract</td>
</tr>
<tr>
<td>IOP increase</td>
</tr>
<tr>
<td>Intraocular hemorrhage</td>
</tr>
<tr>
<td>Retinal breaks</td>
</tr>
<tr>
<td>Glaucoma</td>
</tr>
<tr>
<td>Color vision alteration</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

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

**Data on file. ThromboGenics, Inc. 2012.**

#### 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>Vision alteration</td>
<td>16</td>
<td>(8.6%)</td>
</tr>
<tr>
<td>Intraocular inflammation</td>
<td>8</td>
<td>(4.3%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>18</td>
<td>(9.6%)</td>
</tr>
<tr>
<td>IOP increase</td>
<td>10</td>
<td>(5.3%)</td>
</tr>
<tr>
<td>Intraocular hemorrhage</td>
<td>8</td>
<td>(4.3%)</td>
</tr>
<tr>
<td>Retinal breaks</td>
<td>8</td>
<td>(4.3%)</td>
</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, e.g., “visual acuity reduced,” “visual impairment,” etc, were grouped into relevant categories so as not to underestimate incidence.*
Adverse Events of Special Interest by Category

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

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
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<td>n</td>
<td>(%)</td>
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<tr>
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</tr>
<tr>
<td>Intraocular inflammation</td>
<td>8</td>
<td>(4.3%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>18</td>
<td>(9.6%)</td>
</tr>
<tr>
<td>IOP increase</td>
<td>10</td>
<td>(5.3%)</td>
</tr>
<tr>
<td>Intraocular hemorrhage</td>
<td>8</td>
<td>(4.3%)</td>
</tr>
<tr>
<td>Retinal breaks</td>
<td>8</td>
<td>(4.3%)</td>
</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, e.g., “visual acuity reduced,” “visual impairment,” etc, were grouped into relevant categories so as not to underestimate incidence.


Visual function changes
- Reduced visual acuity
- Dyschromatopsia
- ERG changes
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 ≥2 Line VA Loss

Baseline (66 letters) 7 days post (53 letters)
14 days post (50 letters) 6 months post (72 letters [+6])
Visual Acuity Recovery in Patients With ≥ 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
36 (7.7%)
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>
</tr>
<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>
</tr>
<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>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
</tbody>
</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)

- Occurred in 10 of 820 patients (1.2%)*
  - (8 of 10 had dyschromatopsia)
- 7 of 10 cases resolved
- 3 patients lost to follow-up (VA returned and so patient didn’t return)

- 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

*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
Contemporary Management of Diseases of the Vitreomacular Interface

Course Chair
Szilárd Kiss, MD
Director of Clinical Research
Assistant Professor of Ophthalmology
Weill Cornell Medical College
New York, New York