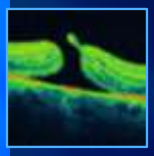

New Approaches to the Treatment of Vitreomacular Interface Disorders

Frontiers and Controversies in Ophthalmology: 2014 Joint Conference

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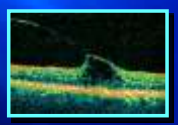
Rush University Medical Center
Chicago, IL

Financial Disclosures

- Consultant
  - Genentech, Regeneron, Allergan, Thrombogenics, Optos, and ArcticDx
- Grant Support
  - Regeneron, Allergan

Vitreoretinal Interface Pathology



- Proliferative diabetic retinopathy (PDR)
- Proliferative vitreoretinopathy (PVR)
- Macular pucker & Macular hole
- Diabetic macular edema (DME)
- Vitreo-macular traction syndrome (VMT)
- *Exudative age-related macular degeneration (AMD) ?*

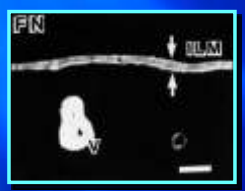
Background

- Vitrectomy is the current treatment vitreoretinal interface pathology
  - Vitreomacular traction syndrome
  - Macular hole
- Pharmacologic vitreolysis using microplasmin has demonstrated potential to induce PVD

Vitreous is an Ideal Matrix For Manipulation With Enzymes

- Rapid diffusion of drugs
- It's mostly water
- Has relatively few molecular components
- It's relatively acellular

The Vitreoretinal Interface



ILM Stain for Fibronectin

- Vitreous adhesion to ILM is mediated by:
  - Fibronectin
  - Laminin
  - Chondroitin
  - Glycoconjugates

G. A. Williams, MD

Plasmin

- Hydrolyzing laminin and fibronectin which bridge collagen fibers between the posterior vitreous cortex and the ILM
- Trese and Williams developed autologous plasmin method
- Induces PVD, especially in young patients, dose and duration dependent
- Cumbersome preparation using patients serum

Structure of Human Plasmin

88 kDa Size

Structure of Microplasmin

Microplasmin

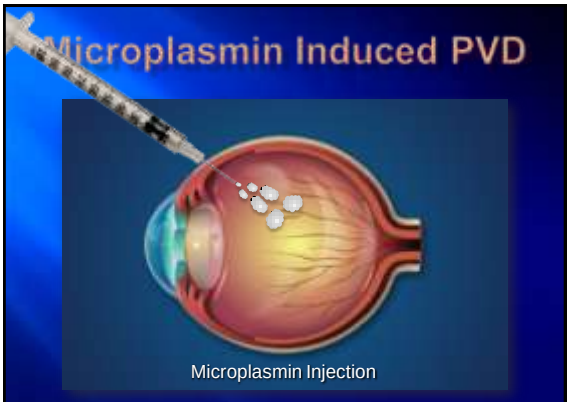
29 kDa Size

Ocriplasmin

Protein Ribbon Structure

- Generic name for microplasmin
- Lacks inactive kringle domains
- Direct-acting thrombolytic *(unlike plasminogen activator)*
- Smaller molecule, allows better retinal penetration
- Recombinant technology
- Induces PVD with single 75µg or 125µg injection

Microplasmin Induced PVD



ThromboGenics

Leuven, Belgium ~ Dublin, Ireland ~ New York NY

The MIVI Trials

"MIcroplasmin for VItreous Injection"

MIVI III ~ Clinical Centers

19 Centers

Data Monitoring Board
- Julia Haller, MD
- William Mieler, MD
- Lloyd-Paul Aiello, MD PhD

MIVI III ~ Study Design

125 Patients without PVD Scheduled for Vitrectomy

Control Saline Injection	25µg Microplasmin Injection	75µg Microplasmin Injection	125µg Microplasmin Injection

- Phase IIb randomized, placebo-controlled, double-masked, parallel-group, dose-ranging US study
- Pars plana vitrectomy 7 days after injection
- Primary analysis after 35 days (full follow-up at 6 months)

MIVI III ~ Primary Endpoint

Posterior Vitreous Detachment

- Assessed by a masked surgeon at the beginning of vitrectomy
- *If vitrectomy not performed:* Based on investigator assessment of OCT or B-Scan

MIVI III ~ Secondary Endpoints

Avoidance of Surgery

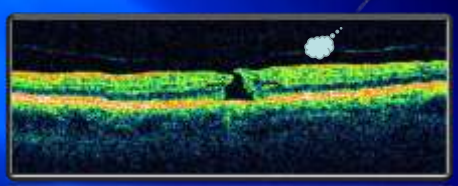
- V-M traction resolution
- Macular hole closure

Safety

- Endophthalmitis
- Uveitis
- Retinal tears
- Vision

Clinical Case

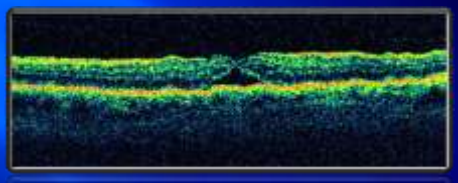
Case 1: 125 µg dose



Pre-injection - Baseline

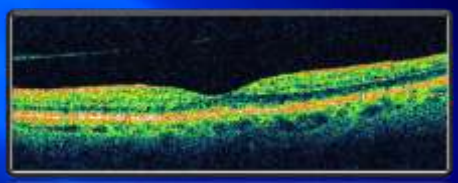
20/63

Case 1: 125 µg dose



Day 7
20/50 → Surgery Cancelled

Case 1: 125 µg dose



1 month
20/32

A Placebo-Controlled Trial of Microplasmin Intravitreous Injection to Facilitate Posterior Vitreous Detachment before Vitrectomy

Matthew T. Benz, MD,[1] Kirk H. Packo, MD,[2] Victor Gonzalez, MD,[3] Stephen Pelletz, MD,[4] Donna Reuter,[4] John A. Maffei, MD,[5] Jason D. Schwartz, MD[6]

Ophthalmology 2010;117:791–797

- *Rate of total PVD noted at time of surgery*:
  Placebo – 10% vs. Microplasmin 125µg – 31%
- *VMT resolution at 35 days precluding need for surgery*:
  Placebo – 3% vs. Microplasmin 125µg – 31%
- *Macular hole closed without surgery at 35 days*:
  Placebo – 0% vs. Microplasmin 125µg – 35%

MIVI-TRUST
Traction Release without Surgical Treatment

- *Design:* Randomized, placebo-injection controlled, double-masked trial
  (same for both studies)
- *Population:* Symptomatic fVMA
  (Patients with VMT or macular holes < 400 µm)
- *Allocation:* Microplasmin 125µg intravitreal injection vs. placebo (vehicle*) injection
  - 2:1: MIVI – 006 (US)
  - 3:1: MIVI – 007 (US & Europe)
- *Follow-Up:* 6 months

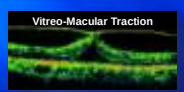
*Vehicle = Mannitol 3.75 mg/mL, Citric Acid Monohydrate 1.051 mg/mL

MIVI-TRUST
Traction Release without Surgical Treatment

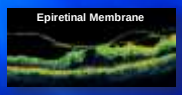
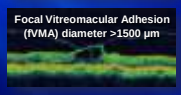
- *Primary endpoint (MIVI-006 & -007):*
  - Nonsurgical resolution of fVMA by Day 28
    (determined by Central Reading Center [CRC])
- *Key Secondary endpoints (MIVI-006 & -007):*
  - Proportion of patients with total posterior vitreous detachment (PVD) at Day 28
    (determined by ultrasound by investigators)
  - Proportion of patients with nonsurgical closure of macular hole *(determined by CRC)*

23

MIVI-006: Baseline Macular Disease

Macular Condition	Placebo (n=106)	Microplasmin (n=220)
 Vitreo-Macular Traction	74 (69.8%)	163 (74.1%)
 Full Thickness Macular Hole	32 (30.2%)	57 (25.9%)

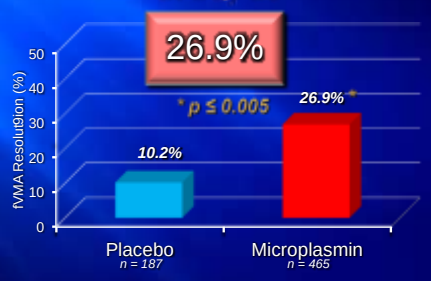
MIVI-006: Other Ocular Characteristics

Ocular Characteristic	Placebo (n=106)	Microplasmin (n=220)
 Epiretinal Membrane	34 (32.1%)	87 (39.7%)
 Focal Vitreomacular Adhesion (fVMA) diameter >1500 µm	19 (17.9%)	47 (21.4%)

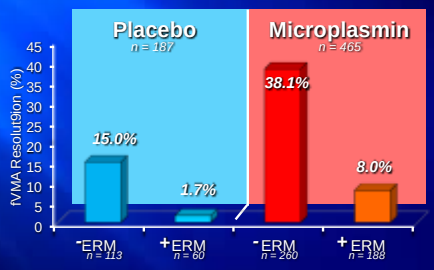
MIVI-TRUST
Traction Release withoUt Surgical Treatment

Primary Efficacy Analysis

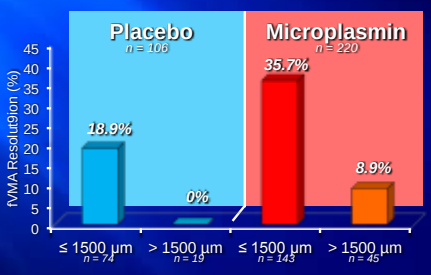
Pooled Data: Primary Endpoint: Nonsurgical fVMA Resolution at Day 28



Pooled Data: Nonsurgical fVMA Resolution at Day 28 Depending on ERM Status

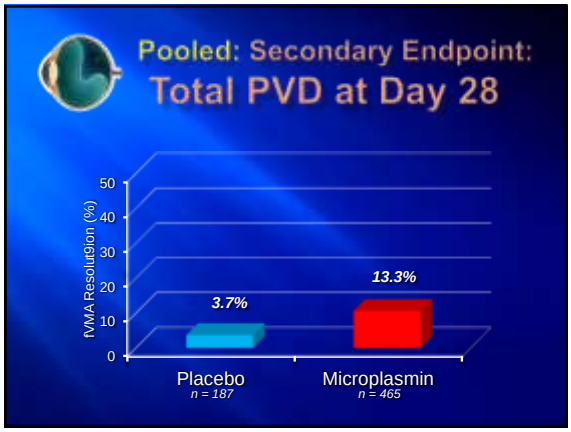


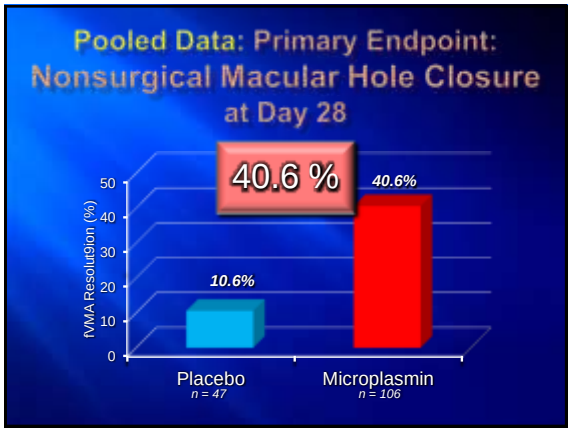
MIVI-006 Nonsurgical fVMA Resolution at Day 28 Depending on fVMA Diameter

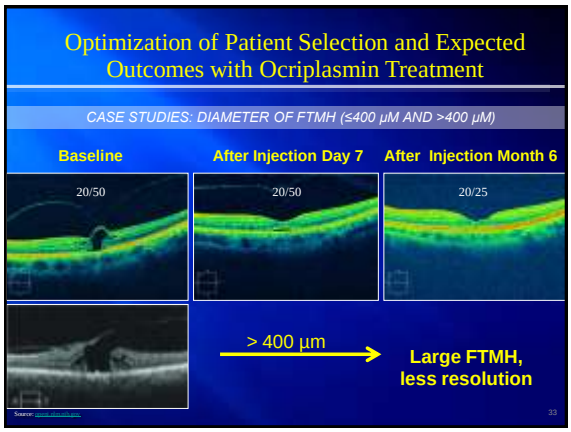


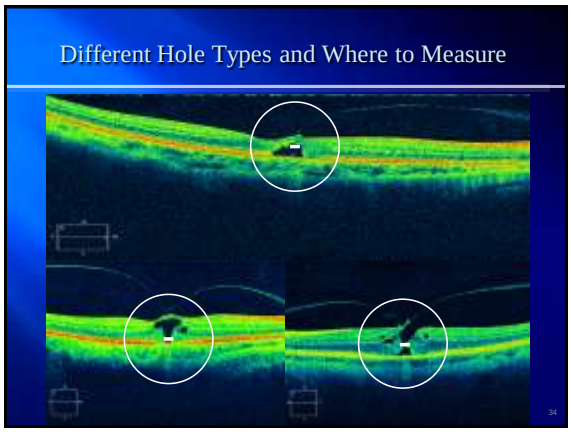
MIVI-TRUST
Traction Release withoUt Surgical Treatment

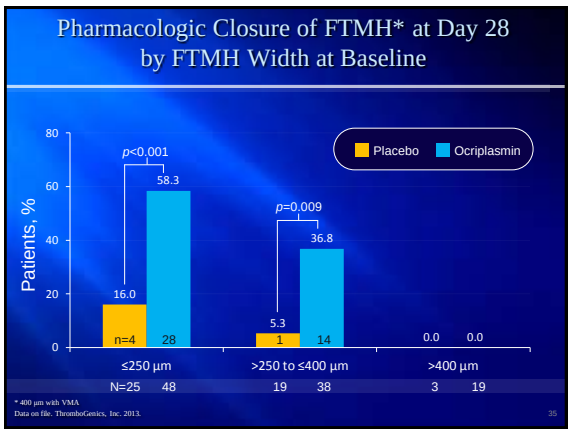
MIVI-006 & MIVI-007 Key Secondary Endpoints

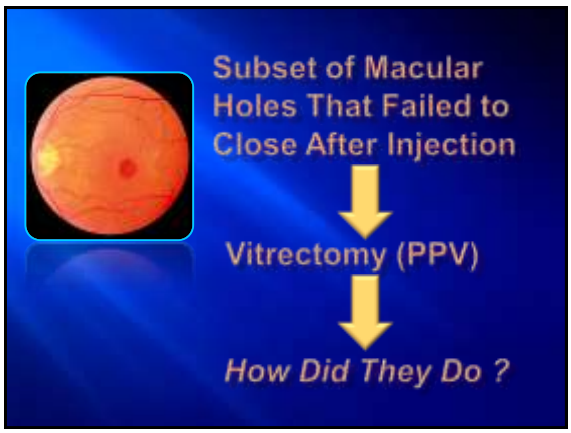

Pooled: Secondary Endpoint:
Total PVD at Day 28
fVMA Resolution (%)
50
40
30
20
10
0
3.7%
13.3%
Placebo
n = 187
Microplasmin
n = 465


Pooled Data: Primary Endpoint:
Nonsurgical Macular Hole Closure
at Day 28
40.6 %
fVMA Resolution (%)
50
40
30
20
10
0
10.6%
40.6%
Placebo
n = 47
Microplasmin
n = 106


Optimization of Patient Selection and Expected
Outcomes with Ocriplasmin Treatment
CASE STUDIES: DIAMETER OF FTMH (≤400 µM AND >400 µM)
Baseline
After Injection Day 7
After Injection Month 6
20/50
20/50
20/25
> 400 µm
Large FTMH,
less resolution


Different Hole Types and Where to Measure


Pharmacologic Closure of FTMH* at Day 28
by FTMH Width at Baseline
Placebo
Ocriplasmin
Patients, %
80
60
40
20
0
p<0.001
58.3
16.0
p=0.009
36.8
5.3
0.0
0.0
n=4
28
1
14
≤250 µm
>250 to ≤400 µm
>400 µm
N=25
48
19
38
3
19
* 400 µm with VMA
Data on file. ThromboGenics, Inc. 2013.


Subset of Macular
Holes That Failed to
Close After Injection
Vitrectomy (PPV)
How Did They Do ?

Macular Hole Closure At End of Study in Patients Who Underwent PPV

% Postop Hole Closure Rate (n)	Placebo (n=19)	Microplasmin (n=26)
	84.2% (16)	84.6% (22)

MIVI-TRUST

Traction Release withoUt Surgical Treatment

MIVI-006

Safety

MIVI-006: Safety Review

AE's with Frequency ≥ 4% in Microplasmin Group

Adverse event (AE) %	Placebo (n=107)	Microplasmin (n=219)
Any ocular AE	55.1	71.7
Any ocular serious AE	10.3	9.6
Vitreous floaters	8.4	19.2
Photopsia	3.7%	16.4%
Retinal edema	0.9	5.9
Anterior chamber cell	3.7	4.6
IOP increase	9.3	4.1
Metamorphopsia	0	4.1

MIVI-006: Safety – Retinal Breaks

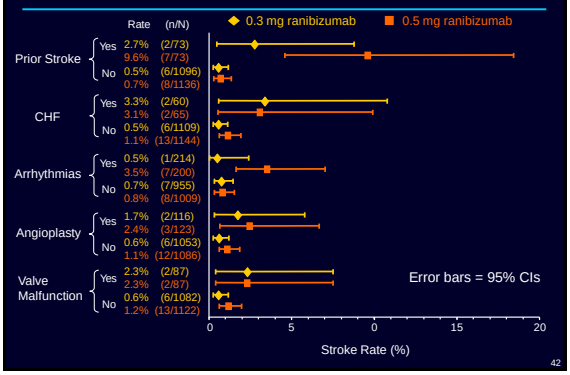
% Retinal Break During 6 mo. Follow-up	Placebo (n=107)	Microplasmin (n=219)
Any Retinal Tear or Retinal Detachment	3.74 %	3.19 %
Intra / Post-Operative Retinal Tear or Detachment	3.74 %	2.28 %
Retinal Tear	1.86 %	1.83 %
Retinal Detachment	1.86 %	0.46 %
Non-Operative Retinal Tear or Detachment	0 %	0.91 %
Retinal Tear	0 %	0 %
Retinal Detachment	0 %	0.91 %

Verteporfin Therapy: All Trials Acute Severe VA Decrease

Study	n/N	%
TAP Investigation[1]	3/402	0.7
VIP Trial[1]	10/225	4.4
VAM[2]	33/4435	0.6
VIM[3]	1/77	1.3
VER[4]	1/323	0.3
JAT[4]	2/64	3.1
VALIO[4]	3/60	5.0
Total	53/5586	0.9

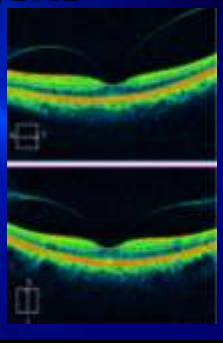
1. TAP and VIP Study Groups. *Am J Ophthalmol*. 2004;137:683–696.
2. VAM Study Writing Committee. *Retina*. 2004;24:512-520.
3. VIM Study Group. *Arch Ophthalmol*. In press.
4. Data on file, Novartis Pharma AG.

Stroke Rate by Potential Risk Factor



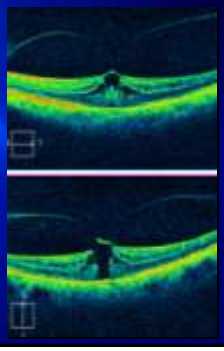
Clinical Case
Dec 5, 2012

- 20/25 OS
- 1+ NS

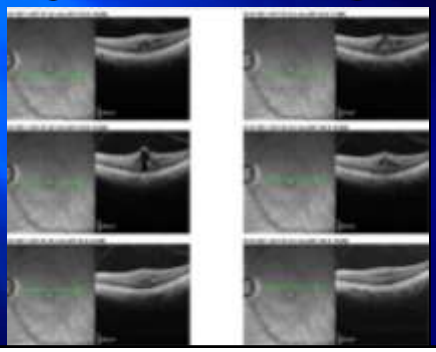


April 3, 2013

- Vision 20/100
- Scheduled Jetrea

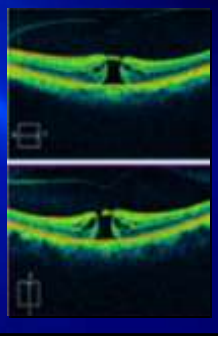


April 10, 2013 – Jetrea given



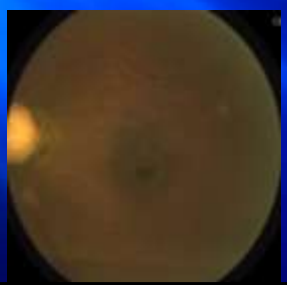
April 11, 2013

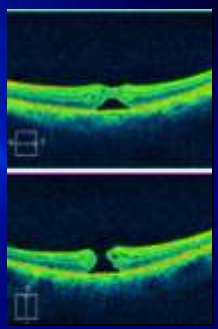
- Vision 20/150
- "Kaleidoscope"
- No holes/tears with SD 360deg



April 24, 2013

- Vision 20/80



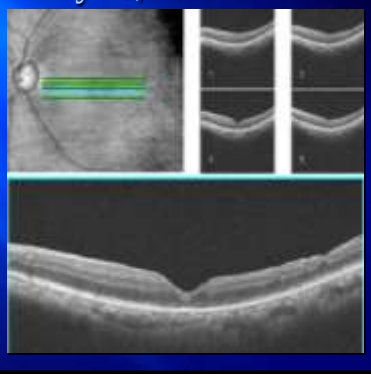


Scleral depression

- Large horseshoe tear 4:00 with SRF
- Plan: vitrectomy/EL/GFX/ILM peeling

Vitrectomy April 26, 2013

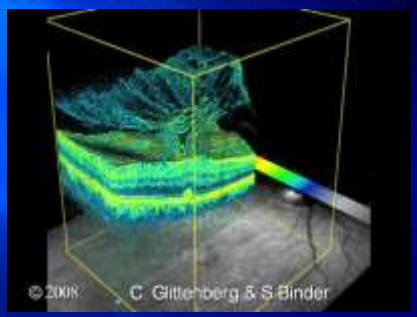
May 18, 2013 – 20/70



Thrombogenics: ORBIT

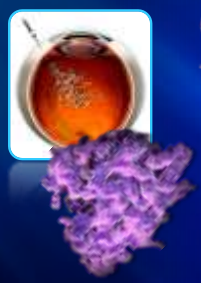
- Ocriplasmin Research to Better Inform Treatment
- Phase 4 prospective clinical study to assess the real-world safety and effectiveness of ocriplasmin treatment for US patients with symptomatic vitreomacular adhesion (VMA)
- Aim is to collect real-time data on 1500 patients at 120 US sites with up to one year follow up
- Enrollment to begin in early 2014

Vitreoretinal Interface – The Future



Patient with exudative AMD

Additional Clinical Trials for Future



- Age-Related Macular Degeneration
- Diabetic Retinopathy
  - Macular Edema
  - Proliferative Disease

Thank You