Ocriplasmina for pharmacologic treatment in VMT

Teresio Avitabile

Introduction

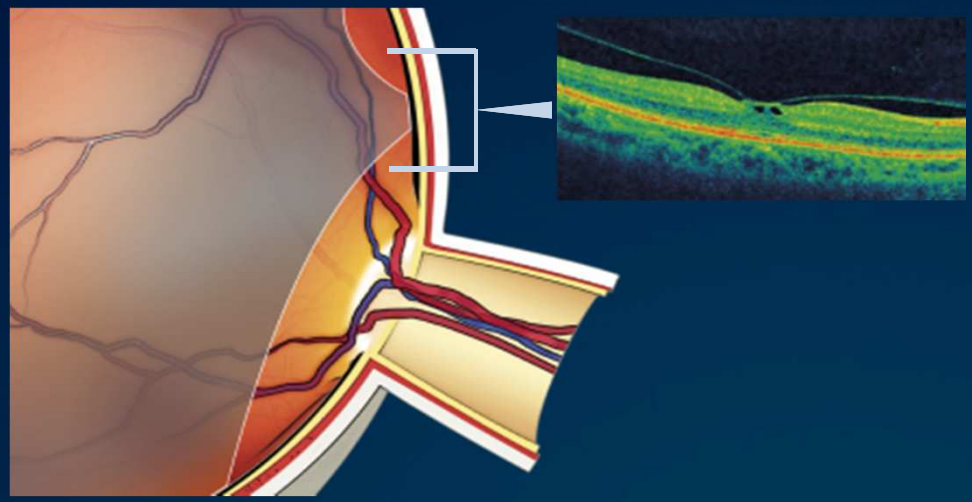
- PVD is a normal, physiologic process that occurs with aging; however, in some cases, PVD is incomplete
- Incomplete PVD localized at the macula is known as VMA and this may result in traction at the site of adherence (known as VMT)
- Clinical manifestations of VMT include visual disturbances and decreased VA
- Untreated VMT can lead to MH, a condition that impacts severely on visual function and, consequently, patient quality of life

MH, macular hole; PVD, posterior vitreous detachment; VA, visual acuity; VMA, vitreomacular adhesion; VMT, vitreomacular traction

Incomplete Posterior Vitreous Detachment

- There should be sufficient weakening at the vitreoretinal interface when the critical level of liquefaction has been achieved[1]
  - If not, incomplete PVD can arise
- VMA:
  - Areas of adhesion between the posterior hyaloid cortex and the fovea, due to incomplete PVD[2]
  - May cause a range of sequelae, e.g.[1]
    - VMT
    - MH
    - Retinal tear

VMA at the macula resulting in VMT

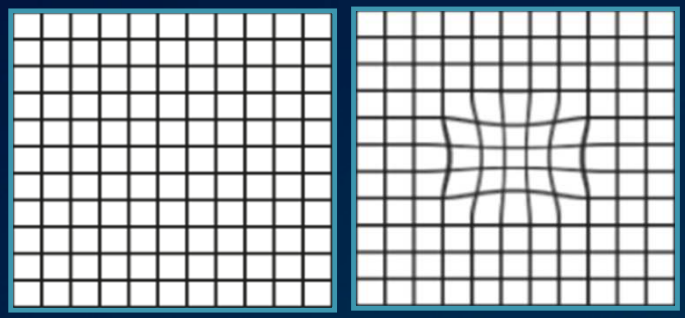


MH, macular hole; PVD, posterior vitreous detachment; VMA, vitreomacular adhesion; VMT, vitreomacular traction

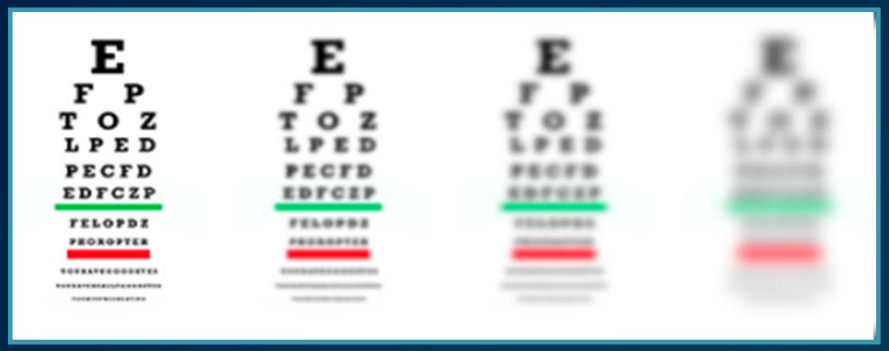
1. Sebag J. *Graefes Arch Clin Exp Ophthalmol* 2004;242:690; 2. Dugel P. *Retina Today* April 2012;50;

Visual Symptoms Associated with Vitreomacular Traction

- Progressive vision loss,[1,2] which can include:
  - Metamorphopsia (distorted vision)[1,2]
  - Photopsia (appearance of flashes of light)[2]
  - Micropsia (objects appear smaller than they are in reality)[2]
  - Central visual field defect[1]



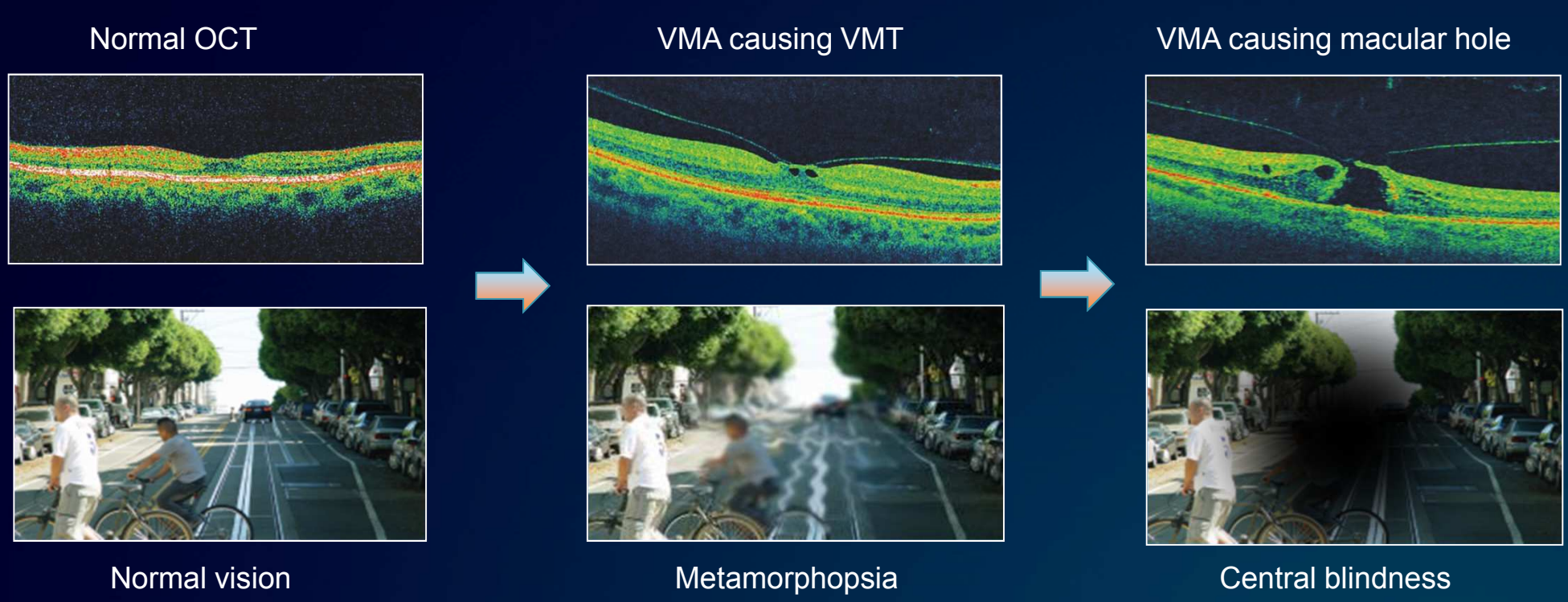
Metamorphopsia



Decreased visual acuity

1. Dugel P. *Retina Today* April 2012;50
2. Hikichi T *et al. Am J Ophthalmol* 1995;119:55

Progression of Vitreomacular Traction to Macular Hole



OCT, optical coherence tomography; VMA, vitreomacular adhesion; VMT, vitreomacular traction

Impact of Macular Hole on Visual Acuity

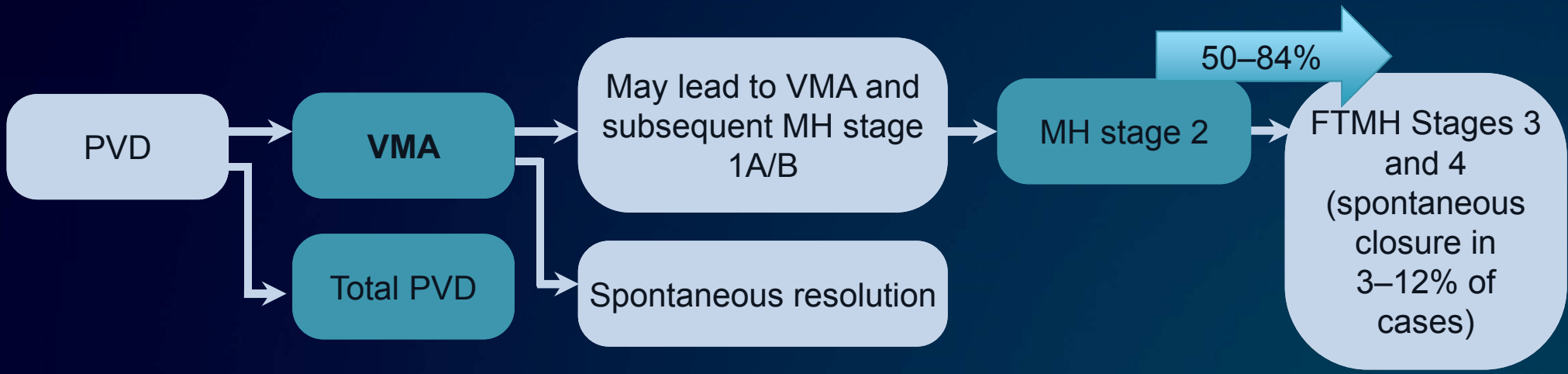
- Stages 1A–2 MH typically associated with a BCVA of 20/25 to 20/80
  - Stages 3–4 MH associated with BCVA of 20/100 to 20/400
- The prognosis of untreated FTMH is poor
  - Only 5% will have 20/50 BCVA or better
  - 55–58% will have BCVA of 20/100 or better
  - Approximately 40% will have BCVA of 20/200 or worse
  - If the FTMH closes (rare), BCVA can recover
  - Most patients retain a BCVA of 20/100 to 20/400

BCVA, best-corrected visual acuity; FTMH, full-thickness macular hole; MH, macular hole

American Academy of Ophthalmology Retina Panel. Preferred Practice Pattern®. Idiopathic Macular Hole, 2008. http://www.aao.org/ppp (accessed November 2012)

Epidemiology of Vitreomacular Adhesion, Vitreomacular Traction, and Macular Hole

- Epidemiologic data on VMA, MH, and FTMH are limited
- The introduction of OCT in the 1990s facilitated the diagnosis of incomplete VMA and its related complications[1]
- 50–84% of Stage 2 MH progress to Stages 3 or 4[2–5]
- Spontaneous FTMH closure occurs in only 3–12% of cases[6]



FTMH, full-thickness macular hole; MH, macular hole; OCT, optical coherence tomography; PVD, posterior vitreous detachment; VMA, vitreomacular adhesion; VMT, vitreomacular traction

1. Carpineto P *et al*. *Eur Ophthalmic Rev* 2011;5:69; 2. Guyer DR *et al. Arch Ophthalmol* 1992;110:1264; 3. Hikichi T *et al. Br J Ophthalmol* 1995;79:517; 4. Kim JW *et al. Ophthalmology* 1995;102:1818; 5. Kim JW *et al. Am J Ophthalmol* 1996;121:605; 6. American Academy of Ophthalmology Retina Panel. Preferred Practice Pattern®. Idiopathic Macular Hole, 2008. http://www.aao.org/ppp (accessed November 2012)

The International Vitreomacular Traction Study Group Classification of Vitreomacular Adhesion, Traction, and Macular Hole

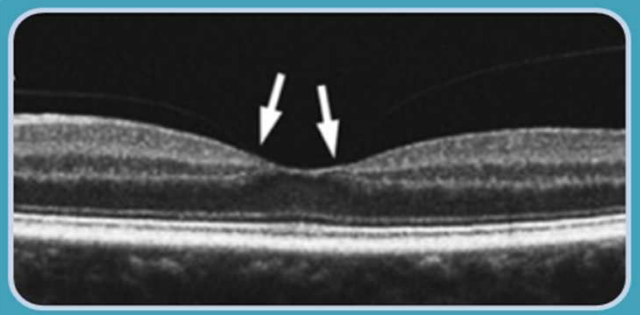
The IVTS Classification System in a Nutshell

Classification	Sub-classification
Vitreomacular adhesion (VMA)	• Focal (≤1500 µm) or broad (>1500 µm) • Isolated or concurrent with other diseases • No structural abnormalities in the retina
Vitreomacular traction (VMT)	• Focal (≤1500 µm) or broad (>1500 µm) • Isolated or concurrent with other diseases • Structural abnormalities in the retina
Full-thickness macular hole (FTMH)	• Small (≤250 µm), medium (>250 µm and ≤400 µm), or large (>400 µm) • With or without VMT • Primary or secondary to other conditions

Duker JS *et al. Ophthalmology* 2013;doi:10.1016/j.ophtha.2013.07.042

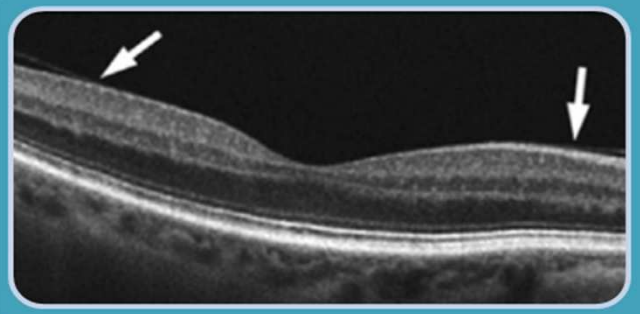
IVTS Definition and Classification of VMA

- VMA represents a specific stage of vitreous separation
  - Partial detachment of the vitreous in the perifoveal area
  - No retinal abnormalities



Focal VMA

- The white arrows mark the sites of vitreous attachment
- The area of attachment is ≤1500 µm, with no detectable change in foveal contour of underlying retinal tissues



Broad VMA

- The white arrows mark the sites of vitreous attachment
- The area of attachment is >1500 µm, with no detectable change in foveal contour of underlying retinal tissues

Duker JS *et al. Ophthalmology* 2013;doi:10.1016/j.ophtha.2013.07.042

IVTS Definition and Classification of VMA

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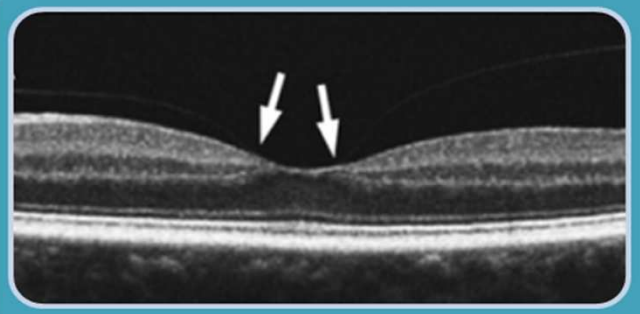
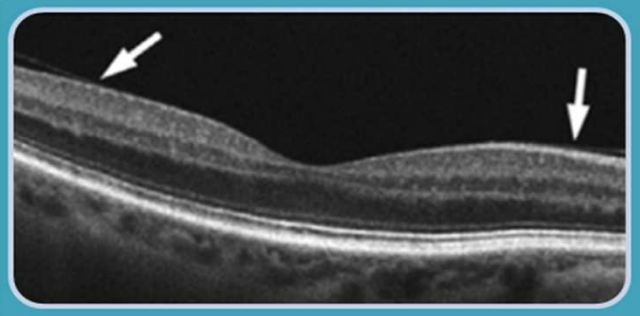


Focal VMA

- The white arrows mark the sites of vitreous attachment
- The area of attachment is ≤1500 µm, with no detectable change in foveal contour of underlying retinal tissues



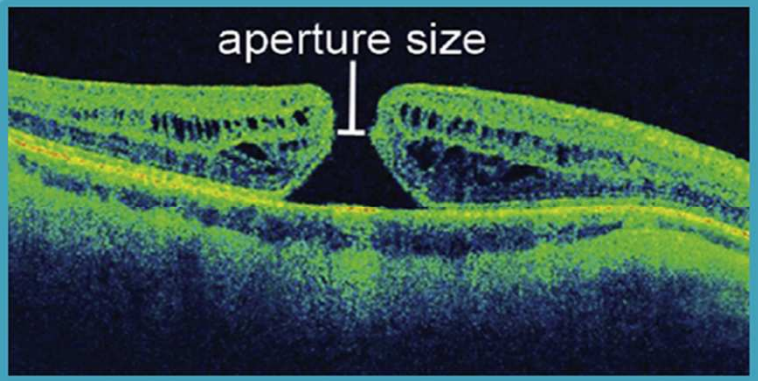
Broad VMA

- The white arrows mark the sites of vitreous attachment
- The area of attachment is >1500 µm, with no detectable change in foveal contour of underlying retinal tissues

Duker JS *et al. Ophthalmology* 2013;doi:10.1016/j.ophtha.2013.07.042

Full-Thickness Macular Hole – Introduction and Definition

- Anatomic defect in the fovea
  - Interruption of all neural retinal layers from the ILM to the RPE
- Clinically evaluated based on the Gass classification
  - Requires careful clinical examination
  - Divides macular holes into 4 stages
- OCT-based anatomic data helped to improve understanding of the pathogenesis and progression of macular hole

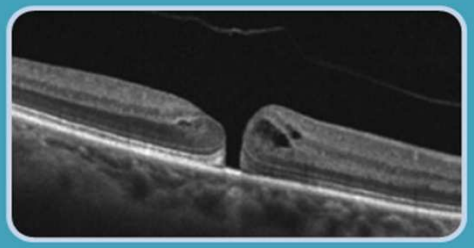


FTMH with aperture size of 192 µm without VMT

- Width-based definition
- The aperture size is measured at the narrowest hole width in the mid retina, parallel to the RPE

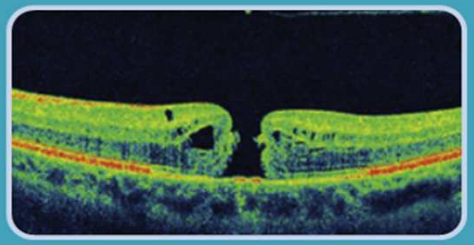
Duker JS *et al. Ophthalmology* 2013;doi:10.1016/j.ophtha.2013.07.042

IVTS Definition and Classification of FTMH



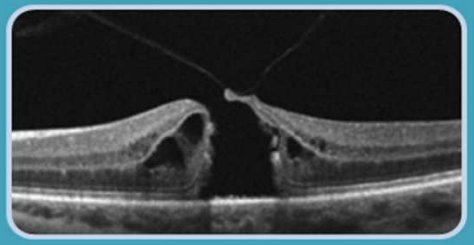
Small FTMH without VMT

- The foveal lesion interrupts all macular layers from the ILM to the RPE and has a narrowest linear width of ≤250 µm
- The vitreous is not attached to the macula or the edge of the hole



Medium FTMH without VMT

- The hole has a narrowest linear width of between 250 µm and 400 µm



Large FTMH with VMT

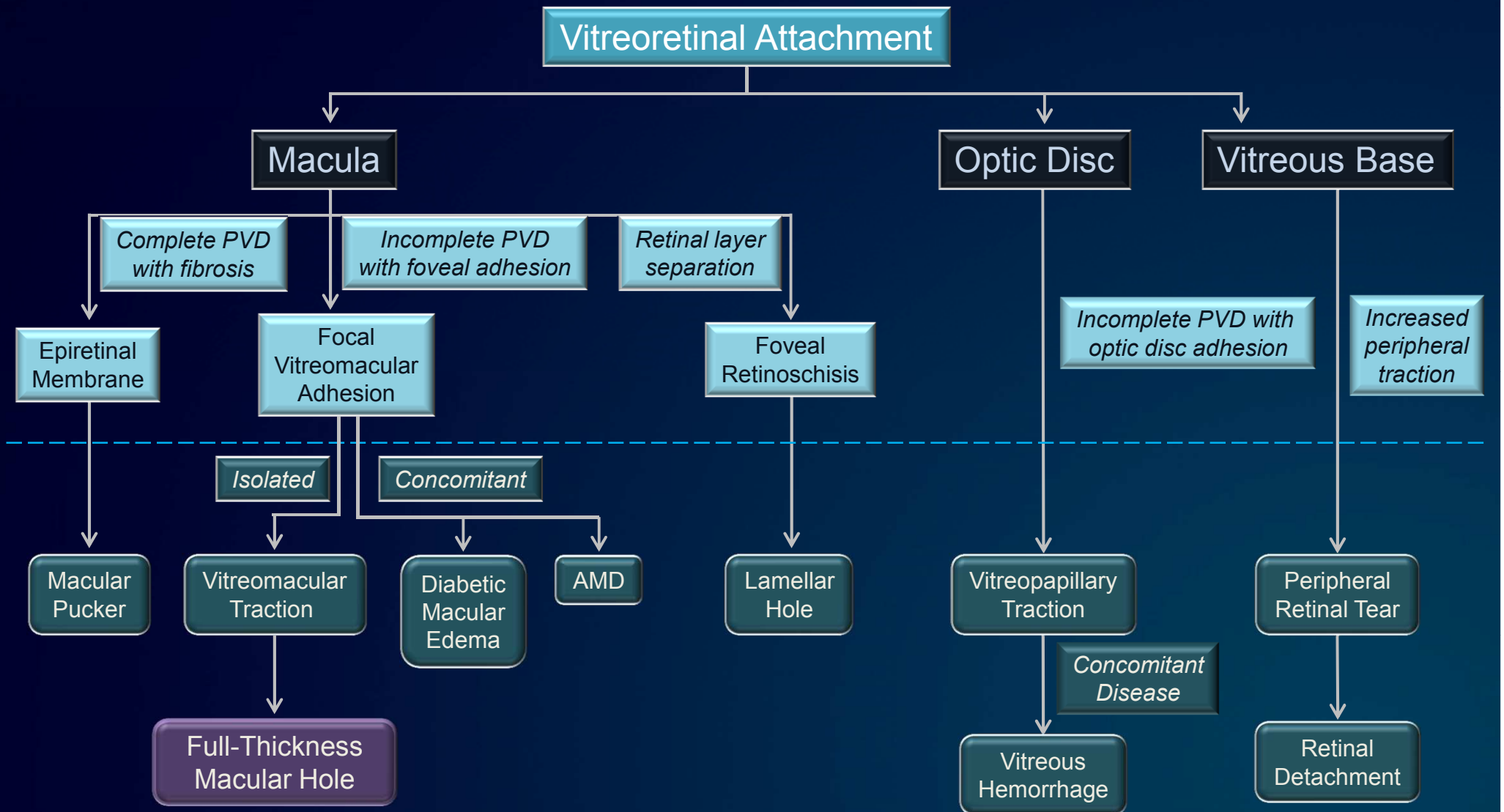
- The narrowest linear width of the hole is >400 µm
- The vitreous is attached to the edge of the hole

Duker JS *et al. Ophthalmology* 2013;doi:10.1016/j.ophtha.2013.07.042

The IVTS Classification System for Vitreomacular Adhesion, Traction, and Macular Hole

Summary Tables and Conclusions

A Comprehensive Overview of the IVTS Classification System



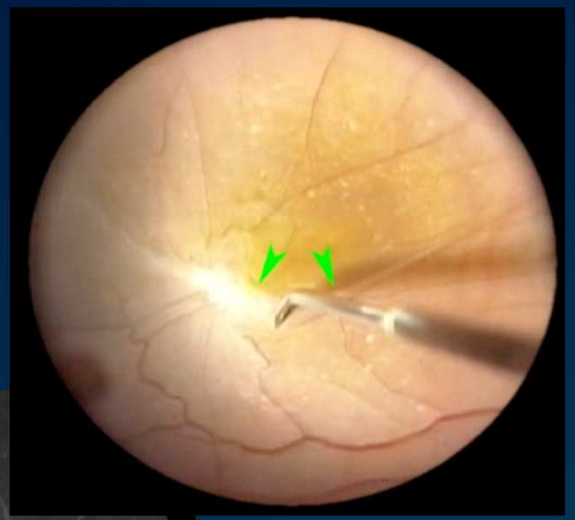
1. Stalmans P *et al. Retina* 2013 Jul 22. Epub, 2. Sebag J. Graefes *Arch Clin Exp Ophthalmol* 2004;242:690, 3. Sebag J. *Br J Ophthalmol* 2009;93:989

LA VITRECTOMIA A FRONTE DI UN MIGLIORAMENTO MORFOLOGICO NON FORNISCE UN MIGLIORE RISULTATO FUNZIONALE [1-3]

Early Postoperative Retinal Thickness Changes and Complications After Vitrectomy for Diabetic Macular Edema

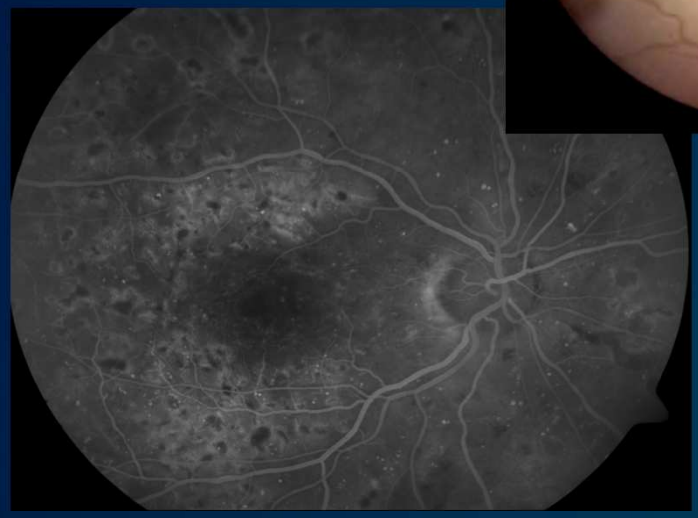
examinations and surgical methods are required. (Am J Ophthalmol 2003;135:14–19. © 2003 by Elsevier Science Inc. All rights reserved.)

TEIKO YAMAMOTO, MD, KOICHIRO HITANI, MD, ITSURO TSUKAHARA, MD, SHUICHI YAMAMOTO, MD, RYO KAWASAKI, MD, HIDETOSHI YAMASHITA, MD, AND SHINOBU TAKEUCHI, MD



COMPLICANZE INTRA E POST-OPERATORIE

- *Rotture retiniche(4.6%)*
- *DR regmatogeno (1.5%)*
- *Glaucoma neovascolare (5%)*
- *Emovitreo (1.5%)*
- *Essudati maculari(4.6%)*
- *Membrane epiretiniche (13.8%)*
- *Fori lamellari (1.5%)*
- *Fori maculari (1.5 %)*



1.Kumar et al. Graefes Arch Clin Exp Ophthalmol. 2007
2.La Heij et al. Graefes Arch Clin Exp Ophthalmol. 2001
3.Patel et al. Eye (Lond).2006

Vitreolytic Agents

Vitreolytic agents under development[1,2]

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

Interfactant: ability to weaken vitreoretinal adhesion

1. Schneider EW, Johnson MW. *Clin Ophthalmol.* 2011;5:1151.
2. Girach A, Pakola S. *Expert Rev Ophthalmol.* 2012;7:311.

Vitreolytic Agents

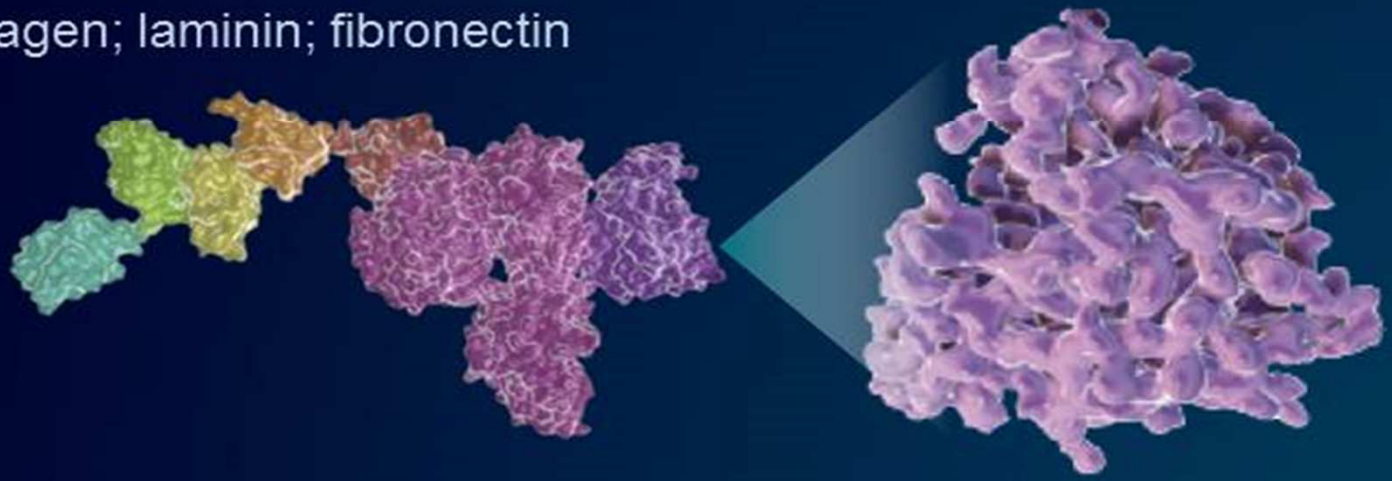
Vitreolytic agents under development[1-4]

Agent	Classification	Mechanism of action	Status
Nattokinase	Liquefactant and interfactant	Fibrinolytic effects by enhancing plasminogen activators and inactivating plasmin activator inhibitors	No evidence of further development
Endogenous plasmin	Liquefactant and interfactant	Mediates fibrinolysis by targeting vitreoretinal interface glycoproteins, including laminin and fibronectin	Independent studies with autologous plasmin enzyme are ongoing
Plasminogen activator	Liquefactant and interfactant	Indirect activation of plasmin	Therapeutic potential limited by need for adequate concentrations of intraocular plasminogen substrate
Ocriplasmin	Liquefactant and interfactant	Cleavage of laminin, fibronectin, and collagen at the vitreoretinal interface	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

1. Schneider EW, Johnson MW. *Clin Ophthalmol* 2011;5:1151.
2. Girach A, Pakola S. *Expert Rev Ophthalmol* 2012;7:311.
3. ThromboGenics, Inc. Jetrea (ocriplasmin) Prescribing Information 2012.
4. ThromboGenics NV. Jetrea(ocriplasmin) Summary of product characteristics 2013.

Ocriplasmin

- Ocriplasmin (previously known as microplasmin) is a recombinant, truncated form of the enzyme plasmin that retains the catalytic activity[1,2]
- Ocriplasmin targets components of the extracellular matrix implicated in VMA, to resolve VMA and release VMT[3–5]
  - Collagen; laminin; fibronectin



Plasmin (88 kDa) **Ocriplasmin (27.2 kDa)**

1. Nagai N *et al. J Thromb Haemost* 2003;1:307
2. de Smet M *et al. Invest Ophthalmol Vis Sci* 2009;50:814
3. Li X *et al. Graefes Arch Clin Exp Ophthalmol* 2002;240:56
4. Liotta LA *et al. Cancer Res* 1981;41:4629
5. Uemura A *et al. Arch Ophthalmol* 2005;123:209

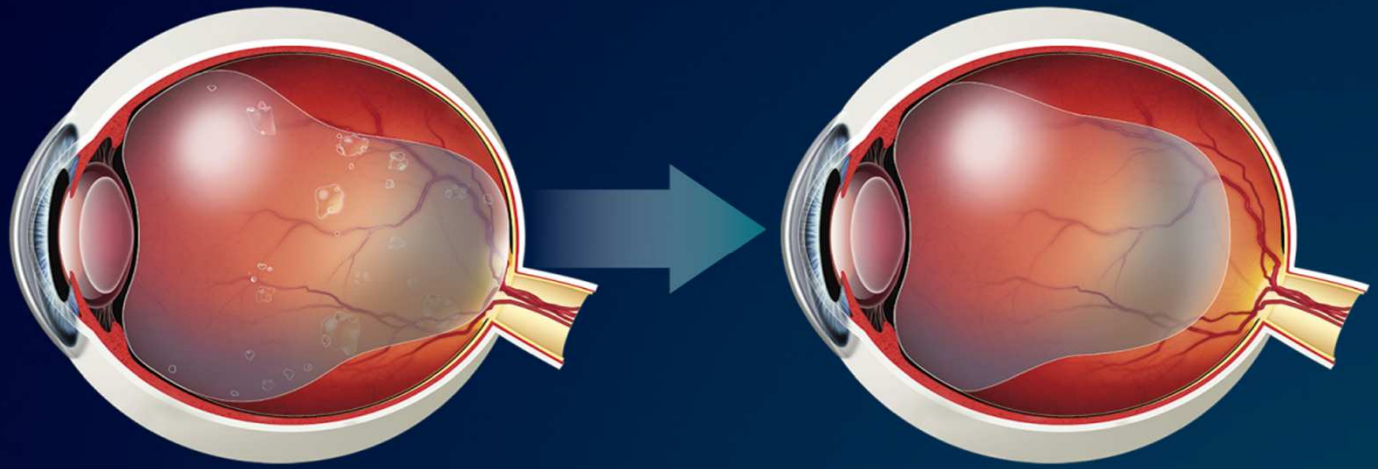
Key Differences: Autologous Plasmin versus Ocriplasmin

Autologous plasmin	Ocriplasmin
• Human protease isolated from serum[1]	• Recombinant, truncated form of plasmin[4]
• Molecular weight: 88 kDa[2]	• Molecular weight: 27.2 kDa[5]
• Harvesting is a time-intensive and expensive process[3]	• Can be developed on an industrial scale

1. Gandorfer A. In *Pharmacology and Vitreoretinal Surgery* 2009;44:26
2. Chen W *et al. Eye (London)* 2008;22:300
3. Schneider E & Johnson M. *Clin Ophthalmol* 2011;5:1151
4. Nagai N *et al. J Thromb Haemost* 2003;1:307
5. de Smet *et al. Invest Ophthalmol Vis Sci* 2012;53:8208

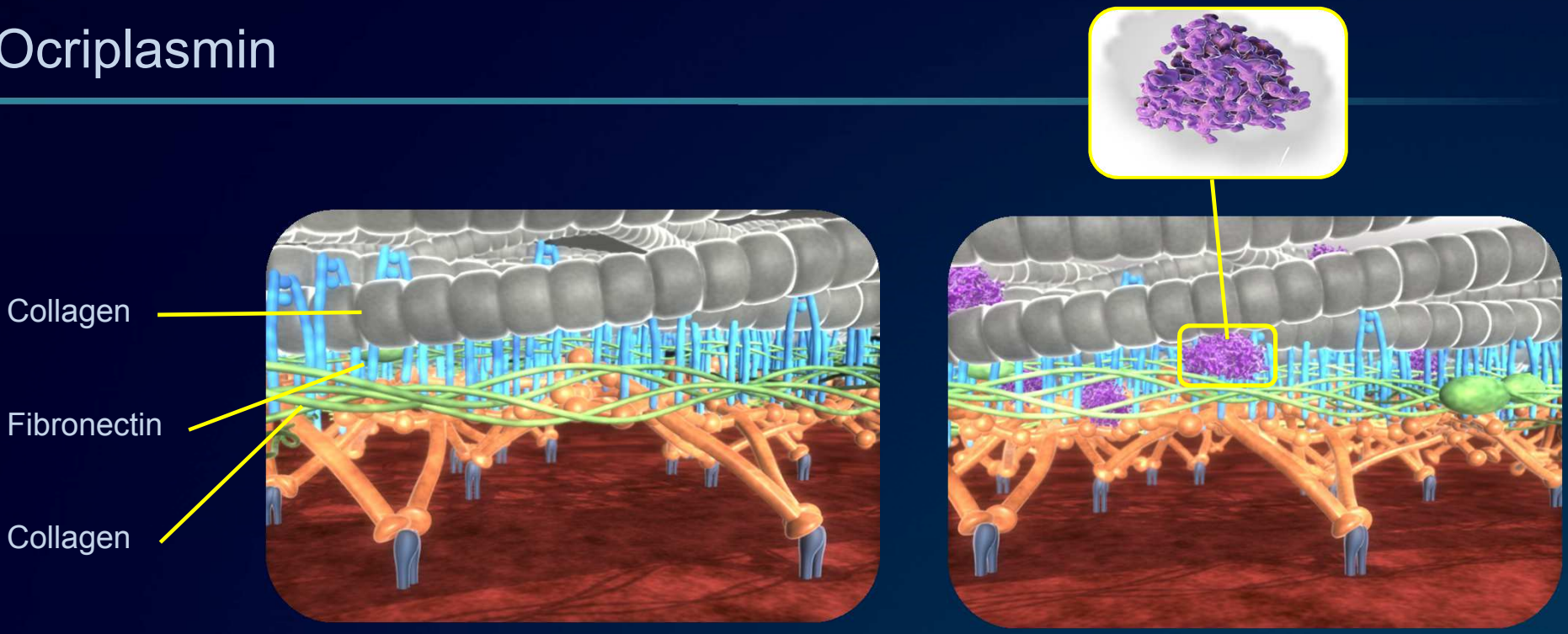
Proteolytic Action of Ocriplasmin

- Ocriplasmin retains the enzymatic activity of plasmin to produce a dual effect of vitreous liquefaction and vitreoretinal separation[1–4]



1. Gandorfer A *et al. Invest Ophthalmol Vis Sci* 2004;45:641
2. Sebag J. *Retina Today* April 2012:55
3. de Smet MD *et al. Invest Ophthalmol Vis Sci* 2009;50:814
4. de Smet MD *et al. Ophthalmology* 2009;116:1349

Ocriplasmin



- Pre-clinical data shows that ocriplasmin[1,2]
  - Targets fibronectin, laminin and collagen
  - Induces vitreous liquefaction and separation of the vitreous at the vitreoretinal interface
  - Cleanly separates vitreous from ILM

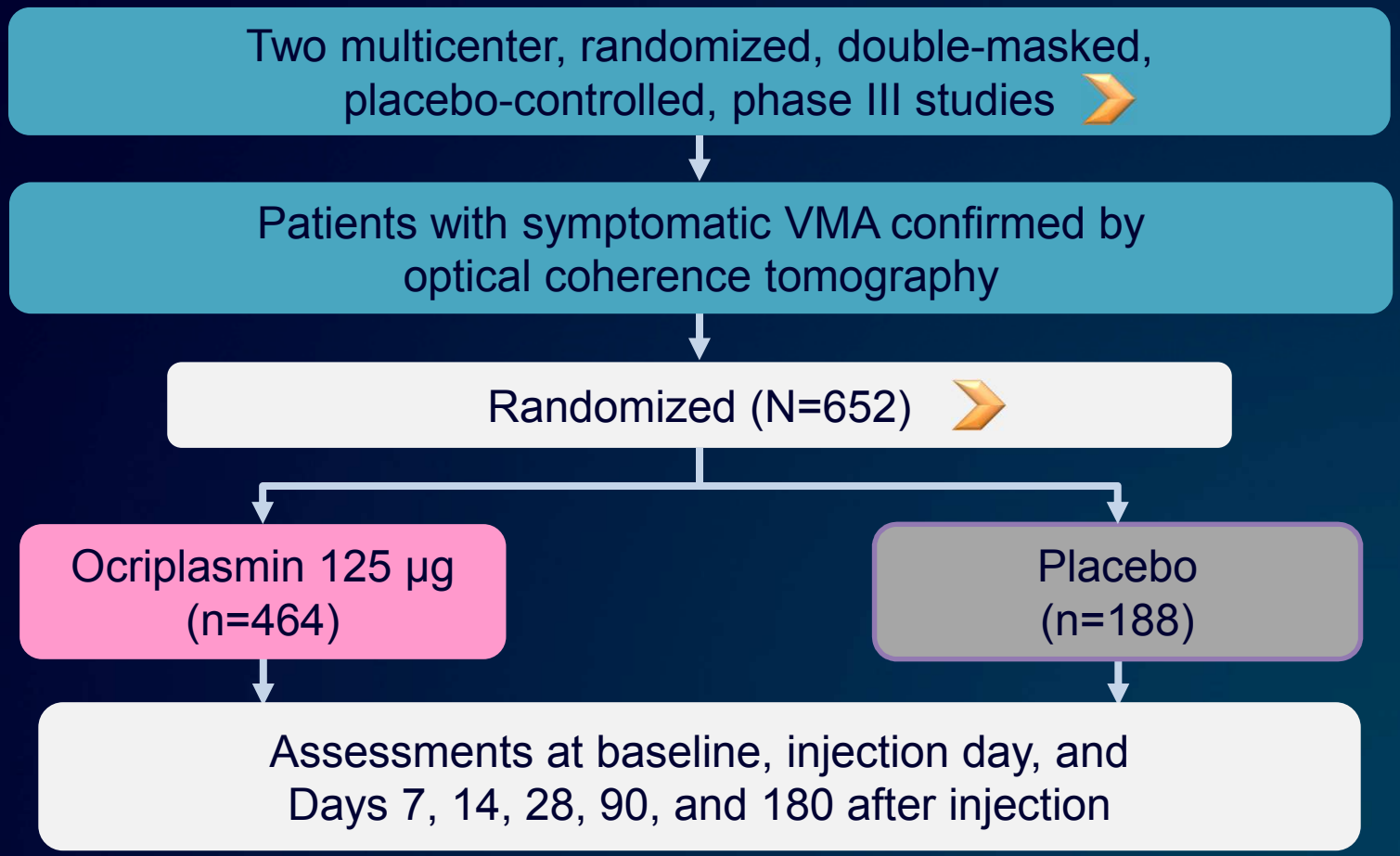
ILM: inner limiting membrane.

1. Gandorfer et al. Invest Ophthalmol Vis Sci. 2004;45:641–647. 2. In vitro experiments.

MIVI 6/7

Enzymatic Vitreolysis with Ocriplasmin for Vitreomacular Traction and Macular Holes

Study Design



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Stalmans P *et al. N Engl J Med* 2012;367:606

Key Inclusion/Exclusion Criteria

Inclusion criteria

- ≥18 years of age
- Focal VMA on OCT
- BCVA ≤20/25 in the study eye
- BCVA ≥20/800 in the non-study eye

Key exclusion criteria

- Concurrent ocular conditions
- Prior vitrectomy
- Prior laser photocoagulation
- Treatment with ocular surgery, intravitreal injection, or retinal laser photocoagulation in the past 3 months

OCT, optical coherence tomography

Stalmans P *et al. N Engl J Med* 2012;367:606

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Treatment

- **Ocriplasmin group**
  - Intravitreal injection of ocriplasmin (125 µg in a 0.10-mL volume)
- **Placebo group**
  - Intravitreal injection of 0.10 mL of the identical drug vehicle diluted with saline
- **Vitrectomy**
  - Investigators could recommend vitrectomy at any time if:
    - The underlying condition deteriorated
    - BCVA in the study eye worsened by >2 lines, or
    - The underlying condition had not improved within 4 weeks after the injection

Stalmans P *et al. N Engl J Med* 2012;367:606

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Study Endpoints

Primary efficacy endpoint

- Non-surgical resolution of VMA at Day 28

Key secondary efficacy endpoints

- Total PVD at Day 28 (main secondary endpoint)
- Non-surgical MH closure
- Avoidance of vitrectomy
- Improvement of ≥3 lines in BCVA without vitrectomy
- BCVA change from baseline at Month 6
- VFQ-25 change from baseline at Month 6

Stalmans P *et al*. *N Engl J Med* 2012;367:606

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Results

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Primary Endpoint

- The proportion of patients with non-surgical resolution of VMA on OCT at Day 28 was significantly higher with ocriplasmin vs placebo in each individual study (p=0.03 in Study 006 and p<0.001 in Study 007)
- For the combined studies, the odds ratio for intervention was 3.28 on the primary endpoint (95% CI 1.93, 5.84; p<0.001)
- Overall, 26.5% of patients in the ocriplasmin group reached the primary endpoint (resolution of VMA) compared with 10.1% of patients in the placebo group
- The magnitude of the effect of ocriplasmin on the primary endpoint varied according to lens status

p-values were not adjusted for multiplicity

Stalmans P *et al*. *N Engl J Med* 2012;367:606

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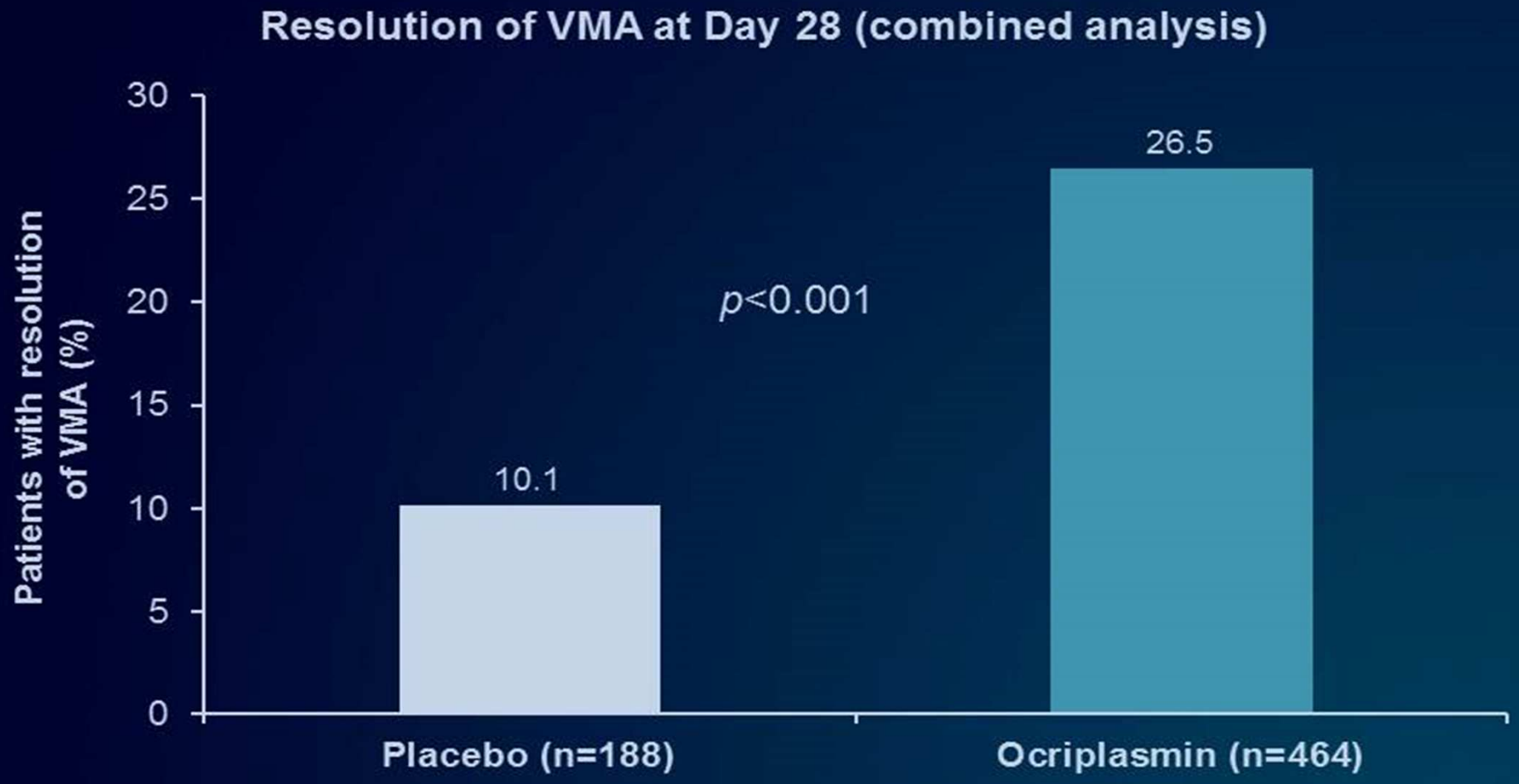
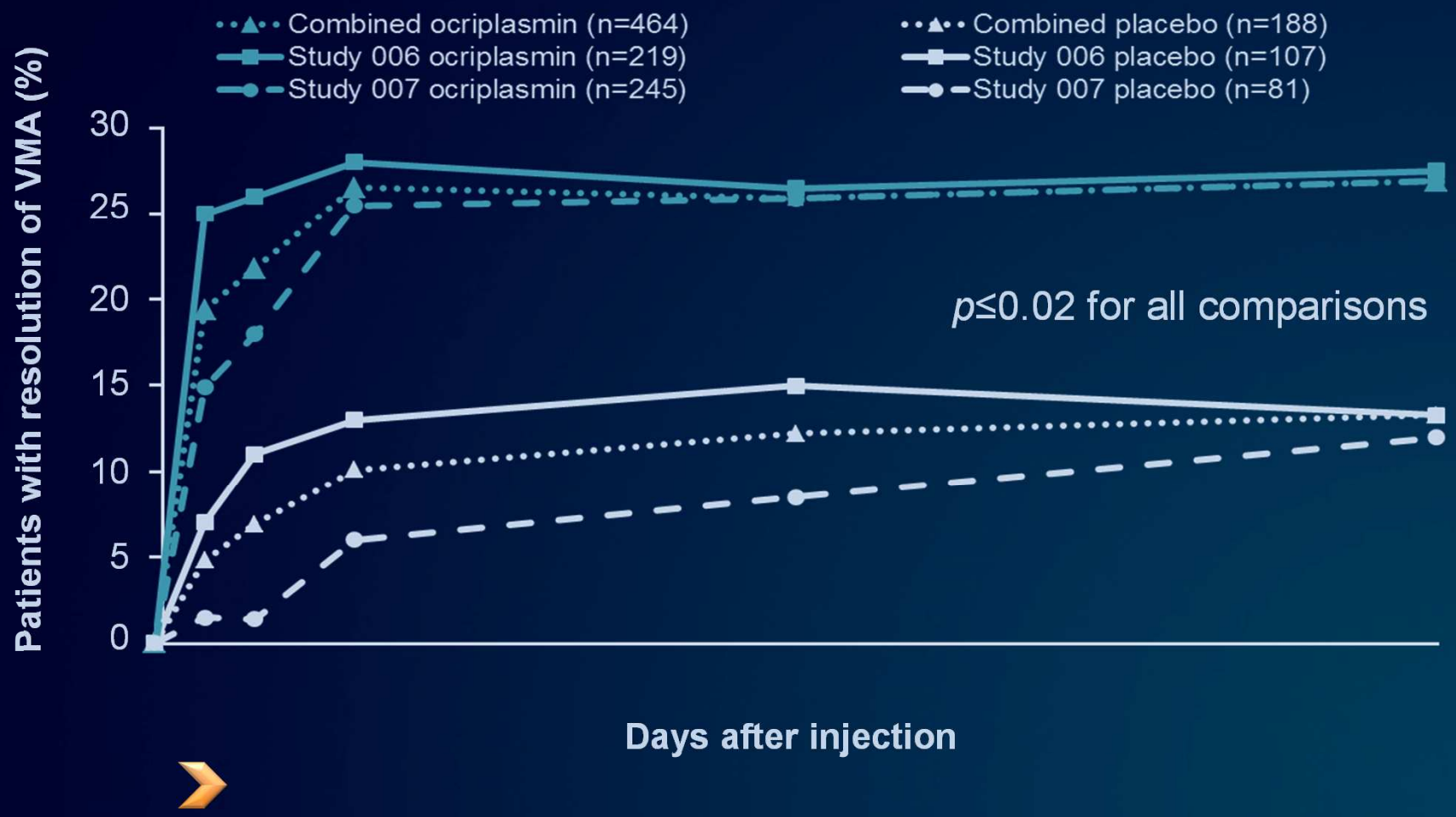
Primary Endpoint Outcome: Resolution of Vitreomacular Adhesion at Day 28



Stalmans P, Benz M, Gandorfer A *et al. N Engl J Med* 2012;367:606

Non-surgical Resolution of Vitreomacular Adhesion with Ocriplasmin Versus Placebo to Day 180



p-values were not adjusted for multiplicity

Stalmans P *et al. N Engl J Med* 2012;367:606

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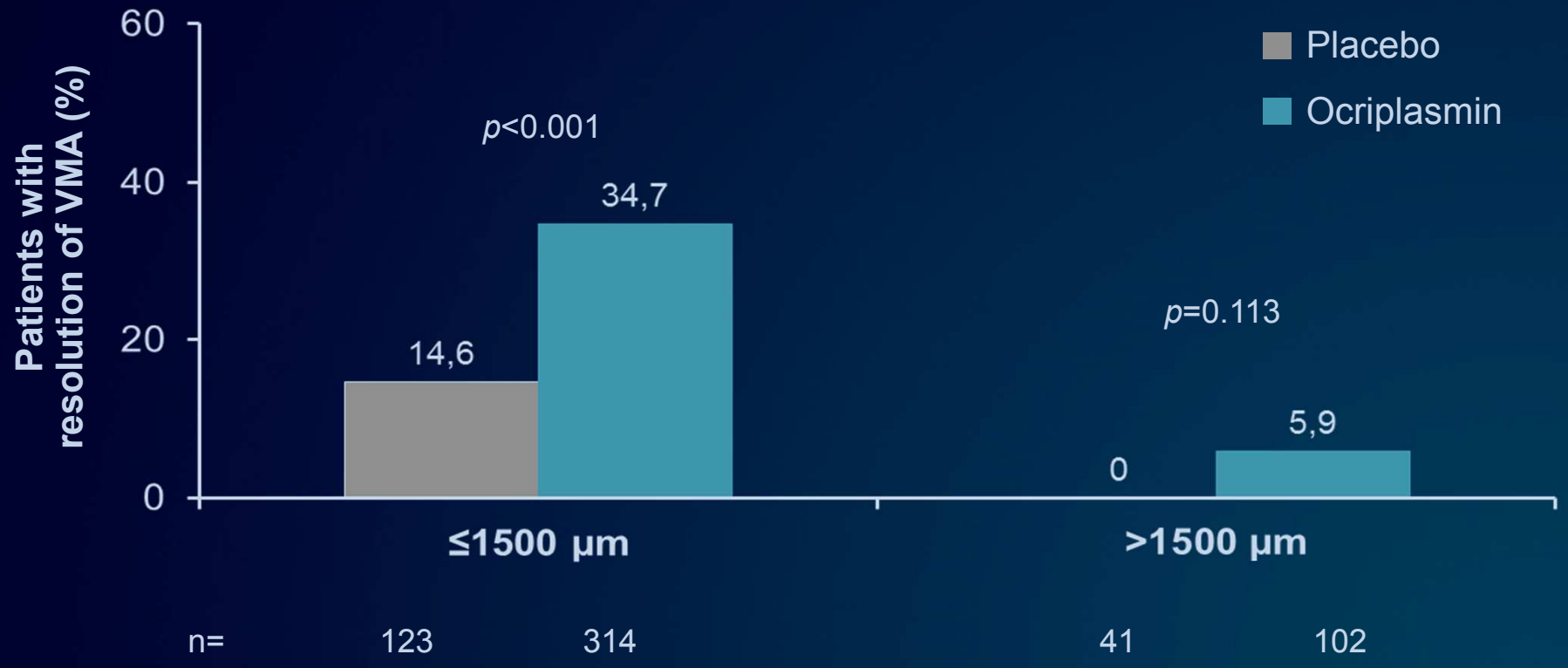
Resolution of Vitreomacular Adhesion Categorized by Vitreomacular Adhesion Diameter

Resolution of VMA at Day 28 categorized by VMA size at baseline



VMA, vitreomacular adhesion

Primary Endpoint According to Lens Status

- Resolution of VMA among phakic eyes:
  - 34.2% in the ocriplasmin group versus 12.6% in the placebo group
  - Odds ratio 3.75; 95% CI 2.09, 7.07; $p<0.001$
- Resolution of VMA among eyes with pseudophakia:
  - 13.4% in the ocriplasmin group versus 3.8% in the placebo group
  - Odds ratio 3.96; 95% CI 0.92, 35.89; $p=0.051$

p-values were not adjusted for multiplicity

Stalmans P *et al*. *N Engl J Med* 2012;367:606

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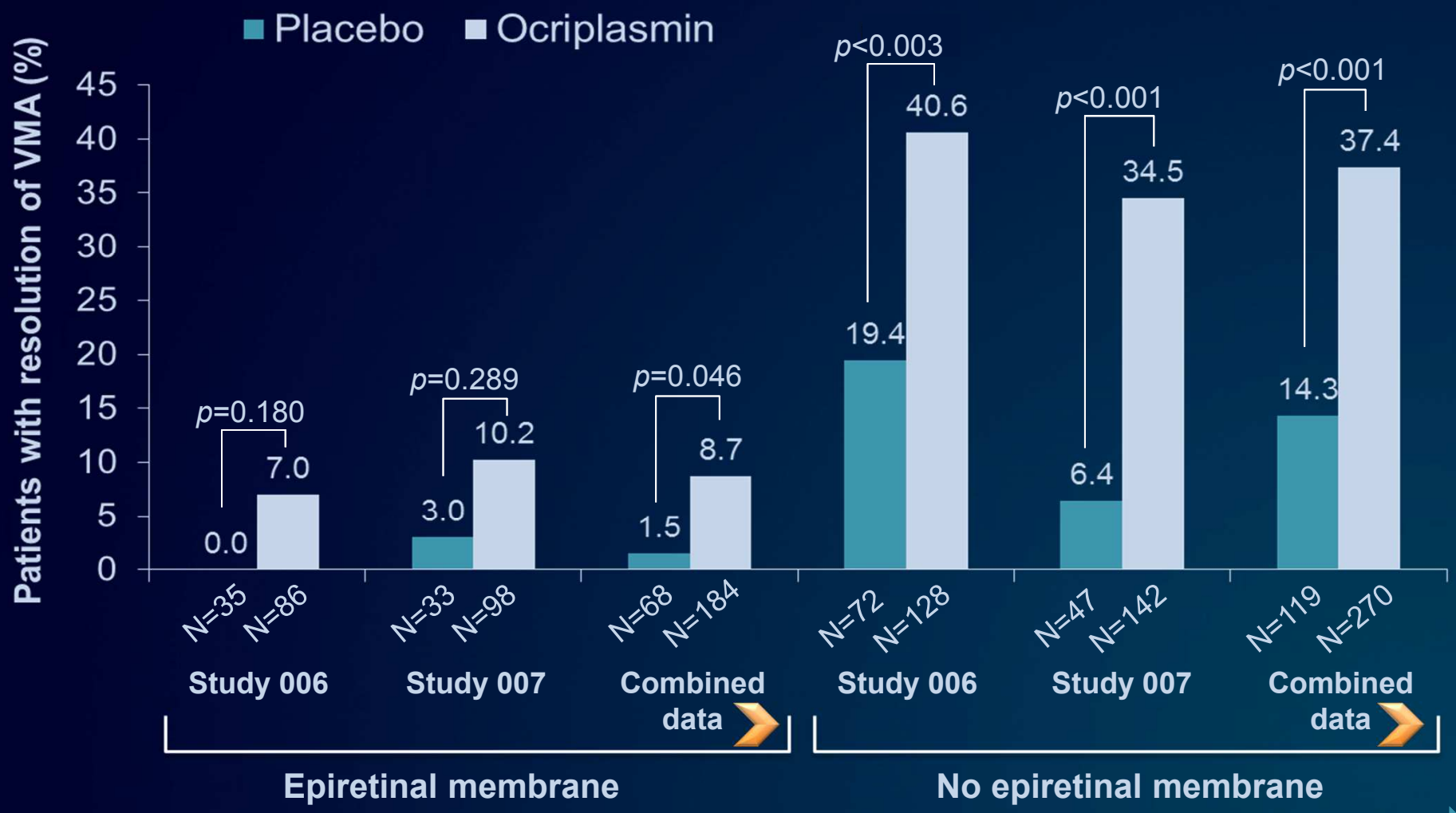
Subgroup Analysis of Non-surgical Resolution of VMA According to Presence of Epiretinal Membrane



p-values were not adjusted for multiplicity

Stalmans P *et al. N Engl J Med* 2012;367:606

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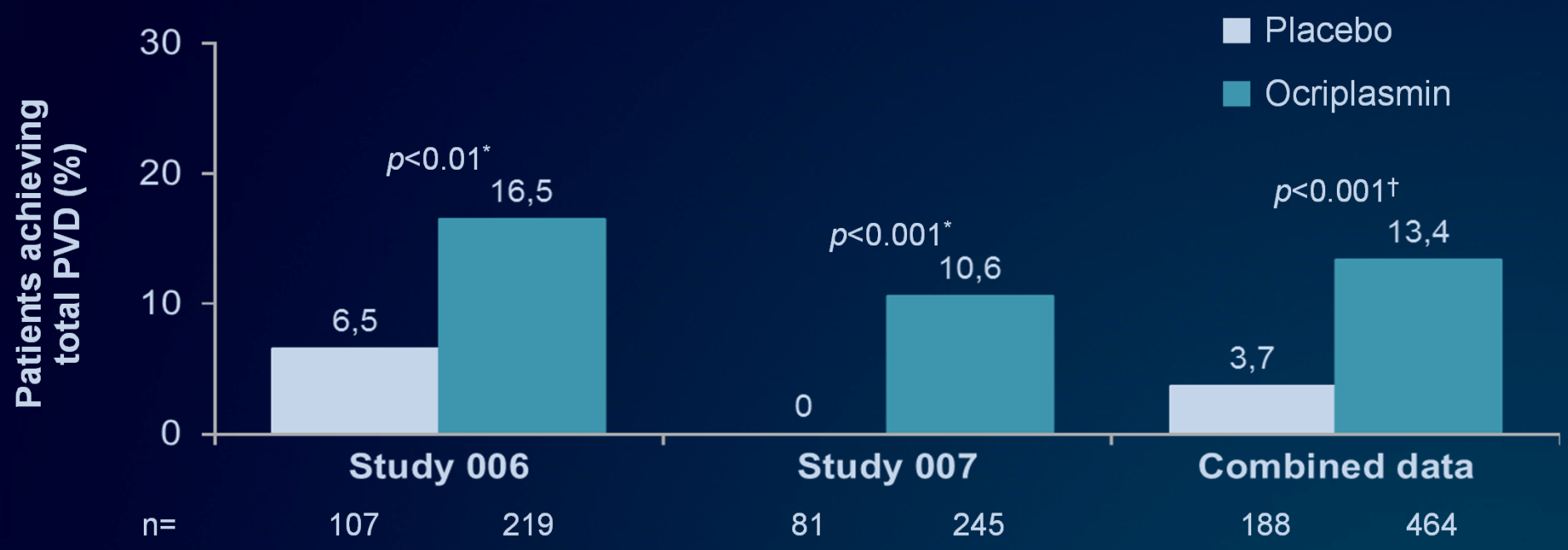
Proportion of Patients with Total PVD at Day 28



*Fisher's exact test; †Cochran–Mantel–Haenszel test, stratified by study

Stalmans P *et al. N Engl J Med* 2012;367:606

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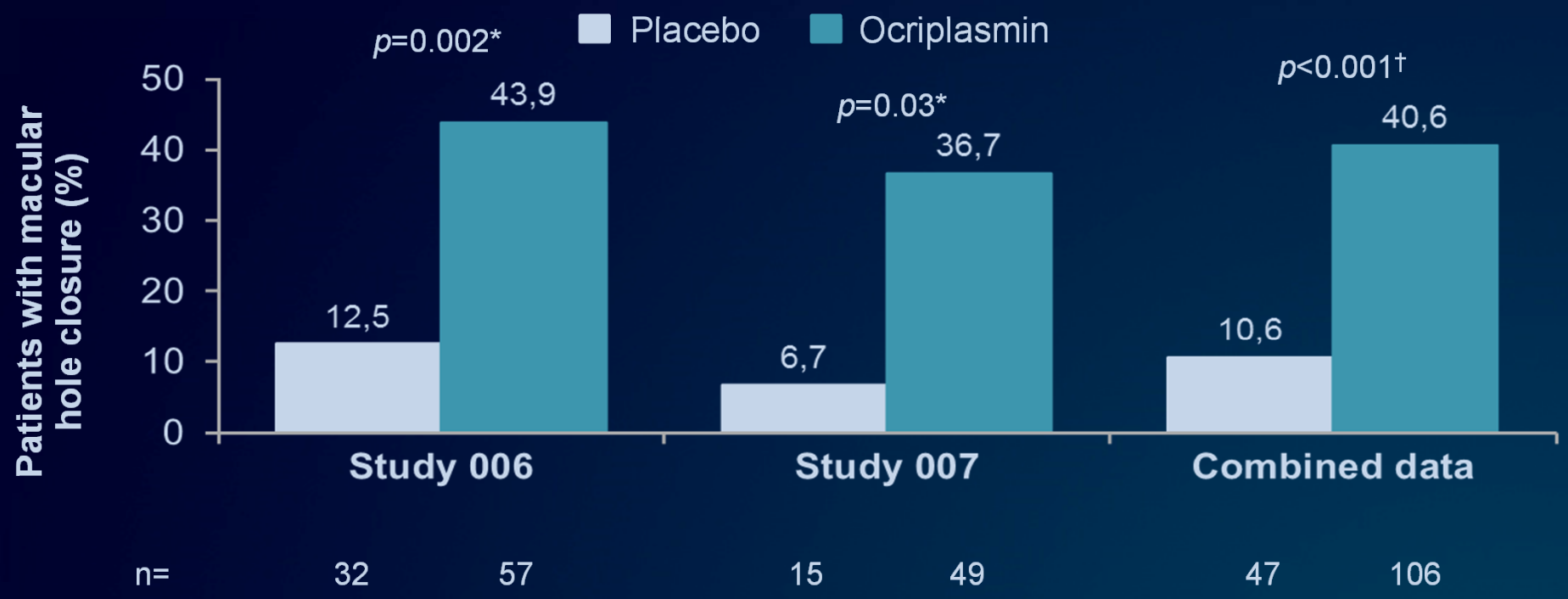
Closure of Macular Hole at Day 28



*Fisher's exact test; †Cochran–Mantel–Haenszel test, stratified by study

p-values were not adjusted for multiplicity

Stalmans P *et al. N Engl J Med* 2012;367:606

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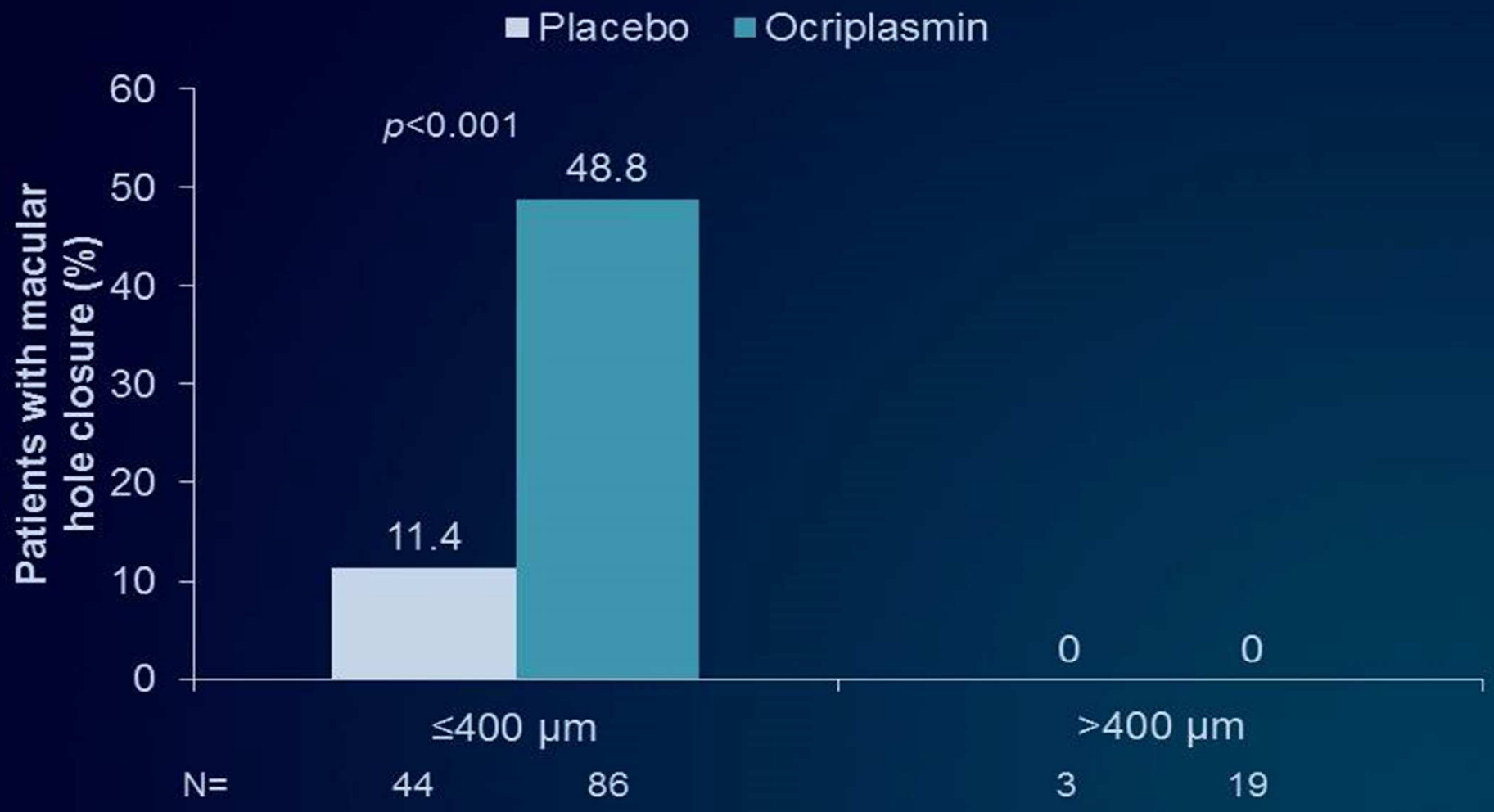
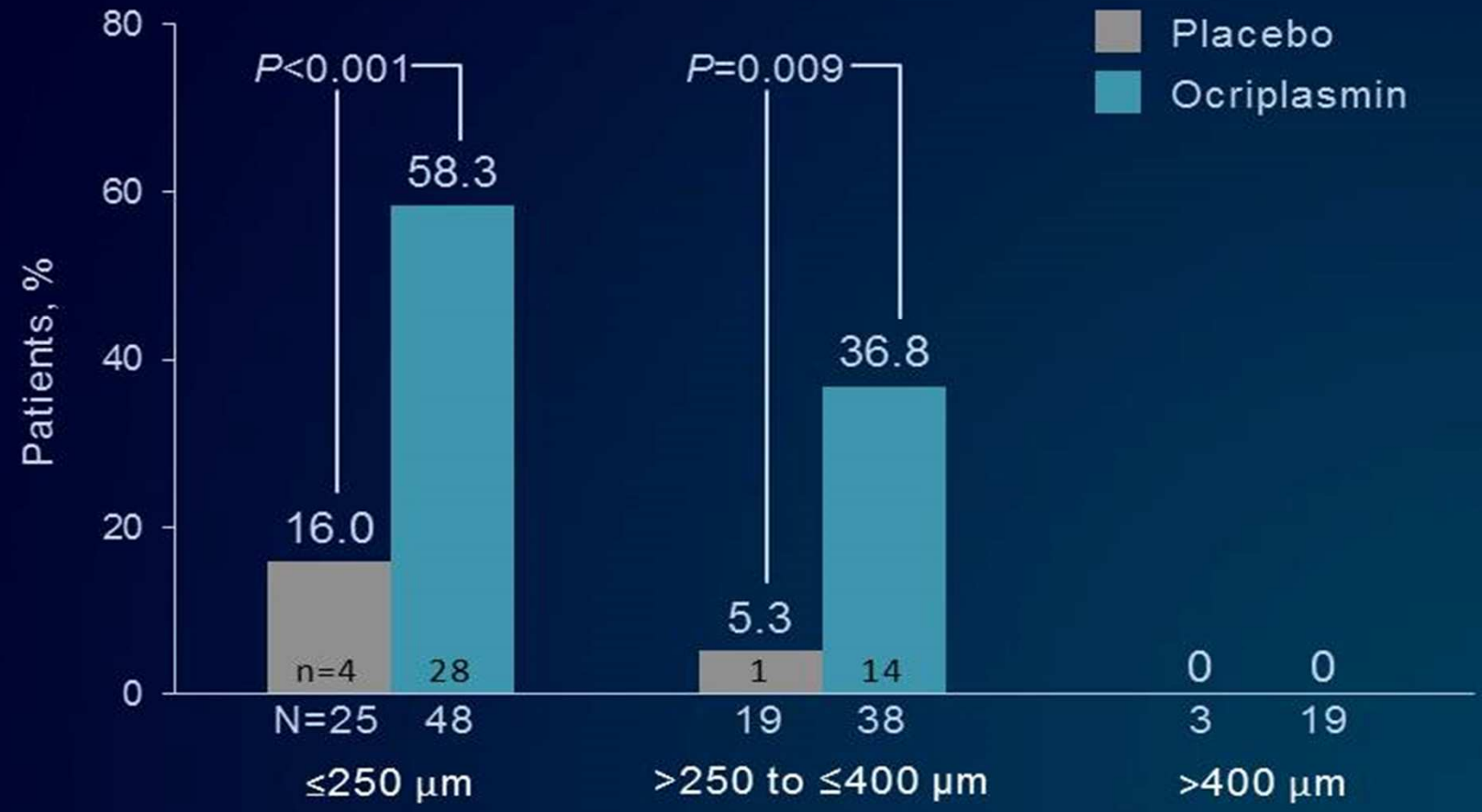
Pharmacologic Closure of FTMH at Day 28 by FTMH Width at Baseline*



Patients with FTMH ≤250 µm More Likely to Achieve Hole Closure at Day 28

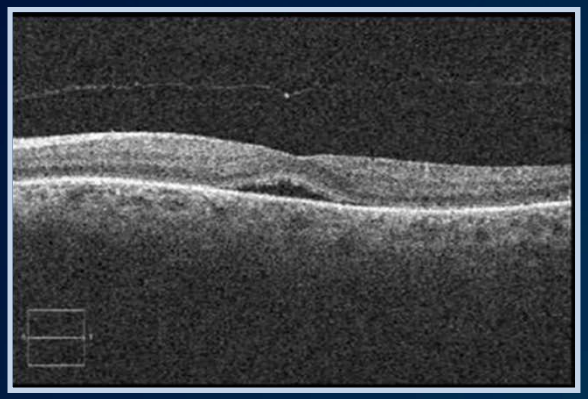


Kaiser, P. Macular Society 2013; Oral

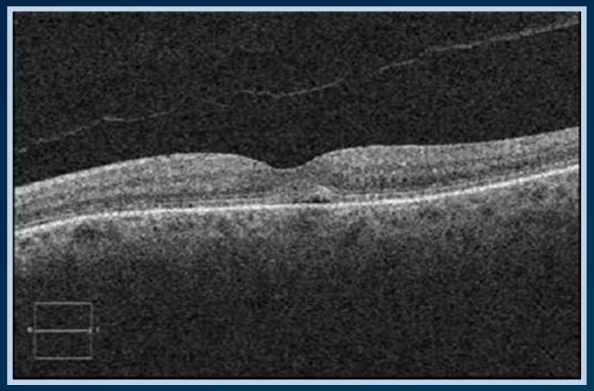
A Case of Macular Hole Closure After Intravitreal Ocriplasmin Injection, shown by Spectral Domain OCT

Baseline retina with MH before injection

MH closure at Day 7 post injection (BCVA improvement +10 letters)



MH remains closed at Month 6 post injection (BCVA improvement +21 letters)



Stalmans P *et al. N Engl J Med* 2012;367:606 (supplementary material)

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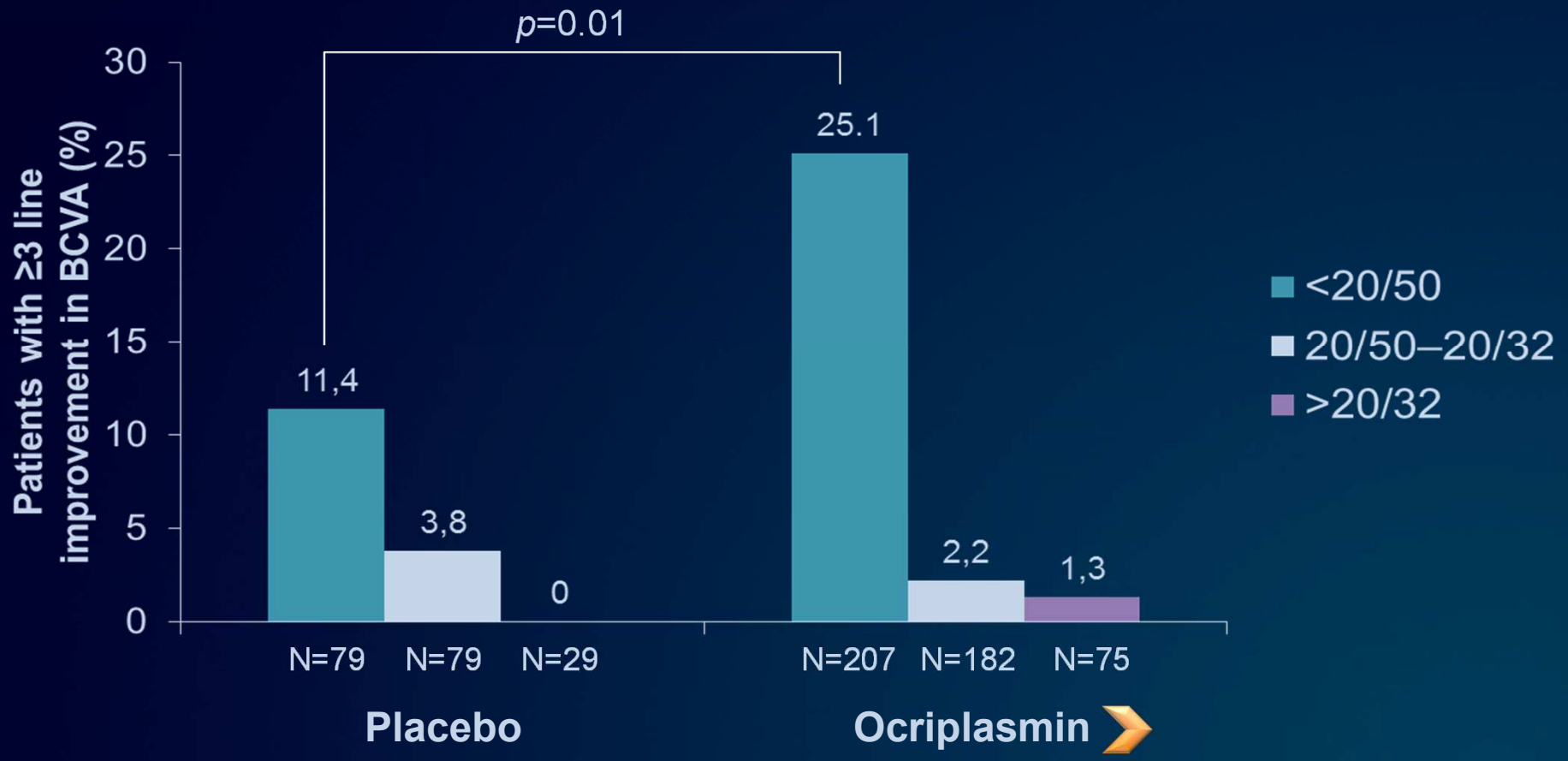
Patients with Baseline BCVA of <20/50, 20/50-20/32, and >20/32 Achieving a ≥3-line Visual Acuity Gain



p-values were not adjusted for multiplicity

Stalmans P *et al*. *N Engl J Med* 2012;367:606 (supplementary material)

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Ocriplasmin Safety Profile

Ocular AEs and serious AEs

	Placebo (n=187)	Ocriplasmin (n=465)	*p*-value
Any ocular AE, n (%)	100 (53.5)	318 (68.4)	<0.001
Any ocular serious AE, n (%)	20 (10.7)	36 (7.7)	0.26

- The difference in the proportion of patients experiencing AEs between the ocriplasmin and placebo groups was driven primarily by those AEs known to be associated with vitreous detachment[1]
- The majority of AEs were transient and mild in severity[1]

AE, adverse event

1. Stalmans P *et al. N Engl J Med* 2012;367:606

Ocular Adverse Events

Event, n (%)	Placebo (n=187)	Ocriplasmin (n=465)	*p*-value*
Any ocular AE, n (%)	100 (53.5)	318 (68.4)	<0.001
Vitreous floaters	14 (7.5)	78 (16.8)	0.002
Photopsia	5 (2.7)	55 (11.8)	<0.001
Conjunctival hemorrhage	24 (12.8)	68 (14.6)	0.53
Injection-related eye pain	11 (5.9)	63 (13.5)	0.005
Blurred vision	6 (3.2)	40 (8.6)	0.01
Visual impairment	3 (1.6)	25 (5.4)	0.02
Increased IOP	10 (5.3)	18 (3.9)	0.50
Retinal tear	5 (2.7)	6 (1.3)	0.25
Cataract	17 (9.1)	26 (5.6)	0.13

**p*-values were calculated with the use of the Cochran–Mantel–Haenszel test, stratified according to study

p-values were not adjusted for multiplicity

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Rates of Ocular Serious Adverse Events

Event, n (%)	Placebo (n=187)	Ocriplasmin (n=465)	p-value*
Any serious AE	20 (10.7)	36 (7.7)	0.26
Macular hole	16 (8.6)	24 (5.2)	0.15
Retinal detachment	3 (1.6)	2 (0.4)	0.16
Reduced VA	1 (0.5)	3 (0.6)	0.94

**p*-values were calculated with the use of the Cochran–Mantel–Haenszel test, stratified according to study

p-values were not adjusted for multiplicity

Stalmans P *et al*. *N Engl J Med* 2012;367:606

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Discussion

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Discussion: Placebo

- Vitreous manipulation effected through intravitreal injection may occasionally result in a PVD, in which case, the placebo injection of 0.1 mL may have induced some treatment response
- The superior therapeutic effects of the ocriplasmin injection would then be indicative of an additional biologic effect of enzymatic vitreolysis over placebo

Stalmans P *et al*. *N Engl J Med* 2012;367:606

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Conclusions

- In conclusion, this study shows that enzymatic vitreolysis represents a means to resolve VMT and to close MH
- Intravitreal injection of ocriplasmin was superior to injection of placebo in altering the vitreoretinal interface of affected eyes, although it was accompanied by some, mainly transient, ocular adverse events

Stalmans P *et al. N Engl J Med* 2012;367:606