

**DX congersso S.O.L.**

**Milano, 16 & 17 dicembre 2005**

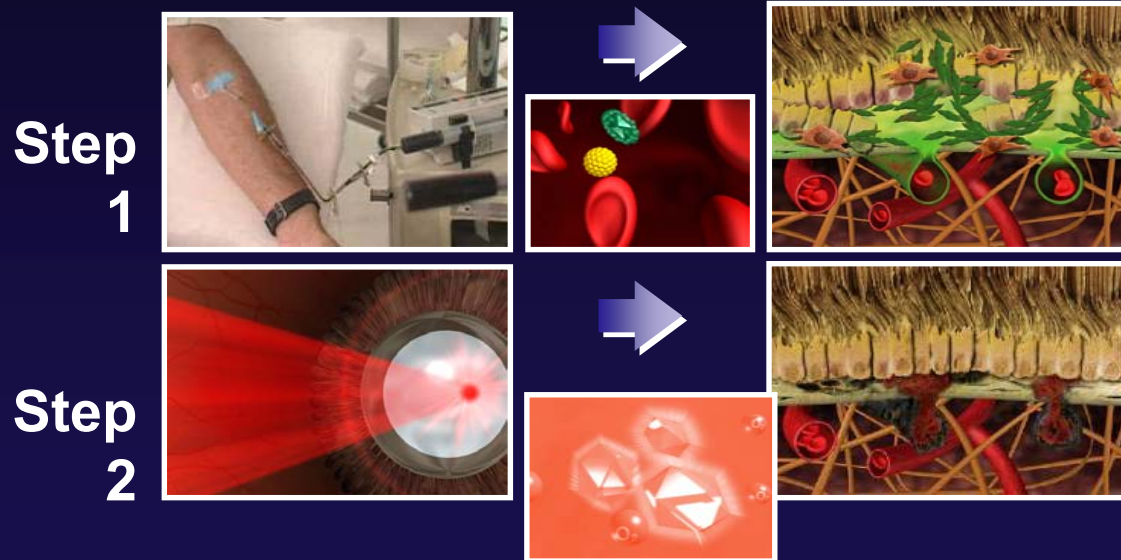
**PDT: lo stato dell'arte**

**Ugo Introini**

**U.O. Oculistica**

**I.R.C.C.S. H San Raffaele, Milano**

# PDT with Verteporfin Therapy: Two-Step Process

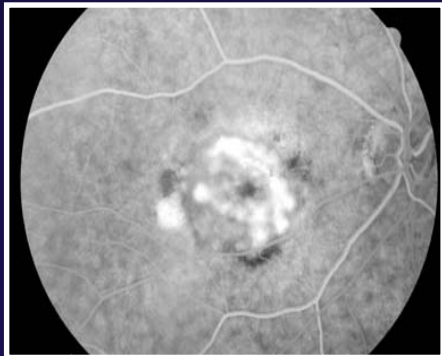
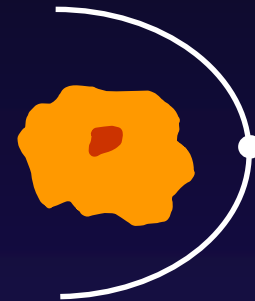
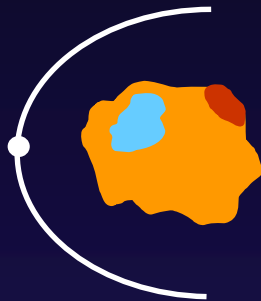
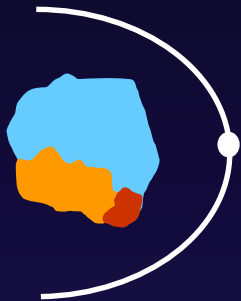


# TAP-VIP: lesion components

Classic CNV

occult CNV

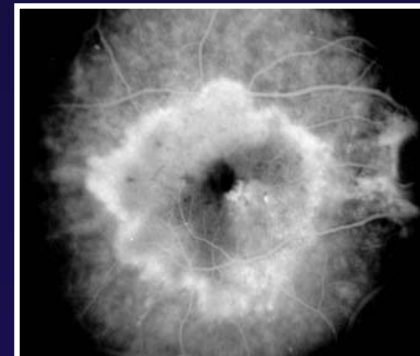
Blood



**Predominantly  
classic**



**Minimally  
classic**



**Occult**

# **Verteporfin therapy in classic CNV**

## **I. TAP Investigation and TAP Extension Study**

# TAP Investigation

- To determine if verteporfin therapy could safely reduce the risk of vision loss in patients  $\geq 50$  years of age with subfoveal CNV due to AMD

**Verteporfin  
therapy n=402**

**2:1**

**Placebo  
n=207**

- Follow-up examinations every 3 months
- Two-year study conducted in 22 centres
- Enrolment completed in 1997

# **TAP Investigation: results in predominantly classic CNV**

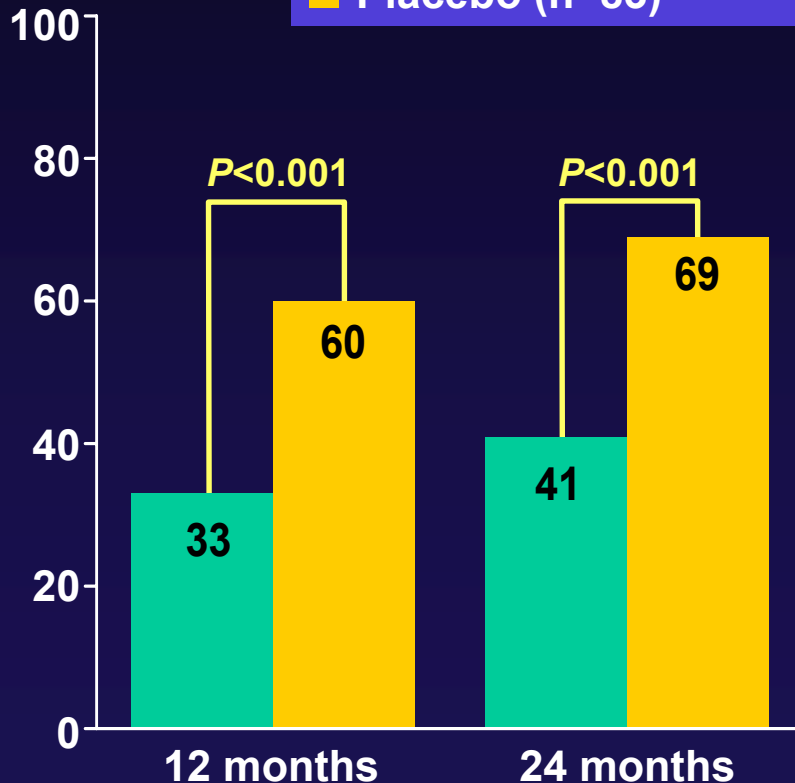
**Verteporfin therapy in classic CNV occupying  $\geq 50\%$  of the entire lesion**

- Reduces the risk of visual acuity loss**
- Reduces the risk of contrast sensitivity loss**
- Leads to preserved quality of vision**
- Reduces the chance of progressive growth of the lesion**

# TAP Investigation: Combined analysis in predominantly classic CNV

Eyes with  $\geq 3$ -line loss (%)

■ Verteporfin therapy (n=159)  
■ Placebo (n=83)

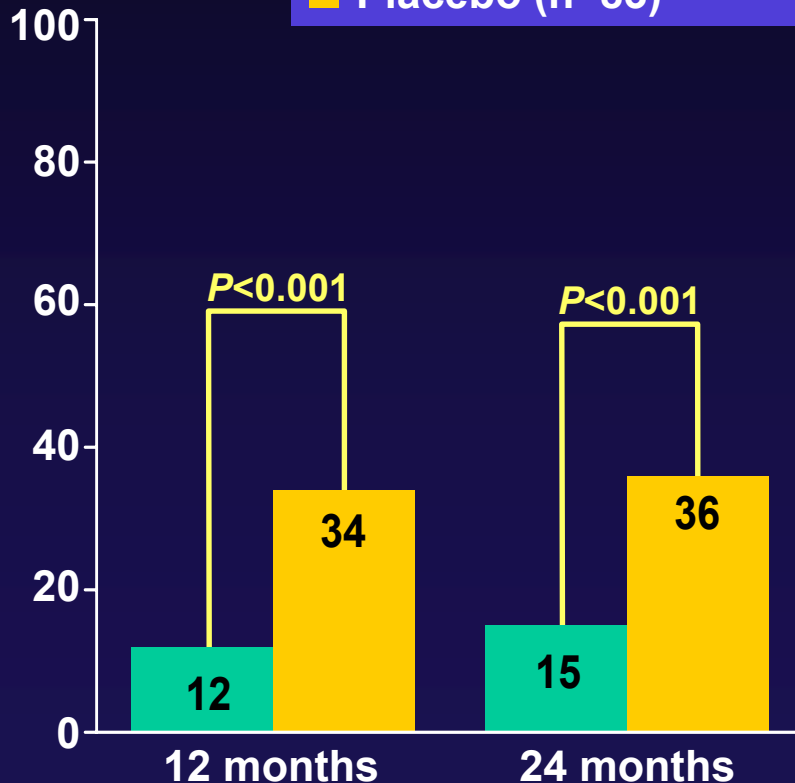


Fewer eyes treated with verteporfin therapy lost 3 or more lines of visual acuity compared with placebo

# TAP Investigation: Combined analysis in predominantly classic CNV

Eyes with  $\geq 6$ -line loss (%)

■ Verteporfin therapy (n=159)  
■ Placebo (n=83)



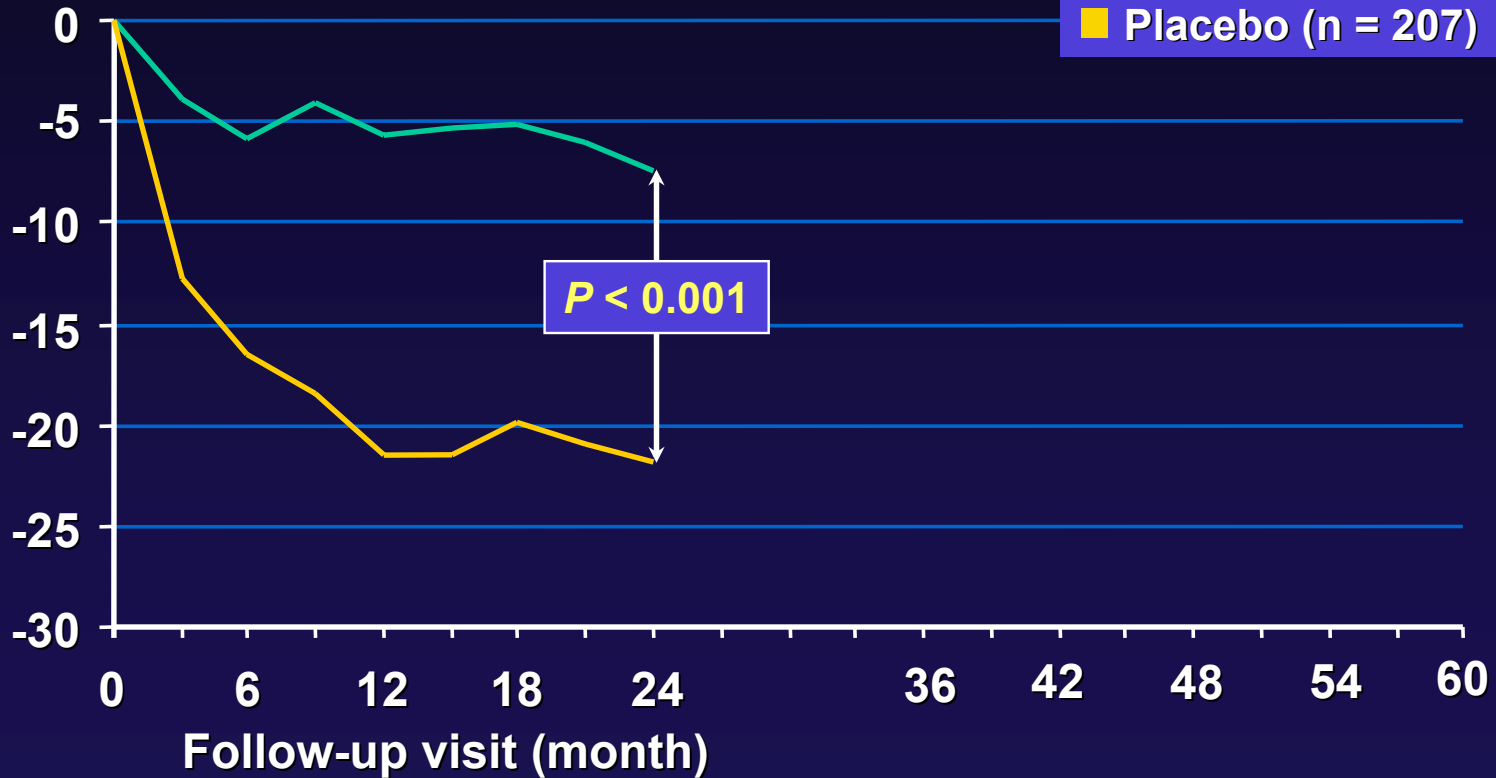
Fewer eyes treated with verteporfin therapy had severe vision loss compared with placebo

# TAP Investigation: Predominantly Classic\*

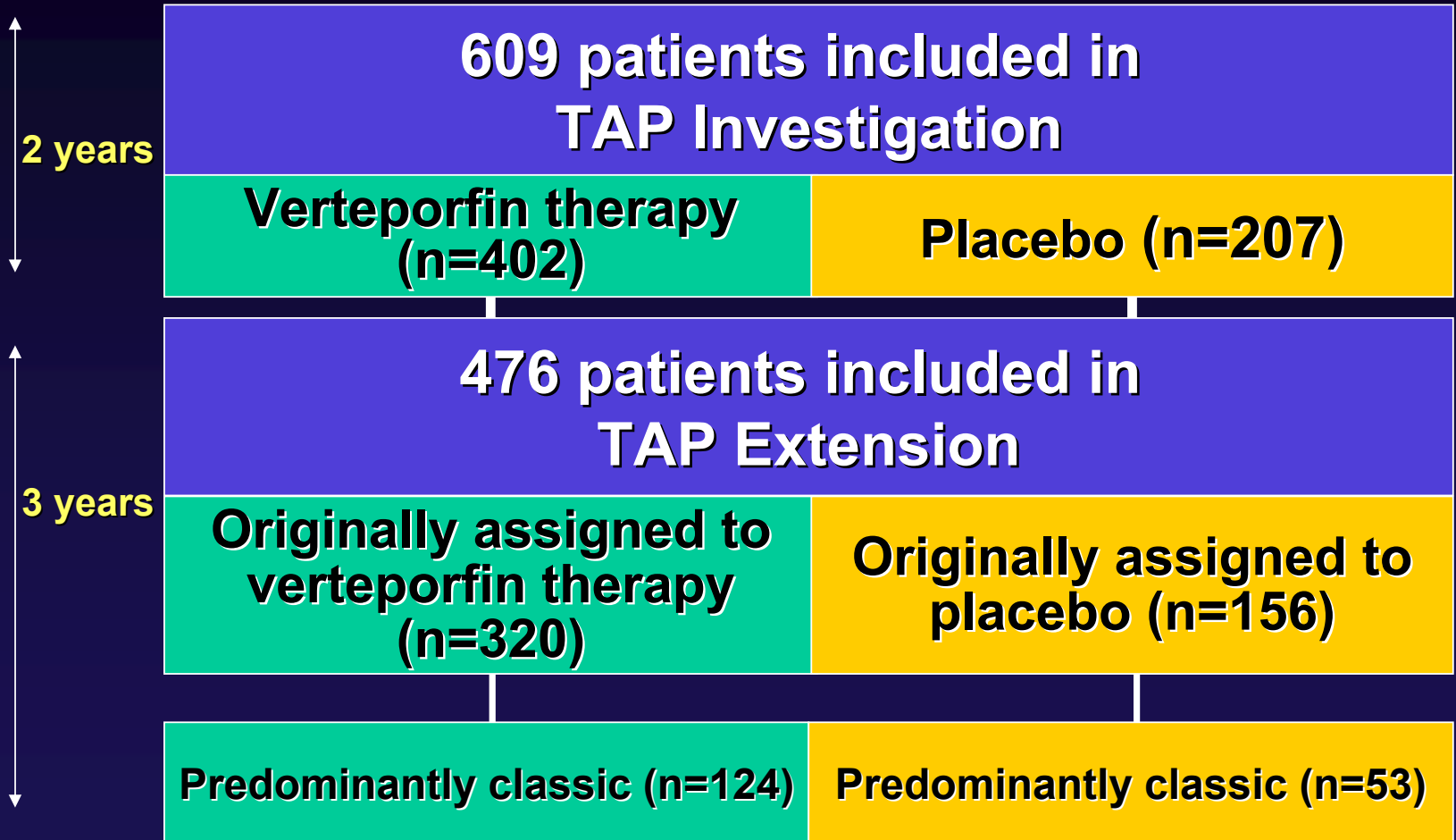
## Change in Visual Acuity from Baseline

Mean change in VA letter score

■ Verteporfin (n = 402)  
■ Placebo (n = 207)



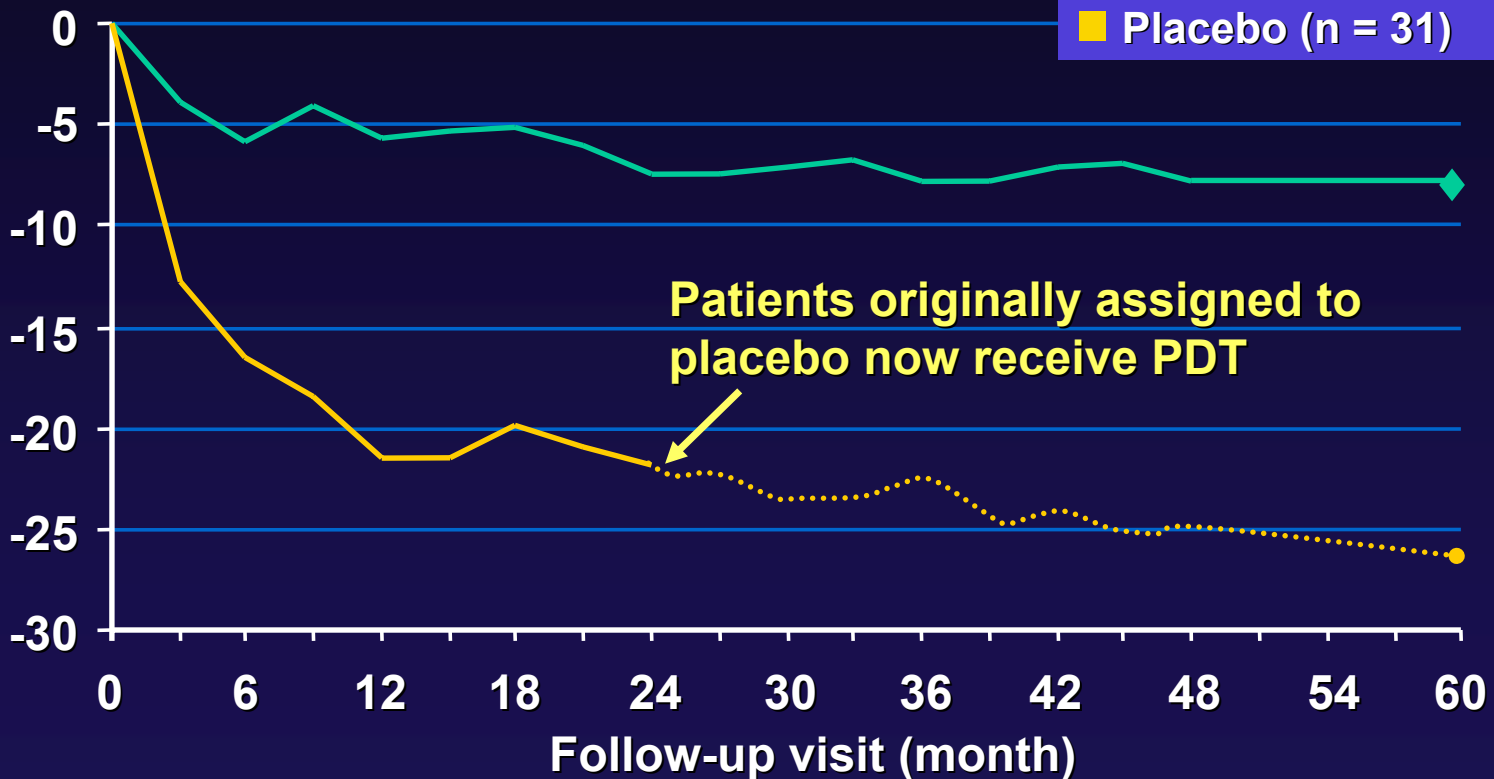
# TAP Extension Study



# TAP Investigation: Predominantly Classic\*

## Change in Visual Acuity from Baseline

Mean change in VA letter score



\* Patients originally treated using PDT with verteporfin, with VA assessment at month 60

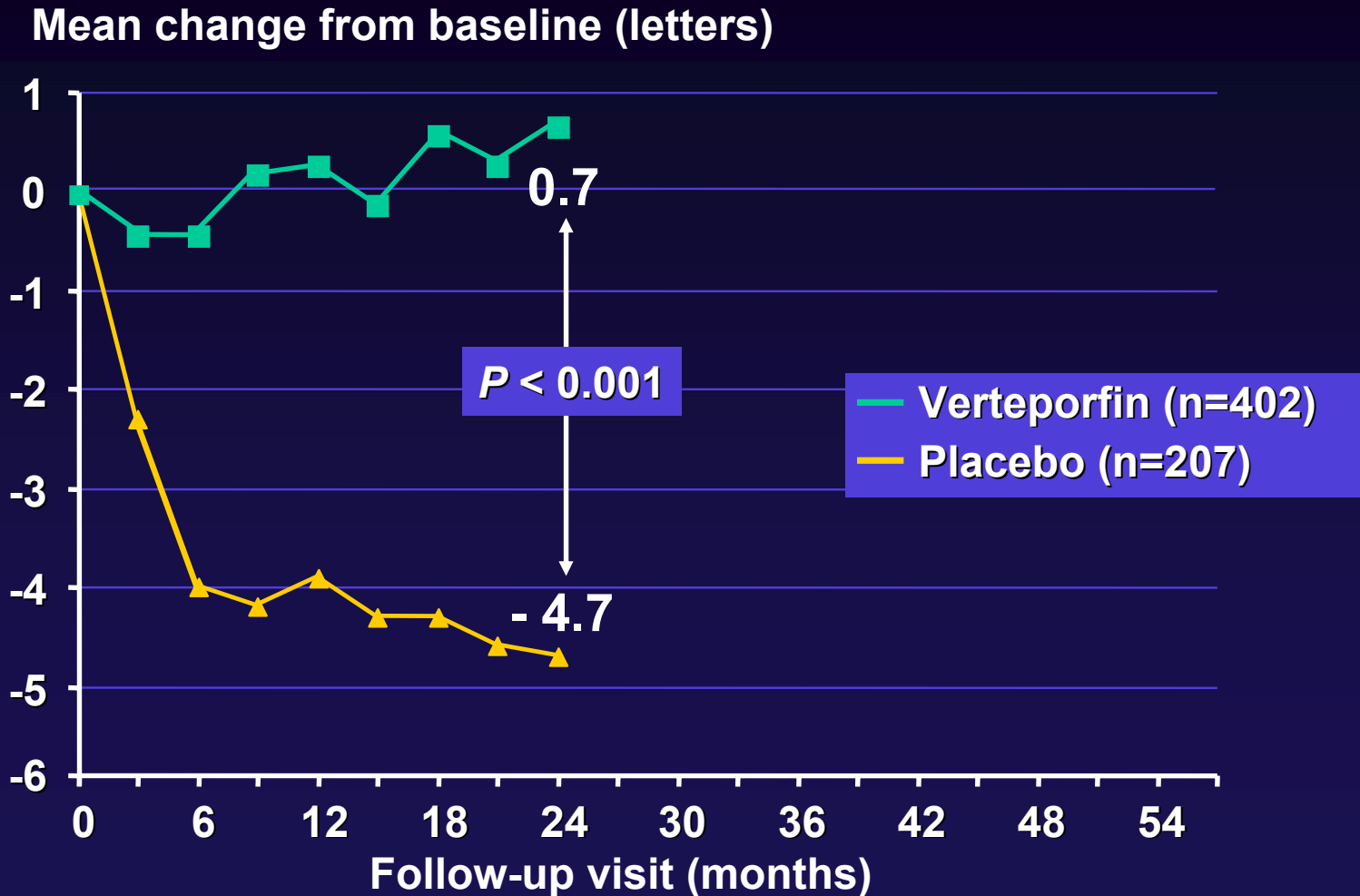
# TAP Investigation: Contrast Sensitivity Outcomes

- Quality of vision depends on contrast sensitivity
- Contrast sensitivity and visual acuity are independent factors in visual disability
- A 6-letter loss of contrast sensitivity has a similar impact on visual disability to a 15-letter loss of visual acuity



# TAP Investigation: Predominantly Classic\*

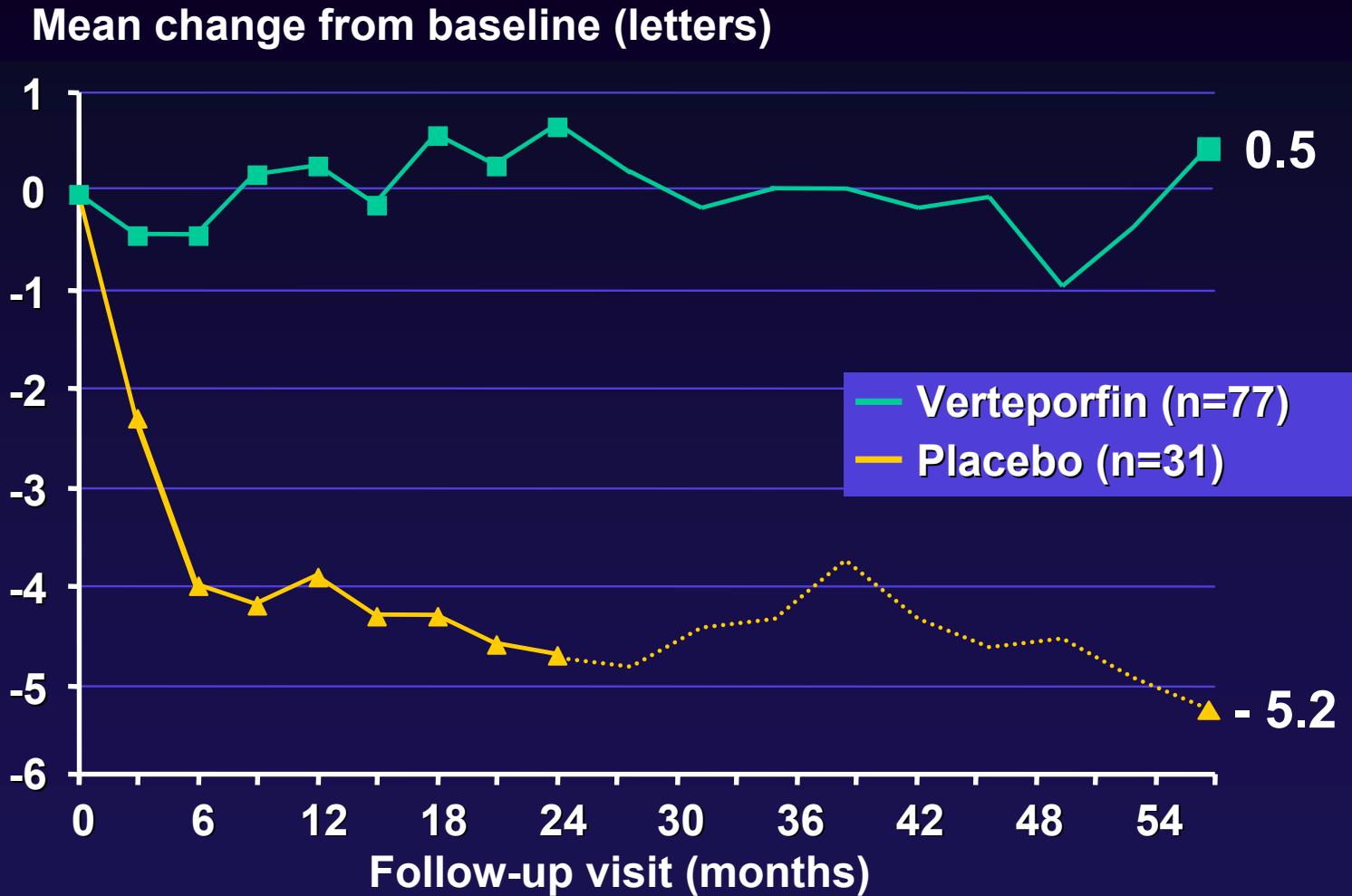
## Mean Change in Contrast Sensitivity



\* Patients originally treated using PDT with verteporfin, with VA assessment at month 60

# TAP Extension: Predominantly Classic\*

## Mean Change in Contrast Sensitivity



\* Patients originally treated using PDT with verteporfin, with VA assessment at month 60

# Number of study eye treatments\*

## Mean number of verteporfin treatments

---

|               |            |
|---------------|------------|
| <b>Year 1</b> | <b>3.5</b> |
| <b>Year 2</b> | <b>2.3</b> |
| <b>Year 3</b> | <b>1.2</b> |
| <b>Year 4</b> | <b>0.5</b> |
| <b>Year 5</b> | <b>0.1</b> |

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\* Patients with predominantly classic CNV originally treated with verteporfin therapy with VA assessment at month 60, n=77

# TAP Extension safety: clinically relevant adverse events

Eyes originally assigned to verteporfin therapy

|                            | TAP Investigation<br>months 0–24<br>(n=402) | TAP Extension<br>months 0–60<br>(n = 320) |
|----------------------------|---|---|
| Injection-site events      | 64 (15.9%)                                  | 60 (19%)                                  |
| Infusion-related back pain | 10 (2.5%)                                   | 10 (3%)                                   |
| Photosensitivity reaction  | 14 (3.5%)                                   | 10 (3%)                                   |
| Visual disturbance         | 89 (22.1%)                                  | 97 (30%)                                  |
| Severe vision decrease     | 3 (0.7%)                                    | 0 (0%)                                    |

## **TAP Extension: conclusions**

- **Verteporfin therapy is proven as best practice in the long-term management of classic neovascular AMD**
  - **Vision outcomes remained relatively stable through 5 years**
    - **35% fewer verteporfin-treated eyes had visual acuities of 20/200 or worse compared with placebo recipients**
  - **Contrast sensitivity was preserved compared with placebo**
  - **No additional safety concerns up to the 5-year final study visit**

# **Verteporfin therapy in classic CNV**

## **II. Japanese AMD Trial (JAT)**

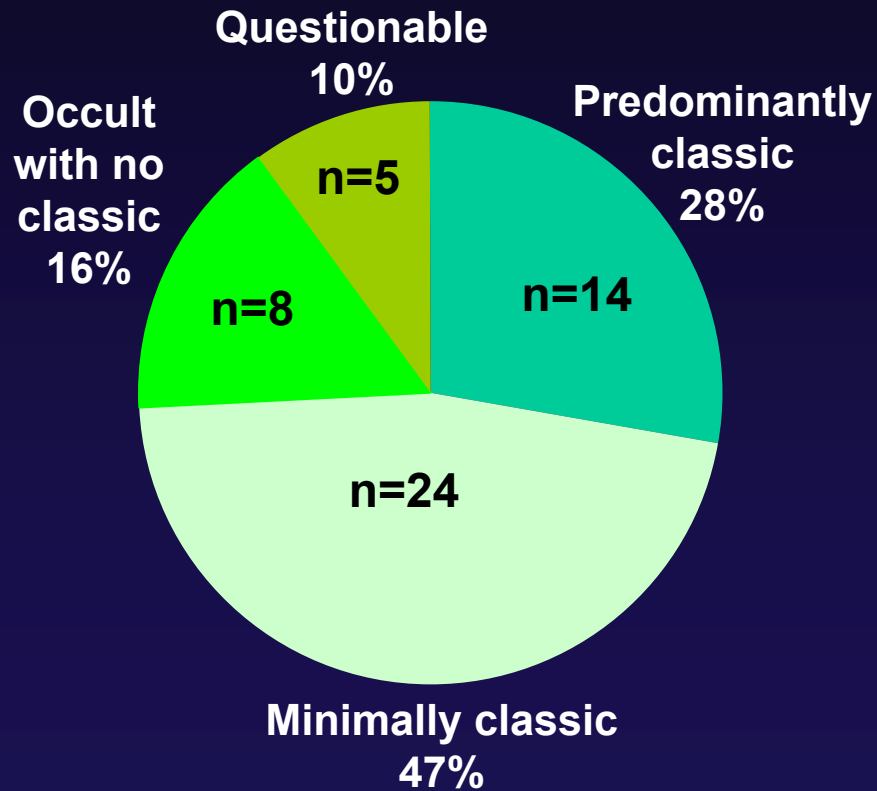


# JAT Trial

- **To investigate safety and effect of verteporfin therapy in Japanese patients with neovascular AMD**
  - **5 centres**
  - **Open-label study of 64 patients**
  - **Classic-containing lesions +/- occult CNV**

# Baseline Lesion Characteristics\*

## Lesion composition



\*Baseline data for patients enrolled in the Extension, n=51

# **JAT Trial: month 12 results and conclusions**

- **At month 12 examination eyes treated with verteporfin therapy had stable or improved visual acuity on average**
  - **Mean change in VA score from baseline was +3.0 letters**
  - **55 eyes (86%) had <3-line loss or improved vision**
- **These results confirm the safety of verteporfin therapy, and are consistent with effectiveness observed in previous studies**

# **Verteporfin therapy in classic CNV**

## **III. Verteporfin Early Retreatment (VER) Trial**

# VER Trial

- To determine whether early treatment intervals (every 6 weeks during the first 6 months) improve treatment outcomes in eyes with predominantly classic CNV due to AMD

**Standard treatment**  
n=159

1:1

**Early treatment**  
n=164

- At month 12 examination, 51% of eyes in the early-treatment group had stable vision\* compared with 52% in the standard-treatment group

\*defined as less than 3-line vision loss

# VER Trial

- **PDT with verteporfin applied at 3-monthly intervals remains the treatment of choice for eyes with predominantly classic CNV**
  - **Early additional treatments did not improve outcomes compared with standard treatment**
  - **No additional safety concerns were identified with early treatment compared with standard treatment intervals**

# **Verteporfin therapy in classic CNV**

## **IV. Verteporfin In Minimally classic CNV (VIM) Trial**

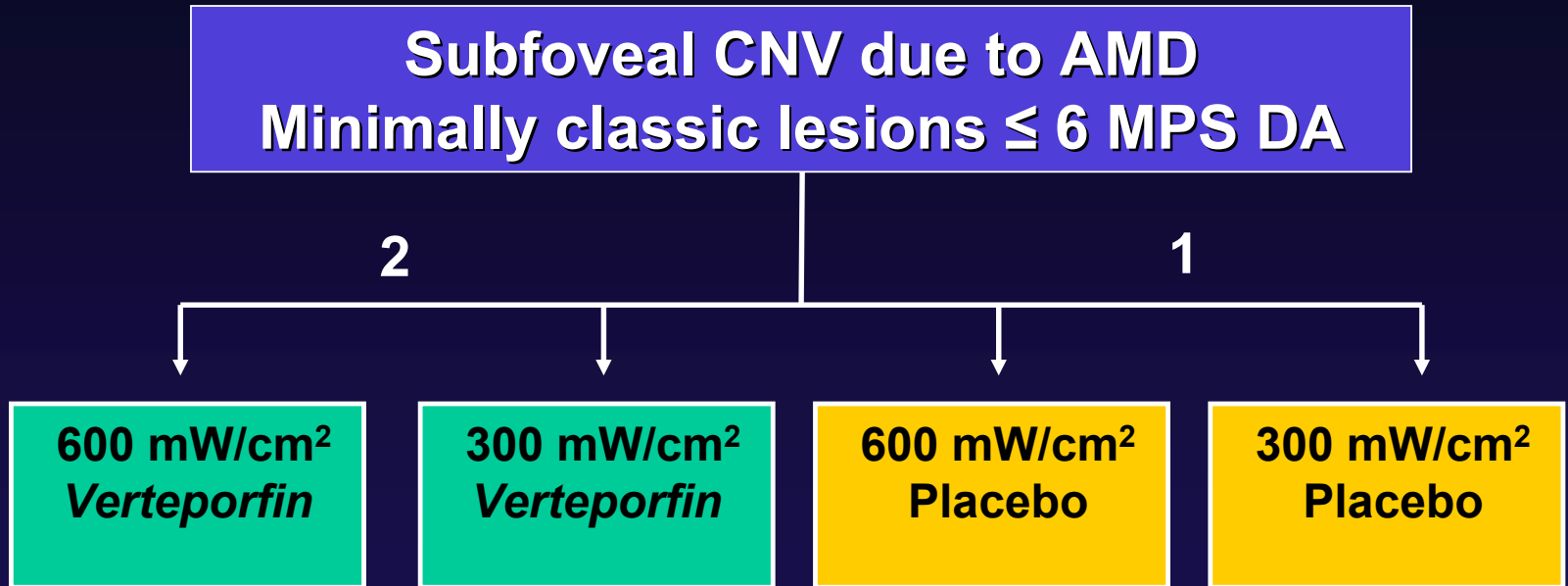
## VIM: study objective

- To determine if verteporfin therapy with either:
  - **Standard light dose and fluence rate**  
(50 J/cm<sup>2</sup> at 600 mW/cm<sup>2</sup>) or
  - **Reduced light dose and fluence rate**  
(25 J/cm<sup>2</sup> at 300 mW/cm<sup>2</sup>)
- In eyes with subfoveal CNV with minimally classic lesions:
  - Reduces the risk of vision loss
  - Has an acceptable safety profile at 12 months

# VIM: principal eligibility criteria and study design

- **Open-label study of subfoveal CNV secondary to AMD**
  - **CNV  $\geq 50\%$  of entire lesion**
  - **Minimally classic CNV (occult CNV with classic CNV covering  $\leq 50\%$  of entire lesion)**
- **Lesion size:  $\leq 4$  MPS DA**  
**4–6 MPS DA**
- **Baseline protocol visual acuity (approximate Snellen equivalent):**
  - **VA  $\geq 20/250$  ( $\leq 4$  MPS DA)**
  - **VA 20/250 to 20/50 (4–6 MPS DA)**
- **Additional therapy as often as every 3 months if fluorescein leakage from CNV**

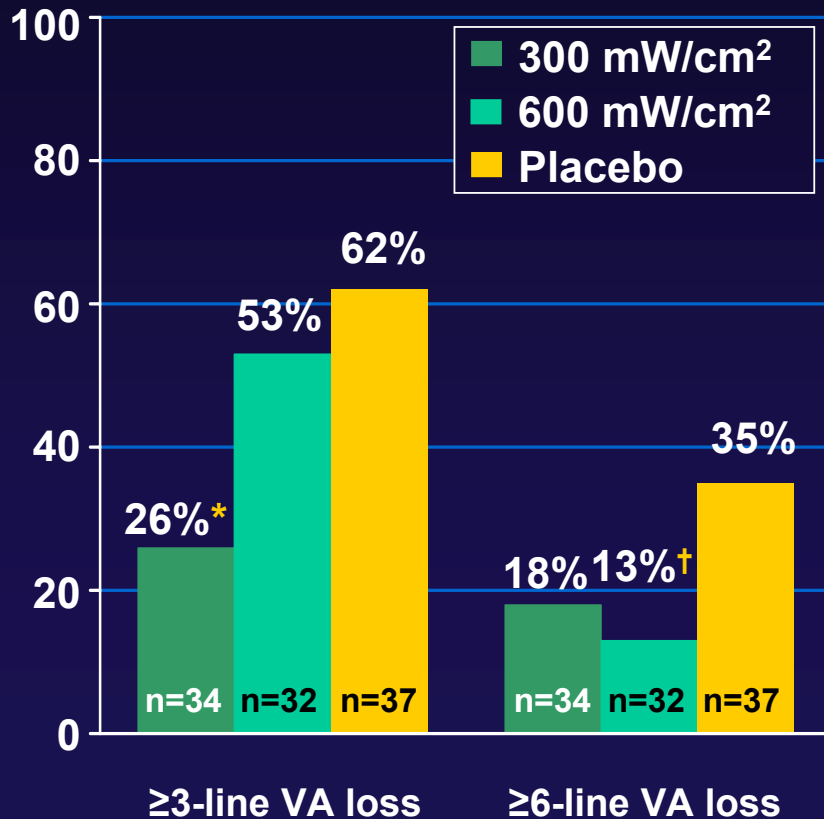
# VIM Trial: Phase II – Treatment Protocol



Additional therapy as often as every 3 months if fluorescein leakage from CNV; open label PDT with verteporfin if predominantly classic lesion confirmed by Reading Center and Investigator

# Month 24 Visual Acuity Outcomes: Observed Data

Eyes with  $\geq 3$ - or  $\geq 6$ -line VA  
loss (%) at month 24, %



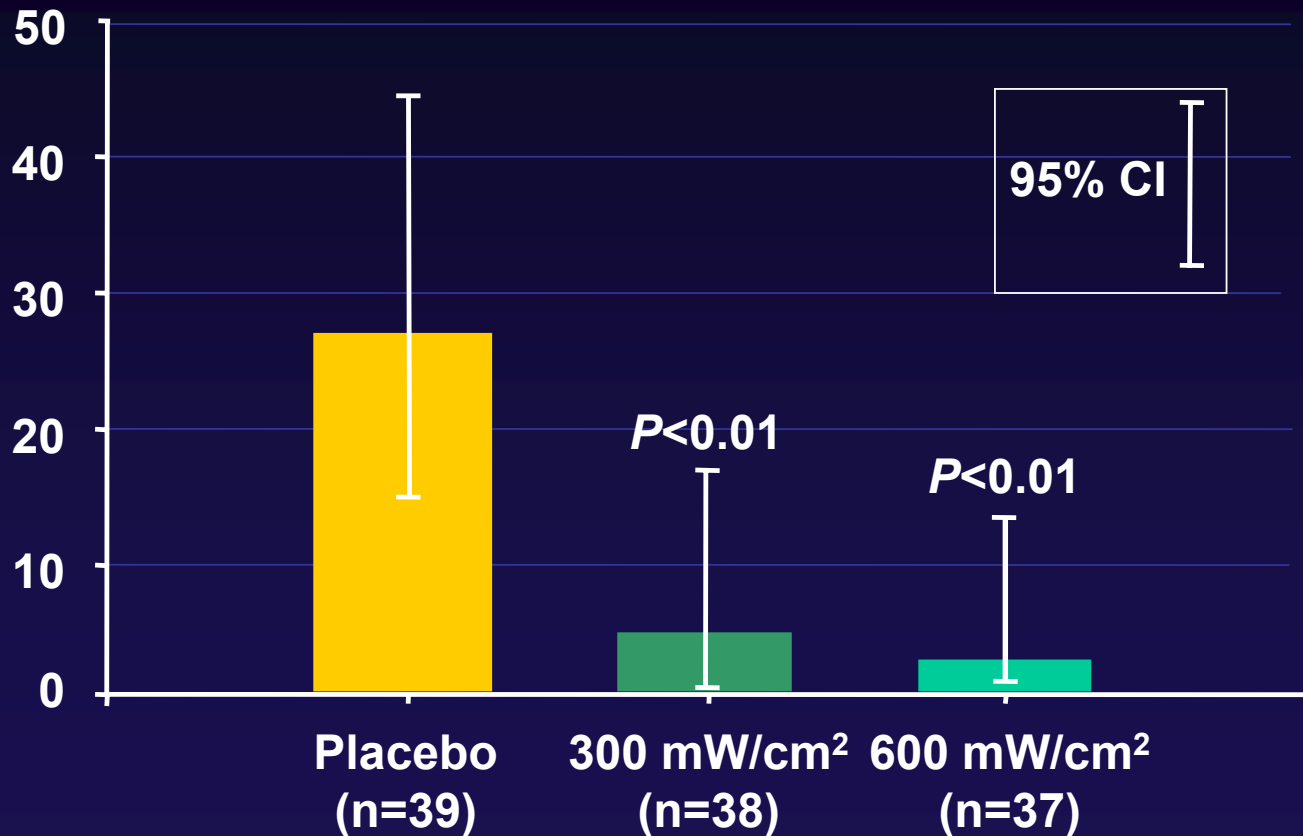
\*  $P$  value  $< 0.01$  in favor of verteporfin group with reduced fluence rate

†  $P$  value = 0.03 in favor of verteporfin group with standard fluence rate

**NOTE:**  $P$  value = 0.03 and 0.02 in favor of total verteporfin group for  $\geq 3$ -line loss, and  $\geq 6$ -line loss, respectively

# Fluorescein Angiographic Outcomes\*

Conversion to predominantly classic CNV by *month 24* examination, %



\* Patients who converted to predominantly classic CNV during the study could receive open-label verteporfin treatments

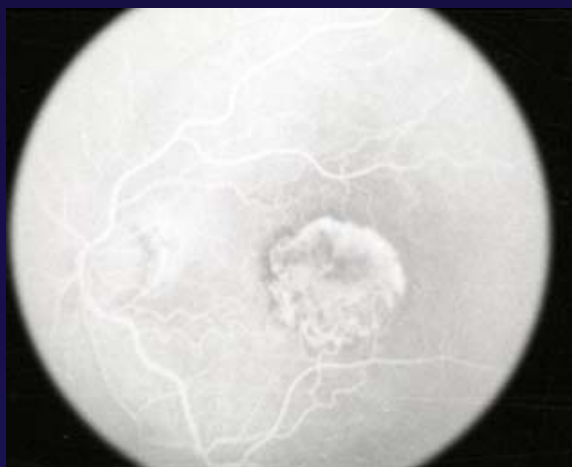
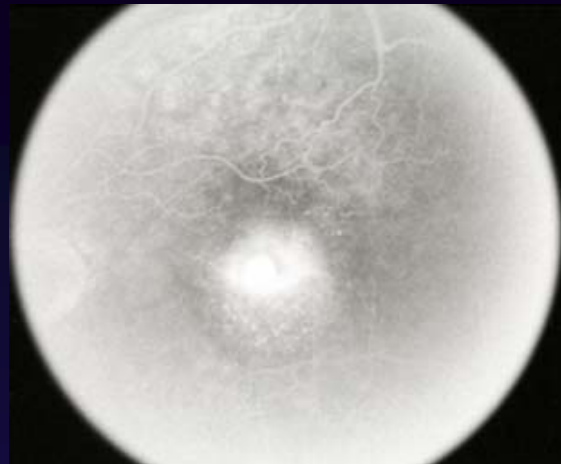
## **Progression to predominantly classic CNV in VIM Trial**

- **By month 24, 14 cases of progression to predominantly classic CNV were identified**
- **Progression to predominantly classic CNV was identified either by the treating ophthalmologist or the reading centre and subsequently patients could receive open-label verteporfin therapy**

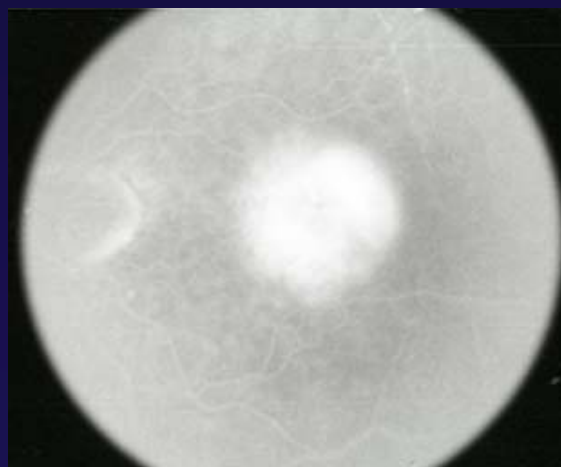
# Conversion at month 3



**Baseline: minimally classic lesion**



**Month 3: predominantly classic lesion**



# **VIM Trial: progression to predominantly classic CNV**

- **Verteporfin therapy reduced the risk of progression to predominantly classic CNV**
- **9 of 14 conversions occurred by month 3**
- **Almost all lesions that progressed were of a size and visual acuity at which verteporfin therapy would be considered**

# Safety

| <b>Treatment-related events</b>                         | <b>Placebo<br/>(n=40)<br/>n (%)</b> | <b>300 mW/cm<sup>2</sup><br/>(n=38)<br/>n (%)</b> | <b>600 mW/cm<sup>2</sup><br/>(n=39)<br/>n (%)</b> |
|---|-------------------------------------|---|---|
| <b>Visual disturbance</b>                               | <b>4 (10)</b>                       | <b>2 (5)</b>                                      | <b>5 (13)</b>                                     |
| <b>Acute severe visual acuity decrease in study eye</b> | <b>1 (3)</b>                        | <b>0 (0)</b>                                      | <b>1 (3)</b>                                      |
| <b>Infusion-related pain*</b>                           | <b>1 (3)</b>                        | <b>3 (8)</b>                                      | <b>6 (15)</b>                                     |
| <b>Injection-site event</b>                             | <b>4 (10)</b>                       | <b>1 (3)</b>                                      | <b>2 (5)</b>                                      |

\* Includes infusion-related back pain, neck pain, and chest pain

## VIM: conclusions

Results *suggest* that verteporfin therapy, using either reduced light fluence or standard light fluence, in eyes with *subfoveal minimally classic CNV* ( $\leq 6$  MPS DA):

- Reduced the risk of vision loss
- Reduced the risk of progressing to predominantly classic CNV
- Had an overall favourable safety profile

# **Verteporfin therapy in occult CNV**

## **I. Verteporfin In Photodynamic therapy (VIP) Trial**

# VIP Trial

- To determine if verteporfin therapy will significantly reduce the risk of  $\geq 15$ -letter and  $\geq 30$ -letter vision loss in AMD eyes including occult with no classic lesions with recent disease progression

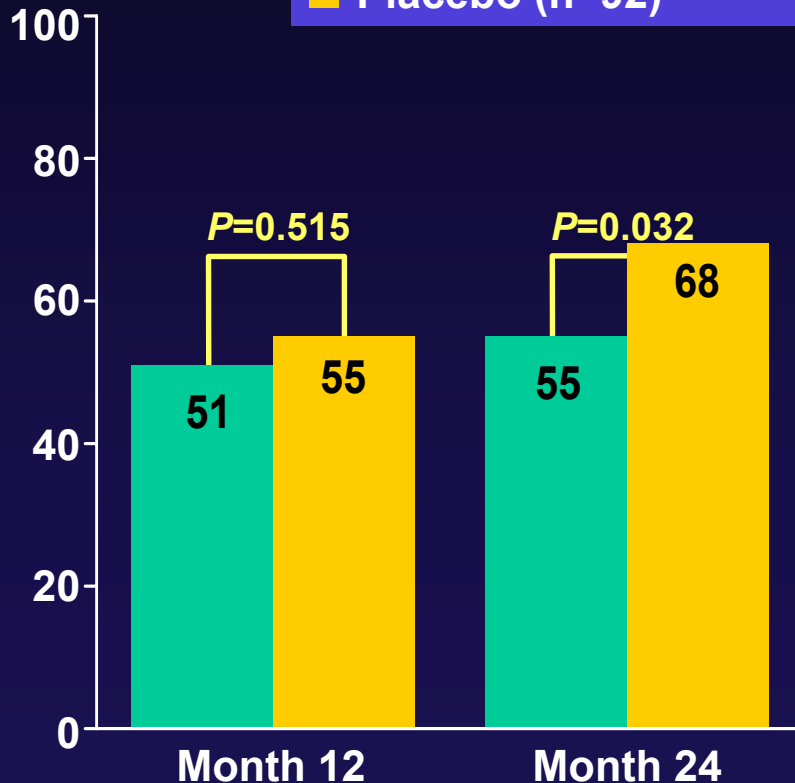
## VIP Trial: selection

- VA score  $\geq 50$  letters  
(approx. Snellen equivalent  $\geq 20/100$ )
- Occult with no classic CNV
- Recent disease progression:
  - Subretinal blood or
  - Anatomic deterioration (increase of lesion GLD by  $\geq 10\%$  within 12 weeks) or
  - Visual acuity deterioration ( $>5$  letters,  $\approx >1$  line, within 12 weeks)

# VIP Trial: $\geq 3$ -line vision loss

Eyes with  
 $\geq 3$ -line loss (%)

■ Verteporfin therapy (n=166)  
■ Placebo (n=92)

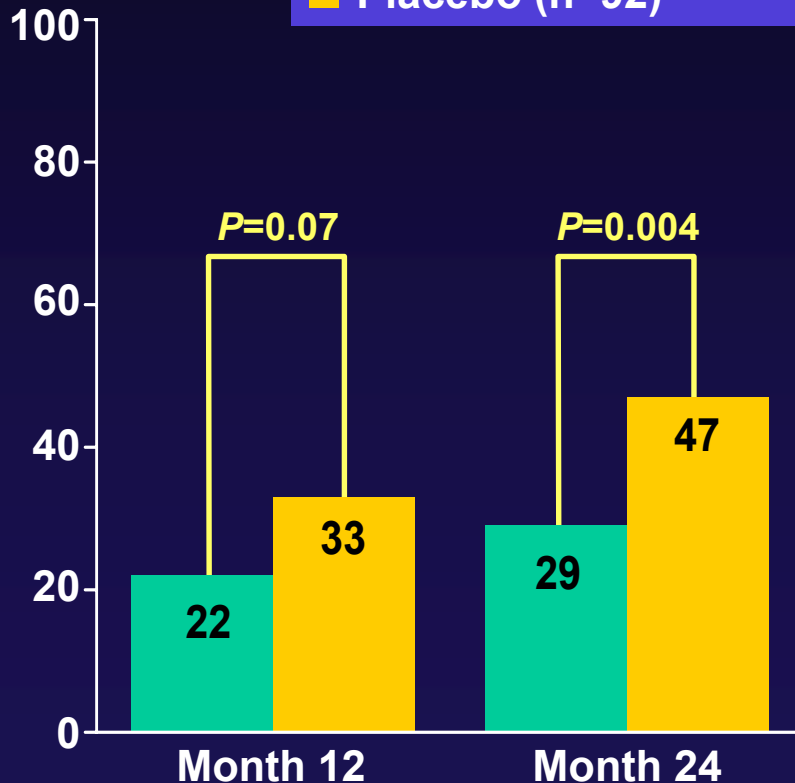


Fewer eyes treated with verteporfin therapy lost 3 or more lines of visual acuity compared with placebo

# VIP Trial: $\geq 6$ -line vision loss

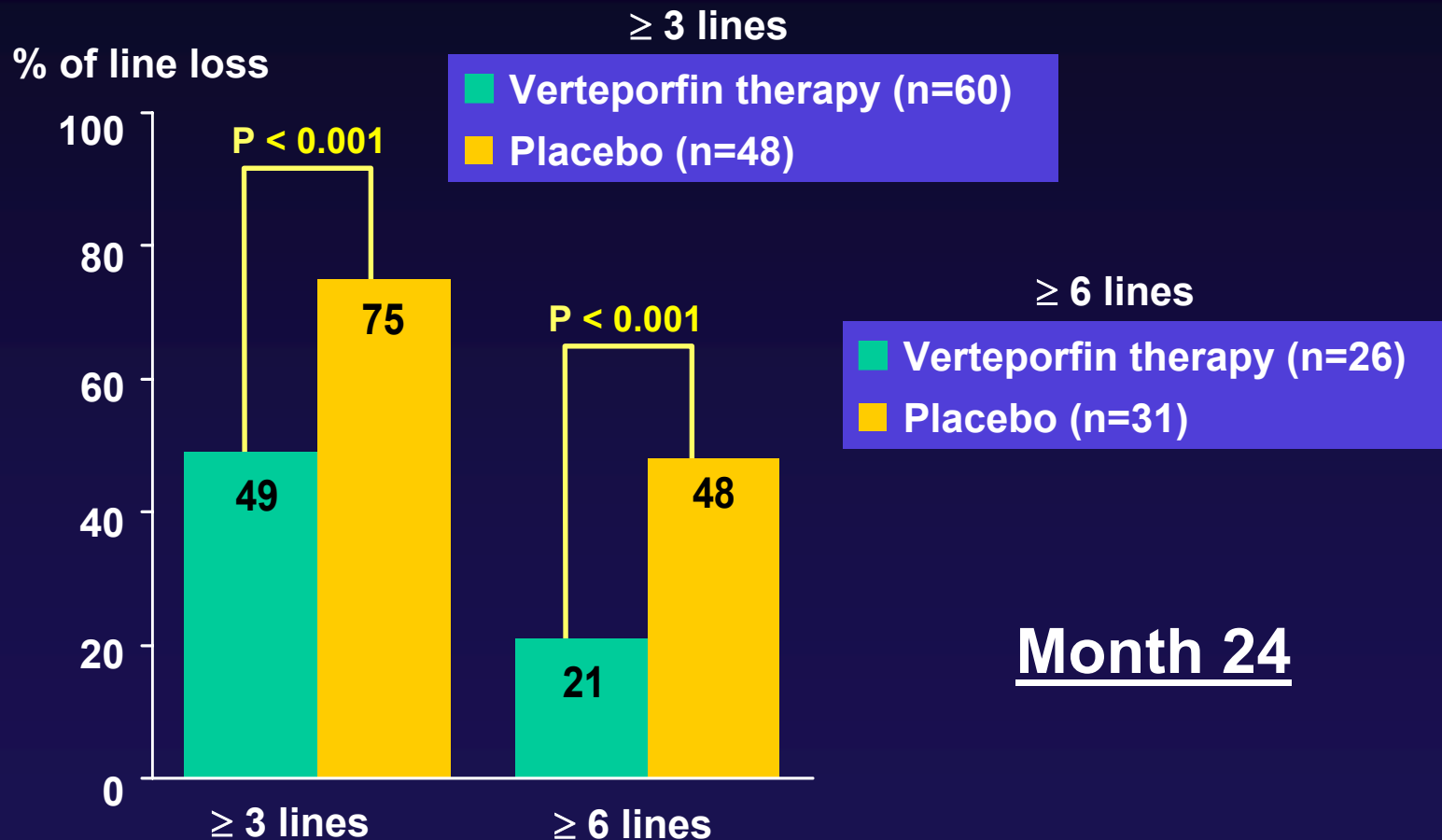
Eyes with  
 $\geq 6$ -line loss (%)

■ Verteporfin therapy (n=166)  
■ Placebo (n=92)



Fewer eyes treated with verteporfin therapy had severe vision loss compared with placebo

# VIP Trial: eyes with *either* smaller lesions ( $\leq 4$ MPS DA) or lower levels of visual acuity



# VIP Trial: number of study eye treatments

|        | Mean number of treatments    |                  |
|--------|------------------------------|------------------|
|        | Verteporfin therapy<br>n=225 | Placebo<br>n=114 |
| Year 1 | 3.1                          | 3.6              |
| Year 2 | 1.9                          | 2.3              |
| Total  | 5.0                          | 5.9              |

Maximum possible treatments = 8.0

## VIP Trial: conclusion

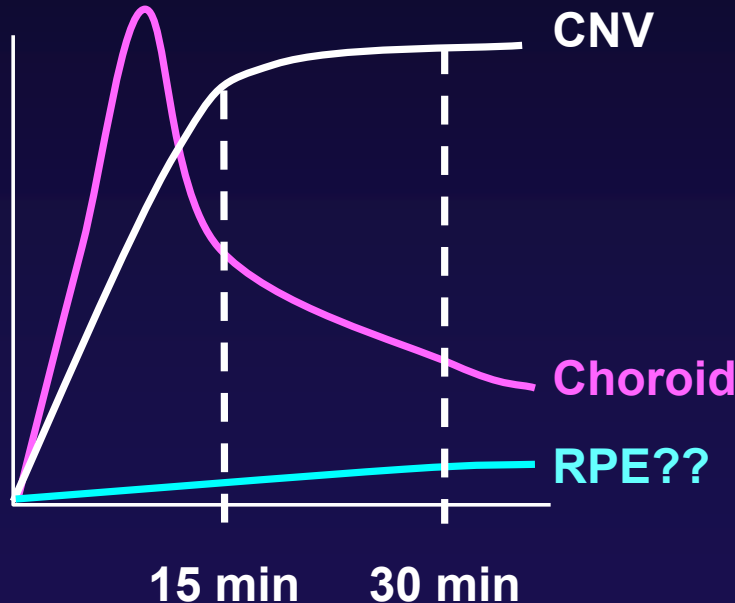
- The VIP Study Group recommends verteporfin therapy for eyes with occult CNV with recent disease progression
  - Particularly for those with *either* smaller lesions ( $\leq 4$  MPS DA) *or* lower levels of visual acuity

# **PDT in occult CNV**

**II. Verteporfin with Altered  
(delayed) Light In Occult (no  
classic) CNV (VALIO) Study**

# Verteporfin therapy of occult CNV: hypothesis for delayed light

Verteporfin  
concentration



- 50% less verteporfin in choroidal circulation at 30 minutes than at 15 minutes
- Less non-selective choroidal injury
- Different characteristics of occult with no classic CNV
- Increased selectivity of the photodynamic effect

## **VALIO study**

- **To determine if visual and angiographic outcomes in eyes with subfoveal occult CNV with no classic component improve by delaying time of light application to 30 minutes after start of infusion compared with standard light application 15 minutes after infusion**
- **To assess safety of verteporfin therapy with delayed light application**

# VALIO study design

|                       |                      |
|-----------------------|----------------------|
| 60 eyes               |                      |
| Standard light (n=28) | Delayed light (n=32) |

- **Pre-screening and evaluation of all fluorescein angiograms before enrolment by Digital Angiographic Reading Center (DARC)**
- **Visual acuity and angiographies (fluorescein and ICG) performed at baseline and follow-up (6 weeks, 3 months and 6 months)**

# VALIO: discussion

- **Imbalances at baseline**
  - **Standard (15-minute) light application group – more lesions with better VA therefore likely to lose more vision**

## **VALIO: conclusions**

- **VALIO Study Group recommends standard (15-minute) light application when considering verteporfin therapy for occult with no classic CNV**
  - **No differences in vision or angiographic outcomes identified for either group**
  - **No additional safety concerns were identified with delayed light application compared with standard light application**

# **Safety in Verteporfin Clinical Trials**

# Verteporfin Therapy: All Trials

## Acute Severe Visual Acuity Decrease

| Study                          | n/N            | %          |
|--------------------------------|----------------|------------|
| TAP Investigation <sup>1</sup> | 3/402          | 0.7        |
| VIP Trial <sup>1</sup>         | 10/225         | 4.4        |
| VAM <sup>2</sup>               | 25/4435        | 0.6        |
| VIM <sup>3</sup>               | 1/77           | 1.3        |
| VER <sup>4</sup>               | 1/323          | 0.3        |
| JAT <sup>4</sup>               | 2/64           | 3.1        |
| VALIO <sup>4</sup>             | 3/60           | 5.0        |
| <b>Total</b>                   | <b>45/5586</b> | <b>0.8</b> |

1. TAP and VIP Study Groups. Acute Severe Visual Acuity Decrease After Photodynamic Therapy with Verteporfin: Case Reports from Randomized Clinical Trials – TAP and VIP Report No. 3. *Am J Ophthalmol.* 2004; 683–696

2. VAM Study Writing Committee. Verteporfin Therapy in Age-Related Macular Degeneration (AMD): An Open-Label Multicenter Photodynamic Therapy Study of 4,435 Patients. *Retina.* 2004; 512–20


3. VIM Study Group. Verteporfin Therapy of Subfoveal Minimally Classic Choroidal Neovascularization in Age-Related Macular Degeneration. *Arch Ophthalmol.* In Press

4. Data on file. Novartis Pharma AG

# Management of CNV: Treatment Algorithm

 Laser photocoagulation

 Visudyne therapy

 Observation

**CNV on fluorescein angiography**

**Lesion location**


Extrafoveal 

Juxtafoveal 

Subfoveal

**Lesion composition**

Predominantly classic 

Minimally classic\* 

Occult with no classic

**Recent disease progression**

No 

Yes


**Lesion size**

$\leq 4$  MPS disc areas 

$> 4$  MPS disc areas

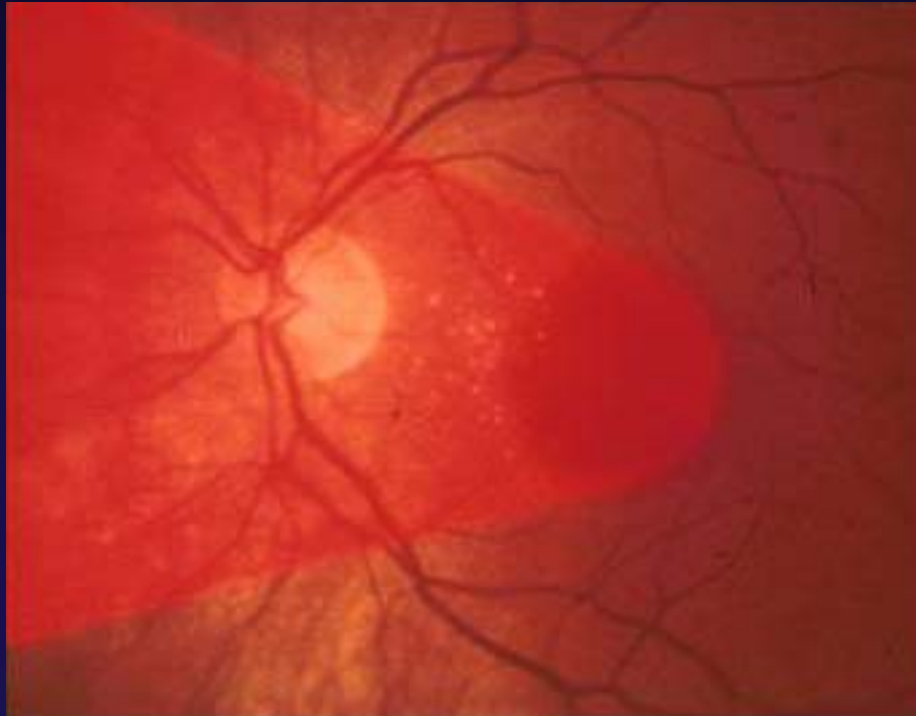
**Visual acuity**

Lower ( $\leq 20/50$ ) 

Higher ( $\geq 20/50$ ) 

\* Consider if lesion  $\leq 4$  MPS disc areas

# Photodynamic Therapy



Barbazetto I, Schmidt-Erfurth U. In Holz FG et al. *Age-Related Macular Degeneration*. Springer-Verlog; 2004.  
Schmidt-Erfurth U. *Acta Ophthalmol Scand*. 2004;82:357.

# Adjunctive Therapy

# Adjunctive Therapy Options

- **Adjunctive therapies under evaluation:**
  - **Anti-angiogenic or angiostatic drugs**
    - **Glucocorticoids (triamcinolone acetonide)**
    - **VEGF inhibitors (pegaptanib; ranibizumab)**
    - **Angiostatic cortisene (anecortave acetate)**
  - **NSAIDs**
    - **COX-2 inhibitors (Celebrex)**
    - **COX-1/COX-2 inhibitors (diclofenac eyedrops)**

# Verteporfin + Adjunctive IVTA review

| Author                             | N  | CNV types | TA dose                | Results   |
|------------------------------------|----|-----------|------------------------|---|
| Spaide<br>(published)              | 26 | All       | 4 mg same day          | Significant improvement in VA at 3 and 6 months, no VA loss $\geq 3$ lines                                      |
| Rechtman<br>(published)            | 14 | All       | 4 mg, +1 to +42 days   | 7% of eyes improved, 50% of eyes stable   |
| Augustin<br>(submitted)            | 41 | Occult    | 25 mg (18hrs post PDT) | VA improved in 22 eyes (54%) and stabilized in 16 eyes (39%)  |
| Rosenfeld<br>(Retina Society 2004) | 81 | All       | 4 mg same day          | No difference in VA from baseline, 15-17% of eyes had $\geq 3$ line gain, 17-35% of eyes had $\geq 3$ line loss |
| Roth<br>(AAO 2004)                 | 72 | All       | 4 mg, 1 wk prior       | VA stable in 81% of eyes, and improved $\geq 2$ lines in 21% of eyes  |

# Verteporfin + Adjunctive IVTA review

| Author                                   | N  | CNV types     | TA dose                                   | Results   |
|--|----|---------------|---|---|
| <b>Bhavsar</b><br>(AAO 2004)             | 26 | MC            | 4 mg same day                             | 23 eyes (88%) had improved VA, or a decrease of <3 lines  |
| <b>Balles</b><br>(ASRS 2004)             | 39 | All           | 4 mg within 72 hrs                        | Average: gain 1.5 lines, no eyes lost > 2 lines   |
| <b>Moshfegi</b><br>(Retina Society 2004) | 35 | Subfoveal     | Verteporfin therapy combined with IVTA    | VA improved by 3 or more lines in 21% of 19 patients with prior verteporfin therapy and in 6% of patients without prior verteporfin therapy |
| <b>El Matri</b><br>(E-abstract 2004)     | 34 | Not specified | Single 4mg dose IVTA                      | VA increased in 65% of patients   |
| <b>Johnson</b><br>(AAO 2004)             | 24 | Subfoveal     | Single dose IVTA 1 week after verteporfin | 270 days after treatment, 3 eyes (13%) had VA improvement >2 lines and 19 eyes (79%) had stable VA  |

# Steroid Adjunctive Therapy Studies

## Intravitreal triamcinolone

- **VISIT**
  - 200 patients; all CNV types; 0 or 4 mg TA + PDT with verteporfin
- **VISTA**
  - 120 patients; MC and occult only; 0, 1 or 4 mg TA + PDT with verteporfin
- **Retina (Canada)**
  - 120 patients; PC CNV; 0 or 4 mg TA + PDT with verteporfin
- **NEI (sponsored by QLT)**
  - 300 patients; all CNV types; 0, 1 or 4 mg TA + PDT with verteporfin

## Subtenon triamcinolone

- **Hopkins**
  - 100 patients; all CNV types; 0 or 40 mg TA + PDT with verteporfin

# Conclusions

- **Adjunctive therapies appear to further improve the long-term efficacy outcomes of PDT with verteporfin**
- **Further studies are ongoing**