

# Safety Evaluation of Second-year Treatment of Age-related Macular Degeneration With Pegaptanib Sodium (Macugen®): VEGF Inhibition Study in Ocular Neovascularization (VISION)

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## INTRODUCTION

The VEGF Inhibition Study in Ocular Neovascularization (VISION) trial<sup>1</sup> evaluated pegaptanib sodium injection (Macugen®, Eyetech Pharmaceuticals), a selective vascular endothelial growth factor (VEGF) antagonist, in the treatment of neovascular age-related macular degeneration (AMD). All 3 doses of pegaptanib (0.3 mg, 1 mg, and 3 mg) employed had favorable safety profiles during the initial 54 weeks of therapy. Most adverse events were transient, mild to moderate in severity, and attributed to the injection procedure itself rather than to the study drug. At week 54, the per injection rates of endophthalmitis, retinal detachment, and traumatic lens injury were 0.16%, 0.07%, and 0.08%, respectively; the rates for endophthalmitis and retinal detachment were lower than or comparable to those identified in a comprehensive review of more than 15,000 intravitreal (IVT) injections.<sup>2</sup>

Although week 54 was the prespecified time point for analysis of the primary efficacy endpoint, the study was designed to continue for 102 weeks. Safety endpoints were measured throughout the study, providing an opportunity to evaluate the longer term safety of pegaptanib therapy in patients with AMD.

\*Please see full prescribing information.

## PURPOSE

To evaluate the second-year safety of pegaptanib sodium injection in the treatment of neovascular AMD

## METHODS

- Patients with all angiographic subtypes of AMD were enrolled in two pivotal phase 2/3 multicenter, randomized, double-masked, controlled trials.<sup>1</sup> Broad entry criteria for vision and lesion size were established.
- During the first year of the study, IVT pegaptanib (0.3 mg, 1 mg, or 3 mg) or sham injection was administered every 6 weeks for 54 weeks (9 injections).
- After the first year, subjects receiving pegaptanib were rerandomized (1:1) at week 54 to either continue treatment for 48 additional weeks (8 injections) or discontinue treatment. Those rerandomized to continue pegaptanib were the only patients who received pegaptanib for year 2.
- Sham-treated patients also were rerandomized (1:1:1:1) at week 54 to either continue in the sham group, receive one of the three pegaptanib doses, or discontinue treatment entirely.
- During the entire 102 weeks, masked investigators were permitted to administer photodynamic therapy with verteporfin at their discretion according to FDA-approved use (i.e., for predominantly classic lesions only).
- Only patients who received a second year of pegaptanib or 2 years of sham are included in this analysis.

### References

- Gragoudas ES, et al. *N Engl J Med* 2004;351:2805-16.
- Jager RD, et al. *Retina* 2004;24:676-98.
- Avastin [package insert]. Genentech, Inc; South San Francisco, CA; 2004.
- Verteporfin in Photodynamic Therapy Study Group. *Am J Ophthalmol* 2001;131:541-60.

## RESULTS

- In all, 374 patients received 2663 IVT injections during the second year (0.3 mg, N=128; 1 mg, N=126; 3 mg, N=120) and 51 patients received 388 sham injections. The mean number of treatments for all patients rerandomized to continue therapy was 7 out of a possible 8 treatments.

- An overall summary of adverse events is provided in Table 1.

**Table 1. Adverse Event Summary,\* N (%)**

	Pegaptanib Sodium				Sham (N=51)
	0.3 mg (N=128)	1 mg (N=126)	3 mg (N=120)		
Patients with an adverse event	122 (95)	118 (94)	109 (91)	46 (90)	
Patients with an ocular adverse event					
Study eye	92 (72)	98 (78)	92 (77)	39 (76)	
Fellow eye	45 (35)	44 (35)	45 (38)	23 (45)	
Patients with a serious adverse event	22 (17)	23 (18)	18 (15)	14 (27)	

\*Data for second year of treatment.

- Pegaptanib sodium was well tolerated at all three doses (Table 2).

**Table 2. Ocular Adverse Events in ≥10% of Patients,\* N (%)**

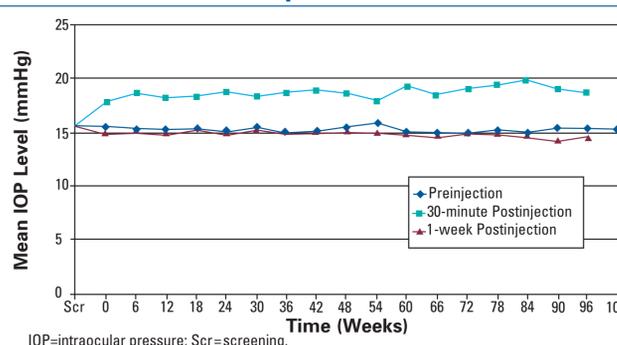
	Pegaptanib Sodium				Sham (N=51)
	0.3 mg (N=128)	1 mg (N=126)	3 mg (N=120)		
Eye pain					
Study eye	27 (21)	35 (28)	31 (26)	9 (18)	
Fellow eye	0	1 (1)	5 (4)	0	
Vitreous floaters					
Study eye	28 (22)	24 (19)	31 (26)	2 (4)	
Fellow eye	3 (2)	2 (2)	2 (2)	3 (6)	
Punctate keratitis					
Study eye	31 (24)	26 (21)	29 (24)	14 (27)	
Fellow eye	2 (2)	1 (1)	0	1 (2)	
IOP increased					
Study eye	26 (20)	22 (17)	42 (35)	4 (8)	
Fellow eye	2 (2)	2 (2)	1 (1)	0	
Vitreous opacities					
Study eye	13 (10)	12 (10)	21 (18)	6 (12)	
Fellow eye	3 (2)	2 (2)	0	1 (2)	
Corneal edema					
Study eye	12 (9)	10 (8)	13 (11)	4 (8)	
Fellow eye	0	0	0	0	
Lacrimation increased					
Study eye	6 (5)	15 (12)	10 (8)	6 (12)	
Fellow eye	1 (1)	3 (2)	0	2 (4)	
Number of phakic study eyes	78	79	87	34	
Cataract in study eye, N (%)	14 (18)	18 (23)	15 (17)	8 (24)	

\*Data for second year of treatment. Adverse events reported in ≥10% of patients receiving pegaptanib sodium. IOP = intraocular pressure.

## Results - Continued

- Ocular adverse events occurred at a frequency similar to that observed during the first year of the study:
  - The majority of adverse events reported in study eyes were transient, mild to moderate in severity, and attributed by investigators to the injection procedure itself rather than the study drug.
  - The incidence of these ocular events was higher in the sham arm than in the fellow eye of any pegaptanib treatment arm, suggesting that the treatment preparation (use of an eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine drops or flush, and subconjunctival injection of anesthetic) rather than the IVT injection itself may be involved in causing these events.
  - In the 374 patients receiving a second year of pegaptanib sodium, anterior chamber inflammation was reported in 21 (6%) patients; the event was mild in all but 1 patient (0.3%) who had moderate inflammation, and no patient had severe anterior chamber inflammation.
- As in year 1, patients experienced an increase in intraocular pressure (IOP) at the 30-minute postinjection assessment compared with preinjection at each visit. IOP returned to preinjection levels at the 1-week postinjection visit (Figure).

**Figure. Mean IOP Levels, 0.3 mg Pegaptanib Treatment Group**



- Pegaptanib sodium continued to have a favorable injection safety profile during the second year (Table 3). There were no reports of endophthalmitis or traumatic cataract occurring within the second year of treatment with pegaptanib sodium. Four cases of rhegmatogenous retinal detachment were reported (0.15% per injection).

**Table 3. Injection-related Serious Adverse Events in Patients Receiving Pegaptanib Sodium\***

Condition	Rate		Severe Vision Loss <sup>†</sup>	
	Patients	Percent per Injection	Patients	Percent per Injection
Endophthalmitis	0	0	-	-
Traumatic cataract	0	0	-	-
Rhegmatogenous retinal detachment	4	0.15	1 <sup>‡</sup>	0.04

\*Data for second year of treatment. Pegaptanib patients rerandomized to pegaptanib, N=374; total injections, N=2663. <sup>†</sup>Severe vision loss is defined as a loss of ≥30 letters. <sup>‡</sup>Follow-up not available for 1 patient.

## Results - Continued

- All doses of pegaptanib were well tolerated systemically (Table 4). No serious adverse events definitely attributed to the study drug were identified.

**Table 4. All Causality Nonocular Adverse Events in >5% of Patients,\* N (%)**

Adverse Event (Preferred Term)	Pegaptanib Sodium			Sham (N=51)
	0.3 mg (N=128)	1 mg (N=126)	3 mg (N=120)	
Blood and lymphatic system disorders				
Anemia	5 (4)	7 (6)	4 (3)	2 (4)
Infections				
Upper respiratory tract infection	4 (3)	9 (7)	2 (2)	2 (4)
Urinary tract infection	8 (6)	2 (2)	3 (3)	3 (6)
Musculoskeletal and connective tissue disorders				
Back pain	3 (2)	4 (3)	6 (5)	3 (6)
Nervous system disorders				
Headache	4 (3)	7 (6)	8 (7)	1 (2)
Respiratory, thoracic, and mediastinal disorders				
Nasopharyngitis	12 (9)	8 (6)	10 (8)	3 (6)
Vascular disorders				
Hypertension	8 (6)	5 (4)	8 (7)	3 (6)

\*Data for second year of treatment. Adverse events reported in >5% of patients receiving pegaptanib sodium.

- There was no evidence that pegaptanib sodium was associated with the potential VEGF inhibition related adverse events seen with the systemically administered nonselective VEGF inhibitor bevacizumab (Avastin®)<sup>3</sup> (Table 5).

**Table 5. Potential VEGF Inhibition Related Adverse Events,\* N (%)**

	Pegaptanib Sodium (N=374)	Sham (N=51)
All thromboembolic adverse events	17 (5)	4 (8)
Arterial events	12 (3)	3 (6)
Venous events	5 (1)	1 (2)
All serious thromboembolic events	12 (3)	4 (8)
Serious arterial events	9 (2)	3 (6)
Serious venous events	3 (1)	1 (2)
Vascular hypertensive disorders	28 (7)	3 (6)
Heart failure	6 (2)	4 (8)
Serious hemorrhagic adverse events	2 (1)	1 (2)

\*Data for second year of treatment.

- In the 2-year pegaptanib cohort, 7 of 374 subjects reported visual loss of any degree within 7 days of injection (7/374, 1.9%), with only 1 documented case of severe (≥20 letters) visual loss (1/374, 0.27%).
- No clinically meaningful pattern of change or findings to suggest a relationship to treatment was identified for any of the hematology or chemistry analytes evaluated.

## CONCLUSIONS

In patients with neovascular AMD, pegaptanib sodium was well tolerated during the second year of treatment, and no new safety concerns were identified. In the 2-year report of verteporfin therapy in AMD, 10 patients (total N=225) reported severe visual acuity decrease within 7 days after treatment and were documented to have lost at least 20 letters of visual acuity compared to pretreatment acuity (10/225, 4.4%). Given the relative risk for acute visual loss pursuant to pegaptanib therapy, even given the small albeit finite risk of endophthalmitis, pegaptanib's safety profile, when compared to other available agents, seems superior.