



**Division of Anti-inflammatory, Analgesic and
Ophthalmic Drug Products
Advisory Committee Meeting
Briefing Package**

For

**Macugen (pegaptanib sodium injection) for the
Treatment of Neovascular Age-Related Macular
Degeneration**

Sponsor:

**Eyetech Pharmaceuticals, Inc
500 Seventh Avenue, 18th floor
New York, New York 10018**



Table of Contents

Table of Contents.....2

I. Introduction and Background 3

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor’s
Proposed Indication(s), Dose, Regimens, Age Groups.....3

B. State of Armamentarium for Indication(s).....4

**II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and
Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other
Consultant Reviews..... 4**

III. Human Pharmacokinetics..... 5

IV. Description of Clinical Data and Sources 6

VI. Integrated Review of Efficacy..... 8

A. General Approach to Review of the Efficacy of the Drug.....8

B. Detailed Review of Trials by Indication8

VII. Integrated Review of Safety 39

A. Description of Patient Exposure39

B. Methods and Specific Findings of Safety Review40

VIII. Appendix

Advisory Committee Questions.....55

I. Introduction and Background

AMD is the leading cause of blindness in developed countries with approximately 15 million people with the disease in the United States. AMD is characterized as a progressive degenerative disease of the macula. There are two forms of AMD: neovascular and non-neovascular. The non-neovascular form of AMD is more common and leads to a slow deterioration of the macula with a gradual loss of vision over a period of years. The neovascular form of the disease is responsible for the majority of cases of severe vision loss and is due to proliferation of abnormal blood vessels behind the retina. These blood vessels leak blood and fluid into the retina, which results in visual abnormalities. The development of these abnormal blood vessels is due in part to the activity of VEGF (vascular endothelial growth factor) and its inhibition is expected to impact on the onset and/or severity of vision loss associated with the proliferation of abnormal blood vessels.

Macugen (pegaptanib sodium injection) has been developed for the treatment of the neovascular form of age-related macular degeneration (AMD). In vitro studies have suggested that pegaptanib binds to VEGF and inhibits its binding to cellular receptors. Macugen's anti-VEGF activity is expected to inhibit abnormal blood vessel proliferation and therefore decrease the vision loss associated with the neovascular form of AMD.

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Proprietary Name:	Macugen
Established name:	pegaptanib sodium injection
Sponsor:	Eyetechnopharmaceuticals 500 Seventh Avenue, 18 th Floor New York, New York 10018
NDA Drug Classification:	1P
Pharmacologic Category	Vascular Endothelial Growth Factor (VEGF) Inhibitor
Proposed Indication:	The treatment of the neovascular form of age-related macular degeneration.
Dosage Form and Route of Administration	Intravitreal Injection

B. State of Armamentarium for Indication(s)

Macugen (pegaptanib sodium) has been developed for the treatment of the neovascular form of age-related macular degeneration (AMD). Currently, there is only one treatment approved for use in AMD. Photodynamic therapy (PDT) with verteporfin is approved for patients with the predominantly classic form of AMD.

II. Chemical Composition and Specifications

Composition of Macugen (pegaptanib sodium injection) 0.3 mg/90 µL^a

Name of Ingredients	Reference to Standards	Function	Solution Composition mg/mL	Unit Dosage Composition 0.3 mg/90 µL	Percent (w/v)
Pegaptanib Sodium	In-house standard	Drug substance	3.47 ^b	0.3 mg ^b	0.3 ^b
Monobasic Sodium Phosphate Monohydrate	USP	pH buffering agent	0.77	0.069 mg	0.077
Dibasic Sodium Phosphate Heptahydrate	USP	pH buffering agent	1.2	0.11 mg	0.12
Sodium Chloride	USP	Tonicity adjuster	9.0	0.8 mg	0.9
Hydrochloric Acid	NF	pH adjuster	As needed ^c	As needed ^c	
Sodium Hydroxide	NF	pH adjuster	As needed ^c	As needed ^c	--
Water for Injection	USP	Diluent	q.s.	q.s.	--
Nitrogen	NF	Processing aid/inert atmosphere	q.s.	q.s.	--
Total Volume			1 mL	90 µL	

^a Quantities are calculated

^b Based on a theoretical potency of 100% for pegaptanib sodium with no overage. The actual weight varies according to the actual potency of pegaptanib sodium used. Compositions calculated based on oligonucleotide moiety

^c For pH adjustment

Proposed analytical specifications for pegaptanib sodium are presented below. Final specifications are currently undergoing revisions to meet the Agency’s acceptance criteria.

Analytical Specification for Macugen Injection, 0.3 mg

Test	Method	Method Reference	Acceptance Criteria
-------------	---------------	-------------------------	----------------------------

TABLE REMOVED

III. Human Pharmacokinetics

The pharmacokinetic profile of pegaptanib has been studied in a total of five trials: one single dose study and four repeated dose studies. The repeated dose studies were conducted with the 3 mg dose injected every 4 weeks or every 6 weeks. The results of these trials show that maximum plasma concentrations of pegaptanib sodium are approximately 90 ng/mL and are reached within 1 to 4 days after injection. These levels declined over 4 weeks. Low circulating levels of pegaptanib are seen 4 to 6 weeks after an intravitreal dose of 3 mg. These levels approach the lower limit of quantification in the majority of patients. The “terminal” half-life of pegaptanib in the plasma after dosing 3mg is 10±4 days. This “terminal” half-life represents the exit of pegaptanib out of the eye into the systemic circulation.

IV. Description of Clinical Data and Sources

Protocol	Design	Dose	Patients Treated	Study Assessments
Studies in Age-related Macular Degeneration (AMD)				
Controlled AMD Trials				
EOP1003	Phase 2/3 multi-center, randomized, sham-injection controlled, double masked, dose finding	Intravitreal injections of either 0.3, 1 or 3 mg pegaptanib sodium/eye or sham every 6 weeks for 54 weeks	622 patients 50 years of age active subfoveal CNV secondary to exudative AMD	BCVA, Fluorescein angiography and fundus photography, AEs, IOP, laboratory parameters, vital signs, PDT administration, local ocular events
EOP1004	Phase 2/3 multi-center, randomized, sham-injection controlled, double masked, dose finding	Intravitreal injections of either 0.3, 1 or 3 mg pegaptanib sodium/eye or sham every 6 weeks for 54 weeks	586 patients 50 years of age active subfoveal CNV secondary to exudative AMD	BCVA, Fluorescein angiography and fundus photography, AEs, IOP, laboratory parameters, vital signs, PDT administration, local ocular events, PK, QOL
Uncontrolled AMD Trials				
NX109-01	Phase 1, multi-center, open label escalating dose, dose finding	Single intravitreal injection of either 0.25, 0.5, 1, 2 or 3 mg pegaptanib sodium/ eye	15 patients 50 years of age with exudative AMD	DLT, AEs, vital signs, BCVA, IOP, laboratory parameters, immune response, PK parameters, local ocular events
EOP1000	Phase 1/2, multi-center, open label, multiple dose in patients without PDT	Total of 3 consecutive intravitreal injections of 3 mg pegaptanib sodium/eye, 28 days apart	10 patients 50 years of age with subfoveal CNV secondary to exudative AMD	BCVA, AEs, IOP, laboratory parameters, vital signs, DLT, PK parameters, immune response, local ocular events

EOP1001	Phase 1/2, multi-center, open label, multiple dose in patients following PDT administration	Total of 3 intravitreal injections of 3 mg pegaptanib sodium/ eye, 28 days apart	11 patients 50 years of age with predominantly classic subfoveal CNV secondary to exudative AMD	BCVA, AEs, IOP, laboratory parameters, vital signs, DLT, PK parameters, immune response, requirement for PDT administration, local ocular events
EOP1006	Phase 2 multi-center, randomized, multiple dose, open label cohort	Intravitreal injections of 3 mg pegaptanib sodium/ eye every 6 weeks for 54 weeks	37 patients 50 years of age with subfoveal CNV secondary to exudative AMD (Study is ongoing in 147 patients)	AE, local ocular events, IOP, laboratory parameters, vital signs, PK parameters, immune response
Development Trials for Additional Indications				
Studies in Diabetic Macular Edema (DME)				
EOP1002	Phase 1/2, multi-center, multiple dose open label,	Intravitreal injections of 3 mg pegaptanib sodium/ eye every 6 weeks for 12 to 30 weeks	10 patients 18 years of age with clinically significant DME	AEs, BCVA, laboratory parameters, IOP, retinal thickening, local ocular events
EOP1005	Phase 2, multi-center, randomized, sham-injection controlled, double masked, dose finding	Intravitreal injections of either 0.3, 1.0 and 3 mg pegaptanib sodium/ eye or sham every 6 weeks for 12 to 30 weeks	169 patients 18 years of age with clinically significant DME (Study is ongoing)	Retinal thickening, BCVA, AEs, IOP, laboratory parameters, local ocular events, need for laser at 12 weeks
Studies in Von Hippel-Lindau Disease (VHL)				
EOP1007	Phase 1/2, open-label, non-randomized, pilot	Intravitreal injections of 3 mg pegaptanib sodium/ eye every 6 weeks for 30 to 54 weeks	5 patients 18 years of age with severe ocular VHL tumors	BCVA, macular thickening, fluorescein leakage, disease progression, AEs, local ocular events, IOP.
CNV = Choroidal neovascularization; PDT = Photodynamic therapy with verteporfin; DLT = Dose limiting toxicity; AE = Adverse event; BCVA = Best corrected visual acuity; IOP = Intraocular pressure; PK = Pharmacokinetics; QOL = quality of life.				

VI. Integrated Review of Efficacy

A. General Approach to Review of the Efficacy of the Drug

Each of the submitted phase 3 studies (EOP1003 and EOP1004) are presented independently to determine if the results of each trial demonstrated efficacy for the primary efficacy endpoint. The primary efficacy end point for each trial was a responder analysis of the proportion of patients who loss less than 15 letters of visual acuity from baseline (doubling of the visual angle) at 54 weeks. This analyses was done for two populations which represent the extreme ends of the spectrum to evaluate the robustness of the results; an all randomized patient population with last-observation-carried-forward (LOCF) and the per-protocol population with observed cased only.

B. Detailed Review of Trials by Indication

Proposed Indication: The treatment of the neovascular form of age-related macular degeneration.

Study 1 – Study EOP1003

Title: A Phase 2/3 Randomized, Double-Masked, Controlled, Dose-Ranging, Multi-Center Comparative Trial, in Parallel Groups, to Establish the Safety and Efficacy of Intravitreal Injections of Pegaptanib Sodium (Anti-Vascular Endothelial Growth Factor [VEGF] Pegylated Aptamer) Given Every 6 Weeks for 54 Weeks, in Patients with Exudative Age- Related Macular Degeneration (AMD)

Objective: The objective of this study was to establish the safe and efficacious dose of pegaptanib sodium when given as an intravitreal injection (0.3 mg, 1 mg or 3 mg/eye) compared with control sham injections every 6 weeks over a 54-week period (9 treatments) in patients with subfoveal choroidal neovascularization (CNV) secondary to AMD.

Study Design: This was a randomized, double-masked, controlled, dose-ranging, multi-center, comparative, Phase 2/3 trial, in parallel groups. The study was conducted internationally in Europe, Israel, Australia, South America and North America. The study has a 2 year duration with two randomization steps and is ongoing. Data from the first year on study are included in this report.

Clinical sites – Study EOP1003

Center Number	Principal Investigator	Center Location	Number of Subjects
Australia			
114	Andrew Chang, MD	Sydney	7
64	Jennifer Arnold, MD	Parramatta	34
65	Ian Constable, MD	St. Nedlands	12
66	Paul Mitchell, MD	Westmead	5
73	Robyn Guyer, MD	East Melbourne	16
131	Mark Gillies, MD	Sydney	12
Austria			
67	Michael Stur, MD	Vienna	11
116	Anton Haas, MD	Graz	4
Belgium			
113	Anita Leys, MD	Leuven	38
Brazil			
70	Michel Fara, MD	Sao Paulo	7
108	Marcos de Avila, MD	Sector Bureno	6
112	Carlos Moreira, MD	Curitiba	3
134	Jaco Lavinsky	Poro Alegre	5
Chile			
71	Jose Manuel Lopez, MD	Santiago	7
Colombia			
104	Franciso Rodriguez, MD	Colombia	18
Czech Republic			
119	Ivan Fiser, MD	Prague	11
Denmark			
72	Michael Larsen, MD	Herlev	9

Center Number	Principal Investigator	Center Location	Number of Subjects
France			
74	Francois Koenig, MD	Lyon	2
75	Gisele Soubrane, MD	Creteil	25
76	Jean-Francois Korobelnik, MD	Bordeau	5
78	Alain Gaudric, MD	Paris	3
Germany			
79	Stefan Dithmar, MD	Heidelberg	10
80	Daniel Pauleikhoff, MD	Munstser	1
81	Ulrike Schneider, MD	Tubingen	6
82	Peter Wiedemann, MD	Leipzig	14
83	B Kirchhof, MD	Koln	8
Hungary			
122	Ildiko Suveges, MD	Budapest	3
137	Jozsef Gyory, MD	Veszprem Korhaz	3
Israel			
84	Anat Loewenstein, MD	Tel-Aviv	11
85	Irit Rosenblatt, MD	Petach Tikva	11
103	Ayala Pollack, MD	Rehovot	7
Italy			
86	Rosario Brancato, MD	Milano	6
87	Francesco Bandello, MD	Udine	16
88	Felice Cardillo Piccolino, MD	Torino	10
89	Lfonso Giovannini, MD	Torrette Ancona	18
123	Ugo Menchini	Firenze	8
Poland			
127	Krystna Pecold, MD	Poznan	5
128	Jozef Kaluzny, MD	Bydgoszcz	5
Portugal			
93	Jose Cunha-Vaz, MD	Coimbra	25
Spain			
94	Marta Figueroa, MD	Madrid	7
136	Jose Ruiz Moreno, MD	Alicante	10
95	Jordi Mones, MD	Barcelona	14
Switzerland			
98	Constantin Pournaras, MD	Geneva	2
99	Leonides Zografos, MD	Lausanne	1
The Netherlands			
91	August Deutman, MD	Nijmegen	7
92	Reiner Schlingemann, MD	Amsterdam	15
United Kingdom			
100	Iain Chisholm, MD	Southampton	14
101	Noemi Lois, MD	Scotland	9
102	Usha Chakravarthy, MD	Belfast	18
130	Phil Hykin, MD	London	15
United States			
143	David Chow, MD	Illinois	4
144	K. Bailey Freund, MD	New York	4
145	Alexander Eaton, MD	Florida	15
146	Philip M. Falcone, MD	Connecticut	4
147	Patrick Higgins, MD	New Jersey	9
148	Keye Wong, MD	Florida	9

Center Number	Principal Investigator	Center Location	Number of Subjects
149	Matthew Thomas, MD	Missouri	-
153	Leonard Joffe, MD	Arizona	16
154	Jeffrey Heier, MD	Massachusetts	21
156	John Thompson, MD	Maryland	-
Canada			
151	Murray Ersmus, MD	Saskatoon	-
155	Raul Garcia, MD	Saskatchewan	8

First Randomization

The trial had a parallel group design. At study entry, patients were allocated to one of the four treatment arms according to a stratified randomization system. The treatment groups were:

Arm A: pegaptanib sodium 0.3 mg intravitreal injection every 6 weeks for 48 weeks

Arm B: pegaptanib sodium 1 mg intravitreal injection every 6 weeks for 48 weeks

Arm C: pegaptanib sodium 3 mg intravitreal injection every 6 weeks for 48 weeks

Arm D: sham intravitreal injection every 6 weeks for 48 weeks

Patients were stratified by center and the following factors:

- Type of lesion (visible classic CNV area divided by total lesion area); defined as predominantly classic (>50% classic CNV), minimally classic (1-49% classic CNV), or occult with no classic (0% classic CNV)
- Whether the patient had received prior PDT therapy (one treatment maximum)

Second Randomization

At one year (54 weeks), patients were re-randomized for a total study period of 102 weeks.

Patients who were treated with pegaptanib sodium during the first year were re-randomized at week 54 in a ratio of 1:1 to either stop therapy (no further treatment) or to continue with the same dose and dosing regimen of pegaptanib sodium.

Patients who were receiving sham injections during the first year were re-randomized at week 54 in a ratio of 1:1:1:1 to either stop therapy, continue with sham injections or to continue on study receiving one of the three pegaptanib sodium doses.

Study Population – Inclusion and Exclusion Criteria

Inclusion Criteria

Ophthalmic Inclusion Criteria

1. BCVA in the study eye between 20/40 and 20/320, and better than or equal to 20/800 in the fellow eye.
2. Subfoveal CNV, secondary to AMD, with a total lesion size (including blood, scar/atrophy and neovascularization) of <12 total disc areas, of which at least 50% had to be active CNV.

3. Any subretinal hemorrhage could comprise no more than 50% of total lesion size.
4. For patients with minimally classic and occult with no classic CNV, there had to be the presence of subretinal hemorrhage (but comprising no more than 50% of the lesion) and/or lipid and/or documented evidence of 3 or more lines of vision loss (ETDRS or equivalent) during the previous 12 weeks.
5. Clear ocular media and adequate pupillary dilatation to permit good-quality stereoscopic fundus photography.
6. Intraocular pressure (IOP) of 23 mmHg or less.
7. PDT with verteporfin was permitted in this protocol only for patients with predominantly classic lesions determined by the investigator, and additionally they had to meet the criteria described in the product label (eligibility for PDT was confirmed retrospectively by the IRC). All PDT therapies given during the study were scheduled to occur within a 5- to 10-day window prior to treatment so that the study injection occurred after the period of photosensitivity, and any angiograms required by this protocol would be used to confirm eligibility for any subsequent PDT treatments wherever possible in order to minimize the number of additional angiograms required.

General Inclusion Criteria

1. Patients of either gender, aged >50 years.
2. Performance status = 2 according to Eastern Cooperative Oncology Group (ECOG) scale.
3. Normal electrocardiogram (ECG) or clinically non-significant changes.
4. Women had to be using two forms of effective contraception, be post-menopausal for at least 12 months prior to study entry, or be surgically sterile. If the woman was of child-bearing potential, a serum pregnancy test was performed within 48 hours prior to treatment and the result made available prior to treatment initiation. The two forms of effective contraception had to be implemented during the study and continue for at least 60 days following the last dose of test medication.
5. Adequate hematological function: hemoglobin >10g/dL, platelet count >130 x 10⁹/L and white blood cell count (WBC) >3.8 x 10⁹/L.
6. Adequate renal function: serum creatinine and blood urea nitrogen (BUN) within 2 x the upper limit of normal (ULN) of the institution.
7. Adequate liver function: serum bilirubin < 1.5 mg/dL, and gamma glutamyl transferase (GGT), alanine amino transferase (ALT/SGOT), aspartame amino transferase (AST/SGPT), and alkaline phosphatase within 2 x ULN of the institution.
8. Written informed consent.
9. Ability to return for all study visits.

Exclusion Criteria:

1. Previous subfoveal thermal laser therapy.
2. Any subfoveal scarring or atrophy, and no more than 25% of the total lesion size could be made up of scarring or atrophy.
3. More than one prior PDT with verteporfin was not permitted. In addition, patients could not have received their one prior PDT within less than eight weeks or more than 13 weeks prior to the baseline angiography/photography for the study. Patients could have their first "on study" PDT (if eligible) after baseline angiography/photography, but at least 5 days prior to the first study treatment.

4. Significant media opacities, including cataract, that might interfere with visual acuity, assessment of toxicity or fundus photography. Patients could not be entered if there was a likelihood that they would require cataract surgery within the following 2 years.
5. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of - 8 diopters or more, or axial length of 25mm or more), the ocular histoplasmosis syndrome, angioid streaks, choroidal rupture and multifocal choroiditis.
6. Any intraocular surgery within 3 months, or extrafoveal/juxtafoveal laser within 2 weeks, of study entry.
7. Previous posterior vitrectomy or scleral buckling surgery.
8. Previous or concomitant therapy with another investigational agent, including PDT with verteporfin for lesions other than predominantly classic (i.e., currently not approved in the majority of participating countries) to treat AMD, except multivitamins and trace minerals.
9. Presence of pigment epithelial tears or rips.
10. Any of the following underlying diseases:
 - Diabetic retinopathy
 - History or evidence of severe cardiac disease, e.g., New York Heart Association (NYHA) Functional Class III or IV, myocardial infarction within 6 months, ventricular tachyarrhythmias requiring ongoing treatment or unstable angina
 - History or evidence of peripheral vascular disease
 - Clinically significant impaired renal or hepatic function
 - Stroke (within 12 months of study entry)
 - Acute ocular or periocular infection
11. Previous therapeutic radiation to the eye, head, or neck.
12. Any treatment with an investigational agent in the past 60 days for any condition.
13. Known serious allergies to the fluorescein dye used in angiography (and indocyanine green if used) or to the components of the pegaptanib sodium formulation.

Primary Efficacy Variable

The primary efficacy endpoint was the proportion of patients losing <15 letters of VA from baseline to 54 weeks (responders).

Secondary Efficacy Endpoints:

- Proportion of patients gaining >15 letters of VA from baseline to 54 weeks
- Proportion of patients gaining >0 letter of VA from baseline to 54 weeks
- Mean change in VA from baseline to 6, 12 and 54 weeks

Other Planned Efficacy Endpoints:

- Change in VA from baseline, prior to every treatment from baseline to 54 weeks
- Proportion of patients with Snellen Equivalent equal to or worse than 20/200 in the study eye at baseline, 6 weeks, 12 weeks and 54 weeks post baseline
- Change in total lesion size in disc areas from baseline to 30 weeks and 54 weeks

- Change in total CNV size in disc areas from baseline to 30 weeks and 54 weeks
- Change in CNV leak size in disc areas from baseline to 30 weeks and 54 weeks
- Proportion of patients with progression in lesion subtype from baseline to 54 weeks (pure occult to minimally classic or predominantly classic, and minimally classic to predominantly classic)
- Proportion of patients receiving PDT at any time during the course of the study.

Safety Endpoints

- All AEs, whether deemed related to treatment or not
- All serious adverse events (SAEs), whether deemed related to treatment or not
- All laboratory abnormalities, whether deemed clinically relevant or not
- A loss of 20 letters of vision on the ETDRS chart between consecutive treatments

Safety assessments included documentation of local ocular events in the study eye such as diffuse retinal hemorrhage; acute cataract; increase in IOP; retinal detachment, acute retinal arterial or venous occlusions; and sterile or infectious endophthalmitis. If there was an adverse event relating to the fellow eye, it was captured on the AE page of the CRF.

Protocol Defined Analysis Populations

Safety Population: consisted of all patients who received at least one treatment, regardless of their eligibility for the study.

Intent-To-Treat Population: all randomized patients who received double-masked treatment and who had complete baseline vision assessments.

Per-Protocol Population: patients in the ITT population who did not experience any major violations of the protocol or of ophthalmic inclusion/exclusion criteria which could have had an impact on VA, for example cataract removal, were included in the per-protocol population. Additionally patients without post-baseline VA assessments were excluded.

All-randomized Population: Included all patients randomized to take part in the study, regardless of whether they received the study treatment or not.

Week 54 observed patient population: included patients from the ITT population who also had week 54 VA data (whether or not they were still receiving study treatment).

Note: The Intent-To-Treat population as defined in the protocol is not a “true” ITT population that is accepted by the Agency. The “true” ITT population is defined as all patients randomized to the study regardless of whether they received an study treatments. The primary efficacy results presented are based on the all-randomized patient population.

Study Flow Chart - Assessments and Timing – Study EOP1003

Week	BL	Randomization 1									Randomization 2							
	-1	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Treatment number		1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8
Informed consent	X																	
Medical history	X																	
Ophthalmic history	X																	
Pregnancy test	X																	
Randomization	X										X							
Pegaptanib sodium or sham injection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy																		
Refraction and VA (ETDRS)	B		S	S	S	S	B	S	S	S	B	S	S	S	B	S	S	S
Color fundus photographs ¹	B ²						B				B				B			
Fluorescein angiogram ¹	B ²						B				B				B			
ICG/OCT ³	B										B							
Safety																		
Physical examination ⁴	X																	
Adverse events / serious adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intraocular pressure ⁵	B	S ⁶	S ⁶	S ⁶	S ⁶	S ⁶	B ⁶	S ⁶	S ⁶	S ⁶	B ⁶	S ⁶	S ⁶	S ⁶	B ⁶	S ⁶	S ⁶	S ⁶
Ophthalmic examination	B	S ⁶	S ⁶	S ⁶	S ⁶	S ⁶	B ⁶	S ⁶	S ⁶	S ⁶	B ⁶	S ⁶	S ⁶	S ⁶	B ⁶	S ⁶	S ⁶	S ⁶
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X		X	X	X	X	X	X	X	X	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸
ECG	X																	
Telephone safety check ⁷		X	X	X	X	X	X	X	X	X	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸

B = Assessment on both eyes

BL = Baseline, performed within 7 days of first treatment

S = Assessment on study eye only

EW = Early withdrawal (prior to Week 102)

¹ Sent to Independent Reading Center (IRC) for efficacy and safety assessments

² Reviewed by Eligibility and Classification Quality Assurance Team (ECQAT) for eligibility and randomization stratification

³ Some selected sites performed optional indocyanine green angiograms (ICG) or optical coherence tomography (OCT), but no analyses of data were performed

⁴ Physical examination performed post baseline only if indicated

⁵ Applanation tonometry at baseline and for confirmation of IOP>30 mmHg

⁶ Before treatment, at least 30 minutes after treatment and 1 week after treatment

⁷ Telephone safety check carried out 3 days post treatment

⁸ Treated (active or sham) patients only

Subject Disposition and Demographics – Study EOP1003

Treatment	Patients Randomized and Treated (N=612)	Patients Discontinued (n=53)
0.3 mg	151	11
1 mg	155	13
3 mg	153	17
Sham	153	12

Discontinued Patients and Reason – Study EOP1003

Patient	Treatment	Reason	Study day
064-012	Sham	Died	342
064-019	Sham	Patient request/frustrated with vision	376
084-010	Sham	Patient request/requested other treatment options	68
085-007	Sham	Patient request/pain on injection	332
087-014	Sham	Worsening macular hemorrhage	391
089-016	Sham	Personal/economic problems -noncompliant with visits	428
093-018	Sham	Osteoarticular pain	355
102-009	Sham	Patient request/refused further injections	294
098-002	Sham	Died	35
130-013	Sham	Died	273
145-018	Sham	Died	350
154-026	Sham	Adverse event/colon cancer	137
075-005	0.3 mg	Patient request/pain on injection	130
081-005	0.3 mg	Patient request/refused further injections	378
087-010	0.3 mg	Patient request/palpitations prior to injection	57
089-019	0.3 mg	Endophthalmitis	385
100-002	0.3 mg	Investigator decision/Transient ischemic attack	39
108-007	0.3 mg	Died	312
123-002	0.3 mg	Protocol deviation/noncompliant with visits	404
123-010	0.3 mg	Patient request/cannot attend follow-up visits	248
136-011	0.3 mg	Died	130
154-001	0.3 mg	Patient request/refused further injections	35
154-017	0.3 mg	Patient request/poor health-unable to make visits	213
064-014	1 mg	Patient request/frustrated with vision	377
065-010	1 mg	Patient request/frustrated with vision	217
070-001	1 mg	Patient request/refused further injections	376
073-008	1 mg	Patient request/visit schedule too rigorous	27
073-014	1 mg	Patient request/developed cataract 2° to injection/had surgery	344
075-028	1 mg	Pulmonary embolism	260
083-002	1 mg	Poor health/pneumonia	137
084-009	1 mg	Patient request/refused further injections	76
101-010	1 mg	Adverse event/shortness of breath-suspected pulmonary embolism	252
102-026	1 mg	Adverse event/ refused further injections(watery eyes)	90

Patient	Treatment	Reason	Study day
104-001	1 mg	Panuveitis	217
130-001	1 mg	Died	358
136-005	1 mg	Died	281
075-006	3 mg	Patient request/travel problems	453
082-006	3 mg	Cerebrovascular accident	271
085-001	3 mg	Died	202
089-015	3 mg	Metastatic lung cancer	248
089-018	3 mg	Patient request/no improvement in vision	419
092-012	3 mg	Angina pectoris	294
093-028	3 mg	Investigator/sponsor decision-worsening AMD	214
095-003	3 mg	Adverse event/worsening general condition	475
104-011	3 mg	Died	195
108-004	3 mg	Patient request/refused further injections	169
113-015	3 mg	Patient request/refused further participation	134
119-012	3 mg	Died	341
122-002	3 mg	Adverse event/lung cancer	260
123-005	3 mg	Patient request/refused further treatment	440
147-003	3 mg	Investigator/sponsor decision/abnormal EKG	48
155-004	3 mg	Patient request/spouse died	135

Demographics – Safety Population – Study EOP1003

		0.3 mg (N=151)	1 mg (N=155)	3 mg (N=153)	Sham (N=153)
Gender					
Male		69 (46%)	68 (44%)	60 (39%)	57 (37%)
Female		82 (54%)	87 (56%)	93 (61%)	96 (63%)
Race					
White		143 (95%)	148 (95%)	145 (95%)	144 (94%)
Asian		0	1 (1%)	1 (1%)	1 (1%)
Black		0	1 (1%)	0	1 (1%)
Hispanic		7 (5%)	5 (3%)	7 (5%)	5 (3%)
Other		1 (1%)	0	0	2 (1%)
Age					
Mean		74.9	74.5	75.4	74.9
Range		53-90	53-90	53-89	52-92
Smoking status					
Yes		24 (16%)	15 (10%)	15 (10%)	14 (9%)
% Classic AMD	= 50%	35 (23%)	40 (26%)	39 (25%)	39 (25%)
	1% - 49%	60 (40%)	57 (37%)	55 (36%)	52 (34%)
	0%	56 (37%)	58 (37%)	59 (39%)	62 (41%)
Prior PDT with verteporfin		6 (4%)	10 (6%)	6 (4%)	4 (3%)
ETDRS Vision					
Mean		53	50.9	50.1	51.3
Range		11-75	22-77	22-76	21-75

Efficacy Analysis

The primary efficacy results are presented below. The statistically significant findings are highlighted in the table. Statistical significance was determined by the protocol defined Hochberg procedure to correct for multiple dose comparisons. The bolded entries indicate a trend for efficacy although formal statistical testing was not performed.

Primary Efficacy Results – All Randomized Patients LOCF – Study 1003

Number of Patients (%)		0.3 mg N= 153	1 mg N= 158	3 mg N= 155	Sham N= 156
Responders ¹	Month 3	134 (87.6%)	146 (92.4%)	136 (87.7%)	130 (83.3%)
	Month 6	127 (83%)	137 (86.7%)	128 (82.6%)	112 (71.8%)
	Month 9	117 (76.5%)	126 (79.8%)	125 (80.7%)	105 (67.3%)
	Month 12	112 (73.2%) p=0.01	119 (75.3%) p=0.002	108 (69.7%) p=0.06	93 (59.6%)

¹ Patients who lost < 15 letters of vision. Note: Patients who lost < 15 letters of vision from baseline to 54 weeks is the primary efficacy endpoint

Primary Efficacy Results – PP population observed cases only– Study 1003

Number of Patients (%)		0.3 mg	1 mg	3 mg	Sham
Responders ¹	Month 3	122 (87.8%) N=139	131 (92.9%) N= 141	122 (86.5%) N= 141	120 (82.8%) N= 145
	Month 6	110 (85.3%) N= 129	125 (86.8%) N= 144	116 (82.3%) N= 141	101 (69.7%) N= 145
	Month 9	103 (78.3%) N= 131	115 (78.9%) N= 144	110 (79.1%) N= 139	93 (66%) N= 141
	Month 12	98 (73.7%) p=0.01 N= 133	105 (75.5%) 0.005 N= 139	90 (66.7%) p=0.26 N= 135	82 (58.6%) N= 140

¹ Patients who lost < 15 letters of vision. Note: Patients who lost < 15 letters of vision from baseline to 54 weeks is the primary efficacy endpoint

² 3 mg dose was omitted from statistical analysis prior to unmasking data

Primary Efficacy Results – Sensitivity Analyses – Study 1003

Worst Case Analysis*	N=153	N=158	N=155	N=156
Responders ¹	104 (68%)	109 (69%)	93 (60%)	96 (61.5%)
p-value	0.15	0.11	-	-
Week 54 Observed population	N=139	N=144	N=139	N=142
Responders ¹	103 (74%)	109 (76%)	93 (67%)	82 (58%)
p-value	0.005	0.003	-	-
¹ Patients who lost < 15 letters of vision from baseline to 54 weeks – primary efficacy endpoint				
² 3 mg dose was omitted from statistical analysis prior to unmasking data				

* In the worst case analysis, all patients in the sham group with missing VA measurements are assumed to be Responders and all patients in the pegaptanib group with missing VA measurements are assumed to be Non-Responders.

Number of Patients Receiving On-Study PDT Treatment in the Study Eye – ITT Population – Study EOP1003

Number of patients		0.3 mg N=150	1 mg N=154	3 mg N=153	Sham N=152
All patients					
PDT treatment	Yes	17 (11%)	19 (12%)	20 (13%)	19 (13%)
Predominantly Classic CNV		n=35	n=39	n=39	n=39
PDT Treatment	Yes	14 (40%)	15 (38%)	16 (41%)	13 (33%)
Minimally Classic CNV		n=59	n=57	n=55	n=52
PDT Treatment	Yes	2 (3%)	3 (5%)	3 (5%)	5 (10%)
Occult CNV		n=56	n=58	n=59	n=61
PDT Treatment	Yes	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Pairwise Comparison		0.3 mg vs. sham	1 mg vs. sham	3 mg vs. sham	
		p=0.68	p=1.0	p=0.92	

Number of On-Study PDT Treatments Received in The Study Eye – ITT population – Study EOP1003

Number of patients	0.3 mg N=150	1 mg N=154	3 mg N=153	Sham N=152
Total number of PDT treatments	n=28	n=36	n=41	n=32
Predominantly classic CNV	23 (82%)	30 (83%)	35 (85%)	20 (63%)
Minimally classic CNV	3 (11%)	4 (11%)	5 (12%)	10 (31%)
Occult CNV	2 (7%)	2 (6%)	1 (2%)	2 (6%)

Responder Analysis for PDT Treatment Interaction– Study 1003

Number of Patients (%) who never received PDT before or during the study		0.3 mg N= 131	1 mg N= 132	3 mg N= 127	Sham N= 127
Responders ¹	Month 3	116 (88.6%)	123 (93.2%)	114 (89.8%)	106 (83.5%)
	Month 6	110 (84%)	117 (88.6%)	109 (85.8%)	92 (72.4%)
	Month 9	102 (78%)	109 (82.6%)	105 (82.7%)	85 (67%)
	Month 12	97 (74%)	103 (78%)	92 (72.4%)	78 (61.4%)

¹Patients who lost < 15 letters of vision.

Number of Patients (%) who only received PDT before the study		0.3 mg N= 2	1 mg N= 5	3 mg N= 6	Sham N= 4
Responders ¹	Month 3	1 (50%)	5 (100%)	6 (100%)	3 (75%)
	Month 6	2 (100%)	5 (100%)	4 (66.7%)	3 (75%)
	Month 9	2 (100%)	5 (100%)	5 (83.3%)	3 (75%)
	Month 12	2 (100%)	3 (60%)	5 (83.3%)	3 (75%)

¹Patients who lost < 15 letters of vision.

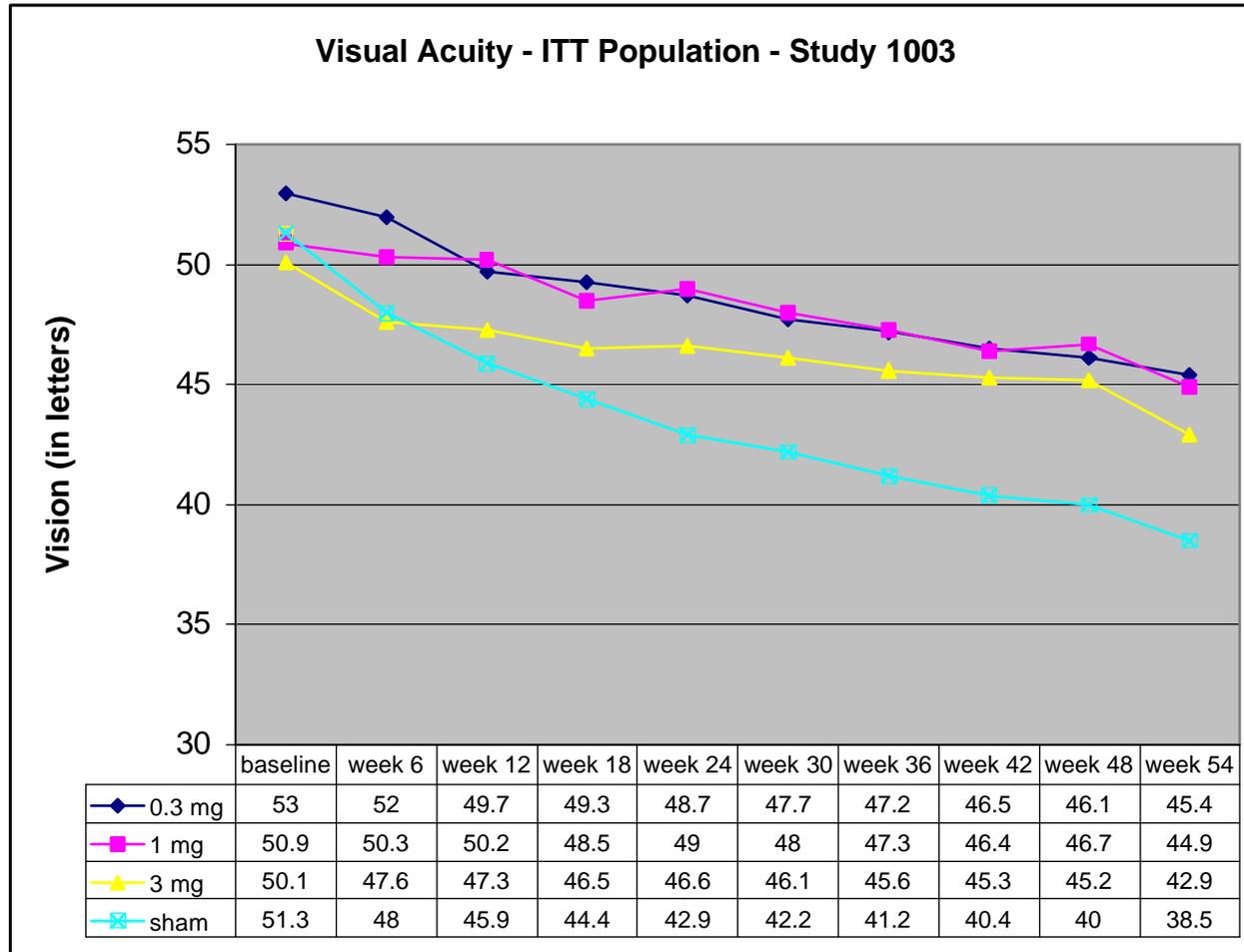
Number of Patients (%) who only received PDT during the study		0.3 mg N= 16	1 mg N= 17	3 mg N= 20	Sham N= 25
Responders ¹	Month 3	13 (81.3%)	15 (88.2%)	14 (70%)	21 (84%)
	Month 6	12 (75%)	11 (64.7%)	13 (65%)	17 (68%)
	Month 9	9 (56.3%)	8 (47%)	13 (65%)	17 (68%)
	Month 12	9 (56.3%)	9 (53%)	10 (50%)	12 (48%)

¹Patients who lost < 15 letters of vision.

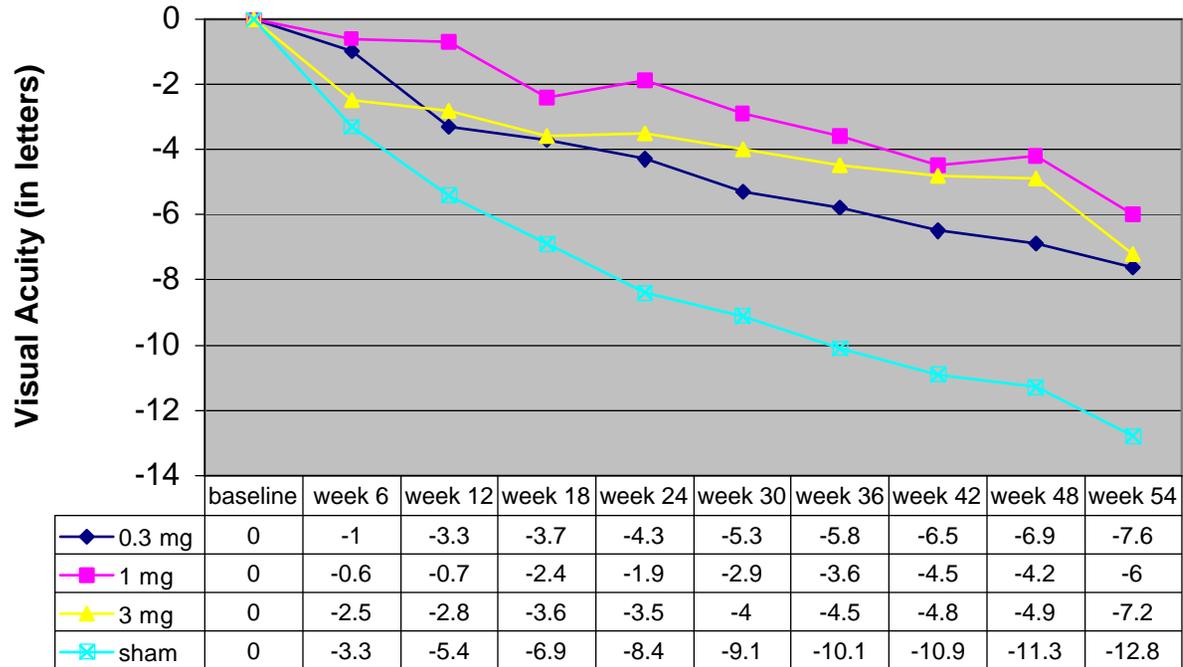
Number of Patients (%) who received PDT before and during the study		0.3 mg N= 4	1 mg N= 4	3 mg N= 2	Sham N= 0
Responders ¹	Month 3	4 (100%)	3 (75%)	2 (100%)	0
	Month 6	3 (75%)	4 (100%)	2 (100%)	0
	Month 9	4 (100%)	4 (100%)	2 (100%)	0
	Month 12	4 (100%)	4 (100%)	1 (50%)	0

¹Patients who lost < 15 letters of vision.

Additional Efficacy Analyses



Change in Visual Acuity - ITT Population - Study 1003



Mean Total Lesion Size, CNV Size and Leak Size – Study 1003

	0.3 mg n=150	1 mg n=154	3 mg n=153	Sham N=152
Total Lesion size¹				
Baseline	3.9	3.7	3.7	4.0
Week 30	4.9	4.7	5.1	5.5
Week 54	5.6	5.6	6.0	6.4
Total CNV Size¹				
Baseline	3.1	3.2	3.2	3.5
Week 30	3.9	3.9	4.3	4.8
Week 54	4.7	4.6	5.0	5.7
Total Leak Size¹				
Baseline	3.4	3.3	3.3	3.5
Week 30	4.1	3.4	4.2	4.9
Week 54	4.5	3.9	4.4	5.1

¹ size given in DA (disc area)

Vision Gain – Study EOP1003

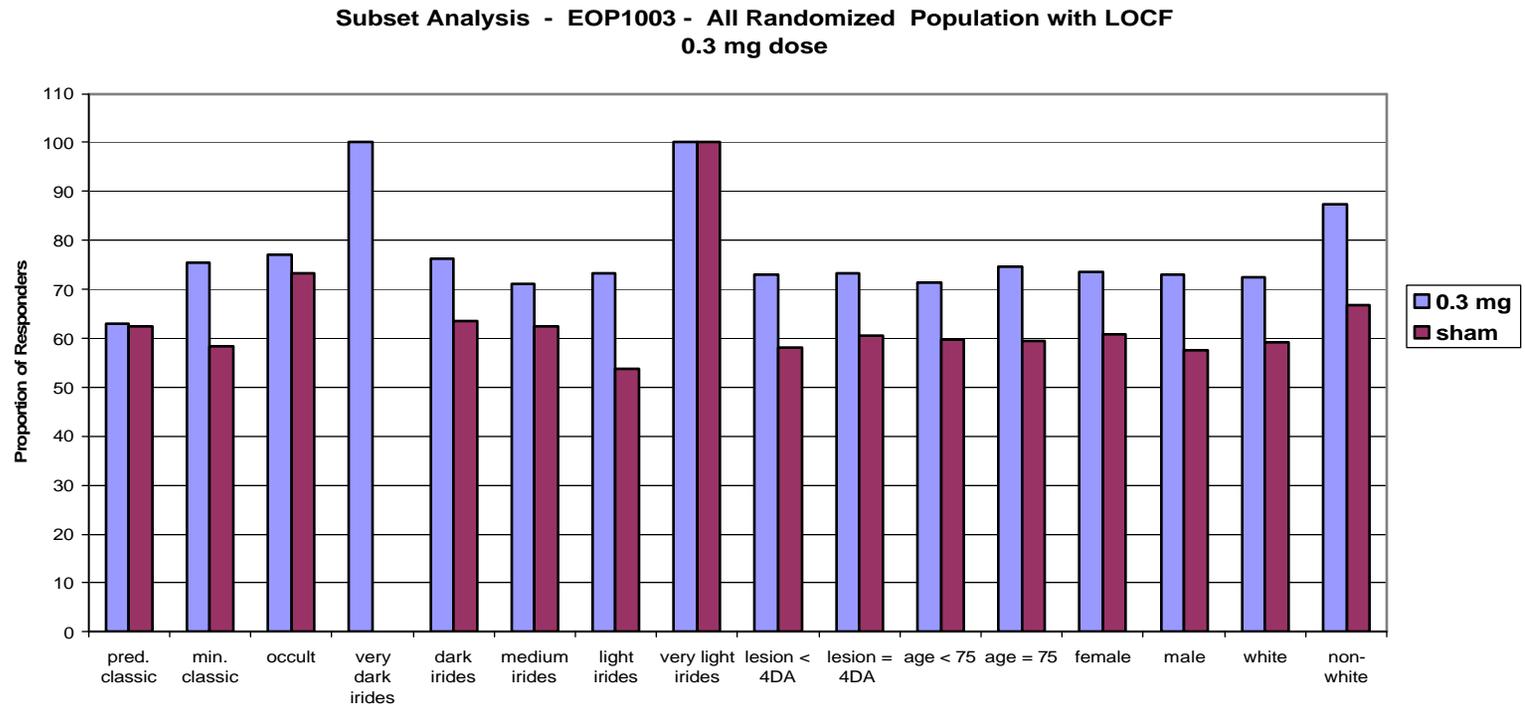
		0.3 mg n=150	1 mg n=154	3 mg n=153	Sham N=152
Number of Patients (%)					
Vision gain = 15 letters ¹	Yes	6 (4%)	10 (6%)	7 (5%)	5 (3%)
	p-value	0.93	0.49	- ³	-
Vision gain = 0 letters ²	Yes	49 (33%)	59 (38%)	60 (39%)	42 (28%)
	p-value	0.38	0.08	- ³	-

¹ patients who gained = 15 letters of vision from baseline to 54 weeks

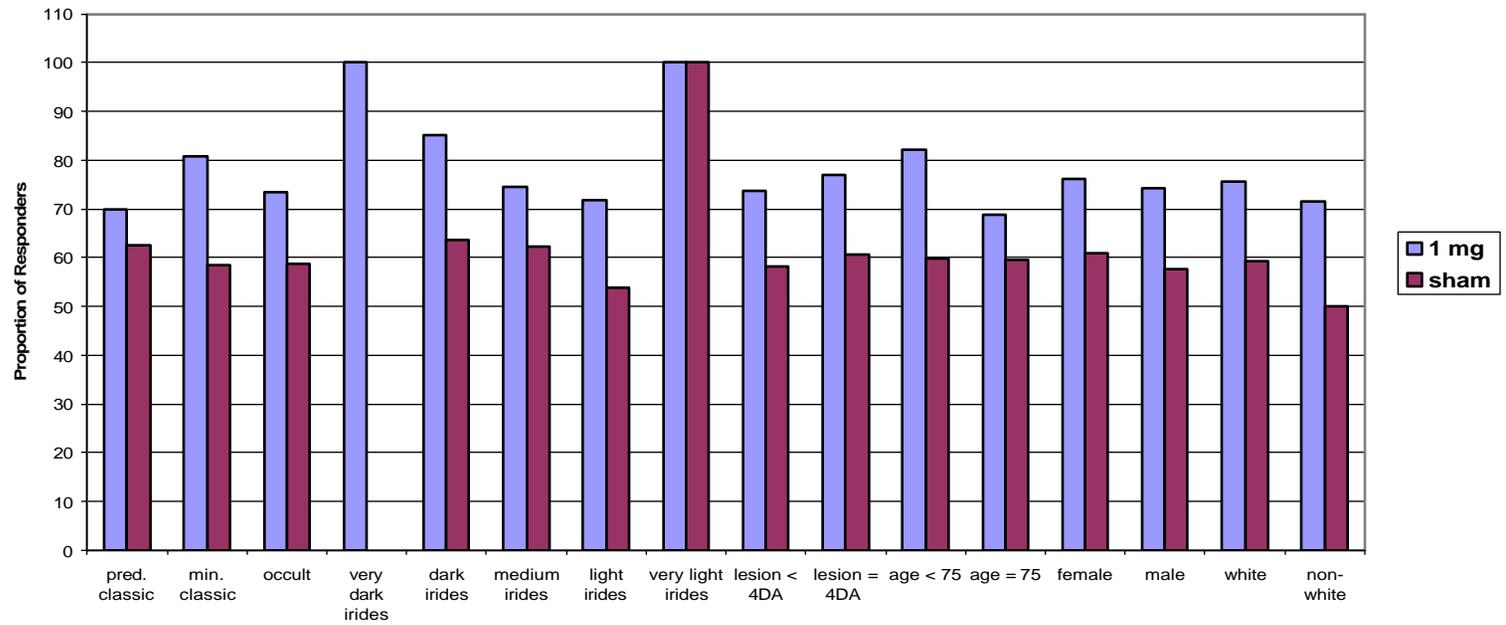
² patients who gained = 0 letters of vision from baseline to 54 weeks

³ 3 mg dose was omitted from statistical analyses prior to unmasking data

Responder analyses based on baseline characteristics for study EOP1003



**Subset Analysis - EOP1003 - All Randomized Population with LOCF
1 mg dose**



Study 2 – Study EOP1004

Title: Same as Study EOP1003

Objective: Same as Study EOP1003

Study Design: Same as Study EOP1003. This study was conducted in North America.

Clinical sites – Study EOP1004

Center Number	Principal Investigator	Center Location	Number of Patients
01	Julia Haller, MD	Baltimore, MD	4
02	Michael Klein, MD	Portland, OR	6
03	Daniel F. Martin, MD	Atlanta, GA	-
04	Gary Fish, MD	Dallas TX	6
05	Allen Ho, MD	Philadelphia, PA	11
06	Scott D. Pendergast, MD	Lakewood, OH	33
07	Christine Gonzales, MD	Los Angeles, CA	30
08	Antonia Capone, MD	Royal Oak, MI	23
09	Jorge Arroyo, MD	Boston, MA	8
10	Steve Sanislo, MD	Menlo Park, CA	9
12	Richard Rosen, MD	New York, NY	6
13	Dean Eliot, MD	Detroit, MI	1
14	Jean Daniel Arbour, MD	Montreal, Quebec	-
15	Robert Avery, MD	Santa Barbara, CA	3
17	Paul Bernstein, MD	Salt Lake City, UT	7
18	Francis Cangemi, MD	Belleville, NJ	6
19	David Boyer, MD	Beverly Hills, CA	22
20	Sandy Brucker, MD	Philadelphia, PA	12
21	Herbert Cantrill, MD	Minneapolis, MN	20
22	Gaetano Barille, MD	New York, NY	-
23	Steven Charles, MD	Memphis, TN	5
24	Thomas A. Ciuilla, MD	Indianapolis, IN	-
25	Thomas Connor, MD	Milwaukee, WI	8
26	Brian P. Conway, MD	Charlottesville, VA	13
27	Alan F. Cruess, MD	Kingston, ON	-
28	John a. Wells, III, MD	Columbia, SC	15
29	Thomas Friberg, MD	Pittsburgh, PA	10
30	Richard Garfinkel, MD	Chevy Chase, MD	10
31	Bert Glaser, MD	Chevy Chase, MD	1
32	W. Sanderson Grizzard, MD	Tampa, FL	14
33	Barry Taney, MD	Fort Lauderdale, FL	8
34	Howard Cummings, MD	Knoxville, TN	17
35	Henry Hudson, MD	Tucson, AZ	25
36	Sharon Fekrat, MD	Durham, NC	14
37	Mark W. Johnson, MD	Ann Arbor, MI	2
38	Baruch Kuppermann, MD	Irvine, CA	1
40	Hilel Lewis, MD	Cleveland, OH	9
41	Jennifer Lim, MD	Los Angeles, CA	7

Center Number	Principal Investigator	Center Location	Number of Patients
43	Naresh Mandava, MD	Aurora, CO	4
44	H. Richard McDonald, MD	San Francisco, CA	12
45	William Mieler, MD	Houston TX	3
46	Mohit Nanda, MD	Santa Ana, CA	7
47	Robert Leonard, MD	Oklahoma City, OK	8
48	Elias Reichel, MD	Boston, MA	13
49	Philip Rosenfeld, MD	Miami, FL	9
50	Ronald Wilson, MD	New Orleans, LA	18
51	Nelson Sabates, MD	Kansas City, MO	12
52	Vincent Deramo, MD	Great Neck, NY	8
53	M. Madison Slusher, MD	Winston-Salem, NC	7
54	Scott Sneed, MD	Phoenix, AZ	14
55	Glen Stoller, MD	Rockville Center, NY	8
56	Paul Tornambe, MD	Poway, CA	3
57	Michael Varenhorst, MD	Wichita, KS	13
58	Lloyd Wilcox, MD	Concord, NH	1
60	Marco Zarbin, MD	Newark, NJ	-
61	Patricia Harvey, MD	Toronto, ON	-
62	David Tom, MD	Hamden, CT	15
110	Alice T. Lyon, MD	Chicago, IL	3
115	David J. Weissgold, MD	Burlington, CT	8
140	Dennis Marcus, MD	Augusta, GA	2
141	John Wroblewski, MD	Hagerstown, MD	15
142	Leonard Joffe, MD	Tucson, AZ	5
39	Brian Leonard, MD	Ottawa, ON	6
42	David Maberley, MD	Vancouver, BC	12
59	Geoff Williams, MD	Calgary, AB	5

Inclusion/Exclusion Criteria – Same as Study EOP1003

Safety and Efficacy Endpoints – Same as Study EOP1003

Study Schedule – Same as Study EOP1003. In addition, plasma samples for nested pharmacokinetic (PK) study were conducted at week 6 and week 18.

Subject Disposition and Demographics

Treatment	Patients Randomized and Treated (N=578)	Patients Discontinued (n=60)
0.3 mg	144	12
1 mg	146	17
3 mg	143	20
Sham	145	11

Discontinued Patients and Reason – Study EOP1004

Patient	Treatment	Reason	Study Day
004-007	Sham	Patient request/did not feel study was helping	84
012-001	Sham	Patient request/felt injections were making eyes worse	126
017-001	Sham	Patient request/refused further injection	378
019-004	Sham	Patient request/vision loss	173
021-012	Sham	Patient died	335
023-001	Sham	Investigator decision/no injection for 12 weeks	241
028-021	Sham	Patient request/vision loss	276
035-021	Sham	Adverse event/acute congestive heart failure	128
040-003	Sham	Patient died	328
049-013	Sham	Patient request/withdrew consent	238
052-007	Sham	Patient request/progressive loss of vision	133
007-033	0.3 mg	Investigator decision/pt too fragile s/p hip replacement surgery	231
009-005	0.3 mg	Patient request/felt vision was getting worse	148
017-008	0.3 mg	Patient request/transportation issues	378
019-026	0.3 mg	Patient request/recovery time too long	205
021-010	0.3 mg	Patient died	231
032-002	0.3 mg	Patient request/withdrew consent	126
034-013	0.3 mg	Lost to follow-up	85
041-003	0.3 mg	Patient request/did not what to continue	288
042-001	0.3 mg	Adverse event/endophthalmitis	63
048-002	0.3 mg	Patient died	185
050-012	0.3 mg	Patient died	140
055-017	0.3 mg	Adverse event/subretinal hemorrhage, retinal detachment	95
007-015	1 mg	Lost to follow-up	217
008-018	1 mg	Patient died	228
015-002	1 mg	Patient died	301
019-009	1 mg	Patient request/no longer wants to participate	465
019-033	1 mg	Move to nursing home	306
020-007	1 mg	Patient request/withdrew consent	358
033-006	1 mg	Patient died	62
036-017	1 mg	Unable to return for visits	343
041-001	1 mg	Patient died	187
043-001	1 mg	Adverse event/subretinal & vitreous hemorrhage	452
050-009	1 mg	Patient request/does not want tx from new PI	260
050-021	1 mg	Patient died	323
055-014	1 mg	Lost to follow-up	205
057-004	1 mg	Patient request/poor health	299
059-006	1 mg	Patient died	101
062-006	1 mg	Patient request/withdrew consent	165
062-009	1 mg	Patient request/anxiety	126
006-002	3 mg	Patient request/withdrew consent	377
006-010	3 mg	Patient died	372
015-003	3 mg	Patient request/moving to another state	130

Patient	Treatment	Reason	Study Day
017-006	3 mg	Patient request/not able to follow-up	377
017-007	3 mg	Investigator decision/poor clinical response	383
019-007	3 mg	Alzheimer's – unable to follow protocol	378
021-005	3 mg	Patient request/study not helping vision	166
026-003	3 mg	Patient died	256
030-001	3 mg	Investigator decision/missed injection due to retinal detachment	210
030-009	3 mg	Patient request/withdrew consent	393
033-009	3 mg	Patient request/withdrew consent	401
034-011	3 mg	Patient died	116
042-009	3 mg	Patient request/withdrew consent	378
046-008	3 mg	Patient request/family illness	356
050-004	3 mg	Patient request/move out of state	378
050-013	3 mg	Patient request/ does not want tx from new PI	251
052-006	3 mg	Adverse event/myocardial infarction, cerebral hemorrhage	36
052-011	3 mg	Patient request/failure to respond to treatment	308
053-006	3 mg	Patient request/general health reasons	127
062-010	3 mg	Adverse event/retinal detachment	300

Demographics – Safety Population – Study EOP1004

		0.3 mg (N=144)	1 mg (N=146)	3 mg (N=143)	Sham (N=145)
Gender					
Male		64 (44%)	68 (47%)	45 (31%)	63 (43%)
Female		80 (56%)	78 (53%)	98 (69%)	82 (57%)
Race					
White		140 (97%)	143 (98%)	141 (99%)	140 (97%)
Asian		2 (1%)	0	0	0
Black		0	0	0	0
Hispanic		2 (1%)	2 (1%)	2 (1%)	4 (3%)
Other		0	1 (1%)	0	1 (1%)
Age					
Mean		78	76.5	77.1	76.7
Range		58-92	52-92	56-97	55-89
Smoking status					
Yes		14 (10%)	15 (10%)	15 (10%)	15 (10%)
% Classic AMD	= 50%	37 (26%)	38 (26%)	41 (29%)	37 (26%)
	1% -49%	51 (35%)	51 (35%)	50 (35%)	50 (34%)
	0%	56 (39%)	57 (39%)	52 (36%)	58 (40%)
Prior PDT with verteporfin		18 (13%)	20 (14%)	20 (14%)	16 (11%)
ETDRS Vision					
Mean		52.5	50.5	52.1	54
Range		23-74	19-73	14-73	27-74

Efficacy Analysis

The primary efficacy results are presented below. The statistically significant findings are highlighted in the table. Statistical significance was determined by the protocol defined Hochberg multiple comparison procedure to correct for multiple dose comparisons. The bolded entries indicate a trend for efficacy although formal statistical testing was not performed.

Primary Efficacy Results – All Randomized Patients LOCF – Study 1004

Number of Patients (%)		0.3 mg N= 144	1 mg N= 147	3 mg N= 147	Sham N= 148
Responders ¹	Month 3	125 (86.8%)	118 (80.3%)	121 (82.3%)	115 (77.7%)
	Month 6	118 (81.9%)	106 (72.1%)	102 (69.4%)	85 (57.4%)
	Month 9	106 (73.6%)	108 (73.5%)	103 (70.1%)	78 (52.7%)
	Month 12	97 (67.4%) p=0.016	98 (66.7%) 0.032	91 (61.9%) 0.13	79 (53.4%)

¹ Patients who lost < 15 letters of vision. Note: Patients who lost < 15 letters of vision from baseline to 54 weeks is the primary efficacy endpoint

Primary Efficacy Results – PP population observed cases only– Study 1004

Number of Patients (%)		0.3 mg	1 mg	3 mg	Sham
Responders ¹	Month 3	122 (87.4%) N=140	114 (81.4%) N=140	110 (81.5%) N=135	104 (77%) N=135
	Month 6	112 (82.4%) N=136	96 (72.2%) N=133	91 (67.4%) N=135	77 (58.8%) N=131
	Month 9	94 (74.6%) N=126	94 (75.2%) N= 125	90 (70.9%) N=127	70 (53.4%) N=131
	Month 12	89 (67.9%) p=0.008 N=131	85 (66.9%) p=0.06 N=127	70 (57.4%) p=0.59 N=122	69 (53.9%) N=128

¹ Patients who lost < 15 letters of vision. Note: Patients who lost < 15 letters of vision from baseline to 54 weeks is the primary efficacy endpoint

Primary Efficacy Results – Sensitivity Analyses – Study 1004

Worst Case Analysis	N=144	N=147	N=147	N=148
Responders ¹	89 (61.8%)	89 (60.5%)	73 (49.7%)	87 (58.8%)
p-value	0.27	0.76	0.36	-
Week 54 Observed population	N=132	N=131	N=125	N=133
Responders ¹	89 (67%)	89 (68%)	73 (58%)	72 (54%)
p-value	0.01	0.032	0.5	-

¹ Patients who lost < 15 letters of vision from baseline to 54 weeks – primary efficacy endpoint

Number of Patients Receiving On-Study PDT Treatment in the Study Eye – ITT Population – Study EOP1004

Number of patients		0.3 mg N=144	1 mg N=146	3 mg N=143	Sham N=144
All patients					
PDT treatment	Yes	32 (22%)	36 (25%)	37 (26%)	43 (30%)
Predominantly Classic CNV		n=37	n=38	n=41	n=37
PDT Treatment	Yes	24 (65%)	23 (61%)	24 (59%)	25 (68%)
Minimally Classic CNV		n=51	n=51	n=50	n=49
PDT Treatment	Yes	5 (10%)	12 (24%)	8 (16%)	13 (27%)
Occult CNV		n=144	n=146	n=143	n=144
PDT Treatment	Yes	3 (5%)	1 (2%)	5 (10%)	5 (9%)
Pairwise Comparison		0.3 mg vs. sham	1 mg vs. sham	3 mg vs. sham	
		p=0.05	p=0.22	p=0.26	

Number of On-Study PDT Treatments Received in The Study Eye – ITT population – Study EOP1004

Number of patients	0.3 mg N=144	1 mg N=146	3 mg N=143	Sham N=144
Total number of PDT treatments	n=56	n=72	n=73	n=94
Predominantly classic CNV	42 (75%)	45 (63%)	48 (66%)	59 (63%)
Minimally classic CNV	10 (18%)	26 (36%)	18 (25%)	27 (29%)
Occult CNV	4 (7%)	1 (1%)	7 (10%)	8 (9%)

Responder Analysis for PDT Treatment Interaction– Study 1004

Number of Patients (%) who never received PDT before or during the study		0.3 mg N= 101	1 mg N= 99	3 mg N= 99	Sham N= 93
Responders ¹	Month 3	87 (86.1%)	83 (83.8%)	86 (86.9%)	74 (79.6%)
	Month 6	80 (79.2%)	77 (77.8%)	70 (70.7%)	57 (61.3%)
	Month 9	74 (73.2%)	75 (75.8%)	72 (72.7%)	52 (55.9%)
	Month 12	65 (64.4%)	70 (70.7%)	65 (65.7%)	54 (58%)

¹Patients who lost < 15 letters of vision.

Number of Patients (%) who only received PDT before the study		0.3 mg N= 5	1 mg N= 8	3 mg N= 5	Sham N= 4
Responders ¹	Month 3	4 (80%)	5 (62.5%)	5 (100%)	3 (75%)
	Month 6	4 (80%)	2 (25%)	5 (100%)	3 (75%)
	Month 9	3 (60%)	5 (62.5%)	3 (60%)	2 (50%)
	Month 12	4 (80%)	3 (37.5%)	3 (60%)	2 (50%)

¹Patients who lost < 15 letters of vision.

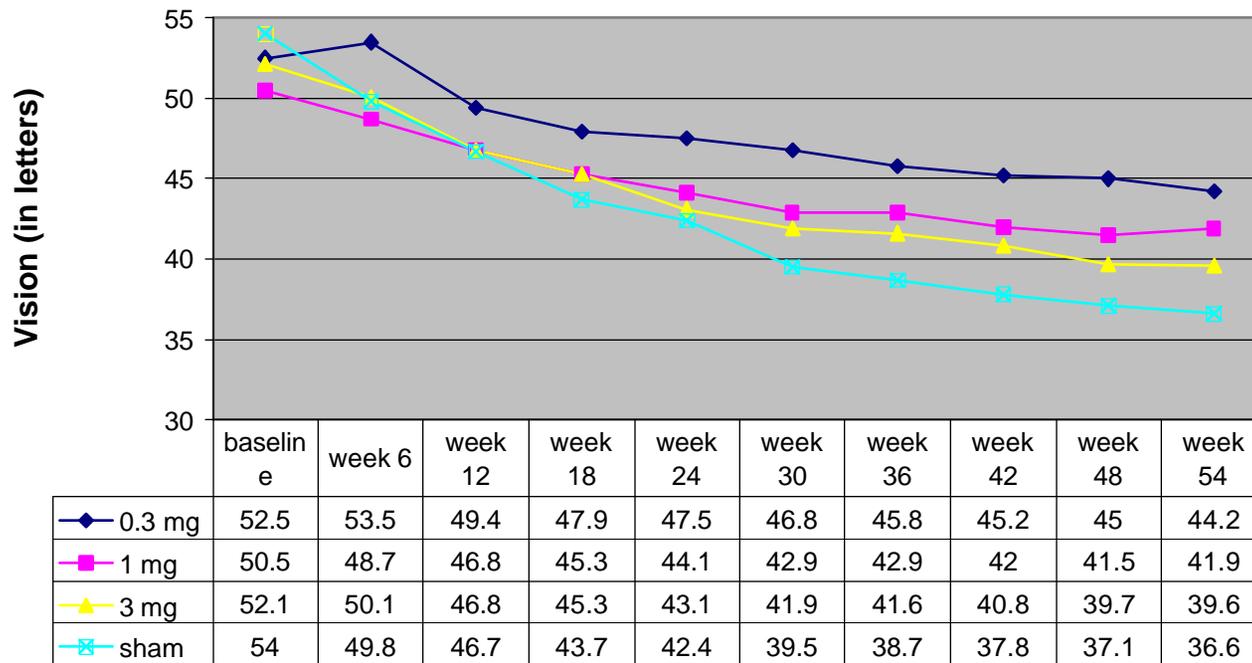
Number of Patients (%) who only received PDT during the study		0.3 mg N= 25	1 mg N= 28	3 mg N= 29	Sham N= 39
Responders ¹	Month 3	22 (88%)	21 (75%)	20 (69%)	30 (77%)
	Month 6	22 (88%)	18 (64%)	16 (57.2%)	19 (48.7%)
	Month 9	18 (72%)	17 (60.7%)	15 (51.7%)	18 (46.2%)
	Month 12	18 (72%)	16 (57.1%)	15 (51.7%)	18 (46.2%)

¹Patients who lost < 15 letters of vision.

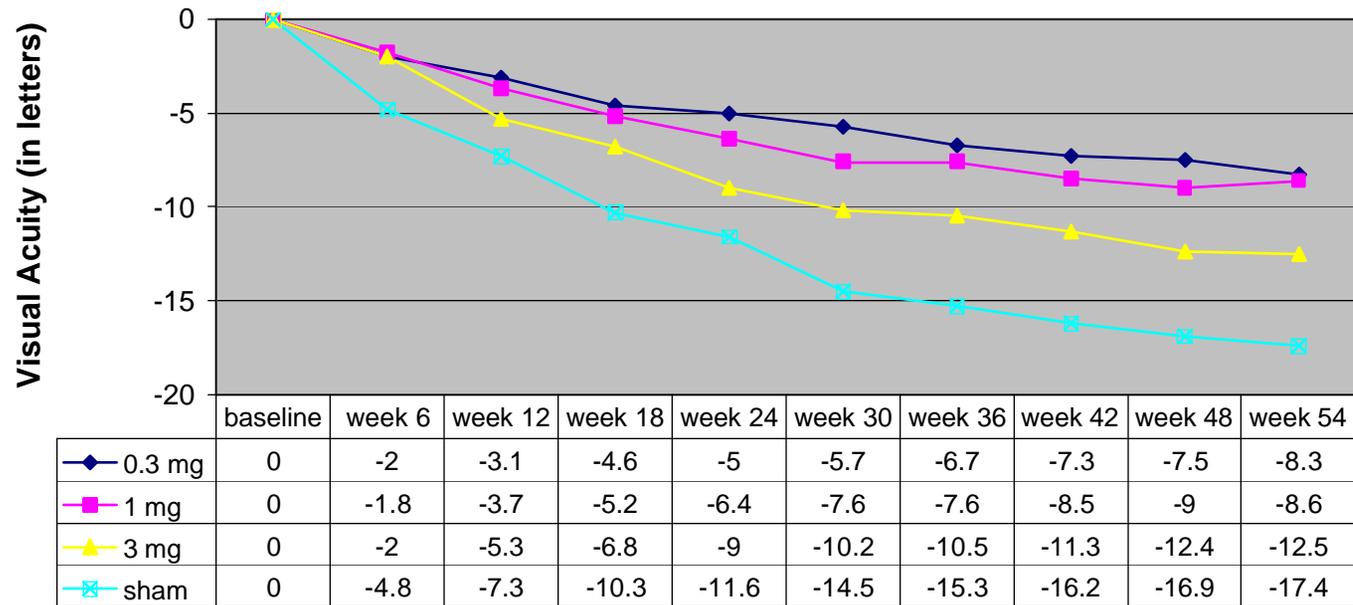
Number of Patients (%) who received PDT before and during the study		0.3 mg N= 13	1 mg N= 12	3 mg N= 14	Sham N= 12
Responders ¹	Month 3	12 (92.3%)	9 (75%)	10 (71.4%)	8 (66.7%)
	Month 6	12 (92.3%)	9 (75%)	11 (78.6%)	6 (50%)
	Month 9	11 (84.6%)	11 (91.7%)	13 (93%)	6 (50%)
	Month 12	10 (76.9%)	9 (75%)	8 (57.1%)	5 (41.7%)

¹Patients who lost < 15 letters of vision.

Visual Acuity - ITT Population - Study EOP1004



Change in Visual Acuity - ITT Population - Study 1004



Mean Total Lesion Size, CNV Size and Leak Size – Study 1004

	0.3 mg n=144	1 mg n=146	3 mg n=143	Sham N=144
Total Lesion size¹				
Baseline	3.6	4.4	3.6	4.4
Week 30	5	5.4	5.3	5.8
Week 54	5.5	6	6.3	7
Total CNV Size¹				
Baseline	3.1	3.8	3.2	3.9
Week 30	4	4.5	4.2	5
Week 54	4.7	5	5	5.8
Total Leak Size¹				
Baseline	3.2	3.6	3.5	3.7
Week 30	3.8	3.9	4.2	4.9
Week 54	4.1	4	4.9	5.2
¹ size given in DA (disc area)				

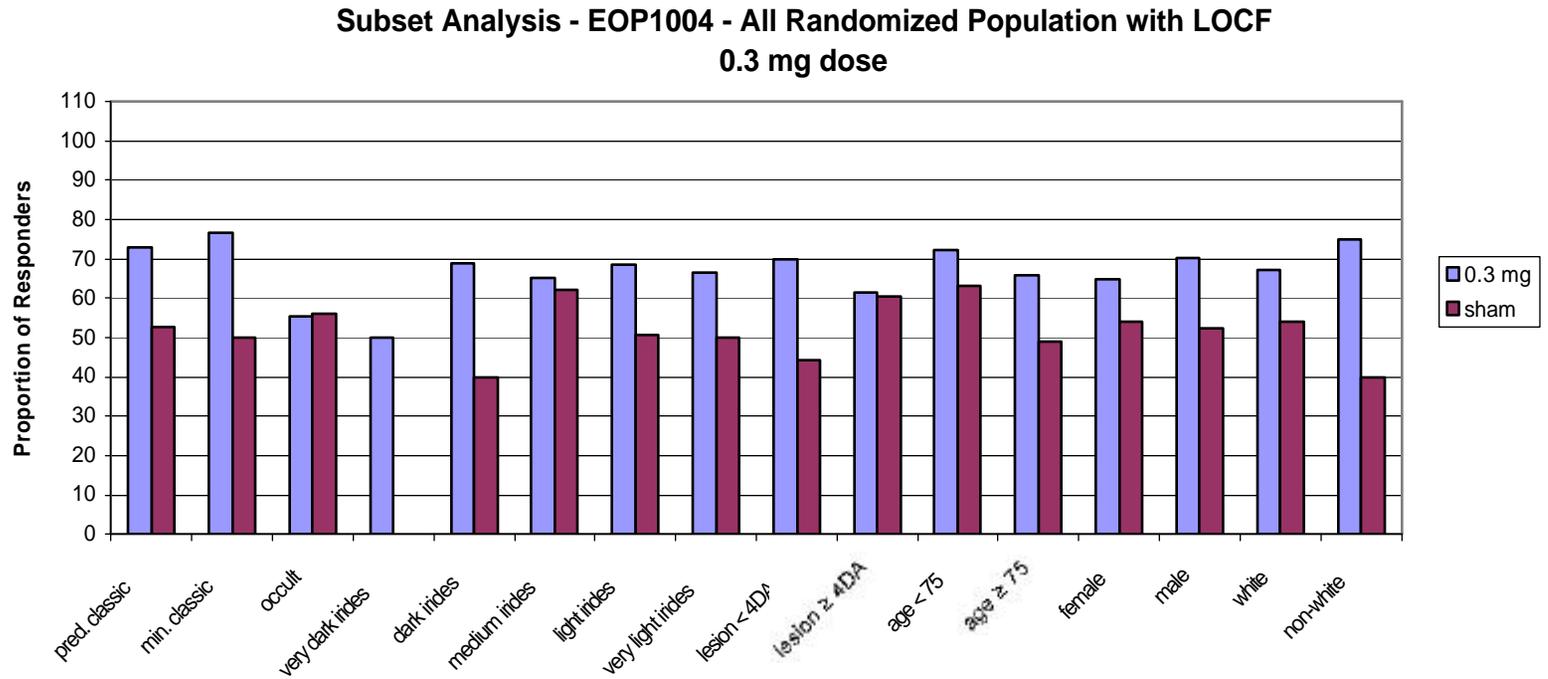
Vision Gain – Study EOP1004

		0.3 mg n=144	1 mg n=146	3 mg n=143	Sham N=144
Number of Patients (%)					
Vision gain = 15 letters ¹	Yes	12 (8%)	10 (7%)	6 (4%)	1 (1%)
	p-value	0.005	0.01	0.04	-
Vision gain = 0 letters ²	Yes	49 (34%)	51 (35%)	33 (23%)	25 (17%)
	p-value	0.0006	0.002	0.17	-

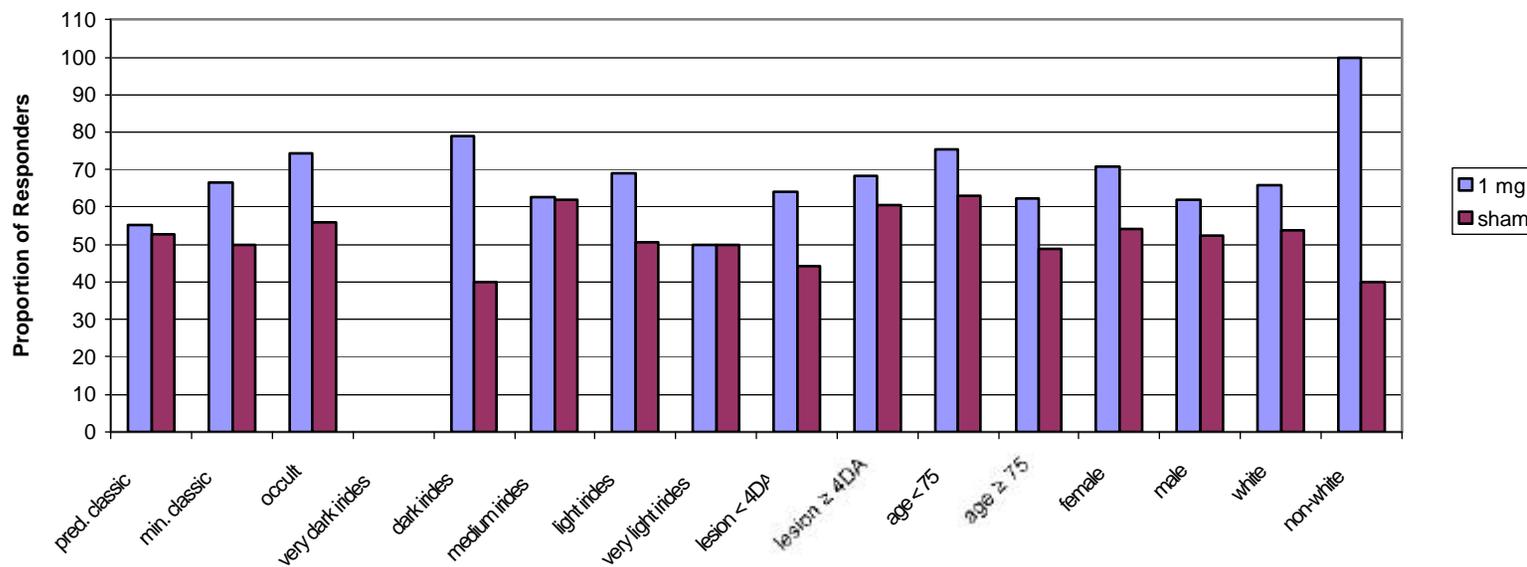
¹patients who gained = 15 letters of vision from baseline to 54 weeks

²patients who gained = 0 letters of vision from baseline to 54 weeks

Responder analyses based on baseline characteristics for study EOP1004



**Subset Analysis - EOP1004 - All Randomized Population with LOCF
1 mg dose**



VII. Integrated Review of Safety

A. Description of Patient Exposure

In the overall development program, almost all patients received doses of either 0.3, 1 or 3 mg of pegaptanib sodium as intravitreal injections. A small number of patients received doses of 0.25 mg (3 patients), 0.5 mg (3 patients), or 2 mg (3 patients).

Number of Patients per Treatment Group in Completed cohorts in the Pegaptanib Sodium Development Program

Number of Patients	0.3 mg	1 mg	3 mg	Sham injection
Controlled exudative AMD, all patients	295	301	296	298
Non-controlled exudative AMD, all patients ¹	0	3	61	0
DME Patients ² , EOP1002	0	0	10	0
Overall Total	295	304	367	298
*Includes 0.25 mg, 0.5 mg and 2 mg doses from study NX109-01; ¹ Only the completed cohort from study EOP1006 is included; ² Study EOP1005 is not included as it is ongoing and has not been unmasked.				

Number of Injections Administered

Total number of injections	0.3 mg	1 mg	3 mg	Sham injection
Studies 1003 and 1004 AMD	2478	2568	2499	2557
Phase 1/2 exudative AMD studies	0	3	62	0
Study 1006 ¹ exudative AMD	0	0	218	0
Study 1002 ² DME	0	0	53	0
*Includes 0.25 mg, 0.5 mg and 2 mg doses from study NX109-01; ¹ Only the completed cohort is included ; ² Study EOP1005 is not included as it is ongoing and has not been unmasked.				

Almost 1000 patients have been treated at or above the recommended dose (0.3 mg) for beyond 1 year at the time of NDA filing.

Number (%) of Patients per Treatment Group Receiving the Specified Number of Study Treatments in the Week 54 Cohort of Studies EOP1003 and EOP1004

Number of Treatments*	0.3 mg N=295	1 mg N=301	3 mg N=296	All Doses N=892	Sham N=298
1	4(1)	2(1)	3(1)	9(1)	2(1)
2	1(0)	3(1)	1(0)	5(1)	1(0)
3	7(2)	3(1)	4(1)	14(2)	3(1)
4	4(1)	4(1)	2(1)	10(1)	5(2)
5	2(1)	2(1)	5(2)	9(1)	1(0)
6	5(2)	5(2)	7(2)	17(2)	7(2)
7	8(3)	10(3)	12 (4)	30 (3)	3(1)
8	37(13)	23(8)	35(12)	95(11)	28(9)
9	227(77)	249(83)	227(77)	703(79)	248(83)
Total number of treatments	2478	2568	2499	7545	2557
Mean	8.4	8.5	8.4	8.5	8.6
SD	1.5	1.4	1.4	1.4	1.3
Median	9.0	9.0	9.0	9.0	9.0
Range	1-9	1-9	1-9	1-9	1-9

* Pegaptanib sodium intravitreal injection or sham treatment

B. Methods and Specific Findings of Safety Review

All safety data were reported for the safety patient population which included all patients who had received at least one study drug injection. Only data relating to the first year of study treatment were analyzed for this review. This included all adverse events up to 6 weeks after the week 48 injection for all patients who received an injection at week 48 or 378 days post the first injection for all other patients. For patient deaths, the cut-off date

for inclusion in this report on the first part of the study was within 42 days (6 weeks) of the week 48 injection.

Overall Summary of Adverse Events – Safety Population – Studies EOP1003 and EOP1004

Number of Patients (%)	0.3 mg n=295	1 mg n=301	3 mg n=296	Sham N=298
Patients with at least one AE	286 (97%)	286 (95%)	288 (97%)	283 (95%)
Patients with at least one ophthalmic AE (study eye)	269 (91%)	270 (90%)	270 (91%)	254 (85%)
Patients with at least one SAE	55 (19%)	50 (17%)	64 (22%)	45 (15%)
Patients with an AE leading to treatment interruption or study discontinuation	7 (2%)	5 (2%)	10 (3%)	7 (2%)

Adverse Events Reported in = 1% of Subjects in Any Treatment Group – Safety Population – Studies EOP1003 and EOP1004

Note: Adverse events seen more frequently in the 0.3 mg group versus sham are highlighted.

Number of subjects System organ class and preferred term	0.3 mg N=295	1 mg N=301	3 mg N=296	Sham N=298
Blood and lymphatic system disorders				
Anemia NOS	2 (1%)	5 (2%)	12 (4%)	8 (3%)
Cardiac disorders				
Arrhythmia NOS	1 (<1%)	3 (1%)	5 (2%)	0 (0%)
Atrial fibrillation	4 (1%)	2 (1%)	2 (1%)	7 (2%)
Bradycardia NOS	2 (1%)	1 (<1%)	4 (1%)	2 (1%)
Myocardial infarction	3 (1%)	2 (1%)	2 (%)	3 (1%)
Coronary artery disease NOS	1 (<1%)	0 (0%)	1 (<1%)	3 (1%)
Ear and labyrinth disorders				
Vertigo	6 (2%)	8 (3%)	4 (1%)	2 (1%)
Endocrine disorders				
Acquired hypothyroidism	0 (0%)	2 (1%)	4 (1%)	3 (1%)
Eye disorders				
Eye pain	101 (34%)	97 (32%)	108 (36%)	85 (29%)
Punctate keratitis	97 (33%)	91 (30%)	98 (33%)	79 (27%)
Vitreous floaters	90 (31%)	105 (35%)	104 (35%)	24 (8%)
Visual acuity reduced	82 (28%)	58 (19%)	62 (21%)	82 (28%)
Cataract	64 (22%)	78 (26%)	85 (29%)	68 (23%)
Vitreous opacities	55 (19%)	56 (19%)	56 (19%)	29 (10%)
Anterior chamber inflammation	47 (16%)	42 (14%)	40 (14%)	17 (6%)
Visual disturbance NOS	40 (14%)	45 (15%)	45 (15%)	38 (13%)

Number of subjects	0.3 mg	1 mg	3 mg	Sham
System organ class and preferred term	N=295	N=301	N=296	N=298
Eye discharge	31 (11%)	22 (7%)	26 (9%)	25 (8%)
Corneal edema	26 (9%)	23 (8%)	37 (13%)	21 (7%)
Vision blurred	27 (9%)	26 (9%)	20 (7%)	15 (5%)
Abnormal sensation in eye	23 (8%)	21 (7%)	26 (9%)	30 (10%)
Conjunctival hemorrhage	23 (8%)	27 (9%)	22 (7%)	18 (6%)
Lacrimation increased	25 (8%)	31 (10%)	29 (10%)	30 (10%)
Macular degeneration	25 (8%)	31 (10%)	29 (10%)	36 (12%)
Blepharitis	20 (7%)	26 (9%)	22 (7%)	19 (6%)
Eye irritation	22 (7%)	24 (8%)	29 (10%)	20 (7%)
Photophobia	22 (7%)	21 (7%)	30 (10%)	23 (8%)
Photopsia	22 (7%)	14 (5%)	25 (8%)	10 (3%)
Eye pruritus	22 (7%)	18 (6%)	27 (9%)	23 (8%)
Eye redness	21 (7%)	23 (8%)	19 (6%)	21 (7%)
Dry eye NOS	17 (6%)	11 (4%)	13 (4%)	15 (5%)
Ocular discomfort	19 (6%)	10 (3%)	11 (4%)	13 (4%)
Vitreous disorder NOS	17 (6%)	22 (7%)	23 (8%)	5 (2%)
Conjunctivitis	15 (5%)	10 (3%)	9 (3%)	10 (3%)
Vitreous detachment	12 (4%)	23 (8%)	14 (5%)	14 (5%)
Conjunctival edema	12 (4%)	16 (5%)	18 (6%)	13 (4%)
Corneal epithelium disorder	13 (4%)	15 (5%)	17 (6%)	18 (6%)
Corneal epithelium defect	10 (3%)	8 (3%)	18 (6%)	14 (5%)
Endophthalmitis	6 (2%)	3 (1%)	3 (1%)	0 (0%)
Eye hemorrhage NOS	5 (2%)	0 (0%)	0 (0%)	1 (<1%)
Eyelid edema	7 (2%)	12 (4%)	17 (6%)	13 (4%)
Conjunctival hyperemia	7 (2%)	8 (3%)	8 (3%)	9 (3%)
Retinal exudates	6 (2%)	3 (1%)	0 (0%)	6 (2%)
Vitreous hemorrhage	5 (2%)	7 (2%)	6 (2%)	0 (0%)
Chalazion	2 (1%)	1 (<1%)	4 (1%)	1 (<1%)
Conjunctivitis allergic	4 (1%)	0 (0%)	4 (1%)	0 (0%)
Corneal deposits	2 (1%)	2 (1%)	6 (2%)	1 (0%)
Corneal dystrophy	4 (1%)	6 (2%)	6 (2%)	2 (1%)
Eye inflammation NOS	4 (1%)	1 (<1%)	1 (<1%)	0 (0%)
Eye swelling	3 (1%)	2 (1%)	4 (1%)	0 (0%)
Eyelids pruritus	3 (1%)	3 (1%)	4 (1%)	1 (0%)
Eyelid ptosis	3 (1%)	5 (2%)	8 (3%)	6 (2%)
Keratitis	4 (1%)	7 (2%)	8 (3%)	9 (3%)
Meibomianitis	3 (1%)	3 (1%)	3 (1%)	0 (0%)
Mydriasis	4 (1%)	2 (1%)	4 (1%)	1 (0%)
Ocular hypertension	4 (1%)	7 (2%)	7 (2%)	6 (2%)
Posterior capsule opacification	2 (1%)	3 (1%)	4 (1%)	2 (1%)
Pupillary reflex impaired	3 (1%)	2 (1%)	2 (1%)	5 (2%)
Retinal artery embolism	4 (1%)	1 (0%)	2 (1%)	2 (1%)
Retinal degeneration	3 (1%)	1 (<1%)	4 (1%)	1 (<1%)
Arcus lipoides	1 (<1%)	1 (<1%)	3 (1%)	1 (<1%)
Eye allergy	1 (<1%)	0 (0%)	2 (1%)	3 (1%)
Eyelid margin crusting	1 (<1%)	1 (<1%)	2 (1%)	3 (1%)
Macular edema	1 (<1%)	2 (1%)	3 (1%)	4 (1%)
Retinal artery occlusion	1 (<1%)	4 (1%)	0 (0%)	0 (0%)
Retinal scar	1 (<1%)	2 (1%)	4 (1%)	7 (2%)
Erythema of eyelid	0 (0%)	1 (<1%)	4 (1%)	3 (1%)
Corneal scar	0 (0%)	1 (<1%)	1 (<1%)	3 (1%)

Number of subjects	0.3 mg	1 mg	3 mg	Sham
System organ class and preferred term	N=295	N=301	N=296	N=298
Iris adhesions	0 (0%)	1 (<1%)	3 (1%)	0 (0%)
Maculopathy	0 (0%)	3 (1%)	3 (1%)	1 (<1%)
Uveitis NOS	0 (0%)	4 (1%)	1 (<1%)	0 (0%)
Gastrointestinal disorders				
Nausea	13 (4%)	7 (2%)	16 (5%)	13 (4%)
Diarrhea NOS	8 (3%)	4 (1%)	9 (3%)	6 (2%)
Vomiting NOS	9 (3%)	1 (<1%)	5 (2%)	1 (<1%)
Constipation	7 (2%)	5 (2%)	9 (3%)	5 (2%)
Dyspepsia	6 (2%)	4 (1%)	7 (2%)	2 (1%)
Gastroesophageal reflux disease	7 (2%)	3 (1%)	2 (1%)	6 (2%)
Abdominal pain NOS	3 (1%)	2 (1%)	1 (0%)	3 (1%)
Hiatus hernia	1 (<1%)	0 (0%)	3 (1%)	1 (<1%)
Abdominal pain upper	0 (0%)	1 (<1%)	3 (1%)	1 (<1%)
Diverticulitis NOS	0 (0%)	1 (<1%)	4 (1%)	4 (1%)
General disorders and administration site conditions				
Edema peripheral	6 (2%)	1 (<1%)	9 (3%)	3 (1%)
Chest pain	7 (2%)	3 (1%)	5 (2%)	4 (1%)
Fatigue	5 (2%)	5 (2%)	4 (1%)	4 (1%)
Fall	2 (1%)	1 (<1%)	5 (2%)	2 (1%)
Pyrexia	4 (1%)	5 (2%)	0 (0%)	2 (1%)
Influenza like illness	1 (<1%)	4 (1%)	0 (0%)	2 (1%)
Malaise	1 (<1%)	1 (<1%)	3 (1%)	0 (0%)
Asthenia	0	1 (<1%)	4 (1%)	2 (1%)
Immune system disorders				
Drug hypersensitivity	2 (1%)	2 (1%)	5 (2%)	3 (1%)
Seasonal allergy	2 (1%)	0 (0%)	5 (2%)	6 (2%)
Infections and infestations				
Upper respiratory tract infection NOS	13 (4%)	10 (3%)	12 (4%)	11 (4%)
Urinary tract infection NOS	11 (4%)	5 (2%)	6 (2%)	6 (2%)
Influenza	10 (3%)	8 (3%)	7 (2%)	13 (4%)
Pneumonia NOS	6 (2%)	7 (2%)	10 (3%)	4 (1%)
Sinusitis NOS	6 (2%)	3 (1%)	10 (3%)	7 (2%)
Gastroenteritis viral NOS	2 (1%)	4 (1%)	3 (1%)	1 (0%)
Lower respiratory tract infection NOS	2 (1%)	1 (<1%)	2 (1%)	3 (1%)
Herpes zoster	1 (<1%)	2 (1%)	4 (1%)	2 (1%)
Respiratory tract infection NOS	1 (<1%)	2 (1%)	2 (1%)	8 (3%)
Tooth abscess	1 (<1%)	3 (1%)	3 (1%)	5 (2%)
Tooth caries NOS	1 (<1%)	2 (1%)	3 (1%)	3 (1%)
Bladder infection NOS	0 (0%)	4 (1%)	0 (0%)	8 (3%)
Ear infection NOS	0 (0%)	1 (<1%)	4 (1%)	3 (1%)
Hordeolum	0 (0%)	1 (<1%)	2 (1%)	3 (1%)
Injury, poisoning and procedural complications				
Periorbital hematoma	7 (2%)	5 (2%)	5 (2%)	7 (2%)
Abrasion NOS	5 (2%)	0 (0%)	2 (1%)	4 (1%)
Corneal abrasion	3 (1%)	8 (3%)	2 (1%)	1 (<1%)
Hip fracture	4 (1%)	1 (<1%)	0 (0%)	1 (<1%)
Post procedural pain	4 (1%)	2 (1%)	2 (1%)	4 (1%)
Skin laceration	3 (1%)	3 (1%)	2 (1%)	4 (1%)
Corneal erosion	1 (0%)	1 (<1%)	3 (1%)	1 (<1%)
Muscle strain	0 (0%)	1 (<1%)	2 (1%)	3 (1%)

Number of subjects	0.3 mg	1 mg	3 mg	Sham
System organ class and preferred term	N=295	N=301	N=296	N=298
Investigations				
Intraocular pressure increased	42 (14%)	59 (20%)	77 (26%)	8 (3%)
Weight increased	2 (1%)	3 (1%)	6 (2%)	3 (1%)
Weight decreased	1 (<1%)	2 (1%)	6 (2%)	1 (<1%)
Gamma-glutamyl transferase increased	1 (<1%)	0 (0%)	0 (0%)	3 (1%)
Metabolism and nutrition disorders				
Hypercholesterolemia	7 (2%)	10 (3%)	3 (1%)	9 (3%)
Dehydration	2 (1%)	2 (1%)	3 (1%)	4 (1%)
Diabetes mellitus NOS	3 (1%)	1 (<1%)	1 (<1%)	0 (0%)
Hyperlipidemia NOS	3 (1%)	2 (1%)	2 (1%)	4 (1%)
Hypocalcaemia	3 (1%)	1 (<1%)	3 (1%)	4 (1%)
Musculoskeletal and connective tissue disorders				
Arthralgia	13 (4%)	12 (4%)	11 (4%)	17 (6%)
Back pain	11 (4%)	10 (3%)	8 (3%)	14 (5%)
Arthritis NOS	9 (3%)	0 (0%)	5 (2%)	2 (1%)
Bone spur	3 (1%)	1 (<1%)	1 (<1%)	0 (0%)
Pain in limb	2 (1%)	7 (2%)	6 (2%)	6 (2%)
Arthritis NOS aggravated	1 (<1%)	2 (1%)	6 (2%)	4 (1%)
Osteoarthritis NOS	1 (<1%)	5 (2%)	3 (1%)	1 (<1%)
Osteoporosis NOS	1 (<1%)	2 (1%)	4 (1%)	6 (2%)
Localized osteoarthritis	0 (0%)	4 (1%)	3 (1%)	2 (1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Basal cell carcinoma	4 (1%)	2 (1%)	4 (1%)	5 (2%)
Prostate cancer NOS	2 (1%)	2 (1%)	1 (<1%)	3 (1%)
Skin carcinoma NOS	4 (1%)	0 (0%)	1 (<1%)	2 (1%)
Lung cancer stage unspecified (excl metastatic tumors to lung)	0 (0%)	0 (0%)	3 (1%)	1 (<1%)
Nervous system disorders				
Headache	19 (6%)	23 (8%)	20 (7%)	11 (4%)
Dizziness	7 (2%)	7 (2%)	9 (3%)	7 (2%)
Transient ischemic attack	5 (2%)	0 (0%)	1 (<1%)	2 (1%)
Carotid artery occlusion	3 (1%)	0 (0%)	2 (1%)	0 (0%)
Carpal tunnel syndrome	2 (1%)	1 (<1%)	0 (0%)	4 (1%)
Cerebrovascular accident	2 (1%)	2 (1%)	3 (1%)	1 (<1%)
Syncope	0 (0%)	3 (1%)	4 (1%)	3 (1%)
Psychiatric disorders				
Depression	11 (4%)	7 (2%)	10 (3%)	11 (4%)
Insomnia	8 (3%)	4 (1%)	9 (3%)	7 (2%)
Anxiety	2 (1%)	8 (3%)	3 (1%)	9 (3%)
Confusional state	3 (1%)	2 (1%)	0 (0%)	1 (<1%)
Renal and urinary disorders				
Hematuria	3 (1%)	1 (<1%)	0 (0%)	1 (<1%)
Urinary retention	3 (1%)	1 (<1%)	1 (<1%)	0 (0%)
Renal failure NOS	0 (0%)	1 (<1%)	1 (<1%)	3 (1%)
Respiratory, thoracic and mediastinal disorders				
Nasopharyngitis	19 (6%)	23 (8%)	27 (9%)	19 (6%)
Bronchitis NOS	16 (5%)	12 (4%)	11 (4%)	10 (3%)
Cough	10 (3%)	9 (3%)	6 (2%)	6 (2%)
Rhinorrhea	5 (2%)	2 (1%)	4 (1%)	2 (1%)
Chronic obstructive airways disease	2 (1%)	1 (<1%)	2 (1%)	3 (1%)

Number of subjects	0.3 mg	1 mg	3 mg	Sham
System organ class and preferred term	N=295	N=301	N=296	N=298
Dyspnea NOS	3 (1%)	3 (1%)	8 (3%)	4 (1%)
Epistaxis	3 (1%)	2 (1%)	3 (1%)	2 (1%)
Pharyngitis	3 (1%)	2 (1%)	5 (2%)	5 (2%)
Pleural effusion	3 (1%)	1 (<1%)	0 (0%)	0 (0%)
Sinus congestion	2 (1%)	4 (1%)	2 (1%)	1 (<1%)
Chronic obstructive airways disease exacerbated	1 (<1%)	4 (1%)	2 (1%)	2 (1%)
Pulmonary congestion	0 (0%)	2 (1%)	3 (1%)	2 (1%)
Skin and subcutaneous tissue disorders				
Contusion	7 (2%)	3 (1%)	5 (2%)	2 (1%)
Dermatitis contact	5 (2%)	1 (<1%)	3 (1%)	1 (<1%)
Cutis laxa	3 (1%)	2 (1%)	2 (1%)	3 (1%)
Rash NOS	3 (1%)	7 (2%)	3 (1%)	3 (1%)
Vascular disorders				
Hypertension NOS	14 (5%)	26 (9%)	29 (10%)	22 (7%)
Hypertension aggravated	12 (4%)	5 (2%)	7 (2%)	8 (3%)
Hypotension NOS	1 (<1%)	2 (1%)	4 (1%)	0 (0%)

Discussion of Vision Threatening Adverse Events:

Endophthalmitis

Endophthalmitis was experienced by 12 pegaptanib sodium-treated patients; no cases occurred in the sham-treated patients. Four (4) additional events of endophthalmitis were reported in pegaptanib sodium-treated patients in the ongoing controlled studies as of the data cutoff date of 26 September 2003. All 16 cases occurred in the study eye and occurred within one week of injection.

The injection procedure as originally described in the study protocols was revised in a protocol amendment to reduce the risk of endophthalmitis.

The amendment required use of:

1. sterile preparation and drape similar to that used for routine intraocular surgery, and
2. use of either pre-injection topical ophthalmic antibiotic drops for three days prior to the injection OR a 10 mL povidone iodine flush immediately prior to injection.

Three of the sixteen (3/16) cases of endophthalmitis occurred after the amendment was distributed to the sites.

Listing of Patients with Endophthalmitis

Patient ID	Sex/ Age	Dose Group	Injections Prior to SAE	Onset Post Last Injection	Baseline VA	VA Before Event	VA After Event	Latest VA Wk 54	Outcome	Culture
EOP1003/1004 Week 54 Cohort										
1003 - 073-015	F/83	3 mg	8	4 days	20/100	20/63	20/125	20/125	d/c'd due to Patient request	Coagulase negative Staph
1003 - 089-019	F/69	0.3 mg	4	4 days	20/320	20/800	<20/800	<20/800	d/c'd due to AE	Staph epidermidis
1003 -102-033	F/76	0.3 mg	2	4 days	20/100	20/160	20/100	20/125	Continued	Coagulase positive Staph
1003 -113-012	F/81	1 mg	5	2 days	20/100	20/50	20/63	20/50	Continued	Negative
1003 -143-006	F/86	0.3 mg	2	4 days	20/125	20/200	20/320	20/125	Continued	Coagulase negative Staph
1003 - 145-013	M/85	3 mg	6	7 days	20/125	20/400	20/400	20/640	Continued	Micrococcus species
1004 -025-001	M/73	0.3 mg	7	3 days	20/40	20/50	20/200	20/80	Continued	Coagulase negative Staph
1004 -026-009	F/69	1 mg	2	3 days	20/80	20/80	20/200	20/200	Continued	Coagulase negative Staph
1004 -034-020	M/80	0.3 mg	1	4 days	20/200	20/200	20/400	20/500	Continued	Staph epidermidis
1004 - 042-001	M/77	0.3 mg	1	4 days	20/63	20/63	20/800	20/800	d/c'd due to AE	Staph lugdunensis
1004 -054-018	F/73	1 mg	1	2 days	20/80	20/80	20/100	20/125	Continued	Negative
1004 - 057-014	M/78	3 mg	5	5 days	20/250	20/320	20/250	20/320	Continued	Negative
EOP1003/1004 Year 2										
1004-025-005	F/81	masked	10	1 day	20/63	20/160	20/200	20/160 Wk 78	Continued	Negative
1004-035-001	M/74	masked	13	4 days	20/160	20/80	20/100	20/160 Wk 103	d/c'd due to AE	Coagulase negative Staph
1004 - 048-017	F/78	masked	9	5 days	20/80	20/250	20/320	20/320 Wk 84	d/c'd due to AE	Negative
EOP1005 Ongoing										
1005-015-001	F/59	masked	1	3 days	20/80	20/63	20/125	20/160 Wk 30	d/c'd due to AE	Negative

Retinal Detachment

The incidence of study eye retinal detachment in the first 54 weeks of Studies EOP1003 and EOP1004 was 0.6% (5/892) in the combined pegaptanib sodium and 0.3% (1/298) in the sham groups. One patient received 0.3 mg, 2 patients received 1 mg, and 2 patients received 3 mg pegaptanib sodium.

The onset of these events did not correlate with the number of treatments received, since the detachments occurred after the third (two patients), fourth, sixth or eighth injection. The event onset varied from 7 to 137 days after the last injection. Two of the patients had detachments that were exudative/hemorrhagic in nature, which may have been secondary to the underlying disease process; these detachments did not have a rhegmatogenous component. The detachment of a third patient was attributed to proliferative vitreoretinopathy and contracture of the retina.

Retinal Tear

Four of 892 patients (0.4%) receiving pegaptanib sodium (2 receiving 0.3 mg; 2 receiving 3 mg) and 1/298 (0.3%) receiving sham treatment experienced a retinal tear in the study eye during the first 54 weeks of Studies EOP1003 and EOP1004. In all 5 cases, the tear was diagnosed at the study visit one week postinjection.

For the 4 patients who were receiving active treatment, the tears occurred after the second, fifth, or sixth (two patients) injection. Four patients were treated with laser photocoagulation and one received no treatment. None of the patients progressed to retinal detachment and none discontinued treatment due to this event. There were no retinal tears in the fellow eye.

Traumatic Cataracts

Five patients developed a traumatic cataract during the first 54 weeks of Studies EOP1003 and EOP1004, all of which were iatrogenic in nature. In 4 of these patients there was contact and/or penetration of the lens with the intravitreal injection needle; two of these events occurred on the same day at the same investigational site (1003-093). In the fifth patient, an anterior chamber paracentesis was performed due to increased IOP after an intravitreal injection, and the paracentesis needle punctured the anterior lens capsule. All of these patients subsequently had a cataract extraction, and all but one continued in the study; the remaining patient requested to be withdrawn from the study after cataract surgery.

Retinal Artery Occlusion

Central retinal artery occlusion (CRAO) in the study eye during the first 54 weeks of Studies EOP1003 and EOP1004 was seen in 4 patients, 1 receiving 0.3 mg pegaptanib sodium and 3 receiving 1 mg. All 4 cases were transient closures of the central artery

which were associated with increased IOP immediately following an injection. All were treated with, and resolved after, paracentesis. These events occurred after the first, third or sixth injection. All events resolved without sequelae and all 4 patients continued in the study.

In addition to the 4 study eye cases described above, one patient receiving pegaptanib sodium 1mg presented with a CRAO in the fellow eye 28 days after the first injection. The patient was treated with paracentesis and acetazolamide.

Deaths

Twenty-five deaths were recorded in the Week 54 cohort of Studies EOP1003 and EOP1004, 19 in patients receiving pegaptanib sodium and 6 patients receiving sham. The incidence of death in all pegaptanib sodium treated patients in the Week 54 cohort of Studies EOP1003 and EOP1004 was 2.1%, with the rate in sham-treated patients from these studies being 2.0%.

Number (%) of Deaths in the Week 54 Cohort of Studies EOP1003 and EOP1004

	0.3 mg	1 mg	3 mg	Sham
	N=295	N=301	N=296	N=298
EOP1003 Wk 54 Cohort	2/151(1.3)	2/155(1.3)	3/153(2.0)	4/153(2.6)
EOP1004 Wk 54 Cohort	3/144(2.1)	6/146(4.1)	3/143(2.1)	2/145(1.4)

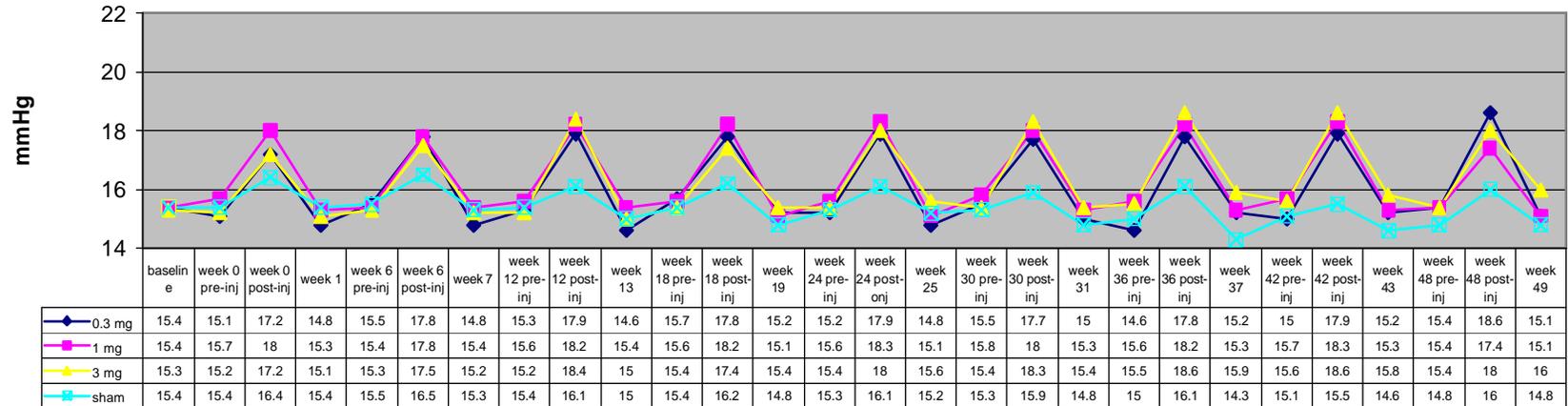
Death Listing in Pegaptanib Sodium Studies by Treatment Group

Patient Identifier	Age/ Gender	Trt Group	Study Day of Death	Last Trt to Death (Days)	Cause(s) of Death (Investigator Term)
Week 54 Cohort of Studies EOP1003 and EOP1004					
EOP1003-108-007	82/M	0.3 mg	312	17	Myocardial Infarction
EOP1003-136-011	80/F	0.3 mg	130	11	Brain Hemorrhage
EOP1004-021-010	68/M	0.3 mg	231	20	Cardiac Arrest
EOP1004-048-002	69/M	0.3 mg	185	17	Abdominal Aortic Aneurysm
EOP1004-050-012	76/M	0.3 mg	140	54	Acute Myeloid Leukemia
EOP1003-130-001	75/F	1 mg	358	22	Heart Attack
EOP1003-136-005	74/M	1 mg	281	31	Stroke
EOP1004-008-018	85/M	1 mg	228	19	Anemia
EOP1004-015-002	76/F	1 mg	307	34	Pneumonia; Worsening Chronic Bronchiectasis; Worsening Mycobacterium Avium Complex Pneumonia
EOP1004-033-006	86/F	1 mg	62	20	Aortic Stenosis; Cardiopulmonary Arrest
EOP1004-041-001	81/F	1 mg	187	55	Renal failure; Septicemia;
EOP1004-050-021	82/M	1 mg	323	48	Poorly Differentiated Large Cell

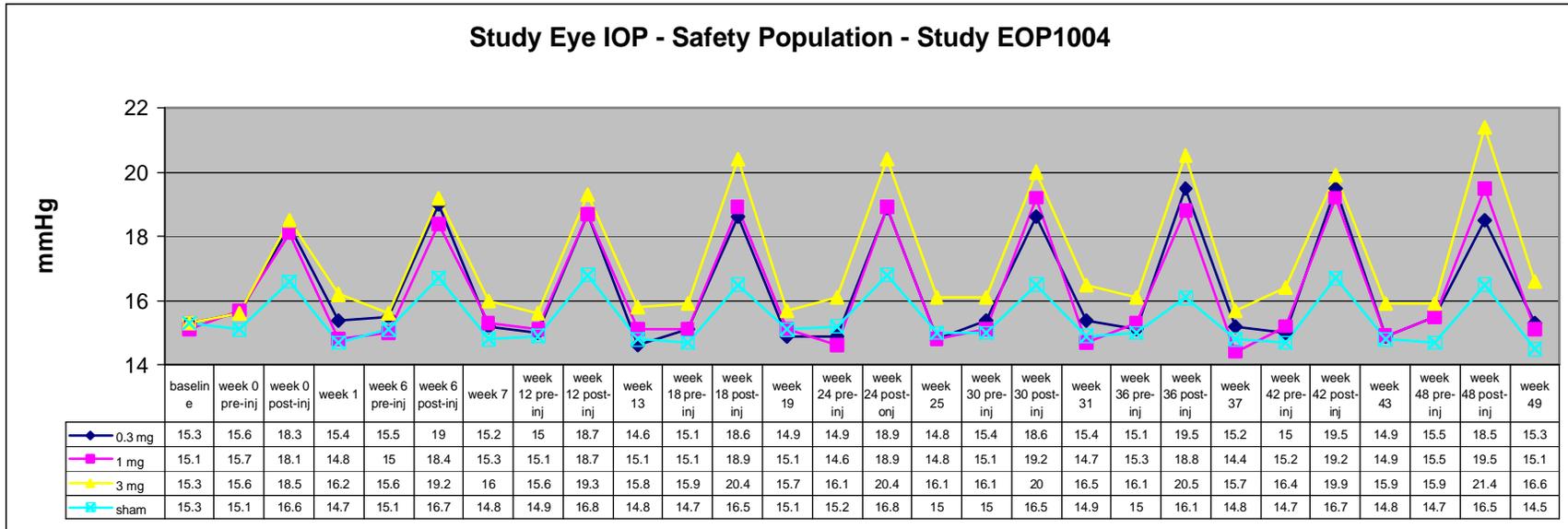
Patient Identifier	Age/ Gender	Trt Group	Study Day of Death	Last Trt to Death (Days)	Cause(s) of Death (Investigator Term)
					Lung Cancer
EOP1004-059-006	75/M	1 mg	101	17	Metastatic Cancer
EOP1003-074-002	89/F	3 mg	183	183	Ischemic Cerebral Vascular Accident
EOP1003-104-011	75/M	3 mg	195	27	Massive Gastric Bleeding
EOP1003-085-001	82/F	3 mg	227	64	Pneumonia
EOP1004-006-010	85/F	3 mg	372	36	Renal Failure
EOP1004-026-003	81/F	3 mg	256	47	Cardiac Arrest; Necrotic Bowel
EOP1004-034-011	86/F	3 mg	116	30	Cardiac Arrest
EOP1003-064-012	82/M	Sham	342	3	Myocardial Infarction; Emphysema
EOP1003-098-002	79/M	Sham	35	35	Acute Myeloid Leukemia
EOP1003-130-013	83/F	Sham	273	63	Bronchopneumonia
EOP1003-145-018	72/M	Sham	350	87	Metastatic Lung Cancer; Multiple Blood Clots
EOP1004-021-012	80/F	Sham	335	79	Bladder Cancer
EOP1004-040-003	76/F	Sham	328	27	Pelvic mass
Deaths Other than in Week 54 Cohort of Studies EOP1003 and EOP1004*					
EOP1005-024-011	80/F	masked	52	10	Acute Myocardial Infarction
EOP1004-141-010**	82/F	0.3 mg	393	58	Gastric Cancer
EOP1003-071-005**	90/M	1 mg	471	136	Cardiorespiratory Arrest
EOP1004-036-017	81/M	1 mg	431	95	Myocardial infarction
EOP1000-006-001	85/F	3 mg	74	18	Myocardial Infarction
EOP1002-HUD-02	73/F	3 mg	67	26	Multisystem Organ Failure
EOP1003-093-005**	74/M	3 mg	401	61	Septic Shock; Intestinal Necrosis
EOP1003-119-012**	75/M	3 mg	381	47	Probable Ischemic Heart Disease
EOP1003-093-018	93/M	Sham	355	142	Pulmonary Embolism
EOP1004-006-034**	84/F	3 mg	415	121	Acute Respiratory Failure
*Study treatment for patients in EOP1003 and EOP1004 given for the Week 54 period					
** No study treatment after Week 54					

Study Eye IOP – Safety population – Study EOP1003

Study Eye IOP - Safety population - Study EOP1003



Study Eye IOP – Safety population – Study EOP1004



Among patients receiving pegaptanib sodium, 9% (0.3 mg), 13% (1 mg) and 15% (3 mg) underwent paracentesis for the treatments of increased intraocular pressure, while no sham-treated patient did. A total of 12% of patients in the 0.3 mg pegaptanib sodium group, 14% in the 1 mg group, and 19% in the 3 mg group received a concomitant medication for increased IOP on one or more injection days.

Concomitant PDT Use

Number (%) of Patients with and Ocular Adverse Events >10% and/or Events that May Have a Significant Effect on Vision in the Study Eye by PDT Use – Study EOP1003 & EOP1004 – Safety Population

Event		0.3 mg	1 mg	3 mg	All Doses	Sham
PDT after 1 st injection	Yes	N=51	N=56	N=59	N=166	N=64
	No	N=244	N=245	N=237	N=726	N=234
Eye Pain	PDT	22 (43%)	23 (41%)	22 (37%)	67 (40%)	25 (39%)
	No PDT	75 (31%)	74 (30%)	83 (35%)	232 (32%)	58 (25%)
Punctate Keratitis	PDT	18 (35%)	19 (34%)	17 (29%)	54 (33%)	12 (19%)
	No PDT	79 (32%)	72 (29%)	81 (34%)	232 (32%)	67 (29%)
Vitreous Floaters	PDT	17 (33%)	22 (39%)	15 (29%)	54 (33%)	6 (9%)
	No PDT	71 (29%)	81 (33%)	88 (37%)	240 (33%)	17 (7%)
Visual Acuity Reduced	PDT	14 (27%)	15 (27%)	14 (24%)	43 (26%)	27 (42%)
	No PDT	53 (22%)	32 (13%)	38 (16%)	123 (17%)	44 (19%)
Anterior Chamber Inflammation	PDT	16 (31%)	12 (21%)	14 (24%)	42 (25%)	5 (8%)
	No PDT	31 (13%)	30 (12%)	25 (11%)	86 (12%)	12 (5%)
Cataract	PDT	11 (22%)	7 (13%)	16 (27%)	34 (20%)	9 (14%)
	No PDT	40 (16%)	54 (22%)	53 (22%)	147 (20%)	45 (19%)
Visual Disturbance NOS	PDT	8 (16%)	6 (11%)	16 (27%)	30 (18%)	9 (14%)
	No PDT	30 (12%)	33 (13%)	24 (10%)	87 (12%)	24 (10%)
Vitreous Opacities	PDT	11 (22%)	11 (20%)	8 (14%)	30 (18%)	6 (9%)
	No PDT	42 (17%)	45 (18%)	40 (20%)	135 (19%)	23 (10%)
Photophobia	PDT	6 (12%)	5 (9%)	9 (15%)	20 (12%)	7 (11%)
	No PDT	16 (7%)	16 (7%)	20 (8%)	52 (7%)	16 (7%)
Vision Blurred	PDT	9 (18%)	6 (11%)	5 (8%)	20 (12%)	5 (8%)
	No PDT	16 (7%)	18 (7%)	12 (5%)	46 (6%)	9 (4%)
Corneal Edema	PDT	7 (14%)	2 (4%)	5 (8%)	14 (8%)	14 (8%)
	No PDT	18 (7%)	21 (9%)	32 (14%)	71 (10%)	16 (7%)
Retinal Hemorrhage	PDT	3 (6%)	8 (14%)	3 (5%)	14 (8%)	6 (9%)
	No PDT	7 (3%)	20 (8%)	16 (7%)	43 (6%)	19 (8%)
Endophthalmitis	PDT	1 (2%)	0	0	1 (1%)	0
	No PDT	5 (2%)	3 (1%)	3 (1%)	11 (2%)	0
Retinal Detachment	PDT	0	1 (2%)	0	1 (1%)	0
	No PDT	1 (0%)	1 (0%)	2 (1%)	4 (1%)	0

Clinical Laboratory Evaluations, Vital Signs, ECG's

Number (%) of Patients with Laboratory Test Abnormalities Meeting the Primary Criteria Occurring at an Incidence of > 1% in Any Treatment Group, Without Regard to Baseline in the Week 54 Cohort of Studies EOP1003 and EOP1004

Laboratory Test	Units	Primary Criteria	0.3 mg	1 mg	3 mg	All Doses	Sham
Hematology			N=293	N=299	N=293	N=885	N=295
Hemoglobin	g/dL	<0.8xBL	3(1)	6(2)	10(3)	19(2)	7(2)
Platelets	10E9/L	< 75	5 (2)	0	0	5 (1)	1 (0)
Neutrophils (Abs)	10E6/L	> 1.5xULN	5 (2)	1 (0)	6 (2)	12 (1)	5 (2)
Eosinophils (Abs)	10E6/L	>1.5x ULN	8(3)	4(1)	2(1)	14(2)	12(4)
Eosinophils	%	>1.5x ULN	11(4)	7(2)	5(2)	23(3)	20(7)
Liver Function			N=295	N=301	N=296	N=892	N=298
GGT	IU/L	>3xULN	5(2)	6(2)	11(4)	22(2)	4(1)
Renal Function			N=295	N=301	N=296	N=892	N=298
BUN	μ MOL/L	>1.3xULN	10(3)	11(4)	12(4)	33(4)	7(2)
Creatinine	μ MOL/L	>1.3xULN	8(3)	10(3)	9(3)	27(3)	11(4)
Electrolytes			N=295	N=301	N=296	N=892	N=298
Potassium	MMOL/L	>1.1xULN	6(2)	8(3)	14(5)	28(3)	8(3)
Carbon dioxide	MMOL/L	< 0.9xLLN	1 (0)	5 (2)	4 (1)	10 (1)	2 (1)
		> 1.1xULN	5 (2)	4 (1)	7 (2)	16 (2)	4 (1)
Phosphorus	MMOL/L	>1.1xULN	3(1)	3(1)	8(3)	14(2)	5(2)

N=No. patients evaluable for laboratory tests

BL=Baseline

ULN=Upper limit of normal

Vital Signs – Studies EOP1003 & EOP1004 – Safety Population

There were no clinically significant changes in vital signs during the course of these studies.

Questions to think about in preparation for the Advisory Committee Meeting

- Has sufficient data been submitted to evaluate the efficacy and safety profile of pegaptanib sodium? If not, what additional data are needed?
- Based on the Inclusion/Exclusion Criteria, are there patients excluded from the studies that you believe need to be studied?
- Are additional analyses of the current data needed to understand the efficacy or safety of pegaptanib sodium for the treatment of age-related macular degeneration?
- Visual acuity measurements were conducted using the ETDRS scale placed at 2 meters from the patient. The validity of the ETDRS scale was established based on readings at 4 meters. Are the visual acuity findings sufficiently robust to overcome the potential bias introduced by visual acuity measurements at 2 meters?
- Has the concomitant use of PDT therapy with pegaptanib been explored sufficiently? Are there concerns with using this product concomitantly with PDT therapy?
- Do the route and/or frequency of administration of the drug raise any concerns that are not addressed by the studies?
- Are there adverse experiences that are of particular concern for this product?
- Endophthalmitis (approximately 2%) was observed in these studies. What is the optimal follow-up needed to minimize the impact of potential endophthalmitis cases?
- Vascular Endothelial Growth Factor (VEGF) has been shown to be an important component in the development of collateral vessels in ischemic heart disease. Inhibition of VEGF in the systemic circulation could present a theoretical increased risk of symptomatic cardiovascular disease in the target population of elderly patients with AMD. Has the adverse event profile of the two randomized phase 3 trials raised any concern over the possible systemic effects of this therapy? Is there additional monitoring that should be in place for patients on pegaptanib sodium therapy?
- Do the benefits of using pegaptanib sodium outweigh the risks in the treatment of age-related macular degeneration?