Eyetech Pharmaceuticals Inc

Three Times Square, 12th Floor,
New York, NY 10036

Pfizer Inc.
Pfizer Global Research and Development
50 Pequot Avenue
New London, CT 06320

Briefing Document for the Dermatologic and Ophthalmic Drugs Advisory Committee

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Pegaptanib Sodium Injection in the Treatment of Neovascular Age-Related Macular Degeneration

EXECUTIVE SUMMARY

The data presented in this briefing document demonstrate that pegaptanib sodium injection (pegaptanib) has a favorable benefit-risk profile to support the following proposed indication:

- Pegaptanib is indicated for the treatment of neovascular age-related macular degeneration (AMD).

The intended dose and regimen for all patients is:

- Pegaptanib 0.3 mg administered every 6 weeks as an intravitreous injection.

BACKGROUND:

AMD is the leading cause of irreversible severe vision loss in Americans over 55 years of age. While the non-neovascular or dry form of the disease is more prevalent, neovascular or wet AMD is responsible for the majority of cases of vision loss. Neovascular AMD is characterized by choroidal neovascularization beneath the retina. The neovascular tissue often leaks blood and fluid, and, untreated, eventually progresses to scarring with destruction of the macula and loss of vision. Neovascular AMD represents a major unmet medical need.

Nonclinical models have shown that VEGF is both necessary and sufficient for the pathological neovascularization and vascular permeability that characterize AMD and other diseases of the eye. Pegaptanib is a pegylated synthetic oligonucleotide that acts as an antagonist of vascular endothelial growth factor isoform 165 ($VEGF_{165}$), the VEGF isoform most associated with ocular disease. Pegaptanib has been developed to treat the pathological choroidal neovascularization associated with neovascular AMD and prevent deterioration of visual acuity. As the different angiographic lesion subtypes of neovascular AMD (i.e., classic and occult) share common pathophysiological features, most importantly abnormal neovascularization and increased vascular permeability, the anti-angiogenic and anti-permeability activity of pegaptanib would be expected to benefit all angiographic lesion subtypes of neovascular AMD.

METHODS:

Two prospective, multi-center, randomized, double-masked, controlled trials with broad entry criteria for vision, lesion size and angiographic subtype were conducted. Intravitreous injections of pegaptanib (0.3 mg, 1 mg, or 3 mg) or sham injections were administered every 6 weeks for 48 weeks with a follow-up period to 54 weeks, totaling a maximum of 9 injections during that time. The doses investigated were selected based on the expectation that VEGF neutralization could be maintained for intervals up to 6 weeks with doses of 0.3 mg or greater. The 3 mg dose was the highest that could be administered due to the viscosity of the injection fluid. The dose interval of 6 weeks was based on the results of earlier nonclinical and clinical studies. The primary efficacy endpoint was the proportion of Responders, defined as patients losing less than 15 letters, of best-corrected visual acuity (VA) in the study eye from baseline up to 54 weeks. Pre-specified secondary endpoints included the proportion of patients maintaining or gaining ≥ 0 and gaining ≥ 15 letters, and the mean change in vision at 6, 12 and 54 weeks. Safety evaluations were performed in patients receiving at least one study treatment.

EFFICACY RESULTS:

Pegaptanib 0.3 mg achieved statistical significance for a clinically meaningful primary efficacy endpoint in two replicate, well-controlled clinical trials in patients with neovascular AMD ($p=0.0031$ Study EOP1004, $p=0.0105$ Study EOP1003 and $p<0.0001$ combined analysis). In addition, pegaptanib 1 mg also showed a statistically significant treatment benefit compared with sham in study EOP1003 ($p=0.0035$) and was near to significance in EOP1004 ($p=0.0273$; significance threshold = 0.025 using the Hochberg statistical procedure; $p=0.0003$ combined analysis). The primary efficacy endpoint was the proportion of Responders, defined as patients avoiding 15 letter loss of visual acuity, a clinically meaningful benefit for a patient.

Eleven hundred eighty-six patients were included in the intent to treat analyses for the combined studies. Approximately 90% of patients across all treatment arms completed the study. The mean number of doses administered (8.5 out of a possible 9, all study arms) was similar among treatment arms.

Analysis of all other endpoints using the combined data set showed a treatment benefit for both the 0.3 mg and 1 mg doses. Onset of efficacy was as early as 6 weeks and appeared to increase up to 54 weeks; at weeks 6, 12, and 54, mean visual acuity loss from baseline was significantly decreased in the 0.3 mg and 1 mg pegaptanib groups compared to sham ($p<0.007$ for each measurement time). Fewer patients treated with pegaptanib progressed to visual acuity levels of 20/200 or worse in the study eye during the study than in the sham group (sham, 56%; 0.3 mg - 38% of patients, $p<0.0001$; 1 mg - 43% of patients, $p=0.001$). Severe vision loss (loss of $\geq$30 letters of visual acuity) was more than twice as likely in sham-treated patients (22%) compared to pegaptanib 0.3 mg (10%) or 1 mg (8%) treated patients ($p<0.0001$). No baseline characteristic precluded a treatment benefit, including angiographic lesion subtype or size, visual acuity at treatment start, age, gender, prior use of PDT with verteporfin or degree of iris pigmentation. Usage of PDT during the studies was low, with increased PDT use in the sham arm. There was no evidence that PDT usage influenced the efficacy of pegaptanib. Dose levels of 1 mg and 3 mg were effective in combined analyses but did not exhibit additional benefit over that seen at the 0.3 mg dose level.

The results of the efficacy analyses validate the importance of $VEGF_{165}$ in the pathogenesis of neovascular AMD, and demonstrate further that continuous inhibition of $VEGF_{165}$ for 54 weeks results in a statistically significant and clinically meaningful benefit for the patient.

SAFETY RESULTS:

Pegaptanib administered by intravitreous injection was well tolerated at the doses investigated with few patients withdrawing from treatment due to adverse events (1-2% of patients across all treatment groups, combined analysis). No systemic safety issues were apparent.

Ocular adverse events were common, predictable, and reported as mostly mild or moderate and resolved without sequelae. The majority of ocular AEs were judged by the investigator to be related to the intravitreous injection procedure. There was no evidence that ocular AEs increased in incidence over time. There were no unexpected retinal vascular or choroidal changes on fluorescein angiography as read by the Independent Reading Center.

Serious ocular adverse events, including endophthalmitis (0.16% per injection or 1.3% per patient per year), traumatic cataract (0.07% per injection or 0.6% per patient per year) and rhegmatogenous retinal detachment (0.04% per injection or 0.3% per patient per year), were infrequent and were likely related to the injection procedure. Of the endophthalmitis cases, only one patient (0.1% per patient per year) lost more than 6 lines (30 letters) of vision from assessments prior to the event until the end of study and 75% of patients with endophthalmitis continued study treatment. In approximately 70% of endophthalmitis cases, there was at least one violation of the injection procedure (e.g., no eyelid speculum used). Other than iatrogenic traumatic cataracts, there was no evidence that pegaptanib treatment resulted in cataract progression.

There is no evidence of a persistent increase in IOP associated with pegaptanib. Transient increases in IOP are expected with intravitreous injections, and such increases were seen with pegaptanib. The increases were manageable and no patient was discontinued due to increased IOP.

There were no differences between doses for almost all safety assessments with the possible exception that transient intraocular pressure elevations of $\geq$ 35 mmHg (a monitoring threshold suggested by the Independent Data Monitoring Committee) were more frequently observed in the 3 mg arm than the 0.3 mg or 1 mg arms.

CONCLUSIONS:

Pegaptanib sodium for injection has a favorable safety profile and is an effective treatment for neovascular AMD. Data from the two pivotal clinical trials indicate a treatment benefit for patients with neovascular AMD treated with pegaptanib at doses of 0.3 mg or 1 mg given by intravitreous injection every six weeks. However, as no additional benefit was apparent with the 1 mg dose, the 0.3 mg dose, the lowest effective dose, is therefore recommended.

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LIST OF ABREVIATIONS

AE	Adverse Event
ALAT	Alanine Aminotransferase (SGPT)
AMD	Age-Related Macular Degeneration
ANCOVA	Analysis of Covariance
AREDS	Age-Related Eye Disease Study
ASAT	Aspartate Aminotransferase (SGOT)
AUC	Area under the Plasma Concentration Time Curve
CNS	Central Nervous System
CNV	Choroidal Neovascularization
CRVO	Central Retinal Vein Occlusion
CV	Cardiovascular
DA	Disc Area
DME	Diabetic Macular Edema
ECG	Electrocardiogram
ECQAT	Eligibility Confirmation and Quality Assurance Team
ERG	Electroretinogram
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICH	International Conference on Harmonisation
IDMC	Independent Data Safety Monitoring Committee
IRC	Independent Reading Center
IOP	Intraocular Pressure
ITT	Intent to Treat
IV	Intravenous
LOCF	Last Observation Carried Forward
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NLP	No Light Perception
NOS	Not Otherwise Specified
OCT	Optical Coherence Tomography
PD	Pharmacodynamics
PDT	Photodynamic Therapy
PEG	Polyethylene Glycol
PK	Pharmacokinetics
RNA	Ribonucleic Acid
SAE	Serious adverse event
SD	Standard Deviation
SOC	System Organ Class
US	United States
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
VHL	Von Hippel-Lindau Disease

1. PURPOSE OF THE DOCUMENT

This document presents an overview of the efficacy and safety data from the clinical development program with pegaptanib sodium injection (pegaptanib) in patients with neovascular age-related macular degeneration (AMD) for discussion at the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting of 27 August 2004.

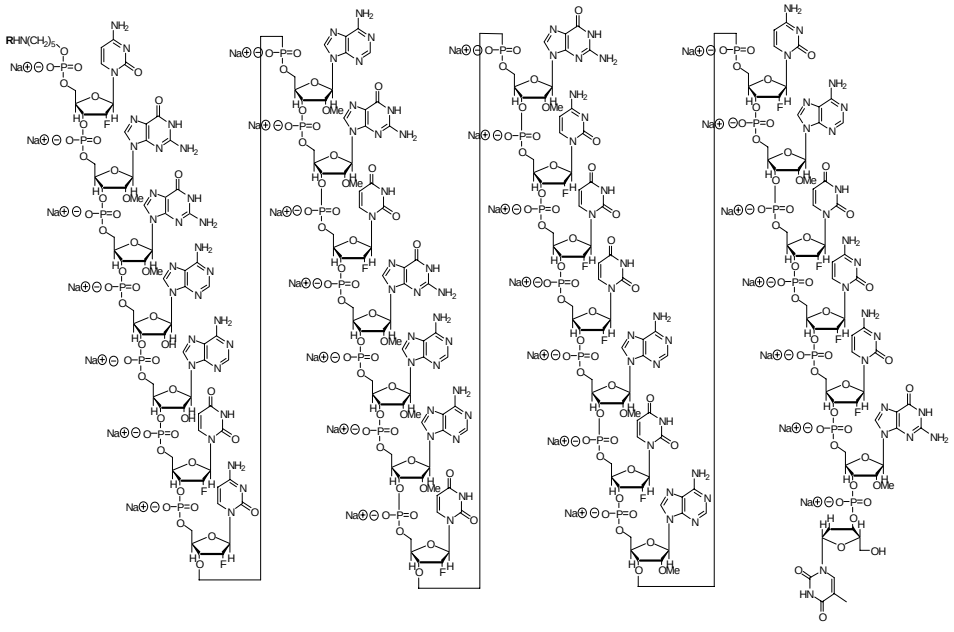
2. PEGAPTANIB OVERVIEW

2.1. Chemical Name and Structure

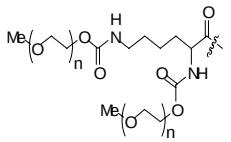
Pegaptanib is a pegylated synthetic ribonucleic acid (RNA)-based oligonucleotide that acts as a vascular endothelial growth factor (VEGF) antagonist. The chemical name for pegaptanib is as follows: RNA, ((2'-deoxy-2'-fluoro)C-G_m-G_m-A-A-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-A_m-G_m-(2'-deoxy-2′-fluoro)U-G_m-A_m-A_m-(2'-deoxy-2'-fluoro)U-G_m-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)U-A_m-(2'-deoxy-2'-fluoro)U-A_m-(2'-deoxy-2'-fluoro)C-A_m-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-G_m-(3'→3')-dT), 5'-ester with α,α'-[4,12-dioxo-6-[[[5-(phosphoonoxy)pentyl]amino]carbonyl]-3,13-dioxa-5,11-diaza-1,15-pentadecanediyl]bis[ω-methoxypoly(oxy-1,2-ethanediyl)], sodium salt.

The molecular formula for pegaptanib sodium is $C_{294}H_{342}F_{13}N_{107}Na_{28}O_{188}P_{28}[C_2H_4O]_n$ (where n is approximately 900) and the molecular weight is approximately 50 kilodaltons.

Figure 1. Chemical Structure of Pegaptanib Sodium



Where R is



and n is approximately 450.

2.2. Proposed Indication

Pegaptanib is indicated for the treatment of neovascular AMD.

2.3. Dosage and Administration

The recommended dose of pegaptanib for the indication of neovascular AMD is 0.3 mg administered every 6 weeks as an intravitreous injection.

Pegaptanib sodium injection is supplied in a single use, pre-filled 1 mL glass syringe and is formulated as a 3.47 mg/mL solution to deliver a dose of 0.3 mg pegaptanib (based on the oligonucleotide weight) in a nominal volume of 90 μL. The product is a sterile, clear, preservative-free solution containing sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, hydrochloric acid and sodium hydroxide in water for injection. Each syringe is fitted with a 27-gauge needle and is contained in an outer package. The accompanying plunger rod and flange are in a separate package.

3. DEVELOPMENT RATIONALE

3.1. Disease Background

AMD is characteristically a disease occurring in patients older than 55 years of age and has long been recognized as the single leading cause of irreversible severe vision loss in developed countries around the world[1,2, 3, 4, 5, 6, 7, 8, 9]. It is a disease characterized by progressive degenerative abnormalities in the macula, a small area in the central portion of the retina.

AMD is classified as two different types: the non-neovascular (or dry) form and the neovascular (or wet) form of the disease. The dry form is the most prevalent, accounting for 90% of cases of the disease however, neovascular AMD is responsible for the majority of cases of severe vision loss[10].

Neovascular AMD is characterized by choroidal neovascularization beneath the retina. The neovascular tissue leaks blood and fluid, and, untreated, eventually progresses to scarring with destruction of the macula[11] and loss of vision. The angiogenesis and hyperpermeability that characterize neovascular AMD are common to all angiographic lesion subtypes.

Patients suffer a loss of the ability to recognize faces, read and drive, and require assistance with activities of daily living[12]. For these elderly patients, the impact of the disease is devastating. Neovascular AMD is a major public health concern, will increase in incidence as a direct result of the increasing age of the population and is a significant humanistic and economic burden to individuals and societies throughout the world[8, 13].

It has been estimated that there are approximately 200,000 new cases of neovascular AMD each year in the United States (US)[14]. In the US at present, as many as 15 million people suffer from some form of AMD with more than 1.6 million experiencing the active blood vessel growth and leakage associated with neovascular AMD[15, 16]. Rates are now considered to be similar between men and women[17] although in previous studies it was found that women might have a higher incidence of AMD than men[18, 19]. AMD appears more prevalent among Caucasians [17, 20, 21, 22].

3.2. Unmet Medical Need

There is no Food and Drug Administration (FDA) approved therapy for the treatment of most patients with neovascular AMD.

Thermal laser photocoagulation therapy has been available since the 1980s as a treatment for a very small group of neovascular AMD patients with well-defined extrafoveal, or juxtafoveal lesions. Thermal laser treatment results in an immediate scotoma when applied to subfoveal lesions[23, 24, 25]. Trials with this therapy were performed in a very selective patient population and the therapy is not generally applicable to a wider population[26]. The recurrence rate approaches 50% at one year[26].

Photodynamic therapy with verteporfin (PDT), FDA approved in the US in 2000, is an alternative treatment strategy that relies on the interaction of laser light directed at a neovascular AMD lesion in patients pretreated with a systemically administered photosensitizer dye. In the US, PDT with verteporfin has been approved only for patients with the predominantly classic subfoveal choroidal neovascularization angiographic lesion subtype (in which classic choroidal neovascularization [CNV] comprises ≥ 50% of total lesion size). PDT often cannot be applied when the area of active choroidal neovascularization is greater than 9 disc areas in size and/or is obscured by blood[27]. The Centers for Medicare and Medicaid Services recently decided to reimburse a subset of minimally classic and occult with no classic lesions in patients with neovascular AMD.

In conclusion, neovascular AMD remains an area of high unmet medical need and is a major public health issue in an aging population.

3.3. Scientific Background

Pegaptanib belongs to a new class of compounds, with a novel mechanism of action that has not been previously investigated for the indication of neovascular AMD.

Pegaptanib acts as a VEGF antagonist to inhibit the angiogenesis and vascular hyperpermeability induced by VEGF, which collectively contribute to the disease progression and vision loss characteristic of neovascular AMD. Nonclinical models have strongly implicated VEGF in the pathogenesis of ocular neovascularization, including the choroidal neovascularization that characterizes neovascular AMD[28, 29, 30, 31, 32, 33, 34].

Pegaptanib binds to extracellular $VEGF_{165}$ with high affinity (Kd = 200 pM) and specificity, thereby inhibiting $VEGF_{165}$ binding to its receptors. Experimental studies have demonstrated that $VEGF_{165}$ levels are selectively increased in ocular diseases manifesting neovascularization and/or vascular hyperpermeability[35,36]. Also, in contrast with $VEGF_{121}$, another prevalent VEGF isoform, $VEGF_{165}$ more potently triggers vascular inflammation, an important feature of pathological neovascularization and vascular leakage. Pegaptanib does not bind to any significant degree to $VEGF_{121}$ which has been shown to be critical to physiological neovascularization[35]. In an animal model of retinal neovascularization, selective $VEGF_{165}$ inhibition with pegaptanib was as effective at suppressing pathological neovascularization as was non-selective VEGF inhibition[35]. However selective $VEGF_{165}$ blockade specifically spared the normal developing vasculature while non-selective VEGF blockade did not[35].

Clinical findings suggest that the different angiographic lesion subtypes (i.e., classic and occult) share common pathophysiological features, most importantly abnormal neovascularization and increased vascular permeability[37, 38, 39, 40]. Additionally, VEGF is expressed around all neovascular AMD lesions, regardless of angiographic subtype[41, 42, 43]. Therefore, pegaptanib activity in the inhibition of VEGF induced vascular proliferation and fluid leakage was expected to provide benefit in all neovascular AMD lesions.

4. NONCLINICAL PROGRAM

The pegaptanib nonclinical toxicology program supports the safety of pegaptanib at the clinical therapeutic doses of 0.3 up to 3 mg/eye administered by intravitreous injection every 6 weeks.

In the toxicology program, intravenous (IV) pegaptanib doses ranged from 0.1 mg/kg/day to 40 mg/kg/day in subchronic studies and up to 450 mg/kg in acute studies. Intravitreous doses of pegaptanib ranged from 0.25 to 2 mg/eye (single dose) and from 0.1 to 3 mg/eye (multiple dose up to 9 months). In general, no systemic or local compound-related findings were observed following acute and chronic intravitreous administration of pegaptanib (bilateral injections). Due to the high tolerability of pegaptanib following both systemic and intravitreous administration, no maximum tolerated dose (MTD) was established. The maximum intravitreous dose of pegaptanib was limited by drug viscosity and ocular vitreous volume. Pegaptanib was not teratogenic in mice at doses up to 40 mg/kg/day IV; limited effects on fetal body weight and delayed ossification of forepaw phalanges were observed at the highest dose (40 mg/kg/day, which is approximately 4000 times higher exposure than the highest dose, 3 mg, investigated in clinical studies). No maternal toxicity was observed.

The cardiovascular (CV), respiratory and neurobehavioral (central nervous system, CNS) safety of pegaptanib was assessed in a standard battery of the International Conference on Harmonisation (ICH) compliant studies. Pegaptanib was administered IV to Beagle dogs (CV) and Sprague Dawley rats (respiratory and CNS studies) to achieve systemic concentrations up to 10-fold higher than those observed in humans after a 3 mg/eye monocular dose. Pegaptanib had no effects on CV, CNS or respiratory parameters. Renal functional parameters from the chronic intravitreous toxicology studies in dogs (0.3 to 3 mg/eye every 2 weeks for 9 months) and monkeys (0.1 to 1 mg/eye every 2 weeks for 3 months) were used to assess renal safety. There were no compound-related changes in renal function based on urinalysis and clinical chemistry in these studies.

Ocular adverse effects (fibrin deposition, ocular discharge, conjunctival irritation, vitreous floaters, traumatic cataracts, retinal detachments) noted in the non-clinical intravitreous repeat-dose studies were considered related to the intravitreous injection procedure, including the pre-operative preparative procedure, because they were observed across treatment groups including sham. A transient increase in intraocular pressure (IOP) was consistently observed in all treatment groups including vehicle controls. The risk of injection-related effects is inherent with the intravitreous route of administration. There were no electroretinogram (ERG) findings suggestive of toxicity to the retina in dogs given the 3 mg dose every 2 weeks for 9 months.

5. CLINICAL PHARMACOLOGY

The clinical pharmacology program has been conducted in AMD patients with concomitant diseases typical of the elderly and is therefore representative of potential recipients of pegaptanib injection in the general patient population.

5.1. Pharmacokinetics

Pegaptanib plasma concentrations in patients with neovascular AMD were quantified by a validated, dual hybridization method. The lower limit of quantification of the dual hybridization assay is 8 ng/mL, and pegaptanib was found to be stable in EDTA-formed plasma.

Characterization of pegaptanib pharmacokinetics (PK) in humans is limited to plasma concentrations at high doses. Vitreous PK in humans have not been described due to ethical concerns with regard to the safety risks associated with vitreous sampling. In animals, following 0.5 mg/eye doses to both eyes, systemic concentrations of pegaptanib are low (0.03% to 0.15% of those levels in the vitreous humor). IV doses which would allow characterization of pegaptanib's systemic clearance and absolute bioavailability have not been administered to humans. However, given the local route of administration, an understanding of the systemic disposition of pegaptanib was not expected to be decisive in identifying the optimal dose/regimen of pegaptanib injection for human use.

In animals, pegaptanib is slowly absorbed into the systemic circulation from the eye after intravitreous administration. The rate of absorption from the eye is the rate limiting step in the disposition of pegaptanib in animals (systemic plasma concentrations parallel vitreous concentrations after an intravitreous dose) and is likely to be in humans also.

A mean maximum plasma concentration of about 80 ng/mL occurs within 1 to 4 days after a 3 mg monocular dose of pegaptanib in humans. The mean area under the plasma concentration-time curve (AUC) is about 25 μg·hr/mL at this dose. At doses below 0.3 mg/eye, pegaptanib plasma concentrations are not likely to exceed 10 ng/ml. The maximum systemic plasma concentrations following a 0.3 mg intravitreous dose are more than 100-fold less than the concentrations observed in the nonclinical toxicology studies at the no-observed-adverse-effect-level (NOAEL) doses. Low circulating levels of pegaptanib are seen 4 to 6 weeks after an intravitreous 3 mg dose, and are below the lower limits of quantification (LLOQ, 8 ng/ml) of the assay after a 0.3 mg dose.

In animals, pegaptanib distributes primarily into plasma volume and is not extensively distributed to peripheral tissues after intravenous administration. Twenty-four hours after intravitreous administration of a radiolabeled dose of pegaptanib to both eyes of rabbits, radioactivity was mainly distributed in vitreous fluid, retina and aqueous fluid. After intravitreous and IV administrations of radiolabeled pegaptanib to rabbits, the highest concentrations of radioactivity (excluding the eye for the intravitreous dose) were obtained in the kidney.

In AMD patients, there is no accumulation of pegaptanib in plasma after multiple dosing every 6 weeks regardless of dose. The mean ± standard deviation apparent terminal half-life of pegaptanib in plasma after intravitreous dosing is 10 ± 4 days at the 3 mg dose. This half-life is

called an apparent half-life because it does not represent the elimination of the drug from the plasma; instead it represents the exit of pegaptanib out of the eye into the systemic circulation. This fact has implications in how the systemic exposure to pegaptanib is viewed; low circulating levels of pegaptanib relative to that in the vitreous humor will be present as pegaptanib slowly enters the circulation. Once in the systemic circulation, pegaptanib is readily cleared from the body. In rabbits, it is eliminated as parent drug and metabolites primarily in the urine.

Data in AMD patients after a 3 mg intravitreous dose indicate that pegaptanib plasma concentrations are similar in women to those in men and in patients whose age ranged from 50 to 90 years. Patients with severe renal insufficiency (creatinine clearance < 30 mL/min) have not been studied. Based on a clinical study (EOP1006) with pegaptanib 3 mg, reduced renal clearance, as described as a decrease in creatinine clearance from 70 mL/min to 30 mL/min, was associated with a 2-3 fold increase in AUC. However, a dosage adjustment is not warranted for patients whose creatinine clearance is > 30 mL/min and who are treated with 0.3 mg pegaptanib, as the pharmacokinetic data indicate that this dose would not produce exposures exceeding those seen with the 3 mg dose. No anti-pegaptanib immunoglobulin IgG antibodies were detected in patients dosed with pegaptanib.

6. CLINICAL PROGRAM

Data from six clinical studies with pegaptanib in patients with neovascular AMD are discussed in this document. Two of these studies are still ongoing, in addition to other studies in neovascular AMD and other indications. An overview of all the studies is given in Table 1.

Clinical phase 1/2 safety studies NX 109-01, EOP1000 and EOP1001 were without dose-limiting toxicities. No unexpected retinal vascular or choroidal changes or abnormalities were observed on angiography as read by the Independent Reading Center. The studies showed preliminary evidence of efficacy in patients with neovascular AMD.

The prospective, pivotal phase 2/3 efficacy studies, EOP1003 and EOP1004, were powered to detect a clinically meaningful treatment benefit (the proportion of patients losing less than 15 letters of VA) between active treatment and sham after 54 weeks of treatment. The natural history of neovascular AMD is of rapid progression,[44, 45, 46, 47, 48] and usually significant vision loss is observed within 1 year of onset. The selection of one year endpoints for efficacy data was thus appropriate for this indication and has a historical precedent in the marketing approval for Visudyne® (verteporfin for injection). The patients are being following into the second year for continued safety assessment and to evaluate the requirement for further treatment, however, all primary and secondary endpoints relate to data collected up to the first 54 weeks on study. Thus data from these studies are presented in accordance with the protocol and statistical analysis plan and represent the pre-specified time points for reporting.

At this time, only the indication for neovascular AMD is being sought and this document focuses on the pivotal studies EOP1003 and EOP1004 which support the safety and efficacy of pegaptanib in this indication. Other clinical studies with pegaptanib are currently ongoing; in diabetic macular edema (DME, EOP1002 and EOP1005, phase I and phase II studies); Von Hippel-Lindau Disease (VHL, EOP1007; a five-patient pilot study); macular edema secondary to central retinal vein occlusion (CRVO, EOP1011; a phase II study); neovascular AMD, including a safety and PK study (1006; phase 2), a study of the effect of pegaptanib on foveal

thickening as measured by optical coherence tomography (OCT) and the correlation between foveal thickening and visual acuity (EOP1009; a phase II study) and a compassionate use protocol using 0.3 mg pegaptanib (EOP1010) (Table 1).

Table 1. Overview of All Clinical Studies with Pegaptanib

Protocol	Design	Dose	Patients	Study Assessments
NX109-01	Phase 1, multi-center, open-label escalating dose, dose finding	Single intravitreous injection of either 0.25, 0.5, 1, 2 or 3 mg pegaptanib/ eye	15 patients ≥ 50 years of age with neovascular 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 intravitreous injections of 3 mg pegaptanib/eye, 28 days apart	10 patients ≥ 50 years of age with subfoveal CNV secondary to neovascular 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 intravitreous injections of 3 mg pegaptanib/ eye, 28 days apart	11 patients ≥ 50 years of age with predominantly classic subfoveal CNV secondary to neovascular AMD	BCVA, AEs, IOP, laboratory parameters, vital signs, DLT, PK parameters, immune response, requirement for PDT administration, local ocular events
EOP1002	Phase 1/2, multi-center, open-label, single dose	3 to 6 intravitreous injections of 3 mg pegaptanib/eye every 6 weeks	10 patients ≥ 18 years of age with clinically significant ME secondary to DR	AEs, laboratory parameters, BCVA
EOP1003	Phase 2/3 multi-center, randomized, controlled, double masked, dose finding	Intravitreous injections of either 0.3, 1 or 3 mg pegaptanib/eye or sham every 6 weeks for 54 weeks	622 patients ≥ 50 years of age with subfoveal CNV secondary to neovascular AMD	BCVA, fluorescein angiography and fundus photography, AEs, IOP, laboratory parameters, vital signs, local ocular events
EOP1004	Phase 2/3 multi-center, randomized, controlled, double masked, dose finding	Intravitreous injections of either 0.3, 1 or 3 mg pegaptanib/eye or sham every 6 weeks for 54 weeks	586 patients ≥ 50 years of age with subfoveal CNV secondary to neovascular AMD	BCVA, fluorescein angiography and fundus photography, AEs, IOP, laboratory parameters, vital signs, local ocular events, PK, QOL
EOP 1005	Phase 2, multicenter, randomized, controlled, double masked, dose finding	Intravitreous injections of either 0.3, 1 or 3 mg pegaptanib/eye or sham every 6 weeks for 80 weeks	169 patients with DME	BCVA, retinal thickening by OCT, angiography and fundus photography, AEs, IOP, laboratory parameters, vital signs, local ocular events.

Table 1. Overview of All Clinical Studies with Pegaptanib (cont)

Protocol	Design	Dose	Patients	Study Assessments
EOP1006	Phase 2 multi-center, randomized, multiple dose (partially open-label, partially masked)	Intravitreous injections of 3 mg (or 1mg in double masked phase) pegaptanib/ eye every 6 weeks for 54 weeks	147 patients ≥ 50 years of age with subfoveal CNV secondary to neovascular AMD	AE, local ocular events, IOP, laboratory parameters, vital signs, PK parameters, immune response
EOP1007	Phase 1/2 single center, non-randomized, multiple dose, open-label	Intravitreous injections of 3 mg pegaptanib/ eye every 6 weeks for 54 weeks	5 patients with Von Hippel Lindau Disease.	BCVA, fluorescein angiography and fundus photography, AEs, IOP, laboratory parameters, vital signs, local ocular events
EOP1009	Phase 2 multi-center, randomized, controlled, double masked, multiple dose	Intravitreous injections of 0.3 or 1.0 mg pegaptanib/ eye every 6 weeks for 54 weeks	135 patients ≥ 50 years of age with subfoveal CNV secondary to neovascular AMD and retinal thickness ≥ 300 microns.	BCVA, retinal thickening by OCT, angiography and fundus photography, AEs, IOP, laboratory parameters, vital signs, local ocular events.
EOP1010	Open-label, non-comparative, compassionate use protocol, 0.3 mg dose	Intravitreous injections of 0.3 pegaptanib/eye every 6 weeks	Maximum 1000 patients, ≥50 years of age, with subfoveal CNV secondary to AMD and with BCVA of 20/40 to 20/320 in the absence of subfoveal atrophy. Patients should not be eligible for PDT with Visudyne®.	AEs
EOP1011	Phase 2 multi-center, randomized, controlled, double masked, multiple dose	Intravitreous injections of 0.3 or 1.0 mg pegaptanib/ eye or sham every 6 weeks for 30 weeks	90 patients ≥ 18 years of age, with macular edema secondary to CRVO, diagnosed within 6 months of study start. BCVA 20/50 to 20/400, center point macular thickness by OCT ≥ 250 μm.	AEs, laboratory parameters, OCT, fluorescein angiography, color fundus photography, PK

AE = Adverse Event; BCVA = Best Corrected Visual Acuity; CNV = Choroidal Neovascularization; CRVO = Central Retinal Vein Occlusion; DLT = Dose Limiting Toxicity; DE = Diabetic Retinopathy; IOP = Intraocular Pressure; ME = Macular Edema; PK = Pharmacokinetics; QOL = Quality of Life: PDT = Photodynamic Therapy with Verteporfin; OCT = Optical Coherence Tomography.

7. PIVOTAL STUDIES

7.1. Study Design

Studies EOP1003 and EOP1004 were conducted according to Good Clinical Practice (GCP) and were prospective, multi-center, randomized, controlled, double masked, parallel group, fixed dose comparison studies. Study EOP1003 was conducted in Europe (EU), Israel, Australia, US, Canada and South America; study EOP1004 was conducted in the US and Canada. EOP1003 and EOP1004 were conducted under identical protocols with the exception that QOL assessments were only included in study EOP1004.

Patients in each study were randomized to one of four treatment groups (0.3 mg pegaptanib, 1 mg pegaptanib, 3 mg pegaptanib or sham injections once every 6 weeks) and were scheduled to receive 9 intravitreous or sham injections for 48 weeks with a follow up period to 54 weeks. At 54 weeks, patients in the pegaptanib arms were re-randomized (1:1) to either discontinue or continue on treatment for a further 48 weeks (8 injections) primarily to assess the safety and need for longer term therapy. Those patients receiving sham injections were re-randomized at week 54 on a 1:1:1:1:1 basis to discontinue treatment, to continue on study receiving one of the 3 active treatments, or to continue on sham therapy.

The randomization was stratified by study center, by percentage of classic CNV: predominantly classic (≥50% classic CNV), minimally classic (1-49% classic CNV), occult with no classic (0% classic CNV); and according to whether or not study patients had received prior PDT (no more than one prior PDT was permitted).

The objective of both studies was to establish the safe and efficacious dose of pegaptanib when given as intravitreous injection compared with sham every 6 weeks over a 54-week period in patients with CNV secondary to AMD.

Substantial efforts were made to minimize bias in these trials and double-masking was implemented to minimize the chance that treatment allocation would be revealed to any of the study participants or investigators conducting the clinical assessments. The double-masking procedures included the following:

- The physician involved in patient assessments or decisions was masked as a different physician was responsible for administering treatment;
- The patients were masked as the sham injection procedures were identical to active drug procedures (including application of lid speculum, instillation of topical anti-infective, and injection of subconjunctival anesthetic) except for the actual penetration into the vitreous (pressure was applied against the globe with a needle-less syringe for the sham injection);
- The visual acuity examiners were masked to treatment arm and previous vision assessments;
- The Reading Center was masked to treatment arm.

Independent monitoring of aspects of the study was undertaken by an Independent Reading Center (IRC) to confirm eligibility and angiographic subtype for purposes of stratification at randomization. Note that during the study, however, the masked investigator was responsible for assessing angiographic subtype and leakage to determine whether patients qualified for

PDT (which was permitted only for patients with predominantly classic lesions, per the approved label) and if treatment was advised. This was an important feature of the study design, simulating ordinary patient management by allowing physicians to determine appropriate PDT usage. The IRC was, however, responsible for surveillance of inappropriate PDT administration.

An Independent Data Safety Monitoring Committee (IDMC) reviewed safety on an ongoing basis.

All VA examiners were required to be certified to perform refraction and VA testing and each site was required to have at least 2 certified VA examiners on site. The physical facility and all equipment was certified to ensure all sites were using equivalent techniques. The sites were to be visited for assessment on at least a yearly basis.

Only one eye was treated for each patient (study eye); the other eye (fellow eye) was always untreated.

The data from the pre-specified time point for the primary analysis (54 weeks, up to 9 injections) have been analyzed and form the basis for the claim of efficacy for pegaptanib injection in the treatment of neovascular AMD.

7.1.1. Doses Investigated

The doses investigated (0.3 mg, 1 mg and 3 mg) were selected on the basis of nonclinical and clinical pharmacology and pharmacokinetic information with the expectation that VEGF neutralization could be maintained for intervals up to 6 weeks with doses of 0.3 mg or greater. No doses above 3 mg could be investigated due to the viscosity of the injection solution. All doses investigated were expected to have the potential for efficacy based on VEGF neutralization. The highest dose (3 mg) had not been associated with any significant toxicities in Phase 1/2 clinical trials.

7.2. Patient Population

The entry criteria for these prospective trials were very broad in order to ensure that the study population resembled the general neovascular AMD population as closely as possible.

- Patients with all neovascular AMD angiographic lesion subtypes (predominantly classic, minimally classic and occult with no classic) were included;
- Patients with a broad range of lesion sizes (up to 12 disc areas of which 50% had to be active CNV and no more than 50% blood) were included;
- Patients with a broad range of baseline VA (20/40 to 20/320) for the study eye were included;
- Patients with typical concomitant diseases of the elderly were not excluded (about half of the population was hypertensive at baseline, over a quarter were using statin-class drugs, and one in five had cardiovascular disease at baseline);

- PDT was permitted to be used concomitantly with pegaptanib at the discretion of the masked investigators only in patients with predominantly classic angiographic lesion subtype as per the approved label.
- The studies had considerably wider entry criteria than previously reported AMD studies with other agents[48, 49].

The study population included patients of either gender, aged ≥50 years with subfoveal CNV secondary to AMD and with best-corrected VA in the study eye between 20/40 and 20/320 and better than or equal to 20/800 in the fellow eye. Subretinal hemorrhage and/or lipid and/or ≥3 line loss in VA in previous the 12 weeks were to be documented for minimally classic and occult with no classic angiographic lesion subtypes. Excluded were patients with previous subfoveal thermal laser therapy, posterior vitrectomy, or scleral buckling surgery; recent intraocular surgery; acute ocular or periocular infection; history of more than one prior PDT; significant media opacities that might interfere with visual acuity, assessment of toxicity or fundus photography. Also excluded were patients with a history or evidence of severe cardiac disease: myocardial infarction within 6 months, ventricular tachyarrythmias or unstable angina; history or evidence of peripheral vascular disease; clinically significant impaired renal or hepatic function, stroke (within 12 months of study entry) or previous therapeutic radiation to the eye, head, or neck.

Classification of the angiographic lesion subtypes was implemented prospectively by an Eligibility Confirmation and Quality Assurance Team (ECQAT) using the Wilmer Technology Assessment Program based at the Wilmer Ophthalmological Institute, Baltimore, Maryland, to verify patient eligibility and classify the lesions using angiograms at baseline for purposes of stratification at randomization. Consistent classification of the angiographic subtypes was thought at the time to be potentially important, and the reading center ensured that the same criteria (often subjective) were being applied between centers and regions, particularly given the geographical separation of the two studies.

Patients with a history of up to one past PDT could be enrolled only if the PDT occurred 8 – 13 weeks prior to their first study treatment.

PDT was permitted during the studies at the discretion of the masked treating physician only for patients with predominantly classic lesions according to the approved label. Therefore, PDT use during the studies was not randomized. This permitted patients to receive PDT according to the prevalent practice patterns. Although the ultimate decision of whether a lesion was predominantly classic, and thus eligible for treatment, and the decision to treat a patient with PDT was investigator based, the reading center reviewed usage and provided feedback for violations.

7.3. Efficacy Endpoints

7.3.1. Primary Efficacy Endpoint

In both studies, the primary efficacy endpoint was the proportion of Responders, defined as patients losing less than 15 letters of best-corrected VA in the study eye from baseline up to 54 weeks, using the Early Treatment Diabetic Retinopathy Study [ETDRS] chart[50].

Distance VA is considered a clinically meaningful measure of visual outcome in patients with neovascular AMD. The threshold of 15 letters corresponds to approximately 3 lines on the ETDRS vision chart, which is a doubling of the visual angle and is regarded as a clinically meaningful change for an individual patient. The endpoint was selected following FDA advice and has a historical precedent in the marketing approval of Visudyne® (verteporfin for injection).

The natural history of neovascular AMD is of rapid progression[45, 46, 47, 48, 49,] and usually significant vision loss is observed within 1 year of onset. Thus, the selection of one year time points for efficacy data was appropriate for this indication and has a historical precedent in the marketing approval of Visudyne® (verteporfin for injection) as well.

7.3.2. Secondary Efficacy Parameters

Pre-specified secondary efficacy endpoints were:

- The proportion of patients gaining ≥15 letters of vision from baseline to 54 weeks;
- The proportion of patients maintaining or gaining ≥ 0 letters of vision from baseline to 54 weeks; and
- The change in mean VA from baseline to 6, 12 and 54 weeks.

7.3.3. Other Pre-specified Efficacy Endpoints

In addition to the primary and secondary efficacy endpoints, additional efficacy data were collected and other efficacy endpoints included:

- Mean change in visual acuity from baseline to 54 weeks prior to every injection
- 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
- Proportion of patients receiving PDT at any time during the course of the study
- National Eye Institute Visual Function Questionnaire 25 measurements (QOL, EOP1004 only)

7.4. Safety Endpoints

Safety was assessed by adverse event reporting, ophthalmic examination, tonometry (intraocular pressure (IOP) measurements), laboratory assessments and vital signs. Safety endpoints were adverse events (AE) (including ocular AEs and serious adverse events [SAE]), IOP, clinical laboratory data, vital signs and loss of 20 letters (4 lines) of visual acuity between injections.

7.5. Summary of Statistical Analysis Plan

7.5.1. Sample Size

Sample size calculations were based on the estimation that approximately 50% of untreated patients would lose ≥15 letters of vision at 54 weeks. All tests of significance were two-sided

and the significance level was set at 5%. With the assumption that treatment would reduce the proportion of patients losing ≥15 letters of vision at 54 weeks by 20% and assuming that 10% of all patients would be ineligible or unevaluable, 135 patients per group were recruited and randomized in each study to provide an overall power of 95%.

7.5.2. Treatment Comparisons

A pre-specified statistical test was required due to multiple dose comparisons in the individual studies. After discussion with the FDA, the Hochberg's statistical procedure was chosen to control Type I error from multiple testing at 0.05.

Following discussion with the FDA, the EOP1004 trial, which was recruited and thus completed before study EOP1003, was unmasked and analyzed prior to the EOP1003 trial. This was undertaken to enable the selection of doses to be analyzed in the primary comparisons of the EOP1003 trial before it was unmasked. The analysis of the study EOP1004 showed that the 3 mg dose group did not reach statistical significance for the primary endpoint compared to the sham injection. Consequently, prior to unmasking of the EOP1003 trial, the Sponsor notified the FDA that the pre-specified comparisons to the sham group in study EOP1003 would be restricted only to the 0.3 mg and the 1 mg dose groups.

For the analysis of the primary endpoint, a pre-specified Cochran-Mantel-Haenszel statistic was used with the following pre-specified baseline characteristics: prior PDT use, baseline angiographic lesion subtype, baseline visual acuity and baseline lesion size. This was implemented to account for the potential contributions of baseline characteristics on the analysis.

The main population used for analysis of the primary efficacy endpoint was a pre-specified intent-to-treat (ITT) population, defined as all patients receiving treatment in the studies who had baseline VA assessments, with the last observation carried forward to account for missing data at week 54.

7.5.3. Combined and Baseline Characteristics Analyses

The two trials EOP1003 and EOP1004 were sufficiently similar in design and patient recruitment to enable statistical analyses to be planned and performed on the data from both trials combined. In all analyses of the combined data, study effect (i.e., 1003 or 1004) was included in the statistical model. Listed p-values for the combined data analyses are nominal.

The individual trials were not designed to assess efficacy by baseline characteristics. A combined analysis was performed for descriptive purposes to assess potential trends in patients with baseline characteristics such as: angiographic lesion subtype, age, gender, history of prior PDT, degree if iris pigmentation (post-hoc), baseline visual acuity, and lesion size.

7.5.4. Post-hoc Analyses

The FDA requested an analysis of the proportion of patients losing at least 15 letters of vision over time (at 3 months, 6 months, 9 months, and 12 months) for each treatment group. Additionally, an analysis of the proportion of patients experiencing severe vision loss (loss of ≥ 30 letters from baseline to week 54) was performed.

8. PATIENT POPULATIONS AND DEMOGRAPHICS

8.1. Patient Populations

The analysis populations from each of the studies included a similar proportion of patients (Table 2). The rates of protocol violation were low and similar between treatment groups and across studies. The majority of patients in each treatment group for both studies were available for assessment at week 54.

Table 2. Patient Populations

Number (%) of Patients*	Pegaptanib 0.3 mg	Pegaptanib 1 mg	Pegaptanib 3 mg	Sham
EOP1004				
All-randomized[1]	144 (100%)	147 (100%)	147 (100%)	148 (100%)
Safety[2]	144 (100%)	146 (99%)	143 (97%)	145 (98%)
Intention to treat[3]	144 (100%)	146 (99%)	143 (97%)	144 (97%)
Per-protocol[4]	142 (99%)	141 (96%)	139 (95%)	139 (94%)
Week 54 observed[5]	132 (92%)	131 (89%)	125 (85%)	133 (90%)
EOP1003				
All-randomized[1]	153 (100%)	158 (100%)	155 (100%)	156 (100%)
Safety[2]	151 (99%)	155 (98%)	153 (99%)	153 (98%)
Intention to treat[3]	150 (98%)	154 (97%)	153 (99%)	152 (97%)
Per-protocol[4]	142 (93%)	147 (93%)	147 (95%)	147 (94%)
Week 54 observed[5]	139 (91%)	144 (91%)	139 (90%)	142 (91%)
Combined Analysis				
All-randomized[1]	297 (100%)	305 (100%)	302 (100%)	304 (100%)
Safety[2]	295 (99%)	301 (99%)	296 (98%)	298 (98%)
Intention to treat[3]	294 (99%)	300 (98%)	296 (98%)	296 (97%)
Per-protocol[4]	284 (96%)	288 (94%)	286 (95%)	286 (94%)
Week 54 observed[5]	271 (91%)	275 (90%)	264 (87%)	275 (90%)

[*] Percentage of All-randomized population
[1] All patients who were randomized to receive study treatment (whether treated or not)
[2] All patients who received at least one study treatment (treated population)
[3] Patients who received masked study treatment and had complete baseline visual acuity assessments
[4] Patients in the ITT population without any major protocol deviations and with at least one post-baseline VA measurement.
[5] Patients in the ITT population who had visual acuity assessments at baseline and week 54.
ITT = Intent to Treat

8.2. Treatment Discontinuations

The rate of patient discontinuation was low and similar across treatment groups and between studies. Very few patients withdrew consent or dropped out for any reason. Overall, 90% of patients in the pegaptanib arms and 92% in the sham arm (combined analysis) completed the study. The mean number of doses administered (8.5 of a maximum of 9) was similar among treatment arms (Table 3).

Table 3. Patients Discontinued from Treatment and Study Treatments Administered

	Pegaptanib			Sham
Number of Patients*	**0.3 mg**	**1 mg**	**3 mg**	
EOP1004	N=144	N=146	N=143	N=145
Total Discontinuations	12 (8%)	17 (12%)	20 (14%)	11 (8%)
Reason: Patient request[1]	5 (3%)	6 (4%)	12 (8%)	7 (5%)
Death	3 (2%)	6 (4%)	3 (2%)	2 (1%)
Adverse event	2 (1%)	1 (1%)	2 (1%)	1 (1%)
Lost to follow up	1 (1%)	2 (1%)	0 (0%)	0 (0%)
Investigator/ Sponsor decision	1 (1%)	0 (0%)	2 (1%)	1 (1%)
Other	0 (0%)	2 (1%)	1 (1%)	0 (0%)
Mean (SD) number of injections**	8.4 (1.5)	8.4 (1.4)	8.4 (1.4)	8.5 (1.4)
EOP1003	N=151	N=155	N=153	N=153
Total Discontinuations	11 (7%)	13 (8%)	17 (11%)	12 (8%)
Reason: Patient request[1]	6 (4%)	8 (5%)	7 (5%)	4 (3%)
Death	2 (1%)	2 (1%)	3 (2%)	4 (3%)
Adverse event	1 (1%)	3 (2%)	4 (3%)	3 (2%)
Lost to follow up	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Investigator/ Sponsor decision	1 (1%)	0 (0%)	2 (1%)	0 (0%)
Other	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Mean (SD) number of injections**	8.4 (1.6)	8.6 (1.3)	8.5 (1.4)	8.6 (1.2)
Combined Analysis	N=295	N=301	N=296	N=298
Total Discontinuations	23 (8%)	30 (10%)	37 (13%)	23 (8%)
Reason: Patient request[1]	11 (4%)	14 (5%)	19 (6%)	11 (4%)
Death	5 (2%)	8 (3%)	6 (2%)	6 (2%)
Adverse event	3 (1%)	4 (1%)	6 (2%)	4 (1%)
Lost to follow up	1 (0%)	2 (1%)	1 (0%)	0 (0%)
Investigator/ Sponsor decision	2 (1%)	0 (0%)	4 (1%)	1 (0%)
Other	1 (0%)	2 (1%)	1 (0%)	1 (0%)
Mean (SD) number of injections**	8.4 (1.5)	8.5 (1.4)	8.4 (1.4)	8.6 (1.3)

* Safety population
** From maximum of 9 injections
[1] Patient request included: withdrawal of consent, patients no longer wished to participate, change in family or home circumstances, withdrawal of consent following adverse events, general poor health reasons.
SD = Standard Deviation

8.3. Patient Demographics

The baseline and demographic data reflect that the inclusion and exclusion criteria delivered study populations generally in accordance with the neovascular AMD population described in the literature [18, 19, 20, 21, 22].

Both studies exhibited a slight excess in the female to male ratio and the majority of patients (96% of the total population) were Caucasian. The mostly Caucasian population in the studies reflects the demographics of this disease[20, 21]. The median age of all patients was 77 years and was similar between the studies. The demographic data within each study were as expected for a neovascular AMD patient population (Table 4).

Lesion size at baseline was comparable between groups. Both studies were stratified and thus well balanced by angiographic lesion subtype across the four treatment arms and the distribution was similar between the two studies (Table 4). The overall enrollment by angiographic lesion subtype in both studies was 26% predominantly classic, 36% minimally classic and 38% occult with no classic, which is representative of the general neovascular AMD population[51, 52, 53].

Mean baseline VA in the study eye was comparable across all treatment arms in both studies (Table 4). The use of prior PDT was balanced across treatment arms within each trial although there was a slightly greater incidence of PDT use in EOP1004 (North America) as compared with EOP1003 (mainly Europe) which seems to reflect geographical and cultural variations in clinical practice at that time. Other baseline data were similar among treatment arms and between studies.

In both studies, the concomitant medical history and medications used suggest that the patients in the two studies are representative of a general elderly population of patients with AMD. At baseline, approximately half of the population was hypertensive, one in five had cardiovascular disease, and more than 25% of patients were on a statin (HMG CoA reductase inhibitor) cholesterol-lowering agent.

Table 4. Demographic and Baseline Data

	Study EOP1004				Study EOP1003				Combined Analysis			
	Pegaptanib			Sham	Pegaptanib			Sham	Pegaptanib			Sham
	0.3 mg	1 mg	3 mg		0.3 mg	1 mg	3 mg		0.3 mg	1 mg	3 mg	
Safety Population	**N=144**	**N=146**	**N=143**	**N=145**	**N=151**	**N=155**	**N=153**	**N=153**	**N=295**	**N=301**	**N=296**	**N=298**
Demographic Data												
Female/ Male (%)	56/44	53/47	69/31	57/43	54/46	56/44	61/39	63/37	55/45	55/45	65/35	60/40
Mean (SD) age	78.0 (7.0)	76.5 (6.8)	77.1 (7.5)	76.7 (6.6)	74.9 (7.4)	74.5 (7.2)	75.4 (7.1)	74.9 (7.6)	76.4 (7.4)	75.5 (7.1)	76.2 (7.3)	75.7 (7.2)
Range (years)	58 - 92	52 - 92	56 - 97	55 - 89	53 - 90	53 - 90	53 - 89	52 - 92	53 - 92	52 - 92	53 - 97	52 - 92
Race												
Caucasian	97%	98%	99%	97%	95%	95%	95%	94%	96%	97%	97%	95%
Hispanic	1%	1%	1%	3%	5%	3%	5%	3%	3%	2%	3%	3%
Asian	1%	0%	0%	0%	0%	1%	1%	1%	1%	0%	0%	0%
Black	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%
Other	0%	1%	0%	1%	1%	0%	0%	0%	0%	0%	0%	1%
Baseline Lesion Size (DA) Mean (SD)	3.6 (2.2)	4.4 (2.5)	3.6 (2.5)	4.3 (2.6)	3.8 (2.5)	3.7 (2.3)	3.7 (2.4)	4.0 (2.9)	3.7 (2.4)	4.0 (2.4)	3.7 (2.5)	4.2 (2.8)
Baseline Stratification Factors												
Angiographic lesion subtype												
Predominantly classic	26%	26%	29%	26%	23%	26%	25%	25%	24%	26%	27%	26%
Minimally classic	35%	35%	35%	34%	40%	37%	36%	34%	38%	36%	35%	34%
Occult	39%	39%	36%	40%	37%	37%	39%	41%	38%	38%	38%	40%
Prior PDT with verteporfin	13%	14%	14%	11%	4%	6%	4%	3%	8%	10%	9%	7%
Baseline Visual Assessments – Study Eye												
Visual Acuity Score[1]	N=144	N=146	N=143	N=144	N=150	N=154	N=153	N=152	N=295	N=300	N=296	N=296
Mean[2]	52.5	50.5	52.1	54.0	53.0	50.9	50.1	51.3	52.8	50.7	51.1	52.7
Range	23 - 74	19 - 73	14 - 73	27 - 74	11 - 75	22 - 77	22 - 76	21 – 75	11 – 95	19 - 77	14 - 76	21 - 75

[1] Measured in Early Treatment Diabetic Retinopathy Study (ETDRS) letters;
[2] Baseline Snellen Equivalent Visual Acuity approximately 20/80 to 20/100
SD = Standard Deviation, DA = Disc Area

9. EFFICACY DATA

9.1. Summary of Efficacy

Data from the two pivotal clinical trials clearly indicate a treatment benefit for patients with neovascular AMD treated with pegaptanib at a dose of 0.3 mg or 1 mg given by intravitreous injection every six weeks over a period of 54 weeks.

- Pegaptanib 0.3 mg achieved statistical significance for a clinically meaningful primary efficacy endpoint (% of patients losing less than 15 letters of VA) in two replicate, well-controlled clinical trials (EOP1004, p=0.0031, EOP1003, p=0.0115).
- In addition, pegaptanib 1 mg also showed a statistically significant treatment benefit for the primary efficacy endpoint compared with sham in study EOP1003 (p=0.0035) and was near to significance in EOP1004 (p=0.0273; significance threshold = 0.025 using Hochberg).
- Results for the other pre-specified endpoints consistently supported the treatment benefit demonstrated by pegaptanib 0.3 mg and 1 mg for the primary efficacy endpoint in both studies.
- Patients receiving 0.3 mg or 1 mg pegaptanib were more likely to maintain or gain VA (0.3 mg, 33%, p=0.0032; 1 mg 37%, p=0.0006) than sham patients (23%) at 54 weeks in the combined analysis. Patients receiving 0.3 mg or 1 mg pegaptanib were also more likely to gain three lines of VA than sham (p=0.0401 for 0.3 mg and p=0.0238 for 1 mg versus sham for three line gain) at 54 weeks.
- The onset of pegaptanib efficacy was evident as early as the first post-treatment study visit (Week 6) and increased over time up to Week 54, as measured by mean visual acuity loss from baseline to each study visit, in the combined analysis compared with sham ($p \leq 0.007$ at every time point).
- Fewer patients progressed to 20/200 or worse visual acuity in the pegaptanib 0.3 mg (38%, $p \leq 0.0001$) or 1 mg (43%, $p \leq 0.0001$) group compared with sham (56%) in the combined analysis from baseline to Week 54.
- Severe vision loss (loss of ≥30 letters of VA) was more than twice as likely in sham treated patients (22%) as in pegaptanib 0.3 mg (10%, p<0.0001) or 1 mg (8%, p<0.0001) treated patients in the combined analyses.
- Treatment benefit with pegaptanib was present in patients in the combined data set with all analyzed baseline characteristics, including baseline angiographic subtype or size, baseline visual acuity, age, gender, prior PDT usage and degree of iris pigmentation.
- Pegaptanib 0.3 mg is the lowest efficacious dose that was studied, as the treatment benefit conferred by pegaptanib 1 mg and 3 mg was not above that seen at the 0.3 mg dose level.

The results of the efficacy analyses validate the importance of $VEGF_{165}$ in the pathogenesis of neovascular AMD, and demonstrate further that continuous inhibition of $VEGF_{165}$ for 54 weeks results in a statistically significant and clinically meaningful benefit for the patient.

9.2. Primary Efficacy Endpoint

The statistically significant treatment benefit of pegaptanib 0.3 mg compared with sham treatment has been replicated in 2 prospective trials in the analysis of the primary endpoint using the pre-specified ITT population with the Hochberg procedure (Table 5).

Table 5. Primary Efficacy Endpoint

	Pegaptanib			Sham
	0.3 mg	**1 mg**	**3 mg**	
EOP1004				
ITT population	N=144	N=146	N=143	N=144
Responders*	67%	66%	61%	52%
p-value	0.0031	0.0273	0.1294	-
EOP1003				
ITT population	N=150	N=154	N=153	N=152
Responders*	73%	75%	69%	59%
p-value	0.0105	0.0035	Not applicable	-
Combined Analysis				
ITT population	N=294	N=300	N=296	N=296
Responders*	70%	71%	65%	55%
p-value	<0.0001	0.0003	0.0310	-

*Responders = patients who lost <15 letters VA from baseline to week 54.
Not applicable as the 3 mg dose level was excluded from analysis in Study EOP1003;
For missing data, the Last Observation Carried Forward method was used. Adjusted for study (combined analysis), angiographic lesion subtype, prior photodynamic therapy with verteporfin, baseline vision and baseline lesion size
ITT = Intent to Treat

In addition, in study EOP1003, pegaptanib 1 mg also showed a statistically significant treatment benefit compared with sham (p=0.0035) and was near to significance in EOP1004 (p=0.0273; significance threshold = 0.025 using Hochberg).

In the combined primary analysis, a positive treatment effect was demonstrated for all three active dose groups compared with sham (0.3 mg: p<0.0001, 1 mg: p=0.0003, 3 mg: p=0.0310). The 1 mg and 3 mg doses showed no additional benefit over the 0.3 mg dose.

Due to low rates of discontinuation and low rates of protocol violation, other analyses of the primary efficacy endpoint that account for missing data and protocol violations supported the primary analysis in both studies.

9.3. Other Visual Acuity Endpoints

The results from the primary efficacy analysis were comparable between the studies. In addition, the design of the study and patient analysis populations were sufficiently similar to permit combination of the studies. Data for secondary and additional endpoints, which are mainly for supportive purposes, are therefore presented for the combined studies analysis.

9.3.1. Pre-specified Secondary Efficacy Endpoints

Table 6. Efficacy Data – Secondary Endpoints (Combined Analysis)

	Pegaptanib			Sham
ITT Population	0.3 mg N=294	1 mg N=300	3 mg N=296	N=296
Secondary Efficacy Endpoint - % Patients Gaining ≥ 15 Letters VA, Baseline - Week 54				
Vision gain ≥ 15 letters	6%	7%	4%	2%
p-value	0.0401	0.0238	0.1588	
Secondary Efficacy Endpoint - % Patients Maintaining or Gaining ≥ 0 Letters VA, Baseline - Week 54				
Maintaining or gaining ≥ 0 letters	33%	37%	31%	23%
p-value	0.0032	0.0006	0.0210	
Secondary Efficacy Endpoint – Mean Changes in VA, Weeks 6, 12 and 54*				
Mean change in VA Week 6	-1.53	-1.20	-2.29	-4.03
p-value	0.0069	0.0036	0.1722	
Mean change in VA Week 12	-3.22	-2.14	-4.01	-6.32
p-value	0.0037	0.0002	0.0898	
Mean change in VA Week 54	-7.99	-7.27	-9.78	-15.03
p-value	<0.0001	<0.0001	0.0017	

* Letters of Visual Acuity. Analysis of covariance model
VA = Visual Acuity

Patients Gaining ≥15 Letters

Vision gain of 15 letters or more from baseline to Week 54 was seen in a small proportion of patients in each treatment arm (Table 6). For the combined analysis, 6% of patients in the 0.3 mg (p=0.0401) and 7% of patients in the 1 mg (p=0.0238) arms compared with 2% in the sham arm showed vision gain of 15 or more letters. For the 3 mg arm, 4% of patients showed a vision gain of ≥15 letters compared with sham (2%).

Patients Maintaining or Gaining ≥0 Letters

Maintaining or gaining ≥0 letters of VA was seen more frequently following pegaptanib treatment, demonstrating the ability of pegaptanib to not only prevent moderate VA loss but also to stabilize and even improve VA as well. For the combined analysis, 33% of patients in the 0.3 mg arm (p=0.0032), 37% in the 1 mg arm (p=0.006) and 31% in the 3 mg arm (p=0.0210) maintained vision or gained vision compared with 23% in the sham arm (Table 6).

Mean Change in VA

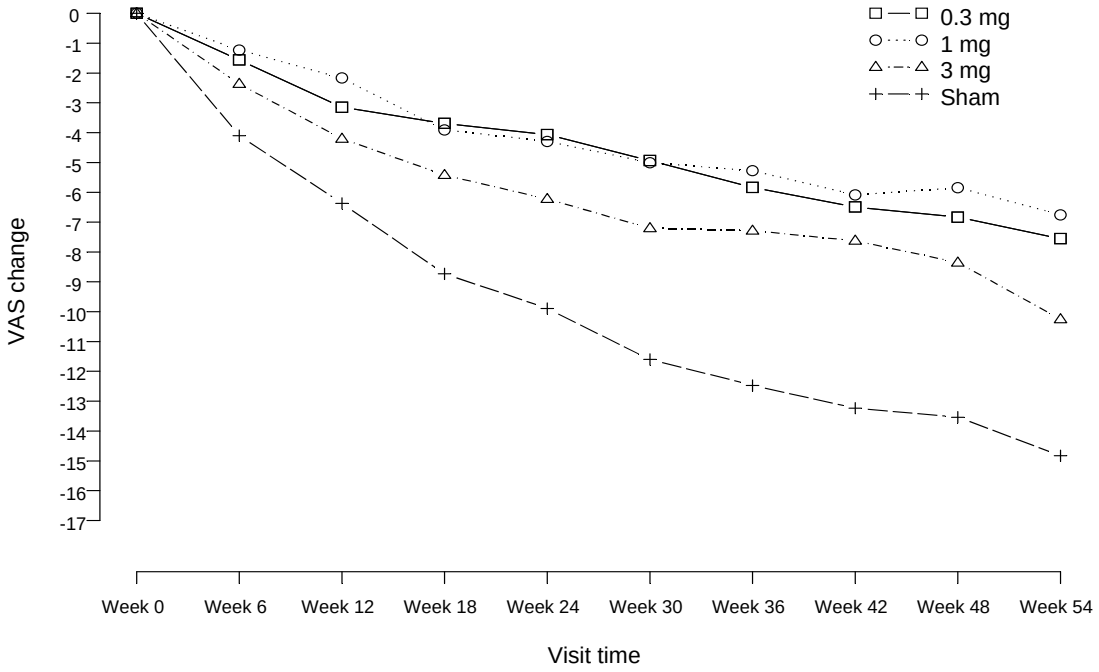
The change in visual acuity from baseline to 6, 12 and 54 weeks was analyzed for each time point (Table 6). In both studies, patients lost more vision in the sham arm than in any active treatment arm. In the combined analysis this effect was evident at the earliest measured time point and continued to increase through 54 weeks, with very low p-values for all active doses at all time points compared with sham.

9.3.2. Other Pre-specified Efficacy Endpoints

Mean VA Over Time

The change in VA from baseline to prior to every injection up to 54 weeks is shown for the combined analysis in Figure 2. The data in the figure are the actual observed data without imputing missing values.

Figure 2. Mean Change in VA Over Time (Combined Analysis)



VAS = Visual Acuity Score

At every time point, a smaller mean decrease in visual acuity from baseline is shown in the active treatment arms compared with the sham arm. The beneficial treatment effect is seen as early as Week 6 and is increased throughout the treatment period. As depicted by the graph, the slope representing the rate of mean vision loss in the control group is not linear. Rather, it is steeper during the first 6 months, with about two thirds of year-end mean vision loss occurring by Week 24, and thereafter the slope begins to flatten out. This feature is in accord with expectations of rapid vision loss early in the natural history of neovascular AMD followed by a slower rate of change[45, 46, 47, 48, 49,]. In contrast, the rate of mean VA loss is slower for all the active treatment arms, indicating that pegaptanib appears to prevent the otherwise immediate, precipitous drop in vision typical of neovascular AMD (reflected in the sham arm).

Table 7. Efficacy Data – Other Endpoints and Post-hoc Analyses (Combined Analysis)

	Pegaptanib			Sham
ITT Population	0.3 mg N=294	1 mg N=300	3 mg N=296	N=296
Other Efficacy Endpoint - % Patients with 20/200 or Worse VA at Baseline and Week 54				
Patients with 20/200 vision or worse				
Baseline	15%	21%	18%	15%
Week 54	38%	43%	44%	56%
p-value	<0.0001	0.0001	0.0014	
Post-hoc Efficacy Endpoint - % Patients with Severe Vision Loss (≥ 30 Letters VA)				
Patients losing ≥ 30 letters VA from Baseline to Week 54	10%	8%	14%	22%
p-value	<0.0001	<0.0001	0.0142	
Post-hoc Efficacy Endpoint - % Patients Losing ≥15 Letters VA from Baseline to Months 3, 6, 9 and 12				
Patients Losing ≥15 letters from Baseline to Month 3	13%	14%	15%	20%
p-value	0.0121	0.0490	0.1320	
Month 6	18%	20%	24%	36%
p-value	<0.0001	<0.0001	0.0034	
Month 9	25%	24%	25%	41%
p-value	<0.0001	<0.0001	0.0001	
Month 12	30%	29%	35%	45%
p-value	<0.0001	0.0003	0.0310	

VA = Visual Acuity

Snellen Equivalent VA 20/200 or Worse in the Study Eye at Week 54

Visual acuity of 20/200 or worse in both eyes constitutes legal blindness in many states/countries. The pegaptanib treatment arms showed superior activity in slowing the progression of the disease as shown by the smaller percentage of patients with Snellen equivalent vision of 20/200 or worse in the study eye for the active arms compared with the sham arm (Table 7). In both studies at week 54, the percentage of patients with a Snellen Equivalent 20/200 VA or worse was smaller in all active treatment groups (0.3 mg group 38%, 1 mg group 43%, 3 mg group 44%) compared with sham (56%).

9.3.3. Post-hoc Efficacy Analyses

Patients losing ≥15 Letters of Vision at 3, 6, 9 and 12 Months

In both studies, a smaller proportion of patients in the active treatment groups lost 15 or more letters of VA than in the sham group at all measured time points during the 54 weeks (Table 7). The treatment benefit of all active doses compared with sham was evident in the combined analysis at the earliest analyzed time point (3 months) and was increased at 12 months. The treatment benefit observed was associated with small p-values for the 0.3 mg and 1 mg treatment arms compared with sham at every time point. The 3 mg arms also showed small p-values compared with sham from 6 months onwards.

Severe Vision Loss

Patients in the sham group (22%) were more than twice as likely to experience severe vision loss (loss of ≥30 letters) as patients treated with pegaptanib 0.3 mg (10%, $p<0.0001$) or 1 mg (8%, $p<0.0001$). In the 3 mg arm, 14% of patients experienced severe vision loss(Table 7).

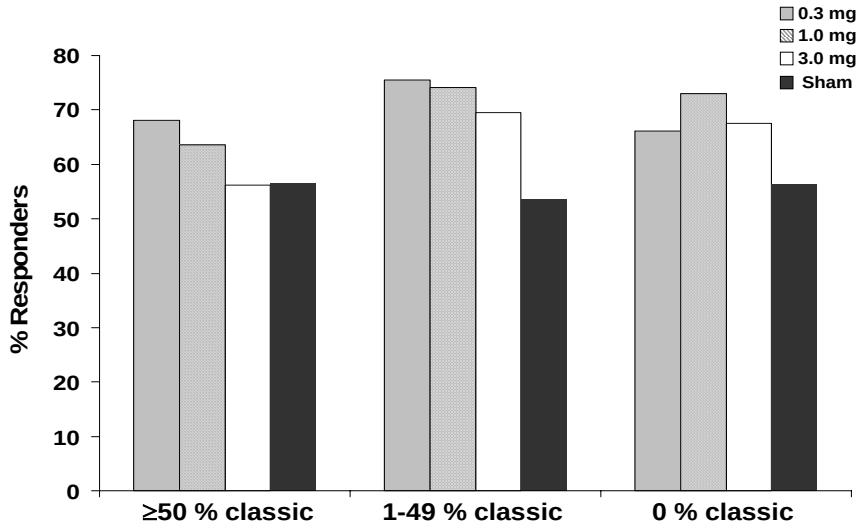
9.4. Influence of Baseline Characteristics on Overall Efficacy

Since pathological neovascularization and VEGF expression are common to all patients with neovascular AMD, it was hypothesized that inhibition of angiogenesis with pegaptanib would provide a broad based treatment benefit. Therefore, the studies enrolled patients with a wide spectrum of baseline characteristics. Although the individual studies were only powered to detect a treatment effect in the overall patient population, it was of interest to understand the influence of various patient baseline characteristics on efficacy. Therefore, analysis of the primary endpoint was performed in patients with various baseline characteristics, including angiographic lesion subtype, age, gender, baseline visual acuity, baseline lesion size, history of prior PDT use, and degree of iris pigmentation (post-hoc), to determine if the efficacy demonstrated for the overall study patient population appeared concentrated in one particular group of patients.

For the primary efficacy endpoint, in the combined analysis patients with each of the analyzed baseline characteristics received a treatment benefit with pegaptanib. Of particular interest was angiographic lesion subtype and baseline lesion size, because in studies of a previously approved treatment for neovascular AMD (Visudyne®, verteporfin for injection) efficacy appeared to be concentrated in patients with predominantly classic lesions and smaller lesions. In contrast, for pegaptanib, statistical tests (Breslow-Day tests for homogeneity) indicated that none of the analyzed baseline characteristics listed above, including angiographic lesion subtype and size, contributed disproportionately to the overall efficacy observed (this is represented with $p>0.05$ for all doses and all analyzed baseline characteristics).

An analysis of the primary endpoint according to angiographic lesion subtype using the combined data is shown in Figure 3 .

Figure 3. Proportion of Responders (losing less than 15 letters of VA) by Angiographic Lesion Subtype, Combined Analysis (54 Weeks)

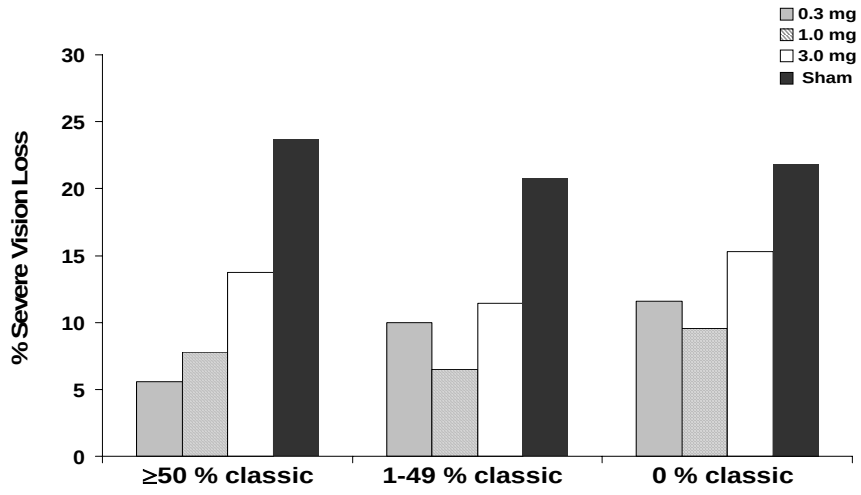


Responders: decrease of less than 15 letters of VA.

The proportion of Responders (primary efficacy endpoint, % of patients losing less than15 letters of VA) was higher in pegaptanib 0.3 and 1 mg treated patients than in sham patients for all angiographic subtypes.

To provide further evidence of treatment benefit in all angiographic subtypes, an analysis demonstrating the ability of pegaptanib to prevent severe vision loss (% of patients losing ≥ 30 letters of VA) was performed (Figure 4).

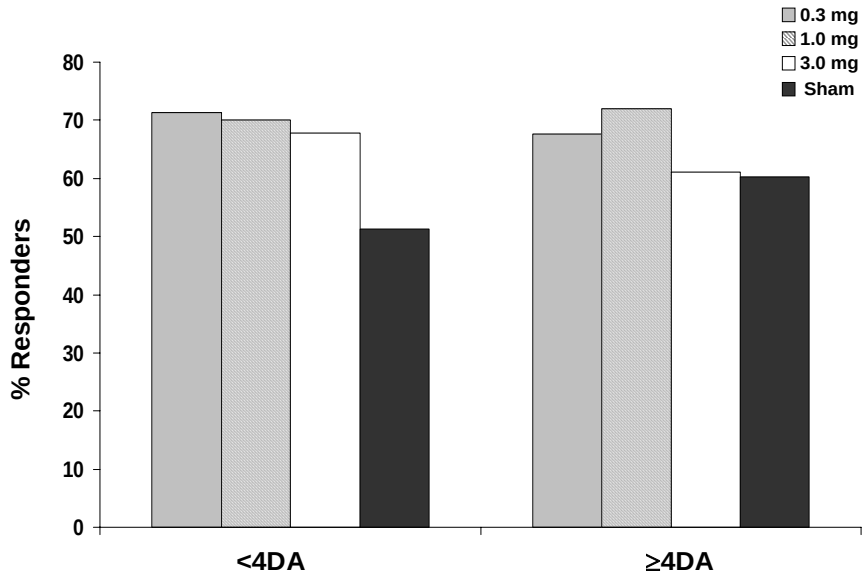
Figure 4. Proportion of Patients with Severe Vision Loss (losing ≥ 30 letters of VA) by Angiographic Lesion Subtype, Combined Analysis (54 Weeks)



For every angiographic subtype, a substantially lower proportion of treated patients progressed to severe vision loss relative to sham. This treatment benefit was evident for all 3 doses of pegaptanib.

The mean total lesion size for all treatment groups at baseline was approximately 4 disc areas. To assess the potential influence of baseline lesion size on efficacy, the primary endpoint was therefore assessed according to whether lesions were greater than or equal, to 4 disc areas or less than 4 disc areas at baseline.

Figure 5. Proportion of Responders (losing less than 15 letters of VA) by Lesion Size, Combined Analysis (54 Weeks)



Responders: decrease of less than 15 letters of VA.
DA = Disc Area

The proportion of Responders (primary efficacy endpoint, % of patients losing less than 15 letters of VA) was higher in pegaptanib 0.3 and 1 mg treated patients than in sham patients for both categories of lesion size.

9.5. PDT Use

At the time the studies were being planned and initiated, PDT with verteporfin was approved for patients with the predominantly classic angiographic subtype in the US and EU but the pattern of usage was not yet established. Ethical considerations required that PDT be permitted in patients with predominantly classic lesions at the discretion of the investigators as per the approved label. The inclusion of PDT represented an important feature of the study design, in which pegaptanib efficacy was tested against a background of usual care so that results could be more reasonably extrapolated to the general population. Of a total 577 PDT treatments administered in the combined studies from baseline to Week 54, the Independent Reading Center agreed with investigators that PDT use was appropriate 92% of the time.

Prior PDT

Patients were permitted to have had a history of up to one PDT in the study eye prior to the studies if it had been administered between 8 and 13 weeks before their baseline study visit. To provide comparable treatment groups, patients were stratified at randomization based on whether or not they had a history of prior PDT (Table 8).

On-Study PDT

At the patient's baseline visit (from 2 weeks before the first injection up to 2 weeks after the first injection) and thereafter during the study period (post-baseline), physicians were permitted to use their clinical judgment in determining PDT use, provided that PDT was administered only to patients with predominantly classic lesions, in accordance with the approved label. The investigators were masked as to the treatment arm of the patients when they decided if the patients could benefit from PDT administration during the studies.

The majority (78%) of study patients never received PDT while on study (at or post-baseline), and 75% of study patients never received PDT at any time (no history of prior PDT or on study PDT).

Because patients were not randomized to receive on-study PDT, inherent bias limits the interpretation of efficacy with and without it. For instance, the patient's response to study treatment might have influenced the physicians' decision to use PDT; i.e., physicians might have been more likely to administer PDT to those patients experiencing a poor response to treatment (channeling bias). As a result, assessment of efficacy in only those patients who did not receive PDT, for example, would select for the subset of patients who were either ineligible for PDT or who were responding relatively well to study treatment, thereby leaving the assessment of pure pegaptanib treatment effect unanswered for the general study patient population.

Demonstrating this analytical problem and the potential effects of channeling bias, patients in the control group who never received PDT on-study were more likely to be Responders than those who did receive PDT on-study (59% vs. 45%, respectively).

One indirect way of ascertaining whether concomitant PDT use contributed to pegaptanib efficacy is to assess relative PDT usage between treatment arms. The pegaptanib and sham groups were well-balanced with respect to prior and baseline PDT use (Table 8). In contrast, a higher proportion of patients in the sham group than in the pegaptanib group received post-baseline PDT (Table 8). Further, the average number of post-baseline PDT treatments per patient was higher in the sham arm (2.33) than in any active treatment arm (1.44 in the 0.3 mg arm, 1.92 in the 1 mg arm, 2.13 in the 3 mg arm) in patients receiving baseline PDT (Table 8), all suggesting, if anything, a possible bias against pegaptanib. It can therefore be concluded that the pegaptanib treatment benefit was present despite increased PDT usage in the sham patients.

Table 8. PDT Use in the Study Eye (Combined Analysis)

	Pegaptanib			Sham
	0.3 mg N=294	1 mg N=300	3 mg N=296	N=296
% Patients Receiving PDT with Verteporfin Prior to the Study[1]				
Patients with prior PDT	8%	10%	9%	7%
% Patients Receiving PDT with Verteporfin at Baseline[2]				
Patients with baseline PDT	13%	10%	13%	14%
% Patients Receiving PDT with Verteporfin Post-Baseline[3]				
Patients with post-baseline PDT	17%	18%	19%	21%
Mean number post-baseline PDT treatments*	1.44	1.92	2.13	2.33

[1] One PDT administration permitted if between 8 and 13 weeks prior to the study; based on stratification data, safety population (Table 2)
[2] PDT administration within 2 weeks before or after first injection; ITT population (Table 2)
[3] PDT administration thereafter during study period; ITT population (Table 2)
* Mean number of post-baseline PDT treatments per patient in those patients who received PDT at baseline.
PDT = Photodynamic Therapy , ITT = Intent to Treat

9.6. Quality of Life (EOP1004)

Quality of life was assessed only in study EOP1004, conducted in the US and Canada, as the questionnaire was only validated in the English language. Study 1004 provided evidence of positive trends in quality of life benefit associated with effective treatment of AMD using pegaptanib. The size of the study was, however, insufficient to show statistically significant differences in the primary or secondary quality of life scale scores between the effective doses and sham.

9.7. Efficacy Conclusions

- Pegaptanib 0.3 mg achieved statistical significance for a clinically meaningful primary efficacy endpoint (% of patients losing less than 15 letters of VA) in two replicate, well-controlled clinical trials (EOP1004, p=0.0031, EOP1003, p=0.0115).
- In addition, pegaptanib 1 mg also showed a statistically significant treatment benefit for the primary efficacy endpoint compared with sham in study EOP1003 (p=0.0035) and was near to significance in EOP1004 (p=0.0273; significance threshold = 0.025 using Hochberg).
- Results for the other pre-specified endpoints consistently supported the treatment benefit demonstrated by pegaptanib 0.3 mg and 1 mg for the primary efficacy endpoint in both studies.
- Patients receiving 0.3 mg or 1 mg pegaptanib were more likely to maintain or gain VA (0.3 mg, 33%, p=0.0032; 1 mg 37%, p=0.0006) than sham patients (23%) at 54 weeks in the combined analysis. Patients receiving 0.3 mg or 1 mg pegaptanib were also more likely to gain three lines of VA than sham (p=0.0401 for 0.3 mg and p=0.0238 for 1 mg versus sham for three line gain) at 54 weeks.
- The onset of pegaptanib efficacy was evident as early as the first post-treatment study visit (Week 6) and increased over time up to Week 54, as measured by mean visual acuity loss

from baseline to each study visit in the combined analysis compared with sham ($p \leq 0.007$ at every time point).

- Fewer patients progressed to 20/200 or worse visual acuity in the pegaptanib 0.3 mg (38%, $p \leq 0.0001$) or 1 mg (43%, $p \leq 0.0001$) group compared with sham (56%) in the combined analysis from baseline to Week 54.
- Severe vision loss (loss of ≥30 letters of VA) was more than twice as likely in sham treated patients (22%) as in pegaptanib 0.3 mg (10%, $p<0.0001$) or 1 mg (8%, $p<0.0001$) treated patients in the combined analyses.
- Treatment benefit with pegaptanib was present in patients in the combined data set with all analyzed baseline characteristics, including baseline angiographic subtype or size, baseline visual acuity, age, gender, prior PDT usage and degree of iris pigmentation.
- Pegaptanib 0.3 mg is the lowest efficacious dose that was studied, as the treatment benefit conferred by pegaptanib 1 mg and 3 mg was not above that seen at the 0.3 mg dose level.

10. SAFETY DATA

Safety data are based primarily on the combined analysis of the first year (54 weeks, 9 injection regimen) data from the pivotal studies EOP1003 and EOP1004. Significant adverse events from other studies were described in the NDA submission as well as in the Safety Update submitted to the FDA in July 2004. No new safety concerns have emerged and the conclusions regarding the safety of pegaptanib are lent further support.

10.1. Summary of Safety

Pegaptanib administered by intravitreous injection was well tolerated at the doses investigated with few patients withdrawing from the studies due to adverse events (1-2% of patients across all treatment groups, combined analysis).

There was no evidence of any systemic toxicity. Most serious systemic adverse events were those that would be expected in an elderly patient population and were similar to those in sham patients.

Ocular adverse events were common, predictable and reported as mostly mild or moderate and resolved without sequelae (Table 16). The majority of the events in the study eye were attributed by the investigators to the injection procedure, and relatively few events were attributed to study drug. Ocular adverse events were generally reported in a higher proportion of patients in the sham study eye than in the fellow (contralateral) eye for any treatment arm. This suggests that many of these events may be related to the pre-intravitreous injection procedure (including use of an eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine drops or flush and subconjunctival injection of anesthetic) rather than the intravitreous injection procedure itself.

Ocular serious adverse events, such as endophthalmitis, iatrogenic traumatic cataract and retinal detachment, were infrequent and were assessed by the investigators to be mostly related to the injection procedure. No unexpected retinal vascular or choroidal changes were seen on fluorescein angiograms as read by the Independent Reading Center. There were no sustained vascular occlusions in the study eye at any time during the study.

The incidence of endophthalmitis was low (12 out of 892 patients in the active arms, 1.3% patients per year of treatment, or 12 out of 7545 injections, 0.16% per injection). Only one patient with endophthalmitis experienced severe vision loss (≥ 30 letters). In approximately 70% of endophthalmitis cases, there was at least one violation of the injection procedure (e.g., no eyelid speculum). Of the 12 endophthalmitis cases, 9 (75%) patients remained in the study.

There is no evidence that pegaptanib treatment resulted in cataract progression, other than the iatrogenic traumatic cataracts. The risk of iatrogenic traumatic cataract events (5 out of 892 patients, 0.6% patients per year of treatment or 5 out of 7545 injections, 0.07% per injection) may be reduced with greater experience in performing intravitreous injections.

There were 5 retinal detachments, two of which were exudative/hemorrhagic in nature and may have been secondary to the underlying disease process. The other 3 retinal detachments had a rhegmatogenous component (3 out of 892 patients, 0.3% patients per year of treatment or 3 out of 7545 injections, 0.04% per injection). In one patient the rhegmatogenous retinal detachment was status post vitrectomy/lensectomy for vitreous hemorrhage, and was attributed to proliferative vitreoretinopathy with contracture of the retina. One patient had a history of lattice degeneration in the study eye and a retinal detachment in the fellow eye; this patient had two retinal tears and a supero-nasal rhegmatogenous retinal detachment in the study eye. The third patient had a history of retinoschisis and had a superior rhegmatogenous retinal detachment with multiple small holes in the study eye. Investigators were instructed to administer the intravitreous injections in the infero-temporal quadrant of the eye.

There is some evidence that pegaptanib injection is associated with mild anterior chamber inflammation although this was also seen in the sham arm. This was not dose dependent and is considered to be due to, at least in part, the injection preparation procedure (eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine drops or flush, subconjunctival injection of anesthetic) as well as to the intravitreous injection. The condition was almost always reported as mild. There were no reports of severe or serious anterior chamber inflammation, nor did any patient discontinue due to this event.

There is no evidence that ocular AEs increase in incidence over time. The AEs were compared according to occurrence during the 1^{st} - 3^{rd} injections vs. 4^{th} –6^{th} vs. 7^{th} –9^{th} injections by the number of patients who received injections within those periods. Within the ocular AEs, there was no increase in anterior chamber inflammation over time, which is important as it provides evidence that pegaptanib does not sensitize the eye to inflammation.

There is no evidence of a persistent increase in IOP associated with pegaptanib. As would be anticipated, a transient increase in intraocular pressure was noted after intravitreous injections. The mean IOP measured 30 minutes post-injection was 2-4 mm Hg higher than pre-injection IOP, with the highest mean increases seen in the 3 mg group. Investigators were instructed to not permit patients to leave the physician's office until the IOP returned to below 30 mm Hg.

The post-injection increases in intraocular pressure were manageable and did not require intervention in the majority of cases. There were no discontinuations due to increased IOP.

There were no differences between doses for almost all safety assessments with the possible exception that transient intraocular pressure (IOP) elevations of ≥ 35 mmHg (a monitoring

threshold suggested by the IDMC) were more frequently observed in the 3 mg arm than the 0.3 mg or 1 mg arms.

10.2. Exposure to Pegaptanib

Data from 1273 patients in 6 clinical studies of pegaptanib in neovascular AMD and 2 studies of pegaptanib in DME (EOP1002, 10 patients; study EOP1005 is ongoing - only SAEs from the 169 patients are reported) were assessed for safety. This included 975 patients receiving active therapy and 298 patients receiving sham injections (study EOP1005 is still masked) (Table 9).

In the overall clinical development program, almost all patients received doses of either 0.3 mg, 1 mg or 3 mg of pegaptanib as intravitreous injections (Table 10). A small number of patients in study NX109-01 received single doses of 0.25 mg (3 patients), 0.5 mg (3 patients), or 2 mg (3 patients) in additional to those receiving the 1 mg and 3 mg doses (3 patients each).

Table 9. Exposure

	Pegaptanib				Sham
Number of Patients	**0.3 mg**	**1 mg**	**3 mg**	**All Doses***	
Controlled trials, neovascular AMD, all patients	295	301	296	**892**	**298**
Non-controlled trials, neovascular AMD, all patients[1]	0	3	61	**73**	**0**
DME Patients[2], EOP1002	0	0	10	**10**	**0**
Overall Total	295	304	367	**975**	**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 (37 patients);
[2]Study EOP1005 is not included as it is ongoing and has not been unmasked.
AMD = Age-related macular degeneration; DME = Diabetic Macular Edema

Table 10. Number of Injections Administered

	Pegaptanib				Sham
Total number of injections	**0.3 mg N=295**	**1 mg N=304**	**3 mg N=367**	**All Doses* N=975**	**N=298**
Studies 1003 and 1004 AMD	2478	2568	2499	**7545**	**2557**
Phase 1/2 AMD studies		3	62	**74**	
Study 1006[1] AMD			218	**218**	
Study 1002[2] DME			53	**53**	
Total	2478	2571	2832	**7890**	**2557**

*Includes 0.25 mg , 0.5 mg and 2 mg doses from study NX109-01
[1]Only completed cohort is included
[2]Study EOP1005 is not included as it is ongoing and has not been unmasked
AMD = Age-related macular degeneration; DME = Diabetic Macular Edema

Almost 1000 patients have been treated at or above the recommended dose (0.3 mg), with treatment continuing up to or beyond 1 year for approximately 700 patients in the ongoing pivotal Phase 2/3 studies in neovascular AMD.

10.3. Safety Overview

The assessment of adverse events in neovascular AMD is primarily based on the combined safety database of the first year of the two pivotal studies.

All adverse events occurring during the study period for the pivotal studies were reported, including AEs in patients who had discontinued treatment but were still being followed to assess disease progression. This means that not only treatment emergent AEs but also adverse events collected throughout the whole period of study, regardless of the number of injections, are included in the analysis.

AEs were differentiated according to whether they were considered by the investigator to be related to the injection procedure (including use of an eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine drops or flush and subconjunctival injection of anesthetic, as well as the actual insertion of the intravitreous needle) or related to the actual study drug therapy.

Serious adverse events (SAE) are events that resulted in death, were life-threatening, resulted in hospitalization or prolonged hospitalization, led to significant disability, or were judged to be other important medical events by the investigator.

The majority of patients in the pivotal studies experienced at least one adverse event during the study period (95 to 97% of patients in the active arms and 95% of patients in the sham arm, combined data) (Table 11). There were no notable differences among treatment groups, including sham, in the incidence of all causality adverse events.

Table 11. Patients Experiencing At Least One Adverse Event (All Causality) in the Pivotal Studies

	Pegaptanib				Sham
	0.3 mg N=295	**1 mg N=301**	**3 mg N=296**	**All Doses N=892**	**N=298**
Patients with an AE	286 (97%)	286 (95%)	288 (97%)	**860 (96%)**	**283 (95%)**
Patients with an ocular AE*	272 (92%)	276 (92%)	272 (92%)	**820 (92%)**	**260 (87%)**
Ocular AE in the study eye	269 (91%)	270 (90%)	270 (91%)	**809 (91%)**	**254 (85%)**
Ocular AE in the fellow eye	119 (40%)	125 (42%)	133 (45%)	**377 (42%)**	**132 (44%)**
Patients with an SAE	55 (19%)	50 (17%)	64 (22%)	**169 (19%)**	**45 (15%)**
Patients with a severe AE	50 (17%)	41 (14%)	52 (18%)	**143 (16%)**	**46 (15%)**
Patients with treatment discontinuation due to an AE	3 (1%)	4 (1%)	6 (2%)	**13 (1%)**	**4 (1%)**

*AEs coded primarily or secondarily to the System Organ Class Eye Disorders
AE = Adverse Event, SAE = Serious Adverse Event

10.4. Deaths

The rate of deaths during the study period was low and similar to that observed in other studies[54,] and is not unexpected in an elderly population. The incidence of death across all pegaptanib-treated patients in the week 54 cohorts of studies EOP1003 and EOP1004 was 2%, the same as in the sham patients from these studies. In the combined data for the pivotal studies, 5 patients (1.7%) in the 0.3 mg arm, 8 (2.7%) in the 1 mg arm, 6 (2.0%) in the 3 mg arm and 6 (2.0%) in the sham arm died.

10.5. Withdrawals

In the combined pivotal studies, few patients on either active or sham discontinued from the study (from 8% to 13%). FO the few who did, most discontinued for reasons other than adverse events with the most common reason being patient request (Table 3).

The proportion of patients who discontinued study treatment due to adverse events was low and similar in the pegaptanib treatment groups (1-2%) and sham group (1%). There were no clinically meaningful differences in the frequency of discontinuations due to adverse events when the data were examined by race, gender, PDT use and exposure to pegaptanib.

10.6. Overview of Serious Adverse Events

The incidence of SAEs in the pivotal studies was 19% among all pegaptanib-treated patients and 15% among sham patients. The System Organ Classes (SOC) with the most frequent SAEs are listed in Table 12. These SAEs are spread out among organ systems and are expected in this age group with this disease. The SAEs are relatively well balanced among the treated and sham groups.

Table 12. System Organ Classes with the Most Frequent All Causality Serious Adverse Events in the Pivotal Studies

SOC	Pegaptanib				Sham
	0.3 mg N=295	1 mg N=301	3 mg N=296	All Doses N=892	N=298
Patients with at least 1 SAE	**55 (19%)**	**50 (17%)**	**64 (22%)**	**169 (19%)**	**45 (15%)**
Cardiac Disorders	11 (4%)	4 (1%)	10 (3%)	**25 (3%)**	**14 (5%)**
Neoplasms: Benign, Malignant, and Unspecified	11 (4%)	7 (2%)	8 (3%)	**26 (3%)**	**12 (4%)**
Injury and Procedural Complications*	10 (3%)	9 (3%)	8 (3%)	**27 (3%)**	**3 (1%)**
Nervous System Disorders	10 (3%)	5 (2%)	10 (3%)	**25 (3%)**	**7 (2%)**
Eye Disorders	9 (3%)	4 (1%)	10 (3%)	**23 (3%)**	**2 (1%)**
Infections and Infestations	2 (1%)	7 (2%)	11 (4%)	**20 (2%)**	**5 (2%)**
General Disorders and Admin. Site Conditions	5 (2%)	3 (1%)	7 (2%)	**15 (2%)**	**4 (1%)**
Gastrointestinal Disorders	3 (1%)	6 (2%)	5 (2%)	**14 (2%)**	**4 (1%)**
Respiratory, Thoracic, and Mediastinal Disorders	2 (1%)	5 (2%)	5 (2%)	**12 (1%)**	**4 (1%)**
Musculoskeletal and Connective Tissue Disorders	1 (0%)	5 (2%)	3 (1%)	**9 (1%)**	**2 (1%)**
Renal and Urinary Disorders	2 (1%)	3 (1%)	2 (1%)	**7 (1%)**	**3 (1%)**
Vascular Disorders	3 (1%)	2 (1%)	2 (1%)	**7 (1%)**	**3 (1%)**
Surgical and Medical Procedures	1 (0%)	0 (0%)	3 (1%)	**4 (0%)**	**1 (0%)**
Hepatobiliary Disorders	1 (0%)	0 (0%)	2 (1%)	**3 (0%)**	**0 (0%)**
Metabolism And Nutrition Disorders	0 (0%)	1 (0%)	2 (1%)	**3 (0%)**	**3 (1%)**

* Mostly fractures and injuries, but also includes traumatic cataracts

There did not appear to be important differences in SAE frequencies with the exception of SAEs in the System Organ Class (SOC) Eye Disorders (discussed in Section 10.10.1).

10.7. Systemic Clinical Safety

There was no evidence of systemic toxicity.

10.7.1. Systemic Serious Adverse Events

The most commonly occurring SAEs in the combined studies were cardiac disorders and neoplasms (Table 12). These events were distributed proportionally across the four treatment arms. The types and incidence of systemic adverse events observed are not unexpected in this elderly patient population.

Overall, the incidence of cardiac disorder AEs within the studies was higher in the sham arm (5%) than the pooled active arms (3%) (Table 12).

Injury and Procedural Complications SAEs were slightly higher in the pegaptanib treatment arms. These were mainly fractures and injuries, which were unrelated to treatment although 3 reports of traumatic cataracts in the pegaptanib arms were also included.

10.7.2. Common Systemic Adverse Events

Adverse events by preferred term occurring in ≥ 5% of patients in any treatment group are presented in Table 13 for all events.

Table 13. Patients with All Causality Systemic Adverse Events by System Organ Class and Preferred Term Occurring in ≥ 5% of Patients in the Pivotal Studies

	Pegaptanib				Sham
Number (%) of Patients	**0.3 mg N=295**	**1 mg N=301**	**3 mg N=296**	**All Doses N=892**	**N=298**
Gastrointestinal disorders					
Nausea	13 (4%)	7 (2%)	16 (5%)	**36 (4%)**	**13 (4%)**
Musculoskeletal and connective tissue disorders					
Arthralgia	13 (4%)	12 (4%)	11 (4%)	**36 (4%)**	**17 (6%)**
Nervous system disorders					
Headache	19 (6%)	23 (8%)	20 (7%)	**62 (7%)**	**11 (4%)**
Respiratory, thoracic and mediastinal disorders					
Nasopharyngitis	19 (6%)	23 (8%)	27 (9%)	**69 (8%)**	**19 (6%)**
Bronchitis NOS*	16 (5%)	12 (4%)	11 (4%)	**39 (4%)**	**10 (3%)**
Vascular disorders					
Hypertension NOS*	14 (5%)	26 (9%)	29 (10%)	**69 (8%)**	**22 (7%)**

NOS* = not otherwise specified

There was no evidence of an overall increase in the proportion of patients with AEs related to elevated blood pressure after administration of pegaptanib. The incidence of systemic Vascular Hypertensive Disorders (a MedDRA high level term which includes the preferred terms of hypertension NOS, hypertension aggravated and systolic hypertension) was similar in the pegaptanib (10%) and sham (10%) patients. In addition, in the open-label cohort of Study EOP1006 where blood pressure was examined prospectively and more frequently for up to 30 weeks, there was no evidence of an increase in blood pressure after administration of pegaptanib 3 mg.

There were no notable differences among the three pegaptanib dose groups in the incidence of systemic AEs, consistent with the low systemic levels of pegaptanib at all dose levels.

10.8. VEGF Antagonism

Effects associated with generalized VEGF-antagonism were not expected. Intravitreous administration of pegaptanib is associated with low systemic exposure at the dose levels investigated in the pivotal studies. Additionally, pegaptanib shows high specificity for $VEGF_{165}$ and does not bind to any significant degree to $VEGF_{121}$.

The nonclinical assessment of pegaptanib showed no evidence of physiological changes or toxic consequences that would be regarded as reasonably related to VEGF-antagonism, either systemically or in the eye. Nonclinical exposures from the IV or intravitreous routes were considerably higher than in humans administered 3 mg in one eye. Toxicology and safety pharmacology studies showed no evidence of hypertension, proteinuria or thromboembolic or bleeding phenomenon.

Although there was no evidence from nonclinical studies to suggest a risk of theoretical VEGF-inhibition related safety events, the pegaptanib clinical safety database was nevertheless scanned for AEs that might theoretically occur with anti-VEGF therapies. Several anti-VEGF therapies are under study, and one has been recently FDA approved for systemic use in an oncologic indication (Avastin™, Genentech). Adverse events noted with Avastin™ included hypertension and associated proteinuria, superficial and deep vein phlebitis at the site of intravenous injection, and tumor-related bleeding.

Given the intravitreous route of administration, it would be expected that undesirable VEGF-mediated effects, if they were to occur, would be observed in the eye. No evidence of any VEGF-mediated effects related to thromboembolic and bleeding phenomena in the eye was, however, found. There were no vascular AEs seen on fluorescein angiography in any patient receiving pegaptanib. There were no sustained vascular occlusions in the study eye at any time during the study. These factors suggest that non-ocular AEs related to the systemic inhibition of VEGF would not be expected to occur, which was found to be true.

There was no signal for systemic thromboembolic and hemorrhagic SAEs. There was no indication that pegaptanib administration was associated with any significant rise in blood pressure related to an anti-VEGF effect. In addition, in the open-label cohort of Study EOP1006 where blood pressure and proteinuria were examined prospectively and more frequently for up to 30 weeks, there was no evidence of an increase in blood pressure or proteinuria after administration of pegaptanib 3 mg.

10.9. Concomitant PDT with Verteporfin

An analysis was performed to examine adverse events with an onset around the time of PDT treatment. The analysis included all PDT treatments given within 2 weeks before and after a study treatment, and thus approximately 80% of PDT treatments were examined. A 6 week window of time was defined for each study treatment (2 weeks before and 4 weeks after each pegaptanib or sham injection) to capture all adverse events with a start date during this period. Only PDT given in the study eye and adverse events in the study eye were considered. A total of 7492 pegaptanib sodium injections and 2530 sham treatments were included; only 5% of pegaptanib (360) and sham (138) injections were associated with PDT treatment (Table 14). In the pegaptanib group (all doses) there were 2 ocular adverse events reported at a rate more than 2% higher in the periods that included PDT as compared to the periods without PDT - eye

pain and corneal epithelium disorder. As these events are also more frequent in the sham group in the periods that included PDT treatment as compared to the periods without PDT, they may reflect an effect of PDT treatment (e.g., contact lens placement) and/or the combination of pegaptanib and PDT treatment. Systemic adverse events were also examined. As expected due to the relatively low overall incidence of non-ocular adverse events, few adverse events were reported during the 6-week windows that included PDT. There is no evidence that a combination of pegaptanib sodium and PDT treatment increases the incidence of any systemic adverse event.

Table 14. Number (%) of Study Eye Ocular Adverse Events Reported per Study Treatment for those Events with an Incidence > 2% higher in (+) PDT group

	0.3 mg	1 mg	3 mg	All Doses	Sham
Total no. of injections	2465	2545	2482	**7492**	**2530**
No. (%) Study Treatments with PDT	106 (4%)	114 (4%)	140 (6%)	**360 (5%)**	**138 (5%)**
No. (%) Study Treatments without PDT	2359 (96%)	2431 (96%)	2342 (94%)	**7132 (95%)**	**2392 (95%)**
Eye pain					
Study treatments with PDT	14 (13%)	16 (14%)	12 (9%)	**42 (12%)**	**10 (7%)**
Study treatments without PDT	185 (8%)	161 (7%)	198 (8%)	**544 (8%)**	**142 (6%)**
Corneal epithelium disorder					
Study treatments with PDT	4 (4%)	10 (9%)	17 (12%)	**31 (9%)**	**9 (7%)**
Study treatments without PDT	68 (3%)	72 (3%)	52 (2%)	**192 (3%)**	**79 (3%)**

PDT = Photodynamic Therapy

10.10. Ocular Clinical Safety

The ocular AE profile of pegaptanib is not unusual for a product administered by intravitreous injection[55,56,57,58,59,60,61,62,63].

10.10.1. Ocular Serious Adverse Events

Ocular SAEs were not frequently observed in the pivotal studies (Table 15). There was no apparent dose relationship observed in relation to ocular SAEs.

Table 15. Summary of Ocular Serious Adverse Events in the Study Eye in the Pivotal Studies

Preferred term	Pegaptanib				Sham
	0.3 mg N = 295	1 mg N = 301	3 mg N = 296	All Doses N = 892	N = 298
Eye Disorders					
Endophthalmitis	6 (2%)	3 (1%)	3 (1%)	**12 (1%)**	**0 (0%)**
Retinal detachment*	1 (0%)	2 (1%)	2 (0%)	**5 (1%)**	**0 (0%)**
Traumatic Cataract**	1 (0%)	2 (1%)	2 (1%)	**5 (1%)**	**0 (0%)**
Retinal hemorrhage	1 (1%)	0 (0%)	1 (0%)	**2 (0%)**	**0 (0%)**
Vitreous hemorrhage	0 (0%)	0 (0%)	1 (0%)	**1 (0%)**	**0 (0%)**
Uveitis NOS	0 (0%)	0 (0%)	1 (0%)	**1 (0%)**	**0 (0%)**
Papilloedema	0 (0%)	0 (0%)	0 (0%)	**0 (0%)**	**1 (0%)**
Investigations					
Intraocular pressure increased	1 (0%)	0 (0%)	0 (0%)	**1 (0%)**	**0 (0%)**

* Three of these retinal detachments were rhegmatogenous retinal detachments and two were exudative in nature. One of the rhegmatogenous detachments was not coded by the investigator as serious per ICH terminology, but is included here for completeness. All five retinal detachments are discussed in the text.

** Three of the 5 traumatic cataracts were coded to the Injury and Procedures SOC but are included here in the Eye Disorder System Organ Class for ease of presentation.

NOS = not otherwise specified, ICH = International Conference on Harmonisation

The most common ocular SAE was endophthalmitis. There were 12 instances of endophthalmitis in the first year of the pivotal studies, all occurring in the pegaptanib treatment arms. There were 5 cases of retinal detachment. It is important to note that two of these cases were exudative and may have been due to the natural history of the disease. Three were rhegmatogenous retinal detachments. There were 5 traumatic cataracts reported. The SAEs endophthalmitis, traumatic cataract, and retinal detachment are discussed in detail below.

There were few other ocular SAEs. There were two patients with retinal hemorrhage – one had a large subretinal hemorrhage treated with pneumatic displacement that resolved and was judged to be unrelated to study treatment; one had a subretinal hemorrhage associated with an exudative retinal detachment. The patient with vitreous hemorrhage was hospitalized for treatment (vitrectomy) of a vitreous hemorrhage that was likely secondary to underlying AMD; this event was judged not related to study treatment. The patient with uveitis had herpes zoster ophthalmicus and keratouveitis in the study eye, both of which were judged to be unrelated to study treatment. The one SAE of increased intraocular pressure occurred in a country where it is standard practice to hospitalize patients for intravenous therapy. The patient was hospitalized with a post-injection IOP of 51 mm Hg for treatment with intravenous glycerine and acetazolamide and was subsequently discharged with an IOP of 17 mm Hg and continued on study. The SAEs macular degeneration and papilloedema were in sham patients.

Endophthalmitis: Endophthalmitis was assessed to be related to the injection procedure in all cases. A slightly higher incidence was observed in the 0.3 mg arm compared to the other active arms, but, based upon the pathogenesis of the event, this is almost certainly due to chance. Of the 12 patients who experienced endophthalmitis, only one patient (0.1% per patient year) experienced severe vision loss (≥ 30 letters) as determined from assessments prior to the event and assessments at the end of the study period. None of the patients progressed to NLP (no light perception) vision. Nine of the 12 patients (75%) continued in the study after resolution of the endophthalmitis.

Three additional SAEs of endophthalmitis have been reported in ongoing AMD masked studies leading to a total incidence of 15 cases in the AMD population. There was also one case in the ongoing DME masked study.

In 11/16 or approximately 70% of the cases of endophthalmitis, there was at least one violation of the original injection procedure (for instance, no eyelid speculum used) identified in audits.

To address the occurrence of endophthalmitis, an amendment to the protocol for preparation and administration of study drug was introduced which 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.

Following the introduction of the revised injection procedure in March 2003, the rate of endophthalmitis may have been reduced. The last case of endophthalmitis occurred on 19 May 2003, and there were no additional cases as of the data cutoff date of 30 April 2004. The precise impact of the protocol amendment cannot be measured. The attention to these events following independent audit of all endophthalmitis cases, and the revision of the injection procedure likely focused the attention of the investigators on the specific elements of the injection protocol, and may also have increased compliance with measures that were common to both the original and revised injection procedures. It is not clear if the rate reduction was resultant from the protocol amendment or was associated with greater adherence of investigators to the good practice of aseptic technique. Also during this time period, the investigators may have gained important clinical experience with intravitreous injections through prevalent off-label use of intravitreous corticosteroids for retinal diseases. The rate of infection following ocular surgery has been reduced with experience and with the practice of aseptic technique[64]. Given the lack of compelling comparative data one cannot interpret the results of this study as indicating a particular injection protocol should be recommended. However, it is essential to stress that adequate asepsis is necessary to limit the rate of endophthalmitis.

Retinal Detachment: There were five cases of retinal detachment in the study eye reported in the active arms (four of which were coded by the investigator as serious per ICH terminology). All five cases of retinal detachment are discussed here.

Two of the patients (one each in the 0.3 mg and 3 mg arms) had retinal detachments that were exudative/hemorrhagic in nature and may have been secondary to the underlying disease process. The other three patients (2 in the 1 mg arm and 1 in the 3 mg arm) had retinal detachments with a rhegmatogenous component. In one patient the retinal detachment was status post vitrectomy/lensectomy for vitreous hemorrhage, and was attributed to proliferative vitreoretinopathy with contracture of the retina. One patient had a history of lattice degeneration in the study eye and a retinal detachment in the fellow eye; this patient had two retinal tears and a supero-nasal retinal detachment in the study eye. The third patient had a history of retinoschisis and had a superior retinal detachment with multiple small holes in the study eye.

There were also four reports of retinal tears in patients receiving pegaptanib (0.4% of active patients or 0.05% of injections), and 1 patient receiving sham treatment (0.3% of sham patients or 0.04% of sham injections) experienced a retinal tear in the study eye during the first 54 weeks of the pivotal studies. Four of the five patients were given laser treatment. None of these patients progressed to retinal detachment.

Traumatic Cataract: Five patients developed a traumatic cataract, all of which were iatrogenic in nature. In 4 of these patients (1 each in the 0.3 mg and 1 mg arms, and 2 in the 3 mg arm) there was contact and/or penetration of the lens with the intravitreous injection needle; two of these events occurred on the same day at the same clinical site, a result of the same investigator's poor technique. In the fifth patient (1 mg arm), an anterior chamber paracentesis was performed due to increased IOP after an intravitreous 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. Only one patient had a severe vision loss (≥ 30 letters) following the event, most likely due to progression of the underlying AMD.

Vitreous Hemorrhage: Only one patient had a vitreous hemorrhage that was coded by the investigator as serious per ICH terminology, as the patient was hospitalized for treatment (vitrectomy). A total of 16 pegaptanib-treated patients (2%) and no sham-treated patients had a vitreous hemorrhage in the study eye. The hemorrhage was likely related to underlying CNV in 7 patients. The event was likely related to the injection procedure in 9 patients; in all of these cases the hemorrhage was mild in nature and in 8/9 patients the visual acuity after the event was unchanged or within 1 line of the pre-event acuity (the remaining patient was within 2 lines of pre-event acuity). None of the vitreous hemorrhages were associated with retinal tears or detachments.

10.10.2. Common Ocular Adverse Events

Ocular AEs were predictable and, with the exception of uncommon events related to the intravitreous injection procedure, were reported as mild to moderate in severity (Table 16).

Table 16. Ocular Adverse Events Occurring in ≥10% of Patients in the Pivotal Studies

	Pegaptanib				Sham
System Organ Class	**0.3 mg**	**1 mg**	**3 mg**	**All Doses**	
Preferred Term	**N=295**	**N=301**	**N=296**	**N=892**	**N=298**
Eye Disorders					
Study eye	269 (91%)	270 (90%)	270 (91%)	**809 (91%)**	**254 (85%)**
Fellow eye	119 (40%)	125 (42%)	133 (45%)	**377 (42%)**	**132 (44%)**
Eye pain					
Study eye	97 (33%)	97 (32%)	105 (35%)	**299 (34%)**	**83 (28%)**
Fellow eye	9 (3%)	3 (1%)	5 (2%)	**17 (2%)**	**7 (2%)**
Vitreous floaters					
Study eye	88 (30%)	103 (34%)	103 (35%)	**294 (33%)**	**23 (8%)**
Fellow eye	7 (2%)	7 (2%)	7 (2%)	**21 (2%)**	**3 (1%)**
Punctate keratitis					
Study eye	97 (33%)	91 (30%)	98 (33%)	**286 (32%)**	**79 (27%)**
Fellow eye	6 (2%)	7 (2%)	3 (1%)	**16 (2%)**	**7 (2%)**
IOP increased (transient)[1]					
Study eye	42 (14%)	58 (19%)	77 (26%)	**177 (20%)**	**8 (3%)**
Fellow eye	1 (0%)	3 (1%)	3 (1%)	**7 (1%)**	**0 (0%)**
Visual acuity reduced					
Study eye	67 (23%)	47 (16%)	52 (18%)	**166 (19%)**	**71 (24%)**
Fellow eye	22 (7%)	15 (5%)	12 (4%)	**49 (5%)**	**18 (6%)**
Vitreous opacities					
Study eye	53 (18%)	56 (19%)	56 (19%)	**165 (18%)**	**29 (10%)**
Fellow eye	6 (2%)	3 (1%)	2 (1%)	**11 (1%)**	**2 (1%)**
Anterior chamber inflammation					
Study eye	47 (16%)	42 (14%)	39 (13%)	**128 (14%)**	**17 (6%)**
Fellow eye	2 (1%)	1 (0%)	1 (0%)	**4 (0%)**	**0 (0%)**
Visual Disturbance NOS					
Study eye	38 (13%)	39 (13%)	40 (14%)	**117 (13%)**	**33 (11%)**
Fellow eye	9 (3%)	13 (4%)	12 (4%)	**34 (4%)**	**17 (6%)**
Corneal Edema					
Study eye	25 (8%)	23 (8%)	37 (13%)	**85 (10%)**	**21 (7%)**
Fellow eye	1 (0%)	0 (0%)	2 (1%)	**3 (0%)**	**0 (0%)**
Abnormal sensation in eye					
Study eye	23 (8%)	20 (7%)	25 (8%)	**68 (8%)**	**30 (10%)**
Fellow eye	1 (0%)	2 (1%)	2 (1%)	**5 (1%)**	**3 (1%)**
Cataract[2]					
Study eye (phakic)	N=184	N=205	N=198	**N=587**	**N=201**
	50 (27%)	60 (29%)	67 (34%)	**177 (30%)**	**53 (26%)**
Fellow eye (phakic)	N=198	N=209	N=209	**N=615**	**N=204**
	27 (14%)	41 (20%)	39 (19%)	**107 (17%)**	**31 (15%)**

[1] These events reflect the transient post-injection increase in IOP
[2] Cataract assessed only for patients with phakic eyes (traumatic cataracts excluded)
NOS = Not Otherwise Specified; IOP = Intraocular Pressure

The majority of the adverse events in the study eye were attributed by the investigators to the injection procedure, and relatively few events were attributed to study drug. These events were generally reported in a higher proportion of patients in the sham study eye than in the fellow eye for any treatment arm. This suggests that many of these events may be related to the pre-intravitreous injection preparation procedure rather than the intravitreous injection procedure alone. For example, the incidence of eye pain and punctate keratitis in the sham study eye was more than ten times that in the fellow eye in any treatment group. Thus, these events are almost certainly related, at least in part, to the injection preparation procedure and not the

intravitreal injection alone. While these events were reported at increased frequency in the pegaptanib arms compared with sham, there was no dose response observed. The majority of the more commonly occurring ocular AEs were reported as mild, with the exception of reduced visual acuity (the incidence of which was higher in sham).

There is no evidence that pegaptanib treatment resulted in cataract progression. Cataract was reported with a slightly higher incidence in the active treatment arms compared with the sham arm for the combined data but there was considerable variation between the reporting in the two pivotal studies possibly due to multiple observers and the random noise associated with a low threshold definition of cataract progression (one unit change in either nuclear, cortical or posterior subcapsular) as an adverse event. No consistent trends in relation to cataract incidence could be identified. The actual Age-Related Eye Disease Study (AREDS) lens opacity gradings were also compared from baseline to the last visit. There was little difference between the active and sham arms, and almost all of the increases were of one grade only. Furthermore, AREDS lens opacity grading data from the fellow eye was very similar (Table 17). There was no evident increase in posterior subcapsular cataracts. This type of cataract is the one most commonly associated with pharmacological toxicity. Taken together, these data show no evidence that the drug leads to cataract progression.

Table 17. Number (%) of Phakic Patients with any Increased Lens Grade: Last Visit Compared to Baseline

	Pegaptanib				Sham
Number of Patients:	**0.3 mg**	**1 mg**	**3 mg**	**All Doses**	
Study Eye	**N=183**	**N=205**	**N=197**	**N=585**	**N=201**
Fellow Eye	**N=189**	**N=205**	**N=202**	**N=596**	**N=197**
Nuclear					
Study eye	29 (16%)	37 (18%)	43 (22%)	**109 (19%)**	**37 (18%)**
Fellow eye	30 (16%)	36 (18%)	31 (15%)	**97 (16%)**	**24 (12%)**
Posterior Subcapsular					
Study eye	16 (9%)	26 (13%)	20 (10%)	**62 (11%)**	**23 (11%)**
Fellow eye	12 (6%)	18 (9%)	15 (7%)	**45 (8%)**	**18 (9%)**
Cortical					
Study eye	31 (17%)	33 (16%)	41 (21%)	**105 (18%)**	**30 (15%)**
Fellow eye	20 (11%)	25 (12%)	31 (15%)	**76 (13%)**	**26 (13%)**

Reduced visual acuity was to be reported as an adverse event if patients lost more than 20 letters of VA between visits but was also reported at the investigator's discretion. Reduced visual acuity is likely to be associated with the underlying disease rather than the treatment. This is consistent with a slightly higher incidence of > 20 letter loss in the study eye in the sham arm compared to the pegaptanib arms.

Anterior chamber inflammation was observed with higher frequency in sham study eyes than in the fellow eyes, and so may be attributed at least in part to the external procedures and treatments used in the injection preparation protocol (including use of an eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine drops or flush and subconjunctival injection of anesthetic) as well as to the intravitreous injection. The condition was almost always mild and transient and there were no reports of severe or serious anterior chamber inflammation. The event did not increase in frequency over the study period. Anterior chamber inflammation did not result in study discontinuation in any patient.

Vitreous floaters were reported with higher frequency in pegaptanib study eyes than in the sham study eyes. This may be due to the movement of the vitreous gel secondary to the intravitreous injection. This event was also reported more frequently in the sham study eyes than in the fellow eyes; since vitreous floaters is a subjective event, this difference between the sham and fellow eyes may also be partly explained by a placebo-like response, since both the investigator and the patient focus closer attention on the study eye. No events of vitreous floaters were severe, and in the great majority of patients (276/294 pegaptanib patients, 20/23 sham patients) the event was mild. The median duration of vitreous floaters in the study eye was 3 days in pegaptanib-treated patients, while in sham-treated patients the median was 7 days. There was a decrease over time in the incidence of vitreous floaters. No patient discontinued because of vitreous floaters. Vitreous opacities were almost exclusively reported with the verbatim term of vitreous haze and were mostly mild. The incidence of this event decreased over time and no patient discontinued due to the event.

Occurrence by Time Period of Ocular Study Eye Adverse Events

All adverse events and ocular adverse events were analyzed by the time period of occurrence: 1-3 injections, 4-6 injections and 7-9 injections. The incidence of Eye Disorders adverse events was slightly higher in the pegaptanib-treated patients during the first 3 injections (74-75%) compared to during injections 4-6 (66-69%) or 7-9 (62-68%). The same decrease over time was seen in the sham-treated patients. This small decrease might have been due to toleration of certain events over time.

There appears to be a decrease over time in the incidence of the more common ocular adverse events, including eye pain, vitreous floaters, reduced visual acuity, and vitreous opacities in pegaptanib-treated patients.

10.11. Changes in Intraocular Pressure

There is no evidence of a persistent increase in IOP associated with pegaptanib. Transient increases in IOP are expected with intravitreal injections, and such increases were seen with pegaptanib. The mean IOP measured 30 minutes post-injection was 2-4 mm Hg higher than pre-injection IOP, with the highest mean increases seen in the 3 mg group. The increases were manageable and did not require intervention in the majority of cases. No patient was discontinued due to increased IOP, nor did any patient require a trabeculoplasty or trabeculectomy.

Pattern of IOP Changes: Baseline IOP values as well as pre-injection values in the study eye were similar across all study groups. There was no evidence of an increase in mean values of IOP over time, since pre-injection values at later visits were similar to those at baseline within each study group. As would be anticipated based on injection volume, mean IOP was increased compared to pre-injection in all active treatment groups 30 minutes after injection. By the next scheduled follow-up, one week post-injection, mean IOP values had returned to pre-injection levels in all treatment groups (Table 18).

Table 18. Mean Values of Intraocular Pressure (mmHg) in the Pivotal Studies

	Pegaptanib			
	0.3 mg N=295	**1 mg N=301**	**3 mg N=296**	**Sham N=298**
Screening Baseline	15.4	15.2	15.3	15.4
Pre-injection				
Week 0	15.3	15.7	15.4	15.2
Week 6	15.5	15.2	15.5	15.3
Week 12	15.2	15.4	15.4	15.2
Week 18	15.4	15.4	15.6	15.1
Week 24	15.1	15.1	15.7	15.2
Week 30	15.4	15.5	15.7	15.1
Week 36	14.8	15.5	15.8	15.0
Week 42	15.0	15.5	16.0	14.9
Week 48	15.4	15.4	15.6	14.7
30 min post-injection				
Week 0	17.7	18.1	17.8	16.5
Week 6	18.4	18.1	18.3	16.6
Week 12	18.3	18.4	18.8	16.4
Week 18	18.2	18.5	18.9	16.3
Week 24	18.4	18.6	19.2	16.4
Week 30	18.1	18.5	19.1	16.2
Week 36	18.6	18.5	19.5	16.1
Week 42	18.7	18.7	19.3	16.1
Week 48	18.6	18.4	19.6	16.2
1 week post-injection				
Week 0	15.1	15.0	15.6	15.0
Week 6	15.0	15.3	15.6	15.1
Week 12	14.6	15.2	15.4	14.9
Week 18	15.1	15.1	15.5	15.0
Week 24	14.8	15.0	15.9	15.1
Week 30	15.2	15.0	16.0	14.8
Week 36	15.2	14.9	15.8	14.5
Week 42	15.1	15.1	15.8	14.7
Week 48	15.2	15.1	16.3	14.6

IOP Increases: The mean 30 minute post-injection IOP was 2-4 mm Hg higher than pre-injection IOP, with the highest mean increases seen in the 3 mg group. In the sham treatment group a somewhat smaller increase (1-1.5 mmHg higher than pre-injection) was seen. No meaningful or consistent differences were seen in any treatment group between pre-injection and 1 week post-injection mean values (Table 19).

Table 19. Mean Changes in Intraocular Pressure (mmHg) in the Pivotal Studies

	0.3 mg N=295	1 mg N=301	3 mg N=296	Sham N=298
Pre-injection to 30 min post-injection mean change				
Week 0	2.4	2.4	2.4	1.2
Week 6	2.8	2.8	3.0	1.3
Week 12	3.1	3.0	3.4	1.2
Week 18	2.9	3.1	3.2	1.3
Week 24	3.3	3.4	3.5	1.2
Week 30	2.6	3.0	3.4	1.0
Week 36	3.7	3.1	3.8	1.1
Week 42	3.7	3.3	3.3	1.1
Week 48	3.1	2.9	4.0	1.5
Pre-injection to 1 week post-injection mean change				
Week 0	- 0.2	- 0.7	0.2	- 0.2
Week 6	- 0.5	0.1	0.2	- 0.2
Week 12	- 0.6	- 0.2	- 0.1	- 0.3
Week 18	- 0.3	- 0.3	- 0.1	- 0.1
Week 24	- 0.2	- 0.2	0.1	- 0.1
Week 30	- 0.3	- 0.5	0.2	- 0.3
Week 36	0.3	- 0.6	0.0	- 0.5
Week 42	0.1	- 0.4	- 0.1	- 0.2
Week 48	- 0.2	- 0.4	0.7	- 0.1

Almost 90% of all pegaptanib treated patients did not experience a post-injection transient IOP of ≥ 35 mmHg (a monitoring threshold suggested by the IDMC) at any time during the study. One sham-treated patient developed an IOP ≥ 35 mmHg, while 27 (9%), 28 (9%) and 44 (15%) patients in the 0.3 mg, 1 mg, and 3 mg pegaptanib sodium groups, respectively, experienced values of ≥ 35 mmHg. These transient increases in IOP are expected with intravitreous injections, and they were manageable and did not require intervention in the majority of cases. Investigators were instructed to not permit patients to leave the physicians' office until the IOP returned to below 30 mmHg.

History of Increased IOP: Although there were few patients with a history of increased IOP, a higher percentage of such patients had an IOP of ≥ 35 mm Hg at 30 minutes after injection. When all pegaptanib-treated patients were evaluated for a history of increased IOP, 8% (68/892) were found to have such a history. Of these 68 patients, 32% (22/68) had IOP values ≥ 35 mmHg on at least one injection day. Of the 824 pegaptanib-treated patients who did NOT have a history of increased IOP, only 9% (77/824) had IOP values ≥ 35 mmHg on at least one injection day.

Treatment of Increased IOP: The majority of patients with increased IOP did not require concomitant treatment. Eighty-five percent of patients did not require concomitant pharmacological therapy for increased IOP (12% of patients in the 0.3 mg pegaptanib group, 14% in the 1 mg group, and 19% in the 3 mg group received concomitant medication for increased IOP on one or more injection days). The overall frequency of paracentesis per number of injections was low (3%) and was affected by practice patterns at a small number of sites, i.e., paracenteses performed at 10/117 (9%) sites accounted for almost ¾ of the procedures performed, and one site alone accounted for almost ¼ of the procedures. No patient

required a trabeculoplasty or trabeculectomy, and no patient was discontinued due to increased IOP.

In summary, increases in IOP were transient, and a return to baseline or near baseline levels was seen within one week of injection. There was no evidence of a persistent increase in IOP after one year of treatment. There were no discontinuations due to increased intraocular pressure.

10.12. Clinical Laboratory Evaluations

A total of 885 patients who received pegaptanib and 296 patients who received sham treatment were evaluable for laboratory test abnormalities in the Pivotal Studies. A comparable proportion of patients in each of the pegaptanib treatment groups and sham group experienced at least one clinically significant laboratory test abnormality during the study, whether considered without regard to baseline abnormality (20-26%) or with normal baseline (14-16%). The incidence of clinically significant laboratory test abnormalities appeared similar between the sham and active treatment arms.

Median changes from baseline to last observation were analyzed. In general, the median values were comparable at baseline among the pegaptanib treatment groups and between the pegaptanib groups and sham. The median changes from baseline for all laboratory parameters were small, not clinically meaningful, and comparable across all treatment groups.

Six patients experienced laboratory abnormalities which were considered as SAEs. Two patients were in the active arms (0.2% of patients) and four were in the sham arms (1.3% of patients). None of the SAEs involving laboratory abnormalities were assessed to be related to study treatment. There were no discontinuations from treatment due to a laboratory test abnormality.

There were four patients with concurrent clinically significant abnormalities of AST, ALT and/or total bilirubin which were not recorded as adverse events and which were likely due to pre-existing conditions. Three patients in the 3 mg arms and one patient in the 0.3 mg arm experienced clinically significant abnormalities which were not considered to be related to study therapy and, as mentioned, were not reported as adverse events. One patient had these abnormalities at baseline, one had concomitant pancreatic carcinoma, one had concomitant chemotherapy for gastric lymphoma, and one had elevated bilirubin at baseline and a spike in ALT and AST that resolved on continued treatment.

10.13. Vital Signs, Physical Findings, and Other Observations Related to Safety

There were no clinically significant findings in relation to vital signs in the pivotal studies.

Study EOP1006 assessed blood pressure in patients who were receiving pegaptanib 3 mg per eye every 6 weeks. Blood pressure was determined at baseline and before each injection at Day 0 and Weeks 6, 12, 18, 24, and 30, and 4 and 24 hours after the first and fourth injections (Day 0 and Week 18).

The mean changes from baseline in systolic and diastolic blood pressures on Day 0 (pre-dose) were –3.9 mmHg and –2.1 mmHg, respectively. Four hours after injection on Day 0, the mean changes from baseline in systolic and diastolic blood pressures were -3.9 mmHg and -3.0

mmHg, respectively. At no time over the course of the study was an increase in mean blood pressure observed; decreases in systolic pressure ranged from 3.3 to 9.5 mmHg, and decreases in diastolic pressure from 2.1 to 7.4 mmHg.

Patients Losing ≥20 Letters of Vision

The proportion of patients who lost 20 or more letters of vision between any two consecutive treatment visits (6 week intervals) was assessed. In the combined pivotal studies 15% to 17% of patients in the pegaptanib arms lost 20 letters or more compared with 22% in the sham arm. This difference may be indicative of the positive treatment effect of pegaptanib.

Other Observations Related to Safety

The Independent Reading Center reviewed all fluorescein angiograms for events that were unrelated to AMD. A central retinal vein occlusion in the study eye of a sham-treated patient was identified at the Week 54 visit. A magnetic resonance image (MRI) revealed thrombosis of the left internal carotid artery. Otherwise, these examinations revealed no retinal vascular or choroidal abnormalities that are unexpected in the natural history of neovascular AMD. There were no notable delays in arterio-venous transit time, abnormalities in choroidal perfusion, or arteriolar occlusions.

The development of serum antibodies to pegaptanib was investigated in Studies NX109-01, EOP1000, EOP1001, and EOP1006. No anti-pegaptanib IgG antibodies have been detected as of the cutoff date for this safety summary in serum samples of patients with AMD who have been treated with pegaptanib.

10.14. Safety Conclusions

- From the perspective of safety, pegaptanib is well tolerated at all doses studied and few patients withdrew from the studies for adverse events (1-2 % of patients across all treatment groups, combined data).
- Adverse events were mostly ocular, predictable, and, with the exception of infrequent events related to the intravitreous injection, mild or moderate in severity.
- No unexpected retinal vascular or choroidal changes were seen in fluorescein angiograms as read by the Independent Reading Center.
- There was no evidence that pegaptanib treatment resulted in cataract progression, other than the iatrogenic traumatic cataracts.
- There was no evidence of a persistent increase in IOP associated with pegaptanib. Mild, transient increases in intraocular pressure were expected with intravitreous injection of pegaptanib but were manageable and did not require intervention in the majority of cases.
- Ocular serious adverse events were infrequent and included endophthalmitis (0.16% per injection or 1.3% per patient per year), traumatic cataract (0.07% per injection or 0.6% per patient per year) and rhegmatogenous retinal detachment (0.04% per injection or 0.3% per patient per year).
- The serious ocular events were principally considered to be related to the injection procedure and not to pegaptanib.

- Of the endophthalmitis cases, only one patient (0.1%) lost more than 6 lines (30 letters) of vision from assessments prior to the event until the end of study and 75% of patients remained in the trial and received subsequent injections. In approximately 70% of endophthalmitis cases, there was at least one violation of the injection procedure (e.g., no eyelid speculum used).
- Laboratory and vital sign assessments did not show any treatment related trends or significant findings.
- There were no differences between doses for almost all safety assessments with the possible exception that post-injection intraocular pressure (IOP) elevations of ≥ 35 mm Hg (a monitoring threshold set by the IDMC) were more frequently observed in the 3 mg arm than the 0.3 mg or 1 mg arms.

11. DISCUSSION AND CONCLUSIONS

11.1. Discussion

The pivotal studies were well-controlled and of identical design with the exception of quality of life assessments in EOP1004. Both trials were conducted according to GCP and were prospective, multi-center, randomized, controlled, double masked, parallel group studies. They were adequately powered to detect statistically and clinically meaningful treatment differences (the proportion of patients losing less than 15 letters of visual acuity at week 54).

Distance visual acuity was chosen as the primary efficacy assessment because it is considered one of the most clinically relevant measures of visual outcome for individual patients with neovascular AMD. The primary endpoint of loss of less than 15 letters (approximately 3 lines) of visual acuity at week 54 was selected following discussion with the FDA. Three lines on the ETDRS eye chart represents a doubling of the visual angle which is a clinically meaningful change for an individual patient and historically has been an approvable endpoint in ophthalmology studies. Study assessments were designed to be simple to perform. The selection of one-year endpoints was appropriate based on the natural history of the disease. A precedent also exists in that Visudyne® was approved with one year data.

Since pegaptanib selectively inhibits $VEGF_{165}$, its effect on CNV was not expected to vary by angiographic lesion subtype, lesion size, baseline visual acuity, age or gender. Therefore, the study was designed with broad inclusion criteria and not powered to examine the efficacy in patients with any one baseline characteristic. The entry criteria for these studies were very broad in order to ensure that the study population resembled the general neovascular AMD population as closely as possible. Patients were stratified at randomization by study center, angiographic lesion subtype and prior PDT to try to ensure comparable distribution to treatment groups.

Despite the geographic differences in the investigational sites involved in the two studies, the patient populations in the two studies were similar and representative of the general AMD population.

Overall treatment compliance was high. The majority of patients (90% overall in the pegaptanib arms and 92% in the sham arms) completed the first year of study treatment. The

mean number of doses administered (8.5 out of a possible 9) was similar among treatment arms.

The results of the efficacy analyses validate the importance of $VEGF_{165}$ in the pathogenesis of neovascular AMD, and demonstrate further that continuous inhibition of $VEGF_{165}$ for 54 weeks results in a statistically significant and clinically meaningful benefit for the patient.

Data from the two pivotal clinical trials clearly indicate a treatment benefit for patients with neovascular AMD treated with pegaptanib at a dose of 0.3 mg or 1 mg given by intravitreous injection with a treatment regimen of every six weeks.

All doses investigated offer a treatment benefit in comparison with sham. The 0.3 mg dose is the lowest effective dose studied. The 0.3 mg dose was statistically significant in both pivotal trials, the efficacy was supported by analyses showing negligible effects of missing data and protocol violations, and the 0.3 mg dose conferred a consistent benefit in relevant patient subgroups. The 1 mg and 3 mg doses also showed efficacy but overall did not show any advantages over the 0.3 mg dose.

It appears that the broad dose range investigated in studies EOP1003 and EOP1004 defines the efficacy plateau, and the 0.3 mg dose represents the lowest effective dose.

All three doses appear to be well tolerated. There were no differences between doses for almost all safety assessments. There was a possible finding in relation to the 3 mg dose level in that transient IOP elevations of $\geq$ 35 mm Hg (a monitoring threshold suggested by the IDMC) were more frequently observed in the 3 mg arm than the 0.3 mg or 1 mg arms. However, most patients in all dose groups did not experience significant elevations of IOP, there was no evidence of a persistent increase in IOP associated with pegaptanib, and no patients discontinued for IOP related AEs. The most significant safety findings were related to the incidence of ocular AEs including endophthalmitis, traumatic cataract and retinal detachment. These were almost certainly (endophthalmitis, traumatic cataract) or likely (retinal detachment) related to the injection procedure rather than the study drug and consequently there is no suggestion that dose level has an impact on the occurrence of these events. Other than iatrogenic traumatic cataracts, there was no evidence that pegaptanib treatment resulted in cataract progression.

There are no apparent safety concerns in relation to systemic exposure given the very low systemic circulation of the drug. Most serious systemic adverse events were those that would be expected in this elderly patient population.

The results of the pivotal studies confirm 0.3 mg pegaptanib as the lowest efficacious dose thus providing the widest margin of safety. Therefore, 0.3 mg pegaptanib administered once every 6 weeks is the recommended dose regimen.

11.2. Benefit and Risk Conclusions

Introduction

Neovascular AMD is the leading cause of severe irreversible vision loss in individuals older than 55 years of age in the developed world. Deterioration of vision often leading to blindness poses an immense humanistic and economic burden to society. As there is no FDA approved treatment for most patients with neovascular AMD, there is a substantial unmet medical need to establish a safe and effective therapy for neovascular AMD.

Pegaptanib belongs to a new class of drugs aimed at the underlying pathophysiological causes of CNV in AMD; namely $VEGF_{165}$ involvement in pathological ocular neovascularization. Current therapies for neovascular AMD rely entirely on the physical obliteration of visible CNV with thermal laser or PDT and hence are applicable only to subgroups of patients with defined angiographic lesion characteristics. The present pivotal studies have, in a scientifically rigorous manner, shown that this mechanism of action is valid for the treatment of neovascular AMD and also that it is valid for all demographic and lesion characteristics. Data from the two pivotal clinical trials clearly indicate a treatment benefit for patients with neovascular AMD treated with pegaptanib at a dose of 0.3 mg or 1 mg given by intravitreous injection every six weeks.

Benefits

Pegaptanib reduced moderate and severe vision loss for patients with neovascular AMD in two large clinical trials conducted in geographically distinct regions. The study populations were representative of the broad range of clinical features and demographic characteristics described in the literature for the general neovascular AMD patient population[18, 19, 20, 21, 22].

Pegaptanib 0.3 mg achieved statistical significance for a clinically meaningful primary efficacy endpoint in two replicate, well-controlled trials ($p=0.0031$ Study EOP1004, $p=0.0105$ Study EOP1003 and $p<0.0001$ combined analysis). In addition, pegaptanib 1 mg also showed a statistically significant treatment benefit compared with sham in study EOP1003 ($p=0.0035$) and was near to significance in EOP1004 ($p=0.0273$; significance threshold = 0.025 using the Hochberg statistical procedure; $p=0.0003$ combined analysis). The primary efficacy endpoint was the proportion of Responders, defined as patients avoiding 15 letter loss of visual acuity, a clinically meaningful benefit for the patient.

Severe vision loss, defined as a loss of ≥30 letters of VA, was more than halved in pegaptanib 0.3 mg and 1 mg treated patients (10% and 8% of patients respectively experienced severe vision loss, $p<0.0001$) compared with sham (22% of patients) in the combined analysis. The consequence of this degree of vision loss is quite devastating.

The level of vision of 20/200 or worse in both eyes constitutes legal blindness in many states/countries. Analysis of the combined data showed that patients receiving 0.3 mg or 1 mg pegaptanib were less likely to progress to 20/200 vision or worse at 54 weeks than those receiving sham (38% and 43% respectively versus 56%, combined data, $p\leq0.0001$) in the treated eye.

Patients receiving 0.3 mg or 1 mg pegaptanib were more likely to maintain or gain VA (0.3 mg, 33%, p=0.0032; 1 mg 37%, p=0.0006) at 54 weeks than patients receiving sham (23%) in the combined analysis. Patients receiving 0.3 mg or 1 mg pegaptanib were also more likely to gain three lines of VA at week 54 than those receiving sham (6% and 7% respectively versus 2%, p=0.0401 and p=0.0238 respectively, combined data).

In addition, pegaptanib at 0.3 mg and 1 mg showed an early onset of action with an apparent increasing effect up to 54 weeks. Patient baseline characteristics such as angiographic lesion subtype, prior PDT usage, visual acuity, lesion size, gender, degree of iris pigmentation and age did not preclude a treatment benefit with pegaptanib. As the only available treatments for neovascular AMD are currently thermal laser photocoagulation therapy and PDT (the latter being FDA approved only for patients with predominantly classic lesions), an available treatment indicated for all patients is of major importance.

Risks

From the safety perspective pegaptanib is well tolerated at all doses studied and few patients withdrew from the studies due to AEs (1-2% across all treatment arms). Ocular AEs are common but, with the exception of infrequent events related to intravitreous injection, are mild or moderate in severity, transient and predictable.

The potential risks are mainly confined to the injection procedure. The majority of serious ocular adverse events (endophthalmitis, traumatic cataract and retinal detachment) are related to the intravitreous injection procedure rather than the drug substance. Hence they are understandable, predictable and may be reduced in practice. Aseptic technique is important to keep the rate of endophthalmitis low.

Intravitreous injection of pegaptanib was associated with the risk of elevated IOP. Mild, transient increases in IOP are to be expected with intravitreous injection but are manageable and do not require intervention in the majority of cases.

- A risk of 1.3% per patient year or 0.16% per injection of developing endophthalmitis was shown in the pivotal studies and only one patient showed severe vision loss (≥ 30 letters) which equated to a risk of 0.1% per patient per year for severe vision loss associated with endophthalmitis in these studies.
- The risk of iatrogenic traumatic cataract events was 0.6% patients per year of treatment or 0.07% per injection and, for rhegmatogenous retinal detachments, 0.3% patients per year of treatment or 0.04% per injection.

The high completion rate seen in the studies is indicative of the ability of the patient population to accept a course of intravitreous injection-based therapy at the prescribed regimen. Although the studies involved repeated intravitreous injections in an aged patient population, very few patients withdrew consent or dropped out for any reason. In the combined analysis, 90% of patients in the pegaptanib arms and 92% in the sham arms completed the study. The mean number of injections administered was 8.5 of a possible 9 for all patients, showing high compliance.

The conclusion of these studies is that the benefits associated with pegaptanib treatment strongly outweigh the risks. An early onset of action and significant reduction in moderate and

severe vision loss was seen and, additionally, more patients receiving pegaptanib than sham obtained visual stability and gain. Efficacy was observed with pegaptanib in a wide range of patients, regardless of baseline angiographic lesion subtype, baseline lesion size, gender and age. The majority of significant AEs were injection related and should be minimized with adherence to appropriate technique.

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