CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-756

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA 21-756
Pegaptanib DFS Copy

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-756/000

Brand Name:	Macugen
Generic Name:	Pegaptanib sodium for intravitreous injection
Dosage Form:	Intravitreous injection
Dosage Strength:	Single use 1 mL glass syringe containing 0.3 mg in a 90 uL deliverable volume
Proposed Dosing:	0.3mg once every six weeks by intravitreous injection
Indication:	For the treatment of exudative (wet) age-related macular degeneration
NDA Type:	Original NDA/NME (P)
Submission Date(s):	3/17/2004, 06/17/04, 07/29/04, 08/19/04
Sponsors:	EyeTech Pharmaceuticals, Inc., NY and Pfizer Inc., NY
Reviewers:	Arzu Selen, Ph.D./Chandra S. Chaurasia, Ph.D.
Deputy Division Director:	Arzu Selen, Ph.D.
OCPB Division:	DPE III/HFD-880
OND Division:	AIAOD/HFD-550

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1. Executive Summary

The Sponsors, EyeTech Pharmaceuticals and Pfizer, are developing pegaptanib (Macugen) for age-related macular degeneration (AMD) which is the leading cause of blindness in developed countries with approximately 15 million people with the disease in the United States.

Vascular endothelial growth factor (VEGF) is one of several growth factors involved in angiogenesis. Literature data suggest that VEGF is the principal angiogenic growth factor contributing to the pathogenesis of AMD. Inhibition of VEGF is expected to

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impact on the onset and/or severity of vision loss associated with vascular growth and subretinal hemorrhage that are characteristic of the disease. This hypothesis is the basis for the development of a VEGF inhibitor as a potential treatment for the neovascular form of AMD.

For the majority of patients with neovascular AMD there is currently no standard and effective therapy. Photodynamic therapy (PDT) with verteporfin (VisudyneTM) has been approved by the FDA for a subgroup of patients with predominantly classic AMD. Another treatment option is thermal laser treatment (photocoagulation), in which the abnormal blood vessels are destroyed, however, this approach is only for a small subset of patients with well-defined small lesions, in the extrafoveal and juxtafoveal location.

Pegaptanib sodium is a pegylated synthetic ribonucleic acid (RNA)-based oligonucleotide composed of 28 nucleotide bases. The oligonucleotide is composed of modified pyrimidine and purine nucleotides (2'-fluoropyrimidines and 2'-methoxypurines).The oligonucleotide has a molecular weight of   . To increase the in vivo residence time, a 40 kD branched polyethylene glycol (PEG) molecule (each PEG arm composed of an approximately 20 kD PEG moiety) has been conjugated to the 5'-terminus of the oligonucleotide.

In support of the NDA 21-756, the Sponsor submitted data from two pivotal clinical studies (EOP1003 AND 1004) and 4 clinical pharmacology studies:

NX109-01: First in human study
EOP1000
EOP1001
EOP1006
And trough (Cmin) data from EOP1004.

Individual study reviews are in Appendix 4.2

Rationale for dose selection: The proposed dose is 0.3 mg/eye. In the two Phase II/III studies (EOP1003 AND EOP1004), a wide range of doses (0.3 mg/eye, 1 mg/eye, 3 mg/eye) were studied. The primary (proportion of patients losing < 15 letters of VA from baseline to 54 weeks) and secondary (proportion of patients gaining > 15 letters of VA) efficacy endpoints were measured. For both endpoints, lower doses (0.3 mg/eye and 1.0 mg/eye) exhibit significant efficacy ($p \leq 0.01$) compared to sham group in patients with neovascular AMD. Higher dose (3 mg/eye) did not consistently demonstrate efficacy in patients with neovascular AMD.

PK characteristics:
- Following intravitreous administration, pegaptanib is systemically available, and displays non-linear pharmacokinetics at doses above 1 mg. In 2 mg/eye and 3 mg/eye dose treatment groups, plasma pegaptanib concentrations increased disproportionately with dose.
- Following intravitreous injection of pegaptanib sodium, pegaptanib is systemically available.

- At the proposed dose of 0.3 mg pegaptanib concentrations in plasma are close to the limit of detection
- Mean terminal elimination half-life of pegaptanib is 10 days with individual values ranging from 2 to 19 days. During repeated dosing when administered every 4 or 6 weeks, pegaptanib accumulation is minimal/negligible, if any.
- Pegaptanib metabolism is not characterized, however, it is expected to be metabolized by nucleases to shorter chains of nucleotides. Because of its molecular structure, typical P450 drug-drug interactions are not expected.
- Based on the pharmacokinetic results in study report EOP1006, higher Cmax and AUClast values were seen in patients with reduced renal function as represented by lower CLcr values. The relationship between creatinine clearance and AUClast and Cmax, respectively for both the 1st and 4th doses appear biphasic. Thus, the relationship between CLcr and AUClast and CLcr and Cmax with a single slope covering the entire range of CLcr (20-80 mL/min) is not meaningful.

  To better characterize the increases in pegaptanib exposure in patients with renal impairment, the pharmacokinetic data should be reanalyzed by grouping patients according to their CLcr values (per Guidance: Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling, issued in May 1998) in three groups representing mild renal impairment (CLcr = 50-80 mL/min), moderate renal impairment (CLcr = 30-50 mL/min) and severe renal impairment (CLcr <30 mL/min).
- The proposed labeling

Adverse events of pegaptanib therapy:
Vascular Endothelial Growth Factor (VEGF) has been shown to be an important component in the development of collateral vessels in ischemic heart disease. Inhibition of VEGF in the systemic circulation could present a theoretical increased risk of symptomatic cardiovascular disease in the target population of elderly patients with AMD.

1.1. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Clinical Pharmacology and Biopharmaceutics information submitted in support of the Macugen (pegaptanib sodium for intravitreous injection, 0.3 mg) and found it to be acceptable for meeting the requirements of 21CFR320 provided that the Sponsor adequately addresses Macugen dosing in patients with renal impairment particularly in patients with CLcr of < 50 mL/min.

1.2 Phase IV Study Commitments

None is being requested at this time.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

A list of studies conducted in the clinical and clinical pharmacology drug development program is provided in Table 1 below.

Table 1 List of Clinical and Clinical Pharmacology and Biopharmaceutics studies Data and Sources.

Protocol	Design	Dose	Patients Treated	Study Assessments
Studies in Age-related Macular Degeneration (AMD)				
Controlled AMD Trials				
EOP1003	Phase 2/3 multi-center, randomized, sham-injection controlled, double masked, dose finding	Intravitreous injections of either 0.3, 1 or 3 mg pegaptanib sodium/eye or sham every 6 weeks for 54 weeks	622 patients 50 years of age active subfoveal CNV secondary to exudative AMD	BCVA, Fluorescein angiography and fundus photography, AEs, IOP, laboratory parameters, vital signs, PDT administration, local ocular events
EOP1004	Phase 2/3 multi-center, randomized, sham-injection controlled, double masked, dose finding	Intravitreous injections of either 0.3, 1 or 3 mg pegaptanib sodium/eye or sham every 6 weeks for 54 weeks	586 patients 50 years of age active subfoveal CNV secondary to exudative AMD	BCVA, Fluorescein angiography and fundus photography, AEs, IOP, laboratory parameters, vital signs, PDT administration, local ocular events, PK, QOL
Uncontrolled AMD Trials				
NX109-01	Phase 1, multi-center, open label escalating dose, dose finding	Single intravitreous injection of either 0.25, 0.5, 1, 2 or 3 mg pegaptanib sodium/ eye	15 patients 50 years of age with exudative AMD	DLT, AEs, vital signs, BCVA, IOP, laboratory parameters, immune response, PK parameters, local ocular events
EOP1000	Phase 1/2, multi-center, open label, multiple dose in patients without PDT	Total of 3 consecutive intravitreous injections of 3 mg pegaptanib sodium/eye, 28 days apart	10 patients 50 years of age with subfoveal CNV secondary to exudative AMD	BCVA, AEs, IOP, laboratory parameters, vital signs, DLT, PK parameters, immune response, local ocular events
EOP1001	Phase 1/2, multi-center, open label, multiple dose in patients following PDT administration	Total of 3 intravitreous injections of 3 mg pegaptanib sodium/ eye, 28 days apart	11 patients 50 years of age with predominantly classic subfoveal CNV secondary to exudative AMD	BCVA, AEs, IOP, laboratory parameters, vital signs, DLT, PK parameters, immune response, requirement for PDT administration, local ocular events
EOP1006	Phase 2 multi-center, randomized, multiple dose, open label cohort	Intravitreous injections of 3 mg pegaptanib sodium/ eye every 6 weeks for 54 weeks	37 patients 50 years of age with subfoveal CNV secondary to exudative AMD (Study is ongoing in 147 patients)	AE, local ocular events, IOP, laboratory parameters, vital signs, PK parameters, immune response
Development Trials for Additional Indications				
Studies in Diabetic Macular Edema (DME)				

EOP1002	Phase 1/2, multi-center, multiple dose open label,	Intravitreous injections of 3 mg pegaptanib sodium/ eye every 6 weeks for 12 to 30 weeks	10 patients 18 years of age with clinically significant DME	AEs, BCVA, laboratory parameters, IOP, retinal thickening, local ocular events
EOP1005	Phase 2, multi-center, randomized, sham-injection controlled, double masked, dose finding	Intravitreous injections of either 0.3, 1.0 and 3 mg pegaptanib sodium/ eye or sham every 6 weeks for 12 to 30 weeks	169 patients 18 years of age with clinically significant DME (Study is ongoing)	Retinal thickening, BCVA, AEs, IOP, laboratory parameters, local ocular events, need for laser at 12 weeks
Studies in Von Hippel-Lindau Disease (VHL)				
EOP1007	Phase 1/2, open-label, non-randomized, pilot	Intravitreous injections of 3 mg pegaptanib sodium/ eye every 6 weeks for 30 to 54 weeks	5 patients 18 years of age with severe ocular VHL tumors	BCVA, macular thickening, fluorescein leakage, disease progression, AEs, local ocular events, IOP.

CNV = Choroidal neovascularization; PDT = Photodynamic therapy with verteporfin; DLT = Dose limiting toxicity; AE = Adverse event;
BCVA = Best corrected visual acuity; IOP = Intraocular pressure; PK = Pharmacokinetics; QOL = quality of life.

There are five PK studies in AMD patients (Study# NX109-01, EOP1000, EOP 1001, EOP1004 and EOP 1006). Results of the PK studies are summarized below:

- Following intravitreous injection of pegaptanib sodium, pegaptanib is systemically available. At low doses (1 mg/eye or less) pegaptanib concentrations in plasma are close to the limit of detection ($\sim$ g/mL), whereas, in 2 mg/eye and 3 mg/eye dose treatment groups, plasma pegaptanib concentrations increased disproportionately with dose (Study NX109-01).

- Highest pegaptanib plasma concentrations were seen within one week of dosing of 3mg pegaptanib sodium and ranged from $\sim$ ng/mL. In patients receiving 0.3 or 1 mg dose (N=64 to 71) plasma pegaptanib trough concentrations (Cmin) were below the limit of detection on weeks 12, 30, 42 and 54, where as approximately 15% of patients (N=71) receiving 3 mg pegaptanib showed detectable plasma pegaptanib trough concentrations ranging from $\sim$ ng/mL (Study EOP 1004).

- In 35 to 37 patients, following every six-week dose of 3-mg of pegaptanib sodium, pegaptanib mean (+/-SD) of Cmax values were 77(+/-29), and 75(+/-30) ng/mL, for the first (N=35), and the fourth or the fifth doses (N=37), respectively. The corresponding extent of exposure values were 28 (+/- 8) µg.hr/mL (AUC0-inf) and 25(+/-6) µg.hr/mL AUC (0-tau), respectively (Study EOP1006).

- Mean terminal elimination half-life of pegaptanib was approximately 10 days with individual values ranging from $\sim$ days.

- The tmax following the first 3 mg dose of pegaptanib was 60 hr (range $\sim$ nours, N=37) and 60(+/-46) hours (range $\sim$ nours, N=35) following every six week dosing was after the fourth dose.

- In general, higher Cmax and AUClast values were seen in patients with reduced renal function as represented by lower CLcr values. For the first dose, there was not a statistically significant relationship between CLcr and AUClast. For the fourth dose, a statistically significant relationship between CLcr (range: $\sim$ .nL/min) and AUClast was found (p=0.0027).

- Pegaptanib metabolism is not fully characterized, however, like other oligonucleatides, it is expected to be metabolized by nucleases to shorter chains of nucleotides.
- A potential pharmacokinetic and pharmacodynamic interaction between pegaptanib and verteporfin was assessed in two clinical studies, and no differences were noted in pharmacokinetics of pegaptanib due to treatment with PDT with verteporfin (EOP 1000 and EOP 1001).

Chandra S. Chaurasia, Ph.D. _____ Date: 9/17/04
Clinical Pharmacology and Biopharmaceutics Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by   Arzu Selen, Ph. D. _____   Date: _____
                      Deputy Director, DPE III

CC: NDA 21-756, HFD-850 (P. Lee), HFD-550 (M. Puglisi), HFD-880 (J. Lazor, A. Selen, E. D. Bashaw, C. Chaurasia)

2. Question Based Review

2.1 General Attributes of Pegaptanib sodium for intravitreous injection

2.1.1 What regulatory background or history information contributes to the assessment of the clinical pharmacology and biopharmaceutics of this drug?

Based on literature, VEGF is the principal angiogenic growth factor contributing to the pathogenesis of AMD. This has lead to development of pegaptanib, a VEGF inhibitor, as a potential treatment for the neovascular form of AMD because it is claimed to inhibit angiogenesis and vascular leakage.

Because of its potential impact, pegaptanib NDA has been given priority review status and it is also being reviewed as a Continuing Marketing Application (CMA). Per the CMA, pilot program, the comments to the reviewable units are made 6 months after their submission, and the final action is taken 6 months after submission of the last reviewable unit.

At the Advisory Committee Meeting (Dermatology and Ophthalmology) that took place on 8/27/2004, the Sponsor also indicated that they will be submitting a POP PK analysis report in September. The POP PK analysis report is expected to have impact on the labeling and as a result, this review summarizes current findings and communicates questions for clarification to the Sponsor. The labeling comments will be provided when all clinical pharmacology reports are submitted and reviewed.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the product?

The active moiety of pegaptanib sodium is an aptamer, a novel class of oligonucleotide-based therapeutic agents. Specifically, pegaptanib sodium is a pegylated synthetic ribonucleic acid (RNA)-based oligonucleotide composed of 28 nucleotide bases. The oligonucleotide is composed of modified pyrimidine and purine nucleotides (2'-fluoropyrimidines and 2'-methoxypurines). It also contains two unmodified nucleotides, 2'-hydroxyadenosines that are required to maintain binding affinity to the VEGF165 protein. These modifications serve to increase resistance of pegaptanib sodium to nuclease degradation. The oligonucleotide has a molecular weight of ⌐ Daltons. To increase the in vivo residence time, a 40 kD branched polyethylene glycol (PEG) molecule (each PEG arm composed of an approximately 20 kD PEG moiety) has been conjugated to the 5'-terminus of the oligonucleotide. The 2 PEG arms are attached through a lysine, linked to the aptamer portion of the molecule via an amide bond formed with a phosphate linked pentyl amine. The 3'-terminus is capped with a reverse thymidine.

The dosage unit of active ingredient is based on the molecular weight of the oligonucleotide moiety of pegaptanib excluding the polyethylene glycol amino linker and excluding 28 sodium atoms that associate with phosphate groups of each nucleotide.

**Chemical Name:** The chemical name for pegaptanib sodium 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

Structural formula

Pegaptanib sodium is represented by the following structural formula:
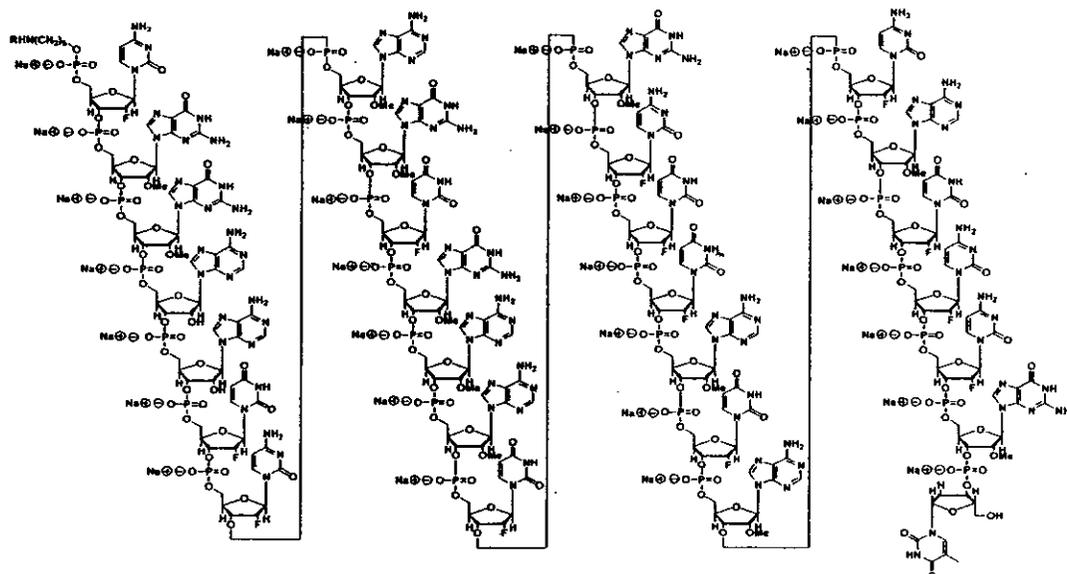
Where R is
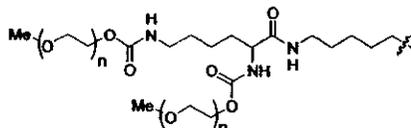
and n is approximately 450.

Empirical Formula: $C_{294}H_{342}F_{13}N_{107}Na_{28}O_{188}P_{28}[C_2H_4O]_n$ (where n is approximately 900)

Molecular Weight: Approximately 50 kilodaltons.

**Physicochemical Properties**:

Macugen™ (pegaptanib sodium for intravitreous injection) is a sterile, aqueous solution containing pegaptanib sodium for intravitreous injection. 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.

What are the proposed mechanism of action and therapeutic indication of Pegaptanib sodium for intravitreous injection?

Pegaptanib is claimed to be a VEGF inhibitor and the Sponsor has submitted the following data in support of their claim:

Two separate experiments to determine IC50 for pegaptanib's anti-VEGF activity in HUVEC (human umbilical vein endothelial cells.

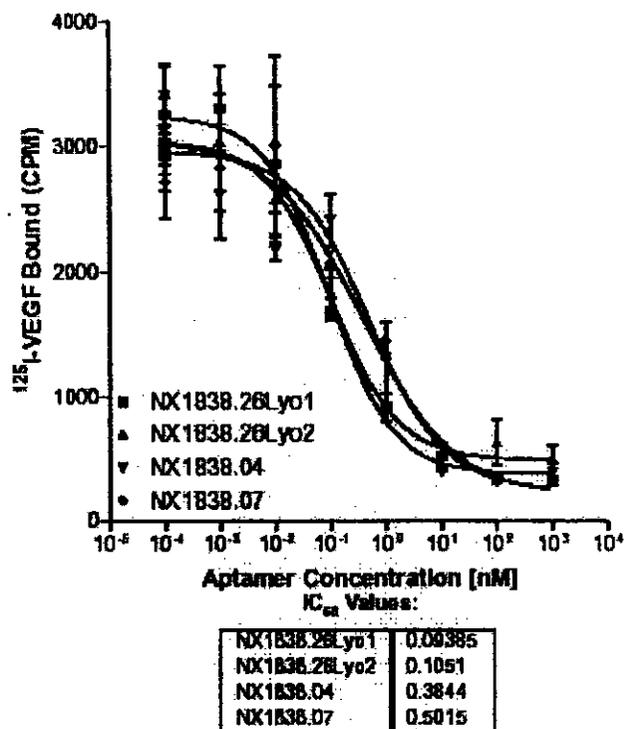**Aptamer Inhibition of ^{125}I-VEGF Binding to HUVECs *In Vitro***

[Reference Date: 10-17-97]
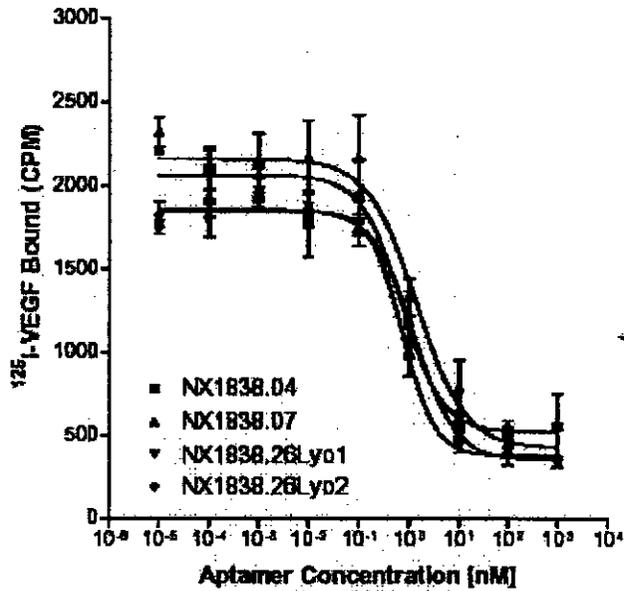
NX1838.04	0.7189
NX1838.07	1.415
NX1838.26Lyo1	0.7528
NX1838.26Lyo2	1.281

**APPEARS THIS WAY
ON ORIGINAL**

Aptamer Inhibition of ^{125}I-VEGF Binding to HUVECs *in Vitro*
[Reference Date: 10-10-97]

IC$_{50}$ Values:

NX1838.26Lyo1	0.03385
NX1838.26Lyo2	0.1051
NX1838.04	0.3844
NX1838.07	0.5015

Results from these experiments demonstrate that binding of 125I-VEGF (10ng/mL) to HUVECs was inhibited - in a dose-dependent manner – by NX1838, resulting in IC50 values for NX1838 of 0.03-1.4nM.

APPEARS THIS WAY
ON ORIGINAL

Inhibition of ^{125}I-VEGF Binding to HUVECs In Vitro
[Reference Date: 2-8-96]
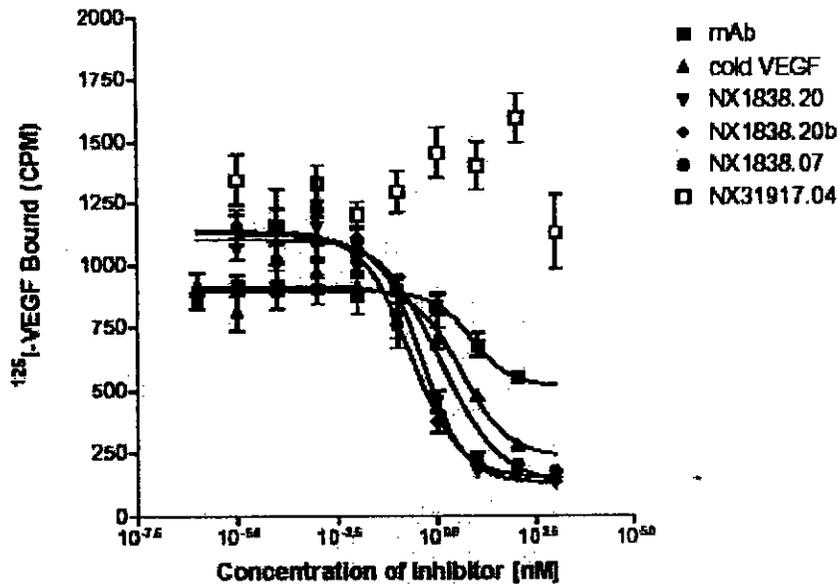
mAb	7.359
cold VEGF	3.083
NX1838.20	0.4283
NX1838.20b	0.2118
NX1838.07	1.126

VEGF mAb was also found to inhibit 125I-VEGF binding to HUVECs [IC50 values of 7.4nM]. Irrelevant antibodies and scrambled sequence aptamer controls failed to inhibit 125I-VEGF binding. These findings are submitted by the Sponsor to support that NX1838 is a specific inhibitor of VEGF binding to endothelium *in vitro*.

Note: The above results are from the nonclinical study (*In Vitro Inhibition of VEGF Receptor Binding by VEGF Aptamer NX1838, Protocol 109-97001-1*).

Indication: Pegaptanib sodium is indicated for the treatment of exudative (wet) age-related macular degeneration.

2.1.4   What is the proposed dosage and route of administration?

The proposed dose is 0.3 mg/eye once every 6 weeks administered intravitreously.

2.2. General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The first time to humans study suggests some non-linearity at 1 mg and higher doses following intravitreous administration of pegaptanib. The response as measured by the primary efficacy endpoint (proportion of patients losing < 15 letters of VA from baseline to 54 weeks (responders)) was significant for the 0.3 mg and 1 mg dose group in EOP1003 and EOP1004. While the response to the high dose (3 mg dose/eye) was not statistically significant, the overall results are comparable for the three doses as illustrated in the following tables (please see Section 2.2.4.1).

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

The efficacy endpoints in two Phase II/III studies (EOP 1003 and EOP 1004) were as follows:
Primary efficacy endpoint
   • Proportion of patients losing < 15 letters of VA from baseline to 54 weeks (responders)
Secondary efficacy endpoints
   • Proportion of patients gaining > 15 letters of VA
   • Proportion of patients gaining > 0 letters
   • Mean change in VA

There have been no clinical studies conducted that had a primary objective of correlating pegaptanib plasma concentration at the time of treatment, and subsequent clinical efficacy. Because of intravitreal administration the plasma concentration may not be related to efficacy.

2.2.3 Are the active moieties in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Exposure-response relationships have not been carried out, however, analytical method used is validated for analysis of pegaptanib in human plasma.

2.2.4. Exposure-response evaluations

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

In the two Phase II/III studies (EOP1003 AND EOP1004), a wide range of doses (0.3 mg. 1 mg, 3 mg) was studied. The primary and secondary efficacy endpoints (please see Section 2.2.2 above) were measured. The efficacy endpoint results are summarized below:

Primary Efficacy Endpoint EOP1003

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

Primary Efficacy Endpoint EOP1004

Number of patients (%)		0.3 mg, N=153	1 mg, N=158	3 mg, N=155	Sham, N=156
Responders	Month 3	125 (86.8%)	118 (80.3%)	121 (82.3%)	115 (77.7%)
	Month 6	118 (81.9%)	106 (72.1%)	102 (69.4%)	85 (57.1%)
	Month 9	106 (73.6%)	108 (73.5%)	103 (70.1%)	78 (52.7%)
	Month 12	97 (67.4%) p=0.016	98 (66.7%) p=0.03	91 (61.9%) p=0.13	79 (53.4%)

Secondary Efficacy Endpoint Vision Gain ≥15 letters

		0.3 mg	1 mg	3 mg	Sham
EOP1003		N=150	N=154	N=153	N=152
	Yes	6 (4%)	10 (6%)	7 (5%)	5 (3%)
	P-value	0.93	0.49	-	-
EOP1004		N=144	N=146	N=143	N=144
	Yes	12 (8%)	10 (7%)	6 (4%)	1 (1%)
	P-value	0.005	0.01	0.04	-

For primary endpoint, lower doses (0.3 mg/eye and 1.0 mg/eye) exhibit significant efficacy ($p \leq 0.01$) compared to the sham group. However, the higher dose (3 mg/eye) did not consistently demonstrate efficacy in patients with neovascular AMD.

For the secondary endpoint, 1 mg/eye or less dose of pegaptanib has treatment effect of approximately 15% compared to sham ($p \leq 0.01$). As in the primary efficacy endpoint, the higher dose (3 mg/eye) did not consistently demonstrate efficacy in patients with neovascular AMD.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

In the main efficacy and safety trials (EOP1003 AND EOP1004):
- Similar events seen in all dose groups (0.3 mg, 1 mg and 3 mg), no dose-dependent events
- Most events are likely to be related to intraocular injection

Given the nature of these events, further ER analyses of these data have not been pursued.

2.2.4.3 Does this drug prolong the QT or QTc interval?

Not studied.

2.2.4.4 Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

As mentioned above (Section 2.2.1), the primary efficacy response was significant for the 0.3 mg and 1 mg dose group in EOP1003 and EOP1004, while the response to the high dose (3 mg dose/eye) was not statistically significant. Thus, a dose-concentration-response relationship could not be satisfactorily explained with the existing data. The pharmacometric analysis and review of the upcoming submission may assist in better understanding the key components of the

ER relationships and address the lack of demonstration of effect at the high dose. The future PM review will be attached to this review as an amendment.

2.2.5. What are the pharmacokinetic characteristics of the drug and its metabolite?

The pharmacokinetic profile of pegaptanib has been studied in a total of five trials: one single dose study and four repeated dose studies. The repeated dose studies were conducted with the 3 mg dose injected every 4 weeks or every 6 weeks. The results of these trials are summarized below:

- In 35 to 37 patients, following every six-week dose of 3-mg of pegaptanib sodium, pegaptanib mean (+/-SD) of Cmax values were 77(+/-29), and 75(+/-30) ng/mL, for the first (N=35), and the fourth or the fifth doses (N=37), respectively. The corresponding extent of exposure values were 28 (+/- 8) μg.hr/mL (AUC0-inf) and 25(+/-6) μg.hr/mL AUC(0-tau), respectively (Study EOP1006).
- Mean terminal elimination half-life of pegaptanib was approximately 10 days with individual values ranging from ⸺ days.
- The tmax following the first 3 mg dose of pegaptanib was 60 hr (range ⸺ hours, N=37) and 60(+/-46) hours (range ⸺ hours, N=35) following every six week dosing was after the fourth dose.
- In general, higher Cmax and AUClast values were seen in patients with reduced renal function as represented by lower CLcr values.

2.2.5.1 What are the single dose and multiple dose pharmacokinetic parameters?

Single Dose PK was obtained in the Phase I dose escalating study NX 109-91 following intravitreous administrations of 0.25 mg, 0.5 mg, 1 mg, 2 mg, and 3 mg/eye of pegaptanib. This was first in human preliminary PK dose escalating study, and as such complete PK profile has not been reported in the submission. Samples were collected on Day 1, 7, 14 and 28 (in all patients), and additionally, on Days 6, 9, 13, 17, 26, 27, 29, 30 or 32 Days (in some patients).

Following intravitreous injection of pegaptanib sodium, pegaptanib is systemically available. At low doses (1 mg/eye or less) pegaptanib concentrations in plasma are close to the limit of detection (7 ng/mL), whereas, in 2 mg/eye and 3 mg/eye dose treatment groups, plasma pegaptanib concentrations increased disproportionately with dose. In the 2 mg/eye group (n=3) maximum pegaptanib plasma concentrations of ⸺ ng/mL were observed, on Day 1, 7, and 14, respectively. In the 3 mg/eye group (n=3) maximum pegaptanib plasma concentrations of ⸺ ng/mL were observed, on Day 1, 7, and 14, respectively.

Multiple Dose PK: please see above Section 2.2.5

2.2.5.2 How does the pharmacokinetics of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Pegaptanib is studied only in patients.

2.2.5.3 What are the characteristics of drug absorption?

The absolute bioavailability of Macugen (parent drug) after intravitreous administration has not been assessed in humans, but is approximately 70-100% in rabbits, dogs, and monkeys. In animals that received doses of Macugen of up to 3 mg/eye to both eyes, plasma concentrations were 0.03% to 0.15% of those in the vitreous humor.

2.2.5.4 What are the characteristics of drug distribution?

In mice, rats, rabbits, dogs and monkeys, Macugen 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 Macugen to both eyes of rabbits, radioactivity was mainly distributed in vitreous fluid, retina and aqueous fluid. After intravitreous and intravenous administrations of radiolabeled Macugen to rabbits, the highest concentrations of radioactivity (excluding the eye for the intravitreous dose) were obtained in the kidney. In rabbits, the component nucleotide, 2'-fluorouridine is found in plasma and urine after single radiolabeled Macugen intravenous and intravitreous doses.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Macugen is metabolized by endo- and exonucleases. In rabbits, Macugen is eliminated as parent drug and metabolites primarily in the urine. No human data have been provided.

2.2.5.6 What are the characteristics of drug metabolism?

Report from rabbit studies indicate that pegaptanib is largely (28-49%) metabolized to 2'-flouro-2'-deoxyruidine following intravitreal and intravenous administration.

2.2.5.7 What are the characteristics of drug excretion?

Human data have not been provided. Based on animal (rabbit) data pegaptanib is eliminated as parent drug and metabolites primarily in the urine.

2.2.5.8 Based on pharmacokinetic parameters, what is the degree of linearity in the dose-concentration relationship?

The first time to humans study suggests some non-linearity at 1 mg and higher doses. While the analytical method may account for differences up to 30%, it is also evident that the increase in exposure for doses of 1 mg and higher is greater than dose-proportional. The exact deviation from non-linearity can not be assessed from this study, however, according to the proposed dose and dosing regimen and availability of the 54 week safety data at 3-mg dose, further exploration of non-linearity is not considered necessary.

2.2.5.9 How do the pharmacokinetic parameters change with time following chronic dosing?

Submitted data do not indicate a time-dependent change in the PK parameters of pegaptanib.

2.2.5.10 What is the inter- and intra-subject variability of pharmacokinetic parameters in volunteers and patients, and what are the major causes of variability?

2.3. Intrinsic Factors

Gender: Plasma concentrations of Macugen following intravitreous administration in male and female patients are similar.

<u>Geriatric:</u> Plasma concentrations of Macugen following intravitreous administration were similar among patients 50 to 90 years of age.

<u>Renal Insufficiency</u>

In general, higher Cmax and AUClast values were seen in patients with reduced renal function (40-70 mL/min) as represented by lower CLcr values following intravitreous injection of 3mg/eye dose of pegaptanib. Patients with moderate to severe renal insufficiency (creatinine clearance < 40mL/min) have not been studied.

<u>Hepatic Impairment:</u> Macugen has not been studied in patients with hepatic impairment.

2.4. Extrinsic factors

Drug interaction studies have not been conducted with Macugen. Macugen is metabolized by nucleases and therefore cytochrome P450 mediated drug interactions are unlikely.

Two early clinical studies conducted in patients who received Macugen alone and in combination with photodynamic therapy revealed no apparent difference in the plasma pharmacokinetics of Macugen.

2.5   General Biopharmaceutics

2.5.1   Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility and permeability data support this classification?

The applicant has not provided any permeability data. There are inadequate data for BCS classification. No further action is necessary.

2.5.2. What is composition of the to-be-marketed formulation?

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

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

a Quantities are calculated

2.5.3 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

Because this NDA is submitted as a Continuing Marketing Application and CMC review is currently on going, we are not able to address this question at this time.

2.5.4 What moieties should be assessed in bioequivalence studies?
No bioequivalence (BE) study was conducted as part of this submission.

2.5.5 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable.

2.5.6 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?
Not applicable

2.6 Analytical Section

2.6.1 Were relevant metabolite concentration measured in the clinical pharmacology and biopharmaceutics studies?
No information on any circulating metabolites of pegaptanib in human plasma have been provided.

2.6.2 For all moieties measured, was free, bound, or total measured? What is the basis of that decision, and is it appropriate?
Total drug concentration in plasma was measured.

2.6.3 Were the analytical procedures used to determine drug concentration in this NDA acceptable?
Yes.

3. Detailed Labeling Recommendations

The labeling comments will be provided when all clinical pharmacology reports are submitted and reviewed (Please refer to Section 2.1.1).

_____ *10* _____ **Draft Labeling Page(s) Withheld**

4.2. Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

Study Title: A Phase 1 Open-Label Trial of PEGAPTANIB Sodium (anti-VEGF) to Establish the Safety and Pharmacokinetic Profile in Patients with Age-Related Macular Degeneration

Compound: EYE001 (pegaptanib)
Compound Name: Pegaptanib Sodium/ MacugenTM
Protocol: NX109-01
Study Dates: 06 January 1999 to 15 August 2000
Issue Date: January 26, 2004

Primary Study Objective:

1) To establish the acute maximum tolerated dose (MTD), which is defined as the dose associated with <33% of patients experiencing acute dose limiting toxicity (DLT).
2) If no DLT occurred, the primary objective was to determine, if the highest practical dose of the PEGylated aptamer pegaptanib sodium (MacugenTM) could be given safely as a single intravitreous injection in patients with neovascular age-related macular degeneration (AMD).

Secondary Study Objectives:

1) To reject any dosing regimen inducing DLT in > 33% of patients.

2 To evaluate the safety, pharmacokinetic (PK) profile and immune response to pegaptanib sodium.
3) To identify unexpected and acute toxicities in a subset of patients with best corrected visual acuity (BCVA) worse than 20/200 for whom the risk of acute toxicity is more acceptable.

Study Design: This was a multi-center, open-label, dose-escalation phase 1 study of a single, unilateral, intravitreous injection of pegaptanib sodium. Three patients were enrolled in each of 5 cohorts to receive the following doses of pegaptanib sodium: 0.25, 0.5, 1, 2 and 3 mg. Enrollment was opened to the next higher dose cohort until a MTD was established or the maximum dose reached.

Please see the Medical Officer's review for the main inclusion and exclusion criteria.

Treatments:
Dosage Form Pegaptanib sodium was provided at nominal active drug concentrations of 2.5, 5, 10, 20, or 30 mg/mL in a nominal 100-μL volume to deliver 95 μl consistently with doses of 0.25, 0.5, 1, 2, or 3 mg of drug, respectively. The investigational drug was a preservative-free and ready-to-use, sterile, intravitreous injection solution of pegaptanib sodium dissolved in 10 mM sodium phosphate and 0.9% sodium chloride buffer solution (weight expresses the oligonucleotide content of pegaptanib). The drug product was presented in a 1-cc USP Type 1 graduated glass body syringe barrel, with a pre-attached 27-gauge needle. The content of the

syringe was administered with local anesthetic consisting of subconjuctival, peribulbar, or retrobulbar 2% xylocaine devoid of epinephrine.

Batch numbers: 151805E, 101804E, 111803E, 201901E, 121802E, 211901E, 131901E

Dosing and Duration:
Patients were treated with a single intravitreous administration of 0.25, 0.5, 1, 2, or 3 mg pegaptanib sodium, respectively. Patients were followed for 12 weeks.

METHODOLOGY:

Safety endpoints:
The primary safety endpoint was the presence of any DLT.
Secondary safety endpoints included:

- Adverse events (AEs)
- Vital signs: Heart rate, systolic and diastolic blood pressure, electrocardiography (ECG) and physical examination
- Ophthalmic variables: BCVA, IOP in the study eye, ophthalmic examination, lens photography, stereoscopic fundus photography, and fluorescein angiograms.
- Laboratory variables such as hematology, renal function, hepatic function and electrolytes
- Immune response: Detection of IgG-directed serum antibodies against pegaptanib.

Analytical Methodology:

Pegaptanib assay:

Determinations of pegaptanib plasma concentrations were performed by a non-GLP dual hybridization assay by　　　　—

Blood samples were collected in Vacutainers containing potassium EDTA for the purpose of determining plasma concentrations of pegaptanib. Serial blood samples were collected over a 1-month period following drug injection for pharmacokinetic analysis (Days 1, 2, 7, 14, 21 and 28, Table 7). Plasma concentrations of pegaptanib were detected using a dual hybridization procedure

. Thus, the dual hybridization assay detects the presence of the oligonucleotide portion of the molecule, and the oligonucleotide portion of the molecule is likely to be intact given the — Pegaptanib plasma concentrations are expressed in terms of the weight of the oligonucleotide portion of the molecule and are based on a theoretical molar extinction coefficient.

Note that in the bioanalytical report, pegaptanib refers to both the drug substance and the biologically active species.

Assay for IgG antibodies for pegaptanib:

Levels of IgG antibody against pegaptanib were measured with a non-GLP — immunoassay using an alkaline phosphatase-conjugated goat anti-human IgG antibody. This non-GLP assay was performed by ⎯

Pharmacokinetics:

The PK parameters Cmax, Tmax, AUClast and t1/2 were calculated by noncompartmental methods. Descriptive statistics were used to summarize the mean data.

Statistical Methods:

No formal hypothesis testing was performed. Descriptive statistics were used to analyze the primary and secondary endpoints.

RESULTS:

Subject Disposition:
Doses were going to be escalated up to a maximum of 4 mg/eye (cohort 6), but due to the drug viscosity at 4 mg dose, the study was stopped after the 3 mg/eye cohort. The sample size was then reduced by one cohort (3 patients) from 18 to 15.

Demographic Characteristics:
All 15 patients in the study were Caucasian. Eight patients were male (53 %), 7 patients were female (47 %), aged between 64 and 92. The most noteworthy difference among cohorts is that all patients in cohort 5 (3 mg) were male and were younger (mean age 67.7+0.6 years) than those in other cohorts (overall mean age 75.8 ± 8.2 years).

Safety:
Please see Medical Officer's review for detailed safety assessment.

The Sponsor's report states that evaluation of laboratory tests and vital signs showed no clinically significant safety concerns associated with pegaptanib sodium administration and that there was no evidence of IgG-directed serum antibodies against the study drug.

Pharmacokinetics:

In the lower dose cohorts (0.25, 0.5 and 1 mg/eye), pegaptanib plasma concentrations were below or close to the limit of detection ___ throughout most of the 28 to 32-day sampling period.
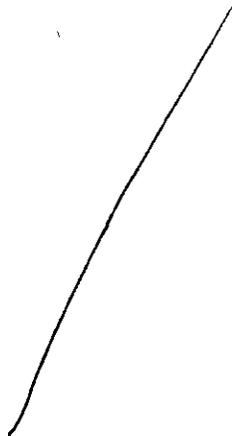
In patients receiving a single dose of 2 mg or 3 mg pegaptanib sodium/eye, pegaptanib plasma concentrations were significantly higher than that would be predicted based on lower doses.

For 2 and 3 mg doses, the maximum pegaptanib plasma concentrations were between ___ ng/ml and the concentrations were measurable for up to 29 days after dosing.

SUMMARY:

- In the 0.25 mg/eye group (n=3):
  Maximum pegaptanib plasma concentration of ～ ng/ML is observed in one patient on Day 7, similar to Day 1 concentration of ― ng/mL in the same patient. The assay limit is ―
- In the 0.5 mg/eye group (n=3):
  Maximum pegaptanib plasma concentrations of ' ― ng/ML and ― ng/ML are observed, on Day 6 and 7, respectively, in two patients.
- In the 1 mg/eye group (n=3):
  Maximum pegaptanib plasma concentrations of ― ng/ML ― mL and ― ng/ML are observed, on Day 1, 0.25, and 7, respectively.
- In the 2 mg/eye group (n=3):

Maximum pegaptanib plasma concentrations of   —
are observed, on Day 1, 1, and 14, respectively.
- In the 3 mg/eye group (n=3):
Maximum pegaptanib plasma concentrations of

                                              are observed, on Day 1, 7, and 14, respectively.
Note: Samples were collected on Day 1, 7, 14 and 28 (in all patients), and additionally,
on Days 6, 9, 13, 17, 26, 27, 29, 30 or 32 Days (in some patients).

REVIWERS' COMMENTS:

1) Pegaptanib following intravitreal administration can be detected in systemic circulation.
2) Due to sampling scheme, that is, there were no samples collected on Day 2 after dosing, one
can not rule out the possibility of Cmax concentrations higher than those observed in this study.
3) There appears to be a disproportionate increase in pegaptanib exposure with dose and this is
greater than the 30% variability that can be at most attributed to the analytical methodology.
Although the study does not allow a full assessment of nonlinearity in pegaptanib
pharmacokinetics, additional work is not considered to be necessary for the proposed dose and
dosing regimen.

APPENDIX:

ANALYTICAL METHOD

Human EDTA-plasma samples were analyzed for pegaptanib, NX1838 (EYE001), according to
     —   procedure   —   This protocol is designed to quantify the levels of the anti-
vascular endothelial growth factor (VEGF) aptamer "NX11838"+40K PEG (or
NX31838+40KPEG) in human EDTA plasma.

The assay is based on a dual hybridization technique   _   —   ... , as
described above.

This method is validated for a range of   —   , ng/mL. This validated range is based on the
oligonucleotide weight of NX1838 and all reported values are reported as the oligonucleotide
weight. The concentration of pegaptanib is based on an approximate extinction coefficient for the
oligonucleotide of 37 µg/mL per A260 unit. The molecular weight of the oligonucleotide portion
is   —

This pegaptanib assay method was used only in this study in this submission. A validated
improved method is used in the subsequent studies.

■■■

STUDY EOP1000

Study Title: A Phase 1/2 Open-Label Multi-Center Trial to Establish the Safety and Pharmacokinetic Profile of Three Consecutive Intravitreal Injections of Pegaptanib Sodium (Anti-VEGF Pegylated Aptamer) in Patients with Exudative Age-Related Macular Degeneration, Without Previous or Concomitant Photodynamic Therapy (PDT) with VisudyneTM

Study Dates: 10 October 2000 to 07 November 2001

Primary Study Objective:
The primary objective was to evaluate the safety of 3 repeat doses of pegaptanib sodium.

Secondary Study Objectives:
Secondary objectives included the evaluation of the plasma pharmacokinetic (PK) profile, the preliminary efficacy by best corrected distance visual acuity, and the development of serum antibodies to pegaptanib, when pegaptanib sodium is given as intravitreous injections (3 mg/eye) once every 28 days for 3 doses in patients with the neovascular form of age-related macular degeneration (AMD).

Study Design:

This was a multi-center, open-label, repeat-dose, phase 1/2 study in patients with subfoveal choroidal neovascular AMD without previous or concomitant photodynamic therapy (PDT) with VisudyneTM. Patients received 3 consecutive unilateral, intravitreous injections of 3 mg pegaptanib sodium/eye at 28-day intervals and were followed for a total of 52 weeks. If 3 or more patients experienced dose limiting toxicities (DLTs), the dose was to be reduced to 2 mg/eye and, if necessary, to 1 mg/eye, each in an additional 10 patients. The intended number of patients to be treated was 10, but enrollment would increase to a maximum of 30, if dose reductions were required.

Please see the medical Officer's review for main **inclusion and exclusion criteria.**

Treatments:
Dosage Form
Ready-to-use, sterile, intravitreous injection solution intended for single use only and supplied in a single-dose, pre-filled syringe. Each syringe delivers 3 mg pegaptanib sodium based on the oligonucleotide weight) in a nominal volume of 95 µL of a sterile, clear, preservative-free solution containing sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, hydrochloric acid, sodium hydroxide in water for injection. The drug product was presented in a 1 cc USP Type 1 glass syringe, with a pre-attached 27-gauge needle. The injections were administered under topical anesthetic, or with local anesthetic consisting of subconjunctival, peribulbar, or retrobulbar 2% xylocaine devoid of epinephrine.

Dosing and Duration
Patients were treated during the first 57 days of the study with 3 consecutive injections of 3 mg pegaptanib sodium/eye at 28-day intervals. Patients were followed for 52 weeks.

METHODOLOGY

Pharmacokinetics:

PK parameters Cmax, tmax, Tlast, Clast, AUClast, AUCinf, AUCtau, t1/2, CL/F were determined.

• Patient's immune response measured by serum IgG antibodies to pegaptanib

For assessment of the patients' immune response to pegaptanib, blood samples were collected prior to the first, second, and third intravitreous injection as well as on Day 85 (i.e. about 28 days after the third injection). Serum samples were assayed for the presence of IgG antibodies directed against pegaptanib by a non-GLP— ___ . immunoassay.

Pegaptanib plasma concentrations were measured by a validated dual hybridization assay with a lower quantitation limit of ⸺ . (same method described in detail for EOP1006). Pegaptanib plasma PK parameters were calculated by noncompartmental methods. Descriptive statistics were used to summarize these PK parameters for each dose administered.

RESULTS

A total of 10 patients were screened and enrolled at 7 of the 11 study centers. Three patients did not complete the study.
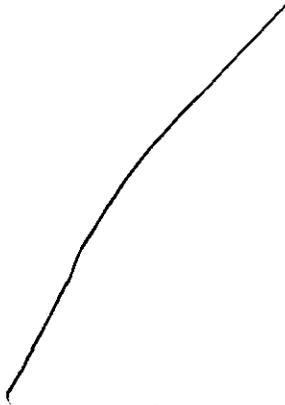
Figure 1. Mean Pegaptanib Plasma Concentrations after Intravitreous Injection of 3mg/study eye Pegaptanib Sodium every 28 Days
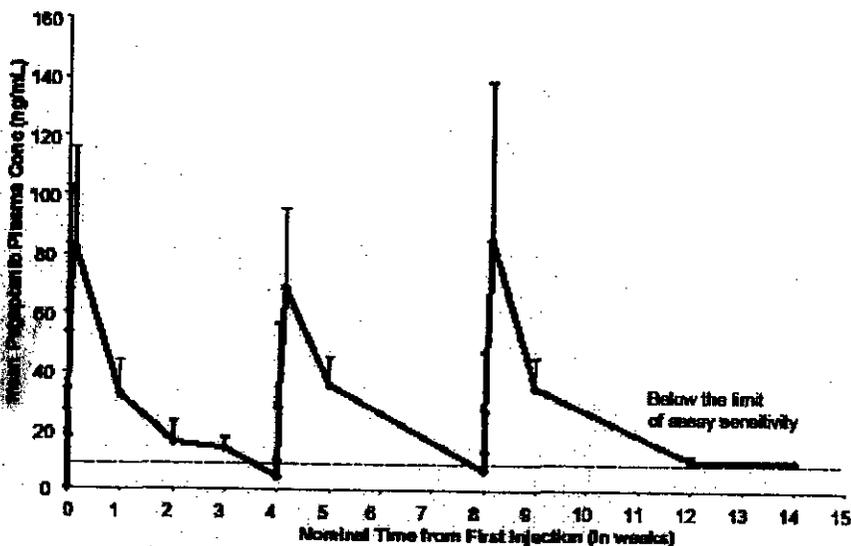
Pegaptanib plasma concentrations = mean +1 SD

Pegaptinib AUC values after 3 mg IVT doses once every 4 weeks (EOP1000)

■ First dose

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....

STUDY EOP1001

Study Title: A Phase 1/2 Open-Label Multi-Center Trial to Establish the Safety and Pharmacokinetic Profile of Three Consecutive Intravitreal Injections of Pegaptanib Sodium (Anti-VEGF Pegylated Aptamer) in Patients With Exudative Age-Related Macular Degeneration who are Scheduled to Receive Photodynamic Therapy (PDT) with VisudyneTM

Primary Study Objective:
The primary objective was to evaluate the safety of 3 repeat doses of pegaptanib sodium administered after photodynamic therapy (PDT) with VisudyneTM.
Secondary Study Objectives:
Secondary objectives included the evaluation of the plasma pharmacokinetic (PK) profile, the preliminary efficacy by best corrected distance visual acuity, and the development of serum antibodies to pegaptanib, when pegaptanib sodium is given as intravitreous injections (3 mg/eye) once every 28 days for 3 doses in patients with the neovascular form of age-related macular degeneration (AMD).

Methods

I) For study design, patient demographics and clinical results, please see the Medical Officer's review.

II) Plasma pegaptanib assay

Analytical Methodology: Assay performed by —
Validated, GLP assay and fully described in the review of Study EOP1006

III) Blood samples were collected during repeated dosing (3 consecutive doses) for pegaptanib assay and assessment of pegaptanib multiple dose PK.

Results:

- Following three repeat intravitreous 3 mg doses, pegaptanib mean (+/-SD) of Cmax values were 68(+/-26), 67(+/-35) and 74(+/-40) ng/ML, for the first, second and third doses, respectively, administered once every 6 weeks.
- Following the first intravitreous 3 mg dose, pegaptanib mean (+/-SD) of AUC(0-inf) values were 21(+/-5) μg.hr/ML and following the third dose, AUC(0-Tau) values were 25(+/-12) μg.hr/ML.

These results suggest minimal if any, accumulation of pegaptanib.

- Mean Pegaptanib elimination half-lives were approximately 10 days with individual values ranging from 2 to 14 days.
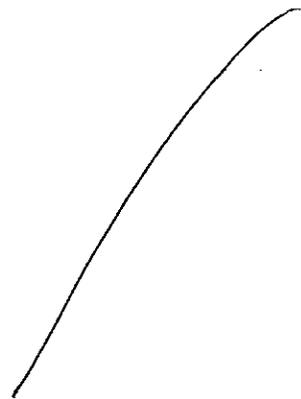
Patient numbers

REVIEWERS' COMMENTS:

Significant systemic exposure is observed at 3mg/eye dose when pegaptanib is administered once every 6 weeks. Although, there does not appear to be drug accumulation, given that pegaptanib is a potent VEGF antagonist, it is important to characterize the source of individual variability (i.e. t1/2 values ranging from 2 to 19 days).

The PK report indicated to be submitted in September 2004 may assist in better characterization of pegaptanib pharmacokinetics and the factors that may be critical for labeling.

■■

STUDY EOP1004

Study title: A Phase 2/3 Randomized, Double-masked, Controlled, Dose-ranging, Multi-center Comparative Trial, in Parallel Groups, to Establish the Safety and Efficacy of Intravitreous Injections of Pegaptanib Sodium Given Every 6 Weeks for 54 Weeks, in Patients with Exudative Age-related Macular Degeneration.

Objectives: The objective of this study was to establish the safe and efficacious dose of pegaptanib sodium when given as an intravenous injections (0.3 mg, 1 mg and 3 mg/eye) compared with control sham injections every 6 weeks over a 54-week period to AMD.

Methods:

IV) For study design, patient demographics and clinical results, please see the Medical Officer's review.
V) Plasma pegaptanib assay
Analytical Methodology:
Performed by —
Validated, GLP assay and fully described in the review of Study EOP1006
VI) Blood samples were collected at trough time points for pegaptanib assay.

Results:
- In almost all patients (n= 64 to 69) receiving 0.3 mg pegaptanib sodium, plasma pegaptanib trough concentrations were below limit of detection on weeks 12, 30, 42 and 54 (prior to administration of study medication).
- In almost all patients (n= 64 to 71) receiving 1 mg pegaptanib sodium, plasma pegaptanib trough concentrations (Cmin) were below limit of detection on weeks 12, 30, 42 and 54.
- Approximately 15% of patients (n= 71 to 75) receiving 3 mg pegaptanib sodium, had detectable plasma pegaptanib trough concentrations ranging from — ıg/mL.
- Highest pegaptanib plasma concentrations were seen within one week of dosing of 3mg pegaptanib sodium and ranged from — ng/mL.
- Only one patient (out of approximately 70) had measurable (— /mL) pegaptanib concentrations 6 weeks after the 1st and the 4th dose.

REVIEWERS' COMMENTS:

Although a different analytical method (same principle) is used, concentrations are similar to those seen in the first study confirming systemic availability of pegaptanib and its slow clearance from the body and validating results from the first study (NX109-01).

PROTOCOL EOP1006: A Randomized, Double-Masked, Multicenter Trial of the Safety, Tolerability and Pharmacokinetics of 1 mg/Eye and 3 mg/Eye Intravitreal Injections of Pegaptanib Sodium (Anti-VEGF Pegylated Aptamer) Given Every 6 Weeks for 54 Weeks, in Patients with Exudative Age-Related Macular Degeneration (AMD)

**Pharmacokinetic Assessments**

Pharmacokinetic Sampling

The study report 1006 includes safety and pharmacokinetic data from the first 37 patients enrolled in the open-label cohort and received 3 mg pegaptanib sodium intravitreous injections every 6 weeks. Pharmacokinetic data were obtained on two occasions, i.e., after the first and fourth 3 mg pegaptanib sodium doses. Data were reported up to 30 weeks.

Nominal blood sampling times were before the injection (predose), and at 4 ± 2 and 24 ± 4 hours, and 3 ± 1 days, 7 ± 2 days, 21 ± 3 days and 42 ± 3 days after (postdose) the first and fourth doses.

Analytical Methods
Pegaptanib plasma concentration determinations were performed using a validated assay by ⎯
⎯ Blood samples were collected in
⎯ containing potassium ethylene diamine tetraacetic acid [K3EDTA]; plasma samples were stored at a nominal temperature of -20°C or below.

Plasma concentrations of pegaptanib were measured using a dual hybridization procedure that is
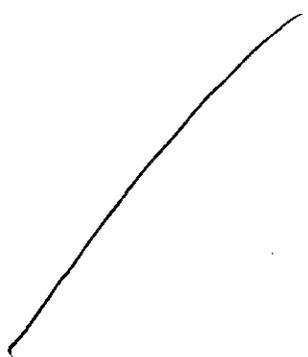
Long-term stability of pegaptanib in plasma samples stored at -20°C has been shown for up to one year. All samples were assayed within 6 months of collections.

Pharmacokinetic Endpoints:

Pegaptanib plasma pharmacokinetic parameters (Cmax, Tmax, apparent terminal half-life [t½], AUC, CL/F, Clast, Tlast) were derived from pegaptanib plasma concentration-time data using noncompartmental methods.

Creatinine clearance was estimated from serum creatinine concentrations using the method Cockcroft and Gault:

$$CLcr = F \times [(140\text{-}Age) \times LBW/(72 \times C)]$$

where:

F = 1.0 for men and 0.85 for women

Age = patient's age in years

Male Lean Body Weight (LBW) = 0.3281W + 0.33929H -29.5336

Female Lean Body Weight (LBW) = 0.29569W + 0.41813H – 43.2933

W = weight in kilograms

H = height in centimeters

C = creatinine concentration in serum (mg/100mL)

Creatinine clearance was reported in units of mL/min.

A ANOVA model was used to assess the relationship between CLcr and pegaptanib's plasma pharmacokinetic parameters AUClast and Cmax.

Results:

The pharmacokinetic and creatinine clearance data were evaluated for 35 patients receiving the first dose and for 33 patients receiving the fourth dose. Mean PK measures are summarized in the Table below. Intersubject and intrasubject variability in the PK parameters were 26% and 23% for AUClast and 27% and 28% for Cmax, respectively.

Table 1. Pegaptanib Plasma Pharmacokinetic Parameters after per Study Eye Every 6 Weeks (Protocol EOP1006:).

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| Pharmacokinetic Parameter	Mean ± SD (Range)	
	First Dose (N=37)	Fourth or Fifth Dose (N=35)
T_{max} (hr)	60 ± 42	60 ± 46
C_{max} (ng/mL)	77 ± 29	75 ± 30
T_{last} (hr)	501 ± 185	504 ± 237
C_{last} (ng/mL)	20 ± 11	21 ± 13
AUC_{last} (µg·hr/mL)	21 ± 7	19 ± 8
AUC_{inf} (µg·hr/mL)	28 ± 8	NC
AUC_{tau} (µg·hr/mL)	26 ± 7	25 ± 6
$t_{1/2}$ [1] (days)	10 ± 3	10 ± 4
CL/F [2] (mL/hr)	132 ± 118	128 ± 35

[1] $t_{1/2}$ is an apparent terminal half-life
[2] $CL/F=Dose/AUC_{inf}$ for first dose or $CL/F=Dose/AUC_{tau}$ for multiple dosing
Abbreviations: SD, standard deviation; NC, not calculated because not applicable to repeat dose; hr, hour; ng, nanogram; mL, milliliter; µg, microgram

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Figure 1 Relationship between Creatinine Clearance and AUClast for Dose 1 and Dose 4
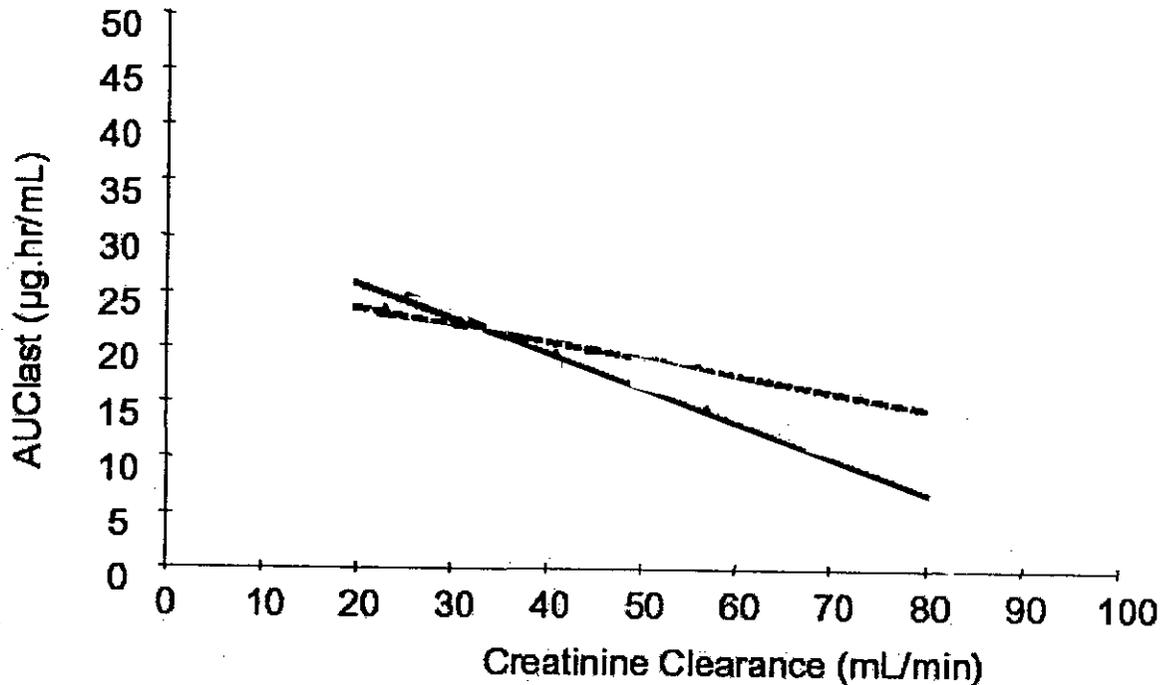
Note: Dashed lines represent a relationship that is not statistically significant. Solid lines represent a relationship that is statistically significant in that the slope of the relationship is different from zero. Open triangles are individual patient values for first dose; dashed line represents the relationship for first dose: AUClast = 26.6357 − 0.1514*CLcr (Test for slope = 0: p=0.1177; not statistically significant); filled triangles are individual patient values for fourth dose; solid line represents the relationship for fourth dose: AUClast = 32.1143 − 0.3155*CLcr (Test for slope=0: p=0.0027; statistically significant).
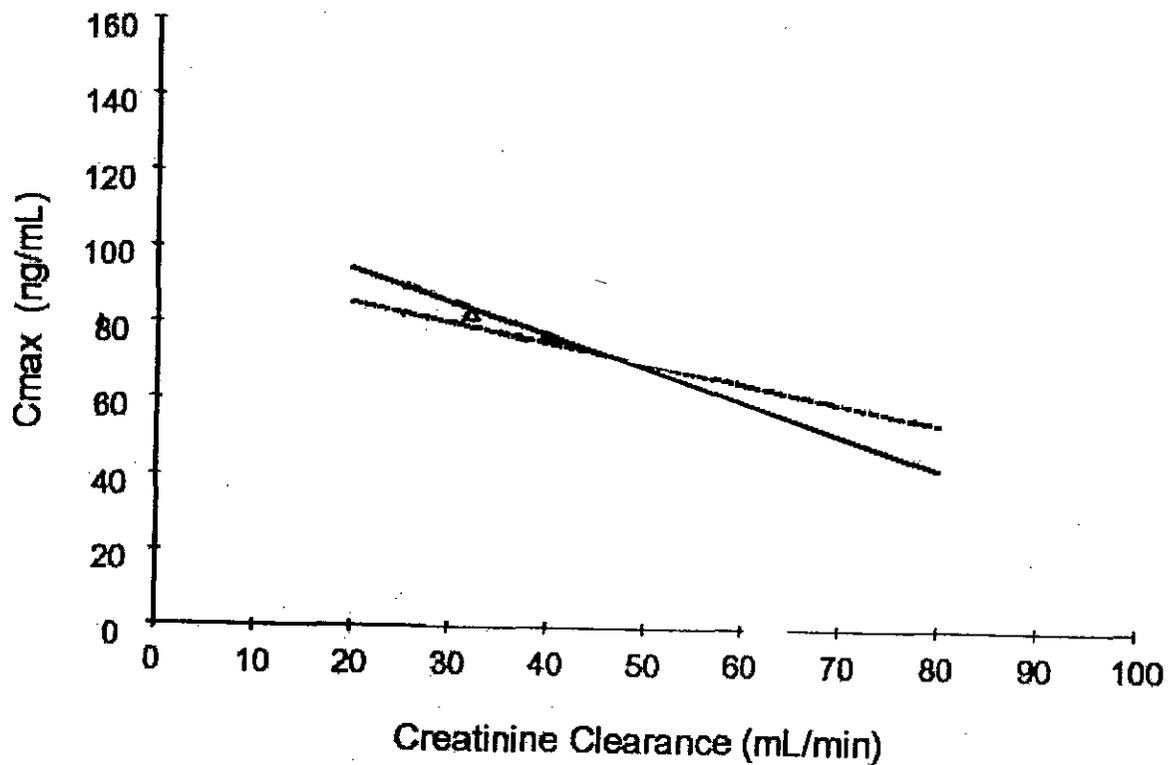
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Figure 2 Relationship between Creatinine Clearance and Cmax for Dose 1 and Dose 4

Note: Dashed lines represent a relationship that is not statistically significant. Solid lines represent a relationship that is statistically significant in that the slope of the relationship is different from zero. Open triangles are individual patient values for first dose; solid line represents the relationship for first dose: $Cmax = 111.66 - 0.8631*CLcr$ (Test for slope = 0; p=0.0415; statistically significant); filled triangles are individual patient values for fourth dose; dashed line represents the relationship for fourth dose: $Cmax = 95.81 - 0.5180*CLcr$ (Test for slope=0; p=0.2217; not statistically significant)

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The pharmacokinetic and creatinine clearance data were evaluated for 35 patients receiving the first dose and for 33 patients receiving the fourth dose.

Reviewer's Comments:

1. Due to limited sampling scheme the reported Cmax of approximately 77± 29 may be considered <u>observed</u> at best. A higher Cmax than that observed in the study may not be ruled out. The Agency requests the Sponsor including frequent sampling times to adequately measure Cmax in any future PK study of this product.

2. In general, higher Cmax and AUClast values were seen in patients with reduced renal function as represented by lower CLcr values. As observed in Figures 1 and 2, the relationship between creatinine clearance and AUClast and Cmax, respectively for both the 1st and 4th doses appear biphasic. Thus, the relationship between CLcr and AUClast and CLcr and Cmax with a single slope covering the entire range of CLcr (20-80 mL/min) is not meaningful.

3. To better characterize the increases in pegaptanib exposure in patients with renal impairment, the pharmacokinetic data should be reanalyzed by grouping patients according to their CLcr values (per Guidance: Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling, issued in May 1998) in three groups representing mild renal impairment (CLcr = 50-80 mL/min), moderate renal impairment (CLcr = 30-50 mL/min) and severe renal impairment (CLcr <30 mL/min).

4. The proposed labeling

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/s/

Chandra S. Chaurasia
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John Lazor
9/17/04 01:12:48 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-756/013

Brand Name:	Macugen
Generic Name:	Pegaptanib sodium for intravitreous injection
Dosage Form:	Intravitreous injection
Dosage Strength:	Single use 1 mL glass syringe containing 0.3 mg in a 90 uL deliverable volume
Proposed Dosing:	0.3mg once every six weeks by intravitreous injection
Indication:	For the treatment of exudative (wet) age-related macular degeneration
NDA Type:	Original NDA/NME
Submission Date(s):	09/30/04
Sponsors:	EyeTech Pharmaceuticals, Inc., NY and Pfizer Inc., NY
Reviewers:	Chandra S. Chaurasia, Ph.D. and Arzu Selen, Ph.D.
Deputy Division Director:	Arzu Selen, Ph.D.
OCPB Division:	DPE III/HFD-880
OND Division:	DOAAODP /HFD-550

1.   BACKGROUND

During the original review of this NDA 21-756, the following comments were noted by this reviewer based on the pharmacokinetic results in study report EOP1006:

- Higher Cmax and AUClast values were seen in patients with reduced renal function as represented by lower CLcr values. The relationships between creatinine clearance and AUClast and Cmax, respectively for both the 1st and 4th doses appear biphasic. Thus, the relationship between CLcr and AUClast and CLcr and Cmax with a single slope covering the entire range of CLcr (20-80 mL/min) is not meaningful.
- To better characterize the increases in pegaptanib exposure in patients with renal impairment, the pharmacokinetic data should be reanalyzed by grouping patients according to their CLcr values (per Guidance: Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling, issued in May 1998) in three groups representing mild renal impairment (CLcr = 50-80 mL/min), moderate renal impairment (CLcr = 30-50 mL/min) and severe renal impairment (CLcr <30 mL/min).

In the Discipline Review letter, dated Sep 17, 2004, for evaluation of impact of stages of renal impairment on pegaptanib pharmacokinetics, the Agency requested the firm to reanalyze the pharmacokinetic data by grouping patients according to their creatinine clearance (CLcr) values

in three groups representing mild renal impairment (CLcr = 50–80 mL/min), moderate renal impairment (CLcr = 30-50 mL/min) and severe renal impairment (CLcr < 30 mL/min).

In the current submission, the Sponsor has provided results of reanalyzed data as requested by the Agency.

Sponsor's Response to the FDA Request and Review of the Sponsor's Response:

The Sponsor provided regression equations describing the relationship between CLcr and pegaptanib parameters (AUClast after Dose 4 and Cmax after Dose1) and utilized the regression equations to predict pegaptanib exposure parameters at the respective midpoint values of the CLcr ranges, specifically at 15 mL/min, 40 mL/min and 65 mL/min.

This approach provides a general description of the exposure parameters as a function of CLcr. The mid-point exposure comparisons do not reflect individual variability or the variability among the three patients groups. Furthermore, it assumes equal weighting among groups in terms of distribution of patients to severe, moderate and mild renal impairment and does not allow a comparison of variability in each one of the renal impairment groups.

For the above reasons, the Sponsor's approach although informative, was considered incomplete and further analysis of pegaptanib exposure data and creatinine clearance values were carried out to determine the impact of renal impairment on pegaptanib pharmacokinetics and the extent of variability within and across the three groups.

Note: The Sponsor's response dated Sep 29, 2004 is in Appendix 2 of this review.

Results

Inspection of individual pharmacokinetic data after Doses 1 and 4, showed that the concentration-time profiles after the first dose were better-defined and thus, were considered adequate for assessment of impact of renal impairment on pegaptanib pharmacokinetics.

The Table below represents mean pegaptanib AUC and Cmax values following a single 3 mg dose (Dose 1). Patients were grouped according to their creatinine clearance values reflecting the stage of the impairment of their renal function.

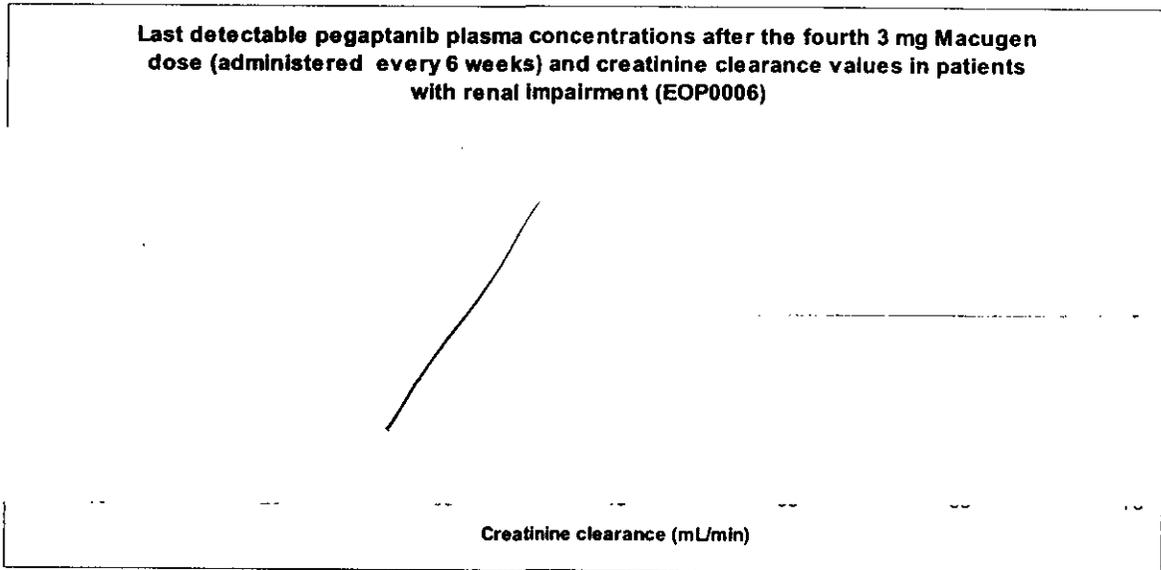| Dose No. 1								
	CLCr < 30 mL/min (actual range: 21-29)			CLCr 30-50 mL/min (actual range: 31-48)			CLCr 50-80 mL/min (actual range: 51-62)		
	Mean (N=7)	% CV	Median	Mean (N=18)	% CV	Median	Mean (N=10)	% CV	Median
Cmax (ng/mL)	96.8	23	▓▓▓	81.6 (N=17)	29.2	88.0	66.5	47	55.5
AUC (µg.hr/mL)	37.8	17	37	26.7	▓	28	23.6	21	24.5
T1/2 (Hr)	270	32	262	214	29	231	226	42	232.5

The data in the Table above indicate an increase in pegaptanib exposure with increasing renal impairment. The differences are more pronounced among patients who have severe and mild renal impairment. The mean pegaptanib Cmax values for patients with severe renal impairment is 96.8 ng/ML and represent an 18.6% and a 41.5% increase, respectively, compared to the patients with moderate and mild renal impairment. Similarly; the mean pegaptanib AUC values for patients with severe renal impairment is 37.8 (μg.hr/mL) and represent a 41.5 % and a 60.2% increase, respectively, compared to the patients with moderate and mild renal impairment.

The results obtained for the mild impairment group are consistent with the other data in this NDA as in general, mean pegaptanib AUC values are approximately 25 ug.h/mL after a 3 mg Macugen dose.

To better understand the overall impact of this difference and the extent of variability among groups, last detectable pegaptanib concentrations after the 4th dose were evaluated against creatinine clearances and are illustrated in the following graph.

Last detectable pegaptanib plasma concentrations after the fourth 3 mg Macugen dose (administered every 6 weeks) and creatinine clearance values in patients with renal impairment (EOP0006)

Creatinine clearance (mL/min)

The last detectable pegaptanib concentrations in plasma after the fourth dose as shown above are highly variable (ranging from ⌐ ⌐ ⌐) and occur at times that range from 6 to 43 days after the fourth dose. While it is difficult to ascertain the source of variability which can be attributed to multiple factors, it is noted that in the patients enrolled in this study (creatinine clearance values ranging from ⌐ mL/min), the last detectable concentrations for most patients are below 35 ng/mL and the variability appears to be more pronounced in patients with moderate to severe and severe renal impairment.

Based on these results, while exposure to pegaptanib increases with reduced renal function, the range of exposure at 0.3 mg pegaptanib dose remains within the dose studied in the Phase III trials over 24 months. As such, within the constraints determined in Phase III trials, dose-adjustment for patients with renal impairment is not recommended.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information resubmitted on Sep 29, 2004 in support of NDA 21-756, pegaptanib sodium for intravitreous injection 0.3mg once every six weeks, and found it to be acceptable for meeting the requirements of 21CFR320 provided the recommendations under Clinical Pharmacokinetics and Precaution sections are incorporated in the proposed labeling of the drug product.

Chandra S. Chaurasia, Ph.D. _____   Date: _____
Clinical Pharmacology and Biopharmaceutics Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by   Arzu Selen, Ph. D. _____   Date: _____
                       Deputy Director, DPE III

CC: NDA 21-756, HFD-850 (P. Lee), HFD-550 (M. Puglisi), HFD-880 (J. Lazor, A. Selen, E. D. Bashaw, C. Chaurasia)

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3.2. Appendix 2

THE SPONSOR'S RESPONSE TO FDA REQUEST:

Methods. The regression equations for the relationship between CLcr and pegaptanib AUClast after Dose 4 and CLcr and Cmax after Dose 1 were used to calculate AUClast and Cmax values corresponding to CLcr values of 15, 40, and 65 mL/min, i.e., the midpoint of the severe, moderate and mild renal impairment CLcr ranges, respectively. These equations were chosen because their slope value was significantly different from zero, and best predicted the increase in AUClast and Cmax that would occur with decreasing CLcr. Percent change in AUClast and Cmax values at the CLcr values corresponding to the severe and moderate renal impairment ranges were calculated relative to the value for the mild renal impairment CLcr range. The results are shown in Table 1.

Table 1 Percent Change in AUClast Values for Dose 4 and Cmax Values for Dose 1 Corresponding to the Midpoint of Sever and Moderate CLcr Ranges Relative to the AUClast and Cmax Values Corresponding to the Midpoint of the Mild CLcr Range. Study EOP1006

CLcr Range (mL/min)	Range Midpoint	Dose 4 AUC$_{last}$[1] (μg·hr/mL)	% Change[2]	Dose 1 C$_{max}$[1] (ng/mL)	% Change[2]
Severe: <30	15	27.4	136	98.7	77.7
Moderate: 30-50	40	19.5	68.0	77.1	38.8
Mild: 50-80	65	11.6		55.6	

1: The regression equations for the relationship between CLcr and pegaptanib AUC$_{last}$ after Dose 4 (AUC$_{last}$ = 32.1143 – 0.3155*CLcr) and CLcr and C$_{max}$ after Dose 1 (C$_{max}$ = 111.66 – 0.8631*CLcr) were used to calculate C$_{max}$ and AUC$_{last}$ values corresponding to CLcr values of 15, 40, and 65 mL/min, i.e., the midpoint of the severe, moderate and mild renal impairment CLcr ranges, respectively. Percent change in AUC$_{last}$ and C$_{max}$ values at the CLcr values corresponding to the severe and moderate renal impairment ranges were calculated relative to AUC$_{last}$ and C$_{max}$ values corresponding to the value for the mild CLcr range.
2: Percent change = (Moderate or Severe PK parameter – Mild PK parameter)/ Mild PK parameter * 100

Results. Data in Table 1 show that AUClast increased 68.0% and 136% in patients with moderate (CLcr = 30-50 mL/min) and severe renal impairment (CLcr <30 mL/min) relative to patients with mild renal impairment (CLcr = 50-80 mL/min). Cmax increased 38.8% in patients with moderate renal impairment and 77.7% in patients with severe renal impairment relative to patients with mild renal impairment, respectively.

For informational purposes, AUClast and Cmax values for Doses 1 and 4 have been ranked by CLcr and univariate statistics have been calculated corresponding to severe, mild, and moderate renal impairment CLcr ranges (Table 2 and Table 3, respectively). Four patients did not have CLcr values and their AUClast and Cmax values are listed in Table 4. For Tables 2-4, please see Appendix under section 4.2.

Tables for Pegaptanib Pharmacokinetic Measures and Estimated Creatinine Clearance

Table 2. **Pegaptanib Cmax and AUClast Values for Dose 1, Sorted by CLcr and Grouped by Nominal CLcr Ranges of <30, 30-50, and 50-80 mL/min. Study EOP1006**

		Nominal CLcr Range: 50 to 80 mL/min		
Patient ID	Dose Number	CLcr (mL/min)	Cmax (ng/mL)	AUClast (µg·hr/mL)
007-227	1			
047-329	1			
157-526	1			
006-375	1			
010-426	1			
025-178	1			
008-158	1			
035-278	1			
047-327	1			
047-328	1			
n		10	10	10
Mean		56.3	66.5	19.5
SD		3.8	31.6	5.2
%CV		6.8	47.5	26.5

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Table 3. **Pegaptanib Cmax and AUClast Values for Dose 4, Sorted by CLcr and Grouped by Nominal CLcr Ranges of <30, 30-50, and 50-80 mL/min. Study EOP1006**

			Nominal CLcr Range < 30 mL/min	
Patient ID	Dose Number	CLcr (mL/min)	Cmax (ng/mL)	AUClast (μg·hr/mL)
025-176	4			
008-155	4			
006-554	4			
028-502	4			
047-330	4			
021-601	4			
057-451	4			
n		7	7	7
Mean		25.7	84.9	27.7
SD		3.2	29.3	6.8
%CV		12.4	34.5	24.6

		Nominal CLcr Range: 30 to 50 mL/min		
006-552	4			
008-151	4			
047-332	4			
028-501	4			
057-452	4			
008-157	4			
049-152	4			
047-331	4			
006-553	4			
035-277	4			
028-503	4			
047-326	4			
035-276	4			
006-551	4			
007-227	4			
047-328	4			
008-154	4			
035-278	4			
n		18	18	18
Mean		38.1	77.8	18.5
SD		6.0	29.7	6.5
%CV		15.9	38.1	35.1

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Table 3. Pegaptanib Cmax and AUClast Values for Dose 4, Sorted by CLcr and Grouped by Nominal CLcr Ranges of <30, 30-50, and 50-80 mL/min. Study EOP1006

		Nominal CLcr Range: 50 to 80 mL/min		
Patient ID	Dose Number	CLcr (mL/min)	Cmax (ng/mL)	AUClast (μg·hr/mL)
006-375	4			
157-526	4			
008-153	4			
047-329	4			
010-426	4			
025-178	4			
047-327	4			
008-158	4			
n		8	8	8
Mean		57.0	63.1	15.4
SD		6.3	33.0	6.3
%CV		11.1	52.2	40.8

Table 4. Cmax and AUClast Values for Patients with No CLcr values. Study EOP1006

Patient ID	Dose Number	CLcr (mL/min)	Cmax (ng/mL)	AUClast (μg·hr/mL)
007-226	1			
008-156	1			
007-226	4			
008-156	4			

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