SCIENTIFIC DISCUSSION

1. Introduction

Age-related macular degeneration

Age-related macular degeneration (AMD) is a disease characterized by progressive degenerative abnormalities in the macula, a small area in the central portion of the retina with the highest visual acuity.

AMD is the major cause of vision loss in the elderly population in the Western world. Although the disease rarely results in complete blindness and peripheral vision may remain unaffected, central vision is gradually blurred, severely affecting ordinary daily activities.

AMD is characteristically a disease occurring in older patients. Population-based epidemiologic studies have provided estimates of prevalence and incidence of AMD among various racial/ethnic groups around the world and have shown that AMD is rare before 55 years of age, that it is more common in persons 75 years of age or older, and that it is less common in blacks than whites.

AMD is classified as two different types: the non-exudative (or dry) form and the exudative (or wet) form of the disease. The dry from is the most prevalent, accounting for 90% of cases of the disease. It is not uncommon that the dry form develops into the wet, neo-vascular form of AMD. Exudative AMD, the neovascular form of the disease, is responsible for the majority of cases of severe vision loss. Exudative AMD is characterized by the formation of a choroidal neovascular network beneath the retina (CNV). This neovascular membrane leaks blood and fluid under the retina and eventually progresses to scar formation with destruction of the macula and loss of vision. The prevalence of exudative AMD in developed countries rises exponentially with age, with near absence at age 50 to 1% at age 70 and 5% at age 80.

The pathogenesis of CNV formation is poorly understood and involves, among many factors, vascular growth factors (including but not limited to VEGF), proteases (serine- and metallo-proteases and their inhibitors) and inflammation (inflammatory cells, bone marrow-derived progenitors, chemokines).

There is no curative treatment for AMD. Treatment available includes low vision rehabilitation. A certain percentage of patients with exudative AMD can benefit from laser treatment with traditional photocoagulation laser or photodynamic therapy (PDT). Photodynamic therapy with verteporfin (Visudyne™) has been approved for the treatment of predominantly classic or occult subfoveal exudative (neovascular) AMD on the basis of decreased visual deterioration in treated patients compared to controls. AMD is currently an area with a need for more efficacious treatments and for treatments applicable to all forms of neovascular AMD.

Pegaptanib

Pegaptanib belongs to the pharmacotherapeutic group of "other ophthalmologicals", ATC code: 01XA17. Pegaptanib is a pegylated modified oligonucleotide that binds with high specificity and affinity to extracellular Vascular Endothelial Growth Factor ($VEGF_{165}$) inhibiting its activity. VEGF is a secreted protein that induces angiogenesis, vascular permeability and inflammation, all of which are thought to contribute to the progression of the neovascular (wet) form of AMD. $VEGF_{165}$ is the VEGF isoform preferentially involved in pathological ocular neovascularisation. The selective inhibition in animals with pegaptanib proved as effective at suppressing pathological neovascularisation as pan-VEGF inhibition, however pegaptanib spared the normal vasculature whereas pan-VEGF inhibition did not.

To increase the intravitreal residence time, a 40 kD branched polyethylene glycol (PEG) molecule has been conjugated to the oligonucleotide. Pegaptanib has the following sequence of nucleotides and functional groups:

5’-[40kD]-[HN-$(CH_2)_5$O]-pC_fpG_mpG_mpA_rpA_rpU_fpC_fpA_mpG_mpU_fpG_mpA_mpA_m pU_fpG_mpC_fpU_fpU_fpA_mpU_fpA_mpC_fpA_mpU_fpC_fpC_fpG_m3’-p-dT

Secondary structure:

where

- [40kD] represents the two 20 kD PEG chains.
- [HN-$(CH_2)_5$O] represents the amino linker connecting PEG and the oligonucleotide via a phosphodiester bond.
- p represents the negatively charged phosphodiester functional groups that have Na^+ counter ions.
- G_m or A_m and C_f or U_f and A_r represent 2-methoxy, 2-fluoro and 2-hydroxy variants of their respective purines and pyrimidines.
- C, A, U and G code for cytidylic, adenylic, uridylic and guanylic acids.

A clinical development program to investigate the use of pegaptanib sodium in the treatment of exudative AMD began in 1999. The nonclinical program began in 1996 and spans the duration of clinical development. The development program has been conducted entirely in male and female over 50-yr patients with exudative AMD (N= 1210) instead of normal volunteers as the product is delivered by an intravitreous injection. The risks of such injections were felt to be inappropriate for healthy volunteers.

GMP inspections were performed at the site of manufacture of the active substance and of the finished product manufacturing site. Both sites were found to operate in compliance with EU GMP.

2. Part II: Chemical, pharmaceutical and biological aspects

Introduction

Pegaptanib is a synthetic oligonucleotide. Pharmaceutically, the product is presented as a sterilised injection 3.47 mg/ml (based on the oligonucleotide weight). The proposed posology is 0.3 mg, every six weeks by means of an intravitreal injection (IVT) into the eye using a single-dose, pre-filled syringe. Each syringe contains a nominal delivered volume of 90 µl. The drug product is presented in a 1 ml glass barrel syringe sealed with a rubber plunger stopper. The syringe has a fixed needle with a rubber needle shield and a rigid plastic outer shield. A plastic syringe plunger and flange adapter are also supplied for administration purposes.

Evidence has suggested a causal role of vascular endothelial growth factor (VEGF) in several diseases of the human eye in which neovascularization and increased vascular permeability occur. Pegaptanib has been developed to bind and block the activity of extracellular VEGF, specifically the 165-amino-acid isoform ($VEGF_{165}$).

Active Substance

The active substance is present as the sodium salt, Pegaptanib Sodium, and is a 28-mer oligonucleotide aptamer (L. *aptus,* to fit; Gk. *meros,* part or region) covalently linked to two 20-kD polyethylene glycol (PEG) chains. Two of the nucleotides are ribonucleotides, one is a deoxy ribonucleotide, while the rest of the nucleotides contain modified sugars. The modified sugars confer increased resistance towards nuclease degradation of the oligonucleotide. The different nucleotides are linked via 5’- to 3’-phosphodiester linkages to yield the 28-mer oligonucleotide. The 3’-end thymidine contains a 3’-3-linkage to the penultimate 2’methoxyguanosine. The 5’-end of the oligonucleotide contains a lysine residue (pentylaminolinker), whose amino groups serve to attach the two PEG units.

Pegaptanib sodium is hydrophilic and very soluble in water and soluble in a number of organic solvents.

- Manufacture

The manufacture of pegaptanib sodium includes the following steps

- Oligonucleotide Synthesis, Purification of nonPEGylated Oligonucleotide, PEGylation Reaction, PEGylated Oligonucleotide Purification and drying.

The oligonucleotide is manufactured by solid phase organic synthesis using well-established methodology.

- Characterisation

The drug substance is an aptamer, meaning it is the secondary structure (i.e. folding) of the oligonucleotide chain that governs the structure which is required for its effect on binding to $VEGF_{165}$. The folding is in turn governed by the primary structure (i.e. nucleotide sequence); hence structural characterisation of drug substance involves determination of primary as well as secondary structure.

The methodologies applied for structural characterisation are well covered. The molecular sequence for the pegaptanib sodium molecule was established through a combination of spectroscopic, physicochemical and biological techniques. The impurities present in oligonucleotides have been investigated.

- Specification

A variety of tests have confirmed the qualitative and quantitative characteristics of the active substance by means of a combination of relevant physicochemical and biological methods.

Batch analyses indicate satisfactory compliance with the agreed specification and uniformity from batch to batch.

- Stability

The active substance is stored in sealed glass vials. Validated stability-indicating methods have been developed and stress studies have demonstrated that it is prone to degradation from light, oxidation and heat ($40^{o}C/75\%RH$). Formal studies according to ICH guidelines have been performed at –20 °C (± 5 °C), recommended storage conditions, and 5 °C (± 3 °C), accelerated storage conditions, for three batches. Supportive data for three batches stored at recommended and accelerated storage conditions, up to 24 months is also presented. The results confirm the retest period and storage conditions of the active substance.

Medicinal Product

- Pharmaceutical Development

Aptamers bind with high specificity and affinity to target molecules, including proteins, and as expected, the binding relies on the specific three-dimensional conformation of the properly folded aptamer. In order to prolong activity at the site of action, the sugar backbone of pegaptanib was modified to prevent degradation by endogenous endonucleases and exonucleases, and the polyethylene glycol moieties were added to increase the half-life of the drug in the vitreous humour.

A sterile aqueous parenteral solution was developed as a rational presentation for this product.

Compatability studies have demonstrate that monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, sodium chloride, hydrochloric acid and sodium hydroxide, at the concentrations used in the formulation, are all compatible with pegaptanib sodium in solution.

Due to the instability of the active substance to terminal sterilisation , an aseptic, filter sterilisation process has been developed.

- Manufacture of the Product

Macugen is manufactured by dissolving pegaptanib sodium into a physiologically-compatible solution. This is followed by pH adjustment, assay, and dilution to the desired strength. The solution is sterilized by filtration and filled into syringes under aseptic conditions. The syringes are labelled and then packaged into a foil pouch. The process uses conventional equipment and facilities. There are no unduly critical steps and the validation of this standard process is satisfactory.

- Product Specification

The specification of the product is based on that of the active substance with additional pharmaceutical tests. Fully characterised reference standards are used in the tests. In addition the specification also includes tests for delivered volume, osmolality, pH, sterility, endotoxin, and particulate contamination..

Batch analyses indicate satisfactory compliance with the agreed specification and uniformity from batch to batch.

- Stability of the Product

Stability results have been provided for three primary stability lots at the 0.3 mg strength the product in the configuration as intended for market. In addition three supportive stability lots at the 1 mg strength are presented in the proposed commercial packaging (syringe in foil pouch).

Tests were performed at 2 – 8°C long term, and 25 °C accelerated, under ICH conditions and the characteristics were monitored using stability-indicating methods.

Results support the shelf-life and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

This synthetic peptide has been manufactured characterised and controlled in a way that indicates satisfactory purity and uniformity, and the medicinal product has been developed utilising molecular development aspects in addition to standard pharmaceutical ones in order to achieve the desired clinical effect.

The finished product is manufactured and tested in a way that indicates a reliable and reproducible product in the clinic, throughout the shelflife.

Macugen should be inspected visually for particulate matter and discoloration prior to administration (see SPC section 6.6).

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
At the time of the CHMP opinion, a number of minor quality issues related chiefly to method development and validation and ongoing stability studies were unresolved; the applicant agreed to resolve these as FollowUp Measures within an agreed timeframe.

3. Part III: Toxico-pharmacological aspects

Introduction

The non-clinical pharmacokinetics and toxicity of pegaptanib was evaluated after of both IVT and intravenous (IV) administration with the main studies performed in rats, rabbits and dogs. A limited reproductive toxicology program was conducted. While no carcinogenicity studies were performed, pegaptanib and its potential metabolites, the component's nucleosides, were evaluated with respect to genotoxicity. Most pivotal non-clinical studies were done according to GLP.

Pharmacology

Inhibition of VEGF has been shown to, at least partially, prevent neovascularisation in several models, both in models using pegaptanib, as those submitted with this application, but also in published studies utilising antibodies and small molecules.

The aptamer of pegaptanib was isolated from RNA libraries containing random nucleotides and further modified to obtain high selectivity and affinity (picomolar region) towards especially $VEGF_{165}$. Addition of the PEG-moiety reduced the affinity ~4-fold.

The pharmacology studies were undertaken to demonstrate the following attributes of pegaptanib sodium:

- High affinity and selectivity for the $VEGF_{165}$ isoform over $VEGF_{121}$ isoform.

- *In vitro* functional studies to confirm that pegaptanib's high affinity for this isoform translates to

$VEGF_{165}$ antagonism.

- *In vivo* studies to demonstrate functional antagonism of VEGF- mediated changes in angiogenesis and vascular permeability.

- Primary pharmacodynamics (*in vitro/in vivo*)

The pharmacological characterisation of pegaptanib included *in vitro* studies on pegaptanib binding to $VEGF_{165}$ and related ligands, inhibition of VEGF-binding to its receptors, inhibition of functional effects following $VEGF_{165}$ binding to its receptors (cellular proliferation, calcium flux, and tissue factor gene expression), and *in vivo* effects on vascular permeability and angiogenesis.

– *In vitro* studies

The series of *in vitro* studies that characterized pegaptanib antiangiogenic and anti-permeability pharmacology included studies on binding affinity and selectivity of pegaptanib to $VEGF_{165}$ relative to other VEGF isoforms and associated proteins, pegaptanib $VEGF_{165}$ antagonist activity in human umbilical vascular endothelial cell (HUVEC) proliferation and tissue factor expression assays, pegaptanib inhibitory effects on VEGF binding to VEGF receptor Fc constructs, and pegaptanib inhibition of calcium mobilization in HUVECs.

Pegaptanib binds *in vitro* to purified recombinant $VEGF_{165}$ with high affinity but does not bind to the smaller isoform $VEGF_{121}$ or any of the VEGF-related proteins tested (VEGF-B, VEGF-C, and PlGF). Pegaptanib also binds to $VEGF_{188}$, the murine ortholog of human $VEGF_{189}$, which is normally bound to the cell surface. Binding to $VEGF_{188}$ was significant, albeit less than obtained with purified $VEGF_{165}$. Pegaptanib effectively inhibits $VEGF_{165}$ binding to its cellular receptors, as seen with both purified constructs of the Flt-1 (VEGFR-1), KDR (VEGFR-2), and NP-1 receptors and on the cell surface of cultured human endothelial cells. Pegaptanib sodium has a three-dimensional conformation that enables it to bind $VEGF_{165}$ much like an antibody.

In addition, $VEGF_{165}$-induced cellular proliferation, calcium mobilization, and tissue factor gene expression are effectively inhibited in cultured human umbilical vein endothelial cells (HUVECs) treated with pegaptanib sodium. No investigations have been carried out on choroidal endothelial cells. The binding of the aptamer portion of pegaptanib is strong, short-lived and reversible. There is no data to show that the sequence does not bind to any off-target ligands/receptors.

– *In vivo* studies

In vivo, administration of pegaptanib sodium inhibited hypoxia-induced retinal neovascularization in a murine model of retinopathy of prematurity, VEGF-induced corneal angiogenesis in a rat corneal pocket model, and dermal vascular leakage in a dermal vascular permeability (modified Miles) assay in guinea pigs. Pegaptanib has not been tested in an animal model for choroidal neovascularisation. In the hypoxia induced neovascularisation model (retinopathy of prematurity, ROP) in rodents, the key role of VEGF in abnormal vascular growth was confirmed. The Applicant has generated additional data showing that the intravitreal injections in the ROP model caused a high variability and poor recovery of intravitreal concentrations of pegaptanib. Therefore, the i.p. route of administration was chosen. In the new studies, ocular neovascularisation could be prevented and a 50% inhibition of retinal vascular growth was achieved at 0.21 nM (~1.95 ng/ml). Extrapolation of data indicates that levels above the IC_{50}-values are obtained clinically at a 6-week dosing interval if the human vitreous T½ exceeds 4 days. Even if the data obtained have their weaknesses, the submitted study is reasonable. Further, the Applicant plans a program to evaluate the applicability of ^{19}F-pegaptanib MRS to obtain repeated non-invasive measures of pegaptanib levels in the human eye.

- Secondary pharmacodynamics

Even though pegaptanib is highly selective for $VEGF_{165}$ compared to closely related targets, no data was presented to show that it does not bind to any off-target ligands/receptors, or whether the de-pegylated (intact or degraded) aptamer may have antisense properties.

- Safety pharmacology

Pegaptanib sodium was evaluated in animal models for cardiovascular, respiratory and neurobehavioral effects, at IV administered doses with associated systemic exposures up to 10-fold

above the exposures observed after a 3 mg/eye clinical dose. All studies were claimed to be performed according to GLP. Pegaptanib did not affect these parameters, nor were any renal parameter changes found following up to 3 mg/eye of pegaptanib administered to animals as frequently as every 2 weeks.

- Pharmacodynamic drug interactions

No pharmacodynamic interaction studies were performed. The Applicant claimed that no pharmacodynamic drug interactions are expected based on the high specificity of pegaptanib and affinity for $VEGF_{165}$ other than interactions associated with the use of agents with VEGF agonistic or anti-agonistic activity. Inhibitors of other anti-angiogenic growth factors as well as anti-VEGF agents may enhance the anti-angiogenic activity and some pharmacodynamic actions of pegaptanib when given concomitantly. .

There is a high probability that pegaptanib will be combined with currently applied therapies for AMD (e.g. PDT). However, in clinical trials, the concomitant use of PDT and pegaptanib did not seem to induce particular safety concerns, nor introduce particular biases. The Applicant has indicated that a randomised and double blind clinical study has been initiated to compare the risks and benefits of pegaptanib in the presence and absence of PDT treatments.

Pharmacokinetics

The pharmacokinetics of pegaptanib have been characterised after IV and IVT administration to rabbits, dogs and monkeys and after IV administration to mouse.

Analytical procedures were generated to determine pegaptanib in plasma, vitreous fluid and amniotic fluid. Pegaptanib was analysed with HPLC (unchanged molecule) and with a dual hybridisation assay (DH, oligonucleotide portion of pegaptanib). Additional methods to analyse serum antibodies to pegaptanib (ELISA) and 2'-FU (LC-MS/MS) were developed. There is no assay to measure the other individual nucleosides. Overall, the analytical assays are considered sufficiently validated, but large variations are allowed. The antibody assay has several weaknesses and its usefulness is not clear. Besides the lack of positive control, there is no LOQ and it is not known if plasma pegaptanib affects the assay, or whether the assay recognises pegaptanib-antibody complexes. Nevertheless, a significant antibody response is not expected and difficulties in developing an assay are recognised.

- Absorption- Bioavailability

Pegaptanib plasma and vitreous PK were characterized in a broad range of animal species: mice, rat, rabbit, dog and monkey. Following IVT administration, pegaptanib was slowly absorbed into the systemic circulation. Systemic bioavailability was high in all species and varied between 70 - 100% as determined from comparisons of AUC values after IV and IVT administration.

There were no apparent signs of accumulation of pegaptanib in plasma after repeated dosing to rabbits, dogs and monkeys and there were no significant gender differences.

The plasma terminal half-life of pegaptanib following IVT administration was ~2 to 4 days in animals, reflecting the slow exit from the vitreous into systemic circulation.

After IV administration, plasma pegaptanib increased linearly with dose. Clearance was not affected by dose. In a rat study, elimination half lives increased with the weight of the PEG-moiety. In all species, the pharmacokinetic profile was similar, even though the half-life of pegaptanib was shorter in the dog. The volume of distribution approximately equalled the plasma volume (close to 60 ml/kg), suggesting little tissue distribution of pegaptanib.

Interspecies differences in the pegaptanib plasma pharmacokinetic profile suggest that in the dog pegaptanib exits the eye and enters the systemic circulation more rapidly than that seen in other species.

- Distribution

In distribution studies, pegaptanib was labelled with ^{14}C in the lysine residue. After IVT administration, radioactivity was mainly located in the vitreous fluid, retina and aqueous humour at 24 hours post-dose. Over the study duration of 6 weeks, radioactivity remained high in the retina, but

diffused particularly to the sclera and choroid, iris and optic nerve. The 15 days half-life of pegaptanib related radioactivity in sclera/choroid may support a low frequency posology. A lower increase of radioactivity over the study duration was observed in the cornea and also in the lens at the last time point, suggesting a diffusion of pegaptanib also to the anterior part of the eye. Compared to ocular levels of radioactivity, extraocular tissue levels of radioactivity were very low. After both IVT and IV administrations, the highest systemic concentrations of radioactivity (AUC) were obtained in the kidney > spleen > bone marrow (vertebra) > lymph node (mesenteric) and liver. The lowest concentrations were found in the brain, spinal cord, skeletal muscle (dorsal) and bone (vertebra). Following IV administration, low levels of radioactivity were also found in the eye. Generally, after IV administration, the tissue to plasma ratios increased over the study interval suggesting that radioactivity was cleared faster from plasma than from tissues. No such consistent pattern was seen after IVT administration. Pegaptanib does not seem to be associated with red blood cells or melanin.

Pegaptanib is designed to remain in the eye for an extended period of time and to be cleared from the eye by slow passive diffusion into the systemic circulation, from where it should rapidly be cleared.

Pegaptanib is probably not highly associated with plasma proteins as indicated by its capacity to inhibit VEGF induced tissue factor expression both in the presence or absence of plasma proteins.

Low levels of pegaptanib passes the placenta and approximately 0.04 % of the plasma levels were found in amniotic fluid 1 hour (=T_{max}) after IV administration of 40 mg/kg pegaptanib to pregnant mice.

- Metabolism (*in vitro/in vivo*)

In vitro, pegaptanib appears to be metabolized to a greater extent in nuclease and in plasma of lower mammal species than in monkey and human plasma. Pegaptanib is metabolized *in vivo*; the component nucleotide, 2'-FU was detected in plasma and urine of DB rabbit following IV and IVT pegaptanib administration. Both pegaptanib and 2'-FU are eliminated primarily by the kidney and secondarily by the liver.
Pegaptanib appears to be more metabolically stable in monkeys as the pegaptanib plasma concentrations after IVT administration to both eyes are substantially higher in monkeys compared to other animals for a given IVT dose.
In the monkey, it appears that little if any pegaptanib is metabolized in the vitreous. High absolute IVT bioavailability of pegaptanib 70% to 100% suggests only a small amount of metabolism is occurring in the vitreous of rabbits and dogs. IVT

- Excretion

Labelled pegaptanib was mainly excreted renally, both intact, as 2'-FU and as unidentified radio-activity. After iv. dosing, > 90 % of the dose was recovered in urine. Excretion into bile and passage into breast milk were not investigated.

Toxicology

The toxicology of pegaptanib was evaluated in mice, rats, rabbits, dogs and monkeys using the clinical route, IVT, and using SC and IV pegaptanib sodium administration. Because pegaptanib was well tolerated, and because of limits on pegaptanib sodium dose size administrable to the vitreous chamber, no maximum tolerated dose was established.

- Single dose toxicity

The acute systemic toxicity of pegaptanib sodium was low, with no adverse effects observed at the highest dose evaluated (450 mg/kg IV in rats).

Study ID/ Report No	Species/ Sex/Number/ Group	Dose/Route	GLP	Major findings
109-97002-T	Rabbits/NZW/ 6m	0.5 mg in 40 µl, one eye, PBS in control eye IVT, ocular exam d. 1, 5, 12.	No	No ocular pegaptanib - related effects. Injection-related effects in both eyes.
109-98006-B (0647-35)	Monkeys/ Rhesus/ 6 f, non-naive	0.5 mg /eye in 67 µl, IVT 7 or 28 d. observation	No	None

109-980142-T (0699-35)	Monkeys/ Rhesus 1/sex/group – cross over between lots, wash-out 29-35 d.	1st lot: 0, 0.25, 0.5, 1 mg in 65 µl /eye, IVT 2nd lot: 0.25, 0.5, 1, 1.5, 2 mg in 65 µl /eye, IVT Up to 29 d. observation.	No	No ocular pegaptanib-related effects. Slight injection-related effects in control and treated eyes.
109-97003-T (804-001)	Rats/SD, 5/sex/group	0, 50, 150, 450 mg/kg, IV bolus	Yes	None
109-98011-T (0654-35)	Monkeys/ Rhesus, 1 control/sex, 2 m + 1 f treated.	0, 5 mg/kg, IV, 1 hr infusion, 7 d. observation	No	None

- Repeat dose toxicity (with toxicokinetics)

From the total of studies performed, the 6-month rabbit and 9-month dog studies are considered pivotal.

Study ID/ Report No	**Species/Sex/ Number/Group**	**Dose/Route**	**Duration**	**NOAEL (drug)**	**Major findings**
109-98003-T	Rabbits/DB, 5/sex/group	Group 1: 0 Group 2: 0.1 (first 4 doses)/ 2 (2 doses) Group 3: 0.3 Group 4:1 mg/eye IVT in 50 µl	11 weeks 1 dose/2 weeks (6 doses)	1 mg/eye for 6 doses and 2 mg/eye for 2 doses	Slight to moderate dose-dependent presence vitreal macrophages and mild cyclitis. Injection-related ocular effects.
144-002 Non-GLP	Dogs/Beagles, control 2f, treated 1/sex	0, 2 mg in 100 µl/eye, IVT	3 weeks 1 dose/week (3 doses)	2 mg/eye	No treatment-related effects. Injection-related ocular effects.
109-98010-T Initial Lot: 11838.26 2nd Lot: 97000690	Monkeys/ Rhesus 0.5 mg: 4m+2f 1-2 mg: 4/sex Naïve animals (3/sex/group) were assigned to the 0, 0.1 and 0.25 mg/eye groups	Initially: 0, 0.5, 1, 2 mg in 66 µl/eye, IVT After 1st dose: 0.1 (dose 1-4), 1 (dose 5-6), 0.25, 0.5 in 66 µl/eye, IVT	3 months (LD only) 1 dose/2 weeks (6 doses)	1 mg/eye after 2 doses	Dose-dependent endotoxin-induced ocular inflammation after 1st dose. Severe at 1 and 2 mg. (Drug lot 11838.26) No treatment-related effects with Drug lot 97000690. Injection-related ocular effects.
109-98004-T (804-002)	Rats/SD 10/sex/group	0, 0.1, 1, 10 mg/kg/day, IV bolus	13 weeks	1 mg/kg	10 mg/kg: Organ weights ↑. Trace chronic progressive nephropathy (m). From 1 mg/kg: mild lymphoid depletion (splenic white pulp) (m), vacuolated macrophages in several organs.
0460LE15.001 Pivotal	Rabbits/NZW, 7-9/sex/group. Reversibility 2/sex in control and 2 mg groups.	0, 0.2, 0.67, 2 mg in 67 µl/eye IVT	6 months with 6 week recovery 1 dose/2 weeks (13 doses)	2 mg OU	No treatment-related effects. Injection-related ocular effects.

Study ID/ Report No	Species/Sex/ Number/Group	Dose/Route	Duration	NOAEL (drug)	Major findings
0472DE15.001 Pivotal	Dogs/Beagle 5-7/sex/group. Reversibility 2/sex in control and 3 mg groups.	0, 0.3, 1, 3 in 100µl/eye, IVT	9 months with 6 week recovery 1 dose/2 weeks (20 doses)	3 mg OU	Minimal to mild lymphocytic infiltration in a variety of tissues. Vitreal floaters/ strands. No other treatment-related effects. Injection-related ocular effects.

OU= both eyes

In IV dose studies, systemic effects were observed in rats only and were limited to vacuolated cells in multiple organs and a mild increase in severity and incidence of chronic progressive nephropathy. There were no pegaptanib sodium-related systemic adverse effects observed in IVT repeat-dose studies. The vacuolated cells, observed in multiple organs in both male and female rats are considered to reflect phagocytosis of the 40 kD PEG moiety of the pegaptanib molecule by macrophages. The increase in absolute organ weights noted in this study might have been associated with the vacuolated cells. There was no cell damage associated with these vacuoles and this finding was not considered adverse. The slight to mild chronic progressive nephropathy was observed in all groups in the repeat IV dose rat study including controls; however, in male rats administered 10 mg/kg/day pegaptanib sodium IV the incidence and severity were mildly increased as compared to the other groups. In these males, a slight decrease in serum protein and albumin was also observed and was likely related to the observed chronic progressive nephropathy. The NOAEL for this study, based on this finding, was 1 mg/kg/day in males. The pegaptanib plasma concentration (30 minutes postdose on Day 91) at the NOAEL was approximately 240-fold higher than human maximum pegaptanib plasma concentrations following 3 mg/eye IVT doses.

There were no relevant pegaptanib sodium-related local adverse effects in single- and repeat-dose toxicity studies by the IVT route of administration. In the 11-week Dutch-Belted rabbit study there was an apparent attenuation of retinal vessels and ocular macrophage infiltrate. The presence of retinal vessel attenuation was considered a spurious finding in this study as it was not supported by fundus photographic data. Electroretinograms (ERG) appeared normal with the exception of an increase in the week 7 latency following single flash with scotopic white light in high-dose animals (1 mg/eye). In addition, retinal vessel attenuation was not observed in any of the other repeat-dose studies, which included studies in New Zealand White rabbits. The macrophage infiltrate likely represents a physiological clearing response to the large pegaptanib molecule; comprised primarily of the PEG moiety. There was no evidence of inflammation or cellular damage associated with the macrophages and this finding was not observed in other IVT toxicity studies. Therefore, the retinal vessel attenuation and macrophage infiltration were not considered relevant local adverse effects.

When ocular adverse effects (fibrin deposition, ocular discharge, conjunctival irritation, vitreal floaters, cataracts, retinal detachments) were noted in the IVT repeat-dose studies, they were considered related to the IVT injection procedure because they were observed across treatment groups including controls. The risk of injection-related effects is inherent with the IVT route of administration.

The injection related findings were typically ocular irritation, conjunctival hyperaemia/redness and traumatic injuries to the retina and lens. Pegaptanib-related effects were limited. In none of the ocular studies, did the severity of findings worsen during the course of the studies (up to 18 injections). Effects essentially resolved between injections and resolved fully during recovery. Immediately after injection, intraocular pressure (IOP) increased abruptly with no relation to dose, which is in contrast to what was observed clinically. The IOPs were normalised at the time of the next injection. Since pegaptanib is believed to leave the eye intact, there might be a concern that when parts of the large molecule diffuses anteriorly, it may get trapped in aqueous outflow pathways e.g. the cribriform meshwork and add to the elevated IOP. The risks with the injection procedure and the high IOPs are significant and addressed clinically.

In the pivotal 9-month dog study, at the early ocular examinations, there were several observations of traumatic damage to the retina (tears/detachments/haemorrhages) and posterior lens capsule. After

improving the injection technique, traumatic changes recovered, e.g. retinal tears healed and turned into scars. Vitreal strands/floaters, occasionally with involvement of pigmented cells, were seen in all groups, but were more pronounced in the high dose group (3 mg/eye) and tended to increase over time. The findings may be a result of infiltration of phagocytosing cells attracted by the PEG-moiety of pegaptanib, since there was no associated inflammation. Due to the poor correlation between ophthalmological evaluations and histopathology, a blinded peer-review of the histological slides was asked for. In the peer-review, additional injection-related, but no drug-related findings were observed and a NOAEL of 3 mg/eye was confirmed. Ocular adverse effects in the repeat IVT dose monkey study were associated with excessive levels of endotoxin (≥ 0.13 EU/mg) in the drug substance. The risk of adverse effects from endotoxin contamination has been mitigated by establishing an endotoxin specification for the drug product.

- Genotoxicity *in vitro* and *in vivo* (with toxicokinetics)

Intact pegaptanib is not suspected to pose a genotoxic risk since the 50kD molecule hardly enters the cell. Therefore, the carcinogenicity potential for pegaptanib sodium is considered low, based on the negative *in vitro* and *in vivo* genotoxicity assays for pegaptanib sodium and its component modified nucleotides. All genotoxicity studies were performed in compliance with GLP. In a battery of genotoxicity assays, 2'-FU and 2'-FC were negative in the *Salmonella* strains of the Ames assay, the SHE cell and the micronucleus assay but produced a small increase in revertant frequency with no relationship to dose in a single bacterial mutagenicity tester strain (*E. coli*). Based on the overall weight of the evidence, 2'-FU and 2'-FC are not considered genotoxic and the genotoxic potential of the monomers of pegaptanib is considered low. No neoplastic or pre-neoplastic lesions were found in the pivotal chronic IVT pegaptanib sodium studies (6-month rabbit and 9-month dog).

- Carcinogenicity (with toxicokinetics)

Carcinogenicity studies were not conducted.

- Reproductive and developmental studies

The reproductive toxicology program included range-finding embryo-foetal development studies in rabbit and mouse and a final embryo-foetal development study in the mouse. Mice (CD-1) which were dosed IV to maximise exposure were selected in accordance with ICH S5A. A full embryo-foetal toxicity in a non-rodent species (e.g., rabbits) was not conducted, but a non-GLP, rabbit dose-range-finding study with IVT administered pegaptanib was performed. This was justified with the advanced age and limited reproductive potential of the patient population with AMD.

Pegaptanib sodium was not found teratogenic in the range-finding studies in rabbits (IVT) or mice (IV), or in the definitive study in mice by the IV route of administration. Developmental toxicity, characterized by a mild decrease in fetal body weight and a reduction in ossification of phalanges, was observed in the 40 mg/kg/day (GD 6 through15) pegaptanib sodium dose group. The NOAEL for developmental toxicity in this study was 6.5 mg/kg. No maternal toxicity was observed. Maternal peak plasma concentration at 40 mg/kg was approximately 2000 µg/mL, which is over 20,000-fold greater than relevant clinical exposure levels. Pegaptanib crosses the placenta and is found in the amniotic fluid. A very small percent (see Pharmacokinetics, Distribution) of the maternal dose is found in the amniotic fluid. No pegaptanib sodium-related effects on ECG parameters or cardiac histopathology were noted in satellite F_1 animals, suggesting a lack of effect of maternal pegaptanib sodium treatment on normal fetal cardiac angiogenesis.

- Local tolerance

No additional studies besides the ocular toxicity studies have been performed. Comprehensive clinical, macroscopic and microscopic evaluations of ocular tissues from animals treated with pegaptanib IVT were conducted in the majority of repeat-dose IVT toxicity studies (Report Numbers 109-98003T, 144-002, 109-98010T; 0460LE15.001; 0472DE15.001). In addition, visual and ocular physiologic functional assays (ERG analysis and tonometry) were included in most of the toxicity studies where pegaptanib was administered IVT. Injection site tissues from the acute toxicity study of pegaptanib administered IV to rhesus monkeys were evaluated by histopathological examination (109-98011T). Pegaptanib sodium was well tolerated locally by both the IVT and IV routes of administration.

- Other toxicity studies

As pegaptanib metabolism may result in systemic exposure to nucleosides structurally related to FIAU, a known hepatotoxicant (e.g., 2'-FU and 2'-FC). An investigative study was undertaken to confirm the hepatic safety of these pegaptanib component nucleosides with particular emphasis on mitochondrial toxicity.

The two pegaptanib component modified nucleotides (2'-FU and 2'-FC) were evaluated in 90-day IV toxicity studies in woodchucks and rats. In contrast to what has been seen with FIAU treatment, there was no evidence of mitochondrial toxicity of the hepatocytes, as measured by the endpoints of cytochrome C oxidase, citrate synthase activity, and mitochondrial DNA content, in either rats or woodchucks administered 2'-FC and 2'-FU IV for 90 days. An increase in the incidence and severity of microvesicular and/or macrovesicular periportal vacuolization was observed in woodchucks after 2'-FC and 2'-FU treatment; however, at a much lower incidence and severity than previously observed with FIAU administration. It should be noted that the studies involved IV administration while studies with FIAU involved oral and peritoneal administration. A small amount of 2'-FU may have been incorporated into the DNA of rats (kidney, liver, muscle, spleen and testes) and woodchucks (liver only), however this did not result in any mitochondrial toxicity. Similarly, a small amount of 2'-FU may have been incorporated into DNA following repeat IV dose administration of pegaptanib sodium in rats. This finding is consistent with pegaptanib being metabolized in vivo to the component modified nucleotide 2'-FU. Overall, pegaptanib sodium and its component modified nucleotides do not exhibit mitochondrial toxicity.

Qualitatively, the impurity profile for pegaptanib sodium has been consistent throughout the nonclinical toxicology program and the clinical development of pegaptanib sodium. No new impurities have been observed in long-term stability testing. The Applicant states that the impurities that are expected to exceed the limit for qualification for new drug products (≥ 1%) have been qualified based on exposures in the pivotal repeat dose and embryo-fetal toxicity studies.

Ecotoxicity/environmental risk assessment

The pegabtanib sodium $PEC_{SURFACEWATER}$ is estimated to be approximately two orders of magnitude less than the action limit of 0.01 µg/L and no other environmental concerns are apparent.

Based on this Phase I Environmental Exposure Assessment, pegabtanib sodium is unlikely to represent a risk for the environment following the prescribed usage in patients.

Discussion on the non-clinical aspects

No primary pharmacodynamic investigations have been carried out on choroidal endothelial cells. The binding of the aptamer portion of pegaptanib is strong, short-lived and reversible. There are no data to show that the sequence does not bind to any off-target ligands/receptors. However, sequence homology analysis comparing the homology of the heparin binding domain of VEGF with other protein candidates (i.e., FGF2) did not identify any potential targets for a significant interaction with pegaptanib. Therefore, it seems reasonable to assume that no clinically meaningful interactions with pegaptanib are to be expected and the lack of secondary pharmacodynamic or drug-drug interaction studies is accepted. VEGF seems highly conserved between species and has an identical binding sequence in the pivotal toxicity species (rabbit and dog) as in humans.

No data were presented to show that pegaptanib does not bind to any off-target ligands/receptors, or whether the de-pegylated (intact or degraded) aptamer may have antisense properties. However, the aptamer portion has very little homology with any mammalian sequence and it does not seem likely that pegaptanib (intact or partly degraded) has any antisense properties. Further, there is no significant homology of the heparin-binding domain of VEGF when compared to other protein candidates (i.e., FGF2). Based on this it seems reasonable to assume that no clinically meaningful interactions with pegaptanib are to be expected, and additional binding studies are therefore not requested.

Overall, the analytical assays are considered sufficiently validated, but large variations are allowed. The antibody assay has several weaknesses and its usefulness is not clear. Besides the lack of positive control, there is no LOQ and it is not known if plasma pegaptanib affects the assay, or whether the assay recognises pegaptanib-antibody complexes. Nevertheless, a significant antibody response is not expected and difficulties in developing an assay are recognised.

Pegaptanib after IVT administration is predominantly a locally acting drug. Compared to vitreous concentrations, pegaptanib plasma concentrations are a very small percentage of these concentrations. Given the recommended dose of 0.3 mg for patients with AMD, relatively low systemic levels of pegaptanib will be seen. As pegaptanib is not extensively distributed to peripheral tissues, tissue levels of pegaptanib will be even lower than those seen in the plasma after IVT administration. There is no apparent accumulation of pegaptanib in plasma after repeat biweekly and twice monthly bilateral IVT administration to animals. These PK characteristics suggest pegaptanib acts locally after IVT administration.

The lack of characterisation of excretion into bile is accepted since faecal excretion was only a minor route, suggesting little biliary elimination of radioactivity. The lack of information regarding passage of pegaptanib into breast milk is acceptable due to the age of the intended population.

No particular safety issues were identified in preclinical studies of pegaptanib sodium in acute, subchronic and chronic toxicology studies using the intravitreous route of administration. In repeat IV dose studies in rats only, systemic effects were observed and were limited to vacuolated cells in multiple organs and a mild increase in severity and incidence of chronic progressive nephropathy. A number of important studies were not fully GLP-compliant, but the quality of these studies seems adequate.

The maximum tolerated dose (MTD) for intravitreous administration was not identified in animals. When ocular adverse effects (fibrin deposition, ocular discharge, conjunctival irritation, cataracts, retinal detachments) were noted in the intravitreous repeat-dose studies, they were considered related to the injection procedure itself, because they were observed across treatment groups including controls, with the exception of vitreous floaters which were more common in actively treated eyes. Pivotal long term-studies in up to 9 months with intravitreous injections every 2 weeks did not cause any apparent toxic effects and there was no evidence of increased intra-ocular inflammation during the course of the studies. A transient increase in IOP was consistently observed in all treatment groups including vehicle controls.

Oligonucleotides may be potent inducers of immune reactions. Pegylation has, however, been shown to reduce the antibody recognition of proteins and the backbone of pegaptanib is made up of phosphate diesters instead of phosphothioate linkages, the latter associated with inflammatory reactions. The compound did not induce lymphocyte proliferation and no induction of antibodies was observed, but the accuracy of the antibody assay is not clear. Overall, there were no indications that pegaptanib induced a local or systemic immune response and there were only minor effects on immune cells and organs at high exposures. Therefore, there are no concerns regarding antigenicity or immunotoxicity.

The main argument considered by the CHMP in order to accept the lack of carcinogenicity studies was due to the very low systemic exposure obtained in the clinical population together with the apparent difficulty to perform relevant study obtaining both high systemic and intraocular exposure.

Concerning impurities, there are no concerns with respect to systemic toxicity since there are large safety margins to the maximum clinical exposure. With respect to intraocular toxicity, the safety margins are 2-3 fold. However, taking into account the larger human eye as compared to dogs and rabbits, the ratio to clinical local exposure is further increased and thus considered acceptable. Regarding genotoxicity, the different impurities are considered qualified.

4. Part IV: Clinical aspects

Introduction

The marketing authorisation for Macugen has been submitted as a complete and independent application based on Article 8.3 (i) of Directive 2001/83/EC as amended. Macugen is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD). Macugen 0.3 mg should be administered once every six weeks (9 injections per year) by intravitreal injection into the affected eye. Instructions for use, handling and disposal are described in section 6.6 of the SPC.

The clinical development included affected patients only, since the mode of administration consisting of repeated injections in the vitreous body precludes the participation of healthy control subjects for

ethical reasons. Patients were all suffering from age-related macular degeneration (AMD) of the exudative or wet kind. The clinical program consists of an open label Phase 1/2 dose finding PK/safety study (NX109-01) with 15 patients conducted in 1999 which was followed in 2000 by two Phase 1/2 open-label, multi-centre trials (EOP1000 and EOP1001) to establish the safety and pharmacokinetic profile of three consecutive intravitreous injections of pegaptanib sodium 3mg given every 4 weeks in 10 +11 patients.

The Phase 2/3 program, which began in 2001, was designed to assess the safety and efficacy of pegaptanib sodium in two sham controlled, double-masked, dose-ranging clinical trials of practically identical design (EOP1003 and EOP1004) with 294 patients on 0.3 mg, the proposed dose for registration and 596 patients on higher doses (1.0 and 3.0 mg) of the study drug and 296 patients on sham treatment. Inclusion criteria were representative of the targeted patient group in terms of retinal changes (confirmed angiographically), visual acuity and the presence of age dependent concomitant diseases and medications. Besides these dose-escalating/efficacy trials, there is another 1-year clinical study ongoing, EOP1006, started in January 2003 designed to assess the safety and pharmacokinetics of pegaptanib. Data from the 30 week cut-off date are included in the safety dossier.

In addition to studies relating to the claimed indication, the dossier contains serious adverse events reporting from 3 studies targeting diabetic maculopathy and von Hippel-Lindau disease, Table 1 summarises the program.

Table 1. Overview of Clinical Studies with Pegaptanib Sodium

Protocol Design Dose	Patients Treated	Study Assessments
Studies in Age-related Macular Degeneration (AMD)		
NX109-01 Phase 1, multi- center, open label dose-escalating study with 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-centre, open-label. Total of 3 consecutive injections of 3 mg/ sodium/eye, 28 days apart in patients without PDT	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- centre, open label Total of 3 intravitreous injections of 3 mg pegaptanib sodium/ eye 28 days apart in patients following PDT administration	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
EOP1003 Phase 2/3 multi-center, randomized, double-masked, sham-injection controlled dose finding study of intravitreous injections of either 0.3, 1 or 3 mg pegaptanib sodium/eye every 6 weeks for 54 weeks.	612 patients ≥50 years of age with 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, double-masked, sham-injection controlled dose finding study of intravitreous injections of either 0.3, 1 or 3 mg pegaptanib sodium/eye every 6 weeks for 54 weeks	578 patients ≥50 years of age with active subfoveal CNV secondary to exudative AMD	BCVA, Fluorescein angiography and fundus photography, AEs, IOP, laboratory parameters, vital signs, PDT administration local ocular events BCVA, QOL

Protocol	Design	Dose	Patients Treated	Study Assessments
Studies in Age-related Macular Degeneration (AMD)				
EOP1006	Phase 2 multi-center, randomized study with intravitreous injections of 1 or 3 mg pegaptanib sodium/ eye every 6 weeks for 54 weeks (study ongoing)		37 open-label (3 mg) and 110 masked patients ≥50 years of age with subfoveal CNV secondary to exudative AMD	AE, local ocular events, IOP, laboratory parameters, vital signs, PK parameters, immune response
Studies in Diabetic Macular Edema (DME)				
EOP1002	Phase 1/2, multi- center open-label study 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, randomised, sham-injection controlled, double-masked dose-finding study with intravitreous injections of either 0.3, 1.0 and 3 mg pegaptanib sodium/ eye 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-randomised pilot study with 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.

Paediatric development of this therapeutic principle is not relevant, since AMD is a disease of the elderly population. No scientific advice has been obtained from the CHMP.

Pharmacokinetics

The clinical pharmacology of pegaptanib sodium has been characterized after single and multiple monocular IVT dosing in six clinical trials (NX109-01, EOP1000, EOP1001, EOP1003, EOP1004 and EOP1006) conducted in patients with neovascular or exudative AMD. Plasma concentrations of pegaptanib have been determined in these studies.

Table 2 . Overview of Clinical Studies containing pharmacokinetic information

Protocol	Design	Dose	Patients Treated	PK Assessments
Studies in Age-related Macular Degeneration (AMD)				
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	PK data (blood samples at 4 h, 22-26 h, day 7, 14 and 28) in 6 patients after administration of 2 or 3 mg/study eye
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	EPO1000 and 1001: PK data after first, second and third dose (samples were taken on Day 1 pre-dose, at 30 min, 1, 2, 4, 6, and 8 hr post-dose, Day 2

Protocol	Design	Dose	Patients Treated	PK Assessments
Studies in Age-related Macular Degeneration (AMD)				
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	(between 22-26 hr post-dose), Days 8, 15, and 22, Day 29 (prior to and 4-hr post-dose), Day 30 (between 22-26 hr post-dose), Day 36, Day 57 (prior to and 4-hr post-dose), Day 58 (between 22-26 hr post-dose) and Days 64, 85, 99, 113, and 141 post-dose)
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	612 patients ≥ 50 years of age active subfoveal CNV secondary to exudative AMD	EOP1003 and 1004 Pre-dose samples week 12, 30, 42 and 54 in 222 patients. Serial blood samples taken in a small number of patients
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	578 patients ≥ 50 years of age active subfoveal CNV secondary to exudative AMD	
EOP1006	Phase 2 multi-center, randomized, multiple dose, cohort	Intravitreous injections of 1 or 3 mg pegaptanib sodium/ eye every 6 weeks for 54 weeks	37 open-label (3 mg) and 110 masked patients ≥ 50 years of age with subfoveal CNV secondary to exudative AMD	Interim report for the open-label part with 37 patients. Samples for PK analysis were taken on Day 1 pre-dose, at 4 and 24 hr post-dose and Days 3, 7, 21, and 42 post-dose of the first and fourth dosing intervals

Most of the pegaptanib PK data in humans was obtained after administration of a 3-mg/eye dose in the target population. PK data were not obtained for the recommended dose (0.3 mg/eye) because of limited assay sensitivity. The MTD could not be determined due to high viscosity of concentrated pegaptanib solutions and the impossibility to inject large volumes in the eyes. Only plasma concentrations of pegaptanib have been determined in these studies; no data on intravitreous concentration of pegaptanib are available in humans.

- Absorption

After intravitreal (IVT) injection of 2 or 3 mg/study eye, release into plasma is slow and maximum pegaptanib plasma concentration is usually reached within 1-4 days. Plasma concentrations were measurable within 4 hours and for up to 28 to 32 days. Cmax values with the 2- and 3-mg/eye doses were between 50 and 130 ng/mL (mean = 80 ng/mL). The AUC is approximately 25 µg·hr/mL for the 3-mg/study eye dosing regimen. It is expected to be <3 µg.hr/ml at the recommended dose of 0.3 mg/eye. No sex- or age-related effects on plasma concentration were observed. The apparent terminal half-life (t½) is 10 ± 4 days and probably represents absorption from the IVT injection site into the systemic circulation; it is not an elimination half-life.

- Distribution

Pegaptanib does not accumulate in the plasma when administered IVT every 6 weeks. At doses below 0.5 mg/eye, it would be unlikely that maximal pegaptanib plasma concentrations would exceed 10 ng/mL. The absolute bioavailability of pegaptanib after IVT administration has not been assessed in humans, but is approximately 70% to 100% in rabbits, dogs, and monkeys (see non-clinical assessment).

The apparent volume of distribution of pegaptanib (Vz/F) in humans after intraocular injection was not accurately estimated by noncompartmental pharmacokinetic methods. This is because the terminal-phase rate constant needed to calculate Vz/F likely represents pegaptanib's exit out of the eye and entrance of pegaptanib into the systemic circulation rather than elimination from the systemic circulation. In animal studies, the volume of distribution of pegaptanib after IV administration is about

60 mL/kg, suggesting that pegaptanib remains mainly in plasma and is not extensively distributed to peripheral tissues, as would be expected for a large molecule.

Protein binding has not been determined in humans.

No bioequivalence or bioavailability studies were performed with pegaptanib sodium as there have been no major changes to the drug substance manufacturing process and no changes to the drug product container-closure system or the formulation during clinical development or in the proposed commercial product.

- Elimination

In vitro data suggest that pegaptanib is metabolised by endo- and exonucleases to shorter chains of nucleotides, which are eventually broken down to some extent to the individual component nucleosides. The primary route of elimination for both pegaptanib and its 2'-FU metabolite is renal.

- Dose proportionality and time dependencies

The pharmacokinetics of pegaptanib is not time dependent. Data are too limited to draw conclusions regarding dose proportionality. However, preclinical data suggest dose proportional pharmacokinetics.

- Special populations

Increased exposure is observed in reduced renal function (2.3-fold increase in exposure in patients with creatinine clearance of 30 ml/min compared with a patient with a creatinine clearance of 70 ml/min). A population PK study (EOP1006) has shown that decreases in renal function (down to a value of 20 ml/min) increase systemic exposure in a way (up to 2.3-fold) that does not impact on clinical use. A dosage adjustment is not warranted for patients whose CLcr is >20 ml/min and who are treated with the recommended dose of 0.3 mg pegaptanib sodium as the PK data indicate that this dose would not produce exposures which would exceed those seen with the 3 mg dose. There are no data in case of severely affected renal or hepatic function, but the same reasoning could be applied. There was no significant influence of age, sex or previous PDT treatment with verteporfin on pegaptanib exposure.

Children were not evaluated due to the nature of the disease.

In study 1006 intersubject variability in AUC was estimated to be 26% and intrasubject variability to 23%.

- Pharmacokinetic interaction studies

No interaction studies have been conducted. The applicant claims that based on information about other oligonucleotide compounds and the large molecular size of pegaptanib, which impedes intracellular uptake, the potential for cytochrome P450 mediated drug interactions with pegaptanib appears to be very low. Oligonucleotides are metabolized by extracellular endo- and exonucleases and are claimed not to inhibit the metabolism of other drugs by the cytochrome P450 system.

Discussion on Pharmacokinetics

In animals, pegaptanib is slowly absorbed into the systemic circulation from the eye after intravitreal administration. The rate of absorption from the eye is the rate-limiting step in the disposition of pegaptanib in animals and is likely to be in humans. In humans, the average ± standard deviation apparent plasma half-life of pegaptanib after a 3 mg (10-times the recommended dose) monocular dose is 10 ± 4 days. A mean maximum plasma concentration of about 80 ng/ml occurs within 1 to 4 days after a 3 mg monocular dose in humans. The mean area under the plasma concentration-time curve (AUC) is about 25 µg·hr/ml at this dose. Pegaptanib does not accumulate in the plasma when administered intravitreally every 6 weeks. At doses below 0.5 mg/eye, pegaptanib plasma concentrations do not likely exceed 10 ng/ml. The absolute bioavailability of pegaptanib after intravitreal administration has not been assessed in humans, but is approximately 70-100% in rabbits, dogs and monkeys.

In animals that received doses of pegaptanib up to 0.5 mg/eye to both eyes, plasma concentrations were 0.03% to 0.15% of those in the vitreous humour.

The apparent volume of distribution of pegaptanib in humans after intraocular injection was not accurately estimated by noncompartmental pharmacokinetic methods. In mice, rats, rabbits, dogs and monkeys, 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 humour, retina and aqueous humour. After intravitreal and intravenous administrations of radiolabeled pegaptanib to rabbits, the highest concentrations of radioactivity (excluding the eye for the intravitreal dose) were obtained in the kidney. In rabbits, the component nucleotide, 2'- fluorouridine is found in plasma and urine after single radiolabeled pegaptanib intravenous and intravitreal doses. Pegaptanib is metabolised by endo- and exonucleases. In rabbits, pegaptanib is eliminated as parent drug and metabolites primarily in the urine.

Pegaptanib pharmacokinetics is similar in female and male patients and within the age range 50 to 90 years.

Pegaptanib sodium has not been adequately studied in patients with creatinine clearance below 20 ml/min. A decrease in creatinine clearance down to 20 ml/min may be associated with up to a 2.3-fold increase in pegaptanib AUC. No special considerations are needed in patients with creatinine clearance above 20 ml/min who are treated with the recommended dose of pegaptanib sodium 0.3 mg.

Pegaptanib pharmacokinetics have not been studied in patients with hepatic impairment. The systemic exposure is expected to be within a well tolerated range in patients with hepatic impairment, as a 10 fold higher dose (3 mg/eye) was well tolerated.

Pharmacodynamics

The clinical development has sought to identify the dose and the regimen needed to inhibit further neovessel formation and macular edema in patients with exudative AMD, a disease with a progressive course ultimately leading to blindness. The ultimate selection of dose and the dosing interval for the 2 pivotal clinical studies EOP1003 and 1004 studies was based on preclinical data and results from the preliminary open label clinical studies, NX-109-01, EOP1000 and 1001. All study participants suffered from AMD according to angiograpical and visual function criteria. In the pivotal studies, three doses of pegaptanib, 0.3 mg, 1 mg and 3 mg, administered in the vitreous by injection every 6 weeks during a 54 weeks trial period were the study medications yielding a per protocol 9 injections per study eye.

- Primary pharmacology and mechanism of action

Pegaptanib acts as a selective VEGF antagonist by binding soluble, extracellular $VEGF_{165}$ in a manner similar to an antibody and preventing it's binding to cell surface VEGF receptors, thus inhibiting the downstream intracellular events that facilitate increased vascular permeability, angiogenesis and neovascularization. The large size (~50 kD) of the pegylated moiety makes entry into cellular targets unlikely or very inefficient, thus pegaptanib is highly unlikely to exhibit any antisense properties.

Clinically, in the efficacy studies (EOP1003 and EOP1004), the applicant claims that pegaptanib sodium treatment provided anti-angiogenic effects in the retina by reducing the growth of mean total lesion size and CNV size, as assessed by angiography. This suggested to the Applicant that pegaptanib sodium was acting as a VEGF antagonist. However, baseline values for these two important objective parameters are significantly different in treated patients compared to controls. Furthermore, it is not clear that the treatment reduced the growth of new vessels. There is no dose-effect relationship, and the size of the CNV does not seem to predict pegaptanib's effects.

It is concluded that the mechanism of action of pegaptanib sodium has not been clearly elucidated.

Extrapolation from non-clinical data indicate that the recommended 0.3 mg dose/eye may be sufficient to maintain vitreous IC_{50} concentrations during 6 weeks.

- Secondary pharmacology

The potential for pharmacodynamic drug-drug interactions with pegaptanib has not been specifically addressed. The only other treatment authorised and available for exudative AMD, photodynamic treatment (PDT) with Visudyne, was indeed used concomitantly in the clinical program. In the pivotal studies, PDT was allowed in patients with predominately classical CNV lesions at the discretion of the

investigator. PDT treatment was given post-baseline to 19% of subjects across all treatment arms, but more so in EOP1004 than in EOP1003. In sub-analyses of patients receiving PDT before the start of the pegaptanib pivotal studies or at baseline, no evidence of an impact of the PDT on the response to the pegaptanib treatment could be demonstrated. As for patients receiving PDT in the course of EOP1003 and 1004, the analyses were not presented, due to a presumed bias in patient selection for this add-on treatment.

Clinical efficacy

- Dose response studies

The maximum tolerated dose (MTD) of pegaptanib sodium after IVT injection has not been determined in humans or animals as the drug is well tolerated in humans up to 3 mg/eye. The 3-mg/study eye dose was the maximal dose used in clinical trials due to the drug product's viscosity at doses higher than this.

Doses and dosing intervals were selected based on the assumption that pegaptanib vitreous concentrations would be maintained above the concentration required to produce 90% of the maximal inhibition (IC_{90}) associated with anti-vascular endothelial growth factor (VEGF) activity in animal models. The selection of doses and the 6-week dosing interval were supported by early indications of pharmacological activity in Phase I/II trials and the presence of low circulating pegaptanib concentrations 4 to 6 weeks post dosing. These low circulating levels suggest that effective vitreous concentrations are present in patients receiving 3 mg/study eye every 6 weeks.

- Main studies

No healthy volunteers participated in the studies. Initially, 36 patients were included in Phase 1/2 studies. Then, without solid preclinical or phase 1/2 data, the Phase 2/3 clinical program began in 2001 and enrolled 1208 patients. It was designed to assess the safety and efficacy of IVT pegaptanib at 0.3-mg, 1-mg or 3-mg given every 6 weeks, in the treatment of exudative AMD in two controlled, double-masked, dose-ranging clinical trials of practically identical design (EOP1003 and EOP1004).

The two studies were of identical design with respect to efficacy endpoints except that Quality of Life (QOL) data were collected in EOP1004 in addition to all the parameters defined in EOP1003.

Patient evaluations in the first study year occurred at each treatment visit, i.e. every six weeks and at an additional final evaluation visit at week 54 when no injection was given. Assessment of visual acuity, IOP, ocular signs was performed at every visit and CNV assessment evaluated with fundus photography and fluorescein angiography were carried out at weeks 30 and 54.

The efficacy data from the first year (54 weeks, 9 planned injections) of these 2-year studies have been analysed and form the basis for the claim of efficacy for pegaptanib sodium in the treatment of exudative (wet) AMD. The second-year results should support this claim.

Retrospective analyses using a combined database have been used to explore the efficacy of pegaptanib sodium in different subgroups of the population defined by certain disease characteristics (CNV lesion subtype, lesion size, baseline vision) and demographic characteristics (age, gender, iris pigmentation) in relation to the dosing regimen.

Studies EOP1003 and EOP1004

METHODS

Study Participants

Ambulatory patients of either gender, aged >50 years, with active subfoveal CNV secondary to AMD were recruited. The two trials enrolled patients, including all neovascular AMD lesion subtypes (25% predominantly classic, 39% occult with no classic and 36% minimally classic), Patients with lesion sizes up to 12 disc area in the study eye, of which up to 50% could be comprised of subretinal haemorrhage and/or up to 25% fibrotic scar or atrophic damage were included. Patients had up to one prior PDT and baseline best corrected visual acuity (BCVA) in the study eye between 20/40 and 20/320, and better than or equal to 20/800 in the fellow eye. Excluded were patients with

- previous subfoveal thermal laser therapy

- recent intraocular surgery
- more than one prior photodynamic therapy (PDT) with verteporfin
- significant media opacities that might interfere with visual acuity assessment of toxicity or fundus photography
- severe cardiac or peripheral vascular disease or diabetic retinopathy
- clinically significant impaired renal or hepatic function.

Treatments

Intravitreous injection of 0.3 mg, 1 mg, 3 mg pegaptanib sodium or sham injection administered once every 6 weeks. PDT with verteporfin was allowed at the discretion of the investigators (average rate of combined treatment : 19 %, similar in all arms of the study).

Patients were given dilation eye drops. Antiseptic and sterility measures included use of diluted povidone iodine as an irrigation flush in the conjunctival sac **(**antibiotic eye drops were given as an alternative in the case of iodine allergy), plastic draping of the eyelids and use of sterile gloves. A speculum was inserted. Subconjunctival anaesthetics with 2% Xylocaine injected in the inferior temporal quadrant was given before the procedure. Patients then received intra-vitreous injections through the pars plana of 0.3 mg, 1 mg or 3 mg pegaptanib in a 95 micro-litres single use pre-filled syringe or control sham procedure involving a syringe without a needle being pressed against the globe every 6 weeks up to 54 weeks (9 planned injections). Re-randomisation among actively (to stop or continue as previously) and sham treated patients (to stop or continue on sham or any of the active treatments) took place at week 54 for another 8 injections during the following 48 weeks for a second study year, the data of which was not part of the initial submission.

Objectives

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

As for the ongoing extension, data of which are not included in this dossier, the purpose is to determine whether 54 weeks is a sufficient treatment period (50% of the actively treated group is randomised to treatment discontinuation) or additional injections are needed to preserve vision, and to further characterize the safety of continued treatment to 102 weeks.

Outcomes/endpoints

In both studies, the primary efficacy endpoint was the proportion of patients losing < 15 letters of BCVA from baseline up to week 54. Secondary efficacy endpoints were the proportion of patients who remained at baseline or gained ≥0 0 letter of vision at week 54, gaining at least ≥ 15 letters of vision at week 54. or severely deteriorating (losing > 30 letters of BCVAfrom baseline up to week 54. Fluorescein angiography and fundus photography were used both to assess the change in total lesion size, total CNV size and CNV leak size from baseline to 30 weeks and 54 weeks.

Sample size

In both studies, a sample size of 540 expected to result in 122 evaluable patients in each arm (calculating a drop-out of 13 patients per arm), was based on the assumption that the proportion of patients losing 15 letters or more on the ETDRS chart at 1 year would be 50% in the sham group and that the corresponding proportions would be reduced to 35, 30 and 25% in the 0.3mg, 1mg and 3mg groups, respectively. With these assumptions the power calculations for the pair-wise comparisons would be 60% for the 0.3 mg, 80% for the 1 mg and 95% for the 3.0 mg arm.

Randomisation

Randomisation on a 1:1:1:1 basis (three active arms and sham) was practiced with a stratification at each study site considering CNV features and the presence of previous PDT therapy.

At 54 weeks, subjects were randomly assigned to undergo controlled discontinuation or continue therapy for a further 48 weeks. All patients assigned to pegaptanib sodium were re-randomised (on a 1:1 basis) after 54 weeks of treatment to either continue or discontinue therapy for a further 48 weeks. All sham control patients were re-randomized in a ratio of 1:1:1:1:1.

Blinding (masking)

The study was double-masked. Proper masking was maintained by ensuring the physician who administered the treatments was not involved in any assessments or decisions during the study. The procedures involved in the administration of the sham were identical to those required for intravitreous injection with the exception that a needleless syringe was pressed against the eye rather than an injection being administered. The main efficacy assessment was distance VA assessed by a masked examiner.

Statistical methods

Primary analyses were performed on the ITT population, defined as all patients with complete baseline data and who had received masked treatment. Premature discontinuation was treated with the last observation carried forward method (LOCF). The PP population, defined as patients without major violations of the protocol was used in sensitivity analyses. Two other populations were analysed as well: The all randomised population meaning all allocated patients regardless if they received any treatment, and the week-54 observed population including ITT participants with VA data at week 54 regardless if they were still receiving medication.

Statistical significance was defined at a p-level of 0.05. Multiple comparisons, i.e. pair-wise comparisons with sham for each treatment arm was analysed with the Hochberg procedure. After the implementation of a protocol amendment, the results of EOP1004 were analysed before those of EOP1003 allowing for the exclusion of one or two of the treatment arms in EOP1003 to increase the statistical power.

The primary analysis was based on the Cochran-Mantel-Haenszel statistics adjusted for the following factors: lesion subtype (predominantly classic, minimally classic, occult with no classic), prior PDT (yes/no), baseline vision (patients with ≥54 letters vs. <54 letters) and baseline lesion size (<4 disc areas vs. ≥4 disc areas). Continuous data were analysed with ANCOVA. Time-related data were summarised in life-tables with Kaplan-Meier curves. Pooling of data of the identical pivotal studies was performed

While both trials were still masked it was decided that the EOP1004 trial would be analyzed first so that, based on the results of this trial, one or two doses could be dropped from the primary comparisons of the EOP1003 trial before it was unmasked. In this case, each of the remaining dose(s) would be compared against sham using Hochberg's multiple comparison adjustments.

RESULTS

EOP 1003 recruited patients from September 27th 2001 and last patient's 54 week visit was on August 15th 2003. The corresponding dates for EOP 1004 were August 3rd 2001 and August 29th 2003.

– Participant flow

Figure 1. Participant flow (Study EOP1003)

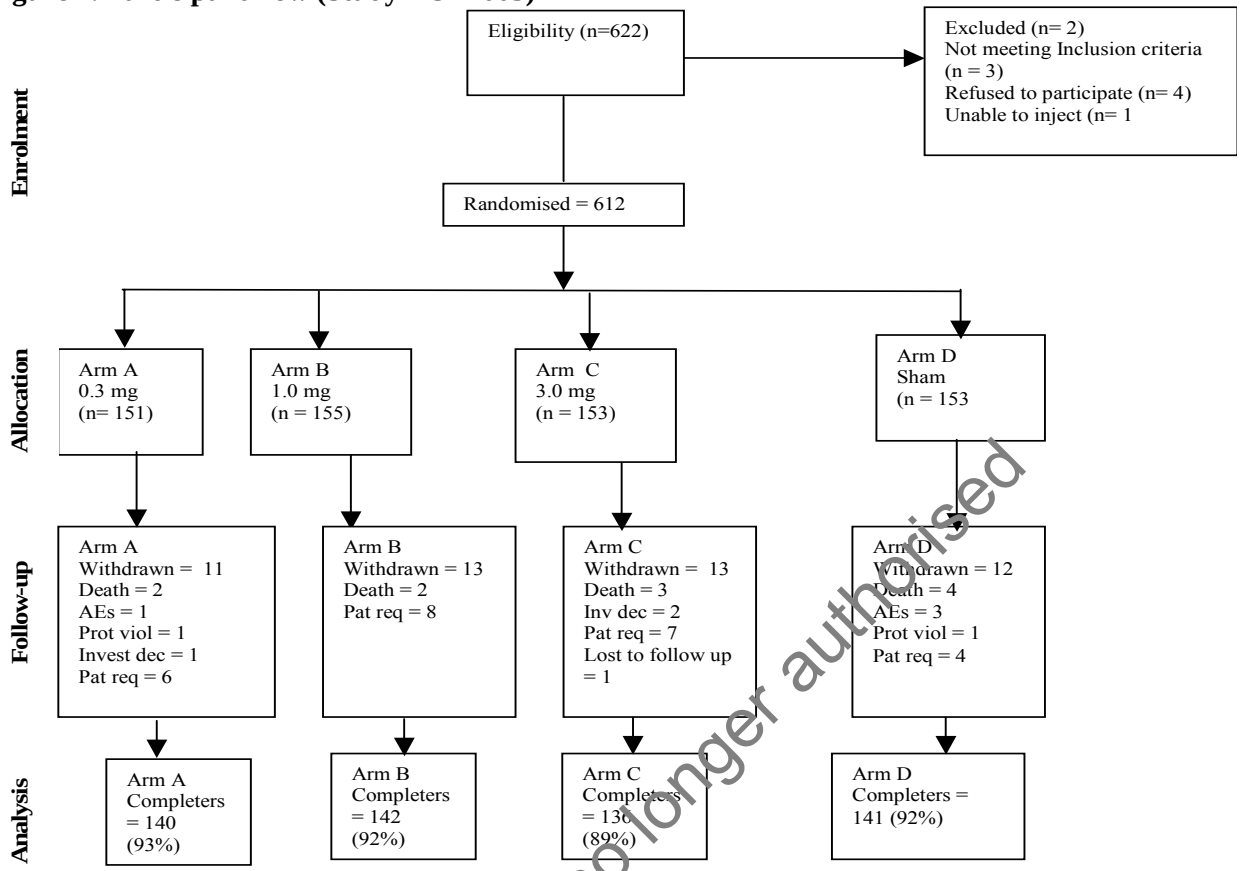
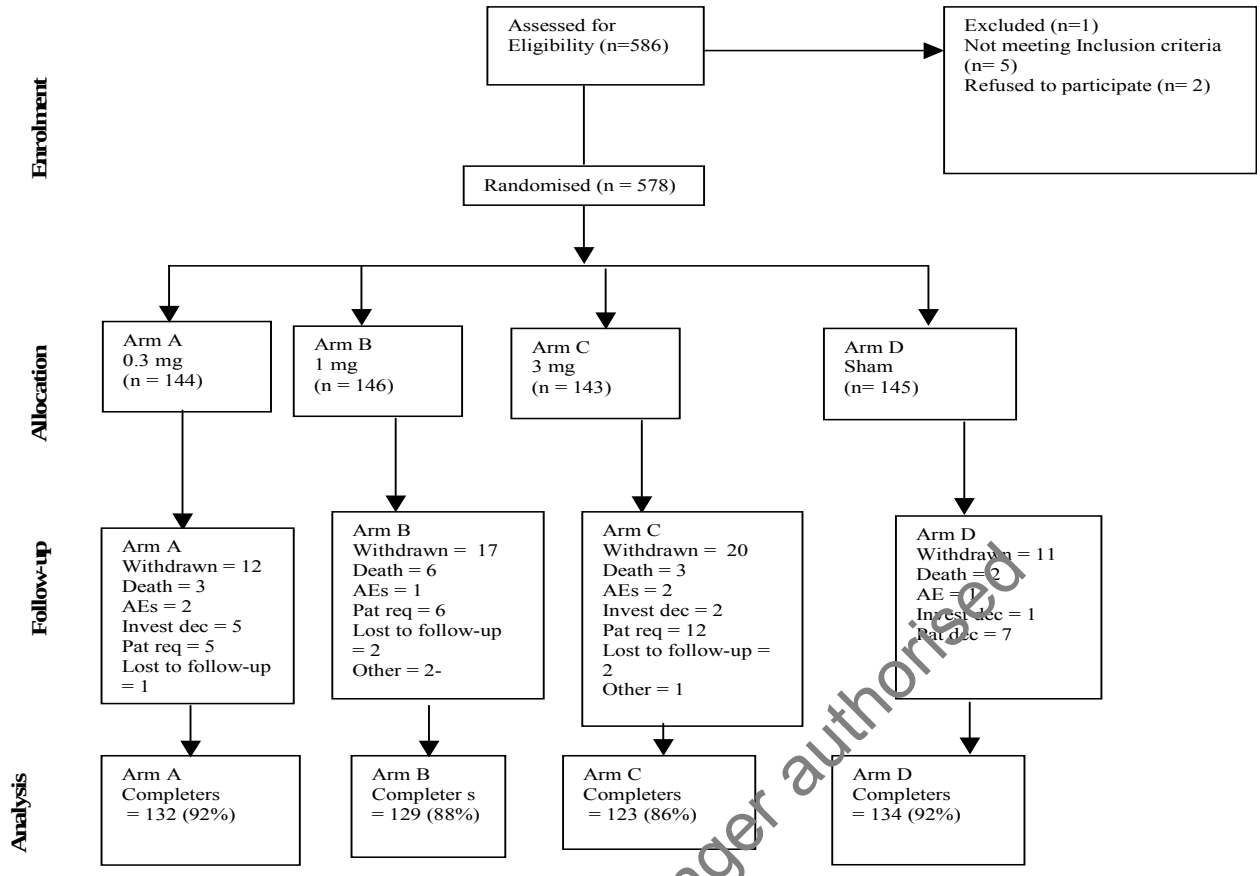


Figure 2. Participant flow (Study EOP1004)



Conduct of the study

Major amendments were not made. Minor amendments included inclusion criteria (presence of active CNV), evaluation of primary endpoint (3 lines loss instead of best corrected visual acuity), and pre-injection procedure to decrease the risk of endophthalmitis.

No special measures were used to assess treatment compliance as all treatments were administered by trained study personnel at the study centers.

Treatment compliance was high with the majority of patients (90%) receiving all 9 study treatments. Discontinuations were few and only in a small number of cases due to adverse events.

Baseline characteristics

Both studies enrolled more women than men, reflecting the demographics of AMD. The ratio of female to male patients across treatment groups and between studies was broadly similar. Some imbalances in baseline covariates were observed in terms of baseline lesion characteristics as evaluated from fluorescein angiograms, with total CNV size, total lesion size and leakage being higher in the sham group than in treated groups. The mean difference in CNV size was 0.6 (the size of the neovascular membrane was 17% higher in the control group) and mean difference in total lesion size = 0.5 (the total size of the lesion was 9% greater in control group).

Table 2. Demographic Data

	Pegaptanib Sodium			
	0.3 mg	1 mg	3 mg	Sham
EOP1004				
Number of patients	144	146	143	145
Female/ Male (%)	56/44	53/47	69/31	57/43
Median age	80	76.5	78	78
Range (years)	58 - 92	52 - 92	56 - 97	55 - 89
Race: *W/ A/ B/ H/ O	140/ 0/ 2/ 2/ 0	143/ 0/ 0/ 2/ 1	141/ 0/ 0/ 2/ 0	140/ 0/ 0/ 4/ 1
EOP1003				
Number of patients	151	155	153	153
Female/ Male (%)	54/46	56/44	61/39	63/37
Median age	75	75	76	75
Range (years)	53 - 90	53 - 90	53 - 89	52 - 92
Race: *W/ A/ B/ H/ O	143/ 0/ 0/ 7/ 1	148/ 1/ 1/ 5/ 0	145/ 0/ 1/ 7/ 0	144/ 1/ 1/ 5/ 2

*W/ A/ B/ H/ O: White/ Asian/ Black/ Hispanic/ Other
Source: Table 2.1., safety population

Table 4. Ophthalmic History – Study Eye

	Pegaptanib Sodium			
	0.3 mg	1 mg	3 mg	Sham
EOP1004				
Number of patients	144	146	143	145
Prior PDT with verteporfin	18 (13%)	20 (14%)	20 (14%)	16 (11%)
Previous non-surgical ocular disease/condition/ trauma	135 (94%)	131 (90%)	134 (94%)	134 (92%)
Previous ocular surgery or laser treatment	78 (54%)	73 (50%)	79 (55%)	80 (55%)
Ocular infection or inflammation within previous 4 weeks	2 (1%)	0 (0%)	1 (1%)	0 (0%)
EOP1003				
Number of patients	151	155	153	153
Prior PDT with verteporfin	6 (4%)	10 (6%)	[illegible]	4 (3%)
Previous non-surgical ocular disease/condition/ trauma	78 (52%)	70 (45%)	85 (56%)	79 (52%)
Previous ocular surgery or laser treatment	45 (30%)	44 (28%)	45 (29%)	44 (29%)
Ocular infection or inflammation within previous 4 weeks	0 (0)%	1 (1%)	3 (2%)	0 (0%)

Source: Table 2.4.1, safety population

Table 6. Baseline Stratification Factors: Lesion Subtype and Prior PDT Use, Study Eye

	Pegaptanib Sodium			
	0.3 mg N (%)	1 mg N (%)	3 mg N (%)	Sham N (%)
Lesion type				
EOP1004				
Predominantly classic	37 (26%)	38 (26%)	41 (29%)	37 (26%)
Minimally classic	51 (35%)	51 (35%)	50 (35%)	50 (34%)
Occult (no classic)	56 (39%)	57 (39%)	52 (36%)	58 (40%)
EOP1003				
Predominantly classic	35 (23%)	40 (26%)	39 (25%)	39 (25%)
Minimally classic	60 (40%)	57 (37%)	55 (36%)	52 (34%)
Occult (no classic)	56 (37%)	58 (37%)	59 (39%)	62 (41%)
Prior PDT				
EOP1004				
Prior PDT	18 (13%)	20 (14%)	20 (14%)	16 (11%)
EOP1003				
Prior PDT	6 (4%)	10 (6%)	6 (4%)	4 (3%)

Source: Tables 2.7, 2.4.1, safety population

Table 3a, baseline VA expressed as number of letters

	0.3 mg	1 mg	3 mg	Sham
EOP1004				
Number of patients	144	146	143	145
Mean (letters)	52.5	50.5	52.1	54.0

Median	56.0	52.0	54.0	55.5
Range	23 - 74	19 - 73	14 - 73	27 - 74
EOP1003				
Number of patients	151	155	153	153
Mean (letters)	53.0	50.9	50.1	51.3
Median	54.0	51.0	51.0	53.0
Range	11 - 75	22 - 77	22 - 76	21 – 75

Table 3b Proportion of patients with baseline visual acuity > 20/80

	0.3 mg	1.0 mg	3.0 mg	sham
EOP 1003	54%	45%	45%	52%
EOP 1004	57%	48%	51%	55%

Numbers analysed

Subset EOP1003	0.3 mg	1 mg	3 mg	sham
Randomised	153	158	155	156
Safety (R_x at least once)	151/153	155/158	153/155	153/156
ITT	150/153	154/158	153/155	152/156
PP	142/153	147/158	147/153	147/156
Week 54 observed	139/153	144/158	139/155	142/156
Subset EOP1004				
Randomised	144	147	147	148
Safety	144/144	146/147	143/147	145/148
ITT	144/144	146/147	143/147	144/148
PP	142/144	141/147	139/147	139/148
Week 54 observed	132/144	131/147	125/147	133/148

Outcomes and estimation

A summary of the number of treatments administered and the number of patients with treatment delays, defined as more than a 56-day interval between any two consecutive injections, is provided in Table 7. The mean number of injections was approximately 8.5 across all treatment arms and in both studies; the median number of injections administered in each treatment group was 9 out of a possible total of 9, indicating high treatment compliance. Overall, a total of approximately 80% of patients received all nine injections in the 2 studies.

Table 7. Drug Administration

	Pegaptanib Sodium			
	0.3 mg	**1 mg**	**3 mg**	**Sham**
EOP1004				
Number of injections Mean/Median	8.4/9	8.4/9	8.4/9	8.5/9
No. of patients who received 9 injections (%)	110 (76%)	115 (79%)	104 (73%)	121 (83%)
No. of patients with one or more treatment delay (%)	28 (19%)	17 (12%)	22 (15%)	17 (12%)
EOP1003				
Number of injections Mean/Median	8.4/9	8.6/9	8.5/9	8.6/9
No. of patients who received 9 injections (%)	116 (77%)	131 (85%)	116 (76%)	126 (82%)
No. of patients with one or more treatment delay (%)	23 (15%)	12 (8%)	20 (13%)	15 (10%)

Source, Tables 3.1, 3.2, safety population

The Table below presents a summary of the first year efficacy results in the two pivotal studies.

	Study EOP1003 Pegaptanib Sodium				Study EOP1004 Pegaptanib Sodium			
ITT population	**0.3 mg N=150**	**1 mg N=154**	**3 mg N=153**	**Sham N=152**	**0.3 mg N=144**	**1 mg N=146**	**3 mg N=143**	**Sham N=144**
	Primary Efficacy Endpoint - % of Patients Losing <15 Letters VA, Baseline - Week 54**							
Vision loss < 15 letters	73%	75%	69%	59%	67%	66%	61%	52%
p-value	0.0105*	0.0035*	-		0.0031*	0.0273	0.1294	
	Secondary Efficacy Endpoint - % Patients Gaining ≥15 Letters VA, Baseline-Week 54**							
Vision gain ≥15 letters	4%	6%	5%	3%	8%	7%	4%	1%
p-value	0.9304	0.4934	-		0.0047*	0.0095*	0.0421*	
	Secondary Efficacy Endpoint - % Patients Gaining ≥0 Letters VA, Baseline - Week 54**							
Vision gain ≥0 letters	33%	38%	39%	28%	34%	35%	23%	17%
p-value	0.3783	0.0749	-		0.0006*	0.0015*	0.1712	
	Secondary Efficacy Endpoint – Mean Changes in VA, Weeks 6, 12 and 54**							
Mean change in VA Week 6	-1.01	-0.60	-2.52	-3.31	-2.08	-1.84	-2.03	-4.78
p-value	0.0375*	0.0273*	--		0.1881	0.1009	0.1653	
Mean change in VA Week 12	-3.31	-0.69	-2.83	-5.38	-3.12	-3.67	-5.27	-7.31
p-value	0.1539	0.0006*	--		0.0316	0.1028	0.5934	
Mean change in VA Week 54	-7.58	-6.03	-7.20	-12.78	-8.42	-8.58	-12.53	-17.38
p-value	0.0059*	0.0014*	--		0.0001*	0.0004*	0.1069	
	Other Efficacy Endpoint - % Patients Receiving PDT with Verteporfin During Study****							
Patients with PDT	13%	14%	14%	16%	26%	27%	30%	35%
	Other Efficacy Endpoint - % Patients with 20/200 or Worse VA at Week 54**							
Patients with 20/200 vision or worse at Week 54	51 (34%)	61 (40%)	60 (39%)	82 (54%)	60 (42%)	67 (46%)	69 (48%)	83 (58%)
p-value	0.0005	0.0041	0.0110		0.0026	0.0110	0.0509	
	Retrospective Efficacy Endpoint - % Patients with Severe Vision Loss (≥30 Letters VA)**							
Patients losing ≥30 letters VA at Week 54	13 (9%)	9 (6%)	17 (11%)	30 (20%)	15 (10%)	15 (10%)	23 (16%)	35 (24%)
p-value	0.0022	0.0007	0.1020		0.0007	0.0102	0.0675	

***** Significantly different from sham treatment, Hochberg Multiple Comparison Procedure
** adjusted for lesion subtype, prior PDT, baseline vision and lesion size
*** Letters of VA ANCOVA model
**** Patients receiving PDT at baseline and/or PDT received after 2 weeks from first study treatment in the study eye.

For the primary endpoint, i.e. the proportion of responders (loss of < 15 letters of VA from baseline to week 54), in study EOP1004, in study EOP1003 and in combined analysis, pegaptanib sodium 0.3 mg showed a statistically significant treatment benefit compared with sham treatment using the Hochberg procedure (pegaptanib 0.3mg 70% versus Sham 55%, p=0.0001; EOP 1003 pegaptanib 0.3mg 73% versus Sham 59%, p = 0.0105; EOP 1004 pegaptanib 0.3 mg 67% versus sham 52%, p=0.0031). The 1-mg dose had some significant effect, but the 3-mg dose had none. Subgroup analyses did not reveal any factor that would predict a better response to pegaptanib sodium. However, prior PDT therapy seemed to be a favorable factor for the 0.3-mg dose while curtailing the effect of the 3-mg dose (although none of the statistical interaction analyses gave significant results). Lesion subtype did not influence the outcome).

For mean change of VA at 6, 12 and 54 weeks, a consistently superior effect vs. sham was demonstrated in both studies at the last follow-up for both 0.3 mg and 1 mg of pegaptanib, but not for 3 mg (see Figures below). No dose response treatment effects were observed.

Figure 1. EOP 1003. Mean change of VA over time.

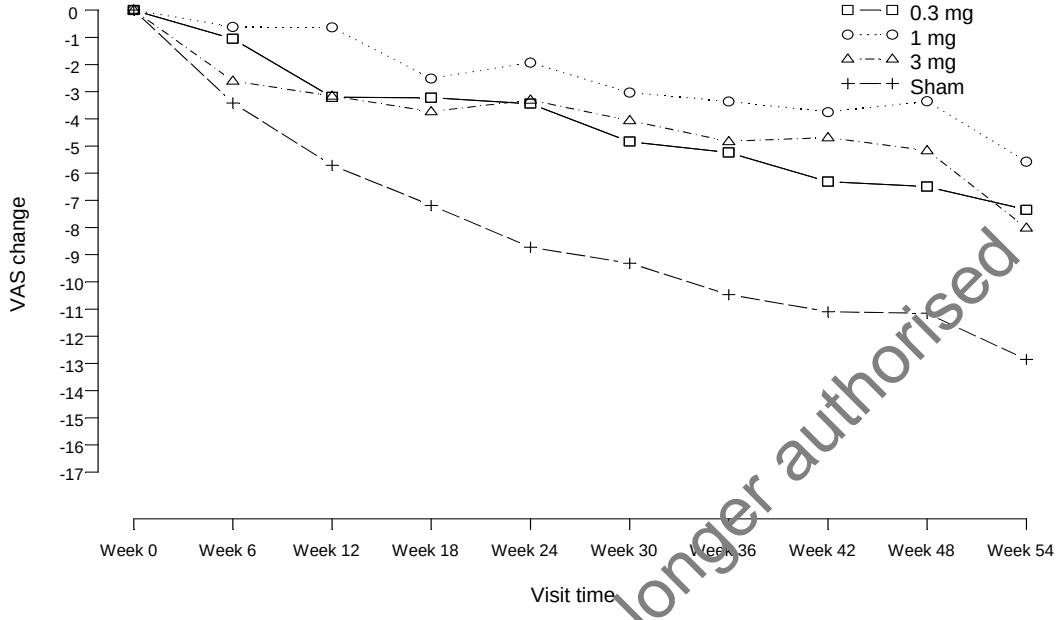


Figure 2, EOP1004 mean change in VA over time

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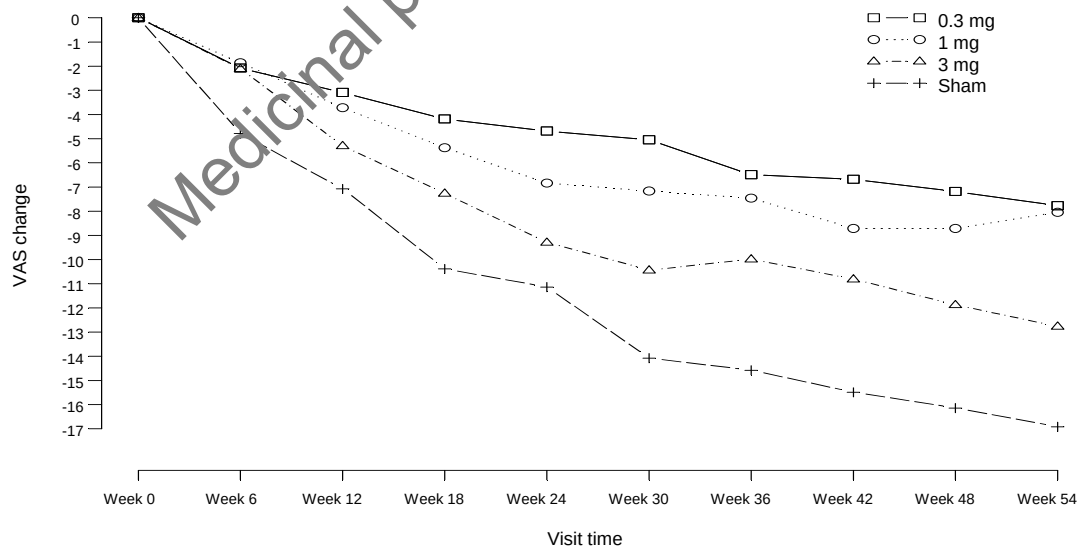


Mean Change in Total Lesion Size from Baseline to 30 and 54 Weeks

Pegaptanib Sodium

Lesion size (DA)[1]	0.3 mg	1 mg	3 mg	Sham
EOP1004				
ITT population	N=144	N=146	N=143	N=144
Baseline	3.6	4.4	3.6	4.4
Mean change at week 30	1.39	0.98	1.65	1.44
Mean change at week 54	1.90	1.56	2.68	2.59
EOP1003				
ITT population	N=150	N=154	N=153	N=152
Baseline	3.9	3.7	3.7	4.0
Mean change at week 30	1.07	1.00	1.45	1.52
Mean change at week 54	1.74	1.88	2.34	2.38
Combined Analysis				
ITT population	N=294	N=300	N=296	N=296
Baseline	3.7	4.0	3.7	4.2
Mean change at week 30	1.22	0.99	1.54	1.48
Mean change at week 54	1.82	1.73	2.50	2.48

[1] Lesion size given in DA (disc area)

Mean Change in Total CNV Size from Baseline to 30 and 54 Weeks

Pegaptanib Sodium

CNV size (DA)[1]	0.3 mg	1 mg	3 mg	Sham
EOP1004				
ITT population	N=144	N=146	N=143	N=144
Baseline	3.1	3.8	3.2	3.9
Mean change at week 30	0.93	0.79	1.00	1.13
Mean change at week 54	1.55	1.20	1.77	1.92
EOP1003				
ITT population	N=150	N=154	N=153	N=152
Baseline	3.1	3.2	3.2	3.5
Mean change at week 30	0.85	0.68	1.13	1.28
Mean change at week 54	1.58	1.35	1.89	2.20
Combined Analysis				
ITT population	N=294	N=300	N=296	N=296
Baseline	3.1	3.5	3.2	3.7
Mean change at week 30	0.89	0.73	1.07	1.21
Mean change at week 54	1.57	1.28	1.83	2.06

[1] CNV size given in DA (disc area)

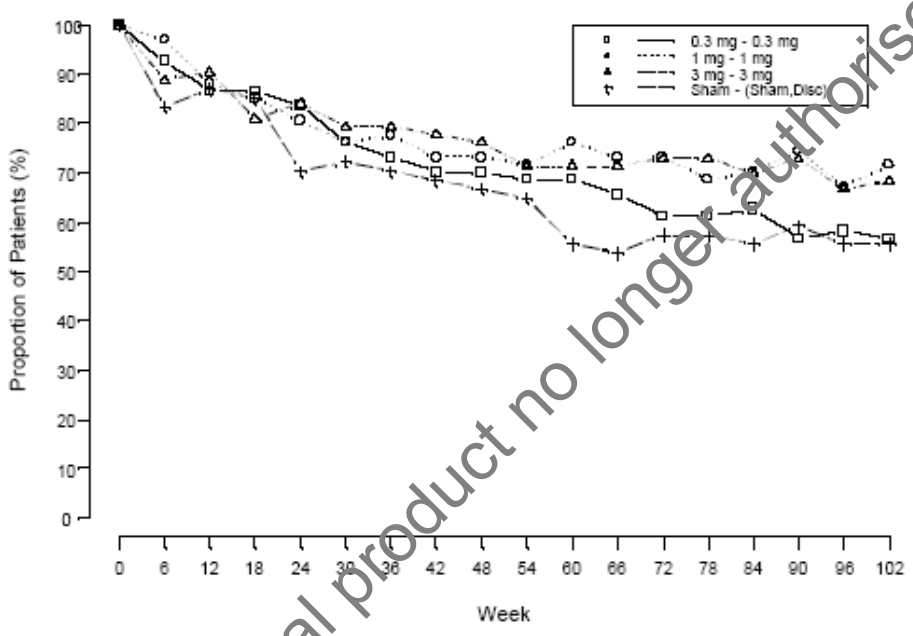
Summary of Mean Changes in Visual Acuity from Baseline to Weeks 6, 12, 54 and 102 (LOCF)

	EOP 1003			EOP 1004		
	0.3-0.3	0.3-discontinued	Sham-sham/sham+discontinued	0.3-0.3	0.3-discontinued	Sham-sham/sham+discontinued
N	67	66	54	66	66	53
Mean change in VA Week 6	-1.9	-0.0	-4.4	-1.9	-2.0	-3.4
Mean change in VA Week 12	-4.3	-2.0	-4.8	-2.8	-2.2	-4.7
Mean change in VA Week 54	-9.6	-4.3	-11.7	-8.0	-7.6	-15.6

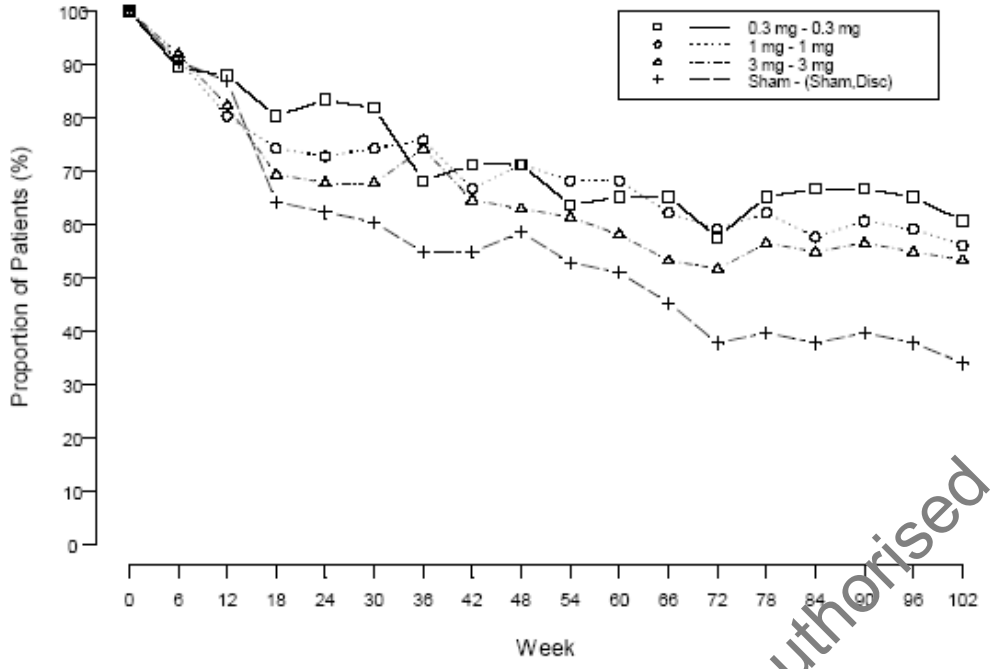
Mean change in VA Week 102	-10.8	-9.7	-13.1	-8.0	-12.7	-21.1

On average, the treatment benefit was maintained at 102 weeks with continuing preservation of visual acuity for patients re-randomized to continue pegaptanib. Patients who were re-randomized to discontinue pegaptanib after one year, lost visual acuity during the second year.
For clinically important secondary efficacy endpoints such as vision stabilization (% of patients losing <15 letters of VA from baseline; % of patients maintaining baseline vision), pegaptanib showed a benefit in EOP1004 but not in EOP1003.

EOP 1003. Mean proportion of responders (patients losing < 15 letters of VA) over time.



EOP 1004. Mean proportion of responders (patients losing < 15 letters of VA) over time.



Ancillary analyses

CNV size and leakage analysis revealed less pronounced changes with both 0.3 mg and 1 mg dosing but differences vs. sham were not statistically significant, view the section presenting pooled data. The quality of life assessment evaluating visual performance and disturbances did not result in any statistically significant findings favouring the active treatments.

- Clinical studies in special populations

Analyses of the primary endpoint by CNV lesion subtype, lesion size, age, gender, race, iris pigment (retrospective), baseline visual acuity, PDT use prior to baseline or at baseline, did not overtly show that pegaptanib sodium treatment with the doses 0.3 mg or 1 mg confer a particular benefit in these specific subgroups).

- Analysis performed across trials (pooled analyses and meta-analysis)

As the two trials EOP1003 and EOP1004 were sufficiently similar in design and patient recruitment, a statistical analysis was performed on the combined data from both trials up to week 54 assessment. For the pooled ITT data from the two studies, 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. Vision gain of 0 letters or more (no vision loss) was achieved by 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) vs. 23% in sham treatment arm. For the angiographic endpoint, change in the mean total CNV size was significantly less with the 1 mg pegaptanib sodium treatment arm for the pooled data at the week 30 and 54 time points and for the 0.3 mg treatment arm at week 54.

- Discussion on clinical efficacy

Reductions in the growth of mean total lesion size, choroidal neovascularisation (CNV) size, and fluorescein leak size have been shown in patients with AMD treated with Macugen. A 1-year treatment with pegaptanib 0.3 mg or 1.0 mg increases the chances of not losing more then 3 lines of vision in active exudative AMD as compared with sham. Since the 0.3 mg and 1 mg doses produced almost identical results, the selection of the 0.3 mg dose for market authorisation appears justified with the given regimen.

The clinical effect of pegaptanib in all subtypes of AMD seems to be in the order of that the reference treatment, i.e. photodynamic therapy (PDT, Visudyne, centrally authorised), in the subtypes where the latter is indicated. There is no study comparing pegaptanib sodium and PDT, and this is a shortcoming of the development plan since it makes it difficult for physicians to choose the most appropriate treatment in the subgroup of patients for which either treatment might be indicated. Although not addressing this issue, a randomized and double masked clinical study (EOP1012) of patients with predominantly classic lesion subtype has been initiated to compare the efficacy and safety of pegaptanib treatment alone to pegaptanib plus PDT treatment.

There appears to be no specific CNV lesion more responsive to the treatment than others rendering the labelling non-restricted in terms of lesion size and type much obviating the need for repetitious angiography and detailed delineation of the lesion.

Some imbalances were observed in terms of baseline lesion characteristics. A meta-analysis performed for photodynamic therapy (PDT) recently suggested that lesion size was a more significant predictive factor for the magnitude of treatment benefit than either lesion composition or visual acuity (Blinder et al, 2003). However, based on exploratory analyses, lesion size was not a significant parameter for determining the effect of pegaptanib. The CHMP concluded that the difference observed in CNV and total lesion size at baseline was unlikely to be an important confounding factor in the interpretation of the results after one-year treatment.

On the other hand, baseline VA had an influence on the response, both in the active or sham treatments, but exactly to the same extent, with a better outcome for patients with <54 letters at baseline. The influence of baseline VA may also translate the natural history of AMD, with a growth phase of the CNV complex along with loss of vision that is followed by a phase of stable, lower vision accompanied by an involution and remodeling of the lesion to disciform scar. On this background, the CHMP also agreed that there is no evidence that pegaptanib treatment benefit would be different for patients with initially good or poor VA, and that individual patients with very poor baseline VA may still benefit from pegaptanib. No predictors of response to pegaptanib have been identified.

The Applicant provided the final study reports of the 2nd year of treatment of EOP 1003 and 1004 to provide reassurance on long-term safety and benefit as regards preservation of useful visual acuity. At the Week 54 visit, patients in the active therapy groups were re-consented and re-randomized on a 1:1 basis to either discontinue or continue treatment for a further 48 weeks (8 injections). Patients receiving sham treatments were re-consented and re-randomized on a 1:1:1:1:1 basis to discontinue the masked treatment, continue in the study receiving one of the 3 active treatments, or continue receiving sham treatments. The Week 54 randomization was stratified by center and visual acuity (VA) in the study eye at Week 54 (better than 20/100 versus equal to, or worse than 20/100). The number of patients per treatment group was thus considerably reduced, especially in the sham control group.

The main problem with the 2-year efficacy data was the lack of difference in responders and the virtual lack of difference in VA worsening between the 0.3-mg pegaptanib active group (as well as other groups) and the sham group in study, EOP 1003, conducted mostly in Europe. When comparing EOP 1003 and 1004, it appears that the evolution is similar in the two lowest active dose groups across both studies, whereas progression towards poor VA is much more pronounced in the sham+DC group in EOP 1004 than in EOP 1003. Thus, the efficacy of pegaptanib seems to have been consistent across both studies. An ITT analysis over the 2-year period based on the original randomisation supported this conclusion.

Clinical safety

- Patient exposure

The safety documentation submitted consisted of data collected from all phase I-III trials as well as the 30-week results of an open-label cohort of the 1-year safety/PK study EOP1006. In addition, safety results were reported from clinical studies with the indication diabetic macular oedema EOP1002 and 1005 and von Hippel-Lindau EOP1007, the last two still ongoing. All safety data were included up to 26-09-2003. For the ongoing studies (post Week 54 cohorts of EOP1003 and EOP1004; EOP1005;

EOP1006; and EOP1007), SAEs and deaths as of a 30-04-2004 data cut-off date were included in the dossier.

Safety endpoints included all ocular and non-ocular reported adverse events (regardless of the perceived relationship to study treatment), serious adverse events and deaths, discontinuations, clinical laboratory values, and vital signs (blood pressure, pulse rate and body weight). All adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) 5.1. If a patient experienced more than one occurrence of the same event, only the event with the highest severity value was counted.

Approximately 1000 patients have been treated at or above the recommended dose on a long-term basis and close to 8000 IVT injections of pegaptanib have been performed. Macugen was administered to 892 patients in controlled studies for one year (total number of injections = 7545, mean number of injections/patient = 8.5) at doses of 0.3, 1.0 and 3.0 mg (Tables 1-2). All three doses shared a similar safety profile.

Table 1. Exposure

Number of Patients	0.3 mg	1 mg	3 mg	All active doses*	Sham injection
Studies 1003 and 1004 AMD, 54 Week Cohort	295	301	296	892	298
Non-controlled exudative 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; [2]Study EOP1005 is not included as it is ongoing and has not been unmasked.

Table 2 Number of Injections Administered

Total number of injections	0.3 mg	1 mg	3 mg	All Doses*	Sham
	N=295	N=304	N=367	N=975	N=298
Studies 1003 and 1004 AMD, 54 Week Cohort	2478	2568	2499	7545	2557
Phase 1/2 exudative AMD studies		3	62	74	
Study 1006[1] exudative 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 the completed cohort from study EOP1006 is included; [2]Study EOP1005 is not included as it is ongoing and has not been unmasked.

- Adverse events

In the 295 patients who were treated with the recommended dose of 0.3 mg for one year (total number of injections = 2478, mean number of injections/patient = 8.4), 84% of the patients experienced an adverse event attributed by the investigators as being related to the injection procedure, 3% of the patients experienced a Serious Adverse Event potentially related to the injection procedure, and 1% experienced an adverse event potentially related to the injection procedure that led to study treatment interruption or discontinuation. Twenty seven percent (27%) of the patients experienced an adverse event attributed by the investigators as being related to the study drug. Two patients (0.7%) experienced Serious Adverse Events potentially related to study drug. One of these patients had an aortic aneurysm; the other had a retinal detachment and retinal haemorrhage, which led to discontinuation of treatment.

Overall pegaptanib sodium injection was well tolerated at all doses studied, since the discontinuation rates in the pivotal studies were 8-13% (1-2% for adverse events) and consistent across the treatment arms.

Most of the adverse events were ocular, predictable and judged by the investigator to be related to the IVT injection procedure (Table 4). Common ocular adverse events included eye pain, vitreous floaters, punctate keratitis, iatrogenic cataract, reduced visual acuity, vitreous opacity, anterior chamber inflammation, increased intraocular pressure (IOP) and visual disturbance. Mild, transient

increases in IOP were expected with IVT injection of pegaptanib sodium but were manageable. Increases in IOP > 10 mmHg in comparison to pre-treatment values were seen after injection in 6-11% of patients. A few cases needed pharmacological interventions to restore IOP to pre-injection levels.

Table 4 Most Frequently Occurring Adverse Events in the SOC Eye Disorders in Completed Controlled Exudative AMD Studies

Number of Patients (%)	**Pegaptanib Sodium Dose**				
	0.3 mg	**1 mg**	**3 mg**	**All doses**	**Sham**
Eye Disorder SOC:	N=295	N=301	N=296	N=892	N=298
Preferred Term:					
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)
Cataracts					
Study eye	51 (17)	61 (20)	69 (23)	181 (20)	54 (18)
Fellow eye	28 (9)	41 (14)	40 (14)	109 (12)	32 (11)
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					

The most commonly occurring non-ocular adverse events by preferred term occurring in ≥ 5% of patients in any treatment group included nausea, arthralgia, headache, nasopharyngitis, bronchitis and hypertension. Few systemic events occurred with meaningful excess in pegaptanib sodium arms compared with sham. This determination was based upon examination of all causality and study drug related SOC/preferred terms and assessed in terms of absolute increase in frequency of patients reporting events, the presence of a dose response, and the number of AEs and their severity. There was no evidence of an overall increase in the proportion of patients with AEs related to elevated blood pressure after administration of pegaptanib sodium. The incidence of systemic vascular hypertensive disorders (including the preferred adverse event terms of hypertension, hypertension aggravated and systolic hypertension) was similar in the pegaptanib sodium (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 sodium 3 mg. Headache was reported with a slightly higher incidence in the pegaptanib sodium arms (7%) compared with the sham arms (4%). Headaches were predominantly mild in severity and approximately half of the cases in the active and sham arms were assessed to be related to the injection procedure. It was very infrequently (3 patients in the active arms, <1%) assessed to be related to the study drug. There were no notable differences among the three pegaptanib sodium dose groups in the incidence of systemic AEs, consistent with the low systemic levels of pegaptanib sodium at all dose levels.

The safety data described below summarise all procedure and drug potentially related adverse events in the 295 patients in the 0.3 mg treatment group. The adverse reactions are described by system organ class and frequency (very common (≥1/10), common (≥1/100 and <1/10), and uncommon (≥1/1000 and <1/100).

Psychiatric disorders (uncommon: nightmare, depression). Nervous system disorders (common: headache).

Eye disorders: these ocular adverse reactions were considered potentially related to treatment with Macugen (either injection procedure or due to Macugen), and for the most part were considered related to the injection procedure, very common: anterior chamber inflammation, eye pain, increased intraocular pressure, punctate keratitis, vitreous floaters and vitreous opacities; common: abnormal

sensation in eye, cataract, conjunctival haemorrhage, conjunctival hyperaemia, conjunctival oedema, conjunctivitis, corneal dystrophy, corneal epithelium defect, corneal epithelium disorder, corneal oedema, dry eye, endophthalmitis, eye discharge, eye inflammation, eye irritation, eye pruritus, eye redness, eye swelling, eyelid oedema, lacrimation increased, macular degeneration, mydriasis, ocular discomfort, ocular hypertension, periorbital haematoma, photophobia, photopsia, retinal haemorrhage, vision blurred, visual acuity reduced, visual disturbance, vitreous detachment, and vitreous disorder; uncommon: asthenopia, blepharitis, conjunctivitis allergic, corneal deposits, eye haemorrhage, eyelids pruritus, keratitis, vitreous haemorrhage, pupillary reflex impaired, corneal abrasion, retinal exudates, eyelid ptosis, retinal scar, chalazion, corneal erosion, decreased intraocular pressure, injection site reaction, injection site vesicles, retinal detachment, corneal disorder, retinal artery occlusion, retinal tear, ectropion, eye movement disorder, eyelid irritation, hyphaema, pupillary disorder, iris disorder, ocular icterus, anterior uveitis, deposit eye, iritis, optic nerve cupping, pupillary deformity, retinal vein occlusion, and vitreous prolapse.

Ear and labyrinth disorders (uncommon: deafness, Meniere's disease aggravated, vertigo).

Cardiac disorders (uncommon: palpitations). Vascular disorders (uncommon: hypertension, aortic aneurysm). Respiratory, thoracic and mediastinal disorders (common: rhinorrhea; uncommon: nasopharyngitis). Gastrointestinal disorders (uncommon : vomiting, dyspepsia). Skin and subcutaneous tissue disorder (uncommon: contact dermatitis, eczema, hair colour changes, rash, pruritus, night sweats).

Musculoskeletal and connective tissue disorders (uncommon: back pain). General disorders and administration site conditions (uncommon: fatigue, rigors, tenderness, chest pain, influenza like illness). Investigations (uncommon: increased gamma-glutamyltransferase). Injury, poisoning and procedural complications (uncommon: abrasion)

- Serious adverse event/deaths/other significant events

Serious ocular Adverse Events reported in Macugen treated patients included endophthalmitis (12 cases, 1%), retinal haemorrhage (3 cases, <1%), vitreous haemorrhage (2 cases, <1%) and retinal detachment (4 cases, < 1%). The serious ocular events were principally judged by the investigator to be related to the injection procedure and not to the study drug itself. A low number of traumatic cataracts were reported in the pivotal studies, all of which were iatrogenic in nature. All of these patients subsequently had a cataract extraction.

Among patients experiencing any of these complications, only one (the AE being a vitreous haemorrhage) sustained severe vision loss (≥ 6 lines) as compared to vision prior to the event.

All adverse events and ocular adverse events were analysed by the time period of occurrence: in relation to injections n°'s 1-3, 4-6 and 7-9. The incidence of adverse events was slightly higher in the pegaptanib-treated patients during the first 3 injections (74-75%) compared to those occurring during injections 4-6 (66-69%) or 7-9 (62-68%). The same decrease over time was seen in the sham-treated patients. In general terms, dose related AEs were not noted.
Following the CHMP opinion of 15 September 2005 for Macugen, cases of anaphylaxis/anaphylactoid reactions, including angioedema, in patients following administration of pegaptanib along with various medications administered as part of the injection preparation procedure, have been reported. In particular, 5 serious cases and 2 moderate cases of anaphylaxis/hypersensitivity with a clear temporal relationship to Macugen injection have been reported in the US over the course of 5 months. A direct causal relationship to Macugen or any of the various medications administered as part of the injection preparation procedure, or to other factors has not been established in these cases (see SPC sections 4.4 and 4.5).

- Laboratory findings

Not analysed.

- Safety in special populations

SAEs were analysed with respect to age and gender. There was an increase in SAEs with increasing age across all treatment arms, No gender-related differences of SAEs were identified.

- Safety related to drug-drug interactions and other interactions

PDT was allowed only once prior to the study, at baseline upon entry into the study, and during the course of the study (post-baseline).The administration of PDT with verteporfin was allowed for patients with predominately classic lesions, the only lesion subtype for which it was approved at the time of study planning. Prior PDT was a stratification factor during randomization, ensuring the proportion of patients who had prior PDT was balanced across treatment groups. Based on exploratory analyses there was no evidence of a significant adverse interaction between concomitantly administered pegaptanib sodium and PDT with verteporfin.

- Discontinuation due to adverse events

In the combined pivotal studies, few patients on either active or sham treatment discontinued from the study (from 8% to 13%) and these were distributed proportionally between the treatment groups. Most patients discontinued for reasons other than adverse events; the most common reason being patient request. The proportion of patients who discontinued study treatment due to adverse events was low and similar in the pegaptanib sodium treatment groups (1-2%) and sham group (1%). The incidence of ocular AEs leading to study discontinuation was higher in the active treatment arms compared to sham, as would be expected given the generally higher incidence of ocular AEs in the active arms.

Safety during the second year of the trial
Three hundred seventy four (374) patients received continuous treatment with Macugen for up to 2 years (128 at 0.3 mg, 126 at 1 mg, and 120 at 3 mg). The overall safety data were consistent with the Year 1 safety data, and no new safety signals emerged. The frequency of endophthalmitis and retinal detachment remained around 1% - 2%. The rate of withdrawals continued to be low also during the second year of treatment. In the 128 patients who were treated with the recommended dose of 0.3 mg for up to 2 years (total number of injections in second year = 913, mean number of injections in the second year = 6.9), there was no evidence of increased in frequency of adverse events compared to those seen during the first year.

- Post marketing experience

See previous section on serious adverse events.

- Discussion on clinical safety

A sufficient exposure to the study medication has been achieved. Overall pegaptanib sodium injection was well tolerated at all doses studied with low proportions of patients discontinuing treatment due to adverse events. Due to the low systemic exposure following intravitreous injection, there was no apparent evidence that treatment with pegaptanib sodium is associated with the systemic safety issues.

Overall, the frequency of serious systemic AEs is not in excess of what can be expected in the elderly study population with typical concomitant diseases. This part of safety file does not raise any specific concerns.
The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent) and the availability of sterile paracentesis (if required). Adequate anaesthesia and a broad-spectrum topical microbicide should be administered prior to the injection (see SPC section 4.2).

There is a small risk of endophthalmitis associated with the intravitreal injection procedure; 0.1 % per injection for Macugen (see SPC secftion 4.4). Endophthalmitis is a potentially devastating SAE and is a major concern. The applicant has committed to follow up the occurrence of retinal detachment in future studies and during post-marketing.

Overall, the rate of ocular serious adverse effects appears acceptable provided that the intraocular injections are performed under aseptic conditions to reduce the risk of endophthalmitis. The real risk of traumatic ocular adverse-events (such as traumatic cataract, intraocular bleeding) might be underestimated since the studies were performed mostly in excellence centers and by ophthalmologists trained in IVT injections, which will not necessarily be the case after release of the product. Moreover, haemorrhage, retinal tears and artery occlusions raise concerns since they are injection related and with the foreseen multiple procedures they may shift the benefit/risk balance during long-term

treatment with pegaptanib. Second year safety data of the pivotal studies was requested and provided reassurance in this respect. Most AEs were less common in year 2 than in year 1.

Following the injection, transient increases in intraocular pressure were seen in Macugen treated patients. Therefore, the perfusion of the optic nerve head and intraocular pressure should be monitored. Elevation of intraocular pressure should be managed appropriately post injection. Moreover patients should be closely monitored for endophthalmitis in the two weeks following the injection. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay. Immediate (on the day of injection) and delayed intravitreous haemorrhages may occur following pegaptanib injections (see SPC sections 4.2 and 4.4).

The potential for hypersensitivity of intravitreous injections, either of antibiotics or of biological products, is not well known. Post-marketing reports of cases of anaphylaxis/anaphylactoid reactions, including angioedema, in patients following administration of pegaptanib along with various medications administered as part of the injection preparation procedure, have been reported. A direct relationship to Macugen or any of the various medications administered as part of the injection preparation procedure, or to other factors has not been established in these cases. The SPC and package leaflet have been revised, requiring careful evaluation of the patient's medical history for hypersensitivity reactions prior to performing the intravitreal procedure, and introducing specific warning and further information about undesirable effects. The applicant also committed as follow-up measures to seek expert advice on these hypersensitivity cases and on the risk of hypersensitivity reactions to latex for e.g. gloves when used during this kind of ocular procedure and to amend the epidemiological studies to collect systemic anaphylactic/hypersensitivity reaction information.

Macugen is contraindicated in case of active or suspected ocular or periocular infection or known hypersensitivity to the active substance or to any of the excipients (see SPC section 4.3).

Macugen has not been studied in patients with hepatic impairment. However, no special considerations are needed in this population (see SPC section 4.2). Macugen has not been adequately studied in patients with creatinine clearance < 20 ml/min. No special considerations are needed in patients with creatinine clearance above 20 ml/min (see SPC section 4.2). Macugen has not been studied for use in patients below the age of 18 years. No special considerations on posology and method of administration are needed for elderly patients or in relationship to gender.

The applicant did not provide (studies are ongoing) any clue concerning the necessity (and safety) of continuing treatment after 102 weeks. It is clear from the results that the disease is still active after 54 weeks (CNV and total lesion size are progressing, vision is decreasing) and that the treatment is symptomatic, without any evidence of curative effect on the disease. Therefore, the total number of intravitreal injections that might be tolerated before there is an unacceptable increase in serious local AEs is not known.

Drug interaction studies have not been conducted with Macugen. Pegaptanib is metabolised 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 PDT (photodynamic therapy) revealed no apparent difference in the plasma pharmacokinetics of pegaptanib (see SPC section 4.5).
Macugen has not been studied in pregnant women. Pegaptanib produced no maternal toxicity and no evidence of teratogenicity or foetal mortality in mice at intravenous doses of 1 to 40 mg/kg/day. Reduced body weight (5%) and minimal delayed ossification in forepaw phalanges were observed, only at exposure levels based on AUC of over 300 fold greater than that expected in humans. These finding are therefore considered to be of limited clinical relevance. In the 40 mg/kg/day group, pegaptanib concentrations in the amniotic fluid were 0.05% of the maternal plasma levels. There are no reproductive toxicity studies in rabbits. No data are available to evaluate male or female mating or fertility indices (see SPC section 5.3).

The potential risk to humans is unknown. The systemic exposure to pegaptanib is expected to be very low after ocular administration. Nevertheless, Macugen should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus (see SPC section 4.6).

It is not known whether Macugen is excreted in human milk. Macugen is not recommended during breast-feeding (see SPC section 4.6).

Patients may experience temporary visual blurring after receiving Macugen by intravitreal injection. They should not drive or use machines until this has resolved (see SPC section 4.7).

Overdosage with Macugen has not been reported in clinical trials (see SPC section 4.9).

5. Overall conclusions and benefit/risk assessment

Quality

Quality aspects are satisfactory for a product of this type. It is developed, manufactured and controlled in a way that indicates satisfactory uniformity from batch to batch. This in turn should give rise to a reliable and consistent performance in the clinic, reproducing the results of the clinical trials upon which evidence of efficacy and safety is based. There are no unresolved quality issues that have a negative impact on the benefit/risk balance.

Non-clinical pharmacology and toxicology

Macugen is a pegylated modified oligonucleotide that binds with high specificity and affinity to extracellular Vascular Endothelial Growth Factor $(VEGF)_{165}$ inhibiting its activity. VEGF is a secreted protein that induces angiogenesis, vascular permeability and inflammation, all of which are thought to contribute to the progression of the neovascular (wet) form of (AMD). $VEGF_{165}$ is the VEGF isoform believed to be preferentially involved in pathological ocular neovascularisation. The selective inhibition in animals with pegaptanib proved as effective at suppressing pathological neovascularization as pan-VEGF inhibition, however pegaptanib spared the normal vasculature whereas pan-VEGF inhibition did not.

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. There are no studies on the carcinogenic potential of pegaptanib.

Pegaptanib produced no maternal toxicity and no evidence of teratogenicity or foetal mortality in mice at intravenous doses of 1 to 40 mg/kg/day. Reduced body weight (5%) and minimal delayed ossification in forepaw phalanges were observed only at exposure levels based on AUC of over 300 fold greater than that expected in humans. These finding are therefore considered to be of limited clinical relevance. In the 40 mg/kg/day group, pegaptanib concentrations in the amniotic fluid were 0.05% of the maternal plasma levels. There are no reproductive toxicity studies in rabbits.

No data are available to evaluate male or female mating or fertility indices.

Efficacy

Macugen was studied in two controlled, double-masked randomised studies (EOP1003; EOP1004) in patients with neovascular AMD. A total of 1208 patients were enrolled and 1190 were treated (892 Macugen, 298 sham) with a median age of 77 years. Patients received a mean of between 8.4-8.6 treatments out of a possible 9 total across all treatment arms in the first year. Patients were randomised to receive sham or 0.3 mg, 1 mg or 3 mg pegaptanib administered as intravitreal injections every 6 weeks for 48 weeks. Verteporfin photodynamic therapy (PDT) was permitted in patients with predominantly classic lesions at the discretion of the investigators. The two trials enrolled patients including all neovascular AMD lesion subtypes (25% predominantly classic, 39% occult with no classic and 36% minimally classic), lesion sizes up to 12 disc areas, of which up to 50% could be comprised of subretinal haemorrhage and/or up to 25% fibrotic scar or atrophic damage. Patients had up to one prior PDT and baseline visual acuity in the study eye between 20/40 and 20/320.

The primary efficacy endpoint was the proportion of patients losing less than 15 letters of visual acuity from baseline up to 54 weeks assessment. At one year, pegaptanib 0.3 mg exhibited a statistically significant treatment benefit for the primary efficacy endpoint; proportion of patients losing less than 15 letters of visual acuity (prespecified pooled analysis, pegaptanib 0.3 mg 70% versus sham 55%, $p = 0.0001$; EOP 1003 pegaptanib 0.3 mg 73% versus sham 59%, $p = 0.0105$; EOP1004 pegaptanib 0.3 mg 67% versus sham 52%, $p = 0.0031$). Pegaptanib 0.3mg showed treatment benefit regardless of baseline lesion subtype, lesion size and visual acuity as well as age, gender, iris pigmentation and prior and/or baseline PDT usage.

At the end of the first year (week 54), approximately 1050 of the original 1200 patients were re-randomized to either continue the same treatment or to discontinue treatment through week 102. On average, the treatment benefit was maintained at 102 weeks with continuing preservation of visual acuity for patients re-randomized to continue pegaptanib. Patients who were re-randomized to discontinue pegaptanib after one year, lost visual acuity during the second year.

Data over a two-year period indicate that Macugen treatment should be initiated as early as possible. In advanced disease the initiation and continuation of Macugen therapy should consider the potential for useful vision in the eye. Macugen therapy administered to both eyes concurrently has not been studied.

Safety

In the 295 patients who were treated with the recommended dose of 0.3 mg for one year, 84% of the patients experienced an adverse event attributed by the investigators as being related to the injection procedure, 3% of the patients experienced a Serious Adverse Event potentially related to the injection procedure, and 1% experienced an adverse event potentially related to the injection procedure that led to study treatment interruption or discontinuation. Twenty seven percent (27%) of the patients experienced an adverse event attributed by the investigators as being related to the study drug; 1% of the patients experienced a Serious Adverse Event potentially related to study drug, and 0.3% experienced an adverse event potentially related to the study drug that led to study treatment interruption or discontinuation.

The potential for hypersensitivity of intravitreous injections, either of antibiotics or of biological products, is not well known. Post-marketing reports of cases of anaphylaxis/anaphylactoid reactions, including angioedema, in patients following administration of pegaptanib along with various medications administered as part of the injection preparation procedure, have been reported. A direct relationship to Macugen or any of the various medications administered as part of the injection preparation procedure, or to other factors has not been established in these cases.

Risk management plan

The Applicant has provided a risk management plan that includes:

- Continued monitoring of the safety data with detailed evaluation of all intravitreous injection procedure related adverse events of several ongoing clinical trials that will increase the number of patients treated with pegaptanib within the next five years to 2,870, representing 31,309 pegaptanib sodium injections, most of them given over the course of 1 year or more;

- Two epidemiological studies, one based on Medicare data in the USA, the other an epidemiological cohort study in the EU that may define risk factors and subgroups of patients with a higher risk of adverse events;

- An educational plan for physicians and health care providers which is aimed at risk minimisation and to support the safe and effective use of the product. This plan shall consist of measures aiming to minimise adverse events associated with the intravitreous injection procedure (e.g. endophthalmitis) through adequate education about:
  - The intravitreal procedure as it was performed in the pivotal clinical studies
  - Sterile techniques to minimize risk of infection
  - Use of antibiotics
  - Use of povidone iodine
  - Performing lid scrubs
  - Use of anesthetic to ensure patient comfort
  - Techniques for the intravitreal injection
  - Management of IOP
  - Management of endophthalmitis
  - Understanding the risk factors involved in developing endophthalmitis
  - Reporting of serious adverse events

- An educational plan for patients which is aimed at risk minimisation and to support safe and effective use for the product. This plan shall consist of measures to provide adequate education on:

- Key signs and symptoms of serious adverse events
- When to seek urgent attention from the health care provider

In addition, the applicant has committed to implementation of the educational plans nationally based on these elements, and to provide these elements as elaborated to the competent authorities prior to marketing for checking and agreement.

The Member States will ensure that the education plans for physicians and health care providers, and patients contain the key elements as detailed in the RMP and are suitable for minimising adverse events associated with the intravitreous injection procedure (e.g. endophthalmitis) prior to marketing.

Furthermore, the applicant committed to provide a proposal for a methodology to assess the effectiveness of risk minimisation measures across the EU, including milestones for such assessment. This should be in line with the CHMP Guideline on Risk Management Systems for Medicinal Products for Human use and should be submitted within 30 days after the Commission Decision. The RMP should be updated as recommended in the CHMP Guideline on Risk Management Systems for Medicinal Products for Human use, and submitted at the same time as PSURs, when new information is received, within 60 days of an important milestones being reached or the results of a study becoming available (see follow-up measures timeline), and upon request of a Competent authority.

Lastly, the applicant committed to update the RMP to include specific surveillance measures for anaphylactic/hypersensitivity reactions, and to provide 6-monthly Periodic Safety Update Reports to the EMEA including a section devoted to the issue of anaphylaxis/hypersensitivity.

Benefit/risk assessment

Clinically, a 1-year treatment with pegaptanib, 0.3 mg or 1.0 mg every 6 weeks intravitreously in the affected eye, increases the chances of not losing more then 15 lines of vision (= responder rate) in active exudative AMD as compared with sham. Since the 0.3 mg and 1 mg doses produced almost identical results, the selection of the 0.3 mg-dose for market authorisation is justified, although the very low efficacy of the 3.0-mg dose, and the lack of dose-response relationship, are puzzling. There is no way of telling whether a lower dose or a longer treatment interval could not have achieved similar effects as those obtained at Week 54 in EOP 1003 and 1004.
The results obtained during the second year of the study, during which patients were re-randomised to either continue or stop study medication, are still statistically significant although less convincing mainly due to an unexpected behaviour of the control group in one of study (EOP 1003). However, patients who stopped active treatment after one year had a much faster deterioration in the affected eye than those who continued on active treatment. The safety and efficacy of Macugen beyond two years have not been demonstrated. The applicant has committed to optimise the recommendations for treatment duration.

The clinical effect of pegaptanib in all subtypes of AMD (predominantly classic, minimally classic and occult) over 1 year approximates that of reference photodynamic therapy (Visudyne, centrally authorised) in the subtypes where the latter is indicated.

The injection procedure is considered a matter of safety concern given the occurrence of alarming injection-related ocular serious adverse effects (SAEs). Overall, these SAEs led to few incidents of severe visual loss or treatment discontinuations and may not, by themselves, reverse the benefit/risk ratio. The procedure of intravitreous injection of Macugen could induce anaphylactic/hypersensitivity reactions. A direct relationship to Macugen or any of the various medications administered as part of the injection preparation procedure, or to other factors has not been established in the cases reported.

Treatment with Macugen is for intravitreal injection only and should be administered by ophthalmologists experienced in intravitreal injections.

In conclusion, the benefit/risk balance is positive. Although the absolute benefit in terms of slowing the loss in visual acuity may be modest, the severity of the disease and the paucity of current treatments must be taken into account. There is risk of intraocular adverse events, notably endophthalmitis, especially if rigourous injection techniques are not followed; this risk should be kept under control with the RMP proposed by the Applicant, and according to the conditions and restrictions for safe and effective use put in place and addressed to the marketing authorisation holder and the Member States.

Recommendation

”Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of Macugen in the treatment of for the treatment of neovascular (wet) age-related macular degeneration was favourable and therefore recommended the granting of the marketing authorisation.