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Committee for Medicinal Products for Human Use (CHMP)

WITHDRAWAL ASSESSMENT REPORT
FOR
MACUGEN

International Nonproprietary Name: pegaptanib sodium

Procedure No. EMEA/H/C/000620/II/0044

This withdrawal Assessment Report is based on the latest assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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LIST OF ABBREVIATIONS

AE	adverse event
APTC	Antiplatelet Trialists' Collaboration
ATE	arterial thromboembolic event
BCVA	best corrected visual acuity
BP	blood pressure
CMH	Cochran-Mantel-Haenszel
CRT	retinal thickness in the central subfield
CSME	clinically significant macular edema
CSR	clinical study report
DA	disc area
DME	diabetic macular oedema
DR	diabetic retinopathy
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMITT	extended MITT
ETDRS	Early treatment diabetic retinopathy study
FAZ	foveal avascular zone
GD	gestation day
IOP	intraocular pressure
ITT	intent-to-treat
IVT	intravitreal
LOCF	last observation carried forward
MI	myocardial infarction
MITT	modified intent-to-treat
OCT	optical coherence tomography
PDR	proliferative diabetic retinopathy
PE	physical exam
PP	per-protocol
PROs	patient reported outcomes
RPE	retinal pigment epithelium atrophy
SAE	serious adverse event
TIA	transient ischaemic attack
PRC	Photographic Reading Center
VA	visual acuity
VFQ-25	Visual Function Questionnaire
WOC	World Ophthalmology Congress
WOCF	worst observation carried forward

RECOMMENDATION

Based on the CHMP review of the data on safety and efficacy, the CHMP considers that the application EMEA/H/C/620/II/44 for Macugen (pegaptanib), in the treatment of neovascular (wet) age-related macular degeneration (AMD, for the proposed change to extend the indication to also include treatment of diabetic macular edema (DME)

is not approvable since "major objections" are still present, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (see section VI). In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

1. EXECUTIVE SUMMARY

Problem statement

DME is characterised by swelling of the central part of the retina, the macula, which mediates high-resolution visual acuity (VA). DME is one of the most sight-threatening complications in diabetes mellitus. DME has been estimated to occur in around 10% of the diabetic population, with a prevalence as high as 30% in patients with more than a 25-year history of diabetes.

The natural progression of DME leads to vision loss of two or more lines (≥ 10 letters) of VA within 2 years in approximately 50% of patients (Ferris, et al 1984). The current standard of care in the treatment of DME is laser photocoagulation as it has been demonstrated to slow the progression of vision loss. In the Early Treatment of Diabetic Retinopathy Study (ETDRS), a key study within the field of diabetic eye disease, patients with mild to moderate DR (diabetic retinopathy) and DME assigned to early focal laser photocoagulation were half as likely to lose 15 or more letters on the ETDRS visual chart compared to non-treated subjects. In the non-treated population, 8, 16 and 24 % lost more than 15 letters after 12, 24 and 36 months, respectively (ETDRS Report No 1, 1985).

On average, laser photocoagulation stabilised VA over 3 years, however visual improvement was uncommon (<3%) which leaves 13% or more patients losing 15 or more letters after three years. (ETDRS Reports No 1, 1985; No 2, 1987 and No 9, 1991).

DME arises from breakdown of the blood retinal barrier (BRB), leading to leakage of fluid and plasma constituents in the surrounding retina, resulting in retinal oedema. It is well established through non-clinical as well as clinical data that VEGF has a major role in the disruption of the BRB. For example, in the study by Vinores et al (1997), a dramatic increase in VEGF staining of the retina from diabetic patients compared to that observed in the normal human retina that contained little or no VEGF, was demonstrated. Elevated VEGF concentrations were also present in the vitreous humour of patients with diabetic retinopathy (Aiello et al., 1994).

Since VEGF appears to be a major endogenous mediator of macular oedema in diabetic retinopathy (DR), pharmacological therapy with pegaptanib to inhibit VEGF aims to address this underlying cause of the pathology. As a consequence, this effect is intended to translate into a reduction in vascular permeability and thus reducing macular oedema and subsequent loss of vision.

About the product

Pegaptanib is a pegylated synthetic ribonucleic acid (RNA)-based oligonucleotide that acts as a selective VEGF165 antagonist.

Macugen 0.3 mg was approved for the treatment of neovascular (wet) age-related macular degeneration (AMD) in January 2006. The approval was based on two controlled, double-masked, and identically designed randomised studies (EOP1003; EOP1004) which included 1190 patients.

In wet AMD, Macugen should be administered once every six weeks.

In AMD, there was a significant proportion of patients experiencing important adverse events (AE), including intraocular pressure (IOP) and occasional cases of endophthalmitis. However, these problems were considered to be outweighed by the efficacy of the study drug.

The development programme/Compliance with CHMP Guidance/Scientific Advice

For the proposed indication, there are no changes related to quality.

To support safety and efficacy of Macugen in the treatment of DME, the MAH has performed non-clinical and clinical studies. In addition, supportive safety data from diabetic patients from the AMD development programme are included in the file.

No centralised, but a number of national scientific advices have been given. The MAH has been granted a paediatric waiver for all paediatric subpopulations in diabetic retinopathy.

General comments on compliance with GMP, GLP, GCP

The MAH states that the clinical trials were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all ICH GCP Guidelines. However, a need for a GCP-inspection has been identified as detailed below.

Proposal for Inspection
The concern regarding a potential need for a GCP-inspection remain:
In view of the below, the CHMP considered that a GCP-inspection addressing the overall quality of the pivotal study EOP1013 is to be performed.

- There is a lack of transparency with regards to the change of primary endpoint (i.e. lowering the requirements) that was made approximately one year after the first patient entered the study. Although the clinical relevance of the changed endpoint is not questioned, no prospectively generated documentation behind the decision for the change has been presented.
- The MAH has identified quality problems (serious GCP-violations) at two (in FR and BR) centres and excluded these from analysis of efficacy. Although the MAH made additional audits in 2 other FR centres and one centre in each of DE, UK and PT without identifying additional violations, the MAH's routines to guarantee an adequate level of quality at the many study centres (56 centres for 260 patients) needs to be further reassured. It is also surprising that the major CZ centre that included 16% of subjects was not part of the additional audits. Finally, the MAH made an internal decision to terminate the trial for all sites in the US in 2007, this leading to a high proportion of discontinuations. This is surprising, in view of these centra being part of a pivotal study.

The outcome of this inspection and the satisfactory responses to its findings are part of the responses to the LoQ as detailed in section VI of this report.

2. SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

N/A

Non clinical aspects

With this application, the MAH has submitted a Nonclinical Overview discussing the rationale for the new indication and relevant issues on pharmacology, pharmacokinetics and toxicology mainly based on data from the original submission. New to this overview are (a) updates to the exposure margins based on the PK parameter obtained from patients with a recommended clinical dose from Study A5751010 and (b) additional studies supporting the DME indication in the following sections:

- Pharmacology: In vivo pharmacology studies in mouse corneal neovascularization model and retinopathy of prematurity model.
- Pharmacokinetics: Protein binding study in rabbit and human plasma and in vitro cytochrome P450 inhibition assay.
- Toxicology: General fertility and reproduction study in mice and embryofetal developmental study in rabbits.

Pharmacology

The nonclinical pharmacology program was developed to characterize the effect of pegaptanib sodium on pathological VEGF165 -induced activities and to assess its effect on other processes that may pose safety issues for its use in humans. The primary pharmacology program for pegaptanib sodium included a series of in vitro and in vivo studies demonstrating the high affinity and specificity of pegaptanib for VEGF165 and its in vivo anti-angiogenic and anti-permeability properties. To support the in vivo angiogenesis inhibitory effects of pegaptanib in DME/AMD the applicant refers to a set a set of pharmacology studies (**Table 1**).

Table 1: Pegaptanib in vivo pharmacology studies

Organ/ System	Species/Strain/Route/ Dose[a] / n	Findings	Report No
Eye – Pegaptanib inhibition of hypoxia-induced neovascularisation	Neonatal C57BL/6 mice, i.p. on postnatal days 12 – 16, Study 1: 0, 10 mg/kg, 7 and 9/sex Study 2: 0, 1, 3, 10 mg/kg, 7-8/sex/group	Study 1: No reduction of neovascularisation. Study 2: 80% reduction of neovascularisation at 3 and 10 mg/kg	109-97004-P
Eye - Pegaptanib inhibition of corneal pocket model. VEGF-induced angiogenesis	SD rats, i.v. bolus 2x/day for 5 days following VEGF-implant. Study 1: 0, 10 mg/kg, 4 m/group Study 2: 0, 1, 3, 10 mg/kg, 4 m/group	Study 1: Significant inhibition of angiogenesis. Study 2: Significant, dose-dependent inhibition of angiogenesis.	109-97002-P
Skin - modified Miles assay – VEGF-induced vascular permeability	Guinea pig, intradermal, single dose. 3f/group/study Study 1: 0, 100, 300, 1000 nM Study 2: 0, 10, 30, 100 nM	Inhibition of vascular leakage. IC_{50} = 30-100 nM (≈ 0.3-1 µg/ml)	109-97001-P
Eye – corneal neovascularisation and retinopathy of prematurity	Mouse, i.p., Corneal neovascularisation model; 0, 5, 10, 50, 100 or 200 mg/kg, 6/group. Retinopathy of prematurity model; 0.0625, 1.25, 2.5, 5, 25 mg/kg, 6/group	The inhibition of corneal neovascularization by pegaptanib was determined by nonlinear regression analysis of the log dose/concentration-angiogenesis response (% vascular growth), with calculated ID50 = 22.5 mg/kg, and IC50 = 0.59 nM (approximately 5.48 ng/mL). In the retinopathy model the inhibition of retinal neovascularization by pegaptanib was determined by nonlinear regression analysis of the log dose/concentration-angiogenesis response (Mean number of endothelial cell nuclei present), with calculated occurred at an ID50 = 3.7 mg/kg, with an IC50 = 0.21 nM (approximately 1.95 ng/mL).	RD-RPT-0005

With the exception of study RD-RPT-0005 all presented pharmacology studies were part of the non-clinical program which was approved with the original marketing authorization application. In the pharmacology overview the MAH claims that pegaptanib treatment can reduce/inhibit neovascularization in a murine corneal neovascularisation model and in a similar fashion in a murine retinopathy prematurity model by referring to study RD-RPT-0005.This study report has not been submitted and the data can therefore not be assessed. The CHMP therefore requested that the MAH should submit this study report for assessment and to further clarify whether there are any other new non-clinical data available to support the DME indication.

In response the MAH submitted the study report for study RD-RPT-0005. Overall the CHMP considered that the data showed that Pegaptanib is able to decrease the percentage of vascularization in the CoNV model. In this model the MAH also shows Pegaptanib presents in the corneal tissue. The data from the ROP model is less convincing as to the effect of Pegaptanib to decrease endothelial cell nuclei (neovessels) extending through the internal limiting membrane into the vitreous due to overlapping standard deviations and lack of data showing exposure (except for the 25 mg/kg group). The clinical effect of Pegaptanib in DME patients is addressed in the clinical assessment and from a non-clinical point of view the issue is considered resolved by the CHMP.

Pharmacokinetics

Protein binding in human and rabbit plasma

With this application the MAH submitted the report for study 400012. The purpose of the study was to evaluate the extent of binding of pegaptanib sodium to human and Dutch Belted rabbit plasma proteins, to assess whether the binding to protein was test article concentration-dependent and if there was any interference from the low-molecular-weight heparin (**Table 2**). No significant protein binding for pegaptanib sodium in both human and rabbit plasma was detected by the gel shift assay at 25-500 ng/mL pegaptanib. Due to the heparin-binding domain residing in pegaptanib, low-molecular-weight heparin was also investigated for its potential role in protein binding. Pegaptanib at 25 ng/mL showed some binding to human plasma proteins that decreased from 49% to 21% with increasing concentrations of heparin (0.2-2.0 IU/mL). However the heparin effect was not observed at 100 ng/mL pegaptanib incubations with human plasma. The binding studies performed at 25 ng/mL 33P-pegaptanib was likely not at optimal conditions as 33P-pegaptanib aggregates in phosphate buffer in a more pronounced fashion at lower concentrations than higher concentrations; conditions which are not optimal for the determination of the free and bound fraction. Based on the discrepancies observed with the binding profile of 33P-pegaptanib to proteins in the presence of heparin the MAH concluded that further investigation would be required. The CHMP therefore requested that these data should be submitted when available.

Table 2. Protein binding of Pegaptanib in rabbit and human plasma

	Fb (5) of the oligonucleotide portion concentration tested (ng/ml)[a]				
Species	**25**	**50**	**100**	**250**	**500**
Rabbit, n=3	-74[c]	-8[c]	-4[c]	6	4
Human, n=3	-8[c]	-27[c]	-14[c]	-1[c]	0

Fb= bound fraction, [a]Target concentration based on oligonucleotide portion of Pegaptanib sodium, [c]Negative Fb values are considered as 0% binding.

In response, the MAH argued that at the time that the plasma protein binding study (400012) was conducted (Nov 2004 – Jan 2005), the specific nature of the molecular interaction between pegaptanib and its molecular target, VEGF165, may not have been fully elucidated. Studies conducted subsequent to the time of the plasma protein binding study demonstrate that pegaptanib specifically targets/binds to the heparin binding domain (HBD) of VEGF165 (Lee et al., 2005; Ng et al., 2006). Report 400012, therefore, inaccurately states that pegaptanib (i.e., the drug) contains a HBD where in fact, it is the drug target (VEGF165) that contains this domain. Consequently, concerns with respect to possible heparin-mediated interference of binding of pegaptanib to plasma proteins are not warranted. Thus, the MAH is of the opinion that no additional investigation is necessary. The CHMP agreed, based on the new information provided, that it was not reasonable to further investigate heparin-mediated interference of binding of pegaptanib to plasma proteins.

In vitro cytochrome P450 inhibition potential

Experiments were carried out in human liver microsomes to determine the potential of pegaptanib sodium to inhibit the 7 major human liver CYP isozymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5) using selective probe substrates (**Table 3**).

Table 3. Inhibition/induction of drug-metabolizing enzymes

	Pegaptanib concentration (ug/ml)/ Oligonucleotide content (ug/ml)								
Enzyme activity (pmol/mg/min)	**0**	**0.010/ 0.002**	**0.030/ 0.0057**	**0.10/ 0.0189**	**0.30/ 0.0567**	**1.0/ 0.189**	**3.0/ 0.567**	**10/ 1.89**	**25/ 4.725**
EROD (CYP1A2)[a]	2.47	2.54	2.55	2.70	2.50	2.56	2.48	2.75	2.48
CMH (CYP2A6)[a]	0.329	0.316	0.346	0.340	0.350	0.350	0.324	0.384	0.355
TBMH (CYP2C9)[b]	20.1	20.5	20.0	20.8	20.7	20.0	19.0	20.5	18.8
MPTH (CYP2C19)[b]	30.9	31.5	31.4	26.4	25.1	26.2	26.4	28.3	27.8
DMOD (CYP2D6)[b]	74.2	74.3	75.4	75.1	74.5	73.8	74.5	73.8	74.8
CZXH (CYP2E1)[b]	0.985	0.973	0.968	0.999	0.968	0.944	0.933	0.979	0.940
TESH (CYP3A4)[c]	6.71	7.71	7.89	8.70	7.75	6.45	7.61	7.79	7.70

CYP450 =Cytochrome P450; EROD=7-Ethoxyresorufin O-Deethylase; CMH=Coumarin 7-Hydroxylase; TBMH=Tolbutamide Methyl-Hydroxylase. MPTH =S-Mephenytoin 4'-Hydroxylase; DMOD=Dextromethorphan O-Demethylase; CZXH=Chlorzoxazone 6-Hydroxylase. TESH=Testosterone 6□-Hydroxylase.
[a]Activity was determined spectrofluorometrically.
[b]Activity was determined by liquid chromatography/mass spectrometry.
[c]Activity was determined by high performance liquid chromatography with ultraviolet detection.

The results showed that pegaptanib at concentrations of 0.01 to 25 µg/mL (0 to 4.725 µg/mL for the oligonucleotide portion), did not significantly affect any of the CYP450 activities tested. In contrast, the inhibition observed for the CYP450 selective inhibitors were in accordance with their inhibition potency reported for various CYP in different species. The CHMP considered that for oligonucleotides a low potential to interact with CYPs was expected. The CHMP further concluded that Pegaptanib is not an inhibitor of any of the CYPs tested (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5) and that these data need to be summarised in sections 4.5 and 5.2 of the SPC.

Toxicology

The sequence homology of the VEGF gene is highly conserved across species. VEGF proteins in the mouse, rat, rabbit, and dog display remarkable similarities to human VEGF22. The cDNA sequences of VEGFs from cynomolgus monkeys predict protein sequences that are identical to the respective human orthologs. In addition, widespread, cross-species biological activity has been demonstrated. These findings support the extrapolation of the results from studies in animal models to humans (Ferrara, N. et al. Nat Med, 2003; Shima, DT. et al. Invest Ophthalmol Vis Scin, 1996; Drake, CJ. et al. Proc Natl Acad Sci USA, 1995). Rabbit and mouse are therefore considered as relevant species for reproductive toxicity testing.

Single and repeat dose toxicity

The nonclinical safety of systemically (IV) and locally (IVT) administered pegaptanib sodium was evaluated in mice, rat, rabbit, dog and monkey. IV doses ranged from 0.1 to 40 mg/kg/day in subchronic studies and up to 450 mg/kg in acute studies. The toxicity of IVT administered pegaptanib sodium was also evaluated in acute, subchronic and chronic studies at doses ranging from 0.1 to 3 mg/eye up to every 2 weeks for 9 months. In general, no systemic or local compound related findings were observed in animals administered pegaptanib sodium IVT after acute or chronic bilateral injections. Due to the high tolerability of pegaptanib following both systemic and local administration, and limitation on IVT dose volume, an MTD for pegaptanib was not established in the toxicology program.

Genotoxicity

Pegaptanib sodium was tested in an ICH compliant standard battery of genotoxicity assays: in vitro bacterial mutation assay, in vitro mouse lymphoma assay, and in vivo mouse micronucleus assay. Pegaptanib genotoxic risk is expected to be nil based on the intact pegylated aptamer size and the physicochemical properties conferred on the molecule by pegylation making it too large (50 kD) for intracellular accessibility to initiate the requisite cascade of events such as DNA incorporation, etc (Caliceti & Veronese, 2003). However, possible degradative or metabolic products, the modified monomer nucleosides, would possibly have unhindered intracellular access, and hence, opportunity to

influence important genetic cellular function (Derelanko, 1995). In order to further characterize the genotoxic risk for theorized monomer metabolites, the O-methylated purines (2'-O-methyladenosine [2'-MA] and 2'-O-methylguanosine [2'-MG]) and the fluorinated pyrimidines (2'-fluorouridine [2'-FU] and 2'-fluorocytidine [2'-FC]) were evaluated in *in vitro* chromosomal aberration and bacterial mutation assays. The bacterial mutation assays were non-GLP compliant for the purine monomers, but GLP compliant for the pyrimidine monomers; for the purines, no QA audit of the data was performed. While the chromosomal aberration studies were not ICH compliant in that no evaluation was conducted under conditions of metabolic activation (Aroclor-induced rat liver S9 microsomal fraction), this is justified since the monomers would represent "preformed" potential metabolites. The studies were of sound quality and provided scientifically valid outcomes. Controls and procedures were conducted in concordance with ICH guidelines. The SHE cell morphological transformation assay was conducted on pegaptanib, 2'-FU and 2'-FC; all were GLP compliant studies. No safety signals emerged from these studies.

Carcinogenicity

No carcinogenicity studies have been performed. The CHMP considered this acceptable as the clinical systemic exposure is very low.

Reproductive and developmental toxicity studies

For the AMD application, it was accepted to not study the potential effects of pegaptanib on embryo-foetal development since the median age of the AMD-population is over 70 years. However, for the present submission, treatment of visual impairment due to DME, a younger population is to be treated and therefore, complementary segment II studies for the embryo-foetal development were undertaken.

- Reproductive and developmental toxicity – Fertility and Early Embryonic Development to Implantation (study 1005-005)

Male and female CD-1 mice (n=25/sex) were administered Pegaptanib (1, 6.5, and 40 mg/kg) intravenously once daily in males beginning 28 days before cohabitation (maximum 14 days) and continuing through the day before sacrifice (immediately after observation of copulatory plug or until the end of cohabitation); and to the female mice once daily beginning 15 days before cohabitation (maximum 14 days) and continuing through day 7 of gestation (DG 7). An additional 30 mice per sex were assigned to each of the dosage Groups II though IV, for toxicokinetic sample collection.

Dosages of pegaptanib as high as 40 mg/kg/day did not affect estrous cycling, mating or the fertility of the male or female mice. Twenty-four of the 25 male mice in each group mated and sired litters. All matings except for one control group male mouse occurred during the first week of cohabitation. No parameter evaluated at Caesarean section was affected by dosages as high as 40 mg/kg/day. No necropsy findings related to the test article occurred. One control group mouse had a small left testis and two 40 mg/kg/day dosage group mice each had small epididymides and testes. No other gross lesions occurred in the male or female mice. Terminal body weights in the male mice were significantly increased ($p \leq 0.01$) in the 40 mg/kg/day dosage group. No other differences related to the test article occurred for terminal body weights, or absolute male reproductive organ or the ratio of the organ weight to the terminal body weight. Epididymal sperm density was significantly decreased ($p \leq 0.05$) 25% and 23% in the 6.5 and 40 mg/kg/day dosage groups, respectively, while dosages as high as 40 mg/kg/day did not affect sperm count or motility.

Based on the results of this study, the male and female NOAEL for fertility and reproduction of pegaptanib is 40 mg/kg/day. This corresponds to AUC(last) value of at least 3264 µg/hr/mL and Cmax value of at least 586 µg/mL, which is approximately 49,000-fold (Cmax) and 1,300-fold (AUC) greater than the clinical exposure at the recommended dose (based on the female exposure on DG 6, which is less than the male exposure on DS 21).

The CHMP considered that the toxicological significance of the decrease in sperm density is unknown as sperm count, sperm motility, mating and fertility were unaffected. In addition, safety margins are high as compared to the recommended clinical exposure. For the recommended clinical dose of 0.3 mg/eye every 6 weeks, the AUC is 2,51 µg/hr/mL and the Cmax is 0.012 µg/mL Based on the male exposures on GD21, at 1 mg/kg/day (no effect on epididymal sperm density at this dose), the Cmax (19 µg/mL) and AUC (136 µg/hr/mL), results in safety margins for female mice of approximately 1600-fold (Cmax) and 54-fold (AUC) greater than the clinical exposure at the recommended dose. Therefore, the CHMP did not consider the finding to be clinically relevant.

- IV EFD Study in Mice (1005-004)

Pegaptanib sodium was administered IV to presumed pregnant CD-1 mice (Main: 21/group; Satellite: 4/group) at doses of 0 (5 mL/kg PBS), 1, 6.5, or 40 mg/kg on GD 6 through 15 (main) or GD 6 through 17 (satellite). The satellite cohort of animals was included to evaluate pharmacological (anti-angiogenesis) endpoints in F1 offspring. In addition to the first two cohorts, a third cohort of animals (36 animals) was administered 40 mg/kg pegaptanib sodium IV on GD 6 through 15 for toxicokinetic analysis of pegaptanib concentration in plasma (sampled on GDs 6 and 15) and amniotic fluid and fetal tissue (sampled on GD 15).

All surviving main study mice were sacrificed on GD 18, and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. The number of corpora lutea and the number and distribution of implantations, live and dead fetuses and early and late resorptions were recorded. Each fetus was weighed, sexed and examined for external alterations. Approximately one half of the fetuses in each litter were dissected and examined for soft tissue abnormalities. The remaining fetuses were eviscerated, stained with Alizarin red and examined for skeletal abnormalities.

The cohort of satellite animals was allowed to deliver and wean their F1 generation pups. Electrocardiographic data were collected on all surviving pups on approximately lactation Day 10. All surviving pups were sacrificed on lactation Day 15 or 20, and a gross and histological evaluation was conducted on the hearts.

There was a slight accumulation of pegaptanib in the plasma as would be expected given the t1/2 and the daily dosing frequency. Mean pegaptanib plasma t1/2 was 4 hours. Pegaptanib crosses the placenta and is found in the amniotic fluid. The mean amniotic fluid concentration was maximal 1 hour postdose (0.58 µg/mL). Pegaptanib amniotic fluid concentration, 1 hour postdose, was 0.04% of the corresponding pegaptanib plasma concentrations of 1400 µg/mL. Based on AUCtau values, the percent of the dose that is found in the amniotic fluid after 10 days of IV dosing is 0.05% (i.e., AUCtau amniotic fluid of 3.8 µg·hr/mL/AUCtau plasma of 8190 µg/hr/mL x 100%).

No evidence of maternal toxicity was noted among in the main study dams. Compound-related effects in fetuses delivered of these dams were limited to the high dose (40 mg/kg/day) and included a decrease (4 to 5% vs. control) in mean fetal body weight and a reduction in the average number of fetal ossification sites in forelimb phalanges.

No compound-related effects on ECG parameters or cardiac histopathology were noted in satellite F1 animals, suggesting a lack of effect of maternal pegaptanib treatment on angiogenic processes within fetal cardiac tissues.

The NOAELs for maternal and fetal effects were considered by the MAH to be 40 and 6.5 mg/kg/day, respectively. The mean C5min and AUCtau on GD 15, at the maternal NOAEL, are 2170 µg/mL and 8190 µg/hr/mL, respectively. This is approximately 180,000- and 3260-fold greater than the human Cmax (0.012 µg/mL) and AUCtau (2.51 µg/hr/mL) at the recommended clinical dose of 0.3 mg in one eye given every 6 weeks (Study A5751010).

The CHMP concluded that this study is not new and there are no new mouse TK data available. Nevertheless, the MAH proposes to change the safety margin mentioned in the SPC from 300 to 3200 (for reduced body weight and minimal delayed ossification in forepaw phalanges). This can be accepted by the Committee, since the maximal recommended clinical dose is 0.3 mg per eye and not 3 mg per eye. In this mouse EFD study, the mean C5min and AUCtau on GD 15, at 40 mg/kg/day, are 2170 µg/mL and 8190 µg/hr/mL, respectively.

This is approximately 24,000- and 300-fold greater than the human Cmax (0.09 µg/mL) and AUCtau (25 µg/hr/mL) at the clinical dose of 3 mg in one eye given every 4 weeks. However, this is approximately 180,000- and 3200-fold greater than the human Cmax (0.012 µg/mL) and AUCtau (2.51 µg/hr/mL) at the recommended clinical dose of 0.3 mg in one eye given every 6 weeks (Study A5751010).

- Intravitreal Embryo-Fetal developmental toxicity study of Pegaptanib in Rabbits (study LIA00580)

Pegaptanib was administered to time-mated [Hra:(NZW)SPF] female rabbits (n=20) at 0.2, 0.6, or 2.0 mg/eye on gestation days (GD) 7 and 13 of presumed gestation (GDs 7 and 13) via IVT injection. On GD 13, blood samples (0.9 mL to 1.1 mL) were collected from 10 rabbits per group via the medial auricular artery. Samples were collected prior to dosage administration, and 1, 9, 24, 48, 96, 144 and 168 hours post dosage (five rabbits/group at predose and 9, 48 and 144 hours post dosage, and five rabbits/group at 1, 24, 96 and 168 hours post dosage). On GD 29, all rabbits were euthanized, Caesarean-sectioned and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed.

All rabbits survived until scheduled euthanasia. IVT administration of pegaptanib did not increase the incidence of clinical signs or cause any test article-related gross lesions. No significant ocular observations were noted following the two intravitreal injections of pegaptanib. Of all analyzed parameters the only statistically significant finding was an increase in angulations of one or both hyoid alae in 4, 2, 3 and 13 ($p \leq 0.01$) fetuses from 3, 2, 3 and 8 litters in the 0 (Vehicle), 0.2, 0.6 and 2.0 mg aptamer/eye dosage groups, respectively. The MAH also presented historical data of fetal incidence of angulated hyoid alae from June 2007 to June 2009 to try to put the results into context. The study in question was performed in February 2010. Fifty full studies are summarised by the MAH, totalling 1010 pregnant rabbits. Angulated hyloid alae occurred in 193 litters out of 977 (19,75%) and 283 fetuses out of 8021 (3,53%). Textbook data refers to much lower incidences (0.77 % in fetuses, see CRC Handbook of toxicology Eds Derelanko and Hollinger). The MAH was therefore requested by the Committee to provide historical data including studies performed before and after February 2010.

Mean Tmax on DG 13 was observed at 24, 9.0, and 9.0 hours for the 0.2, 0.6, and 2.0 mg aptamer/eye dose groups, respectively. Systemic exposure [assessed by Cmax and AUC(0-168)] increased with increasing dosage. On DG 13, the mean Cmax and AUC(0-168) increased by 3.5x and 3.0x, respectively, with a 3x increase in dosage (from 0.2 to 0.6 mg aptamer/eye). On DG 13, additional 3.3x increase in dosage (from 0.6 to 2.0 mg aptamer/eye) resulted in 5.9x and 3.9x increase in mean Cmax and AUC(0-168), respectively. (**Table 4**).

Table 4. Mean toxicity parameters for Pegaptanib in rabbits on DG13 after two doses of intravitreal administration of Pegaptanib.

Dose level (mg/eye)	Cmax (ng/ml)	Tmax (h)	AUC (0-168h, ug*h/ml)
0.2	76.4	24	9.87
0.6	269	9.0	29.5
2.0	1580	9.0	115.0

Overall, the CHMP considered that data depicting the systemic exposure in subjects with DME has not yet been confirmed due to missing study reports. Thus, the exposure margins between humans with DME and mouse/rabbit claimed by the MAH cannot be satisfactorily verified. In turn, the clinical relevance of the findings of increased angulations of one or both hyoid alaes in rabbit can equally not be assessed appropriately at this time. The MAH was therefore requested to submit the missing human PK study reports for assessment in order to facilitate an evaluation of the reproductive toxicity potential of pegaptanib. In response to this the MAH submitted the missing human PK study reports and also updated the non-clinical parts of the dossier by changing exposure margins between DME patients and the species used in the various safety testing studies. The human PK data are discussed in more detail later in this report. As a consequence, the safety margin for the iv EFD study in mice mentioned in section 5.3 of the SPC needed to be adapted.

With regards to the incidences of angulated hyoid alae, the MAH provided details of the incidences of angulated hyoid alae observed in the questioned rabbit embryo-foetal development (EFD) study, historical control data from June 2007 to June 2009 that were attached to the study report, and historical data from June 2008 to June 2010.

Based on the MAH response the CHMP concluded that the only developmental toxicity seen in the rabbit was an increase in the incidence of a common skeletal variation, angulated hyoid alae, at the highest dose tested. The argumentation of the MAH stating that his observation is not related to pegaptanib treatment is not convincing, since the increase (although not significantly) in the number of litters at the highest dose group with angulated hyoid alae cannot be ignored. The range of the incidences of angulated hyoid alae is comparable. However, results from studies performed between June 2008 and June 2009 are overlapping for both periods and thus it could well be that only 1 or a few studies showed these high incidence rates. Taking into account the 70-fold safety margin (for AUC ratio expected in humans), this finding seems to be of limited clinical relevance. Nevertheless, it is uncertain whether the fetuses have been adequately exposed during the early stages of organogenesis. The MAH was therefore requested to update the SmPC to reflect that the final outcome of the study is inconclusive. As CHMP agrees that relevant fetal exposure to pegaptanib after intravitreal administration is very unlikely, additional embryofetal development studies are not warranted.

The MAH was also asked to comment on the fact that administration of the rabbits started on GD 7 when current understanding makes clear that rabbit organogenesis starts on GD6 (Shepard, T.H., 1992, Catalog of Teratogenic Agents, 7th ed. The Johns Hopkins University Press, Baltimore). Taken the PK of pegaptanib after IVT injection into account the applicant should also estimate the time to maximum foetal exposure in this study.

The literature references presented by the MAH on the issue of organogenesis in rabbit suggest that it starts between day 6 and day 7 after gestation. Thus, the issue of rabbit gestation is considered resolved by the CHMP.

As toxicokinetic data after the first dose (administered on GD7) is missing from the rabbit embryo-foetal study, data from rabbit absorption studies presented in the MAA could be used as guidance on the issue of rabbit PK after intravitreal administration.

This data indicate that Pegaptanib T_{max} is reached 24 hours after intravitreal administration. In mouse Pegaptanib crosses the placenta and is found in amniotic fluid (0.05% of the maternal dose). The amount of Pegaptanib found in rabbit amniotic fluid is unknown since no such data is presented in the LIA00580 study report. Thus, it is unknown to what extent the rabbit fetuses are exposed to Pegaptanib, but the presented mouse data support that Pegaptanib also cross the rabbit placenta. In addition, the PK of Pegaptanib after single intravitreal administration to rabbit shows that maximum serum level is reached 24 hours after administration. This gives that maximum foetal exposure in the presented rabbit embryo-foetal study is most likely reached 24 hours after administration, i.e. on GD 8. Together with literature data, stating that organogenesis in rabbit starts between day 6 and day 7 after gestation, it is uncertain whether the fetuses have been adequately exposed during the early stages of organogenesis (delayed for 24 to 48 hours after initiation of organogenesis).

The rabbit embryo-foetal study shows a significant incidence increase of angulated hyoid alae in the highest dose group which could be related to pegaptanib treatment. The highest dose used corresponds to a 316-fold (Cmax) and 71-fold (AUC) greater than the PK found in DME patients (Cmax; 0.005 μg/mL and AUC0-inf; 1.63 μg·hr/mL) at the recommended clinical dose of 0.3 mg in one eye given every 6 weeks (study PMAR-00174). In the rat IV study mild decrease in fetal body weight and a reduction in ossification of phalanges were observed in the 40 mg/kg/day (GD 6 through 15) pegaptanib sodium dose group in (study 1005-004). This is approximately 434,000- and 5,020-fold greater than DME patient Cmax (0.005 μg/mL) and AUC0-inf (1.63 μg·hr/mL) at the recommended clinical dose of 0.3 mg in one eye given every 6 weeks (study PMAR-00174).

Altogether, the CHMP concluded that the findings in the rabbit embryo-foetal study should be adequately presented in the SmPC, as should the questionable early exposure levels in this study.

The CHMP also requested the MAH to amend the proposed text in the SPC to include the fetal skeletal variations. The MAH agreed and updated the SPC accordingly.

Peri-/post-natal development studies

Prenatal and postnatal developmental studies are being planning by the MAH and will be supplemented to this submission when completed. The CHMP considered that the systemic exposure after intravitreal administration is very low and human placental transfer is probably poor. However, given the fact that VEGF is crucial in development, the absence of a peri-/post-natal developmental toxicity study for the requested new indication is not acceptable. The MAH was therefore requested to provide the protocol and the time table of the submission of the results from the planned peri-/post-natal development study. In addition, the MAH was requested to include information in section 5.3 of the SPC that there is currently no data on pre- and postnatal development available.

The MAH responded that the plan is to conduct the peri-/post-natal development study during 2011. The protocol for that study, which will include the study timeline, will be submitted to the CHMP as soon as it is available.

Ecotoxicity/environmental risk assessment

Screening for Persistence, Bioaccumulation and Toxicity (PBT)

Log D < -3 at pH 6.2

Log D values at environmentally relevant pH's are less than the 'PBT' action criteria of 4.5.

Calculation of the Predicted Environmental Concentration in Surface Water (PECsw)

$$PECsw\ [mg/L] = \frac{0.3\ mg/inh/d * 0.01}{} = 1.5 \times 10\text{-}6\ mg/L = 0.0015\ \mu g/L$$

200 L/inh/d * 10

The dose is 0.3 mg every 6 weeks (essentially 7.1 x 10-3 mg/day),
PECsw= 0.0015 µg/L < Action limit of 0.01 µg/L

Based on the above shown calculations the CHMP concluded that the ERA provided by the MAH is adequate. The PECSURFACEWATER value is less than the 0.01 µg/L action limit and no other environmental concerns are apparent. A Phase II environmental fate and effects analysis of pegaptanib sodium is not required. Pegaptanib is therefore not considered to pose a risk to the environment.

Clinical aspects

Tabular overview of clinical studies

A Phase 1b exploratory study (EOP1002) was initially performed followed by one Phase 2 dose-finding study (EOP1005) and one Phase 2/3 pivotal study (EOP1013) to support the claim for the safety and efficacy of Macugen administration. The single pivotal, Phase 2/3, efficacy and safety study was conducted to support the efficacy of Macugen in the treatment of patients with DME for up to 2 years. The Phase 2 dose-finding study provides supportive efficacy data based on the primary and key secondary endpoints. The recommended dosing regimen for Macugen is supported by the pivotal study in conjunction with a PK modeling analysis based on data from the Phase 2 study. An overview of these studies is presented in Table 5 below.

Table 5. Overview of Clinical Studies with Pegaptanib Sodium in Support of the DME Indication

Protocol and Countries	Study Design	Dose	No. Patients Treated	Study Assessments
Phase 1b				
EOP1002 United States	Phase 1b, open-label, single-arm, repeat dose, multicentre	3-6 IVT injections of pegaptanib sodium 3 mg/eye every 6 weeks	10 patients ≥18 years of age with clinically significant macular edema and DME in the study eye, involving the centre of the macula	AEs, SAEs, ECGs, vital signs, PE, clinical laboratory, BCVA, fluorescein angiograms, tonometry, fundus photography, ophthalmologic exam
Phase 2				
EOP1005 United States, Canada, France, Spain, Portugal, Austria, Australia	Phase 2, randomized, controlled, double-masked, dose-finding, multicentre, comparative in parallel groups	Pegaptanib sodium given by IVT injection at doses of 0.3, 1, or 3 mg/eye or sham every 6 weeks for 12-30 weeks; follow up to 82 weeks	172 patients ≥18 years with clinically significant DME, involving the centre of the macula	BCVA, retinal thickening by OCT angiograph and fundus photography, tonometry, AEs, SAEs, ECGs, vital signs, PE, clinical laboratory, local ocular events
Pivotal				
EOP1013 Australia, Austria, Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, France, Germany, Greece, India, Italy, Netherlands, Portugal, Switzerland, United Kingdom, United States	Phase 2/3, randomized, double-masked, sham-controlled, multicentre, comparative trial in parallel groups	Pegaptanib sodium given by IVT injection at a dose of 0.3 mg/eye* or sham every 6 weeks for 2 years (with a 3 year open-label extension)	286 patients ≥18 years with DME involving the centre of the macula	BCVA, applanation tonometry, ophthalmological exam, fundus photography, fluorscein angiography, retinal thickness, OCT3, PROs, ECG, AEs, SAEs, vital signs, clinical laboratory

DME=Diabetic macular edema; IVT=Intravitreal; AE=Adverse event; SAE=Serious adverse event; BCVA=Best corrected visual acuity; IOP=Intraocular pressure; OCT=Optical coherence tomography; PROs=Patient Reported Outcomes; ECG=electrocardiogram; PE=Physical exam *Protocol EOP1013 amendment D allowed for patients previously randomized to 0.03 or 0.003 mg pegaptanib sodium the option of either receiving 0.3 mg injections or withdrawing from the study. Refer to Module 5.3.5.11 for a detailed discussion of the protocol amendments.

Pharmacokinetics

In summary, the MAH argued based on previous observations in patients with AMD, that pegaptanib sodium administered IVT every 6 weeks results in relatively low systemic exposure, does not accumulate in the plasma with repeated dosing and does not appear to elicit an anti-drug antibody response. While renal impairment, as reflected in CLcr, increases systemic exposure (Cmax, AUC) to pegaptanib, the elevation is within the 10 fold safety margin observed for this drug. Consequently, the MAH stated that no adjustment of the 0.3 mg/eye dose is required for AMD patients with CLcr > 30 mL/min and body weight > 39 kg. A population pharmacokinetic (PK) analysis of data obtained from the earlier DME study EOP1005 was performed to provide insights into the PK of pegaptanib in DME patients, as well as to investigate the influence of covariates on pegaptanib PK. Data from the pivotal study EOP1013 in DME was further analysed to provide information on a dosing regimen for pegaptanib in the treatment of DME. The CHMP highlighted that no results from the pharmacokinetic substudy are actually included in the study report for EOP1005 hence it was assumed that all results from this substudy are included and adequately presented in the population PK report. The information on study EOP1005 included below should therefore be considered preliminary as based on summary documents. As the actual population PK reports were not included in the originally submitted documentation no proper assessment of the population PK data has been possible. The MAH was therefore requested by the CHMP to submit all population PK (and PKPD) reports referred to in 2.7.2 Summary of clinical pharmacology studies, including the underlying bioanalytical reports. Until a proper assessment of the population PK analyses has been made possible, the proposed changes to the SPC based on these analyses are not acceptable.

In response, the MAH submitted the requested population PK reports, but not all bioanalytical reports for the underlying data. For completeness and for proper evaluation of observed Cmax levels in DME patients, the CHMP requested that the raw data including the bioanalytical report for the PK data obtained in study EOP1005 should be submitted.

As further described in the MAH response, the separate population PK models were developed based on DME and AMD PK data as described in reports [PMAR-00174] and [PMAR-00173] respectively. In both the DME and AMD data, a large proportion of the data was below limit of quantification. This issue was appropriately handled in both analyses to avoid bias. The DME data only included 58 subjects hence the covariate analysis is considered to be exploratory for the covariates tested. The final model included creatinine clearance as predictor of clearance and sex as predictor of Ka (resulting in lower Cmax in women). In the submitted AMD data analysis [00173], creatinine clearance and weight was included *a priori* on clearance and age on Ka. Specifically only the impact of race (Asian or other) was tested and was not found to be significant when differences in creatinine clearance and size were accounted for. Although slightly different modeling approaches were used for the DME and AMD population analyses respectively, where only a few covariate relations were tested, none of the identified covariate relations were considered to be clinically relevant given that the effects were resulting in exposure differences well below the 10-fold safety margin, i.e., no dose adjustments are warranted based on anticipated differences in AUC for the studied populations. There is no (or very limited) information in subjects with creatinine clearance <30 ml/min which is appropriately described in section 4.2 and 5.2.

The visual predictive plots suggested that the overall profile is reasonably well described by the model. However, there is uncertainty whether Cmax is adequately described by the model. Shrinkage was relatively large (at least for Volume of distribution and Ka). Hence, for the evaluation of systemic exposure in different subgroups it is considered more adequate to use typical values and changes in typical values over the covariate range rather than looking at individual predictions of AUC and Cmax.

It is not entirely clear to the CHMP whether the figures in the SPC are observed values, based on noncompartmental calculations based on individual predicted parameters or based on typical parameter estimates and this should be clarified by the MAH.

The AUC values agree with typical parameter estimates but it should be considered that in AMD patients the typical clearance is corresponding to a patient of 70 kg with creatinine clearance of 45 ml/min and for DME patients the value corresponding to a creatinine clearance of 80 ml/min (0.13 l/h for AMD and 0.19 l/h for DME patients respectively). The difference in typical renal (median renal function) could explain some of the apparent difference in exposure between the two populations. The AMD model (based on 262 patients) suggests that a patient with CrCL of 80 ml/min (still 70 kg) would have a CL of 0.15 l/h. The MAH was therefore requested by the CHMP to include relevant exposure measures to be present in the SPC Section 5.2.

Study EOP1005

Study EOP1005 was a trial conducted in Type I or II diabetic patients diagnosed with clinically significant DME. These patients were randomized into 0.3 mg, 1 mg, 3 mg, and sham treatment groups. Patients received a minimum of 3 and a maximum of 6 IVT injections of Macugen or sham-control applications. Results from 20 patients who received 6 treatments with the therapeutic dose of 0.3 mg/eye for which there are full data are discussed below.

Serial blood samples for the determination of pegaptanib concentrations were to be collected after the first and third pegaptanib or sham injections. A validated, GLP, dual hybridization assay was used to determine pegaptanib plasma concentrations from the samples. A targeted set of covariates was evaluated on the PK parameters and all the covariate effects were added and estimated simultaneously to establish a full model. Clinical judgment was used to determine testing of covariates on PK parameters: for Ka, age and sex; for V, sex and weight (WGT); for CL, age, CLcr, sex and weight. Using a normalized prediction to 0.3 mg, AUC(0-∞) was similar between males and females, and was 18% higher in Blacks compared to Whites. Subjects with AGE > 68 years had a 57% higher AUC relative to subjects with AGE ≤ 57 years. Subjects with WGT ≤ 79 kg or CLCR ≤ 63 ml/min had a 45−48% higher AUC than subjects with WGT > 93 kg or CLCR >86 ml/min.

Females had a 14% lower CMAX than males and Blacks had a 24% greater CMAX than Whites. However, the differences in CMAX by gender or race over the range of CLCR observed are not expected to yield a clinically significant outcome. For the covariates AGE and WGT, the discrepancy between the groups with a 50% increase in CMAX for subjects > 68 years relative to subjects with AGE ≤ 57 years was due to CLCR values. Females had a 9% longer t1/2z. The other covariates had similar values across their respective covariate values. An exception was the influence of CLCR on pegaptanib exposure (CMAX, AUC(0-∞)). However, the predicted change in exposures (AUC(0-∞) and CMAX) over the CLCR range of 30 – 190 ml/min for males and females is less than the 10-fold range of doses administered. No dose adjustment is considered warranted given the safety profile observed over the dose range of 0.3 – 3.0 mg. Moreover, the clinical significance of the effects of the other covariates (e.g., Race, Age, and Weight) on pegaptanib exposure is not expected to warrant an adjustment in pegaptanib dose or dosing interval. Finally, no evidence for the accumulation of pegaptanib in the plasma was observed following repeated actual or predicted dosing.

In addition, due to the similarity of oligonucleotide pharmacokinetics across species, a method was developed to predict vitreous humor PK in humans based upon plasma PK and physiologically-based estimates of vitreous humor volume of distribution using data collated from nonclinical studies in rabbits and monkeys. The resulting predicted concentrations of pegaptanib may be used to inform recommendations for dosing intervals. Details of this study are found in report LI-900015/192611. Predicted vitreous humor clearance values were within 2-fold of observed values for all simulations.

In more detail, the study results showed at the end of approximately 7 weeks (1187 hours or 49.5 days) that the estimated concentrations of pegaptanib in the vitreous humor (mean ± SD) were 26.5 ± 4.03 µg/mL following the 3.0 mg/eye dose, and 3.97 ± 1.16 µg/mL following the 0.3 mg/eye dose. These levels are approximately dose-proportionate. At 7 weeks after the 0.3 mg/eye dose, 26 of 41 (63%) of subjects modeled are predicted to have pegaptanib concentrations in the vitreous humor ≥1 µg/mL. This threshold concentration is equivalent to the EC90 for suppressing VEGF-induced vascular permeability in a guinea pig model, and is in excess of concentrations needed to suppress VEGF-induced neovascularization in the cornea and retina. This suggests that sufficient amounts of pegaptanib (3.97 ± 1.16 µg/mL) would be present in a majority (>50%) of patients at 7 weeks after dosing to functionally inactivate any VEGF165 that may be present. Moreover, 95% of the patients will have vitreous pegaptanib concentrations in excess of the lower limit of efficacy of ca 5 ng/mL. By 12 weeks after administration of the 0.3 mg/eye dose, vitreous concentrations of pegaptanib will drop below 1 µg/mL in 80% and below 5 ng/mL in 10% of the patients. These predictions suggest that clinical efficacy may be expected in a significant percentage of patients for some time beyond the current, 6 week interdose interval for pegaptanib.

In addition, the dossier submitted contained the MAH's analyses to develop a dosing regimen for the treatment of DME patients with pegaptanib sodium and to quickly discriminate between those individuals who would benefit from treatment and those who would not, in parallel with the current recommendations for AMD treatment. The dosing regimen is intended to provide optimal treatment of responding patients, while reducing the relative risk of an IVT injection to patients who will not respond to pegaptanib sodium, and allow them to pursue alternative treatments. To this end, DME patients from studies A57510052 and A57510103 were used. Details of this process are provided in Report PMAR-00176. The first step in achieving the goal of an individualized therapeutic regimen was to identify those patients treated with pegaptanib sodium whose VA improved, deteriorated or stabilized.

This was achieved by stratifying patients into subpopulations on the basis of the change in visual acuity from baseline.

The results suggest that >80% of the patients who stand to benefit from treatment with Macugen will manifest a VA gain of ≥ 5 letters after no fewer than 2 doses, while the minimum time to achieve maximum benefit (100%) by the greatest number of potential responders (100%) is 5 doses. Conversely, almost 80% of the patients who will ultimately show no sustained benefit from Macugen therapy will manifest an improvement in VA of < 5 letters after having received 2 doses.

Taking into account the duration of treatment effect in DME, the results of the MAH's analyses support an individualised dosing regimen for the treatment of DME patients using Macugen. Both direct observations and predictive modeling indicated that the >80% of patients who stand to benefit (Responders) from Macugen therapy will manifest a significant improvement in VA after no fewer than 2 doses, and will continue to improve their vision with subsequent doses. In contrast, >70% of patients who will not respond to Macugen therapy (Combined Intermediate and Non-Responders) will not show significant VA gains at 2 doses. Subsequent treatment of Macugen responding patients is recommended at the physician's discretion. This is based on both model predictions of disease progression and observed data on the decay in VA after a hiatus of 2 consecutive doses. These suggest that the VA of the majority (>70%) of Macugen responding patients will deteriorate by less than 5 letters if one dose is withheld. The outcome after a 2 dose hiatus of pegaptanib is less clear, but as many as 50% of patients may lose more than 5 letters of VA.

As a result of this analysis, the MAH recommends the following dosing instructions for the treatment of DME: "*Macugen 0.3 mg should initially be administered once every 6 weeks into the affected eye, and the patient should be evaluated for clinical benefit after no fewer than 2 doses. Those patients who show a clinical benefit from therapy should continue receiving Macugen at the discretion of the physician. The interval between any subsequent doses should not be shorter than 6 weeks.*"

The CHMP acknowledged the MAH conclusions as they are considered similar to the instructions given to AMD patients.

Comments on the immunogenicity of pegaptanib
In AMD, despite the observations that pegylation reduces the antigenicity of protein therapeutics, and that no anti-pegaptanib IgGs were observed in nonclinical and clinical samples from subjects repeatedly exposed to Macugen, reports of possible hypersensitivity reactions to pegaptanib led to the investigation of the presence of anti-pegaptanib, and anti-nonpegylated pegaptanib IgG and IgE antibodies in the serum of AMD patients repeatedly exposed to pegaptanib as part of study A5751006 (in AMD). Although no IgG or IgE antibodies to pegaptanib were observed in the serum samples of patients with AMD following treatment with Macugen for over 1 year as part of trial A5751006, 4 of 131 patients who were negative at baseline demonstrated an IgG antibody response to nonpegylated pegaptanib. However, these titers were low and close to the assay LLOQ. These data suggest that pegaptanib was not immunogenic in AMD patients. In addition, the presence of anti-pegaptanib antibodies was investigated in individuals positive for anti-nuclear antibodies who did not receive pegaptanib therapy. Only 5/100 individuals were positive for anti-pegaptanib IgG, and 13/100 were positive for anti-nonpegylated pegaptanib IgG. None were positive for IgE. The low incidence of positive individuals coupled with no clear correlation to ANA titer or pattern suggests that there is no or minimal cross reactivity between anti-nuclear antibodies and either pegaptanib or nonpegylated pegaptanib.

The CHMP considered that despite the data in AMD patients, it appears that no immunogenic data have been collected in DME patients. The MAH was therefore requested to commit to collect such data through a post authorization commitment if the application for an extension of indication is accepted.

In response the MAH provided the results of studies in which the MAH showed that diabetics actually seem to have a reduced immune response, especially those with poor glucose control. Therefore, the MAH's comment suggesting that "it is not anticipated that diabetics will have a greater tendency to produce anti-pegaptanib antibodies than what has been observed in the AMD population" is endorsed by the CHMP. In addition, the number of cases of hypersensitivity reactions associated with pegaptanib sodium DME clinical program was similar to those observed with sham treatment. The MAH is committed to continue monitoring the safety data relating to anaphylaxis/hypersensitivity-related events as outlined in the Risk Management Plan. This ADR should also be clearly monitored in the EU safety study, A5751036 (open-label, multi-centre, non-comparative, interventional) planned.

Pharmacodynamics

No new, dedicated clinical pharmacology studies have been conducted in support of the DME submission. This was considered acceptable by the CHMP since the mechanism of action of pegaptanib sodium is expected to be similar in AMD and DME.

Clinical efficacy

Dose-response studies

Study EOP1002
This study is an open-label, single-arm, multicenter, Phase 1b exploratory study to investigate the safety and preliminary efficacy (visual acuity data only) of at least 3 consecutive IVT injections of Macugen (3 mg) given at 6-week intervals in diabetic patients with DME. A maximum of 6 injections of study drug could be given based on the investigator's assessment of clinical need. Patients were followed for a total of 82 weeks (up to 1 year after the last dose of study drug was injected). Safety and efficacy assessments were to be performed at baseline, at each injection visit (Weeks 0, 6, 12, 18, 24, and 30), and at follow-up Weeks 36, 48, and 82. Ten (10) patients entered the study and 6 completed it. No formal hypothesis testing was performed.

In this preliminary study, most of the AEs were mild or moderate in intensity and not considered as study drug-related events except one case of elevated increased intraocular pressure (IOP). One patient died 26 days after the last injection of study drug due to multisystem organ failure and pneumonia; this was not considered study drug-related. In terms of efficacy, one of the 8 (12.5%) patients who remained in the study at Week 36 (6 weeks after the last injection of study drug) lost ≥15 letters of VA in the study eye, and none lost ≥30 letters of VA. Most patients exhibited stable VA following administration of Macugen therapy, with 9 of 10 (90%) patients having no loss of vision in the study eye after the first injection (Week 6), and 4 of 5 (80%) remaining patients having no loss of vision at study completion (Week 82). At the end of the study period, 2 patients had gained ≥5 letters of VA and 1 patient had gained ≥15 letters of VA compared with baseline.

The CHMP considered that the Phase 1b study of Macugen in 10 patients with DME was satisfactory.

Study EOP1005

Methods
This is a Phase 2, multi-centre, dose-finding (0.3, 1.0 or 3.0 mg/eye) study designed to explore the safety and efficacy of pegaptanib administered as intravitreal (IVT) injections every 6 weeks in comparison to sham (needleless syringe pressed towards the conjunctiva) in 169 subjects (128 treated and 41 sham subjects) with DME. Focal laser therapy was deferred for 18 weeks after randomisation. Patients were planned to receive between 3 and up to a maximum of 6 injections for 12 to 30 weeks with a follow up period to 82 weeks. Randomisation was stratified by site, area of retinal thickening (<2.5 vs. >2.5 disc areas [DAs]), and VA (>58 vs. <58 letters on the ETDRS chart).

- **Study Participants**

The study was conducted at 39 sites in Europe, Canada, Australia and in the US to provide 4-10 subjects per site.

Main inclusion criteria: Type I or II diabetic patients, ≥18 years, diagnosed with clinically significant DME, with BCVA between 68 and 25 ETDRS letters (~20/50 to 20/320 Snellen equivalents) in the study eye, and ≥ 35 ETDRS letters in the fellow eye. The area of retinal thickening was to have been at least one-half a disc area in size and involve the centre of the macula as determined by the Photographic Reading Center (PRC).

Main exclusion criteria: Intraocular pressure (IOP) > 23 mmHg, panretinal or focal/grid photocoagulation within 6 months prior to baseline, need of scatter photocoagulation therapy (at study entry or anticipated need it within 9 months). Women of childbearing potential were to use two effective forms of contraception throughout the duration of the study. History of severe cardiac disease, significant peripheral vascular disease, significant impaired renal or hepatic function. Systolic blood pressure (BP) > 155 mmHg or diastolic BP > 95 mmHg, HbA1C ≥13%.

The CHMP commented that despite that retinal thickness is the selected primary outcome measure, there were no enrolment criteria regarding the thickness of the retina, only with regards to the area.

- **Treatments**

Pegaptanib sodium (0.3 mg in 90 μl) or sham was administered once every 6 weeks for 12 to 30 weeks (3 initial planned doses and an additional 3 doses at the discretion of the investigator to a maximum of 6 injections). Focal/grid photocoagulation was allowed from 1 week after the third treatment at the discretion of the investigator. Following the treatment period, patients were followed up for a further 52 weeks, for 82 weeks in total; no study treatments were applied during the follow up period.

- **Objectives**

To establish the safe and efficacious dose of pegaptanib as compared to control sham injection every 6 weeks for 12 to 30 weeks in patients with clinically significant DME involving the centre of the macula.

- **Outcomes/endpoints**

Primary efficacy endpoint: Change in retinal thickness in the central subfield (CRT) as a whole, as measured by OCT, between baseline and week 36.

Key secondary efficacy endpoint: Change in VA between baseline and week 36.

Other endpoints included: - Proportion of patients who received focal/grid laser at week 12 or later, - Proportion of patients with a loss ≥ 15 letters on the ETDRS chart at week 36, - Change in macular capillary loss, fluorescein leakage and cystoid changes in the grid as a whole.

Post hoc endpoint: The proportions of patients gaining ≥ 0, 5, 10 or 15 letters on the ETDRS chart at week 36.

Efficacy and safety analyses were repeated for the week 52 and week 82 time points.

The CHMP concluded that a primary endpoint based on a functional measure over an anatomical one would have been preferred. In view of the exploratory nature of the study, this is however acceptable as vision-related endpoints have been included in the study as well.

- **Sample size**

Sample size calculations were based on changes in CRT where a 75 μm reduction was considered clinically important and an estimated SD (reported from reading centre) of 100 μm. Since the trial was designed to compare each treatment group with control, the significance level of each of the comparisons was set to 1.67% (Bonferroni correction). Based on these assumptions, the sample size required was 152 patients (38 evaluable patients per group) to detect a 75 μm reduction with an 80% power and an alpha of 5 %. Accounting for at most 15% un-evaluable patients, the trial was planned to accrue a total of 176 patients (44 patients per group).

The CHMP considered the sample size calculations to be acceptable.

- **Randomisation**

Patients were assigned to treatment according to the randomisation scheme. The dynamic minimisation used a stochastic treatment-allocation algorithm based on the variance method. Randomization was stratified by centre, area of retinal thickening (<2.5 vs. >2.5 DAs), and VA (>58 vs. <58 letters). Since the primary endpoint is based on the central retinal thickness, the CHMP did not understand why stratification was based on the area of retinal thickening and not the thickness.

- **Blinding (masking)**

Masking was achieved by requiring that the ophthalmologist who administered the pegaptanib or sham injection should be distinct from the examiner responsible for VA measurement, AE recording and assessment and decisions regarding need for laser treatment. It is stated by the MAH that masking of individual patients was not compromised for the week 36 analysis (see Conduct of study below).

- **Statistical Methods**

Analysis population: All randomised patients, whether treated or not, were included in the intent-to-treat (ITT) population. The safety population consisted of all treated patients. The per-protocol (PP) population included all treated patients who did not experience any major violation of the protocol and excluded patients without or with only baseline RT values. All efficacy analyses were conducted on the intent-to-treat (ITT) population. Analysis on the primary efficacy endpoint was also performed on the PP population. Missing data were imputed with the last observation carried forward (LOCF) method.

Analyses: Summary statistics were presented for all endpoints at relevant time points. The 95% CIs were calculated for selected treatment contrasts. All tests were two-sided. The primary efficacy analysis was analysed using ANCOVA which included main effects of treatment and stratification factors as a covariate. Hochberg's multiple comparison procedure was implemented to test doses successively against sham for the primary efficacy endpoint only (type I error controlled at α =0.05).

Interim analysis: The original protocol for study EOP1005 included a planned primary analysis at week 82, after the follow-up period, and an interim analysis at 36 weeks. However, it was decided to make the week 36 analysis the primary analysis of this trial. This decision was made prospectively, prior to unmasking.

The CHMP considered the statistical methods used acceptable.

Results

- **Participant flow**

Table 6. Patient Populations Evaluated for Efficacy and Safety

Number of Patients	Pegaptanib				Sham
(%)	0.3 mg	1 mg	3 mg	All Doses	
Intent-to-Treat[1] (ITT)	44 (100%)	44 (100%)	42 (100%)	130 (100%)	42 (100%)
Safety[2]	44 (100%)	42 (95%)	42 (100%)	128 (98%)	41 (98%)
Per-protocol[3]	41 (93%)	42 (95%)	40 (95%)	123 (95%)	38 (90%)

[1] All patients who randomized by the ID-Net randomization system
[2] All patients who received at least one double masked treatment
[3] All treated patients without any major protocol deviations during the study, excluding those without or with only baseline OCT measurements
Source: Table 1.1 in Section 15

Table 7. Patients Excluded from the Per-Protocol Population

Reason for Exclusion	Number of Patients	Patient Numbers (Treatment Arm)
Not treated	3	012-001 (1 mg), 029-002 (sham), 041-001 (1 mg)
Protocol violation	4	002-003 (3 mg), 032-003 (sham), 037-003 (0.3 mg), 078-007 (0.3 mg)
Missing baseline, or only baseline OCT measurements	4	025-001 (0.3 mg), 031-003 (3 mg), 036-009 (sham), 037-001 (sham)

OCT - Optical Coherence Tomography
Data derived from List 5.1 in Section 16.2.

Table 8. Patient Discontinuations from Study up to Week 36 with Reason for Discontinuation

	Pegaptanib				Sham
Safety Population	0.3 mg	1 mg	3 mg	All Doses	
Number of Patients (%)	N = 44	N = 42	N = 42	N=128	N = 41
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Adverse event	1 (2%)	0 (0%)	1 (2%)	2 (2%)	0 (0%)
Patient request	0 (0%)	0 (0%)	1 (2%)	1 (1%)	5 (12%)
Total	1 (2%)	0 (0%)	2 (5%)	3 (2%)	6 (15%)

Source: Table 4.1a in Section 15 and List 11 in Section 16.

Table 9. Patient Discontinuations from Study after Week 36 with Reason for Discontinuation

	Pegaptanib				Sham
Safety Population	**0.3 mg**	**1 mg**	**3 mg**	**All Doses**	
Number of Patients (%)	**N = 44**	**N = 42**	**N = 42**	**N=128**	**N = 41**
Death	0 (0%)	1 (2%)	1 (2%)	2 (2%)	0 (0%)
Adverse event	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Protocol violation	0 (0%)	0 (0%)	1 (2%)	1 (1%)	1 (2%)
Patient request	2 (5%)	3 (7%)	2 (5%)	7 (5%)	2 (5%)
Lost to follow up	0 (0%)	1 (2%)	2 (5%)	3 (2%)	0 (0%)
Other	0 (0%)	1 (2%)	1 (2%)	2 (2%)	0 (0%)
Total	2 (5%)	6 (14%)	7 (17%)	15 (12%)	3 (7%)

Source: Table 4.1b in Section 15 and List 11 in Section 16.

There were few discontinuations during the active treatment phase, especially in the pegaptanib treatment groups. A larger dropout rate is to be expected during the follow up period, but also this rate is within a reasonable range.

- **Conduct of the study**

The study was performed from October 4, 2002 to February 10, 2005.

Protocol amendments: There were two protocol amendments (last amendment March 2003) that included changes to secondary endpoints and changes to the IVT administration procedure to further reduce the risk for infections. In addition, the originally planned 82 week endpoint for the efficacy analysis was changed to week 36. This decision was made prospectively, prior to unmasking, and is documented in the SAP.

The CHMP considered that the protocol amendment raises no concern, they were made prior to unmasking and the shortening of the study is acceptable in view of the exploratory nature of the study.

- **Baseline data**

Demographic data were generally similar across treatment groups. The median age was 62.5 years and was similar in each treatment group. The majority of patients were White (> 80%), were non-smokers (94%) and had an Eastern Cooperative Oncology Group (ECOG) performance scores of 0 (69%) with a somewhat lower proportion in the 3 mg dose group (52%). (ECOG performance status abbreviated: 0: Fully active; 1: Restricted in physically strenuous activity, but ambulatory; 3: Capable of only limited self care; confined to bed or chair more than 50% of waking hours. 4: Completely disabled. Totally confined to bed or chair.)

With regards to ophthalmic history the proportions of patients who had previous non-surgical ocular disease, ocular conditions, trauma, previous ocular surgery or laser treatment were similar across treatment groups.

Baseline ocular diabetic disease status in the study eye is summarised in the Tables below.

Table 10. Baseline Stereoscopic Fundus Photographs, Fluorescein Angiograms and OCT – Study Eye

		Pegaptanib			Sham
ITT Population		**0.3 mg**	**1 mg**	**3 mg**	
Number of Patients (%)		**N = 44**	**N = 44**	**N = 42**	**N = 42**
Area of retinal thickening ≥ 2 DA involving center of the macula	Yes	44 (100%)	43 (98%)	42 (100%)	41 (98%)
	No	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Not done	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Other retinal abnormalities	Yes	14 (32%)	8 (18%)	10 (24%)	10 (24%)
	No	30 (68%)	35 (80%)	32 (76%)	31 (74%)
	Not done	0 (0%)	1 (2%)	0 (0%)	1 (2%)

DA=disc area;

Table 11 Baseline Visual Acuity Scores and Snellen Equivalents

		Pegaptanib		Sham
ITT Population	**0.3 mg**	**1 mg**	**3 mg**	
Number of Patients (%)	**N = 44**	**N = 44**	**N = 42**	**N = 42**
ETDRS VAS (letters)				
Mean (SD)	57.1 (11.5)	55.0 (10.5)	57.0 (9.1)	55.8 (9.5)
Median	61.0	59.0	57.5	58.0
Range	30 - 79	27 - 70	30 - 70	26 - 69
Snellen Equivalent VAS				
20/20 to 20/80	31 (69%)	28 (63%)	29 (71%)	29 (69%)
20/100 to 20/160	10 (23%)	12 (27%)	12 (29%)	9 (22%)
20/200 to ≤ 20/800	3 (7%)	4 (9%)	1 (2%)	4 (8%)

ETDRS=Early Treatment Diabetic Retinopathy Study; VAS=visual acuity score; SD=standard deviation.

Mean IOP was 15.7 ± 3.0 mmHg in the ITT population with very little variation among treatment groups. Baseline retinal thickness was slightly higher in the 0.3 mg treatment group, but fairly similar between groups, see **Table 13** below.

The CHMP noted that, in all treatment groups, a few subjects with a better baseline VA are included, than defined by the inclusion criteria.

Baseline stratification factors were fairly well balanced across the treatment groups. Twenty-two percent of all ITT patients had less than or equal to 2.5 (DAs) of retinal thickening, and 78% had greater than 2.5 DA of retinal thickening. Baseline VA was less than 58 letters in 53% of all patients and was at least 58 letters in 47%.

With regards to baseline diabetes status, 75 (44%) had Type II, 12 (7%) with Type I, and 86 (50%) were reported as having "diabetes mellitus NOS [not otherwise specified]". Mean HbA1c were similar across treatment arms (7.1-7.7%, range 4.7-11.7) and the use of concomitant medication for diabetes was consistent across the treatment arms.

The CHMP considered that there were few included subjects with type I diabetes and a high number of subjects where the type of diabetes was not defined. This is considered a severe shortcoming, even for a Phase 2 study. Of those who were classified, 84% had type II DM. Therefore the results are not easily applicable to type I patients. Further, information on the duration of DME would be of certain interest as a long-standing oedema may reduce the chances of gaining VA.

Extent of exposure

Table 12. Study Drug Administration

Number of Patients (%)	**Pegaptanib 0.3 mg N=44**	**Pegaptanib 1 mg N=42**	**Pegaptanib 3 mg N=42**	**Sham N=41**
Mean (SD)	5.0 (1.2)	5.2 (1.0)	5.0 (1.3)	4.5 (1.5)
Median number of injections	5.0	6.0	6.0	5.0
Mean (SD) treatment duration (weeks)	24.4 (10.4)	26.6 (6.3)	25.8 (7.9)	23.2 (9.4)
Median treatment duration (weeks)	30.1	30.0	30.1	29.3

Overall, 95% of all patients received all of the first three injections and 83% remained on therapy after the first three injections. Over 90% of patients received an injection at each visit until week 12. Thereafter, the proportion of patients receiving treatment declined with 69%, 67% and 63% overall receiving injections at weeks 18, 24 and 30 respectively. A greater proportion of patients in the active arms received treatment from week 18 than in the sham arm. Twenty-one percent of patients, similar between treatment groups, experienced one treatment delay (>8 weeks between two consecutive injections).

Primary endpoint

Table 13. Mean Changes in CRT from Baseline to Week 36 – ITT Population

	Pegaptanib			Sham
	0.3 mg N = 44	1 mg N = 44	3 mg N = 42	N = 42
Evaluable patients*	n = 43	n = 42	n = 42	n = 41
Retinal thickness (µm)				
Mean baseline thickness	465.5	436.8	442.0	432.7
Mean (SD) change at week 36	-50.8 (114.9)	-15.9 (102.1)	-21.0 (143.8)	-12.7 (112.4)
p-value**	0.2052	0.9315	0.7987	-

SD – standard deviation
For missing data, the LOCF method was used
* For missing data at baseline, day 0 was used; when no baseline or day 0 data were available, the patient was non-evaluable.
** ANCOVA model, adjusted for baseline retinal thickening area, baseline vision and baseline retinal thickness as a covariate; p-values of pair wise comparisons, unadjusted for multiplicity
Source: Table 5.1.1a in Section 15

There was a trend towards a treatment effect in the 0.3 mg dose group. This trend was also seen in the PP population with a tendency towards a greater decrease in the 0.3 mg pegaptanib dose group (-49.4 ± 101.9 µm) versus the sham control group (-19.3 ± 111.3 µm; p=0.38).

Data from weeks 52 and 82 show that the mean RT continued to decrease, most noticeably in the 0.3 mg (-71 and -100 µm) and 3 mg (-58 and -102 µm) arms in comparison with sham (-32 and -42 µm). In the 0.3 mg arm, 42% of patients compared with 27% in the sham arm had a decrease of ≥ 75 µm at week 36. Thirty-three percent of patients in the 0.3 mg arm compared with 17% in the sham arm had a decrease in RT of ≥ 100 µm at week 36.

The CHMP concluded that the mean decrease in CRT is modest, not statistically significant in any treatment group and borderline clinically significant only in the 0.3 mg dose group at the time for assessment of the primary endpoint (week 36). However, the observation that there appears to be a continued decrease in CRT after discontinuing treatment is of interest. As in AMD, there is no dose response relationship and the 0.3 mg dose tends to be the most effective.

Key secondary endpoint
Mean change in VA are summarised in the table below.

Table 14. Mean Changes in Visual Acuity from Baseline to Week 36 – ITT Population

	Pegaptanib			Sham
	0.3 mg N = 44	1 mg N = 44	3 mg N = 42	N = 42
Evaluable patients*	n = 44	n = 43	n = 42	n = 41
Visual Acuity (letters)				
Mean baseline score	57.1	55.0	57.0	55.8
Mean (SD) change at Week 36	4.7 (11.8)	4.7 (10.7)	1.1 (11.5)	-0.4 (13.9)
p-value**	0.0419	0.0543	0.5499	

*Day 0 was used for missing data at baseline.
**ANCOVA model, adjusted for baseline retinal thickening area and baseline vision; p values of pair-wise comparisons, unadjusted for multiplicity

At weeks 52 and 82, mean VA decreased slightly from the week 36 levels in all treatment arms. In the 0.3 mg arm, mean VA at week 82 still showed a slight numerical improvement over baseline levels (+1.3 letters) vs. a decline of 2.4 letters in the sham group.

Selected secondary efficacy endpoints

Table 15 Proportion of Patients Receiving Focal/Grid Laser Treatment after Week 12 and up to Week 36 – ITT Population

Number of Patients (%)		Pegaptanib 0.3 mg N = 44	Pegaptanib 1 mg N = 44	Pegaptanib 3 mg N = 42	Sham N = 42
Evaluable patients		n = 44	n = 44	n = 42	n = 42
Focal/grid laser after Week 12	Yes	11 (25%)	13 (30%)	17 (40%)	20 (48%)
	No	33 (75%)	31 (70%)	25 (60%)	22 (52%)

Estimates of the Odds Ratio and CMH Test *

Treatment Comparison	Odds Ratio	p-value** (CMH)
0.3 mg vs sham	0.37	0.0425
1 mg vs sham	0.46	0.0897
3 mg vs sham	0.75	0.5368

*Cochran-Mantel-Haenszel (CMH) test, adjusted for baseline retinal thickening area and baseline vision
** For pair wise comparison, not adjusted for multiple comparisons

Very few patients lost ≥ 15 letters of VA up to week 36 (6% of patients in all treatment groups combined) with slightly lower, but non-significant proportions in the active arms, the 1.0 mg arm numerically in favour of the other arms (1/44 subjects (2%) lost ≥ 15 letters, p = 0.1790). The corresponding figures in the 0.3, 3.0 and sham group were 7, 7 and 10%, respectively.

Table 16. Proportion of ITT Patients Gaining ≥ 0, 5, 10 or 15 Letters of VA at Week 36 –ITT Population

Number of Patients (%)	Pegaptanib 0.3 mg N = 44	Pegaptanib 1 mg N=44	Pegaptanib 3 mg N=42	Sham N = 42
Evaluable patients	n = 44	n = 43	n = 42	n = 41
≥ 0 letter(s) gained	32 (73%)	31 (72%)	25 (60%)	21 (51%)
p-value*	0.0231	0.0244	0.3766	-
≥ 5 letter(s) gained	26 (59%)	19 (44%)	13 (31%)	14 (34%)
p-value*	0.0103	0.2597	0.7795	-
≥ 10 letter(s) gained	15 (34%)	13 (30%)	6 (14%)	4 (10%)
p-value*	0.0030	0.0135	0.3873	-
≥ 15 letter(s) gained	8 (18%)	6 (14%)	3 (7%)	3 (7%)
p-value*	0.1181	0.2115	0.7575	-

*CMH test adjusted for baseline retinal thickening area and baseline vision. Pairwise comparison not adjusted for multiple comparisons.
Source: Table 5.7.1a-4a

The proportion of patients with vision gain, showed a gradual decrease from week 36 for most treatment arms, although the increase of ≥ 10 letters remained statistically significant in the 0.3 mg dose group at week 82 (p= 0.0446).

With regards to macular capillary loss, fluorescein leakage, there were no clear differences between active treatment groups and sham.

There was a modest, trend towards a negative correlation between VA and CRT in all dose groups, with reduction in macular thickness associated with improvement in VA (Pearson's correlation coefficient =-0.38; p=0.074). Additional anatomical analyses tended to show a benefit in favour of the 0.3 mg dose.

The CHMP concluded that also with regards to the secondary outcome measures, there is no, or an inverse, dose response but in all analyses, 0.3 mg was in favour over the 3 mg dose group, and in most analyses in favour over the 1 mg dose group. A potential effect of lower doses were planned to be investigated in the pivotal study, however, lower concentrations of pegaptanib were not stable (see Main study).

In the 0.3 mg dose group, VA outcomes indicate a mean 5 letter increase in VA vs. sham at week 36 and that 34 vs. 10 % in the sham arm gains ≥ 10 letters. Such outcome is clearly of clinical importance. It is also interesting that there appears to be a tendency towards a sustained treatment effect in some subjects, although this effect is modest. Further, fewer pegaptanib-treated subjects – especially in the 0.3 mg treatment arm – received laser treatment as rescue. Although the VA data are not fully supported by anatomical outcome measures, overall the data points in the same direction. It

is considered important from a safety perspective that there were no negative effects on macular capillaries.

The selection of the dose of 0.3 mg per injection and the interval of 6 weeks is also considered acceptable by the CHMP for DME as it was for AMD.

Main clinical study

Study: EOP1013

A Phase 2/3 Randomized, Controlled, Double-Masked, Multi-Center, Comparative Trial, in Parallel Groups, to Compare the Safety and Efficacy of Intravitreous Injections of 0.3 mg Pegaptanib Sodium (Macugen), Given as Often as Every 6 Weeks for 2 Years, to Sham Injections, in Subjects with Diabetic Macular Edema (DME) Involving the Center of the Macula with an Open-Label Macugen Year 3 Extension.

Methods

The study initially explored three doses of pegaptanib (0.3, 0.03 or 0.003 mg/eye) vs. sham. During the course of the study (see conduct of the study below), the lower concentrations of pegaptanib were dropped and subjects were given the option of either receiving injections of 0.3 mg/eye or withdrawing from the study. For the 0.3 mg dose, subjects were randomised (1:1) in a masked fashion to receive sham or 0.3 mg (90 μl) of pegaptanib (IVT injections) every sixth week during the first year, and on a "when needed" basis the 2nd year. After that, subjects have the option of receiving Macugen in a one-year, open label extension-phase with the primary purpose of collecting safety data (ongoing).

Assessments were made according to **Table 17**.

Table 17 Activities during the 1 and 2 years of the study.

Page 1 of 6										
Week	**Baseline[a]**	**0 (Before Injection)**	**0 (After Injection)**	**0+3 Days**	**6 (Before Injection)**	**6 (After Injection)**	**6 + 3 Days**	**12 (Before Injection)**	**12 (After Injection)**	**12 + 3 Days**
Randomisation		M								
Pegaptanib sodium injection / sham injection		X			X			X		
Informed consent, medical history	X									
Ophthalmologic/DMO history	X									
Physical examination/weight/vital signs	X	X[b]			X[b]			X[b]		
Telephone safety check				M			M			M
Protocol refraction and distance visual acuity (ETDRS chart)	B	S			S			S		
Tonometry	B	S[c]	S		S[c]	S		S[c]	S	
Ophthalmologic examination	B	S	S		S	S		S	S	
Stereoscopic colour fundus photos	B[d, e]									
Fluorescein angiogram, OCT	B[e]									
ECG	X									
Pregnancy test	X[f]	X[f]			X[f]			X[f]		
Laboratory tests	X[g]				X[g]					
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X
NEI-VFQ 25 and EQ-5D	M									

Source: Appendix A1

Eye Assessments: A = as indicated, B = both eyes, M = mandatory, S = study eye

- **Study Participants**

The study was conducted at 56 centres.

Main inclusion criteria:

- Ocular
  - Macular oedema with centre involvement and corresponding leakage.
  - Foveal thickness ≥ 250 microns (OCT3, centre point)
  - BCVA between 65 and 35 letters (20/50 to 20/200 Snellen equivalents).
  - Clear ocular media and adequate pupillary dilatation to permit fundus photography.
  - IOP ≤ 21 mmHg
  - Laser (focal/grid) can be deferred for at least 18 weeks, even though indicated.
- General
  - Type I, or Type II diabetic subjects (WHO criteria) ≥ 18 years old
  - Performance Status ≤ 2 according to the ECOG/ WHO scale.
  - Normal ECG
  - Women must be using effective contraception until 60 days after the last dose, be post-menopausal, or surgically sterile.
  - Adequate haematological, liver, renal function

Main exclusion criteria:

- Ocular
  - Prior scatter (panretinal) photocoagulation < 6 months prior to baseline, or needed/ likely to be needed within the next 9 months.
  - Presence of any abnormality that is likely to confound assessment of VA improvement, incl. non-perfusion for >1 disc area involving the foveal avascular zone (FAZ - involving 2 or more quadrants centred around the foveal avascular zone), atrophy/scarring/fibrosis involving the centre of the macula
  - Any other cause of macular oedema
  - Any subfoveal hard exudates, or RPE atrophy
  - YAG laser, or peripheral retinal cryoablation, or laser retinopexy (for retinal tears only), or focal or grid photocoagulation, within the previous 16 weeks.
  - Significant media opacities, including cataract, which might interfere with assessments.
  - Any intraocular surgery within 6 months of trial entry, previous vitrectomy or filtering surgery.
  - Acute ocular or periocular infection

- General
  - HbA1C >10% or recent signs of uncontrolled diabetes
  - Systemic diseases incl. severe cardiac disease (e.g. NYHA Functional Class III or IV), unstable angina, acute coronary syndrome, myocardial infarction (MI), peripheral vascular disease, stroke (within 12 months prior entry), systolic BP >160, diastolic BP >100
  - Clinically significant renal or hepatic function
  - Women currently nursing

By excluding subjects with severe central retinal ischaemia, recent (previous 16 weeks) or indicated focal or grid laser photocoagulation and unstable diabetes the CHMP questioned whether the study population can be extrapolated to the overall target population. Further, very few subjects with type I diabetes were included. Considering that vision loss in type I diabetes is predominantly due to proliferative complications of retinopathy, whereas vision loss in type II diabetes is mainly due to DME, it may not be possible to extrapolate the results from type II to type I diabetes. In addition, the strict exclusion criteria will have to be taken into account when extrapolating these results to the broad type II DM population and section 4.4 of the SPC should be updated to reflect these. In particular, treatment with scatter (panretinal) photocoagulation < 6 months prior to baseline, or needed/likely to be needed within the next 9 months. Patients with YAG laser, or peripheral retinal cryoablation, or laser retinopexy (for retinal tears only) were also excluded. Mentioning these criteria in the SPC may be required. More importantly, the lack of experience in DM patients with major ischemic edema or with coexistent epiretinal fibrosis should be addressed in the SPC.

The MAH's responded that the pathophysiology of DME does not differ between type I and II diabetic patients. This was acknowledged by the CHMP as were the reasons for restricting the patient population to fairly stable patients. Subgroup analyses of subjects with type I diabetes did not indicate a better effect of Macugen over sham, however the sample size was too limited to draw any conclusions and the MAH was therefore requested to commit to address the effect in subjects with type I diabetes in future studies. In the Macugen file, 22 subjects with typ1 diabetes were included. Consequently, this information should be given in section 4.4.

The CHMP further considered that a larger clinical study (RCT) exploring pegaptanib treatment in subjects with DME type I and type II, using inclusion criteria that are less restrictive concerning blood pressure and HbA1 level should be undertaken. As long as the results of these additional trials aren't known, the limited experience of pegaptanib-treatment in subjects with DME due to type I diabetes and in diabetic subjects with an HbA1 over 12% should be added to the SPC, section 4.4.

The MAH further explained the reasons for not including subjects with a need for laser coagulation. However, patients who would seek treatment for symptoms associated with DME and then are deferred laser treatment for over 4 months are not considered representative of the target population. This translates into the fact that there is no experience of initiating Macugen treatment in subjects with a need for laser photocoagulation. In addition, the CHMP acknowledged that the aim of the inclusion/exclusion criteria regarding laser therapy was not to select 'healthy' patients but to remove the bias of laser treatment in the early stages of the study. While this may justify excluding patients who received laser therapy within 16 weeks prior to the inclusion in the study, it does not justify excluding patients with an anticipated (within 18 weeks) need for laser therapy. Indeed, the primary efficacy outcome is one year improvement from baseline. Reiterating their concerns, the use of pegaptanib in relation to laser therapy was considered to be further studied by the CHMP.

A small study (Chung et al., Retina. 2008 28(7):957-63) including patients with retinal ischaemia indicated that the VEGF-inhibitor bevacizumab decreased VA in these subjects. The MAH was therefore requested by the CHMP to justify this exclusion criterion in view of the proposed indication and this should be addressed in the RMP. The MAH should also explain whether any subjects with significant central retinal ischaemia of < one disc area (e.g. > 500 μm2) and whether any subjects with ischaemic areas involving the foveal zone were included in the study.

In the response the MAH argued that the effect of selective anti-VEGF use in the presence of macular edema is unknown. In order to reduce the confounder of macular ischemia in the assessment of the safety and efficacy of pegaptanib sodium in the treatment of DME, this characteristic was excluded from the EOP1005 and EOP1013 study at enrolment. Although, excluded at enrolment, there were no adverse event reports of "Macular ischaemia", "Worsening macular ischaemia" or "Ocular ischaemia" in either study. Macular ischaemia has not been identified as a risk associated with treatment with pegaptanib sodium. Thus there are no data to present.

The CHMP acknowledged that macular ischemia in relation with the use of anti-VEGF compounds as described for bevacizumab, cannot necessarily be extrapolated to pegaptanib which differs from bevacizumab in that it is a pegylated modified oligonucleotide and specifically binds to the VEGF165 isoform. In studies EOP1005 and 1013, subjects with non-perfusion for >1 disc area involving the foveal avascular zone (FAZ - involving 2 or more quadrants centred around the foveal avascular zone) were excluded. Subjects with a lesser, but still significant, degree of retinal ischaemia may thus have been included. The MAH states that this information was not collected when the patient was enrolled in the study and that there is no information available for analysis. However, fluorescein angiograms were captured for the reading centres at baseline (Final protocol for study EOP1013, Appendix 16.4: Color fundus photography and Fluorescein angiography) for EOP1013, while change in macular capillary loss was evaluated in study EOP1005). Thus the requested information should in the view if the CHMP be possible to extract. The MAH is requested to present data on whether there were any subjects with retinal ischemia included in the two studies and should presented key efficacy (and safety) data from these patients.

- **Treatments**

Pegaptanib sodium (0.3 mg in 90 μl) or sham were given to subjects at 6-week intervals up through 48 weeks in Year 1, and, thereafter, at 6-week intervals, if deemed necessary as per protocol specifications, up through Week 96 in Year 2. Criteria for administering study medication after Week 48 were based on VA, clinical examination, OCT, and the opinion of the Investigator.

Subjects should not be re-treated if: - VA ≥ 20/25, - CRT< 175 μm, - serious adverse event (SAE) that would make immediate injection unwise. If none of the above criteria are met, additional courses of therapy are to be performed after Week 48. If the efficacy (positive risk/benefit) of Macugen is confirmed in the primary 1-year analysis, subjects who have not completed the Week 102 visit will have the option to convert to the Macugen treatment arm or continue their original treatment assignment until Week 102. To maintain the subject masking, subjects will not be informed of his/her treatment arm. The study will continue a 3rd year, in an open-label extension phase. Concomitant treatment with other investigational drugs and with IVT, subconjunctival or subtenon corticosteroid is not permitted. Laser treatment is allowed 1 week after injection (at week 18 or later), but not more often than every 17 weeks unless VA is ≥ 80 letters and OCT central retinal thickness < 175 μm.

- **Objectives**

The objective of this study was to confirm the safety and compare the efficacy of pegaptanib sodium when subjects were given intravitreous injections of 0.3 mg/eye vs. sham injections.

- **Outcomes/endpoints**

Primary efficacy endpoint:

- Proportion of subjects who experience a >10 letter (2-line) improvement in BCVA (ETDRS, 4 meter distance) from baseline at 1 year.

Secondary efficacy endpoints included:

- Proportion of subjects who experience a >10 letter (2-line) improvement in vision (ETDRS) from baseline at 2 years.
- Proportion of subjects with a >15 letter improvement at 1 and 2 years
- Proportion of eyes experiencing a change in the degree of retinopathy by 2 or more steps at 1 and 2 years

- Changes in mean VA over time
- Proportion of subjects requiring focal or grid laser at 1 and 2 years.
- Laser-free survival rates at Year 1 and Year 2

Other efficacy endpoints:
- Proportion of subjects exhibiting a decreased retinal thickness (centre point) by at least 25% and 50% using OCT
- Health related outcome measures e.g. Visual Function Questionnaire (VFQ-25)

The year-two endpoints (Week 102) will be analyzed using only the data from those subjects who have completed the study (Week 102 or Early Withdrawal). Applicable safety and efficacy variables will be evaluated for the year-three extension phase.

The CHMP considered that the primary outcome measure addresses the functional measure VA, not an anatomical measure. This is appropriate. However, the outcome does not match the sought indication which reflects an anatomical change. Consequently, the initially proposed indication was not acceptable.

- **Sample size**

With the assumptions that 15% more pegaptanib-treated subjects over sham will experience a ≥10 letter improvement at 1 year, with a two-sided alpha of 5 % and a power of 85%, 270 evaluable subjects are needed. A total of 300 individuals will be enrolled to account for ineligible or inevaluable subjects.

- **Randomisation**

Subjects will be centrally allocated to one of the two treatment arms (0.3 mg pegaptanib sodium or sham) by a dynamic minimization procedure in a 1:1 ratio, using centre and the following factors: HbA1c (<7.6% vs. ≥7.6%), systemic blood pressure (systolic <140 mm Hg vs. ≥140 mm Hg/diastolic <80 mm Hg vs. ≥80 mm Hg), and baseline visual acuity (VA) (<54 letters vs. ≥54 letters). Four to ten subjects per site were to be provided.

- **Blinding (masking)**

VA measurements were to be performed by examiners masked to the previous VA measurement and treatment assignment. The ophthalmologist who injects the subject must not be the study ophthalmologist (responsible for subject's care), who should remain masked to the subject's treatment (intravitreous pegaptanib sodium vs. sham injection). In the event that the study ophthalmologist must administer the treatment, an ophthalmologist masked to the subject's treatment should assess any adverse events reported during the visit.

The CHMP considered that measures to maintain masking appears reasonable. However, since 20% of subjects had not finalised the 2 years at the time of the MAH submission of the dossier, it was questioned whether the remaining, still ongoing part of the study was remained masked.

- **Statistical methods**

Analysis population:
- Modified Intent-to-Treat (MITT)1: Included all randomised subjects with at least 1 dose of study treatment, who had completed the baseline VA assessment, and had at least 1 post baseline VA within 1 year [excluding subjects from Sites 134 (Pfizer Site 1032) and 77 (Pfizer Site 1035) due to GCP-violations].
- MITT2: As for MITT1, but had completed the Week 102 visit or any visit post Week 102.
- Extended MITT (EMITT): As MITT1, but subjects from sites 134 and 77 were included.
- Per Protocol (PP)1: Subjects from the MITT1 population without any major protocol deviation within 1 year.
- PP2: Subjects from the MITT2 population without any major protocol deviation within 2 years.

Analysis:
Descriptive and summary statistics was to be provided. Missing values would be imputed using the LOCF approach (baseline values are not carried forward). Imputation using the worst observation carried forward (WOCF) will also be applied in the responder analyses.

The primary analysis of the primary efficacy endpoint will be performed on the MITT1 population (LOCF) and confirmed with sensitivity analyses using different populations and different schema to

impute missing values. Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factors will be used to compare the 2 treatment groups; odds ratio and the corresponding 95% CI will be reported for the primary analysis as well as for the other responder analyses.

Laser-free survival rates at Year 1 and Year 2 will be computed using Kaplan-Meier estimates together with the 95% CIs, Log-rank test. The mean change from baseline in BCVA and health related outcomes at Week 54 (MITT1) and Week 102 (MITT2) will be computed with ANCOVA.

In addition, a logistic regression model will be used to explore any prognostic or predictive impact of baseline covariates on the effect of treatment. Clinically meaningful subsets may be explored, including those defined by the covariates used in the stratification procedure.

An interim analysis was initially planned to be performed determine if pegaptanib sodium, at doses of 0.003 mg, 0.03 mg, and 0.3 mg, was efficacious for subjects with DMO after up to 1 year of therapy. This analysis was not completed as the pegaptanib sodium 0.003 mg and 0.03 mg doses were removed from the study (protocol EOP1013D), see further Conduct of study, Protocol amendments.

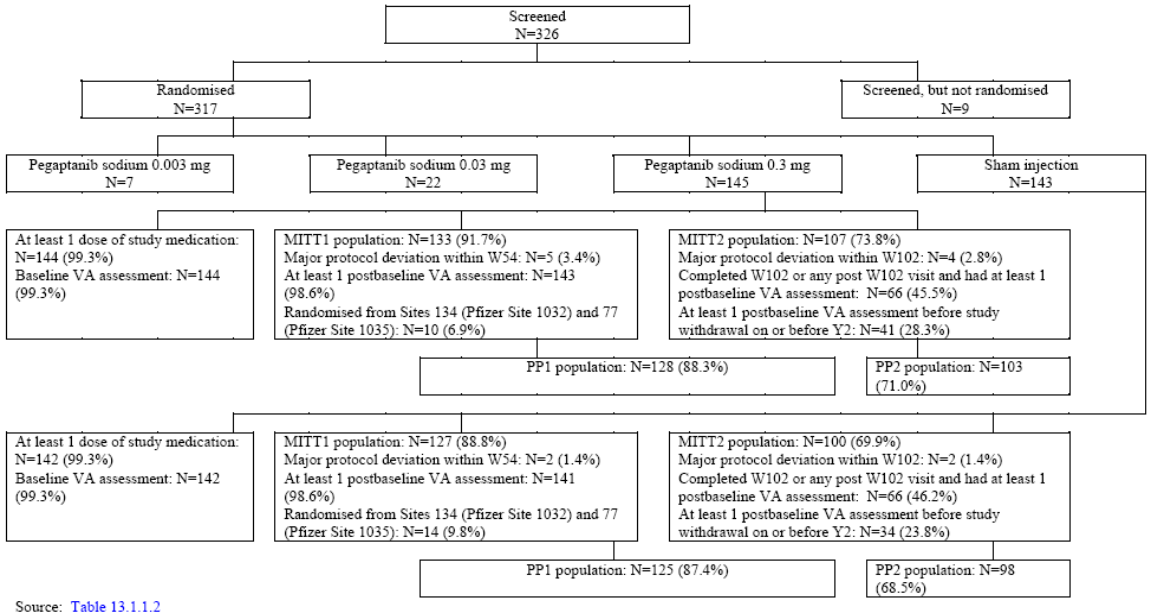
An interim analysis for futility was planned for (protocol EOP1013G) to evaluate the probability of attaining the primary efficacy endpoint (futility) when at least 54 subjects complete the study VA assessment at Week-54 post-baseline. No endpoints were to be analyzed for this purpose however, subject disposition, as well as baseline clinical and demographic information was to be summarised. An efficacy evaluation committee not involved in the activity of the study, was to be given prespecified criterion (probability of success > 80%) to provide Sponsor management with a stop/go recommendation, while the results of the interim analysis were not be shared with anyone outside the committee while the trial was on-going.

The CHMP considered that the statistical plan is reasonable. Given a similar withdrawal rate between arms, the WOCF approach tends to give a conservative estimate in responder analyses. Parts of the protocol amendments give however rise to concern, see further comments to conduct of the study.

Results

- **Participant flow**

Figure 1 Participant flow



Source: Table 13.1.1.2
A major protocol violation was a violation that was considered to be significant enough to remove the subject from analysis.
Abbreviations: MITT = modified intent-to-treat, N = number of subjects, PP = per protocol, VA = visual acuity, W = Week, Y = Year

With regards to the sites (134 and 77) that were excluded from the MITT populations, see Conduct of study.

Table 18 Subject discontinuations

No. of Discontinued Subjects Before Week 54 (MITT1 Population)	Pegaptanib Sodium (0.3 mg) N=133 n (%)	Sham Injection N=127 n (%)
Adverse event	3 (2.3)	3 (2.4)
Protocol violation	0	0
Investigator or Sponsor decision	7 (5.3)	6 (4.7)
Subject request	2 (1.5)	3 (2.4)
Lost to follow-up or subject noncompliance	4 (3.0)	1 (0.8)
Other	1 (0.8)	0
Total	**17 (12.8)**	**13 (10.2)**
No. of Subjects Discontinued Before Week 102 (MITT2 Population)	**Pegaptanib Sodium (0.3 mg) N=107 n (%)**	**Sham Injection N=100 n (%)**
Subjects discontinued before Week 54 (MITT2 Population)		
Adverse event	3 (2.8)	3 (3.0)
Protocol violation	0	0
Investigator or Sponsor decision	7 (6.5)	6 (6.0)
Subject request	2 (1.9)	3 (3.0)
Lost to follow-up or subject noncompliance	4 (3.7)	1 (1.0)
Other	1 (0.9)	0
Total	**17 (15.9)**	**13 (13.0)**
Subjects discontinued after Week 54 and before Week 102 (MITT2 Population)		
Adverse event	4 (3.7)	3 (3.0)
Protocol violation	0	0
Investigator or Sponsor decision	11 (10.3)	11 (11.0)
Subject request	4 (3.7)	4 (4.0)
Lost to follow-up or subject noncompliance	4 (3.7)	2 (2.0)
Other	1 (0.9)	1 (1.0)
Total	**24 (22.4)**	**21 (21.0)**

Source: Tables 13.1.3 and 13.1.4

Besides subjects from sites 134 and 77, the majority of protocol violations included abnormal laboratory data, foveal thickness < 250 μm and use of prohibited intraocular medication.

In the view of the CHMP the discontinuation rates were of an expected frequency and comparable between treatment arms. A relatively high proportion of discontinuations, especially during the 2nd year, were due to the investigator's or sponsor's decision. The CHMMP therefore requested that the MAH should address the reasons behind these decisions.

The MAH explain that in 2007, an internal decision was taken to terminate the trial for all sites in the US; all ongoing patients at those sites were required to discontinue from the protocol. When the site selected Investigator/Sponsor Decision as the reason for discontinuation, it was also to enter a text statement with more specific details. A total of 18 pegaptanib sodium and 17 sham patients discontinued due to Investigator/Sponsor Decision. The majority of patients who discontinued for this reason did so because the trial was closed by the Sponsor, i.e., 11 of 18 pegaptanib sodium and 13 of 17 sham patients.

The CHMP acknowledged the MAH response, but considered that the MAH should investigate whether patients dropping out from the study are different from those remaining in the study, not only in terms of patient characteristics (baseline characteristics) but also in terms of the outcome values observed. For example, is the baseline outcome value of those dropping out from the study during the first year different from the baseline outcome value of the others? Also, is the change at year one from baseline of those dropping out from the study during the second year different from the change at year one from baseline of the others? The interaction between laser therapy and Sham/Pegaptanib Sodium should be formally tested, rather than performing three separate tests comparing the Sham group without laser therapy with each of the other three groups.

Table 19. Subject Evaluation Groups; All Randomised Subjects

No. of Subjects	Pegaptanib Sodium (0.3 mg) N=145 n (%)	Sham Injection N=143 n (%)
All randomised subjects	145 (100)	143 (100)
MITT1 population	133 (91.7)	127 (88.8)
MITT2 population	107 (73.8)	100 (69.9)
PP1 population	128 (88.3)	125 (87.4)
PP2 population	103 (71.0)	98 (68.5)
Safety1 population	144 (99.3)	142 (99.3)
Safety2 population	134 (92.4)	128 (89.5)

Abbreviations: MITT = modified intent-to-treat, N = number of subjects, n = number of subjects meeting specified criteria, No. = number, PP = per protocol

- **Conduct of the study**

Recruitment: First Subject Visit: 26 September 2005; Last Subject Visit: 20 November 2009 (date of data cut-off); Final Signoff Date: 01 April 2010

Protocol amendments: The protocol (EOP1013, 21 June, 2005) was amended 7 times (Amendments EOP1013B through EOP1013H). The majority of amendments were related to changes in visits, examinations, inclusion/exclusion criteria and study duration. In amendment EOP1013D (18 September 2006) major changes were introduced:

- Pegaptanib 0.003 mg and 0.03 mg doses were removed from the study, subjects were given the option of either receiving pegaptanib 0.3 mg/eye or withdrawing from the study. Subjects electing to receive the injections (n=29) were not included as part of the efficacy population, but were included in the safety population. Sample size changed from 816 to 270 evaluable subjects. The lower dose groups were discontinued since they were chemically unstable. The FDA and EMA were apprised of this situation, and concurred with the removal of the 0.03 and 0.003 mg doses of pegaptanib sodium from study in this protocol.
- Change of primary endpoint from 3 lines to 2 lines gain in VA.

In amendment EOP1013H (Pfizer Protocol A5751013, March 2009) an addition of the provision for sham-injection subjects remaining in the 2-year study to convert to pegaptanib for the remainder of the study was introduced.

The interim analysis for futility was performed on 70 subjects (EOP1013G). The EEC met in June 2008 and recommended that the study continue. The actual 80% criterion has not been disseminated outside those immediately responsible for the study at Pfizer as the study continues.

During routine monitoring at Sites 134 (Pfizer Site 1032) and 77 (Pfizer Site 1035), suspected significant deviations from GCP were identified. Due to these audit findings, subjects from these sites were excluded from the MITT set for efficacy analyses but included in the safety analyses. The nature of these violations was not found in the initial documentation and the MAH was therefore requested to explain.

The MAH acknowledged that it had identified quality problems (serious GCP-violations like changing CRFs, site 1035 (FR) and baseline source data lost in a flood, site 134 (BR)) and subsequently excluded these from analysis of efficacy. The appropriateness of the MAH to exclude these sites from the main analyses is acknowledged by the CHMP. Although the MAH made additional audits in 2 other FR centres and one centre in each of DE, UK and PT without identifying additional violations, the MAH's routines to guarantee an adequate level of quality at the many study centres (56 centres for 260 patients) needs to be further reassured. It is also surprising to the CHMP that the major CZ centre that included 16% of subjects was not part of the additional audits. It was therefore considered by the CHMP that a GCP-inspection would give further reassurance of the quality of the study.

The SAP (v. 1.0) was written at the time of Protocol Amendment EOP1013G and v. 2 was written at the time of Protocol Amendment EOP1013H; both versions of the SAP were written to reflect the changes in the protocol. V. 3.0 of the SAP was written to exclude subjects from Sites 134 (Pfizer Site 1032) and 77 (Pfizer Site 1035). V. 4 of the SAP was written to detail the analyses of the CSR. The most recent version of the SAP (v. 5.0) was written to reflect the change in PP populations (i.e., PP1 and PP2).

The CHMP concluded that with regards to the amendment D, the rationale behind discontinuing the lower dose groups have been clarified, however, the reason for changing the primary endpoint is not clear and the lack of transparency is a major concern. In addition, this amendment is contradictory to the statement in the Clinical Overview that the study is still being masked and that the full 2-year data are expected in July (see Safety). The data were made public in June 2010. A GCP-inspection is warranted. In amendment H, subjects in the sham group were allowed to cross over to active treatment. It is a risk that there will be a selection of subjects that crosses over, i.e. those who are better tend to favour treatment. It is also not clear how these subjects have been analysed. It further appears that the first version of the SAP was written while the study was ongoing and after major amendments, including the change of the primary endpoint, was introduced. This appears somewhat late. The CHMP further requested the MAH to discuss the reasons for decreasing the planned sample size dramatically (from 816 to 270) and how this could have influenced the overall results and statistical significance of the trial.

In response the MAH further explained the flow of subjects that crossed over to receive pegaptanib treatment. In total, four subjects converted from sham to pegaptanib-treatment after the original study report was completed and were not included in the 2-year assessment of efficacy while they were included in the sham treatment group until the visit at which these patients converted to active treatment. Efficacy data for these subjects are stated to be included in the supplemental CSR but were not found in the response submission, however, since only 4 subjects converted, this is not likely to add significant information and the response is deemed acceptable by the CHMP. However, it is highlighted by the CHMP that the requested full study report was not submitted as response to the LoQ. In conclusion the CHMP considered that although the full 2-year study report hasn't been submitted, the response is considered acceptable.

- **Baseline data**

Table 20. Demographic Characteristics and Diabetes History; MITT1 Population

No. of Subjects		Pegaptanib Sodium (0.3 mg) N=133 n (%)	Sham Injection N=127 n (%)
Sex	Male	81 (60.9)	68 (53.5)
	Female	52 (39.1)	59 (46.5)
	Treatment comparison (Chi-square test): p-value = 0.2305		
Race	Caucasian/White	104 (78.2)	107 (84.3)
	Asian	13 (9.8)	15 (11.8)
	Black	3 (2.3)	2 (1.6)
	Hispanic/Latino	8 (6.0)	3 (2.4)
	Other	5 (3.8)	0
	Treatment comparison (Chi-square test): p-value = 0.1107		
Age (years)	Mean	62.3	62.5
	SD	9.33	10.22
	Median	62.0	63.0
	Range	28;83	20;80
	N	133	127
	Treatment comparison (T-test): p-value = 0.8731		
ECOG performance status	0	65 (48.9)	67 (52.8)
	1	66 (49.6)	57 (44.9)
	2	2 (1.5)	3 (2.4)
	3	0	0
	4	0	0
	Treatment comparison (Chi-square test): p-value = 0.6870		
Baseline smoking status	Active	6 (4.5)	10 (7.9)
	Not active	127 (95.5)	117 (92.1)
	Treatment comparison (Chi-square test): p-value = 0.2594		
Type of diabetes	Type I	10 (7.5)	8 (6.3)
	Type II	123 (92.5)	119 (93.7)
	Missing	0	0
	Treatment comparison (Chi-square test): p-value = 0.6986		
Diabetes medication	None	0	0
	Oral	53 (39.8)	55 (43.3)
	Insulin	40 (30.1)	44 (34.6)
	Oral and insulin	40 (30.1)	28 (22.0)
	Missing	0	0
	Treatment comparison (Chi-square test): p-value = 0.3316		
Duration of vision problems in the study eye related to diabetes	None	1 (0.8)	0
	<1 year	53 (39.8)	50 (39.4)
	1-5 years	67 (50.4)	68 (53.5)
	6-10 years	9 (6.8)	7 (5.5)
	≥11 years	3 (2.3)	2 (1.6)
	Missing	0	0
	Treatment comparison (Chi-square test): p-value = 0.8430		

N = number of subjects, n = number of subjects meeting specified criteria

Table 21. Baseline VA Score; MITT1 Population

Study Eye; MITT1 Population			
No. of Subjects		**Pegaptanib Sodium (0.3 mg) N=133 n (%)**	**Sham Injection N=127 n (%)**
Visual acuity score (number of letters)	Mean	57.0	57.5
	SD	8.85	8.11
	Median	60.0	60.0
	Range	35;73	35;70
	N	133	127
Distribution of approximate Snellen equivalent[a]	Better than 20/40	1 (0.8)	0
	20/40	1 (0.8)	3 (2.4)
	20/50	41 (30.8)	33 (26.0)
	20/63	33 (24.8)	42 (33.1)
	20/80	23 (17.3)	17 (13.4)
	20/100	7 (5.3)	14 (11.0)
	20/125	17 (12.8)	7 (5.5)
	20/160	5 (3.8)	4 (3.1)
	20/200	4 (3.0)	6 (4.7)
	Worse than 20/200	1 (0.8)	1 (0.8)

[a] VA score within the range of 70 to 35 is equivalent to Snellen score within the range of 20/40 to 20/200.

Baseline ocular and non-ocular concomitant medications as well as baseline ocular disorders were balanced between treatment arms. In the pegaptanib and sham treatment arm, 61 and 64 % of subjects had had a previous laser treatment.

The distribution of stratification factors were, with the exception of baseline VA scores (70 % of subjects in the sham group had a VA score ≥54 letters vs. 63 in the pegaptanib group), nearly equal between the treatment groups.

Table 22 Summary of ophthalmic history at baseline.

Number of Subjects System organ class and Preferred term (MedDRA v 12.0)	Macugen N=133	Sham N=127
Subjects with at least one ocular disease	133 (100%)	127 (100%)
Congenital, familial and genetic disorders	1 (0.8%)	1 (0.8%)
Corneal dystrophy	1 (0.8%)	1 (0.8%)
Eye disorders	133 (100%)	127 (100%)
Diabetic retinal oedema	120 (90.2%)	115 (90.6%)
Diabetic retinopathy	103 (77.4%)	92 (72.4%)
Cataract	52 (39.1%)	48 (37.8%)
Macular oedema	23 (17.3%)	24 (18.9%)
Retinal exudates	23 (17.3%)	21 (16.5%)
Retinal haemorrhage	16 (12.0%)	15 (11.8%)
Retinal aneurysm	13 (9.8%)	13 (10.2%)
Glaucoma	3 (2.3%)	7 (5.5%)
Maculopathy	5 (3.8%)	3 (2.4%)
Open angle glaucoma	4 (3.0%)	2 (1.6%)
Blepharitis	2 (1.5%)	3 (2.4%)
Iris atrophy	2 (1.5%)	3 (2.4%)
Retinal vascular disorder	2 (1.5%)	3 (2.4%)
Dry eye	2 (1.5%)	2 (1.6%)
Eyelid ptosis	3 (2.3%)	1 (0.8%)
Macular degeneration	3 (2.3%)	1 (0.8%)
Posterior capsule opacification	3 (2.3%)	1 (0.8%)
Retinal neovascularisation	3 (2.3%)	1 (0.8%)
Vitreous detachment	2 (1.5%)	2 (1.6%)

Source: Table 13.2.3.1

Baseline CRT was 442±148 and 464±136 μm in the pegaptanib and sham treatment arm, respectively.

Baseline demographics were fairly balanced, but also in this study a number of subjects with a better baseline VA than defined in the inclusion criteria were enrolled. These were however few and do not likely impact the overall outcome of the study.

With regards to the presentation of ophthalmic disease history, a presence of DME would be expected in 100% of the population and it is surprising that only 90 % of included subjects were regarded to have diabetic retinal oedema, ~75% had diabetic retinopathy and ~ 18% had macular oedema. The

definition of these terms in relation to the inclusion criteria should be clarified as well as the proportion of subjects with focal/diffuse DME. It is assumed that, but not clear that at least parts of diabetes-related vision problems displayed in Table 20 were related to DME, i.e. the indication applied for, however, the CHMP requested the MAH to confirm whether these problems were due to DME, and if not, the duration of DME should be presented. The mean age was 62 years. The CHMP therefore requested that the MAH should discuss the extrapolation of the results to the very old DM population, since the effect of treatment with Macugen appeared better in younger patients as discussed below. In addition, most of the population had vision score of 35-65 (Snellen equivalent 20/200-20/50): the MAH was subsequently requested to include this as well in the proposed indication.

In response, the MAH provided results from subgroup analysis of proportion of responders at week 54 by age and change in VA stratified by age. The CHMP acknowledged that potential differences in treatment effects amongst different age groups have been studied using subgroup analyses (<62 years, >=62 years).However, not only may the reduced sample sizes imply lack of power, the results may severely depend on the chosen cut-off value of 62 years. An alternative analysis would be to test for the presence of an interaction between age and Sham/Pegaptanib. The MAH was therefore requested by the CHMP to perform this analysis.

Regarding the CHMP request to the MAH to justify or reconsider the sought indication the MAH argued that DME is an important visual consequence of abnormal retinal vascular permeability in diabetic retinopathy. DME is defined by anatomic features which include retinal thickening (RT) with or without lipid exudates, and with or without cystoid changes. The MAH further acknowledged that it is apparent in the ophthalmic community that differing opinions exist regarding the association between visual acuity and retinal thickness. Although OCT measurements of retinal thickness represent an important tool in clinical evaluation, these measurements serve as one of several factors that evaluate the DME disease process in this complex, and not yet fully understood disease. The strength of correlation between OCT and Visual Acuity varies widely. The vision criteria were selected as an endpoint by the MAH in the 1013 study in an effort to appreciate and assess the efficacy of pegaptanib, Vision variables are well accepted as the most clinically meaningful measures of the patients disease process; however, they should not be evaluated in isolation from the disease process. For the reasons cited above, the MAH was of the opinion that the data justify the indication of Diabetic Macular Edema.

The CHMP acknowledged that the use of a combination of different techniques for the diagnostic work-up of the ocular complications in DM is good.

However, the CHMP considered that there are still unresolved uncertainties as follows:

- Conflicting data on the relationship between visual acuity and ocular coherence tomography measurements.
- No clear-cut endpoint was validated for the evaluation of DME before the start of the clinical studies.

The MAH further sought justification for the treatment of "diabetic" ME in the scientific literature, quoting the effects of VEGF165 on vascular leakage and blood retinal barrier breakdown and the effect (which is questionable) of pegaptanib in clinical studies. Results claimed in this regard are the trends and statistically significant findings obtained for secondary and other endpoints (DR, QoL). The MAH justifies a broader target population in order not to preclude any patients from treatment with a potentially beneficial product. This justification is not considered acceptable by the CHMP. The effect of pegaptanib has only been studied in subjects with an impaired VA due to DME and there is no information on the short and long-term benefit/risk in subjects with DME without VA loss. The sought indication should consequently be restricted to treatment of visual impairment due to DME.

Overall, the CHMP consider, in opposition to the MAH, that there is no objective effect on DME, and that the indication has to be limited to patients with visual loss secondary to DME to correlate with the population evaluated in EOP1003.

- **Outcomes and estimation**

Extent of exposure

Table 23 Number of IVT Injections Administered in the MITT1 Population

Number of Patients		**Pegaptanib N=133 n (%)**	**Sham N=127 n (%)**
Number of injections	Mean (SD)	8.3 (1.67)	8.4 (1.44)
	Median	9.0	9.0
	Range	1 – 9	2 – 9
Treatment duration (weeks)	Mean (SD)	45.0 (10.09)	45.6 (8.32)
	Median	48.1	48.1
	Range	0 – 52	6 – 51
Mean time between 2 injections (weeks)	Mean (SD)	6.2 (0.397)	6.2 (0.607)
	Median	6.0	6.0
	Range	5.0 – 8.0	5.8 – 10.0

In the MITT2 set, the mean number of injections (Day 0 to Week 102) was 12.7 ±4.6 (range 1-17, median 14) injections for the pegaptanib group, and 12.9 ±4.4 (range 2-17, median 15) for the sham group. The mean treatment duration was 74 (median 90) weeks and the mean time between injections remained close to 6 weeks (mean 6.4±0.7, range 5-10, median 6) in both treatment arms.

Primary endpoint

Table 24. Proportion of patients with ≥ 10 and ≥ 15 letters gain in vision compared to baseline at Week 54 (MITT1) and Week 102 (MITT2 for the subgroups:

MITT1	**Sham (N = 127)**		**Pegaptanib Sodium (N=133)**	
≥ 10 letter gain w .54	**No Laser (n=74)**	**Laser (n=53)**	**No Laser (n=102)**	**Laser (n=31)**
	10 (13.5%)	15 (28.3%)	37 (36.3%)	12 (38.7%)
P-Value vs. Sham/No Laser		0.0738	0.0030	0.0194
MITT2	**Sham (N = 100)**		**Pegaptanib Sodium (N=107)**	
≥ 10 letter gain w.102	**No Laser (n=55)**	**Laser (n=45)**	**No Laser (n=80)**	**Laser (n=27)**
	12 (21.8%)	18 (40.0%)	32 (40.0%)	9 (33.3%)
P-Value vs. Sham/No Laser		0.0572	0.0121	0.2639
MITT1	**Sham (N = 127)**		**Pegaptanib Sodium (N=133)**	
≥ 15 letter gain w .54	**No Laser (n=74)**	**Laser (n=53)**	**No Laser (n=102)**	**Laser (n=31)**
	4 (5.4%)	9 (17.0%)	18 (17.6%)	4 (12.9%)
P-Value vs. Sham/No Laser		0.0454	0.0295	0.3996
MITT2	**Sham (N = 100)**		**Pegaptanib Sodium (N=107)**	
≥ 15 letter gain w.102	**No Laser (n=55)**	**Laser (n=45)**	**No Laser (n=80)**	**Laser (n=27)**
	2 (3.6%)	13 (28.9%)	18 (22.5%)	7 (25.9%)
P-Value vs. Sham/No Laser		0.0007	0.0014	0.0314

The proportion of subjects improved was significantly larger in the pegaptanib group at each time point except for at weeks 18 and 48 (2/9 time points), but numerically in favour of pegaptanib at all time

points. Analyses with and without adjustment for stratification factors did not affect the outcome of the study.

The CHMP considered that at the end of the first treatment year there was a statistically significant and clinically meaningful effect in favour of pegaptanib, with approximately 17 % more pegaptanib-treated subjects that gained ≥ 10 letters in VA compared to sham. The outcome of the primary analysis (MITT1) is supported by analyses of the PP population and of analyses using WOCF, i.e. imputing missing data as failures which points to a robustness of data. However, the CHMP considered it questionable whether the outcome in this trial may be possible to extrapolate to the intended target population as the inclusion/exclusion criteria restricted the study population.

The CHMP further considered that the available 2-year results are of concern. The difference in the primary endpoint is no longer statistically significant. A number of sham-treated patients had improvement in VA, perhaps due to laser therapy or to other factors that the MAH is invited to discuss. In addition, a relatively high proportion of discontinuations, especially during the 2nd year, were due to the investigator's or sponsor's decision. The reasons for these decisions should be further addressed. Overall, the full 2-year results should be provided and extensively discussed. It should be made clear if these results were obtained in a blinded fashion. The CHMP is concerned that the 2-year results may not confirm the 1-year results, which would be considered a serious shortcoming in this type of setting.

In response, the MAH acknowledged that that the primary endpoint of the trial was the proportion of patients who experienced a ≥ 10 letter gain in VA at Week 54 of the trial, and the study was powered to detect a difference between pegaptanib sodium and sham treatment at this time point. The study was not powered, however, to detect this difference at Week 102. In addition to the study not being powered for Week 102 differences, the lack of significance between treatment groups at the end of Year 2 may have been due to the increase in VA in the sham treatment group. In study EOP1013 there is an increase in the proportion of sham-treated patients that gain >10 and >15 letters. There may be several reasons for these findings including the use of laser treatment after Week 18 in this trial, as well as good metabolic control. Regarding the secondary endpoint data presented in the 11 June 2010 Clinical Study Report (CSR), although the study was not powered to detect significant treatment differences at endpoints other than the primary at Week 54, the majority of measures of VA over the course of the study, the degree of retinopathy, and Quality of Life data reinforced the conclusions of the primary endpoint. In summary, the MAH is of the opinion the 2-year data support and confirm the Week 54 primary endpoint of the trial, i.e., that pegaptanib sodium is significantly superior to sham treatment. The 2-year data display strong trends in the effectiveness of pegaptanib sodium in maintaining improvement in visual acuity and the overall status of diabetic retinopathy and in decreasing the need for laser therapy. The results and conclusions of the June CSR are supported by the Supplemental Study Report 1. These results taken together illustrate the greater effectiveness of pegaptanib sodium versus sham treatment; this effectiveness is clinically meaningful and is maintained up through Week 102.

The methodological flaws of this study were acknowledged by the CHMP:

- The study was not designed to have power to demonstrate differences at the end of year 2.
- There were confounding factors.
- The drop out rate, especially during the second year, has to be taken into account.

The MAH proposes the increase in visual acuity (by laser therapy or good diabetic control status) in the sham treated patients, as an explanation for the loss of significance for the proportion of subjects who experience a > 10 letter (2-line) improvement in vision between treatment groups at year two. This is possible, although not formally proved. The MAH suggests that the 2 year results support the idea that pegaptanib is statistically superior to sham treatment. However, the difference in visual acuity during 106 weeks of follow-up is never higher than 5 letters between pegaptanib and sham group. That represents less than a single snellen line and is not considered clinically relevant. The CHMP therefore does not believe that the 2-year data support the 1-year results.

Full 2-year data: The submitted study report linked to the response still has a cut-off data as per November 20, 2009 – i.e. as in the original submission. Updated report, even though the MAH summarises the full data and refers to an update, could not be found in the MAH's response. A supplementary report discussing the > 10 letter improvement in vision (primary and secondary endpoint) for the entire study duration until 04 June 2010 should therefore be provided.

High proportion of discontinuations due to the investigator's or sponsor's decision: The MAH has explained that the majority of these subjects discontinued because the MAH's internal decision to terminate the trial for all sites in the US. This decision is surprising, in view of these centres being part

of a pivotal study. The CHMP therefore considered that a GCP-inspection is required to address this issue.

As discussed earlier in this report the CHMP also considered that the MAH should further investigate whether patients dropping out from the study are different from those remaining in the study, not only in terms of patient characteristics (baseline characteristics) but also in terms of the outcome values observed. Masking of data during Year 2: The statement in the clinical overview submitted with the original application that the study was still being masked and that the full data were expected in July did not agree with the presentation of the study that was made public in June (WOC, June 4 2010). The MAH has explained that although results of the trial were presented at the WOC, the sites participating in the trial remained masked to each subject's individual treatment assignment and that Principal Investigators will not receive the unmasked treatment assignment until the trial is fully closed in 2011.

Following the results of the pivotal trial, whereby the effect of laser therapy was much more marked in the sham patients than in the pegaptanib arm, there are concerns in the CHMP regarding how pegaptanib should be used in relation to conventional laser therapy and this must be addressed by the MAH. The MAH should explore the options to further address how Macugen should be used in relation to laser photocoagulation. A three armed study comparing Macugen plus laser, Macugen as monotherapy, and laser therapy alone (including escape options to VEGF-inhibitory) may be considered. The MAH was therefore requested by the CHMP to discuss this option and commit to investigate this further.

Secondary endpoints

Table 25. Key secondary endpoints.

Mean BCVA (letters) change from baseline, MITT / LOCF (Tables 13.4.4.1-2)			
Week 54		**Pegaptanib N=133**	**Sham N=127**
	Mean (SD)	5.2 (9.9)	1.2 (11.8)
	95% CI for difference	(1.25, 6.54)	
	Odds ratio	3.90	
	p-value	0.0040	
Week 102		**N=107**	**N=100**
	Mean (SD)	6.1 (10.6)	1.3 (12.0)
	95% CI for difference	(1.86, 8.01)	
	Odds ratio	4.94	
	p-value	0.0018	

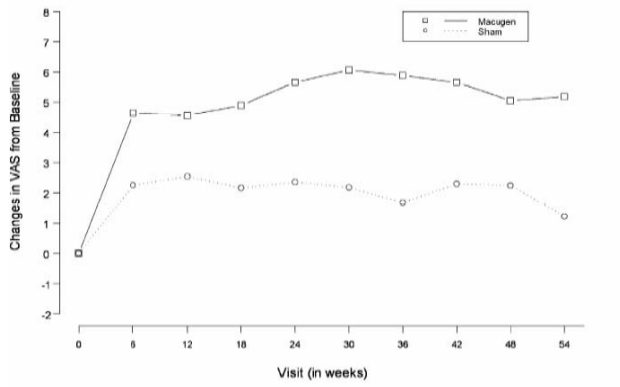
Proportion of Subjects With a Gain of ≥10 Letters of Vision at Week 102			
No. of Patients	**Pegaptanib N=107** n (%)		**Sham N=100** n (%)
Evaluable patients (LOCF, MITT2)	n=107		n=100
Gain of ≥10 letters:	41 (38.3)		30 (30.0)
Pegaptanib vs. Sham	Odds Ratio	95% CI	p value[1]
	1.57	(0.83, 2.97)	0.1729
No. of Patients	**Pegaptanib N=103** n (%)		**Sham N=98** n (%)
Evaluable patients (LOCF, PP2 population)	n=103		N=98
Gain of ≥10 letters:	41 (39.8)		31 (31.6)
Pegaptanib vs. Sham	Odds Ratio	95% CI	p value[1]
	1.50	(0.80, 2.80)	0.2075

[1] CMH adjusted for HbA1c, systolic BP, diastolic BP, and baseline VA

The proportion of subjects improved with ≥ 10 letters over the 2 years, was numerically larger in the pegaptanib group at each time point and statistically significant at 8/17 time points, however not at week 102.

Figure 2. Key secondary endpoint: Change in Visual Acuity Score From Baseline Over Time (LOCF); MITT

Week 54 (MITT1)



Week 102 (MITT2)

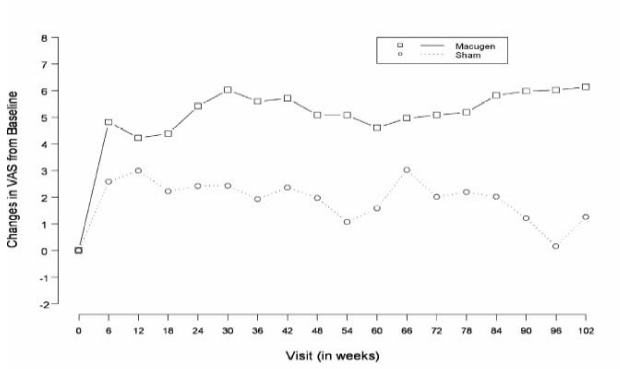


Table 26 Selected secondary and additional endpoints

Parameter	Statistic	Macugen	Sham
Proportion of Subjects with ≥15-Letter Improvement in VA, MITT/LOCF (Tables 13.4.2.1-2)			
Week 54		**N=133**	**N=127**
	Gain of ≥ 15 letters	22 (16.5%)	13 (10.2%)
	95% CI for difference	(0.74, 3.34)	
	Odds ratio	1.57	
	p-value	0.2466	
Week 102		**N=107**	**N=100**
	Gain of ≥ 15 letters	25 (23.4%)	15 (15.0%)
	95% CI for difference	(0.80, 3.58)	
	Odds ratio	1.70	
	p-value	0.1582	
Proportion of Subjects Requiring Focal or Grid Laser, MITT / LOCF (Tables 13.4.5.1-2)			
By end of Week 54		**N=133**	**N=127**
	Focal/grid laser received[a]	31 (23.3%)	53 (41.7%)
	95% CI for difference	(0.24, 0.74)	
	Odds ratio	0.42	
	p-value	0.0023	
By end of Week 102		**N=107**	**N=100**
	Focal/grid laser received[a]	27 (25.2%)	45 (45.0%)
	95% CI for difference	(0.22, 0.75)	
	Odds ratio	0.41	
	p-value	0.0032	
Proportion of Subjects with loss of VA, MITT / LOCF (Table 13.5.1.1-2)			
Week 54		**N=133**	**N=127**
	Loss of ≥ 15 letters	5 (3.8%)	9 (7.1%)
	Loss of ≥ 10 letters	4 (3.0%)	8 (6.3%)
Week 102	Loss of ≥ 15 letters	4 (3.7%)	9 (9.0%)
	Loss of ≥ 10 letters	4 (3.7%)	7 (7.0%)
Decrease in retinal thickness at the centre point by ≥25% MITT / LOCF (Tables 13.5.3.1.1-2)			
Week 54 Evaluable subjects		**N=123**	**N=118**
	Decrease in retinal thickness, proportion	39 (31.7%)	28 (23.7%)
	p-value	0.3489	
Week 102 Evaluable subjects		**N=99**	**N=92**
	Decrease in retinal thickness, proportion	40 (40.4%)	41 (44.6%)
	p-value	0.2871	
Proportion with a Change in the Degree of Retinopathy by ≥2 Steps MITT / LOCF (Tables 13.4.3.1-3)			
Week 54 Evaluable subjects		**N=98**	**N=97**
	Increase in retinopathy severity score by ≥2 steps	4 (4.1%)	12 (12.4%)
	95% CI for difference	(0.07, 0.99)	
	Odds ratio	0.27	
	p-value	0.0468	
Week 102 Evaluable subjects		**N=80**	**N=80**
	Increase in retinopathy severity score by ≥2 steps	5 (6.3%)	11 (13.8%)
	95% CI for difference	(0.15, 1.60)	

	Odds ratio	0.48	
	p-value	0.2295	
Week 54 Evaluable subjects		**N=98**	**N=97**
	Decrease in retinopathy severity score by ≥2 steps	10 (10.2%)	3 (3.1%)
	95% CI for difference	(0.73, 11.55)	
	Odds ratio	2.90	
	p-value	0.1124	
Week 102 Evaluable subjects		**N=80**	**N=80**
	Decrease in retinopathy severity score by ≥2 steps	13 (16.3%)	3 (3.8%)
	95% CI for difference	(1.02, 14.57)	
	Odds ratio	3.86	
	p-value	0.0296	

[a] Included focal laser coagulation, focal laser photocoagulation, panretinal laser photocoagulation, retinal laser coagulation, and retinal laser photocoagulation as per MedDRA (v12.0) lower level terms

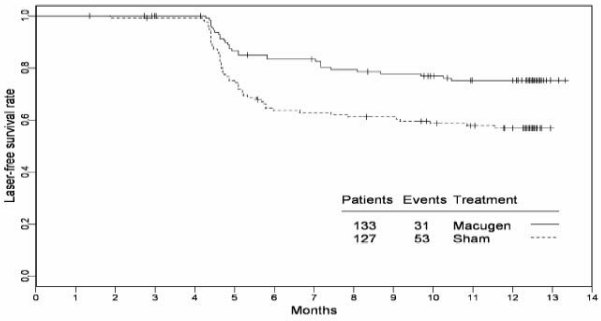
Retinal thickness, as measured by OCT, showed positive trends (numerical decrease in the Macugen group) although no statistically significant difference was observed between both treatment groups. The MAH suggests that the relative retinal thickness may be impacted by laser use, that this relationship remains an area of controversy, and that the clinical value of retinal thickness relative to VA remains a topic of discussion in ophthalmology. Nevertheless, the absence of significant decrease in retinal thickness, which is supposed to be the mechanism of action of pegaptanib sodium, remains a concern and the CHMP requested that it should be discussed in greater length by the MAH.

In the response, regarding the absence of objective effect on oedema, the MAH elaborated on the absence of direct relations between OCT oedema measures and visual acuity. This is known in the literature; one of the reasons is that in atrophy, retina becomes very thin while vision becomes very low. However, that does not mean that a drug might increase visual acuity in macular oedema without reducing the volume of the oedema. In the view of the CHMP, anti-VEGF therapy is not associated to any biological protective effect. In addition, other anti-VEGF agents used in the same indication induce a significant reduction in retinal thickness (Massin P et al, Diabetes Care, 2010, 33, 2399-2405). The MAH did not explain why, if pegaptanib is really reducing blood retina barrier permeability, there is no effect on objective measures of oedema (which currently are only performed with OCT machines). This remains a real concern to the CHMP and the MAH was requested to further comment.

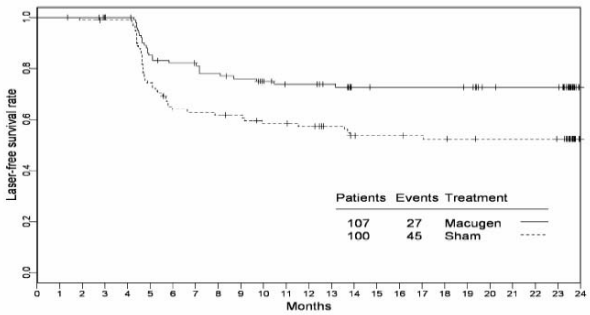
Laser-free survival rate for pegaptanib (75.3%) was statistically significantly better than sham (56.9%) at Year 1 (p=0.0015). Similarly, laser-free survival rate for pegaptanib (72.6%) was significantly better than sham (52.4%) at Year 2 (p-value=0.0042), see Figure 3 below.

Figure 3.

Laser-Free Survival Rate Within 1 Year Post baseline; MITT1 Population



Laser-Free Survival Rate Within 2 Year Post baseline; MITT2 Population



The mean number of laser treatments were 0.3±0.56 and 0.6±0.75 during the first year, 0.2±0.48 and 0.2±0.57 additional treatments during weeks 54 to 102 in the pegaptanib and sham arm, respectively

During the 2nd year, the benefit with regards to the mean change in VA vs. baseline remained in favour of pegaptanib treatment. However, the difference in treatment difference between pegaptanib- and sham-treated subjects in terms of proportion subjects that gained ≥ 10 letters in VA was reduced due to an (unexpected) improvement in the sham group while the proportion of pegaptanib-treated subjects remained stable. This gives rise to questions regarding the included patient population – were parts of the population too healthy. The mean difference in VA between both treatment groups across the study is less than 5 letters, which the CHMP considered to be barely clinically significant or at least not impressive.

Health related questionnaires

For the NEI-VFQ-25, there was no, or a very limited effect on some of the parameters, however, for others like distance vision activities and social function, pegaptanib was statistically and clinically (> 5 units difference) in favour of sham. No beneficial effects of pegaptanib were observed in the Quality of Life (EQ-5D) questionnaire.

- **Ancillary analyses**

Subset analyses

A logistic regression model on the primary efficacy variable was carried out to explore the predictive impact of the stratification factors (HbA1c, systolic and diastolic blood pressure, baseline VA stratifications) as well as other prognostic factors or baseline covariates, including age, race, gender, country, duration of diabetes, type of diabetes, prior laser treatment, baseline RT in OCT centre point, baseline RT in OCT central subfield, and baseline total macular volume on the effect of treatment (as patients were randomised to receive).

The independent covariates, treatment group ($p = 0.0062$), age ($p = 0.0058$), baseline VA ($p = 0.0187$), and baseline total macular volume ($p = 0.0020$) were selected from the backward selection procedure. With a 1 year increase in age, the expected odds of patients with ≥10 letter improvement in VA would be decreased (expected odds ratio 0.951, 95% CI of 0.918, 0.986). With a 1 letter increase in baseline in VA, the mean odds of patients who had ≥10 letter improvement in VA would be decreased (odds ratio 0.946, 95% CI 0.903, 0.991). With a 1 mm3 increase in baseline macular volume, the mean odds of patients who had ≥10 letter improvement in VA would be decreased (mean odds ratio 0.716, 95% CI 0.580, 0.885).

A better treatment effect was indicated in younger subjects and for subjects with a worse VA or a larger macular volume. Other parameters did not appear to have any impact. However, outcomes based on covariates on a continuous scale are difficult to interpret. For example, at which age, VA or macular volume is there no clinical relevant benefit of treatment (taking the risks into account)?

- **Choice of dose and dosing frequency**

Dose: The dose-range finding study EOP1005 investigating the efficacy of 0.3, 1 and 3 mg doses of pegaptanib generally showed a treatment effect of the 0.3 and 1 mg dose in favour over sham and 3 mg with the 0.3 mg dose tended to be slightly better. Although no safety concerns for the treatment of DME patients with pegaptanib were identified in this study, the pivotal Phase 3 study aimed to explore the lower doses, also including 0.003 and 0.03 mg. However, it was found that the 0.003 and 0.03 mg pegaptanib formulations were chemically unstable. The potential for lower doses was further evaluated using a simulation of the concentrations of pegaptanib sodium in human vitreous humour which suggested that 0.03 or 0.003 mg of pegaptanib would not be sustained at the concentrations (≥1 µg/mL) believed to be effective for the duration of the proposed dosing interval (6 weeks) while the 0.3 mg dose would maintain the vitreal concentrations above this level throughout the inter-dose interval.

Dosing frequency

Previous preclinical studies and simulations formed the basis for the 6 week dosing interval, i.e. predicted concentrations of pegaptanib in the vitreous humour 7 weeks after dosing with 0.3 mg/eye would be ≥ 1 µg/ml in > 50% of the patients, which is a concentration equivalent to the EC90 for suppressing VEGF-induced vascular permeability in a guinea pig model, and is in excess of concentrations needed to suppress VEGF-induced neovascularisation in the cornea and retina.

Directly observed changes in VA following missed doses of pegaptanib were obtained from Study EOP1013. The 14 patients that did not receive pegaptanib on 2 consecutive occasions (12 weeks) during the 2nd year, only 1/14 patients lost ≥5 letters in VA. Two of the 4 patients who lost VA after the first dose got worse after having not received the second dose. A similar analysis was made using data obtained from study EOP1005 at the follow up exams (time points equivalent to 16 and 46 weeks after the last dose) and with the disease progression model. Taken together, the observations from Studies EOP1013 and EOP1005 suggest that ~30 - 50% of patients may lose ≥5 letters in VA between 12 and 16 weeks after their last injection. Given the limitations of the disease progression model (see below), it nevertheless suggests that the majority (>70%) of responding patients will lose < 5 letters if one dose is withheld, but 50 % may lose > 5 letters if more than 2 doses are withheld.

Dosing recommendations by stratification of patients into subpopulations based on treatment response: Patients experiencing an average change in VA ≥ 5 letters over 54 weeks of treatment were considered Responders. Patients whose VA changed from 0 to < 5 letters from baseline averaged over 54 weeks of treatment were considered Intermediate Responders while those whose average VA declined from baseline (change in VA < 0 letters) over 54 weeks were considered Non-Responders.

A disease-progression based model (based on data from EIOP1013) of the changes in VA over time was developed and used to estimate the maximum improvement in VA in response to pegaptanib treatment and to aid in determining the number of doses required to achieve a given response level. The mean increase in VA at each dose was determined for the Responding subpopulation, see Table below.

Table 27. Average Increase in VA over Doses 1 Through 5 in the Pegaptanib Responder Subpopulation.

Pegaptanib Dose (No.)	Change in Visual Acuity, Pegaptanib Responders (mean ± SD)	Percent of Maximum Response (Maximum Improvement = 12.9 letters gained)
1	8.82 ± 6.94	68
2	10.2 ± 6.52	79
3	10.9 ± 6.89	85
4	11.7 ± 6.41	90
5	12.9 ± 5.13	100

Source: Regimen for Intravitreal Dosing of Pegaptanib Sodium (Macugen®) in the Treatment of Diabetic Macular Edema, PMAR-00176, Table 2.

The maximum improvement in VA (13 letters) was observed after 30 weeks of treatment, or the fifth dose (significantly different from first dose, maintained for doses 6-7) and almost 80% of the maximum effect was achieved after 2 doses.

In order to better discriminate between Responders and Non-responders after as few doses as possible, subpopulations were combined in an analysis of the proportion of patients who fell into either a ≥5 or < 5 letters of VA gain after each dose of pegaptanib (observed data and the disease progression-based model).

This analysis indicated that after 5 doses, 100% of the potential responding patients would achieve a ≥ 5 letter improvement in VA relative to baseline, while 85% of non-responders would have gained < 5 letters. After fewer (2-4) doses, the probability that a patient in the Non-responder subpopulation would manifest a VA change of < 5 letters remained high (78-90%). However, the probability that a potential responding patient would not manifest an increase in VA ≥ 5 letters after 2 to 4 doses ranged from 19-11%, respectively, with the probability of a "false negative" decreasing with an increasing number of doses, see Table 28. There were no significant differences in probabilities between doses 2 and 3, and 3 and 4 for the Responding population and no significant difference between the probabilities for the Non-Responding subpopulation after any of the doses.

Table 28. Probabilities that Members of Responder/Intermediate and Non-Responder Subpopulations Fall into VA Improvement Categories after each Dose of Pegaptanib (Patients from EOP1013)

Cut-off Criteria	Pegaptanib Sodium Dose (#)	Pegaptanib Sodium Responders (≥5 letters ΔVA)			Intermediate and Non-responders combined (< 5 letters ΔVA)		
		Observed		Predicted	Observed		Predicted
		Proportion	Percentage	Percentage	Proportion	Percentage	Percentage
Pts with ΔVA ≥5 letters	1	44/65	67.7	75.1	14/68	20.6	29.2
	2	53/65	81.5	85.8	15/68	22.1	20.3
	3	56/65	86.2	88.6	14/68	20.6	12.4
	4	58/65	89.2	91.4	7/68	10.3	10.0
	5	65/65	100	92.1	10/68	14.7	8.7
Pts with ΔVA <5 letters	1	21/65	32.3	24.9	54/68	79.4	70.8
	2	12/65	18.5	14.2	53/68	77.9	79.7
	3	9/65	13.9	11.4	54/68	79.4	87.6
	4	7/65	10.8	8.6	61/68	89.7	90.0
	5	0/65	0.00	7.9	58/68	85.3	91.3

Source: PMAR-00176, Tables 3 and 7

Taken together, the analysis suggests that >80% of the patients who stand to benefit from treatment will manifest a VA gain of ≥ 5 letters after no fewer than 2 doses, while the minimum time to achieve maximum benefit (100%) by the greatest number of potential responders (100%) is 5 doses. Conversely, 77.9% of the patients who will ultimately show no sustained benefit from pegaptanib therapy will manifest an improvement in VA of < 5 letters after having received 2 doses.

- **Conclusion on posology**

The MAH recommends (Clinical overview) monitoring patients regardless of whether they are to receive a dose of pegaptanib, and that dosing resumed if there is a significant loss in VA. The MAH proposes the following treatment recommendation in the SPC, section 4.2: *"Macugen 0.3 mg should initially be administered once every 6 weeks into the affected eye, and the patient should be evaluated for clinical benefit after no fewer than 2 doses. Those patients who show a clinical benefit from therapy should continue receiving Macugen at the discretion of the physician. The interval between any subsequent doses should not be shorter than 6 weeks."*

The CHMP concluded that the choice of the 0.3 mg dose also in DME is considered reasonable as it is supported by data and it is clear that lower concentrations of pegaptanib are not feasible. The rationale for monitoring subjects that have been responders and treat those subjects when they lose VA appears reasonable, however, the MAH's recommendation in the clinical overview does not match the information proposed in the SPC, section 4.2. In section 4.2, it is not stated whether re-treatment should be based on a decrease in VA or an increased oedema. Since there was only a modest correlation between an increased oedema and a decreased VA and all assessments and models (all study reports not yet submitted and not assessed, see Clinical Pharmacology) are based on VA, it appears reasonable that re-treatment recommendations are based on a decrease in VA, however, this needs to be further explored. It is also not clear how non-responders should be handled and treatment recommendations, including criteria when to stop treatment, for this group of patients needs to be further discussed. It may also be of value to add the information (to section 5.1 in the SPC) that the minimum time to achieve maximum benefit by the greatest number of potential responders was 5 doses. In addition, it should be further explored whether any of the disease characteristics (DME – type and extent, duration of DME, degree of DR, capillary non-perfusion, previous laser treatment etc) can aid in predicting which patients who are likely to respond/not respond to treatment.

Clinical studies in special populations
N/A

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

Supportive study
N/A

Clinical safety

The primary safety database consists of data from 465 patients in three clinical studies of pegaptanib for DME; 282 patients received pegaptanib, and 183 patients received sham, see table below.

Table 29. Primary safety database: Patient exposure during the DME development programme

Study	Pegaptanib 0.3 mg	Pegaptanib 1.0 mg	Pegaptanib 3.0 mg	Any Pegaptanib Dose	Sham
EOP1002	--	--	10	10	--
(Phase 1b)					
EOP1005	44	42	42	128	41
(Phase 2)					
EOP1013[a]	144	--	--	144	142
(pivotal)					
Total[a]	188	42	52	282	183

[a] Included 10 subjects from Sites 134 (Pfizer Site 1032) and 77 (Pfizer Site 1035) that were not part of efficacy evaluation

In addition, the AE profile in 165 pegaptanib-treated (0.3 mg) AMD-subjects with diabetes have been compared with 1421 AMD-subjects without diabetes as a supportive safety data set.

Study EOP1013 is still ongoing at the time of the MAH submission of this application. The MAH states that the full 2 year data from the remaining 20% of patients yet to reach that time point will be

provided in a Year 2 Supplemental Report, at which time all sponsors, investigators and patients will be unmasked. The full 2 year data are expected to be available by July 2010; the target date for the Year 2 Supplemental Report is November 2010 (during clock stop). A Year 3 Supplemental Report will be provided to confirm the safety profile, including analyses of all safety endpoints and a summary of efficacy endpoints. The 3 year data are expected to be available in July 2011, and the target date for the Year 3 Supplemental Report is January 2012. Given the information above that the two year data have been made public (June 2010), it is not clear to the CHMP how the remaining data that are expected to be available in July 2010 can still be masked.

In response the MAH explained that although results of the trial were presented at the WOC, the sites participating in the trial remained masked to each subject's individual treatment assignment and that Principal Investigators will not receive the unmasked treatment assignment until the trial is fully closed in 2011. This confirmation that the data were obtained in a blinded fashion was acknowledged by the CHMP

Patient exposure
From study EOP1013, the safety database includes 282 patients completed 2 years of treatment with either 0.3 mg pegaptanib sodium or sham and for ongoing patients in this study, routine AEs were reported as of 15 January 2010; deaths and other SAEs reported as of 12 February 2010 were included as part of the safety evaluation. The mean and median numbers of pegaptanib injections administered during the studies were comparable overall when pegaptanib sodium and sham treatment was administered. In the pivotal study, the mean (±SD) pegaptanib and sham injections administered were 13.1±4.3 and 13.2 ±4.4, respectively. More than 85 % of subjects received 8-9 injections during the first year (116 pegaptanib-treated, 109 sham-treated), while 48 and 51 pegaptanib and sham-treated subjects received in total 15-17 injections during the two years.

Less than 300 subjects with DME are exposed to pegaptanib. Although some support is given from AMD-patients with diabetes, the AMD- population has no DME and, likely, a less advanced vascular disease and these patients may not be fully representative for the targeted population. A long-term treatment is foreseen and it is possible that a notable proportion of subjects will receive injections every 6th week. Only 116 subjects have been treated with such frequency (8-9 injections) for 1 year while ~50 subjects have received most of the injections (15-17) for two 2 years. Consequently, the CHMP concluded that safety database is limited. When AEs were assessed by exposure, there did not appear to be any important differences in the incidence or severity of AEs reported with increasing exposure. No new risks associated with the IVT procedure have been identified in the DME program.
However, only a limited number of patients with DME (282) were exposed to Macugen, 144 of whom for at least one year.

Adverse events
In study EOP1002, most AEs were assessed as mild or moderate in intensity (one severe case of reduced VA) although there was a high incidence of increased IOP (7/10). There was one event of retinal microaneurysm, other AEs were similar as previously reported in patients with AMD.

In study EOP1005, the majority of patients in all treatment groups (>90% and 85 % in pegaptanib and sham groups) experienced at least one AE during the study, with ocular AEs being the most common (> 60% in all groups). The number of AEs was higher in the 3 mg treatment group (n=321) than in the 0.3 mg (n=244) or 1 mg (n=225) arms, but was higher in all the active arms than the sham arm (n=167).

In study EOP1013, the proportions of patients who had reports of AEs were overall similar between pegaptanib (83.3%) and sham (91.5%) groups. The majority of AEs were ocular and mostly related to the injection procedure, with most AEs/injection-related complications being mild or moderate in severity. The proportions of pegaptanib (19.4%) and sham patients (19.7%) with reports of severe AEs were comparable.

Below are the incidences of ocular and non-ocular AEs, irrespective of causality that were reported in >1 % of patients in studies EOP1005 and EOP1013 (pooled) that were treated for up to 36 weeks and AEs from available data from study EOP1013 (**Tables 30** and **31**).

Table 30 Incidence of ocular adverse events reported in ≥ 1% of patients in the pegaptanib treatment group in any of the studies, all causalities in subjects included up to week 36, Studies EOP1005 and EOP1013 and from available data (up to Feb 16, 2010) from study EOP1013.

	EOP1005 and EOP1013	**EOP1013**

	Pegap 0.3 mg	Sham	Pegap 0.3 mg	Sham
Number of Patients	**N=188**	**N=183**	**N=144**	**N=142**
Patients with at least one AE	136 (72.3%)	141 (77.0%)	118 (81.9%)	127 (89.4%)
Eye disorders	115 (61.2%)	117 (63.9%)	95 (66.0%)	102 (71.8%)
Conjunctival haemorrhage	31 (16.5%)	17 (9.3%)	32 (22.2%)	20 (14.1%)
Eye pain	29 (15.4%)	15 (8.2%)	16 (11.1%)	10 (7.0%)
Myodesopsia (perception of floaters)	19 (10.1%)	4 (2.2%)	7 (4.9%)	2 (1.4%)
Cataract	18 (9.6%)	11 (6.0%)	12 (8.3%)	13 (9.2%)
Punctate keratitis	18 (9.6%)	16 (8.7%)	18 (12.5%)	9 (6.3%)
Lacrimation increased	13 (6.9%)	7 (3.8%)	8 (5.6%)	4 (2.8%)
Diabetic retinal oedema	12 (6.4%)	18 (9.8%)	16 (11.1%)	26 (18.3%)
Visual acuity reduced	11 (5.9%)	8 (4.4%)	13 (9.0%)	14 (9.9%)
Vitreous opacities	9 (4.8%)	3 (1.6%)	5 (3.5%)	7 (4.9%)
Macular oedema	8 (4.3%)	11 (6.0%)	14 (9.7%)	16 (11.3%)
Vitreous haemorrhage	8 (4.3%)	9 (4.9%)	9 (6.3%)	12 (8.5%)
Eye discharge	7 (3.7%)	9 (4.9%)	3 (2.1%)	6 (4.2%)
Photophobia	7 (3.7%)	3 (1.6%)	4 (2.8%)	0
Vision blurred	7 (3.7%)	4 (2.2%)	2 (1.4%)	2 (1.4%)
Corneal oedema	6 (3.2%)	0	4 (2.8%)	2 (1.4%)
Diabetic retinopathy	6 (3.2%)	9 (4.9%)	6 (4.2%)	15 (10.6%)
Foreign body sensation in eyes	6 (3.2%)	7 (3.8%)	2 (1.4%)	3 (2.1%)
Retinal exudates	6 (3.2%)	6 (3.3%)	9 (6.3%)	8 (5.6%)
Visual impairment	6 (3.2%)	3 (1.6%)	3 (2.1%)	1 (0.7%)
Vitreous disorder	6 (3.2%)	1 (0.5%)	3 (2.1%)	1 (0.7%)
Conjunctival hyperaemia	5 (2.7%)	5 (2.7%)	4 (2.8%)	2 (1.4%)
Corneal disorder	5 (2.7%)	0	4 (2.8%)	0
Keratitis	5 (2.7%)	2 (1.1%)	3 (2.1%)	0
Maculopathy	5 (2.7%)	5 (2.7%)	4 (2.8%)	6 (4.2%)
Ocular hyperaemia	5 (2.7%)	2 (1.1%)	4 (2.8%)	3 (2.1%)
Conjunctivitis	4 (2.1%)	3 (1.6%)	7 (4.9%)	6 (4.2%)
Eye pruritus	4 (2.1%)	4 (2.2%)	0	1 (0.7%)
Retinal aneurysm	4 (2.1%)	7 (3.8%)	6 (4.2%)	8 (5.6%)
Vitreous detachment	4 (2.1%)	1 (0.5%)	6 (4.2%)	1 (0.7%)
Blepharitis	3 (1.6%)	4 (2.2%)	6 (4.2%)	3 (2.1%)
Conjunctival oedema	3 (1.6%)	3 (1.6%)	2 (1.4%)	2 (1.4%)
Corneal erosion	3 (1.6%)	3 (1.6%)	3 (2.1%)	4 (2.8%)
Ocular discomfort	3 (1.6%)	1 (0.5%)	1 (0.7%)	1 (0.7%)
Retinal haemorrhage	3 (1.6%)	10 (5.5%)	9 (6.3%)	16 (11.3%)
Angle closure glaucoma	2 (1.1%)	2 (1.1%)	2 (1.4%)	1 (0.7%)
Anterior chamber inflammation	2 (1.1%)	0	1 (0.7%)	0
Dry eye	2 (1.1%)	4 (2.2%)	0	0
Photopsia	2 (1.1%)	0	1 (0.7%)	0
Retinal neovascularisation	2 (1.1%)	2 (1.1%)	2 (1.4%)	3 (2.1%)
Chalazion	0	1 (0.5%)	3 (2.1%)	1 (0.7%)
Corneal opacity	1 (0.5%)	0	3 (2.1%)	1 (0.7%)
Posterior capsule opacification	0	5 (2.7%)	3 (2.1%)	5 (3.5%)
Eyelid bleeding	0	0	2 (1.4%)	0
Eyelid ptosis	0	0	2 (1.4%)	0
Ocular hypertension	1 (0.5%)	1 (0.5%)	2 (1.4%)	1 (0.7%)
Retinal degeneration	0	0	2 (1.4%)	0
Retinal vascular disorder	1 (0.5%)	3 (1.6%)	2 (1.4%)	2 (1.4%)
Injury, poisoning and procedural complications				
Retinal scar	2 (1.1%)	1 (0.5%)	2 (1.4%)	3 (2.1%)
Corneal abrasion			2 (1.4%)	1 (0.7%)
Investigations				
Intraocular pressure increased	18 (9.6%)	12 (6.6%)	25 (17.4%)	9 (6.3%)

All injection procedure related AEs were mild or moderate in severity, except for one event of endophthalmitis and two events of increased IOP (see below). With exception of an increased incidence of increased IOP, the duration of exposure did not appear to have an effect on the occurrence of the reported ocular AEs

Table 31 Incidence of non-ocular adverse events reported in ≥ 1% of patients in the pegaptanib treatment group (in any of the studies), all causalities in subjects included up to week 36, Studies EOP1005 and EOP1013 and from available data (up to Feb 16, 2010) from study EOP1013.

	EOP1005 and EOP1013		**EOP1013**	
	Pegap 0.3 mg	**Sham**	**Pegap 0.3 mg**	**Sham**
Number of Patients	**N=188**	**N=183**	**N=144**	**N=142**
Patients with at least one adverse event[1]	136 (72.3%)	141 (77.0%)	118 (81.9%)	127 (89.4%)
Blood and lymphatic system disorders	7 (3.7%)	5 (2.7%)	5 (3.5%)	6 (4.2%)
Anaemia	7 (3.7%)	2 (1.1%)	5 (3.5%)	4 (2.8%)
Thrombocytopenia	2 (1.1%)	3 (1.6%)	2 (1.4%)	2 (1.4%)
Cardiac disorders	2 (1.1%)	2 (1.1%)	6 (4.2%)	6 (4.2%)
Coronary artery disease	2 (1.1%)	0	2 (1.4%)	2 (1.4%)
Angina pectoris	1 (0.5%)	0	2 (1.4%)	1 (0.7%)
Angina unstable	1 (0.5%)	0	2 (1.4%)	0
Gastrointestinal disorders	8 (4.3%)	11 (6.0%)	6 (4.2%)	15 (10.6%)
Diarrhoea	2 (1.1%)	3 (1.6%)	1 (0.7%)	1 (0.7%)
Gastrooesophageal reflux disease	2 (1.1%)	2 (1.1%)	2 (1.4%)	1 (0.7%)
Hiatus hernia	2 (1.1%)	0	1 (0.7%)	0
General disorders/adm site conditions	6 (3.2%)	3 (1.6%)	2 (1.4%)	0
Drug intolerance	1 (0.5%)	0	2 (1.4%)	0
Hepatobiliary disorders	3 (1.6%)	0	3 (2.1%)	0
Cholelithiasis	3 (1.6%)	0	3 (2.1%)	0
Immune system disorders	1 (0.5%)	2 (1.1%)	2 (1.4%)	0
Drug hypersensitivity	1 (0.5%)	2 (1.1%)	2 (1.4%)	0
Infections and infestations	22 (11.7%)	20 (10.9%)	28 (19.4%)	31 (21.8%)
Nasopharyngitis	7 (3.7%)	6 (3.3%)	13 (9.0%)	8 (5.6%)
Bronchitis	3 (1.6%)	1 (0.5%)	6 (4.2%)	7 (4.9%)
Influenza	3 (1.6%)	3 (1.6%)	4 (2.8%)	2 (1.4%)
Lower respiratory tract infection	3 (1.6%)	0	3 (2.1%)	0
Urinary tract infection	3 (1.6%)	2 (1.1%)	3 (2.1%)	4 (2.8%)
Viral infection	0	1 (0.5%)	4 (2.8%)	1 (0.7%)
Rhinitis	1 (0.5%)	0	3 (2.1%)	0
Laryngitis	1 (0.5%)	0	2 (1.4%)	0
Pneumonia	1 (0.5%)	4 (2.2%)	2 (1.4%)	5 (3.5%)
Injury, poisoning and procedural complications	2 (1.1%)	3 (1.6%)	10 (6.9%)	10 (7.0%)
Contusion	1 (0.5%)	1 (0.5%)	2 (1.4%)	0
Joint sprain	0	1 (0.5%)	2 (1.4%)	1 (0.7%)
Investigations	25 (13.3%)	18 (9.8%)	33 (22.9%)	24 (16.9%)
Blood urea increased	3 (1.6%)	3 (1.6%)	5 (3.5%)	3 (2.1%)
Alanine aminotransferase increased	2 (1.1%)	1 (0.5%)	4 (2.8%)	1 (0.7%)
Blood creatinine increased	2 (1.1%)	4 (2.2%)	4 (2.8%)	4 (2.8%)
Glycosylated haemoglobin increased	2 (1.1%)	1 (0.5%)	6 (4.2%)	2 (1.4%)
Weight increased	2 (1.1%)	0	1 (0.7%)	4 (2.8%)
Blood pressure increased	0	1 (0.5%)	2 (1.4%)	1 (0.7%)
Gamma-glutamyltransferase increased	0	2 (1.1%)	2 (1.4%)	3 (2.1%)
Metabolism and nutrition disorders	10 (5.3%)	10 (5.5%)	17 (11.8%)	14 (9.9%)
Diabetes mellitus	5 (2.7%)	5 (2.7%)	10 (6.9%)	5 (3.5%)
Hypercholesterolaemia	3 (1.6%)	1 (0.5%)	6 (4.2%)	3 (2.1%)
Hyperlipidaemia	3 (1.6%)	2 (1.1%)	3 (2.1%)	3 (2.1%)
Musculoskeletal and connective tissue disorders	2 (1.1%)	3 (1.6%)	4 (2.8%)	7 (4.9%)
Musculoskeletal pain	2 (1.1%)	1 (0.5%)	2 (1.4%)	2 (1.4%)
Osteoarthritis	1 (0.5%)	1 (0.5%)	2 (1.4%)	1 (0.7%)
Nervous system disorders	9 (4.8%)	7 (3.8%)	9 (6.3%)	10 (7.0%)
Headache	4 (2.1%)	4 (2.2%)	3 (2.1%)	3(2.1%)
Dizziness	3 (1.6%)	3 (1.6%)	3 (2.1%)	3 (2.1%)
Sciatica	2 (1.1%)	1 (0.5%)	1 (0.7%)	1 (0.7%)
Cerebrovascular accident	1 (0.5%)	1 (0.5%)	2 (1.4%)	1 (0.7%)
Psychiatric disorders	3 (1.6%)	6 (3.3%)	3 (2.1%)	5 (3.5%)
Anxiety	2 (1.1%)	1 (0.5%)	3 (2.1%)	2 (1.4%)
Insomnia	2 (1.1%)	1 (0.5%)	1 (0.7%)	1 (0.7%)
Depression	1 (0.5%)	4 (2.2%)	2 (1.4%)	3 (2.1%)
Renal and urinary disorders	1 (0.5%)	2 (1.1%)	7 (4.9%)	9 (6.3%)
Renal failure	0	1 (0.5%)	3 (2.1%)	1 (0.7%)
Diabetic nephropathy	1 (0.5%)	2 (1.1%)	2 (1.4%)	4 (2.8%)
Nephropathy	1 (0.5%)	1 (0.5%)	2 (1.4%)	2 (1.4%)
Respiratory, thoracic and mediastinal	5 (2.7%)	0	5 (3.5%)	2 (1.4%)

disorders				
Dyspnoea	3 (1.6%)	0	2 (1.4%)	0
Cough	2 (1.1%)	0	2 (1.4%)	2 (1.4%)
Epistaxis	0	0	2 (1.4%)	0
Skin and subcutaneous tissue disorders	3 (1.6%)	4 (2.2%)	3 (2.1%)	2 (1.4%)
Eczema	3 (1.6%)	0	3 (2.1%)	0
Vascular disorders	14 (7.4%)	8 (4.4%)	20 (13.9%)	14 (9.9%)
Hypertension	14 (7.4%)	8 (4.4%)	20 (13.9%)	14 (9.9%)

Source: TABLES A64, A67, Summary of clinical safety
[1] Incidence in each SOC row based on AEs appearing in > 1% of patients.

In general, non-ocular AEs reported were those that might be expected in the diabetic population and comparable between treatment groups. Besides an increased frequency of hypertension and an increased AAT and HbA1c, there were no noteworthy differences when comparing the 36 weeks of the pooled studies with EOP1013 which included subjects with 2 years treatment. However, the MAH was requested to discuss the apparently increased frequency of Macugen-treatment related increased glycosylated haemoglobin (17.4% vs. 6.3% in sham patients) and cholesterol (6.9% vs. 3.5%) as well as systemic hypertension (13.9% vs. 9.9%). There were no important differences in the reports of non ocular AEs between male and female patients, or based on age group.

During the follow up phase of study EOP1005, ocular AEs during this period consisted of cataracts, vitreous haemorrhage, vitreous detachment, macular oedema and vitreous floaters. 16 AEs reported by 14 patients (11%) across the pegaptanib arms and 3 AEs reported by 3 patients (7%) in the sham arm were assessed to have a relationship to the injection/procedure or study drug. The majority of non ophthalmic AEs were reported by one patient only and none of the systemic AEs during this period were considered related to treatment.

The CHMP considered that there is a further concern that VEGF-inhibitors may not be beneficial in subjects with a poor retinal perfusion (Chung, 2008). The MAH was therefore requested to summarise the subjects with some degree of central retinal ischaemia (e.g. sum of central ischaemic areas ≥500 μm2) and compare these with subjects without any notable ischaemia with regards to ocular AEs. Similarly, the AE profiles of subjects receiving/not receiving laser rescue during the studies should be presented.

The MAH has chosen to report only the AEs from the pivotal study in the proposed section 4.8 of the SPC. To increase the figure of DME-subjects exposed to 0.3 mg pegaptanib, AEs of subjects received 0.3 mg from study EOP1005 the CHMP considered that these should be pooled with those of study EOP1013. Further, a conservative approach should be taken, since there are apparently a number of AEs that appears to develop over time, e.g. AAT increased, and are seen at a higher frequency in pegaptanib-treated subjects compared to sham only in EOP1013. Finally, the frequency of some AEs needs to be changed as well or justified why placed in a certain frequency category. Consequently, there are a number of changes that the CHMP requested the MAH to introduce to the table of AEs in section 4.8 (see details in appended SPC). For those AEs appearing only in subjects with DME, it would be acceptable to the CHMP to mark these with an asterisk with this information under the table.

Serious adverse events and deaths

- **Deaths**

Thirteen of 465 patients enrolled in the three studies died, six pegaptanib patients and seven sham patients. None of the deaths was considered related to the study therapy or injection procedure.

In the pivotal study, nine patients died, see Table below.

Table 32. Listing of Subject Deaths; EOP1013

Subject Information (Number, Age [Years], Sex)	Cause of Death[a]	Treatment-Emergent Status (Yes vs No)	Relationship to Treatment	Severity
Pegaptanib sodium (0.3 mg) treatment group				
0028-3060; 80; F	Cerebrovascular accident	Yes	Not related	Severe
0319-3333; 67; M	Death	Yes	Not related	Severe
0410-3346; 79; F	Cardiac arrest	No	Not related	Severe
0410-3442; 65; M	Cardiac arrest	Yes	Not related	Severe
Sham injection treatment group				
0074-3093; 76; M	Colorectal cancer	Yes	Not related	Severe
0077-3282; 51; F	Breast cancer	Yes	Not related	Severe
0077-3373; 61; M	Ascites	Yes	Not related	Severe
0134-3319; 69; M	Acute myocardial infarction; arrhythmia	Yes	Not related	Severe
0313-3419; 44; M	Myocardial infarction	Yes	Not related	Severe

Source: Appendix B6.6.5
Abbreviations: F = female, M = male, MedDRA = Medical Dictionary for Regulatory Activities,
[a] MedDRA (v12.0) Coding Dictionary applied; preferred term listed.

Three patients died in the Phase 2 study (EOP1005), one during the active phase (sham patient) and two during the follow-up phase (pegaptanib 1 and 3 mg patients). The causes of death for the pegaptanib patients who died during the follow-up period were congestive heart failure following mitral valve replacement surgery for one patient and cardiac arrest for the other patient. Both of the pegaptanib patients had existing medical conditions that could have contributed to the deaths. In the Phase 1b study, one patient died post injection of multi-organ failure.

The CHMP considered that although the systemic exposure of pegaptanib is low, there is a potential association with VEGF-inhibition and cardio/cerebrovascular adverse reactions. Considering that this is a population with cardiovascular co-morbidity, an increased risk in this population and a relation to treatment cannot be excluded.

- **Serious adverse events**

EOP1002
SAEs consisted of multiorgan failure (leading to death), pneumonia NOS, renal failure, and respiratory failure plus one additional patient with intervertebral disc herniation, none considered related to treatment.

EOP1005
Overall, the proportions of patients with SAEs for all pegaptanib groups combined and sham were low (8.6% pegaptanib sodium patients and 9.8% sham). During the follow-up phase, six patients experienced 11 non-fatal SAEs. The following SAEs were reported:

- 0.3 mg pegaptanib 9 SAEs: Up to week 36: 1 each Vascular disorders, Cardiac disorders, Gastrointestinal disorders, Eye disorders, Hepatobiliary disorders. After week 36: 2 Cardiac disorders, 1 Psychiatric disorder, 1 Renal/urinary disorders.
- 1 mg pegaptanib – 3 SAEs: Up to week 36: 1 Cardiac disorders. After week 36: 1 Cardiac disorders, 1 Nervous system disorder.
- 3 mg pegaptanib -17 SAEs: Up to week 36: 3 Metabolism/Nutrition disorders, 3 Nervous system disorders, 2 Vascular disorders, 1 Gastrointestinal disorders, 1 General disorders/administration site disorders, 1 Renal/and Urinary disorders, 1 Reproductive system and breast disorders. After week 36: 1 Cardiac disorders, 2 General/Administration site disorders, 2 Metabolism/nutrition disorders.
- Sham – 4 SAEs: Up to week 36: 1 Cardiac disorders, 2 Eye disorders, 1 Infections/infestations. After week 36: 0.

Two non ocular SAEs reported in patients led to hospitalisation (TIA or a Chiari I malformation/pegaptanib 3 mg) and MI/pegaptanib 1 mg); one led to study discontinuation (Guillian-Barre syndrome/pegaptanib 3 mg, in a patient with pre-existing neurological symptoms); and two led to death (MI/sham; and cardiac arrest/pegaptanib 3 mg). None of the SAEs were considered related to study drug, but here was one report of endophthalmitis (0.3 mg pegaptanib, subject discontinued from the study) and one report of vitreous haemorrhage (sham group), which was considered related to the injection procedure.

EOP1013
The proportions of pegaptanib sodium (24.3%) and sham patients (24.6%) who had SAEs reported were comparable in the pivotal study. The incidence of reported non ocular SAEs was low for both the pegaptanib and sham treatment groups.

Most SAEs were cardiovascular in nature in both pegaptanib sodium (6.9%) and sham (5.6%) patients. The most frequently reported SAEs in patients in the pivotal study were: Vitreous haemorrhage (2.1%, sham 2.1%), Angina pectoris (1.4%, sham 0.7%), Angina unstable (1.4%, sham 0), Coronary artery disease (1.4%, sham 0.7%), IOP increased (1.4%, sham 0), and Cerebrovascular accident (1.4%, sham 0.7%).

Below are the SAEs considered related to study therapy.

Table 33 Incidence of serious adverse events in study EOP1013, considered study therapy related

Number of Patients SOC, HLGT and PT	Pegap 0.3 mg N=144	Sham N=142
Cardiac disorders	0	1 (0.7%)
Coronary artery disorders	0	1 (0.7%)
Angina pectoris	0	1 (0.7%)
Coronary artery disease	0	1 (0.7%)
Eye disorders	1 (0.7%)	0
Retina, choroid and vitreous haemorrhages and vascular disorders	1 (0.7%)	0
Vitreous haemorrhage	1 (0.7%)	0
Nervous system disorders	1 (0.7%)	0
Central nervous system vascular disorders	1 (0.7%)	0
Cerebrovascular accident	1 (0.7%)	0

The cerebrovascular accident event was considered related to the study therapy; however, the patient had underlying disease factors. In addition, there were 2 events (1.4%) of serious IOP increase in the pegaptanib treatment arm vs. 0 in the sham arm that were considered related to the injection procedure. No additional SAEs have been reported for the ongoing patients in the study.

The CHMP considered that the SAE profile appears reassuring and treatment-emergent events considered related to study drug or the injection were few, however, the patient database is limited. Further, the presentation of SAEs in the submitted documentation is difficult to penetrate. The MAH was therefore requested to pool and tabulate all and SAEs not suspected as well as suspected related to study drug/sham or injection from studies EOP1005 and 1013 by SOC and preferred term, displaying frequencies at the different doses vs. sham.

Laboratory findings
Overall, the incidence of clinically significant laboratory test abnormalities appeared similar between the sham and active treatment arms and likely related to the underlying metabolic disease. The median changes from baseline for all laboratory parameters were small, not clinically meaningful, and comparable for the pegaptanib and sham groups. HbA1c the mean baseline values were between 6.35% and 7.80% (all dose groups, all studies) and remained essentially stable during the course of the studies.

Discontinuation due to AES
For overall discontinuation rates, see Table 8 and 18. In the pivotal study, 4.9% of pegaptanib sodium and 6.3% of sham patients discontinued due to AEs. The AEs (Increasing rigidity of sclera and Increased IOP) were considered related to the injection procedure for three of the six pegaptanib patients and related to the study therapy (Apoplexy) for one of the patients. In the Phase 2 study, 3.1% and 2.4%, pegaptanib and sham patients, respectively, discontinued due to an AE: one of the events (Endophthalmitis, 0.3 mg pegaptanib, injection-related), and the other (Guillian-Barre Syndrome, 3 mg pegaptanib, not considered related). One patient discontinued from the Phase 1b study due to a non-related SAE. There was no apparent relationship between the number of injections administered and the rate of discontinuation.

The CHMP was of the opinion that an increased rigidity of the sclera is a complication that may be expected after repeated injections. Considering that the now targeted population is substantially younger than the AMD-population and may need therapy for many years, this may be a future problem.

- **Adverse events of special interest**

Adverse events of special interest, which included specific ocular events, hypersensitivity events, and other important events (cardiovascular, cerebrovascular, and peripheral vascular thrombotic events) were assessed in the three clinical studies.

Ocular AEs of special interest

Endophthalmitis: No pegaptanib or sham patients developed endophthalmitis during the pivotal or Phase 1b studies. During the Phase 2 study, there was one report of severe endophthalmitis in the study eye of a patient receiving 0.3 mg pegaptanib sodium. The event resolved after 6 weeks of treatment with antibiotics. It was later discovered that the ophthalmologist had not followed appropriate pre-injection and injection techniques.

Intraocular pressure increased: Changes in IOP were transient, mild for the majority of patients. In the pivotal study, almost three times as many pegaptanib patients (17.4%) had AE reports of IOP increased compared with sham patients (6.3%). The majority of patients who received pegaptanib sodium injections (96.5%) and sham treatment (100%) did not have an IOP ≥ 35 mmHg. At any point during the Phase 2 study, 7.8% of pegaptanib patients and 2.4% of sham patients had IOP increases ≥35 mmHg. Clinically relevant elevated IOPs were handled with paracentesis or pharmacological intervention. No increase in the frequency of IOP ≥35 mmHg was seen with increasing numbers of injections, and the frequency of increases in IOP to ≥35 mmHg was not dose-dependent, as was evidenced in the Phase 2 study where 0.3, 1, and 3 mg of pegaptanib sodium or sham were administered.

Ocular hypertension/Glaucoma: Ocular hypertension was reported for 2 (1.4%) pegaptanib sodium patients and 1 (0.7%) sham patient during the pivotal study and none in the other studies. Reports of glaucoma during the pivotal study were low in both treatment groups.

Retinal detachment: No pegaptanib-treated patient experienced retinal detachment.

Retinal Haemorrhage: In the pivotal study, 6.3% of pegaptanib sodium patients (non-severe) and 11.3% of sham patients experienced a retinal haemorrhage during the pivotal study. No action was taken for any of the events. No additional events were identified in the other studies.

Retinal pigment epitheliopathy: In the pivotal study, 0.7% of pegaptanib sodium and 1.4% of sham patients had retinal pigment epitheliopathy reported in the study eye, which was not considered related to treatment. No additional events were identified in the other studies.

Vitreous haemorrhage: During the pivotal study 6.3% of pegaptanib and 8.5% of sham patients experienced a vitreous haemorrhage. During the Phase 2 study, vitreous haemorrhage was reported in 5.5% of patients across all pegaptanib and in 4.9% of patients in the sham group. One of the reports was reported as severe in a sham patient. One patient had a vitreous haemorrhage reported in the Phase 1b study, which resolved the next day and was considered unrelated to treatment.

In addition to the AEs of special interest discussed above, the following AEs of special interest were also assessed: Panophthalmitis, Retinal tear, Glaucoma traumatic, Retinal toxicity, Retinal injury, Detachment of the retinal epithelium, Eye haemorrhage, and Cataract traumatic. None of these AEs of special interest were reported in the three studies.

The CHMP considered that since diabetic subjects are susceptible to infections, and may be also more susceptible to ocular infections, it is reassuring that only one event of endophthalmitis was reported from the three studies. The frequency of elevated IOP (with the exception of the phase I study) appears in the similar range as reported in subjects with AMD (6-11% during the 1st year) and clinically significant IOP elevations (defined as pressures >35 mmHg) were not frequent and could be managed**.** Although the frequency was increased during the 2nd year (9.6% up to week 36 in studies EOP1005 and EOP 1013, vs. 17.4 % in the 2-year study EOP13), there appears to be no increase in frequency of IOP values ≥ 35 mmHg with increasing numbers of injections. In the phase II study, there was no increased incidence of IOP > 35 mmHg at higher doses. However, in subjects with AMD as well as in the phase I study, where 3 mg pegaptanib was administered, the overall incidence of increased

IOP was higher. The frequency of the other ocular AEs of special interest does not raise any new concerns compared to the AMD-population.

Non-Ocular AEs of special interest

Hypersensitivity reactions were reported in four pegaptanib patients (not considered treatment-related) and included: Hypersensitivity, drug hypersensitivity, and rash. Blepharitis allergic was reported in four patients receiving sham. No additional events were identified in pegaptanib-treated subjects in the other studies.

Cardiovascular events were reported at a low frequency in the pivotal study (4.9% in both arms). Three of these were fatal, one in a pegaptanib patient (not considered related) and two in sham patients. In the Phase 2 study, four pegaptanib patients had five cardiovascular events reported; three of the events resulted in death (two pegaptanib patients during the follow up phase of the study and one sham patient during the active phase of the study). None of the events was considered related to the study treatment. No patient in the Phase 1b study had a cardiovascular event reported.

Cerebrovascular events were reported for 2 patients in each of the pegaptanib and sham treatment groups in the pivotal study. One of the reports in a patient receiving pegaptanib (not considered related to treatment) was fatal. In the Phase 2 study, one patient receiving pegaptanib (3 mg) reported a cluster of symptoms that could be explained by a TIA or by a Chiari I malformation. After hospitalization, the patient recovered and continued in the study. No cerebrovascular events were reported in the Phase 1b study.

No patients in either the pegaptanib or sham groups in the pivotal study experienced a **peripheral vascular thrombotic event**, nor did any patient in the Phase 1b study. One patient who received pegaptanib in the Phase 2 study (0.3 mg) experienced a deep vein thrombosis (considered not related to study therapy).

The CHMP also considered that the non-ocular AE profile of events of special interest is assuring, but again, the number of treated subjects is limited. CV events are of special interest in a diabetic population due to their underlying disease status and it cannot be excluded that these subjects may be more susceptible towards even a low degree of systemic VEGF-inhibition. Further, there were restrictions with regards to the inclusion of patients with severe cardiac disease, pervious MI, peripheral vascular disease, stroke (within 12 months prior entry) and uncontrolled blood pressure. Consequently, the information on the safety of pegaptanib in such population is missing and this should be further addressed in the RMP, in the SPC, section 4.4 as well as in the planned European safety study.

- **Supportive safety data**

Methods

Clinical trial safety data obtained from the pooled AMD patient population treated with pegaptanib and diagnosed with a history of diabetes mellitus were compared with similar data from the pooled AMD patient population who did not have diabetes mellitus. The comparison was based on the incidence of pre-specified related to endophthalmitis, increased IOP, retinal injury, intraocular haemorrhage, traumatic cataract (18 ocular terms in total) and hypersensitivity reactions (34 terms), as well as stroke, MI, and any other arterial thromboembolic events (ATEs) according to the Antiplatelet Trialists' Collaboration (APTC) criteria. The ocular and hypersensitivity-related terms are listed in the pegaptanib RMP. Only the period when subjects received 0.3 mg was taken into account regarding AEs, concomitant medications and discontinuations and only the treatment emergent AEs having occurred after the first drug injection of 0.3 mg and within 42 days (6 weeks) after the last injection of 0.3 mg have been considered. There were 1586 subjects enrolled in the 9 clinical studies selected for this analysis. Among the 1586 subjects, 165 (10.4%) were identified with a history of diabetes mellitus and 1421 were non-diabetics, see table below.

Table 34 Patient disposition - all treated patients with pegaptanib 0.3 mg

Protocol ID	Duration of Treatment	Diabetic	Non-Diabetic
		N=165	N=1421
EOP1003 Randomized	2 year (only pts on same treatment)	22 (13.3%)	208 (14.6%)
EOP1004 Randomized	2-year (only pts on same treatment)	20 (12.1%)	182 (12.8%)
EOP1006 Randomized	1 year	1 (0.6%)	41 (2.9%)
EOP1009 Randomized	1 year No treatment between w.12 and 24	4 (2.4%)	60 (4.2%)
EOP1010 Open-label	Different duration of treatment	67 (40.6%)	370 (26.0%)
EOP1012 Randomized	An early stopped trial planned for 2-year	16 (9.7%)	149 (10.5%)
A5751010/15 Open-label	A5751015 is the extension of A5751010	7 (4.2%)	72 (5.1%)
A5751016 Open-label	1 year	11 (6.7%)	70 (4.9%)
A5751017 Open-label	2 year	17 (10.3%)	269 (18.9%)

Demographic characteristics

There was a higher proportion of diabetic males (51.5%) than non-diabetic males (42.6%) and a lower proportion of diabetic females (48.5%) than non-diabetic females (57.4%). The mean age of the diabetic group was 75.3 years (ranging from 56 to 89 years) which was similar to the mean age of the non-diabetic group of 75.9 (ranging from 40 to 94 years). In both groups, most subjects were Caucasian/White.

Adverse events

Overall, AEs presented were reported by 117 (70.9%) subjects in the diabetic group and 1095 (77.1%) subjects in the non-diabetic group. Reporting rates in the different SOCs were similar between diabetic and non-diabetic groups. For particular SOCs of interest, the reporting rates for the diabetic group compared with the non-diabetic group included Cardiac disorders (6.7 vs. 7.0%), Eye disorders (65.5 vs. 66.6%), Immune system disorders (1.2 vs. 2.1%), Nervous system disorders (12.7 vs. 11.5%) and Vascular disorders (8.5 vs. 9.0%). There were no major differences in reporting of AEs in any SOC between the two patient populations.

There were 28 (17.0%) subjects in the diabetic group who reported 50 pre-selected ocular AEs and 294 (20.7%) in the non-diabetic group who reported 601 pre-specified ocular AEs regardless of causality, see Table below.

Table 35 Incidence and severity of pre-specified ocular AEs, all causality - Study eye - pegaptanib 0.3 mg

Number of Subjects	Diabetic (N=165)				Non-Diabetic (N=1421)			
		Severity [1]				Severity [1]		
Preferred term *	n (%)	Mild	Mod.	Sev.	n (%)	Mild	Mod.	Sev.
Cataract traumatic	0	0	0	0	1 (0.1)	0	1	0
Detachment of retinal pigment epithelium	0	0	0	0	3 (0.2)	2	1	0
Endophthalmitis	1 (0.6)	0	0	1	16 (1.1)	0	2	14
Eye haemorrhage	0	0	0	0	6 (0.4)	1	3	2
Eye haemorrhage NOS	0	0	0	0	3 (0.2)	3	0	0
Glaucoma	0	0	0	0	2 (0.1)	1	1	0
Glaucoma NOS	0	0	0	0	2 (0.1)	0	2	0
Intraocular pressure increased	13 (7.9)	12	1	0	155 (10.9)	97	52	6
Ocular hypertension	0	0	0	0	11 (0.8)	8	3	0
Retinal detachment	1 (0.6)	1	0	0	9 (0.6)	2	2	5
Retinal haemorrhage	8 (4.8)	3	4	1	64 (4.5)	42	16	6
Retinal pigment epitheliopathy	4 (2.4)	3	1	0	10 (0.7)	9	1	0
Retinal tear	1 (0.6)	1	0	0	5 (0.4)	3	2	0
Vitreous haemorrhage	3 (1.8)	3	0	0	21 (1.5)	16	3	2

Of the pre-specified ocular AEs, the majority of the events endophthalmitis, elevated IOP and vitreous haemorrhage were deemed relation to the injection. Four events in the diabetic treatment group (2 each of IOP increased and retinal haemorrhage) were considered related to pegaptanib.

There were few events associated with hypersensitivity reactions in the diabetic subjects (2 events of rash) and none considered related to treatment.

There was a somewhat higher proportions of subjects in the diabetic population reporting pre-specified APTC AEs, see **Tables 36** and **37** below.

Table 36 Summary of pre-specified APTC AEs, all causality - pegaptanib 0.3 mg

	Diabetic	Non-Diabetic	All Patients

Number of subjects	N=165	N=1421	N=1586
Number of subjects with at least one *			
APTC AE	10 (6.1%)	60 (4.2%)	70 (4.4%)
Serious APTC AE	10 (6.1%)	48 (3.4%)	58 (3.7%)
Severe APTC AE **	6 (3.6%)	34 (2.4%)	40 (2.5%)
APTC AE leading to death	0	7 (0.5%)	7 (0.4%)
APTC AE leading to study drug discontinuation	0	8 (0.6%)	8 (0.5%)

Table 37 Incidence and severity of pre-specified APTC AEs, all causality - pegaptanib 0.3 mg

Number of Subjects	Diabetic (N=165)					Non-Diabetic (N=1421)				
		Severity [1]					Severity [1]			
Preferred term **	n (%)	Mild	Mod.	Sev.	Lt*	n (%)	Mild	Mod.	Sev.	Lt*
Acute myocardial infarction	0	0	0	0	0	1 (0.1)	0	0	0	1
Angina pectoris	1 (0.6)	0	0	1	0	8 (0.6)	1	4	2	1
Angina unstable	0	0	0	0	0	4 (0.3)	0	2	2	0
Cardiac arrest	0	0	0	0	0	2 (0.1)	0	0	0	2
Cardiac failure congestive	0	0	0	0	0	5 (0.4)	0	2	1	2
Cerebral haemorrhage	0	0	0	0	0	1 (0.1)	0	0	0	1
Cerebrovascular accident	3 (1.8)	0	0	3	0	9 (0.6)	2	1	5	1
Coronary artery atherosclerosis	2 (1.2)	0	1	1	0	0	0	0	0	0
Coronary artery disease NOS	1 (0.6)	0	1	0	0	9 (0.6)	1	5	3	0
Coronary artery occlusion	0	0	0	0	0	1 (0.1)	0	0	1	0
Myocardial infarction	2 (1.2)	0	1	1	0	10 (0.7)	1	0	7	2
Pulmonary embolism	1 (0.6)	0	0	1	0	7 (0.5)	0	2	4	1
Retroperitoneal haemorrhage	0	0	0	0	0	1 (0.1)	0	0	1	0
Thrombosis	1 (0.6)	0	0	1	0	0	0	0	0	0
Transient ischaemic attack	1 (0.6)	0	1	0	0	8 (0.6)	1	5	2	0
Silent myocardial infarction	1 (0.6)	0	1	0	0	0	0	0	0	0
Ischaemia NOS	0	0	0	0	0	1 (0.1)	0	1	0	0
Deep vein thrombosis	0	0	0	0	0	4 (0.3)	2	1	1	0

Only one cerebrovascular accident was considered related to treatment in the diabetic population.

Based on the provided data the CHMP concluded that including the elderly subjects with AMD and diabetes adds to the information on age-related risk factors in this group (10-15 years older subjects in the AMD-trials). On the other hand, considering that the general DME patient is younger, additional number of years with IVT treatment may be expected. There is consequently a need for long-term data in this indication. There was no information on the duration of diabetes in these patients, however, it is likely shorter than in the target population since these subjects had no ocular manifestations of diabetes (DR was an exclusion criterion). Therefore, it is assumed that these subjects also have less advanced diabetes including other manifestations of vascular complications. This limits the safety bridging strategy, not only with regards to ocular AEs, but also to the assessment of systemic AEs like ATEs, which appeared at a somewhat higher frequency in the diabetic population. The MAH was therefore requested by the CHMP to summarise the pre-specified Antiplatelet Trialists' Collaboration (APTC) AEs in the controlled AMD-studies and compare the diabetic subjects treated with pegaptanib with the diabetic subjects that were sham-treated (baseline data included). Any differences between treated and non-treated subjects should be addressed in depth.

In response the MAH submitted a comparison of ATEs in diabetic subjects treated with pegaptanib with the diabetic subjects that were sham-treated. Surprisingly few sham-treated diabetic subjects were included in the AMD-studies and the comparison was considered by the CHMP to be of limited use. However, appropriate information has been added to the SPC, section 4.4 and 4.8. Potential risks with systemic VEGF-inhibition will also be further addressed in the RMP.

Pharmacovigilance system
N/A

Risk Management plan
The RMP submitted (version 8.0) has been updated to reflect the proposed new indication for pegaptanib. Data on the DME clinical development program and epidemiology of DME in diabetic population have been included.

Pharmacovigilance Plan
In addition to routine pharmacovigilance practices, at the time of launch of the AMD indication, an educational program to better inform physicians of potential risks associated with intravitreal injection

of pegaptanib was implemented. This program will be continued. Additionally, a one year safety study (A5751036) is being planned.

Summary of safety concerns and planned pharmacovigilance actions

Safety concern	Planned action(s)
Important identified risks	
Ocular Risks: • Endophthalmitis • Increased IOP • Retinal injury • Intraocular haemorrhage • Traumatic cataract Non-ocular Risks: Hypersensitivity	Routine pharmacovigilance and reporting through the PSUR system. Enhanced pharmacovigilance activities: • Independent Data Monitoring Committee to review clinical study data – Committee members concluded that external monitoring was no longer necessary on 30 October 2007 • Macugen Educational Program – ongoing • EU Epidemiological Cohort Study (A5751019) • Data Capture Aid for reported ocular and systemic events • Expert panel meetings, as needed for review of hypersensitivity data
Important potential risks	
No additional ocular or systemic risks in the diabetic population have been identified.	• As above. • To monitor the safety profile of the diabetic patient who receives pegaptanib sodium, the European Safety Study (A5751036) in patients with DME is planned.
Important missing information	
None	

Evaluation of the need for a Risk Minimisation plan

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide description of routine activity and justification
Important identified risks:		
Endophthalmitis	No	See Section 4
Increased intraocular pressure	No	See Section 4
Retinal injury	No	See Section 4
Intraocular haemorrhage	No	See Section 4
Traumatic cataract	No	See Section 4
Hypersensitivity	No	See Section 4
Important potential risks:	Yes	No new risks have been identified in DME population at this time.
Important missing information: None		

Risk Minimisation plan

Safety Concern: Endophthalmitis	
Routine risk minimisation activities	**SPC:** Section 4.2 instructs use of aseptic procedures and topical microbicide, and monitoring for endophthalmitis following injection. Section 4.3 contraindicates use in presence of known or suspected ocular or periocular infection. Sections 4.4 and 4.8 contain warnings/precautions and events.
Additional risk minimisation activity: Educational Program	**Objective and rationale** To minimize the risks associated with intravitreal therapy, the MAH undertook (in the US and in the EU) several initiatives designed to educate physicians on appropriate aseptic procedure with the aim of minimizing the potential for infection and other adverse events. The educational program materials also reflected the hypersensitivity information provided within the SPC and patient information leaflet. Objectives and rationales for individual components of the Educational Program and results of the program are provided in Annex 8.
	Proposed actions The educational program was designed to focus the attention of physicians on the need for appropriate aseptic technique for the intravitreal injection procedure. The MAH provided details of the aseptic technique used during pivotal clinical trials, which was associated with a low rate of adverse events related to the procedure, together with information on those elements of the technique on which consensus exists within the ophthalmic community. This was communicated in a variety of modalities (peer reviewed publications, video/CD ROM.). Further details of the Education program are provided in Annex 8.
	Criteria to be used to verify the success of proposed risk minimisation activity The MAH has developed a survey (the Education Program Implementation Survey or EPIS) to evaluate whether the educational program was being effectively implemented and information pertaining to aseptic technique effectively communicated. Objectives of EPIS were to measure the proportion of target physicians to whom educational materials were communicated, to understand the nature and timing of educational materials from the MAH to the physician, and to assess the usefulness of the educational material and the unmet educational needs of the physician.
	Proposed review period Data received from EPIS have been reviewed during each RMP update. See Annex 8 for final update through 30 June 2009, when the collection of surveys was completed. Between 01 January 2008 and 30 June 2009, the collection of surveys was sporadic. Only 32 additional surveys were collected during that time. The planned launch of pegaptanib sodium for wet AMD in the EU is completed.
Safety Concern: Increased IOP	
Routine risk minimisation activities	**SPC:** Section 4.2 instructs on monitoring for perfusion of optic nerve head and intraocular pressure. Sections 4.4 and 4.8 contain warnings/precautions and events.
Additional risk minimisation activity: Educational Program	**See description above under Endophthalmitis**
Safety Concern: Retinal Injury	
Routine risk minimisation activities	**SPC:** Section 4.8 contains relevant retinal adverse events.
Additional risk minimisation activity:	**See description above under Endophthalmitis**

Additional risk minimisation activity: Educational Program	**See description above under Endophthalmitis**
Safety Concern: Intraocular haemorrhage	
Routine risk minimisation activities	**SPC:** Sections 4.4 and 4.8 contain warnings and events.
Additional risk minimisation activity: Educational Program	**See description above under Endophthalmitis**
Safety Concern: Traumatic cataract	
Routine risk minimisation activities	**SPC:** Section 4.8 contains the adverse event, cataract.
Additional risk minimisation activity: Educational Program	**See description above under Endophthalmitis**
Safety Concern: Hypersensitivity	
Routine risk minimisation activities	**SPC:** Section 4.2 instructs evaluation of patient medical history of hypersensitivity prior to use. Section 4.3 contraindicates use in patients with known hypersensitivity to the active substance or excipients. Sections 4.4 and 4.8 contain warnings and events.
Additional risk minimisation activity: Educational Program	**See description above under Endophthalmitis**

The educational program consists of a package provided to physicians including eight items:

1. A Supplement to journal Retina (Aiello LP) published in 2004 outlining a recommended injection procedure for physicians to use in a clinical setting, The recommendations were a result of an MAH-sponsored consensus round-table discussion in May 2004 in which thirteen physicians with expertise in performing IVT injections, infectious diseases of the eye and their prevention, and glaucoma took part.
2. Two articles published in Retina following an MAH-sponsored review:.
    a. "Minimizing the Risk of Endophthalmitis Following Intravitreal Injections": Review paper by Dr. Christopher Ta 2004
    b. "Risks of Intravitreal Injection: A comprehensive review": Review paper by Jager et al. 2004.
3. An excerpt of the VISION protocol including descriptions of the IVT injection procedure as it was performed in the pivotal AMD clinical studies after the introduction of more conservative and prophylactic activities.
4. An educational video/CD and speaker slide set reflecting the recommended injection procedure developed in the Consensus Roundtable described above, and also incorporating the recommendations in the two review papers outlined above.
5. A set of sterile drapes and a lid speculum
6. Brochures with safety information along with an intravitreal injection procedure perforated pad with follow-up information, to be given to the patients by the physician. These will include descriptions of key symptoms and reasons for rapid reporting.
7. A reminder aid to physicians with key information regarding the process of adverse event reporting to the MAH (contact information including telephone/fax numbers etc.).
8. The Macugen webpage includes safety information and the ability to print the Package Leaflet (PL).

The educational program materials also reflect the hypersensitivity information provided within the SPC and patient information leaflet.

A survey to evaluate the effectiveness of the educational program was performed between May 2006 and June 2009.

The MAH will continue the program as pegaptanib becomes available to the DME population. No changes to the educational programme are proposed. Each identified physician receives the customized base educational package.

III.3.4.5 Summary of the EU-RMP

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Endophthalmitis	• Routine pharmacovigilance • Data Capture Aid • Epidemiology studies (EU Cohort/AMD; EU Safety/DME)	• Sections 4.2, 4.3, 4.4 and 4.8 of SPC • Educational Program
Increased intraocular pressure	• Routine pharmacovigilance • Data Capture Aid • EU Cohort study/AMD; EU Safety/DME	• Sections 4.2, 4.4 and 4.8 of SPC • Educational Program
Retinal injury	• Routine pharmacovigilance • Data Capture Aid • EU Cohort study	• Section 4.8 of SPC • Educational Program
Intraocular haemorrhage	• Routine pharmacovigilance • Data Capture Aid • EU Cohort study/AMD; EU Safety/DME	• Sections 4.4 and 4.8 of SPC • Educational Program
Traumatic cataract	• Routine pharmacovigilance • Data Capture Aid • EU Cohort study/AMD; EU Safety/DME	• Section 4.8 of SPC • Educational Program

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Hypersensitivity	• Routine pharmacovigilance • Data Capture Aid • Epidemiology studies (EU Cohort/AMD; EU Safety/DME) • External Hypersensitivity Expert Panel as needed	• Sections 4.2, 4.3, 4.4 and 4.8 of SPC • Educational Program

The CHMP considered that the RMP is written in adherence to the guidelines of Vol 9A, although some sections need revision. The safety database is limited to a small number of exposed patients (less than 300 in pivotal study EOP1013). The safety database is also limited to patients having well-controlled type 2 diabetes without significant history of cardiovascular disease. It was questioned by the CHMP whether these findings in the safety database can be extrapolated to the proposed target population. However, at present, there are no new safety findings that warrant an immediate change to risk minimisation activities ongoing or planned.

Supplementary information was requested by the CHMP in relation to the definition of DME and the different types of retinal detachments in the epidemiology section (1.7). Further, the following areas of missing information required amendments in the RMP: Macular ischemia, Long-term safety beyond 2 years, Effect of Macugen on progression of overall DR, Effects of stopping Macugen treatment on DR, Relation of anti-VEGF-therapy to standard care grid/focal photocoagulation, Risk for ATEs including MI in diabetic patients, Adverse events related to bilateral treatment and Adverse events related to off-label use.

Additionally, it was stated in Section 2.1 (Routine pharmacovigilance practices) that in addition to the pharmacovigilance activities, a one year European safety study (A5751036) is being planned to further evaluate safety and tolerability in the DME population. The MAH should comment on the short duration of this study. Important safety information should come from a long-term study (>3 years). No information is provided about the number of patients that will be enrolled. The protocol status is planned. This should be submitted for assessment by the CHMP.

ORPHAN MEDICINAL PRODUCTS

N/A

3. BENEFIT RISK ASSESSMENT

Benefits
The mechanism of action of pegaptanib is to decrease permeability of leaking blood vessels. This mechanism of action is valid independent on whether targeting retinal vessels in DME or choroidal vessels in AMD. Therefore, available data from the AMD-population adds to the basic understanding of the drug. This is of relevance also for understanding the treatment of subjects with DME.

To support the sought indication - treatment of DME - the effect of pegaptanib has been studied in one phase II (EOP1005) and one phase III (EOP1013) study were subjects with an impaired vision and macular oedema were included. The sought indication is not acceptable and would, in a best case, read "Treatment of visual impairment due to DME". Although the primary outcome measure in the phase II study evaluated the macular oedema (with non-convincing signs of efficacy), in the pivotal study, the primary outcome measure assessed the proportion of subjects that gained ≥ 10 letters of VA. Further, the decrease in vision and the increase of the DME did not correlate very well. Since subjects with DME may have a perfect VA, it is considered doubtful whether these subjects should be treated with IVT injections and no such subjects were included in the clinical trials.

In both studies, the effect of pegaptanib 0.3 mg with regards to improvement in VA was clinically relevant and statistically significant at the primary time point for evaluation. The proportion that gained ≥ 10 letters was 24% (phase II, week 36, p=0.0030) and 17 % (phase III, 1 year, p=0.0047) more in the pegaptanib-groups than in the sham-groups. Further, the mean increase in VA vs. baseline was +4-5 letters over sham in the two trials. Sensitivity analyses supported these outcomes. There were also benefits of pegaptanib with regards to the need for laser photocoagulation as rescue and some vision-related outcomes in the VFQ-25 health questionnaire (EOP1013). However, there were no major differences in the proportions of subjects that gained ≥ 15 letters, no effects on anatomical endpoints like retinal thickness and at the end of the 2nd year in the pivotal study, the proportion that gained ≥ 10 letters was not statistically significant (p=0.1729) compared to sham even though the mean increase in VA remained in pegaptanib-treated subjects (5 letters over sham, p=0.0018). Taken together, although not impressing, a treatment effect of pegaptanib has been demonstrated.

Although fairly consistent across subgroups, some limited analyses indicated a slightly better effect in subjects with lower baseline VA (< 54 letters), in subjects with thicker retina (>300 μm).

In EIOP1005, 0.3, 1.0 and 3.0 mg of pegaptanib was studied. As in the AMD-studies, there was no dose-response and the 0.3 mg dose tended to be the most effective. In EOP1013, two lower doses were included, however, lower concentrations of pegaptanib were found unstable and these dose groups were terminated. No additional attempts to test other doses were performed. Taken together, the choice of the 0.3 mg dose is considered reasonable.

Uncertainty in the knowledge about the beneficial effects
A number of uncertainties with regards to the pivotal study remain. These relates to the internal (indications of potential bias) and external validity (suitable to extrapolate study population to target population?).

- External validity: The sought indication includes all subsets of patients with DME. However, almost no subjects with type I diabetes and only fairly controlled subjects were enrolled. This has to be addressed in the SPC.

  Further, only subjects with no relatively recent (prior 16 weeks) or an anticipated (within 18 weeks) need for laser photocoagulation were included. Subjects with prior laser treatment appeared to have a limited benefit of pegaptanib-treatment. This subgroup was fairly large and adds to the uncertainties on when and how pegaptanib should be used in relation to laser photocoagulation. Finally, it is not clear to what extent subjects with significant central retinal ischaemia (e.g. ≥ 500 μm^2) were included in the study. Since a small study (Chung et al., 2008) including patients with retinal ischaemia indicated that the VEGF-inhibitor bevacizumab

decreased VA in these subjects. It is consequently uncertain to which extent the studied population can be extrapolated to the target population.

- Internal validity: The primary endpoint was changed in Amendment EOP1013D (from proportion ≥3 lines to ≥2 lines gain in VA). No prospectively generated documentation behind the actual decision to change the primary end point has been presented.

- Lack of consistency: The CHMP estimates that consistency of the results within this trial is low, mostly when it comes to comparing the two-year data versus one year data. There is a benefit of treatment during the first year. A significant proportion of subjects gained ≥ 10 letters in VA (primary endpoint). However the proportion that gain ≥ 10 letters was no longer statistically significantly different vs. sham the 2nd year (38 vs. 30% in pegaptanib and sham groups, p=0.1729).

The full 2-year data hasn't yet been submitted and together with the limited additional trials that are ongoing or planned to address the above uncertainties, the deficiencies remain as major concerns.

In none of the studies, there was a direct comparison vs. the standard of care, i.e. laser photocoagulation. Although the benefits, of laser are well characterised, i.e. the disease progression with and without laser treatment, this is of concern.

In clinical practice, it is not unlikely that IVT injections may be performed in conjunction with laser treatment. In none of the studies, the efficacy (and safety) of the combination was evaluated. Further, it is not known if an early, and maybe not lasting, gain in VA due to pegaptanib-treatment will result in a loss of the well characterised long-term preservation of vision due to laser treatment if laser is halted or deferred. The MAH has performed sub-group analyses by use of laser photocoagulation as rescue. In these analyses, it appears that the unexpectedly high proportion of responders in the sham treatment group at the end of the 2nd year was due to rescue laser, but that the effect of pegaptanib appeared to be sustained. However, the MAH must explore the options to further address how pegaptanib should be used in relation to laser photocoagulation in clinical studies, e.g. in a study comparing Macugen+ concomitant laser vs. Macugen as monotherapy including also a laser-treatment arm (with escape options to VEGF-inhibitory therapy).

The selected 0.3 mg dose of pegaptanib appears reasonable, however some uncertainties remain regarding the criteria for withholding and resuming therapy as well as how frequent the patients need to be monitored. Consequently, additional evaluations are needed before final treatment recommendation can be given.

In subgroup analyses, a number of the subgroups were too small to draw any conclusions or to suggest any changes to the treatment recommendations. It remains nevertheless of concern that pegaptanib wasn't even numerically in favour of sham-treatment in subjects with type I diabetes, in subjects on thiazolidinediones and this has to be addressed. There are yet no efficacy data from subjects with focal vs. diffuse DME, different degrees of retinal ischaemia and different durations of visual impairment due to diabetes.
A long treatment may be expected since the current target population is 10-15 years younger than the previously studied AMD-population. A long term benefit of treatment (> 2 years) has not been demonstrated and must be confirmed, potentially post approval.

Risks
Pegaptanib is given by IVT injections. The risks with such injections are characterised from the previous development programme including patients with AMD and consists mainly of increased IOP that is, in most cases are non-serious, transient and can be managed. In addition, there are risks for injection-related damage to intraocular tissues including increased risks for haemorrhages, retinal tears and detachment as well as potentially sight-threatening endophthalmitis, although only one event of endophthalmitis was detected in the studies submitted by the Applicant. Overall, data indicate that the risks are fairly similar for patients with DME compared with the AMD-population, no new adverse events were reported and, overall, the reporting of AEs is reassuring in subjects with DME. In addition, since Macugen is presented in a pre-filled syringe, the risk for contamination that may lead to ocular infections and inadvertently overdosing may be reduced.

With regards to non-ocular AEs, as in the AMD-population, the majority was mild to moderate in severity and generally those that might be expected in the diabetic population. Few non-ocular AEs were suspected related to study drug and/or ocular injection and only one event of a cerebrovascular

accident was considered related to treatment. Although a low systemic exposure of pegaptanib is expected, the potential risk for ATEs is also the most important non-ocular risk in this population, a population with significant co-morbidities due to their disease. This has been adequately addressed in the SPC.

Uncertainty in the knowledge about the unfavourable effects
Less than 300 subjects with DME are exposed to pegaptanib and due to the limited number of subjects, there is a reasonable probability only to detect an AE that appears with a frequency of 1 in a 100 patients, i.e. a common AE. Some reassurance is given from an additional 165 AMD-patients with diabetes, which adds to the information on age-related risk factors in this group. On the other hand, the AMD-population had no DME and, likely, a less advanced vascular disease. Therefore, these patients may not be fully representative for the targeted population.

Considering that the general DME patient is younger than subjects with AMD, additional number of years with IVT treatment may be expected and it is possible that a notable proportion of subjects will receive injections every 6^{th} week. Only 116 subjects have been treated with such frequency (8-9 injections) for 1 year, while ~50 subjects have received most of the injections (15-17) for two 2 years. Consequently, the safety database is limited and there is an uncertainty regarding the long-term risks in the target population. For example, there are appears to be a number of AEs that seems to develop over time, e.g. AAT increased and hypertension as well as an increased rigidity of the sclera, the latter a complication that may be expected after repeated injections. In addition, the younger target population may be pregnant. In the segment II study in rabbits, reprotoxicity was observed. The assessment of the clinical relevance of these findings is pending since exposure margins to maximal clinical exposures have not yet been verified.

There is a recent report (Chung, 2008) that the VEGF-inhibitor bevacizumab decreased VA in DME-patients with retina ischaemia, while VA increased in those without ischaemia. It is not clear to what extent subjects with a significant (central) retinal ischaemia were included in the study. Since such subjects may be treated with pegaptanib in clinical practice, it is consequently not known whether patients with major retinal ischaemia may have a higher risk for an impaired vision if treated. Since fluorescein angiograms were captured for the reading centres in Study EOP1013, while change in macular capillary loss was evaluated in study EOP1005 at baseline, the missing information should be possible to extract. It is also not known whether there are any additional risks in case of concomitant laser photocoagulation, if treating subjects with recent laser photocoagulation, proliferative diabetic retinopathy or whether there is an increased risk for endophthalmitis bearing in mind the possibility of an increased susceptibility towards also ocular infections in diabetic subjects.

Cardiovascular events are of special interest in a diabetic population due to their underlying disease status and it cannot be excluded that these subjects may be more susceptible towards even a low degree of systemic VEGF-inhibition. There is also no, or limited information on any increased risks for, for example, ATEs if treating subjects with severe cardiac disease, pervious MI, peripheral vascular disease, stroke (within 12 months prior entry) and uncontrolled blood pressure (exclusion criteria).

Consequently, information on the safety of pegaptanib in parts of the target population is missing and this should be addressed in the planned European Safety Study (A5751036) as well as in the RMP and in the SPC.

Balance
Although the short-term benefit of pegaptanib is considered clinically relevant and may outweigh the risks, there are too many remaining uncertainties. Further, data do not support the sought indication, treatment of DME. The extrapolation to Type I diabetes is at least questionable

Uncertainties regarding the short and long-term benefit risk of pegaptanib treatment in relation to the current standard of care, laser photocoagulation, whether and how the two can be combined and the long-term effect of pegaptanib remain. Together with this arises the concern related to uncertainty if the gain in VA due to pegaptanib-treatment will result in a loss of the well characterised long-term preservation of vision due to laser treatment if laser is halted or deferred. Consequently, there is a need for additional long-term efficacy data.

Although reassuring, the safety database is very limited and does not include the full target population. Even though the similarity of the risk profile in diabetic subjects is supported by an additional 165 subjects with AMD and diabetes, these subjects likely had less advanced vascular complications (no significant DME). Thus, it cannot be excluded that the diabetes co-morbidity profile, including a potentially increased susceptibility towards infections, may put the target population at a higher risk.

Other matters of concern that have to be resolved include potential risks associated with concomitant laser photocoagulation and whether subjects with retinal ischaemia should be treated with pegaptanib. These concerns may be addressed with additional analyses, studies, or registries or, potentially, in the planned European Safety Study, however, the proposed one year duration of this study is not considered sufficient.

While it is not known whether there is a long-term benefit of pegaptanib-treatment in subjects with oedema only (as established with laser), the information to treat only the visual impairment has to reach the physicians. Although a large proportion of the retinal specialists now are familiar with intravitreal VEGF-inhibitors in the treatment of AMD, it is possible that a new subset of specialist will be introduced to treatment. As there are major risks if the injection procedure is handled incorrect, there is a need for a continuous education of physicians in this field. Taken together with the concern that diabetes patients have additional co-morbidities and may have an increased susceptibility to ocular infections, the educational programme for the AMD-population has to be updated.

Taken together, the potential to improve vision should not be deferred the target population, presently, no other treatment option exists. However, before an approval can be considered, the major issues as outlined in the LoOI have to be resolved.

Conclusions

As a result of the above considerations, in December 2010, the overall B/R of Macugen in the treatment of DME was considered by the CHMP to be negative, and the following 16 questions were sent to the MAH.

4. CHMP LIST OF QUESTIONS ADOPTED IN DECEMBER 2010 AND ASSESSMENT OF THE MAH RESPONSES

MAJOR OBJECTIONS:

Question 1:

"The MAH is requested to provide the protocol and the time table of the submission of the results from the planned peri-/post-natal development study."

In their response, the MAH explained that the protocol of the planned study is in preparation. The draft protocol *for "A Developmental and Perinatal/Postnatal Reproduction Study of Macugen by Intravenous Injection in Mice, Including a Postnatal Behavioral/Functional Evaluation"* was submitted *(Testing Facility Study No. LIA00583, Sponsor Reference No. 11LJ025*). The objective of the study is to detect adverse effects of Macugen on development of the offspring consequent to exposure from implantation through lactation and weaning (ICHS5 stages C to F). Observations will be continued through sexual maturity of the F1 generation mice.

The MAH plan was to start the study in June 2011. The results will be submitted based on the audited draft final report, which will be available in March 2012.

The CHMP considered that the proposed protocol and time-table of submission of the draft final report can be accepted.

Question 2

"The sought indication, to treat DME, is not acceptable. Only subjects with an impaired VA due to DME were included and treated in the studies and there is no information on the short and long-term benefit/risk in subjects with DME without visual acuity loss. To extend the indication to a broader patient population including in addition patients with diabetes, DME as observed by OCT and no visual impairment, clinical studies specifically examining the short and long term benefit/risk in this broader population need to be undertaken. The sought indication should thus be restricted to treatment of visual impairment due to DME."

The MAH accepted the comments and justifications provided by the CHMP in respect of restricting the sought indication and proposed to update section 4.1 of the SPC to read as follows in accordance with the CHMP's recommendations:

4.1 Therapeutic indications
Macugen is indicated in adults for:

- *the treatment of neovascular (wet) age-related macular degeneration (AMD) (see section 5.1).*
- *the treatment of visual impairment due to diabetic macular oedema (DME) (see section 5.1)*

The CHMP noted that the MAH agreed to rephrase the indication, as requested, and considered additionally that section 4.4 of the SPC sufficiently addresses the limitations of the study population. The proposed indication above is therefore accepted (see also assessment of Question 4a below). Therefore, the issue is resolved, pending approval of the new indication.

Question 3

"Following the results of the pivotal trial, whereby the effect of laser therapy was much more marked in the sham patients than in the pegaptanib arm, there are concerns regarding how pegaptanib should be used in relation to conventional laser therapy and this must be addressed by the MAH. The MAH should explore the options to further address how Macugen should be used in relation to laser photocoagulation. A three armed study comparing Macugen plus laser, Macugen as monotherapy, and laser therapy alone (including escape options to VEGF-inhibitory) may be considered. The MAH should discuss this option and commit to investigate this further."

The MAH explained that a three-armed study comparing pegaptanib plus laser, pegaptanib as monotherapy, and laser therapy alone was considered. However, several considerations including (1) the findings in the A5751013 study, (2) the established efficacy of laser in the treatment of DME (Aiello et al. in Retina-Vitreous-Macula, WB Saunders 1999), (3) the recent approval of Lucentis for the treatment of visual impairment due to DME and as such potential challenges to enrolling a laser arm in any future study, as well as (4) the discussions at the recent Clarifications Meeting (internal minutes) on 17 Feb 2011, the MAH will not plan to include a third, laser arm in the future study. As such, to further understand how pegaptanib should be used in relation to conventional laser therapy, and more specifically to understand whether pegaptanib in combination with laser (no deferral time) is not inferior to pegaptanib monotherapy, the MAH proposes a post approval two-arm study in patients with diabetic macular edema, evaluating (1)Pegaptanib vs. (2) Pegaptanib/plus active Laser. Treatment in both arms would be as follows:

> Pegaptanib
> Two pegaptanib injections will be required initially (Baseline and Week 6) and then pegaptanib will be administered at six week intervals based on visual acuity (section 4.2 posology).
>
> Laser
> Active laser or sham laser will be administered at the Baseline visit. After Baseline active laser and sham/laser will be administered as per ETDRS criteria. After Week 54 active laser may be given in both arms. Pegaptanib injection/sham laser and pegaptanib injection/laser will be administered at the same visit.

The primary endpoint will be the proportion of subjects exhibiting an improvement of ≥10 letters (or 2-lines) of vision (ETDRS) from baseline at Week 54. The study would be continued in a double-masked fashion through Week 102, with the final injection and/or laser treatment to be administered no later than Week 96. Rescue therapy will be restricted to objective criteria for non-responsive patients.

The MAH sought scientific advice and indicated that will share this protocol within three months of opinion of Macugen for the treatment of visual impairment in DME.

The CHMP acknowledged the MAH's plan to perform a two-armed study with pegapbtanib+active laser in one treatment arm and pegaptanib+sham laser in the other treatment arm as the difficulties recruiting subjects to a laser arm are recognised. This study is planned to elucidate a number of efficacy and safety issues including criteria for re-dosing (OC7). The issue can be considered resolved provided that the MAH adhered to the recommendations given in the final advice (unless there would be strong and scientifically valid justifications).

Question 4

"There are still major unresolved issues with regards to (primarily) the pivotal study. These relate to the external validity (suitable to extrapolate study population to target population) and the internal validity (indications of potential bias).

External validity:

a. *Assuming that local mechanisms in the retina might be the same for type I and type II patients is not sufficient to state that treatment can be extrapolated. The MAH must commit to address the effect in subjects with type I diabetes in future studies. A larger clinical study (RCT) exploring pegaptanib treatment in subjects with DME type I and type II, using inclusion criteria that are less restrictive concerning blood pressure and HbA1 level should be undertaken. As long as the results of these additional trials aren't known, the limited experience of pegaptanib-treatment in subjects with DME due to type I diabetes and in diabetic subjects with an HbA1 over 12% (CSR Table 13.7.2.09) should be added to the SPC, section 4.4.*
b. *Full 2-year data should be submitted: The submitted study report linked to the response still has a cut-off date as per November 20, 2009 – i.e. as in the original submission.*
c. *A supplementary report discussing the > 10 letter improvement in vision (primary and secondary endpoint) for the entire study duration until 04 June 2010 should therefore be provided.*
d. *It should be investigated whether patients dropping out from the study are different from those remaining in the study, not only in terms of patient characteristics (baseline characteristics) but also in terms of the outcome values observed. For example, is the baseline outcome value of those dropping out from the study during the first year different from the baseline outcome value of the others? Also, is the change at year one from baseline of those dropping out from the study during the second year different from the change at year one from baseline of the others?*
e. *There are concerns with regards to efficacy (and potentially also safety) when treating subjects with significant retinal ischaemia. The MAH was asked to analyse whether there were any subjects with significant retinal ischaemia included in the study but states that this information was not collected when patient was enrolled in the study and that there is no information available for analysis. However, baseline fluorescein angiograms were captured for the reading centres (Final protocol for study EOP1013, Appendix 16.4: Color fundus photography and Fluorescein angiography), while change in macular capillary loss was evaluated in study EOP1005. Thus the information (from both studies) should be possible to extract. The MAH is requested to present data on whether there were any subjects with retinal ischemia (e.g. any subjects with a centrally located retinal ischaemia of an area < one disc area, e.g. > 500 μm2 and any of these involving the foveal zone) included in the two studies and should presented key efficacy and ocular safety data from these patients.*

Internal validity:

f. *In view of the lack of transparency with regards to the change of primary endpoint, the identified quality problems (serious GCP-violations) at two (in FR and BR) centres, the lack of additional audits at the major CZ centre that included 16% of subjects and the MAH internal decision to terminate the study for all sites in the US in 2007 leading to a high proportion of discontinuations, a GCP-inspection addressing the overall quality of the pivotal study EOP1013 is to be performed. The MAH should therefore provide the response to the questions put forward in the integrated inspection report. "*

For Q4a, the MAH reiterated that they are committed to obtaining a better understanding of the effect of pegaptanib use in diabetic macular oedema (DME) in patients with type I diabetes. They will strive to encouraging enrolment of type I diabetics and in future studies, they will seek to enhance enrollment of type I diabetics with DME through interaction with learned societies, investigators, and Patient Advocacy Groups (A5751034, A5751036, and any future studies).

The MAH modified their future plans and has executed a post-hoc analysis further reviewing the HbA1c and Blood Pressure of the patients in the 1013 study.

Patients with HbA1c level >10% or recent signs of uncontrolled diabetes (3 or more episodes of severe hypoglycemia by DCCT (Diabetes Control and Complications Trial) definition1 within 3 months of

baseline, or 2 or more episodes of ketoacidosis within 1 year of baseline, or an episode of ketoacidosis within 3 months of baseline).were excluded from the study; during the study randomized patients HbA1c levels were well controlled in both treatment groups throughout the study. Additionally, for patients who had baseline HbA1c1 < 10, their maximum values while on study treatment were found to be greater than or equal to 10 in less than 22% of patients of either treatment group (21.5% in Macugen; 17.6% in Sham).

In the 1034 study, the MAH broadened inclusion criteria with regard to HbA1c levels, allowing HbA1c to 12 (protocol A5751034). The MAH is in the process of amending Study 1036 and, as part of that amendment, will broaden the inclusion criteria to include patients with HbA1c to12. In addition, the MAH will use this criterion in future studies.

With regard to blood pressure, inclusion criteria for the 1013 study was limited to patients with blood pressure less than 160/100, during the study the blood pressure of included patients was well controlled with few patients that had even one occurrence of blood pressure over 160/100.
Reference:

1. Early Treatment Diabetic Retinopathy Study Research Group; Focal photocoagulation treatment of diabetic macular edema; Relationship of treatment effect to fluorescein angiographic and other retinal characteristics at baseline: ETDRS Report No. 19: Archives of Ophthalmology, September 1995, Vol 113; Pages 1144-1155

With regards to the above aspects covered by Q4a, the CHMP acknowledged that the MAH was committed to obtaining more data on the effect and safety of pegaptanib use in diabetic macular oedema in patients with type I diabetes. The Committee also considered that a post hoc analysis on the full 2 year data of study A7571013 showed that both blood pressure and HbA1c levels were well controlled throughout the study.

As recommended by the CHMP in the December 2010 RSI, exclusion criteria with regards to HbA1c and BP were made less restrictive for future studies allowing HbA1c level to 12 (studies A5751034 and A5751036 amendment) and BP less than 180/110 (study A5751036).

The MAH has submitted a protocol for A5751034, a new study for the indication of Diabetic Macular edema (ongoing) and amendments to the protocol of study A5751036 (for the indication of Diabetic Macular Oedema). This is captured by FUMs 2, 3 and 4 described in the table 'Recommended Conditions For Marketing Authorisation' at the end of this document.

At the time of issuing of this document, the data and study reports of studies A5751034 and A5751036 are not yet available for assessment.

The MAH proposed to add the following text to section 4.4 of the SPC:
«*There is only limited experience in the treatment of subjects with DME due to type I diabetes, in patients treated with thiazolidinediones and in diabetic patients with an HbA1c over 10% and uncontrolled hypertension*»

However, given that the addition of «*the indication of the treatment of visual impairment due to diabetic macular oedema (DME) (see section 5.1)*» to the indications section 4.1 of the SPC is not acceptable at present, based on the evidence provided within this submission (2-year cut-off data of the pivotal study 1013), the addition of these restrictions to Section 4.4 are not applicable.

For detailed comments on the proposed SPC, please refer to the attachment in section VIII.1.

In conclusion, the CHMP requests in Q4A were satisfactorily addressed by the MAH**.** The MAH plans the Japanese sham-controlled study (A5751034), the up to 3-year EU extension study (A5751036) as well as the study requested in MO 3 to respond to the request. Together with the clear definition of the limitations of the study populations given in section 4.4, it is the CHMP's opinion that this issue can be considered resolved, pending approval of the new indication.

With regards to Q4b, the MAH informed the CHMP that submission of the original A5751013 Clinical Study Report with a data cut-off point of 20 November 2009 was provided in error as part of the original documentation submitted on 11 June 2009.

In accordance with the request in Q4b, a supplement report with a cut-off point of 4 June 2010, which included the information on the remaining 20 % of patients, was provided. Its main findings are summarised in the tables below:

Final 2-year outcome:
Discontinuations

Table 2. Subject Discontinuations; SafetyS1 Population

No. of Discontinued Subjects Before Week 102	Pegaptanib Sodium (0.3 mg) N=144 n (%)	Sham treatment N=142 n (%)
Adverse event	7 (4.9)	8 (5.6)
Protocol violation	0	1 (0.7)
Investigator or Sponsor decision	18 (12.5)	17 (12.0)
Subject request	6 (4.2)	8 (5.6)
Lost to follow-up or subject noncompliance	9 (6.3)	5 (3.5)
Other	2 (1.4)	1 (0.7)
Total	**42 (29.2)**	**40 (28.2)**

Source: Table 13.1.3.1
Abbreviations: N = number of subjects, n = number of subjects meeting specified criteria, No. = number

Proportion of Subjects Who Experienced ≥10-Letter (or 2-Line) Improvement in Vision (Early Treatment of Diabetic Retinopathy Study [ETDRS]) at Year 2 (Week 102) Postbaseline:

Table 4. Proportion of Subjects With a Gain of ≥10 Letters of Vision at Week 102 (LOCF Data); FAS2 Population

No. of Subjects	Pegaptanib Sodium (0.3 mg) N=133 n (%)		Sham treatment N=123 n (%)
Evaluable subjects (LOCF data, FAS2 population)	n=133		n=123
Gain of ≥10 letters of vision at Week 102: Yes	51 (38.3)		37 (30.1)
Gain of ≥10 letters of vision at Week 102: No	82 (61.7)		86 (69.9)
Estimates of the odds ratio and Cochran-Mantel-Haenszel (CMH) test[a]			
Pegaptanib sodium vs sham treatment	Odds Ratio	Confidence Interval (95%)	p-value (CMH)
	1.46	(0.85, 2.53)	0.1904
Breslow-Day test on homogeneity:	p-value = 0.6683		

Source: Table 13.4.1
Baseline values were not carried forward for any missing postbaseline data.
Abbreviations: CMH = Cochran-Mantel-Haenszel, FAS = full analysis set, HbA1c = glycohemoglobin A1c, LOCF = last observation carried forward, N = number of subjects, n = number of subjects meeting specified criteria, No. = number, VA = visual acuity
[a] CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Proportion of Subjects Who Experienced ≥15-Letter Improvement in Vision at Year 2 (Week 102):

Table 5. Proportion of Subjects With a Gain of ≥15 Letters of Vision at Week 102 (LOCF Data); FAS2 Population

No. of Subjects	Pegaptanib Sodium (0.3 mg) N=133 n (%)	Sham treatment N=123 n (%)
Evaluable subjects (LOCF data, FAS2 population)	n=133	n=123
Gain of ≥15 letters of vision at Week 102: Yes	31 (23.3)	18 (14.6)
Gain of ≥15 letters of vision at Week 102: No	102 (76.7)	105 (85.4)

Estimates of the odds ratio and Cochran-Mantel-Haenszel (CMH) test[a]			
Pegaptanib sodium vs sham treatment	Odds Ratio	Confidence Interval (95%)	p-value (CMH)
	1.72	(0.89, 3.34)	0.1140
Breslow-Day test on homogeneity:	p-value = 0.2691		

Source: Table 13.4.2
Baseline values were not carried forward for any missing postbaseline data.
Abbreviations: CMH = Cochran-Mantel-Haenszel, FAS = full analysis set, HbA1c = glycohemoglobin A1c, LOCF = last observation carried forward, N = number of subjects, n = number of subjects meeting specified criteria, No. = number, VA = visual acuity
[a] CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Proportion of Eyes Experiencing a Change in the Degree of Retinopathy by 2 or More Steps at Year 2 (Week 102):

Table 6. Proportion of Eyes Experiencing an Increase in the Degree of Retinopathy by ≥2 Steps at Year 2 (LOCF Data); FAS2 Populations

Parameter		Pegaptanib Sodium (0.3 mg) N=133	Sham treatment N=123
Evaluable subjects (FAS2 population)		103	102
Increase in retinopathy severity by ≥2 steps (at Week 102)	Yes	6 (5.8%)	13 (12.7%)
	No	97 (94.2%)	89 (87.3%)

Estimates of the odds ratio and Cochran-Mantel-Haenszel (CMH) test[a]			
Pegaptanib sodium vs sham treatment	**Odds Ratio**	**Confidence Interval (95%)**	**p-value (CMH)**
	0.48	(0.16, 1.42)	0.1788

Source: Table 13.4.3.1
Baseline values were not carried forward for any missing postbaseline data.
Abbreviations: CMH = Cochran-Mantel-Haenszel, FAS = full analysis set, HbA1c = glycohemoglobin A1c, LOCF = last observation carried forward, N = number of subjects
[a] CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline visual acuity.

Table 7. Proportion of Eyes Experiencing a Decrease in the Degree of Retinopathy by ≥2 Steps at Year 2 (LOCF Data); FAS2 Populations

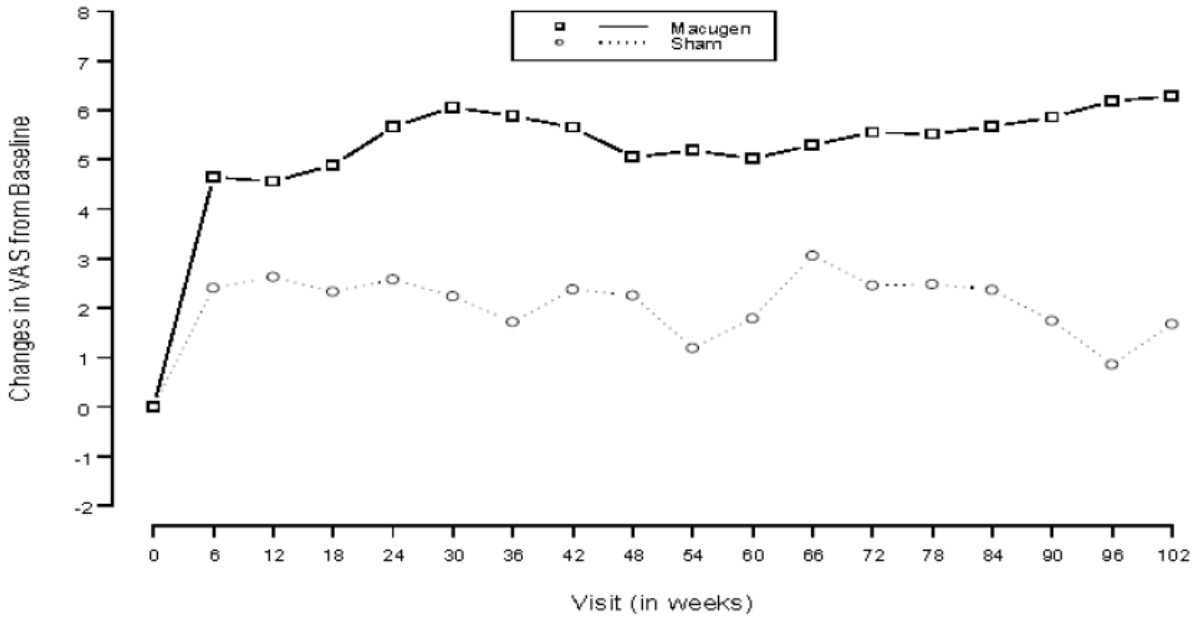
Parameter		Pegaptanib Sodium (0.3 mg) N=133	Sham treatment N=123
Evaluable subjects (FAS2 population)		103	102
Decrease in retinopathy severity by ≥2 steps (at Week 102)	Yes	17 (16.5%)	3 (2.9%)
	No	86 (83.5%)	99 (97.1%)

Estimates of the odds ratio and Cochran-Mantel-Haenszel (CMH) test[a]			
Pegaptanib sodium vs sham treatment	**Odds Ratio**	**Confidence Interval (95%)**	**p-value (CMH)**
	5.12	(1.45, 18.06)	0.0048

Source: Table 13.4.3.2
Baseline values were not carried forward for any missing postbaseline data.
Abbreviations: CMH = Cochran-Mantel-Haenszel, FAS = full analysis set, HbA1c = glycohemoglobin A1c, LOCF = last observation carried forward, N = number of subjects
[a] CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline visual acuity.

Changes in Mean Visual Acuity Over Time:

Figure 1. Change in Visual Acuity Score From Baseline Over Time (LOCF Data); FAS2 Population



CHANGE IN VISUAL ACUITY SCORE FROM BASELINE BY VISITS (LOCF DATA) - MITT2 POPULATION

Number of patients		Macugen N=107	Sham N=100	All N=207
Change from Baseline:				
Week 102	Mean	6.1	1.3	3.8
	Std Dev	10.63	12.04	11.57
	Median	6.0	1.0	5.0
	Range	-19;28	-37;30	-37;30
	N	107	100	207

Comparison between Macugen and Sham:

ANCOVA [1] on VA Change LSMean of Macugen - Sham (95% CI): 4.94 (1.86, 8.01) P-value: 0.0018

[1] Adjusted for HbA1c, systolic blood pressure, diastolic blood pressure and baseline visual acuity.
Note: Baseline values are not carried forward for any missing post-baseline data.

Proportion of Subjects Requiring Focal or Grid Laser by the End of Year 2 (Week 102):
From Week 18 onwards, subjects were permitted to receive focal or grid laser treatments during the study provided that a minimum of 17 weeks occurred between treatments (maximum of 3 focal or grid laser treatments per year)

Table 8. Proportion of Subjects Treated With Focal/Grid Laser at Year 2; FAS2 Population (Study Eye)

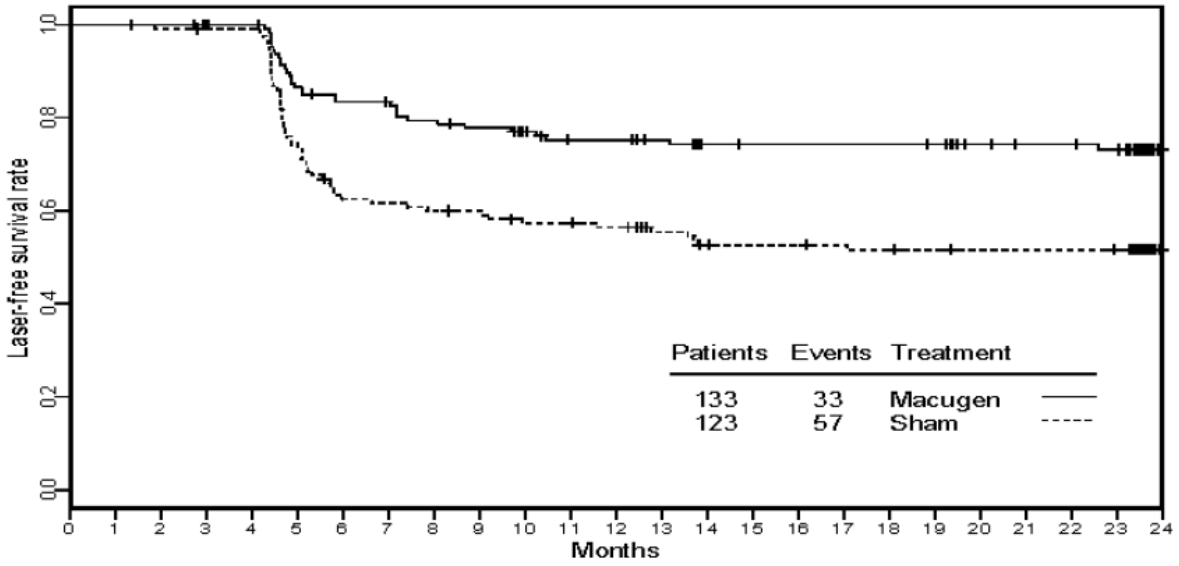
Parameter		Pegaptanib Sodium (0.3 mg) N=133	Sham treatment N=123
Evaluable subjects (FAS2 population)		133	123
Focal/grid laser received[a]	Yes	33 (24.8%)	57 (46.3%)
	No	100 (75.2%)	66 (53.7%)

Estimates of the odds ratio and Cochran-Mantel-Haenszel (CMH) test[b]			
Pegaptanib sodium vs sham treatment	**Odds Ratio**	**Confidence Interval (95%)**	**p-value (CMH)**
	0.38	(0.22, 0.66)	0.0004

Source: Table 13.4.5.1
Abbreviations: CMH = Cochran-Mantel-Haenszel, FAS = full analysis set, HbA1c = glycohemoglobin A1c, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects
[a] Included focal laser coagulation, focal laser photocoagulation, panretinal laser photocoagulation, retinal laser coagulatio and retinal laser photocoagulation as per MedDRA (v12.1) lower level terms
[b] CMH test adjusted for glycohemoglobin A1c (HbA1c), systolic blood pressure, diastolic blood pressure, and baseline visual acuity.

Laser-Free Survival Rates (i.e. proportion of subjects who did not require laser treatment):

Figure 2. Laser-Free Survival Rate Within 2 Years Postbaseline; FAS2 Population



Source: Figure A10.5.6.1
Note that "+" represents censored subjects.
Abbreviation: FAS = full analysis set

Proportion of Subjects With a ≥0 Letter Improvement of Vision From Baseline by Visit:

Table 9. Proportion of Subjects With a Gain of ≥0 Letters of Vision at Week 102 (LOCF Data); FAS2 Population

No. of Subjects	Pegaptanib Sodium (0.3 mg) N=133 n (%)	Sham treatment N=123 n (%)
Evaluable subjects (LOCF data, FAS2 population)	n=133	n=123
Gain of ≥0 letters of vision at Week 102: Yes	96 (72.2)	67 (54.5)
Gain of ≥0 letters of vision at Week 102: No	37 (27.8)	56 (45.5)
P-value (Chi-Square)	0.0032	
P-value Cochran-Mantel-Haenszel (CMH) test[a]	0.0030	

Source: Table 13.5.2.3
Baseline values were not carried forward for any missing postbaseline data.
Abbreviations: CMH = Cochran-Mantel-Haenszel, FAS = full analysis set, HbA1c = glycohemoglobin A1c, LOCF = last observation carried forward, N = number of subjects, n = number of subjects meeting specified criteria, No. = number, VA = visual acuity
[a] CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Retinal Thickness:

Table 10. Proportion of Subjects With Decrease in Retinal Thickness at the Centre Point by ≥25% at Week 102 (LOCF Data); FAS2 Population

Number of Subjects	Pegaptanib Sodium N=133	Sham N=123
Evaluable subjects at Week 102	n=123	n=114
Decrease in retinal thickness by ≥25% from baseline: Yes	59 (48.0%)	51 (44.7%)
Decrease in retinal thickness by ≥25% from baseline: No	64 (52.0%)	63 (55.3%)
p-value (CMH)[a]	0.8943	
Odds Ratio (Confidence Interval 95%)	1.05 (0.61, 1.79)	

Source: Table 13.5.3.1
Baseline values were not carried forward for any missing post-baseline data.
Abbreviations: CMH = Cochran-Mantel-Haenszel, FAS = full analysis set, HbA1c = glycohemoglobin A1c, LOCF = last observation carried forward, N = number of subjects, n = number of subjects meeting specified criteria,
[a] CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline visual acuity.

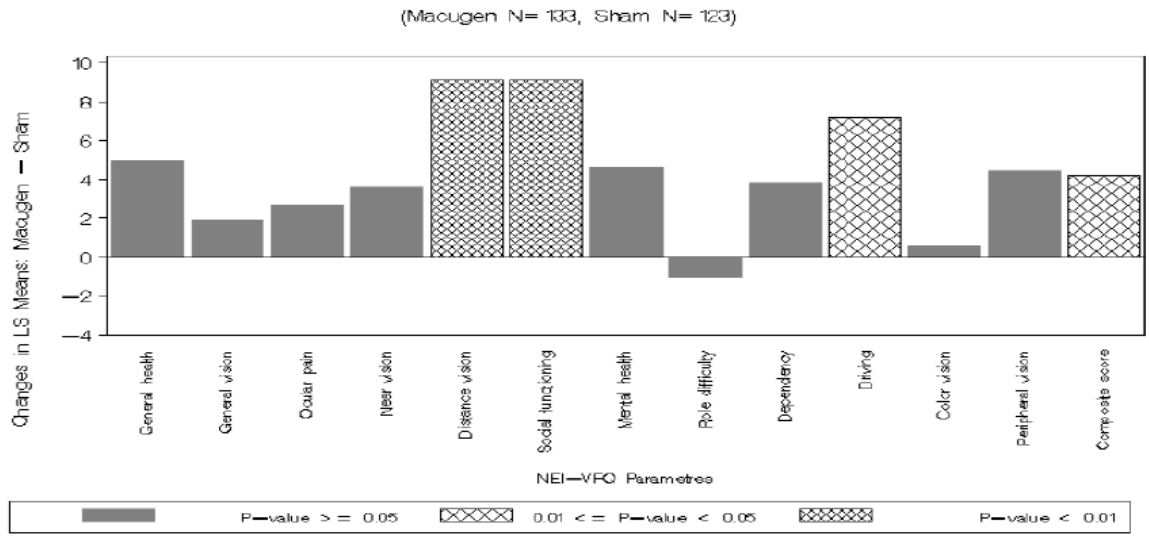
Table 11. Proportion of Subjects With a Decrease in Retinal Thickness at Centre Point by ≥50% at Week 102 (LOCF Data); FAS2 Population

Number of Subjects	Pegaptanib Sodium N=133	Sham N=123
Evaluable subjects at Week 102	n=123	n=114
Decrease in retinal thickness by ≥50% from baseline: Yes	27 (22.0%)	31 (27.2%)
Decrease in retinal thickness by ≥50% from baseline: No	96 (78.0%)	83 (72.8%)
p-value (CMH)[a]	0.0989	
Odds Ratio (Confidence Interval 95%)	0.59 (0.31, 1.11)	

Source: Table 13.5.3.2
Baseline values were not carried forward for any missing post-baseline data.
Abbreviations: CMH = Cochran-Mantel-Haenszel, FAS = full analysis set, HbA1c = glycohemoglobin A1c, LOCF = last observation carried forward, N = number of subjects, n = number of subjects meeting specified criteria,
[a] CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline visual acuity.

Vision-related quality of life

Figure 3. Changes in LS Means in NEI-VFQ 25 Composite Score and Subscales at Week 102 (Pegaptanib Sodium - Sham); FAS2 Population



Having taken the above arguments from the MAH in consideration, the CHMP considered that, at the end of the 2-year study, no statistically significant difference between study groups was observed for the following parameters: > 10 letter improvement in VA, > 15 letter improvement in VA, the proportion of subjects with a decrease in retinal thickness at centre point by ≥25% or ≥50%. The MAH was therefore requested discuss why the > 10 letter improvement in visual acuity at 1 year is not maintained at 2 year (primary and secondary efficacy endpoints) - ***(see remaining major issue on Clinical Efficacy to be addressed in writing 1a).***

In response to Q4c, a supplementary report with a data cut-off point of 4 June 2010 was provided by the MAH. Based on the data obtained over the entire study duration until 4 June 2010, no statistically significant difference between pegaptanib treatment and sham could be demonstrated for the endpoint > 10 letter improvement in vision. The MAH pointed out that this was in line with the conclusion in the previously provided report (data cut-off point of 20 November 2009). The CHMP noted that no further discussion of this final (negative) result was provided, which would have been desirable. The issue was considered by the CHMP to be resolved.

With regards to Q4d, the MAH further investigated patient discontinuations. The total number of discontinuations before Year 1 or before Year-2 was limited, and as a result the subgroup analyses should be considered exploratory and suggestive rather than conclusive.

MITT1: patient demographics and baseline characteristics

For MITT1 population (Table 1), the distribution of race was slightly different, all other demographics and baseline characteristics were similar between patients who discontinued before Year-1 and those who completed Year-1.

Table 1. Demographic Characteristics and Key Baseline Characteristics (Study Eye) – MITT1 Population

	Dropped out before Year-1			Completing Year-1		
	Macugen (N=17)	Sham (N=13)	Both (N=30)	Macugen (N=116)	Sham (N=114)	Both (N=230
Sex						
Male	10 (58.8%)	9 (69.2%)	19 (63.3%)	71 (61.2%)	59 (51.8%)	130 (56.5%)
Female	7 (41.2%)	4 (30.8%)	11 (36.7%)	45 (38.8%)	55 (48.2%)	100 (43.5%)
Race						
Caucasian/White	10 (58.8%)	8 (61.5%)	18 (60.0%)	94 (81.0%)	99 (86.8%)	193 (83.9%)
Asian	2 (11.8%)	3 (23.1%)	5 (16.7%)	11 (9.5%)	12 (10.5%)	23 (10.0%)
Black	3 (17.6%)	0	3 (10.0%)	0	2 (1.8%)	2 (0.9%)
Hispanic/Latino	2 (11.8%)	2 (15.4%)	4 (13.3%)	6 (5.2%)	1 (0.9%)	7 (3.0%)
Other	0	0	0	5 (4.3%)	0	5 (2.2%)
Age (Years)						
Mean	62.9	62.2	62.6	62.2	62.5	62.3
Std Dev	10.31	7.96	9.22	9.22	10.48	9.85
Median	62.0	63.0	62.5	61.5	63.0	62.0
Range	43;80	52;77	43;80	28;83	20;80	20;83
N	17	13	30	116	114	230
Height (cm)						
Mean	170.3	165.8	168.4	167.6	166.4	167.0
Std Dev	8.36	11.18	9.76	8.82	8.64	8.74
Median	168.0	168.0	168.0	166.0	165.5	166.0
Range	157;185	150;193	150;193	144;188	147;186	144;188
N	17	13	30	116	114	230
Weight (kg)						

Table 1. Demographic Characteristics and Key Baseline Characteristics (Study Eye) – MITT1 Population

	Dropped out before Year-1			Completing Year-1		
	Macugen (N=17)	Sham (N=13)	Both (N=30)	Macugen (N=116)	Sham (N=114)	Both (N=230
Mean	90.8	85.7	88.6	82.8	80.4	81.6
Std Dev	20.10	25.01	22.10	16.44	17.83	17.14
Median	93.0	76.0	88.0	82.0	80.0	81.0
Range	57;135	55;125	55;135	54;140	44;137	44;140
N	17	13	30	116	113	229
ECOG performance status[1]						
0	8 (47.1%)	8 (61.5%)	16 (53.3%)	57 (49.1%)	59 (51.8%)	116 (50.4%)
1	8 (47.1%)	5 (38.5%)	13 (43.3%)	58 (50.0%)	52 (45.6%)	110 (47.8%)
2	1 (5.9%)	0	1 (3.3%)	1 (0.9%)	3 (2.6%)	4 (1.7%)
3	0	0	0	0	0	0
4	0	0	0	0	0	0
Baseline Smoking Status						
Active	2 (11.8%)	0	2 (6.7%)	4 (3.4%)	10 (8.8%)	14 (6.1%)
Not Active	15 (88.2%)	13 (100%)	28 (93.3%)	112 (96.6%)	104 (91.2%)	216 (93.9%)
Type of Diabetes						
Type I	1 (5.9%)	2 (15.4%)	3 (10.0%)	9 (7.8%)	6 (5.3%)	15 (6.5%)
Type II	16 (94.1%)	11 (84.6%)	27 (90.0%)	107 (92.2%)	108 (94.7%)	215 (93.5%)
Diabetes Medication						
None	0	0	0	0	0	0
Oral	4 (23.5%)	7 (53.8%)	11 (36.7%)	49 (42.2%)	48 (42.1%)	97 (42.2%)
Insulin	5 (29.4%)	4 (30.8%)	9 (30.0%)	35 (30.2%)	40 (35.1%)	75 (32.6%)
Oral and Insulin	8 (47.1%)	2 (15.4%)	10 (33.3%)	32 (27.6%)	26 (22.8%)	58 (25.2%)
Duration of visual problems in the study eye related to Diabetes						
None	0	0	0	1 (0.9%)	0	1 (0.4%)
<1 year	5 (29.4%)	8 (61.5%)	13 (43.3%)	48 (41.4%)	42 (36.8%)	90 (39.1%)
1-5 years	9 (52.9%)	4 (30.8%)	13 (43.3%)	58 (50.0%)	64 (56.1%)	122 (53.0%)
6-10 years	3 (17.6%)	1 (7.7%)	4 (13.3%)	6 (5.2%)	6 (5.3%)	12 (5.2%)
>11 years	0	0	0	3 (2.6%)	2 (1.8%)	5 (2.2%)

[1] Eastern Cooperative Oncology Group (ECOG) performance status:
0: Fully active, able to carry on all pre-disease performance without restriction.
1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4: Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

Source: Table 1.1a

MITT1: Outcome variables at baseline
The outcome variables (Table 2) at baseline were similar between patients who discontinued before Year-1 and those who completed Year-1.

Table 2. Baseline Outcome Variables (Study Eye) – MITT1 Population						
	Dropped out before Year-1			Completing Year-1		
	Macugen (N=17)	Sham (N=13)	Both (N=30)	Macugen (N=116)	Sham (N=114)	Both (N=230
Baseline VAS (in letters)						
Mean	57.3	60.7	58.8	57.0	57.1	57.0
Std Dev	9.44	7.13	8.55	8.80	8.16	8.47
Median	61.0	63.0	62.0	59.0	60.0	59.5

Table 2. Baseline Outcome Variables (Study Eye) – MITT1 Population						
	Dropped out before Year-1			Completing Year-1		
	Macugen (N=17)	Sham (N=13)	Both (N=30)	Macugen (N=116)	Sham (N=114)	Both (N=230
Range	35;68	42;70	35;70	35;73	35;69	35;73
N	17	13	30	116	114	230
Baseline Severity of Retinopathy						
Mean	4.7	5.5	5.0	5.5	5.4	5.5
Std Dev	1.29	1.00	1.22	1.51	1.57	1.54
Median	5.0	5.0	5.0	5.0	5.0	5.0
Range	3;7	4;7	3;7	2;9	3;9	2;9
N	15	12	27	105	103	208
Baseline Center Point Thickness (in microns)						
Mean	439.4	434.3	437.2	441.9	467.9	454.7
Std Dev	112.4	130.2	117.8	153.6	136.2	145.5
Median	454.0	437.5	454.0	444.0	468.5	451.0
Range	198;680	255;667	198;680	125;884	165;787	125;884
N	17	12	29	113	110	223
Baseline Center Point Thickness (in microns)						
Mean	439.4	434.3	437.2	441.9	467.9	454.7
Std Dev	112.4	130.2	117.8	153.6	136.2	145.5
Median	454.0	437.5	454.0	444.0	468.5	451.0
Range	198;680	255;667	198;680	125;884	165;787	125;884
N	17	12	29	113	110	223
Baseline Central Subfield Thickness (in microns)						
Mean	449.1	433.5	441.9	454.5	473.1	463.8
Std Dev	104.7	101.5	101.4	133.6	119.1	126.5
Median	453.0	441.0	444.5	440.5	477.0	456.0
Range	321;686	278;632	278;686	240;852	244;784	240;852
N	14	12	26	94	95	189
Baseline Total Macular Volume (in cubic millimeters)						
Mean	8.7	9.5	9.1	9.6	9.7	9.7
Std Dev	1.22	1.64	1.46	2.11	2.09	2.10
Median	8.5	9.5	8.7	9.1	9.2	9.2
Range	7;11	7;12	7;12	6;17	7;17	6;17
N	13	11	24	89	93	182

Source: Table 1.1a

MITT1: Primary and Secondary outcomes at Year-1.

Patients who discontinued before Year-1 had greater VA improvement compared to those who completed Year-1. In this analysis the proportion of patients with a decrease or increase in severity of retinopathy of ≥ 2 steps was higher in patients who completed Year 1 compared to those who discontinued prior to Year 1; however, the number of patients in each subgroup was small; thus, the results may not be conclusive. Given the nature of this disease state, the duration of time required to assess a change in the degree of retinopathy is important in ascertaining meaningful information.

The mean change in macular volume was similar between the two groups. For center point thickness (Table 3), there was a negligible change in patients who discontinued before Year-1. However, patients who completed Year 1 had a mean decrease of 37.9 microns. A similar trend was seen with the central subfield parameter.

Table 3. Primary and Secondary Outcomes at Week 54 – MITT1 Population

	Dropped out before Year-1 [1]			Completing Year-1		
	Macugen (N=17)	Sham (N=13)	Both (N=30)	Macugen (N=116)	Sham (N=114)	Both (N=230
Change in VA (in letters)						
Mean	8.9	-1.5	4.4	4.6	1.5	3.1
Std Dev	9.80	14.59	13.00	9.88	11.44	10.77
Median	10.0	-2.0	4.0	6.0	3.0	4.0
Range	-12;25	-29;30	-29;30	-28;27	-65;25	-65;27
N	17	13	30	116	114	230
10 Letters Improvement						
Yes	9 (52.9%)	2 (15.4%)	11 (36.7%)	40 (34.5%)	23 (20.2%)	63 (27.4%)
No	8 (47.1%)	11 (84.6%)	19 (63.3%)	76 (65.5%)	91 (79.8%)	167 (72.6%)
Decrease in Retinopathy by >=2 steps						
Yes	0	0	0	10 (8.6%)	3 (2.6%)	13 (5.7%)
No	4 (23.5%)	7 (53.8%)	11 (36.7%)	84 (72.4%)	87 (76.3%)	171 (74.3%)
Not available	13 (76.5%)	6 (46.2%)	19 (63.3%)	22 (19.0%)	24 (21.1%)	46 (20.0%)
Increase in Retinopathy by >=2 steps						
Yes	0	2 (15.4%)	2 (6.7%)	4 (3.4%)	10 (8.8%)	14 (6.1%)
No	4 (23.5%)	5 (38.5%)	9 (30.0%)	90 (77.6%)	80 (70.2%)	170 (73.9%)
Not available	13 (76.5%)	6 (46.2%)	19 (63.3%)	22 (19.0%)	24 (21.1%)	46 (20.0%)
Change in Center Point Thickness (in microns)						
Mean	-31.5	38.78	0.10	-31.9	-44.0	-37.9
Std Dev	168.82	89.583	140.24	177.49	155.59	166.78
Median	3.00	31.00	6.00	-29.0	-45.0	-39.0
Range	-390;196.0	-131;157.0	-390;196.0	-469;465.0	-494;328.0	-494;465.0
N	11	9	20	112	109	221
Change in Central Subfield Thickness (in microns)						
Mean	-35.1	27.78	-3.67	-7.20	-42.2	-25.3
Std Dev	142.52	93.035	121.16	133.94	119.73	127.64
Median	3.00	28.00	9.50	-13.0	-42.0	-22.0
Range	-330;128.0	-139;149.0	-330;149.0	-398;385.0	-454;289.0	-454;385.0
N	9	9	18	85	91	176
Change in Macular Volume (in mm^3)						
Mean	-0.34	0.17	-0.08	0.02	-0.29	-0.14
Std Dev	0.682	0.641	0.692	1.240	1.444	1.354
Median	-0.48	0.30	0.13	-0.17	-0.08	-0.13
Range	-1.4;0.8	-1.1;0.9	-1.4;0.9	-2.3;3.8	-5.0;5.7	-5.0;5.7
N	8	8	16	79	85	164

[1] The change from baseline was assessed at the time of discontinuation for patients who dropped out before year-1.
Source: Table 1.2a

MITT2: patient demographics and baseline characteristics The distribution of race and gender were different in patients who discontinued prior to Year 1, patients who discontinued during Year 2 and patients who completed Year 2. All other characteristics were similar among the three groups.

Table 4. Demographic Characteristics and Key Baseline Characteristics (Study Eye) – MITT2 Population

	Dropped out before Year-1			Dropped out during Year-2			Completing Year-2		
	Macugen	Sham	Both	Macugen	Sham	Both	Macugen	Sham	Both
	N=17	N=13	N=30	N=24	N=21	N=45	N=66	N=66	N=132
Sex									
Male	10 (58.8%)	9 (69.2%)	19 (63.3%)	15 (62.5%)	13 (61.9%)	28 (62.2%)	37 (56.1%)	31 (47.0%)	68 (51.5%)
Female	7 (41.2%)	4 (30.8%)	11 (36.7%)	9 (37.5%)	8 (38.1%)	17 (37.8%)	29 (43.9%)	35 (53.0%)	64 (48.5%)
Race									
Caucasian/White	10 (58.8%)	8 (61.5%)	18 (60.0%)	16 (66.7%)	13 (61.9%)	29 (64.4%)	58 (87.9%)	62 (93.9%)	120 (90.9%)
Asian	2 (11.8%)	3 (23.1%)	5 (16.7%)	3 (12.5%)	6 (28.6%)	9 (20.0%)	5 (7.6%)	3 (4.5%)	8 (6.1%)
Black	3 (17.6%)	0	3 (10.0%)	0	1 (4.8%)	1 (2.2%)	0	1 (1.5%)	1 (0.8%)
Hispanic/Latino	2 (11.8%)	2 (15.4%)	4 (13.3%)	4 (16.7%)	1 (4.8%)	5 (11.1%)	2 (3.0%)	0	2 (1.5%)
Other	0	0	0	1 (4.2%)	0	1 (2.2%)	1 (1.5%)	0	1 (0.8%)
Age (years)									
Mean	62.9	62.2	62.6	64.5	63.3	64.0	61.5	62.2	61.8
Std Dev	10.31	7.96	9.22	9.57	9.87	9.62	9.99	10.64	10.28
Median	62.0	63.0	62.5	64.0	63.0	63.0	60.0	63.5	62.0
Range	43;80	52;77	43;80	50;83	44;77	44;83	28;82	20;79	20;82
N	17	13	30	24	21	45	66	66	132
Height (cm)									
Mean	170.3	165.8	168.4	167.8	167.1	167.4	166.2	166.2	166.2
Std Dev	8.36	11.18	9.76	6.78	9.00	7.81	8.97	8.67	8.79
Median	168.0	168.0	168.0	167.0	168.0	168.0	165.0	165.5	165.0
Range	157;185	150;193	150;193	155;180	152;183	152;183	144;188	147;186	144;188
N	17	13	30	24	21	45	66	66	132
Weight (kg)									
Mean	90.8	85.7	88.6	83.8	79.1	81.7	82.3	80.5	81.4
Std Dev	20.10	25.01	22.10	14.63	23.73	19.20	16.26	16.98	16.58
Median	93.0	76.0	88.0	82.9	77.0	80.1	81.5	79.0	80.0
Range	57;135	55;125	55;135	60;112	50;137	50;137	54;133	47;132	47;133
N	17	13	30	24	20	44	66	66	132
ECOG performance status [1]									
0	8 (47.1%)	8 (61.5%)	16 (53.3%)	14 (58.3%)	10 (47.6%)	24 (53.3%)	32 (48.5%)	36 (54.5%)	68 (51.5%)
1	8 (47.1%)	5 (38.5%)	13 (43.3%)	10 (41.7%)	9 (42.9%)	19 (42.2%)	33 (50.0%)	30 (45.5%)	63 (47.7%)
2	1 (5.9%)	0	1 (3.3%)	0	2 (9.5%)	2 (4.4%)	1 (1.5%)	0	1 (0.8%)
3	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0
Baseline Smoking Status									
Active	2 (11.8%)	0	2 (6.7%)	0	1 (4.8%)	1 (2.2%)	1 (1.5%)	9 (13.6%)	10 (7.6%)
Not Active	15 (88.2%)	13 (100%)	28 (93.3%)	24 (100%)	20 (95.2%)	44 (97.8%)	65 (98.5%)	57 (86.4%)	122 (92.4%)
Type of Diabetes									
Type I	1 (5.9%)	2 (15.4%)	3 (10.0%)	1 (4.2%)	0	1 (2.2%)	7 (10.6%)	5 (7.6%)	12 (9.1%)
Type II	16 (94.1%)	11 (84.6%)	27 (90.0%)	23 (95.8%)	21 (100%)	44 (97.8%)	59 (89.4%)	61 (92.4%)	120 (90.9%)
Diabetes Medication									
None	0	0	0	0	0	0	0	0	0
Oral	4 (23.5%)	7 (53.8%)	11 (36.7%)	11 (45.8%)	11 (52.4%)	22 (48.9%)	25 (37.9%)	26 (39.4%)	51 (38.6%)
Insulin	5 (29.4%)	4 (30.8%)	9 (30.0%)	6 (25.0%)	6 (28.6%)	12 (26.7%)	22 (33.3%)	25 (37.9%)	47 (35.6%)
Oral and Insulin	8 (47.1%)	2 (15.4%)	10 (33.3%)	7 (29.2%)	4 (19.0%)	11 (24.4%)	19 (28.8%)	15 (22.7%)	34 (25.8%)
Duration of visual problems in the study eye related to Diabetes									
None	0	0	0	1 (4.2%)	0	1 (2.2%)	0	0	0
<1 year	5 (29.4%)	8 (61.5%)	13 (43.3%)	12 (50.0%)	11 (52.4%)	23 (51.1%)	24 (36.4%)	20 (30.3%)	44 (33.3%)
1-5 years	9 (52.9%)	4 (30.8%)	13 (43.3%)	10 (41.7%)	8 (38.1%)	18 (40.0%)	35 (53.0%)	40 (60.6%)	75 (56.8%)
6-10 years	3 (17.6%)	1 (7.7%)	4 (13.3%)	1 (4.2%)	2 (9.5%)	3 (6.7%)	5 (7.6%)	4 (6.1%)	9 (6.8%)
>11 years	0	0	0	0	0	0	2 (3.0%)	2 (3.0%)	4 (3.0%)

[1] Eastern Cooperative Oncology Group (ECOG) performance status:
0: Fully active, able to carry on all pre-disease performance without restriction.
1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4: Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

Source: Table 1.1b

Table 5. Baseline Outcome Variables (Study Eye) – MITT2 Population									
	Dropped out before Year-1			Dropped out during Year-2			Completing Year-2		
	Macugen	Sham	Both	Macugen	Sham	Both	Macugen	Sham	Both
	N=17	N=13	N=30	N=24	N=21	N=45	N=66	N=66	N=132
Baseline VAS (in letters)									
Mean	57.3	60.7	58.8	57.7	56.7	57.2	57.3	57.6	57.5
Std Dev	9.44	7.13	8.55	8.49	9.07	8.68	8.84	7.76	8.29
Median	61.0	63.0	62.0	60.5	60.0	60.0	60.0	60.0	60.0
Range	35;68	42;70	35;70	35;68	35;65	35;68	35;73	35;69	35;73
N	17	13	30	24	21	45	66	66	132
Baseline Severity of Retinopathy									
Mean	4.7	5.5	5.0	5.3	5.3	5.3	5.6	5.5	5.5
Std Dev	1.29	1.00	1.22	1.45	1.45	1.43	1.42	1.64	1.53
Median	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Range	3;7	4;7	3;7	3;8	3;8	3;8	2;7	3;9	2;9
N	15	12	27	20	17	37	61	61	122
Baseline Center Point Thickness (in microns)									
Mean	439.4	434.3	437.2	457.5	438.8	448.6	439.2	467.7	453.1
Std Dev	112.4	130.2	117.8	138.7	148.2	142.0	157.1	143.3	150.6
Median	454.0	437.5	454.0	482.0	428.0	457.5	431.5	466.0	448.0
Range	198;680	255;667	198;680	205;738	165;784	165;784	196;884	180;787	180;884
N	17	12	29	23	21	44	66	63	129
Baseline Central Subfield Thickness (in microns)									
Mean	449.1	433.5	441.9	457.4	455.3	456.3	451.2	473.9	462.3
Std Dev	104.7	101.5	101.4	113.0	119.0	114.4	138.5	125.4	132.1
Median	453.0	441.0	444.5	460.0	458.0	458.0	433.0	481.5	445.5
Range	321;686	278;632	278;686	297;676	272;784	272;784	240;852	244;771	240;852
N	14	12	26	20	19	39	56	54	110
Baseline Total Macular Volume (in mm3)									
Mean	8.7	9.5	9.1	10.1	9.6	9.9	9.5	9.5	9.5
Std Dev	1.22	1.64	1.46	2.38	1.69	2.05	1.99	2.28	2.13
Median	8.5	9.5	8.7	9.8	9.5	9.6	9.2	9.1	9.2
Range	7;11	7;12	7;12	7;16	7;14	7;16	7;17	7;17	7;17
N	13	11	24	19	19	38	52	52	104

Source: Table 1.1b

MITT2: Outcome variables at baseline For MITT2 population, the outcome variables at baseline were similar across all three groups. MITT2: Primary and secondary outcomes at Week 102 (Table 6) Patients who discontinued before Year-1 had similar VA improvement compared to those who completed Year-2 (4.4 and 4.7 letters respectively), while patients who discontinued during Year-2 had less VA improvement (0.7 letters). The proportions of VA improvement of ≥10 letters was also similar between patients who discontinued before Year-1 and patients who completed Year-2 (36.7% and 37.1% respectively), but was lower in patients who discontinued during Year-2 (24.4%). The decrease in severity of retinopathy by ≥ 2 steps was distributed similar between patients who discontinued before year-1 and patients who discontinued during year-2; but within patients who completed Year-2, there were more patients (10.6%) who had a decrease in severity of retinopathy by ≥2 steps. However, the MAH did not find notable differences in increase in severity of retinopathy by ≥ 2 steps among the three groups. Regarding OCT center point thickness, there was a negligible change in patients who discontinued before Year-1; however, patients who discontinued during Year 2 had a mean decrease of 16.1 microns and patients who completed Year-2 had a mean decrease of 117 microns. A similar trend was seen in central subfield thickness. The change in macular volume was negligible in patients who discontinued before Year 1 and in patients who discontinued during Year 2; but it had a mean decrease of 0.34 mm3 in patients who completed year 2.

Table 6. Primary and Secondary Outcomes at Week 102 – MITT2 Population

	Dropped out before Year-1 [1]			Dropped out during Year-2 [2]			Completing Year-2		
	Macugen	Sham	Both	Macugen	Sham	Both	Macugen	Sham	Both
	N=17	N=13	N=30	N=24	N=21	N=45	N=66	N=66	N=132
Change in VA (in letters)									
Mean	8.9	-1.5	4.4	2.2	-1.0	0.7	6.8	2.5	4.7
Std Dev	9.80	14.59	13.00	9.62	12.05	10.81	10.94	11.49	11.38
Median	10.0	-2.0	4.0	3.0	-3.0	1.0	7.5	3.5	5.5
Range	-12;25	-29;30	-29;30	-15;18	-25;20	-25;20	-19;28	-37;22	-37;28
N	17	13	30	24	21	45	66	66	132
10 Letters Improvement									
Yes	9 (52.9%)	2 (15.4%)	11 (36.7%)	6 (25.0%)	5 (23.8%)	11 (24.4%)	26 (39.4%)	23 (34.8%)	49 (37.1%)
No	8 (47.1%)	11 (84.6%)	19 (63.3%)	18 (75.0%)	16 (76.2%)	34 (75.6%)	40 (60.6%)	43 (65.2%)	83 (62.9%)
Decrease in Retinopathy by >=2 steps									
Yes	0	0	0	1 (4.2%)	1 (4.8%)	2 (4.4%)	12 (18.2%)	2 (3.0%)	14 (10.6%)
No	4 (23.5%)	7 (53.8%)	11 (36.7%)	15 (62.5%)	13 (61.9%)	28 (62.2%)	48 (72.7%)	57 (86.4%)	105 (79.5%)
Not available	13 (76.5%)	6 (46.2%)	19 (63.3%)	8 (33.3%)	7 (33.3%)	15 (33.3%)	6 (9.1%)	7 (10.6%)	13 (9.8%)
Increase in Retinopathy by >=2 steps									
Yes	0	2 (15.4%)	2 (6.7%)	1 (4.2%)	3 (14.3%)	4 (8.9%)	4 (6.1%)	6 (9.1%)	10 (7.6%)
No	4 (23.5%)	5 (38.5%)	9 (30.0%)	15 (62.5%)	11 (52.4%)	26 (57.8%)	56 (84.8%)	53 (80.3%)	109 (82.6%)
Not available	13 (76.5%)	6 (46.2%)	19 (63.3%)	8 (33.3%)	7 (33.3%)	15 (33.3%)	6 (9.1%)	7 (10.6%)	13 (9.8%)
Change in Center Point Thickness (in microns)									
Mean	-31.5	38.78	0.10	-11.7	-21.0	-16.1	-74.2	-162	-117
Std Dev	168.82	89.583	140.24	230.57	103.41	179.47	179.85	197.17	192.82
Median	3.00	31.00	6.00	28.50	-42.0	-33.0	-85.0	-152	-112
Range	-390;196.0	-131;157.0	-390;196.0	-469;303.0	-196;195.0	-469;303.0	-377;356.0	-626;310.0	-626;356.0
N	11	9	20	22	20	42	66	63	129
Change in Central Subfield Thickness (in microns)									
Mean	-35.1	27.78	-3.67	-3.67	-37.9	-20.8	-42.9	-107	-75.5
Std Dev	142.52	93.035	121.16	172.24	94.578	138.04	146.55	157.42	154.82
Median	3.00	28.00	9.50	7.50	-45.5	-28.0	-62.0	-93.5	-77.0
Range	-330;128.0	-139;149.0	-330;149.0	-398;233.0	-246;172.0	-398;233.0	-291;353.0	-490;308.0	-490;353.0
N	9	9	18	18	18	36	51	52	103
Change in Macular Volume (in mm3)									
Mean	-0.34	0.17	-0.08	0.15	-0.32	-0.08	-0.23	-0.45	-0.34
Std Dev	0.682	0.641	0.692	1.687	1.176	1.452	1.775	2.181	1.985
Median	-0.48	0.30	0.13	0.12	-0.20	-0.06	-0.42	-0.44	-0.43
Range	-1.4;0.8	-1.1;0.9	-1.4;0.9	-2.5;3.8	-2.5;1.9	-2.5;3.8	-3.2;7.9	-6.1;7.4	-6.1;7.9
N	8	8	16	17	17	34	47	49	96

[1] The change from baseline was assessed at the time of discontinuation for patients who dropped out before year-1.
[2] The change from baseline was assessed at the time of discontinuation for patients who dropped out during year-2.
Source: Table 1.2b.

In summary, patient demographics, baseline characteristics and the outcome variables at baseline were similar between patients who discontinued early as compared to those completing Year-1 or Year-2. However, for VA improvement at Week 54, patients who discontinued before Year-1 had slightly greater improvement than those completing Week 54; but for VA improvement at Week 102, patients who discontinued before Year-1 showed similar improvement compared to those who completed Year-2, both had shown greater improvement than those who discontinued during Year-2. For all other outcome variables, some differences were found among patients who discontinued before Year-1, who completed Year-1, who discontinued during Year-2 or who completed Year-2; however, these differences did not exhibit consistent patterns. Thus, the MAH concluded that with regards to Q4d it was reasonable to believe that the early discontinuations should not have impacted the result of the primary efficacy analysis.

The CHMP noted that, as an outcome of the inspection, the high discontinuation due to closing the US centre was apparently a strategic issue decided by. No specific differences in baseline criteria for patients that discontinued vs. those who did not. It was interesting to note that more patients that did better in terms of VA improvement discontinued treatment during the 1st year, while the opposite was indicated the 2nd year (as may be expected). Issue 4d was considered by the CHMP to be resolved.

For Q4e, the MAH explained that the objective of Protocol 1013 was to evaluate '*subjects with diabetic macular oedema (DME) involving the center of the macula associated with vision loss not due to*

ischemia.' In order to assure appropriate subjects entered the trial, the protocol specified Exclusion Criterion 7.3.1.2 as follows:
Presence of any abnormality that is likely to confound assessment of visual acuity improvement in eyes in which macular edema resolves, or improves, such as non-perfusion for >1 disc area involving the foveal avascular zone (FAZ - involving 2 or more quadrants centered around the foveal avascular zone), epiretinal membrane associated with signs of contraction and/or significant opacification (i.e. striae within 1 disc diameter of the foveal center), or presence of chorioretinal atrophy involving the center of the macula.

The Reading Center independently verified that patients met this criteria upon study entry. In order to more adequately address the request of the EMA, the MAH obtained and summarised information regarding capillary loss in Protocol 1013. Within the grading system applied by the central reader, the variable "capillary loss" represents (i.e., is generally synonymous with) the term "ischemia" as used clinically. In the ETDRS severity of capillary loss was estimated in each of the subdivisions (subfields) of a grid covering the central 16 disc areas of the 30 degree photographic field that is centered on the macula. A 6-step scale was used: none (Code 0); questionable (Code 1); definitely present mild (Code 2); definitely present moderate (Code 3); definitely present severe (Code 4 or 5); cannot grade (Code 8 or Indeterminable). The reading center modified the ETDRS grading system to estimate area of definite capillary loss in each of the 9 subfields of the grid and to combine them into an estimate for the grid as a whole and for the central plus 4 inner subfields.

The tables below summarize capillary loss noted within the Central Subfield and the ETDRS Grid at Baseline, Week 54 and Week 102 for angiograms that were readable. No capillary loss >1 disc area for the Central Subfield was noted for any subject at any time. Only a handful of subjects had a capillary loss >1 disc area within the ETDRS Grid at any time point, and these were all within the Macugen treatment group.

Capillary Loss Within Central Subfield at Week 54 – MITT1

Capillary Loss in Disc Areas	*Baseline*		*Week 54*	
	Macugen (N=133)	Sham (N=127)	Macugen (N=133)	Sham (N=127)
None	91 (68.4%)	76 (59.8%)	75 (56.4%)	57 (44.9%)
< 0.13 DA	8 (6.0%)	12 (9.4%)	3 (2.3%)	10 (7.9%)
0.13-0.28	7 (5.3%)	8 (6.3%)	4 (3.0%)	3 (2.4%)
0.29-0.50	0	0	0	0
0.51-1.00	0	0	0	0
1.01-2.00	0	0	0	0
2.01-3.00	0	0	0	0
3.01-4.00	0	0	0	0
>=4.01 DA	0	0	0	0
Missing	7 (5.3%)	6 (4.7%)	28 (21.1%)	27 (21.3%)
Unable to read/grade	20 (15.0%)	25 (19.7%)	23 (17.3%)	30 (23.6%)

Source Table 1.6.2a

Capillary Loss Within Central Subfield at Week 102 – MITT2

Capillary Loss in Disc Areas	*Baseline*		*Week 102*	
	Macugen (N=107)	Sham (N=100)	Macugen (N=107)	Sham (N=100)
None	71 (66.4%)	53 (53.0%)	37 (34.6%)	23 (23.0%)
< 0.13 DA	8 (7.5%)	11 (11.0%)	1 (0.9%)	4 (4.0%)
0.13-0.28	4 (3.7%)	8 (8.0%)	1 (0.9%)	4 (4.0%)
0.29-0.50	0	0	0	0
0.51-1.00	0	0	0	0
1.01-2.00	0	0	0	0
2.01-3.00	0	0	0	0
3.01-4.00	0	0	0	0
>=4.01 DA	0	0	0	0
Missing	5 (4.7%)	5 (5.0%)	53 (49.5%)	45 (45.0%)
Unable to read/grade	19 (17.8%)	23 (23.0%)	15 (14.0%)	24 (24.0%)

Source Table 1.6.2b

Capillary Loss Within ETDRS Grid at Week 54 – MITT1

Capillary Loss in Disc Areas	*Baseline*		*Week 54*	
	Macugen (N=133)	Sham (N=127)	Macugen (N=133)	Sham (N=127)
None	69 (51.9%)	62 (48.8%)	54 (40.6%)	49 (38.6%)
< 0.13 DA	16 (12.0%)	11 (8.7%)	11 (8.3%)	9 (7.1%)
0.13-0.28	7 (5.3%)	15 (11.8%)	5 (3.8%)	6 (4.7%)
0.29-0.50	5 (3.8%)	6 (4.7%)	5 (3.8%)	5 (3.9%)
0.51-1.00	2 (1.5%)	2 (1.6%)	3 (2.3%)	1 (0.8%)
1.01-2.00	3 (2.3%)	0	2 (1.5%)	0
2.01-3.00	3 (2.3%)	0	1 (0.8%)	0
3.01-4.00	1 (0.8%)	0	1 (0.8%)	0
>=4.01 DA	0	0	0	0
Missing	7 (5.3%)	6 (4.7%)	28 (21.1%)	27 (21.3%)
Unable to read/grade	20 (15.0%)	25 (19.7%)	23 (17.3%)	30 (23.6%)

Source Table 1.6.1a

Capillary Loss Within ETDRS Grid at Week 102 – MITT2

Capillary Loss in Disc Areas	*Baseline*		*Week 102*	
	Macugen (N=107)	Sham (N=100)	Macugen (N=107)	Sham (N=100)
None	54 (50.5%)	44 (44.0%)	29 (27.1%)	16 (16.0%)
< 0.13 DA	15 (14.0%)	9 (9.0%)	1 (0.9%)	4 (4.0%)
0.13-0.28	4 (3.7%)	14 (14.0%)	4 (3.7%)	3 (3.0%)
0.29-0.50	3 (2.8%)	3 (3.0%)	3 (2.8%)	5 (5.0%)
0.51-1.00	2 (1.9%)	2 (2.0%)	1 (0.9%)	3 (3.0%)
1.01-2.00	2 (1.9%)	0	1 (0.9%)	0
2.01-3.00	2 (1.9%)	0	0	0
3.01-4.00	1 (0.9%)	0	0	0
>=4.01 DA	0	0	0	0
Missing	5 (4.7%)	5 (5.0%)	53 (49.5%)	45 (45.0%)
Unable to read/grade	19 (17.8%)	23 (23.0%)	15 (14.0%)	24 (24.0%)

Source Table 1.6.1b

No subjects demonstrated capillary loss in the central subfield of >0.29 disc area (centrally located retinal ischaemia), as such, the MAH was unable to perform additional sub-analyses of key efficacy and safety data on patients with centrally located retinal ischaemia of an area > 1 disc area.

With regard to Protocol 1005, the objective was to evaluate 'Clinically Significant Diabetic Macular Edema (CSME) Involving the Center of the Macula.' and, as for Protocol 1013, subjects with non-perfusion for >1 disc area involving the foveal avascular zone were excluded. Upon entry into the study, the Reading Center verified that patients met these criteria and no patients with non-perfusion of >1 disc area involving the foveal avascular zone were included in the study.

In this study, the maximum grade recorded for any subfield, and the number of subfields with that grade, were used to characterize capillary loss:

Severity level	Maximum grade/Number of subfields with maximum
0	0
1	1/1 – 10, 2/1
2	2/2 – 10, 3/1
3	3/2 – 10, 4/1
4	4/2 – 3
5	4/4-10
8	Indeterminable

The information indicates the following at baseline: 57% had no capillary loss, 20% had at worst mild capillary loss in one of ten subfields, 7% had at worst moderate capillary loss in one of ten subfields, 9% had at worst severe capillary loss in one of ten subfields, 4% had severe capillary loss in two or three of ten subfields, 1% had severe capillary loss in more than 3 of ten subfields, and 2% were indeterminate for capillary loss. The distribution is concentrated in the range of no-to-mild capillary loss.

Table 5.1.10.1a (initial application) summarizes the capillary loss grades over all ten subfields in the ETDRS FA grading: central subfield, four inner subfields, four outer subfields and far temporal subfield. Looking at the results for all ten subfields brings the far temporal subfield (which is outside the ETDRS grid proper) into play. This means that eyes with far temporal capillary dropout can show up in the upper end of the summary scale – even if they have no or only mild capillary dropout near the center of the macula.

Additional exploratory efficacy endpoints evaluated change in macular capillary loss during the study. In this work, the macula was divided into nine subfields according to the ETDRS macular grid, each abnormality was graded against a series of standards for each subfield of the grid. For each of the relevant areas, a summary variable for the entire area was computed. This variable gave the maximum grade assigned in any subfield concatenated with the number of subfields receiving that grade. For example, "4/1" denotes a maximum grade of 4 occurring in one of nine subfields (or ten subfields, for capillary loss). Since this created a rather extensive scale, a scheme to pool the compound grades into a manageable scale recommended by was used. The distribution of change in fluorescein angiographic variables from baseline to follow-up between treatment groups was compared using these summary scales.

A χ^2 test (Cochran-Amitage test) for trend was carried out on the proportion of patients falling in each category of these scales. In case that the expected frequency in any one of the cells of the contingency table was less than 5, the exact trend test, for stratified 2 x C contingency tables in StatXact 4.0, was used.

Since no subjects demonstrated capillary loss in the central subfield of >1.0 disc area (centrally located retinal ischaemia), the MAH was unable to perform additional sub-analyses of key efficacy and safety data; however, a summary of capillary loss of the grid as a whole for the ITT population at baseline is shown in Table 5.10.1a in Section 15 of the Clinical Study Report. The data for active treatment groups and the sham control group did not show any clear differences. This information was previously reported.

In summary, upon entry into the 1013 and 1005 study, the Reading Center independently verified that patients did not demonstrate non-perfusion of >1 disc area involving the foveal avascular zone.

The CHMP acknowledged the efforts from the MAH in addressing Q4e, and particularly their submission of an evaluation on the extent of retinal ischaemia in the study by analyses within the ETDRS grid and by specifically analysing capillary loss in the central subfield. In none of the studies, subjects with a significant capillary loss were included. In EOP1013, there were no subjects with a central loss of >0.28 DAs while only 5 subjects with a > 1 DA of capillary loss within the ETDRS grid were defined. Due to the few cases, the MAH was unable to perform additional sub-analyses of key efficacy and safety data. The same was evident for study EOP1005. Of importance is, however, that the number of subjects with some degree of ischaemia at baseline did not appear increase during treatment with pegaptanib. However, a large number of patients ware missing for evaluation, especially at week 102, and the outcome is thus inconclusive. Although the data are very limited, this is of some reassurance, since it is not unlikely that such subjects will be treated in clinical practice. The SPC (section 4.4) contains the information on the lack of/limited experience in treating subjects with major ischaemia and relevant information is also given in the RMP (missing data). Finally, the MAH has indicated that they will further address this in the EU DME safety study. Overall, the issue will be considered resolved once the results of the EU DME safety study (A5751036), which has now been extended to 3 years (see RMP), will be available.

In conclusion, the CHMP considered that the lack of data in subjects with retinal ischaemia has been adequately addressed in the SPC, in the RMP and efforts to gain experience in these subjects will be made in the EU DME safety study (study A5751039).

With regards to Q4f, the MAH's response to GCP queries received following the investigator and sponsor site inspections that took place in February and March 2011 were included as annexes to their response document, including the original inspector reports.

What follows summarises the MAH's position on the findings:

- The audit approach adopted for the A5751013 program was to initially focus on three of the highest recruiting centers (– Czech Republic, – France) as well as one identified by the study team for suspected GCP violations related to source records (– Brazil).
- The first two investigator site audits were performed at sites in the Czech Republic– Drs. and (enrollment accounted for approximately 16% of the overall study enrollment numbers) – and were the subject of subsequent EMA inspections related to this regulatory submission.
- The third investigator site audit was performed at a site in France – Dr.. Significant GCP violations were noted at this site (report subsequently provided to the EMA inspectors) and the findings led to the subsequent performance of 5 additional site audits (2 France, 1 UK, 1 Germany, 1 Portugal) to assess if similar issues to those identified in France were present at other sites and/or if there was anything suggestive of systemic oversight failures.
- The fourth investigator site audit was performed in Brazil – Dr. . Significant GCP violations related to source were identified.
- Actions taken in relation to the and sponsor audits included the following:
    - site: Data from the 4 properly randomized subjects were excluded from primary efficacy analysis due to inability to verify baseline visit source data; data from all subjects who received at least one dose of treatment were included in the safety analysis
    - site: Data from one subject were excluded from primary efficacy analysis due to repeated steroid injection related to concurrent participation in a second study; due to GCP noncompliance findings at the site, data from the 17 remaining randomized subjects were excluded from primary efficacy analysis but included in a sensitivity analysis; safety tables was generated both with and without data from the 18 randomized subjects
- While audits at the 5 additional sites(referenced in bullet 3 above) resulted in a number of observations, none were deemed critical by the MAH and results were not suggestive of pattern; hence, additional investigator site audits and/or re-audit of the sites in the Czech Republic were not deemed necessary
- Additional information related to audit activities performed in support of the A5751013 program will be addressed during the sponsor inspection as well as in the MAH responses to the integrated inspection report

The CHMP considered that the main issues behind the inspection were:
1) Question regarding the lack of transparency behind the change of primary endpoint one year after the first patient entered the study;
2) The quality problems identified by the MAH at certain sites and a concern regarding the MAH's routines to guarantee an adequate level of quality at the 56 centres for 260 patients;
3) The MAH internal decision to terminate the study for all sites in the US in 2007 leading to a high proportion of discontinuations.

had marketing rights in North America and Pfizer for the rest of the world. At onset of the study was the official sponsor of the study. In 2006, declared that they would not pursue the DME indication in the US and the implication of this decision was to terminate the US sites, delete the two lower doses, and change the primary efficacy parameter from 3 to a 2 line improvement. Pfizer took over the responsibility of the study and the transfer of the sponsorship to Pfizer was completed on 31 October 2008.

The inspection included visits at the two Czech Republic sites and at the Sponsor site (US). The inspection report revealed the key findings below and the following conclusions:
- the sponsor did not have acceptable routines or system to ensure adequate overview of the study conduct (critical finding)
- the electronic trial master file did not comply with the regulation (critical finding)
- major findings included, for example: introduction of a waiver system, data not always reported back to the investigators, incorrect descriptions (eligibility criteria, safety issues) in study report.

Data recorded and reported by the study sites appeared reliable. The previous sponsor lacked overview of the conduct of the study. The quality of the overview improved substantially when Pfizer gained the sponsorship and took control of the study, but even today there is a tendency of insufficient oversight. New processes are being, or have been implemented in order to ensure complete compliance.

The responses received from the two clinical sites and Pfizer's site verified the findings described in the individual reports. The responses also indicated an understanding of the findings. The deviations identified were concluded likely not to have in any major sense influenced or changed the results as they were presented in the final study report. The recommendation of the inspectors was that the study report can be used for evaluation and assessment of the application.

In conclusion, the CHMP considered that the previous sponsor, , lacked overview of the conduct of the study. The situation improved substantially since Pfizer gained the sponsorship. The inspection concluded that the study report can be used for evaluation and assessment of the application. The issue was considered resolved.

OTHER CONCERNS

Question 5 (Pharmacokinetics)

"*To be able to adequately assess the Cmax levels observed in DME patients [Study EOP1005] and for completeness, the raw data and bioanalytical report from study EOP1005 should be submitted. The applicant should discuss whether Cmax is appropriately described by the model and whether Cmax in the SPC is the mean of observed values, typical predictions or individual predictions (considering the large shrinkage in Ka and V). Further the applicant should clarify the origin of the exposure data presented in the SPC for the two populations (DME and AMD). Relevant exposure measures should be presented and differences in renal function between the two populations should be considered.****"***

The MAH articulated their response in three parts, as summarised below:

A) The final bioanalytical report (Project EQM) determining plasma pegaptanib levels in patients from study EOP1005 was submitted. This contained the requested listings of the raw data.

B) The Cmax values (as well as the AUC) reported in Table 5 of the SPC are arithmetic means of the individual predictions, which were derived by plugging the empirical Bayes (post-hoc) estimates of the random effects and the fixed effects estimates into the final model. The MAH agreed with the CHMP that the shrinkage of Ka and V is on the larger side (31% for V and 58% for Ka – Appendix 5 of PMAR-00174). However, these larger shrinkages do not appear to indicate that the individual predictions of Cmax are inappropriate or inaccurate. A summary of the individual Bayes predictions of the NCA parameters were similar to the same summaries of simulated data, which would not suffer from shrinkage. An excerpt of this comparison is provided below (Table 6-1.):

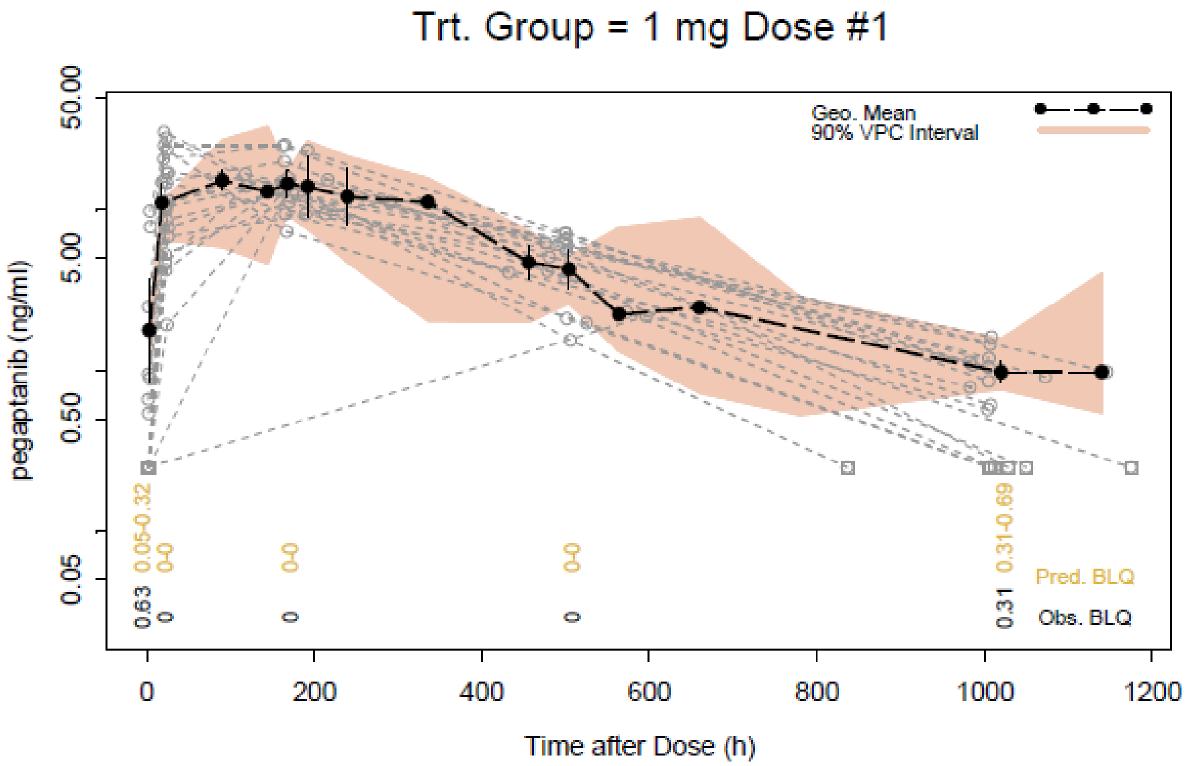
Table 6-1. Summary of NCA Parameter Predictions for the Final Model Scaled to 0.3 mg

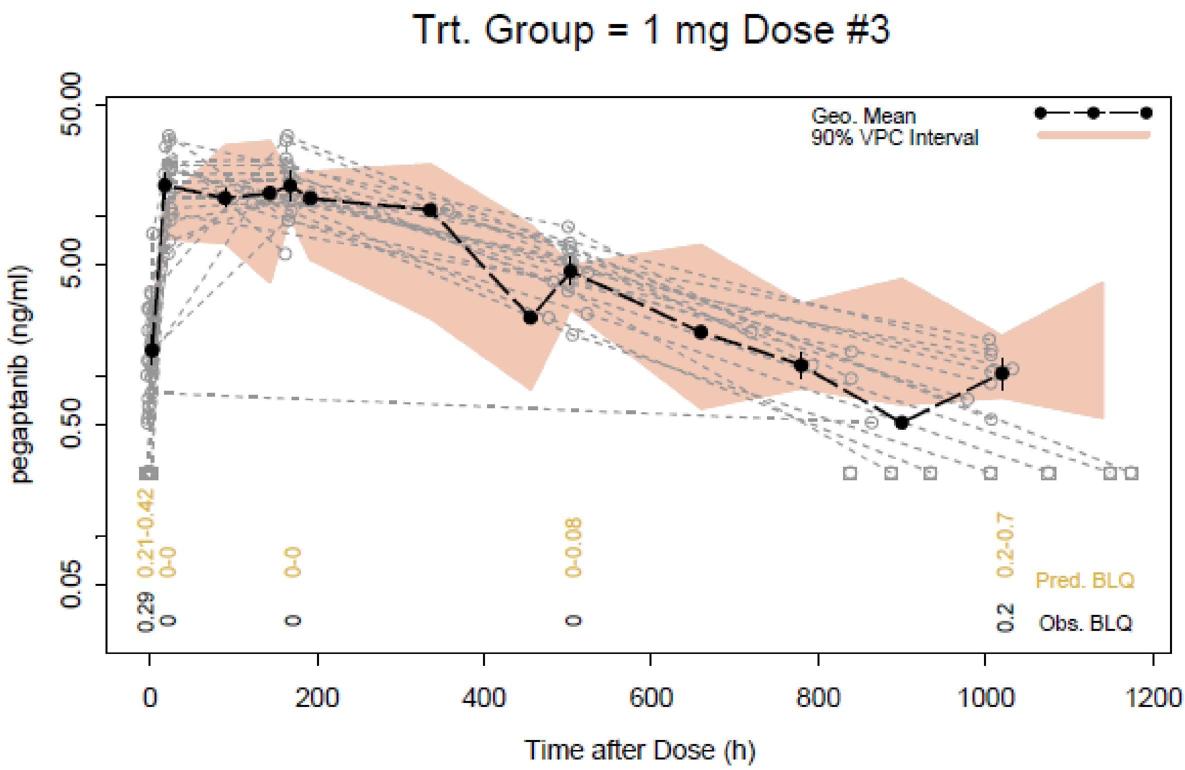
Covariate		AUC(0-inf) (ng.h/ml)			Cmax (Single Dose) (ng/ml)			Tmax (Single Dose) (h)			$T_{½}z$ (d)		
Value	N	Mean	Med	%CV	Mean	Med	%CV	Mean	Med	%CV	Mean	Med	%CV
						...							
Total	58	1608	1727	40.0	4.6	4.8	37.5	86.8	92.7	41.0	6.8	6.7	12.9
Sim. Total[a]		1592	1590	45.2	4.5	4.5	40.8	85.0	86.7	51.1	6.8	6.8	19.7

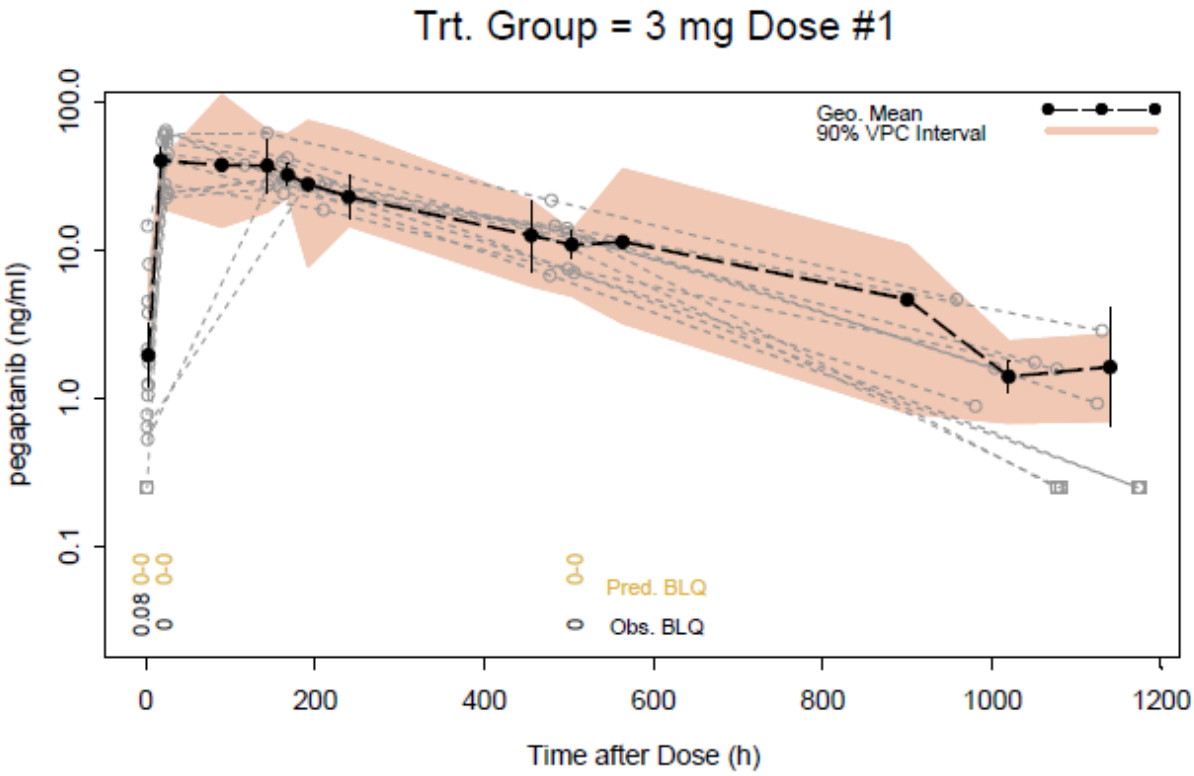
[a]Simulation considered 100,000 virtual subjects

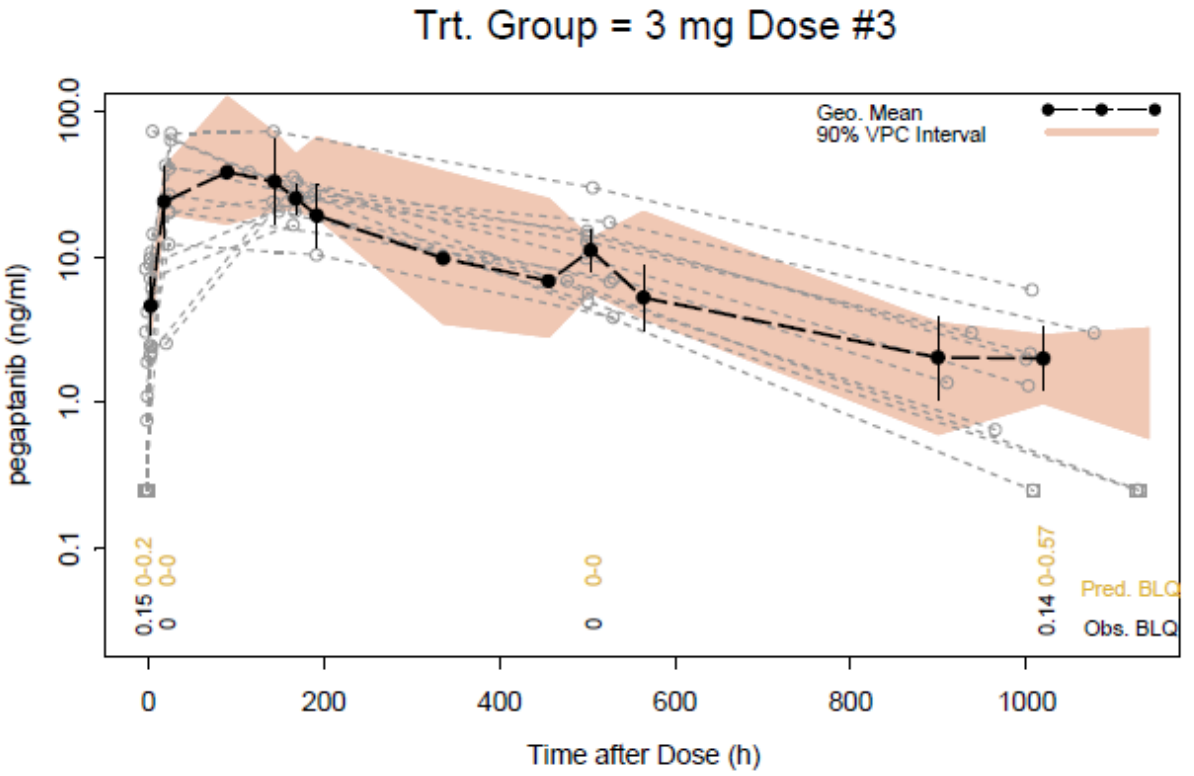
The arithmetic means of the predictions of Cmax (and AUC) and the %CV's are similar for the empirical Bayes predictions (Line entry 'Total') and those from a Monte Carlo simulation, which used the estimate of the variance components (and hence do not suffer from shrinkage) to generate the predictions. This similarity in variability between the individual predictions and the simulations might not seem intuitive. However, pegaptanib has flip-flop kinetics, where the ascending phase of the concentration profile could be determined (heuristically) to be driven by Ke = CL/V, so Cmax is primarily determined by Ke and V, not Ka and V as with regular kinetics. Thus, the shrinkage in Ka might not play as much of a role in predicting Cmax for pegaptanib. Additionally, the shrinkage estimate of the IWRES, individually weighted residuals, which are calculated as [y – IPRED]/(σ) (y is natural logarithm of a concentrations and IPRED is a natural logarithm of an individual prediction of y), was 35%. The shrinkage indicates that the IPRED were closer to the y values than the residual

variance estimate indicated (that is, the variance of the IPRED is 35% less than the estimate of σ). Thus, despite the shrinkage in Ka and V, model predictions are not affected – the model is sufficiently flexible to predict the data. A visual predictive check of the concentration data was performed to evaluate if the model was compatible with the data. This was performed to evaluate whether quantities such as Cmax are predicted accurately by the model. This figure is reproduced below for convenience. From the plots, Tmax might be over-predicted, but the model does predict Cmax adequately.









C) The demographics of the populations from Study EOP1005 (DME) and from study (AMD) were outlined in the Table below (Table 6-2).

Table 6-2. Comparison of the Population Demographics of Patients with DME and AMD utilized in Population PK Analyses.

Population	n	Sex		Age (yrs)			Baseline Weight (kg)			Race				Baseline CLCR (mL/min)		
		M	F	Mean	Median	SD	Mean	Median	SD	W	B	H	A	Mean	Median	SD
DME	58	32	26	61.7	61.5	11.6	86.6	85.2	19.2	44	8	4	2	77.7**	70.5	32.8
AMD	262	127	135	75.5	76	7.52	69.1	67.2	15.2	162	3	1	94	60.6	58.4	18.7

**: P<0.01, unpaired two-way t-test. Data taken from table 5, PMAR-000173 and Table 4, PMAR-000174

Baseline creatinine clearances of the DME patients from study A5751005 and 1013 are 28.2% greater than those of AMD patients from studies A5751000, 1001, 1006 and 1010. This may reflect the significantly greater (22%) average age of the AMD patients enrolled in the 4 studies, and the concomitant decrease in renal function with age (Lindeman, 1985). Nonetheless, the mean CLCR values of the patients in both disease groups are within the range of CLCR defining mild renal insufficiency. The influence of CLCR on systemic exposure to pegaptanib in both patient populations was investigated in detail in two population PK analyses (PMAR-000173 and 000174). These population PK studies determined the basic PK parameters of pegaptanib and describe the changes in CL, Cmax and AUC of pegaptanib with CLCR and other covariates for both patient populations. To summarize, CLCR significantly influenced CL, with an approximately 2 (2.3-2.5) fold decrease in CL over the range of CLCR studied (30-120 mL/min). This result was qualitatively similar for DME and AMD patients. However, the magnitude of the decrease in CL with diminished renal function is such that systemic exposure (Cmax, AUC) following administration of the therapeutic 0.3 mg dose of pegaptanib to patients with CLCR less or equal to 30 mL/min is predicted to be much less than the 10 fold higher plasma levels of pegaptanib observed following the well-tolerated 3 mg dose.

The CHMP noted that the raw data ranged from <LOQ for all samples in some subjects to above 70 ng/ml in a few subjects.

The Committee also noted that the MAH explained that the data included in the SPC section 5.2 is arithmetic means of individual predictions based on the population PK model. This PK 'flip-flop' behaviour means that elimination rate is of larger importance for the Cmax than the absorption rate constant hence that shrinkage in Ka would not be influencing these calculations. Although it is agreed that 'flip-flop' kinetics are applicable, the shrinkage in V is still rather large (31%), hence calculating arithmetic means of individual predictions may be inaccurate (model based or based on non-compartmental analysis made on these individual predicted profiles). Geometric mean of observed Cmax and/or Cmax in the typical profile (i.e. based on typical parameter estimates) would be preferred. Information regarding % of subjects with Cmax observations below LLOQ would also be of interest. AUCs for a typical individual in the respective population (for a given weight and renal function) would also be of interest, and it would be desirable to have the half-life for the typical profile submitted.

The following amendments to the SPC section 5.2 were recommended by the CHMP (X and Ys are numbers to be provided by the MAH)

In patients with DME or AMD treated with the recommended 0.3 mg/eye dose, ***observed Cmax ranged from X to Y. X and Y% of the subjects had all observations less than 0.5 ng/ml (lowest measurable concentration). Based on population PK the typical*** maximum plasma concentration (C_{max}) of pegaptanib ***were X and Y for DME and AMD respectively.*** ~~ranges from an average of 5 to 7.6 ng/ml, which is~~ ***Cmax was predicted to typically be*** reached within ***X and Y*** ~~an average of 2.7 to 3.1~~ days (T_{max}). The ~~mean~~ ***typical*** area under the plasma concentration-time curve (AUC) ***for a 70 kg subject with CLCr 80 ml/min were X and Y*** ~~is 1.6-2.3~~ µg hr/mL, and the apparent plasma half-life ***were X and Y*** ~~averages 6.9 to 7.8~~ days, ***for AMD and DME patients respectively***. Pegaptanib was not observed to accumulate in the plasma following repeated intravitreal administrations.

The CHMP recommended also that no detailed information on the above should be included in section 4.2

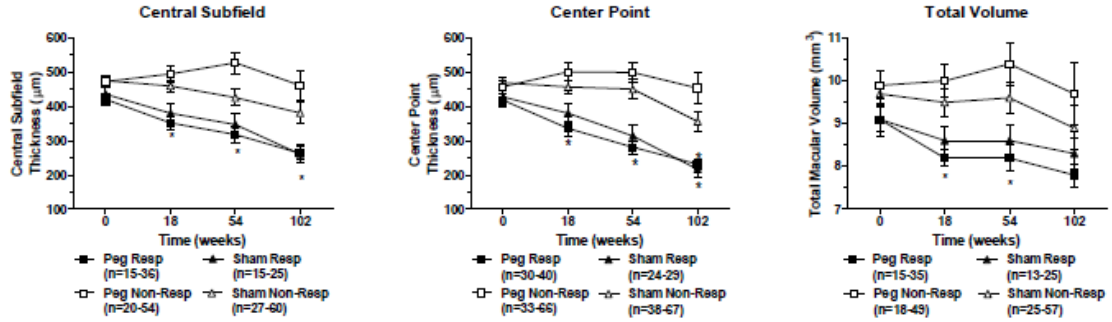
Question 6 (Efficacy)
"The MAH is requested to explain why, if pegaptanib is really reducing blood retina barrier permeability, there is no effect on objective measures of oedema (which currently are only performed with OCT machines)."

The MAH Responded that vascular endothelial growth factor (VEGF) potently increases vascular permeability (Senger, 1983), contributing to oedematous states in diseases such as diabetic retinopathy/diabetic macular oedema (Aiello, 1994). Reducing intraocular VEGF levels may be expected to reduce retinal vascular permeability, and therefore retinal edema/thickening with a resulting improvement in visual acuity (VA), (Moss, 1988). However, VEGF also regulates osmotic swelling of retinal glia, such that reducing ocular VEGF levels may increase glial swelling with deleterious effects on retinal function (Wurm, 2008; Krugel, 2010). Thus, changes in retinal thickness per se may not be sufficient to predict retinal function or visual acuity. Instead, changes in the thickness of specific retinal layers or cell populations may be more indicative of improvements in retinal function. Given that multiple factors contribute to diabetic macula edema (Funatsu, 2002), reducing ocular levels of VEGF alone, while sufficient to enhance visual function, may not measurably decrease overall retinal thickness Relatively recently, OCT and its application have evolved to the point where moderate correlations between changes in retinal thickness and visual acuity in DR/DME have been reported (Al-latyfeh, 2010; Kim, 2006; Murakami, 2011).

However, at the time of initiation of the A5751013 study, the maturity of the technology, its application, and intraindividual variability acted as substantial impediments to the ability of OCT to correlate changes in visual acuity with retinal thickness. This situation was not inconsistent with the wide variation in reported strength of the correlation between OCT and visual acuity (DRCR 2007; Bandello, 2005; Goebel, 2002; Hee, 1995; Otani, 2001), suggesting that OCT measured retinal thickness may not adequately predict visual acuity. This information contributed to the decision to use visual acuity measurements as the primary endpoint in the 1013 study and to assess changes in retinal thickness as measured by OCT parameters (eg, central subfield thickness, centerpoint thickness, macular volume) as a secondary endpoint. Nonetheless, the outcome in the 1013 study did not support a significant association between the changes in retinal thickness parameters as determined by OCT and improvement in visual acuity from cohorts evaluated in toto. Post-hoc analysis of the treatment cohorts indicated that a sub-population of patients manifested a significant improvement in visual acuity. Figure 7-1 below illustrates the absolute values of central retinal subfield thickness (Csub), center point thickness (CPT) and total volume over time for patients achieving a clinical response asdefined by ≥10 letter gain versus patients who did not achieve a full response. The change in Csub, CPT and total volume values relative to baseline for VA responders and VA non-responders to pegaptanib and sham treatment over time are illustrated in Figure 7-2. While no significant changes in total macular volume were observed for either cohort, significant changes in Csub and CPT were observed for all patients treated with pegaptanib who manifested a ≥10 letter gain in visual acuity after 54 weeks of treatment. In contrast, significant changes in retinal thickness parameters were not observed in pegaptanib treated patients who did not achieve ≥10 letter gain in VA. This decrease in retinal thickness among treatment responders was manifested as early as 18 weeks after the initiation of treatment, and was sustained for up to 102 weeks (54 weeks after the suspension of treatment). The decrease in Csub in pegaptanib treated responding patients ranged from 47 to 99 μm over 18 to 102 weeks, respectively. Similarly, the decrease in CPT in pegaptanib treated responding patients ranged from 97 to 140 μm over 18 to 102 weeks, respectively. In contrast, the retinal thickness parameters between the sham treated patients who showed a ≥ 10 letter gain at 54 weeks were not significantly different from the non-responding patients, with the exception of absolute and relative changes in CPT at 102 weeks.

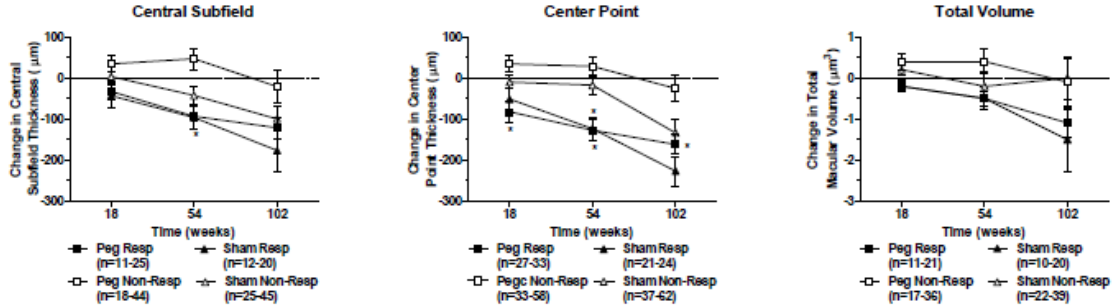
Furthermore, there was no significant difference in retinal thickness parameters between sham and pegaptanib treated patients who responded with a ≥10 letter gain at 54 weeks. In conclusion, the MAH reiterated that subgroup analyses should be considered as hypotheses generating, with the only valid scientific conclusions arising from analyses of the entire population. Nonetheless, post hoc analysis of treatment subpopulations revealed that the Csub and CPT, as measured by OCT, decrease significantly over time in those patients who show a ≥10 letter improvement in visual acuity at Week 54. However, the change in retinal thickness of those patients with improved VA who received pegaptanib was not significantly different from those sham treated patients with similar gains in VA.

Figure 7-1. Temporal Changes in Absolute Values of Retinal Thickness Parameters of Treatment Subpopulations



Absolute measures of central subfield thickness, center point thickness and total volume in patients receiving pegaptanib (Mac, squares) or sham (triangles) treatment. Data is from the MITT2 Population of Study A5751013. Each point represents the Mean ± SEM of n observations. The Responder population was defined as anyone with a ≥ 10 letter gain in ETDRS BCVA at 54 weeks of treatment. *: Statistically significantly different from corresponding Non-Responder group within the same cohort, P<0.01. 2-way ANOVA followed by Bonferroni's multiple comparison matrix.

Figure 7-2. Temporal Changes in Retinal Thickness Parameters Relative to Baseline of Treatment Subpopulations



The changes in central subfield thickness, center point thickness and total volume relative to baseline in patients receiving pegaptanib (Peg, squares) or sham (triangles) treatment. Data is from the MITT2 Population of Study A5751013. Each point represents the Mean ± SEM of n observations listed. The Responder population was defined as anyone with a ≥ 10 letter gain in ETDRS BCVA at 54 weeks of treatment *: Statistically significantly different from corresponding Non-Responder group within the same cohort, P<0.01. 2-way ANOVA followed by Bonferroni's multiple comparison matrix.

Having considered the MAH response on this question, the CHMP considered that the MAH did not explain why, if pegaptanib is really reducing the blood retina barrier permeability, there is no effect on objective measures of oedema (which currently are only performed with OCT machines). The MAH was therefore requested discuss - ***(see remaining point for consideration on Clinical Efficacy to be addressed in writing 2).***

Question 7

"There are still some uncertainties regarding the criteria for withholding and resuming therapy as well as how frequent the patients should be monitored. Such information i.e. was a stable VA the main criterion for withholding treatment, was a decrease in VA was the main criterion to resume treatment and how frequent was VA evaluated, should be extracted from the 2nd year of EOP 1013. This should translate into treatment recommendations for the SPC, section 4.2."

With regard to this question on re-treatment criteria, the MAH explained that they recommend that stable (i.e., less than 5 letter change) visual acuity serves as the primary criterion after administration of the first 2 doses. This criterion was chosen on the basis of a post-hoc analysis of the responses of subpopulations of patients with DME during the first 54 weeks of treatment. It is the recommendation

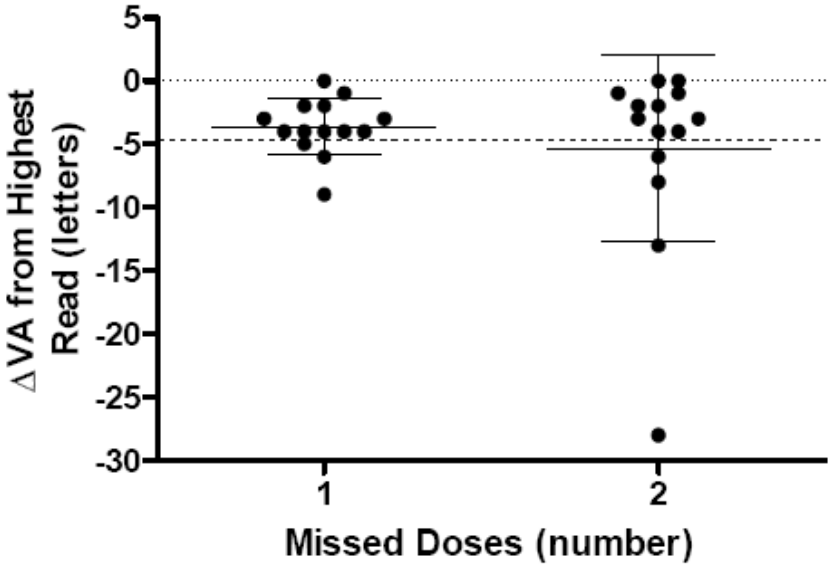
of the MAH that patients who do not respond after two Macugen treatments with a ≥ 5 letter gain in visual acuity above their baseline level be precluded from further treatment with Macugen alone. Because of the number of alternative therapies, and the unique features of a patient's medical history, the MAH believes that the treating physician is best able to determine the appropriate therapy for patients who do not respond to Macugen.

To reach this decision, post-hoc assessments of the relationship between retinal thickness parameters and response to Macugen treatment were performed. The outcome of this analysis is discussed in greater detail in the response to question 6. Briefly, retinal thickness decreased over the 102 week course of the study in patients who manifested improvements in visual acuity. Retinal thickness measures (OCT) were collected at Week 54 and 102 in the 1013 Study. In contrast, visual acuity measures were collected every 6 weeks over the course of the study, with an average of 101 ± 17 measures taken (out of 143 possible per dosing interval) over this period. Because of the limited number of OCT collections, further analysis of the relationship between patient outcome and re-dosing based on retinal thickness parameters or visual acuity is limited. Moreover, subgroup analyses should be considered as hypotheses generating. These findings lead the MAH to recommend that re-dosing be based solely on visual acuity.

Issues regarding the duration of action of pegaptanib were addressed by simulations based on preclinical data, direct observations and disease progression models based on the 1013 Study.

The simulations based on preclinical pharmacokinetics indicate that concentrations of pegaptanib in the vitreous humor 7 weeks after dosing with 0.3 mg/eye would be ≥ 1 μg/mL in > 50% of the patients treated. This concentration is equivalent to the EC90 for suppressing VEGF-induced vascular permeability in a guinea pig model, and is in excess of concentrations needed to suppress VEGF-induced neo-vascularization in models of corneal angiogenesis and retinopathy of prematurity.

Figure 7-1. Change in VA Associated With One or Two Missed Doses of Pegaptanib in Macugen Responders: EOP1013



Directly observed changes in VA following missed doses of pegaptanib sodium were obtained from the second year of study 1013 (PMAR-00176). On average, 101 of 143 possible doses were administered every 6 weeks from Weeks 54 to 102 (second year of the study). Fourteen (14) patients did not receive pegaptanib on two consecutive occasions (12 weeks) after having received at least 54 weeks (9 doses) of prior pegaptanib therapy. When the change in VA was determined by comparing the current reading against the highest VA reading attained, 3/14 patients lost ≥5 letters after withholding the first dose and 4/14 after withholding the second dose (Figure 7-1). The average (±SD) decline from the highest attained VA measured was -3.64 ± 2.41 letters after missing one dose, and -5.36 ±7.40 letters after missing 2 doses (Figure 7-1). Two of the 4 patients who lost VA after the first dose got

worse after having not received the second dose. One patient who had lost ≥ 5 letters after the first missed dose improved by the second missed dose, and one patient who was within criteria after the first missed dose lost ≥ 5 letters at the second time point. These results suggest that patients may not experience a significant decline in visual acuity after having missed a single dose (e.g., a 12 week interdose interval). However, observations from no more than 14 patients form this conclusion.

The model developed to describe the change in VA of patients from the 1013 study contained a disease progression function (Summary of Clinical Pharmacology and PMAR-00176). This model predicts that the estimated disease progression rate in patients responding to pegaptanib therapy is 0.005296/day, with 95% of responding patients not losing more than 0.85 letters over a 6 week period. A missed dose would result in no more than a 1.6 letter loss in VA over the 12 week interdose interval.

In conclusion, for the MAH extrapolations from preclinical models, direct measures from Year 2 of the 1013 Study and disease progression simulations based on the 1013 Study data suggested that a 12 week interdose interval may be tolerated by patients who have responded to pegaptanib. Nonetheless, the paucity of information underlying these analyses prevented them from making the recommendation that the interdose interval be extended to 12 weeks in patients who respond to pegaptanib. Given these limitations, and the reliance of their observations on visual acuity measures, the MAH adopted the recommended language of the CHMP for section 4.2 of the proposed SPC, which now read as follows:

Treatment of visual impairment due to DME:
Macugen 0.3 mg should initially be administered once every 6 weeks into the affected eye, and the patient should be evaluated for clinical benefit after no fewer than 2 doses. Those patients who gain ≥ 5 ETDRS letters (or Snellen equivalent) of visual acuity should continue receiving Macugen until no additional improvement in visual acuity is achieved.

The minimum interval between evaluations and any subsequent doses should not be shorter than 6 weeks.

If there is no improvement in visual acuity after two injections, continued treatment with Macugen alone is not recommended.

The CHMP acknowledged the additional analyses that had been presented. They considered that analysis of the relationship between patient outcome and re-dosing based on retinal thickness parameters or visual acuity was limited since OCT-data were limited (see Question 6). Thus, the Committee endorsed that MAH recommendation that re-dosing be based solely on visual acuity.

In view of the availability of alternative therapies, in clinical practice, it is reasonable that patients who do not respond following two pegaptanib injections are not further treated, and consequently it is reasonable not to continue treatment in these patients. However, the sentence *"If there is no improvement in visual acuity after two injections, continued treatment with Macugen alone is not recommended"* was not acceptable since it indicates that a combination treatment may be of benefit. The CHMP view was that no such combination treatment had been established.

Only 14 subjects did not receive pegaptanib on two consecutive occasions. Of these, 3 and 4 subjects lost ≥5 letters after withholding the 1st and 2nd dose respectively. As illustrated in the figure above, the effect of a missed dose appeared highly individual (from no loss to almost -10 letters) and the loss of VA tended to increase if two doses were missed. However, the number of patients for this analysis was too few to allow a conclusion. The MAH also refers to non-clinical data and the clinical pharmacology model with disease progression function and suggests, taking the 2 year EOP13-data into account, that a 12 week interdose interval may be tolerated by patients who have responded to pegaptanib, but realises the limitations of data. The CHMP noted that the MAH will perform a study to gain further information on how to use pegaptanib in relation to laser photocoagulation. In that study, additional information on the posology – with and without concomitant laser photocoagulation – should be generated and there may be a potential to further refine the posology. At present, however, updating the SPC according to CHMP recommendations was considered necessary. This additional amendment of the SPC will resolve the issue, whilst waiting for potential additional information to be generated in the planned study.

Question 8

"It is assumed that, but not clear that at least parts of diabetes-related vision problems were related to DME, i.e. the indication applied for, however, it should be confirmed whether these problems were due to DME, and if not, other causes of the impaired vision should be addressed."

In their response, the MAH argued that inclusion and exclusion criteria secured enrolment of 100% of patients in the study who suffered from DME with visual impairment upon trial entry. The MAH pointed out that this issue had been raised in the first RSI of September 2010, and that at that time the concern with regard to patients enrolment was resolved. The duration of the patients' DME prior to entry is difficult to ascertain. However, at the time of entry into the trial, a question on the 'duration of visual problems in the study eye related to diabetes' was asked to patients and this information collected as part of the study. However, it cannot be assumed by the answer to the question that DME is the sole source of their visual impairment in the time that they have experienced diabetes. The ocular complications of diabetes mellitus which can result in visual impairment are numerous and include retinopathy, cataract, uveitis, and neurophthalmic disorders among many others (Stanga, 1999).

Since the A5751013 study specifically evaluated the safety and efficacy of pegaptanib sodium in the treatment of DME, the MAH explained that it would be difficult to discern the impact of timing of visual impairment due to DME on the patient based upon the answer to this question alone. However, in review of the answer to the question of 'duration of visual problems due to diabetes', 60% of the patients in both the pegaptanib and sham treatment groups answered the question, in that they had 'visual problems' for greater than or equal to 1 year.

Table 3 below presents the mean change in VA at Week 54 for patients with less than 12 months and ≥12 months 'duration of visual problems in the study eye related to diabetes'; for patients with symptoms less than 12 months, those treated with pegaptanib sodium showed a significant improvement in VA compared to sham (p value = 0.0033).

Table 3. Mean VA Change from Baseline at Week 54, Subgroup by Shorter and Longer Duration Due to Diabetes (LOCF) – MITT1

Subset	Treatment Group	N	Mean at Baseline	Mean Change from Baseline	LSmeans of Change from Baseline [95% CI]	P-value[1]
Duration of visual problems in the study eye related to diabetes						
<12 months	Pegaptanib	54	56.81	7.87	6.07 [2.35, 9.78]	0.0033
	Sham	50	57.24	2.20		
≥12 months	Pegaptanib	79	57.14	3.35	2.70 [-0.86, 6.25]	0.1361
	Sham	77	57.64	0.58		

[1] ANCOVA model adjusted for HbA1c, systolic blood pressure, diastolic blood pressure and baseline visual acuity.
Source: Table 1.3.1.

Table 4 presents the proportion of responders (VA improvement of ≥10 letters at Week 54) for patients with less than 12 months and ≥12 months of 'duration of visual problems in the study eye related to diabetes.' Similar to the results above, for patients with symptoms less than 12 months, significantly more pegaptanib sodium-treated patients than sham (p value = 0.0155) experience an improvement of ≥ 10 letters. For patients with symptoms ≥12 months, the data were not statistically significant (p-value= 0.0522), but were in favor of pegaptanib sodium.

Table 4. Proportion of Responders (Gain ≥ 10 Letters) at Week 54, Subgroup by Shorter and Longer Duration Due to Diabetes (LOCF) – MITT1

Subset	Treatment Group	N	Patients with a Gain of ≥ 10 Letters of Vision at Week 54			
			n (%)	Difference (Percentage)	95% CI of Difference[1]	P-value[2]
Duration of visual problems in the study eye related to diabetes						
<12 months	Pegaptanib	54	24 (44.4%)	22.4%	[4.9%, 40.0%]	0.0155
	Sham	50	11 (22.0%)			
≥12 months	Pegaptanib	79	25 (31.6%)	13.5%	[0.1%, 26.9%]	0.0522
	Sham	77	14 (18.2%)			

[1] The difference and its corresponding confidence intervals were calculated using normal z-test.
[2] Chi-square test for treatment effect between Macugen and Sham.
Source: Table 1.3.2.A.

Further to understanding the patients' ocular status, upon entry into the study, the patients' ophthalmic history and prior ocular surgeries were collected.

The summary of ophthalmic history demonstrated that the majority of eye disorders in the study eye were likely related to or associated with diabetes mellitus. These included diabetic retinal oedema (Macugen 90%, sham 91%), diabetic retinopathy (Macugen 77%, sham 72%), cataract (Macugen 39%, sham 38%), macular oedema (Macugen 17%, sham 19%), retinal exudate (Macugen 17%, sham 17%), retinal hemorrhage (Macugen 12%, sham 12%), retinal aneurysm (Macugen 10%, sham 10%), and glaucoma (Macugen 2%, sham 6%). All other eye disorders demonstrated an occurrence of less than or equal to 10% with the majority of other disorders less than or equal to 2%. Additionally, as noted in the paragraph below, most subjects with an incoming history of cataracts had received treatment for the condition prior to entering the trial. Given this, the fact that most of the conditions are related to the disease under study, i.e. DME and the fact that all these conditions were approximately equal in both treatment groups, it is unlikely they affected the results and conclusions of the study in relation to the effect of Macugen on vision loss due to DME.

In terms of prior ocular surgeries, the majority of surgical and medical procedures in the study eye were retinal laser coagulation (Macugen 61%, sham 64%), and cataract operation (Macugen 17%, sham 17%). All other procedures occurred less than 4%.

In addition to the question upon entry regarding the duration of vision problems due to diabetes, the ophthalmic history and prior ocular surgeries, during the study, concomitant ocular medications, surgeries and adverse events were collected.

In terms of concomitant medications, the use of medications was similar between treatment groups and not suggestive of any significant ocular disease that would confound the presence and treatment of DME.

In terms of concomitant ocular surgeries, the majority of surgical and medical procedures in the study eye were retinal laser coagulation (Macugen 25%, sham 46%), vitrectomy (Macugen 2%, sham 5%), cataract operation (Macugen 2%, sham 2%) and eye laser surgery (Macugen 1%, sham 3%). All other procedures occurred less than 2%.

During the trial, the incidence of ocular treatment–emergent adverse events (all causality) was Macugen 65%, sham 73%. With the highest incidences in conjunctival hemorrhage (Macugen 22%, Sham 14%), diabetic retinal oedema (Macugen 6%, Sham 14%), eye pain (Macugen 11%, Sham 7%), punctate keratitis (Macugen 12%, Sham 6%) and macular oedema (Macugen 7%, Sham 9%). All other procedures occurred less than or equal to 10% (with the majority less than 3%). None of these AEs suggest a condition other than DME exerted a substantial contribution to visual acuity during the trial; therefore, they also would not be expected to affect the results and interpretation of the data.

In summary, the MAH undertook subgroup analyses which should be considered as hypotheses generating, with the only valid scientific conclusions arising from analyses of the entire population. Analyses of these subgroups suggest that patients with less than 12 months of duration of 'visual problems in the study eye related to diabetes' may respond better to pegaptanib sodium treatment than those with ≥12 months of duration of 'visual problems in the study eye related to diabetes.' It is

possible that DME is not the only ocular complication of diabetes that the patients may have experienced over the course of their disease. However, inclusion and exclusion criteria secured enrolment of 100% of patients in the study who suffered from DME with visual impairment upon trial entry. Further, the patients' ophthalmic history and prior ocular surgeries suggest that diabetes is the primary disease process affecting the eye, and during the study the concomitant medications, surgeries and adverse events additionally corroborate these findings. The MAH claimed that they were confident that adequate steps were taken to ensure that all patients entering into this trial suffered primarily from DME with visual impairment.

In response to the above, the CHMP considered that visual acuity is influenced by a large number of pre-existing factors. These factors should be equally distributed between the different treatment groups. The MAH was therefore asked to show that the potentially confounding factors (including, but not limited to the duration of visual problems due to diabetes mellitus, type of DME (focal or diffuse), age of the patient, other underlying systemic complications such as chronic kidney failure, heart failure and peripheral vascular micro/macro-angiopathy) are equally distributed between the treatment arms. The MAH was also asked to further discuss whether and to what extent any of these factors could have affected the 1 and 2-year outcome (visual acuity, macular thickness) in the two study arms. - ***(see remaining major issue on Clinical Efficacy to be addressed in writing 1b)***

Question 9

"Some of the requested subgroup analyses were not performed (see also MO above).

a. *Fluorescein angiograms were captured for the reading centres (Final protocol for study EOP1013, Appendix 16.4: Color fundus photography and Fluorescein angiography) and information on subjects with focal vs. diffuse DME should thus be available. The MAH should classify the types of DME (focal/diffuse) from these photographs and evaluate the effect (baseline data included) in the two groups.*
b. *Unfortunately, there appears to be no information on the exact duration of DME, however, there is information on the duration of visual problems due to diabetes. The MAH is requested to perform a subgroup analysis by shorter and longer duration (e.g. 12 months) of visual problems due to diabetes."*

The MAH performed the requested subgroup analyses. However, as these subgroup analyses have statistical limitations, the MAH acknowledged that they should be considered exploratory and suggestive rather than conclusive. Moreover, the MAH pointed out that the only scientifically valid conclusion from study EOP1013 comes from the overall population, where the patients treated with pegaptanib sodium responded significantly better in terms of improvement in visual acuity when compared to Sham treatments.

9.a The EOP1013 study enrolled patients with DME. At the time of enrollment, patients were not classified into focal or diffuse macular edema. At the request of the Agency, the MAH has utilized fluorescein leakage source data from the independent reading center and has classified DME as focal, diffuse and intermediate DME. The actual data used is derived from the assessment made by the masked grader. It is the proportion of fluorescein leakage that appears to be (focally) from retinal capillary microaneurysms (MA) as opposed to (diffusely) from dilated retinal capillaries or the retinal pigment epithelium. As per the ETDRS report (ETDRS Report # 11, Ophthalmology 1991; 98:807-822) : >= 67% from MA is classified as focal, 33-66% from MA is classified as intermediate, <33% from MA is classified as diffuse.

Using this classification, the study contained 80 patients (33.3%) with focal, 62 patients (25.9%) classified as intermediate, 97 patients (40.6%) as diffuse (see Table 1 below). The demographic and baseline characteristics were similar across all patients with focal, diffuse, intermediate DME (Table 1). Baseline visual acuity, severity of retinopathy, center point thickness, central subfield and macular volume were also similar across all patients with focal, diffuse and intermediate DME (Table 2 below).

Table 1. Demographic Characteristics and Key Baseline Characteristics (Study Eye) – MITT1 Population

	Focal DME			Diffuse DME			Intermediate DME		
	Macugen (N=40)	Sham (N=40)	Both (N=80)	Macugen (N=54)	Sham (N=43)	Both (N=97)	Macugen (N=30)	Sham (N=32)	All (N=62)
Sex									
Male	21 (52.5%)	19 (47.5%)	40 (50.0%)	37 (68.5%)	25 (58.1%)	62 (63.9%)	18 (60.0%)	17 (53.1%)	35 (56.5%)
Female	19 (47.5%)	21 (52.5%)	40 (50.0%)	17 (31.5%)	18 (41.9%)	35 (36.1%)	12 (40.0%)	15 (46.9%)	27 (43.5%)
Race									
Caucasian/White	33 (82.5%)	34 (85.0%)	67 (83.8%)	44 (81.5%)	38 (88.4%)	82 (84.5%)	22 (73.3%)	29 (90.6%)	51 (82.3%)
Asian	1 (2.5%)	4 (10.0%)	5 (6.3%)	5 (9.3%)	3 (7.0%)	8 (8.2%)	3 (10.0%)	2 (6.3%)	5 (8.1%)
Black	1 (2.5%)	0	1 (1.3%)	0	2 (4.7%)	2 (2.1%)	2 (6.7%)	0	2 (3.2%)
Hispanic/Latino	4 (10.0%)	2 (5.0%)	6 (7.5%)	2 (3.7%)	0	2 (2.1%)	2 (6.7%)	1 (3.1%)	3 (4.8%)
Other	1 (2.5%)	0	1 (1.3%)	3 (5.6%)	0	3 (3.1%)	1 (3.3%)	0	1 (1.6%)
Age (Years)									
Mean	63.4	60.9	62.1	61.6	64.4	62.8	62.8	61.8	62.3
Std Dev	8.57	11.01	9.89	10.01	10.07	10.09	9.88	9.72	9.73
Median	63.0	63.0	63.0	61.0	65.0	62.0	61.0	62.5	61.5
Range	48;80	20;77	20;80	28;82	32;80	28;82	45;83	31;78	31;83
N	40	40	80	54	43	97	30	32	62
Height (cm)									
Mean	169.5	166.5	168.0	168.3	167.6	168.0	166.2	165.5	165.9
Std Dev	9.25	8.98	9.18	8.26	9.17	8.64	8.59	8.98	8.73
Median	168.0	167.0	168.0	169.0	166.0	168.0	165.5	167.5	166.0
Range	152;188	150;193	150;193	152;187	148;186	148;187	144;183	147;180	144;183
N	40	40	80	54	43	97	30	32	62
Weight (kg)									
Mean	82.8	80.0	81.4	83.7	82.8	83.3	85.7	83.5	84.6
Std Dev	15.44	19.16	17.34	16.05	19.32	17.49	16.01	17.21	16.53
Median	83.5	78.0	79.9	82.0	82.0	82.0	85.0	84.0	85.0
Range	54;106	47;132	47;132	56;140	44;137	44;140	60;135	52;129	52;135
N	40	40	80	54	43	97	30	31	61
ECOG performance status[1]									
0	19 (47.5%)	23 (57.5%)	42 (52.5%)	26 (48.1%)	20 (46.5%)	46 (47.4%)	13 (43.3%)	17 (53.1%)	30 (48.4%)
1	20 (50.0%)	17 (42.5%)	37 (46.3%)	27 (50.0%)	20 (46.5%)	47 (48.5%)	17 (56.7%)	15 (46.9%)	32 (51.6%)
2	1 (2.5%)	0	1 (1.3%)	1 (1.9%)	3 (7.0%)	4 (4.1%)	0	0	0
3	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0
Baseline Smoking Status									
Active	2 (5.0%)	5 (12.5%)	7 (8.8%)	3 (5.6%)	1 (2.3%)	4 (4.1%)	1 (3.3%)	2 (6.3%)	3 (4.8%)
Not Active	38 (95.0%)	35 (87.5%)	73 (91.3%)	51 (94.4%)	42 (97.7%)	93 (95.9%)	29 (96.7%)	30 (93.8%)	59 (95.2%)
Type of Diabetes									
Type I	2 (5.0%)	4 (10.0%)	6 (7.5%)	4 (7.4%)	1 (2.3%)	5 (5.2%)	4 (13.3%)	3 (9.4%)	7 (11.3%)
Type II	38 (95.0%)	36 (90.0%)	74 (92.5%)	50 (92.6%)	42 (97.7%)	92 (94.8%)	26 (86.7%)	29 (90.6%)	55 (88.7%)
Diabetes Medication									
None	0	0	0	0	0	0	0	0	0
Oral	17 (42.5%)	19 (47.5%)	36 (45.0%)	22 (40.7%)	15 (34.9%)	37 (38.1%)	8 (26.7%)	12 (37.5%)	20 (32.3%)
Insulin	11 (27.5%)	13 (32.5%)	24 (30.0%)	17 (31.5%)	19 (44.2%)	36 (37.1%)	12 (40.0%)	10 (31.3%)	22 (35.5%)
Oral and Insulin	12 (30.0%)	8 (20.0%)	20 (25.0%)	15 (27.8%)	9 (20.9%)	24 (24.7%)	10 (33.3%)	10 (31.3%)	20 (32.3%)
Duration of visual problems in the study eye related to Diabetes									
None	0	0	0	1 (1.9%)	0	1 (1.0%)	0	0	0
<1 year	15 (37.5%)	19 (47.5%)	34 (42.5%)	24 (44.4%)	17 (39.5%)	41 (42.3%)	10 (33.3%)	10 (31.3%)	20 (32.3%)

	Focal DME			Diffuse DME			Intermediate DME		
	Macugen (N=40)	Sham (N=40)	Both (N=80)	Macugen (N=54)	Sham (N=43)	Both (N=97)	Macugen (N=30)	Sham (N=32)	All (N=62)
1-5 years	24 (60.0%)	17 (42.5%)	41 (51.3%)	22 (40.7%)	25 (58.1%)	47 (48.5%)	17 (56.7%)	18 (56.3%)	35 (56.5%)
6-10 years	1 (2.5%)	3 (7.5%)	4 (5.0%)	4 (7.4%)	1 (2.3%)	5 (5.2%)	3 (10.0%)	3 (9.4%)	6 (9.7%)
>11 years	0	1 (2.5%)	1 (1.3%)	3 (5.6%)	0	3 (3.1%)	0	1 (3.1%)	1 (1.6%)

[1] Eastern Cooperative Oncology Group (ECOG) performance status:
0: Fully active, able to carry on all pre-disease performance without restriction.
1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4: Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

Source: Table 1.

Table 2. Baseline Outcome Variables – MITT1 Population (Study Eye) – MITT1 Population

	Focal DME			Diffuse DME			Intermediate DME		
	Macugen (N=40)	Sham (N=40)	Both (N=80)	Macugen (N=54)	Sham (N=43)	Both (N=97)	Macugen (N=30)	Sham (N=32)	All (N=62)
Baseline VAS (in letters)									
Mean	60.4	59.9	60.1	55.5	57.1	56.2	55.0	55.2	55.1
Std Dev	7.28	5.75	6.53	9.07	9.44	9.22	8.91	8.28	8.52
Median	63.0	62.0	63.0	57.0	61.0	59.0	58.0	57.5	58.0
Range	40;70	47;69	40;70	35;70	35;70	35;70	35;68	35;65	35;68
N	40	40	80	54	43	97	30	32	62
Baseline Severity of Retinopathy									
Mean	4.8	5.2	5.0	5.9	5.5	5.7	5.5	5.5	5.5
Std Dev	1.28	1.44	1.37	1.30	1.52	1.41	1.78	1.67	1.71
Median	5.0	5.0	5.0	6.0	5.0	5.0	6.0	5.0	5.5
Range	3;7	3;9	3;9	3;9	3;9	3;9	3;8	3;8	3;8
N	39	38	77	50	42	92	27	31	58
Baseline Center Point Thickness (in microns)									
Mean	445.5	447.5	446.5	449.4	504.6	474.1	428.6	447.0	437.9
Std Dev	132.4	141.3	136.0	157.2	124.7	145.5	166.8	134.8	150.4
Median	452.0	452.0	452.0	450.0	479.0	467.5	402.0	443.0	427.0
Range	207;751	199;700	199;751	125;871	244;787	125;871	198;884	180;681	180;884
N	40	39	79	53	43	96	30	31	61
Baseline Central Subfield Thickness (in microns)									
Mean	449.3	458.0	453.6	467.3	501.4	483.1	443.4	451.6	447.8
Std Dev	114.1	121.1	116.8	136.7	117.1	128.3	148.9	115.2	130.6
Median	460.5	476.0	461.0	450.0	477.5	464.5	413.0	473.0	428.5
Range	274;733	244;675	244;733	240;852	319;784	240;852	262;834	295;681	262;834
N	34	33	67	44	38	82	25	29	54
Baseline Total Macular Volume (in cubic millimeters)									
Mean	9.1	9.1	9.1	9.9	10.4	10.1	9.6	9.3	9.5
Std Dev	1.82	1.59	1.70	2.24	2.43	2.33	2.12	1.61	1.84
Median	8.9	8.9	8.9	9.3	9.9	9.5	8.9	9.2	9.2
Range	6;15	7;13	6;15	7;17	7;17	7;17	7;14	7;13	7;14
N	33	32	65	41	38	79	23	28	51

Source: Table 1.

9.b The results of the subgroup analyses on duration of visual problems in the study eye due to diabetes are presented below in Table 3 and Table 4. Because these subgroup analyses have statistical limitations, they should be considered exploratory and suggestive rather than conclusive. Note that the only scientifically valid conclusion from study EOP1013 comes from the overall population, where the patients treated with pegaptanib sodium responded significantly better in terms of improvement in visual acuity when compared to Sham treatments.

Table 3 below presents the mean change in VA at Week 54 for patients with <12 months and ≥12 months of visual problems in the study eye related to diabetes; for patients with duration <12 months,

patients treated with pegaptanib sodium showed a significant improvement in VA compared to sham (p-value = 0.0033).

Table 3. Mean VA Change from Baseline at Week 54, Subgroup by Shorter and Longer Duration Due to Diabetes (LOCF) – MITT1

Subset	Treatment Group	N	Mean at Baseline	Mean Change in VA from Baseline	LSmeans of Change in VA at Week 54 [95% CI]	P-value[1]
Duration of visual problems in the study eye related to diabetes						
<12 months	Pegaptanib	54	56.81	7.87	6.07 [2.35, 9.78]	0.0033
	Sham	50	57.24	2.20		
≥12 months	Pegaptanib	79	57.14	3.35	2.70 [-0.86, 6.25]	0.1361
	Sham	77	57.64	0.58		

[1] ANCOVA model adjusted for HbA1c, systolic blood pressure, diastolic blood pressure and baseline visual acuity.
Source: Table 1.3.1.

Table 4 presents the proportion of responders (VA improvement of ≥10 letters at Week 54) for patients with <12 months and ≥12 months of visual problems in the study eye related to diabetes. Similar to the results above, for patients with duration <12 months, significantly more pegaptanib sodium-treated patients (p-value = 0.0155) experienced an improvement of ≥ 10 letters. For patients with duration ≥12 months, the numerical difference was in favor of pegaptanib sodium, but it was not statistically significant (p-value=0.0522).

Table 4. Proportion of Responders (Gain ≥ 10 Letters) at Week 54, Subgroup by Shorter and Longer Duration Due to Diabetes (LOCF) – MITT1

Subset	Treatment Group	N	Patients with a Gain of ≥ 10 Letters of Vision at Week 54			
			n (%)	Difference (Percentage)	95% CI of Difference[1]	P-value[2]
Duration of visual problems in the study eye related to diabetes						
<12 months	Pegaptanib	54	24 (44.4%)	22.4%	[4.9%, 40.0%]	0.0155
	Sham	50	11 (22.0%)			
≥12 months	Pegaptanib	79	25 (31.6%)	13.5%	[0.1%, 26.9%]	0.0522
	Sham	77	14 (18.2%)			

[1] The difference and its corresponding confidence intervals were calculated using normal z-test.
[2] Chi-square test for treatment effect between Macugen and Sham.
Source: Table 1.3.2.

In summary, the analyses of these subgroups performed by the MAH suggested that patients with intermediate DME, patients with less than 12 months of duration of visual problems in the study eye related to diabetes' may respond better to pegaptanib sodium treatment than those with ≥12 months of duration of visual problems in the study eye related to diabetes. However, the MAH reiterated that subgroup analyses should be considered as hypotheses generating, with the only valid scientific conclusions arising from analyses of the entire population.

The CHMP acknowledged that the MAH had, as requested, classified the types of DME (focal/diffuse) from fluorescein angiograms. However, the Committee considered that the MAH had not evaluated the effect of Macugen/sham in these subgroups. Key efficacy analyses are expected. ***(see remaining point for consideration on Clinical Efficacy to be addressed in writing 3).***

Question 10

"In the EOP1013 study, Potential differences in treatment effects amongst different age groups have been studied using subgroup analyses (<62 years, >=62 years). Not only may the reduced sample sizes imply lack of power, the results may severely depend on the chosen cut-off value of 62 years. An

alternative analysis should be performed to test for the presence of an interaction between age and Sham/Pegaptanib."

The MAH pointed out that in response to a previous CHMP query (Response #20, 5 October 2010) the MAH performed a sub-group analysis evaluating the treatment benefits in patients of different age groups. Given the Agency's concerns about the chosen cut-off of 62 years, the MAH performed a logistic analysis (Maura, 2000) to further characterize the interaction between age and treatment. The outcome variable was the proportion of responders with ≥ 10 letter improvement in VA at Week 54. The full model included the variables in Table 1 below. The interaction between age and treatment group was not statistically significant. The logistic regression analysis (Maura, 2000) demonstrated that the proportion of subjects gaining ≥10 letters in visual acuity decreases as age increases, irrespective of treatment group.

Table 1. Logistic Regression Analysis – MITT1 (LOCF).

Variable	Estimate	Standard Error	Wald Chi-Square	P-value
Intercept	1.6288	1.3208	1.5206	0.2175
Treatment: Macugen vs. Sham	0.2978	1.8106	0.0271	0.8694
Baseline VA: < 54 vs. ≥ 54 letters	0.0294	0.1521	0.0373	0.8468
Systolic Blood Pressure: <140 vs. ≥ 140 mmHg	-0.0936	0.1519	0.3798	0.5377
Diastolic Blood Pressure: < 80 vs. ≥ 80 mmHg	0.1864	0.1551	1.4450	0.2293
HbA1C: < 7.6% vs. ≥ 7.6%	0.2078	0.1440	2.0837	0.1489
Age	-0.0485	0.0215	5.1025	0.0239
Age-Treatment interaction	0.0095	0.0294	0.1045	0.7465

Source: Table 1.7.1.

In conclusion, it was the opinion of the MAH that the above logistic regression analyses have demonstrated that the proportion of subjects gaining ≥10 letters in visual acuity will decrease with the increase of age irrespective of Pegaptanib/Sham treatment.

The CHMP considered that, in order to study potential differences in treatment effects amongst different age groups, a logistic regression model was used including the interaction between age and treatment. The CHMP agrees that this is the correct approach provided that the assumed linear effect of age (on logit scale) is appropriate. This should be explored by the MAH, and evidence should be given that this model fits the data well. – ***(see remaining point for consideration on Clinical Efficacy to be addressed in writing 4).***

Question 11

"The LOCF analysis should be backed by sensitivity analyses for all endpoints, by which the sensitivity of the final conclusions with respect to the way missing data has been handled is investigated."

The MAH pointed out that they had performed longitudinal analyses as recommended in Question 22 of September 2010 RSI, when missing data were not imputed for these analyses. The MAH highlighted that these sensitivity analyses were performed to confirm the results from the primary and secondary efficacy analyses as reported in EOP1013 clinical study report.

The following four major efficacy endpoints were evaluated: the proportion of subjects who experience a ≥ 10 letter (or 2-line) improvement in vision (ETDRS) at Year-1 post-baseline; the proportion of subjects who experience a ≥ 10 letter (or 2-line) improvement in vision (ETDRS) at Year-2 post-baseline; changes in mean visual acuity within 1-year; changes in mean visual acuity within 2-year.

Responder analyses re-evaluated using a generalized estimating equations (GEE) analysis of repeated measures1 with all variables (BP, HbA1c, baseline VA, treatment group, visits, treatment + visit interaction).

Mean changes in visual acuity re-evaluated using a mixed model analysis of repeated measures on MITT1 population; baseline stratification factors, treatment groups, visits, the interaction of treatment group and visits were included in the model.

The MAH concluded that results were consistent with what was presented in the Clinical Study Report.

The CHMP, however, considered that statistically significant effect for efficacy endpoints was not fully demonstrated. Sensitivity analysis for the binary outcomes was based on generalized estimating equations (GEE) which assume missingness completely at random. Regarding, the continuous outcomes, the proposed mixed model makes very strict, often unrealistic, assumptions about the variance and correlation structure in the data. The MAH was asked to explain how those assumptions will be justified. Additionally, it should be explained what alternative (less restrictive) models will be used in case the assumptions are not satisfied - ***(see remaining point for consideration on Clinical Efficacy to be addressed in writing 5).***

Question 12 (Safety)
"The MAH should justify why not including Coronary artery disease, Angina pectoris, Angina unstable, Cholelithiasis and Lower respiratory tract infection (increased in pegaptanib-treated subjects) in the SPC, section 4.8".

In response to this question, the MAH explained that Section 4.8 in the SPC was revised as follows.

The incidence of adverse events for the 2 pivotal AMD studies (EOP1003 and EOP1004) was combined, and the adverse events for the phase 2 and phase 2/3 DME studies (EOP1005 and EOP1013) were also combined, as suggested by the CHMP. The data for EOP1013 were collected as of 25 March 2011. A table will include all causality adverse events that occurred at a higher rate (at least 2 percentage points) in patients receiving treatment with pegaptanib 0.3 mg and in those receiving sham treatment. This table will also include all adverse events suspected of being at least potentially related to the injection procedure or study drug in 2 or more patients.

Under these criteria, the adverse event cholelithiasis appears as Common frequency (≥1/100 and <1/10). The other adverse events noted above did not meet, in the view of the MAH either of the above specified criteria, and therefore are not included in Section 4.8.

The response from the MAH was acceptable to the CHMP, who considered this issue to be resolved.

Question 13
"The MAH should summarise and present the ocular adverse events of subjects receiving/not receiving laser rescue during the studies."

The MAH argued that, as per the EOP1013 study, patients with prior scatter (panretinal) photocoagulation at least 6 months prior to baseline angiography/photography or YAG laser, laser retinopexy, focal or grid photocoagulation at least 16 weeks prior to baseline were eligible for inclusion in the study. During the study, patients were permitted to receive focal or grid photocoagulation beginning after week 18 following randomisation (maximum of 3 focal or grid laser treatments per year - provided that a minimum of 17 weeks occurs between treatments). The laser treatment was to be applied at least 1 week after injection of the trial/sham drug is given. The administration of laser therapy was considered standard of care, not rescue therapy.

By designing the protocol in this manner, all patients could receive the current standard of care, laser, as needed, regardless of the randomised treatment assignment.

A secondary efficacy endpoint in the study is the proportion of patients who received focal or grid laser at 1 and 2 years. The rates of focal/grid laser are:
- Year 1: Pegaptanib sodium 0.3 mg group – 23.3% (n=133), Sham 41.7%(n=127)
- Year 2: Pegaptanib sodium 0.3 mg group – 25.2% (n=107), Sham 45% (n=100)

The EOP1013 study was not designed to evaluate the safety of laser treatment, and after Week 18, laser treatment was permitted as per investigator discretion. Laser treatment could have been administered at varying times during the course of the study. The number of patients who did not receive laser versus the number receiving laser treatment was changing over the course of the study. Thus, it is difficult to fully assess the incidence of adverse events for patients receiving laser compared to those who did not receive laser. However, the MAH prepared post-hoc evaluations of the adverse events associated with the following four subgroups based on the actual treatment each patient received before Week 54: 1) pegaptanib sodium alone; 2) pegaptanib sodium + laser; 3) sham alone;

4) sham + laser, as follows: Adverse events were tabulated up to Week 18 in one assessment and after Week 18 through Week 54 in a second assessment for the 4 subgroups outlined above. The numbers of patients in the groups are not balanced, with the least number in the pegaptanib sodium + laser group.

Not taken into account are the following: 1) the number of laser treatments received by each patient; 2) the timing of the laser treatment before Week 54; and 3) the temporal relationship of adverse events to laser treatment.

NOTE: Unless otherwise stated, events summarised in the text below refer to the study eye.

Patients in the pegaptanib sodium and sham treatment groups had more all causality treatment emergent AEs reported from Week 18 to Week 54 when laser therapy could be added compared with those patients who received pegaptanib sodium or sham without laser. (See Table 1 below)

Table 1. Summary of Treatment-Emergent Adverse Events in Study Eye for Patients Receiving Study Treatment Alone and Study Treatment + Laser

No. Pts with at least one AE in study eye:	Pegaptanib alone N=102		Pegatanib + Laser N=31		Sham alone N=74		Sham + Laser N=53	
	BL* – Wk 18	Wk 18 – Wk 54	BL* – Wk 18	Wk 18 – Wk 54	BL* – Wk 18	Wk 18 – Wk 54	BL* – Wk 18	Wk 18 – Wk 54
All Cause %								
AE	35.3	39.2	35.5	64.5	31.1	37.8	41.5	69.8
SAE	1.0	1.0	0	0	1.4	0	0	1.9
Severe AE	1.0	1.0	0	6.5	4.1	0	0	1.9
AE leading to death	2.0	1.0	0	0	0	0	0	0
AE leading to D/C	0	2.9	0	0	0	0	1.9	1.9
Inject Procedure Related %								
AE	27.5	28.4	25.8	32.3	18.9	20.3	24.5	26.4
SAE	1.0	1.0	0	0	0	0	0	0
Severe AE	1.0	1.0	0	3.2	1.4	0	0	0
AE leading to death	0	0	0	0	0	0	0	0
AE leading to D/C	0	1.0	0	0	0	0	0	0
Study Drug Related %								
AE	2.0	2.0	6.5	3.2	0	2.7	1.9	3.8
SAE	0	0	0	0	0	0	0	0
Severe AE	0	0	0	0	0	0	0	0
AE leading to death	0	0	0	0	0	0	0	0
AE leading to D/C	0	0	0	0	0	0	0	1.9

Source: Tables 13.6.1.1a; 13.6.1.1b; 13.6.1.2a; 13.6.1.2b; 13.6.1.3a; 13.6.1.3b
*BL = Baseline; Laser was not permitted from BL-Week 18

All Causality Treatment Emergent AEs:
There were 67 AEs reported in 31 patients for the pegaptanib sodium + laser group compared with 119 AEs reported in 102 patients for the pegaptanib sodium alone group. There were 78 AEs reported in 53 sham + laser patients compared with 79 AEs reported in 74 sham alone patients. There was a higher incidence of AEs reported in the groups that received study treatment plus laser (Wk18-Wk54) compared with the groups that received study treatment alone. Across all treatment groups, 20.3% – 32.3% of the adverse events were injection procedure related and 2.0% - 3.8% were deemed related to the study drug Most of the AEs reported occurred in the Eye disorders SOC. There were no findings of note for systemic AEs reported for patients who received pegaptanib sodium + laser and sham + laser. The all causality ophthalmic AEs reported for patients who received pegaptanib sodium + laser, and sham + laser are shown in the table below (Table 2). Only AE terms that occurred in at least one of the laser groups are included in the table.

Table 2. **Incidence of Ophthalmic Treatment-Emergent Adverse Events in the Study Eye for Pegaptanib Sodium + Laser and Sham + Laser Groups at Baseline – Week 18 and Week 18 – Week 54* – All Causality**

No. Pts with at least one All Cause AE (%)	Pegaptanib alone N=102		Pegaptanib + laser N=31		Sham alone N=74		Sham + Laser N=53	
Eye Disorders Study Eye	**BL** – Wk 18**	**Wk 18-Wk 54**	**BL* – Wk 18**	**Wk 18-Wk 54**	**BL** – Wk 18**	**Wk 18-Wk 54**	**BL** – Wk 18**	**Wk 18-Wk 54**
Conjunctival haemorrhage	12 (11.8)	13 (12.7)	**4 (12.9)**	**6 (19.4)**	4 (5.4)	7 (9.5)	**4 (7.5)**	**3 (5.7)**
Eye pain	7 (6.9)	6 (5.9)	**2 (6.5)**	**5 (16.1)**	4 (5.4)	3 (4.1)	**2 (3.8)**	**2 (3.8)**
Corneal disorder	2 (2.0)	--	**2 (6.5)**	--	0	--	**0**	--
Visual acuity reduced	2 (2.0)	3 (2.9)	**2 (6.5)**	**0**	3 (4.1)	2 (2.7)	**2 (3.8)**	**1 (1.9)**
Eye discharge	0	0	**2 (6.5)**	**3 (9.7)**	2 (2.7)	2 (2.7)	**2 (3.8)**	**1 (1.9)**
Myodesopsia	1 (1.0)	1 (1.0)	**2 (6.5)**	**0**	0	1 (1.4)	**0**	**0**
Photophobia	1 (1.0)	0	**2 (6.5)**	**3 (9.7)**	0	0	**0**	**0**
Retinal exudates	2 (2.0)	4 (3.9)	**1 (3.2)**	**1 (3.2)**	2 (2.7)	3 (4.1)	**1 (1.9)**	**2 (3.8)**
Lacrimation increased	3 (2.9)	3 (2.9)	**1 (3.2)**	**1 (3.2)**	2 (2.7)	0	**0**	**2 (3.8)**
Vitreous opactities	1 (1.0)	2 (2.0)	**1 (3.2)**	**0**	0	0	**1 (1.9)**	**2 (3.8)**
Diabetic retinal oedema	0	1 (1.0)	**1 (3.2)**	**4 (12.9)**	0	0	**2 (3.8)**	**13 (24.5)**
Meibomianitis	0	--	**1 (3.2)**	--	0	--	**0**	--
Ocular hyperemia	0	1 (1.0)	**1 (3.2)**	**1 (3.2)**	0	0	**1 (1.9)**	**1 (1.9)**
Anterior chamber inflammation	0	0	**1 (3.2)**	**1 (3.2)**	0	0	**0**	**0**
Corneal abrasion	0	0	**1 (3.2)**	**0**	0	0	**0**	**1 (1.9)**
Foreign body sensation in eyes	1 (1.0)	0	**1 (3.2)**	**0**	1 (1.4)	0	**2 (3.8)**	**1 (1.9)**
Vision blurred	1 (1.0)	0	**1 (3.2)**	**0**	0	0	**1 (1.9)**	**1 (1.9)**
Vitreous haemorrhage	1 (1.0)	0	**1 (3.2)**	**0**	1 (1.4)	1 (1.4)	**0**	**1 (1.9)**
Punctate keratitis	4 (3.9)	7 (6.9)	**0**	**2 (6.5)**	2 (2.7)	2 (2.7)	**4 (7.5)**	**4 (7.5)**
Retinal haemorrhage	0	3 (2.9)	**0**	**1 (3.2)**	1 (1.4)	5 (6.8)	**2 (3.8)**	**2 (3.8)**
Angle closure glaucoma	1 (1.0)	1 (1.0)	**0**	**0**	0	0	**1 (1.9)**	**0**
Cataract	1 (1.0)	2 (2.0)	**0**	**1 (3.2)**	0	1 (1.4)	**0**	**1 (1.9)**
Conjunctivitis	1 (1.0)	2 (2.0)	**0**	**1 (3.2)**	1 (1.4)	1 (1.4)	**0**	**0**
Corneal erosion	1 (1.0)	2 (2.0)	**0**	**0**	0	2 (2.7)	**1 (1.9)**	**2 (3.8)**
Retinal aneurysm	0	2 (2.0)	**0**	**2 (6.5)**	1 (1.4)	1 (1.4)	**2 (3.8)**	**3 (5.7)**
Diabetic retinopathy	1 (1.0)	1 (1.0)	**0**	**0**	1 (1.4)	1 (1.4)	**1 (1.9)**	**2 (3.8)**
Maculopathy	0	1 (1.0)	**0**	**1 (3.2)**	0	0	**2 (3.8)**	**4 (7.5)**
Posterior capsule opacification	0	1 (1.0)	**0**	**0**	1 (1.4)	1 (1.4)	**2 (3.8)**	**0**
Retinal vascular disorder	0	1 (1.0)	**0**	**1 (3.2)**	0	1 (1.4)	**1 (1.9)**	**1 (1.9)**
Retinopathy proliferative	0	--	**0**	--	0	--	**1 (1.9)**	--

No. Pts with at least one All Cause AE (%)	Pegaptanib alone N=102		Pegaptanib + laser N=31		Sham alone N=74		Sham + Laser N=53	
	BL** – Wk 18	Wk 18-Wk 54	BL* – Wk 18	Wk 18-Wk 54	BL** – Wk 18	Wk 18-Wk 54	BL** – Wk 18	Wk 18-Wk 54
Vitreous detachment	1 (1.0)	1 (1.0)	0	1 (3.2)	0	0	0	0
Blepharitis	1 (1.0)	0	0	1 (3.2)	0	0	1 (1.9)	1 (1.9)
Eye irritation	0	0	0	1 (3.2)	0	0	2 (3.8)	1 (1.9)
Macular oedema	0	0	0	6 (19.4)	0	2 (2.7)	2 (3.8)	6 (11.3)
Macular scar	--	0	--	0	--	0	--	1 (1.9)
Ocular discomfort	0	0	0	1 (3.2)	0	0	1 (1.9)	0
Retinal neovascularisation	0	0	0	1 (3.2)	1 (1.4)	0	0	0
Intraocular pressure increased	6 (5.9)	10 (9.8)	0	1 (3.2)	3 (4.1)	3 (4.1)	0	3 (5.7)
Chalazian	--	1 (1.0)	--	1 (3.2)	--	1 (1.4)	--	0
Blepharitis allergic	--	0	--	0	--	1 (1.4)	--	2 (3.8)
Blepharochalasis	--	0	--	1 (3.2)	--	0	--	0
Conjunctivitis allergic	--	0	--	0	--	2 (2.7)	--	1 (1.9)
Eyelid bleeding	--	0	--	1 (3.2)	--	0	--	0
Eyelid pain	--	0	--	1 (3.2)	--	0	--	0
Eyelid ptosis	--	0	--	1 (3.2)	--	0	--	0
Iris neovascularisation	--	0	--	0	--	0	--	1 (1.9)
Retinal scar	--	0	--	1 (3.2)	--	0	--	2 (3.8)
Uveitis	--	0	--	0	--	0	--	1 (1.9)

Source: Tables 13.6.4.1a; 13.6.4.1b
Note: double dash (--) means not reported for that cohort
*(data for patients receiving pegaptanib sodium alone and sham alone shown for reference)
**BL = Baseline; Laser was not permitted from BL-Week 18

After Week 18, a statistically significant greater number of patients in the sham group received laser treatment than in the pegaptanib sodium group (reference secondary endpoint info in CSR).

In summary, in the view of the MAH, in review of the post hoc analysis, the overall incidence of adverse events reported by the 4 subgroups from Baseline to Week 18, before laser could be administered per protocol, were similar among the 4 subgroups, except for the pegaptanib sodium + laser group, in which the overall incidence was higher. No specific safety issue was noted to be the source of this difference. However, the small number of patients in that group (n=31) makes it difficult to draw any conclusions. After Week 18, the overall incidence of adverse events increased in all groups, the greatest increase occurred in the sham + laser group. The overall increased incidence of adverse events might be explained, in part, by the longer period of data collection (36 weeks from Week 18 – Week 54 compared to 18 weeks from Baseline – Week 18).

The CHMP, however, considered the above analysis inconclusive, and requested the MAH to re-analyse the safety data (classification of recorded AE) on a per patient basis for the small numbers of subjects concerned - ***(see remaining point for consideration on Clinical Safety to be addressed in writing 6).***

Question 14 (Risk Management Plan)
"Section 1.7.2 of the RMP should be revised to have focus on prevalence and incidence of clinically significant macular oedema constituting a threat to visual acuity as defined in the ETDRS study and study EOP 1013."

As requested, the MAH revised Section 1.7.2 of the RMP and created a separate section that focuses on the prevalence and incidence of clinically significant macular edema constituting a threat to visual acuity. The revised sections read as follows:

1.7.2 Diabetic Macular Oedema (DME)
Diabetes mellitus (DM) is a serious condition which affects more than 220 million people worldwide (WHO 2009) and is among the leading causes of death, disability and economic loss through the world. Diabetic retinopathy (DR) and its frequent manifestation, diabetic macular oedema (DME), are

common microvascular complications in patients with diabetes and may have a sudden and debilitating impact on visual acuity (VA), eventually leading to blindness (Ciulla 2003). DR correlates with the duration of diabetes; thus, with increasing life expectancy, DR and the ensuing blindness will tend to increase (WHO 2005). Advanced stages of DR are characterized by the growth of abnormal retinal blood vessels secondary to ischemia. These blood vessels grow in an attempt to supply oxygenated blood to the hypoxic retina. At any time during the progression of DR, patients with diabetes can also develop DME, which involves retinal thickening in the macular area. DME occurs after breakdown of the blood-retinal barrier because of leakage of dilated hyperpermeable capillaries and microaneurysms (Ciulla 2003). Diabetic macular oedema is designated as clinically significant if at least one of the following characteristics is present: retinal thickening at or within 500 µm of the center of the macula; and/or hard exudates at or within 500 µm of the center of the macula, if associated with thickening of adjacent retina; and/or a zone or zones of retinal thickening 1 disc area or larger in size, any part of which is within 1 disc diameter of the macular center (ETDRS study).
Tables were updated accordingly.

The CHMP noted that the MAH revised Section 1.7.2 of the RMP and created a separate section that focuses on the prevalence and incidence of clinically significant macular edema constituting a threat to visual acuity. The definition of Diabetic Macular Edema (DME) is now clearly stated as well as the latest data on the Incidence in the target population. Prevalence and incidence of Clinically Significant Macular Edema (CSME) have been added. The issue was considered resolved.

Question 15 (Risk Management Plan)
"(from OC30) Additional changes to the areas of important missing information (section 1.10) are required:

a. *Macular ischaemia: a broader search including other PTs indicating deterioration of retinal blood flow should be applied.*
b. *Effects of stopping Macugen treatment on diabetic retinopathy: There is at present very limited information on the effect of stopping pegaptanib sodium treatment on diabetic retinopathy and the RMP should be amended accordingly.*
c. *Relation to laser photocoagulation: There is at present very limited information on the relation of anti-VEGF-therapy to standard care grid/focal photocoagulation with regards to efficacy and recommendations for optimising the treatment strategy for the individual patient. Section 1.10 should thus be amended.*
d. *There is limited information with regards to possible systemic side effects following bilateral treatment with Macugen. The RMP and the SmPC section 4.4 should be amended accordingly.*
e. *The section should be updated with the information that there is limited information concerning efficacy and safety of pegaptanib sodium in uncontrolled or poorly controlled diabetes.*
f. *Scleral effects after long-term of IVT injections are not known, this should be amended to the RMP as missing information."*

The MAH addresses each point as follows:

a. Macular ischaemia: a broader search including other PTs indicating deterioration of retinal blood flow should be applied.

The MAH conducted a search of MedDRA v 13.1 System Organ Class (SOC) Eye disorders to identify Preferred Terms (PT) indicating macular ischaemia, deterioration of retinal blood flow, or macular capillary loss.
The following High Level Terms (HLT) were reviewed: Choroid and vitreous haemorrhages and vascular disorders, Retinal bleeding and vascular disorders (excl retinopathy), and Retinopathies NEC (Not Elsewhere Classified) in the High Level Group Term (HLGT) Retina, choroid and vitreous haemorrhages and vascular disorders; Retinal structural change, deposit and degeneration in the HLGT Ocular structural change, deposit and degeneration NEC.

It was determined the following PTs would be appropriate terms to search:
• Retinal vascular disorder – could signify deterioration of retinal blood flow
• Venous stasis retinopathy, Macular ischaemia, Retinal ischaemia, Retinal infarction – are consequences of change or deterioration of retinal blood flow

It was determined that the following PTs would not be appropriate terms to search:

• Retinal artery occlusion, Retinal artery stenosis, Retinal artery thrombosis, retinal vascular occlusion, Retinal vascular thrombosis, Retinal vein occlusion, Retinal vein thrombosis – these conditions may lead to ischaemia but do not represent ischaemia
• Arteriosclerotic retinopathy – can occur concomitantly with diabetic disease, but is the ocular manifestation of arteriosclerosis

	EOP1005		EOP1013	
	Pegap (all)	Sham	Pegap 0.3 mg	Sham
	128	41	144	142
Retinal vascular disorder	0	1 (2%)	2 (1.4%)	2 (1.4%)
Venous stasis retinopathy	0	0	0	0
Macular ischaemia	0	0	0	0
Retinal ischaemia	1 (1%)	0	0	0
Retinal infarction	0	0	0	0
Source: EOP1005 CSR, Table 6.3.2.5a, Table 6.3.3.2a, Table List 3.1. Source: EOP1013 CSR Supplemental Study Report 1, Table Listing B6.3.4.1, Table 13.6.2.1a, Table 13.6.3.1a, Table 13.6.4.1a; SCS Table A159.3.3				

In study EOP1005:
• Patient 004-001: Preferred term Retinal vascular disorder NOS; start date was study day 46; occurred in study eye; moderate severity; deemed related to procedure; sham group. This event was reported during the active phase.
• Patient 075-005: Preferred term Retinal ischaemia; start date was study day 126; occurred in study eye, mild severity; deemed possibly related to study therapy; pegaptanib sodium 3.0 mg group. This event was reported during the active phase.

In study EOP1013:
• Patient 0087-3206: Preferred term Retinal vascular disorder; start day was study day 294; occurred in study eye (subject reported same AE in fellow eye on the same day); moderate severity; deemed not related; pegaptanib sodium 0.3 mg group.
• Patient 0409-3286: Preferred term Retinal vascular disorder; start day was study day 251; occurred in study eye; mild severity; deemed not related; pegaptanib sodium 0.3 mg group.
• Patient 0087-3216; Preferred term Retinal vascular disorder; start day was study day 169 (subject reported same AE study day 588); occurred in study eye; severity; deemed not related; sham group.
• Patient 0169-3086; Preferred term Retinal vascular disorder; start day was study day 0 (subject reported same AE study day 42, and study day 125, 210, and 252 in fellow eye); occurred in study eye; severity; deemed not related; sham group.

b. Effects of stopping Macugen treatment on diabetic retinopathy: There is at present very limited information on the effect of stopping pegaptanib sodium treatment on diabetic retinopathy and the RMP should be amended accordingly.

c. Relation to laser photocoagulation: There is at present very limited information on the relation of anti-VEGF-therapy to standard care grid/focal photocoagulation with regards to efficacy and recommendations for optimising the treatment strategy for the individual patient. Section 1.10 should thus be amended.

d. There is limited information with regards to possible systemic side effects following bilateral treatment with Macugen. The RMP and the SPC section 4.4 should be amended accordingly.

e. The section should be updated with the information that there is limited information concerning efficacy and safety of pegaptanib sodium in uncontrolled or poorly controlled diabetes.

f. Scleral effects after long-term of IVT injections are not known, this should be amended to the RMP as missing information.

The MAH confirmed that RMP Section 1.10 will be amended accordingly for each topic, see below. Each topic will be addressed in Section 2 Planned Pharmacovigilance Actions

1.10 Summary – Ongoing safety concerns

Table Summary of ongoing Safety Concerns

Important identified risks	Endophthalmitis, increased intraocular pressure, retinal injury, intraocular haemorrhage, traumatic cataract, hypersensitivity
Important potential risks	No additional ocular or systemic risks in the diabetic population have been identified.
Important missing information	Patients with retinal ischaemia, macular ischaemia Long term safety in diabetic patients with respect to ATE events Effect of stopping treatment on progression of diabetic retinopathy Long term effect of treatment on progression of diabetic retinopathy Limited information on the relation of Pegaptanib sodium therapy to standard care photocoagulation Information on optimal treatment strategy for combining Pegaptanib sodium with standard care grid/focal photocoagulation Possible systemic effects following bilateral treatment Limited information on patients with uncontrolled or poorly controlled diabetes Long term effect of IVT injections and Pegaptanib sodium therapy on scleral rigidity

With regards to point a., concerning Macular ischaemia, the MAH performed a broader search including other PTs indicating deterioration of retinal blood flow. Retinal vascular disorder, venous stasis retinopathy, macular ischaemia, retinal ischaemia, and retinal infarction were considered in both studies EOP1005 and EOP1013. No new safety signal was raised with this search. This satisfactorily addressed the concern of the CHMP.

With regards to points b, c, d and e., the RMP Section 1.10 was amended accordingly for each topic: Effect of stopping treatment on progression of diabetic retinopathy, limited information on the relation of Pegaptanib sodium therapy to standard care photocoagulation, possible systemic effects following bilateral treatment, limited information on patients with uncontrolled or poorly controlled diabetes, long term effect of IVT injections and Pegaptanib sodium therapy on scleral rigidity. Each topic is adequately addressed in Section 2 Planned Pharmacovigilance Actions. This was satisfactory to the CHMP.

Question 16 (Risk Management Plan)
"(from OC30 and 32) Extension of study A5751036 to 3 years is acknowledged. The minimum number of patient to be enrolled should be 500 (from 0C 23). The updated study protocol A5751036 should be submitted for review. The RMP should be updated accordingly."

The MAH acknowledged the comments made by the CHMP in respect of the ongoing study A5751036, entitled "A phase IIIb, one year, open-label, multi-centre, non-comparative study to evaluate the safety and tolerability of intravitreal pegaptanib sodium injection in subjects with diabetic macular oedema (DME)" . The MAH explained that they intended to enrol a minimum of 500 patients as previously indicated.

In accordance with the guidance provided in the previous RfSI (16 December 2011), the intent of the MAH is to institute the proposed revisions to the stated sections of the study protocol A5751036 via a CTA amendment:
• Extension of study duration to 3 years (section Summary, 3, 5)
• Incidence of specific pertinent ocular and systemic adverse events (section 2.2)
• Exclusion criteria for BP and HbA1c have been modified (section 4.2)
The MAH proposed to permit patients with bilateral DME access to pegaptanib treatment in both eyes if in the opinion of the investigator, they could benefit from pegaptanib anti- VEGF therapy, based upon the rationale that DME often presents bilaterally in patients.

The clinical trials that have been performed to date have administered intravitreally (IVT) 0.3 to 3 mg/eye doses of pegaptanib sodium unilaterally into patients with diabetic macular oedema (DME). It may be reasonably anticipated that concurrent, bilateral, IVT administration of a therapeutic, 0.3

mg/eye dose of pegaptanib sodium would result in at least a doubling of systemic exposure (i.e., plasma concentrations) to the drug. However based on a population PK study of pegaptanib in DME patients, it is not likely that bilateral administration of the 0.3 mg/eye dose of pegaptanib to DME patients would result in an increase in plasma pegaptanib concentrations exceeding those observed in patients receiving the well-tolerated 3 mg/eye dose (VISION and EOP1005 studies). By allowing bilateral dosing in the study the MAH was convinced that they will better understand the safety and efficacy of pegaptanib when administered under these conditions.

At the same time the MAH took the opportunity of correcting some typographical errors within the body of the text. Clean and tracked versions of the draft protocol submitted as per request for review (protocol A5751036) were submitted. In accordance with the request of the CHMP, Section 2 of the Risk Management Plan (RMP) was updated accordingly (section 2, RMP vs. 8.1).

The CHMP noted that the MAH proposed an updated version of the study protocol A5751036, entitled "A Phase Iiib, Three Year, Open Label, Multicentre, Non-Comparative Study To Evaluate The Safety And Tolerability Of Intravitreal Pegaptanib Sodium Injection In Subjects With Diabetic Macular Edema (DME)". The CTA amendment includes
• Extension of study duration to 3 years (section Summary, 3, 5)
• Incidence of specific pertinent ocular and systemic adverse events (section 2.2)
• Exclusion criteria for BP and HbA1c have been modified (section 4.2)

The Primary endpoints are:
The incidence of Adverse Events (both ocular and non ocular).
Pertinent ocular AE's include:
- Endophthalmitis
- Retinal detachment
- Retinal tear
- Traumatic cataract
- Increased ocular pressure

Secondary endpoints:
- Mean total number of injections per subject.
- Mean changes in BCVA from baseline to 12 months, baseline to 24 months and baseline to 36 months of treatment
- The incidence of Non-ocular events including
- Anaphylaxis/hypersensitivity-related adverse events.
- Cardiovascular adverse events
- Cerebrovascular adverse events
- Peripheral vascular adverse events
- Incidence of SAEs, both ocular and non-ocular

The MAH also proposed to permit patients with bilateral DME access to pegaptanib treatment in both eyes if in the opinion of the investigator, they could benefit from pegaptanib anti-VEGF therapy, based upon the rationale that DME often presents bilaterally in patients. This proposal will provide important new data since clinical trials performed to date have administered intravitreally (IVT) 0.3 to 3 mg/eye doses of pegaptanib sodium unilaterally into patients with diabetic macular oedema (DME). As pointed out by the MAH, there is a theoretical possibility that concurrent, bilateral, IVT administration of a therapeutic, 0.3 mg/eye dose of pegaptanib sodium would result in at least a doubling of systemic exposure (i.e., plasma concentrations) to the drug and therefore an increased risk of systemic ADRs. The safety and efficacy of pegaptanib when administered under these conditions need to be specifically investigated. This is taken into consideration in the updated protocol: "Patients who enter the study with one eye requiring treatment and later develop the need for treatment in both eyes providing the second eye fulfils all the entry criteria, can receive pegaptanib sodium treatment to both eyes. In such cases, the primary efficacy data analysis will be based on the first treated eye. Data from the second eye will be summarised separately. Ocular AE's will be summarised in a similar manner. Non-ocular AE's will be summarised by patients with 1 eye treated, 2 eyes treated and all patients.

In either of these situations, both eyes must not be injected at the same visit and the interval between treatments in any single eye must be at least 6 weeks, The interval between treatment in alternate eyes must be at least 3 weeks. Where both eyes require treatment, all inclusion and exclusion criteria apply equally to both eyes and both treated eyes will be assessed clinically on the days of injection of either eye, as under Study Procedures". This was acceptable to the CHMP.

5. FURTHER REQUEST FOR SUPPLEMENTARY INFORMATION TO BE ADDRESSED IN WRITING AND IN AN ORAL EXPLANATION

Major objection - to be addressed in writing and in an oral explanation

Benefit risk

The magnitude of effect of Macugen is not convincing. In addition there are concerns about the lack of a statistical significance at the end of the 2nd year (unexpected efficacy in the sham group) and the potential factors that contributed to this lack of difference between the treatment groups. This translates into an issue on the internal and external validity of the trial. In view of the modest effect and the uncertainties about both this effect as well as its applicability to the target population, the MAH should justify a positive benefit/risk in the treatment of patients with visual impairment due to macular oedema.

Major issues - to be addressed in writing

Clinical Efficacy

In view of the modest effect and the uncertainties about both this effect as well as its applicability to the target population, the MAH should elaborate on the below and justify the positive benefit/risk in the treatment of patients with visual impairment due to macular oedema.

a. At the end of the 2-year study, no statistically significant difference between study groups was observed for the following parameters: > 10 letter improvement in VA, > 15 letter improvement in VA, the proportion of subjects with a decrease in retinal thickness at centre point by ≥25% or ≥50%. The applicant should discuss why the > 10 letter improvement in visual acuity at 1 year is not maintained at 2 year (primary and secondary efficacy endpoints).
b. Visual acuity is influenced by a large number of pre-existing factors. These factors should be equally distributed between the different treatment groups. The MAH is asked to show the CHMP that the potentially confounding factors (including, but not limited to the duration of visual problems due to diabetes mellitus, type of DME (focal or diffuse), age of the patient, other underlying systemic complications such as chronic kidney failure, heart failure and peripheral vascular micro/macro-angiopathy) are equally distributed between the treatment arms. The MAH should further discuss whether and to what extent any of these factors could have affected the 1 and 2-year outcome (visual acuity, macular thickness) in the two study arms.

Other concerns - Points for consideration - to be addressed in writing

Clinical Efficacy

1. The MAH has been asked to provide the full 2-year efficacy data. In the MAH's response, summarising tables were provided. However, the raw data and the tables referred to in the supplementary clinical study report concerning the FAS2 population are still lacking and should be provided.

2. The MAH did not explain why, if pegaptanib is really reducing the blood retina barrier permeability, there is no effect on objective measures of oedema (which currently are only performed with OCT machines)

3. The MAH have, as requested, classified the types of DME (focal/diffuse) from fluorescein angiograms but have not evaluated the effect of Macugen/sham in these subgroups. Key efficacy analyses are expected.

4. In order to study potential differences in treatment effects amongst different age groups, a logistic regression model was used including the interaction between age and treatment. The CHMP agrees that this is the correct approach provided that the assumed linear effect of age (on logit scale) is appropriate. This should be explored, and evidence should be given that this model fits the data well.

5. Statistically significant effect for efficacy endpoints is not fully demonstrated. Sensitivity analysis for the binary outcomes was based on generalized estimating equations (GEE) which assume missingness completely at random. Regarding the continuous outcomes, the proposed mixed model makes very strict, often unrealistic assumptions about the variance and correlation structure in the data. How will those assumptions be justified? What alternative (less restrictive) models will be used in case the assumptions are not satisfied?

Clinical Safety

6. The MAH is requested to re-analyse the safety data (classification of recorded AE) on a per patient basis for the small numbers of subjects concerned.

The Timetable below will apply to the continuation of this assessment:

Submission	Restart	(Co)-Rapporteurs Assessment Report	Comments from CHMP Members	Opinion (or additional List of Outstanding Issues)
29 June 2011	30 June 2011	7 July 2011	12 July 2011	21 July 2011

RECOMMENDED CONDITIONS FOR MARKETING AUTHORISATION

Follow-up measures

Area[1]	Description	Due date[2]/Fulfilled
1. Non-clinical	The MAH is requested to provide the protocol and the time table of the submission of the results from the planned peri-/post-natal development study	As soon as it is available.
2. Clinical	The MAH should perform additional clinical study(ies) to • further evaluate the effect and safety in subjects with type I diabetes, subjects with different severity of diabetic retinopathy and subjects on treatment with thiazolidinediones. • Investigate the efficacy and safety of Macugen in relation to and in combination with laser photocoagulation	A synopsis of the study(ies), including a time plane, should be submitted within three months after opinion.
3. Clinical	The MAH should collect and analyse non-responder data from all planned and ongoing studies including the finalised studies in an attempt to define characteristics of patients that are likely to respond to treatment and those who are likely not to respond to treatment. If	Within 6 months after finalising the respective studies and within 12 months after finalising the last study.

	warranted, the Applicant should revise the treatment recommendations for the groups of patients.	
4. Clinical	The MAH should report back on study A5751034 in Japanese patients.	Within 6 months after finalising the study
5. Clinical/Pharmacovigilance	The MAH should report back on study A5751036. The minimum number of patient to be enrolled should be 500. The protocol of this study should be agreed by the CHMP	The outcome of the study should be reported back within 6 months after finalising the study.
6. Pharmacovigilance	The MAH should report back on the 3-year outcome of EOP1013	Within 6 month after the end of the study.
7. Pharmacovigilance	The educational package should be updated with relevant information with regards to the new proposed indication. The MAH is requested to perform and present results form a survey to demonstrate that the updated educational package has been distributed to relevant physicians.	The educational package should be updated and submitted for review before marketing in the respective countries. The survey should be performed within 12 months after marketing. The outcome of the survey should be submitted for review within 6 months after finalising the survey.
8. Pharmacovigilance	In the upcoming FU studies, occurrence of cardiovascular, cerebrovascular, and peripheral vascular adverse events should be specifically monitored.	

Conditions for the marketing authorisation

No changes. Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2). The need for an updated educational material to physicians is discussed in the RMP.

[1] Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.