Report on the Deliberation Results

May 13, 2008

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Macugen Intravitreous Injection Kit 0.3 mg
[Non-proprietary name]	Pegaptanib Sodium
[Applicant]	Pfizer Japan Inc.
[Date of application]	March 30, 2007

[Results of deliberation]
In the meeting held on April 25, 2008, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

In addition, the following conclusions were reached: the product is not classified as a biological product or a specified biological product; the re-examination period is 10 years; and the drug substance and the drug product are both classified as powerful drugs.

All-case surveillance is imposed as a condition for approval as follows:
Due to the limited number of patients treated in Japanese clinical studies, conduct a post-marketing drug use-results survey, covering all patients treated with the product, until data from a certain number of cases will be collected, in order to obtain the background information of patients treated with the product, collect data on the safety and efficacy of the product as soon as possible, and take necessary measures to ensure proper use of the product.

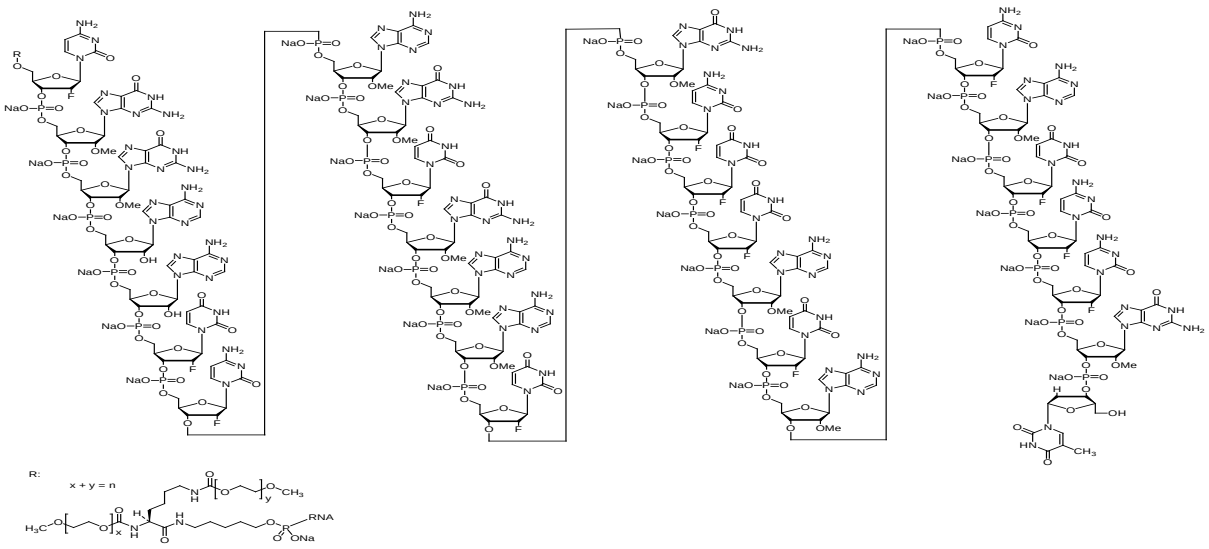
Review Report

April 9, 2008
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Macugen Intravitreous Injection Kit 0.3 mg
[Non-proprietary name]	Pegaptanib Sodium
[Name of applicant]	Pfizer Japan Inc.
[Date of application]	March 30, 2007
[Dosage form/Strength]	A solution for intravitreous injection containing 0.3 mg of pegaptanib sodium (as the free acid form of the oligonucleotide) in a prefilled syringe (90 μL)
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



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

Molecular weight: Approximately 50,000

Chemical name:

Modified oligo RNA (molecular weight: ca. 50,000) consisting of 28 sodium salt of (2'-deoxy-2'-fluoro)C-G_m-G_m-A-A-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-A_m-G_m-(2'-deoxy-2'-fluoro)U-G_m-A_m-A_m-(2'-deoxy-2'-fluoro)U-G_m-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro

)U-(2'-deoxy-2'-fluoro)U-A_m-(2'-deoxy-2'-fluoro)U-A_m-(2'-deoxy-2'-fluoro)C-A_m-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-G_m-(3'→3')dT attached to α,α'-{[(1*S*)-1-{[5-(phosphonooxy)pentyl]carbamoyl}pentane-1,5-diyl]bis(iminocarbonyl)}bis [ω-methoxypoly(oxyethane-1,2-diyl)] in an ester linkage at the 5' end

[Items warranting special mention]	Orphan drug
[Reviewing office]	Office of New Drug III

Review Results

April 9, 2008

[Brand name] Macugen Intravitreous Injection Kit 0.3 mg
[Non-proprietary name] Pegaptanib Sodium
[Name of applicant] Pfizer Japan Inc.
[Date of application] March 30, 2007

[Results of review]
It is determined that the submitted data have demonstrated the efficacy and safety of the product in the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration. Subfoveal choroidal neovascularization secondary to age-related macular degeneration for which the product is indicated has a poor prognosis and could lead to blindness, the product has been designated as an orphan drug, and the number of patients studied in Japan is limited. Therefore, it is necessary to conduct a post-marketing survey, covering all patients treated with the product, in order to further investigate the occurrence of local ocular and systemic adverse events and the association of the efficacy and safety of the product with the baseline visual acuity, lesion size, lesion subtype, and concomitant photodynamic therapy, etc.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indication and dosage and administration as described below, with the following condition.

[Indications]
Subfoveal choroidal neovascularization secondary to age-related macular degeneration

[Dosage and administration]
Pegaptanib sodium 0.3 mg (as the free acid form of the oligonucleotide) should be administered once every 6 weeks by intravitreous injection into the affected eye.

[Condition for approval]
Due to the limited number of patients treated in Japanese clinical studies, conduct a post-marketing drug use-results survey, covering all patients treated with the product, until data from a certain number of cases will be collected, in order to obtain the background information of patients treated with the product, collect data on the safety and efficacy of the product as soon as possible, and take necessary measures to ensure proper use of the product.

Review Report (1)

March 14, 2008

I. Product Submitted for Registration

[Brand name] Macugen Intravitreous Injection Kit 0.3 mg

[Non-proprietary name] Pegaptanib Sodium

[Name of applicant] Pfizer Japan Inc.

[Date of application] March 30, 2007

[Dosage form/Strength] A solution for intravitreous injection containing 0.3 mg of pegaptanib sodium (as the free acid form of the oligonucleotide) in a prefilled syringe (90 μL)

[Proposed indications] Subfoveal choroidal neovascularization secondary to age-related macular degeneration

[Proposed dosage and administration]

Pegaptanib sodium 0.3 mg (as the free acid form of the oligonucleotide) should be administered once every 6 weeks by intravitreous injection into the affected eye.

II. Summary of the Submitted Data and the Outline of Review

For this application, the data submitted by the applicant and the applicant's responses to the questions from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Age-related macular degeneration (AMD) is an age-related, chronic, progressive disease of the macula, which causes a deterioration of central vision and is associated with the risk of blindness. AMD is classified into the atrophic form which is characterized by atrophy of the retinal pigment epithelium and choriocapillaris in the macula and the exudative form which is characterized by the formation of choroidal neovascularization (CNV). Exudative AMD progresses more rapidly than does the atrophic form and is associated with a poor prognosis for vision and especially when CNV involves the fovea, it leads to blindness in not a few cases. In CNV secondary to exudative AMD, it has been reported that abnormalities of the retinal pigment epithelium due to aging or oxidative stress lead to excessive secretion of vascular endothelial growth factor (VEGF), resulting in an imbalance between VEGF and pigment epithelium derived factor (PEDF), which induces CNV (Lu M et al. *Ophthalmol Clin North Am.* 2006; 19: 323-334, Witmer AN et al. *Prog Retin Eye Res.* 2003; 22: 1-29).

Pegaptanib sodium is a selective VEGF inhibitor developed by [redacted] (a predecessor of [redacted]) and is a polyethylene glycol (PEG)-conjugated oligonucleotide. The oligonucleotide portion is an aptamer (a nucleic acid molecule that specifically binds to a target protein) designed to selectively bind to $VEGF_{165}$. In foreign countries, the clinical development program for pegaptanib sodium began in 19[redacted] and approval was granted in the US in December 2004. As of January 2008, the product has been approved in 53 countries.

In Japan, only verteporfin ([redacted]® for intravenous infusion) has been approved as a drug indicated for the treatment of AMD.

Pegaptanib sodium being developed for AMD (indication: subfoveal choroidal neovascularization secondary to age-related macular degeneration) was designated as an orphan drug as of July 7, 2004 and a clinical trial was initiated in [redacted] 20[redacted]. As the efficacy and safety of pegaptanib sodium in the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration have been confirmed, the applicant has filed an application for marketing approval for this product.

2. Data relating to quality

2.A *Summary of the submitted data*

2.A.(1) Drug substance

The drug substance, i.e. pegaptanib sodium is a 28-mer synthetic oligonucleotide aptamer covalently linked to polyethylene glycol chains. The drug substance is white to slightly colored powder and the following physicochemical properties were determined: physical description, solubility, hygroscopicity, thermal analysis and melting point, pH, dissociation constant (pKa), partition coefficient, crystalline polymorphism, and optical activity, and its biological properties and biological activity. The drug substance has a hygroscopicity value of [redacted]% at [redacted]°C[redacted]%RH and is deliquescent. The peaks in a powder X-ray diffraction pattern of the drug substance are derived from the PEG chains and no peaks derived from the oligonucleotide moiety have been observed. The oligonucleotide portion of the drug substance has 111 chiral centers and the PEG chains are achiral.

The manufacturing process for the drug substance consists of Stage 1 ([redacted] step), Stage 2 ([redacted] step), Stage 3 (PEGylation step), Stage 4 (PEGylated [redacted] step), and Stage 5 (freeze-drying step). In Stages [redacted] to [redacted], in-process tests are carried out and action limits have been established. As in-process controls of intermediates, the purity of [redacted] has been set for Step [redacted] of Stage [redacted], Step [redacted] of Stage [redacted], and Step [redacted] and Step [redacted] of Stage [redacted] and [redacted] has been set for Stage [redacted] and action limits for moving into the next process step have been established. Step [redacted] and Step [redacted] of Stage [redacted] have been defined as critical process steps and the purity of [redacted] in each fraction and the quantity of endotoxins in each fraction have been selected as process control parameters, respectively. As there are no intermediates isolated during the manufacturing process for the drug substance, no critical

process intermediates exist.

The structure of the drug substance has been confirmed by nucleotide base sequencing using a molecular biological method, nucleotide base sequencing using mass spectrum (analysis of non-PEGylated oligonucleotide, analysis of the drug substance), nucleoside profile, nuclear magnetic resonance spectrum (^{1}H-NMR, a spectrum of non-PEGylated oligonucleotide and a spectrum of the drug substance), ultraviolet (UV) spectrum, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrum, melting temperature (Tm), and circular dichroism (CD) spectrum. Potential impurities in the drug substance have been investigated: impurities derived from the oligonucleotide moiety (and PEG chain process-related impurities, PEGylated impurities [process-related impurities], PEGylated impurities [process-related impurities], impurities); impurities derived from the PEG chains (PEG chain oligonucleotide impurities, PEG chain oligonucleotide impurities, oligonucleotide impurities with different PEG chain structures); and other impurities. These impurities are controlled as band X (PEGylated impurities), band Y (PEGylated impurities, degradation products arising from of the PEG chains [Z*]), and band Z* (degradation products arising from of the PEG chains). Residual solvents including , , , , and have been determined and the specifications have been established. Inorganic compounds are controlled by monitoring of in process at Step of Stage and heavy metals are controlled by purity test.

The proposed specifications for the drug substance are description (appearance), identification (Method B*), pH, purity (clarity and color of solution, heavy metals [spectral analysis], related substances (1) [HPLC], related substances (2) [HPLC], residual solvents [gas chromatography]), water content, bacterial endotoxins, microbial limit, nucleoside profile (HPLC), (HPLC), (HPLC), sodium (HPLC), and assay (HPLC). The specification limits for related substances have been set as follows: band X ≤ %, band Y ≤ %, others ≤ %, and the total ≤ % for related substances (1); and Z* ≤ % for related substances (2). Although chromatographic retention time and have been investigated as possible identification tests, they are not included in the specifications. The safety of related substances has been discussed based on toxicity studies [see "2.A.(2) Drug product"]. Although identification test (Method A*) was included in the specifications at the time of regulatory submission, it was changed to the identification test (Method B*) in the course of regulatory review.

In order to assess the stability of the drug substance, long-term testing (-20 ± 5°C, 24 months), stress testing (temperature [5 ± 3°C, 6 months]), and stress testing (light [cool white fluorescent lamp, 1.2 million lx·hr; near ultraviolet fluorescent lamp, 200 W·hr/m^2]) were performed with the drug substance produced at a commercial scale packaged in glass vials sealed with a rubber stopper. The attributes tested

*Original information is masked in this document for disclosure.

in these studies were description (appearance), identification (Method A*), pH, clarity and color of solution, related substances (1), related substances (2), water content, [redacted], [redacted], and assay. The long-term testing showed no changes in the attributes tested over time. In the stress testing (temperature), there were increases in band Y and band Z*, suggesting increases in degradation products derived from the PEG chains, which were within the specification ranges. In the stress testing (light), there were increases in band Y and band Z*, and related substances and it is recommended that the drug substance should be stored protected from light. Based on the results of these studies, a storage condition of -25°C to -15°C and a re-test period of [redacted] months have been proposed for the drug substance.

2.A.(2) Drug product

The drug product is filled into single-use, glass pre-filled syringes (without a needle). Each injection (90 μL) contains 0.3 mg of the drug substance as the oligonucleotide pegaptanib free acid. The drug product contains the active ingredient, pH buffering agents, a tonicity adjuster, pH adjusters, and a diluent, and the specifications have been established separately for monobasic sodium phosphate [redacted]hydrate, dibasic sodium phosphate [redacted]hydrate, and water for injection and the other excipients are those listed in the Japanese Pharmacopoeia. Dibasic sodium phosphate [redacted]hydrate is a novel excipient.

In formulation development, the viscosity of the drug solution was investigated since a fine gauge needle is used for injection, and the appropriateness of the volume to be delivered was evaluated based on the risk of increased intraocular pressure and the viscosity of the drug solution. Pre-filled syringes with 27 gauge needles have been used for the commercial product in foreign countries and the same syringes were used also in Japanese clinical studies. However, an application for approval of a drug product presented in a pre-filled syringe without a needle has been filed so that a 30 gauge needle can be used to alleviate pain during injection. The commercial product in foreign countries will also be switched gradually to the drug product presented in a pre-filled syringe without a needle.

The manufacturing process for the drug product consists of Step 1 (buffer preparation), Step 2 (dissolution of the drug substance), Step 3 (pH adjustment), Step 4 (volume adjustment), Step 5 (filtration), Step 6 (filling), Step 7 (assembly and packaging for sterilization), Step 8 ([redacted] sterilization), and Step 9 (packaging) and in-process controls are included in Steps [redacted], [redacted], and [redacted]. Although no critical process step was identified initially, Step [redacted] has been defined as a critical process step in the course of regulatory review.

The proposed specifications for the drug product are description (appearance), identification (Method B*), osmolarity, viscosity, pH, related substance (1) (HPLC), related substance (2) (HPLC), bacterial endotoxins test, foreign insoluble matter test, insoluble particulate matter test, sterility test, test for delivered volume, [redacted] (HPLC), [redacted] (HPLC), and assay (HPLC). The specification limits for related substances have been set as follows: band X ≤ [redacted]%, band Y ≤ [redacted]%, others ≤ [redacted]%, and the total ≤ [redacted]% for related substance (1); and Z* ≤ [redacted]% for related substance (2). The safety of

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related substances has been evaluated in a rabbit 6-month intravitreous toxicity study and a dog 9-month intravitreous toxicity study, which have assured the safety of band X, band Y, and band Z* at doses up to 6.4 times, 6 times, and 4 times the estimated maximum daily intake in humans, respectively. As with the drug substance, identification test (Method A*) was changed to the identification test (Method B*) in the course of regulatory review.

In order to assess the stability of the drug product, long-term testing (5 ± 3°C, 12 months) and accelerated testing (25 ± 2°C, 6 months) were conducted with 3 lots of the drug product presented in a pre-filled syringe without a needle produced at a commercial scale (the proposed commercial drug product). Also using the drug product presented in a pre-filled syringe with a needle, long-term testing (5 ± 3°C, 24 months), accelerated testing (25 ± 2°C, 6 months), and stress testing (light [cool white fluorescent lamp, 1.2 million lx·hr; near ultraviolet fluorescent lamp, 200 W·hr/m^2]) were performed. The attributes tested in these studies were description (appearance), identification (Method A*), osmolarity, viscosity, pH, related substances (1), related substances (2), bacterial endotoxins, foreign insoluble matter, insoluble particulate matter, sterility, delivered volume (measured with pre-filled syringes with needles only), [redacted], [redacted], and assay. Bacterial endotoxins, insoluble particulate matter, and sterility were not included in the test attributes for the stress testing (light). In the long-term testing, variations in assay results were observed, but there were no changes or variations in other attributes tested. The stability testing with the drug product presented in a pre-filled syringe with a needle showed that the drug product was stable at 2°C to 8°C for 2 years. In the stress testing (light), there were increases in band Y and band Z* for the drug product exposed to light, which were within the specification ranges. Based on the results of the long-term testing with the proposed commercial drug product, the proposed expiration period for the drug product is 12 months when stored at 2°C to 8°C. The long-term testing with the proposed commercial drug product will continue for up to 36 months of storage.

2.B *Outline of the review by PMDA*

2.B.(1) Drug substance

PMDA asked the applicant to explain whether the assay method described in the specification for the drug substance is adequate to assure the activity of pegaptanib sodium and whether it is necessary to newly establish a specification for biological activity such as inhibitory activity against VEGF receptor.

The applicant explained as follows:

The effects of temperature, pH, salt concentration, and ion concentration on the secondary structure of the oligonucleotide moiety of pegaptanib sodium were investigated. As a result, the secondary structure was shown to be thermodynamically stable and robust under physiological conditions and very reversible upon temperature changes (Melanie B et al. *Biochemistry.* 2006;45: 7639-7643). Thus, adequate quality control can be ensured even without a specification for biological activity.

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Then, the applicant described as follows:
In the identification test (Method A*), pegaptanib sodium at a concentration of [redacted] mol/L competitively inhibited the binding of [redacted] DNA to $VEGF_{165}$ while PEGylated [redacted] oligonucleotide (an impurity lacking [redacted] in the oligonucleotide sequence) or PEGylated [redacted] oligonucleotide (an impurity in which [redacted] is added to the oligonucleotide sequence) even at concentrations of [redacted] mol/L did not inhibit the binding of [redacted] DNA to $VEGF_{165}$, indicating that the inhibitory activity of pegaptanib sodium is oligonucleotide sequence-specific. Therefore, the quality of the drug substance is properly controlled by quantitatively controlling the content of the oligonucleotide having the correct sequence and confirming the nucleotide sequence using the identification test (Method A*).

PMDA asked the applicant to explain why the test procedure and acceptance criteria for identification are different between Japan and [redacted] and instructed the applicant to change the proposed identification test to the identification test (Method B*) employed in [redacted] so that the biological activity of this proposed product can be controlled appropriately.

The applicant explained as follows:
According to the proposed test procedure, the [redacted] ratio of the reference standard to sample at concentrations corresponding to [redacted] is used as the test result. On the other hand, for [redacted] commercial product, [redacted] is calculated respectively from [redacted] of the reference standard and sample and its ratio is used as the test result. This calculation method was established in the course of regulatory review in [redacted] and identification test (Method A*) has been employed in the remaining foreign countries.

Then, the applicant responded as follows:
The test procedure for identification in Japan will be changed to Method B* and the specification will be re-established, improving the test procedure in [redacted] so as to enable an appropriate calculation via Method B*.

PMDA asked the applicant to explain the possibility of residual [redacted] and [redacted] derived from the PEG chains of pegaptanib sodium.

The applicant explained as follows:
(a) The PEG chain itself of pegaptanib sodium is stable and we consider that impurities derived from the PEG chain will not occur even upon heating etc, (b) In the anion exchange liquid chromatography process [redacted] at Step [redacted] of Stage [redacted] after the PEGylation process, [redacted], which can function even as [redacted] and [redacted], is used. However, as this process step is kept under [redacted] condition, [redacted] and [redacted] are unlikely to occur and even if these occur, they will be removed in the next [redacted] step. Therefore, the safety is assured.

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2.B.(2) Drug product

Syringes that are different from those of the foreign commercial product used in clinical studies are used for the proposed commercial drug product. PMDA asked the applicant to explain whether this change may possibly affect the efficacy and safety of the product.

The applicant explained as follows:

The syringe was compared between the foreign commercial product and the proposed commercial drug product. As a result, (a) The materials of construction of the syringe (excluding a needle) are the same except for the use of a synthetic rubber* cap in the proposed commercial drug product and the synthetic rubber* has been evaluated in the test for extractable substances, (b) Test for delivered volume was conducted [redacted] times with the proposed commercial drug product by [redacted] testers and the test results were compared to those with [redacted] lots of the foreign commercial product. As a result, the mean volume was [redacted] μL and [redacted] μL, respectively, and there was also little difference in the minimum and maximum values, (c) [redacted] sterilization has been introduced into the manufacturing process for the proposed commercial drug product and [redacted] is present at concentrations below the quantitation limit ([redacted] ppm). However, given that the vitreous [redacted] concentration ([redacted] μmol/L) following the administration of this drug product is very low compared to [redacted] concentration in the normal human vitreous humour ([redacted] μmol/L: Bhuyan KC et al. *Life Sci.* 1986;38: 1463-1471), its effects on the safety of the product should be insignificant. Therefore, the efficacy and safety of the two drug products should be comparable.

PMDA asked the applicant to explain the necessity of including the test for extractable volume in the specifications, in addition to a test for delivered volume.

The applicant explained as follows:

The test for extractable volume confirms that a slightly excess volume is withdrawn for the nominal volume (90 μL) after transferring the entire contents of each container. Meanwhile, the test for delivered volume with this drug product has confirmed that [redacted] to [redacted] μL can be delivered after the plunger is aligned with the dose line. Thus, the acceptance criteria are more stringent for the test for delivered volume compared to the test for extractable volume. The OC curve indicates that the consumer's risk level is almost comparable (when the true fraction defective is ≤ [redacted]%) or lower (when the true fraction defective is ≥ [redacted]%) for the test for delivered volume with this drug product compared to the test for extractable volume. Therefore, the test for extractable volume is unnecessary for this product.

PMDA accepted the above response and determined that the specifications, test methods, storage, and re-test period for the drug substance and the specifications, test methods, storage, and expiration period for the drug product are appropriate.

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2.B.(3) A novel excipient

The drug product contains a novel excipient, i.e. dibasic sodium phosphate [redacted]hydrate, as a buffering agent.

The specification for this excipient was re-established referring to the Japanese Pharmacopoeia etc. Initially, no relevant data on the stability of this excipient were submitted and data submission was requested. As a result, there were no particular problems. Also regarding safety, since sufficiently high doses of dibasic sodium phosphate [redacted]hydrate, which is a different hydrate form of this excipient, have been used for intraocular application, it has been determined that there are no safety concerns.

Based on the above, PMDA has determined that there are no particular problems with the use of this excipient in the drug product.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A *Summary of the submitted data*

The doses of pegaptanib are expressed as the oligonucleotide weight of pegaptanib. Unless otherwise specified, pharmacokinetic parameters in "(2) Safety pharmacology" are expressed as the mean.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Selectivity of non-PEGylated aptamer to $VEGF_{165}$ (4.2.1.1.1, 4.2.1.1.2)

The selectivity of ^{32}P-non-PEGylated aptamer of pegaptanib to human $VEGF_{165}$, mouse $VEGF_{164}$, human $VEGF_{121}$, or human placental growth factor $(PlGF)_{129}$ was investigated in binding studies. The non-PEGylated aptamer bound to human $VEGF_{165}$ with a dissociation constant of 49 ± 6 pmol/L (mean ± SE) and also bound to $VEGF_{164}$, the murine ortholog of human $VEGF_{165}$ with similar affinity, but did not bind to human $VEGF_{121}$ or human $PlGF_{129}$ even at 100 nmol/L. The non-PEGylated aptamer showed weak affinity for human platelet-derived growth factor (PDGF)-BB, but did not bind to human VEGF-related proteins (VEGF-B_{167}, VEGF-C, PlGF). On the other hand, when the binding of the non-PEGylated aptamer to mouse VEGF isoforms ($VEGF_{120}$, $VEGF_{164}$, $VEGF_{188}$) was determined by Far Western Blot assay, the non-PEGylated aptamer also showed affinity for $VEGF_{188}$, the murine ortholog of human $VEGF_{189}$, which was weaker than for human $VEGF_{165}$. The non-PEGylated aptamer had no affinity for human $VEGF_{121}$ and bound to human $VEGF_{165}$ and mouse $VEGF_{188}$, which suggested that the aptamer binding to the VEGF molecule depends on the presence of exon 7.[1)]

3.(i).A.(1).2) Inhibition of $VEGF_{165}$ binding to its VEGF receptors by pegaptanib

(a) Inhibition of VEGF receptor binding by pegaptanib in a cell-free system (4.2.1.1.3)

The inhibitory effects of pegaptanib on $VEGF_{165}$ binding to its VEGF receptors (Flt-1, KDR, NP-1) were

1) All VEGF isoforms share exons 1 to 5, covering the binding sites for the VEGF tyrosine kinase receptors (Flt-1 and KDR). Furthermore, different isoforms have different biological properties depending on the presence or absence of exons 6 and 7 (heparin or NP-1 binding site).

determined by radioimmunoassay using anti-human IgG antibody and ^{125}I-VEGF$_{165}$. Pegaptanib inhibited VEGF$_{165}$ binding to Flt-1, KDR, and NP-1 and its IC$_{50}$ values were 0.47 nmol/L for Flt-1, 1.10 nmol/L for KDR, and 0.23 nmol/L for NP-1.

(b) Inhibition of VEGF binding to human umbilical vein vascular endothelial cells (HUVECs) by pegaptanib in a cell system (4.2.1.1.4)

The inhibitory effects of pegaptanib on VEGF$_{165}$ binding to HUVECs expressing Flt-1 and KDR were assessed in a binding study using ^{125}I-VEGF$_{165}$. Pegaptanib concentration-dependently inhibited the binding of VEGF$_{165}$ to HUVECs with the IC$_{50}$ ranging from 0.03 to 1.41 nmol/L. The IC$_{50}$ value of anti-VEGF monoclonal antibody (mAb) was 7.36 nmol/L.

3.(i).A.(1).3) Inhibition of VEGF receptor functions by pegaptanib

(a) HUVEC proliferation (4.2.1.1.5)

The inhibitory effects of pegaptanib on VEGF$_{165}$-induced HUVEC proliferation were assessed based on cellular incorporation of ^{3}H-thymidine into DNA. Pegaptanib concentration-dependently inhibited VEGF$_{165}$-induced cellular proliferation with an IC$_{50}$ of 0.43 to 2.90 nmol/L. The IC$_{50}$ value of anti-VEGF mAb was 0.07 to 0.11 nmol/L.

(b) Calcium mobilization (4.2.1.1.6)

When VEGF induces cellular proliferation and vascular permeability, intracellular calcium mobilization is induced. Thus, the inhibitory effects of pegaptanib on VEGF were assessed based on calcium concentrations in HUVECs by fluorometry. Pegaptanib inhibited VEGF$_{165}$-induced calcium mobilization in a concentration-dependent manner with the IC$_{50}$ ranging from 0.74 to 3.18 nmol/L. The IC$_{50}$ value of anti-VEGF mAb was 2.66 nmol/L.

(c) Blood coagulation tissue factor mRNA expression (4.2.1.1.7)

Tissue factor, which forms a complex with factor VII, acting as a cellular initiator of the blood coagulation cascade (Viles-Gonzalez JF and Badimon JJ. *Int J Biochem Cell Biol.* 2004;36:25-30, Morrissey JH. *Thromb Haemost.* 2001;86: 66-74), has been reported to be associated with neovascularization in ocular vascular proliferative diseases (choroidal neovascularization, diabetic retinopathy) and tumors (Grossniklaus HE et al. *Mol Vis.* 2002;8: 119-126, Ishibashi T. *J Jpn Ophthalmol Soc*. 1999;103: 923-947). As VEGF$_{165}$ induces tissue factor expression in HUVECs, the inhibitory effects of pegaptanib on VEGF$_{165}$ were examined based on tissue factor mRNA expression levels by RT-PCR. Pegaptanib inhibited VEGF$_{165}$-induced tissue factor mRNA expression in HUVECs in a concentration-dependent manner with the IC$_{50}$ ranging from 0.39 to 0.64 nmol/L. The IC$_{50}$ value was 0.53 to 1.38 nmol/L when HUVECs were incubated with VEGF$_{165}$ in the presence of 50% normal human plasma.

The above results suggest that pegaptanib inhibits VEGF$_{165}$-induced tissue factor expression and its

inhibitory effects are little affected by plasma.

3.(i).A.(1).4) *In vivo* effects of pegaptanib

(a) Mouse model of retinopathy of prematurity (4.2.1.1.8)

As it has been reported that in a mouse model of hypoxia-induced retinopathy of prematurity, VEGF expression in the retina increases, inducing neovascularization, which is inhibited by VEGF-neutralizing protein and antisense DNA against VEGF (Smith LEH et al. *Invest Ophthalmol Vis Sci*. 1994;35: 101-111, Aiello LP et al. *Arch Ophthalmol*. 1995;113: 1538-1544, Aiello LP et al. *Proc Natl Acad Sci USA.* 1995;92: 10457-10461, Robinson GS et al. *Proc Natl Acad Sci USA.* 1996;93: 4851-4856), the inhibitory effects of pegaptanib on retinal neovascularization in this model were investigated.

When pegaptanib sodium (0.625, 1.25, 2.5, 5, and 25 mg/kg) or phosphate-buffered saline (PBS, vehicle) was intraperitoneally administered once daily for 5 days to mouse models of retinopathy of prematurity, pegaptanib inhibited retinal neovascularization in a dose-dependent manner and the ED_{50} value was 3.70 mg/kg and the IC_{50} value was 0.21 nmol/L (Retinal neovascularization was quantified by counting endothelial nuclei extending beyond the inner limiting membrane into the vitreous and intraocular concentrations of pegaptanib in each treatment group were determined).

(b) Mouse model of corneal angiogenesis (4.2.1.1.8)

Corneal angiogenesis was induced in mice by application of sodium hydroxide followed by debridement of the corneal epithelium and pegaptanib sodium (5, 10, 50, 100, and 200 mg/kg) or PBS (vehicle) was intraperitoneally administered twice daily for 10 days to the mouse models of corneal angiogenesis from the day of debridement of the corneal epithelium. Pegaptanib inhibited corneal angiogenesis in a dose-dependent manner and the ED_{50} value was 22.50 mg/kg and the IC_{50} value was 0.59 nmol/L.

(c) Guinea pig model of dermal vascular leakage (4.2.1.1.1, 4.2.1.1.9)

VEGF was intradermally administered to guinea pigs to induce vascular leakage and the inhibitory effects of pegaptanib and its non-PEGylated aptamer on increased dermal vascular permeability were investigated. Pegaptanib exhibited little inhibitory effects on $VEGF_{165}$-induced vascular leakage at 10 and 30 nmol/L, but almost fully inhibited vascular leakage at 100, 300, and 1000 nmol/L, which was similar to the inhibitory effects of 1000 nmol/L of anti-VEGF mAb. In contrast, the inhibitory effects of the non-PEGylated aptamer on vascular leakage were weaker than those of the PEGylated pegaptanib.

3.(i).A.(1).5) Anti-tumor activity of pegaptanib(4.2.1.1.10)

Mice were transplanted with human A673 tumors. Then, 14 to 16 hours later (a model of non-established tumors) or after tumors were grown until 200 mm^3 in size (a model of established tumors), pegaptanib sodium or PBS (vehicle) was intraperitoneally administered. Pegaptanib inhibited the growth of both non-established and established tumors as follows.

Treatment of mice with pegaptanib sodium at a dose of 10 mg/kg administered twice daily for 13 days inhibited the growth of non-established tumors by 80% compared to the control group, which were similar to the inhibition achieved by anti-VEGF mAb at a dose of 100 μg administered intraperitoneally twice weekly for 2 weeks (83%). Also, when pegaptanib sodium at a dose of 10 mg/kg was administered once daily for 16 days, tumor growth was inhibited by 70%. Furthermore, pegaptanib sodium at doses of 0.03, 0.3, 3, and 10 mg/kg administered once daily for 14 days showed dose-dependent anti-tumor activity (inhibition rate, 49%, 63%, 77%, and 84%, respectively).

The growth of established tumors was also inhibited by 59% with pegaptanib sodium at a dose of 10 mg/kg administered once daily for 12 days, demonstrating pegaptanib's anti-tumor activity.

The above-mentioned anti-VEGF mAb inhibited A673 tumor growth by 90% or more in the human A673 rhabdomyosarcoma mouse xenograft model, but had no direct effects on A673 cells *in vitro* (Kim KJ et al. *Nature.* 1993;362: 841-844). Therefore, it is considered that anti-VEGF mAb inhibited tumor growth by acting on VEGF-induced neovascularization, instead of directly acting on tumor cells.

3.(i).A.(2) Safety pharmacology

In order to assess the effects of pegaptanib on the cardiovascular system, conscious dogs were treated with single intravenous bolus doses of pegaptanib sodium (0, 4.5, 13.5, and 45 μg/kg) followed by 60-minute infusions (0, 2, 6, and 20 μg/kg/h, respectively). The maximum plasma pegaptanib concentrations[2)] were 114 ng/mL in the 4.5 μg/kg + 2 μg/kg/h group (9 times[3)] and 1 time[4)] the human C_{max}), 302 ng/mL in the 13.5 μg/kg + 6 μg/kg/h group (25 times and 3 times the human C_{max}), and 1080 ng/mL in the 45 μg/kg + 20 μg/kg/h group (90 times and 12 times the human C_{max}). Pegaptanib had no effects on heart rate, blood pressure, or ECG parameters (QT, QRS, and PR intervals) in any dose groups (4.2.1.3.1).

In order to assess the effects of pegaptanib on the respiratory system, rats were treated with a single intravenous dose of 0, 7, 20, or 65 μg/kg pegaptanib sodium. Pegaptanib had no effects on respiratory rate or tidal volume at 15, 30, 60, 240, and 480 minutes post-dose in any dose groups (4.2.1.3.2).

In order to assess the effects of pegaptanib on the central nervous system, pegaptanib sodium at a dose of 0, 7, 20, or 65 μg/kg was intravenously administered to rats and gross behavior[5)] was observed at 15, 60, 240, and 480 minutes post-dose. The estimated plasma pegaptanib concentrations immediately after

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[2)] The maximum value of plasma pegaptanib concentrations measured at 15 minutes, 30 minutes, 1 hour, and 2 hours post-dose.

[3)] Compared to the mean C_{max} following the administration of pegaptanib sodium 0.3 mg every 6 weeks for 48 weeks in humans: approximately 12 ng/mL (5.3.5.1.1, Study A5751010).

[4)] Compared to the maximum individual C_{max} following the administration of pegaptanib sodium 0.3 mg every 6 weeks for 48 hours in humans: 86.5 ng/mL (5.3.5.1.1, Study A5751010).

[5)] Gross behavior was evaluated by Irwin's multidimensional observation.

dosing were 177 ng/mL in the 7 μg/kg group (14 times[3] and 2 times the human C_{max}[4]), 567 ng/mL in the 20 μg/kg group (47 times and 6 times the human C_{max}), and 1371 ng/mL in the 65 μg/kg group (114 times and 15 times the human C_{max}). Pegaptanib had no CNS-related effects on gross behavior in any dose groups (4.2.1.3.3, 4.2.1.3.4).

In order to assess the effects of pegaptanib on the renal function, urinalysis and blood chemistry test results obtained from dog 9-month and monkey 3-month repeated dose toxicity studies were evaluated. Pegaptanib sodium was administered by intravitreous injection to both eyes once every 2 weeks to dogs at doses of 0.3, 1, and 3 mg/eye and to monkeys at doses of 0.1/1[6], 0.25, and 0.5 mg/eye. The plasma pegaptanib concentrations following repeated administration[7] were 1746 ng/mL in the 3 mg/eye group in dogs (145 times[3] and 20 times[4] the human C_{max}) and 1003 ng/mL in the 0.1/1 mg/eye group in monkeys (83 times and 11 times the human C_{max}). Pegaptanib had no effects on the renal function in any dose groups (4.2.3.2.6, 4.2.3.2.3).

Based on the above, the applicant explained that pegaptanib has no effects on the cardiovascular, respiratory, central nervous, or renal function at exposure levels up to 11 to 20 times the maximum plasma concentrations observed in human patients receiving pegaptanib sodium.

3.(i).B *Outline of the review by PMDA*

3.(i).B. (1) Mode of action of pegaptanib

PMDA asked the applicant to explain the mode of action of pegaptanib in the treatment of CNV secondary to exudative AMD.

The applicant explained as follows:

Normal choroidal vasculature is maintained through the balance between VEGF secreted by the retinal pigment epithelium (RPE) and pigment epithelium derived factor (PEDF), which is an anti-angiogenic factor (Tong JP and Yao YF. *Clin Biochem.* 2006;39: 267-276) and it is known that in CNV secondary to exudative AMD, RPE abnormalities due to aging or oxidative stress lead to excessive secretion of VEGF, resulting in an imbalance between VEGF and PEDF, which induces choroidal neovascularization (Lu M and Adamis AP. *Ophthalmol Clin North Am.* 2006;19: 323-334, Witmer AN et al. *Prog Retin Eye Res.* 2003;22: 1-29). When oversecreted VEGF binds to Flt-1 (VEGFR-1) and KDR (VEGFR-2) receptors on the surface of endothelial cells, the receptor tyrosine kinase is activated, increased vascular permeability and proliferation of vascular endothelial cells are induced, the surrounding matrix structure is changed, and due to the migration of proliferating endothelial cells and tube formation, new blood vessels sprout and branch, leading to the formation of CNV.

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[6] The dose was increased from 0.1 mg/eye to 1 mg/eye for the last two doses.

[7] Plasma concentrations in dogs refer to C_{max} and plasma concentrations in monkeys refer to the levels at 24 hours after the last dose.

Then the applicant described as follows:

VEGF exists in four major isoforms and of which $VEGF_{165}$ has been reported to be preferentially involved in ocular vascular proliferative diseases (Usui T et al. *Invest Ophthalmol Vis Sci.* 2004 ;45: 368-374, Ishida S et al. *J Exp Med.* 2003;198: 483-489, Spilsbury K et al. *Am J Pathol.* 2000;157: 135-144). Pegaptanib suppresses CNV formation by binding to $VEGF_{165}$ and inhibiting $VEGF_{165}$ binding to its VEGF receptors (Flt-1 and KDR). Severe visual impairment associated with AMD is due to CNV and hemorrhage and leakage of plasma components comprising fat from this premature vascular plexus is the direct cause of the functional impairment of the neural retina. VEGF not only promotes the division and proliferation of vascular endothelial cells, but also increases vascular permeability, functioning as an inflammatory cytokine as well. The pathological conditions of VEGF-dependent diseases like exudative AMD are neovascularization due to VEGF's vascular endothelial proliferative effects complicated by oedema and exudative lesions etc. in which VEGF is involved as an inflammatory cytokine. Therefore, not only anti-angiogenetic effect but also anti-inflammatory and anti-vascular permeability effects can be expected through inhibition of VEGF (Ishida S et al. *Ophthalmology.* 2006;48: 187-192, 2006) and even if neovascularization already exists, alleviation or improvement of symptoms can be expected through inhibition of VEGF-induced inflammation and increased vascular permeability by pegaptanib.

The PDMA understands that the mode of action of pegaptanib is based on the inhibition of $VEGF_{165}$. However, although the applicant explains that even if neovascularization already exists, alleviation or improvement of exudative AMD symptoms can be expected through the anti-VEGF effects of pegaptanib, this claim needs to be judged taking account of clinical study data.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A *Summary of the submitted data*

The results from absorption, distribution, metabolism, and excretion studies in mice, rats, rabbits, dogs, and monkeys were submitted. In studies using pegaptanib sodium labeled with ^{14}C in the lysine residue connecting the aptamer of pegaptanib and PEG (^{14}C-pegaptanib sodium), the radioactivity was determined by liquid scintillation counter (lower limit of quantification, 1.5 times the background radioactivity) or a quantitative whole-body autoradiography (QWBA) (lower limit of quantification, 0.4 or 0.5 nCi/g). Plasma pegaptanib concentrations were determined by a validated HPLC-UV method (lower limit of quantification, 0.025-0.21 μg/mL) and a validated nucleic acid hybridization assay (lower limit of quantification, 8 ng/mL). With respect to metabolites, one of the nucleotides that may be formed from the aptamer portion of pegaptanib was determined as nucleoside (2'-fluorouridine: 2'-FU) by HPLC-tandem mass spectrometry (LC-MS/MS) (lower limit of quantification, 75 pg/mL in plasma; 250 pg/mL in urine). Pegaptanib concentrations in samples are expressed as concentrations of the oligonucleotide of pegaptanib. Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean ± SD.

3.(ii).A .(1) Absorption

Following a single intravitreous injection of pegaptanib sodium 1 mg (0.5 mg/eye) in male white rabbits, the pegaptanib concentration in the vitreous fluid at 6 hours after dosing was 357.7 ± 74.3 μg/mL, the elimination half-life ($t_{1/2}$) was 83 hours, and the $AUC_{0-\infty}$ was 47 129 μg·h/mL. The plasma level of pegaptanib reached its maximum (C_{max}) (0.092 ± 0.051 μg/mL) at 24 hours after dosing, the $t_{1/2}$ was 84 hours, and the $AUC_{0-\infty}$ was 15.7 μg·h/mL (4.2.2.3.1).

Following a single intravitreous injection of pegaptanib sodium 1 mg (0.5 mg/eye) in male colored rabbits, the pegaptanib concentration in the vitreous fluid at 1 hour after dosing was 491.6 μg/mL, the $t_{1/2}$ was 111 hours, and the $AUC_{0-\infty}$ was 42 824 μg·h/mL. The plasma level of pegaptanib reached C_{max} (0.364 ± 0.232 μg/mL) at 24 hours after dosing, the $t_{1/2}$ was 51.3 hours, and the $AUC_{0-\infty}$ was 22.5 μg·h/mL (4.2.2.3.2).

Following a single intravitreous injection of pegaptanib sodium 1 mg (0.5 mg/eye) in female monkeys, the pegaptanib concentration in the vitreous fluid on Day 7 and Day 28 were 49.2 ± 12.7 and 1.5 ± 0.6 μg/mL, respectively. The plasma level of pegaptanib reached C_{max} (0.318 ± 0.047 μg/mL) at 12.7 hours after dosing, the $t_{1/2}$ was 104.8 ± 14.4 hours, and the $AUC_{0-\infty}$ was 38.2 ± 3.6 μg·h/mL (4.2.3.1.2).

Following a single intravitreous injection of pegaptanib sodium 3 or 4 mg (1.5 or 2 mg/eye) in male and female monkeys, the C_{max} of plasma pegaptanib was 1.05 or 1.99 μg/mL, respectively, the $AUC_{0-\infty}$ was 135 or 239 μg·h/mL, respectively, and the plasma levels of pegaptanib increased dose-dependently (4.2.3.1.3).

Following a single intravenous injection of pegaptanib sodium 0.1, 1, or 10 mg/kg in female mice, the $AUC_{0-\infty}$ of pegaptanib was 5.42, 82.8, or 691 μg·h/mL, respectively, indicating a dose-dependent increase, while $t_{1/2}$, CL, and V_{SS} values were almost constant regardless of the administered dose (4.2.2.3.3).

Following a single intravenous injection of pegaptanib sodium 1 mg/kg in male rats, the $t_{1/2}$ of plasma pegaptanib was 6.0 hours and the $AUC_{0-\infty}$ was 129 μg·h/mL (4.2.2.3.4).

Following a single intravenous injection of pegaptanib sodium 1 mg/kg in male colored rabbits, the $t_{1/2}$ of plasma pegaptanib was 3.5 hours, which was shorter than the $t_{1/2}$ of plasma pegaptanib after intravitreous administration (51.3 hours), suggesting that plasma levels of pegaptanib over time following intravitreous administration depend on the elimination of pegaptanib from the globe. The $AUC_{0-\infty}$ following intravenous administration was 69.3 μg·h/mL and comparison of the dose-adjusted $AUC_{0-\infty}$ indicated that 67% of pegaptanib administered intravitreously enters the systemic circulation as the unchanged drug (4.2.2.3.5).

Following a single intravenous dose of pegaptanib sodium 5 or 50 μg/kg in male dogs, the $AUC_{0-\infty}$ of pegaptanib was 0.247 or 2.320 μg·h/mL, respectively, indicating a dose-dependent increase, while $t_{1/2}$, CL,

and V_{SS} values were almost constant regardless of the administered dose (4.2.2.3.6).

Following a single intravenous dose of pegaptanib sodium 1 mg/kg in female monkeys, the $t_{1/2}$ of plasma pegaptanib was 9.3 ± 1.5 hours, which was shorter than the $t_{1/2}$ of plasma pegaptanib after intravitreous administration (104.8 ± 14.4 hours), as with in colored rabbits. The $AUC_{0-\infty}$ after intravenous administration was 165 ± 22.9 μg·h/mL and comparison of the dose-adjusted $AUC_{0-\infty}$ indicated that 95% of pegaptanib administered intravitreously enters the systemic circulation as the unchanged drug (4.2.2.3.7).

Following a single subcutaneous injection of pegaptanib sodium 1 mg/kg in female monkeys, the plasma level of pegaptanib reached C_{max} (4.9 ± 1.5 μg/mL) at 9.3 ± 2.1 hours after dosing, the $t_{1/2}$ was 12 ± 0.8 hours, and the $AUC_{0-\infty}$ was 128.5 ± 33.2 μg·h/mL and comparison with the dose-adjusted $AUC_{0-\infty}$after intravenous administration indicated that 78% of pegaptanib administered subcutaneously enters the systemic circulation as the unchanged drug (4.2.2.3.8).

Following a single intravenous injection of 1 mg/kg of the non-PEGylated aptamer, the 20 kD-PEGylated aptamer, or pegaptanib (the 40kD-PEGylated aptamer) in male rats, the $t_{1/2}$ of plasma pegaptanib was 0.3, 3.2, or 6.0 hours, respectively. The non-PEGylated aptamer was eliminated from plasma more rapidly than the PEGylated aptamers and pegaptanib had the longest $t_{1/2}$. The above results suggest that PEGylation is useful for increasing the aptamer residence time *in vivo* (4.2.2.3.4).

When pegaptanib sodium 0.4, 1.34 or 4 mg (0.2, 0.67, or 2 mg/eye, respectively) was administered to male and female white rabbits by intravitreous injection once every 2 weeks for 6 months (a total of 12 injections), no increases in plasma pegaptanib concentrations were observed after repeated administration and there was no evidence of drug accumulation. The $t_{1/2}$ also remained unchanged, indicating that clearance is unaffected by multiple dosing (4.2.3.2.5).

When pegaptanib sodium 0.6, 2, or 6 mg (0.3, 1, or 3 mg/eye, respectively) was administered to male and female dogs by intravitreous injection once every 2 weeks for 9 months (a total of 18 injections), plasma pharmacokinetic parameters are as shown in the following table. No increases in plasma pegaptanib concentrations were observed following repeated administration and there was no evidence of drug accumulation. The $t_{1/2}$ tended to be longer with increasing dose, which is considered attributable to the detection of terminal phase plasma concentrations due to elevations of plasma levels with increasing dose (4.2.3.2.6).

Table. Plasma pharmacokinetic parameters following repeated intravitreous administration of pegaptanib in dogs

Dose	No. of injections	C_{max} (μg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{τ} (μg·h/mL) ($AUC_{0-\infty}$ after the 1st dose)
0.6 mg	1	0.109 ± 0.068	4 ± 2	35 ± 20	2.2 ± 0.8
	9	0.154 ± 0.071	4 ± 2	21 ± 17	1.9 ± 0.4
	18	0.107 ± 0.042	6 ± 7	18 ± 8	2.1 ± 0.3
2 mg	1	0.496 ± 0.163	3 ± 1	52 ± 18	8.2 ± 1.4
	9	0.573 ± 0.230	4 ± 1	45 ± 22	8.7 ± 1.9
	18	0.453 ± 0.169	5 ± 2	37 ± 23	8.5 ± 1.5
6 mg	1	1.548 ± 0.822	5 ± 2	59 ± 18	26.4 ± 5.1
	9	1.329 ± 0.640	6 ± 5	55 ± 14	26.2 ± 4.0
	18	1.746 ± 0.473	4 ± 2	45 ± 16	28.8 ± 5.0

When pegaptanib sodium 0.2 to 2 mg (0.1-1 mg/eye)[8)] was administered to male and female monkeys by intravitreous injection once every 2 weeks for 3 months (a total of 6 injections), the vitreous pegaptanib concentrations at 2 weeks after the last dose were 6.3 ± 2.5 μg/mL at 0.5 mg and 12 ± 6.3 μg/mL at 1 mg. The plasma pegaptanib concentrations at 24 hours after the first dose and at 24 hours after the last dose were similar, i.e. 0.22 ± 0.05 and 0.19 ± 0.04 μg/mL, respectively, at 0.5 mg and 0.48 ± 0.07 and 0.45 ± 0.15 μg/mL, respectively at 1 mg (4.2.3.2.3).

3.(ii).A .(2) Distribution

The systemic distribution of radioactivity was determined following a single intravitreal injection of ^{14}C-pegaptanib sodium 2.36 mg (1.18 mg/eye) in male colored rabbits. The ocular levels of radioactivity at 24 hours post-dose were highest in the vitreous fluid (523.7 μg eq./g) followed by the retina (192.2 μg eq./g), aqueous humor (33.7 μg eq./g), optic nerve (15.6 μg eq./g), and cornea (15.5 μg eq./g) and the plasma radioactivity level at 24 hours post-dose was 0.2 μg eq./g. At 24 hours post-dose, the ocular level of radioactivity determined by QWBA was 199.4 μg eq./g. Compared to ocular levels of radioactivity, extraocular tissue levels of radioactivity were very low. Tissue radioactivity levels were lower than the plasma radioactivity level except for the kidney (9.0 μg eq./g), spleen (5.8 μg eq./g), bone marrow (1.7 μg eq./g), mesenteric lymph node (1.3 μg eq./g), and liver (1.0 μg eq./g). Then ocular radioactivity diffused from the vitreous fluid to the entire ocular tissue and reached its maximum level in each part of the eye at 168 to 312 hours post-dose. Radioactivity was detected in the eye even at 1008 hours post-dose (6 weeks) and the level of radioactivity in the vitreous fluid declined to 3.9 μg eq./g, but 30.6 to 75.3 μg eq./g of radioactivity was detected in the iris; retina; and sclera and choroid. The plasma radioactivity level at 1008 hours post-dose was 0.019 μg eq./g. On the other hand, radioactivity levels in systemic tissues declined with decreasing plasma radioactivity and levels of radioactivity at 1008 hours post-dose were below the lower limit of quantification in most tissues except for the eye (4.2.2.3.9).

The systemic distribution of radioactivity was determined following a single intravenous injection of ^{14}C-pegaptanib sodium 1.38 mg/kg in male colored rabbits. Tissue radioactivity levels in the kidney, spleen, and bone marrow at 2 hours post-dose were higher than the plasma radioactivity level (2.50 μg

8) 0.2 mg (0.1 mg/eye) was administered for the 1st to 4th doses and 2 mg (1 mg/eye) was administered for the 5th and 6th doses or 0.5 or 1 mg (0.25 or 0.5 mg/eye, respectively) was administered for the 1st to 6th doses.

eq./g) and radioactivity level in the liver was similar to the plasma radioactivity level. At 6 hours post-dose, the kidney, spleen, bone marrow, liver, and mesenteric lymph node had radioactivity levels higher than plasma (1.44 μg eq./g) and then plasma and tissue radioactivity levels declined over time. At all timepoints, the tissues except for the kidney, spleen, bone marrow, liver, and mesenteric lymph node had radioactivity levels similar to or lower than plasma (4.2.2.3.9).

Plasma protein binding was measured *in vitro* after the addition of 25 to 500 ng/mL of ^{33}P-pegaptanib sodium[9)]. The unbound fraction in rabbit plasma was ≥ 94%, suggesting that pegaptanib is little bound to plasma proteins (5.3.2.1.1).

Following a single intravitreal (2.36 mg [1.18 mg/eye]) or intravenous (1.38 mg/kg) injection of ^{14}C-pegaptanib sodium in male colored rabbits, red blood cells to plasma ratio of radioactivity ranged from 0.1 to 0.3 up to 1008 hours post-dose (for intravitreal administration) and up to 504 hours post-dose (for intravenous administration), indicating little distribution of pegaptanib or its metabolites into red blood cells (4.2.2.3.9).

Following repeated intravenous injections of pegaptanib sodium 40 mg/kg/day in pregnant mice from gestation day 6 to gestation day 15, less than 1% of the maternal plasma concentrations of pegaptanib was detected in the amniotic fluid on gestation day 15 (4.2.3.5.2.3).

3.(ii).A .(3) Metabolism

Following a single intravitreal injection of ^{14}C-pegaptanib sodium 2.36 mg (1.18 mg/eye) or a single intravenous injection of 1.38 mg/kg in male colored rabbits, 2'-FU as well as the unchanged drug were detected in plasma and urine (4.2.2.3.9).

In vitro metabolic stability of pegaptanib sodium was assessed using a nuclease solution (a mixture of endonuclease, 3'-exonuclease, 5'-exonuclease, and ribonuclease) and rabbit, dog, and monkey plasma. When 50, 100, and 250 ng/mL of ^{14}C-pegaptanib sodium were added to a nuclease solution, the parent compound disappeared over time regardless of concentration, ≥ 75% in 2.5 hours and ≥ 80% in 5 hours were metabolized, and 2'-FU concentrations increased in almost proportion to the dose of pegaptanib sodium added. In plasma samples, the extent of disappearance of the parent compound was not concentration-dependent while 2'-FU concentrations increased with increasing dose of pegaptanib sodium added. The disappearance rate of the parent compound was fastest in dog plasma, followed by rabbit plasma and then monkey plasma, but the difference is considered not directly associated with species difference as the possible influence of the amount of nucleases released from the red blood cells during the preparation of plasma can not be excluded (5.3.2.3.1).

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9) The aptamer portion of pegaptanib was radiolabeled at the 5' end using [γ-^{33}P]-ATP and T4 polynucleotide kinase.

3.(ii).A .(4) Excretion (4.2.2.5)

Following a single intravitreal injection of ^{14}C-pegaptanib sodium 2.36 mg (1.18 mg/eye) in male colored rabbits, 40% of the administered radioactivity was excreted in urine up to 1008 hours post-dose. Following a single intravenous injection of ^{14}C-pegaptanib sodium 1.38 mg/kg in male colored rabbits, 85.7% and 2.7% of the administered radioactivity were excreted in urine and feces, respectively, up to 168 hours post-dose (4.2.2.3.9).

3.(ii).B *Outline of the review by PMDA*

3.(ii).B.(1) Accumulation of pegaptanib in ocular tissue

After intravitreal administration of pegaptanib, the iris, retina, and sclera and choroid still had radioactivity levels higher than the vitreous fluid at 6 weeks post-dose. PMDA asked the applicant to explain the safety of pegaptanib in the ocular tissue and the safety in humans at the recommended clinical dosage regimen.

The applicant explained as follows:

Based on the measurements (n = 1 per timepoint) in distribution studies, the theoretical accumulation ratios in different tissues after the administration of pegaptanib sodium at a dosing interval of 2 weeks (employed in toxicity studies) and at a dosing interval of 6 weeks (the recommended clinical dosage regimen) are as presented in the following table. Even if accumulation occurs, the accumulation ratios would be less than 1.2 at the recommended clinical dosage regimen and around 2.1 in the sclera and choroid at the dosing interval of toxicity studies.

Table. Tissue radioactivity elimination half-life and accumulation ratio in colored rabbits

	Plasma	Iris*)	Retina	Sclera and choroid	Whole eye
Elimination half life (hr)	290		202	359	151
Accumulation ratio (at 6-week intervals)	1.10		1.03	1.17	1.01
Accumulation ratio (at 2-week intervals)	1.81		1.46	2.10	1.27

*) $t_{1/2}$ was not calculated for the iris due to insufficient sampling points, but based on comparison of the time course of concentrations among different tissues, it is estimated that the $t_{1/2}$ in the iris is similar to that in the retina and therefore, it is inferred that the accumulation ratio in the iris is also similar to that in the retina.

Then the applicant described as follows:

A 6-month repeated intravitreal toxicity study in white rabbits (at doses up to 2 mg/eye) and a 9-month repeated intravitreal toxicity study in dogs (at doses up to 3 mg/eye) showed no pegaptanib-related changes in the eye including the iris, retina, sclera, and choroid. Adverse events involving the iris, retina, sclera, and choroid for which a causal relationship to pegaptanib could not be denied, reported in clinical studies were iritis, retinal haemorrhage, retinal detachment, retinal exudates, retinal artery occlusion, retinal vein occlusion, and retinal scar, of which retinal haemorrhage had the highest incidence. However, since retinal haemorrhage is a basic pathology of age-related macular degeneration, the target disease of pegaptanib sodium and this event has been reported also in sham groups, retinal haemorrhage is very likely associated with the primary disease. Iritis, retinal exudates, retinal artery occlusion, retinal vein

occlusion, and retinal scar were reported as mild adverse events in most cases. Therefore, pegaptanib sodium is unlikely to cause significant adverse events involving the ocular tissue.

As the repeated-dose pharmacokinetics of pegaptanib has been investigated in white animals only, PMDA asked the applicant to explain the potential differences in the pharmacokinetics between white and colored animals and the potential differences in the efficacy and safety of pegaptanib sodium between different races (melanin content).

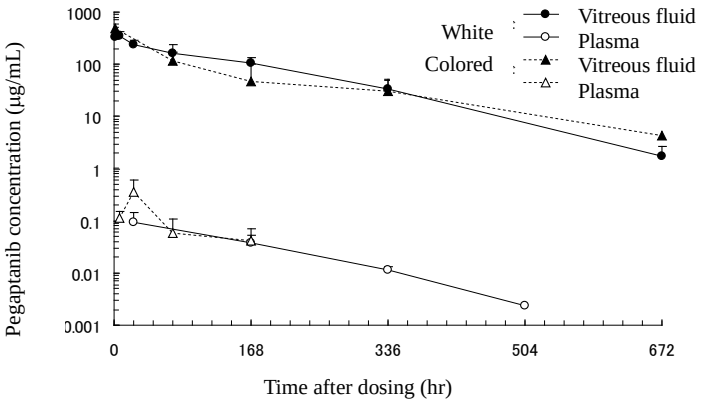


Figure. Vitreous and plasma pegaptanib concentrations following single intravitreal injection of pegaptanib sodium 1 mg (0.5 mg/eye) in rabbits (mean or mean + SD, n = 1-6/timepoint)

The applicant explained as follows:

With respect to the pharmacokinetic parameters of vitreous and plasma pegaptanib after a single intravitreal injection of pegaptanib sodium 1 mg (0.5 mg/eye) in white and colored rabbits, differences were seen in the mean values of plasma C_{max} and half-life and vitreous half-life (4.2.2.3.1, 4.2.2.3.2), but as shown in the figure on the left, there were no major differences in the time course of drug concentrations between white and colored rabbits. Timing of sampling and the number of samples at each timepoint differed between the studies and the lower limit of quantification for plasma pegaptanib concentrations was also different between the studies (white rabbits, 0.004 μg/mL; colored rabbits, 0.030 μg/mL). Taking account of these findings, it has been determined that there are no clear differences in the pharmacokinetics of pegaptanib between white and colored rabbits. Furthermore, repeated-dose toxicity studies in dogs and monkeys, i.e. colored animals, showed no accumulation of plasma and vitreous pegaptanib concentrations following the administration of pegaptanib sodium, as with the results in white rabbits. Since QWBA following a single intravitreal or intravenous injection of ^{14}C-pegaptanib sodium in colored rabbits did not show high levels of radioactivity in the retina or skin suggestive of melanin affinity, there should be no differences between white and colored animals. Foreign clinical studies and post-marketing information have also revealed no differences in the efficacy and safety of pegaptanib sodium among different iris colors (different melanin contents).

PMDA accepts the above response and considers that there are no major problems with the pharmacokinetic profile of pegaptanib, but the safety of pegaptanib in human ocular tissue needs to be judged taking account of clinical study data.

3.(iii) Summary of toxicology studies

3.(iii).A *Summary of the submitted data*

Toxicity studies of pegaptanib sodium were conducted mainly using intravitreous administration, i.e. the clinical route of administration, in non-rodents, and using intravenous administration in rodents. The doses of pegaptanib sodium are expressed as the oligonucleotide weight of pegaptanib.

3.(iii).A.(1) Single-dose toxicity

Single dose toxicity studies were conducted using intravitreous and intravenous injections in rats, rabbits, and monkeys.

A single intravitreous dose toxicity study in rabbits was conducted as a pilot study for a repeated-dose study and pegaptanib sodium 0.5 mg was administered to one eye and vehicle to the other eye. There were no drug-related toxic changes and just changes considered related to the intravitreous injection procedure were noted in both the study eye and the control eye (4.2.3.1.1).

A single intravitreous dose of pegaptanib sodium 0.5 mg/eye was administered to both eyes of monkeys and there were no drug-related or injection procedure-related changes (4.2.3.1.2).

Pegaptanib sodium from two lots at doses up to 2.0 mg/eye were administered to both eyes of monkeys by single intravitreous injection. There were no drug-related changes with either lot, but mild ocular discharge and conjunctival hyperaemia related to the injection procedure were noted at around 24 hours after dosing, which resolved by Day 4 (the day of dosing was designated as Day 1). In one animal in the 2 mg/eye group, conjunctival hyperaemia was still observed on Day 8 and pupillary hyporesponsiveness to a mydriatic was also noted, which resolved on Day 29 (4.2.3.1.3).

Single intravenous doses of 50, 150, and 450 mg/kg of pegaptanib sodium were administered in rats. There were no deaths or drug-related changes and the approximate lethal dose in rats by intravenous route is considered to be over 450 mg/kg (4.2.3.1.4).

Pegaptanib sodium 5 mg/kg[10)] was administered over 1 hour as a continuous intravenous infusion in monkeys. No deaths occurred and a slight prolongation of activated partial thromboplastin time (APTT) from the baseline value was noted at the end of continuous infusion, but there were no complement split products (C4d and Bb) or drug-related changes at the injection site, and the approximate lethal dose in

[10)] A dose of 5 mg/kg was chosen for this study because it has been reported that when blood drug concentrations reach 40-50 μg/mL following the administration of the phosphorothioated oligonucleotide in monkeys, serious toxicities such as transient complement activation associated with marked cardiovascular effects (decreases in heart rate, blood pressure, and cardiac output), increased APTT, and death occur (Levin AA. *Biochim Biophys Acta*. 1999;1489: 69-84, Galbraith WM et al. *Antisense Res Dev.* 1994;4: 201-206) and the plasma concentration at 5 minutes after an intravenous bolus dose of pegaptanib sodium 1 mg/kg in monkeys was 24.7 μg/mL (4.2.2.3.7) and pegaptanib sodium has linear pharmacokinetics.

monkeys by continuous intravenous infusion is considered to be over 5 mg/kg (4.2.3.1.5).

3.(iii).A.(2) Repeated-dose toxicity

Pegaptanib sodium 0.1/2 (2 mg/eye for the last two doses), 0.3, or 1 mg/eye was intravitreously administered into both eyes of rabbits (5 males and 5 females in each group) once every 2 weeks for 11 weeks (total 6 doses). The plasma and vitreous levels of pegaptanib increased with increasing dose and the plasma levels were lower than the vitreous levels throughout the study period. One animal in the 0.3 mg/eye group died due to anesthetic administration for intravitreal injection in Week 5 (the 3rd injection). Ophthalmologic examinations revealed dose-dependent mild attenuation of the retinal vessels. However, reevaluation of the fundus photographs showed no differences in the morphology of the retinal vessels between baseline and Day 55 (prior to the 5th injection) or Day 77 (1 week after the 6th injection), the incidence was not dose-related, there were no changes in electroretinograms, and no associated histopathological findings were observed. Thus, the retinal vessel attenuation is considered remotely related to the drug. Vitreal cells appeared to a mild to moderate degree in a dose-dependent manner and were confirmed to be macrophages by histopathological examinations, which is considered to be a physiological response to foreign bodies. Injection procedure-related, ocular oedema, mild signs of irritation, focal cataract, and iritis were observed in all groups, but there were no changes in intraocular pressure. Therefore, the no observed adverse effect level (NOAEL) in this study was determined to be 1 mg/eye for 6 doses and 2 mg/eye for 2 doses (4.2.3.2.1).

Pegaptanib sodium 2 mg/eye was intravitreously administered into both eyes of dogs (one male and one female) once weekly for 3 weeks (total 3 doses). Injection procedure-related preretinal haemorrhage (one animal in the control group) and fibrin deposition in the vitreous cavity (pegaptanib-treated and control animals) were noted, but there were no drug-related changes. Thus, the NOAEL in this study was determined to be 2 mg/eye (4.2.3.2.2).

Pegaptanib sodium 0.5, 1, or 2 mg/eye was intravitreously administered into both eyes of monkeys and the control group received 66 μL/eye of PBS. Twenty-four hours after the initial dose, dose-related ocular inflammation occurred and it was considered difficult to continue treatment with 1 or 2 mg/eye of pegaptanib sodium and the animals in the 1 and 2 mg/eye groups did not receive additional treatment and were sacrificed on Day 3 or Day 32. Ophthalmologic and histopathological examinations revealed moderate to severe uveitis (conjunctival hyperaemia/oedema; aqueous flare; diminished light reflex; increased intraocular pressure; fibrin deposition; inflammatory cell infiltration and hemorrhage), but these changes almost resolved by Day 32. The endotoxin level in the lot used for the initial dose (lot number, 11838.26) (0.130-0.156 EU/mg) was higher than that of the lot used in the re-designed study (lot number, [redacted]000690) (less than 0.05 EU/mg) and ophthalmic inflammation did not occur after 2 injections of pegaptanib sodium at a dose of 1 mg/eye in the re-designed study. Therefore, uveitis observed after the initial dose is considered associated with the higher endotoxin level in drug preparation.

In the re-designed study with a different lot (lot number, [redacted]000690), pegaptanib sodium 0.1/1 (1 mg/eye for the last two doses), 0.25, or 0.5 mg/eye was intravitreously administered into both eyes of monkeys (2-4 males and 2-4 females/group) once every 2 weeks for 3 months (total 6 doses). Plasma and vitreous levels of pegaptanib increased with increasing dose, but plasma levels after the first dose were similar to those after the last dose. Although injection procedure-related changes (transient conjunctival hyperaemia, eye discharge, and fibrosis of the ciliary body, choroid, or sclera) were noted in all groups, as there were no drug-related changes and anti-pegaptanib IgG antibody production was not detected, the NOAEL in this study was determined to be 0.5 mg/eye for 6 doses and 1 mg/eye for 2 doses (4.2.3.2.3).

Rats (10 males and 10 females in each group) were treated with daily intravenous doses of pegaptanib sodium 0.1, 1, or 10 mg/kg/day for 13 weeks and the control group received 1 mL/kg of PBS. Plasma levels increased in a dose-proportional manner and the plasma levels on Day 91 were higher than those on Day 1. One female each in the 1 mg/kg/day and control groups died or was euthanized when moribund, but the cause of death could not be identified. However, as no deaths occurred at the high dose, the death in the 1 mg/kg/day group is considered unlikely related to the drug. Mild lymphopenia in the spleen was noted in males treated with 1 mg/kg/day and males and females treated with 10 mg/kg/day, but hematology tests revealed no changes in white blood cell or lymphocyte count. Although vacuolated macrophages and vacuolated renal tubular epithelial cells were noted at ≥ 1 mg/kg/day, as similar vacuolation has been observed also with repeated administration of PEGylated proteins (Bendele A et al. *Toxicol Sci.* 1998;42: 152-157, Conover C et al. *Art Cells Blood Subs & Immob Biotech.* 1996;24: 599-611), these changes are considered associated with the phagocytosis of pegaptanib and its metabolite, i.e. PEGylated oligonucleotide, into cells. Chronic nephropathy was observed in all groups, and decreases in total protein and albumin and increased kidney weight etc. in males receiving 10 mg/kg may also be related to chronic nephropathy. Males in the 10 mg/kg group had statistically significant increases in cholesterol. Based on the above, as lymphopenia in the spleen was noted at ≥ 1 mg/kg/day, the NOAEL in this study was determined to be 0.1 mg/kg/day. At the NOAEL, the plasma level at 30 minutes post-dose on Day 91 was 1.489 μg/mL, which was about 124-fold higher than the C_{max} (12.0 ng/mL) at the recommended clinical dose (0.3 mg) in Japanese patients.

Pegaptanib sodium (0.2, 0.67, or 2 mg/eye) or PBS (67 μL/eye) was intravitreously administered into both eyes of rabbits (7-9 males and 7-9 females in each group) once every 2 weeks for 6 months (total 13 doses) (a 6-week recovery period was scheduled for 2 males and 2 females from the 2 mg/eye and control groups). Plasma levels of pegaptanib increased in a dose-proportional manner and plasma levels after repeated dosing were similar to or slightly lower than those after the first dose. One male in the 2 mg/eye group died after the 1st injection only in one eye and histopathological examination findings included hemorrhage and autolysis in extensive tissues and nuclear pyknosis in renal medulla, but no other lesions consistent with hypoxia were noted. The cause of death was unknown, but since the systemic exposure immediately after intravitreal injection is low and toxicity is unlikely to occur immediately after injection and no toxic signs were noted in other surviving rabbits, its relationship to the drug is considered remote.

Increased intraocular pressure was observed immediately after injection in all groups, which is considered a transient change as intraocular pressure was within the normal range at 7 to 13 days after injection. Clear bubbles on the surface of the sclera were noted after the injection of pegaptanib sodium, which resolved at 1 to 2 days after injection. This finding is considered attributable to the leakage of the drug solution or the vitreous fluid due to an increased volume of the vitreous fluid or a transient increase in intraocular pressure following intravitreal injection. Findings probably related to injection procedure were observed in the anterior segment of the eye in all groups that included vitreous cells, iritis, capsular ectasia, punctate vitreal opacities, fibrin deposition in the vitreous cavity, cortical cataract, corneal erosion, conjunctivitis, conjunctival hyperemia and swelling, cellular infiltration, and transmural fibrosis, and any of these findings was not observed at the end of the recovery period. Based on the above, the NOAEL in this study was determined to be 2 mg/eye (4.2.3.2.5).

Pegaptanib sodium (0.3, 1, or 3 mg/eye) or PBS (100 μL/eye) was intravitreously administered into both eyes of dogs (5 or 7 males and 5 or 7 females in each group) once every 2 weeks for 9 months (total 20 doses) (a 6-week recovery period was scheduled for 2 males and 2 females from the 3 mg/eye and control groups). Plasma levels of pegaptanib increased in a dose-proportional manner and plasma levels after repeated dosing were similar to those after the first dose. No drug-related changes were noted and no neoplastic or pre-neoplastic lesions were found in any of the organs including the globe. Increased intraocular pressure (2.3-3.9 times the baseline levels) was observed immediately after injection in all groups, which is considered a transient change as intraocular pressure was within the normal range at 7 days after injection. Injection procedure-related findings were tapetal or retinal scars or hemorrhage, conjunctival hyperemia, ecchymosis or hemorrhage, retinal detachment, vitreal floaters or strands, vitreous haemorrhage, lens capsular or cortical opacities, cataract, corneal erosion, capsular ectasia, miosis, and lymphocytic infiltration in the episcleral tissue associated with the injection tract, which were not observed at the end of the recovery period.
Based on the above, the NOAEL in this study was determined to be 3 mg/eye (4.2.3.2.6).

3.(iii).A.(3) Genotoxicity (4.2.3.3.1.1, 4.2.3.3.1.2, 4.2.3.3.1.3, 4.2.3.3.2.1)

Genotoxicity studies performed include a bacterial reverse mutation assay, a mouse lymphoma TK assay, a cell transformation assay with Syrian hamster embryo (SHE) cells, and a mouse bone marrow micronucleus test, all of which produced negative results.

3.(iii).A.(4) Carcinogenicity

According to “Guidelines for Carcinogenicity Studies of Drugs” (PMSB/ELD Notification No. 1607 dated November 1, 1999), pharmaceuticals administered by the ocular route etc. may not require carcinogenicity studies if there is little systemic exposure. Pegaptanib sodium and its component nucleosides have no genotoxic potential, a marked increase in systemic exposure is unlikely to occur in a long-term treatment with pegaptanib sodium at the clinical dosage regimen (0.3 mg should be administered once every 6 weeks by intravitreous injection), and VEGF inhibitors have been confirmed to

exert anti-tumor activity (4.2.1.1.10), etc. Therefore, pegaptanib sodium is considered to have a low carcinogenic potential and carcinogenicity studies have not been conducted.

3.(iii).A.(5) Reproductive and developmental toxicity

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation (4.2.3.5.1.1)

Mice (25 males and 25 females in each group) were treated by daily intravenous injection with pegaptanib sodium (1, 6.5, or 40 mg/kg/day) or PBS (5 mL/kg) from 28 days prior to, and throughout mating for males and from 15 days prior to mating, throughout mating, and until gestation day 7 for females. One male in the 40 mg/kg/day group died on Day 43, which was considered unlikely related to pegaptanib sodium since only redness and oedema at the injection site were noted, there were no other changes in general condition or body weight, necropsy also revealed no abnormal findings, and no other animals died or had drug-related serious changes. There were no changes in estrous cycle, copulation index, or fertility index. Smaller testis and epididymis in males treated with 40 mg/kg/day and decreased sperm density in the epididymis at ≥ 6.5 mg/kg/day were noted, but there were no changes in sperm count or sperm motility. Based on the above, the NOAELs for paternal and maternal general and reproductive toxicity and for the fetus were determined to be 40 mg/kg/day.

3.(iii).A.(5).2) Embryo-fetal development studies

(a) Intravitreous dosage-range embryo-fetal developmental toxicity study in rabbits (4.2.3.5.2.1)

Pregnant rabbits were treated by intravitreous injection with pegaptanib sodium (0.067, 0.2, 0.67, or 2 mg/eye) or PBS (67 μL/eye) on gestation days 6, 13, and 19. Plasma levels of pegaptanib increased with increasing dose and plasma levels after the 3rd dose were higher than those after the first dose. There were no changes suggestive of maternal or embryo-fetal toxicity. Some animals in the pegaptanib sodium 0.067 and 2 mg/eye groups had infection symptoms including corneal oedema, small pupil, iris congestion, and injection site swelling and redness, which were considered related to the injection procedure and unlikely related to the drug. Based on the above, the NOAELs in this study were determined to be 2 mg/eye for maternal general and reproductive toxicity and for the fetus.

(b) Intravenous dosage-range embryo-fetal developmental toxicity study in mice (4.2.3.5.2.2)

Pregnant mice were treated by daily intravenous injection with pegaptanib sodium (0.2, 1.2, or 8 mg/kg/day) or PBS (5 mL/kg) on gestation days 6 through 15. Plasma levels of pegaptanib increased with increasing dose and pegaptanib was detected in the amniotic fluid in the 8 mg/kg/day group, indicating that pegaptanib crosses the placenta. There were no changes suggestive of maternal or embryo-fetal toxicity. Based on the above, the NOAELs for maternal general and reproductive toxicity and for the fetus in this study were determined to be 8 mg/kg/day.

(c) Intravenous embryo-fetal development toxicity study in mice (4.2.3.5.2.3)

Pregnant mice were treated by daily intravenous injection with pegaptanib sodium (1, 6.5, or 40 mg/kg/day) or PBS (5 mL/kg) on gestation days 6 through 15. No deaths occurred and there were no

changes suggestive of maternal toxicity. In the fetuses, decreased fetal weights (-4% to -5% compared to the control group) and delayed ossification in phalanges were noted at 40 mg/kg/day. In this study, in order to evaluate the pharmacologic effect (anti-angiogenic effect) on F1 fetuses, satellite groups of pregnant mice were treated with pegaptanib sodium or PBS on gestation days 6 through 17 and delivered naturally and the effects of pegaptanib on the cardiovascular function and cardiovascular structure of the pups were assessed. As a result, the pup ECG and cardiac histopathology revealed no drug-related changes. Based on the above, the NOAELs in this study were determined to be 40 mg/kg/day for maternal general and reproductive toxicity and 6.5 mg/kg/day for the fetus.

3.(iii).A.(6) Local tolerance study (4.2.3.2.4)

No local tolerance study of pegaptanib sodium has been performed. In repeated intravitreal dose toxicity studies in rabbits, dogs, and monkeys, there were injection procedure-related changes at the injection site but no drug-related signs of irritation were noted.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Antigenicity/immunogenicity studies

(a) *In vitro* lymphocyte stimulation assay (4.2.3.7.1.1)

Pegaptanib was incubated with human peripheral blood lymphocytes and murine spleen lymphocytes from C3H/He mice and thymidine uptake was measured. No increase in thymidine uptake was observed, indicating that pegaptanib induces little stimulation of lymphocytes.

(b) Immunogenicity studies in mice, rats, and rabbits (4.2.3.7.1.2)

Serum samples collected from mice, rats, and rabbits treated with pegaptanib sodium were assayed by an ELISA for the presence of anti-pegaptanib IgG antibody. As a result, no anti-pegaptanib IgG antibody was detected and pegaptanib is considered to have no immunogenicity.

3.(iii).A.(7).2) A study on the mechanism of toxicity (4.2.3.7.3.1)

Incorporation of 2'-FU into DNA of the kidney, liver, spleen, muscle, and testis was determined following intravenous administration of pegaptanib sodium at a dose of 10 mg/kg/day in a 13-week, repeated intravenous dose toxicity study in rats (4.2.3.2.4). As a result, 2'-FU was present in DNA, suggesting that pegaptanib is metabolized in the body to 2'-FU that can subsequently be incorporated into DNA.

3.(iii).A.(7).3) Toxicity studies of its component nucleosides (potential metabolites)

(a) *In vitro* studies

2'-O-methyladenosine (2'-MA) did not induce reverse mutations in bacteria and was nonclastogenic in human lymphocytes (4.2.3.7.5.1, 4.2.3.7.5.5).

2'-O-methylguanosine (2'-MG) did not induce reverse mutations in bacteria and was nonclastogenic in human lymphocytes (4.2.3.7.5.2, 4.2.3.7.5.6).

In the bacterial reverse mutation assay, 2'-fluoro-cytidine hydrochloride (2'-FC) was negative with *S. typhimurium* strain, but produced a non-dose related increase in the number of revertant colonies with *E. coli* WP2*uvrA* in the presence and absence of metabolic activation at ≥ 33.3 μg/mL. Thus, another assay was performed with *E. coli* WP2*uvrA*. As a result, as observed in the initial assay, a non-dose related increase in the number of revertant colonies was observed at ≥ 33.3 μg/mL. 2'-FC was nonclastogenic in the chromosomal aberration assay in human lymphocytes (4.2.3.7.5.3, 4.2.3.7.5.7).

In the bacterial reverse mutation assay, 2'-fluoro-uridine (2'-FU) was negative with *S. typhimurium* strain, but produced a non-dose related increase in the number of revertant colonies with *E. coli* WP2*uvrA* in the presence and absence of metabolic activation at ≥ 33.3 μg/mL. Another assay was performed with *E. coli* WP2*uvrA*. As a result, like in the initial assay, a non-dose related increase in the number of revertant colonies was observed at ≥ 33.3 μg/mL. 2'-FU was nonclastogenic in the chromosomal aberration assay in human lymphocytes (4.2.3.7.5.4, 4.2.3.7.5.8).

2'-FC and 2'-FU were tested in the Syrian hamster embryo (SHE) cell transformation assay, which showed no increases in the number of transformed colonies (4.2.3.7.5.9, 4.2.3.7.5.10).

Using tissues from 90-day intravenous toxicity studies of 2'-FU in rats and woodchucks (4.2.3.7.5.12, 4.2.3.7.5.13), its incorporation into DNA and RNA was determined. As a result, 2'-FU was incorporated into cellular DNA of all tissues examined in a dose-dependent manner. 2'-FU was also incorporated into the RNA of the rat liver, which was lower than the level of incorporation in DNA (4.2.3.7.5.11).

(b) *In vivo* studies

90-day intravenous toxicity studies of 2'-FU and 2'-FC in rats and woodchucks were conducted. As a result, no toxicity findings exceeding those with pegaptanib were noted (4.2.3.7.5.12, 4.2.3.7.5.13).

3.(iii).B *Outline of the review by PMDA*

Despite that dose-dependent retinal vessel attenuation was observed in colored rabbits, but not in white rabbits or other animal species, the applicant considers that there are no differences in the toxicity of pegaptanib between the strains. PMDA asked the applicant to explain its reason.

The applicant explained as follows:

In a 11-week repeated dose toxicity study in colored rabbits (4.2.3.2.1), ophthalmologic examination revealed dose-dependent attenuation of the retinal vessels, which was not observed in toxicity studies in white rabbits (4.2.3.2.5), dogs (4.2.3.2.6), or monkeys (4.2.3.2.3). Concerning attenuation of the retinal vessels observed in colored rabbits, the ophthalmologist closely examined the fundus photographs. As a result, there were no morphological abnormalities in the retinal vessels on Day 55 or Day 77 compared to baseline in all groups and there were also no changes in electroretinograms. Furthermore, there were no

pegaptanib-related histopathological changes in the melanin-containing tissues, i.e. the retina, choroid, ciliary body, and iris, and no differences in the pharmacokinetics after a single intravitreal injection of pegaptanib sodium were seen between white and colored rabbits. Therefore, pegaptanib seems to be insignificantly associated with melanin and we consider that there are no differences in the toxicity of pegaptanib sodium between the strains.

Chronic nephropathy was noted in a 13-week intravenous toxicity study in rats (4.2.3.2.4). PMDA asked the applicant to explain the effects of pegaptanib sodium and its extrapolation to humans.

The applicant explained as follows:
The mechanism of an increased incidence and severity of chronic nephropathy is unknown. Minimal chronic nephropathy was noted also in the control group. $VEGF_{165}$ is present in the kidney and contributes to the maintenance of glomerular structure and function, and it has been reported that the administration of anti-human $VGEF_{165}$ antibody to mice resulted in vacuolation, swelling, and obstruction of glomerular capillary vessels (Kitamoto Y et al. *Tohoku J Exp Med*. 2001;195: 43-54). A study investigating the effects of $VEGF_{165}$ on the glomerulus (Ostendorf T et al. *J Clin Invest.* 1999;104: 913-923) indicates that $VEGF_{165}$ inhibitors do not affect the glomerulus when glomerular endothelial cells are normal, but affect the regeneration/maintenance of glomerular endothelial cells and can augment glomerular capillary injuries when glomerular endothelial cells are injured. Taking account of these findings, it was very likely that pegaptanib exacerbated naturally occurring chronic nephropathy, and also in humans, when glomerular endothelial cells are injured, pegaptanib can exacerbate the lesion. However, when chronic nephropathy was exacerbated in rats, the dose of pegaptanib sodium administered was 10 mg/kg/day and the plasma level at 30 minutes post-dose was 176.9 μg/mL, which was about 14 700 times the maximum plasma level (12.0 ng/mL) at the Japanese recommended clinical dose (0.3 mg). Therefore, serious adverse events involving the kidney are unlikely to occur following the administration of pegaptanib sodium in humans.

PMDA accepted the above response. Based on the submitted data, except for injection procedure-related events, pegaptanib sodium is considered to have low toxicities in humans at the proposed dosage regimen and there should be no particular problems with its clinical use from a toxicological point of view.

4. Clinical data

4.(i) Summary of human pharmacokinetic and pharmacodynamic studies

4.(i).A *Summary of the submitted data*

As the evaluation data, the results from a pharmacokinetic study in Japanese patients (5.3.5.1.1, A5751010) and pharmacokinetic studies in foreign patients (5.3.3.2.1, NX-109-01; 5.3.3.2.2, EOP1000; 5.3.3.2.3, EOP1001; 5.3.5.1.4, EOP1004; 5.3.5.1.7, EOP1006) were submitted. Plasma pegaptanib concentrations are expressed in terms of the weight of the oligonucleotide portion of pegaptanib and were determined by a validated nucleic acid hybridization assay (lower limit of quantification: NX109-01, 7

ng/mL; EOP1000, EOP1001, EOP1004, and EOP1006, 8 ng/mL; A5751010, 0.5 ng/mL). IgG antibodies against pegaptanib were measured by a validated, non-GLP, sandwich enzyme immunoassay (A lower limit of quantification has not been established). The results from *in vitro* studies using human biomaterials (5.3.2.1.1, 5.3.2.2.1, 5.3.2.3.1) were also submitted. Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean ± SD.

4.(i).A.(1) Studies using human biomaterials

^{33}P-pegaptanib sodium, when added to human plasma at concentrations of 25 to 500 ng/mL as the oligonucleotide moiety of pegaptanib, was little bound to plasma proteins (5.3.2.1.1).

When ^{14}C-pegaptanib sodium was added to human plasma at concentrations of 50 to 250 ng/mL, 2'-FU was detected as a metabolite (5.3.2.3.1).

Using specific substrates for 7 cytochrome P450 species (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5), inhibition of the activities of cytochrome P450 species by pegaptanib in human liver microsome was investigated. Pegaptanib sodium did not inhibit the activity of any of the species studied at concentrations of 0.01 to 25 μg/mL (0.002-4.725 μg/mL as the oligonucleotide moiety of pegaptanib, which is equivalent to 0.17- to 395-fold the C_{max} [11.96 ng/mL] observed in Japanese patients treated with 0.3 mg of pegaptanib sodium) (5.3.2.2.1).

4.(i).A.(2) Studies in patients

Japanese data

Ninety-five Japanese patients with exudative AMD received 9 consecutive unilateral, intravitreous injections of pegaptanib sodium (0.3 or 1 mg as the oligonucleotide weight of pegaptanib) at 6-week intervals (up to Week 48). Plasma concentrations of the unchanged drug reached C_{max} within 7 days after the first dose and the apparent $t_{1/2}$ was about 10 days. The C_{max} after the first dose and the AUC between the first dose and the next dose (AUC_{τ}) were 12.0 ± 13.2 ng/mL and 2.5 ± 0.9 μg·h/mL, respectively in the 0.3 mg group and 37.2 ± 27.2 ng/mL and 8.6 ± 2.2 μg·h/mL, respectively in the 1 mg group. Trough levels immediately before injections during repeated administration were below the quantification limit (quantification limit, 0.5 ng/mL) in most subjects treated with 0.3 mg and the mean trough level in the 1 mg group was constant (about 1.5 ng/mL), and there was no accumulation higher than that would be predicted based on the results of the first dose (5.3.5.1.1).

Foreign data

A single, unilateral, intravitreous injection of pegaptanib sodium (0.25, 0.5, 1, 2, and 3 mg as the oligonucleotide weight of pegaptanib) was given to 15 foreign patients with exudative AMD. Plasma pegaptanib concentrations were below the quantification limit (quantification limit, 7 ng/mL) in most subjects at 0.25, 0.5, and 1 mg. Plasma pegaptanib concentrations were below the quantification limit at 4

hours after dosing in most of the subjects receiving 2 or 3 mg, but the plasma concentrations were measurable for 28 to 32 days after dosing in some subjects and in these subjects, C_{max} was reached within 1 to 7 days after dosing and the $t_{1/2}$ was 4 to 11 days. As to the C_{max} and AUC up to the last measured concentration (AUC_{last}) in each patient in the 2 and 3 mg groups (2 patients per group[11]), the C_{max} was 98 and 52 ng/mL and the AUC_{last} was 18 and 9 μg·h/mL in the 2 mg group and the C_{max} was 148 and 70 ng/mL and the AUC_{last} was 36 and 28 μg·h/mL in the 3 mg group (5.3.3.2.1).

Ten foreign patients with exudative AMD received 3 consecutive unilateral, intravitreous injections of pegaptanib sodium (3 mg as the oligonucleotide weight of pegaptanib) at 4-week intervals (up to Week 8). The t_{max} and $t_{1/2}$ values for plasma pegaptanib concentrations in individual patients treated with 3 doses were 4 to 189 hours and 3 to 17 days, respectively, and the C_{max} values were 32 to 200 ng/mL, showing large inter-individual variability, but the mean C_{max} values for the 1st, 2nd, and 3rd doses were similar, i.e. 83, 70, and 87 ng/mL, respectively. The $AUC_{0-\infty}$ after the 1st dose and the AUC_{τ} after the 3rd dose were similar, i.e. 20 ± 6 and 24 ± 7 μg·h/mL, respectively, indicating that repeated administration does not alter the pharmacokinetics of pegaptanib (5.3.3.2.2).

Eleven foreign patients with exudative AMD received 3 consecutive unilateral, intravitreous injections of pegaptanib sodium (3 mg as the oligonucleotide weight of pegaptanib) at 4-week intervals (up to Week 8) in combination with PDT (verteporfin PDT treatment was scheduled to be given within 5-10 days prior to the first dose of pegaptanib sodium). The t_{max} and $t_{1/2}$ values in individual patients treated with 3 doses were 4 to 163 hours and 2 to 14 days, respectively, and the C_{max} values were 30 to 152 ng/mL, showing large inter-individual variability, but the mean C_{max} values for the 1st, 2nd, and 3rd doses were similar, i.e. 68, 67, and 74 ng/mL, respectively and there was no accumulation higher than that would be predicted based on the results of the first dose. The $AUC_{0-\infty}$ following the 1st dose and the AUC_{τ} following the 3rd dose were similar, i.e. 21 ± 5 and 25 ± 12 μg·h/mL, respectively, indicating that repeated administration does not alter the pharmacokinetics of pegaptanib (5.3.3.2.3).

Foreign patients with exudative AMD (222 patients included in the pharmacokinetic analysis) received 9 consecutive unilateral, intravitreous injections of pegaptanib sodium (0.3, 1, and 3 mg as the oligonucleotide weight of pegaptanib) at 6-week intervals (up to Week 48). Plasma pegaptanib trough concentrations in Weeks 12, 30, 42, and 54 were below the lower limit of quantification in almost all patients receiving 0.3 or 1 mg and 1 of 73 patients in the 0.3 mg group and 2 of 74 patients in the 1 mg group had at least one measurable plasma pegaptanib trough concentration, which was 17.8 ng/mL and 8.9 and 20.8 ng/mL, respectively. Also in the 3 mg group, almost all patients had plasma pegaptanib trough concentrations below the quantitation limit, but 4 of 75 patients had measurable plasma pegaptanib trough concentrations at more than one time point, the means of which at Weeks 12, 30, 42, and 54 were

[11] Of the 3 patients in each group, neither Cmax nor AUClast was calculated due to insufficient sampling points for 1 patient in the 2 mg group and Cmax was not calculated but AUClast was 17 μg·h/mL for 1 patient in the 3 mg group.

10.3, 8.7, 11.5, and 9.8 ng/mL, respectively. The pharmacokinetics of pegaptanib was investigated in more detail in 13 patients together with 7 patients from Study EOP1003 that was conducted at a similar dosing regimen (5.3.5.1.2) and plasma pegaptanib concentrations at pre-dose, 4 hours and 24 hours after dosing and 1, 3, and 6 weeks after dosing for the first dose and the 4th dose (Week 18) were measured. As a result, 2 of 4 patients in the 0.3 mg group had measurable plasma pegaptanib concentrations (range, 8.8-10.7 ng/mL) at 24 hours after dosing. In 4 of 4 patients in the 1 mg group, plasma pegaptanib concentrations were measurable between 24 hours and 3 weeks after dosing (range, 9.4-35.8 ng/mL) and C_{max} was reached within 1 week after dosing. In the 3 mg group, 8 of 8 patients had measurable plasma concentrations (range, 8.1-202 ng/mL) and C_{max} was observed within 1 week after dosing. Only 1 patient in the 3 mg group had measurable plasma pegaptanib concentrations at 6 weeks after the 1st and the 4th dose, which were 8.7 and 8.1 ng/mL, respectively. In other patients, plasma pegaptanib concentrations at 6 weeks after dosing were all below the quantitation limit (5.3.5.1.4).

Thirty-seven foreign patients with exudative AMD received 4 or 5 consecutive unilateral, intravitreous injections of pegaptanib sodium (3 mg as the oligonucleotide weight of pegaptanib) at 6-week intervals (up to Week 18 or 24). Plasma pegaptanib concentrations over time after the 1st dose were similar to those after the 4th or 5th dose as shown in the table below, indicating that repeated administration does not alter the pharmacokinetics of pegaptanib (5.3.5.1.7).

Table. Pharmacokinetic parameters of plasma pegaptanib in foreign patients (Study EOP1006, 5.3.5.1.7)

	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (day)	AUC_{τ} (μg·h/mL)
After the first dose (n) (range)	77 ± 29 (37) (19-136)	60 ± 42 (37) (21–170)	10 ± 3 (34) (4-18)	26 ± 7 (34) (4-44)
After the 4th or 5th dose (n) (range)	75 ± 30 (35) (27-142)	60 ± 46 (35) (19-167)	10 ± 4 (32) (3-19)	25 ± 6 (32) (13-39)

4.(i).A.(3) Population pharmacokinetic (PPK) analysis

Using plasma pegaptanib concentration data (3536 points) (168 patients) obtained from 3 studies involving foreign patients with exudative AMD (EOP1000, EOP1001, EOP1006), PPK analysis was performed to identify factors affecting the pharmacokinetics of pegaptanib. As a result, creatinine clearance and body weight were found to be significant factors influencing clearance (CL) and age was found to be a significant factor influencing the transfer rate constant (Ka) from the vitreous into the systemic circulation (5.3.3.5.1).

4.(i).B *Outline of the review by PMDA*

4.(i).B.(1) Pharmacokinetic similarities between Japanese and foreign patients

PMDA asked the applicant to explain differences in the pharmacokinetics of pegaptanib at the clinical dose of 0.3 mg/eye given every 6 weeks between Japanese and foreign subjects.

The applicant explained differences in plasma pegaptanib concentrations at a dose of 0.3 mg/eye as follows:

Since the quantitation limit was higher in foreign clinical studies than in a Japanese clinical study (foreign

clinical studies, 7-8 ng/mL; Japanese clinical study, 0.5 ng/mL), more foreign subjects had plasma concentrations below the quantitation limit.

Then the applicant described as follows:

Plasma pegaptanib concentrations in Japanese and foreign subjects treated with the same doses of pegaptanib sodium are not available. However, when the doses were normalized to 1 mg, the data distribution for C_{max} and AUC_{τ} values was similar between Japanese subjects treated with repeated intravitreous injections of 0.3 or 1 mg and foreign subjects treated with repeated intravitreous injections of 3 mg as shown in the following figures and the $t_{1/2}$ values were similar between Japanese and foreign subjects, i.e. 9.6 ± 4.2 (0.3 mg), 11.4 ± 3.9 (1 mg), and 10 ± 3 days (3 mg). Therefore, we consider that there are no major differences in the pharmacokinetics of pegaptanib between Japanese and foreign subjects.

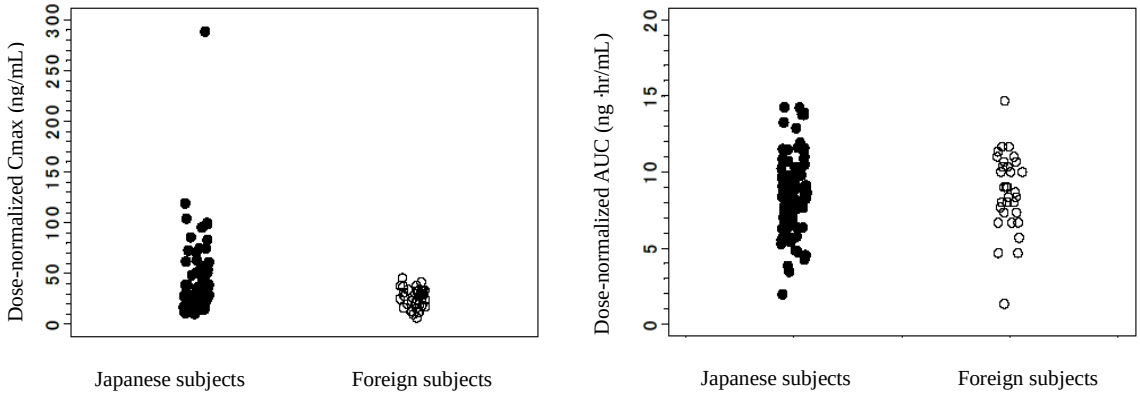


Figure. C_{max} (figure on the left) and AUC_{τ} (figure on the right) after the first dosing in the repeated intravitreous administration studies of pegaptanib sodium every 6 weeks to Japanese and foreign patients with exudative AMD (5.3.5.1.1, Study A5751010; 5.3.5.1.7, Study EOP1006) when the first doses are normalized to 1 mg.

PMDA considers as follows:

Although there are no study data allowing for the comparison of plasma pegaptanib concentrations at the same doses between Japanese and foreign patients with AMD, no major differences were observed in the pharmacokinetics of pegaptanib when the doses were normalized to 1 mg and there should also be no major differences in the pharmacokinetics at the clinical dosage regimen between Japanese and foreign patients. However, the safety of pegaptanib sodium in Japanese AMD patients needs to be judged taking account of clinical study data.

4.(i).B.(2) Factors affecting excretion into the systemic circulation

Although pegaptanib sodium is delivered by intravitreal injection, pegaptanib is detected also in plasma and plasma pegaptanib concentrations vary considerably. Therefore, PMDA asked the applicant to explain the factors affecting its excretion into the systemic circulation and the safety in patients with high plasma pegaptanib levels in view of the pharmacologic effects of pegaptanib.

The applicant explained as follows:

Although the mechanism of excretion of pegaptanib from the eye into the systemic circulation in humans

is unknown, since non-clinical studies using the radiolabeled drug showed that radioactivity was detected in the posterior retina and choroid, and since blood vessels are present mainly in the posterior segment of the eye, pegaptanib is considered to be excreted mainly via the posterior segment of the eye into the systemic circulation. Any factors influencing the tissue of the posterior segment of the eye may affect its absorption into the systemic circulation. The results of PPK analysis in foreign patients have shown that age is a factor influencing the rate of excretion from the vitreous into the systemic circulation and it is inferred that such excretion tends to be delayed with increasing age, which is considered attributable to age-related, decreased choroidal permeability and decreased choroidal blood flow associated with reduced choroidal vessels. Concerning its elimination from plasma, non-clinical studies have indicated that the primary route of excretion of pegaptanib is renal and PPK analysis has suggested that creatinine clearance and body weight affect the total body clearance of pegaptanib. Taking account of these findings, inter-individual differences in these factors (age, body weight and creatinine clearance) are considered to be one of the causes for the variability in plasma pegaptanib concentrations in Japanese and foreign clinical studies.

Then the applicant described as follows:

Regarding the safety of treatment with pegaptanib sodium, pegaptanib has anti-VEGF activity and when it enters the systemic circulation, adverse events such as hypertension and proteinuria, as reported with bevacizumab ([redacted]®), i.e. an anti-VEGF antibody as an anti-cancer drug, can occur. However, (a) There were no effects of pegaptanib sodium on the cardiovascular system in a safety pharmacology study (4.2.1.3.1) where dogs were treated with intravenous doses of pegaptanib sodium (4.5-45 μg/kg), which were equivalent to 9- to 90-fold the plasma concentrations observed in humans at the clinical intravitreous dose (0.3 mg/eye), (b) The maximum plasma pegaptanib concentration following the intravitreal administration of the clinical dose (0.3 mg/eye) of pegaptanib sodium (C_{max}, 12.0 ± 13.2 ng/mL = 1.3 ± 1.4 nM) was low, i.e. one-several thousandth of the maximum plasma bevacizumab concentrations following the administration of the clinical doses of bevacizumab (5 or 10 mg/kg) (C_{max} at a dose of 5 mg/kg, 152.8 ± 23.8 μg/mL = 1.0 ± 0.2 μM; C_{max} at a dose of 10 mg/kg, 404.0 ± 47.9 μg/mL = 2.7 ± 0.3 μM) in terms of molar concentration, (c) While pegaptanib has high affinity for the $VEGF_{165}$ isoform, which has been reported to be responsible for pathologic neovascularization (Usui T et al. *Invest Ophthalmol Vis Sci.* 2004;45: 368-374, Ishida S et al. *J Exp Med.* 2003;198: 483-489, Spilsbury K et al. *Am J Pathol.* 2000;157: 135-144), bevacizumab binds also to other VEGF isoforms that are involved in normal neovascularization. Taking account of these findings, unlike other drugs with anti-VEGF activity, pegaptanib sodium is unlikely at present to cause systemic adverse events, and actually, Japanese and foreign clinical studies and overseas post-marketing safety information have suggested no association between pegaptanib sodium and systemic adverse events related to anti-VEGF activity and increased incidences of such events have not been reported either.

With respect to a patient with a high plasma pegaptanib concentration and a short t_{max} in a Japanese phase II study (A5751010), PMDA asked the applicant to explain the cause for the abnormal values and the

efficacy and safety of pegaptanib sodium in this patient.

The applicant explained as follows:
There were no remarkable differences in the factors that have been suggested by PPK analysis to potentially affect the pharmacokinetics of pegaptanib (age, body weight, creatinine clearance) between the patient with a high plasma pegaptanib concentration (C_{max}, 86.5 ng/mL) and a short t_{max} (2.05 hours) (case number 10141001, 0.3 mg/eye) and other patients in the Japanese phase II study (A5751010) and the cause for the abnormally high value is unknown. The AUC_{τ} (4.1 μg·h/mL) in this patient was higher than the mean value of the 0.3 mg group (2.5 μg·h/mL), but was not highest in the population. Adverse events observed in this patient include cataract, conjunctival haemorrhage, punctate keratitis, and hypertension, of which cataract is considered associated with aging and conjunctival haemorrhage and punctate keratitis are considered related to the intravitreous injection procedure. Hypertension was examined for possible association with anti-VEGF activity. The incidence of hypertension (6%) in the 0.3 mg group from a Japanese clinical study (A5751010) was similar to that in the 0.3 mg group from foreign clinical studies (5%, EOP1003 and EOP1004). In foreign clinical studies EOP1003 and EOP1004, where patients treated with 3 mg/eye had similar plasma pegaptanib concentrations as this patient, the incidence of hypertension was almost comparable between the pegaptanib sodium 3 mg/eye group (10%) and the sham group (7%). Taking account of these findings, it is unlikely that the hypertension occurring in this patient was related to pegaptanib sodium. Furthermore, as to the efficacy of pegaptanib sodium in this patient, since the t_{max} was short, an increased rate of excretion from the vitreous into the systemic circulation could have resulted in failure to maintain vitreous pegaptanib concentrations, affecting the efficacy of pegaptanib sodium. However, although the change in visual acuity from baseline (in letters) in this patient was -7 letters at Week 6, which was a greater loss compared to the change in visual acuity in the 0.3 mg group (-0.7 ± 8.8 letters, mean ± SD), the loss was considered within the variation range. Also, the primary efficacy endpoint, i.e. the change in visual acuity from baseline to Week 54 in this patient was -3 letters, which was comparable to that in the 0.3 mg group (-3.8 ± 15.0 letters). Thus, there should be no major problems with the efficacy as well.

PMDA asked the applicant to explain about ocular safety concerns since high concentrations of pegaptanib stay in the vitreous humor for a long time.

The applicant explained as follows:
Since PPK analysis has suggested that age is a factor affecting the pharmacokinetics of pegaptanib, the occurrence of ocular adverse events (excluding those related to the injection procedure) by age group (< 65 years, 65-74 years, 75-84 years, ≥ 85 years) in Japanese and foreign clinical studies was investigated. As a result, in a Japanese clinical study (A5751010), although it is shown that the incidence of reduced visual acuity increased with increasing age, the incidences in the 0.3 mg and 1 mg groups were similar for each age group and it is very unlikely that vitreous levels of pegaptanib affect the occurrence of reduced visual acuity. For other events, no apparent increase in the incidence with increasing age was observed

and there was no consistent trend also in foreign clinical studies (EOP1003 and EOP1004). Therefore, even if high concentrations of pegaptanib stay in the vitreous body for a long time in the elderly, there should be no major problem with ocular safety.

PMDA considers as follows:
Although aging may affect the drug's excretion into the systemic circulation, an increased incidence of systemic adverse events associated with the drug has not been reported according to the overseas post-marketing safety information, and there is no need at present to advise particular caution. However, based on the results of the PPK analysis, the efficacy and safety (local ocular and systemic) of pegaptanib sodium in patients with factors affecting the pharmacokinetics of pegaptanib, e.g. elderly patients and patients with renal impairment, need to be confirmed via post-marketing surveillance.

4.(i).B.(3) Drug interactions

As pegaptanib sodium is injected into the vitreous body of the eye, the concomitant use of antibiotic and anesthetic drugs etc. is expected. PMDA asked the applicant to explain possible drug interactions with these medications.

The applicant explained as follows:
Antibiotic and anesthetic eye drops are used before the injection of pegaptanib sodium and antibiotic eye drops are given after the injection. It has been reported that these drugs are localized in the lacrimal fluid immediately after instillation and are primarily distributed into the anterior segment of the eye (cornea, anterior chamber) when distributed in the eye (Kanamoto N et al. *Complete guide of ophthalmology.* 2004;428-430). Since pegaptanib sodium is directly injected into the vitreous body of the eye by inserting an injection needle into the globe, pegaptanib sodium administered is not directly mixed with eye drops and local drug interactions are unlikely to occur. Concerning antibiotic eye drops given after the injection of pegaptanib sodium, following the distribution of the antibiotic into the anterior segment of the eye, its distribution into the posterior chamber is limited in view of the outflow route of aqueous humor via the Schlemm's canal, and the drug not distributed to the eye will be excreted into the systemic circulation via the conjunctiva or nasal mucosa (Kanamoto N et al. *Complete guide of ophthalmology.* 2004;428-430). Thus, it is unlikely that high concentrations of the drug are distributed into the posterior segment of the eye and the potential for physical drug interactions is low. Moreover, regarding possible drug interactions when these eye drops and pegaptanib enter the systemic circulation, as pegaptanib is metabolized by nucleases, drug interactions with these eye drops are unlikely to occur from the point of view of metabolism in plasma. In Japanese and foreign clinical studies, such antibiotic and anesthetic drugs were always used concomitantly and their safety in combination with the intravitreal injection of pegaptanib sodium has been confirmed. After the market launch, information on the intravitreous injection procedure, including the handling of concomitant drugs, will be provided.

PMDA understands the applicant's explanation that physical and metabolism-related drug interactions

between pegaptanib and concomitant eye drops are unlikely to occur and considers at present that there is no need to advise particular caution, but physicians etc. need to be fully informed about the procedure for administering pegaptanib sodium etc. PMDA also considers that it is necessary to identify the occurrence of adverse events associated with these concomitant medications after the market launch.

4.(ii) Summary of clinical efficacy and safety

4.(ii).A *Summary of the submitted data*

As the efficacy and safety evaluation data, the results from one Japanese phase II study (5.3.5.1.1, A5751010) and foreign phase II/III studies (5.3.5.1.2 and 5.3.5.1.3, EOP1003; 5.3.5.1.4 and 5.3.5.1.5, EOP1004; 5.3.5.1.6 and 5.3.5.1.10, EOP1003/EOP1004) were submitted. As the safety evaluation data, the results from a foreign phase I study (5.3.3.2.1, NX109-01), foreign phase I/II studies (5.3.3.2.2, EOP1000; 5.3.3.2.3, EOP1001), and a foreign phase II/III study (5.3.5.1.7, 5.3.5.1.8, 5.3.5.1.11, EOP1006) were submitted. As the reference data, the results from a foreign phase II study (5.3.5.1.9, EOP1009) were submitted.

4.(ii).A.(1) Japanese clinical study

4.(ii).A.(1).1) Phase II study (5.3.5.1.1, A5751010 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-masked, parallel-group, comparative study in Japanese patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) (target number of cases of 90 [45 cases per group]) was conducted to assess the efficacy, safety, and pharmacokinetics of pegaptanib [see "4.(i) Summary of human pharmacokinetic and pharmacodynamic studies" for pharmacokinetics].

Subjects were to receive a total of 9 intravitreal injections of 0.3 or 1 mg pegaptanib sodium at 6-week intervals and the study period was 54 weeks.

All of the 95 treated patients (47 patients in the 0.3 mg group, 48 patients in the 1 mg group) were included in the efficacy (FAS: Full Analysis Set) and safety analyses.

The primary endpoint, i.e. the changes in visual acuity from baseline to Week 54 in the FAS using the ETDRS (Early Treatment Diabetic Retinopathy study) chart are as presented below.

	0.3 mg group (N=47)	1 mg group (N=48)
Visual acuity measured at baseline	47.1 ± 11.2	46.5 ± 10. 9
Visual acuity measured at Week 54	43.2 ± 15.5	44.3 ± 16.6
Change up to Week 54 *	−3.8±15.0	−4.3 ± 16.4

mean ± SD * Missing values were imputed using LOCF.

Adverse events (including abnormal laboratory values) were reported in 100% of the 0.3 mg group (47 of 47 patients) and 100% of the 1 mg group (48 of 48 patients). Of which, those related to the injection procedure were observed in 87.2% of the 0.3 mg group (41 of 47 patients) and 87.5% of the 1.0 mg group (42 of 48 patients). Two deaths occurred in the 0.3 mg group (1 case with gastric cancer, spinal ligament

ossification, epididymitis, staphylococcal infection, malignant pleural effusion, and respiratory failure, 1 case with pneumonia and cardiac failure), but their causal relationship to the drug was denied. Other serious adverse events occurred in 5 patients in the 0.3 mg group and 10 patients in the 1 mg group (0.3 mg group, gastric cancer, hyperglycaemia, aortic dissection, chest pain, and intestinal obstruction [one case each]; 1 mg group, cholecystitis and macular degeneration [2 cases each], retinal haemorrhage, vitreous haemorrhage, and retinal detachment; retinal haemorrhage; increased intraocular pressure; malaise; conjunctival disorder; and bronchopneumonia [one case each]) and a causal relationship to the drug could not be denied for 2 cases in the 1 mg group (1 case with retinal haemorrhage, vitreous haemorrhage, and retinal detachment [a causal relationship was denied for retinal detachment] and 1 case with retinal haemorrhage). Except for 2 cases with macular degeneration and 1 case with hyperglycaemia that existed prior to the start of study drug administration, all events resolved or resolved with sequela (reduced visual acuity).

Adverse events for which a causal relationship to the drug could not be denied (including abnormal laboratory values) were reported in 31.9% of the 0.3 mg group (15 of 47 patients) and 27.1% of the 1 mg group (13 of 48 patients) and the main events are as shown in the following table.

Name of event	0.3 mg group (N=47)	1 mg group (N=48)
Anterior chamber inflammation	2 (4.3)	3 (6.3)
Corneal erosion	1 (2.1)	3 (6.3)
Corneal oedema	3 (6.4)	2 (4.2)
Foreign body sensation in eyes	0	2 (4.2)
Retinal haemorrhage	0	2 (4.2)
Vitreous floaters	2 (4.3)	2 (4.2)
Vitreous haemorrhage	0	2 (4.2)

n (%)

There were no apparent changes from baseline in blood pressure, pulse rate, or body weight in either the 0.3 or 1 mg group.

Based on the above, the applicant explained that the study results were similar between the pegaptanib sodium 0.3 and 1 mg groups and pegaptanib sodium 0.3 and 1 mg were shown to preserve visual acuity and were well tolerated.

4.(ii).A.(2) Foreign clinical studies

4.(ii).A.(2).1) Phase I study (5.3.3.2.1, NX109-01 [19 to 20])

An open-label, uncontrolled study in foreign patients with subfoveal CNV secondary to AMD (at least 3 cases per dose group, the total number of cases to be treated was not specified as the final dose was to be determined by a dose escalation method.) was conducted to establish the maximum tolerated dose of a single intravitreal injection of pegaptanib sodium (defined as the dose associated with < 33% of subjects experiencing acute dose limiting toxicity [DLT]) and evaluate the pharmacokinetic profile [see "4.(i) Summary of human pharmacokinetic and pharmacodynamic studies" for pharmacokinetics].

First, a starting dose of 0.25 mg was to be administered to 1 patient and if no DLT occurred, an additional

2 patients were to be treated. If no DLT occurred also in the additional 2 patients, the dose was to be escalated. If at least one of the additional 2 patients had DLT, a further 3 patients were to be treated with the same dose. Then if no DLT occurred, the dose was to be escalated and if at least 1 patient had DLT, dose escalation was to be stopped. Also if the first patient had DLT, an additional 2 patients were to be treated. If at least one of the additional 2 patients had DLT, dose escalation was to be stopped. If neither of the 2 additional patients had DLT, a further 3 patients were to be treated with the same dose. Then if at least one of the additional 3 patients had DLT, dose escalation was to be stopped and if no DLT occurred, the dose was to be escalated. The doses selected were 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg.

A total of 15 patients were treated (3 patients each for 0.25, 0.5, 1, 2, and 3 mg). Doses were going to be escalated up to a maximum of 4 mg, but due to high viscosity of the drug solution at 4 mg dose, the study was stopped after the 3 mg cohort.

Adverse events (including abnormal laboratory values) occurred in 66.7% of the 0.25 mg group (2 of 3 patients), 100% of the 0.5 mg group (3 of 3 patients), 66.7% of the 1 mg group (2 of 3 patients), 66.7% of the 2 mg group (2 of 3 patients), and 100% of the 3 mg group (3 of 3 patients). No deaths occurred and other serious adverse events were reported in 1 patient in the 2 mg group (breast cancer), but its causal relationship to the drug was denied. Adverse events for which a causal relationship to the drug could not be denied were observed in 1 patient in the 0.25 mg group (condition aggravated), 2 patients in the 0.5 mg group (blind spot enlarged and visual acuity reduced, one case each), 0 patient in the 1 mg group, 2 patients in the 2 mg group (eye pain and urticaria, one case each), and 1 patient in the 3 mg group (fatigue).

One day after dosing, transient increased intraocular pressure ≥ 23 mmHg occurred in a total of 4 patients (27%), but returned to normal within 24 hours in all cases, and no adverse events related to intraocular pressure were reported.

Based on the above, the applicant explained that no significant toxicities occurred following a single intravitreal injection of pegaptanib sodium at doses up to 3 mg in AMD patients.

4.(ii).A.(2).2) Phase I/II study (5.3.3.2.2, EOP1000 [[redacted] to [redacted]])

An open-label, uncontrolled study in patients with subfoveal CNV secondary to AMD (target number of cases of 10) was conducted to evaluate the safety and pharmacokinetics of 3 repeated intravitreal injections of pegaptanib sodium [see "4.(i) Summary of human pharmacokinetic and pharmacodynamic studies" for pharmacokinetics].

Subjects were to receive 3 consecutive unilateral, intravitreous injections of 3 mg pegaptanib sodium/eye at 28-day intervals. If 3 or more patients experienced DLTs, the dose was to be reduced to 2 mg/eye, and then, if necessary, to 1 mg/eye, each in a further 10 patients.

All of the 10 treated patients were included in the safety analysis.

Adverse events (including laboratory test abnormalities) occurred in 100% of the patients (10 of 10 patients). One death occurred (myocardial infarction), but its causal relationship to the drug was denied. Other serious adverse events were reported in 1 patient (atrial fibrillation and palpitations; supraventricular tachycardia), but their causal relationship to the drug was denied. Adverse events for which a causal relationship to the drug could not be denied were observed in 90% of the patients (9 of 10 patients), which include anterior chamber inflammation (3 patients), eye pain (2 patients), vitreous opacities (2 patients), and eye pruritus (2 patients).

With respect to vital signs, physical examination, and ECG findings, there were no changes for which a causal relationship to the drug could not be denied. The production of anti-pegaptanib IgG antibodies was not induced.

Based on the above, the applicant explained that 3 repeated intravitreal injections of 3 mg pegaptanib sodium were well-tolerated and anti-pegaptanib IgG antibodies were not detected.

4.(ii).A.(2).3) Phase I/II study (5.3.3.2.3, EOP1001 [20 to 20])

An open-label, uncontrolled study in patients with subfoveal CNV secondary to AMD (target number of cases of 10) was conducted to evaluate the safety and pharmacokinetics of 3 repeated doses of pegaptanib sodium administered after photodynamic therapy (PDT) with verteporfin.

Subjects were to undergo the initial PDT with verteporfin within 5 to 10 days prior to the intravitreal injection of pegaptanib sodium and then receive 3 consecutive intravitreal injections of 3 mg pegaptanib sodium in the study eye at 28 day-intervals. If 3 or more patients experienced DLTs, the dose was to be reduced to 2 mg/eye, and then, if necessary, to 1 mg/eye, each in a further 10 patients.

All of the 11 treated patients were included in the safety analysis.

Adverse events (including abnormal laboratory values) were reported in 100% of the patients (11 of 11 patients). No deaths occurred. Other serious adverse events were observed in 1 patient (suicide attempt), but its causal relationship to the drug was denied. Adverse events for which a causal relationship to the investigational product could not be denied were eye pain (4 patients), anterior chamber inflammation (3 patients), and abnormal sensation in eye (2 patients). Concerning clinical laboratory tests, vital signs, physical examination, and ECG findings, there were no significant changes from baseline or no adverse events for which a causal relationship to the investigational product could not be denied. The production of anti-pegaptanib IgG antibodies was not induced in 4 patients tested.

Based on the above, the applicant explained that 3 repeated doses of 3 mg pegaptanib sodium after PDT were well-tolerated.

4.(ii).A.(2).4) Phase II/III study (5.3.5.1.2, EOP1003 [Weeks 0-54 data] [20 to , 20 (data cutoff date)])

A randomized, double-masked, parallel-group, sham injection-controlled, comparative study in patients with subfoveal CNV secondary to AMD (target number of cases of 540 [135 cases per group]) was conducted to assess the efficacy and safety of pegaptanib sodium.

A sham injection (a procedure in which a needleless syringe was pressed against the globe under local anesthesia, instead of an intravitreous injection being administered) or an intravitreous injection of 0.3, 1, or 3 mg pegaptanib sodium was to be administered once every 6 weeks for a total of 9 treatments and a follow-up was to be conducted up to 6 weeks after the last dose (Week 54).

All of the 612 treated patients (153 patients in the sham group, 151 patients in the pegaptanib sodium 0.3 mg group, 155 patients in the pegaptanib sodium 1 mg group, 153 patients in the pegaptanib sodium 3 mg group) were included in the safety analysis and 609 patients (152 patients in the sham group, 150 patients in the 0.3 mg group, 154 patients in the 1 mg group, 153 patients in the 3 mg group) excluding 3 patients with incomplete baseline vision data (1 patient each in the sham, 0.3 mg, and 1 mg groups) were included in the efficacy analysis (Intent-to-treat: ITT).

The primary endpoint, i.e. the proportion of responders (patients losing < 15 letters of visual acuity from baseline to Week 54) in the ITT population is presented below. Pegaptanib sodium 0.3 mg and 1 mg statistically significantly reduced the loss of vision compared to the sham group ($P < 0.05$, CMH [Cochran-Mantel-Haenszel] test, adjustment for multiplicity was performed using the Hochberg procedure).

Proportion of responders (LOCF) (ITT population)

Treatment group	pegaptanib sodium			Sham
	0.3 mg	1 mg	3 mg	
Number of evaluable patients	150	154	153	152
Responders[a] (%)	109 (73)	116 (75)	106 (69)	89 (59)
P-value	0.0105*	0.0035*	—[b]	—

*: Pair-wise comparison with sham control, CMH test, Hochberg procedure
a) Subjects losing < 15 letters of visual acuity from baseline to Week 54
b) While this clinical study (EOP1003) was still masked, the analysis of EOP1004 was conducted before that of EOP1003, and it was decided that the 3 mg group should be excluded from the primary and secondary analyses.

Adverse events (including abnormal laboratory values) were reported in 90% of the sham group (138 of 153 patients), 95% of the 0.3 mg group (144 of 151 patients), 91% of the 1 mg group (141 of 155 patients), and 95% of the 3 mg group (145 of 153 patients). The deaths included 5 patients in the sham group (emphysema and myocardial infarction; chronic obstructive airways disease, microcytic anaemia, and pulmonary embolism; acute myeloid leukaemia; mediastinal neoplasm and bronchopneumonia; and deep vein thrombosis, thrombosis, and lung cancer, one case each), 2 patients in the 0.3 mg group

(myocardial infarction; and atrial fibrillation, atrial flutter, tachycardia, and cerebral haemorrhage; one case each), 2 patients in the 1 mg group (myocardial infarction and cerebrovascular accident; one case each), and 3 patients in the 3 mg group (cerebrovascular accident; cerebrovascular accident and pneumonia; and spinal compression fracture and gastric haemorrhage; one case each), but a causal relationship to study treatment was denied for all cases.

Other serious adverse events observed in each group are presented in the following table and a causal relationship to study treatment could not be denied for one case in the 0.3 mg group (night sweats) only.

Sham group (14 patients)	macular degeneration; colon cancer and resection of rectum; atrial fibrillation; transient ischaemic attack; hyperglycaemia; breast hyperplasia; coronary artery insufficiency; plasmacytoma; acute pulmonary oedema; atrial fibrillation and hypokalaemia; syncope; squamous cell carcinoma of skin; chest pressure and palpitations; colon adenoma, colon cancer, dehydration, and drug toxicity (1 case each)
Pegaptanib sodium 0.3 mg group (25 patients)	endophthalmitis (3 cases), cholelithiasis and inguinal hernia; atrial fibrillation; angina pectoris; prostatic adenoma and cerebrovascular accident; leukopenia, thrombocytopenia, and transient ischaemic attack; night sweats; increased intraocular pressure; myocardial ischaemia and coronary artery surgery; endometrial cancer; cataract; transient ischaemic attack; fall and humerus fracture; lung squamous cell carcinoma (stage unspecified); cerebral thrombosis; lymphoma; carotid artery stenosis; pulmonary embolism; rectal cancer and granuloma; forearm fracture; basal cell carcinoma; prostate cancer; hip fracture (1 case each)
Pegaptanib sodium 1 mg group (19 patients)	inguinal hernia (2 cases), dehydration and vertigo; urethral caruncle; traumatic cataract; injury and loss of consciousness; pulmonary embolism; leukopenia; chest pain; pneumonia; arthritis aggravated; dyspnoea and deep vein thrombosis; general physical health deterioration, nasopharyngitis, and therapeutic agent poisoning; endophthalmitis; prostate cancer; sepsis; colon spastic; malignant melanoma and basal cell carcinoma; neck pain and retinal detachment (1 case each)
Pegaptanib sodium 3 mg group (28 patients)	syncope (2 cases), endophthalmitis (2 cases), pancreatitis and cholecystectomy; parathyroid tumour benign; bronchopneumonia and localised osteoarthritis; vitreous haemorrhage; heart valve operation; cerebrovascular accident; cholelithiasis and urosepsis; cataract and traumatic cataract; lung cancer (stage unspecified); hospitalisation; angina pectoris; atrial flutter, chest pain, herpes zoster ophthalmic, and uveitis; prostate cancer; cataract; therapeutic agent poisoning; lung cancer (stage unspecified) and metastases to liver; fall and joint dislocation; urinary tract infection; pyelonephritis; cardiac failure; pancreatitis and lung cancer (stage unspecified); pelvic tumour; coronary artery disease aggravated; atrial fibrillation and dyspnoea (1 case each)

Adverse events for which a causal relationship to study treatment could not be denied (including abnormal laboratory values) were reported in 20.9% of the sham group (32 of 153 patients), 27.2% of the 0.3 mg group (41 of 151 patients), 27.7% of the 1 mg group (43 of 155 patients), and 31.4% of the 3 mg group (48 of 153 patients) and the main events are as shown below.

Adverse event	0.3 mg (N=151)	1 mg (N=155)	3 mg (N=153)	Sham (N=153)
Cataract	6 (4.0)	8 (5.2)	10 (6.5)	8 (5.2)
Visual acuity reduced	8 (5.3)	3 (1.9)	2 (1.3)	7 (4.6)
Vitreous floaters	10 (6.6)	16 (10.3)	15 (9.8)	2 (1.3)
Vitreous opacities	11 (7.3)	12 (7.7)	12 (7.8)	8 (5.2)
Anterior chamber inflammation	4 (2.6)	5 (3.2)	3 (2.0)	1 (0.7)
Eye discharge	1 (0.7)	4 (2.6)	0	0
Eye pain	0	2 (1.3)	0	0
Retinal haemorrhage	1 (0.7)	3 (1.9)	1 (0.7)	7 (4.6)
Vision blurred	2 (1.3)	2 (1.3)	0	1 (0.7)
Visual disturbance	1 (0.7)	4 (2.6)	5 (3.3)	0
Increased intraocular pressure	2 (1.3)	3 (1.9)	4 (2.6)	0
Macular degeneration	1 (0.7)	1 (0.6)	2 (1.3)	3 (2.0)

n (%)

There were no clinically relevant findings in vital signs or ECGs. There were no abnormal laboratory values leading to treatment discontinuation or interruption.

Based on the above, the applicant explained that pegaptanib sodium 0.3 mg and 1 mg were shown to be

effective in patients with exudative AMD, with a statistically significant difference in the proportion of responders compared to the sham group, and all doses were well-tolerated.

4.(ii).A.(2).5) Phase II/III study (5.3.5.1.3, EOP1003 [Weeks 54-102 data] [up to [redacted] 20[redacted] (up to the end of assessment at Week 102 [12)])])

A randomized, double-masked, parallel-group, sham injection-controlled, comparative study in patients with subfoveal CNV secondary to AMD who participated in Study EOP1003 was conducted to assess the efficacy and safety of 2-year treatment with pegaptanib sodium and compare the efficacy and safety between patients who discontinued therapy and those who continued therapy.

At Week 54, subjects who were treated with pegaptanib sodium (0.3, 1, and 3 mg) were re-randomized to either discontinue or continue therapy (for a further 48 weeks, 8 injections) and subjects receiving sham injections were re-randomized to either stop therapy, receive pegaptanib sodium (0.3, 1, or 3 mg), or continue with sham injections (a total of 5 arms). Cohort 1 was defined as all subjects re-randomized to continue the same treatment in Weeks 54 to 102 as in Weeks 0 to 54, Cohort 2 was defined as all subjects re-randomized to discontinue treatment in Weeks 54 to 102, and Cohort 3 was defined as all subjects receiving sham injections in Weeks 0 to 48 who were re-randomized to either pegaptanib sodium (0.3, 1, or 3 mg) or sham injections in Weeks 54 to 102 (Subjects in the sham-sham group of Cohort 3 overlap with subjects in the sham-sham group of Cohort 1).

All of the 533 randomized patients were included in the efficacy analysis (ITT). The number of patients in each cohort is as follows: Cohort 1 (67 patients in the 0.3 mg-0.3 mg [first year treatment-second year treatment] group, 67 patients in the 1 mg-1 mg group, 63 patients in the 3 mg-3 mg group, 27 patients in the sham-sham group); Cohort 2 (66 patients in the 0.3 mg-discontinued group, 68 patients in the 1 mg-discontinued group, 64 patients in the 3 mg-discontinued group, 27 patients in the sham-discontinued group); and Cohort 3 (26 patients in the sham-0.3 mg group, 29 patients in the sham-1 mg group, 29 patients in the sham-3 mg group, 27 patients in the sham-sham group). The safety analysis population included 524 patients excluding a total of 9 patients (patients who withdrew consent, patients who did not wish to continue study, but were randomized mistakenly, and patients who did not visit or had no assessments after randomization) from the ITT population.

The efficacy endpoints, i.e. the mean change in visual acuity and the proportion of responders in the ITT population are presented below and the mean reduction in visual acuity was smaller in patients treated with pegaptanib sodium for 2 years compared to the sham group.

12) The cutoff date for the second year data was Week 102 visit if visual acuity was assessed at Week 102 or the planned last visit if visual acuity was not assessed at Week 102.

Table. Mean changes in visual acuity (number of letters, mean ± SD) (LOCF)

Treatment group	Pegaptanib Sodium[a)]			Sham[b)]
	0.3 mg	1 mg	3 mg	
Number of evaluable patients	67	67	63	54 [b)]
Baseline visual acuity	53.6 ± 12.0	53.4 ± 13.2	50.1 ± 12.7	49.8 ± 13.2
Week 6	- 1.9 ± 9.1	- 0.5 ± 7.0	- 1.8 ± 10.6	- 4.4 ± 8.2
Week 24	- 4.7 ± 14.9	- 3.6 ± 11.8	- 3.2 ± 12.5	- 7.7 ± 13.5
Week 54	- 9.6 ± 16.3	- 7.0 ± 15.6	- 6.5 ± 15.0	- 11.7 ± 18.5
Week 78	- 10.3 ± 17.3	- 8.3 ± 15.8	- 6.4 ± 17.0	- 13.6 ± 20.0
Week 102	- 10.8 ± 18.8	- 8.1 ± 16.9	- 9.2 ± 18.7	- 13.1 ± 18.6

a) The results of the pegaptanib sodium groups refer to the results of Cohort 1 (patients who continued with the same dose as the first year).
b) Patients receiving sham injections in the first year who were randomized to continue sham injections or discontinue treatment in the second year (the combined data from Cohort 1 and Cohort 2).

Figure. Mean changes in visual acuity over time (LOCF)

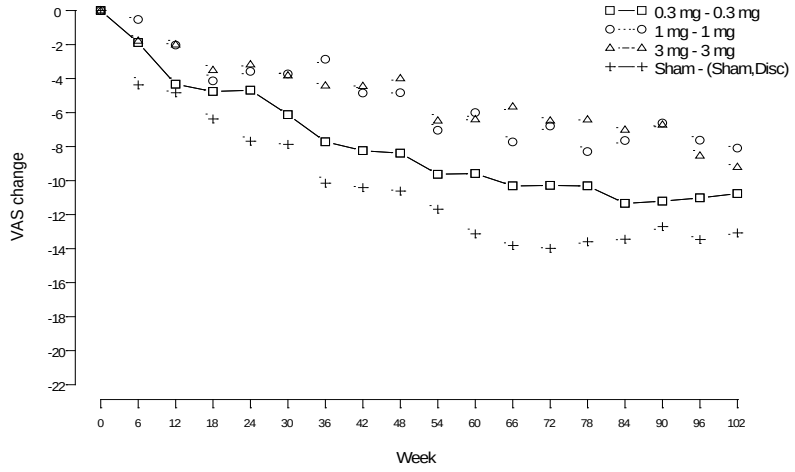


Table. Proportion of responders (Week 102)

Treatment group	Pegaptanib Sodium[a)]			Sham[b)]
	0.3 mg	1 mg	3 mg	
Number of evaluable patients	67	67	63	54 [b)]
Responders	38 (57%)	48 (72%)	43 (68%)	30 (56%)
Non-responders	29 (43%)	19 (28%)	20 (32%)	24 (44%)
P-value[c)]	0.9784	0.0983	0.2259	—

a) The results of the pegaptanib sodium groups refer to the results of Cohort 1 (patients who continued with the same dose as the first year).
b) Patients receiving sham injections in the first year who were randomized to continue sham injections or discontinue treatment in the second year (the combined data from Cohort 1 and Cohort 2).
c) CMH test, adjusted for prior PDT and lesion subtype

Adverse events (including abnormal laboratory values) were reported as follows: Cohort 1 (91% of the 0.3 mg-0.3 mg group [59 of 65 patients], 89% of the 1 mg-1 mg group [58 of 65 patients], 87% of the 3 mg-3 mg group [54 of 62 patients], 81% of the sham-sham group [21 of 26 patients]); Cohort 2 (74% of the 0.3 mg-discontinued group [48 of 65 patients], 71% of the 1 mg-discontinued group [48 of 68 patients], 73% of the 3 mg-discontinued group [46 of 63 patients], 63% of the sham-discontinued group [17 of 27 patients]); and Cohort 3 (76% of the sham-0.3 mg group [19 of 25 patients], 90% of the sham-1 mg group [26 of 29 patients], 97% of the sham-3 mg group [28 of 29 patients], 81% of the sham-sham group [21 of 26 patients]). Eight patients died (Cohort 1 [1 case with brain metastases and lung squamous cell carcinoma (stage unspecified) (0.3 mg-0.3 mg group)], Cohort 2 [1 case with cardio-respiratory arrest (1 mg-discontinued group); 1 case with prostate cancer, urinary retention, intestinal obstruction, gastrointestinal necrosis, multi-organ disorder, and septic shock (3 mg-discontinued group); 1 case with lung cancer (stage unspecified) and metastases to liver (3

mg-discontinued group)], Cohort 3 [1 case with metastatic prostate cancer (sham-0.3 mg group); 1 case with cardio-respiratory arrest, transient ischaemic attack, and traumatic cataract (sham-3 mg group); 1 case with intestinal obstruction, pneumonia aspiration, myocardial infarction, and cellulitis (sham-3 mg group)], and others [1 case with myocardial ischaemia (3 mg-not re-randomized group)]), but a causal relationship to study treatment was denied for all cases.

Other serious adverse events observed in each group (events observed in the second year of the study) are shown in the following table and a causal relationship to study treatment could not be denied for one case in the 0.3 mg-0.3 mg group of Cohort 1 (tachycardia) only.

Cohort 1	0.3 mg-0.3 mg group (10 patients)	urinary retention, hypertension, angina pectoris, cerebrovascular insufficiency, and orthostatic hypotension; localised osteoarthritis; atrial fibrillation; carotid sinus syndrome; tachycardia; cerebrovascular accident; atrial fibrillation and pulmonary embolism; pubic rami fracture; cerebrovascular accident; renal cell carcinoma (stage unspecified) (1 case each)
	1 mg-1 mg group (8 patients)	pelvic fracture and femur fracture; nasopharyngeal cancer; hiatus hernia, oesophagitis, and uterine fibroids; deep vein thrombosis; chest pain; joint sprain; retinal detachment; osteoarthritis aggravated (1 case each)
	3 mg-3 mg group (9 patients)	subdural haematoma, osteoarthritis, retinal tear, retinal detachment, increased intraocular pressure, myocardial infarction, prostate cancer, angina pectoris, breast cancer (1 case each)
	Sham-sham group (7 patients)	pneumonia; colon cancer; macular degeneration; chest pain, cardiac failure congestive, bradycardia, acute myocardial infarction, enteritis, enterocolitis infectious, and gastroenteritis; angina pectoris aggravated; nerve root compression; cardiac failure congestive and emphysema (1 case each)
Cohort 2	0.3 mg-discontinued group (9 patients)	myocardial infarction and coronary artery disease; gastroenteritis; breast cancer; atrial flutter; lymphoma; cerebrovascular accident; femoral neck fracture; chronic obstructive airways disease exacerbated; cerebrovascular accident (1case each)
	1 mg-discontinued group (4 patients)	chest pain; cerebrovascular accident and myocardial infarction; angina pectoris; coronary artery disease (1 case each)
	3 mg-discontinued group (3 patients)	cerebrovascular accident, epistaxis, fall (1 case each)
	Sham-discontinued group (3 patients)	pneumonia, rectal haemorrhage, cardiac arrest (1 case each)
Cohort 3	Sham-0.3 mg group (2 patients)	prostatic hyperplasia and coronary artery disease; clostridium colitis (1 case each)
	Sham-1 mg group (4 patients)	atrial fibrillation; skin ulcer; arrhythmia and cardiac failure; hip fracture (1 case each)
	Sham-3 mg group (3 patients)	peripheral vascular disorder, femoral neck fracture, endophthalmitis (1 case each)
	Sham-sham group (7 patients)	Same as Cohort 1.

The main adverse events for which a causal relationship to study treatment could not be denied (including abnormal laboratory values) are shown in the following table.

	Cohort 1				Cohort 2				Cohort 3			
Name of adverse event	0.3-0.3 mg (n=65)	1-1 mg (n=65)	3-3 mg (n=62)	Sham-sham (n=26)	0.3 mg-discontinued (n=65)	1 mg-discontinued (n=68)	3 mg-discontinued (n=63)	Sham-discontinued (n=27)	Sham-0.3 mg (n=25)	Sham-1 mg (n=29)	Sham-3 mg (n=29)	Sham-sham (n=26)
Total	12 (18)	13 (20)	12 (19)	1 (4)	6 (9)	3 (4)	5 (8)	0	6 (24)	6 (21)	9 (31)	1 (4)
Cataract	1 (1.5)	5 (7.7)	0	0	2 (3.1)	0	1 (1.6)	0	0	0	3 (10.3)	0
Visual acuity reduced	0	0	2 (3.2)	1 (3.8)	2 (3.1)	0	0	0	1 (4.0)	0	1 (3.4)	1 (3.8)
Vitreous floaters	3 (4.6)	3 (4.6)	6 (9.7)	0	1 (1.5)	1 (1.5)	1 (1.6)	0	3 (12.0)	2 (6.9)	1 (3.4)	0
Vitreous opacities	3 (4.6)	1 (1.5)	4 (6.5)	0	0	1 (1.5)	3 (4.8)	0	3 (12.0)	0	4 (13.8)	0
Increased intraocular pressure	2 (3.1)	1 (1.5)	1 (1.6)	0	0	0	0	0	1 (4.0)	0	1 (3.4)	0

n (%)

There were no clinically relevant findings in vital signs or ECGs.

Based on the above, the applicant explained that the treatment benefit was maintained in AMD patients

treated with pegaptanib sodium, patients who continued therapy lost less visual acuity compared to those who discontinued therapy, and there were no major differences in the safety between the first year and second year of the study.

4.(ii).A.(2).6) Phase II/III study (5.3.5.1.4, EOP1004 [Weeks 0-54 data] [[redacted] 20[redacted] to [redacted] [redacted], 20[redacted] (data cutoff date)])

A randomized, double-masked, parallel-group, sham injection-controlled, comparative study in patients with subfoveal CNV secondary to AMD (target number of cases of 540 [135 cases per group]) was conducted to assess the efficacy and safety of pegaptanib sodium.

A sham injection or an intravitreous injection of pegaptanib sodium (0.3, 1, or 3 mg) was to be administered once every 6 weeks for a total of 9 treatments and a follow-up was to be conducted up to 6 weeks after the last dose (Week 54).

All of the 578 treated patients (pegaptanib sodium groups [144 patients in the 0.3 mg group, 146 patients in the 1 mg group, 143 patients in the 3 mg group], 145 patients in the sham group) were included in the safety analysis and 577 patients (pegaptanib sodium groups [144 patients in the 0.3 mg group, 146 patients in the 1 mg group, 143 patients in the 3 mg group], 144 patients in the sham group) excluding 1 patient with incomplete baseline vision data (sham group) were included in the efficacy analysis (ITT).

The primary endpoint, i.e. the proportion of responders (subjects losing < 15 letters of visual acuity from baseline to Week 54) in the ITT population is presented in the following table. Pegaptanib sodium 0.3 mg statistically significantly reduced the loss of visual acuity ($P = 0.0031$, CMH test, the level of significance using the Hochberg procedure $P \leq 0.0167$), whereas pegaptanib sodium 1 mg showed no statistically significant difference compared to the sham group ($P = 0.0273$, CMH test, the level of significance using the Hochberg procedure $P \leq 0.0250$).

Table. Proportion of responders (LOCF)

Treatment group	Pegaptanib Sodium			Sham
	0.3 mg	1 mg	3 mg	
Number of evaluable patients	144	146	143	144
Responders[a] (%)	97 (67)	97 (66)	87 (61)	75 (52)
P-value	0.0031*	0.0273	0.1294	—

*: Pair-wise comparison with sham control, CMH test, Hochberg procedure
a) Subjects losing < 15 letters of visual acuity from baseline to Week 54

Adverse events (including abnormal laboratory values) were reported in 100% of the sham group (145 of 145 patients), 99% of the 0.3 mg group (142 of 144 patients), 99% of the 1 mg group (145 of 146 patients), and 100% of the 3 mg group (143 of 143 patients). The deaths included 2 patients in the sham group (1 case with urinary calculus, proctitis, and pelvic mass; 1 case with bladder cancer), 3 patients in the 0.3 mg group (1 case with cardiac arrest; 1 case with aortic aneurysm; 1 case with acute myeloid leukaemia and urinary tract infection), 6 patients in the 1 mg group (chronic gastrointestinal bleeding; bronchiectasis, lung infection, and pneumonia; aortic stenosis and cardio-respiratory arrest; renal failure

and sepsis; large cell carcinoma of the respiratory tract [stage unspecified] and urinary tract infection; metastasis; one case each), and 3 patients in the 3 mg group (1 case with humerus fracture and renal failure, 1 case with cardiac arrest, gastrointestinal necrosis, and hiatus hernia, 1 case with cardiac arrest). Of which, a causal relationship to study treatment could not be denied for one death in the 0.3 mg group (aortic aneurysm) only.

Other serious adverse events observed in each group are shown in the following table and a causal relationship to the investigational product could not be denied for 1 case in the 0.3 mg group (retinal detachment and retinal haemorrhage) and 2 cases in the 3 mg group (chest pain; myocardial infarction and syncope) only.

Sham group (24 patients)	prostate cancer and orchitis; dizziness; coronary artery disease; pneumonia viral; asthenia and dizziness; prostate cancer metastatic; papilloedema; acute myocardial infarction; aortic aneurysm and pneumonia; transient ischaemic attack; myocardial infarction and renal failure; gastrointestinal haemorrhage, cardiac failure acute, and constipation; angina pectoris; stress urinary incontinence and rotator cuff syndrome; arthritis aggravated; radiculopathy; atrioventricular block; hip fracture; diverticulitis; chronic obstructive airways disease exacerbated, atrial fibrillation, anaemia, haemorrhage subcutaneous, cerebrovascular accident, and coronary artery disease; gastrointestinal ulcer haemorrhage and peripheral artery aneurysm; chronic obstructive airways disease exacerbated; basal cell carcinoma; liver abscess, pyrexia, atrial fibrillation, and basal cell carcinoma (1 case each)
Pegaptanib sodium 0.3 mg group (25 patients)	myocardial infarction, atrial fibrillation, and chest pain; supraventricular tachycardia and cerebrovascular accident; hip fracture; haematuria and urinary retention; meniscal tear and sepsis; chest pain; rib fracture and thoracic vertebral fracture; depression; aortic aneurysm and endophthalmitis; nephrolithiasis; glaucoma, retinal haemorrhage, vitreous haemorrhage, and hypertensive crisis; transient ischaemic attack and hip fracture; endophthalmitis, arthropathy, and myocardial infarction; pancreatitis; endophthalmitis; transient ischaemic attack; hip fracture and breast cancer; incisional hernia and chest pain; vertigo; head injury; carotid artery occlusion and pulmonary oedema; retinal detachment and retinal haemorrhage; prostate cancer; cardiac failure congestive; gastric cancer, dyspnoea, and gastrointestinal haemorrhage (1 case each)
Pegaptanib sodium 1 mg group (23 patients)	localised osteoarthritis (2 cases), endophthalmitis (2 cases), traumatic cataract; drug hypersensitivity; lumbar vertebral fracture; kidney infection; colonic polyp and myocardial infarction; lumbar vertebral fracture and vascular dementia; syncope; osteoarthritis aggravated and chronic obstructive airways disease exacerbated; bladder prolapse, rectal prolapse, and uterine prolapse; carotid artery stenosis; prostate cancer; fall, multiple fractures, and lower limb fracture; pneumonia; skull fracture; dislocation of joint prosthesis and dermal cyst; squamous cell carcinoma of skin; atrial fibrillation; multiple myeloma; chronic obstructive airways disease exacerbated (1 case each)
Pegaptanib sodium 3 mg group (30 patients)	dehydration (2 cases), chest pain (2 cases), pneumonia and fall; chronic obstructive airways disease exacerbated and pneumonia; lymphoma; cerebral infarction; pancreatic carcinoma and cholecystitis acute; pneumothorax; small intestinal obstruction; femoral neck fracture and renal artery stenosis; retinal detachment; migraine; bradycardia, hypertension, and hypotension; arthritis; chest pain and dizziness; pelvic fracture; meniscus lesion; epistaxis; localised osteoarthritis and bacterial infection; transient ischaemic attack; cerebral haemorrhage, myocardial infarction, and syncope; endophthalmitis; coronary artery thrombosis, bradycardia, chest pain, and dyspnoea; aortic stenosis and retinal detachment; breast cancer; retinal haemorrhage; urosepsis; myocardial infarction (1 case each)

The main adverse events for which a causal relationship to study treatment could not be denied (including abnormal laboratory values) are shown in the following table.

Name of adverse event	0.3 mg (n=144)	1 mg (n=146)	3 mg (n=143)	Sham (n=145)
No. of patients with events	38 (26)	47 (32)	50 (35)	25 (17)
Anterior chamber inflammation	7 (4.9)	4 (2.7)	2 (1.4)	2 (1.4)
Cataract	6 (4.2)	14 (9.6)	11 (7.7)	10 (6.9)
Eye pruritus	0	2 (1.4)	0	0
Vitritis	0	2 (1.4)	0	0
Photophobia	4 (2.8)	4 (2.7)	2 (1.4)	2 (1.4)
Pupillary reflex impaired	2 (1.4)	0	0	1 (0.7)
Vision blurred	3 (2.1)	1 (0.7)	4 (2.8)	2 (1.4)
Reduced visual acuity	6 (4.2)	0	5 (3.5)	8 (5.5)
Visual disturbance	6 (4.2)	5 (3.4)	9 (6.3)	1 (0.7)
Vitreous detachment	1 (0.7)	3 (2.1)	0	1 (0.7)
Vitreous floaters	4 (2.8)	18 (12.3)	12 (8.4)	0
Vitreous opacities	4 (2.8)	9 (6.2)	10 (7.0)	1 (0.7)
Increased intraocular pressure	1 (0.7)	3 (2.1)	8 (5.6)	0
Eye pain	0	0	3 (2.1)	0
Macular degeneration	1 (0.7)	2 (1.4)	2 (1.4)	0
Retinal scar	1 (0.7)	0	1 (0.7)	2 (1.4)

n (%)

There were no clinically relevant findings in vital signs or ECGs.

Based on the above, the applicant explained that pegaptanib sodium 0.3 mg was effective in patients with exudative AMD and also regarding safety, just mild ocular adverse events were noted.

4.(ii).A.(2).7) Phase II/III study (5.3.5.1.5, EOP1004 [Weeks 54-102 data] [up to [redacted] 20[redacted] (up to the end of assessment at Week 102 [13)])])

A randomized, double-masked, parallel-group, sham injection-controlled, comparative study in patients with subfoveal CNV secondary to AMD who participated in Study EOP1004 was conducted to assess the efficacy and safety of 2-year treatment with pegaptanib sodium and compare the efficacy and safety between patients who discontinued therapy and those who continued therapy.

At Week 54, subjects who were treated with pegaptanib sodium (0.3, 1, or 3 mg) were re-randomized to either discontinue or continue therapy (for a further 48 weeks, 8 injections) and subjects receiving sham injections were re-randomized to either stop therapy, receive pegaptanib sodium (0.3, 1, or 3 mg), or continue with sham injections (a total of 5 arms). Cohort 1 was defined as all subjects re-randomized to continue the same treatment in Weeks 54 to 102 as in Weeks 0 to 54, Cohort 2 was defined as all subjects re-randomized to discontinue treatment in Weeks 54 to 102, and Cohort 3 was defined as all subjects receiving sham injections in Weeks 0 to 48 who were re-randomized to either pegaptanib sodium (0.3, 1, or 3 mg) or sham injections in Weeks 54 to 102 (Subjects in the sham-sham group of Cohort 3 overlap

13) The cutoff date for the second year data was Week 102 visit if visual acuity was assessed at Week 102 or the planned last visit if visual acuity was not assessed at Week 102.

with subjects in the sham-sham group of Cohort 1).

All of the 520 randomized patients were included in the efficacy analysis (ITT). The number of patients in each cohort is as follows: Cohort 1 (66 patients in the 0.3 mg-0.3 mg (first year treatment-second year treatment) group, 66 patients in the 1 mg-1 mg group, 62 patients in the 3 mg-3 mg group, 26 patients in the sham-sham group); Cohort 2 (66 patients in the 0.3 mg-discontinued group, 63 patients in the 1 mg-discontinued group, 63 patients in the 3 mg-discontinued group, 27 patients in the sham-discontinued group); and Cohort 3 (27 patients in the sham-0.3 mg group, 26 patients in the sham-1 mg group, 28 patients in the sham-3 mg group, 26 patients in the sham-sham group). The safety analysis population included 500 patients excluding a total of 20 patients (patients who did not receive study treatment in the second year, patients who were withdrawn from the study without receiving study treatment in the second year, patients who withdrew consent after randomization, patients who did not visit and had no assessments, being withdrawn from the study due to adverse events, and patients who were unable to comply with the visit schedule) from the ITT population.

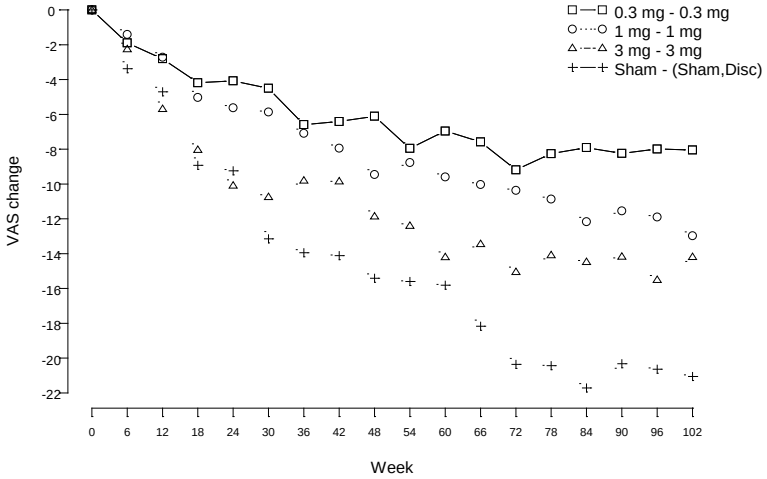
The efficacy endpoints, i.e. the mean change in visual acuity and the proportion of responders in the ITT population are presented in the table below and the reduction in visual acuity was smaller in patients treated with pegaptanib sodium for 2 years compared to the sham group.

Table. Mean changes in visual acuity (number of letters, mean ± SD) (LOCF)

Treatment group	Pegaptanib Sodium[a)]			Sham[b)]
	0.3 mg	1 mg	3 mg	
Number of evaluable patients	66	66	62	53 [b)]
Baseline visual acuity	52.3 ± 13.9	50.8 ± 12.6	55.0 ± 11.4	55.7 ± 11.5
Week 6	-1.9 ± 10.1	-1.4 ± 9.9	-2.3 ± 10.5	-3.4 ± 8.9
Week 24	-4.1 ± 13.2	-5.6 ± 14.5	-10.1 ± 14.4	-9.2 ± 12.4
Week 54	-8.0 ± 16.7	-8.8 ± 16.2	-12.4 ± 17.0	-15.6 ± 17.3
Week 78	-8.3 ± 17.4	-10.9 ± 16.2	-14.1 ± 20.1	-20.4 ± 20.0
Week 102	-8.0 ± 18.1	-13.0 ± 18.8	-14.2 ± 20.3	-21.1 ± 20.7

a) The results of the pegaptanib sodium groups refer to the results of Cohort 1 (patients who continued with the same dose as the first year).
b) Patients receiving sham injections in the first year who were randomized to continue sham injections or discontinue treatment in the second year (the combined data from Cohort 1 and Cohort 2).

Figure. Mean changes in visual acuity over time (LOCF)



Proportion of responders (Week 102)

Treatment group	Pegaptanib sodium			Sham[a)]
	0.3 mg	1 mg	3 mg	
Number of evaluable patients	66	66	62	53 [a)]
Responders (%)	40 (61%)	37 (56%)	33 (53%)	18 (34%)
Non-responders (%)	26 (39%)	29 (44%)	29 (47%)	35 (66%)
P-value[b)]	0.0022	0.0195	0.0177	—

a) Patients receiving sham injections in the first year who were randomized to continue sham injections or discontinue treatment in the second year (the combined data from Cohort 1 and Cohort 2).
b) CMH test, adjusted for prior PDT and lesion subtype

Adverse events (including abnormal laboratory values) were reported as follows: Cohort 1 (100% of the 0.3 mg-0.3 mg group [63 of 63 patients], 98% of the 1 mg-1 mg group [60 of 61 patients], 95% of the 3 mg-3 mg group [55 of 58 patients], 100% of the sham-sham group [25 of 25 patients]); Cohort 2 (82% of the 0.3 mg-discontinued group [53 of 65 patients], 89% of the 1 mg-discontinued group [55 of 62 patients], 95% of the 3 mg-discontinued group [59 of 62 patients], 93% of the sham-discontinued group [25 of 27 patients]); and Cohort 3 (100% of the sham-0.3 mg group [26 of 26 patients], 96% of the sham-1 mg group [22 of 23 patients], 93% of the sham-3 mg group [26 of 28 patients], 100% of the sham-sham group [25 of 25 patients]). Nine patients died (Cohort 1 [1 case with congestive cardiac failure (0.3 mg-0.3 mg group); 1 case with arrhythmia and cardiac failure (1 mg-1 mg group)], Cohort 2 [1 case with congestive cardiac failure and cerebrovascular accident (3 mg-discontinued group); 1 case with pneumothorax and chronic obstructive airways disease (3 mg-discontinued group); 1 case with arrhythmia (3 mg-discontinued group); 1 case with gastrointestinal ulcer haemorrhage, peripheral artery aneurysm, pneumonia, and hip fracture (sham-discontinued group)], and others [1 case with gastric cancer and gastrointestinal haemorrhage (0.3 mg-not re-randomized group); 1 case with pulmonary embolism and chronic obstructive airways disease exacerbated (3 mg-not re-randomized group); 1 case with colon cancer, metastases to liver, and metastases to lymph nodes (0.3 mg-discontinued group)]), but a causal relationship to the investigational product was denied for all cases.

Other serious adverse events observed in each group are shown in the following table and a causal relationship to study treatment was denied for all events.

Cohort 1	0.3 mg-0.3 mg group (10 patients)	chest pain (2 cases), pelvic fracture; atrial fibrillation; cardiac failure congestive, chronic obstructive airways disease exacerbated, and pneumonia; confusional state and pneumonia; gastrointestinal candidiasis, duodenal stricture, and pulmonary embolism; fall, parkinson's disease, and silent myocardial infarction; dizziness and coronary artery occlusion; post procedural pain (1 case each)
	1 mg-1 mg group (14 patients)	myocardial infarction and cardiac failure congestive; femur fracture; pelvic fracture and pneumothorax; adnexa uteri mass; skin laceration; angioneurotic oedema; asthenia; retinal detachment; prostatic hyperplasia; osteoarthritis aggravated; chronic obstructive airways disease exacerbated, bradycardia, and sinus arrest; osteoarthritis; squamous cell carcinoma of skin; chronic obstructive airways disease exacerbated (1 case each)
	3 mg-3 mg group (9 patients)	subdural haematoma; retinal detachment; atrioventricular block; myocardial infarction; anaemia; bladder cancer and wound dehiscence; atrial fibrillation and cardiac failure congestive; anxiety, peptic ulcer, and chest pain; chest pain and hiatus hernia (1 case each)
	Sham-sham group (7 patients)	extrusion of device; hip fracture and pulmonary embolism; myocardial infarction; pancreatitis and prostate cancer; atrioventricular block; gastric ulcer haemorrhage; ketoacidosis (1 case each)
Cohort 2	0.3 mg-discontinued group (9 patients)	gastritis and gastrointestinal haemorrhage; pneumonia; colon cancer; asthma and chronic obstructive airways disease exacerbated; arthritis aggravated and cholecystitis; cerebrovascular accident; chronic obstructive airways disease; atrial tachycardia and breast cancer metastatic; syncope (1 case each)
	1 mg-discontinued group (7 patients)	limb injury; hip fracture; osteoarthritis aggravated and breast cancer; cerebrovascular accident; retinal detachment; localised osteoarthritis; arterial occlusion and peripheral occlusion (1 case each)
	3 mg-discontinued group (8 patients)	chest pain (2 cases), bradycardia; anxiety aggravated and depression aggravated; osteoarthritis aggravated; epistaxis and pneumonia; pneumonia; calculus bladder and urinary retention (1 case each)
	Sham-discontinued group (3 patients)	sinusitis and metastasis; hip fracture and pneumonia; atrial fibrillation and cardiac failure congestive (1 case each)
Cohort 3	Sham-0.3 mg group (3 patients)	aortic valve stenosis; pneumonia; hip fracture (1 case each)
	Sham-1 mg group (6 patients)	deep vein thrombosis; acute bronchitis and obstructive airways disease; colon cancer; endophthalmitis; cholecystitis; pneumonia (1 case each)
	Sham-3 mg group (6 patients)	endophthalmitis (2 cases), diverticulitis; myocardial infarction; lumbar spinal stenosis; gastroenteritis (1 case each)
	Sham-sham group (7 patients)	Same as Cohort 1

The main adverse events for which a causal relationship to study treatment could not be denied are shown in the following table.

	Cohort 1				Cohort 2				Cohort 3			
Name of adverse event	0.3-0.3 mg (n=63)	1-1 mg (n=61)	3-3 mg (n=58)	Sham-sham (n=25)	0.3 mg-discontinued (n=65)	1 mg-discontinued (n=62)	3 mg-discontinued (n=62)	Sham-discontinued (n=27)	Sham-0.3 mg (n=26)	Sham-1 mg (n=23)	Sham-3 mg (n=28)	Sham-sham (n=25)
Total	4 (6)	5 (8)	11 (19)	3 (12)	3 (5)	1 (2)	8 (13)	1 (4)	4 (15)	3 (13)	3 (11)	3 (12)
Cataract	1 (1.6)	2 (3.3)	1 (1.7)	0	0	0	2 (3.2)	1 (3.7)	0	0	0	0
Reduced visual acuity	0	1 (1.6)	0	1 (4.0)	1 (1.5)	1 (1.6)	3 (4.8)	0	0	0	1 (3.6)	1 (4.0)
Vitreous floaters	0	1 (1.6)	1 (1.7)	0	0	0	0	0	2 (7.7)	0	0	0
Vitreous opacities	0	2 (3.3)	4 (6.9)	0	1 (1.5)	0	0	0	0	1 (4.3)	1 (3.6)	0
Increased intraocular pressure	0	0	2 (3.4)	0	1 (1.5)	0	0	0	1 (3.8)	0	1 (3.6)	0
Visual disturbance	0	0	3 (5.2)	1 (4.0)	0	0	0	0	2 (7.7)	1 (4.3)	0	1 (4.0)

n (%)

There were no clinically relevant findings in vital signs or ECGs.

Based on the above, the applicant explained that the treatment benefit was maintained in AMD patients treated with pegaptanib sodium, patients who continued therapy lost less visual acuity compared to those who discontinued therapy, and there were no major differences in the safety between the first year and

second year of the study.

4.(ii).A.(2).8) Phase II/III study (5.3.5.1.8, EOP1006 [60 weeks data] [[redacted] 20[redacted] to [redacted], 20[redacted] (data cutoff date)])

A randomized, double-masked, parallel-group, comparative study in patients with subfoveal CNV secondary to AMD (target number of cases of 125) was conducted to evaluate the tolerability, safety, and pharmacokinetics of pegaptanib sodium.

Initially, the study was intended to be conducted in an open-label manner with intravitreous injections of pegaptanib sodium 3 mg given once every 6 weeks for 54 weeks but the protocol was amended later and the study design was changed to a randomized, double-masked, parallel-group, comparative study in which pegaptanib sodium 1 or 3 mg was to be given once every 6 weeks by intravitreous injection.

All of the 147 treated patients (37 patients who received open-label pegaptanib sodium 3 mg, 54 patients who received masked pegaptanib sodium 1 mg, 56 patients who received masked pegaptanib sodium 3 mg) were included in the safety analysis.

Adverse events (including abnormal laboratory values) were reported in 100% of the open-label 3 mg group (37 of 37 patients), 100% of the masked 1 mg group (54 of 54 patients), and 96% of the masked 3 mg group (54 of 56 patients). The deaths included 2 patients in the masked 1 mg group (1 case with cardiac arrest; 1 case with cerebrovascular accident, atrial fibrillation, thrombosis, pneumonitis, and pneumonia) and 4 patients in the masked 3 mg group (1 case with arteriosclerosis and hypertension aggravated; 1 case with congestive cardiac failure and aortic disorder; 1 case with hip fracture and dementia; 1 case with subdural haematoma), but a causal relationship to study treatment was denied for all cases. Other serious adverse events were reported in 8 patients in the open-label 3 mg group (chest pain; explorative laparotomy; hiatus hernia; atrial fibrillation and sick sinus syndrome; prostate cancer; coronary artery stenosis, atrial fibrillation, and inflammatory bowel disease; cerebrovascular accident; dermatitis allergic [1 case each]), 7 patients in the masked 1 mg group (hip fracture [2 cases], coronary artery stenosis; coronary artery disease aggravated; nephrolithiasis; gastroenteritis viral and atrial fibrillation; acute respiratory failure [1 case each]), and 7 patients in the masked 3 mg group (gastroenteritis and diabetic ketoacidosis; colon cancer and abdominal pain; prostate cancer; retinal haemorrhage; wrist fracture; heart valve incompetence, cardiomyopathy, pleural effusion, atelectasis, and atrial fibrillation aggravated; hip fracture) and a causal relationship to study treatment could not be denied for 1 case in the open-label 3 mg group (coronary artery stenosis).

Adverse events for which a causal relationship to study treatment could not be denied (including abnormal laboratory values) were observed in 22% of the open-label 3 mg group (8 of 37 patients), 15% of the masked 1 mg group (8 of 54 patients), and 23% of the masked 3 mg group (13 of 56 patients) and the main events are shown in the following table.

Adverse event	Open-label 3 mg (n=37)	Masked 1 mg (n=54)	Masked 3 mg (n=56)
Cataract	0	4 (7.4)	2 (3.6)
Anterior chamber inflammation	1 (2.7)	0	2 (3.6)
Pupillary reflex impaired	0	2 (3.7)	0
Vitreous floaters	2 (5.4)	1 (1.9)	1 (1.8)
Vitreous opacities	2 (5.4)	3 (5.6)	3 (5.4)
Reduced visual acuity	0	1 (1.9)	2 (3.6)
Visual disturbance	4 (10.8)	2 (3.7)	5 (8.9)

n (%)

Concerning changes from baseline in hematology and clinical chemistry tests, there were no findings suggestive of a relationship to pegaptanib sodium.

Based on the above, the applicant explained that pegaptanib sodium 1 or 3 mg administered for 1 year was well-tolerated and also regarding safety, reported events were mostly ocular and mild to moderate in severity and there were no problems with systemic safety as well.

4.(ii).B *Outline of the review by PMDA*

4.(ii).B.(1) Positioning of pegaptanib sodium

PMDA asked the applicant to explain the clinical positioning of pegaptanib sodium in comparison with verteporfin.

The applicant explained as follows:

In Japan, verteporfin (Visudyne® for intravenous infusion) was approved as a drug indicated for subfoveal CNV secondary to AMD in October 2003 and PDT combining verteporfin and a low-powered laser has been performed for the treatment of the disease. However, there are restrictions on the lesion type, size, and location that are treatable with PDT and patients' daily activities are also restricted, etc. Therefore, not all patients are expected to benefit from PDT.

Then the applicant described as follows:

Pegaptanib sodium has high selectivity for $VEGF_{165}$ that is considered to be involved in pathologic neovascularization and is expected to suppress the pathologic activity of VEGF only, without affecting the normal physiological function of VEGF in the eye or whole body. Therefore, it can offer a new option as an effective therapy for subfoveal CNV secondary to AMD.

PMDA considers as follows:

AMD is a serious disease ultimately leading to blindness and verteporfin for PDT has been approved as a therapeutic drug in Japan, but pegaptanib sodium is expected to show efficacy via a different mode of action and has significance in terms of offering a new pharmacotherapeutic option for the treatment of patients with subfoveal CNV secondary to AMD in Japan.

4.(ii).B.(2) Efficacy

4.(ii).B.(2).1) Comparison of Japanese and foreign clinical study data and the ability to extrapolate foreign clinical data

Since a sham group was not included in a Japanese clinical study, PMDA asked the applicant to compare the natural history of visual acuity loss and clinical study data between Japan and overseas and explain the efficacy of pegaptanib sodium in Japanese patients.

The applicant explained as follows:

In clinical studies in Japanese AMD patients (Kobayashi H et al. *Am J Ophthalmol*. 2000;130: 617-635, Mandai M et al. *Ophthalmology.* 1996;38: 1045-1052, Matsuhashi H et al. *J Jpn Ophthalmol Soc*. 1999;103: 456-463), the changes from baseline to 12 months in the untreated groups were -7 to -24 letters (mean, -16 letters) on the ETDRS chart. In clinical studies in foreign AMD patients (Chakravarthy U et al. *Br J Opthalmol*. 1993;77: 265-273, Ciulla TA et al. *Am J Ophthalmol*. 2002;134: 905-906, Macular photocoagulation Study Group. *Arch Ophthalmol*. 1991;109: 1220-1231, Treatment of age-related macular degeneration with photodynamic therapy (TAP) study group. *Arch Ophthalmol*. 1999;117: 1329-1345, Verteporfin in photodynamic therapy study group. *Am J Ophthalmol*. 2001;131: 541-560), the changes from baseline to 12 months in the untreated groups were -12 to -21 letters (mean, -17 letters) on the ETDRS chart. In foreign clinical studies of pegaptanib sodium (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004), the changes from baseline to 12 months in the sham groups were -13 to -17 letters on the ETDRS chart, which are similar to those in the untreated groups in the Japanese and foreign clinical studies. In the foreign clinical studies of pegaptanib sodium (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004), pegaptanib sodium (0.3 or 1 mg) significantly reduced the loss of visual acuity at 12 months compared to the sham group ($P < 0.01$, analysis of covariance [ANCOVA] including lesion subtype, prior verteporfin PDT, baseline visual acuity, and baseline lesion size as covariates). Changes in visual acuity over time in the pegaptanib sodium groups in a Japanese clinical study (5.3.5.1.1, A5751010) were not inferior to those in the foreign clinical studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004). Taking account of these findings, the changes in visual acuity over time in the pegaptanib sodium groups are considered superior to the natural history of AMD in Japanese patients.

Although a placebo group was not included in the Japanese phase II study (5.3.5.1.1, A5751010), there was a trend towards higher efficacy in terms of the mean change in visual acuity (in letters) and the proportion of responders at Week 54 in the Japanese study compared to the foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004). PMDA asked the applicant to discuss its reason taking also account of differences in the patient background between the Japanese and foreign clinical studies.

The applicant explained as follows:

“Baseline visual acuity,” “baseline lesion size,” “age,” “lesion subtype,” “presence or absence of prior PDT,” and “sex” were analyzed. As a result, in the Japanese phase II study (5.3.5.1.1, A5751010) compared to the foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004), the baseline

visual acuity was worse (Japan, 46.5-47.1 letters; overseas, 50.7-52.8 letters), the baseline lesion size was similar (Japan, 3.8-4.1 DA; overseas, 3.7-4.2 DA), the age was younger (Japan, 72.0-72.9 years; overseas, 75.5-76.4 years), the most predominant lesion subtype was Minimally Classic CNV in the Japanese phase II study (5.3.5.1.1, A5751010) (Japan, 40%-43%; overseas, 34%-38%) and Occult with no Classic CNV in the foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004) (Japan, 30%-33%; overseas, 38%-40%), fewer patients received prior PDT (Japan, 4%; overseas, 7%-10%), and the percentage of male patients was higher (Japan, 74%-83%; overseas, 35%-45%).

Then, the applicant described as follows:
In order to identify the patient background factors influencing the mean change in visual acuity, an analysis of covariance was performed with the mean change in visual acuity as the response variable, region (Study A5751010 [Japan], Study EOP1003 and Study EOP1004 combined [overseas]) and treatment group (sham group, 0.3 mg group + 1 mg group[14)], 3 mg group) as main effects, and either baseline visual acuity, baseline lesion size, age, lesion subtype (Predominantly Classic, Minimally Classic, Occult with no Classic), prior PDT (yes, no), or sex (male, female) as a covariate. As a result, baseline visual acuity and age were considered to influence the mean change in visual acuity. The same results were obtained also when Study EOP1003 and Study EOP1004 were not combined and when the 0.3 mg group and the 1 mg group were not combined. Based on the above, the differences in the effect size between the Japanese and foreign clinical studies are considered attributable to differences in the distribution of baseline visual acuity and age.

PMDA considers as follows:
As a sham group was not included in the Japanese clinical study (5.3.5.1.1, A5751010), the efficacy of pegaptanib sodium in Japanese AMD patients has not been confirmed. However, sham injection-controlled clinical studies conducted overseas have clearly demonstrated the efficacy of pegaptanib sodium, the results of the Japanese clinical study have also suggested the efficacy of pegaptanib sodium, and pegaptanib sodium has been studied under a limited condition as a drug to treat an orphan disease with small number of patietns. In view of these points etc., it may be determined that the submitted clinical study data have shown the efficacy of pegaptanib sodium in Japanese patients.

4.(ii).B.(2).2) Differences in the efficacy of pegaptanib sodium among different lesion subtypes and baseline lesion sizes

PMDA asked the applicant to present the study results by lesion subtype of subfoveal CNV secondary to AMD (Predominantly Classic, Minimally Classic, Occult with no Classic) and by baseline lesion size (< 4DA [disc area] or ≥ 4DA) and explain potential differences in the efficacy of pegaptanib sodium among

[14)] As the mean change in visual acuity was similar between the pegaptanib sodium 0.3 mg and 1 mg groups (Study A5751010, -4.3 to -3.8 letters; combined analysis from Studies EOP1003 and EOP1004, -8.0 to -7.3 letters), the 0.3 mg group and the 1 mg group were combined and an analysis of covariance was performed.

different lesion subtypes or baseline lesion sizes.

Using the data from a Japanese phase II study (5.3.5.1.1, A5751010) and foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004), the applicant analyzed the mean changes in ETDRS visual acuity from baseline to Week 54 by lesion subtype and by baseline lesion size and presented the analysis results in the following table.

The applicant explained as follows:
The Japanese clinical study (5.3.5.1.1, A5751010) suggested a trend towards some differences among different lesion subtypes, and in the pegaptanib sodium 0.3 and 1 mg groups, patients with a baseline lesion size < 4DA lost less visual acuity compared to those with a baseline lesion size ≥ 4DA. Meanwhile, the foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004) showed no major differences among different lesion subtypes or baseline lesion sizes.

Then the applicant described as follows:
The results of ANCOVA as mentioned in 4.(ii).B.(2).1) indicated no trend towards lesion subtype and baseline lesion size influencing the mean change in visual acuity. Since intravitreously administered pegaptanib sodium is considered to diffuse and reach the retina, it is assumed that the same dose of pegaptanib sodium results in the same concentration at the lesion site regardless of the lesion size. The clinical effect of pegaptanib sodium is almost comparable at doses of 0.3 to 3 mg. Taking account of these findings, we consider that there are no major differences in the efficacy of pegaptanib sodium among different lesion subtypes or baseline lesion sizes.

Table. Change in visual acuity from baseline to Week 54

		A5751010				EOP1003 and EOP1004 (Pooled analysis)							
		Pegaptanib Sodium				Pegaptanib Sodium						Sham	
		0.3 mg n=47		1 mg n=48		0.3 mg n=294		1 mg n=300		3 mg n=296		n=296	
		n	Change in visual acuity	n	Change in visual acuity	n	Change in visual acuity	n	Change in visual acuity	n	Change in visual acuity	n	Change in visual acuity
Lesion subtype	Predominantly Classic	13	0.8 ± 15.3	13	-5.7 ± 19.5	72	-7.2 ± 16.4	77	-10.2 ± 16.5	80	-10.4 ± 15.9	76	-13.8 ± 18.5
	Minimally Classic	20	-3.0 ± 9.5	19	-4.8 ± 17.8	109	-7.3 ± 15.1	108	-6.6 ± 15.0	105	-9.5 ± 14.5	101	-14.1 ± 17.3
	Occult with no Classic	14	-9.3 ± 19.9	16	-2.5 ± 12.2	111	-9.1 ± 16.3	115	-5.9 ± 18.2	111	-9.6 ± 18.8	118	-16.6 ± 17.8
Lesion size	< 4 DA	26	0.9 ± 13.5	32	-1.3 ± 15.9	181	-7.5 ± 16.2	157	-8.2 ± 16.0	183	-9.1 ± 16.8	154	-16.4 ± 18.2
	≥ 4 DA	21	-9.7 ± 15.1	16	-10.3 ± 16.2	111	-8.9 ± 15.3	143	-6.3 ± 17.4	113	-10.8 ± 16.1	141	-13.6 ± 17.4

mean ± SD
DA: disc area

PMDA considers as follows:
With respect to the change in ETDRS visual acuity from baseline to Week 54, pegaptanib sodium has been shown to reduce the loss of visual acuity compared to the sham group in all lesion subtypes and baseline lesion sizes in the foreign studies. In the Japanese study, the number of cases was limited and

may not be enough to draw clear conclusions, but the efficacy of pegaptanib sodium has been suggested in all lesion subtypes and baseline lesion sizes. Therefore, also considering that pegaptanib sodium is intended to treat an orphan disease, there is no need to especially restrict the use of pegaptanib sodium to a specific lesion subtype or baseline lesion size.

4.(ii).B.(3) Dosage and administration

4.(ii).B.(3).1) Justification for choosing 0.3 mg as the optimal dose

PMDA asked the applicant to provide a justification for choosing 0.3 mg as the optimal dose of pegaptanib sodium, based on the results from foreign clinical studies, from an efficacy and safety point of view.

The applicant explained regarding the dose response of pegaptanib sodium as follows:

The primary endpoint in the foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004) was the proportion of patients losing < 15 letters of visual acuity from baseline to Week 54 (the proportion of responders) studies and the data is shown in the following table. Although there were no statistically significant differences between the pegaptanib sodium 1 mg group and the sham group in Study EOP1004, a pooled analysis from Studies EOP1003 and EOP1004 of similar design indicated that the clinical effects of pegaptanib sodium 1 mg and 0.3 mg were almost equal. The proportion of responders in the pegaptanib sodium 3 mg group was lower compared to the pegaptanib sodium 0.3 mg and 1 mg groups in each study and its reason is unknown, but the pooled analysis from the foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004) showed a significant difference between the 3 mg and sham groups. When the proportion of patients losing ≥ 15 letters of visual acuity (the proportion of non-responders) was compared between the treatment groups, the proportion of the pegaptanib sodium 0.3, 1, or 3 mg group were significantly different from that of the sham group at all timepoints after 6 months and no significant differences were found among the pegaptanib sodium groups. Taking account of these findings etc., the efficacy of pegaptanib sodium seems to reach a plateau at 0.3 mg.

Table. Summary of the proportion of responders

	Endpoint	Pegaptanib Sodium			Sham
		0.3 mg	1 mg	3 mg	
EOP1003 (5.3.5.1.2)	No. of evaluable patients	150	154	153	152
	Responders	109 (73)	116 (75)	106 (69)	89 (59)
	P-value	0.0105	0.0035	—[a)]	
EOP1004 (5.3.5.1.4)	No. of evaluable patients	144	146	143	144
	Responders	97 (67)	97 (66)	87 (61)	75 (52)
	P-value	0.0031	0.0273[b)]	0.1294[b)]	
Pooled analysis (EOP1003/EOP1004)	No. of evaluable patients	294	300	296	296
	Responders	206 (70)	213 (71)	193 (65)	164 (55)
	P-value	0.0001	0.0003	0.0310	

Responders: n (%)
Missing values were imputed using LOCF.
P-value, CMH test (adjusted for clinical study [only for pooled analysis], lesion subtype, prior PDT, baseline visual acuity, and baseline lesion size)
a) In Study EOP1003, the 3 mg dose was excluded from Hochberg comparison (While Study EOP1003 was masked, the analysis of EOP1004 was conducted before that of EOP1003, and it was decided that the 3 mg group should be excluded from primary and secondary analyses).
b) In Study EOP1004, the *P*-value exceeded 0.05 for 3 mg (p = 0.1294). As the level of significance was 0.025 using the Hochberg procedure, there were no statistically significant differences between the 1 mg and sham groups.

Table. Comparison of the proportion of non-responders over time among the pegaptanib sodium and sham groups (*P*-value)

	P-value [a)]			
	Time after the start of clinical study			
	Month 3	Month 6	Month 9	Month 12
Pegaptanib Sodium vs. Sham				
0.3 mg vs. Sham	0.0121	< 0.0001	< 0.0001	< 0.0001
1 mg vs. Sham	0.0490	< 0.0001	< 0.0001	0.0003
3 mg vs. Sham	0.1320	0.0034	0.0001	0.0310
Comparison among the Pegaptanib Sodium groups				
0.3 mg vs. 1 mg	0.9883	0.3890	0.9039	0.8594
0.3 mg vs. 3 mg	0.5361	0.0585	0.8486	0.2919
1 mg vs. 3 mg	0.7473	0.2548	0.6327	0.1249

a) CMH test, adjusted for clinical study, lesion subtype, prior PDT, baseline visual acuity, and baseline lesion size

The applicant also explained regarding the safety as follows:

There were no differences in almost all safety endpoints among the pegaptanib sodium groups in the foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004). Although it was suggested that increased intraocular pressure ≥ 35 mmHg may occur more frequently in the pegaptanib sodium 3 mg group compared to the pegaptanib sodium 0.3 mg and 1 mg groups, none of the patients discontinued treatment due to increased intraocular pressure. Ocular adverse events such as endophthalmitis, traumatic cataract, and retinal detachment, are considered related to the injection procedure rather than the drug itself and should be unaffected by the dose level of pegaptanib sodium. Based on the above, the optimal dose of pegaptanib sodium has been determined to be 0.3 mg, which is its minimum effective dose and at which the systemic exposure should be low.

PMDA considers as follows:

The results from the foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004) have demonstrated the consistent efficacy of pegaptanib sodium 0.3 mg. The effects of dose increase to 1 and 3 mg of pegaptanib sodium are unclear and there has been a trend towards an inferior effect of 3 mg for some efficacy measures though the cause is unknown. Regarding safety, it has been suggested that increased intraocular pressure may occur more frequently with pegaptanib sodium 3 mg. The Japanese phase II study (5.3.5.1.1, A5751010) has also shown a similar trend as the foreign clinical studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004) did. Therefore, there are no particular problems with choosing 0.3 mg as the optimal dose in Japan.

4.(ii).B.(3).2) Justification for the dosing interval and the criteria for stopping treatment

Since subfoveal CNV secondary to AMD is a progressive disease, PMDA asked the applicant to explain the need for continued injections every 6 weeks with pegaptanib sodium in all patients, taking account of the usage in foreign countries and published literatures from Japan and overseas, etc.

The applicant explained as follows:

The foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004) have confirmed the efficacy and safety of pegaptanib sodium administered every 6 weeks for 48 weeks (54-week observation) and there have been no safety problems with repeated administration for up to 4 years. Pfizer U.S. held a

discussion with 10 ophthalmologists (an external expert meeting) in [redacted] 20[redacted], which concluded that an ophthalmologist should decide whether to continue or stop treatment based on the overall assessments of the patient background and clinical condition and the prediction of the future condition of the patient. The European guidance (Chakravarthy U et al. *Br J Ophthalmol.* 2006;90: 1188-1196) reads that "Patients should receive re-treatment with pegaptanib sodium every 6 weeks, as recommended by the phase II/III study protocol. The end point and the duration of treatment with pegaptanib sodium are yet to be determined." The US practice guidelines (Preferred Practice Pattern. Age-related macular degeneration [September 16, 2006 version]) recommend return exam with retreatments every 6 weeks for pegaptanib sodium, and has not established the duration of treatment or the dosing interval separately for patients with improved visual acuity or halted progression of vision loss. As the mode of action of pegaptanib sodium (inhibition of VEGF binding to its receptors) is different from that of verteporfin (direct occlusion of CNV), it is not appropriate to apply similar retreatment criteria. Therefore, instead of establishing an uniform duration of treatment or retreatment criteria, pegaptanib sodium should be adminsitered once every 6 weeks and an ophthalmologist should determine whether to continue injections, considering the patient's visual acuity, fundal condition, and the level of visual acuity to be maintained for each patient, etc. as a whole.

In the European package insert, the following statement was added as of December 2007: "After 2 consecutive injections of Macugen, if a patient does not demonstrate a treatment benefit (loss of less than 15 letters of visual acuity) at the 12-week visit, consideration should be given to stopping or withholding Macugen therapy." PMDA asked the applicant to explain the background of and basis for including this statement in the package insert and show their view on the necessity of including such statement in the Japanese package insert.

The applicant explained as follows:
In January 2006 when approval was granted, the European Medicines Agency (EMEA) demanded that Pfizer should consider establishing the criteria for stopping treatment with pegaptanib sodium. The criteria for stopping treatment were discussed at an external expert meeting in [redacted] 20[redacted], which concluded that a decision should be made comprehensively in view of all possible indicators of the condition and clinical course of the patient on treatment and that it is not appropriate to apply uniform criteria for stopping treatment to all patients, and this response was submitted to the EMEA in [redacted] 20[redacted]. In [redacted] 20[redacted], Pfizer submitted the response that, based on the results from the phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004), when patients were still non-responders (loss of ≥ 15 letters of visual acuity) after at least 6 months of treatment with pegaptanib sodium, the possibility of visual acuity improvement or conversion to responders (loss of < 15 letters of visual acuity) after more prolonged therapy was low, and they would include this information in the package insert. However, in [redacted] 20[redacted], the EMEA presented the following assessment results: "As the proportion of non-responders converted to responders seems almost constant after Week 12, consideration needs to be given to stopping or withholding treatment with pegaptanib sodium at the Week 12 visit, and a relevant statement should be added to the Posology and

method of administration section." Accordingly, as of December 21, 2007, the sentence "After 2 consecutive injections of Macugen, if a patient does not demonstrate a treatment benefit (loss of less than 15 letters of visual acuity) at the 12-week visit, consideration should be given to stopping or withholding Macugen therapy" was added to the package insert.

Then the applicant described as follows:
Compared to the foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004), a Japanese phase II study (5.3.5.1.1, A5751010) had fewer subjects and a limited number of non-responders and it is difficult to draw a certain conclusion. However, the proportion of non-responders converted to responders tended to be generally higher in the Japanese phase II study (5.3.5.1.1, A5751010) compared to the foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004) and 1 of 5 subjects who had been non-responders at Week 12 was converted to a responder at Week 54, suggesting that it is not easy to predict the clinical response to treatment beforehand. Therefore, whether to stop treatment with pegaptanib sodium should be determined comprehensively, in view of all possible indicators of the condition and clinical course of the patient on treatment, and it is not appropriate to determine whether to stop treatment based uniformly on the clinical response at Week 12.

PMDA considers as follows:
Although the clinical response at Week 12 may be a clue for determining the efficacy of pegaptanib sodium, it is difficult at present to establish uniform criteria for stopping treatment or for retreatment, taking account that pegaptanib sodium is indicated for a serious disease that could lead to blindness, PDT with verteporfin is the only therapy for this disease in Japan, and there are also limitations on the data, etc.. On the other hand, aimless administration of pegaptanib sodium should be avoided and the decision on whether to continue injections of pegaptanib sodium needs to be reviewed regularly, monitoring the patient's condition, and a relevant caution statement should be included in the package insert. It is important to accumulate experience with the use of pegaptanib sodium in Japan and overseas. The efficacy and safety of long-term treatment needs to be investigated after the market launch also in Japan.

4.(ii).B.(4) Safety

4.(ii).B.(4).1) Ocular adverse events

(a) Conjunctival haemorrhage, conjunctivitis, corneal erosion, and keratitis

When a Japanese clinical study (5.3.5.1.1, A5751010) is compared to foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004), adverse events of conjunctival haemorrhage, conjunctivitis, corneal erosion, and keratitis occurred more frequently in Japanese patients. PMDA asked the applicant to explain its reason.

First, the applicant explained about conjunctival haemorrhage and conjunctivitis as follows:
Ophthalmologic examination was performed before and after treatment and 1 week after treatment in the Japanese phase II study (5.3.5.1.1, A5751010) and the foreign phase II/III studies (5.3.5.1.2, EOP1003

and 5.3.5.1.4, EOP1004) and the presence or absence of “conjunctival inflammation or haemorrhage” was assessed as part of ophthalmologic examination. In both Japan and overseas, if conjunctival inflammation or haemorrhage was noted, it was reported as “present” without distinguishing inflammation from haemorrhage. The incidence of “conjunctival inflammation or haemorrhage” after each treatment was 32% to 59% in the Japanese phase II study (5.3.5.1.1, A5751010) while “conjunctival inflammation or haemorrhage” was observed at high incidences of 76% to 82% in the pegaptanib sodium groups in the foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004).

Then the applicant described as follows:
In the foreign phase II/III studies (5.3.5.1.2, EOP1003; 5.3.5.1.4, EOP1004), conjunctival haemorrhage was to be reported as an adverse event only when it was determined by the investigator to be clinically relevant. On the other hand, in the Japanese clinical study (5.3.5.1.1, A5751010), any symptom of conjunctival haemorrhage regardless of clinical relevance was to be reported as an adverse event. Therefore, differences in the incidence between Japan and overseas are considered attributable to differences in the handling of adverse events between Japan and overseas.

Next, the applicant explained about corneal erosion and keratitis as follows:
The incidence of “corneal abnormalities” after each treatment with pegaptanib sodium as detected by ophthalmologic examination was 30% to 60% in the Japanese phase II study (5.3.5.1.1, A5751010), which was higher than that (15%-25%) in the pegaptanib sodium groups in the foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004). With respect to adverse events involving the cornea, the frequencies of corneal erosion and keratitis tended to be higher in the pegaptanib sodium groups (0.3 mg and 1 mg groups) in the Japanese phase II study (5.3.5.1.1, A5751010), while the frequencies of corneal oedema, corneal epithelium defect, and corneal epithelium disorder tended to be slightly higher in the foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004). Thus, there may be possible influences of applying similar adverse event terms differently, but differences in the incidence were also noted when “corneal abnormalities” were observed via ophthalmologic examination. Thus, the reason for higher incidences of especially corneal erosion and keratitis in the Japanese phase II study (5.3.5.1.1, A5751010) is unclear at present.

PMDA asked the applicant to explain the severity and outcome of conjunctival haemorrhage, conjunctivitis, corneal erosion, and keratitis reported in the Japanese phase II study (5.3.5.1.1, A5751010) as these events occurred frequently in Japan.

The applicant explained that conjunctival haemorrhage, conjunctivitis, corneal erosion, and keratitis reported in the Japanese phase II study (5.3.5.1.1, A5751010) were mild in severity and resolved within 1 to 2 weeks in all cases.

PMDA considers as follows:

The reason why conjunctival haemorrhage, conjunctivitis, corneal erosion, and keratitis occurred more frequently in the Japanese clinical study is unclear. However, these events are also related to the intravitreal injection procedure and it is difficult to establish a causal relationship to pegaptanib sodium, and the events reported in Japan were all mild in severity and resolved within 1 to 2 weeks. Taking account of these findings, there should be no major problems at present. It is necessary to identify the occurrence of these events via post-marketing surveillance.

(b) Endophthalmitis

Concerning the risk of endophthalmitis associated with pegaptanib sodium, PMDA asked the applicant to explain about the incidences of endophthalmitis observed in Japanese and foreign clinical studies in comparison to the incidences of endophthalmitis that could occur after common intraocular surgery, e.g. cataract surgery, also in view of published literatures etc.

The applicant explained as follows:

Endophthalmitis was not reported in the Japanese phase II study (5.3.5.1.1, A5751010). In the foreign phase II/III studies (5.3.5.1.2, 5.3.5.1.3, 5.3.5.1.6, EOP1003; 5.3.5.1.4, 5.3.5.1.5, 5.3.5.1.6, EOP1004), there were a total of 18 cases with endophthalmitis in the study eye (12 cases in Weeks 0-54; 4 cases in Weeks 54-102; 2 cases in Weeks 102-156), which were all determined to be related to the injection procedure. After the resolution of endophthalmitis, 9 of 12 subjects in Weeks 0-54, 2 of 4 subjects in Weeks 54-102, and 1 of 2 subjects in Weeks 102-156 continued treatment with pegaptanib sodium. The incidence of endophthalmitis per injection was 0.16% in Weeks 0-54 (12 events/7545 injections), 0.10% in Weeks 54-102 (4 events/4091 injections), and 0.06% in Weeks 102-156 (2 events/3227 injections), indicating lower incidences in the second and third years compared to the first year. By dose level, endophthalmitis occurred in 7 subjects treated with pegaptanib sodium 0.3 mg, 5 subjects treated with 1 mg, and 6 subjects treated with 3 mg and no dose response was observed. The number of injections received prior to the development of endophthalmitis ranged from 1 to 26 and there was also no association with the number of injections received.

Then the applicant described as follows:

The incidence of endophthalmitis after cataract surgery has been reported to be 0.04% to 0.12% (Mitooka K et al. *Ophthalmology.* 2006;48: 755-762). According to a questionnaire survey of the Japanese Society of Cataract and Refractive Surgery (2004), the incidence of endophthalmitis is 0.36 cases per 1000 cataract surgeries (0.036%) in Japan (Mitooka K et al. *Ophthalmology.* 2006;48: 755-762). A similar investigation in the US has also reported that the incidence is 0.04% to 0.09% (Mitooka K et al. *Ophthalmology.* 2006;48: 755-762). It has been reported that the incidence of endophthalmitis after vitreoretinal surgery is 0.04% to 0.14%, which is similar to that after cataract surgery (Horio N et al. *Ophthalmology.* 2006;48: 769-776). Taking account of these reports, the incidences of endophthalmitis of 0.06% to 0.16% in the foreign phase II/III studies of pegaptanib sodium (5.3.5.1.2, 5.3.5.1.3, 5.3.5.1.6, EOP1003; 5.3.5.1.4, 5.3.5.1.5, 5.3.5.1.6, EOP1004) are similar to the reported incidences after cataract

surgery or other vitreoretinal surgery and considering the outcome of AMD, i.e. visual disturbance or blindness, the risk of endophthalmitis associated with the intravitreal injection procedure should be medically acceptable.

PMDA considers as follows:
The incidence of endophthalmitis after injection of pegaptanib sodium is not much different from those after cataract surgery etc. and endophthalmitis is considered related to the intravitreal injection procedure and there should be no major problems at present. Meanwhile, pegaptanib sodium should be administered by ophthalmologists with expertise about retinal diseases and adequate experience in intravitreal injection procedures. It is also necessary to identify the occurrence of endophthalmitis via post-marketing surveillance.

(c) Increased intraocular pressure
Transient increases in intraocular pressure have been noted after the injection of pegaptanib sodium. There are also many glaucoma or ocular hypertension patients among the elderly for whom pegaptanib sodium is indicated. Thus, PMDA asked the applicant to explain the risk of increased intraocular pressure following the injection of pegaptanib sodium.

The applicant explained as follows:
In the Japanese phase II study (5.3.5.1.1, A5751010), adverse events of increased intraocular pressure in the study eye occurred in 10% of the pegaptanib sodium 1 mg group (5 of 48 subjects) and none of the 0.3 mg group. Its severity was mild for 2 subjects, moderate for 2 subjects, and severe for 1 subject, and all resolved with treatment and none of the subjects discontinued pegaptanib sodium. In the foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004), adverse events of increased intraocular pressure in the study eye occurred in 14% of the pegaptanib sodium 0.3 mg group (42 of 295 subjects), 20% of the 1 mg group (59 of 301 subjects), 26% of the 3 mg group (77 of 296 subjects), and 3% of the sham group (8 of 298 subjects), many of which were determined by the investigator to be related to the injection procedure, and its severity was mostly mild or moderate and none of the subjects discontinued treatment with pegaptanib sodium. As to changes in intraocular pressure values over time, in the Japanese phase II study (5.3.5.1.1, A5751010) and foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004), the baseline intraocular pressure and the pre-injection intraocular pressure at each visit (the study eye) were similar across the treatment groups and there was no increase in the mean intraocular pressure over time, and the mean intraocular pressure increased at 30 minutes post-injection compared to the pre-injection value, but returned to the mean pre-injection level within 1 week post-injection.

Then the applicant described as follows:
Patients with an intraocular pressure ≥ 35 mmHg in the Japanese and foreign clinical studies are presented in the following table. The incidence of increased intraocular pressure ≥ 35 mmHg was high in patients with prior or concurrent glaucoma or ocular hypertension, but even patients without prior or

concurrent glaucoma or ocular hypertension had increased intraocular pressure. Since an adequate attention needs to be paid to increased intraocular pressure following the injection of pegaptanib sodium, a caution statement about increased intraocular pressure will be provided.

Table. Subjects with an intraocular pressure ≥ 35 mmHg [Study A5751010, pooled data from Studies EOP1003 and EOP1004 (Weeks 0-54)]

	Study A5751010		Pooled data from Studies EOP1003 and EOP1004				
Treatment group	0.3 mg	1 mg	0.3 mg	1 mg	3 mg	Total	Sham
No. of evaluable subjects	47	48	295	301	296	892	298
Subjects with an intraocular pressure ≥ 35 mmHg	0 (0)	2 (4)	27 (9)	28 (9)	44 (15)	99 (11)	1 (0)
With prior or concurrent glaucoma or ocular hypertension	3	6	26	15	27	68	26
Subjects with an intraocular pressure ≥ 35 mmHg	0 (0)	1 (17)	4 (15)	8 (53)	10 (37)	22 (32)	1 (4)
Without prior or concurrent glaucoma or ocular hypertension	44	42	269	286	269	824	272
Subjects with an intraocular pressure ≥ 35 mmHg	0 (0)	1 (2)	23 (9)	20 (7)	34 (13)	77 (9)	0 (0)

n (%)

PMDA considers as follows:

Increased intraocular pressure following the injection of pegaptanib sodium is an event that we should be cautious about. Taking account of its occurrence in Japan and overseas, of course, caution must be exercised when patients have prior or concurrent glaucoma or ocular hypertension, but even in patients without prior or concurrent glaucoma or ocular hypertension, an adequate attention needs to be paid to increased intraocular pressure. It is necessary to investigate increases in intraocular pressure via post-marketing surveillance.

4.(ii).B.(4).2) Occurrence of systemic adverse events, e.g. hypertension and thrombotic adverse events

Pegaptanib sodium is an anti-VEGF inhibitor, and hypertension and thrombosis and thromboembolic events have been reported with bevacizumab, a systemically administered anti-cancer drug. Thus, systemic exposure to pegaptanib sodium may also result in systemic adverse events. PMDA asked the applicant to explain the occurrence of systemic adverse events associated with pegaptanib sodium.

The applicant explained as follows:

Concerning serious thromboembolic adverse events, chest pain was reported in 1 subject in a Japanese clinical study (5.3.5.1.1, A5751010) but this subject had a history of hypertension, arrhythmia, hyperlipidaemia, and chest pain and its causal relationship to the injection procedure and to pegaptanib sodium were both denied by the investigator. The occurrence of serious thromboembolic and haemorrhagic adverse events in foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004) is shown in the table below and there were no major differences between the pegaptanib sodium groups and the sham group.

Table. Serious adverse events potentially related to VEGF inhibition (excluding “eye disorders”) in Studies EOP1003 and EOP1004 (Weeks 0-54)

Treatment group	Pegaptanib Sodium				Sham
	0.3 mg	1 mg	3 mg	Total	
No. of evaluable subjects	295	301	296	892	298
Serious thromboembolic adverse events (Cardiovascular disorders/Lung disorders)					
Myocardial infarction	3 (1)	2 (1)	2 (1)	7 (1)	2 (1)
Angina pectoris	1 (0)	—	1 (0)	2 (0)	1 (0)
Cardiac arrest	1 (0)	—	1 (0)	2 (0)	—
Cardio-respiratory arrest	—	1 (0) [b)]	—	1 (0)	—
Coronary artery disease aggravated	—	—	1 (0)	1 (0)	—
Coronary artery thrombosis	—	—	1 (0)	1 (0)	—
Myocardial ischaemia	1 (0) [a)]	—	—	1 (0)	—
Acute myocardial infarction	—	—	—	—	1 (0)
Coronary artery disease	—	—	—	—	2 (1) [d)]
Coronary artery insufficiency	—	—	—	—	1 (0)
Coronary artery surgery	1 (0) [a)]	—	—	1 (0)	—
Aortic stenosis	—	1 (0) [b)]	1 (0)	2 (0)	—
Aortic aneurysm	2 (1)	—	—	2 (0)	1 (0)
Deep vein thrombosis	—	1 (0)	—	1 (0)	1 (0) [c)]
Thrombosis	—	—	—	—	1 (0) [c)]
Pulmonary embolism	1 (0)	1 (0)	—	2 (0)	1 (0)
Total	10	6	7	23	11
Serious thromboembolic adverse events (Central nervous system disorders)					
Cerebrovascular accident	2 (1)	1 (0)	3 (1)	6 (1)	1 (0) [d)]
Transient ischaemic attack	4 (1)	—	1 (0)	5 (1)	2 (1)
Carotid artery stenosis	1 (0)	1 (0)	—	2 (0)	—
Carotid artery occlusion	1 (0)	—	—	1 (0)	—
Cerebral infarction	—	—	1 (0)	1 (0)	—
Cerebral thrombosis	1 (0)	—	—	1 (0)	—
Total	9	2	5	16	3
Serious haemorrhagic adverse events					
Cerebral haemorrhage	1 (0)	—	1 (0)	2 (0)	—
Chronic gastrointestinal bleeding	—	1 (0)	—	1 (0)	—
Gastric haemorrhage	—	—	1 (0)	1 (0)	—
Gastrointestinal haemorrhage	1 (0)	—	—	1 (0)	1 (0)
Gastrointestinal ulcer haemorrhage	—	—	—	—	1 (0)
Haematuria	1 (0)	—	—	1 (0)	—
Epistaxis	—	—	1 (0)	1 (0)	—
Total	3	1	3	7	2
Total number of subjects with serious thromboembolic and haemorrhagic adverse events	21	8	15	44	14

(%)

a) Subject ID 1003-085-011 (0.3 mg group in Weeks 0-54) had coronary artery surgery and myocardial ischaemia as serious adverse events.
b) Subject ID 1004-033-006 (1 mg group in Weeks 0-54) had aortic stenosis and cardio-respiratory arrest as serious adverse events.
c) Subject ID 1003-145-018 (Sham group in Weeks 0-54) had deep vein thrombosis and thrombosis as serious adverse events.
d) Subject ID 1004-054-011 (Sham group in Weeks 0-54) had cerebrovascular accident and coronary artery disease as serious adverse events.

The incidence of serious thromboembolic adverse events (central nervous system disorders) tended to be slightly higher in the pegaptanib sodium groups (0.3 mg and 3 mg), which is considered attributable to more patients with the risk factors for thromboembolic events (central nervous system disorders) (hypertension or existing vascular occlusion, etc.) in the pegaptanib sodium groups than in the sham group. The incidence of serious thromboembolic adverse events (central nervous system disorders) was highest in the pegaptanib sodium 0.3 mg group, which was not dose-related.

With respect to blood pressure, the incidences of adverse events related to hypertension in the Japanese phase II study (5.3.5.1.1, A5751010) and foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004) are shown in the following table and pegaptanib sodium was not associated with an increased incidence of adverse events related to hypertension.

Adverse events related to hypertension in Study A5751010 and Studies EOP1003 and EOP1004 (Weeks 0-54)

Treatment group	Study A5751010			Study EOP1003 and Study EOP1004				
	Pegaptanib Sodium			Pegaptanib Sodium				Sham
	0.3 mg	1 mg	Total	0.3 mg	1 mg	3 mg	Total	
No. of evaluable subjects	47	48	95	295	301	296	892	298
MedDRA Term								
Hypertension	3 (6)	0 (0)	3 (3)	14 (5)	26 (9)	29 (10)	69 (8)	22 (7)
Hypertension aggravated	–	–	–	12 (4)	5 (2)	7 (2)	24 (3)	8 (3)
Systolic hypertension	–	–	–	–	–	–	–	1 (0)
Hypertensive crisis	–	–	–	1 (0)	–	–	1 (0)	–

n (%)

Then the applicant explained as follows:

Taking account of the potency of anti-VEGF activity by referring to published data etc., pegaptanib sodium was compared to bevacizumab. As a result, the systemic exposure following intravitreal injection of pegaptanib sodium is very low, pegaptanib sodium has selectively high affinity for $VEGF_{165}$ that has been reported to be involved in pathologic neovascularization, and non-clinical study data showed no effects of pegaptanib sodium on the cardiovascular system. Thus, the possibility of occurrence of systemic adverse events related to anti-VEGF activity, including hypertension, following intravitreal injection of pegaptanib sodium, is considered very low compared to intravenously administered bevacizumab [see "4.(i).B.(2) Factors affecting absorption into the systemic circulation"].

PMDA considers as follows:

Based on the results of pharmacokinetic studies, the potential systemic exposure to pegaptanib sodium is considered very low. There was no clear dose response relationship for the incidence of systemic adverse events potentially related to anti-VEGF activity, and regarding the reported events, it is difficult to establish a causal relationship to pegaptanib sodium, considering the background of patients with various risk factors. Therefore, it can not be said that pegaptanib sodium increases the risk of systemic adverse events, but such events, if they occur, may lead to a serious outcome and this point needs to be confirmed via post-marketing surveillance.

4.(ii).B.(4).3) Hypersensitivity/anaphylaxis

PMDA asked the applicant to explain the risk of hypersensitivity/anaphylaxis to pegaptanib sodium, in view of Japanese and foreign clinical studies, cases of hypersensitivity/anaphylaxis reported in foreign post-marketing experience, and published literatures etc.

The applicant explained as follows:

In a Japanese clinical study (5.3.5.1.1, A5751010), there were no adverse events reported as drug hypersensitivity to pegaptanib sodium. In foreign clinical studies (5.3.5.1.2 and 5.3.5.1.3, EOP1003; 5.3.5.1.4 and 5.3.5.1.5, EOP1004; 5.3.5.1.7 and 5.3.5.1.8, EOP1006), the incidence of adverse events considered related to hypersensitivity regardless of relationship to pegaptanib sodium was similar between the pegaptanib sodium groups and the sham group, and 3 serious adverse events (allergic reaction to ramipril, allergic dermatitis to trimethoprim-sulfamethoxazole, angioneurotic oedema associated with lidocaine [one case each]) were noted. But after the presumed causative drugs were

switched to other drugs, treatment with pegaptanib sodium could be continued without problems. According to foreign post-marketing safety information (from December 17, 2004 to June 30, 2007), a total of 21 patients experienced adverse events related to hypersensitivity/anaphylaxis (including rash) during treatment with pegaptanib sodium, and Pfizer Inc. (U.S.) requested an Expert Panel composed of allergists/immunologists to conduct assessments. As a result, as 14 of 21 patients developed events within several minutes to several hours after the injection of pegaptanib sodium, it was concluded that the possibility of hypersensitivity reactions to pegaptanib sodium could not be denied. However, among about 75 000 patients estimated to have received a total of at least 200 000 injections of pegaptanib sodium between December 17, 2004 and June 2007, adverse events related to hypersensitivity/anaphylaxis were reported by 21 patients, suggesting that the incidence is very low. The applicant is still proceeding with a further investigation in light of the suggestions from the Expert Panel. A caution statement about hypersensitivity/anaphylaxis has been included in the package insert for the proposed product.

PMDA considers as follows:
Since events that are indicative of hypersensitivity/anaphylaxis to pegaptanib sodium have been reported, an adequate attention needs to be paid to the possible occurrence of hypersensitivity/anaphylaxis. Meanwhile, as pegaptanib sodium is administered by intravitreous injection, hypersensitivity/anaphylaxis to concomitant medications including an antiseptic agent, an anesthetic agent, antibiotic eye drops, and a mydriatic are also expected. Thus, we should recognize and be cautious of hypersensitivity/anaphylaxis as events associated with intravitreous injection. Although hypersensitivity/anaphylaxis did not occur in the Japanese clinical study, it is necessary to identify the possible occurrence via post-marketing surveillance. An investigation of these events by the applicant is under way and if any new findings become available, the relevant information should be provided to the clinical practice as soon as possible (A caution statement about these events has already been included in the “CONTRAINDICATIONS”, “Important Precautions”, and “Clinically significant adverse reactions” sections of the package insert).

4.(ii).B.(4).4) The efficacy and safety of pegaptanib sodium in combination with PDT

PMDA asked the applicant to explain the efficacy and safety of pegaptanib sodium in combination with verteporfin PDT.

The applicant explained as follows:
In order to evaluate the effectiveness of pegaptanib sodium in combination with verteporfin PDT, a double-masked, comparative study comparing pegaptanib sodium + PDT vs. pegaptanib sodium + sham-PDT (Study A5751012) was undertaken. However, as patient enrollment was slow and an initial interim analysis (at Week 18) indicated that the effectiveness of the combination of pegaptanib sodium + PDT was not clear, it was decided to terminate the study prematurely and the study was closed with 168 cases (pegaptanib sodium + PDT group, 84 cases; pegaptanib sodium + sham-PDT group, 84 cases), which was less than half the target number of cases (360 cases [180 cases per group]). Regarding efficacy,

changes in visual acuity from baseline to Week 54 are presented in the following table and there were no statistically significant differences between the two groups.

Table. Mean change in visual acuity at Week 54 (in letters)

Item	Pegaptanib sodium + sham PDT	Pegaptanib sodium + PDT
No. of evaluable patients (ITT)	84	83
Baseline visual acuity (in letters)	51.0	52.8
Change at Week 54 (LS mean) ± standard error	-13.93 ± 3.04	-13.74 ± 3.16
Difference between the two arms [95% confidence interval]	-0.19 [-5.40, 5.02]	
P-value*	0.9432	

Adjusted for baseline lesion size and baseline visual acuity. Missing values were imputed using LOCF.
* Analysis of covariance: ANCOVA

The incidences of adverse events are shown in the following table. Most of the reported events were local ocular adverse events. Although serious adverse events occurred more frequently in the combination therapy group, only 1 case of endophthalmitis in the combination therapy group fell under the category of serious adverse events related to injection procedure, pegaptanib sodium or verteporfin/PDT, and the differences in the incidence of serious adverse events regardless of causality were considered to have been incidental. Injection procedure-related adverse events accounted for more than half of all adverse events and the incidence of adverse events related to pegaptanib sodium or verteporfin/PDT was low. Therefore, it is considered that the concomitant use of pegaptanib sodium and PDT would not affect the safety of pegaptanib sodium.

Table. Safety results at Week 54 in Study A5751012

Item	Non-combination therapy group Pegaptanib sodium + sham PDT	Combination therapy group Pegaptanib sodium + PDT
No. of evaluable patients (Safety population)	n=83	n=83
No. of patients with adverse events	66 (80%)	71 (86%)
No. of patients with local ocular adverse events	61 (73%)	62 (75%)
No. of patients with serious adverse events	8 (10%)	15 (18%)
No. of patients with adverse events leading to treatment interruption or discontinuation	4 (5%)	2 (2%)
No. of patients with injection procedure-related adverse events	44 (53%)	42 (51%)
No. of patients with injection procedure-related local ocular adverse events	44 (53%)	41 (49%)
No. of patients with injection procedure-related serious adverse events	0 (0%)	1 (1%)
No. of patients with injection procedure-related adverse events leading to treatment interruption or discontinuation	0 (0%)	0 (0%)
No. of patients with pegaptanib sodium-related adverse events	8 (10%)	4 (5%)
No. of patients with pegaptanib sodium-related local ocular adverse events	8 (10%)	4 (5%)
No. of patients with pegaptanib sodium-related serious adverse events	0 (0%)	0 (0%)
No. of patients with pegaptanib sodium-related adverse events leading to treatment interruption or discontinuation	0 (0%)	1 (1%)
No. of patients with verteporfin/PDT-related adverse events	1 (1%)	3 (4%)
No. of patients with verteporfin/PDT-related local ocular adverse events	1 (1%)	0 (0%)
No. of patients with verteporfin/PDT-related serious adverse events	0 (0%)	0 (0%)
No. of patients with verteporfin/PDT-related adverse events leading to treatment interruption or discontinuation	0 (0%)	0 (0%)

Furthermore, the applicant explained as follows:

Also in foreign phase II/III studies (EOP1003 and EOP1004), the concomitant use of PDT was allowed. When patients are stratified by whether or not they received PDT at baseline or during the course of the study, the incidences of adverse events are as presented in the following table and there were no major differences in the nature or incidence of adverse events between pegaptanib sodium with or without PDT.

Table. Adverse events by the presence or absence of concomitant use of verteporfin PDT in Studies EOP1003 and EOP1004 (Weeks 0-54)

Concomitant use of verteporfin PDT	With verteporfin PDT (at baseline or during the course of the study)				Without verteporfin PDT			
Treatment group	Pegaptanib Sodium group			Sham group	Pegaptanib Sodium group			Sham group
	0.3 mg	1 mg	3 mg		0.3 mg	1 mg	3 mg	
No. of evaluable patients	58	61	65	75	237	240	231	223
No. of patients with adverse events								
Regardless of causality	58 (100)	60 (98)	63 (97)	73 (97)	228 (96)	226 (94)	225 (97)	210 (94)
Regardless of causality (serious)	10 (17)	9 (15)	21 (32)	9 (12)	45 (19)	41 (17)	43 (19)	36 (16)
Injection procedure-related [a)]	51 (88)	55 (90)	57 (88)	54 (72)	197 (83)	187 (78)	192 (83)	149 (67)
Injection procedure-related [a)] (serious)	2 (3)	2 (3)	2 (3)	0 (0)	7 (3)	4 (2)	4 (2)	0 (0)
Causal relationship to the investigational product can not be denied [a)]	19 (33)	17 (28)	27 (42)	17 (23)	60 (25)	73 (30)	71 (31)	40 (18)
Causal relationship to the investigational product can not be denied [a)] (serious)	0 (0)	0 (0)	1 (2)	0 (0)	3 (1)	0 (0)	1 (0)	0 (0)

a) Causal relationship: Causality was assessed using a 4-point scale ("Unrelated," "Relationship can not be denied," "Probably related," "Definitely related") and events assessed as "Relationship can not be denied," "Probably related," and "Definitely related" were included.

PMDA considers as follows:

Although there were no particular safety problems with combination therapy of pegaptanib sodium and verteporfin PDT in Study A5751012, as the efficacy of combination therapy has not been demonstrated, the clinical significance of the concomitant use of pegaptanib sodium and verteporfin PDT has not been determined at present.

4.(ii).B.(4).5) Deaths following treatment with pegaptanib sodium

Concerning deaths reported in Japanese and foreign clinical studies, PMDA asked the applicant to explain the cause of death and its relationship to pegaptanib sodium.

The applicant explained as follows:

Concerning deaths reported in 1 Japanese clinical study (5.3.5.1.1, A5751010) and 7 foreign clinical studies (5.3.3.2.1, NX109-01; 5.3.3.2.2, EOP1000; 5.3.3.2.3, EOP1001; 5.3.5.1.2, 5.3.5.1.3, and 5.3.5.1.6, EOP1003; 5.3.5.1.4, 5.3.5.1.5, and 5.3.5.1.6, EOP1004; 5.3.5.1.7 and 5.3.5.1.8, EOP1006; 5.3.5.1.9, EOP1009), most of the patients enrolled into the clinical studies were elderly and the main causes of death were cardiac disorders (e.g. myocardial infarction, cardiac failure, cardio-respiratory arrest), respiratory disorders (e.g. pneumonia), and cancer etc., which are common causes of death in the elderly. Deaths potentially related to VEGF inhibition in foreign phase II/III studies (EOP1003 and EOP1004 [Weeks 0-156]) were investigated. As a result, except for 1 death (case number EOP-1004-048-002; name of adverse event, aortic aneurysm; cause of death, abdominal aortic aneurysm rupture; Causal relationship to pegaptanib sodium could not be denied), patients who died due to haemorrhagic or embolic adverse events had pre-existing diseases or factors relating to the cause of death before entry into the clinical

study and a causal relationship between death and pegaptanib sodium was denied. Also in other Japanese and foreign clinical studies (A5751010, EOP1006 and EOP1009), the deaths were considered related to the patient's medical history, pre-existing diseases, or factors relating to the cause of death and have been determined to be unrelated to pegaptanib sodium, and there was also no trend towards an increase in specific adverse events causing death with prolonged treatment. Thus, it is considered that there is no possibility that pegaptanib sodium increases the mortality. Furthermore, 5 of the 7 deaths reported in foreign post-marketing experience (from December 17, 2004 to June 30, 2007) were elderly patients aged ≥ 75 years (the age of the remaining two patients is unknown) and the main causes of death were cardiovascular and cerebrovascular events and a causal relationship between death and pegaptanib sodium was denied for 5 cases and unknown (no information) for the remaining 2 cases.

PMDA considers as follows:
When the deaths reported in the clinical studies of pegaptanib sodium were examined in detail, no information suggestive of a relationship to pegaptanib sodium was found and there should be no particular problems. The intended population is elderly patients and it is expected that deaths due to various causes will occur also in future. Therefore, it is necessary to continue to collect and evaluate the information via post-marketing surveillance.

III. Results of Conformity Audit Concerning the Documents Appended to the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based inspection

A document-based inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the documents appended to the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the documents appended to the new drug application (A5751010). As a result, it was found that at some clinical study sites, the IRB's opinion on the appropriateness of continuing the clinical study had not been sought in response to some of the serious and unexpected adverse drug reaction reports notified by the sponsor, but there were no major problems. Therefore, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application dossier.

IV. Overall Evaluation

It is determined that the submitted data have demonstrated the efficacy and safety of pegaptanib sodium in the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration. It is necessary to confirm the safety of long-term treatment with pegaptanib sodium and identify the occurrence of ocular adverse events, systemic adverse events (thromboembolism, haemorrhage, etc.), and hypersensitivity/anaphylaxis etc. via post-marketing surveillance.

Pegaptanib sodium may be approved if it can be determined that there are no particular problems, taking account of the results of the Expert Discussion.

Review Report (2)

April 7, 2008

Based on the results of the Expert Discussion, the Pharmaceuticals and Medical Devices Agency (PMDA) conducted an additional review of the following points and took necessary actions. The expert advisors attending the Expert Discussion have declared that they did not come under the Section 1 or 2 (1) of "Measures against the problem of conflict of interests involving the outside experts of the PMDA", dated May 8, 2007, regarding the product submitted for registration.

(1) Post-marketing surveillance

Subfoveal CNV secondary to AMD for which pegaptanib sodium is indicated has a poor prognosis and could lead to blindness, pegaptanib sodium has been designated as an orphan drug, and the efficacy and safety of long-term treatment with pegaptanib sodium have been evaluated in foreign clinical studies, but have not adequately been investigated in Japan. Thus, it seems necessary to conduct a long-term post-marketing survey, covering all patients treated with pegaptanib sodium, over a certain period of time in order to fully evaluate the efficacy and safety of pegaptanib sodium and PMDA instructed the applicant to consider it.

The applicant responded as follows:

A survey covering all patients treated with pegaptanib sodium in which each patient is monitored for up to 2 years will be conducted. This survey will investigate local ocular adverse events i.e., eye disorders and increased intraocular pressure etc., and especially investigate in detail the occurrence of eye disorders (endophthalmitis, traumatic cataract, vitreous haemorrhage, retinal detachment, retinal tear) as the priority items. The association of baseline visual acuity, lesion size, lesion subtype, and concomitant PDT with the efficacy and safety of pegaptanib sodium will be investigated. The association of age and the severity of renal impairment with adverse events and the occurrence of systemic adverse events related to anti-VEGF activity will be investigated. In addition, changes in visual acuity on the ETDRS chart will also be surveyed actively at some medical institutions.

PMDA accepted the above, but has determined that the following conditions should be imposed on the approval of pegaptanib sodium.

[Conditions for approval]

Due to the limited number of patients treated in Japanese clinical studies, conduct a post-marketing drug use-results survey, covering all patients treated with the product, until data from a certain number of cases will be collected, in order to obtain the background information of patients treated with the product, collect data on the safety and efficacy of the product as soon as possible, and take necessary measures to ensure proper use of the product.

(2) Update on ongoing long-term studies

(2).1) Japanese long-term study (5.3.5.2.1, A5751015 [[redacted] 20[redacted] to [redacted], 20[redacted] (data cutoff date)])

An open-label, uncontrolled study in patients with subfoveal CNV secondary to AMD who participated in a Japanese phase II study (5.3.5.1.1, A5751010) and wished to continue treatment with pegaptanib sodium was conducted to evaluate the efficacy and safety of long-term treatment with pegaptanib sodium.

Pegaptanib sodium 0.3 mg was to be administered from Week 54 of the phase II study (A5751010) and was to be continued until the approval of pegaptanib sodium or the investigator judged that treatment continuation was unnecessary.

All of the 61 treated patients were included in the efficacy and safety analyses.

The efficacy endpoint, i.e. visual acuity changes from baseline to Week 108 using the ETDRS chart are shown in the following table and the change from baseline to Week 54 was similar to the change from Week 54 to Week 108.

Table. Mean change in visual acuity from baseline to each observation timepoint (in letters)
(Baseline refers to the baseline of the preceding phase II study [A5751010])

Observation timepoint	No. of evaluable patients [a)]	Mean ± SD	95% confidence interval
Week 54	53	–3.2 ± 13.36	[–6.8, 0.5]
Week 72	53	–2.8 ± 15.22	[–7.0, 1.4]
Week 90	53	–4.1 ± 16.27	[–8.6, 0.4]
Week 108	53	–6.9 ± 17.53	[–11.7, –2.1]

Missing values were imputed using LOCF.
a) Eight subjects who participated in the clinical study beyond 14 days after the completion of Study A5751010 were excluded.

Adverse events (adverse events that occurred after the start of the study or adverse events that had been pre-existing from the phase II study [A5751010] and increased in severity, including abnormal laboratory values, were counted) were reported in 90.2% (55 of 61 subjects). One death occurred (angina pectoris, aortic aneurysm, arteriosclerosis obliterans, death) at 80 days after the last dose of pegaptanib sodium, but the details were unknown at the time of an interim analysis and a causal relationship with the study treatment could not be denied. Other serious adverse events occurred in 15 subjects (macular degeneration [3 cases], carotid artery stenosis and myocardial infarction; cataract and colonic polyp; herpes zoster; pneumonia; pyrexia; basal cell carcinoma; gastric cancer; haemorrhoids; traumatic cataract; gastric polyps; thoracic vertebral fracture and femur fracture; large intestine carcinoma [1 case each]) and a causal relationship with the study treatment could not be denied for 1 case of macular degeneration. Adverse events for which a causal relationship with the study treatment could not be denied (including abnormal laboratory values) occurred in 18.0% (11 of 61 subjects) and the main events were retinal haemorrhage (3 subjects) and anterior chamber inflammation (2 subjects) etc.

There were no apparent changes from baseline in blood pressure or pulse rate. Intraocular pressure increased transiently at 30 minutes post-injection, but returned to normal within 1 week post-injection.

Based on the above, the applicant explained that visual acuity changes following continued treatment with pegaptanib sodium from Week 54 to Week 108 were similar to those in the phase II study (A5751010) and also regarding safety, events observed were similar to those reported in the phase II study (A5751010) and the safety of 2-year treatment with pegaptanib sodium has been demonstrated.

(2).2) Foreign long-term studies

(a) Phase II/III studies (5.3.5.1.6, EOP1003 and EOP1004 [Weeks 102-156 data] [up to [redacted] 20[redacted] (up to the end of assessment at Week 156)]

The efficacy and safety of 3-year treatment with pegaptanib sodium (0.3 or 1 mg) in patients with subfoveal CNV secondary to AMD who participated in Studies EOP1003 and EOP1004 were evaluated.

Subjects receiving pegaptanib sodium 0.3 or 1 mg in the second year were to continue with the same dose, and subjects assigned to pegaptanib sodium 3 mg or sham injections in the second year were to be re-randomized to pegaptanib sodium 0.3 or 1 mg at Week 102. Subjects who received pegaptanib sodium 0.3 or 1 mg in the first year and were discontinued from treatment in the second year were to resume treatment in the third year at the same dose as in the first year. Subjects who were assigned to pegaptanib sodium 3 mg or sham injections in the first year and were discontinued from treatment in the second year were to be re-randomized to pegaptanib sodium 0.3 or 1 mg and then resume treatment in the third year.

All of the 428 treated subjects (including 54 subjects treated with 0.3 mg and 58 subjects treated with 1 mg throughout the 3 years [Cohort A]) were included in the efficacy analysis (ITT) and 422 subjects excluding a total of 6 subjects (withdrawal due to subject's request [2 subjects], consent withdrawal [1 subject], discontinuation due to adverse events [1 subject], nonparticipation in the third year of study [1 subject], randomization error [1 subject]) (including 52 subjects treated with 0.3 mg and 57 subjects treated with 1 mg throughout the 3 years) were included in the safety analysis.

Regarding efficacy, changes in visual acuity over time in Cohort A are presented in the following table.

Table. Change in visual acuity over time (Cohort A, LOCF)

Study Number	EOP1003		EOP1004		EOP1003/EOP1004	
	0.3 mg	1 mg	0.3 mg	1 mg	0.3 mg	1 mg
n	34	36	20	22	54	58
Visual acuity: Baseline	57.3 ± 10.2	53.3 ± 14.1	51.6 ± 14.1	53.5 ± 12.5	55.2 ± 12.0	53.4 ± 13.4
Week 54	50.8 ± 13.2	46.6 ± 20.8	45.7 ± 23.2	45.4 ± 17.3	48.9 ± 17.6	46.1 ± 19.4
Week 102	49.9 ± 16.4	47.7 ± 18.8	45.5 ± 17.2	39.9 ± 15.3	48.2 ± 16.7	44.7 ± 17.8
Week 156	44.7 ± 17.6	51.1 ± 18.0	45.2 ± 18.4	41.4 ± 16.4	44.9 ± 17.7	47.4 ± 17.9

mean ± SD

Adverse events (including abnormal laboratory values) occurred in 89% of the pegaptanib sodium 0.3 mg group (185 of 207 subjects) and 89% of the pegaptanib sodium 1 mg group (192 of 215 subjects) (In Cohort A, 83% of the 0.3 mg group [43 of 52 subjects] and 91% of the 1 mg group [52 of 57 subjects] experienced adverse events in the third year). There were 6 deaths (glioblastoma; bradyarrhythmia, carotid artery stenosis, syncope, transient ischaemic attack, and cardiac arrest; spinal compression fracture, fall, clostridium colitis, and hip fracture; abdominal pain upper, congestive cardiac failure aggravated, and

cardio-respiratory arrest; acute myocardial infarction, aortic aneurysm rupture, shock haemorrhagic, abdominal compartment syndrome, acute respiratory failure, renal failure acute, sepsis, hepatic failure, and hypotension; lung cancer metastatic, one case each), but a causal relationship to the study treatment was denied for all cases. Other serious adverse events occurred in 32 subjects in the 0.3 mg group and 28 subjects in the 1 mg group (In Cohort A, 7 subjects in the 0.3 mg group and 9 subjects in the 1 mg group) and a causal relationship to the study treatment could not be denied for 1 case of retinal haemorrhage and vitreous haemorrhage. Adverse events for which a causal relationship to the study treatment could not be denied (including abnormal laboratory values) were reported in 16% of the 0.3 mg group (34 of 207 subjects) and 10% of the 1 mg group (22 of 215 subjects) (In Cohort A, such events occurred in 10% of the 0.3 mg group [5 of 52 subjects] and 9% of the 1 mg group [5 of 57 subjects] in the third year) and the main events are shown in the following table.

Adverse event	All treated subjects		Cohort A	
	0.3 mg (n=207)	1 mg (n=215)	0.3 mg (n=52)	1 mg (n=57)
Total	34 (16)	22 (10)	5 (10)	5 (9)
Cataract	3 (1.4)	2 (0.9)	0	1 (1.8)
Macular degeneration	2 (1.0)	0	1 (1.9)	0
Ocular hypertension	2 (1.0)	0	1 (1.9)	0
Punctate keratitis	1 (0.5)	2 (0.9)	0	0
Retinal haemorrhage	1 (0.5)	2 (0.9)	1 (1.9)	0
Reduced visual acuity	3 (1.4)	2 (0.9)	1 (1.9)	0
Visual disturbance	2 (1.0)	4 (1.9)	0	1 (1.8)
Vitreous floaters	8 (3.9)	4 (1.9)	2 (3.8)	0
Vitreous opacities	7 (3.4)	2 (0.9)	1 (1.9)	1 (1.8)
Increased intraocular pressure	5 (2.4)	3 (1.4)	0	1 (1.8)
Anterior chamber inflammation	2 (1.0)	0	0	0

There were no vital sign or ECG findings suggestive of relationship to pegaptanib sodium.

Based on the above, the applicant explained that the treatment benefit was maintained in AMD patients treated with pegaptanib sodium for 3 years and regarding safety, adverse events were not much different from those observed so far.

(b) Phase II/III studies (5.3.5.1.10, EOP1003 and EOP1004 [Weeks 156-204 data] [up to [redacted] 20[redacted] (up to the end of assessment at Week 204)])

The efficacy and safety of 4-year treatment with pegaptanib sodium (0.3 or 1 mg) in patients with subfoveal CNV secondary to AMD who participated in Studies EOP1003 and EOP1004 were evaluated.

Only subjects receiving the same dose of pegaptanib sodium (0.3 or 1 mg) for 3 years at Week 156 were to continue with the same dose of pegaptanib sodium (0.3 or 1 mg) for an additional 108 weeks (a total of 5 years).

All of the 60 treated subjects (26 subjects in the 0.3 mg group, 34 subjects in the 1 mg group) were included in the efficacy analysis (ITT) and safety analysis. Excluding 4 subjects who were enrolled into the 4th year treatment despite that they did not receive 3-year continuous treatment with pegaptanib

sodium 0.3 or 1 mg, 56 subjects (23 subjects in the 0.3 mg group, 33 subjects in the 1 mg group) were included in Cohort A (subjects who received 4-year continuous treatment with the same dose of pegaptanib sodium).

Regarding efficacy, changes in visual acuity over time in all treated subjects and Cohort A are shown in the following table.

Table. Change in visual acuity over time (LOCF)

Treatment group	Cohort A		All treated subjects	
	0.3-0.3-0.3-0.3 mg	1-1-1-1 mg	0.3 mg	1 mg
Pooled analysis (ITT)	23	33	26	34
Visual acuity: Baseline	57.9 ± 12.9	53.9 ± 12.7	58.3 ± 12.4	54.1 ± 12.6
Week 54	52.0 ± 18.4	46.7 ± 18.1	NA	NA
Week 102	49.5 ± 14.6	45.5 ± 16.4	NA	NA
Week 156	46.6 ± 14.5	47.4 ± 17.8	47.8 ± 14.1	47.8 ± 17.7
Week 204	44.3 ± 16.3	46.1 ± 19.7	45.6 ± 15.8	47.0 ± 20.0

mean ± SD

Adverse events (including abnormal laboratory values) occurred in 69% of the pegaptanib sodium 0.3 mg group (18 of 26 subjects) and 76% of the pegaptanib sodium 1 mg group (26 of 34 subjects). There were 2 deaths (1 patient of pulmonary embolism; 1 patient of injury and femur fracture), but a causal relationship to the study treatment was denied for all cases. Other serious adverse events were reported in 2 subjects in the 0.3 mg group and 6 subjects in the 1 mg group, but a causal relationship to the study treatment was denied for all cases. Adverse events for which a causal relationship to the study treatment could not be denied (including abnormal laboratory values) were observed in 12% of the 0.3 mg group (3 of 26 subjects) and 3% of the 1 mg group (1 of 34 subjects), which include cataract in 1 subject (0.3 mg group), vitreous floaters in 2 subjects (both in the 0.3 mg group), and increased intraocular pressure in 1 subject (1 mg group).

There were no vital sign or ECG findings suggestive of relationship to pegaptanib sodium.

Based on the above, the applicant explained that the treatment benefit was maintained in AMD patients treated with pegaptanib sodium for 4 years and regarding safety, adverse events were not much different from those observed so far.

Concerning the above, PMDA considers that there are no major problems with the safety and efficacy of long-term treatment with pegaptanib sodium at present, but this needs to be further confirmed via post-marketing surveillance.

(3) A caution statement about continued injections with pegaptanib sodium

PMDA asked the applicant to explain the subsequent clinical course of patients classified as responders (loss of < 15 letters of visual acuity) at Week 12, in terms of determining whether to continue injections of pegaptanib sodium.

The applicant explained as follows:
In a Japanese phase II study (5.3.5.1.1, A5751010), 85% (35 of 41 patients) of the patients in the pegaptanib sodium 0.3 mg group who had been responders at Week 12 were still responders at Week 54. Also in foreign phase II/III studies (5.3.5.1.2, EOP1003 and 5.3.5.1.4, EOP1004), 76% (195 of 256 patients) of the patients in the pegaptanib sodium 0.3 mg group and 64% (151 of 237 patients) of the patients in the sham group who had been responders at Week 12 were still responders at Week 54. Pegaptanib sodium is considered to preserve visual acuity.

PMDA considers as follows:
Although many of the responders at Week 12 were still responders at Week 54, some responders were later converted to non-responders. Conversely, many of the non-responders (loss of ≥ 15 letters of visual acuity) at Week 12 were still non-responders at Week 54, but some non-responders were converted to responders at Week 54 [see Review Report (1) " 4.(ii).B.(3).2) Justification for the dosing interval and the criteria for stopping treatment"]. Taking account of these findings, as mentioned in the Review Report (1), although the clinical response at Week 12 may be a clue for determining the efficacy of pegaptanib sodium, considering the seriousness of the intended disease, it is not appropriate at present to determine whether to continue injections of pegaptanib sodium based only on the outcome at Week 12. Then, during treatment with pegaptanib sodium, visual acuity etc. should be regularly assessed at Week 12 and subsequent appropriate timings and if no efficacy is observed, action should be taken, such as treatment temination, so as to avoid aimless administration.

PMDA instructed the applicant to include a relevant caution statement in the "Precautions for Dosage and Administration" section of the package insert and the proposed package insert was amended accordingly.

(4) Binding property of PEGylated pegaptanib sodium to VEGF
With respect to the effects of PEGylation on the anti-VEGF activity of pegaptanib sodium, PMDA asked the applicant to explain the possibility that PEGylation may alter the affinity for different VEGF isoforms and other molecules.

The applicant explained as follows:
It has been reported that the *in vitro* affinity of pegaptanib sodium to $VEGF_{165}$ is about one-fourth of that of the non-PEGylated aptamer (Ng EWM et al. *Nat Rev Drug Discov.* 2006;5: 123-132) and a steric hindrance between the PEG moiety and $VEGF_{165}$ seems to contribute to a decrease in the affinity. It is known that PEGylation of a protein prolongs its half-life *in vivo*, reduces its immunogenicity, and improves its resistance to proteases while decreases its *in vitro* affinity to the target molecule (Gaberc-Porekar V et al. *Curr Opin Drug Discov Devel.* 2008;11: 242-250). Since PEGylation of pegaptanib sodium also has improved its *in vivo* stability and decreased its *in vitro* affinity to VEGF, it is considered that the PEG moiety of pegaptanib sodium is flexible and does not form a rigid structure. Thus, it seems difficult for the PEG moiety to form a stable complex with other molecules. On the other hand,

the aptamer portion of pegaptanib sodium has a relatively rigid structure and its structure is considered critical for binding to VEGF (Lee J-H et al. *Proc Natl Acad Sci USA.* 2005;102: 18902-18907) and PEG is introduced via a linker containing a lysine residue at the 5'-end of the aptamer only. Therefore, PEGylation should cause little changes in the conformation of the aptamer portion and there should be little possibility that PEGylation affects the specificity of the aptamer portion to VEGF and alters its affinity to other molecules.

PMDA considers as follows:
Since an investigation of the affinity of the non-PEGylated aptamer to $VEGF_{165}$ has demonstrated that the non-PEGylated aptamer binds to human $VEGF_{165}$ (4.2.1.1.1, 4.2.1.1.2) and pegaptanib sodium has also been shown to inhibit $VEGF_{165}$ binding to its receptors (4.2.1.1.3, 4.2.1.1.4), there should be no major problems with the pharmacological profile of pegaptanib sodium.

As a result of the above review, PMDA has concluded that pegaptanib sodium may be approved for the indication and dosage and administration as described below, with the following condition. The re-examination period is 10 years, the drug substance and the drug product are both classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Indications]
Subfoveal choroidal neovascularization secondary to age-related macular degeneration

[Dosage and administration]
Pegaptanib sodium 0.3 mg (as the free acid form of the oligonucleotide) should be administered once every 6 weeks by intravitreous injection into the affected eye.

[Condition for approval]
Due to the limited number of patients treated in Japanese clinical studies, conduct a post-marketing drug use-results survey, covering all patients treated with the product, until data from a certain number of cases will be collected, in order to obtain the background information of patients treated with the product, collect data on the safety and efficacy of the product as soon as possible, and take necessary measures to ensure proper use of the product.