A PHASE IV, OPEN LABEL, MULTI-CENTER STUDY TO ASSESS THE EFFECT OF INTRAVITREAL INJECTIONS OF MACUGEN® (PEGAPTANIB SODIUM INJECTION) ADMINISTERED EVERY 6 WEEKS FOR 48 WEEKS ON THE CORNEAL ENDOTHELIUM

PROTOCOL NUMBER: EOP 1024 AMENDMENT 3

Dated: September 26, 2018

SPONSOR:

Valeant Pharmaceuticals North America LLC

as engaged by and acting as a service provider to

Valeant International (Barbados) SRL

Address:

400 Somerset Corporate Blvd

Bridgewater, NJ 08807

FOR MEDICAL EMERGENCIES, CALL [redacted]

Confidentiality Statement

The information in this document is confidential and will not be disclosed to others without written authorization from Valeant Pharmaceuticals North America LLC except to the extent necessary to obtain informed consent from persons receiving the investigational procedure or their legal guardians, or for discussions with local regulatory authorities, institutional review boards (IRB), or persons participating in the conduct of the study.

Protocol Amendment No. 3

Amendment rationale and changes to the protocol:

- Change of Medical Monitor
- Change medical emergency phone numbers
- Update revision to 100 evaluable subjects at recommendation of FDA
- Subsections 4.3.1.1-4.3.1.4 have been added to separate clinical trial descriptions for Macugen treatment of wet AMD, diabetic macular edema, central retinal vein occlusion, and branched retinal vein occlusion, respectively
- Update Introduction and Sections, 4.1, 4.3.1, and 4.3.1.1-4.3.1.4 to recognize and describe additional clinical trials and indications that have been completed with Macugen
- Update reference list and links to references for clarification in the Introduction
- Reword Section 12 for clarity

Protocol Amendment No. 2

Amendment rationale and changes to the protocol:

- Modification of study schedule / window period for visits extended to +/- 14 days
- Valeant supplying study drug

Protocol Amendment No. 1

Amendment rationale and changes to the protocol

The purpose of this amendment is to document the change in sponsorship of the protocol; the Sponsor has changed from Eyetech, Inc. to:

Valeant Pharmaceuticals North America LLC

as engaged by and acting as service provider to

Valeant International (Barbados) SRL.

Other changes to the protocol include:

Modifications to Exclusion criteria:

- Unilateral ocular blunt trauma within one year of enrollment and no greater than 5% difference in central endothelial cell density between the 2 eyes
- intraocular surgery (cataract surgery and surgery for glaucoma without tube shunt or mini-shunt) within one year of enrollment,
- Anterior segment laser surgery (laser trabeculoplasty) performed within one year of enrollment
- Glaucoma tube-shunt surgery
- Known serious allergies to the components of pegaptanib sodium formulation
- Significant media opacities, including cataract, which might interfere with visual acuity, or assessment of toxicity. Subjects should not be entered if there is likelihood that they will require cataract or glaucoma surgery in either eye during the study treatment and follow-up period.
- Clarification for corneal specular microscopy results sent to CIARC within 3 days
- Protocol Deviation/Waiver Request instruction

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1.0 GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AMD	Age-Related Macular Degeneration
ANCOVA	Analysis of Covariance
CIARC	Cornea Image Analysis Reading Center
CMH	Cochran-Mantel-Haenszel
CNV	Choroidal neovascularization
EC	Ethics Committee
ECG	Electrocardiogram
EW	Early Withdrawal
FA	Fluorescein Angiography
FDA	Food & Drug Administration
GLP	Good Laboratory Practices
GCP	Good Clinical Practices
IB	Investigator Brochure
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intent To Treat
LOCF	Last Observation Carried Forward
NEI	National Eye Institute
NLP	No Light Perception
PDT	Photodynamic Therapy
PEG	PolyEthylene Glycol
SAE	Serious Adverse Event
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

2.0 SUMMARY OF PROTOCOL EOP 1024

Name of Sponsor / Company:	Valeant Pharmaceuticals North America LLC as engaged by and acting as a service provider to Valeant International (Barbados) SRL
Name of Finished Product:	Macugen® (pegaptanib sodium injection)
Protocol Title:	A Phase IV, open label, multi-center study to assess the effect of intravitreal injections of Macugen® (pegaptanib sodium injection) administered every 6 weeks for 48 weeks on the corneal endothelium.
Protocol Number:	EOP 1024
Investigators:	Multi-center
Study Center(s):	Multi-center (10 sites)
Study Period:	48-week treatment period with 6 week follow-up period
Study Design and Rationale:	This will be a Phase IV, open label, multi-center study. Subjects will receive intravitreal injections of Macugen® (pegaptanib sodium injection) every 6 weeks for 48 weeks. Additional therapy may be employed at the Investigator's discretion for circumstances judged to be clinical deterioration. The Investigator will decide which treatment to provide as an additional therapy. Macugen® (pegaptanib sodium injection) injections should remain on the 6-week schedule defined by the protocol even if an additional therapy is given. Due to the lack of information generated in the pivotal phase III trials assessing potential effects of intravitreal injections of Macugen® on the corneal endothelium, the FDA requested clinical information from a 1-year (minimum) clinical study to support that there are no adverse effects on the corneal endothelium following intravitreal injections of Macugen®.
Number of Subjects:	Approximately 125 subjects will be recruited from 10 sites in order to complete 1-year data on at least 100 subjects. Recruitment will close once this objective is met.
Study Objective	The objective of this study will be to assess the effect of intravitreal injections of Macugen® (pegaptanib sodium injection) administered every 6 weeks for 48 weeks on the corneal endothelium.
Endpoint	Corneal Endothelium assessment by specular microscopy: Mean cell density loss from baseline over time and frequency distribution.

Inclusion Criteria	• Subjects of either gender aged ≥ 50 years diagnosed with Subfoveal Neovascular Age-Related Macular Degeneration (AMD), Diabetic Macular Edema (DME) or Retinal Vein Occlusion (RVO). • Best corrected visual acuity in the study eye between 85 and 20 ETDRS letters or between 20/20 and 20/400 using a Snellen chart. • Ability to return for all study visits. • Women must be using **two forms** of effective contraception, be post-menopausal for at least 12 months prior to study entry, or surgically sterile; **if of child-bearing potential**, a urine pregnancy test must be performed within 7 days prior to the first injection with a negative result. If the test is positive, a serum test must be done to confirm. The **two forms** of effective contraception must be implemented during the study and for at least 60 days following the last dose of test medication. • Provide written informed consent.

Exclusion Criteria	• Unilateral ocular blunt trauma within one year of enrollment and no greater than 5% difference in central endothelial cell density between the 2 eyes.
	• Intraocular surgery (cataract surgery and surgery for glaucoma without tube shunt or mini-shunt) within one year of enrollment
	• Anterior segment laser surgery (laser traberculoplasty) performed within one year of enrollment
	• Glaucoma tube-shunt surgery
	• Previous history of corneal transplant in the study or non-study eye.
	• Presence of vitreous macular traction
	• Previous therapeutic radiation in the region of the study eye.
	• Any treatment with an investigational agent in the past 30 days for any condition.
	• Known serious allergies to the components of pegaptanib sodium (pegaptanib sodium injection) formulation
	• Any of the following underlying diseases including:
	  ○ History or evidence of severe cardiac disease (e.g., NYHA Functional Class III or IV - see Appendix 2, clinical or medical history of unstable angina, acute coronary syndrome, myocardial infarction or revascularization within 6 months, ventricular tachyarrythmias requiring ongoing treatment.
	  ○ History or evidence of clinically significant peripheral vascular disease, such as intermittent claudication or prior amputation.
	  ○ History or evidence of clinically significant impaired renal or hepatic function
	  ○ Stroke (within 12 months of study entry).
	  ○ Any major surgical procedure within one month of study entry.
	• Significant media opacities, including cataract, which might interfere with visual acuity, or assessment of toxicity. Subjects should not be entered if there is likelihood that they will require cataract or glaucoma surgery in either eye during the study treatment and follow-up period.

Statistics	Descriptive statistics will be provided to summarize baseline and on-study measures, including demographic information, treatment administration, study outcomes and protocol deviations.
Safety	All adverse events spontaneously reported, elicited or observed by the Investigators, will be recorded.
Test Product, Dose, Formulation and Mode of Administration:	**Test Product**: Macugen® (pegaptanib sodium injection) **Administration**: intravitreous injection **Dose**: All subjects will receive intravitreous injections of 0.3 mg/eye pegaptanib sodium every 6 weeks for 48 weeks. Other available therapy of the Investigator's choice may be employed at the Investigator's discretion for circumstances judged to be clinical deterioration, such as but not restricted to: $\geq$ 2 line vision loss; retinal thickness at center point $\geq$ 300µm; an increase of retinal thickness at center point $\geq$ 100µm from baseline visit.
Corneal Specular Microscopy	Specular microscopy assessments of the corneal endothelium will be completed and compared individually for central cell density and cell characteristics changes (polymegathism and polymorphism) occurring from baseline. All 10 targeted clinical sites will perform corneal specular microscopy assessments on a total of approximately 125 enrolled subjects. Both contact and non-contact microscopes are permitted, but consistency throughout the entire study is required (same method must be used for each subject throughout the study). Corneal specular microscopy examinations must be performed at Baseline and at Weeks 24 and 54 or early withdrawal. All examinations that are collected for the study must be sent to Central Image Analysis Reading Center (CIARC, Cleveland, OH) within 3 days of collection. For complete procedures for specular microscopy of the corneal endothelium and data transfer, please refer to the Corneal Specular Microscopy Instruction Manual.

3.0 STUDY FLOW CHART

VISIT/WEEK	Baseline[1] Day 0	Week 6	Week 12	Week 18	Week 24	Week 30	Week 36	Week 42	Week 48	Week 54	Early Withdrawal
Informed Consent	X										
Medical & Ophthalmic History	X										
Urine Pregnancy Test[2]	X										
Macugen® (Pegaptanib Sodium Injection)	X	X	X	X	X	X	X	X	X		
Corneal Specular Microscopy[4]	X				X					X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[3]	X	X	X	X	X	X	X	X	X	X	X

All visits for injections must occur within +/- 14 days of the schedule

[1] Baseline assessments should be performed within 7 days prior to study drug injection (Day 0). Baseline assessments can be collected over 2 days if necessary. If all screening is completed during the baseline visit, DAY 0 assessments may be done on the same day.
[2] Only Women who are not post-menopausal for at least 12 months or surgically sterile. If urine pregnancy test comes back positive, a serum test must be done.
[3] Serious adverse events are to be recorded from time of signing of informed consent. All adverse events are to be recorded after first injection.
[4] Corneal Specular Microscopy will be completed on both eyes. All results must be sent to CIARC within 3 days of the procedure completion date.

4.0 INTRODUCTION

4.1 Background

The objective of this study will be to assess the effects of intravitreal injections of Macugen® (pegaptanib sodium injection) administered every 6 weeks for 48 weeks on the corneal endothelium. Macugen® (pegaptanib sodium injection) is the first anti-VEGF inhibitor approved by the FDA for the treatment of wet AMD. Extensive research has been conducted on Macugen® (pegaptanib sodium injection) and it has been shown to be effective at slowing vision loss in patients with such condition. Macugen® (pegaptanib sodium injection) has been studied in phase 2 and phase 3 trials in several other retinal ophthalmic diseases in which VEGF plays a major role, including Age-related macular degeneration (AMD) Diabetic Macular Edema (DME), Branched Retinal Vein Occlusion (BRVO) and Central Retinal Vein Occlusion (CRVO).

Age-related macular degeneration (AMD) is a disease characterized by progressive degenerative abnormalities in the macula of the eye, a small area in the central portion of the retina. Age-related macular degeneration is classified into one of two general subgroups; the non-neovascular (non-exudative or wet) form of the disease and the neovascular (exudative) form of the disease. The non-neovascular form of AMD is more prevalent, accounting for approximately 90% of all AMD cases, and is often characterized by a slow degeneration of the macula resulting in atrophy of the central retina with gradual vision loss over a period of years [1, 2]. By contrast, neovascular AMD, although less prevalent, more commonly causes sudden, often substantial, loss of central vision and is responsible for most cases of severe loss of visual acuity in this disease [3, **4**]. The neovascular form of the disease is responsible for the majority of cases of severe vision loss. This type of AMD results when abnormal blood vessels proliferate under and/or within the retina. These blood vessels leak blood and fluid into the retina, which results in vision loss. The natural history of AMD is that of scarring with progressive destruction of the central retina.

Diabetic Macular Edema (DME) can occur with either non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR) and is the most common cause of diabetic-related visual acuity impairment. Laser photocoagulation or other surgical modalities can help reduce the risk of moderate (3 or more lines) or severe (<20/800) distance visual acuity loss. Panretinal photocoagulation (or scatter laser therapy) is the standard treatment for patients with high risk PDR or patients approaching high risk PDR. Clinically, DME is defined as retinal thickness within 2 disc diameters of the center of the macula, with or without lipid exudates, and with or without cystoids features. Clinically significant macular edema (CSME) is defined as having one or more of the following features: retinal thickness within 500 µm from the center of the macula; hard exudates within 500 µm of the center of the macula with adjacent retinal thickness; retinal thickness of at least 1 disc area of which at least 1 part is within 1 disc diameter of the center of the macula. Hence, patients with CSME have maculopathy that threatens or affects the center of the macula.

Retinal Vein Occlusion (RVO), either BRVO or CRVO, is the second leading cause of blindness (among vascular disorders) after diabetic retinopathy [5]. The estimated annual incidence of RVO is 160,000 cases in the United States and RVO prevalence is much higher, especially in the population over 65 years of age [5, 6]. Blindness from RVO can develop over a long period or occur suddenly. RVO occurs when a blood clot or other substances, such as fat or plaque, obstruct the normal blood flow in a retinal vein. Consequently, during the occlusive event different pathophysiologic mechanisms including over expression of VEGF lead to different degrees of macular edema and

ischemia. Visual loss may result from chronic macular edema, macular ischemia or ocular neovascularization

4.2 Macugen® (pegaptanib sodium injection) (Formerly EYE001 and NX1838)

Macugen® (pegaptanib sodium injection) is composed of 28 nucleotide bases, containing 2'F-substituted pyrimidines and 2'O-methyl-substituted purines, with the exception of two 2'OH adenosines. One molecule of ~40,000 dalton molecular weight polyethylene glycol (40kD PEG) is attached to the 5' end of the oligonucleotide. The 3' end is capped with an inverted thymidine. Pegylated pegaptanib has a molecular weight of approximately 50,000 daltons and is roughly one-third the size of an IgG molecule. Pegaptanib selectively binds $VEGF_{165}$, which is the most abundant isoform of VEGF and is the isoform associated with pathological ocular neovascularization, with high specificity and affinity (K_d approximately 80 pM).

4.2.1 Pre-Clinical Efficacy

The preclinical data demonstrating the anti-angiogenic properties of pegaptanib are described in detail in the Investigator Brochure (IB).

4.2.2 Intravitreous Pharmacokinetics of Pegaptanib

Single and repeat dose pharmacokinetic studies in both the rabbit and monkey are described in full in the Investigator Brochure (IB) for pegaptanib. While there are some differences in the pharmacokinetic parameters of pegaptanib among species, vitreous concentrations of pegaptanib after intravitreous injections are consistently and substantially higher than plasma concentrations by at least several hundred-fold. Thus, after intravitreous injections, there is a low systemic exposure to pegaptanib compared to that seen in the vitreous. Of note, vitreous concentrations appear to remain sufficiently high to allow a dosing interval of 6 weeks.

4.2.3 Toxicology

Studies to evaluate the potential toxicity of pegaptanib include evaluations of genotoxicity, immunogenicity, acute toxicity, and sub-chronic toxicity. Studies were conducted in accordance with GLP and ICH guidelines.

4.3 Clinical Data

4.3.1 Clinical Summary of Phase 1 & 2 Safety, and Phase 2/3 Pivotal Studies

In a dose-finding Phase 1 study (NX109-01) described in the IB, pegaptanib sodium was given to 15 subjects as single doses ranging from 0.25 mg/eye (6.9 mM) to 3 mg/eye (110 mM) [7]. Due to increasing viscosity with increasing dose, 3 mg is the maximal dose that can be given in an acceptable volume (0.1ml) for intravitreous injection with the current formulation. In addition, three repeat doses (4 weeks apart) of 3 mg/eye were given to a total of 21 subjects in two phase 2 studies, EOP1000B and EOP1001 [7].There were no local dose-limiting toxicities observed and no systemic toxicity attributed to pegaptanib sodium in any of the three studies. Approximately 30% of the subjects exhibited a three, or more, line improvement 3 months after starting treatment.

4.3.1.1 Macugen for Exudative (Wet) Age-Related Macular Degeneration (AMD)

A phase 2 dose-ranging study (EOP1009), including a sham treatment cohort, was conducted with 137 subjects with AMD. Pegaptanib intraviteous injections of 0.3 mg

or 1.0 mg were completed with subjects for a 12-week period (3 injections) and a subsequent 24-week periods (5 injections). There was no evidence of specific systemic safety concerns, and one SAE (endophthalmitis) considered related to the injection procedure. The most commonly reported adverse events in the study eye were eye pain and punctate keratitis. Small increases in mean intraocular pressure (IOP) were transient after injections and returned to baseline levels within 1 week of injection. There were no findings in relation to laboratory test results or ECG results suggestive of a relationship to pegaptanib sodium treatment.

Two Phase 2/3 randomized, double-masked, controlled, multi-center, comparative studies (EOP1003 and EOP1004) were done to establish the safety and efficacy of intravitreous injections of pegaptanib sodium (0.3, 1 or 3 mg) as compared to sham injection given every 6 weeks for 54 weeks, in patients with exudative (wet) age-related macular degeneration [8, 9].

A total of 1,200 subjects with wet AMD were randomized for enrollment in studies EOP1003 and EOP1004 and a total of 1,190 of these subjects provided safety data. Data from the first year of these studies demonstrates that pegaptanib sodium was well tolerated. More than 10,000 intravitreous or sham injections have been administered with 25% of subjects receiving a sham injection. A total of 7,545 intravitreous injections of pegaptanib sodium (0.3, 1 or 3 mg) have been administered during the first year of these two studies. The mean number of injections per subject during the studies ranged from 8.4 to 8.6 of a possible 9 total injections. The median age of subjects participating in EOP1003 and EOP1004 was 77 years.

In the combined analysis, all pegaptanib sodium doses tested demonstrated statistically significant efficacy compared with control for the clinically relevant primary efficacy endpoint of the proportion of subjects losing less than 15 letters of VA up to 54 weeks. Pegaptanib sodium activity was observed at the 6-week post-injection visit and was sustained throughout the year. There was no evidence to suggest that the overall effect was derived from any one subject subgroup (e.g., baseline visual acuity, lesion subtype, lesion size, or prior treatment with PDT). Mean visual acuity loss at 1 year was reduced in approximately 50% compared to usual care. In the second year, subjects were re-randomized to either continue or discontinue masked therapy for 48 more weeks. The data revealed that the treatment benefit continued throughout the second year of pegaptanib sodium therapy as compared to usual care controls. During the second year, subjects receiving continued pegaptanib (pegaptanib sodium injection) 0.3mg were less likely to experience a 15-letter loss compared with subjects discontinuing treatment after 1 year. Fifty nine percent (59%) of the subjects receiving pegaptanib (pegaptanib sodium injection) 0.3mg for two years lost less than 15 letters of VA at week 102 compared to 45% of the subjects who continued in the usual care group for two years

Overall, adverse events (AE) in the first year were reported in similar percentages of pegaptanib sodium and sham treated subjects (96% and 95% respectively). The most frequent adverse events were ocular in nature and mild to moderate in severity. The majority of ocular events were attributed by Investigators of the injection procedure, not to pegaptanib sodium. Overall, 92% of pegaptanib sodium and 87% of sham treated subjects experienced one or more ocular events.

Ocular adverse events (i.e., eye pain, vitreous floaters, punctate keratitis, cataract, vitreous opacities, anterior chamber inflammation, visual disturbance and corneal edema) were reported in the study eye in 10% or more of pegaptanib sodium treated subjects. This is comparable with ocular adverse events reported for sham treated subjects. When these most frequent ocular events were analyzed by study and fellow

eye, it was noted that these events were reported in a higher proportion of subjects in the sham study eye than in the fellow eye for all treatment arms. This suggests that some of these events were related to the pre-injection preparation procedure (i.e., eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine drops or flush, and subconjunctival injection of anesthetic), rather than the intravitreous injection alone.

As would be anticipated with intravitreous injections, transient increases in intraocular pressure were noted immediately following intravitreous injection. However, in most of the subjects (90%), IOP values 30 minutes post-injection were less than 35 mmHg. Further, mean values for IOP returned to baseline or near baseline levels within one week of injection. There was no evidence of a persistent increase in IOP after one year of treatment.

Most serious non-ocular adverse events were those that would be expected in this very elderly subject population. A relatively small percentage of subjects (2%) in both pegaptanib sodium and sham treatment groups discontinued treatment because of adverse events in the first year. The percentages of subjects who died during the course of treatment were the same (2%) in pegaptanib sodium and sham treated subjects. There were few injection-related serious adverse events (SAE). These included endophthalmitis, occurring in 12 pegaptanib sodium subjects (0.16% per injection) in the first year. Nine of these subjects continued in the study and only one developed severe visual acuity loss ($\geq$ 6 line loss, ETDRS) at 54 weeks. Iatrogenic traumatic cataract occurred in 5 pegaptanib sodium subjects (0.07% per injection), and retinal detachment occurred in 6 pegaptanib sodium subjects (0.08% per injection). Four of the retinal detachments were rhegmatogenous; two were exudative and thought to be related to underlying AMD.

No new systemic or ocular safety concerns were identified in the second or third year of treatment, third year subjects agreeing to participate in an extension cohort. There were 4 cases of endophthalmitis (0.1% per injection), one case of traumatic cataract (0.02% per injection), and 7 cases of retinal detachment (0.17% per injection; 6 rhegmatogenous and 1 exudative in nature) by the end of the third year.

A three year phase 2 dose-ranging study (EOP1006) of Macugen (pegaptanib sodium injection) given as 1 mg/eye or 3 mg/eye intravitreal injections given every 6 weeks for 54 weeks to patients with wet AMD was conducted at 24 clinical sites in the US. These doses were chosen as the lowest efficacious doses from studies EOP1003 and EOP1004. Safety was assessed by adverse event reporting, ophthalmic examination, tonometry, clinical laboratory tests, electrocardiograms (ECG), vital signs, and $\geq$ 20-letter loss of visual acuity (VA) between 2 consecutive visits. Safety endpoints included all adverse events and serious adverse events, all laboratory data, intraocular pressure (IOP) measurements, vital signs, ECGs, and vision loss of 20 letters or more between injections.

Efficacy was not planned to be assessed in the first year of the study, but VA and fluorescein angiography assessments were performed and were reported as exploratory data. VA endpoints were mean visual acuity over time and change in visual acuity prior to every injection from baseline to 156 weeks. Pharmacodynamics endpoints were change in total lesion size in disc areas from baseline to 156 weeks, change in CNV size in disc areas from baseline to 156 weeks, and change in CNV leak size in disc areas from baseline to 156 weeks.

Studies A5751010 and A5751015 were multicenter studies conducted in Japan for patients with AMD. A total of 95 subjects were enrolled in this study and received intravitreal injections of pegaptanib sodium 0.3 mg or 1 mg/eye once every 6 weeks for

54 weeks. Protocol A5751015 was a multicenter, open label, extension study from protocol A5751010. A total of 61 subjects were continuously received intravitreal injections of pegaptanib sodium 0.3 mg/eye once every 6 weeks for a maximum of 144 weeks. The most common treatment-related adverse events were anterior chamber inflammation (0.3 mg 4.3%, 1 mg 6.3%), corneal oedema (0.3 mg 6.4%, 1 mg 4.2%) with protocol A5751010, and retinal haemorrhage (4.9%), anterior chamber inflammation (3.3%) with protocol A5751015. There were no consistent trends considered to be treatment-related changes in laboratory values, and IOP increases were transient.

Study EOP 1023[10] , was designed primarily to explore the safety and efficacy of intravitreous injections of Macugen® (pegaptanib sodium injection) when given every 6 weeks for 48 weeks in subjects with exudative maculopathy secondary to neovascular AMD who, after previous treatment regimen, have improved based upon clinical and anatomical (OCT) findings as determined by the Investigator. A total of 568 subjects were included in the study. The mean visual acuity over time using last observation carried forward (LOCF) data showed a 3.7-letter loss from baseline to week 54. After 54 weeks of maintenance therapy with Macugen® (pegaptanib sodium injection), 52% of subjects did not receive any additional treatment other than Macugen®(pegaptanib sodium injection). Of those who did receive additional treatment, 46% required only one additional treatment. Safety profile is consistent with phase 2/3 pivotal studies. The most frequently reported treatment emergent adverse events by system organ class are eye disorders (58%), infections and infestations (28%), gastrointestinal disorders (13%), investigations (13%), musculoskeletal and connective tissue disorders (12%), and nervous system disorders (11%). The most frequently reported treatment emergent adverse events (high-level term) were punctate keratitis (13%), eye pain (11%), vitreous floaters (11%), macular degeneration (9%), intraocular pressure increased (9%), and hypertension (8%).

4.3.1.2 Macugen for Treatment of Diabetic Macular Edema (DME)

EOP1002 was an open label study of intravitreal injections of 3 mg pegaptanib sodium/eye every 6 weeks for up to 36 weeks in ten (10) patients with diabetic macular edema (DME). No dose limiting toxicities were reported and there were no premature withdrawals from the EOP1002 study due to treatment-related AEs. A total of 69 AEs were reported, 29 of which were considered treatment related. Treatment-related AEs were mostly (28/29 reports) due to the injection procedure. There were 5 SAEs experienced by two subjects, with one subject dying 26 days after the last injection of study treatment due to multisystem organ failure and pneumonia. None of the SAEs was considered treatment-related.

A phase 2 dose-ranging study, EOP1005 was conducted to evaluate safety and efficacy of Macugen® (pegaptanib sodium injection) in the treatment of diabetic macular edema (DME) [11]. This was a randomized, double-masked, multicenter, dose-ranging, controlled trial. Intravitreous pegaptanib sodium (0.3 mg, 1 mg, 3 mg) or sham injections were given at study entry, week 6, and week 12 with additional injections and/or focal photocoagulation as needed for another 18 weeks. Final assessments were conducted at week 36. A total of 172 subjects were enrolled. Median VA was better at week 36 with pegaptanib sodium 0.3 mg (20/50), as compared with sham (20/63) ($P = 0.04$). A larger proportion of those receiving 0.3 mg gained VAs of $\geq$10 letters (approximately 2 lines) (34% vs. 10%, $P = 0.003$) and $\geq$15 letters (18% vs. 7%, $P = 0.12$). The results of this exploratory Phase 2 study did not identify any safety concerns for the treatment of patients with DME. Pegaptanib sodium was generally well tolerated. The safety profile in this study appears similar to that established in the

age-related macular degeneration (AMD) indication, with additional findings consistent with what would be anticipated in a diabetic population.

A subsequent phase 2/3 study [EOP1013] was conducted to confirm the safety and compare the efficacy of intravitreal Macugen® (pegaptanib sodium injection) 0.3 mg versus sham injections in subjects with DME [12]. This was a 2 year study, with 260 (pegaptanib, n = 133; sham, n = 127) and 207 (pegaptanib, n = 107; sham, n = 100) subjects included in years 1 and 2 intent-to-treat analyses, respectively. Change in mean visual acuity from baseline for pegaptanib sodium was superior to sham injection ($P < 0.05$) at weeks 6, 24, 30, 36, 42, 54, 78, 84, 90, 96, and 102. Additionally pegaptanib-treated subjects gained 6.1 letters on average at week 102 compared to 1.3 letters for sham injection. Pegaptanib was well tolerated, with frequencies of adverse events, treatment-related adverse events, and serious adverse events comparable in both treatment groups.

The analysis of VA and fluorescein angiograms in the EOP1006 study showed a pettern of greater vision loss during the first year of the study followed by a degree of stabilization. Macugen® was generally well tolerated, with AEs predominantly ocular in nature, mild, and predictable. The most frequently o9ccurring ophthalmic adverse events during Yeats 2 and 3 were punctate keratitis, vitreous floaters, and eye pain. Four subjects experienced ophthalmic SAEs during Years 2 and 3, including 3 reports of endophthalmiitis (related to the injection procedure). No generalized systemic safety concerns were observed, as most events other than eye disorders were infrequent and of the types often seen in an elderly population.

4.3.1.3 Macugen for Treatment of Central Retinal Vein Occlusion (CRVO)

The phase 2 study, EOP 1011 assessed the safety and efficacy of intravitreous pegaptanib sodium for the treatment of macular edema following central retinal vein occlusion (CRVO). This was a dose-ranging, double-masked, multicenter trial including subjects with CRVO for 6 month or less duration randomly assigned (1:1:1) to receive pegaptanib sodium or sham injections every 6 weeks for 24 weeks (0.3 mg and 1 mg, n=33; sham, n=32). In the primary analysis at week 30, 12 of 33 (36%) subjects treated with 0.3 mg of pegaptanib sodium and 13 of 33 (39%) treated with 1 mg of pegaptanib sodium gained 15 or more letters from baseline vs. 9 of 32 (28%) sham treated subjects (P=.48 for 0.3 mg and P=.35 for 1 mg of pegaptanib sodium vs. sham). In secondary analyses, subjects treated with pegaptanib sodium were less likely to lose 15 or more letters (9% and 6%; 0.3-mg and 1-mg pegaptanib sodium groups, respectively) compared with sham-treated eyes (31%; P=.03 for 0.3 mg and P=.01 for 1 mg of pegaptanib sodium vs. sham). Pegaptanib sodium was generally well tolerated. AEs were predominantly ocular in nature, mild and predictable. No new safety concerns were detected [13].

4.3.1.4 Macugen for Treatment of Branched Retinal Vein Occlusion (BRVO)

Twenty subjects from three clinical practices in the US with BRVO of 1-6 months duration and central foveal thickness of 250 μm or more were included in this study. Subjects were randomized 3:1 to intravitreous injections of Macugen (pegaptanib sodium) 0.3 or 1.0 mg at baseline and at weeks 6 and 12 with subsequent injections at 6-week intervals at investigator discretion until week 48. Fifteen (15) subjects received 0.3 mg Macugen and Five (5) subjects received 1.0 mg Macugen. The majority of subjects completed the 54-week follow-up visit, and results were similar for both Macugen doses. VA response was rapid after the first dose, with mean BCVA improvement of 11 ± 7 letters at 1 week from baseline. There was one retinal detachment and no cases of endophthalmitis [14].

4.4 Corneal Endothelium and Clinical Specular Microscopy

A specular microscope will be used to assess adverse effects of the corneal endothelium. Results will be compared individually for central cell density and cell characteristics changes (polymegathism and polymorphism) occurring from baseline.

The corneal endothelium is the posterior layer of the cornea consisting of a single layer of cells, about 5 µm thick, bound together and predominantly hexagonal in shape. The posterior border is in direct contact with the aqueous humour while the anterior border is in contact with Descemet's membrane. The endothelium is the structure responsible for the relative dehydration of the corneal stroma. The endothelium receives most of its energy from the oxidative breakdown of carbohydrates via the Krebs cycle. In the normal adult eye the cell density varies from around 3000 cells/mm^2 in the centre of the cornea to about 2000 cells/mm^2 in the periphery. With age, disease or trauma the density of cells decreases but with disease or trauma this reduction may affect corneal transparency, as some fluid then leaks into the cornea.

The corneal endothelial cells do not replicate in general. When destroyed by disease or surgery, the remaining cells enlarge and spread out to cover the posterior corneal surface, thus decreasing the cell density (cell count). Corneas with extremely low endothelial cell densities can no longer maintain a dehydrated state. The corneas may decompensate, swell, and become cloudy over time, with an associated loss of visual acuity. The specular microscope provides a magnified view of a small area of corneal endothelial cells to measure and record endothelial cell counts of the cornea.

5.0 STUDY OBJECTIVE

5.1 Objective

The objective of this study will be to assess the effect of intravitreal injections of Macugen® (pegaptanib sodium injection) administered every 6 weeks for 48 weeks on the corneal endothelium.

6.0 INVESTIGATIONAL PLAN

6.1 Study Design

This will be a Phase IV, open label, multi-center study. Subjects will receive intravitreal injections of Macugen® (pegaptanib sodium) every 6 weeks for 48 weeks. Additional therapy may be employed at the Investigator's discretion for circumstances judged to be deterioration. The Investigator will decide which treatment to provide as additional therapy. Macugen® (pegaptanib sodium injection) injections should remain on the 6-week schedule defined by the protocol even if an additional therapy is given.

6.2 Rationale

Due to the lack of information generated in the pivotal phase III trials assessing potential effects of intravitreal injections of Macugen® on the corneal endothelium, the FDA requested clinical information from a 1-year (minimum) clinical study to support that there are no adverse effects on the corneal endothelium following intravitreal injections of Macugen®.

6.3 Eligibility Criteria

6.3.1 Inclusion Criteria

6.3.1.1 Ophthalmic Criteria

6.3.1.1.1 Subjects of either gender aged ≥ 50 years diagnosed with subfoveal neovascular Age-Related Macular Degeneration (AMD), Diabetic Macular Edema (DME) or Retinal Vein Occlusion (RVO)

6.3.1.1.2 Best corrected visual acuity in the study eye between 85 and 20 ETDRS letters or between 20/20 and 20/400 using a Snellen chart

6.3.1.2 General Criteria

6.3.1.2.1 Women must be using **two forms** of effective contraception, be post-menopausal for at least 12 months prior to study entry, or surgically sterile; **if of child-bearing** potential, a urine pregnancy test must be performed within 7 days prior to the first injection with a negative result. If the test is positive, a serum test must be done to confirm. The **two forms** of effective contraception must be implemented during the study and for at least 60 days following the last dose of test medication.

6.3.1.2.2 Provide written informed consent.

6.3.1.2.3 Ability to return for all study visits.

6.3.2 Exclusion Criteria

Subjects will not be eligible for the study if subjects cannot attend all study-required visits, or if any of the following criteria are present

6.3.2.1 Unilateral ocular blunt trauma within one year of enrollment and no greater than 5% difference in central endothelial cell density between the 2 eyes

6.3.2.2 intraocular surgery (cataract surgery and surgery for glaucoma without tube shunt or mini-shunt) within one year of enrollment

6.3.2.3 Anterior segment laser surgery (laser trabeculoplasty) performed within one year of enrollment

6.3.2.4 Glaucoma tube-shunt surgery

6.3.2.5 Previous history of corneal transplant in the study or non-study eye.

6.3.2.6 Presence of vitreous macular traction

6.3.2.7 Previous therapeutic radiation in the region of the study eye.

6.3.2.8 Any treatment with an investigational agent in the past 30 days for any condition.

6.3.2.9 Known serious allergies to the components of pegaptanib sodium formulation

6.3.2.10 Any of the following underlying diseases including:

6.3.2.10.1 History or evidence of severe cardiac disease (e.g., NYHA Functional Class III or IV - see Appendix 2), clinical or medical history of unstable angina, acute coronary syndrome, myocardial infarction or revascularization within 6 months, ventricular tachyarrythmias requiring ongoing treatment.

6.3.2.10.2 History or evidence of clinically significant peripheral vascular disease, such as intermittent claudication or prior amputation.

6.3.2.10.3 History or evidence of clinically significant impaired renal or hepatic function

6.3.2.10.4 Stroke (within 12 months of study entry).

6.3.2.10.5 Any major surgical procedure within one month of study entry.

6.3.2.11 Significant media opacities, including cataract, which might interfere with visual acuity, or assessment of toxicity. Subjects should not be entered if there is likelihood that they will require cataract or glaucoma surgery in either eye during the study treatment and follow-up period.

7.0 STUDY MEDICATION

7.1 Investigational Drug Supply

Bausch Health will provide study drug to the sites. The drug provided will be specifically labeled as clinical trial materials for this study, utilizing a label on both the primary foil pouch and the carton. The carton will be closed and secured with tamper evident tape.

Pegaptanib sodium drug substance is a pegylated (40 kDa branched PEG molecule consisting of two 20 kDa PEG arms) anti-VEGF aptamer. It is formulated in phosphate

buffered saline at pH 6-7. Sodium hydroxide or hydrochloric acid may be added for pH adjustment.

The drug product is supplied in a sterile foil pouch as a single-use glass pre-filled syringe. After proper preparation, the syringe will contain 0.3mg of Macugen® in a nominal 90µL deliverable volume pack. A sterile packaged BD® single use 30G X ½" Precision Glide® Luer Lok® needle is supplied in a separate pouch. The foil pouch and needle are packaged together in a carton. For a full description of the drug product, please review the package insert located in Appendix 1.

Active Ingredient:	Pegaptanib Sodium Injection formulated as: 3.47mg/mL solution to deliver a dose of 0.3mg pegaptanib sodium injection
Excipients:	Sodium Chloride, USP Sodium Phosphate Monobasic, Monohydrate, USP Sodium Phosphate Dibasic, Heptahydrate, USP Sodium Hydroxide, USP (as needed) Hydrochloric acid, USP (as needed) Water for injection, USP

7.2 Dose and Administration

7.2.1 Preparation

The drug product, pegaptanib sodium, is a ready-to-use sterile solution provided in a single-use glass syringe. Ensure that the drug to be administered is labeled specifically for this study. Preparation of the syringe for drug administration includes the following steps (see Appendix 1 for more details):

1. Remove the syringe from the plastic clip.
2. Twist off cap.
3. Attach the sterile administration needle (included) to the syringe by screwing it into the syringe tip. Another sterile administration needle may be used in lieu of the one included. Remove the plastic needle shield from the needle.
4. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top of the syringe. SLOWLY depress the plunger rod to eliminate all the bubbles and to expel the excess drug so that the top edge of the 3rd rib on the plunger aligns with the pre-printed black dosing line.
5. Inject the entire contents of the syringe.

7.2.2 Treatment Regimen and Duration

Pegaptanib sodium will be administered as 90µl (nominal delivered volume) intravitreous injections every 6 weeks from Day 0 to Week 48 as described in Section 3, Study Flow Chart.

7.2.3 Administration of Study Drug and Controls

The method for intravitreous administration of pegaptanib sodium is described in Appendix 1.

7.2.4 Stability of Final Solution

The drug product should be used without further dilution. Expiration dating will be based on available stability information and will not exceed what is approved for the commercial product.

7.2.5 Storage of Drug product

The Investigator, or an approved representative (e.g. pharmacist), will be using the drug supplied by Valeant Pharmaceuticals NA. The Investigator or representative will be asked to document treatments given to each patient during each visit. The drug will be stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. The pegaptanib sodium is to be stored under standard refrigeration conditions (2-8°C; 36-46°F) and not frozen.

7.3 Previous or Concomitant Medications and Restrictions

Any treatment with any investigational agent for any condition in the past 30 days is not permitted. Additional therapy during the study, with a therapy of the Investigator's choosing (except Macugen®), may be employed at the Investigator's discretion for circumstances judged to be clinical deterioration, *such as but not restricted to*: ≥2 line vision loss; retinal thickness at center point ≥ 300 µm; an increase in retinal thickness of 100µm from baseline visit. Additional treatment of a non-VEGF agent may be given on any day the Investigator prefers. It is recommended that additional treatment with another VEGF agent should be given at least 3-weeks after a Macugen® (pegaptanib sodium injection) injection unless the Investigator does not feel this is in the best interest of the subject.

8.0 STUDY CONDUCT

8.1 Study Evaluations

Written informed consent must be obtained before any of the Baseline procedures listed below are performed. An explanation of the study and discussion of the possible risks and discomforts will be given by the Investigator. Only those subjects who fulfill all eligibility criteria will be entered into the study.

The following assessments will be performed at Baseline and during the treatment and follow-up periods. All visits for injections must occur within +/- 14 days of the schedule.

8.1.1 Baseline Visit

The following Baseline evaluations, as outlined in the Study Flow Chart (see Section 3), will be performed within 7 days prior to receiving Macugen® (Pegaptanib Sodium injection). Baseline assessments can be broken into 2 days if necessary. If all screening is completed during the baseline visit, DAY 0 assessments may be done on the same day.

- Informed consent
- Medical history
- Ophthalmologic/AMD history
- Urine pregnancy test within 7 days of first injection (if applicable)
- Concomitant Medication Assessment and Serious Adverse Events

8.1.2 Day 0

The following assessments will be performed at the Day 0 Visit.

- Macugen® (Pegaptanib Sodium injection) administration
- Corneal Specular Microscopy (Both eyes). Send results to CIARC
- Concomitant Medication Assessment and Adverse Events

8.1.3 Week 6, Week 12, Week 18, Week 30, Week 36, Week 42, Week 48

The following assessments will be performed at the Visit:

- Macugen® (Pegaptanib Sodium injection) administration
- Concomitant Medication Assessment and Adverse Events

8.1.4 Week 24

The following assessments will be performed at the Visit:

- Macugen® (Pegaptanib Sodium injection) administration
- Corneal Specular Microscopy (Both eyes). Send results to CIARC
- Concomitant Medication Assessment and Adverse Events

8.1.5 Week 54

The following assessments will be performed at the Visit:

- Corneal Specular Microscopy (Both Eyes). Send results to CIARC
- Concomitant Medication Assessment and Adverse Events

8.1.6 Early Termination Visit

Due to the critical nature of the corneal specular microscopy data set, any patient who discontinues from the study early outside of a scheduled clinic visit, the study doctor will need to notify the Sponsor for further instruction. The Sponsor should also be notified if a patient is not expected to complete the study.

8.2 Protocol Compliance and Violations

The protocol must be read thoroughly and the instructions should be followed exactly. Either the Sponsor or the Investigator without agreement by both parties will not implement modifications to the study protocol. However, the Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the study subjects without prior IRB/Sponsor approval/favorable opinion. As soon as

possible, the implemented deviation or change, the reasons for it and, if appropriate, the proposed protocol amendment should be submitted to the IRB/Sponsor. Significant protocol deviations or violations may require that the subject be withdrawn from the study. The Investigator is responsible for notifying the IRB of all protocol deviations or violations.

8.3 Subject Discontinuation

Subjects have the right to withdraw from the study at any time for any reason. The Investigator (after consultation with the Sponsor) or Sponsor also have the right to withdraw subjects from the study in the event of concurrent illness, adverse events, treatment-failure after a prescribed procedure, protocol violations, cure, administrative or other reasons. Every reasonable attempt should be made to encourage the subject to return at Week 54 for evaluation.

Final study assessments as outlined in the Study Flow Chart, Section 3, should be performed on all subjects who withdraw. Subjects who withdraw due to an adverse event should be followed until resolution of the adverse event, or an adequate explanation for the event is obtained.

Subjects who withdraw for any reason should have assessments performed according to the Early Withdrawal schedule.

8.4 Study Discontinuation

The reason for a subject discontinuing from the study will be recorded in the case report form. A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. The Investigator must determine the primary reason for discontinuation. A discontinuation must be reported immediately to the Sponsor or his/her designated representative if it is due to a serious adverse event (SAE) (see Section 11). The final evaluation required by the protocol will be performed at the time of study discontinuation. The Investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for such subjects, and document the course of the subject's condition.

Premature termination of this clinical study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, product or procedure safety problems, or at the discretion of the Sponsor.

9.0 OUTCOME MEASURES

9.1 Safety Measurements and Endpoints

9.1.1 Corneal Specular Microscopy

A post marketing study commitment was made to the FDA stating that the sponsor would, "provide clinical information from a 1-year (minimum) clinical study to support that there are no adverse effects on the corneal endothelium following the intravitreal administration of Macugen®." Corneal specular microscopy data will be collected on an enrollment of approximately 125 subjects in order to fulfill the commitment made to the FDA. Assessments of specular microscopy of the corneal endothelium will be completed and compared individually for central cell density and cell characteristics changes (polymegathism and polymorphism) occurring from baseline. All 10 targeted clinical sites will perform Corneal Specular Microscopy assessments on approximately 125 enrolled subjects. Both contact and non-contact microscopes are permitted, but consistency throughout the entire study is required

(same method must be used for each subject at any given site). Corneal Specular Microscopy examinations must be performed at Baseline and at Weeks 24 and 54 or early withdrawal.

The study sites will perform the corneal specular microscopy assessment in accordance with the protocol and the Corneal Specular Microscopy Instruction Manual. At baseline, Week 24, Week 54 or early withdrawal, the site will send all the data to CIARC within 3 days of collection. At the completion of the study, CIARC will perform a final analysis of the corneal specular microspy data. CIARC will calibrate and certify study site Specular Microscopes. For complete procedures for specular microscopy of the corneal endothelium, please refer to the Corneal Specular Microscopy Instruction Manual.

9.2 Efficacy Measurement and Endpoints

This is a safety study and no primary efficacy endpoint is defined. The effect on the corneal endothelium will be assessed by specular microscopy: Mean cell density loss from baseline over time and frequency distribution.

10.0 STATISTICAL METHODS

10.1 Determination of Sample Size

In order to fulfill a commitment to FDA, at least 100 subjects will need to complete the study. To achieve this number of completed subjects, approximately 125 subjects will be enrolled to account for possible early withdrawals.

10.2 Methods of Analysis

The objective of this study will be to assess the effect of intravitreal injections of Macugen® (pegaptanib sodium injection) administered every 6 weeks for 48 weeks on the corneal endothelium. The primary analysis will be carried out when all subjects have reached their Week 54 assessment.

10.2.1 General Statistical Methods

Categorical data will be summarized using frequency tables, presenting the patient counts and the percentage of patients falling into the category. McNemar's chi-square may be used to assess within-subject change in a bivariate response variable.

Confidence intervals will be constructed using traditional large-sample methodology.

The SAS system will be used to perform all analyses.

A final data analysis plan will be developed prior to locking the CRF database at the conclusion of the study. The statistical plan will include mock-ups of all tables, listings, and figures to be included in a summary report, as well as documentation of all data derivations and statistical methods utilized, including any deviations from those described here.

All statistical analyses will be performed by a statistical office independent of the study Sponsor.

10.2.2 Safety Data Analysis

The safety analysis will be conducted on all subjects who had at least one administration of the study drug. Adverse events will be summarized using MedDRA

terms. The incidence and severity of adverse events will be listed and grouped by body system.

Summary statistics will be given on the number of subjects for whom the study medication had to be reduced or permanently stopped.

Safety endpoints are:

- All adverse events reported, whether deemed related to treatment or not
- All serious adverse events (SAE) reported, whether deemed related to treatment or not

11.0 DRUG SAFETY

11.1 Definition of Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. Therefore, any unfavorable, unintended and emergent medical sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study medication must be reported whether or not considered related. Furthermore, in addition to events not present prior to exposure, any event already present that worsens in intensity or frequency following exposure to study medication must also be reported. All AEs, whether or not they are considered related to the product or device are to be recorded in the subject's medical record and the CRF.

The definitions and terminology to be used during the study are those that reflect the International Conference on Harmonization (ICH E6 (R2)) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines for Good Clinical Practice (GCP).

Each subject eye treated must be examined for the presence/absence of adverse events at all visits, whether scheduled or not. If an adverse event occurs, the first concern will be the safety and welfare of the subject; treatment should be provided as appropriate for the event. Depending on the severity and attribution of the event to the investigational device, FDA regulations and GCPs determine how incidences of safety events are to be recorded and/or reported during the study.

11.1.1 Relationship of Adverse Events

The assessment of the relationship of an AE to the administration of study procedure is a clinical decision based on all available information at the time of the completion of the CRF. In this study, adverse events will be assessed for their relationship to the study drug.

The relationship to study treatment (administrative procedure or (drug)) will be assessed using the following definitions.

Related = There is at least a reasonable possibility that the AE/SAE is related to the study drug. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE.

Not Related	=	There is little or no reasonable possibility that the AE/SAE is related to the study drug. This assessment implies that the AE/SAE has little or no temporal relationship to the study drug and/or a more likely or certain alternative etiology exists.

Events may be attributed to either the administrative procedure of the protocol or the drug (and not both), or to neither.

11.2 Severity of Adverse Events

The severity of all adverse events will be categorized as follows (see Appendix 2 for reference):

- Mild: mild events are those that are easily tolerated with no disruption of normal daily activity.
- Moderate: moderate events are those that cause sufficient discomfort to interfere with daily activity and/or require a simple dose medication.
- Severe: severe events are those that incapacitate and prevent usual activity or require complex medication

11.3 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that results in any of the following outcomes and at any dose:

- Death
- Life-threatening situation (the subject was at risk of death at the time of the event. It does not refer to the hypothetical risk of death if the AE were more severe or were to progress)
- Subject Hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect (any structural abnormality in subject offspring that occurs after intrauterine exposure to treatment)
- Other medically important events (important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in subject hospitalization; or the development of drug dependency or drug abuse)

11.4 Reporting of Adverse Events and Serious Adverse Events

The Investigator will follow up on all AEs and SAEs observed or reported by the subject until resolution, stabilization, and loss to follow-up or until an adequate medical explanation is available, whether or not considered related to the study medication. All serious adverse events must be reported with-in 24 hours of being aware of the event by faxing the Serious Adverse Event form to the number below. Any SAE resulting in death

or was life threatening should be immediately telephoned to the Sponsor's medical monitor. The numbers below can be used for both phone and fax reporting.

The contacts for reporting SAEs are:

[redacted]

AND

[redacted]

The vigilance team will notify the regulatory authorities within the required time frames for all serious adverse events subject to expedited reporting, either due to their nature (e.g., "serious") or due to the significant, unexpected information they provide.

It is the Investigator's responsibility to notify the Institutional Review Board (IRB) of all serious adverse events occurring during the study that are likely to affect the safety of study subjects or conduct of the study.

11.5 Exposure in Utero

If any study subject becomes or is found to be pregnant while receiving study drug, the Investigator must inform the Sponsor/designee via a pregnancy report form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. If a pregnancy is associated with an SAE, a pregnancy report form along with a SAE from should be submitted to the Sponsor/designee.

12.0 INVESTIGATOR RESPONSIBILITIES

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigator abide by all ethical principles originating from the Declaration of Helsinki, ICH guidelines, GCP guidelines, and in compliance with local and federal regulatory requirements.Informed Consent.

Prior to participation in this study, the Investigator must fully explain to the subjects all aspects of the study that are relevant to the decision of participating in the study. The Informed Consent Form (ICF) is documented by means of a written, signed and dated consent form prior to the start of the study. The ICF must be written in a language and in a form understandable to the subject. The Investigator and/or site delegate will sign the ICF in conjunction with the subject. An ICF template will be provided to all study sites and any modifications to template must be submitted to the Sponsor or Sponsor

representative for approval prior to the implementation of the ICF, and prior to submission to the IRB/IEC or any changes requested by the IRB/IEC.

A copy of the signed and dated ICF will be given to the subject and the Investigator in the study will file and retain the original signed and dated copy. The Investigator should clearly indicate the subject's enrollment in a clinical study in the study medical chart.

Institutions, Investigators, Contract Research Organizations, etc., under this Protocol shall abide by all requirements applicable to the use and disclosure of subjects' protected health information (such as the requirements provided for under the Health Insurance Portability and Accountability Act (HIPAA), Hospital Trust and Regulatory authorities.)

12.1 Ethics Review

Documented approval from an appropriate IRB/IEC must be obtained for all participating sites prior to study start, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IRB/IEC approval must be obtained and also forwarded to the Sponsor.

Either the Investigator(s) or representatives of the Sponsor must submit progress reports to the IRB/IEC according to local regulations and guidelines. The Principal Investigator(s) must also provide the IRB/IEC with any reports of SAEs from the study site.

12.2 Source Documents

The Investigator must keep a written or electronic subject file for every subject participating in the study. This subject file should contain the available demographic and medical information of the subject, in particular the following: name, date of birth, sex, height, weight, subject history, concomitant diseases and concomitant medications (including changes during the study), statement of entry into the study, study identification, the date of informed consent, all study visit dates, predefined performed examinations and clinical findings, observed AEs (if applicable), and reason for withdrawal from the study if applicable. It should be possible to verify the inclusion and exclusion criteria for the study from the available data in this file.

Any other documents with source data, especially original documents of data that were generated by technical equipment, have to be filed. All these documents have to bear at least the subject identification number and the printing date printed by the recording device, to indicate to which subject and to which study procedure the document belongs. All data are to be recorded directly onto the CRF.

12.3 Training

The record of all individuals involved in the study is to be maintained in the regulatory binder. The Principal Investigator will ensure that appropriate training relevant to the study is given to all the staff included in the study, and that they will receive any new information of relevance to the performance of this study.

12.4 Study Agreements

The Principal Investigator at each center must comply with all the terms, conditions and obligations of the agreements for this study. In the event of any inconsistency between this protocol and the study agreement, the study agreement will prevail.

12.5 Confidentiality

The Investigators must agree to maintain the confidentiality of the study at all times and must not reveal information relating to the Investigator's Brochure, protocol, CRF or associated documents to unauthorized third parties.

13.0 STUDY MANAGEMENT

13.1 Study Initiation Requirements

The following documents must be available prior to the recruitment of the first subject into the study:

- Signed protocol signature page
- Completed and signed Confidentiality Agreement and Clinical Study Agreement, Including an agreed-upon study budget
- Completed and signed FDA 1572 Form and Financial Certification/Disclosure
- Forms for all personnel listed on the FDA 1572 Form signed and dated within two years of the site initiation, a curriculum vitae for all persons listed FDA Form 1572 as an Investigator or sub-Investigators, and their Medical Licenses
- Copy of the IEC/IRB approval of the protocol and the Informed Consent Form approved by the IEC/IRB and appropriate local regulatory agencies
- List of members of the IEC/IRB or an IRB Assurance Number, IEC members and Constitution
- Laboratory licenses/certification/accreditation
- Copy of the most recent Package Insert
- Copy of national regulatory authority approval (e.g. FDA)
- Copy of hospital NHS Trust R&D approval, where applicable.

13.2 Monitoring, Verification of Data, Auditing and Inspection

An appointed representative of the Sponsor will visit each site periodically to discuss the progress of the clinical study and review CRFs against original source documents with the study personnel, for accuracy of data recording, study product or device accountability and correspondence. The Principal Investigator is to ensure that subjects are aware of and consent that personal information may be reviewed during the data verification process as part of monitoring or auditing by properly authorized agents of the sponsor or subject to inspection by regulatory authorities. In addition, participation and personal information must be treated as strictly confidential to the extent the applicable law permits and not publicly available. Audits or inspections may include, for example, a review of all source documents, product or device records, and original clinic medical notes, at some or all of the facilities used in the study.

13.3 Data Management

Once the CRFs have been retrieved from the site, each individual CRF page will be data entered and pre-validated. The data will then be further validated to ensure that the forms were completed properly and that all responses met the standards set forth by the validation specifications. Any suspect data identified during the validation process will be sent to the site as a data query to be compared against source documentation for resolution. The query response will then be returned for resolution in the database. An electronic audit trail will document any changes to all the CRFs. Medical coding will be performed throughout the data cleaning process for required fields.

13.4 Study Drug Accountability

The Investigator will be using the drug supplied by Valeant. They will have a specific amount of study drug. The Investigator or representative will be asked to record the amount given to each patient during each visit. The Investigator will be responsible for the accountability of all used and unused study medication.

13.5 Protocol Compliance

The Sponsor will not compensate the Investigator for evaluation of cases in which the procedures and evaluations are conducted in a manner other than that specified by the protocol.

Under certain circumstances, individual protocol criteria may be waived by the Sponsor and in agreement with the Investigator. Any such waiver will be documented in writing and provided to the Investigator by the Sponsor.

13.6 Ethical Aspects

Local Regulations/Declaration of Helsinki
The Investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, South Africa, and Scotland) and with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (May 9th 1997) and with local law if it affords greater protection to the subject. For studies conducted in the USA or under a US IND, the Investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards".

13.7 Institutional Review Board (IRB) Approval and Informed Consent

The Investigator is responsible for obtaining approval of the study protocol, informed consent, and any advertising used for subject recruitment from the appropriate IRB/EC prior to initiating the study. The Investigator will forward the following documents prior to commencement of subject enrollment:

- IRB/EC approval documentation
- Approved study subject informed consent
- A list of IRB/EC members, or statement of compliance.

Prior to enrollment, written informed consent must be obtained from each subject or his/her legally authorized representative. The informed consent must contain all of the elements prescribed by the relevant regulatory authorities and must be appropriately signed, dated and witnessed. **Any changes by the Investigator or local IRB/EC to the sample consent provided by the Sponsors must be approved by the Sponsors before initiating enrollment.**

13.8 Record Retention

All data derived from the study and all correspondence should be organized in the appropriate file folders. In compliance with the ICH guidelines, GCP, and federal, state

and local laws, regulations and guidelines, the Investigator will retain all essential records related to the study for at least two years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications, and for a longer period if required by federal, state and local laws, regulations and guidelines. To avoid any possible errors, the Investigator must contact the Sponsor prior to the destruction of any study records. If the Investigator moves or withdraws from an investigation, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made and agreed by the Sponsor.

13.9 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Subject names will not be supplied to the sponsor. Only the subject number and subject initials will be recorded in the CRF, and if the subject name appears on any other document (e.g. pathology report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the sponsor ., IRB, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential. The Investigator will maintain a list to enable subjects' records to be identified.

13.10 Use of Data and Publication

All data and results, and all intellectual property rights in the data and results, derived from the study will be the property of the Sponsor, who may utilize the data in various ways, including but not limited to submission to government regulatory authorities or disclosure to other Investigators.

The results of this study shall not be published or communicated in any manner without the expressed written agreement of the Sponsor. Valeant Pharmaceuticals North America LLC (Valeant) will require advance review of any publication, disclosure, presentation or any other communication of the data, results or any other aspect of the study including but not limited to the content and conclusions of any abstract, presentation or paper before consent for publication will be provided. This provision also applies to any amendments that are subsequently requested by the referees or journal editors. The Sponsor will undertake to comment on the draft documents within thirty days of receipt, but additional time for Sponsor review is recommended. If Valeant does not comment within the allocated time, disclosure is still prohibited unless Valeant consents to such disclosure in writing. In case of a difference of opinion between the Sponsor and the Investigator(s), the contents of the publication will be discussed in order to find a solution, which satisfies both parties.

14.0 REFERENCES

1. Vingerling JR et al. Prevalence of age-related maculopathy in the Rotterdam trial. Ophthalmology 102:205-210, 1995.
2. Leibowitz HM et al. The Framingham Eye Trial monograph: an ophthalmological and epidemiological trial of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2,631 adults, 1973-1975. Surv Ophthalmol 24 (suppl): 335-610, 1980.
3. Bressler NM. Early detection and Treatment of neovascular age-related macular degeneration. J Am Board Fam Pract 2002; 15:142-152.
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5. Laouri M, Chen E, Looman M, et al. The burden of disease of retinal vein occlusion: review of the literature. Eye 2011; 25:981-988.
6. Klein R, Moss SE, Meuer SM, et al. The 15-year cumulative incidence of retinal vein occlusion. The Beaver Dam Eye Study. Arch Ophthalmol 2008; 126:513-518.
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9. EOP1004 Final study report: pegaptanib sodium (Macugen™). A Phase II/III randomized, double-masked, controlled, dose-ranging, multi-center comparative trial, in parallel groups, to establish the safety and efficacy of intravitreous injections of pegaptanib sodium (anti-vascular endothelial growth factor [VEGF] pegylated aptamer) given every 6 weeks for 54 weeks, in patients with exudative age-realted macular degeneration (AMD).
10. EOP1023 Final study report: A Phase IV, open label, multi-center trial of maintenance intravitreous injections of Macugen™ (pegaptanib sodium) given every 6 weeks for 48 weeks in subjects with subfoveal neovascular age-related macular degeneration (AMD) initially treated with a modality resulting in maculopathy improvement.
11. EOP1005 Final study report: A Phase 2, randomized, controlled, double-masked, dose-finding, multi-center, comparative trial, in parallel groups, to establish the safety and preliminary efficacy of intravitreous injections of EYE001 (anti-VEGF pegylated

aptamer), given every 6 weeks for 12 to 30 weeks to patients with clinically significant diabetic macular edema (DME) involving the center of the macula.

12. Sultan MB, Zhou D, Loftus J, et al. A phase 2/3, multicenter, randomized, double-masked, 2-year trial of pegaptanib sodium for the treatment of diabetic macular edema. Ophthalmology 2011; 118:1107-1118.
13. Wroblewski JJ, Wells JA, Adamis AP, et al. Pegaptanib sodium for macular edema secondary to central retinal vein occlusion. Arch Ophthalmol 2009; 127:374-380.
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15.0 SIGNATURE PAGE

Signatures confirm that this protocol amendment no. 3 for EOP 1024 has been carefully read and fully understood, and that there is agreement to comply with the conduct and terms of the study specified herein in compliance with Good Clinical Practice and all other regulatory requirements.

PROTOCOL TITLE: A Phase IV, open label, multi-center study to assess the effect of intravitreal injections of Macugen® (pegaptanib sodium injection) administered every 6 weeks for 48 weeks on the corneal endothelium.

Study Sponsor: Valeant Pharmaceuticals North America LLC, as engaged by and acting as a service provider to Valeant International (Barbados) SRL

Address: 400 Somerset Corporate Blvd, Bridgewater, NJ 08807

[redacted]

APPENDIX 1 MACUGEN PRESCRIBING INFORMATION

A09541_70010815_Macugen_Insert_Template - TOP FRONT
Width: 8.25", Height: 17"
Fold Size: 2.8125" x 5.75"

VALEANT
1400 North Goodman Street Rochester, NY 14609, USA
DESCRIPTION: MACUGEN Insert - US - PPS
PART No.: 9405902 SPEC No. or SPEC DIMENSIONS: 8.25" x 17"
SPECIAL INSTRUCTIONS: Figure_1.pdf Figure_2.pdf Figure_3.pdf Figure_4.pdf Figure_5.pdf Figure_6.pdf
Pharmacode 1155.eps
PRINT SUPPLIERS: Please refer to Valeant's *Print Supplier Guidelines*
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MACUGEN®
(pegaptanib sodium injection)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all of the information needed to use MACUGEN safely and effectively. See full prescribing information for MACUGEN.

MACUGEN® (pegaptanib sodium injection)
Intravitreal Injection
Initial U.S. Approval: 2004

INDICATIONS AND USAGE
MACUGEN is indicated for the treatment of neovascular (wet) age-related macular degeneration. (1)

DOSAGE AND ADMINISTRATION
- FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY. (2.1)
- MACUGEN 0.3 mg should be administered once every six weeks by intravitreous injection into the eye to be treated. (2.2)

DOSAGE FORMS AND STRENGTHS
- 0.3 mg/90 μL solution in a single-use syringe for intravitreal injection. (3)

CONTRAINDICATIONS
- Ocular or periocular infections. (4.1)
- Hypersensitivity. (4.2)

WARNINGS AND PRECAUTIONS
- Endophthalmitis may occur following intravitreous injections. Proper aseptic injection technique should always be utilized when administering MACUGEN. Patients should be monitored during the week following the injection. (5.1)
- Increases in intraocular pressure have been seen within 30 minutes of injection of MACUGEN. (5.2)
- Rare cases of anaphylaxis/anaphylactoid reactions, including angioedema, have been reported in the postmarketing experience. (5.3)

ADVERSE REACTIONS
Most common adverse reactions (reported in 10-40% of patients treated with MACUGEN for up to two years) are anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, corneal edema, eye discharge, eye irritation, eye pain, hypertension, increased intraocular pressure (IOP), ocular discomfort, punctate keratitis, reduced visual acuity, visual disturbance, vitreous floaters, and vitreous opacities. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC, at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
MACUGEN® (pegaptanib sodium injection) is indicated for the treatment of neovascular (wet) age-related macular degeneration.

2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY.

2.2 Dosing
MACUGEN 0.3 mg should be administered once every six weeks by intravitreous injection into the eye to be treated.

2.3 Preparation for Administration
MACUGEN should be inspected visually for particulate matter and discoloration prior to administration. If visible particulates are observed and/or the liquid in the syringe is discolored, the syringe must not be used.

Administration of the syringe contents involves assembly of the syringe with the administration needle. The injection procedure should be carried out under controlled aseptic conditions, which includes the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). When ready to assemble syringe and administer injection, carefully peel open pouches, remove contents, and place on sterile field. If upon opening the pouch, the plastic clip is missing or not attached to the syringe, the syringe should not be used.

To avoid compromising the sterility of the product, do not pull back on the plunger.
1. Remove the syringe from the plastic clip.
2. Twist off cap.
3. Attach the sterile, single-use administration needle (included) to the syringe by screwing it into the syringe tip.
– Another sterile, single-use administration needle may be used in lieu of the one included. Remove the plastic needle shield from the needle.
4. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top of the syringe. **SLOWLY** depress the plunger to eliminate all the bubbles and to expel the excess drug so that the top edge of the 3rd rib on the plunger stopper aligns with the preprinted black dosing line (see Figure 2, below).
5. Inject the entire contents of the syringe.

PRIOR to Injection
Figure 1. **Before** expelling air bubble and excess drug

(Actual air bubble formation may vary)

READY for Injection
Figure 2. **After** expelling air bubble and excess drug

2.4 Administration
The injection procedure should be carried out under controlled aseptic conditions, which includes the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.

The patient's medical history for hypersensitivity reactions should be evaluated prior to performing the intravitreal procedure *[see Warnings and Precautions (5) and Adverse Events (6)]*.

Following the injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and monitoring during the week following the injection. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

No special dosage modification is required for any of the populations that have been studied (i.e. gender, elderly).

The safety and efficacy of MACUGEN therapy administered to both eyes concurrently have not been studied.

3 DOSAGE FORMS AND STRENGTHS
Single-use glass syringe pre-filled with 0.3 mg of MACUGEN in a nominal 90 μL solution for intravitreal injection.

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
MACUGEN is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity
MACUGEN is contraindicated in patients with known hypersensitivity to pegaptanib sodium or any other excipient in this product.

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis
Intravitreous injections, including those with MACUGEN, have been associated with endophthalmitis. Proper aseptic injection technique should always be utilized when administering MACUGEN. In addition, patients should be monitored during the week following the injection to permit early treatment, should an infection occur *[see Dosage and Administration (2.4)]*.

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been seen within 30 minutes of injection with MACUGEN. Therefore, intraocular pressure as well as the perfusion of the optic nerve head should be monitored and managed appropriately *[see Dosage and Administration (2.4)]*.

5.3 Anaphylaxis
Rare cases of anaphylaxis/anaphylactoid reactions, including angioedema, have been reported in the postmarketing experience following the MACUGEN intravitreal administration procedure *[see Dosage and Administration (2.4) and Adverse Events (6.3)]*.

6 ADVERSE REACTIONS
6.1 Injection Procedure
Serious adverse events related to the injection procedure occurring in <1% of intravitreous injections included endophthalmitis *[see Warnings and Precautions (5.1)]*, retinal detachment, and iatrogenic traumatic cataract.

6.2 Clinical Studies Experience
The most frequently reported adverse events in patients treated with MACUGEN 0.3 mg for up to two years were anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, corneal edema, eye discharge, eye irritation, eye pain, hypertension, increased intraocular pressure (IOP), ocular discomfort, punctate keratitis, reduced visual acuity, visual disturbance, vitreous floaters, and vitreous opacities. These events occurred in approximately 10-40% of patients.

The following events were reported in 6-10% of patients receiving MACUGEN 0.3 mg therapy:
Ocular: blepharitis, conjunctivitis, photopsia, vitreous disorder.
Non-Ocular: bronchitis, diarrhea, dizziness, headache, nausea, urinary tract infection.

The following events were reported in 1-5% of patients receiving MACUGEN 0.3 mg therapy:
Ocular: allergic conjunctivitis, conjunctival edema, corneal abrasion, corneal deposits, corneal epithelium disorder, endophthalmitis, eye inflammation, eye swelling, eyelid irritation, meibomianitis, mydriasis, periorbital hematoma, retinal edema, vitreous hemorrhage.
Non-Ocular: arthritis, bone spur, carotid artery occlusion, cerebrovascular accident, chest pain, contact dermatitis, contusion, diabetes mellitus, dyspepsia, hearing loss, pleural effusion, transient ischemic attack, urinary retention, vertigo, vomiting.

6.3 Postmarketing Experience
Anaphylaxis/anaphylactoid reactions, including angioedema, have been identified during postapproval use of MACUGEN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure *[see Dosage and Administration (2.4) and Warnings and Precautions (5.3)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Teratogenic Effects: Pregnancy Category B. Pegaptanib produced no maternal toxicity and no evidence of teratogenicity or fetal mortality in mice at intravenous doses of up to 40 mg/kg/day (about 7,000 times the recommended human monocular ophthalmic dose of 0.3 mg/eye). Pegaptanib crosses the placenta in mice.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers
It is not known whether pegaptanib is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when MACUGEN is administered to a nursing woman.

8.4 Pediatric Use
Safety and effectiveness of MACUGEN in pediatric patients have not been established.

8.5 Geriatric Use
Approximately 94% (834/892) of the patients treated with MACUGEN were ≥65 years of age and approximately 62% (553/892) were ≥75 years of age. No difference in treatment effect or systemic exposure was seen with increasing age.

10 OVERDOSAGE
Doses of MACUGEN up to 10 times the recommended dosage of 0.3 mg have been studied. No additional adverse events have been noted but there is decreased efficacy with doses above 1 mg.

11 DESCRIPTION
MACUGEN® (pegaptanib sodium injection) is a sterile, aqueous solution containing pegaptanib sodium for intravitreous injection. MACUGEN is supplied in a single-dose, pre-filled syringe and is formulated as a 3.47 mg/mL solution, measured as the free acid form of the oligonucleotide. The active ingredient is 0.3 mg of the free acid form of the oligonucleotide without polyethylene glycol, in a nominal volume of 90 μL. This dose is equivalent to 1.6 mg of pegaptanib sodium (pegylated oligonucleotide) or 0.32 mg when expressed as the sodium salt form of the oligonucleotide moiety. The product is a sterile,

8.25"

VALEANT
1400 North Goodman Street Rochester, NY 14609, USA

DESCRIPTION: MACUGEN Insert - US - PPS

PART No.: 9405902 **SPEC No. or SPEC DIMENSIONS:** 8.25" x 17"

SPECIAL INSTRUCTIONS: Figure_1.pdf Figure_2.pdf Figure_3.pdf Figure_4.pdf Figue_5.pdf Figure_6.pdf
Pharmacode 1155.eps

PRINT SUPPLIERS: Please refer to Valeant's *Print Supplier Guidelines*

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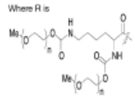
clear, preservative-free solution containing sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, hydrochloric acid, and/or sodium hydroxide to adjust the pH and water for injection.

Pegaptanib sodium is a covalent conjugate of an oligonucleotide of twenty-eight nucleotides in length that terminates in a pentylamino linker, to which two 20-kilodalton monomethoxy polyethylene glycol (PEG) units are covalently attached via the two amino groups on a lysine residue. Pegaptanib sodium is represented by the following structural formula:

Where R is



and n is approximately 450.

The chemical name for pegaptanib sodium is as follows:
RNA, ((2'-deoxy-2'-fluoro)C-G_m-G_m-A-A-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-A_m-G_m-(2'-deoxy-2'-fluoro)U-G_m-A_m-A_m-(2'-deoxy-2'-fluoro)U-G_m-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)U-A_m-(2'-deoxy-2'-fluoro)U-A_m-(2'-deoxy-2'-fluoro)C-A_m-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-G_m-(3'→3')-dT), 5'-ester with α,α'-[4,12-dioxo-6-[[[5-(phosphoonoxy)pentyl]amino]carbonyl]-3,13-dioxa-5,11-diaza-1,15-pentadecanediyl]bis[ω-methoxypoly(oxy-1,2-ethanediyl)], sodium salt.

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

MACUGEN is formulated to have an osmolality of 280-360 mOsm/Kg, and a pH of 6–7.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pegaptanib is a selective vascular endothelial growth factor (VEGF) antagonist. VEGF is a secreted protein that selectively binds and activates its receptors located primarily on the surface of vascular endothelial cells. VEGF induces angiogenesis, and increases vascular permeability and inflammation, all of which are thought to contribute to the progression of the neovascular (wet) form of age-related macular degeneration (AMD), a leading cause of blindness. VEGF has been implicated in blood retinal barrier breakdown and pathological ocular neovascularization.

Pegaptanib is an aptamer, a pegylated modified oligonucleotide, which adopts a three-dimensional conformation that enables it to bind to extracellular VEGF. Under *in vitro* testing conditions, pegaptanib binds to the major pathological VEGF isoform, extracellular $VEGF_{165}$, thereby inhibiting $VEGF_{165}$ binding to its VEGF receptors. The inhibition of $VEGF_{164}$, the rodent counterpart of human $VEGF_{165}$, was effective at suppressing pathological neovascularization.

12.3 Pharmacokinetics

Absorption
In animals, pegaptanib is slowly absorbed into the systemic circulation from the eye after intravitreous administration. The rate of absorption from the eye is the rate limiting step in the disposition of pegaptanib in animals and is likely to be the rate limiting step in humans.

In humans, a mean maximum plasma concentration of about 80 ng/mL occurs within 1 to 4 days after a 3 mg monocular dose (10 times the recommended dose). The mean area under the plasma concentration-time curve (AUC) is about 25 µg•hr/mL at this dose.

Pegaptanib is metabolized by nucleases and is generally not affected by the cytochrome P450 system.

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

Distribution/Metabolism/Excretion
Twenty-four hours after intravitreous administration of a radiolabeled dose of pegaptanib to both eyes of rabbits, radioactivity was mainly distributed in vitreous fluid, retina, and aqueous fluid. After intravitreous and intravenous administrations of radiolabeled pegaptanib to rabbits, the highest concentrations of radioactivity (excluding the eye for the intravitreous dose) were obtained in the kidney. In rabbits, the component nucleotide, 2'-fluorouridine, is found in plasma and urine after single radiolabeled pegaptanib intravenous and intravitreous doses. In rabbits, pegaptanib is eliminated as parent drug and metabolites primarily in the urine.

Based on preclinical data, pegaptanib is metabolized by endo- and exonucleases.

In humans, after a 3 mg monocular dose (10 times the recommended dose), the average (± standard deviation) apparent plasma half-life of pegaptanib is 10 (±4) days.

Special Populations
Plasma concentrations do not appear to be affected by age or gender, but have not been studied in patients under the age of 50.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with pegaptanib have not been conducted. No data are available to evaluate male or female mating or fertility indices.

13.2 Animal Toxicology and/or Pharmacology

Pegaptanib and its monomer component nucleotides (2'-MA, 2'-MG, 2'-FU, 2'-FC) were evaluated for genotoxicity in a battery of *in vitro* and *in vivo* assay systems. Pegaptanib, 2'-O-methyladenosine (2'-MA), and 2'-O-methylguanosine (2'-MG) were negative in all assay systems evaluated. 2'-fluorouridine (2'-FU) and 2'-fluorocytidine (2'-FC) were nonclastogenic and were negative in all *S. typhimurium* tester strains, but produced a nondose-related increase in revertant frequency in a single *E. coli* tester strain. Pegaptanib, 2'-FU, and 2'-FC tested negative in cell transformation assays.

14 CLINICAL STUDIES

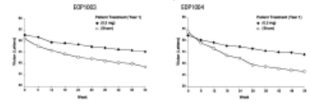
MACUGEN was studied in two controlled, double-masked, and identically designed randomized studies in patients with neovascular AMD. Patients were randomized to receive control (sham treatment) or 0.3 mg, 1 mg or 3 mg MACUGEN administered as intravitreous injections every 6 weeks for 48 weeks. A total of approximately 1200 patients were enrolled with 892 patients receiving MACUGEN and 298 receiving a sham injection. The median age of the patients was 77 years. Patients received a mean 8.5 treatments out of a possible 9 total treatments across all treatment arms. Patients were re-randomized between treatment and no treatment during the second year. Patients who continued treatment in year 2 received a mean of 16 treatments out of a possible total 17 overall.

The two trials enrolled patients with neovascular AMD characteristics including classic, occult, and mixed lesions of up to 12 disc areas and baseline visual acuity in the study eye between 20/40 and 20/320. The primary efficacy endpoint was the proportion of patients losing less than 15 letters of visual acuity, from baseline up to 54 week assessment. Verteporfin PDT usage was permitted at the discretion of the investigators in patients with predominantly classic lesions.

The groups treated with MACUGEN 0.3 mg exhibited a statistically significant result in both trials for the primary efficacy endpoint at 1 year: Study EOP1003, MACUGEN 73% vs. Sham 60%; Study EOP1004, MACUGEN 67% vs. Sham 53%. Concomitant use of PDT overall was low. More sham treated patients (75/296) received PDT than MACUGEN 0.3 mg treated patients (58/294).

On average, MACUGEN 0.3 mg treated patients and sham treated patients continued to experience vision loss. However, the rate of vision decline in the MACUGEN treated group was slower than the rate in the patients who received sham treatment. See Figure 1.

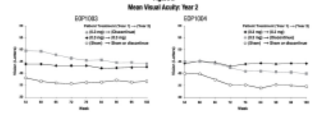
Figure 1
Mean Visual Acuity: Year 1



At the end of the first year (week 54), approximately 1050 of the original 1200 patients were re-randomized to either continue the same treatment or to discontinue treatment through week 102. See Figure 2.

MACUGEN was less effective during the second year than during the first year. The percentage of patients losing less than 15 letters from baseline to week 102 was: Study EOP1003, MACUGEN 38/67 (57%); Sham 30/54 (56%); Study EOP1004, MACUGEN 40/66 (61%); Sham 18/53 (34%).

Figure 2
Mean Visual Acuity: Year 2



Dose levels above 0.3 mg did not demonstrate any additional benefit.

The safety or efficacy of MACUGEN beyond 2 years has not been demonstrated.

16 HOW SUPPLIED/STORAGE AND HANDLING

MACUGEN® (pegaptanib sodium injection) is supplied in a sterile foil pouch with a single-use glass syringe pre-filled with 0.3 mg of MACUGEN in a nominal 90 µL deliverable volume pack. A sterile, single-use administration needle is supplied in a separate pouch. The foil pouch and needle are packaged together in a carton (NDC 68782-001-02).

Store in the refrigerator at 2° to 8°C (36° to 46°F). **Do not freeze or shake vigorously.**

Rx only

17 PATIENT COUNSELING INFORMATION

In the days following MACUGEN administration, patients are at risk for the development of endophthalmitis. If the eye becomes red, sensitive to light, painful or develops a change in vision, the patient should seek the immediate care with their ophthalmologist *[see Warnings and Precautions (5.1)]*.

Manufactured for:
Bausch + Lomb, a division of
Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

By:
Pfizer Manufacturing Belgium NV
Rijksweg 12, B-2870 Puurs
Belgium

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Revised: 07/2016

APPENDIX 2 NYHA FUNCTIONAL CLASSIFICATIONS

Class	Subject Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea (shortness of breath).
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea (shortness of breath).
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.