CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-756

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 21-756
Labeling Review

NDA 21-756	Submission: December 10, 2004 Review Completed: December 13, 2004
Proposed Tradename:	Macugen
Generic Name:	pegaptanib sodium
Sponsor:	Eyetech Pharmaceuticals 3 Time Square, 12th Floor New York, New York, 10036
Pharmacologic Category:	VEGF Inhibitor
Proposed Indication:	The treatment of the neovascular form of age-related macular degeneration
Dosage Form and Route of Administration:	intravitreal injection
Submitted:	Draft Labeling

Reviewer Comments: *Reviewer recommended additions are underlined in red. Recommended deletions are located in the margins.*

6 Draft Labeling Page(s) Withheld

Manufactured by:

Gilead Sciences, Inc
650 Cliffside Drive
San Dimas, CA 91773

For:

Eyetech Pharmaceuticals, Inc.
Three Times Square
New York, NY 10036

Pfizer Inc.
235 E.42nd St.
New York, NY 10017

Comments/Recommendations:

The sponsor has accepted all of the changes proposed by the division. The label is recommended for approval.

Jennifer D. Harris, M.D.
Medical Officer

cc: NDA 21-756
HFD-550/Div Files
HFD-550/CSO/Puglisi
HFD-520/CHEM
HFD-550/PHARM/ZChen
HFD-550/MO/Harris
HFD-550/SMO/Chambers

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jennifer Harris
12/16/04 09:51:37 AM
MEDICAL OFFICER

Wiley Chambers
12/16/04 12:07:05 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-756
NDA Amendment (2nd year study data)

NDA 21-756	Submission: October 7, 2004 Review Completed: October 27, 2004
Proposed Tradename:	Macugen
Established Name:	pegaptanib sodium
Sponsor:	Eyetech Pharmaceuticals 3 Time Square, 12th Floor New York, New York, 10036
Pharmacologic Category:	VEGF Inhibitor
Proposed Indication:	The treatment of the neovascular form of age-related macular degeneration
Dosage Form and Route of Administration:	intravitreal injection

Submitted:

The sponsor has submitted draft safety and efficacy tables for the 2nd year data for this two year study. The results of the 1st year data were submitted in the original NDA application. Full study reports including, case report forms, case report tabulations, subgroup analysis, etc have not been provided. This review is based on an incomplete database for the 2nd year data, however, enough information has been provided to adequately label the product at this time.

Background

At baseline (week 0), patients in each study (EOP1003 and EOP1004) were randomized to one of four treatment groups (0.3 mg pegaptanib, 1 mg pegaptanib, 3 mg pegaptanib or sham injections once every 6 weeks).

At the 54 week time point, patients in the active therapy arms were re-randomized on a 1:1 basis to either discontinue or continue treatment for a further 48 weeks. Patients receiving sham injections were re-randomized on a 1:1:1:1:1 basis to discontinue the masked treatment, to continue on study receiving one of the 3 active treatments, or to continue on sham therapy.

Patients who were randomized to stop treatment were permitted to resume therapy if they had benefited from treatment in the first year and had lost at least 2 lines of vision after discontinuation.

The patient populations for the 2nd year of study were defined as follows:

Cohort 1 - all patients re-randomized to continue the same treatment.
Cohort 2 – all patients re-randomized to discontinue treatment.
Cohort 3 – all sham patients re-randomized to active dose or sham

For the purposes of the review, special attention have been given to patients in cohort 1 since this will give a true picture of the long term safety and efficacy of pegaptanib sodium treatment.

Patient Evaluation Groups – 2nd Year

Populations	**N**	**N**	**N**	**N**
Randomized	265	264	252	272
Intent-to-Treat [1]	265	264	252	272
Safety [2]	258	256	245	265

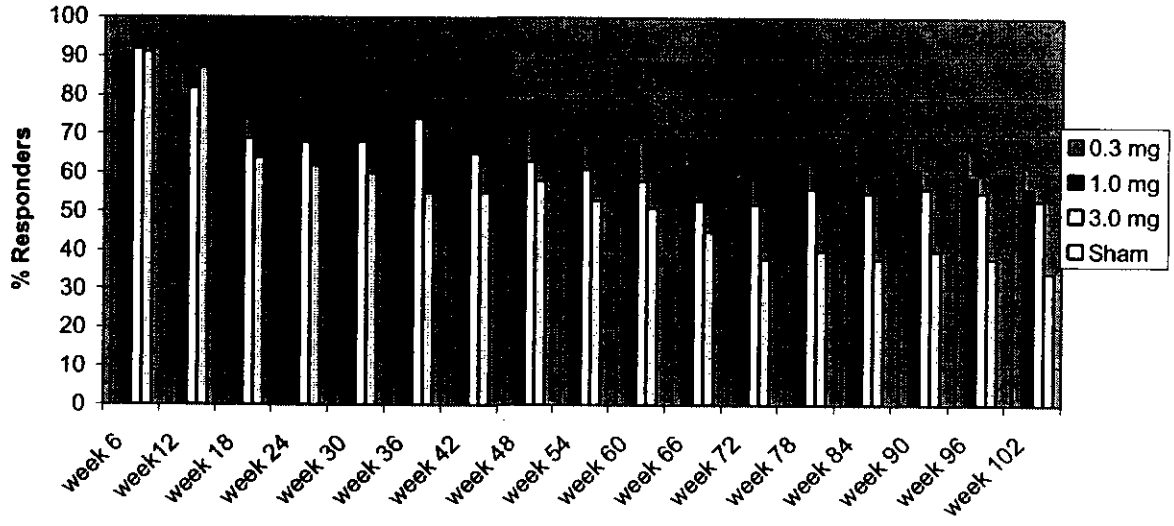
[1] Patients who were re-randomized at week 54, regardless of their eligibility for the study
[2] Patients who received at least one study treatment

Efficacy Analysis

Responder Analysis – ITT Population– Study 1004

	0.3 mg N=66	1.0mg N=66	3.0 mg N=62	Sham N=53
Loss < 15 letters at week 102	40 (61%)	37 (56%)	33 (53%)	18 (34%)
Loss ≥ 15 letters at week 102	26 (39%)	29 (44%)	29 (47%)	35 (66%)
p-value	[redacted]	*0.02*	[redacted]	

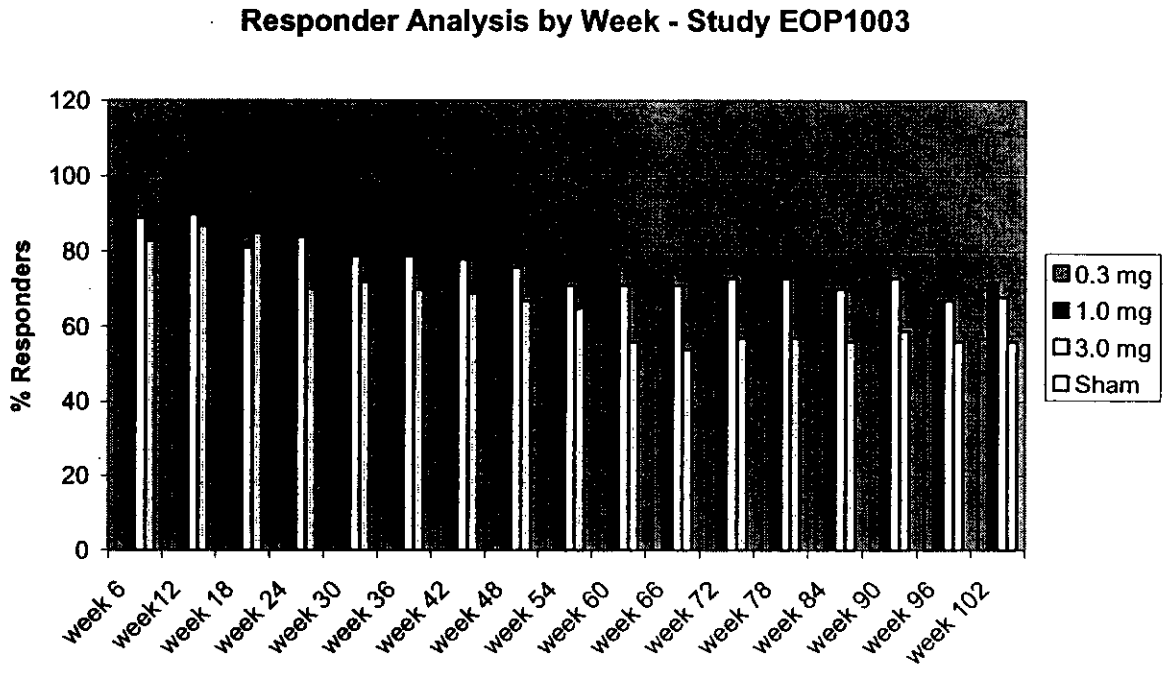
Responder Analysis by Week - Study EOP1004



APPEARS THIS WAY
ON ORIGINAL

Responder Analysis – ITT Population– Study 1003

	0.3 mg N=67	1.0 mg N=67	3.0 mg N=63	Sham N=54
Loss < 15 letters at week 102	38 (57%)	46 (72%)	43 (68%)	30 (56%)
Loss ≥ 15 letters at week 102	29 (43%)	19 (28%)	20 (32%)	24 (44%)
p-value	*0.98*	*0.1*	*0.23*	

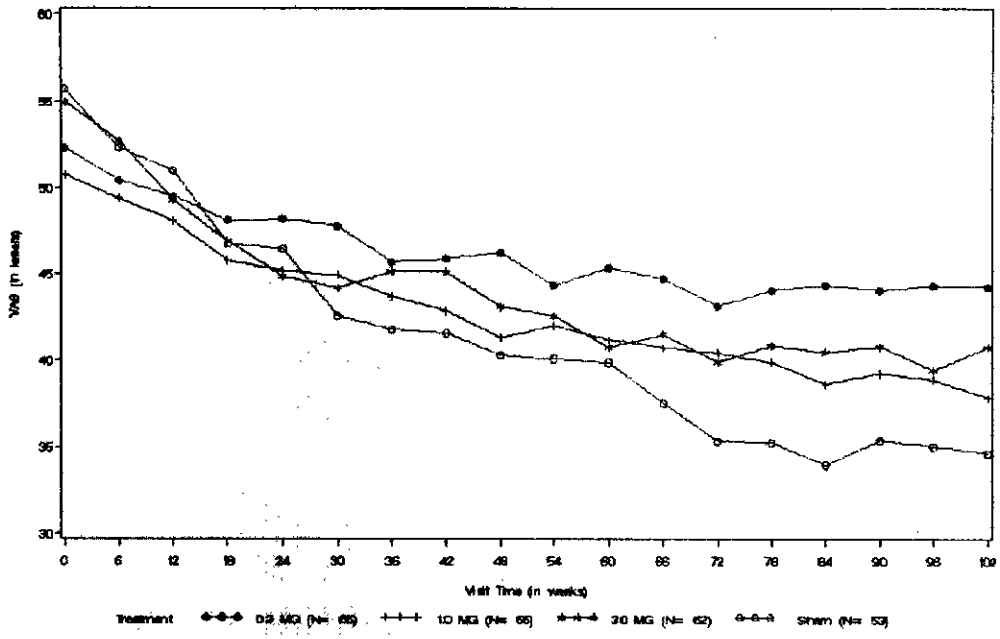


Reviewer's Comments:

The statistically significant findings are highlighted in the table. The efficacy analysis in this review is based on a responder analysis of all patients who lost < 15 letters of visual acuity at week 102. This provides a means of direct comparison of the second year data to the first year data that was submitted in the original NDA.

Based on the same Hochberg multiple comparison procedure used to analyze the first year data, Study 1004 demonstrates efficacy for all active doses of pegaptanib sodium at week 102. However, this effect is not replicated in study 1003 which does not show efficacy for any of the active doses.

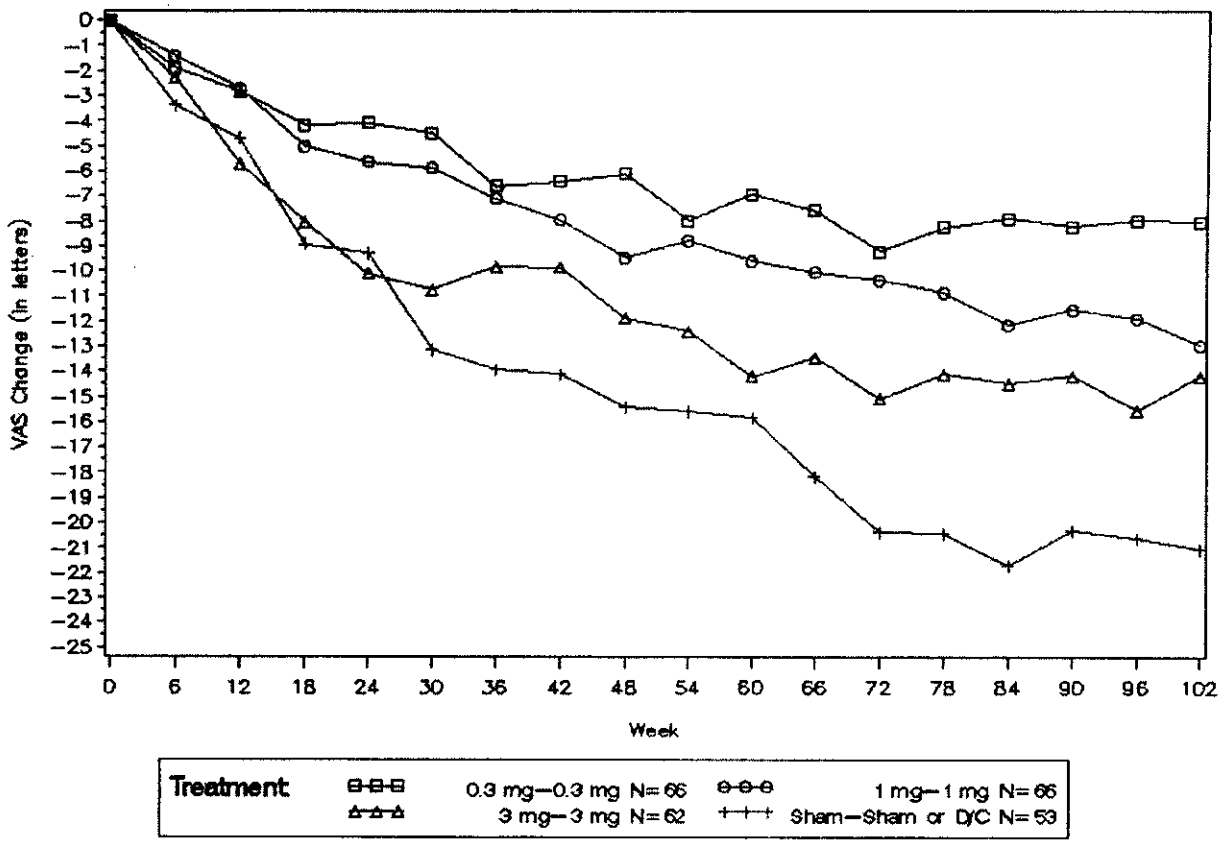
EOP1004: Mean Visual Acuity Over Time ITT (LOCF)



APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

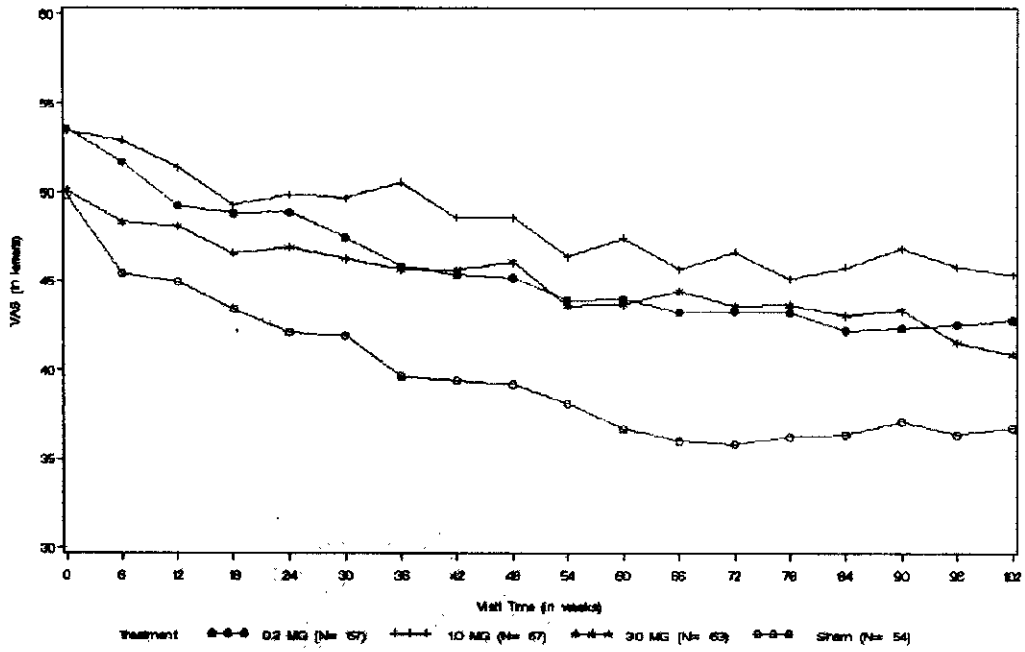
EOP1004 Mean Changes in Visual Acuity (LOCF), Baseline to Week 102



Number of On-Study PDT Treatments Received in the 2nd Year – Study EOP1004

	0.3 mg-0.3mg N=66	**1 mg-1mg N=66**	**3mg-3mg N=62**	**Sham-sham or d/c N=53**
No of PDT treatments	8	14	6	18

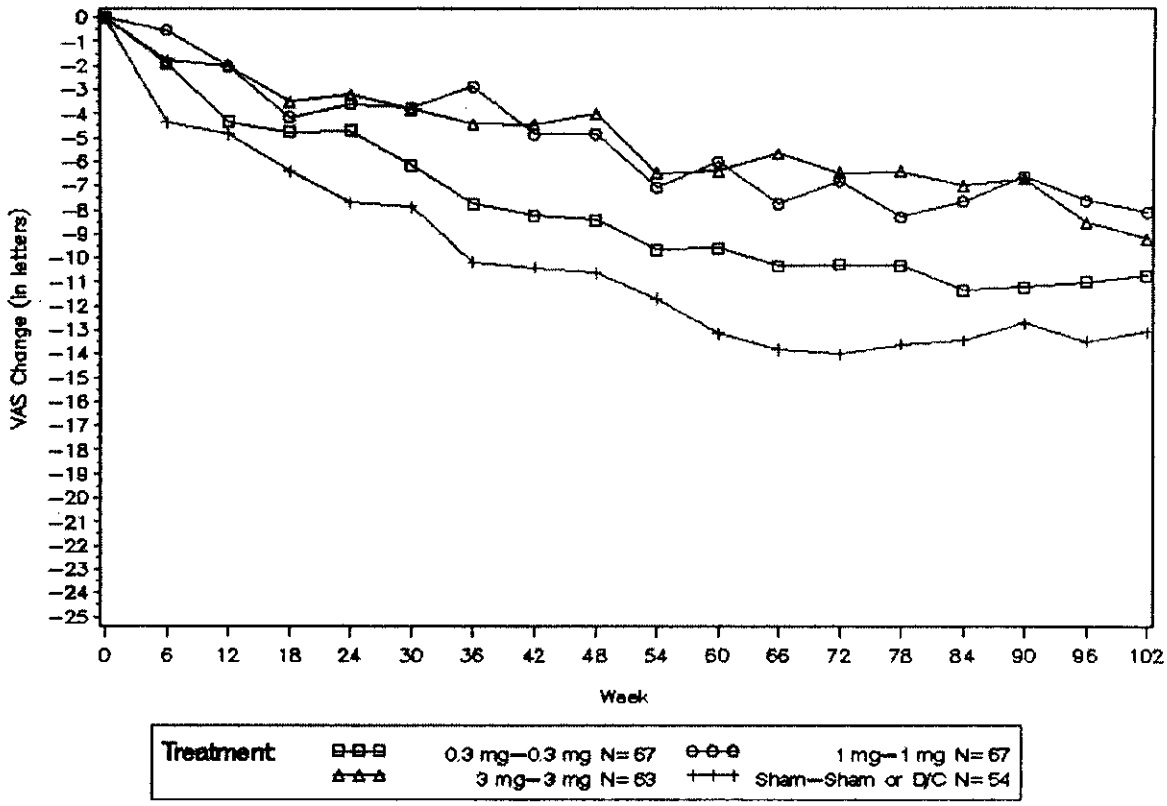
EOP1003: Mean Visual Acuity Over Time ITT (LOCF)



APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

EOP1003 Mean Changes in Visual Acuity (LOCF), Baseline to Week 102



Number of On-Study PDT Treatments Received in the 2nd Year – Study EOP1003

	0.3 mg-0.3mg N=67	1 mg-1mg N=67	3mg-3mg N=63	Sham-sham or d/c N=54
No of PDT treatments	1	6	2	3

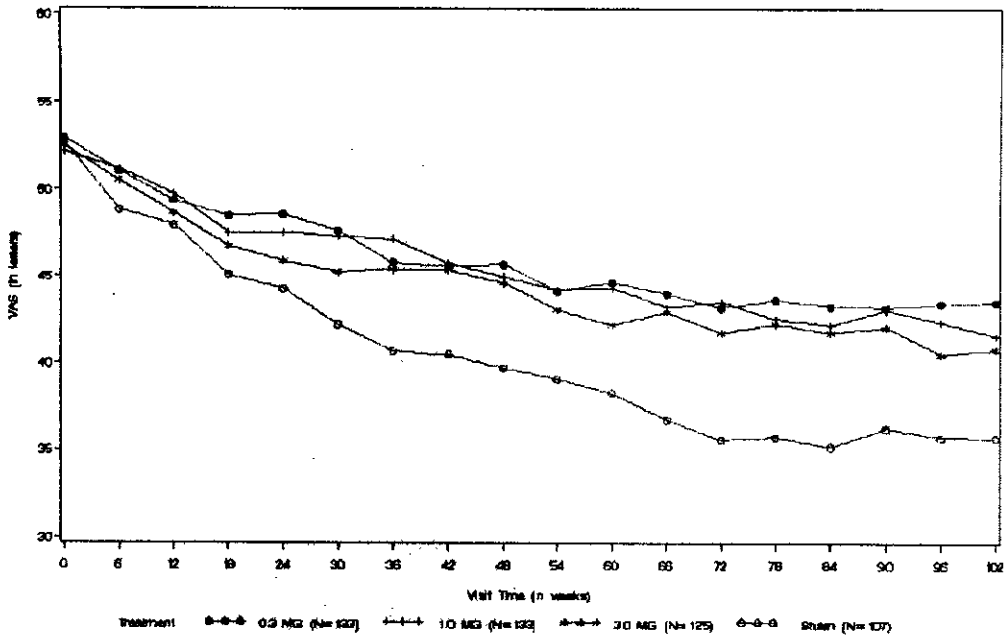
Reviewer's Comments:

Patients in all pegaptanib treatment groups as well as the sham group show a slower rate of vision loss in the 2nd year of study than in the 1st year for both studies EOP1004 and EOP1003. There appears to be stabilization of vision during the second year of treatment in the 0.3 mg and 3 mg treatment groups for study EOP1004. This

stabilization is also seen in Study EOP1003 for the 0.3 mg and 1 mg pegaptanib groups as well as patients in the sham group.

APPEARS THIS WAY
ON ORIGINAL

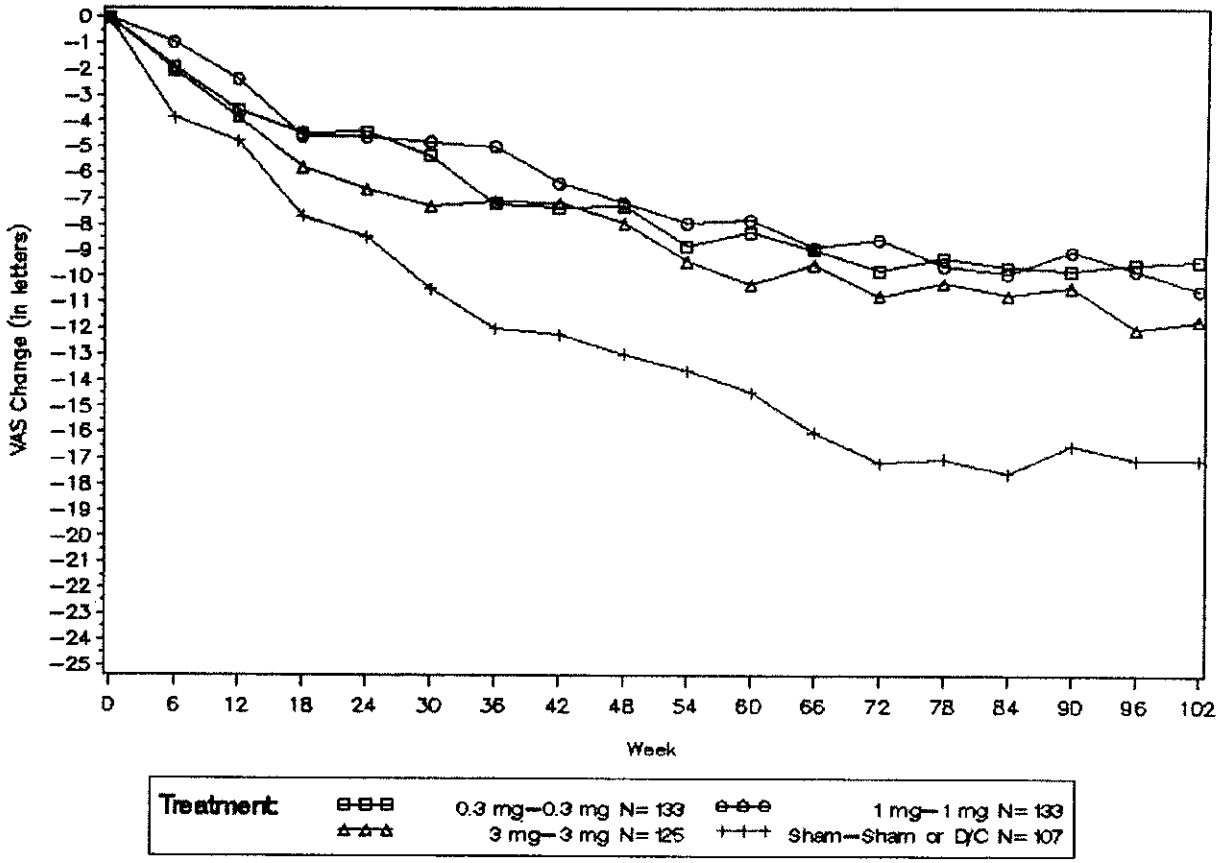
Combined Studies: Mean Visual Acuity Over Time – ITT (LOCF)



APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

EOP1004 & EOP1003 Mean Changes in Visual Acuity (LOCF), Baseline to Week 102



Number of On-Study PDT Treatments Received in the 2nd Year – Combined Studies

	0.3 mg-0.3mg N=133	1 mg-1mg N=133	3mg-3mg N=125	Sham-sham or d/c N=107
No of PDT treatments	9	16	8	21

Reviewer's Comments:

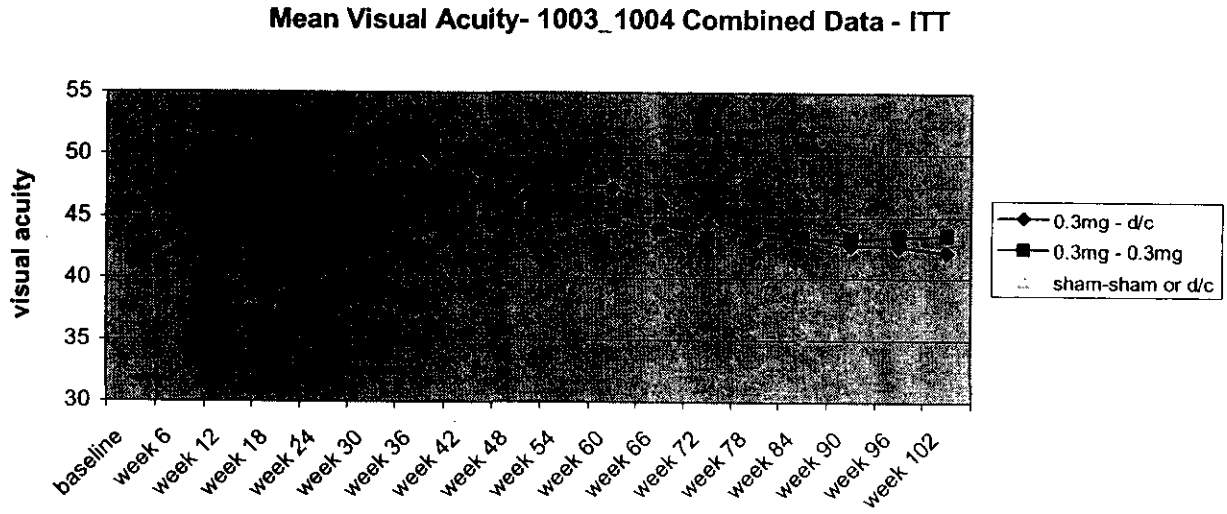
The rate of vision loss in the combined data set is similar for all active treatment groups. The results for all treatment groups including sham demonstrate a progressive vision loss throughout the first year of treatment followed by a plateau effect in the second year. Overall, there is less vision loss in the pegaptanib treatment groups as compared to

sham, however there is minimal differentiation demonstrated between the three doses of pegaptanib studied.

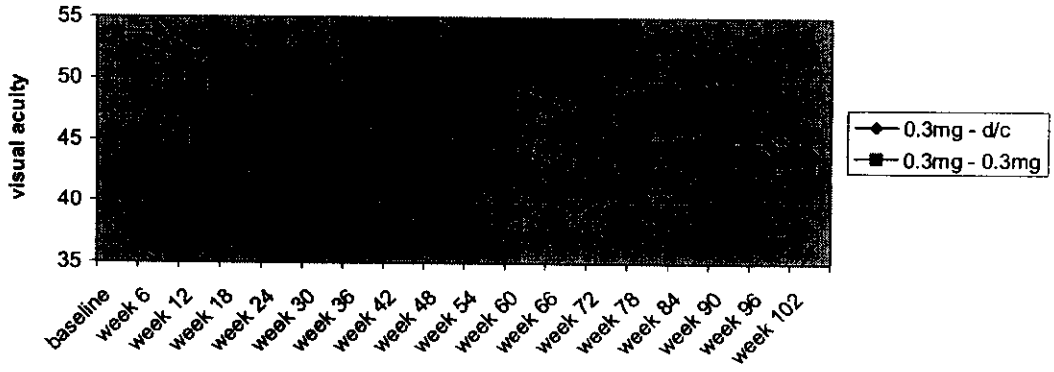
The following section of the review has been done to address the issue of the need for continuing injections of pegaptanib sodium after the 1st year of treatment Based on the results of the responder analysis, the was no demonstration of efficacy for the 0.3 mg dose during the 2nd year of the study based on replicative trials. However, there may still be a reason to continue injections after the first year of treatment despite the lack of demonstrated efficacy. Theoretically, further injections may be needed to maintain the positive visual acuity effects gained during the 1st year of treatment. The questions was addressed by evaluating those patients who were in the 0.3mg group during the 1st year of study and then subsequently discontinued treatment or remained on the 0.3 mg dose.

The three patient populations analyzed were:

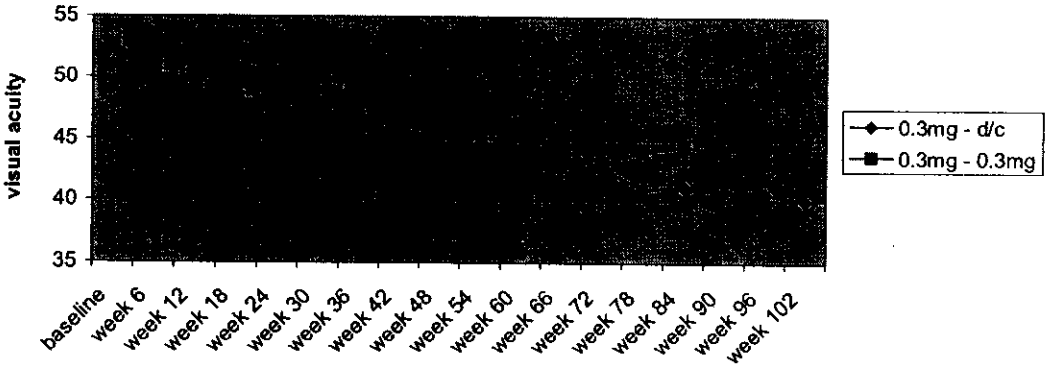
0.3mg-0.3mg: patients who were on 0.3mg for the 1st and 2nd years
0.3mg-sham: patients who were on 0.3mg during the 1st year and were re-randomized to sham during the 2nd year.
Sham-sham or d/c: patients who were in the sham group during the 1st year and re-randomized to sham or to discontinuation of treatment during the second year



Mean Visual Acuity - EOP1003



Mean Visual Acuity - EOP1004



Reviewer's comments:

The mean visual acuity results for study EOP1003 appear to favor the 0.3mg-d/c group in study EOP1003. However, the separation between the two groups during the first year of treatment may be artificial since both groups are receiving the same dose. In study EOP1004, this separation is not seen and the results appear to favor the 0.3mg-0.3mg group. For the combined data set, the results are equivocal concerning the need for further injections beyond the first year of treatment.

Safety Analysis

Number of Patients discontinued Cohort 1

	0.3 mg	1 mg	3 mg	Sham
Study EOP 1004	N=66	N=66	N=62	N=26
	18 (27%)	14 (21%)	13 (21%)	1 (4%)
Study EOP 1003	N=67	N=67	N=63	N=27
	9 (13%)	9 (13%)	8 (13%)	3 (11%)

Reasons for Discontinuation from Treatment Cohort 1 – Study EOP1004 and EOP1003

Number of patients	0.3 mg N=133	1.0 mg N=133	3.0mg N=125	Sham N=53
Death	1 (1%)	1 (1%)	0	0
Adverse event	5 (4%)	2 (2%)	4 (3%)	2 (4%)
Protocol violation	0	0	0	0
Investigator/sponsor decision	2 (2%)	1 (1%)	4 (3%)	0
Patient request	13 (10%)	16 (12%)	12 (10%)	2 (4%)
Lost to follow-up	1 (1%)	1 (1%)	0	0
Other	5 (4%)	2 (2%)	1 (1%)	0

Reviewer's Comments:
The majority of patients were reported as discontinued due to patient request. This may be indicative of adverse experiences associated with the drug that were intolerable to the patient. Case report forms have not been provided in this submission which are needed to adequately evaluate the reasons for discontinuation.

First and Second Year Adverse Events Reported in > 1% of Subjects (Cohort 1)– Safety Population – Studies EOP1003 and EOP1004

Number of subjects System organ class and preferred term	0.3 mg N=128	1 mg N=126	3 mg N=120	Sham N=51
Eye Disorders				
Punctate keratitis	54 (42%)	50 (40%)	50 (42%)	23 (45%)
[redacted]	50 (39%)	50 (40%)	53 (44%)	11 (22%)
[redacted]	48 (38%)	58 (46%)	53 (44%)	17 (33%)
Cataract	42 (33%)	46 (37%)	50 (42%)	19 (37%)
Visual acuity reduced	41 (32%)	32 (25%)	34 (28%)	17 (33%)
[redacted]	35 (27%)	37 (29%)	55 (46%)	4 (8%)
[redacted]	32 (25%)	28 (22%)	34 (28%)	11 (22%)

Number of subjects System organ class and preferred term	0.3 mg N=128	1 mg N=126	3 mg N=120	Sham N=51
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Macular degeneration	19 (15%)	20 (16%)	17 (14%)	12 (24%)
Eye discharge	18 (14%)	16 (13%)	14 (12%)	9 (18%)
Eye irritation	18 (14%)	18 (14%)	14 (12%)	7 (14%)
Abnormal sensation in eye	17 (13%)	17 (13%)	12 (10%)	8 (16%)
Conjunctival hemorrhage	16 (13%)	14 (11%)	8 (7%)	7 (14%)
Vision blurred	16 (13%)	14 911%)	12 (10%)	8 (16%)
Eye redness	15 (12%)	12 (10%)	17 (14%)	7 (14%)
Retinal hemorrhage	15 (12%)	17 (13%)	13 (11%)	6 (12%)
Eye pruritus	14 (11%)	10 (8%)	21 (18%)	8 (16%)
Lacrimation increased	14 (11%)	24 (19%)	17 (14%)	55 (15%)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Photophobia	11 (9%)	11 (9%)	10 (8%)	5 (10%)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Dry eye	10 (8%)	13 (10%)	13 (11%)	7 (14%)
Vitreous detachment	10 (8%)	13 (10%)	8 (7%)	7 (14%)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Conjunctival hyperemia	7 (5%)	7 (6%)	6 (5%)	3 (6%)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Eyelid edema	5 (4%)	10 (8%)	11 (9%)	26 (7%)
Posterior capsule opacification	5 (4%)	1 (1%)	4 (3%)	2 (4%)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Corneal dystrophy	4 (3%)	3 (2%)	2 (2%)	2 (4%)
Corneal epithelium defect	4 (3%)	5 (4%)	8 (7%)	4 (8%)
Eyelid ptosis	4 (3%)	3 (2%)	4 (3%)	2 (4%)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Corneal abrasion	3 (2%)	4 (3%)	5 (4%)	3 (6%)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Keratitis	2 (2%)	3 (2%)	2 (2%)	3 (6%)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Mydriasis	2 (2%)	2 (2%)	0	1 (2%)
Pupillary reflex impaired	2 (2%)	1 (1%)	1 (1%)	2 (4%)

Number of subjects **System organ class and preferred term**	**0.3 mg** **N=128**	**1 mg** **N=126**	**3 mg** **N=120**	**Sham** **N=51**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Retinal exudates	3 (2%)	2 (2%)	0	1 (2%)
Retinal Scar	3 (2%)	2 (2%)	1 (1%)	1 (2%)
Blood and Lymphatic system disorders				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocythemia	0	2 (2%)	0	2 (1%)
Cardiac disorders				
Atrial fibrillation	3 (2%)	3 (2%)	2 (2%)	1 (2%)
Arrhythmia	1 (1%)	4 (3%)	1 (1%)	1 (2%)
Cardiac failure congestive	3 (2%)	2 (2%)	1 (1%)	4 (8%)
Bradycardia	1 (1%)	2 (2%)	2 (2%)	4 (8%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	0	1 (1%)	2 (2%)	1 (2%)
Myocardial ischemia	0	2 (2%)	1 (1%)	0
Atrioventricular block	0	0	2 (2%)	1 (2%)
Cardiomegaly	0	2 (2%)	0	1 (2%)
Ear and Labyrinth				
Vertigo	4 (3%)	8 (6%)	2 (2%)	14 (4%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cerumen impaction	1 (1%)	2 (2%)	0	3 (1%)
Endocrine Disorders				
Acquired hypothyroidism	0	1 (1%)	3 (3%)	4 (1%)
Hyperthyroidism	0	0	2 (2%)	2 (1%)
Gastrointestinal disorders				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	3 (2%)	6 (5%)	2 (2%)	1 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	3 (2%)	4 (3%)	1 (1%)	1 (2%)
General disorders and administration site conditions				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Edema peripheral	4 (3%)	2 (2%)	4 (3%)	2 (4%)
Asthenia	2 (2%)	2 (2%)	2 (2%)	1 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations				

Number of subjects System organ class and preferred term	0.3 mg N=128	1 mg N=126	3 mg N=120	Sham N=51
[redacted]	[redacted]	[redacted]	[redacted]	3 (6%)
Influenza	12 (9%)	5 (4%)	6 (5%)	5 (10%)
Urinary tract infection				
[redacted]	[redacted]	[redacted]	[redacted]	2 (4%)
Sinusitis	3 (2%)	5 (4%)	6 (5%)	3 (6%)
Gastroenteritis viral	2 (2%)	1 (1%)	3 (3%)	2 (4%)
[redacted]	[redacted]	[redacted]	[redacted]	0
Injury, poisoning and procedural complications				
Post procedural pain	3 (2%)	4 (3%)	3 (3%)	1 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	0
Skin laceration	2 (2%)	3 (2%)	3 (3%)	2 (4%)
Abrasion	3 (2%)	0	2 (2%)	3 (6%)
[redacted]	[redacted]	[redacted]	[redacted]	0
Metabolism and nutrition disorders				
[redacted]	[redacted]	[redacted]	[redacted]	2 (4%)
[redacted]	[redacted]	0	[redacted]	1 (2%)
[redacted]	[redacted]	0	[redacted]	0
[redacted]	[redacted]	0	[redacted]	0
[redacted]	[redacted]	[redacted]	0	0
[redacted]	[redacted]	0	[redacted]	0
Musculoskeletal and connective tissue disorders				
Back pain	7 (5%)	8 (6%)	8 (7%)	5 (10%)
Arthralgia	8 (6%)	4 (3%)	4 (3%)	3 (6%)
[redacted]	[redacted]	[redacted]	[redacted]	1 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	1 (2%)
Osteoarthritis	2 (2%)	4 (3%)	2 (2%)	1 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	0
Muscle cramp	2 (2%)	0	3 (3%)	1 (2%)
[redacted]	[redacted]	0	0	0
[redacted]	[redacted]	[redacted]	0	0
Neoplasms				
Basal cell carcinoma	2 (2%)	4 (3%)	2 (2%)	2 (4%)
Prostate cancer	2 (2%)	1 (1%)	2 (2%)	1 (2%)
[redacted]	[redacted]	0	0	0
Nervous system disorders				
[redacted]	[redacted]	[redacted]	[redacted]	1 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	2 (4%)
[redacted]	[redacted]	2 (2%)	0	0
[redacted]	[redacted]	0	[redacted]	0
[redacted]	[redacted]	0	0	0
[redacted]	[redacted]	0	0	0
[redacted]	[redacted]	0	0	0
Psychiatric disorders				

Number of subjects System organ class and preferred term	0.3 mg N=128	1 mg N=126	3 mg N=120	Sham N=51
Depression	6 (5%)	8 (6%)	4 (3%)	1 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	0
[redacted]	[redacted]	0	0	0
Renal and urinary disorders				
[redacted]	[redacted]	[redacted]	0	0
[redacted]	[redacted]	[redacted]	0	0
Reproductive System				
[redacted]	[redacted]	[redacted]	0	0
Respiratory, thoracic and mediastinal disorders				
Nasopharyngitis	15 (12%)	17 (13%)	20 (17%)	7 (14%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	8 (6%)	5 (4%)	6 (5%)	4 (8%)
Pharyngitis	5 (4%)	3 (2%)	2 (2%)	2 (4%)
[redacted]	[redacted]	[redacted]	0	0
Dyspnea	2 (2%)	4 (3%)	7 (6%)	2 (4%)
Emphysema	2 (2%)	1 (1%)	1 (1%)	2 (4%)
Epistaxis	2 (2%)	2 (2%)	2 (2%)	1 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	0
[redacted]	[redacted]	[redacted]	0	0
[redacted]	[redacted]	[redacted]	[redacted]	0
Pulmonary embolism	2 (2%)	0	0	1 (2%)
Rhinorrhea	3 (2%)	1 (1%)	1 (1%)	1 (2%)
Skin and subcutaneous tissue disorders				
[redacted]	[redacted]	0	[redacted]	[redacted]
Cutis laxa	3 (2%)	2 (2%)	0	1 (2%)
Skin lesion	3 (2%)	0	1 (1%)	1 (2%)
Skin cysts	3 (2%)	0	0	1 (2%)
Vascular disorders				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension aggravated	4 (4%)	5 (4%)	3 (3%)	3 (6%)
Hypotension	3 (2%)	4 (3%)	2 (2%)	1 (2%)
[redacted]	[redacted]	0	[redacted]	0

Reviewer's comments:

Similar types of adverse events are seen in this combined second year data compared to the first year data as shown in the original NDA review. There are no new adverse events identified in this submission. Adverse events seen more frequently in the 0.3 mg group versus sham are highlighted. The majority of the most frequently occurring adverse events (i.e. >10%) in the drug group are those commonly seen after intraocular procedures including injections.

First and Second Year Ocular Adverse Events > 10% and/or Events that are Considered Potentially Vision Threatening – Safety Population

Event	0.3 mg N=128	1 mg N=126	3 mg N=120	Sham N=51
Punctate keratitis	54 (42%)	50 (40%)	50 (42%)	23 (45%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cataract	42 (33%)	46 (37%)	50 (42%)	19 (37%)
Visual acuity reduced	41 (32%)	32 (25%)	34 (28%)	17 (33%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Macular degeneration	19 (15%)	20 (16%)	17 (14%)	12 (24%)
Eye discharge	18 (14%)	16 (13%)	14 (12%)	9 (18%)
Eye irritation	18 (14%)	18 (14%)	14 (12%)	7 (14%)
Abnormal sensation in eye	17 (13%)	17 (13%)	12 (10%)	8 (16%)
Conjunctival hemorrhage	16 (13%)	14 (11%)	8 (7%)	7 (14%)
Vision blurred	16 (13%)	14 (11%)	12 (10%)	8 (16%)
Eye redness	15 (12%)	12 (10%)	17 (14%)	7 (14%)
Retinal hemorrhage	15 (12%)	17 (13%)	13 (11%)	6 (12%)
Eye pruritus	14 (11%)	10 (8%)	21 (18%)	8 (16%)
Lacrimation increased	14 (11%)	24 (19%)	17 (14%)	55 (15%)
[redacted]	[redacted]	[redacted]	5 (4%)	[redacted]
[redacted]	[redacted]	[redacted]	0	0
[redacted]	[redacted]	[redacted]	1 (1%)	0
Retinal Artery Occlusion	1 (1%)	3 (2%)	0	1 (2%)
Retinal Detachment	0	4 (3%)	2 (2%)	1 (2%)

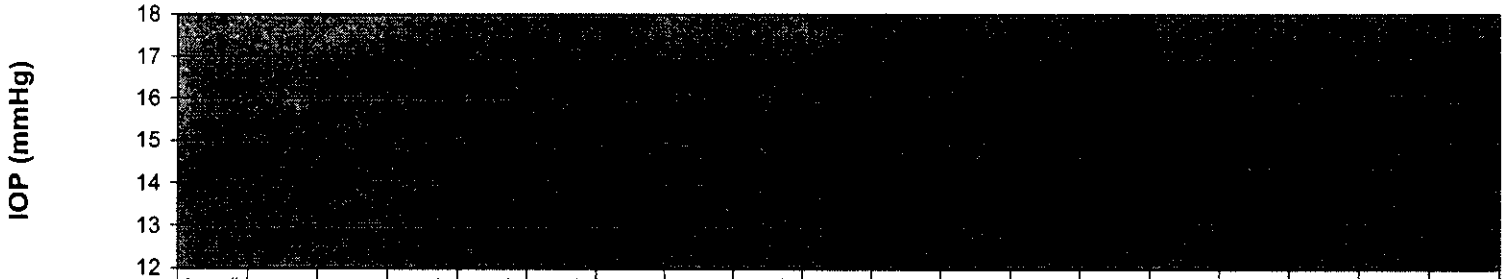
First and Second Year Rate of Endophthalmitis for Each Cohort – Study EOP1003 and EOP1004 – Safety Population

	0.3 mg	**1 mg**	**3 mg**	**Sham**
2nd year data	N=258	N=256	N=245	N=265
Cohort 1	0	0	0	0
Cohort 2	0	0	0	0
Cohort 3	0	**1 (2%)**	**3 (5%)**	0
1st year data	N=295	N=301	N=296	N=298
	6 (2%)	**3 (1%)**	**3 (1%)**	**0**

Reviewer's Comments:
There is a lower risk of endophthalmitis seen in the 2nd year of treatment compared to the 1st year (0.5% vs. 1.4%).

APPEARS THIS WAY
ON ORIGINAL

IOP (mmHg) at All Study Visits - Study EOP1003 and EOP1004 - ITT Population



	baseline	week 1	week 7	week 13	week 19	week 25	week 31	week 37	week 43	week 49	week 55	week 61	week 67	week 73	week 79	week 85	week 91	week 97	week 102
0.3 mg	15.5	14.9	15	14.8	15.2	14.7	15.2	14.9	14.9	15	14.9	14.8	14.6	14.8	14.8	14.5	14.2	14.5	15.2
1 mg	15.2	15.2	15.5	15.2	15.1	15	14.9	14.8	15.3	14.9	14.9	15	15.4	15.2	15.3	14.8	15.1	14.9	15.1
3 mg	15.6	15.9	15.6	15.8	16	16	16.2	16.1	16.2	16.9	16.1	16.3	16.5	15.9	16.3	16.3	16.4	16.2	16.3
Sham	14.8	14.9	15	14.6	15	14.9	15.4	14.4	14.5	14.4	14.5	14.5	13.6	14.3	13.9	14.6	14.6	13.4	14.4

Reviewer's Comments:

During this two year study, the baseline IOP for all treatment groups remains unchanged. There does not appear to be a risk of hypotony associated with multiple penetrations of the globe over a 2 year period.

Conclusions:

- *All active treatment groups of pegaptanib sodium show a diminished effect in the primary efficacy endpoint (number of patients who loss ≤ 15 letters of vision) at week 102.*

- *Visual acuity appears to stabilize in the second year of the study for the 0.3 mg treatment group in replicative studies; however, this phenomenon is also seen in the sham treatment group.*

- *The effectiveness of 0.3mg pegaptanib sodium is less in the second year than in the first.*

- *The need for continued injections every 6 weeks with 0.3 mg pegaptanib sodium cannot be definitively determined from this database.*

- *No new safety concerns were identified in the second year data. The majority of adverse events identified continue to be those commonly seen with intraocular procedures including intravitreous injections.*

- *There was a lower risk of endophthalmitis seen in the 2nd year of treatment compared to the 1st year (0.5% vs. 1.4%).*

Recommendations:

The original conclusions of the NDA review remain unchanged. Pegaptanib sodium 0.3% is approvable from a clinical perspective for the treatment of the neovascular form of age-related macular degeneration. The labeling should reflect the diminished efficacy demonstrated in the second year of the study.

Jennifer D. Harris, M.D.
Medical Officer

cc: NDA 21-756
HFD-550/Div Files
HFD-550/CSO/Puglisi
HFD-520/CHEM
HFD-550/PHARM/ZChen
HFD-550/MO/Harris
HFD-550/SMO/Chambers

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jennifer Harris
12/7/04 09:07:57 AM
MEDICAL OFFICER

Wiley Chambers
12/7/04 04:20:25 PM
MEDICAL OFFICER

CLINICAL REVIEW

Medical Officer's Review of NDA 21-756

Proprietary Name:	**Macugen**
Tradename:	**pegaptanib sodium injection**
Applicant:	**Eyetech Pharmaceuticals** **500 Seventh Avenue, 18th Floor** **New York, New York 10018**
NDA Drug Classification:	**1P**
Proposed Indication:	**The treatment of the neovascular form of age-related macular degeneration.**
Date of Submission:	**March 18, 2004**
Date of Review:	**July 27, 2004**
Reviewer:	**Jennifer Harris, M.D.**

Table of Contents

Clinical Review for NDA 21-756

Executive Summary

I. Recommendations

A. Recommendation on Approvability

NDA 21-756 is approvable for the treatment of the neovascular form of age-related macular degeneration pending the receipt and review of the 120-day safety update; revised drug product specifications and satisfactory labeling.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

It is recommended that the sponsor conduct studies postmarketing to address the possible neurotropic effects of pegaptanib sodium. This was raised as a concern in the advisory committee meeting.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

AMD is the leading cause of blindness in developed countries with approximately 15 million people with the disease in the United States. AMD is characterized as a progressive degenerative disease of the macula. There are two forms of AMD: neovascular and non-neovascular. The non-neovascular form of AMD is more common and leads to a slow deterioration of the macula with a gradual loss of vision over a period of years. The neovascular form of the disease is responsible for the majority of cases of severe vision loss and is due to proliferation of abnormal blood vessels behind the retina. These blood vessels leak blood and fluid into the retina, which results in visual abnormalities. The development of these abnormal blood vessels is due in part to the activity of VEGF (vascular endothelial growth factor) and its inhibition is expected to impact on the onset and/or severity of vision loss associated with the proliferation of abnormal blood vessels.

Macugen (pegaptanib sodium injection) has been developed by Eyetech, Pharmaceuticals for the treatment of the neovascular form of age-related macular

degeneration (AMD). In vitro studies have suggested that pegaptanib binds to VEGF and inhibits its binding to cellular receptors. Macugen's anti-VEGF activity is expected to inhibit abnormal blood vessel proliferation and therefore decrease the vision loss associated with the neovascular form of AMD.

Macugen is administered as an intravitreal injection which is dosed every six (6) weeks. It has been study in approximately 966 patients during the clinical development program. During the two phase 3 trials approximately 295 patients received the 0.3 mg dose, 301 patients received the 1mg dose and 296 patients received the 3 mg dose.

B. Efficacy

The submitted studies in NDA 21-756 are sufficient to establish efficacy for the use of pegaptanib sodium 0.3 mg in the treatment of the neovascular form of age-related macular degeneration. The two phase 3 studies show replicative results in the ability of pegaptanib sodium to reduce the risk of vision loss in patients with neovascular AMD by approximately 15% when administered every six weeks compared to sham.

C. Safety

The majority of safety concerns raised in the review of this application are likely attributed to the procedure required to administer pegaptanib sodium and not to the drug product itself. The majority of adverse events seen in the database are those commonly seen with intraocular procedures including intravitreous injections. There is concern raised in this database over the rate of endophthalmitis. This event is most likely due to contamination during the procedure itself and not to the drug product since most cases were infectious in nature. The labeling will need to reflect the risk of this administration related adverse event and the importance of the use of sterile technique. This will allow for physicians and patients to be adequately informed about this risk and steps to take to minimized its occurrence.

D. Dosing

Adequate dose ranging studies were conducted during drug development. The 0.3 mg dose of pegaptanib sodium has been demonstrated to be safe and effective in two controlled phase 3 trials. The dosing interval (every 6 weeks) chosen by the apllicant was not varied during the development program, therefore there is no clinical data available to assess the adequacy of this dosing interval.

E. Special Populations

The sponsor has adequately evaluated gender effects on both the safety and efficacy outcomes. Sub-group analyses did not reveal any difference in the primary efficacy endpoint between males and females. The safety profile seen in male and females is similar. The types and rates of adverse events seen in the two groups are consistent.

The trials for this indication were conducted in a population that was overwhelmingly elderly and white. This is reflective of the population which is mostly affected by this disease and does not reflect an issue with recruitment. The number of patients outside of this demographic were too small to make any definitive conclusion about the safety and efficacy; however, based on a subset analysis it does not appear that there are any age, race or ethnicity effects.

Pediatric trials have not been conducted for this drug. The indication being sought is for age-related macular degeneration which is a disease seen exclusively in the adult population.

The demographics of the patients enrolled in the trial during the development program for this product are representative of the targeted population. There is no additional data need from other populations.

Clinical Review

I. Introduction and Background

AMD is the leading cause of blindness in developed countries with approximately 15 million people with the disease in the United States. AMD is characterized as a progressive degenerative disease of the macula. There are two forms of AMD: neovascular and non-neovascular. The non-neovascular form of AMD is more common and leads to a slow deterioration of the macula with a gradual loss of vision over a period of years. The neovascular form of the disease is responsible for the majority of cases of severe vision loss and is due to proliferation of abnormal blood vessels behind the retina. These blood vessels leak blood and fluid into the retina, which results in visual abnormalities. The development of these abnormal blood vessels is due in part to the activity of VEGF (vascular endothelial growth factor) and its inhibition is expected to impact on the onset and/or severity of vision loss associated with the proliferation of abnormal blood vessels.

Macugen (pegaptanib sodium injection) has been developed for the treatment of the neovascular form of age-related macular degeneration (AMD). In vitro studies have suggested that pegaptanib binds to VEGF and inhibits its binding to cellular receptors. Macugen's anti-VEGF activity is expected to inhibit abnormal blood vessel proliferation and therefore decrease the vision loss associated with the neovascular form of AMD.

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Proprietary Name:	Macugen
Tradename:	pegaptanib sodium
Sponsor:	Eyetech Pharmaceuticals 500 Seventh Avenue, 18th Floor New York, New York 10018
NDA Drug Classification:	1P
Pharmacologic Category	Vascular Endothelial Growth Factor (VEGF) Inhibitor
Proposed Indication:	The treatment of the neovascular form of age-related macular degeneration.
Dosage Form and Route of Administration	Intravitreal Injection

B. State of Armamentarium for Indication(s)

Macugen (pegaptanib sodium injection) has been developed for the treatment of the neovascular form of age-related macular degeneration (AMD). Currently, there is only one treatment approved for use in AMD. Photodynamic therapy (PDT) with verteporfin is approved for patients with the predominantly classic form of AMD.

C. Important Milestones in Product Development

Milestones leading up to this NDA submission:

4/26/01 – End of Phase 2 Meeting
1/18/01 – Fast Track Designation Granted

8/27/04 – Advisory Committee Meeting

A decision was made to convene an advisory committee meeting for pegaptanib to present the efficacy and safety findings contained in the NDA. This was due to the fact that this drug product is the first in its class that will potentially be approved for this indication. Additionally, the route/regimen and frequency of administration (repeated intravitreal injections) required for this drug product is atypical for any currently approved ophthalmic drug products.

The advisory committee concluded that efficacy had been demonstrated for the use of pegaptanib sodium in the treatment of neovascular age-related macular degeneration. Overall, the committee concluded that the product was safe, however, there were recommendations to monitor for longer-term effects and to educate physicians concerning injection procedures to minimized the rate of endophthalmitis.

D. Other Relevant Information

Pegaptanib Sodium is a new molecular entity. It has not been approved for marketing in or outside of the United States at any time by any sponsor and has not been withdrawn from marketing for any reason.

E. Important Issues with Pharmacologically Related Agents

There are no other drugs in this pharmacologic class currently marketed for ophthalmic use. There are products in this class currently under investigation. There have been no additional issues raised with this class of agents outside of those identified in this NDA review.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

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

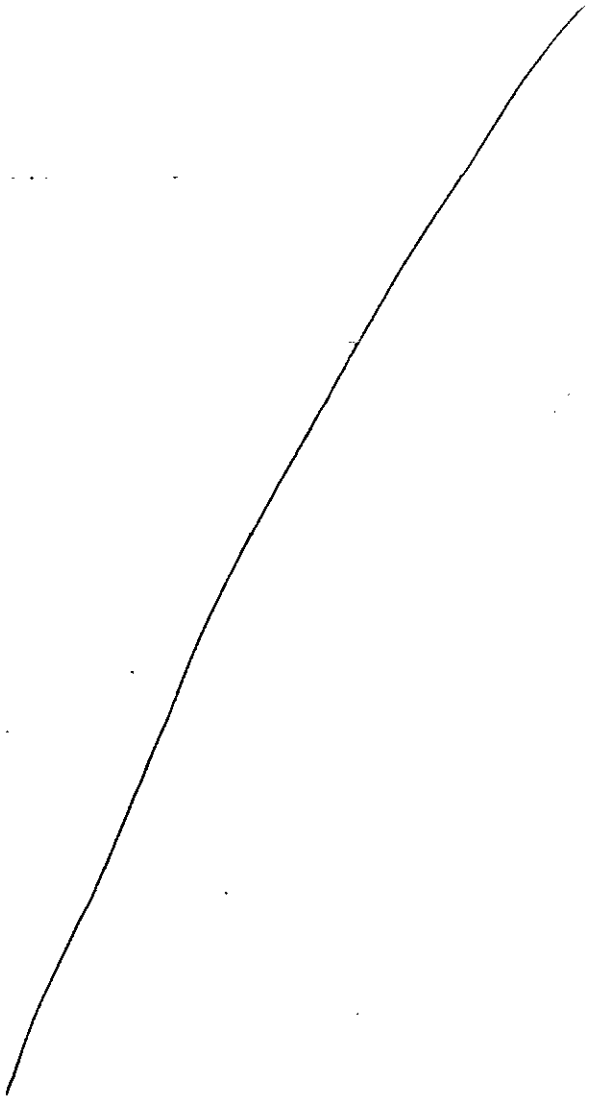
Name of Ingredients	Reference to Standards	Function	Solution Composition mg/mL	Unit Dosage Composition 0.3 mg/90 µL	Percent (w/v)
Pegaptanib Sodium	In-house standard	Drug substance	3.47[b]	0.3 mg[b]	0.3[b]
Monobasic Sodium Phosphate Monohydrate	USP	pH buffering agent	0.77	0.069 mg	0.077
Dibasic Sodium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

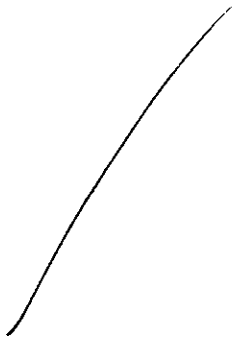
a Quantities are calculated

[b] Based on a theoretical potency of 100% for pegaptanib sodium with no overage. The actual weight varies according to the actual potency of pegaptanib sodium used. Compositions calculated based on oligonucleotide moiety

[c] For pH adjustment

Analytical Specification for Macugen Injection, 0.3 mg





III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

PK characteristics:

- Following intravitreous administration, pegaptanib is systemically available, and displays non-linear pharmacokinetics at or doses above 1 mg. At 2 mg/eye and 3 mg/eye dose treatment groups, plasma pegaptanib concentrations increased disproportionately with dose.
- Mean terminal elimination half-life of pegaptanib is 10 days with individual values ranging from 2 to 19 days. During repeated dosing when administered every 4 or 6 weeks, pegaptanib accumulation is minimal/negligible, if any.
- Pegaptanib metabolism is not fully characterized, however, it is expected to be metabolized by nucleases to shorter chains of nucleotides. Because of its molecular structure, typical P450 drug-drug interactions are not expected. However, pharmacodynamic interactions with patients taking anti-hypertensive or IOP lowering agents have not been studied.
- Renal impairment (<70 mL/min CrCL) results in significant decrease in pegaptanib clearance.

B. Pharmacodynamics

Pharmacodynamic evaluations have not been studied for this drug product.

IV. Description of Clinical Data and Sources

A. Overall Data

This review is based on the results of the applicant supported trials for AMD conducted under IND 56,503. Two phase 3 safety and efficacy trials were submitted to support the indication currently being sought by the applicant. In addition, the results of four early phase 1/2 dose ranging and safety trials were also submitted.

This NDA was submitted in Common Technical Document (CTD) format in electronic and paper media (angiograms only) for review.

B. Tables Listing the Clinical Trials

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

EOP1001	Phase 1/2, multi-center, open label, multiple dose in patients following PDT administration	Total of 3 intravitreous injections of 3 mg pegaptanib sodium/ eye, 28 days apart	11 patients 50 years of age with predominantly classic subfoveal CNV secondary to exudative AMD	BCVA, AEs, IOP, laboratory parameters, vital signs, DLT, PK parameters, immune response, requirement for PDT administration, local ocular events
EOP1006	Phase 2 multi-center, randomized, multiple dose, open label cohort	Intravitreous injections of 3 mg pegaptanib sodium/ eye every 6 weeks for 54 weeks	37 patients 50 years of age with subfoveal CNV secondary to exudative AMD (Study is ongoing in 147 patients)	AE, local ocular events, IOP, laboratory parameters, vital signs, PK parameters, immune response
Development Trials for Additional Indications				
Studies in Diabetic Macular Edema (DME)				
EOP1002	Phase 1/2, multi-center, multiple dose open label,	Intravitreous injections of 3 mg pegaptanib sodium/ eye every 6 weeks for 12 to 30 weeks	10 patients 18 years of age with clinically significant DME	AEs, BCVA, laboratory parameters, IOP, retinal thickening, local ocular events
EOP1005	Phase 2, multi-center, randomized, sham-injection controlled, double masked, dose finding	Intravitreous injections of either 0.3, 1.0 and 3 mg pegaptanib sodium/ eye or sham every 6 weeks for 12 to 30 weeks	169 patients 18 years of age with clinically significant DME **(Study is ongoing)**	Retinal thickening, BCVA, AEs, IOP, laboratory parameters, local ocular events, need for laser at 12 weeks
Studies in Von Hippel-Lindau Disease (VHL)				
EOP1007	Phase 1/2, open-label, non-randomized, pilot	Intravitreous injections of 3 mg pegaptanib sodium/ eye every 6 weeks for 30 to 54 weeks	5 patients 18 years of age with severe ocular VHL tumors	BCVA, macular thickening, fluorescein leakage, disease progression, AEs, local ocular events, IOP.

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

C. Postmarketing Experience

There is no postmarketing experience with this drug. Macugen is not approved in any other country.

D. Literature Review

This product is a new molecular entity developed by the applicant. There is no data in the published literature pertinent to this drug product other than that submitted by the applicant.

V. Clinical Review Methods

A. How the Review was Conducted

This review evaluated the results of the two phase 3 trials submitted by the applicant. Each individual study was evaluated in depth to determine if the data supported the primary efficacy endpoint. The integrated safety and efficacy database was finally evaluated to determine the overall risk/benefit profile for this drug product.

B. Overview of Materials Consulted in Review

This review was based on data submitted by the sponsor submitted in Common Technical Document (CTD) format in electronic and paper media (angiograms only) for review.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI was requested to investigate four of the clinical sites in the phase 3 studies. The audits have not been competed at this time. The results will be reviewed for any data integrity issues once completed.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

These studies were conducted in accordance with the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCPs), the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, South Africa and Scotland), and in compliance with relevant regulations for informed consent and protection of subject rights in the country of conduct.

Before initiation of the study, the protocol and the patient informed consent provisions were reviewed and approved by the appropriate ethics committees (EC) or institutional review boards (IRB) for each of the centers involved in the study. The studies began only after receiving written approval from each EC/IRB.

E. Evaluation of Financial Disclosure

Eyetech has certified that [redacted]

[redacted] Dr [redacted] and Dr [redacted] were certified to hold financial interests with the sponsor however these interests were not significant as defined in 21 CFR 54.2(b). Both were investigators for [redacted] Dr. [redacted] enrolled [redacted] and Dr. [redacted] enrolled [redacted]. The number of patients enrolled by these investigators were to small to have any impact on the outcome of the phase 3 study.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The submitted studies in NDA 21-756 are sufficient to establish efficacy for the use of pegaptanib sodium 0.3 mg in the treatment of the neovascular form of age-related macular degeneration. The two phase 3 studies show replicative results in the ability of pegaptanib sodium to reduce the risk of vision loss in patients with neovascular AMD when administered every six weeks compared to sham.

B. General Approach to Review of the Efficacy of the Drug

The submitted phase 3 studies (EOP1003 and EOP1004) were reviewed independently to determine if the results of each trial demonstrated efficacy for the primary efficacy endpoint. The primary efficacy end point for each trial was a responder analysis of the proportion of patients who loss less than 15 letters of visual acuity from baseline (doubling of the visual angle) at 54 weeks. This analyses was done for two populations which represent ends of the data spectrum to evaluate the robustness of the results; an all randomized patient population with last-observation-carried-forward (LOCF) and the per-protocol population with observed cased only.

C. Detailed Review of Trials by Indication

Proposed Indication: The treatment of the neovascular form of age-related macular degeneration.

Study 1 – Study EOP1003

Title: A Phase 2/3 Randomized, Double-Masked, Controlled, Dose-Ranging, Multi-Center Comparative Trial, in Parallel Groups, to Establish the Safety and Efficacy of Intravitreous Injections of Pegaptanib Sodium (Anti-Vascular Endothelial Growth Factor [VEGF] Pegylated Aptamer) Given Every 6 Weeks for 54 Weeks, in Patients with Exudative Age- Related Macular Degeneration (AMD)

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

Study Design: This was a randomized, double-masked, controlled, dose-ranging, multi-center, comparative, Phase 2/3 trial, in parallel groups. The study was conducted internationally in Europe, Israel, Australia, South America and North America. The study has a 2 year duration with two randomization steps and is ongoing. Data from the first year on study are included in this report.

Clinical sites – Study EOP1003

Center Number	Principal Investigator	Center Location	Number of Subjects
Australia			
114	Andrew Chang, MD	Syndey	7
64	Jennifer Arnold, MD	Parramatta	34
65	Ian Constable, MD	St. Nedlands	12
66	Paul Mitchell, MD	Westmead	5
73	Robyn Guymer, MD	East Melbourne	16
131	Mark Gillies, MD	Sydney	12
Austria			
67	Michael Stur, MD	Vienna	11
116	Anton Haas, MD	Graz	4
Belgium			

Center Number	Principal Investigator	Center Location	Number of Subjects
113	Anita Leys, MD	Leuven	38
Brazil			
70	Michel Fara, MD	Sao Paulo	7
108	Marcos de Avila, MD	Sector Bureno	6
112	Carlos Moreira, MD	Curitiba	3
134	Jaco Lavinsky	Poro Alegre	5
Chile			
71	Jose Manuel Lopez, MD	Satiago	7
Colombia			
104	Franciso Rodriguez, MD	Colombia	18
Czech Republic			
119	Ivan Fiser, MD	Prague	11
Denmark			
72	Michael Larsen, MD	Herlev	9
France			
74	Francois Koenig, MD	Lyon	2
75	Gisele Soubrane, MD	Creteil	25
76	Jean-Francois Korobelnik, MD	Bordeau	5
78	Alain Gaudric, MD	Paris	3
Germany			
79	Stefan Dithmar, MD	Heidelberg	10
80	Daniel Pauleikhoff, MD	Munstser	1
81	Ulrike Schneider, MD	Tubingen	6
82	Peter Wiedemann, MD	Leipzig	14
83	B Kirchhof, MD	Koln	8
Hungary			
122	Ildiko Suveges, MD	Budapest	3
137	Jozsef Gyory, MD	Veszprem Korhaz	3
Israel			
84	Anat Loewenstein, MD	Tel-Aviv	11
85	Irit Rosenblatt, MD	Petach Tikva	11
103	Ayala Pollack, MD	Rehovot	7
Italy			
86	Rosario Brancato, MD	Milano	6
87	Francesco Bandello, MD	Udine	16
88	Felice Cardillo Piccolino, MD	Torino	10
89	Lfonso Giovannini, MD	Torrette Ancona	18
123	Ugo Menchini	Firenze	8
Poland			
127	Krystna Pecold, MD	Poznan	5
128	Jozef Kaluzny, MD	Bydgoszcz	5
Portugal			
93	Jose Cunha-Vaz, MD	Coimbra	25
Spain			
94	Marta Figueroa, MD	Madrid	7
136	Jose Ruiz Moreno, MD	Alicante	10
95	Jordi Mones, MD	Barcelona	14
Switzerland			
98	Constantin Pournaras, MD	Geneva	2
99	Leonides Zografos, MD	Lausanne	1

Center Number	Principal Investigator	Center Location	Number of Subjects
The Netherlands			
91	August Deutman, MD	Nijmegen	7
92	Reiner Schlingemann, MD	Amsterdam	15
United Kingdom			
100	Iain Chisholm, MD	Southampton	14
101	Noemi Lois, MD	Scotland	9
102	Usha Chakravarthy, MD	Belfast	18
130	Phil Hykin, MD	London	15
United States			
143	David Chow, MD	Illinois	4
144	K. Bailey Freund, MD	New York	4
145	Alexander Eaton, MD	Florida	15
146	Philip M. Falcone, MD	Connecticut	4
147	Patrick Higgins, MD	New Jersey	9
148	Keye Wong, MD	Florida	9
149	Matthew Thomas, MD	Missouri	-
153	Leonard Joffe, MD	Arizona	16
154	Jeffrey Heier, MD	Massachuesettes	21
156	John Thompson, MD	Maryland	-
Canada			
151	Murray Ersmus, MD	Saskatoon	-
155	Raul Garcia, MD	Saskatchewan	8

Reviewer's Comment:
The agency prefers patients to be randomized with at least ten patients per arm per center in multicenter trials so that interaction between centers can be evaluated.

Leonard Joffe, MD is also an investigator for study EOP1004 and enrolled 5 patients. This is the only overlap in principle investigators for the two phase three trials.

First Randomization
The trial had a parallel group design. At study entry, patients were allocated to one of the four treatment arms according to a stratified randomization system. The treatment groups were:
Arm A: pegaptanib sodium 0.3 mg intravitreous injection every 6 weeks for 48 weeks
Arm B: pegaptanib sodium 1 mg intravitreous injection every 6 weeks for 48 weeks
Arm C: pegaptanib sodium 3 mg intravitreous injection every 6 weeks for 48 weeks
Arm D: sham intravitreous injection every 6 weeks for 48 weeks

Patients were stratified by center and the following factors:

- Type of lesion (visible classic CNV area divided by total lesion area); defined as predominantly classic (>50% classic CNV), minimally classic (1-49% classic CNV), or occult with no classic (0% classic CNV)
- Whether the patient had received prior PDT therapy (one treatment maximum)

Second Randomization
At one year (54 weeks), patients were re-randomized for a total study period of 102 weeks.

Patients who were treated with pegaptanib sodium during the first year were re-randomized at week 54 in a ratio of 1:1 to either stop therapy (no further treatment) or to continue with the same dose and dosing regimen of pegaptanib sodium.

Patients who were receiving sham injections during the first year were re-randomized at week 54 in a ratio of 1:1:1:1:1 to either stop therapy, continue with sham injections or to continue on study receiving one of the three pegaptanib sodium doses.

Study Population – Inclusion and Exclusion Criteria

Inclusion Criteria
Ophthalmic Inclusion Criteria

1. BCVA in the study eye between 20/40 and 20/320, and better than or equal to 20/800 in the fellow eye.
2. Subfoveal CNV, secondary to AMD, with a total lesion size (including blood, scar/atrophy and neovascularization) of <12 total disc areas, of which at least 50% had to be active CNV.
3. Any subretinal hemorrhage could comprise no more than 50% of total lesion size.
4. For patients with minimally classic and occult with no classic CNV, there had to be the presence of subretinal hemorrhage (but comprising no more than 50% of the lesion) and/or lipid and/or documented evidence of 3 or more lines of vision loss (ETDRS or equivalent) during the previous 12 weeks.
5. Clear ocular media and adequate pupillary dilatation to permit good-quality stereoscopic fundus photography.
6. Intraocular pressure (IOP) of 23 mmHg or less.
7. PDT with verteporfin was permitted in this protocol only for patients with predominantly classic lesions determined by the investigator, and additionally they had to meet the criteria described in the product label (eligibility for PDT was confirmed retrospectively by the IRC). All PDT therapies given during the study were scheduled to occur within a 5- to 10-day window prior to treatment so that the study injection occurred after the period of photosensitivity, and any angiograms required by this protocol would be used to confirm eligibility for any subsequent PDT treatments wherever possible in order to minimize the number of additional angiograms required.

General Inclusion Criteria

1. Patients of either gender, aged >50 years.
2. Performance status ≤ 2 according to Eastern Cooperative Oncology Group (ECOG) scale.
3. Normal electrocardiogram (ECG) or clinically non-significant changes.
4. Women had to be using two forms of effective contraception, be post-menopausal for at least 12 months prior to study entry, or be surgically sterile. If the woman was of child-bearing potential, a serum pregnancy test was performed within 48 hours prior to treatment and the result made available prior to treatment initiation. The two forms of

effective contraception had to be implemented during the study and continue for at least 60 days following the last dose of test medication.

5. Adequate hematological function: hemoglobin >10g/dL, platelet count >130 x 109/L and white blood cell count (WBC) >3.8 x 109/L.
6. Adequate renal function: serum creatinine and blood urea nitrogen (BUN) within 2 x the upper limit of normal (ULN) of the institution.
7. Adequate liver function: serum bilirubin < 1.5 mg/dL, and gamma glutamyl transferase (GGT), alanine amino transferase (ALT/SGOT), aspartame amino transferase (AST/SGPT), and alkaline phosphatase within 2 x ULN of the institution.
8. Written informed consent.
9. Ability to return for all study visits.

Exclusion Criteria:

1. Previous subfoveal thermal laser therapy.
2. Any subfoveal scarring or atrophy, and no more than 25% of the total lesion size could be made up of scarring or atrophy.
3. More than one prior PDT with verteporfin was not permitted. In addition, patients could not have received their one prior PDT within less than eight weeks or more than 13 weeks prior to the baseline angiography/photography for the study. Patients could have their first "on study" PDT (if eligible) after baseline angiography/photography, but at least 5 days prior to the first study treatment.
4. Significant media opacities, including cataract, that might interfere with visual acuity, assessment of toxicity or fundus photography. Patients could not be entered if there was a likelihood that they would require cataract surgery within the following 2 years.
5. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8 diopters or more, or axial length of 25mm or more), the ocular histoplasmosis syndrome, angioid streaks, choroidal rupture and multifocal choroiditis.
6. Any intraocular surgery within 3 months, or extrafoveal/juxtafoveal laser within 2 weeks, of study entry.
7. Previous posterior vitrectomy, or scleral buckling surgery.
8. Previous or concomitant therapy with another investigational agent, including PDT with verteporfin for lesions other than predominantly classic (i.e., currently not approved in the majority of participating countries) to treat AMD, except multivitamins and trace minerals.
9. Presence of pigment epithelial tears or rips.
10. Any of the following underlying diseases:
    - Diabetic retinopathy
    - History or evidence of severe cardiac disease, e.g., New York Heart Association (NYHA) Functional Class III or IV, myocardial infarction within 6 months, ventricular tachyarrhythmia's requiring ongoing treatment or unstable angina
    - History or evidence of peripheral vascular disease
    - Clinically significant impaired renal or hepatic function
    - Stroke (within 12 months of study entry)
    - Acute ocular or periocular infection
11. Previous therapeutic radiation to the eye, head, or neck.

12. Any treatment with an investigational agent in the past 60 days for any condition.
13. Known serious allergies to the fluorescein dye used in angiography (and indocyanine green if used) or to the components of the pegaptanib sodium formulation.

Primary Efficacy Variable
The primary efficacy endpoint was the proportion of patients losing <15 letters of VA from baseline to 54 weeks (responders).

Secondary Efficacy Endpoints:

- Proportion of patients gaining >15 letters of VA from baseline to 54 weeks
- Proportion of patients gaining >0 letter of VA from baseline to 54 weeks
- Mean change in VA from baseline to 6, 12 and 54 weeks

Other Planned Efficacy Endpoints:

- Change in VA from baseline, prior to every treatment from baseline to 54 weeks
- Proportion of patients with Snellen Equivalent equal to or worse than 20/200 in the study eye at baseline, 6 weeks, 12 weeks and 54 weeks post baseline
- Change in total lesion size in disc areas from baseline to 30 weeks and 54 weeks
- Change in total CNV size in disc areas from baseline to 30 weeks and 54 weeks
- Change in CNV leak size in disc areas from baseline to 30 weeks and 54 weeks
- Proportion of patients with progression in lesion subtype from baseline to 54 weeks (pure occult to minimally classic or predominantly classic, and minimally classic to predominantly classic)
- Proportion of patients receiving PDT at any time during the course of the study.

Safety Endpoints

- All AEs, whether deemed related to treatment or not
- All serious adverse events (SAEs), whether deemed related to treatment or not
- All laboratory abnormalities, whether deemed clinically relevant or not
- A loss of 20 letters of vision on the ETDRS chart between consecutive treatments

Safety assessments included documentation of local ocular events in the study eye such as diffuse retinal hemorrhage; acute cataract; increase in IOP; retinal detachment, acute retinal arterial or venous occlusions; and sterile or infectious endophthalmitis. If there was an adverse event relating to the fellow eye, it was captured on the AE page of the CRF.

Protocol Defined Analysis Populations

Safety Population: consisted of all patients who received at least one treatment, regardless of their eligibility for the study.
Intent-To-Treat Population: all randomized patients who received double-masked treatment and who had complete baseline vision assessments.

Per-Protocol Population: patients in the ITT population who did not experience any major violations of the protocol or of ophthalmic inclusion/exclusion criteria which could have had an impact on VA, for example cataract removal, were included in the per-protocol population. Additionally patients without post-baseline VA assessments were excluded.
All-randomized Population: Included all patients randomized to take part in the study, regardless of whether they received the study treatment or not.
Week 54 observed patient population: included patients from the ITT population who also had week 54 VA data (whether or not they were still receiving study treatment).

Reviewer's Comment: *This is not a true intent-to-treat population as defined. A true intent-to-treat population is defined as all randomized patients regardless of whether treatment was received or if baseline visual assessments were completed.*

Study Flow Chart - Assessments and Timing – Study EOP1003

	BL	Randomization 1									Randomization 2							
Week	-1	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Treatment number		1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8
Informed consent	X																	
Medical history	X																	
Ophthalmic history	X																	
Pregnancy test	X																	
Randomization	X										X							
Pegaptanib sodium or sham injection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy																		
Refraction and VA (ETDRS)	B		S	S	S	S	B	S	S	S	B	S	S	S	B	S	S	S
Color fundus photographs[1]	B[2]						B				B				B			
Fluorescein angiogram[1]	B[2]						B				B				B			
ICG/OCT[3]	B										B							
Safety																		
Physical examination[4]	X																	
Adverse events / serious adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intraocular pressure[5]	B	S[6]	S[6]	S[6]	S[6]	S[6]	B[6]	S[6]	S[6]	S[6]	B[6]	S[6]	S[6]	S[6]	B[6]	S[6]	S[6]	S[6]
Ophthalmic examination	B	S[6]	S[6]	S[6]	S[6]	S[6]	B[6]	S[6]	S[6]	S[6]	B[6]	S[6]	S[6]	S[6]	B[6]	S[6]	S[6]	S[6]
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X		X	X	X	X	X	X	X	X	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]
ECG	X																	
Telephone safety check[7]		X	X	X	X	X	X	X	X	X	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]

B = Assessment on both eyes
BL = Baseline, performed within 7 days of first treatment
S = Assessment on study eye only
EW = Early withdrawal (prior to Week 102)
[1] Sent to [redacted] for efficacy and safety assessments
[2] Reviewed by Eligibility and Classification Quality Assurance Team (ECQAT) for eligibility and randomization stratification
[3] Some selected sites performed optional indocyanine green angiograms (ICG) or optical coherence tomography (OCT), but no analyses of data were performed
[4] Physical examination performed post baseline only if indicated
[5] Applanation tonometry at baseline and for confirmation of IOP>30 mmHg
[6] Before treatment, at least 30 minutes after treatment and 1 week after treatment
[7] Telephone safety check carried out 3 days post treatment
[8] Treated (active or sham) patients only

Subject Disposition and Demographics – Study EOP1003

Treatment	Patients Randomized and Treated (N=612)	Patients Discontinued (n=53)
0.3 mg	151	11
1 mg	155	13
3 mg	153	17
Sham	153	12

Discontinued Patients and Reason – Study EOP1003

Patient	Treatment	Reason	Study day
064-012	Sham	Died	342
098-002	Sham	Died	35
130-013	Sham	Died	273
145-018	Sham	Died	350
064-019	Sham	Patient request/frustrated with vision	376
084-010	Sham	Patient request/requested other treatment options	68
085-007	Sham	Patient request/pain on injection	332
102-009	Sham	Patient request/refused further injections	294
087-014	Sham	Worsening macular hemorrhage	391
093-018	Sham	Osteoarticular pain	355
154-026	Sham	Colon cancer	137
089-016	Sham	Personal/economic problems-noncompliant with visits	428
075-005	0.3 mg	Patient request/pain on injection	130
081-005	0.3 mg	Patient request/refused further injections	378
087-010	0.3 mg	Patient request/palpitations prior to injection	57
123-010	0.3 mg	Patient request/cannot attend follow-up visits	248
154-001	0.3 mg	Patient request/refused further injections	35
154-017	0.3 mg	Patient request/poor health-unable to make visits	213
089-019	0.3 mg	Endophthalmitis	385
100-002	0.3 mg	Investigator decision/Transient ischemic attack	39
123-002	0.3 mg	Protocol deviation/noncompliant with visits	404
108-007	0.3 mg	Died	312
136-011	0.3 mg	Died	130
064-014	1 mg	Patient request/frustrated with vision	377
065-010	1 mg	Patient request/frustrated with vision	217
070-001	1 mg	Patient request/refused further injections	376
073-008	1 mg	Patient request/visit schedule too rigorous	27
073-014	1 mg	Patient request/developed cataract 2° to injection/had surgery	344
084-009	1 mg	Patient request/refused further injections	76
075-028	1 mg	Pulmonary embolism	260
083-002	1 mg	Poor health/pneumonia	137
101-010	1 mg	Adverse event/shortness of breath-suspected pulmonary embolism	252
102-026	1 mg	Adverse event/ refused further injections(watery eyes)	90

Patient	Treatment	Reason	Study day
104-001	1 mg	panuveitis	217
130-001	1 mg	Died	358
136-005	1 mg	Died	281
075-006	3 mg	Patient request/travel problems	453
089-018	3 mg	Patient request/no improvement in vision	419
108-004	3 mg	Patient request/refused further injections	169
113-015	3 mg	Patient request/refused further participation	134
123-005	3 mg	Patient request/refused further treatment	440
155-004	3 mg	Patient request/spouse died	135
082-006	3 mg	Cerebrovascular accident	271
089-015	3 mg	metastatic lung cancer	248
092-012	3 mg	Angina pectoris	294
095-003	3 mg	Adverse event/worsening general condition	475
122-002	3 mg	Adverse event/lung cancer	260
085-001	3 mg	Died	202
104-011	3 mg	Died	195
119-012	3 mg	Died	341
093-028	3 mg	Investigator/sponsor decision-worsening AMD	214
147-003	3 mg	Investigator/sponsor decision/abnormal EKG	48

Demographics – Safety Population – Study EOP1003

		0.3 mg (N=151)	1 mg (N=155)	3 mg (N=153)	Sham (N=153)
Gender					
Male		69 (46%)	68 (44%)	60 (39%)	57 (37%)
Female		82 (54%)	87 (56%)	93 (61%)	96 (63%)
Race					
White		143 (95%)	148 (95%)	145 (95%)	144 (94%)
Asian		0	1 (1%)	1 (1%)	1 (1%)
Black		0	1 (1%)	0	1 (1%)
Hispanic		7 (5%)	5 (3%)	7 (5%)	5 (3%)
Other		1 (1%)	0	0	2 (1%)
Age					
Mean		74.9	74.5	75.4	74.9
Range		53-90	53-90	53-89	52-92
Smoking status					
Yes		24 (16%)	15 (10%)	15 (10%)	14 (9%)
% Classic AMD	≥ 50%	35 (23%)	40 (26%)	39 (25%)	39 (25%)
	1% - 49%	60 (40%)	57 (37%)	55 (36%)	52 (34%)
	0%	56 (37%)	58 (37%)	59 (39%)	62 (41%)
Prior PDT with verteporfin		6 (4%)	10 (6%)	6 (4%)	4 (3%)
ETDRS Vision					
Mean		53	50.9	50.1	51.3
Range		11-75	22-77	22-76	21-75

Reviewer's comments:
The overwhelming majority of patients enrolled in this trial were older white adults. This is reflective of the population which is mostly affected by this disease and does not reflect an issue with recruitment. The between group demographics, however, were well balanced for all baseline characteristics.

Efficacy Analysis

Primary Efficacy Results – All Randomized Patients LOCF – Study 1003

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

[1] Patients who lost < 15 letters of vision. Note: Patients who lost < 15 letters of vision from baseline to 54 weeks is the primary efficacy endpoint

Primary Efficacy Results – PP population observed cases only– Study 1003

Number of Patients (%)		0.3 mg	1 mg	3 mg	Sham
Responders[1]	Month 3	122 (87.8%) *N=139*	**131 (92.9%)** *N= 141*	122 (86.5%) *N= 141*	120 (82.8%) *N= 145*
	Month 6	**110 (85.3%)** *N= 129*	**125 (86.8%)** *N= 144*	116 (82.3%) *N= 141*	101 (69.7%) *N= 145*
	Month 9	**103 (78.3%)** *N= 131*	115 (79.9%) *N= 144*	110 (79.1%) *N= 139*	93 (66%) *N= 141*
	Month 12	[redacted] *N= 133*	[redacted] p=0.005 *N= 139*	90 (66.7%) *N= 135*	82 (58.6%) *N= 140*

[1] Patients who lost < 15 letters of vision. Note: Patients who lost < 15 letters of vision from baseline to 54 weeks is the primary efficacy endpoint
[2] 3 mg dose was omitted from statistical analysis prior to unmasking data

Reviewer's Comments:
There were no interim analyses for safety or efficacy performed during the clinical trial. The statistically significant findings are highlighted in the table. The bolded entries indicate a trend for efficacy although statistical significance was not reached. Based on the Hochberg multiple comparison procedure defined in

the protocol, both the 0.3 mg and 1 mg doses demonstrate efficacy in this trial. There is approximately a 15% treatment effect for both doses.

Primary Efficacy Results – Sensitivity Analyses – Study 1003

Worst Case Analysis	**N=153**	**N=158**	**N=155**	**N=156**
Responders[1]	104 (68%)	109 (69%)	93 (60%)	96 (61.5%)
p-value	0.15	0.11	-	-
Week 54 Observed population	**N=139**	**N=144**	**N=139**	**N=142**
Responders[1]	103 (74%)	109 (76%)	93 (67%)	82 (58%)
p-value	0.005	0.003	-	-

[1] Patients who lost < 15 letters of vision from baseline to 54 weeks – primary efficacy endpoint
[2] 3 mg dose was omitted from statistical analysis prior to unmasking data

Number of Patients Receiving On-Study PDT Treatment in the Study Eye – ITT Population – Study EOP1003

Number of patients		**0.3 mg N=150**	**1 mg N=154**	**3 mg N=153**	**Sham N=152**
All patients					
PDT treatment	Yes	17 (11%)	19 (12%)	20 (13%)	19 (13%)
Predominantly Classic CNV		n=35	n=39	n=39	n=39
PDT Treatment	Yes	14 (40%)	15 (38%)	16 (41%)	13 (33%)
Minimally Classic CNV		n=59	n=57	n=55	n=52
PDT Treatment	Yes	2 (3%)	3 (5%)	3 (5%)	5 (10%)
Occult CNV		n=56	n=58	n=59	n=61
PDT Treatment	Yes	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Pairwise Comparison		0.3 mg vs. sham	1 mg vs. sham	3 mg vs. sham	
		p=0.68	p=1.0	p=0.92	

Number of On-Study PDT Treatments Received in The Study Eye – ITT population – Study EOP1003

Number of patients	**0.3 mg** N=150	**1 mg** N=154	**3 mg** N=153	**Sham** N=152
Total number of PDT treatments	**n=28**	**n=36**	**n=41**	**n=32**
Predominantly classic CNV	23 (82%)	30 (83%)	35 (85%)	20 (63%)
Minimally classic CNV	3 (11%)	4 (11%)	5 (12%)	10 (31%)
Occult CNV	2 (7%)	2 (6%)	1 (2%)	2 (6%)

Reviewer's Comments:

The number of patients receiving PDT treatments during the trial as well as the number of treatments received are consistent across the treatment groups. Therefore the efficacy demonstrated in the 0.3 mg and 1 mg groups does not appear to have been confounded by the adjunctive PDT treatment received by the patients in the trial.

It is noted that a small percentage of patients with minimally classic or occult CNV received PDT treatment. PDT treatment is not approved for these indications and is in violation of the study protocol. However, due the small numbers, this does not have any impact on the final efficacy results.

Responder Analysis for PDT Treatment Interaction– Study 1003

Number of Patients (%) who never received PDT before or during the study		**0.3 mg N= 131**	**1 mg N= 132**	**3 mg N= 127**	**Sham N= 127**
Responders[1]	Month 3	116 (88.6%)	123 (93.2%)	114 (89.8%)	106 (83.5%)
	Month 6	110 (84%)	117 (88.6%)	109 (85.8%)	92 (72.4%)
	Month 9	102 (78%)	109 (82.6%)	105 (82.7%)	85 (67%)
	Month 12	97 (74%)	103 (78%)	92 (72.4%)	78 (61.4%)

[1] Patients who lost < 15 letters of vision.

Number of Patients (%) who only received PDT before the study		**0.3 mg N= 2**	**1 mg N= 5**	**3 mg N= 6**	**Sham N= 4**
Responders[1]	Month 3	1 (50%)	5 (100%)	6 (100%)	3 (75%)
	Month 6	2 (100%)	5 (100%)	4 (66.7%)	3 (75%)
	Month 9	2 (100%)	5 (100%)	5 (83.3%)	3 (75%)
	Month 12	2 (100%)	3 (60%)	5 (83.3%)	3 (75%)

[1] Patients who lost < 15 letters of vision.

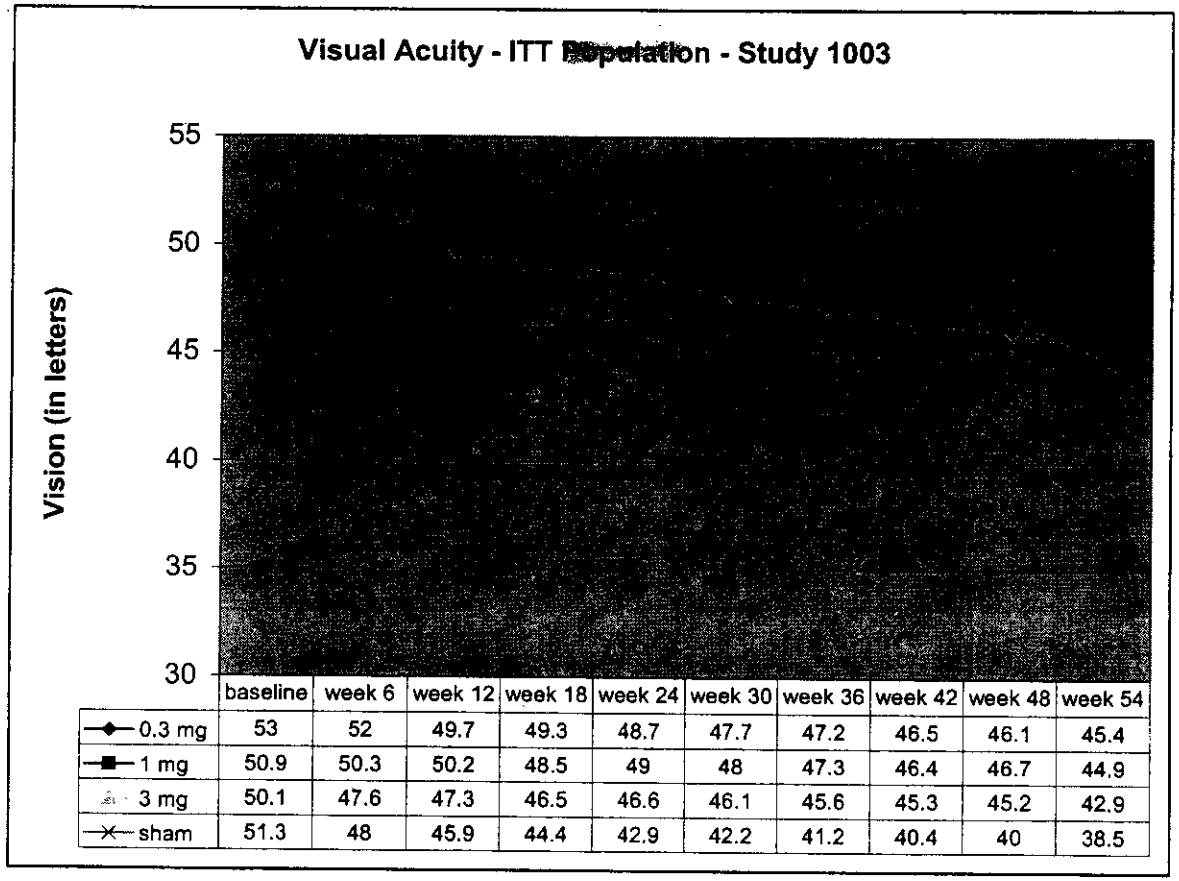
Number of Patients (%) who only received PDT during the study		**0.3 mg N= 16**	**1 mg N= 17**	**3 mg N= 20**	**Sham N= 25**
Responders[1]	Month 3	13 (81.3%)	15 (88.2%)	14 (70%)	21 (84%)
	Month 6	12 (75%)	11 (64.7%)	13 (65%)	17 (68%)
	Month 9	9 (56.3%)	8 (47%)	13 (65%)	17 (68%)
	Month 12	9 (56.3%)	9 (53%)	10 (50%)	12 (48%)

[1] Patients who lost < 15 letters of vision.

Number of Patients (%) who received PDT before and during the study		**0.3 mg N= 4**	**1 mg N= 4**	**3 mg N= 2**	**Sham N= 0**
Responders[1]	Month 3	4 (100%)	3 (75%)	2 (100%)	0
	Month 6	3 (75%)	4 (100%)	2 (100%)	0
	Month 9	4 (100%)	4 (100%)	2 (100%)	0
	Month 12	4 (100%)	4 (100%)	1 (50%)	0

[1] Patients who lost < 15 letters of vision.

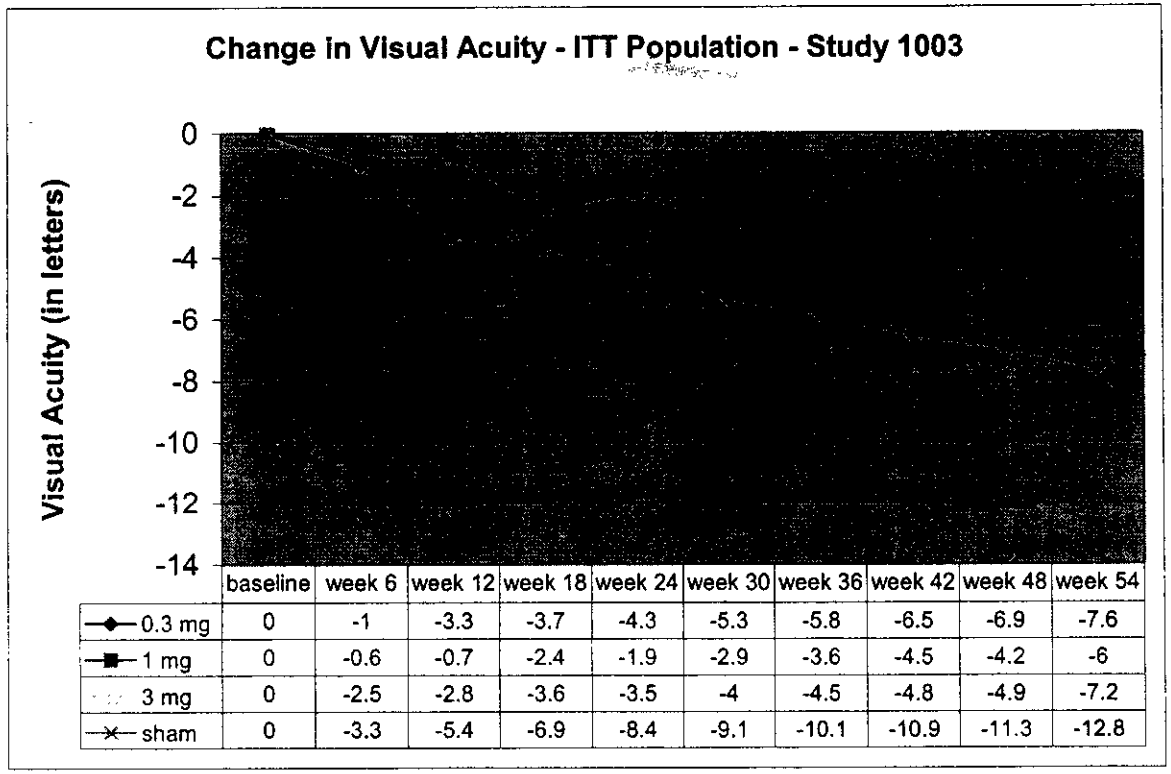
Additional Efficacy Analyses



	baseline	week 6	week 12	week 18	week 24	week 30	week 36	week 42	week 48	week 54
0.3 mg	53	52	49.7	49.3	48.7	47.7	47.2	46.5	46.1	45.4
1 mg	50.9	50.3	50.2	48.5	49	48	47.3	46.4	46.7	44.9
3 mg	50.1	47.6	47.3	46.5	46.6	46.1	45.6	45.3	45.2	42.9
sham	51.3	48	45.9	44.4	42.9	42.2	41.2	40.4	40	38.5

Reviewer's Comments:

The rate of vision loss in the 0.3 mg and 1 mg groups is similar. This vision loss does not appear to plateau which would suggest that there may be continued vision loss despite therapy. This will be further analyzed after the results of the 2 years data is available.



	baseline	week 6	week 12	week 18	week 24	week 30	week 36	week 42	week 48	week 54
0.3 mg	0	-1	-3.3	-3.7	-4.3	-5.3	-5.8	-6.5	-6.9	-7.6
1 mg	0	-0.6	-0.7	-2.4	-1.9	-2.9	-3.6	-4.5	-4.2	-6
3 mg	0	-2.5	-2.8	-3.6	-3.5	-4	-4.5	-4.8	-4.9	-7.2
sham	0	-3.3	-5.4	-6.9	-8.4	-9.1	-10.1	-10.9	-11.3	-12.8

Mean Total Lesion Size, CNV Size and Leak Size – Study 1003

	0.3 mg n=150	1 mg n=154	3 mg n=153	Sham N=152
Total Lesion size[1]				
Baseline	3.9	3.7	3.7	4.0
Week 30	4.9	4.7	5.1	5.5
Week 54	5.6	5.6	6.0	6.4
Total CNV Size[1]				
Baseline	3.1	3.2	3.2	3.5
Week 30	3.9	3.9	4.3	4.8
Week 54	4.7	4.6	5.0	5.7
Total Leak Size[1]				
Baseline	3.4	3.3	3.3	3.5
Week 30	4.1	3.4	4.2	4.9
Week 54	4.5	3.9	4.4	5.1
[1] size given in DA (disc area)				

Reviewer's Comments:
The increase in the total lesion size at week 54 does appear to be less in all of the drug groups compared to sham. Clinically this correlates with the vision results which demonstrate that there is less visual loss in the drug groups compared to sham. However, none of the doses evaluated appear to be able to inhibit the lesion growth.

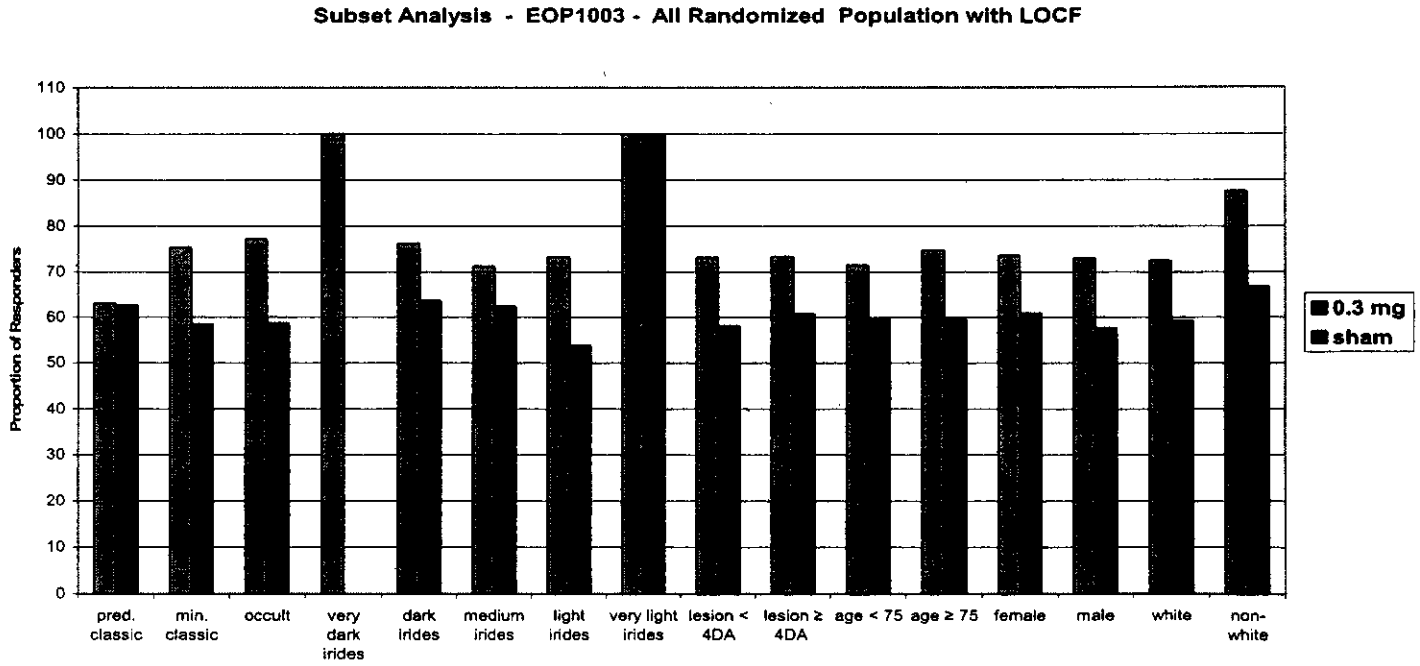
Vision Gain – Study EOP1003

		0.3 mg n=150	1 mg n=154	3 mg n=153	Sham N=152
Number of Patients (%)					
Vision gain ≥ 15 letters[1]	Yes	6 (4%)	10 (6%)	7 (5%)	5 (3%)
	p-value	0.93	0.49	-[3]	-
Vision gain ≥ 0 letters[2]	Yes	49 (33%)	59 (38%)	60 (39%)	42 (28%)
	p-value	0.38	0.08	-[3]	-

[1]patients who gained ≥ 15 letters of vision from baseline to 54 weeks
[2]patients who gained ≥ 0 letters of vision from baseline to 54 weeks
[3]3 mg dose was omitted from statistical analyses prior to unmasking data

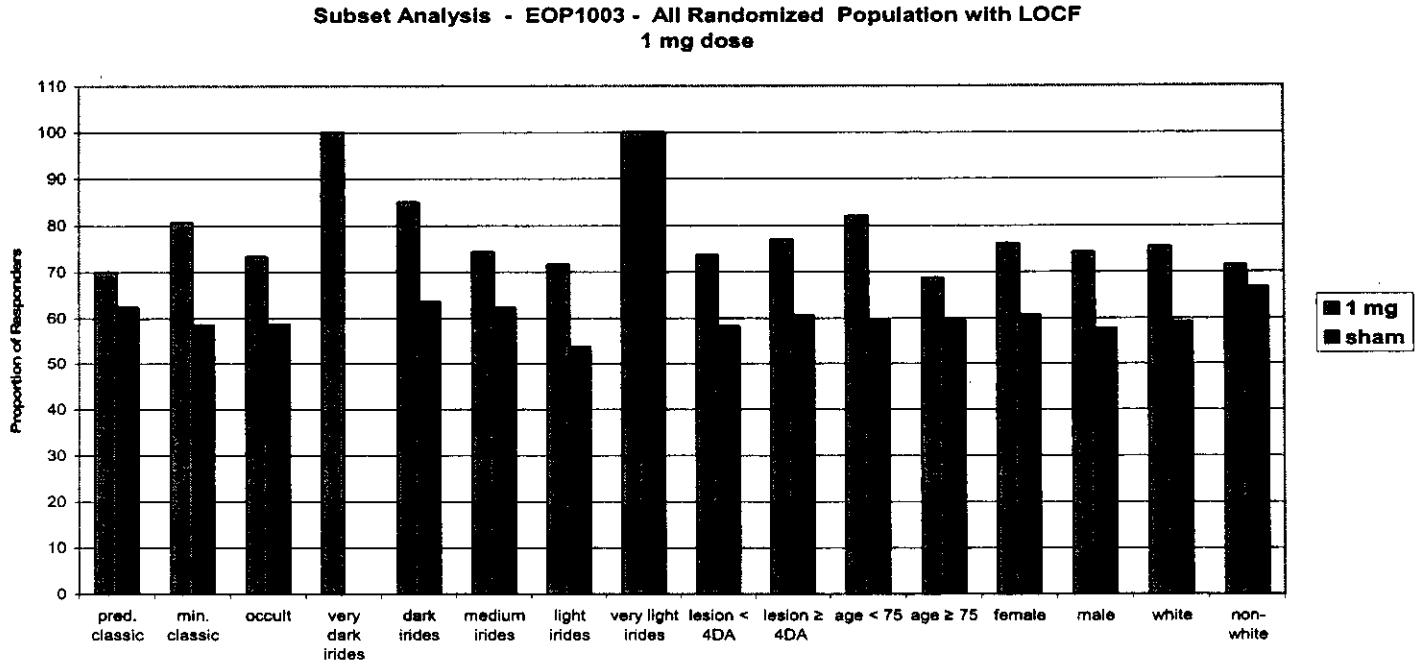
Reviewer's Comments:
There is only a small percentage of patients in each treatment group that show a clinically meaningful increase in vision and the difference seen between the groups is not statistically significant . This is expected based on the disease process being studied.

Responder analyses based on baseline characteristics for study EOP1003



Reviewers Comments:

The white vs. non-white treatment groups are grossly imbalanced (N= 292 vs. N= 17). This is expected due to the indication being studied. There is no evidence that overall efficacy is derived from any one subgroup in any treatment arm.


Subset Analysis - EOP1003 - All Randomized Population with LOCF
1 mg dose
Proportion of Responders
110
100
90
80
70
60
50
40
30
20
10
0
pred. classic
min. classic
occult
very dark irides
dark irides
medium irides
light irides
very light irides
lesion < 4DA
lesion ≥ 4DA
age < 75
age ≥ 75
female
male
white
non-white
1 mg
sham

Study 2 – Study EOP1004

Title: Same as Study EOP1003
Objective: Same as Study EOP1003
Study Design: Same as Study EOP1003. This study was conducted in North America.

Clinical sites – Study EOP1004

Center Number	Principal Investigator	Center Location	Number of Patients
01	Julia Haller, MD	Baltimore, MD	4
02	Michael Klein, MD	Portland, OR	6
03	Daniel F. Martin, MD	Atlanta, GA	-
04	Gary Fish, MD	Dallas TX	6
05	Allen Ho, MD	Philadelphia, PA	11
06	Scott D. Pendergast, MD	Lakewood, OH	33
07	Christine Gonzales, MD	Los Angeles, CA	30
08	Antonia Capone, MD	Royal Oak, MI	23
09	Jorge Arroyo, MD	Boston, MA	8
10	Steve Sanislo, MD	Menlo Park, CA	9
12	Richard Rosen, MD	New York, NY	6
13	Dean Eliot, MD	Detroit, MI	1
14	Jean Daniel Arbour, MD	Montreal, Quebec	-
15	Robert Avery, MD	Santa Barbara, CA	3
17	Paul Bernstein, MD	Salt Lake City, UT	7
18	Francis Cangemi, MD	Belleville, NJ	6
19	David Boyer, MD	Beverly Hills, CA	22
20	Sandy Brucker, MD	Philadelphia, PA	12
21	Herbert Cantrill, MD	Minneapolis, MN	20
22	Gaetano Barille, MD	New York, NY	-
23	Steven Charles, MD	Memphis, TN	5
24	Thomas A. Ciuilla, MD	Indianapolis, IN	-
25	Thomas Connor, MD	Milwaukee, WI	8
26	Brian P. Conway, MD	Charlottesville, VA	13
27	Alan F. Cruess, MD	Kingston, ON	-
28	John a. Wells, III, MD	Columbia, SC	15
29	Thomas Friberg, MD	Pittsburgh, PA	10
30	Richard Garfinkel, MD	Chevy Chase, MD	10
31	Bert Glaser, MD	Chevy Chase, MD	1
32	W. Sanderson Grizzard, MD	Tampa, FL	14
33	Barry Taney, MD	Fort Lauderdale, FL	8
34	Howard Cummings, MD	Knoxville, TN	17
35	Henry Hudson, MD	Tucson, AZ	25
36	Sharon Fekrat, MD	Durham, NC	14
37	Mark W. Johnson, MD	Ann Arbor, MI	2
38	Baruch Kuppermann, MD	Irvine, CA	1
40	Hilel Lewis, MD	Cleveland, OH	9

Center Number	Principal Investigator	Center Location	Number of Patients
41	Jennifer Lim, MD	Los Angeles, CA	7
43	Naresh Mandava, MD	Aurora, CO	4
44	H. Richard McDonald, MD	San Francisco, CA	12
45	William Mieler, MD	Houston TX	3
46	Mohit Nanda, MD	Santa Ana, CA	7
47	Robert Leonard, MD	Oklahoma City, OK	8
48	Elias Reichel, MD	Boston, MA	13
49	Philip Rosenfeld, MD	Miami, FL	9
50	Ronald Wilson, MD	New Orleans, LA	18
51	Nelson Sabates, MD	Kansas City, MO	12
52	Vincent Deramo, MD	Great Neck, NY	8
53	M. Madison Slusher, MD	Winston-Salem, NC	7
54	Scott Sneed, MD	Phoenix, AZ	14
55	Glen Stoller, MD	Rockville Center, NY	8
56	Paul Tornambe, MD	Poway, CA	3
57	Michael Varenhorst, MD	Wichita, KS	13
58	Lloyd Wilcox, MD	Concord, NH	1
60	Marco Zarbin, MD	Newark, NJ	-
61	Patricia Harvey, MD	Toronto, ON	-
62	David Tom, MD	Hamden, CT	15
110	Alice T. Lyon, MD	Chicago, IL	3
115	David J. Weissgold, MD	Burlington, CT	8
140	Dennis Marcus, MD	Augusta, GA	2
141	John Wroblewski, MD	Hagerstown, MD	15
142	Leonard Joffe, MD	Tucson, AZ	5
39	Brian Leonard, MD	Ottawa, ON	6
42	David Maberley, MD	Vancouver, BC	12
59	Geoff Williams, MD	Calgary, AB	5

Reviewer's Comment:
The agency prefers patients to be randomized with at least ten patients per arm per center in multicenter trials so that interaction between centers can be evaluated.

Leonard Joffe, MD is also an investigator for study EOP1003 and enrolled 16 patients. This is the only overlap in principle investigators for the two phase three trials.

Inclusion/Exclusion Criteria – Same as Study EOP1003

Safety and Efficacy Endpoints – Same as Study EOP1003

Study Schedule – Same as Study EOP1003. In addition, plasma samples for nested pharmacokinetic (PK) study was conducted at week 6 and week 18.

Subject Disposition and Demographics

Treatment	Patients Randomized and Treated (N=578)	Patients Discontinued (n=60)
0.3 mg	144	12
1 mg	146	17
3 mg	143	20
Sham	145	11

Discontinued Patients and Reason – Study EOP1004

Patient	Treatment	Reason	Study Day
007-033	0.3 mg	Investigator decision/pt too fragile s/p hip replacement surgery	231
009-005	0.3 mg	Patient request/felt vision was getting worse	148
017-008	0.3 mg	Patient request/transportation issues	378
019-026	0.3 mg	Patient request/recovery time too long	205
021-010	0.3 mg	Patient died	231
032-002	0.3 mg	Patient request/withdrew consent	126
034-013	0.3 mg	Lost to follow-up	85
041-003	0.3 mg	Patient request/did not what to continue	288
042-001	0.3 mg	Adverse event/endophthalmitis	63
048-002	0.3 mg	Patient died	185
050-012	0.3 mg	Patient died	140
055-017	0.3 mg	Adverse event/subretinal hemorrhage, retinal detachment	95
007-015	1 mg	Lost to follow-up	217
008-018	1 mg	Patient died	228
015-002	1 mg	Patient died	301
019-009	1 mg	Patient request/no longer wants to participate	465
019-033	1 mg	Move to nursing home	306
020-007	1 mg	Patient request/withdrew consent	358
033-006	1 mg	Patient died	62
036-017	1 mg	Unable to return for visits	343
041-001	1 mg	Patient died	187
043-001	1 mg	Adverse event/subretinal & vitreous hemorrhage	452
050-009	1 mg	Patient request/does not want tx from new PI	260
050-021	1 mg	Patient died	323
055-014	1 mg	Lost to follow-up	205
057-004	1 mg	Patient request/poor health	299
059-006	1 mg	Patient died	101
062-006	1 mg	Patient request/withdrew consent	165
062-009	1 mg	Patient request/anxiety	126
006-002	3 mg	Patient request/withdrew consent	377
006-010	3 mg	Patient died	372
015-003	3 mg	Patient request/moving to another state	130

Patient	Treatment	Reason	Study Day
017-006	3 mg	Patient request/not able to follow-up	377
017-007	3 mg	Investigator decision/poor clinical response	383
019-007	3 mg	Alzheimer's – unable to follow protocol	378
021-005	3 mg	Patient request/study not helping vision	166
026-003	3 mg	Patient died	256
030-001	3 mg	Investigator decision/missed injection due to retinal detachment	210
030-009	3 mg	Patient request/withdrew consent	393
033-009	3 mg	Patient request/withdrew consent	401
034-011	3 mg	Patient died	116
042-009	3 mg	Patient request/withdrew consent	378
046-008	3 mg	Patient request/family illness	356
050-004	3 mg	Patient request/move out of state	378
050-013	3 mg	Patient request/ does not want tx from new PI	251
052-006	3 mg	Adverse event/myocardial infarction, cerebral hemorrhage	36
052-011	3 mg	Patient request/failure to respond to treatment	308
053-006	3 mg	Patient request/general health reasons	127
062-010	3 mg	Adverse event/retinal detachment	300
004-007	Sham	Patient request/did not feel study was helping	84
012-001	Sham	Patient request/felt injections were making eyes worse	126
017-001	Sham	Patient request/refused further injection	378
019-004	Sham	Patient request/vision loss	173
021-012	Sham	Patient died	335
028-021	Sham	Patient request/vision loss	276
035-021	Sham	Adverse event/acute congestive heart failure	128
040-003	Sham	Patient died	328
049-013	Sham	Patient request/withdrew consent	238
052-007	Sham	Patient request/progressive loss of vision	133
023-001	Sham	Investigator decision/no injection for 12 weeks	241

Demographics – Safety Population – Study EOP1004

	0.3 mg (N=144)	1 mg (N=146)	3 mg (N=143)	Sham (N=145)
Gender				
Male	64 (44%)	68 (47%)	45 (31%)	63 (43%)
Female	80 (56%)	78 (53%)	98 (69%)	82 (57%)
Race				
White	140 (97%)	143 (98%)	141 (99%)	140 (97%)
Asian	2 (1%)	0	0	0
Black	0	0	0	0
Hispanic	2 (1%)	2 (1%)	2 (1%)	4 (3%)
Other	0	1 (1%)	0	1 (1%)

Age					
Mean		78	76.5	77.1	76.7
Range		58-92	52-92	56-97	55-89
Smoking status					
Yes		14 (10%)	15 (10%)	15 (10%)	15 (10%)
% Classic AMD	≥ 50%	37 (26%)	38 (26%)	41 (29%)	37 (26%)
	1%-49%	51 (35%)	51 (35%)	50 (35%)	50 (34%)
	0%	56 (39%)	57 (39%)	52 (36%)	58 (40%)
Prior PDT with verteporfin		18 (13%)	20 (14%)	20 (14%)	16 (11%)
ETDRS Vision					
Mean		52.5	50.5	52.1	54
Range		23-74	19-73	14-73	27-74

Reviewer's comments:

The overwhelming majority of patients enrolled in this trial were older white adults. This is reflective of the population which is mostly affected by this disease and does not reflect an issue with recruitment. The between group demographics, however, were well balanced for all baseline characteristics.

Efficacy Analysis

Primary Efficacy Results – All Randomized Patients LOCF – Study 1004

Number of Patients (%)		**0.3 mg N= 144**	**1 mg N= 147**	**3 mg N= 147**	**Sham N= 148**
Responders[1]	Month 3	125 (86.8%)	118 (80.3%)	121 (82.3%)	115 (77.7%)
	Month 6	**118 (81.9%)**	**106 (72.1%)**	102 (69.4%)	85 (57.4%)
	Month 9	**106 (73.6%)**	**108 (73.5%)**	**103 (70.1%)**	78 (52.7%)
	Month 12	[redacted]	98 (66.7%) p=0.03	91 (61.9%) p=0.13	79 (53.4%)

[1] Patients who lost < 15 letters of vision. Note: Patients who lost < 15 letters of vision from baseline to 54 weeks is the primary efficacy endpoint

Primary Efficacy Results – PP population observed cases only– Study 1004

Number of Patients (%)		0.3 mg	1 mg	3 mg	Sham
Responders[1]	Month 3	122 (87.4%) *N=140*	114 (81.4%) *N=140*	110 (81.5%) *N=135*	104 (77%) *N=135*
	Month 6	**112 (82.4%)** *N=136*	96 (72.2%) *N=133*	91 (67.4%) *N=135*	77 (58.8%) *N=131*
	Month 9	**94 (74.6%)** N=126	**94 (75.2%)** *N= 125*	**90 (70.9%)** *N=127*	70 (53.4%) *N=131*
	Month 12	[redacted] *N=131*	85 (66.9%) p=0.06 *N=127*	70 (57.4%) p=0.59 *N=122*	69 (53.9%) *N=128*

[1] Patients who lost < 15 letters of vision. Note: Patients who lost < 15 letters of vision from baseline to 54 weeks is the primary efficacy endpoint

Reviewer's Comments:

There were no interim analyses for safety or efficacy performed during the clinical trial. The statistically significant findings are highlighted in the table. The bolded entries indicate a trend for efficacy although statistical significance was not reached. Based on the Hochberg multiple comparison procedure defined in the protocol, only the 0.3 mg dose demonstrates efficacy in this trial. There is approximately a 15% treatment effect seen.

Primary Efficacy Results – Sensitivity Analyses – Study 1004

Worst Case Analysis	**N=144**	**N=147**	**N=147**	**N=148**
Responders[1]	89 (61.8%)	89 (60.5%)	73 (49.7%)	87 (58.8%)
p-value	0.27	0.76	0.36	-
Week 54 Observed population	**N=132**	**N=131**	**N=125**	**N=133**
Responders[1]	89 (67%)	89 (68%)	73 (58%)	72 (54%)
p-value	0.01	0.032	0.5	-

[1] Patients who lost < 15 letters of vision from baseline to 54 weeks – primary efficacy endpoint

Number of Patients Receiving On-Study PDT Treatment in the Study Eye – ITT Population – Study EOP1004

Number of patients		0.3 mg N=144	1 mg N=146	3 mg N=143	Sham N=144
All patients					
PDT treatment	Yes	32 (22%)	36 (25%)	37 (26%)	43 (30%)
Predominantly Classic		n=37	n=38	n=41	n=37

CNV					
PDT Treatment	Yes	24 (65%)	23 (61%)	24 (59%)	25 (68%)
Minimally Classic CNV		n=51	n=51	n=50	n=49
PDT Treatment	Yes	5 (10%)	12 (24%)	8 (16%)	13 (27%)
Occult CNV		n=144	n=146	n=143	n=144
PDT Treatment	Yes	3 (5%)	1 (2%)	5 (10%)	5 (9%)
Pairwise Comparison		0.3 mg vs. sham	1 mg vs. sham	3 mg vs. sham	
		p=0.05	p=0.22	p=0.26	

Number of On-Study PDT Treatments Received in The Study Eye – ITT population – Study EOP1004

Number of patients	**0.3 mg N=144**	**1 mg N=146**	**3 mg N=143**	**Sham N=144**
Total number of PDT treatments	**n=56**	**n=72**	**n=73**	**n=94**
Predominantly classic CNV	42 (75%)	45 (63%)	48 (66%)	59 (63%)
Minimally classic CNV	10 (18%)	26 (36%)	18 (25%)	27 (29%)
Occult CNV	4 (7%)	1 (1%)	7 (10%)	8 (9%)

Reviewer's Comments:

The overall number of patients receiving PDT treatments during the trial as well as the number of treatments received are significantly less in the 0.3 mg group versus sham. Therefore, the efficacy demonstrated in the 0.3 mg does not appear to have been confounded by the adjunctive PDT treatment received by the patients in the trial. The lack of PDT treatments in the 0.3 mg group may be supportive of the efficacy of the drug.

It is noted that a small to moderate percentage of patients with minimally classic or occult CNV received PDT treatment. PDT treatment is not approved for these indications and is in violation of the study protocol.

Responder Analysis for PDT Treatment Interaction– Study 1004

Number of Patients (%) who never received PDT before or during the study		**0.3 mg N= 101**	**1 mg N= 99**	**3 mg N= 99**	**Sham N= 93**
Responders[1]	Month 3	87 (86.1%)	83 (83.8%)	86 (86.9%)	74 (79.6%)
	Month 6	80 (79.2%)	77 (77.8%)	70 (70.7%)	57 (61.3%)
	Month 9	74 (73.2%)	75 (75.8%)	72 (72.7%)	52 (55.9%)
	Month 12	65 (64.4%)	70 (70.7%)	65 (65.7%)	54 (58%)

[1] Patients who lost < 15 letters of vision.

Number of Patients (%) who only received PDT before the study		**0.3 mg N= 5**	**1 mg N= 8**	**3 mg N= 5**	**Sham N= 4**
Responders[1]	Month 3	4 (80%)	5 (62.5%)	5 (100%)	3 (75%)
	Month 6	4 (80%)	2 (25%)	5 (100%)	3 (75%)
	Month 9	3 (60%)	5 (62.5%)	3 (60%)	2 (50%)
	Month 12	4 (80%)	3 (37.5%)	3 (60%)	2 (50%)

[1] Patients who lost < 15 letters of vision.

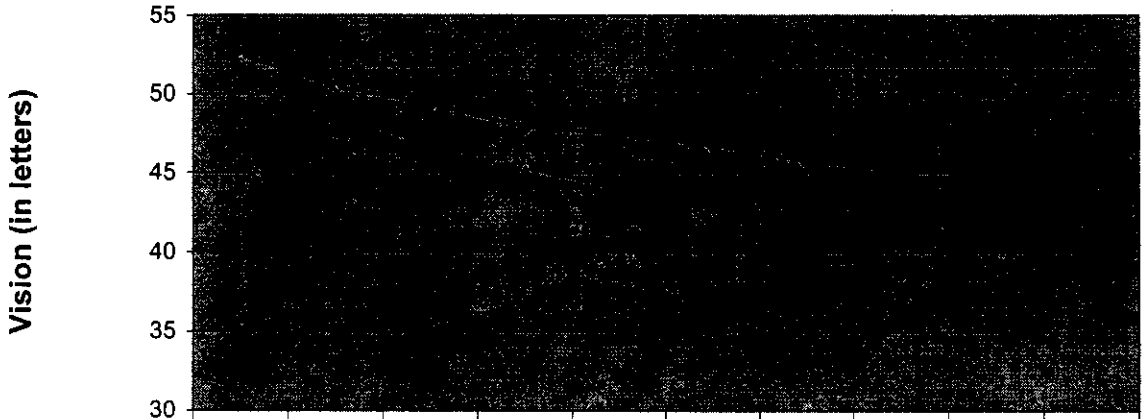
Number of Patients (%) who only received PDT during the study		**0.3 mg N= 25**	**1 mg N= 28**	**3 mg N= 29**	**Sham N= 39**
Responders[1]	Month 3	22 (88%)	21 (75%)	20 (69%)	30 (77%)
	Month 6	22 (88%)	18 (64%)	16 (57.2%)	19 (48.7%)
	Month 9	18 (72%)	17 (60.7%)	15 (51.7%)	18 (46.2%)
	Month 12	18 (72%)	16 (57.1%)	15 (51.7%)	18 (46.2%)

[1] Patients who lost < 15 letters of vision.

Number of Patients (%) who received PDT before and during the study		**0.3 mg N= 13**	**1 mg N= 12**	**3 mg N= 14**	**Sham N= 12**
Responders[1]	Month 3	12 (92.3%)	9 (75%)	10 (71.4%)	8 (66.7%)
	Month 6	12 (92.3%)	9 (75%)	11 (78.6%)	6 (50%)
	Month 9	11 (84.6%)	11 (91.7%)	13 (93%)	6 (50%)
	Month 12	10 (76.9%)	9 (75%)	8 (57.1%)	5 (41.7%)

[1] Patients who lost < 15 letters of vision.

Visual Acuity - ITT Population - Study EOP1004

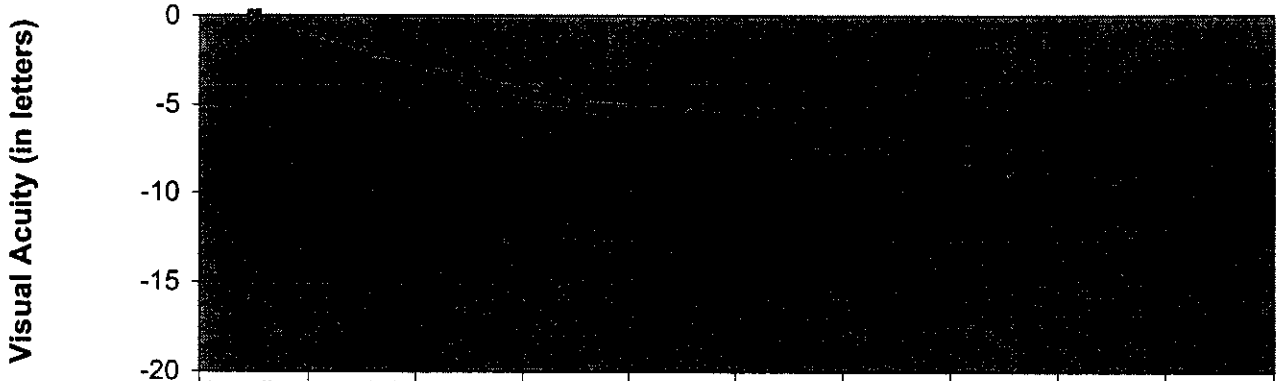


	baseline	week 6	week 12	week 18	week 24	week 30	week 36	week 42	week 48	week 54
0.3 mg	52.5	50.5	49.4	47.9	47.5	46.8	45.8	45.2	45	44.2
1 mg	50.5	48.7	46.8	45.3	44.1	42.9	42.9	42	41.5	41.9
3 mg	52.1	50.1	46.8	45.3	43.1	41.9	41.6	40.8	39.7	39.6
sham	54	49.2	46.7	43.7	42.4	39.5	38.7	37.8	37.1	36.6

Reviewer's Comments:

The rate of vision loss in the 0.3 mg is slightly less than in the other treatment groups. This vision loss does not appear to plateau which would suggest that there is there may be continued vision loss despite therapy. This will be analyzed after the results of the 2 years data is available.

Change in Visual Acuity - ITT Population - Study 1004



	baseline	week 6	week 12	week 18	week 24	week 30	week 36	week 42	week 48	week 54
0.3 mg	0	-2	-3.1	-4.6	-5	-5.7	-6.7	-7.3	-7.5	-8.3
1 mg	0	-1.8	-3.7	-5.2	-6.4	-7.6	-7.6	-8.5	-9	-8.6
3 mg	0	-2	-5.3	-6.8	-9	-10.2	-10.5	-11.3	-12.4	-12.5
sham	0	-4.8	-7.3	-10.3	-11.6	-14.5	-15.3	-16.2	-16.9	-17.4

Mean Total Lesion Size, CNV Size and Leak Size – Study 1004

	0.3 mg n=144	1 mg n=146	3 mg n=143	Sham N=144
Total Lesion size[1]				
Baseline	3.6	4.4	3.6	4.4
Week 30	5	5.4	5.3	5.8
Week 54	5.5	6	6.3	7
Total CNV Size[1]				
Baseline	3.1	3.8	3.2	3.9
Week 30	4	4.5	4.2	5
Week 54	4.7	5	5	5.8
Total Leak Size[1]				
Baseline	3.2	3.6	3.5	3.7
Week 30	3.8	3.9	4.2	4.9
Week 54	4.1	4	4.9	5.2
[1] size given in DA (disc area)				

Reviewer's Comments:

The increase in the total lesion size, total lesion size and total leak size at week 54 appears to be less in the 0.3 mg group compared to sham. Clinically this correlates with the vision results which demonstrate that there is less visual loss in the drug groups compared to sham.

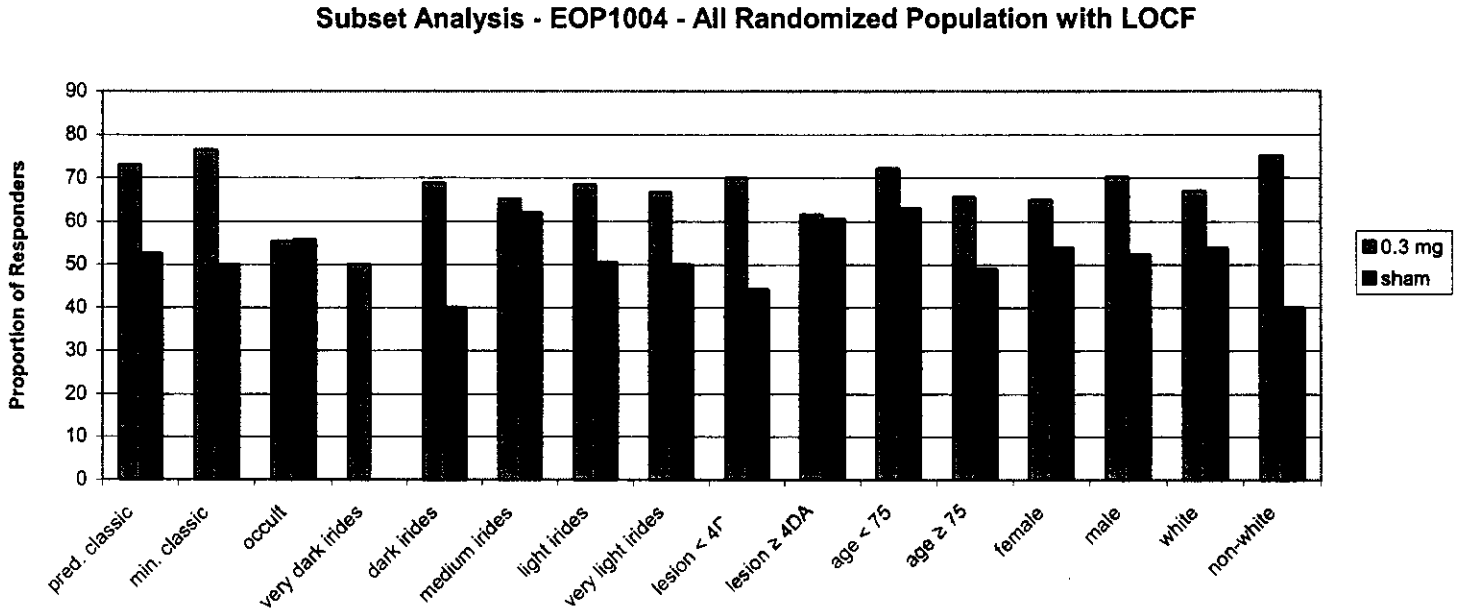
Vision Gain – Study EOP1004

		0.3 mg n=144	1 mg n=146	3 mg n=143	Sham N=144
Number of Patients (%)					
Vision gain ≥ 15 letters[1]	Yes	12 (8%)	10 (7%)	6 (4%)	1 (1%)
	p-value	0.005	0.01	0.04	-
Vision gain ≥ 0 letters[2]	Yes	49 (34%)	51 (35%)	33 (23%)	25 (17%)
	p-value	0.0006	0.002	0.17	-

[1]patients who gained ≥ 15 letters of vision from baseline to 54 weeks
[2]patients who gained ≥ 0 letters of vision from baseline to 54 weeks

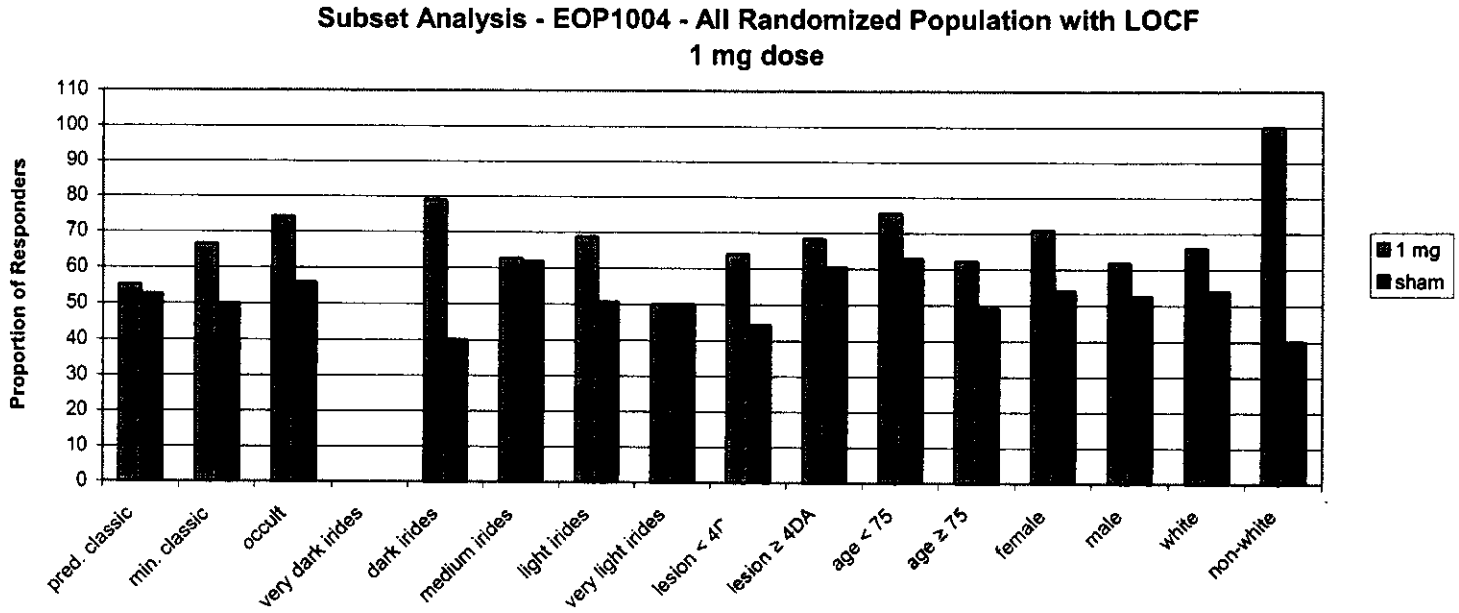
Reviewer's Comments:
There is only a small percentage of patients in each treatment group that show a clinically meaningful increase in vision. This is expected based on the disease process being studied.

Responder analyses based on baseline characteristics for study EOP1004



Reviewers Comments:

The white vs. non-white treatment groups are grossly imbalanced (N= 283 vs. N= 9). This is expected due to the indication being studied. There is no evidence that overall efficacy is derived from any one subgroup in any treatment arm.


Subset Analysis - EOP1004 - All Randomized Population with LOCF
1 mg dose
Proportion of Responders
110
100
90
80
70
60
50
40
30
20
10
0
pred. classic
min. classic
occult
very dark irides
dark irides
medium irides
light irides
very light irides
lesion < 4r
lesion ≥ 4DA
age < 75
age ≥ 75
female
male
white
non-white
1 mg
sham

D. Efficacy Conclusions

The submitted studies in NDA 21-756 are sufficient to establish efficacy for the use of pegaptanib sodium 0.3 mg in the treatment of the neovascular form of age-related macular degeneration. The two phase 3 studies show replicative results in the ability of pegaptanib sodium to reduce the risk of vision loss in patients with neovascular AMD by approximately 15% when administered every six weeks compared to sham.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The majority of safety concerns raised in the review of this application are likely attributed to the procedure required to administer pegaptanib sodium and not the drug product itself. The majority of adverse events seen in the database are those commonly seen with intraocular procedures including intravitreous injections. There are no signals noted in the database submitted to raise a concern over the unacceptable safety of this drug product. However, there is considerable concern raised over the rate of endophthalmitis seen in these trials. Since the cases reported were, in fact, infectious in nature (not sterile), this event is most likely due to contamination during the procedure itself and not the drug product. The injection procedure used to administer this drug product may require refinement before the safety profile is considered acceptable.

B. Description of Patient Exposure

In the overall development program, almost all patients received doses of either 0.3, 1 or 3 mg of pegaptanib sodium as intravitreous injections. A small number of patients received doses of 0.25 mg (3 patients), 0.5 mg (3 patients), or 2 mg (3 patients).

Number of Patients per Treatment Group in Completed cohorts in the Pegaptanib Sodium Development Program

Number of Patients	0.3 mg	1 mg	3 mg	Sham injection
Controlled exudative AMD, all patients	295	301	296	298
Non-controlled exudative AMD, all patients[1]	0	3	61	0
DME Patients[2], EOP1002	0	0	10	0
Overall Total	295	304	367	298

*Includes 0.25 mg, 0.5 mg and 2 mg doses from study NX109-01; [1] Only the completed cohort from study EOP1006 is included ; [2] Study EOP1005 is not included as it is ongoing and has not been unmasked.

Number of Injections Administered

Total number of injections	0.3 mg	1 mg	3 mg	Sham injection
Studies 1003 and 1004 AMD	2478	2568	2499	2557
Phase 1/2 exudative AMD studies	0	3	62	0
Study 1006[1] exudative AMD	0	0	218	0
Study 1002[2] DME	0	0	53	0

*Includes 0.25 mg, 0.5 mg and 2 mg doses from study NX109-01; [1] Only the completed cohort is included ; [2] Study EOP1005 is not included as it is ongoing and has not been unmasked.

Almost 1000 patients have been treated at or above the recommended dose (0.3 mg) for beyond 1 year at the time of NDA filing.

Number (%) of Patients per Treatment Group Receiving the Specified Number Number of Study Treatments in the Week 54 Cohort of Studies EOP1003 and EOP1004

Number of Treatments*	0.3 mg N=295	1 mg N=301	3 mg N=296	All Doses N=892	Sham N=298
1	4(1)	2(1)	3(1)	9(1)	2(1)
2	1(0)	3(1)	1(0)	5(1)	1(0)
3	7(2)	3(1)	4(1)	14(2)	3(1)
4	4(1)	4(1)	2(1)	10(1)	5(2)
5	2(1)	2(1)	5(2)	9(1)	1(0)
6	5(2)	5(2)	7(2)	17(2)	7(2)
7	8(3)	10(3)	12 (4)	30 (3)	3(1)
8	37(13)	23(8)	35(12)	95(11)	28(9)
9	227(77)	249(83)	227(77)	703(79)	248(83)
Total number of treatments	2478	2568	2499	7545	2557
Mean	8.4	8.5	8.4	8.5	8.6
SD	1.5	1.4	1.4	1.4	1.3
Median	9.0	9.0	9.0	9.0	9.0
Range	1-9	1-9	1-9	1-9	1-9

* Pegaptanib sodium intravitreous injection or sham treatment

C. Methods and Specific Findings of Safety Review

All safety data were reported for the safety patient population which included all patients who had received at least one study drug injection. Only data relating to the first year of study treatment were analyzed for this review. This included all adverse events up to 6 weeks after the week 48 injection for all patients who received an injection at week 48 or

378 days post the first injection for all other patients. For patient deaths, the cut-off date for inclusion in this report on the first part of the study was within 42 days (6 weeks) of the week 48 injection.

Overall Summary of Adverse Events – Safety Population – Studies EOP1003 and EOP1004

Number of Patients (%)	0.3 mg n=295	1 mg n=301	3 mg n=296	Sham N=298
Patients with at least one AE	286 (97%)	286 (95%)	288 (97%)	283 (95%)
Patients with at least one ophthalmic AE (study eye)	269 (91%)	270 (90%)	270 (91%)	254 (85%)
Patients with at least one SAE	55 (19%)	50 (17%)	64 (22%)	45 (15%)
Patients with an AE leading to treatment interruption or study discontinuation	7 (2%)	5 (2%)	10 (3%)	7 (2%)

Adverse Events Reported in ≥ 1% of Subjects in Any Treatment Group – Safety Population – Studies EOP1003 and EOP1004

Number of subjects System organ class and preferred term	0.3 mg N=295	1 mg N=301	3 mg N=296	Sham N=298
Blood and lymphatic system disorders				
Anemia NOS	2 (1%)	5 (2%)	12 (4%)	8 (3%)
Cardiac disorders				
Arrhythmia NOS	1 (<1%)	3 (1%)	5 (2%)	0 (0%)
Atrial fibrillation	4 (1%)	2 (1%)	2 (1%)	7 (2%)
Bradycardia NOS	2 (1%)	1 (<1%)	4 (1%)	2 (1%)
Myocardial infarction	3 (1%)	2 (1%)	2 (%)	3 (1%)
Coronary artery disease NOS	1 (<1%)	0 (0%)	1 (<1%)	3 (1%)
Ear and labyrinth disorders				
[redacted]	[redacted]	[redacted]	[redacted]	2 (1%)
Endocrine disorders				
Acquired hypothyroidism	0 (0%)	2 (1%)	4 (1%)	3 (1%)
Eye disorders				
[redacted]	[redacted]	[redacted]	[redacted]	85 (29%)
[redacted]	[redacted]	[redacted]	[redacted]	79 (27%)
[redacted]	[redacted]	[redacted]	[redacted]	24 (8%)
Visual acuity reduced	82 (28%)	58 (19%)	62 (21%)	82 (28%)
Cataract	64 (22%)	78 (26%)	85 (29%)	68 (23%)
[redacted]	[redacted]	[redacted]	[redacted]	29 (10%)
[redacted]	[redacted]	[redacted]	[redacted]	17 (6%)
[redacted]	[redacted]	[redacted]	[redacted]	38 (13%)

Number of subjects System organ class and preferred term	0.3 mg N=295	1 mg N=301	3 mg N=296	Sham N=298
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal sensation in eye	23 (8%)	21 (7%)	26 (9%)	30 (10%)
[redacted]	[redacted]	[redacted]	[redacted]	18 (6%)
Lacrimation increased	25 (8%)	31 (10%)	29 (10%)	30 (10%)
Macular degeneration	25 (8%)	31 (10%)	29 (10%)	36 (12%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye irritation	22 (7%)	24 (8%)	29 (10%)	20 (7%)
Photophobia	22 (7%)	21 (7%)	30 (10%)	23 (8%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye pruritus	22 (7%)	18 (6%)	27 (9%)	23 (8%)
Eye redness	21 (7%)	23 (8%)	19 (6%)	21 (7%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous detachment	12 (4%)	23 (8%)	14 (5%)	14 (5%)
Conjunctival edema	12 (4%)	16 (5%)	18 (6%)	13 (4%)
Corneal epithelium disorder	13 (4%)	15 (5%)	17 (6%)	18 (6%)
Corneal epithelium defect	10 (3%)	8 (3%)	18 (6%)	14 (5%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eyelid edema	7 (2%)	12 (4%)	17 (6%)	13 (4%)
Conjunctival hyperemia	7 (2%)	8 (3%)	8 (3%)	9 (3%)
Retinal exudates	6 (2%)	3 (1%)	0 (0%)	6 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corneal dystrophy	4 (1%)	6 (2%)	6 (2%)	2 (1%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eyelid ptosis	3 (1%)	5 (2%)	8 (3%)	6 (2%)
Keratitis	4 (1%)	7 (2%)	8 (3%)	9 (3%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular hypertension	4 (1%)	7 (2%)	7 (2%)	6 (2%)
Posterior capsule opacification	2 (1%)	3 (1%)	4 (1%)	2 (1%)
Pupillary reflex impaired	3 (1%)	2 (1%)	2 (1%)	5 (2%)
Retinal artery embolism	4 (1%)	1 (0%)	2 (1%)	2 (1%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arcus lipoides	1 (<1%)	1 (<1%)	3 (1%)	1 (<1%)
Eye allergy	1 (<1%)	0 (0%)	2 (1%)	3 (1%)
Eyelid margin crusting	1 (<1%)	1 (<1%)	2 (1%)	3 (1%)
Macular edema	1 (<1%)	2 (1%)	3 (1%)	4 (1%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Retinal scar	1 (<1%)	2 (1%)	4 (1%)	7 (2%)
Erythema of eyelid	0 (0%)	1 (<1%)	4 (1%)	3 (1%)

Number of subjects System organ class and preferred term	0.3 mg N=295	1 mg N=301	3 mg N=296	Sham N=298
Corneal scar	0 (0%)	1 (<1%)	1 (<1%)	3 (1%)
Iris adhesions	0 (0%)	1 (<1%)	3 (1%)	0 (0%)
Maculopathy	0 (0%)	3 (1%)	3 (1%)	1 (<1%)
Uveitis NOS	0 (0%)	4 (1%)	1 (<1%)	0 (0%)
Gastrointestinal disorders				
Nausea	13 (4%)	7 (2%)	16 (5%)	13 (4%)
Diarrhea NOS	8 (3%)	4 (1%)	9 (3%)	6 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	7 (2%)	5 (2%)	9 (3%)	5 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrooesophageal reflux disease	7 (2%)	3 (1%)	2 (1%)	6 (2%)
Abdominal pain NOS	3 (1%)	2 (1%)	1 (0%)	3 (1%)
Hiatus hernia	1 (<1%)	0 (0%)	3 (1%)	1 (<1%)
Abdominal pain upper	0 (0%)	1 (<1%)	3 (1%)	1 (<1%)
Diverticulitis NOS	0 (0%)	1 (<1%)	4 (1%)	4 (1%)
General disorders and administration site conditions				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fall	2 (1%)	1 (<1%)	5 (2%)	2 (1%)
Pyrexia	4 (1%)	5 (2%)	0 (0%)	2 (1%)
Influenza like illness	1 (<1%)	4 (1%)	0 (0%)	2 (1%)
Malaise	1 (<1%)	1 (<1%)	3 (1%)	0 (0%)
Asthenia	0	1 (<1%)	4 (1%)	2 (1%)
Immune system disorders				
Drug hypersensitivity	2 (1%)	2 (1%)	5 (2%)	3 (1%)
Seasonal allergy	2 (1%)	0 (0%)	5 (2%)	6 (2%)
Infections and infestations				
Upper respiratory tract infection NOS	13 (4%)	10 (3%)	12 (4%)	11 (4%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	10 (3%)	8 (3%)	7 (2%)	13 (4%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis NOS	6 (2%)	3 (1%)	10 (3%)	7 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower respiratory tract infection NOS	2 (1%)	1 (<1%)	2 (1%)	3 (1%)
Herpes zoster	1 (<1%)	2 (1%)	4 (1%)	2 (1%)
Respiratory tract infection NOS	1 (<1%)	2 (1%)	2 (1%)	8 (3%)
Tooth abscess	1 (<1%)	3 (1%)	3 (1%)	5 (2%)
Tooth caries NOS	1 (<1%)	2 (1%)	3 (1%)	3 (1%)
Bladder infection NOS	0 (0%)	4 (1%)	0 (0%)	8 (3%)
Ear infection NOS	0 (0%)	1 (<1%)	4 (1%)	3 (1%)
Hordeolum	0 (0%)	1 (<1%)	2 (1%)	3 (1%)
Injury, poisoning and procedural complications				
Periorbital haematoma	7 (2%)	5 (2%)	5 (2%)	7 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post procedural pain	4 (1%)	2 (1%)	2 (1%)	4 (1%)
Skin laceration	3 (1%)	3 (1%)	2 (1%)	4 (1%)

Number of subjects System organ class and preferred term	0.3 mg N=295	1 mg N=301	3 mg N=296	Sham N=298
Corneal erosion	1 (0%)	1 (<1%)	3 (1%)	1 (<1%)
Muscle strain	0 (0%)	1 (<1%)	2 (1%)	3 (1%)
Investigations				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight increased	2 (1%)	3 (1%)	6 (2%)	3 (1%
Weight decreased	1 (<1%)	2 (1%)	6 (2%)	1 (<1%)
Gamma-glutamyltransferase increased	1 (<1%)	0 (0%)	0 (0%)	3 (1%)
Metabolism and nutrition disorders				
Hypercholesterolemia	7 (2%)	10 (3%)	3 (1%)	9 (3%)
Dehydration	2 (1%)	2 (1%)	3 (1%)	4 (1%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperlipidaemia NOS	3 (1%)	2 (1%)	2 (1%)	4 (1%)
Hypokalaemia	3 (1%)	1 (<1%)	3 (1%)	4 (1%)
Musculoskeletal and connective tissue disorders				
Arthralgia	13 (4%)	12 (4%)	11 (4%)	17 (6%)
Back pain	11 (4%)	10 (3%)	8 (3%)	14 (5%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain in limb	2 (1%)	7 (2%)	6 (2%)	6 (2%)
Arthritis NOS aggravated	1 (<1%)	2 (1%)	6 (2%)	4 (1%)
Osteoarthritis NOS	1 (<1%)	5 (2%)	3 (1%)	1 (<1%)
Osteoporosis NOS	1 (<1%)	2 (1%)	4 (1%)	6 (2%)
Localized osteoarthritis	0 (0%)	4 (1%)	3 (1%)	2 (1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Basal cell carcinoma	4 (1%)	2 (1%)	4 (1%)	5 (2%)
Prostate cancer NOS	2 (1%)	2 (1%)	1 (<1%)	3 (1%)
Skin carcinoma NOS	4 (1%)	0 (0%)	1 (<1%)	2 (1%)
Lung cancer stage unspecified (excl metastatic tumours to lung)	0 (0%)	0 (0%)	3 (1%)	1 (<1%)
Nervous system disorders				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	7 (2%)	7 (2%)	9 (3%)	7 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carpal tunnel syndrome	2 (1%)	1 (<1%)	0 (0%)	4 (1%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	0 (0%)	3 (1%)	4 (1%)	3 (1%)
Psychiatric disorders				
Depression	11 (4%)	7 (2%)	10 (3%)	11 (4%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	2 (1%)	8 (3%)	3 (1%)	9 (3%)
Confusional state	3 (1%)	2 (1%)	0 (0%)	1 (<1%)
Renal and urinary disorders				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal failure NOS	0 (0%)	1 (<1%)	1 (<1%)	3 (1%)
Respiratory, thoracic and mediastinal disorders				
Nasopharyngitis	19 (6%)	23 (8%)	27 (9%)	19 (6%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of subjects System organ class and preferred term	0.3 mg N=295	1 mg N=301	3 mg N=296	Sham N=298
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic obstructive airways disease	2 (1%)	1 (<1%)	2 (1%)	3 (1%)
Dyspnea NOS	3 (1%)	3 (1%)	8 (3%)	4 (1%)
Epistaxis	3 (1%)	2 (1%)	3 (1%)	2 (1%)
Pharyngitis	3 (1%)	2 (1%)	5 (2%)	5 (2%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic obstructive airways disease exacerbated	1 (<1%)	4 (1%)	2 (1%)	2 (1%)
Pulmonary congestion	0 (0%)	2 (1%)	3 (1%)	2 (1%)
Skin and subcutaneous tissue disorders				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cutis laxa	3 (1%)	2 (1%)	2 (1%)	3 (1%)
Rash NOS	3 (1%)	7 (2%)	3 (1%)	3 (1%)
Vascular disorders				
Hypertension NOS	14 (5%)	26 (9%)	29 (10%)	22 (7%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension NOS	1 (<1%)	2 (1%)	4 (1%)	0 (0%)

Reviewer's comments:
Adverse events seen more frequently in the 0.3 mg group versus sham are highlighted. The majority of the most frequently occurring adverse events (i.e. >10%) in the drug group are those commonly seen after intraocular procedures including injections. Anterior chamber inflammation, vitreous floaters, vitreous opacities and increased intraocular pressure are reported at a much higher rate in the drug groups than in the sham arm. This may be due to the lack of intraocular penetration in the sham group, however, a drug effect cannot be ruled out.

Discussion of Vision Threatening Adverse Events:

Endophthalmitis

Endophthalmitis was experienced by 12 pegaptanib sodium-treated patients; no cases occurred in the sham-treated patients. Four (4) additional events of endophthalmitis were reported in pegaptanib sodium-treated patients in the ongoing controlled studies as of the data cutoff date of 26 September 2003. All 16 cases occurred in the study eye and occurred within one week of injection.

The injection procedure as originally described in the study protocols was revised in a protocol amendment to reduce the risk of endophthalmitis.

The amendment required use of:

1. sterile preparation and drape similar to that used for routine intraocular surgery, and
2. use of either pre-injection topical ophthalmic antibiotic drops for three days prior to the injection OR a 10 mL povidone iodine flush immediately prior to injection.

Three of the sixteen (3/16) cases of endophthalmitis occurred after the amendment was distributed to the sites.

Reviewer's Comments:

The rate of endophthalmitis seen in the phase three trials is much higher than expected for an intravitreal injection. It is approximately 10 fold higher than the rate seen in cataract surgery. This calls in to question the appropriateness of the technique used to administer this drug. Despite the change in the injection procedure instituted to reduce the risk of endophthalmitis there is still a significant risk of this adverse event.

Listing of Patients with Endophthalmitis

Patient ID	Sex/ Age	Dose Group	Injections Prior to SAE	Onset Post Last Injection	Baseline VA	VA Before Event	VA After Event	Latest VA Wk 54	Outcome	Culture
EOP1003/1004 Week 54 Cohort										
1003 - 073-015	F/83	3 mg	8	4 days	20/100	20/63	20/125	20/125	d/c'd due to Patient request	Coagulase negative Staph
1003 - 089-019	F/69	0.3 mg	4	4 days	20/320	20/800	<20/800	<20/800	d/c'd due to AE	Staph epidermidis
1003 -102-033	F/76	0.3 mg	2	4 days	20/100	20/160	20/100	20/125	Cont't	Coagulase positive Staph
1003 -113-012	F/81	1 mg	5	2 days	20/100	20/50	20/63	20/50	Cont't	Negative
1003 -143-006	F/86	0.3 mg	2	4 days	20/125	20/200	20/320	20/125	Cont't	Coagulase negative Staph
1003 - 145-013	M/85	3 mg	6	7 days	20/125	20/400	20/400	20/640	Cont't	Micrococcus species
1004 -025-001	M/73	0.3 mg	7	3 days	20/40	20/50	20/200	20/80	Cont't	Coagulase negative Staph
1004 -026-009	F/69	1 mg	2	3 days	20/80	20/80	20/200	20/200	Cont't	Coagulase negative Staph
1004 -034-020	M/80	0.3 mg	1	4 days	20/200	20/200	20/400	20/500	Cont't	Staphy epidermidis
1004 - 042-001	M/77	0.3 mg	1	4 days	20/63	20/63	20/800	20/800	d/c'd due to AE	Staph lugdunensis
1004 -054-018	F/73	1 mg	1	2 days	20/80	20/80	20/100	20/125	Cont't	Negative
1004 - 057-014	M/78	3 mg	5	5 days	20/250	20/320	20/250	20/320	Cont't	Negative
EOP1003/1004 Year 2										
1004-025-005	F/81	masked	10	1 day	20/63	20/160	20/200	20/160 Wk 78	Cont't	Negative
1004-035-001	M/74	masked	13	4 days	20/160	20/80	20/100	20/160 Wk 103	d/c'd due to AE	Coagulase negative Staph
1004 - 048-017	F/78	masked	9	5 days	20/80	20/250	20/320	20/320 Wk 84	d/c'd due to AE	Negative
EOP1005 Ongoing										
1005-015-001	F/59	masked	1	3 days	20/80	20/63	20/125	20/160 Wk 30	d/c'd due to AE	Negative

Retinal Detachment

The incidence of study eye retinal detachment in the first 54 weeks of Studies EOP1003 and EOP1004 was 0.6% (5/892) in the combined pegaptanib sodium and 0.3% (1/298) in the sham groups One patient received 0.3 mg, 2 patients received 1 mg, and 2 patients received 3 mg pegaptanib sodium.

The onset of these events did not correlate with the number of treatments received, since the detachments occurred after the third (two patients), fourth, six or eighth injection. The event onset varied from 7 to 137 days after the last injection. Two of the patients had detachments that were exudative/hemorrhagic in nature, which may have been secondary to the underlying disease process; these detachments did not have a rhegmatogenous component. The detachment of a third patient was attributed to proliferative vitreoretinopathy and contracture of the retina.

Retinal Tear

Four of 892 patients (0.4%) receiving pegaptanib sodium (2 receiving 0.3 mg; 2 receiving 3 mg) and 1/298 (0.3%) receiving sham treatment experienced a retinal tear in the study eye during the first 54 weeks of Studies EOP1003 and EOP1004. In all 5 cases, the tear was diagnosed at the study visit one week postinjection.

For the 4 patients who were receiving active treatment, the tears occurred after the second, fifth, or sixth (two patients) injection. Four patients were treated with laser photocoagulation and one received no treatment. None of the patients progressed to retinal detachment and none discontinued treatment due to this event. There were no retinal tears in the fellow eye.

Traumatic Cataracts

Five patients developed a traumatic cataract during the first 54 weeks of Studies EOP1003 and EOP1004, all of which were iatrogenic in nature. In 4 of these patients there was contact and/or penetration of the lens with the intravitreous injection needle; two of these events occurred on the same day at the same investigational site (1003-093). In the fifth patient, an anterior chamber paracentesis was performed due to increased IOP after an intravitreous injection, and the paracentesis needle punctured the anterior lens capsule. All of these patients subsequently had a cataract extraction, and all but one continued in the study; the remaining patient requested to be withdrawn from the study after cataract surgery.

Retinal Artery Occlusion

Central retinal artery occlusion (CRAO) in the study eye during the first 54 weeks of Studies EOP1003 and EOP1004 was seen in 4 patients, 1 receiving 0.3 mg pegaptanib

sodium and 3 receiving 1 mg. All 4 cases were transient closures of the central artery which were associated with increased IOP immediately following an injection. All were treated with, and resolved after, paracentesis. These events occurred after the first, third or sixth injection. All events resolved without sequelae and all 4 patients continued in the study.

In addition to the 4 study eye cases described above, one patient receiving pegaptanib sodium 1mg presented with a CRAO in the fellow eye 28 days after the first injection. The patient was treated with paracentesis and acetazolamide.

Deaths

Twenty-five deaths were recorded in the Week 54 cohort of Studies EOP1003 and EOP1004, 19 in patients receiving pegaptanib sodium and 6 patients receiving sham. The incidence of death in all pegaptanib sodium treated patients in the Week 54 cohort of Studies EOP1003 and EOP1004 was 2.1%, with the rate in sham-treated patients from these studies being 2.0%.

Number (%) of Deaths in the Week 54 Cohort of Studies EOP1003 and EOP1004

	0.3 mg	1 mg	3 mg	Sham
	N=295	N=301	N=296	N=298
EOP1003 Wk 54 Cohort	2/151(1.3)	2/155(1.3)	3/153(2.0)	4/153(2.6)
EOP1004 Wk 54 Cohort	3/144(2.1)	6/146(4.1)	3/143(2.1)	2/145(1.4)

Death Listing in Pegaptanib Sodium Studies by Treatment Group

Patient Identifier	Age/ Gender	Trt Group	Study Day of Death	Last Trt to Death (Days)	Cause(s) of Death (Investigator Term)
Week 54 Cohort of Studies EOP1003 and EOP1004					
EOP1003-108-007	82/M	0.3 mg	312	17	Myocardial Infarction
EOP1003-136-011	80/F	0.3 mg	130	11	Brain Hemorrhage
EOP1004-021-010	68/M	0.3 mg	231	20	Cardiac Arrest
EOP1004-048-002	69/M	0.3 mg	185	17	Abdominal Aortic Aneurysm
EOP1004-050-012	76/M	0.3 mg	140	54	Acute Myeloid Leukemia
EOP1003-130-001	75/F	1 mg	358	22	Heart Attack
EOP1003-136-005	74/M	1 mg	281	31	Stroke
EOP1004-008-018	85/M	1 mg	228	19	Anemia
EOP1004-015-002	76/F	1 mg	307	34	Pneumonia; Worsening Chronic Bronchiectasis; Worsening Mycobacterium Avium Complex Pneumonia
EOP1004-033-006	86/F	1 mg	62	20	Aortic Stenosis; Cardiopulmonary Arrest

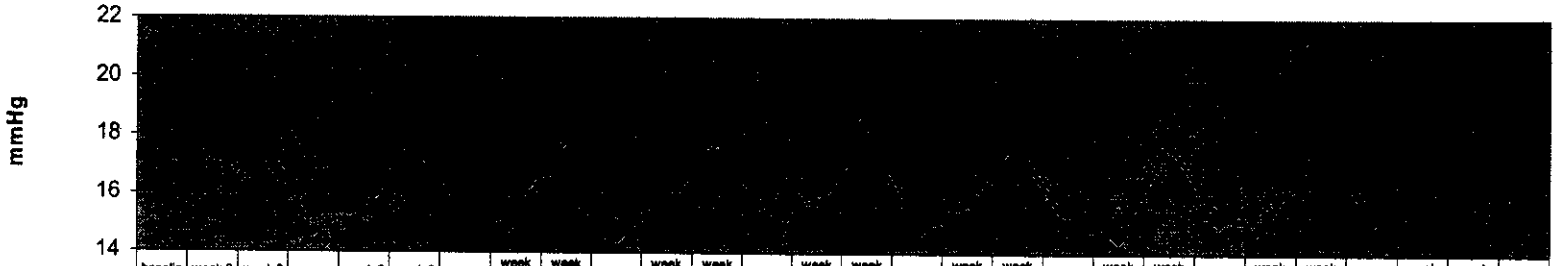
EOP1004-041-001	81/F	1 mg	187	55	Renal failure; Septicemia;
EOP1004-050-021	82/M	1 mg	323	48	Poorly Differentiated Large Cell
					Lung Cancer
EOP1004-059-006	75/M	1 mg	101	17	Metastatic Cancer
EOP1003-074-002	89/F	3 mg	183	183	Ischemic Cerebral Vascular Accident
EOP1003-104-011	75/M	3 mg	195	27	Massive Gastric Bleeding
EOP1003-085-001	82/F	3 mg	227	64	Pneumonia
EOP1004-006-010	85/F	3 mg	372	36	Renal Failure
EOP1004-026-003	81/F	3 mg	256	47	Cardiac Arrest; Necrotic Bowel
EOP1004-034-011	86/F	3 mg	116	30	Cardiac Arrest
EOP1003-064-012	82/M	Sham	342	3	Myocardial Infarction; Emphysema
EOP1003-098-002	79/M	Sham	35	35	Acute Myeloid Leukemia
EOP1003-130-013	83/F	Sham	273	63	Bronchopneumonia
EOP1003-145-018	72/M	Sham	350	87	Metastatic Lung Cancer; Multiple
					Blood Clots
EOP1004-021-012	80/F	Sham	335	79	Bladder Cancer
EOP1004-040-003	76/F	Sham	328	27	Pelvic mass
Deaths Other than in Week 54 Cohort of Studies EOP1003 and EOP1004*					
EOP1005-024-011	80/F	masked	52	10	Acute Myocardial Infarction
EOP1004-141-010**	82/F	0.3 mg	393	58	Gastric Cancer
EOP1003-071-005**	90/M	1 mg	471	136	Cardiorespiratory Arrest
EOP1004-036-017	81/M	1 mg	431	95	Myocardial infarction
EOP1000-006-001	85/F	3 mg	74	18	Myocardial Infarction
EOP1002-HUD-02	73/F	3 mg	67	26	Multisystem Organ Failure
EOP1003-093-005**	74/M	3 mg	401	61	Septic Shock; Intestinal Necrosis
EOP1003-119-012**	75/M	3 mg	381	47	Probable Ischemic Heart Disease
EOP1003-093-018	93/M	Sham	355	142	Pulmonary Embolism
EOP1004-006-034**	84/F	3 mg	415	121	Acute Respiratory Failure
*Study treatment for patients in EOP1003 and EOP1004 given for the Week 54 period					
** No study treatment after Week 54					

Reviewer's Comments:

The death rate in the pooled phase 3 studies is consistent across the treatment groups. The 2% death rate is likely due to the population studied in these trials and not due to the drug or procedure.

Study Eye IOP – Safety population – Study EOP1003

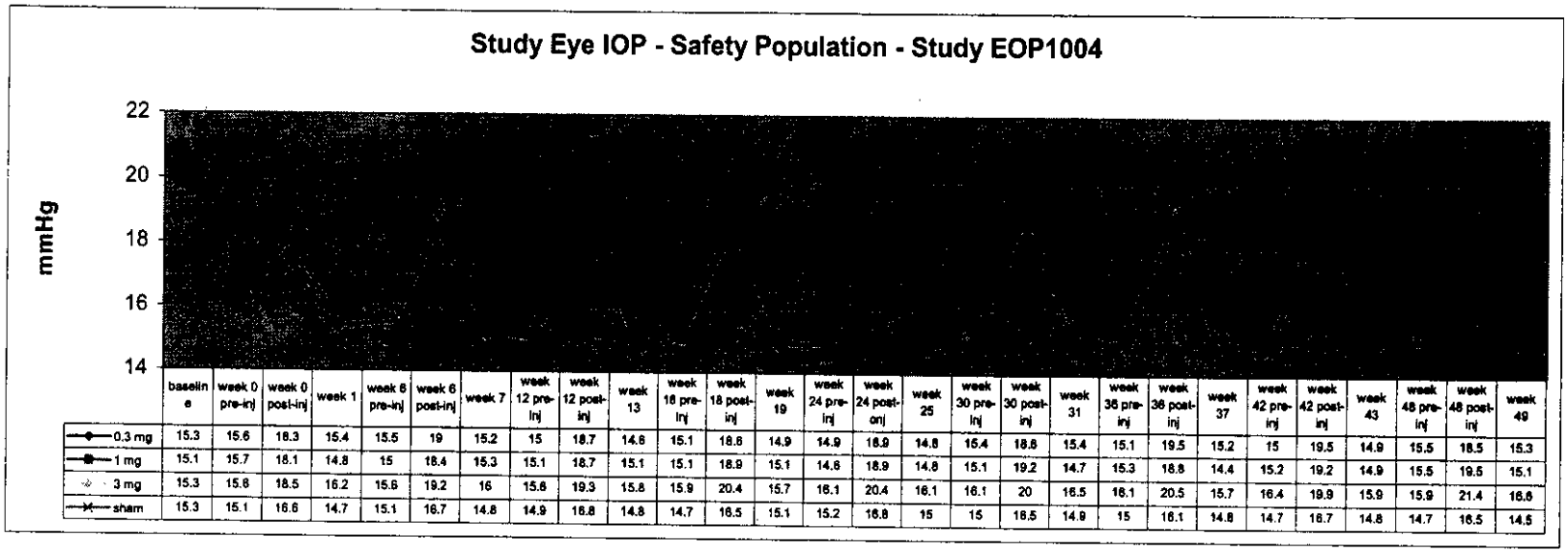
Study Eye IOP - Safety population - Study EOP1003



	baseline	week 0 pre-inj	week 0 post-inj	week 1	week 6 pre-inj	week 6 post-inj	week 7	week 12 pre-inj	week 12 post-inj	week 13	week 18 pre-inj	week 18 post-inj	week 19	week 24 pre-inj	week 24 post-onj	week 25	week 30 pre-inj	week 30 post-inj	week 31	week 36 pre-inj	week 36 post-inj	week 37	week 42 pre-inj	week 42 post-inj	week 43	week 48 pre-inj	week 48 post-inj	week 49
0.3 mg	15.4	15.1	17.2	14.8	15.5	17.8	14.8	15.3	17.9	14.8	15.7	17.8	15.2	15.2	17.9	14.8	15.5	17.7	15	14.6	17.8	15.2	15	17.9	15.2	15.4	18.6	15.1
1 mg	15.4	15.7	18	15.3	15.4	17.8	15.4	15.6	18.2	15.4	15.6	18.2	15.1	15.6	18.3	15.1	15.8	18	15.3	15.6	18.2	15.3	15.7	18.3	15.3	15.4	17.4	15.1
3 mg	15.3	15.2	17.2	15.1	15.3	17.5	15.2	15.2	18.4	15	15.4	17.4	15.4	15.4	18	15.6	15.4	18.3	15.4	15.5	18.6	15.9	15.8	18.6	15.8	15.4	18	16
sham	15.4	15.4	16.4	15.4	15.5	16.5	15.3	15.4	16.1	15	15.4	16.2	14.8	15.3	16.1	15.2	15.3	15.9	14.8	15	16.1	14.3	15.1	15.5	14.6	14.8	16	14.8

APPEARS THIS WAY
ON ORIGINAL

Study Eye IOP – Safety population – Study EOP1004



	baseline	week 0 pre-inj	week 0 post-inj	week 1	week 6 pre-inj	week 6 post-inj	week 7	week 12 pre-inj	week 12 post-inj	week 13	week 18 pre-inj	week 18 post-inj	week 19	week 24 pre-inj	week 24 post-inj	week 25	week 30 pre-inj	week 30 post-inj	week 31	week 36 pre-inj	week 36 post-inj	week 37	week 42 pre-inj	week 42 post-inj	week 43	week 48 pre-inj	week 48 post-inj	week 49
0.3 mg	15.3	15.6	16.3	15.4	15.5	19	15.2	15	16.7	14.6	15.1	16.6	14.9	14.9	16.9	14.8	15.4	16.8	15.4	15.1	19.5	15.2	15	19.5	14.9	15.5	16.5	15.3
1 mg	15.1	15.7	16.1	14.8	15	16.4	15.3	15.1	16.7	15.1	15.1	16.9	15.1	14.6	16.9	14.8	15.1	19.2	14.7	15.3	16.8	14.4	15.2	19.2	14.9	15.5	19.5	15.1
3 mg	15.3	15.6	16.5	16.2	15.6	19.2	16	15.6	19.3	15.6	15.9	20.4	15.7	16.1	20.4	16.1	16.1	20	16.5	16.1	20.5	15.7	16.4	19.9	15.9	15.9	21.4	16.6
sham	15.3	15.1	16.6	14.7	15.1	16.7	14.6	14.9	16.8	14.8	14.7	16.5	15.1	15.2	16.8	15	15	16.5	14.9	15	16.1	14.8	14.7	16.7	14.8	14.7	16.5	14.5

Among patients receiving pegaptanib sodium, 9% (0.3 mg), 13% (1 mg) and 15% (3 mg) underwent paracentesis for the treatments of increased intraocular pressure, while no sham-treated patient did. A total of 12% of patients in the 0.3 mg pegaptanib sodium group, 14% in the 1 mg group, and 19% in the 3 mg group received a concomitant medication for increased IOP on one ore more injection days.

Reviewer's Comments:

The is an expected increase in IOP which occurs post injection in all of the drug treatment groups. The increase in IOP is consistent across drug groups. During the first year of the study, the baseline IOP for all drug groups appears to remain unchanged. There is no trend of hypotony due to multiple penetrations of the globe over the year of treatment.

Concomitant PDT Use

Number (%) of Patients with and Ocular Adverse Events >10% and/or Events that May Have a Significant Effect on Vision in the Study Eye by PDT Use – Study EOP1003 & EOP1004 – Safety Population

Event		0.3 mg	1 mg	3 mg	All Doses	Sham
PDT after 1st injection	Yes	N=51	N=56	N=59	N=166	N=64
	No	N=244	N=245	N=237	N=726	N=234
Eye Pain	PDT	[redacted]	23 (41%)	22 (37%)	67 (40%)	25 (39%)
	No PDT	[redacted]	74 (30%)	83 (35%)	232 (32%)	58 (25%)
Punctate Keratitis	PDT	[redacted]	19 (34%)	17 (29%)	54 (33%)	12 (19%)
	No PDT	[redacted]	72 (29%)	81 (34%)	232 (32%)	67 (29%)
Vitreous Floaters	PDT	[redacted]	22 (39%)	15 (29%)	54 (33%)	6 (9%)
	No PDT	[redacted]	81 (33%)	88 (37%)	240 (33%)	17 (7%)
Visual Acuity Reduced	PDT	[redacted]	15 (27%)	14 (24%)	43 (26%)	27 (42%)
	No PDT	[redacted]	32 (13%)	38 (16%)	123 (17%)	44 (19%)
Anterior Chamber Inflammation	PDT	[redacted]	12 (21%)	14 (24%)	42 (25%)	5 (8%)
	No PDT	[redacted]	30 (12%)	25 (11%)	86 (12%)	12 (5%)
Cataract	PDT	[redacted]	7 (13%)	16 (27%)	34 (20%)	9 (14%)
	No PDT	[redacted]	54 (22%)	53 (22%)	147 (20%)	45 (19%)
Visual Disturbance NOS	PDT	[redacted]	6 (11%)	16 (27%)	30 (18%)	9 (14%)
	No PDT	[redacted]	33 (13%)	24 (10%)	87 (12%)	24 (10%)
Vitreous Opacities	PDT	[redacted]	11 (20%)	8 (14%)	30 (18%)	6 (9%)
	No PDT	[redacted]	45 (18%)	40 (20%)	135 (19%)	23 (10%)
Photophobia	PDT	[redacted]	5 (9%)	9 (15%)	20 (12%)	7 (11%)
	No PDT	[redacted]	16 (7%)	20 (8%)	52 (7%)	16 (7%)
Vision Blurred	PDT	[redacted]	6 (11%)	5 (8%)	20 (12%)	5 (8%)
	No PDT	[redacted]	18 (7%)	12 (5%)	46 (6%)	9 (4%)
Corneal Edema	PDT	[redacted]	2 (4%)	5 (8%)	14 (8%)	14 (8%)
	No PDT	[redacted]	21 (9%)	32 (14%)	71 (10%)	16 (7%)
Retinal Hemorrhage	PDT	[redacted]	8 (14%)	3 (5%)	14 (8%)	6 (9%)
	No PDT	[redacted]	20 (8%)	16 (7%)	43 (6%)	19 (8%)
Endophthalmitis	PDT	1 (2%)	0	0	1 (1%)	0
	No PDT	5 (2%)	3 (1%)	3 (1%)	11 (2%)	0
Retinal Detachment	PDT	0	1 (2%)	0	1 (1%)	0
	No PDT	1 (0%)	1 (0%)	2 (1%)	4 (1%)	0

Reviewer's Comments:

Those adverse events occurring at a higher rate in the group administered PDT during treatment are highlighted. There was an increased risk of the majority of ocular adverse events which occur in >10% of the population as well the majority of events considered vision threatening when concomitant PDT was administered.

Clinical Laboratory Evaluations, Vital Signs, ECG's

Number (%) of Patients with Laboratory Test Abnormalities Meeting the Primary Criteria Occurring at an Incidence of > 1% in Any Treatment Group, Without Regard to Baseline in the Week 54 Cohort of Studies EOP1003 an EOP1004

Laboratory Test	Units	Primary Criteria	0.3 mg	1 mg	3 mg	All Doses	Sham
Hematology			N=293	N=299	N=293	N=885	N=295
Hemoglobin	g/dL	<0.8xBL	3(1)	6(2)	10(3)	19(2)	7(2)
Platelets	10E9/L	< 75	5 (2)	0	0	5 (1)	1 (0)
Neutrophils (Abs)	10E6/L	> 1.5xULN	5 (2)	1 (0)	6 (2)	12 (1)	5 (2)
Eosinophils (Abs)	10E6/L	>1.5x ULN	8(3)	4(1)	2(1)	14(2)	12(4)
Eosinophils	%	>1.5x ULN	11(4)	7(2)	5(2)	23(3)	20(7)
Liver Function			N=295	N=301	N=296	N=892	N=298
GGT	IU/L	>3xULN	5(2)	6(2)	11(4)	22(2)	4(1)
Renal Function			N=295	N=301	N=296	N=892	N=298
BUN	µ MOL/L	>1.3xULN	10(3)	11(4)	12(4)	33(4)	7(2)
Creatinine	µ MOL/L	>1.3xULN	8(3)	10(3)	9(3)	27(3)	11(4)
Electrolytes			N=295	N=301	N=296	N=892	N=298
Potassium	MMOL/L	>1.1xULN	6(2)	8(3)	14(5)	28(3)	8(3)
Carbon dioxide	MMOL/L	< 0.9xLLN	1 (0)	5 (2)	4 (1)	10 (1)	2 (1)
		> 1.1xULN	5 (2)	4 (1)	7 (2)	16 (2)	4 (1)
Phosphorus	MMOL/L	>1.1xULN	3(1)	3(1)	8(3)	14(2)	5(2)

N=No. patients evaluable for laboratory tests
BL=Baseline
ULN=Upper limit of normal

Reviewer's Comments:
There are no dose dependent changes in laboratory values noted.

Vital Signs – Studies EOP1003 & EOP1004 – Safety Population

Reviewer's Comments:
There were no clinically significant changes in diastolic or systolic BP, temperature or pulse in any of the treatment groups during the first year of this study.

D. Adequacy of Safety Testing

The database submitted in this NDA is adequate to assess the safety profile of pegaptanib sodium.

APPEARS THIS WAY
ON ORIGINAL

E. Summary of Critical Safety Findings and Limitations of Data

The majority of safety concerns raised in the review of this application are likely attributed to the procedure required to administer pegaptanib sodium and not the drug product itself. The majority of adverse events seen in the database are those commonly seen with intraocular procedures including intravitreous injections. There is concern raised in this database over the rate of endophthalmitis. This event is most likely due to contamination during the procedure itself and not the drug product since most cases were infectious in nature. The labeling will need to reflect the risk of this administration related adverse event and the importance of the use of sterile technique. This will allow for physicians and patients to be adequately informed about this risk and steps to take to minimized its occurrence.

VIII. Dosing, Regimen, and Administration Issues

Adequate dose ranging studies were conducted during drug development. The 0.3 mg dose of pegaptanib sodium has been demonstrated to be safe and effective in two controlled phase 3 trials. The dosing interval (every 6 weeks) chosen by the applicant was not varied during the development program, therefore there is no clinical data available to assess the adequatcy of this dosing interval.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The sponsor has adequately evaluated gender effects on both the safety and efficacy outcomes. Sub-group analyses did not reveal any difference in the primary efficacy endpoint between males and females. The safety profile seen in male and females is similar. The types and rates of adverse events seen in the two groups are consistent.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The trials for this indication were conducted in a population that was overwhelmingly elderly and white. This is reflective of the population which is mostly affected by this disease and does not reflect an issue with recruitment. The number of patients outside of this demographic were too small to make any

definitive conclusion about the safety and efficacy, however based on a subset analysis it does not appear that there is any age, race or ethnicity effects.

C. Evaluation of Pediatric Program

Pediatric trials have not been conducted for this drug. The indication being sought is for age-related macular degeneration which is a disease seen exclusively in the adult population.

D. Comments on Data Available or Needed in Other Populations

The demographics of the patients enrolled in the trial during the development program for this product are representative of the targeted population. There is no additional data need from other populations.

X. Conclusions and Recommendations

A. Conclusions

The submitted studies in NDA 21-756 are sufficient to establish efficacy for the use of pegaptanib sodium 0.3 mg in the treatment of the neovascular form of age-related macular degeneration. The two phase 3 studies show replicative results in the ability of pegaptanib sodium to reduce the risk of vision loss in patients with neovascular AMD when given every six weeks compared to sham.

B. Recommendations

NDA 21-756 is approvable from a clinical perspective the treatment of the neovascular form of age-related macular degeneration pending the receipt and review of the 120-day safety update, labeling and revised drug product specifications.

XI. Appendix

A. Other Relevant Materials

The labeling for this drug product will be contained in a separate M.O. review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jennifer Harris
9/16/04 10:02:05 AM
MEDICAL OFFICER

Wiley Chambers
9/17/04 07:40:06 AM
MEDICAL OFFICER