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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Macugen® / Pegaptanib sodium

PROTOCOL NO.: A5751013

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

Study Centers: A total of 60 centers took part in the study and randomized subjects; 2 in Australia, 2 in Austria, 3 in Brazil, 1 in Denmark, 5 in France, 4 in India, 1 in the Netherlands, 1 in Switzerland, 2 in Canada, 5 in the Czech Republic, 6 in Germany, 3 in Italy, 1 in Portugal, 2 in the United Kingdom (UK), 21 in the United States (US), and 1 in Greece.

Study Initiation and Final Completion Dates: 15 September 2005 to 15 July 2011

Phase of Development: Phase 2/3

Study Objectives:

Primary Objectives:

- To compare the efficacy and confirm the safety of pegaptanib sodium in subjects with diabetic macular edema (DME) involving the center of the macula associated with vision loss not due to ischemia;

- To collect safety data from subjects enrolled in the study after Year 2 (Phase 3, extension study).

METHODS

Study Design: This study was a Phase 2/3, randomized, double-masked, sham-controlled, multicenter, parallel-group, comparative study. Subjects were stratified by sites, glycosylated hemoglobin (HbA_{1c}) levels (<7.6% versus ≥7.6%), systemic blood pressure (BP, [systolic <140 mm Hg versus ≥140 mm Hg and diastolic <80 mm Hg versus ≥80 mm Hg]), and baseline visual acuity (VA, [subjects with <54 letters versus ≥54 letters]). Intravitreous injections of pegaptanib sodium 0.3 mg (90 μL) or a sham treatment procedure were given to subjects at 6-week intervals through 48 weeks in Year 1 and at 6-week

intervals thereafter, if deemed necessary per protocol specifications through Week 96 in Year 2.

Analysis of data was performed after Years 1 and 2, when 100% of subjects had completed Year 1 and 80% of subjects had completed Year 2.

Subjects who had not yet completed the Week 102 visit had the option to enroll in a Year 3 open-label extension period after completing Week 102. Year 3 was an open-label extension period for this study. The primary objective of the Year 3 extension was to collect safety data the subjects still enrolled in the study.

A full schedule of activities planned for Year 1 (through Week 54) and Year 2 (through Week 102) of this study is presented in Table 1. A schedule of activities planned for the Year 3 (through Week 156) extension period of this study is presented in Table 2.

Table 1. Schedule of Activities; Years 1 and 2

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

Eye Assessments: B = both eyes; M = mandatory; S = study eye.
A maximum of 3 focal/grid laser treatments per year with a minimum of 17 weeks between applications was required.
Note: all visits for injections were required to occur within ±5 days of the Scheduled Visit.
DME = diabetic macular oedema; ECG = electrocardiogram; EQ-5D = self-reported questionnaire developed by the EuroQoL group; ETDRS = early treatment of diabetic retinopathy study; EuroQoL = european quality of life; ILM = internal limiting membrane; NEI-VFQ 25 = 25-item national eye institute – visual functioning questionnaire; OCT = optical coherence tomography; RPE = retinal pigment epithelium.

a. Baseline assessments were performed within 2 weeks before the first study injection.
b. Vital signs measurements and weight were always recorded; physical examination was performed only if indicated.
c. Before injection and again at least 30 minutes after injection for all subjects. Applanation was required at Baseline and Weeks 54 and 102 or early withdrawal.
d. Modified 7 standard fields and stereo fundus reflex (both eyes).
e. Angiograms, photographs and OCTs sent to the Reading Center for both eyes at Baseline and Weeks 54 and 102 or Early Withdrawal, otherwise study eye as noted. OCT center point thickness was required to be at least 250 microns with a standard deviation of <10% and have properly created ILM and RPE borders at Baseline by computer software. At Week 18, an OCT for the study eye was sent to the Reading Center. Fluorescein angiography was obtained in the study eye beginning at Week 18 for the purpose of confirming decision for focal/grid laser to perfused oedema and were not sent to the Reading Center.
f. Only in female subjects who were not postmenopausal for at least 12 months or surgically sterile (serum at Baseline and urine thereafter before each injection).
g. Laboratory tests were performed at Baseline, Week 6, and every 12 weeks thereafter.

Table 1. Schedule of Activities; Years 1 and 2

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Week	**18 (Before Injection)**	**18 (After Injection)**	**18+3 Days**	**19**	**24 (Before Injection)**	**24 (After Injection)**	**24+3 Days**	**30 (Before Injection)**	**30 (After Injection)**	**30+3 Days**
Pegaptanib sodium injection/sham injection	X				X			X		
Decision to laser[a]	A									
Apply focal laser (if indicated)[a]				A[a]						
Physical examination/weight/vital signs	X[b]				X[b]			X[b]		
Telephone safety check (as indicated)			M				M			M
Protocol refraction and distance VA (ETDRS chart)	S				S			S		
Tonometry	S[c]	S			S[c]	S		B[c]	S	
Ophthalmologic examination	S	S			S	S		B	S	
Fluorescein angiography	A[d]									
OCT	S[d]									
Pregnancy test	X[e]				X[e]			X[e]		
Laboratory tests	X[f]							X[f]		
Concomitant medication	X	X	X	X[a]	X	X	X	X	X	X
Adverse events	X	X	X	X[a]	X	X	X	X	X	X
NEI-VFQ 25 and EQ-5D	M									

Eye Assessments: A = as indicated; B = both eyes; M = mandatory; S = study eye.
A maximum of 3 focal/grid laser treatments per year with a minimum of 17 weeks between applications was required.
Note: all visits for injections were required to occur within ±5 days of the Scheduled Visit.
EQ-5D = self-reported questionnaire developed by the EuroQoL group; ETDRS = early treatment of diabetic retinopathy study; EuroQoL = european quality of life; ILM = internal limiting membrane; NEI-VFQ 25 = 25-item national eye institute – visual functioning questionnaire; OCT = optical coherence tomography; RPE = retinal pigment epithelium; VA = visual acuity.

a. Visit only occurred if the decision was made to laser. A maximum of 3 focal/grid laser treatments per year with a minimum of 17 weeks between applications was required. Concomitant medications and adverse events were recorded only if the visit occurred.
b. Vital signs measurements and weight were always recorded; physical examination was performed only if indicated.
c. Before injection and again at least 30 minutes after injection for all subjects. Applanation was required at Baseline and Weeks 54 and 102 or early withdrawal.
d. Angiograms, photographs and OCTs sent to the Reading Center for both eyes at Baseline and Weeks 54 and 102 or Early Withdrawal, otherwise study eye as noted. OCT center point thickness was required to be at least 250 microns with a standard deviation of <10% and have properly created ILM and RPE borders at Baseline by computer software. At Week 18, an OCT for the study eye was sent to the Reading Center. Fluorescein angiography was obtained in the study eye beginning at Week 18 for the purpose of confirming decision for focal/grid laser to perfused oedema and were not sent to the Reading Center.
e. Only in female subjects who were not postmenopausal for at least 12 months or surgically sterile (serum at Baseline and urine thereafter before each injection).
f. Laboratory tests were performed at Baseline, Week 6, and every 12 weeks thereafter.

Table 1. Schedule of Activities; Years 1 and 2

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Week	**36 (Before Injection)**	**36 (After Injection)**	**36+3 Days**	**42 (Before Injection)**	**42 (After Injection)**	**42+3 Days**	**48 (Before Injection)**	**48 (After Injection)**	**48+3 Days**
Pegaptanib sodium injection/ sham injection	X			X			X		
Physical examination/weight/vital signs	X[a]			X[a]			X[a]		
Telephone safety check (as indicated)			M			M			M
Protocol refraction and distance VA (ETDRS chart)	S			S			S		
Tonometry	S[b]	S		S[b]	S		S[b]	S	
Ophthalmologic examination	S	S		S	S		S	S	
Pregnancy test	X[c]			X[c]			X[c]		
Laboratory tests				X[d]					
Concomitant medication	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

Eye Assessments: M = mandatory; S = study eye.
A maximum of 3 focal/grid laser treatments per year with a minimum of 17 weeks between applications was required.
Note: all visits for injections were required to occur within ±5 days of the Scheduled Visit.
ETDRS = early treatment of diabetic retinopathy study; VA = visual acuity.

a. Vital signs measurements and weight were always recorded; physical examination was performed only if indicated.
b. Before injection and again at least 30 minutes after injection for all subjects. Applanation was required at Baseline and Weeks 54 and 102 or early withdrawal.
c. Only in female subjects who were not postmenopausal for at least 12 months or surgically sterile (serum at Baseline and urine thereafter before each injection).
d. Laboratory tests were performed at Baseline, Week 6, and every 12 weeks thereafter.

Table 1. Schedule of Activities; Years 1 and 2

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Week	**54 (Before Injection)**	**54 (After Injection)**	**54+3 Days**	**60 (Before Injection)**	**60 (After Injection)**	**60+3 Days**	**66 (Before Injection)**	**66 (After Injection)**	**66+3 Days**
Pegaptanib sodium injection/sham injection	X[a]			X[a]			X[a]		
Physical examination/weight/vital signs	X[b]			X[b]			X[b]		
Telephone safety check (as indicated)			A			A			A
Protocol refraction and distance VA (ETDRS chart)	B			S			S		
Tonometry	B[c]	S		S[c]	S		S[c]	S	
Ophthalmologic examination	B	S		S	S		S	S	
Stereoscopic colour fundus photos	B[d, e]								
Fluorescein angiography	B[e]								
OCT	B[e]			A[f]			A[f]		
ECG	X								
Pregnancy test	X[g]			X[g]			X[g]		
Laboratory tests	X[h]						X[h]		
Concomitant medication	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
NEI-VFQ 25 and EQ-5D	M								

Eye Assessments: A = as indicated; B = both eyes; M = mandatory; S = study eye.
A maximum of 3 focal/grid laser treatments per year with a minimum of 17 weeks between applications was required.
Note: all visits for injections were required to occur within ±5 days of the Scheduled Visit.
ECG = electrocardiogram; EQ-5D = self-reported questionnaire developed by the EuroQoL group; ETDRS = early treatment of diabetic retinopathy study; EuroQoL = european quality of life; ILM = internal limiting membrane; NEI-VFQ 25 = 25-item national eye institute – visual functioning questionnaire; OCT = optical coherence tomography; RPE = retinal pigment epithelium; VA = visual acuity.

a. Injection of pegaptanib sodium, as indicated.
b. Vital signs measurements and weight were always recorded; physical examination was performed only if indicated.
c. Before injection and again at least 30 minutes after injection for all subjects. Applanation was required at Baseline and Weeks 54 and 102 or early withdrawal.
d. Modified 7 standard fields and stereo fundus reflex (both eyes).
e. Angiograms, photographs and OCTs sent to the Reading Center for both eyes at Baseline and Weeks 54 and 102 or Early Withdrawal, otherwise study eye as noted. OCT center point thickness was required to be at least 250 microns with a standard deviation of <10% and have properly created ILM and RPE borders at Baseline by computer software. At Week 18, an OCT for the study eye was sent to the Reading Center. Fluorescein angiography was obtained in the study eye beginning at Week 18 for the purpose of confirming decision for focal/grid laser to perfused oedema and were not sent to the Reading Center.
f. OCT for study eye as indicated. If obtained, OCTs were not sent to the Reading Center at these visits.
g. Only in female subjects who were not postmenopausal for at least 12 months or surgically sterile (serum at Baseline and urine thereafter before each injection).
h. Laboratory tests were performed at Baseline, Week 6, and every 12 weeks thereafter.

Table 1. Schedule of Activities; Years 1 and 2

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Week	**72 (Before Injection)**	**72 (After Injection)**	**72+3 Days**	**78 (Before Injection)**	**78 (After Injection)**	**78+3 Days**	**84 (Before Injection)**	**84 (After Injection)**	**84+3 Days**
Pegaptanib sodium injection/sham injection	X[a]			X[a]			X[a]		
Physical examination/weight/vital signs	X[b]			X[b]			X[b]		
Telephone safety check (as indicated)			A			A			A
Protocol refraction and distance VA (ETDRS chart)	S			S			S		
Tonometry	S[c]	S		B[c]	S		S[c]	S	
Ophthalmologic examination	S	S		B	S		S	S	
OCT	A[d]			A[d]			A[d]		
Pregnancy test	X[e]			X[e]			X[e]		
Laboratory tests				X[f]					
Concomitant medication	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

Eye Assessments: A = as indicated; B = both eyes; S = study eye.
A maximum of 3 focal/grid laser treatments per year with a minimum of 17 weeks between applications was required.
Note: all visits for injections were required to occur within ±5 days of the Scheduled Visit.
ETDRS = early treatment of diabetic retinopathy study; OCT = optical coherence tomography.

a. Injection of pegaptanib sodium, as indicated.
b. Vital signs measurements and weight were always recorded; physical examination was performed only if indicated.
c. Before injection and again at least 30 minutes after injection for all subjects. Applanation was required at Baseline and Weeks 54 and 102 or early withdrawal.
d. OCT for study eye as indicated. If obtained, OCTs were not sent to the Reading Center at these visits.
e. Only in female subjects who were not postmenopausal for at least 12 months or surgically sterile (serum at Baseline and urine thereafter before each injection).
f. Laboratory tests were performed at Baseline, Week 6, and every 12 weeks thereafter.

Table 1. Schedule of Activities; Years 1 and 2

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Week	90 (Before Injection)	90 (After Injection)	90+3 Days	96 (Before Injection)	96 (After Injection)	96+3 Days	102±5 Days	Early Withdrawal[a]
Pegaptanib sodium injection/sham injection	X[b]			X[b]				
Physical examination/weight/vital signs	X[c]			X[c]			X[c]	X[c]
Telephone safety check (as indicated)			A			A		
Protocol refraction and distance VA (ETDRS chart)	S			S			B	B
Tonometry	S[d]	S		S[d]	S		B[d]	B
Ophthalmologic examination	S	S		S	S		B	B
Stereoscopic colour fundus photos							B[e, f]	B[e, f]
Fluorescein angiography							B[f]	B[f]
OCT	A[g]			A[g]			B[f]	B[f]
ECG							X	X
Pregnancy test	X[h]			X[h]				
Laboratory tests	X[i]						X[i]	X[i]
Concomitant medication	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
NEI-VFQ 25 and EQ-5D							M	M

Eye Assessments: A = as indicated; B = both eyes; M = mandatory; S = study eye.
A maximum of 3 focal/grid laser treatments per year with a minimum of 17 weeks between applications was required.
Note: all visits for injections were required to occur within ±5 days of the Scheduled Visit.
ECG = electrocardiogram; EQ-5D = self-reported questionnaire developed by the EuroQoL group; ETDRS = early treatment of diabetic retinopathy study; EuroQoL = european quality of life; ILM = internal limiting membrane; NEI-VFQ 25 = 25-item national eye institute – visual functioning questionnaire; OCT = optical coherence tomography; RPE = retinal pigment epithelium; VA = visual acuity.

a. Any examination indicated for an early withdrawal was performed before any other treatment was administered.
b. Injection of pegaptanib sodium, as indicated.
c. Vital signs measurements and weight were always recorded; physical examination was performed only if indicated.
d. Before injection and again at least 30 minutes after injection for all subjects. Applanation was required at Baseline and Weeks 54 and 102 or early withdrawal.
e. Modified 7 standard fields and stereo fundus reflex (both eyes).
f. Angiograms, photographs and OCTs sent to the Reading Center for both eyes at Baseline and Weeks 54 and 102 or Early Withdrawal, otherwise study eye as noted. OCT center point thickness was required to be at least 250 microns with a standard deviation of <10% and have properly created ILM and RPE borders at Baseline by computer software. At Week 18, an OCT for the study eye was sent to the Reading Center. Fluorescein angiography was obtained in the study eye beginning at Week 18 for the purpose of confirming decision for focal/grid laser to perfused oedema and were not sent to the Reading Center.
g. OCT for study eye as indicated. If obtained, OCTs were not sent to the Reading Center at these visits.
h. Only in female subjects who were not postmenopausal for at least 12 months or surgically sterile (serum at Baseline and urine thereafter before each injection).
i. Laboratory tests were performed at Baseline, Week 6, and every 12 weeks thereafter.

Table 2. Extension Period Flow Chart; Year 3

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Week	**108; Before Injection**	**108; After Injection**	**108+3 Days**	**114; Before Injection**	**114; After Injection**	**114+3 Days**	**120; Before Injection**	**120; After Injection**	**120+3 Days**
Pegaptanib sodium injection/sham injection	X[a]			X[a]			X[a]		
Decision to laser[b]									
Apply focal laser (if indicated) [b]									
Physical examination/weight/vital signs	X[c]			X[c]			X[c]		
Telephone safety check (as indicated)			A			A			A
Protocol refraction and distance VA (ETDRS chart)	S			S			S		
Tonometry	S[d]	S		S[d]	S		S[d]	S	
Ophthalmologic examination	S	S		S	S		S	S	
OCT	A[e]			A[e]			A[e]		
Pregnancy test	X[f]			X[f]			X[f]		
Laboratory tests				X					
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

Eye Assessments: A = as indicated; S = study eye.
ETDRS = early treatment of diabetic retinopathy study; OCT = optical coherence tomography; VA = visual acuity.

a. Injection of pegaptanib sodium, as indicated.
b. Visit only occurred if the decision was made to laser. A maximum of 3 focal/grid laser treatments per year with a minimum of 17 weeks between applications was required. Concomitant medications and adverse events were recorded only if the visit occurred.
c. Vital signs measurements and weight were always recorded; physical examination was performed only if indicated.
d. Before injection and again at least 30 minutes after injection for all subjects.
e. OCT for study eye as indicated; if obtained, these were not sent to the Reading Center at these visits.
f. Only in female subjects who were not postmenopausal for at least 12 months or surgically sterile (serum at Baseline and urine thereafter before each injection).

Table 2. Extension Period Flow Chart; Year 3

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Week	**126; Before Injection**	**126; After Injection**	**126+3 Days**	**132; Before Injection**	**132; After Injection**	**132+3 Days**	**138; Before Injection**	**138; After Injection**	**138+3 Days**
Pegaptanib sodium injection/sham injection	X[a]			X[a]			X[a]		
Decision to laser[b]									
Apply focal laser (if indicated)[b]									
Physical examination/weight/vital signs	X[c]			X[c]			X[c]		
Telephone safety check (as indicated)			A			A			A
Protocol refraction and distance VA (ETDRS chart)	S			S			S		
Tonometry	S[d]	S		S[d]	S		S[d]	S	
Ophthalmologic examination	S	S		S	S		S	S	
OCT	A[e]			A[e]			A[e]		
Pregnancy test	X[f]			X[f]			X[f]		
Laboratory tests	X								
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

Eye Assessments: A = as indicated; S = study eye.
ETDRS = early treatment of diabetic retinopathy study; OCT = optical coherence tomography; VA = visual acuity.

a. Injection of pegaptanib sodium, as indicated.
b. Visit only occurred if the decision was made to laser. A maximum of 3 focal/grid laser treatments per year with a minimum of 17 weeks between applications was required. Concomitant medications and adverse events were recorded only if the visit occurred.
c. Vital signs measurements and weight were always recorded; physical examination was performed only if indicated.
d. Before injection and again at least 30 minutes after injection for all subjects.
e. OCT for study eye as indicated; if obtained, these were not sent to the Reading Center at these visits.
f. Only in female subjects who were not postmenopausal for at least 12 months or surgically sterile (serum at Baseline and urine thereafter before each injection).

Table 2. Extension Period Flow Chart; Year 3

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Week	**144; Before Injection**	**144; After Injection**	**144+3 Days**	**150; Before Injection**	**150; After Injection**	**150+3 Days**	**156; ±5 Days**	**Early Withdrawal**
Pegaptanib sodium injection/sham injection	X[a]			X[a]				
Decision to laser[b]								
Apply focal laser (if indicated)[b]								
Physical examination/weight/vital signs	X[c]			X[c]			X[c]	X[c]
Telephone safety check (as indicated)			A			A		
Protocol refraction and distance VA (ETDRS chart)	S			S			B	B
Tonometry	S[d]	S		S[d]	S		B[d]	B
Ophthalmologic examination	S	S		S	S		B	B
Stereoscopic colour fundus photos							B[e, f]	B[e, f]
Fluorescein angiography							B[f]	B[f]
OCT	A[g]			A[g]			B[f]	B[f]
Pregnancy test	X[h]			X[h]			X[h]	
ECG							X	X
Laboratory tests				X			X	X
Concomitant medications	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X

Eye Assessments: A = as indicated; B = both eyes; S = study eye.
Any examination indicated for an early withdrawal was to be performed before any other treatment was administered.
ECG = electrocardiogram; ETDRS = early treatment of diabetic retinopathy study; ILM = internal limiting membrane; OCT = optical coherence tomography; RPE = retinal pigment epithelium; VA = visual acuity.

a. Injection of pegaptanib sodium, as indicated.
b. Visit only occurred if the decision was made to laser. A maximum of 3 focal/grid laser treatments per year with a minimum of 17 weeks between applications was required. Concomitant medications and adverse events were recorded only if the visit occurred.
c. Vital signs measurements and weight were always recorded; physical examination was performed only if indicated.
d. Before injection and again at least 30 minutes after injection for all subjects.
e. Modified 7 standard fields and stereo fundus reflex (both eyes).
f. Angiograms, photographs and OCTs sent to the Reading Center for both eyes at Baseline and Week 156 or Early Withdrawal, otherwise study eye as noted. OCT center point thickness was required to be at least 250 microns with a standard deviation of <10% and have properly created ILM and RPE borders at Baseline by computer software. At Week 18, an OCT for the study eye was sent to the Reading Center. Fluorescein angiography was obtained in the study eye beginning at Week 18 for the purpose of confirming decision for focal/grid laser to perfused oedema and were not sent to the Reading Center.
g. OCT for study eye as indicated; if obtained, these were not sent to the Reading Center at these visits.
h. Only in female subjects who were not postmenopausal for at least 12 months or surgically sterile (serum at Baseline and urine thereafter before each injection).

Number of Subjects (Planned and Analyzed): Protocol Amendment D removed the 2 lowest doses of pegaptanib sodium (ie, 0.003 mg and 0.03 mg), which resulted in a change to the sample size and a plan for 270 evaluable subjects. A total of 300 subjects were planned for randomization in this study and to follow for 2 years.

A total of 326 subjects were screened for this study, including 29 subjects who were randomized to pegaptanib sodium 0.003 or 0.03 mg. A total of 317 subjects (5 in Australia, 9 in Austria, 12 in Brazil, 5 in Denmark, 34 in France, 29 in India, 3 in the Netherlands, 3 in Switzerland, 9 in Canada, 83 in the Czech Republic, 26 in Germany, 27 in Italy, 11 in Portugal, 7 in the UK, 52 in the US and 2 in Greece) were enrolled and randomized. Out of the 317 subjects, 174 subjects were assigned to receive pegaptanib sodium 0.3 mg and 143 subjects were assigned to receive sham injection.

Diagnosis and Main Criteria for Inclusion: The study included subjects with macular edema associated with diabetes and VA between 20/50 and 20/200. Subjects with recent signs of uncontrolled diabetes, blood pressure worse than 160/100, severe cardiac disease and who underwent recent laser therapy in the eye were excluded from the study.

Study Treatment: As per protocol treatment criteria, randomized subjects received either intravitreous injections of pegaptanib sodium 0.3 mg (90 μL) or a sham injection procedure at 6-week intervals up through 48 weeks in Year 1. The original protocol included doses of 0.003 mg, 0.03 mg, and 0.3 mg of pegaptanib sodium; however, only the 0.3 mg dose of pegaptanib sodium was administered. During Year 2, treatment was administered at 6-week intervals, if deemed necessary per protocol specifications, up through Week 96 in Year 2. Criteria for administering study medication after Week 48 were based on VA, clinical examination, OCT, and the opinion of the Investigator. The final efficacy assessments for Year 1 were performed at Week 54.

Study medication was not administered during Year 2 (ie, from Week 54 through Week 96) if VA was 20/25 or better, retinal thickness was <175 μm, if a serious adverse event (SAE) occurred in the study eye that would have made immediate injection unwise or, if, in the opinion of the Investigator, a specific situation warranted deferral. This last situation was to be discussed promptly between the Investigator, or personnel designated by the Investigator, and a medically qualified representative of the Sponsor. The final efficacy assessments for Year 2 were performed at Week 102.

During the Year 3, open–label, year-long extension period, all active subjects who completed the Week 102 study assessments and chose to receive open-label pegaptanib sodium in a 1-year extension-phase of the study received 0.3 mg (90 μL) administered every 6 weeks as indicated by the same prespecified criteria that applied to Year 2. The last possible pegaptanib sodium injection occurred at Week 150. The final assessments for Year 3 were performed at Week 156.

The intravitreous injection procedure required 1 of the 2 following options, according to the decision of the ophthalmologist: topical ofloxacin, levofloxacin, or an antibiotic drop with comparable antimicrobial coverage therapy for 3 days prior to the injection, followed by 3 consecutive drops of antibiotic and several drops of 5% povidone-iodine immediately

before the injection; or 3 consecutive drops of antibiotic and a 5% povidone-iodine flush of the fornices and caruncle with at least 10 mL of solution just prior to injection. These procedures were followed for each subject, regardless of whether they received pegaptanib sodium injection or sham injection.

The drug product was a ready-to-use sterile solution provided in a single-use glass syringe. Capped sterile empty syringes without needles were provided for the sham injection.

Efficacy Endpoints:

Primary Efficacy Endpoint**:**

- The primary efficacy endpoint was the proportion of subjects who experienced a ≥10-letter (or 2-line) improvement in vision at the 1-year timepoint (defined as Week 54); the modified Early Treatment of Diabetic Retinopathy Study (ETDRS) eye charts were used to measure this endpoint.

Secondary Efficacy Endpoints:

- The proportion of subjects who experienced a ≥10-letter (or 2-line) improvement in vision from Baseline at the 2-year endpoint;
- The proportion of subjects who experienced a ≥15 letter improvement at 1 and 2 years;
- The proportion of eyes experiencing a change in the degree of retinopathy by ≥2 steps at 1 and 2 years;
- Changes in mean VA over time;
- The proportion of subjects requiring focal or grid laser at 1 and 2 years;
- Distribution of visual changes and actual levels of VA over time;
- The proportion of subjects with a ≥5 letter improvement at 1 and 2 years;
- The proportion of subjects with a ≥0 letter improvement at 1 and 2 years;
- The proportion of subjects exhibiting a decrease in retinal thickness at the center point by at least 25% and 50% using optical coherence tomography (OCT) at 1 and 2 years;
- Quality of life (QoL) measurements were also included as secondary endpoints. Two patient-reported outcome (PRO) questionnaires, the 25-Item National Eye Institute – Visual Functioning Questionnaire (NEI-VFQ 25) and the self-report questionnaire (a QoL instrument) developed by the European Quality of Life (EuroQoL) Group (EQ-5D), were included and the change from Baseline to Week 54 (ie, Year 1) and Week 102 (ie, Year 2) were measured between the pegaptanib sodium treated group and the sham treated group.

Safety and Efficacy Endpoint (Year 3 Extension):

- The primary purpose of the third year was to collect safety data on subjects who consented to enter this optional, open-label, extension phase of the study; however, efficacy-related data were also collected.

Safety Evaluations: Safety endpoints included all reported adverse events (AEs), whether or not deemed related to treatment; all SAEs, whether or not deemed related to treatment; and all laboratory abnormalities, whether or not deemed clinically relevant. Safety was also assessed through the use of electrocardiograms (ECGs), physical examinations, and vital signs measurements (including body weight) at regular intervals throughout the study period.

Statistical Methods:

The following populations were used for analysis of study endpoints as defined:

- Modified Intent-To-Treat 1: Included all randomized subjects with at least 1 dose of study treatment (pegaptanib sodium 0.3 mg or sham injection), who had completed the baseline VA assessment, and had at least 1 postbaseline VA within 1 year (54 weeks [last injection administered at Week 48]), excluding subjects from two sites.

- Modified Intent-To-Treat 2: Included all randomized subjects with at least 1 dose of study treatment (pegaptanib sodium 0.3 mg or sham injection), who had completed the baseline VA assessment, and who met the following criteria: (with the exception of two sites) subjects who completed the Week 102 visit or any visit post Week 102 on or before the date of database cut-off and who had at least 1 postbaseline VA assessment; or subjects who had at least 1 postbaseline VA before withdrawing from the study within the 2-year study period.

- Extended Modified Intent-To-Treat: Included all randomized subjects with at least 1 dose of study treatment (pegaptanib sodium 0.3 mg or sham injection), who had completed the baseline VA assessment, and had at least 1 postbaseline VA within 1 year (54 weeks) (included subjects from the two sites).

- Per Protocol 1: Included all subjects from the modified intent-to-treat 1 (MITT1) population without any major protocol deviation within 1 year (ie, Week 54) postbaseline; a major protocol violation was a violation that was considered to be significant enough to remove the subject from analysis.

- Per Protocol 2: Included all subjects from the MITT2 population without any major protocol deviation within 2 years (ie, Week 102) postbaseline; a major protocol violation was a violation that was considered to be significant enough to remove the subject from analysis.

- Full Analysis Set 2: All randomized subjects who had the same treatment for the entire 102 weeks (ie, pegaptanib sodium 0.3 mg or sham treatment on/before Week 96) with baseline VA assessment and who met the following criteria: subjects who had at least

1 postbaseline VA within 2 years, before entry into the Year 3 open-label extension period, or before withdrawing from the study prior to Week 102. The full analysis set 2 (FAS2) population was used for the evaluation of all secondary efficacy endpoints. Subjects from two sites were not included in this population.

- Full Analysis Set 3: All subjects originally randomized to pegaptanib sodium, with at least 1 dose of pegaptanib sodium prior to Year 2 (on or before Week 96) and with at least 1 dose of pegaptanib sodium after entry into the open-label extension period, who had both the baseline VA assessment and at least 1 VA assessment after entry into the Year 3 open-label extension period (on or after Week 102). Subjects from two sites were not included in this population.

- Observed Cases 2: All subjects who were not included in the MITT2 population, but who had at least 1 dose of study treatment and who completed the baseline and at least 1 postbaseline VA assessment at or prior to Week 102. Subjects from two sites were not included in this population.

- Observed Cases 2∗: All subjects in the observed cases 2 (OBC2) population, with the exception of those subjects who switched from sham to pegaptanib sodium (ie, OBC2∗ = OBC2 minus subjects who switched from sham to pegaptanib sodium).

- Observed Cases 3: All sham-treated subjects who converted to pegaptanib sodium within 2 years, or sham-treated subjects who entered the Year 3 pegaptanib sodium open-label extension period.

- SafetyS1: All evaluable subjects who received at least 1 dose of the study treatment (pegaptanib sodium 0.3 mg or sham treatment). Subjects from the two sites were included in this population.

- SafetyS2: All subjects from the SafetyS1 population, with the exception of subjects from two sites.

- SafetyS3: Included the 29 subjects who were originally randomized to pegaptanib sodium 0.003 mg (7 subjects) or 0.03 mg (22 subjects), and who were not included in any of the populations above.

Note: All subjects previously randomized to the pegaptanib sodium 0.03 or 0.003 mg/eye treatment arms were given the option of receiving injections of pegaptanib sodium 0.3 mg/eye or withdrawing from the study. Subjects electing to receive the injections (N=29) were not included as part of the efficacy population or the safety population.

The primary efficacy endpoint was the proportion of subjects who experienced a ≥10-letter (or 2-line) improvement in VA (ETDRS) at Year 1 (Week 54). The analyses of this endpoint was carried out using Cochran-Mantel-Haenszel test adjusting for stratification factors, including HbA_{1c}, systolic blood pressure, diastolic blood pressure, and baseline VA categories (except center). The odds ratio and the 95% confidence intervals (CIs) were reported for pegaptanib sodium as compared with sham injection. The analysis on the

MITT1 population was deemed primary; missing values were imputed using the last observation carried forward (LOCF) approach.

The proportion of subjects with a VA improvement of ≥15 letters, ≥10 letters, ≥5 letters, and ≥0 letters at each visit, the proportion of subjects with a VA loss of ≥15 letters at each visit, the proportion of eyes experiencing an increase in the degree of retinopathy by ≥2 steps overall, the proportions of eyes experiencing a decrease in the degree of retinopathy by ≥2 steps overall, the proportion of subjects receiving focal or grid laser overall and the proportion of subjects exhibiting a decrease in retinal thickness at the center point by 25% and 50% using OCT, were evaluated.

The mean change from Baseline in distance VA, in vision function (NEI-VFQ 25) in terms of 12 subscales, and quality of life (EQ-5D and EQ-VAS) at Weeks 54 and 102 were computed at each visit. Analysis of covariance model was used; the least square (LS) means were presented together with the 95% CI as a measurement of the treatment difference at each visit.

The Medical Dictionary for Regulatory Activities (MedDRA) coding system was used for classifying AEs. Analysis of AEs was based on all treated subjects and on all eyes.

RESULTS

Subject Disposition and Demography:

Table 3 presents the subject disposition and Table 4 summarizes the study populations and the number of subjects randomized to either pegaptanib sodium 0.3 mg or sham injection.

A total of 317 subjects (174 pegaptanib sodium 0.3 mg; 143 sham injection) were enrolled and randomized; 286 subjects (144 pegaptanib sodium 0.3 mg; 142 sham injection) received at least 1 dose of study treatment. There was 1 subject from each treatment group who was enrolled and randomized, but not treated.

Additionally, during routine monitoring at two sites, some suspected significant deviations from good clinical practices were identified. Due to the subsequent quality audit findings, all subjects from these 2 sites (N=24) were excluded from the analyses of all efficacy endpoints; however, all evaluable subjects were included in the safety analyses.

Table 3. Subject Disposition

	Pegaptanib 0.3 mg	Pegaptanib 0.03 mg	Pegaptanib 0.003 mg	Sham Injection
Year 1				
Started	145	22	7	143
Received 0.3 mg treatment	144	13	3	0
Completed	126	11	6	124
Not completed	19	11	1	19
Adverse events	3	1	1	5
Physician decision	7	4	0	6
Withdrawal by subject	2	4	0	4
Other unspecified	2	1	0	1
Protocol violation	0	0	0	1
Other lost to follow-up or subject non-compliance	5	1	0	2
Year 2				
Started	126	11	6	124
Received 0.3 mg treatment	126	3	2	0
Completed	102	5	0	102
Not completed	24	6	6	22
Adverse events	4	0	2	4
Physician decision	11	6	4	11
Withdrawal by subject	4	0	0	4
Other unspecified	1	0	0	1
Protocol violation	0	0	0	0
Other lost to follow-up or subject non-compliance	4	0	0	2
Year 3				
Completed Year 2	102	5	0	102
Subject completed Year 2 but did not want to participate Year 3	56	5	0	48
Started Year 3	46	0	0	54
Received 0.3 mg treatment	46	0	0	54
Completed	38	0	0	45
Not completed	8	0	0	9
Adverse events	2	0	0	2
Physician decision	0	0	0	2
Withdrawal by subject	2	0	0	5
Other unspecified	2	0	0	0
Protocol violation	0	0	0	0
Other lost to follow-up or subject non-compliance	2	0	0	0

Table 4. Subject Evaluation Groups; All Randomized Subjects

No. of Subjects	Pegaptanib Sodium (0.3 mg) N=174 n (%)	Sham Injection N=143 n (%)
All randomized subjects	174 (100)	143 (100)
MITT1 population	133 (76.4)	127 (88.8)
MITT2 population	107 (61.5)	100 (69.9)
FAS2 population	133 (76.4)	123 (86.0)
OBC2 population	26 (14.9)	27 (18.9)
OBC2* population	26 (14.9)	23 (16.1)
SafetyS1 population	144 (82.8)	142 (99.3)
SafetyS2 population	134 (77.0)	128 (89.5)
SafetyS3 population	29 (16.7)	0
FAS3 population	42 (24.1)	0
OBC3 population	0	51 (35.7)

Subjects from two sites were not included in any of the populations above except SafetyS1 population; FAS = full analysis set; MITT = modified intent-to-treat; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; OBC = observed cases.

A similar number and percent (42/144; 29.2%) of subjects in the pegaptanib sodium group discontinued before Week 102 compared with subjects in the sham injection group (40/142; 28.2%); 9 (6.3%) subjects in the pegaptanib sodium group were lost to follow-up or subject noncompliance compared with 5 (3.5%) subjects in the sham injection group. One subject in the sham injection group was discontinued due to protocol violations before Week 102. It should be noted that in 2007, an internal decision was made to terminate the study for all sites in the US; all ongoing subjects at those sites were required to discontinue from the protocol. A total of 18 pegaptanib sodium and 17 sham subjects discontinued due to Investigator/Sponsor decision. The majority of subjects who discontinued for this reason did so because the study was closed by the Sponsor, ie, 11 of 18 pegaptanib sodium and 13 of 17 sham subjects.

A similar number and percent (14/144; 9.7%) of subjects in the pegaptanib sodium group and in the sham injection group (13/142; 9.2%) discontinued after Week 102 and before Week 156 (Table 5).

Table 5. Subject Discontinuations; SafetyS1 Population

No. of Subjects	Pegaptanib Sodium (0.3 mg) N=144 n (%)	Sham Injection N=142 n (%)
Subjects Discontinued Before Week 102		
Adverse event	7 (4.9)	8 (5.6)
Protocol violation	0	1 (0.7)
Investigator or Sponsor decision	18 (12.5)	17 (12.0)
Subject request	6 (4.2)	8 (5.6)
Lost to follow-up or subject noncompliance	9 (6.3)	5 (3.5)
Other	2 (1.4)	1 (0.7)
Subtotal	42 (29.2)	40 (28.2)
Subject completed Year 2, but did not participate in Year 3	48 (33.3)	43 (30.3)
No. of Subjects Discontinued Between Week 102 and Week 156		
Adverse event	2 (1.4)	2 (1.4)
Protocol violation	0	0
Investigator or Sponsor decision	5 (3.5)	5 (3.5)
Subject request	3 (2.1)	5 (3.5)
Lost to follow-up or subject noncompliance	2 (1.4)	0
Other	2 (1.4)	1 (0.7)
Subtotal	14 (9.7)	13 (9.2)
Total	104 (72.2)	96 (67.6)

N = number of subjects; n = number of subjects meeting specified criteria; No. = number.

Discontinuations before Week 102 for the SafetyS3 population are presented in Table 6.

Table 6. Subject Discontinuations; SafetyS3 Population

No. of Subjects	Pegaptanib Sodium (0.03 mg) N=22 n (%)	Pegaptanib Sodium (0.003 mg) N=7 n (%)
Subjects discontinued before Week 102		
Adverse event	1 (4.5)	3 (42.9)
Protocol violation	0	0
Investigator or Sponsor decision	10 (45.5)	4 (57.1)
Subject request	4 (18.2)	0
Lost to follow-up or subject noncompliance	1 (4.5)	0
Other	1 (4.5)	0
Total	17 (77.3)	7 (100)

N = number of subjects; n = number of subjects meeting specified criteria; No. = number.

Demographic characteristics for all randomized subjects are summarized in Table 7.

Table 7. Demographic Characteristics: All Subjects

No. of Subjects		Pegaptanib Sodium (0.003 mg) N=7 n (%)	Pegaptanib Sodium (0.03 mg) N=22 n (%)	Pegaptanib Sodium (0.3 mg) N=145 n (%)	Sham Injection N=143 n (%)
Sex	Male	3 (42.9)	11 (50.0)	86 (59.3)	78 (54.5)
	Female	4 (57.1)	11 (50.0)	59 (40.7)	65 (45.5)
Race	Caucasian/White	5 (71.4)	17 (77.3)	114 (78.6)	122 (85.3)
	Asian	0	1 (4.5)	14 (9.7)	16 (11.2)
	Black	1 (14.3)	0	4 (2.8)	2 (1.4)
	Hispanic/Latino	1 (14.3)	4 (18.2)	8 (5.5)	3 (2.1)
	Other	0	0	5 (3.4)	0
Age (years)	Mean	57.3	64.7	62.2	62.4
	SD	10.1	8.6	9.2	10.3
	Median	58.0	63.5	62.0	63.0
	Range	39; 72	50; 82	28, 83	20, 80
	N	7	22	145	143
Height (cm)	Mean	166.7	166.3	167.5	166.3
	SD	7.2	8.6	8.8	8.8
	Median	165.0	168.0	166.0	166.0
	Range	157; 177	152; 180	144, 188	147, 193
	N	7	21	145	143
Weight (kg)	Mean	91.2	84.2	82.8	81.1
	SD	15.7	19.7	16.9	18.0
	Median	89.0	79.5	82.0	80.0
	Range	70; 119	62; 134	54, 140	44, 137
	N	7	22	145	141
ECOG performance status	0	3 (42.9)	13 (59.1)	74 (51.0)	81 (56.6)
	1	3 (42.9)	8 (36.4)	69 (47.6)	59 (41.3)
	2	1 (14.3)	1 (4.5)	2 (1.4)	3 (2.1)
	3	0	0	0	0
	4	0	0	0	0
Baseline smoking status	Active	1 (14.3)	2 (9.1)	7 (4.8)	11 (7.7)
	Not active	6 (85.7)	20 (90.9)	138 (95.2)	132 (92.3)

ECOG performance status: 0- Fully active, able to carry on all predisease performance without restriction. 1- Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work. 2- Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about >50% of waking hours. 3- Capable of only limited self-care; confined to bed or chair >50% of waking hours. 4- Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
ECOG = eastern cooperative oncology group; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; SD = standard deviation.

Efficacy Results:

Primary Efficacy Endpoint:

Proportion of Subjects Who Experienced a ≥10-Letter (or 2-line) Improvement in VA (ETDRS) at Year 1:

The primary efficacy evaluation was the proportion of subjects who experienced a ≥10-letter (or 2-line) improvement in VA (ETDRS) at Year 1 (Week 54; last injection at Week 48) as compared from Baseline.

The proportion of subjects with an improvement of ≥10 letters at Week 54 for the MITT1 population (LOCF data) is presented in Table 8. A total of 49 (36.8%) subjects from the pegaptanib sodium group and 25 (19.7%) subjects from the sham injection group

experienced a VA improvement of ≥10 letters (or 2-lines) at Week 54 compared from Baseline; the odds ratio between pegaptanib sodium versus sham injection was 2.38, with 95% CI of (1.32, 4.30). There was a statistically significant difference between the 2 treatment groups (p-value=0.0047) (Table 8).

Table 8. Proportion of Subjects With a Gain of ≥10 Letters of Vision at Week 54; MITT1 Population

No. of Subjects	**Pegaptanib Sodium (0.3 mg) N=133 n (%)**		**Sham Injection N=127 n (%)**
Evaluable Subjects (LOCF Data; MITT1 Population)	133		127
Gain of ≥10 letters of vision: yes	49 (36.8)		25 (19.7)
Gain of ≥10 letters of vision: no	84 (63.2)		102 (80.3)
Estimates of the odds ratio and CMH test[a]			
Pegaptanib Sodium Versus Sham Injection	Odds ratio	Confidence interval (95%)	P-value (CMH)
	2.38	(1.32; 4.30)	0.0047
Breslow-day test on homogeneity:	p-value=0.8219		

CMH = cochran-mantel-haenszel; HbA1c = glycosylated hemoglobin; LOCF = last observation carried forward; MITT = modified intent-to-treat; N = number of subjects; n = number of subjects meeting specified criteria; VA = visual acuity.

a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Secondary Efficacy Endpoints:

Proportion of Subjects Who Experienced ≥10-Letter (or 2-Line) Improvement in Vision (ETDRS)

Year 2: The proportion of subjects who experienced a gain of ≥10 letters of vision at Week 102 for the FAS2 population are presented in Table 9. At Week 102 (FAS2), 51 (38.3%) subjects in the pegaptanib sodium group had a ≥10-letter improvement of vision from Baseline compared with 37 (30.1%) subjects in the sham injection group. The difference between the 2 treatment groups was not statistically significant (p-value=0.1904).

Table 9. Proportion of Subjects With a Gain of ≥10 Letters of Vision at Week 102 (LOCF Data); FAS2 Population

No. of Subjects	Pegaptanib Sodium (0.3 mg) N=133 n (%)		Sham treatment N=123 n (%)
Evaluable Subjects (LOCF Data, FAS2 Population)	133		123
Gain of ≥10 letters of vision at Week 102: yes	51 (38.3)		37 (30.1)
Gain of ≥10 letters of vision at Week 102: no	82 (61.7)		86 (69.9)
Estimates of the odds ratio and CMH test[a]			
Pegaptanib Sodium Versus Sham Treatment	Odds ratio	Confidence interval (95%)	P-value (CMH)
	1.46	(0.85; 2.53)	0.1904
Breslow-day test on homogeneity:	p-value=0.6683		

CMH = cochran-mantel-haenszel; FAS = full analysis set; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; VA = visual acuity.

a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Proportion of Subjects Who Experienced ≥15-Letter Improvement in Vision

Year 1: The proportion of subjects with an improvement of ≥15 letters at Week 54 for the MITT1 (LOCF data) population is summarized in Table 10. At Week 54, a total of 22 (16.5%) subjects from the pegaptanib sodium group and 13 (10.2%) subjects from the sham injection group experienced a VA improvement of ≥15 letters from Baseline; the odds ratio between pegaptanib sodium versus sham injection was 1.57, with 95% CI of (0.74, 3.34). There was no statistically significant difference between the 2 treatment groups (p-value=0.2466) (Table 10).

Table 10. Proportion of Subjects With a Gain of ≥15 Letters of Vision at Week 54 (LOCF Data); MITT1 Population

No. of Subjects (MITT1 Population)	Pegaptanib Sodium (0.3 mg) N=133 n (%)		Sham Injection N=127 n (%)
Evaluable Subjects (LOCF Data; MITT1 Population)	133		127
Gain of ≥15 letters of vision: yes	22 (16.5)		13 (10.2)
Gain of ≥15 letters of vision: no	111 (83.5)		114 (89.8)
Estimates of the odds ratio and CMH test[a]			
Pegaptanib Sodium Versus Sham Injection	Odds ratio	Confidence interval (95%)	P-value (CMH)
	1.57	(0.74; 3.34)	0.2466

CMH = cochran-mantel-haenszel; HbA1c = glycosylated hemoglobin; LOCF = last observation carried forward; MITT = modified intent-to-treat; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; VA = visual acuity.

a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Year 2: The proportion of subjects with a gain of ≥15 letters of vision at Week 102 for the FAS2 population are presented in Table 11. At Week 102, a total of 30 (22.6%) subjects from the pegaptanib sodium group and 18 (14.6%) subjects from the sham injection group experienced a VA improvement of ≥15 letters from Baseline; the odds ratio between

pegaptanib sodium versus sham injection was 1.67, with 95% CI of (0.86, 3.26). There was no statistically significant difference between the 2 treatment groups (p-value=0.1388).

Table 11. Proportion of Subjects With a Gain of ≥15 Letters of Vision at Week 102 (LOCF Data); FAS2 Population

No. of Subjects	Pegaptanib Sodium (0.3 mg) N=133 n (%)		Sham treatment N=123 n (%)
Evaluable Subjects (LOCF Data, FAS2 Population)	133		123
Gain of ≥15 letters of vision at Week 102: yes	30 (22.6)		18 (14.6)
Gain of ≥15 letters of vision at Week 102: no	103 (77.4)		105 (85.4)
Estimates of the odds ratio and CMH test[a]			
Pegaptanib Sodium Versus Sham Treatment	Odds ratio	Confidence interval (95%)	P-value (CMH)
	1.67	(0.86; 3.26)	0.1388
Breslow-Day test on homogeneity:	p-value=0.3141		

Baseline values were not carried forward for any missing postbaseline data.
CMH = cochran-mantel-haenszel; FAS = full analysis set; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; VA = visual acuity.
a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Proportion of Subjects With a ≥5-Letter Improvement of Vision From Baseline by Visit:

Year 1: The proportion of subjects with a ≥5-letter improvement of vision from Baseline by visit for the MITT1 population is presented in Table 12. The proportion of subjects with a ≥5-letter improvement of vision from Baseline through Week 54 (MITT1) showed numeric differences in favour of the pegaptanib sodium group over the sham injection group. These differences were statistically significant at Weeks 12, 18, 24, 30, 36, 42, and 54. At Week 54, 74 (55.6%) subjects in the pegaptanib sodium group had a ≥5-letter improvement of vision from Baseline compared with 52 (40.9%) subjects in the sham injection group; this difference was statistically significant (p-value=0.0121).

Table 12. Proportion of Subjects With a Gain of ≥5 Letters of Vision at Week 54 (LOCF Data); MITT1 Population

No. of Subjects	Pegaptanib Sodium (0.3 mg) N=133 n (%)	Sham treatment N=127 n (%)
Week 54		
Gain of ≥5 letters of vision at Week 54: yes	74 (55.6)	52 (40.9)
Gain of ≥5 letters of vision at Week 54: no	59 (44.4)	75 (59.1)
P-value (chi-square)	0.0178	
P-value CMH test[a]	0.0121	

Baseline values were not carried forward for any missing postbaseline data.
CMH = cochran-mantel-haenszel; MITT1 = modified intent to treat 1; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; VA = visual acuity.
a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Year 2: Table 13 presents the proportion of subjects who experienced a gain of ≥5 letters of vision at Week 102 for the FAS2 population. The proportion of subjects with a ≥5-letter

improvement of vision from Week 60 through Week 102 (FAS2) showed numeric differences in favour of the pegaptanib sodium group over the sham injection group. These differences were statistically significant at Weeks 66, 78, 84, 90, 96, and 102. At Week 102, 79 (59.4%) subjects in the pegaptanib sodium group had a ≥5-letter improvement of vision from Baseline compared with 52 (42.3%) subjects in the sham injection group; this difference was statistically significant (p-value=0.0062).

Table 13. Proportion of Subjects With a Gain of ≥5 Letters of Vision at Week 102 (LOCF Data); FAS2 Population

No. of Subjects	Pegaptanib Sodium (0.3 mg) N=133 n (%)		Sham treatment N=123 n (%)
Week 102			
Gain of ≥5 letters of vision at Week 102: yes	79 (59.4)		52 (42.3)
Gain of ≥5 letters of vision at Week 102: no	54 (40.6)		71 (57.7)
P-value (chi-square)		0.0062	
P-value CMH test[a]		0.0062	

Baseline values were not carried forward for any missing postbaseline data.
CMH = cochran-mantel-haenszel; FAS = full analysis set; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; VA = visual acuity.
a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

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

Year 1: The proportion of subjects with a ≥0-letter improvement of vision from Baseline by visit for the MITT1 population is presented in Table 14. The proportion of subjects with a ≥0-letter improvement of vision from Baseline through Week 54 (MITT1) showed numeric differences in favour of the pegaptanib sodium group over the sham injection group. These differences were statistically significant at Weeks 12, 18, 24, 36, and 54. At Week 54, 98 (73.7%) subjects in the pegaptanib sodium group had a ≥0-letter improvement of vision from Baseline compared with 75 (59.1%) subjects in the sham injection group; this difference was statistically significant (p-value=0.0172).

Table 14. Proportion of Subjects With a Gain of ≥0 Letters of Vision at Week 54 (LOCF Data); MITT1 Population

No. of Subjects	Pegaptanib Sodium (0.3 mg) N=133 n (%)		Sham treatment N=127 n (%)
Evaluable Subjects (LOCF Data, MITT1 Population)			
Gain of ≥0 letters of vision at Week 54: yes	98 (73.7)		75 (59.1)
Gain of ≥0 letters of vision at Week 54: no	35 (26.3)		52 (40.9)
P-value (chi-square)		0.0125	
P-value CMH test[a]		0.0172	

Baseline values were not carried forward for any missing postbaseline data.
CMH = cochran-mantel-haenszel; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; MITT1 = modified intent to treat 1; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; VA = visual acuity.
a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Year 2: The proportion of subjects with a gain of ≥0 letters of vision for the FAS2 population at Week 102; these data are presented in Table 15. The proportion of subjects with a ≥0-letter improvement of vision from Week 60 through Week 102 (FAS2) showed numeric differences in favour of the pegaptanib sodium group over the sham injection group. These differences were statistically significant at Weeks 72, 78, 84, 90, 96, and 102. At Week 102, 96 (72.2%) subjects in the pegaptanib sodium group had a ≥0-letter improvement of vision from Baseline compared with 67 (54.5%) subjects in the sham injection group; this difference was statistically significant (p-value=0.0030).

Table 15. Proportion of Subjects With a Gain of ≥0 Letters of Vision at Week 102 (LOCF Data); FAS2 Population

No. of Subjects	Pegaptanib Sodium (0.3 mg) N=133 n (%)	Sham treatment N=123 n (%)
Evaluable Subjects (LOCF Data, FAS2 Population)		
Gain of ≥0 letters of vision at Week 102: yes	96 (72.2)	67 (54.5)
Gain of ≥0 letters of vision at Week 102: no	37 (27.8)	56 (45.5)
P-value (chi-square)	0.0032	
P-value CMH test[a]	0.0030	

Baseline values were not carried forward for any missing postbaseline data.
CMH = cochran-mantel-haenszel; FAS = full analysis set; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; VA = visual acuity.
a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Proportion of Eyes Experiencing a Change in the Degree of Retinopathy by 2 or More Steps

Year 1: The proportion of eyes experiencing an increase in the degree of retinopathy by ≥2 steps at Year 1 (Week 54) for the MITT1 population is summarized in Table 16. At Week 54, a total of 4 (4.1%) subjects from the pegaptanib sodium group and 12 (12.4%) subjects from the sham injection group experienced an increase in the degree of retinopathy by ≥2 steps from Baseline; the odds ratio between pegaptanib sodium versus sham injection was 0.27, with 95% CI of (0.07, 0.99). The difference between the 2 treatment groups was statistically significant (p-value=0.0468) (Table 16).

Table 16. Proportion of Eyes Experiencing an Increase in the Degree of Retinopathy by ≥2 Steps at Week 54; MITT1 Population

No. of Subjects (MITT1 Population)		Pegaptanib Sodium (0.3 mg) N=133 n (%)	Sham Injection N=127 n (%)
Evaluable Subjects (MITT1 Population)		98	97
Increase in retinopathy severity by ≥2 steps at Week 54	Yes	4 (4.1)	12 (12.4)
	No	94 (95.9)	85 (87.6)
Estimates of the odds ratio and CMH test[a]			

Pegaptanib Sodium Versus Sham Injection	Odds ratio	Confidence interval (95%)	P-value (CMH)
	0.27	(0.07; 0.99)	0.0468

CMH = cochran-mantel-haenszel; HbA_{1c} = glycosylated hemoglobin; MITT = modified intent-to-treat; N = number of subjects; n = number of subjects meeting prespecified criteria; No. = number; VA = visual acuity.
a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

The proportion of eyes experiencing a decrease in the degree of retinopathy by ≥2 steps at Year 1 (Week 54) for the MITT1 population is summarized in Table 17. At Week 54, a total of 10 (10.2%) subjects from the pegaptanib sodium group and 3 (3.1%) subjects from the sham injection group experienced a decrease in the degree of retinopathy by ≥2 steps; the odds ratio between pegaptanib sodium versus sham injection was 2.90, with 95% CI of (0.73, 11.55). The difference between the 2 treatment groups was not statistically significant (p-value=0.1124) (Table 17).

Taken as a whole, the change in the degree of retinopathy was either statistically significant or numerically in favour of the pegaptanib sodium group versus the sham group.

Table 17. Proportion of Eyes Experiencing a Decrease in the Degree of Retinopathy by ≥2 Steps at Week 54; MITT1 Population

No. of Subjects (MITT1 Population)		**Pegaptanib Sodium (0.3 mg) N=133 n (%)**	**Sham Injection N=127 n (%)**
Evaluable Subjects (MITT1 Population)		98	97
Decrease in retinopathy severity by ≥2 steps at Week 54	Yes	10 (10.2)	3 (3.1)
	No	88 (89.8)	94 (96.9)

Estimates of the odds ratio and CMH test[a]			
Pegaptanib Sodium Versus Sham Injection	Odds ratio	Confidence interval (95%)	P-value (CMH)
	2.90	(0.73, 11.55)	0.1124

CMH = cochran-mantel-haenszel; HbA_{1c} = glycosylated hemoglobin; MITT = modified intent-to-treat; N = number of subjects; n = number of subjects meeting prespecified criteria; No. = number; VA = visual acuity.
a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Year 2: The proportion of eyes experiencing an increase in the degree of retinopathy by ≥2 steps at Week 102 for the FAS2 population are presented in Table 18. At Week 102, a total of 6 (5.8%) subjects from the pegaptanib sodium group and 13 (12.7%) subjects from the sham injection group experienced an increase in the degree of retinopathy by ≥2 steps from Baseline; the odds ratio between pegaptanib sodium versus sham injection was 0.48, with 95% CI of (0.16, 1.42). The difference between the 2 treatment groups was not statistically significant (p-value=0.1788).

Table 18. Proportion of Eyes Experiencing an Increase in the Degree of Retinopathy by ≥2 Steps at Year 2 (LOCF Data); FAS2 Population

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

Estimates of the odds ratio and CMH test[a]			
Pegaptanib Sodium Versus Sham Injection	Odds ratio	Confidence interval (95%)	P-value (CMH)
	0.48	(0.16, 1.42)	0.1788

CMH = cochran-mantel-haenszel; FAS = full analysis set; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; N = number of subjects; n = number of subjects meeting prespecified criteria; VA = visual acuity.
a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

The proportion of eyes experiencing a decrease in the degree of retinopathy by ≥2 steps at Week 102 for the FAS2 population are presented in Table 19. At Week 102, a total of 17 (16.5%) subjects from the pegaptanib sodium group and 3 (2.9%) subjects from the sham injection group experienced a decrease in the degree of retinopathy by ≥2 steps from Baseline; the odds ratio between pegaptanib sodium versus sham injection was 5.12, with 95% CI of (1.45, 18.06). The difference between the 2 treatment groups was statistically significant (p-value=0.0048).

Table 19. Proportion of Eyes Experiencing a Decrease in the Degree of Retinopathy by ≥2 Steps at Year 2 (LOCF Data); FAS2 Population

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

Estimates of the odds ratio and CMH test[a]			
Pegaptanib Sodium Versus Sham Treatment	Odds ratio	Confidence interval (95%)	P-value (CMH)
	5.12	(1.45, 18.06)	0.0048

CMH = cochran-mantel-haenszel; FAS = full analysis set; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; N = number of subjects; n = number of subjects meeting prespecified criteria; VA = visual acuity.
a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Changes in Mean Visual Acuity Over Time

Year 1: The changes in VA score from Baseline for the MITT1 (LOCF data) population are presented in Table 20. Over time, the mean change in the VA score from Baseline by visit was primarily in favour of pegaptanib sodium (MITT1, LOCF) in that pegaptanib sodium was statistically superior to sham at Weeks 6 (p-value=0.0069), 18 (p-value=0.0225), 24 (p-value=0.0029), 30 (p-value=0.0013), 36 (p-value=0.0033), 42 (p-value=0.0137), 48 (p-value=0.0372), and 54 (p-value=0.0040).

Table 20. Change in Visual Acuity Score From Baseline at Week 54 (LOCF Data); MITT1 Population

No. of Subjects	Pegaptanib Sodium (0.3 mg) N=133	Sham treatment N=127
Baseline		
Mean	57.0	57.5
Standard deviation	8.85	8.11
Median	60.0	60.0
Range	35; 73	35; 70
Week 54		
Mean	5.2	1.2
Standard deviation	9.94	11.77
Median	6.0	2.0
Range	-28; 27	-65; 30
Comparison between pegaptanib sodium (0.3 mg) and sham		
ANCOVA[a] on VA change LS mean of pegaptanib sodium (0.3 mg)-sham (95% CI)	3.90 (1.25, 6.54)	
P-value	0.0040	

Baseline values were not carried forward for any missing postbaseline data.
ANCOVA = analysis of covariance; CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; LS = least square; MITT = modified intent-to-treat; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; VA = visual acuity.
a. Adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Year 2: The VA scores and changes in VA score from Baseline for the FAS2 (LOCF data) populations are presented in Table 21. From Baseline to Week 102, the mean change in the VA score from Baseline by visit was primarily in favour of pegaptanib sodium (FAS2, LOCF) in that pegaptanib sodium was statistically superior to sham at Weeks 60 (p-value=0.0231), 72 (p-value=0.0254), 78 (p-value=0.0207), 84 (p-value=0.0155), 90 (p-value=0.0036), 96 (p-value=0.0003), and 102 (p-value=0.0011).

Table 21. Change in Visual Acuity Score From Baseline at Week 102 (LOCF Data); FAS2 Population

No. of Subjects	Pegaptanib Sodium (0.3 mg) N=133	Sham treatment N=123
Baseline		
Mean	57.0	57.4
Standard deviation	8.85	8.20
Median	60.0	60.0
Range	35; 73	35; 70
Week 102		
Mean	6.2	1.7
Standard deviation	10.58	11.68
Median	6.0	2.0
Range	-19; 31	-37; 30
Comparison between pegaptanib sodium (0.3 mg) and sham		
ANCOVA[a] on VA change LS mean of pegaptanib sodium (0.3 mg)-sham (95% CI)	4.57 (1.85, 7.29)	
P-value	0.0011	

Baseline values were not carried forward for any missing postbaseline data.
ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; LS = least square; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; VA = visual acuity.
a. Adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Proportion of Subjects Requiring Focal or Grid Laser

Year 1: The proportion of subjects who received focal or grid laser by the end of Year 1 (Week 54; MITT1 population) is summarized in Table 22. For the MITT1 population at Week 54, a total of 31 (23.3%) subjects from the pegaptanib sodium group and 53 (41.7%) subjects from the sham injection group had received focal or grid laser treatment; the odds ratio between pegaptanib sodium versus sham injection was 0.42, with a 95% CI of (0.24, 0.74). The difference between the 2 treatment groups was statistically significant (p-value=0.0023) (Table 22).

Table 22. Proportion of Subjects Treated With Focal/Grid Laser at Year 1; MITT1 Population (Study Eye)

No. of Subjects (MITT1 Population)		Pegaptanib Sodium (0.3 mg) N=133 n (%)	Sham Injection N=127 n (%)
Year 1 (Week 54)			
Evaluable Subjects (MITT1 Population)		133	127
Focal/grid laser received[a]	Yes	31 (23.3)	53 (41.7)
	No	102 (76.7)	74 (58.3)

Estimates of the odds ratio and CMH test[b]			
Pegaptanib Sodium Versus Sham Injection	Odds ratio	Confidence interval (95%)	P-value (CMH)
	0.42	(0.24, 0.74)	0.0023

CMH = cochran-mantel-haenszel; HbA1c = glycosylated haemoglobin; MedDRA = medical dictionary for regulatory activities; MITT = modified intent-to-treat; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; VA = visual acuity.
a. Included focal laser coagulation, focal laser photocoagulation, panretinal laser photocoagulation, retinal laser coagulation, and retinal laser photocoagulation as per MedDRA (Version 12.1) lower level terms.
b. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Year 2: The proportion of subjects treated with focal/grid laser at Year 2 (study eye) for the FAS2 population are presented in Table 23. For the FAS2 population at Week 102, a total of 34 (25.6%) subjects from the pegaptanib sodium group and 57 (46.3%) subjects from the sham injection group had received focal or grid laser treatment; the odds ratio between pegaptanib sodium versus sham injection was 0.40, with a 95% CI of (0.23, 0.69). The difference between the 2 treatment groups was statistically significant (p-value=0.0008).

Table 23. Proportion of Subjects Treated With Focal/Grid Laser at Year 2; FAS2 Population (Study Eye)

Parameter		**Pegaptanib Sodium (0.3 mg) N=133 n (%)**	**Sham treatment N=123 n (%)**
Evaluable Subjects (FAS2 Population)		133	123
Focal/grid laser received[a]	Yes	34 (25.6)	57 (46.3)
	No	99 (74.4)	66 (53.7)

Estimates of the odds ratio and CMH test[b]			
Pegaptanib Sodium Versus Sham Treatment	Odds ratio	Confidence interval (95%)	P-value (CMH)
	0.40	(0.23, 0.69)	0.0008

CMH = cochran-mantel-haenszel; FAS = full analysis set; HbA_{1c} = glycosylated hemoglobin; MedDRA = medical dictionary for regulatory activities; N = number of subjects; n = number of subjects meeting prespecified criteria; VA = visual acuity.

a. Included focal laser coagulation, focal laser photocoagulation, panretinal laser photocoagulation, retinal laser coagulation, and retinal laser photocoagulation as per MedDRA (Version 12.1) lower level terms.
b. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Distribution of Visual Changes and Actual Levels of VA Over Time

Year 1: At Week 54, the mean VA was 62.2±12.16 letters in the pegaptanib sodium group with a median of 64.0 and a range of 24 to 85; the mean VA was 58.7±14.55 in the sham injection group with a median of 61.0 and range of 0 to 88. Table 24 summarizes the results for Baseline and Week 54 for the MITT1 population.

Table 24. Actual Levels of Visual Acuity and Changes From Baseline to Week 54 (LOCF Data); MITT1 (Study Eye)

No. of Subjects (MITT1 Population)		Pegaptanib Sodium (0.3 mg) N=133 n (%)	Sham Injection N=127 n (%)
Baseline	Mean	57.0	57.5
	SD	8.85	8.11
	Median	60.0	60.0
	Range	35; 73	35; 70
	N	133	127
Week 54	Mean	62.2	58.7
	SD	12.16	14.55
	Median	64.0	61.0
	Range	24; 85	0; 88
	N	133	127
Change from	Lost 15 or more	5 (3.8)	9 (7.1)
Baseline at	Lost 10–14	4 (3.0)	8 (6.3)
Week 54	Lost 1–9	26 (19.5)	35 (27.6)
	No change or gained 1–9	49 (36.8)	50 (39.4)
	Gained 10–14	27 (20.3)	12 (9.4)
	Gained 15 or more	22 (16.5)	13 (10.2)

LOCF = last observation carried forward; MITT = modified intent-to-treat; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; SD = standard deviation.

Year 2: At Week 102, the mean VA was 63.2±12.77 letters in the pegaptanib sodium group with a median of 64.0 and a range of 25 to 88; the mean VA was 59.0±14.79 in the sham injection group with a median of 60.0 and range of 14 to 85. Table 25 summarizes the results for Baseline and Week 102 for the FAS2 population.

Table 25. Actual Levels of Visual Acuity and Changes From Baseline to Week 102 (LOCF Data); FAS2 (Study Eye)

No. of Subjects (FAS2 Population)		Pegaptanib Sodium (0.3 mg) N=133 n (%)	Sham Injection N=123 n (%)
Baseline	Mean	57.0	57.4
	SD	8.85	8.20
	Median	60.0	60.0
	Range	35; 73	35; 70
	N	133	123
Week 102	Mean	63.2	59.0
	SD	12.77	14.79
	Median	64.0	60.0
	Range	25; 88	14; 85
	N	133	123
Change from	Lost 15 or more	5 (3.8)	10 (8.1)
Baseline at	Lost 10–14	5 (3.8)	8 (6.5)
Week 102	Lost 1–9	27 (20.3)	38 (30.9)
	No change or gained 1–9	45 (33.8)	30 (24.4)
	Gained 10–14	21 (15.8)	19 (15.4)
	Gained 15 or more	30 (22.6)	18 (14.6)

FAS = full analysis set; LOCF = last observation carried forward; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; SD = standard deviation.

Retinal Thickness

Year 1: After Week 18, subjects were allowed to receive focal or grid laser treatments during the study provided that a minimum of 17 weeks occurred between treatments (maximum of 3 focal or grid laser treatments per year). The proportion of subjects with a decrease in retinal thickness at the center point by ≥25% (LOCF data) for the MITT1 population at Week 54 is summarized in Table 26. At Week 54, 39 (31.7%) subjects in the pegaptanib sodium group had a decrease in retinal thickness at the center point by ≥25% from Baseline compared with 28 (23.7%) subjects in the sham injection group; this difference was not statistically significant (p-value=0.3489).

Table 26. Proportion of Subjects With Decrease in Retinal Thickness at Center Point by ≥25% (LOCF Data) at Week 54; MITT1 Population

No. of Subjects	MITT1	
	Pegaptanib Sodium (0.3 mg) N=133 n (%)	Sham Injection N=127 n (%)
Evaluable Subjects at Week 54	123	118
Decrease in retinal thickness by ≥25% from Baseline: yes	39 (31.7)	28 (23.7)
Decrease in retinal thickness by ≥25% from Baseline: no	84 (68.3)	90 (76.3)
P-value (CMH)[a]	0.3489	

CMH = cochran-mantel-haenszell HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; MITT = modified intent-to-treat; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; VA = visual acuity.
a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

The proportion of subjects with a decrease in retinal thickness at the center point by ≥50% (LOCF data) for the MITT1 population is summarized in Table 27. At Week 54, 18 (14.6%) subjects in the pegaptanib sodium group had a decrease in retinal thickness at the center point by ≥50% from Baseline compared with 14 (11.9%) subjects in the sham injection group; this difference was not statistically significant (p-value=0.7211).

Table 27. Proportion of Subjects With Decrease in Retinal Thickness at Center Point by ≥50% (LOCF Data) at Week 54; MITT1 Population

No. of Subjects	MITT1	
	Pegaptanib Sodium (0.3 mg) N=133 n (%)	Sham Injection N=127 n (%)
Evaluable Subjects at Week 54	123	118
Decrease in retinal thickness by ≥50% from Baseline: yes	18 (14.6)	14 (11.9)
Decrease in retinal thickness by ≥50% from Baseline: no	105 (85.4)	104 (88.1)
P-value (CMH)[a]	0.7211	

CMH = cochran-mantel-haenszel; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; MITT = modified intent-to-treat; N = number of subjects; n = number of subjects meeting specified criteria; No. = number; VA = visual acuity.
a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Year 2: The proportion of subjects with a decrease in retinal thickness at the center point by ≥25% (LOCF data) for the FAS2 population is summarized in Table 28. At Week 102, 60 (48.8%) subjects in the pegaptanib sodium group had a decrease in retinal thickness at the

center point by ≥25% from Baseline compared with 51 (44.7%) subjects in the sham injection group; this difference was not statistically significant (p-value=0.7566).

Table 28. Proportion of Subjects With Decrease in Retinal Thickness at the Center Point by ≥25% at Week 102 (LOCF Data); FAS2 Population

Number of Subjects	Pegaptanib Sodium N=133 n (%)	Sham N=123 n (%)
Evaluable Subjects at Week 102	123	114
Decrease in retinal thickness by ≥25% from Baseline: yes	60 (48.8)	51 (44.7)
Decrease in retinal thickness by ≥25% from Baseline: no	63 (51.2)	63 (55.3)
P-value (CMH)[a]	0.7566	
Odds ratio (confidence interval 95%)	1.10 (0.64, 1.88)	

CMH = cochran-mantel-haenszel; FAS = full analysis set; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; N = number of subjects; n = number of subjects meeting specified criteria; VA = visual acuity.
a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

The proportion of subjects with a decrease in retinal thickness at the center point by ≥50% (LOCF data) for the FAS2 population is summarized in Table 29. At Week 102, 27 (22.0%) subjects in the pegaptanib sodium group had a decrease in retinal thickness at the center point by ≥50% from Baseline compared with 31 (27.2%) subjects in the sham injection group; this difference was not statistically significant (p-value=0.0989).

Table 29. Proportion of Subjects With a Decrease in Retinal Thickness at Center Point by ≥50% at Week 102 (LOCF Data); FAS2 Population

Number of Subjects	Pegaptanib Sodium N=133 n (%)	Sham N=123 n (%)
Evaluable Subjects at Week 102	123	114
Decrease in retinal thickness by ≥50% from Baseline: yes	27 (22.0)	31 (27.2)
Decrease in retinal thickness by ≥50% from Baseline: no	96 (78.0)	83 (72.8)
P-value (CMH)[a]	0.0989	
Odds ratio (confidence interval 95%)	0.59 (0.31, 1.11)	

CMH = cochran-mantel-haenszel; FAS = full analysis set; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; N = number of subjects; n = number of subjects meeting specified criteria; VA = visual acuity.
a. CMH test adjusted for HbA1c, systolic blood pressure, diastolic blood pressure, and baseline VA.

Visual Function and Health-Related Quality of Life (NEI-VFQ 25)

Year 1: Subject's self-reported visual functioning and visual related QoL data were collected using the NEI-VFQ 25. Table 30 presents a summary of the NEI-VFQ 25 scores from Baseline and Week 54 (MITT1 population).

Table 30. Mean NEI-VFQ 25 Scores at Baseline and Week 54 Visits; MITT1 Population

Domain	Pegaptanib Sodium (0.3 mg) Baseline N=133	Pegaptanib Sodium (0.3 mg) Week 54 N=133	Sham Baseline N=127	Sham Injection Week 54 N=127
Composite score[a]	65.9	70.4	67.9	69.2
General health	38.9	40.7	41.7	40.1
General vision	54.7	61.9	54.6	60.5
Ocular pain	78.0	80.0	79.7	83.3
Near vision	56.8	61.9	60.7	59.6
Distance vision	61.4	67.3	67.3	65.1
Social functioning	78.1	80.2	82.3	77.0
Mental health	56.6	63.3	60.0	63.3
Role difficulty	56.8	62.4	52.6	58.8
Dependency	69.2	73.1	71.2	73.7
Driving	50.7	56.7	53.1	55.7
Colour vision	86.9	87.4	87.4	85.8
Peripheral vision	71.0	75.8	71.6	73.1

MITT = modified intent-to-treat; N = number of subjects; NEI-VFQ 25 = 25-item national eye institute – visual functioning questionnaire.
a. The composite score is not a subscale.

Statistical significance is related to the clinically meaningful difference (CMD) observed when using the NEI-VFQ 25 between the 2 treatment groups at the predefined timepoints. The CMD describes the degree and importance of observed QoL score changes in a context that is both important to subjects and health care providers. When a 100-point scale is used, as with the NEI-VFQ 25, a ≥5-point shift or difference is meaningful to subjects.

Table 31 summarizes the outcome for this secondary endpoint: numerical change at Week 54 from Baseline for subjects in the pegaptanib sodium group compared with subjects in the sham group and the accompanying p-value for each subscale.

Table 31. Summary of NEI-VFQ Data; Week 54 Change From Baseline for Pegaptanib Sodium Group Compared With the Sham Group (LOCF Data); MITT1 Population

Domain	P-Value	LS Mean Change From Baseline to Week 54, Pegaptanib Sodium Group - Sham Group (Range)
Composite score[a]	0.0769	2.92 (-0.32; 6.16)
General health	0.3490	2.68 (-2.95; 8.30)
General vision	0.7375	0.8 (-3.90; 5.50)
Ocular pain	0.4751	-2.00 (-7.51; 3.51)
Near vision activities	0.0325	5.70 (0.48; 10.91)
Distance vision activities	0.0040	8.50 (2.74; 14.25)
Social functioning	0.0023	7.99 (2.90; 13.09)
Mental health	0.2721	3.07 (-2.43; 8.57)
Role difficulty	0.8768	-0.59 (-8.03; 6.86)
Dependency	0.7530	-1.10 (-7.97; 5.77)
Driving	0.0554	6.13 (-0.14; 12.41)
Colour vision	0.6785	1.17 (-4.40; 6.74)
Peripheral vision	0.3754	2.91 (-3.55; 9.36)

LOCF = last observation carried forward; LS = least square; MITT = modified intent-to-treat; NEI-VFQ = national eye institute – visual functioning questionnaire.
a. The composite score is not a subscale.

Year 2: Subject's self-reported visual functioning and visual related QoL data were collected using the NEI-VFQ 25. Table 32 presents a summary of the NEI-VFQ 25 scores from Baseline and Week 102 (FAS2 population).

Table 32. Mean NEI-VFQ 25 Mean Scores at Baseline and Week 102 (LOCF Data); FAS2 Population

Subscale	Pegaptanib Sodium (0.3 mg) Baseline	Pegaptanib Sodium (0.3 mg) Week 102	Sham Treatment Baseline	Sham Treatment Week 102
Composite score[a]	65.9	70.7	67.5	67.2
General health	38.9	43.1	41.4	40.0
General vision	54.7	61.7	54.2	59.3
Ocular pain	78.0	83.1	79.4	80.1
Near vision	56.8	63.1	59.9	61.3
Distance vision	61.4	65.9	66.9	61.6
Social functioning	78.1	80.4	82.4	75.2
Mental health	56.6	65.6	59.8	62.6
Role difficulty	56.8	62.1	52.1	58.7
Dependency	69.2	75.0	70.7	69.6
Driving	50.7	56.0	52.8	49.2
Colour vision	86.9	85.4	87.1	84.6
Peripheral vision	71.0	75.0	71.5	70.9

FAS = full analysis set; LOCF = last observation carried forward; NEI-VFQ 25 = 25-item national eye institute – visual functioning questionnaire.

a. The composite score is not a subscale.

Table 33 summarizes the outcome for this secondary endpoint: numeric change at Week 102 (FAS2 population) from Baseline for subjects in the pegaptanib sodium group compared with subjects in the sham group and the accompanying p-value for each domain.

Table 33. Summary of NEI-VFQ 25 Data; Week 102 LS Mean Change From Baseline for Pegaptanib Sodium Group Compared With the Sham Group (LOCF Data); FAS2 Population

Subscale	P-Value	LS Mean Change From Baseline to Week 102, Pegaptanib Sodium Group - Sham Group (Range)[a]
Composite score[b]	0.0249	4.21 (0.54; 7.89)
General health	0.0913	4.90 (-0.79; 10.60)
General vision	0.4119	1.91 (-2.67; 6.49)
Ocular pain	0.3449	2.73 (-2.95; 8.41)
Near vision activities	0.2048	3.56 (-1.95; 9.06)
Distance vision activities	0.0020	9.16 (3.39; 14.93)
Social functioning	0.0013	9.17 (3.62; 14.73)
Mental health	0.1389	4.62 (-1.51; 10.76)
Role difficulty	0.7907	-1.05 (-8.84; 6.74)
Dependency	0.2834	3.86 (-3.22; 10.94)
Driving	0.0460	7.21 (0.13; 14.29)
Colour vision	0.8660	0.54 (-5.75; 6.82)
Peripheral vision	0.1734	4.42 (-1.96; 10.79)

ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; LS = least square; NEI-VFQ 25 = 25-item national eye institute – visual functioning questionnaire; VA = visual acuity.

a. ANCOVA on VA Change LS Mean of pegaptanib sodium-Sham (95% CI). Adjusted for HbA1c, systolic blood pressure, diastolic blood pressure and baseline VA.

b. The composite score is not a subscale.

Safety Results:

The incidence of treatment-emergent AEs (TEAEs) (all causalities, reported by ≥5% subjects in either treatment group) for all randomized subjects (SafetyS1 population) is summarized in Table 34.

Table 34. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term in ≥5% Subjects (All Causalities) – All Randomized Subjects (SafetyS1 Population)

System organ class Preferred term	Pegaptanib Sodium (0.3 mg) N=174 n (%)	Sham Injection N=143 n (%)
Subjects with at least one adverse event	114 (65.5)	100 (69.9)
Eye disorders	97 (55.7)	89 (62.2)
Conjunctival haemorrhage	34 (19.5)	20 (14.0)
Diabetic retinal oedema	17 (9.8)	24 (16.8)
Macular oedema	18 (10.3)	16 (11.2)
Eye pain	20 (11.5)	11 (7.7)
Punctate keratitis	21 (12.1)	10 (7.0)
Visual acuity reduced	16 (9.2)	14 (9.8)
Diabetic retinopathy	11 (6.3)	16 (11.2)
Cataract	16 (9.2)	10 (7.0)
Retinal haemorrhage	11 (6.3)	15 (10.5)
Vitreous haemorrhage	10 (5.7)	12 (8.4)
Retinal exudates	12 (6.9)	8 (5.6)
Conjunctivitis	9 (5.2)	6 (4.2)
Lacrimation increased	9 (5.2)	4 (2.8)
Retinal aneurysm	5 (2.9)	8 (5.6)
Myodesopsia	10 (5.7)	2 (1.4)
Infections and infestations	13 (7.5)	11 (7.7)
Nasopharyngitis	13 (7.5)	11 (7.7)
Investigations	30 (17.2)	9 (6.3)
Intraocular pressure increased	30 (17.2)	9 (6.3)
Metabolism and nutrition disorders	15 (8.6)	5 (3.5)
Diabetes mellitus	15 (8.6)	5 (3.5)
Vascular disorders	21 (12.1)	13 (9.1)
Hypertension	21 (12.1)	13 (9.1)

MedDRA (Version 12.1) coding dictionary applied.
Treatment-emergent adverse events include all adverse events that occurred on or after the first injection and up to and including 6-weeks after the last injection.
For subjects converted from the lower doses to 0.3 mg, only include the events occurred after they converted to 0.3 mg.
For Sham converted subjects, only include the events occurred while they were on Sham, ie, before converting to 0.3 mg.
MedDRA = medical dictionary for regulatory activities; N = number of subjects; n = number of subjects meeting specified criteria.

The incidence of treatment-emergent AEs (TEAEs) (study related) for all randomized subjects (SafetyS1 population) is summarized in Table 35.

Table 35. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (Study Related) – All Randomized Subjects (SafetyS1 Population)

System Organ Class Preferred Term[a]	Pegaptanib Sodium D0-W156[b] N=144 n (%)	Pegaptanib Sodium D0-<W102 N=144 n (%)	Pegaptanib Sodium W102-W156 N=46 n (%)	Sham D0-<CONV N=142 n (%)	Sham CONV-W156[b] N=54 n (%)
Subjects with at least one adverse event	12 (8.3)	12 (8.3)	0	7 (4.9)	0
Blood and lymphatic system disorders	2 (1.4)	2 (1.4)	0	2 (1.4)	0
Thrombocytopenia	2 (1.4)	2 (1.4)	0	2 (1.4)	0
Cardiac disorders	0	0	0	1 (0.7)	0
Angina pectoris	0	0	0	1 (0.7)	0
Coronary artery disease	0	0	0	1 (0.7)	0
Eye disorders	8 (5.6)	8 (5.6)	0	4 (2.8)	0
Myodesopsia	2 (1.4)	2 (1.4)	0	0	0
Cataract	1 (0.7)	1 (0.7)	0	0	0
Cataract subcapsular	1 (0.7)	1 (0.7)	0	0	0
Punctate keratitis	1 (0.7)	1 (0.7)	0	0	0
Retinal aneurysm	1 (0.7)	1 (0.7)	0	0	0
Visual acuity reduced	1 (0.7)	1 (0.7)	0	1 (0.7)	0
Visual impairment	1 (0.7)	1 (0.7)	0	0	0
Vitreous haemorrhage	1 (0.7)	1 (0.7)	0	0	0
Diabetic retinopathy	0	0	0	1 (0.7)	0
Iris neovascularisation	0	0	0	1 (0.7)	0
Macular oedema	0	0	0	2 (1.4)	0
Retinal exudates	0	0	0	1 (0.7)	0
Vitreous opacities	0	0	0	1 (0.7)	0
Investigations	1 (0.7)	1 (0.7)	0	0	0
Intraocular pressure increased	1 (0.7)	1 (0.7)	0	0	0
Nervous system disorders	1 (0.7)	1 (0.7)	0	0	0
Cerebrovascular accident	1 (0.7)	1 (0.7)	0	0	0
Renal and urinary disorders	2 (1.4)	2 (1.4)	0	1 (0.7)	0
Diabetic nephropathy	1 (0.7)	1 (0.7)	0	1 (0.7)	0
Nephropathy	1 (0.7)	1 (0.7)	0	0	0

Treatment-emergent AEs include all AEs that occurred on or after the first injection and up to and including 6 weeks after the last injection.
AE = adverse event; CONV = conversion; D = day; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects meeting prespecified criteria; No. = number; W = week.
a. MedDRA Version 12.1 coding dictionary applied.
b. These columns combined represent the total population exposed to pegaptanib sodium.

The incidence of treatment-emergent SAEs (all causalities) for all randomized subjects (SafetyS1 population) is summarized in Table 36.

Table 36. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) – All Randomized Subjects (SafetyS1 Population)

System Organ Class Preferred Term	Pegaptanib Sodium (0.3 mg) N=174 n (%)	Sham Injection N=143 n (%)
Subjects with at least one adverse event	45 (25.9)	35 (24.5)
Cardiac disorders	10 (5.7)	8 (5.6)
Angina pectoris	2 (1.1)	1 (0.7)
Coronary artery disease	2 (1.1)	1 (0.7)
Myocardial infarction	0	3 (2.1)
Angina unstable	2 (1.1)	0
Arrhythmia	1 (0.6)	1 (0.7)
Cardiac failure congestive	0	2 (1.4)
Acute myocardial infarction	0	1 (0.7)
Arteriosclerosis coronary artery	1 (0.6)	0
Cardiac arrest	1 (0.6)	0
Cardiac failure	0	1 (0.7)
Cardiogenic shock	1 (0.6)	0
Mitral valve stenosis	0	1 (0.7)
Myocardial ischaemia	1 (0.6)	0
Endocrine disorders	1 (0.6)	0
Adrenocortical insufficiency acute	1 (0.6)	0
Eye disorders	8 (4.6)	6 (4.2)
Vitreous haemorrhage	3 (1.7)	3 (2.1)
Cataract	2 (1.1)	3 (2.1)
Retinal detachment	2 (1.1)	0
Diabetic retinal oedema	0	1 (0.7)
Eye haemorrhage	1 (0.6)	0
Iris neovascularisation	1 (0.6)	0
Ocular hypertension	1 (0.6)	0
Gastrointestinal disorders	2 (1.1)	4 (2.8)
Intestinal obstruction	0	2 (1.4)
Ascites	0	1 (0.7)
Constipation	1 (0.6)	0
Nausea	1 (0.6)	0
Polyp colorectal	0	1 (0.7)
Vomiting	1 (0.6)	0
General disorders and administration site conditions	1 (0.6)	1 (0.7)
Death	1 (0.6)	0
Impaired healing	0	1 (0.7)
Hepatobiliary disorders	2 (1.1)	0
Cholangitis	1 (0.6)	0
Cholecystitis	1 (0.6)	0
Cholelithiasis	1 (0.6)	0
Infections and infestations	4 (2.3)	10 (7.0)
Osteomyelitis	1 (0.6)	2 (1.4)
Pneumonia	0	3 (2.1)
Cellulitis	1 (0.6)	1 (0.7)
Gangrene	1 (0.6)	1 (0.7)
Viral infection	1 (0.6)	1 (0.7)
Appendicitis	0	1 (0.7)
Bronchopneumonia	0	1 (0.7)
Erysipelas	0	1 (0.7)
Gastroenteritis	0	1 (0.7)
Lower respiratory tract infection	1 (0.6)	0
Respiratory tract infection	0	1 (0.7)

Table 36. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) – All Randomized Subjects (SafetyS1 Population)

System Organ Class Preferred Term	Pegaptanib Sodium (0.3 mg) N=174 n (%)	Sham Injection N=143 n (%)
Urinary tract infection	0	1 (0.7)
Injury, poisoning and procedural complications	1 (0.6)	3 (2.1)
Facial bones fracture	0	2 (1.4)
Fall	0	2 (1.4)
Joint dislocation	0	2 (1.4)
Hip fracture	1 (0.6)	0
Pelvic fracture	0	1 (0.7)
Tendon rupture	0	1 (0.7)
Investigations	4 (2.3)	0
Intraocular pressure increased	2 (1.1)	0
Liver function test abnormal	1 (0.6)	0
Troponin increased	1 (0.6)	0
Metabolism and Nutrition Disorders	3 (1.7)	3 (2.1)
Hypoglycaemia	2 (1.1)	0
Dehydration	0	1 (0.7)
Hyperglycaemia	0	1 (0.7)
Metabolic disorder	0	1 (0.7)
Overweight	1 (0.6)	0
Musculoskeletal and connective tissue disorders	3 (1.7)	0
Intervertebral disc protrusion	1 (0.6)	0
Muscular weakness	1 (0.6)	0
Musculoskeletal pain	1 (0.6)	0
Rhabdomyolysis	1 (0.6)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.7)	4 (2.8)
Bladder cancer	1 (0.6)	0
Brain neoplasm	1 (0.6)	0
Breast cancer	0	1 (0.7)
Colorectal cancer	0	1 (0.7)
Glioblastoma	1 (0.6)	0
Retroperitoneal neoplasm	0	1 (0.7)
Uterine cancer	0	1 (0.7)
Nervous system disorders	7 (4.0)	2 (1.4)
Cerebrovascular accident	2 (1.1)	1 (0.7)
Carotid artery stenosis	1 (0.6)	0
Cervical myelopathy	1 (0.6)	0
Convulsion	0	1 (0.7)
Diabetic hyperglycaemic coma	1 (0.6)	0
Dizziness	1 (0.6)	0
Headache	1 (0.6)	0
Psychiatric disorders	0	1 (0.7)
Anxiety	0	1 (0.7)
Renal and urinary disorders	3 (1.7)	0
Renal failure	2 (1.1)	0
Renal artery stenosis	1 (0.6)	0
Renal embolism	1 (0.6)	0
Renal failure chronic	1 (0.6)	0
Respiratory, thoracic and mediastinal disorders	1 (0.6)	1 (0.7)
Acute pulmonary oedema	0	1 (0.7)
Lung disorder	1 (0.6)	0
Skin and subcutaneous tissue disorders	1 (0.6)	1 (0.7)

Table 36. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) – All Randomized Subjects (SafetyS1 Population)

System Organ Class Preferred Term	Pegaptanib Sodium (0.3 mg) N=174 n (%)	Sham Injection N=143 n (%)
Dermatitis	0	1 (0.7)
Erythema nodosum	1 (0.6)	0
Vascular disorders	2 (1.1)	1 (0.7)
Hypertension	1 (0.6)	1 (0.7)
Malignant hypertension	1 (0.6)	0

MedDRA (Version 12.1) coding dictionary applied.
Treatment-emergent adverse events include all adverse events that occurred on or after the first injection and up to and including 6-weeks after the last injection.
For subjects converted from the lower doses to 0.3 mg, only include the events occurred after they converted to 0.3 mg.
For Sham converted subjects, only include the events occurred while they were on Sham, ie, before converting to 0.3 mg.
Incl = including; MedDRA = medical dictionary for regulatory activities; N = number of subjects; n = number of subjects meeting specified criteria.

The incidence of SAEs (study related) for all randomized subjects (SafetyS1 population) is summarized in Table 37.

Table 37. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (Study Related) – All Randomized Subjects (SafetyS1 Population)

System Organ Class Preferred Term[a]	Pegaptanib Sodium[b] D0-W156 N=144 n (%)	Pegaptanib Sodium D0-<W102 N=144 n (%)	Pegaptanib Sodium W102-W156 N=46 n (%)	Sham D0-<CONV N=142 n (%)	Sham CONV-W156[b] N=54 n (%)
Subjects with at least one adverse event	2 (1.4)	2 (1.4)	0	1 (0.7)	0
Cardiac disorders	0	0	0	1 (0.7)	0
Angina pectoris	0	0	0	1 (0.7)	0
Coronary artery disease	0	0	0	1 (0.7)	0
Eye disorders	1 (0.7)	1 (0.7)	0	0	0
Vitreous haemorrhage	1 (0.7)	1 (0.7)	0	0	0
Nervous system disorders	1 (0.7)	1 (0.7)	0	0	0
Cerebrovascular accident	1 (0.7)	1 (0.7)	0	0	0

Treatment-emergent AEs include all AEs that occurred on or after the first injection and up to and including 6 weeks after the last injection.
AE = adverse event; CONV = conversion; D = day; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects meeting prespecified criteria; W = week.
a. MedDRA Version 12.1 coding dictionary applied.
b. These columns combined represent the total population exposed to pegaptanib sodium.

The incidence of treatment-emergent AEs (TEAEs) (all causalities, reported by ≥5% subjects in either treatment group) for all treated subjects in Year 3 is summarized in Table 38.

Table 38. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term in ≥5% Subjects (All Causalities) – All Treated Subjects in Year 3

System organ class Preferred term	Pegaptanib Sodium (0.3 mg) N=46 n (%)	Sham Injection N=54 n (%)
Subjects with at least one adverse event	11 (23.9)	10 (18.5)
Eye disorders	7 (15.2)	8 (14.8)
Conjunctival haemorrhage	1 (2.2)	7 (13.0)
Macular oedema	3 (6.5)	4 (7.4)
Cataract	3 (6.5)	0
Investigations	3 (6.5)	3 (5.6)
Intraocular pressure increased	3 (6.5)	3 (5.6)
Metabolism and nutrition disorders	4 (8.7)	0
Diabetes mellitus	4 (8.7)	0

MedDRA (Version 12.1) coding dictionary applied.
Treatment-emergent adverse events include all adverse events that occurred on or after the first injection and up to and including 6-weeks after the last injection.
Events occurred after Week 102 for Pegaptanib sodium randomized Subjects or after conversion for Sham randomized subjects but before Week 156.
MedDRA = medical dictionary for regulatory activities; N = number of subjects; n = number of subjects meeting specified criteria.

The incidence of TEAEs (all causalities) for SafetyS3 population is summarized in Table 39.

Table 39. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All Causalities) – SafetyS3

System organ class Preferred term	Pegaptanib Sodium (0.03 mg) N=22 n (%)	Pegaptanib Sodium (0.003 mg) N=7 n (%)
Subjects with at least one adverse event	19 (86.4)	7 (100)
Eye disorders	15 (68.2)	6 (85.7)
Eye pain	6 (27.3)	2 (28.6)
Conjunctival haemorrhage	4 (18.2)	1 (14.3)
Cataract	2 (9.1)	2 (28.6)
Punctate keratitis	4 (18.2)	0
Visual acuity reduced	1 (4.5)	3 (42.9)
Diabetic retinopathy	1 (4.5)	2 (28.6)
Macular oedema	2 (9.1)	1 (14.3)
Myodesopsia	3 (13.6)	0
Retinal exudates	2 (9.1)	1 (14.3)
Diabetic retinal oedema	2 (9.1)	0
Iris neovascularisation	1 (4.5)	1 (14.3)
Retinal haemorrhage	2 (9.1)	0
Retinal neovascularisation	0	2 (28.6)
Vitreous opacities	2 (9.1)	0
Anterior chamber flare	0	1 (14.3)
Conjunctivitis	0	1 (14.3)
Eye irritation	0	1 (14.3)
Retinal aneurysm	0	1 (14.3)
Retinal detachment	0	1 (14.3)
Vitreous detachment	0	1 (14.3)
Gastrointestinal disorders	7 (31.8)	1 (14.3)
Nausea	4 (18.2)	0
Diarrhoea	2 (9.1)	0
Vomiting	2 (9.1)	0
Dyspepsia	0	1 (14.3)
Infections and infestations	7 (31.8)	2 (28.6)
Bronchitis	2 (9.1)	0
Urinary tract infection	1 (4.5)	1 (14.3)
Upper respiratory tract infection	0	1 (14.3)
Investigations	7 (31.8)	5 (71.4)
Intraocular pressure increased	3 (13.6)	4 (57.1)
Glycosylated hemoglobin increased	0	1 (14.3)
Metabolism and nutrition disorders	4 (18.2)	3 (42.9)
Hyperglycaemia	1 (4.5)	1 (14.3)
Hypoglycaemia	2 (9.1)	0
Hypercholesterolaemia	0	1 (14.3)
Hyperlipidaemia	0	1 (14.3)
Musculoskeletal and connective tissue disorders	5 (22.7)	2 (28.6)
Back pain	2 (9.1)	1 (14.3)
Pain in extremity	2 (9.1)	0
Muscular weakness	0	1 (14.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (9.1)	1 (14.3)
Glioblastoma	0	1 (14.3)
Nervous system disorders	3 (13.6)	0
Headache	2 (9.1)	0
Vascular disorders	6 (27.3)	0
Hypertension	4 (18.2)	0

MedDRA (Version 12.1) coding dictionary applied.
Treatment-emergent adverse events include all adverse events that occurred on or after the first injection and up to and including 6-weeks after the last injection that occurred on or before week-96 or 04 June 2010, whichever was earlier.
Incl = including; MedDRA = medical dictionary for regulatory activities; N = number of subjects; n = number of subjects meeting specified criteria.

The incidence of TEAEs (study drug related) for SafetyS3 population is summarized in Table 40.

Table 40. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (Study Related) – SafetyS3

System Organ Class Preferred Term	Pegaptanib Sodium (0.03 mg) N=22 n (%)	Pegaptanib Sodium (0.003 mg) N=7 n (%)
Subjects with at least one adverse event	1 (4.5)	0
Investigations	1 (4.5)	0
Intraocular pressure increased	1 (4.5)	0

MedDRA (Version 12.1) coding dictionary applied.
Treatment-emergent adverse events include all adverse events that occurred on or after the first injection and up to and including 6-weeks after the last injection that occurred on or before week-96 or 04 June 2010, whichever was earlier.
MedDRA = medical dictionary for regulatory activities; N = number of subjects; n = number of subjects meeting specified criteria.

The incidence of SAEs (all causalities) for SafetyS3 population is summarized in Table 41.

Table 41. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) – SafetyS3

System Organ Class Preferred Term	Pegaptanib Sodium (0.03 mg) N=22 n (%)	Pegaptanib Sodium (0.003 mg) N=7 n (%)
Subjects with at least one adverse event	5 (22.7)	2 (28.6)
Eye disorders	0	1 (14.3)
Iris neovascularisation	0	1 (14.3)
Retinal detachment	0	1 (14.3)
Gastrointestinal disorders	1 (4.5)	0
Nausea	1 (4.5)	0
Vomiting	1 (4.5)	0
Investigations	1 (4.5)	0
Liver function test abnormal	1 (4.5)	0
Metabolism and nutrition disorders	1 (4.5)	0
Hypoglycaemia	1 (4.5)	0
Musculoskeletal and connective tissue disorders	0	1 (14.3)
Muscular weakness	0	1 (14.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (4.5)	1 (14.3)
Brain neoplasm	1 (4.5)	0
Glioblastoma	0	1 (14.3)
Nervous system disorders	2 (9.1)	0
Carotid artery stenosis	1 (4.5)	0
Headache	1 (4.5)	0
Renal and urinary disorders	1 (4.5)	0
Renal artery stenosis	1 (4.5)	0
Renal embolism	1 (4.5)	0
Renal failure	1 (4.5)	0
Vascular disorders	1 (4.5)	0
Malignant hypertension	1 (4.5)	0

MedDRA (Version 12.1) coding dictionary applied.
Treatment-emergent adverse events include all adverse events that occurred on or after the first injection and up to and including 6-weeks after the last injection that occurred on or before week-96 or 04 June 2010, whichever was earlier.
Incl = including; MedDRA = medical dictionary for regulatory activities; N = number of subjects; n = number of subjects meeting specified criteria.

SAEs related to study drug have not been reported for the SafetyS3 population.

A total of 11 subjects died during the study (1 in the pegaptanib sodium 0.003 mg group, 5 in the pegaptanib sodium 0.3 mg group, and 5 in the sham injection group (Table 42).

Table 42. Listing of Subject Deaths

Subject Information (Age [Years]; Sex)	Cause of Death[a]
Pegaptanib Sodium (0.003 mg) Treatment Group	
63[b]; F	Glioblastoma multiforme
Pegaptanib Sodium (0.3 mg) Treatment Group	
80; F	Cerebrovascular accident
67; M	Death[c]
58; M	Sepsis, renal failure, and endocarditis
80; F	Cardiac arrest
66; M	Cardiac arrest
Sham Injection Treatment Group	
78; M	Colorectal cancer and cardiac failure
52; F	Breast cancer
61; M	Ascites
70; M	Acute myocardial infarction; arrhythmia
46; M	Myocardial infarction

Reported age is age at death.
Note that one subject (64-year-old female) died prior to randomization; the cause of death was related to acute pancreatitis.
F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities.

a. MedDRA (Version 12.1) Coding Dictionary applied; preferred term listed.
b. Pegaptanib sodium was administered intravitreously, at a total daily dose of 0.003 mg, once every 6 weeks, from 13 Jun 2006 (Study Day 1) to until 29 Nov 2006 (Week 24). In accordance with the protocol, the subject then received 0.3 mg from 12 Jan 2007 (Week 30) until 06 Feb 2008.
c. The cause of death was unknown.

The incidence of treatment-emergent AEs leading to study drug discontinuation (all causalities) by MedDRA SOC and preferred term is presented in Table 43.

Table 43. Incidence of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (All Causalities); SafetyS1 Population

System Organ Class Preferred Term[a]	Pegaptanib Sodium[b] D0-W156 N=144 n (%)	Pegaptanib Sodium D0-<W102 N=144 n (%)	Pegaptanib Sodium W102-W156 N=46 n (%)	Sham D0-<CONV N=142 n (%)	Sham CONV-W156[b] N=54 n (%)
Cardiac disorders	2 (1.4)	2 (1.4)	0	2 (1.4)	0
Angina unstable	1 (0.7)	1 (0.7)	0	0	0
Cardiac arrest	1 (0.7)	1 (0.7)	0	0	0
Cardiogenic shock	1 (0.7)	1 (0.7)	0	0	0
Acute myocardial infarction	0	0	0	1 (0.7)	0
Angina pectoris	0	0	0	1 (0.7)	0
Arrhythmia	0	0	0	1 (0.7)	0
Coronary artery disease	0	0	0	1 (0.7)	0
Eye disorders	2 (1.4)	1 (0.7)	1 (2.2)	1 (0.7)	0
Retinal detachment	1 (0.7)	0	1 (2.2)	0	0
Scleral disorder	1 (0.7)	1 (0.7)	0	0	0
Retinal haemorrhage	0	0	0	1 (0.7)	0
Retinopathy proliferative	0	0	0	1 (0.7)	0
Investigations	2 (1.4)	2 (1.4)	0	0	0
Intraocular pressure increased	2 (1.4)	2 (1.4)	0	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	0	0	2 (1.4)	1 (1.9)
Breast cancer	0	0	0	1 (0.7)	0
Colorectal cancer	0	0	0	1 (0.7)	0
Prostate cancer	0	0	0	0	1 (1.9)
Nervous system disorders	1 (0.7)	1 (0.7)	0	0	0
Cerebrovascular accident	1 (0.7)	1 (0.7)	0	0	0
Respiratory, thoracic, and mediastinal disorders	0	0	0	0	1 (1.9)
Pulmonary embolism	0	0	0	0	1 (1.9)

Treatment-emergent AEs include all AEs that occurred on or after the first injection and up to and including 6 weeks after the last injection.
AE = adverse event; CONV = conversion; D = day; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects meeting prespecified criteria; No. = number; W = week.
a. MedDRA Version 12.1 coding dictionary applied.
b. These columns combined represent the total population exposed to pegaptanib sodium.

CONCLUSIONS:

This study demonstrated that pegaptanib sodium 0.3 mg was well tolerated and effective in treating DME.

For the primary efficacy endpoint, there was a statistically significant difference in favour of pegaptanib sodium over the sham injection group in the proportion of subjects with ≥10 letters (or 2-lines) VA improvement at Week 54 (ie, through 1 year of treatment). There was a trend in favour of the pegaptanib sodium group regarding VA after 2 years of treatment. Efficacy was maintained for the pegaptanib sodium group at the end of Year 3.

Additionally, the strength of the clinical benefit of pegaptanib sodium was reinforced by the secondary endpoints in relation to the statistical significance, positive trends, and numeric differences in a number of vision, anatomic, and QoL endpoints.

The incidence of most events was similar between the 2 treatment groups or in favour of pegaptanib sodium during the first 2 years of the study. The most common treatment-emergent AEs occurred in the eye. No deaths were related to the injection procedure or study drug. No new safety concerns emerged during the open-label third year of the study.