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

PROTOCOL NO: A5751036

PROTOCOL TITLE: A Phase 3B, 1-Year, Open-Label, Multicenter, Non-Comparative Study to Evaluate the Safety and Tolerability of Intravitreal Pegaptanib Sodium Injection in Subjects With Diabetic Macular Edema (DME)

Study Centers: A total of 12 centers took part in the study and enrolled subjects; 6 in Spain, 2 each in the United Kingdom (UK), Sweden and Finland.

Study Initiation Date and Final Completion Date: 24 January 2011 to 12 July 2012. The study was terminated prematurely.

Phase of Development: Phase 3b

Study Objective: The primary objective of this study was to further evaluate the safety and tolerability of pegaptanib sodium in subjects with DME.

METHODS

Study Design: This was an open-label, multicenter, non-comparative study, where approximately 500 subjects were to be enrolled and participate for ≤54 weeks.

Before Baseline Macugen (0.3 mg) treatment, each subject received a thorough ophthalmologic examination (ie, slit-lamp biomicroscopy, ophthalmoscopy, and tonometry) and a best corrected visual acuity (BCVA) test.

Following pre-treatment examinations, Macugen (0.3 mg) was intravitreally injected into the study eye of each subject. Additional injections were administered once every 6 weeks, as applicable. After the first 2 injections, Additional injections may have been administered less frequently than once every 6 weeks, as per investigator's discretion. Slit-lamp biomicroscopy, ophthalmoscopy, tonometry, and BCVA measurements were performed at each treatment visit.

Clinical benefit was evaluated after ≥2 injections. At the investigator's discretion, subjects who demonstrated a clinical benefit continued to receive intravitreal Macugen (0.3 mg) injections for ≤48 weeks. All time intervals between injections were at least 6 weeks.

Ocular and non-ocular adverse events (AEs) were closely monitored throughout the study, with a follow-up visit scheduled for 6 weeks after the last injection or early subject withdrawal from the study. The schedule of activities is provided in Table 1.

Table 1. Schedule of Activities

Protocol Activity	Screening Visit (Up to 7 Days Prior to Baseline Visit)	Baseline Visit	Treatment Visits	End of Treatment / Early Withdrawal Visit	Day + 3 Post Injection Telephone Follow-Up[a]	Follow-Up Visit (6 Weeks After End of Treatment or Early Withdrawal)
Informed consent	X					
Urine pregnancy test (if required in female subjects)[b]	X	X (pre-injection)	X (pre-injection)	X (pre-injection)		
General medical history	X					
History of diabetes mellitus	X					
Ophthalmologic medical history	X					
Blood pressure and pulse	X					
Visual acuity assessment (BCVA)	X	X (pre-injection)	X (pre-injection)	X (pre-injection)		X
Ophthalmologic examination[c]	X	X	X	X		X
Tonometry[d]	X	X	X	X		X
Enrollment	X					
Study treatment injection		X	X	X[e]		
AE monitoring		X	X	X	X	X
Concomitant medication	X	X	X	X		X

AE = adverse event; BCVA = best corrected visual acuity.

a. For sites in Italy, the Day 3 post injection follow-up telephone call was replaced by a Day 3 post injection subject site visit. A 2-day window was allowed starting on Day 3, allowing subjects to return to the site sometime between Day 3 and Day 5. The change was made to more closely monitor any potential post injection AEs.
b. Performed in all female subjects unless they were postmenopausal for ≥12 months prior to study start.
c. Included biomicroscopy and dilated fundus examinations.
d. Tonometry was performed once at Screening and the Follow-up visits and twice at each treatment visit (ie, before and ≥30 min after treatment injection).
e. Not applicable for early withdrawal subjects.

Number of Subjects (Planned and Analyzed): It was planned to recruit a total of 500 subjects. Fifty-five subjects were screened and a total of 46 subjects (5 in Finland, 25 in Spain, 8 in Sweden and 8 in the UK) were treated with Macugen prior to the early termination of the study.

Diagnosis and Main Criteria for Inclusion: Subjects with a documented clinical diagnosis of DME, with proliferative or non-proliferative diabetic retinopathy, who according to the clinical assessment of the investigator, could have benefited from anti-vascular endothelial growth factor (anti-VEGF) therapy. Subjects had to have distance BCVA in the study eye with a letter score between 78 and 24, inclusive (20/32 to 20/320 Snellen equivalents), and intraocular pressure (IOP) had to be ≤21 mm Hg. The treating investigator had to be comfortable that focal laser (ie, direct and grid as needed) could be deferred for ≥18 weeks in the study eye, even though focal or grid laser was indicated. Subjects had to have type 1 or type 2 diabetes as defined by the World Health Organization criteria, of either gender, be aged ≥18 years, and have clear ocular media and adequate papillary dilatation.

Study Treatment: Subjects were intravitreally injected with Macugen 0.3 mg at Baseline and at each treatment visit (once every 6 weeks) following urine pregnancy tests for applicable females, BCVA, biomicroscopy, and dilated fundus examinations in both eyes, and tonometry measurements. Study treatments were administered by ophthalmologists experienced in intravitreal injections using prefilled syringes. The procedure was performed under aseptic conditions: surgical hand disinfection, sterile gloves, a sterile drape, a sterile eyelid speculum (or equivalent), and the availability of sterile paracentesis (if required). The subject's medical history for hypersensitivity reactions was carefully evaluated prior to performing the intravitreal procedure. Adequate anesthesia and a broad-spectrum topical microbiocide were administered prior to the injection.

Transient increases in IOP have been observed in other clinical studies using Macugen intravitreal injections; therefore, perfusion of the optic nerve head and IOP were monitored closely. Subjects were closely monitored for endophthalmitis in the days following the injection. Subjects were instructed to report any symptoms suggestive of endophthalmitis without delay. Symptoms suggestive of endophthalmitis could have included the following: eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, and increased number of small particles in subject's vision.

Efficacy and Safety Endpoints:

Primary Endpoint:

- The incidence of AEs both ocular and non-ocular.

Secondary Endpoints:

- The incidence of serious adverse events (SAEs) both ocular and non-ocular.
- Mean total number of injections per subject.

- Mean changes in BCVA from Baseline to end of treatment.

Safety Evaluations: Included clinical monitoring, vital signs, ophthalmological examinations (including biomicroscopy and fundus examinations), applanation tonometry, AEs, and concomitant medications.

Statistical Methods:

Population Sets:

- Full Analysis Set (FAS): Defined as all subjects who received ≥1 dose of study medication. The FAS was the primary population of interest for efficacy data.

- Safety Analysis Set (SAS): Defined as all subjects received ≥1 dose of study medication. The SAS was the primary population of interest for safety data.

Efficacy Evaluations:

The BCVA scores and changes from Baseline in BCVA scores to each visit and to the end of treatment were reported using descriptive statistics (i.e, number [n], mean, median, standard deviation, range).

Safety Evaluations:

- IOP: The IOP at Baseline and final visit (prior to injection), and the change in IOP from Baseline to the final visit (prior to injection) were summarized using descriptive statistics (ie, n, mean, median, standard deviation, and range) for the study eye.

- AEs: The incidence of ocular and non-ocular AEs and SAEs were summarized descriptively.

- Other: Use of concomitant medications was summarized. The total number of injections received, the duration of study treatment, and the mean interval between injections were reported using descriptive statistics.

RESULTS:

Subject Disposition and Demography: As summarized in Table 2, 55 subjects were screened and 46 subjects were treated prior to early termination of the study. Overall, 12 subjects completed the study (12/46, 26.1%). A majority of subjects discontinued from the study due to non-AE discontinuations (32/46, 69.6%).

Table 2. Subject Disposition

Number (%) of Subjects	Macugen 0.3 mg (N=46)
Screened, N=55	
Assigned to study treatment	46 (100.0)
Treated	46 (100.0)
Completed	12 (26.1)
Discontinued from study	34 (73.9)
Non AE discontinuations	32 (69.6)
Did not meet entrance criteria	3 (6.5)
Insufficient clinical response	13 (28.3)
Lost to follow-up	1 (2.2)
No longer willing to participate in study	6 (13.0)
Other	8 (17.4)
Protocol violation	1 (2.2)
Related to study drug	1 (2.2)
AE	1 (2.2)
Not related to study drug	1 (2.2)
AE	1 (2.2)

AE = adverse event; N = number of subjects.

All subjects were analyzed for efficacy and safety**.** Overall, most subjects were male (30/46, 65.2%), White (42/46, 91.3%), and between 51 and 75 years old (35/46, 76.1%). Demographic characteristics are summarized in Table 3.

Table 3. Demographic Characteristics

Parameter	Macugen 0.3 mg (N=46) n (%)		
	Male	**Female**	**Total**
Number of subjects	30 (65.2)	16 (34.8)	46 (100.0)
Age (years)			
≤50	3 (10.0)	0	3 (6.5)
51-64	14 (46.7)	7 (43.8)	21 (45.7)
65-75	9 (30.0)	5 (31.3)	14 (30.4)
≥75	4 (13.3)	4 (25.0)	8 (17.4)
Mean [SD]	63.4 [10.5]	68.1 [10.4]	65.0 [10.6]
Range	37-80	52-88	37-88
Race			
White	28 (93.3)	14 (87.5)	42 (91.3)
Black	1 (3.3)	0	1 (2.2)
Asian	1 (3.3)	1 (6.3)	2 (4.3)
Other	0	1 (6.3)	1 (2.2)

n = number of subjects meeting predefined criteria; N = number of subjects; SD = standard deviation.

Efficacy Results:

Mean BCVA scores increased markedly at Week 6 compared with Baseline scores and generally remained constant or slowly increased throughout the study as summarized in Table 4.

Table 4. Mean BCVA Scores by Study Visit (FAS Population)

Study Visit	n (%)	Macugen 0.3 mg (N=46) Mean [SD]
Baseline	42 (91.3)	58.9 [16.5]
Week 6	36 (78.3)	63.1 [14.1]
Week 12	34 (73.9)	63.4 [13.2]
Week 18	32 (69.6)	60.6 [16.5]
Week 24	22 (47.8)	65.6 [12.7]
Week 30	20 (43.5)	65.1 [10.7]
Week 36	12 (26.1)	62.3 [11.7]
Week 40	11 (23.9)	66.6 [10.8]
Week 48	14 (30.4)	65.0 [12.2]
Week 54	5 (10.9)	68.6 [11.8]
>Week 54	1 (2.2)	78.0 [NA]
Final visit	42 (91.3)	63.4 [13.1]

The BCVA score was analyzed using the visit windows.
If subjects were unable to read letters at either 4.0 meters or 1 meter then the BCVA score was recorded as 0. Subjects with a 0 BCVA score were excluded from the descriptive summary; 1 subject had a BCVA score of 0 at Baseline, Week 12, Week 18 and Week 30. One subject had a BCVA score of 0 at Baseline and Week 12.
BCVA = best corrected visual acuity; FAS = full analysis set; n = number of subjects meeting predefined criteria; NA = not available or not applicable; N = number of subjects; SD = standard deviation.

Safety Results:

Incidence of AEs and SAEs: Incidence of AEs is summarized in Table 5.

Table 5. Summary of Treatment-Emergent Adverse Events (Safety Population)

Number (%) of Subjects or Parameter	Macugen 0.3 mg (N=46)	
	All Causality	Treatment-Related
Subjects evaluable for AEs	46 (100.0)	46 (100.0)
Number of AEs	37	5
Subjects with AEs	16 (34.8)	4 (8.7)
Subjects with SAEs	3 (6.5)	0
Subjects with severe AEs	2 (4.3)	0
Subjects discontinued due to AEs	2 (4.3)	1 (2.2)
Subjects with dose reduced or temporary discontinuation due to AEs	1 (2.2)	1 (2.2)

Included data up to 30 days after last dose of study drug.
Except for the number of AEs subjects were counted only once per treatment in each row.
SAEs-according to the investigator's assessment
AE = adverse event; n = number of subjects meeting predefined criteria; N = number of subjects; SAE = serious adverse event.

The summary of treatment-emergent non-serious AEs by System Organ Class and preferred term are presented in Table 6.

Table 6 Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate Greater Than or Equal to 0

	Macugen 0.3 mg n (%)
Number (%) of Subjects with Adverse Events by:	
System Organ Class	
MedDRA (v15.0) Preferred Term	
Blood and lymphatic system disorders	1 (2.2)
Anaemia	1 (2.2)
Eye disorders	10 (21.7)
Cataract	1 (2.2)
Conjunctival haemorrhage	1 (2.2)
Conjunctival hyperaemia	1 (2.2)
Conjunctivitis	1 (2.2)
Eye discharge	1 (2.2)
Eye pain	1 (2.2)
Eye pruritus	1 (2.2)
Eyelid ptosis	1 (2.2)
Macular oedema	3 (6.5)
Maculopathy	1 (2.2)
Uveitis	1 (2.2)
Visual acuity reduced	2 (4.3)
Vitreous floaters	1 (2.2)
Gastrointestinal disorders	3 (6.5)
Diarrhoea	1 (2.2)
Gastric polyps	1 (2.2)
Gastrointestinal hypermotility	1 (2.2)
Hiatus hernia	1 (2.2)
General disorders and administration site conditions	1 (2.2)
Asthenia	1 (2.2)
Infections and infestations	2 (4.3)
Gastroenteritis	1 (2.2)
Upper respiratory tract infection	1 (2.2)
Investigations	3 (6.5)
Biopsy vocal cord	1 (2.2)
Carcinoembryonic antigen increased	1 (2.2)
Intraocular pressure increased	1 (2.2)
Nervous system disorders	1 (2.2)
Headache	1 (2.2)
Psychiatric disorders	1 (2.2)
Anxiety	1 (2.2)
Renal and urinary disorders	1 (2.2)
Renal colic	1 (2.2)
Respiratory, thoracic and mediastinal disorders	2 (4.3)
Cough	1 (2.2)
Wheezing	1 (2.2)
Skin and subcutaneous tissue disorders	1 (2.2)
Skin reaction	1 (2.2)
Vascular disorders	1 (2.2)
Hypertension	1 (2.2)

Table 6 Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate Greater Than or Equal to 0

	Macugen 0.3 mg n (%)
Number (%) of Subjects with Adverse Events by:	
System Organ Class	
MedDRA (v15.0) Preferred Term	

Subjects were only counted once per treatment for each row.
Included data up to 30 days after last dose of study drug.
MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects meeting predefined criteria; v = version.

Three subjects had at least 1 treatment-related ocular AE. One subject had a non-ocular treatment-related AE. The summary of treatment-emergent treatment-related AEs are presented in Table 7.

Table 7. Incidence and Severity of Treatment-Emergent Treatment-Related Adverse Events; Safety Population)

Number (%) of Subjects MedDRA Preferred Term	Macugen 0.3 mg (N=46) Severity Treatment-Related			
	Mild	Moderate	Severe	Total
Ocular AEs	2	2	0	4
Vitreous floaters	1	0	0	1
Cataract	1	0	0	1
Intraocular pressure increased	0	1	0	1
Uveitis	0	1	0	1
Non Ocular AEs	1	0	0	1
Wheezing	1	0	0	1

The SAEs/AEs are not separated out.
If the same subject in a given treatment had more than 1 occurrence in the same preferred term event category, only the most severe occurrence was taken. Subjects were counted only once per treatment in each row. For the TESS algorithm any missing severities were imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity was summarized. Missing Baseline severities were imputed as mild. Included data up to 30 days after last dose of study drug. When a dictionary other than MedDRA was used, percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (version 15.0) coding dictionary was applied.
Data in the table included serious AEs.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; TESS = treatment-emergent signs and symptoms; SAEs = serious adverse events; v = version.

No treatment-related hypersensitivity AEs were reported. Three subjects had SAEs which were unrelated to study treatment as summarized in Table 8.

Table 8 Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate Greater Than or Equal to 0

Number (%) of Subjects with Adverse Events by:System Organ Class and MedDRA (v15.0) Preferred Term	Macugen 0.3 mg n (%)
Cardiac disorders	1 (2.2)
Myocardial infarction	1 (2.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (2.2)
Lung neoplasm malignant	1 (2.2)
Nervous system disorders	1 (2.2)
Cerebrovascular accident	1 (2.2)

Subjects were only counted once per treatment for each row.
Included data up to 30 days after last dose of study drug.
MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects meeting predefined criteria; v = version.

Two subjects discontinued due to AEs; 1 due to a mild treatment-related cataract and 1 due to a mild treatment unrelated cataract. Both events resolved. One subject had a dose reduction due to an AE of mild wheezing which resolved. No deaths were reported in this study.

Mean total number of injections: Overall, the total mean number of injections in all subjects was 3.2, with a median of 3.0, and a range of 1.0 to 6.0. The mean duration of study treatment was 17.7 weeks, with a median of 13.6 weeks, and a range of 0 to 49.4 weeks. The mean interval between injections was 7.7 weeks, with a median of 6.5 weeks, and a range of 5.3 to 16.5 weeks. The extent of exposure is summarized in Table 9.

Table 9. Extent of Exposure

Parameter		Macugen 0.3 mg (N=46)
Total Number of Injections, n (%)		46 (100.0)
Mean [SD]		3.2 [1.0]
Median		3.0
Range		1.0-6.0
Duration of Study Treatment (Weeks), n (%)	46 (100.0)	
Mean [SD]		17.7 [11.1]
Median		13.6
Range		0-49.4
Interval Between Injections (Weeks), n (%)	44 (95.7)	
Mean [SD]		7.7 [2.6]
Median		6.5
Range		5.3-16.5

Duration of treatment per subject was calculated in weeks as: (date of the last injection of Macugen-date of the first injection of Macugen) / 7).
Mean interval between injections was calculated as: duration of treatment (in weeks) / (number of Macugen injections administered per subject-1).
n = number of subjects meeting predefined criteria; N = number of subjects; SD = standard deviation.

Intraocular Pressure:

No clinically significant mean changes in IOP were observed from Baseline to >Week 54 as summarized in Table 10.

Table 10 Mean Intraocular Pressures by Study Visit

Study Visit	n (%)	Macugen 0.3 mg (N=46) Mean [SD]
Baseline	45 (97.8)	15.9 [2.6]
Week 6	34 (73.9)	15.7 [2.8]
Week 12	35 (76.1)	15.5 [2.6]
Week 18	32 (69.6)	15.9 [2.8]
Week 24	23 (50.0)	15.9 [2.2]
Week 30	22 (47.8)	15.9 [2.6]
Week 36	14 (30.4)	16.8 [2.9]
Week 40	10 (21.7)	16.3 [3.2]
Week 48	14 (30.4)	15.5 [2.7]
Week 54	5 (10.9)	14.6 [2.1]
>Week 54	1 (2.2)	15.0 [0]
Final visit	46 (100.0)	16.3 [2.4]

Mean visit results were used for visit summaries and change from Baseline summaries.
One subject discontinued after the Baseline visit therefore the Baseline visit and the final visit were the same visit (ie, both taking place on study Day 1).
At the final visit, the change from Baseline mean visit result for the final mean visit result only included subjects who had the final visit data after study Day 1.
n = number of subjects meeting predefined criteria; N = number of subjects; SD = standard deviation.

CONCLUSIONS:

The safety and tolerability of Macugen in subjects with DME was clearly demonstrated in this study:

- Mean BCVA scores increased markedly at Week 6 compared with Baseline scores and generally remained constant or slowly increased throughout the study.
- Of the 16 subjects who experienced treatment-emergent AEs (34.8%), only 4 experienced treatment-related AEs (8.7%) and all were mild or moderate in severity.
- No subjects died, had treatment-related SAEs, severe AEs, or hypersensitivity AEs; and no clinically significant mean changes in IOP were observed during the study.