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

PROTOCOL NO.: A5751011 (EOP1011B)

PROTOCOL TITLE: A Phase II Randomized, Dose-Ranging, Double-Masked, Multi-Center Trial, in Parallel Groups, to Determine the Safety, Efficacy and Pharmacokinetics of Intravitreous Injections of Pegaptanib Sodium Compared to Sham Injection for 30 Weeks in Patients With Recent Vision Loss Due to Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO).

Other Endpoints:

- Difference in change from Baseline mean Optical Coherence Tomography (OCT) center point value between sham and 0.3 mg at 30 weeks and between sham and 1 mg at 30 weeks.
- OCT data over time - a repeated measure analysis which utilized all of OCT center point values over time was performed to compare between sham and each dose group.
- The proportion of eyes developing retinal or iris neovascularization postbaseline before Week 30 for each dose group.
- The proportion of eyes requiring laser photocoagulation at any time postbaseline before Week 30 for each dose group.
- The change in mean area of macular edema determined from fluorescein angiography at 30 weeks for each dose group.
- The change in mean area of capillary non-perfusion determined from fluorescein angiography at 30 weeks for each dose group.
- The change in mean center point retinal thickness as determined by grading of the color photographs for each dose group.
- Population pharmacokinetics (PKs) was assessed in subjects participating in this trial.

Statistical Methods:

Other Endpoints Analysis: Descriptive statistics of the efficacy endpoints over time and change from Baseline whenever appropriate was presented for the 3 treatment groups

(0.3 mg, 1 mg and sham). Analysis of mean change in visual acuity (VA) from Baseline up to Week 30 between 0.3 mg, 1 mg and sham was performed using an analysis of covariance model. The model included main effects of treatment and stratification factors used at randomization, ie. vision at randomization (>34 vs 34 letters). The difference between the mean changes in VA score was estimated and its 95% confidence intervals was reported as a measure of the treatment effect.

Analysis of change in OCT retinal thickness at center point from Baseline to Week 30, analysis of change in OCT retinal thickness at center subfield from Baseline to Week 30, analysis of change in OCT volume from Baseline to Week 30, analysis of change in mean area of macular edema, change in mean area of capillary non-perfusion was the same as that was used for the mean change in VA, except that Baseline covariate was the corresponding OCT value at Baseline.

RESULTS:

Other Endpoint Results:

- Mean Change From Baseline in OCT Retinal Thickness at Center Point: A summary of the mean change in OCT center point value is shown in Table 1. Mean decrease from Baseline in retinal thickness at center point was greater in both pegaptanib treatment arms than in the sham arm at all time points, although this difference was not significant compared with sham.

Table 1. Mean Change in OCT Retinal Thickness at Week 30

ITT Population Week 30 Endpoints	Pegaptanib		
	0.3 mg	1 mg	Sham
	N=33	N=33	N=32
Mean OCT retinal thickness at center point at Baseline	686.8	642.1	674.4
Mean change at Week 6	-171.6	-131.3	-80.0
Mean change at Week 12	-175.0	-153.1	-94.6
Mean change at Week 30	-252.6	-185.7	-151.2

ITT = intent-to-treat; N = number of subjects; OCT = optical coherence tomography.

All groups showed an early and sustained decline in OCT-measured central retinal thickness. The greatest mean reduction in retinal thickness was seen in the 0.3 mg arm. Mean reduction in retinal thickness at the center point from Baseline to Week 30 was 101 μm lower in the 0.3 mg arm compared with sham. At the center subfield the difference in reduction of retinal thickness was 106 μm lower in the 0.3 mg arm compared with sham.

- OCT Data Over Time: OCT changes over time are summarized in Table 2 for the center point.

Table 2. Summary of Changes in Retinal Thickness From Baseline Over Time

ITT Population Week 30 Endpoints	Pegaptanib		
	0.3 mg	1 mg	Sham
	N=33	N=33	N=32
Mean Baseline retinal thickness[a]	686.8	642.1	674.4
Mean change at Week 6	-185	-141	-86.0
Mean change at Week 12	-188	-152	-123
Mean change at Week 18	-184	-190	-149
Mean change at Week 24	-203	-198	-159
Mean change at Week 30	-286	-181	-168

ITT = intent-to-treat; N = number of subjects.
a. Day 0 data were used as Baseline values. If Day 0 was missing, then Screening data were used.

- The Proportion of Eyes Developing Retinal or Iris Neovascularization: Very few subjects developed retinal or iris neovascularization during the study period (6% of subjects overall) although it occurred slightly more frequently in the sham arm (9%) than in either of the pegaptanib treatment arms (3% in the 0.3 mg arm and 6% in the 1 mg arm; Week 30 analysis Table 3).

Table 3. Proportion of OCT Responders (a Decrease of ≥30% in Baseline Center Point Thickness) at Week 30 (LOCF Data)

ITT Population Week 30 Endpoints	Pegaptanib		
	0.3 mg	1 mg	Sham
	N=33	N=33	N=32
Retinal or iris neovascularization			
Yes	1 (3%)	2 (6%)	3 (9%)
No	32 (97%)	31 (94%)	29 (91%)
Estimates of the Odds Ratio and CMH Test[a]			
	Odds Ratio	**95% CI**	**p-Value[b] (CMH)**
Retinal or iris neovascularization (Treatment comparison)			
0.3 mg vs Sham	0.30	(0.03, 3.07)	0.2910
1 mg vs Sham	0.62	(0.10, 4.00)	0.6189

CMH = Cochran-Mantel-Haenszel; CI = confidence interval; ITT = intent-to-treat; LOCF = Last Observation Carried Forward; N = number of subjects; OCT = optical coherence tomography; vs = versus.
a. CMH test adjusted for Baseline vision.
b. For pairwise comparison, not adjusted for multiple comparisons.

- The Proportion of Eyes Requiring Laser Photocoagulation: Seven subjects overall (7%) required laser photocoagulation during the study period. This included 2 subjects (6%) each in the pegaptanib 0.3 mg and 1 mg arms and 3 subjects (9%) in the sham arm (Week 30 analysis Table 4.

Table 4. Proportion of Eyes Requiring Laser Photocoagulation at Any Time Postbaseline And Before Week 30 - Study Eye

ITT Population Week 30 Endpoints	Pegaptanib		
	0.3 mg	1 mg	Sham
	N=33	N=33	N=32
Eyes requiring laser photocoagulation			
Yes	2 (6%)	2 (6%)	3 (9%)
No	30 (94%)	30 (94%)	29 (91%)
Estimates of Odds Ratio and CMH Test[a]			
	Odds Ratio	**95% CI**	**p-Value[b] (CMH)**
Proportion of Eyes (Treatment comparison)			
0.3 mg vs Sham	0.64	(0.10, 4.14)	0.6657
1 mg vs Sham	0.64	(0.10, 4.14)	0.6542

CMH = Cochran-Mantel-Haenszel; CI = confidence interval; ITT = intent-to-treat; N = number of subjects; vs = versus

a. CMH test adjusted for Baseline vision.
b. For pairwise comparison, not adjusted for multiple comparisons.

- Fluorescein Angiography Endpoints: Mean change in area of macular edema by fluorescein angiography is summarized in Table 5. There were no significant differences in the mean change in area of macular edema between the treatment arms.

Table 5. Mean Change in Area of Macular Edema at Week 30

ITT Population Week 30 Endpoints	Pegaptanib		
	0.3 mg	1 mg	Sham
	N=33	N=33	N=32
Central subfield			
Mean area of macular edema at Baseline	0.4	0.4	0.4
Change at Week 30	-0.1	-0.1	-0.1
Central subfield and inner subfields			
Mean area of macular edema at Baseline	3.4	3.5	3.2
Change at Week 30	-0.4	-0.5	-0.7
Whole macular grid including central, inner and outer subfields			
Mean area of macular edema at Baseline	10.3	10.6	9.8
Change at Week 30	-2.5	-2.6	-2..1

ITT = intent-to-treat; N = number of subjects.

Mean change in area of capillary non-perfusion by fluorescein angiography is summarized in Table 6. The differences in mean change in area between the treatment arms were not statistically significant.

Table 6. Mean Changes in Area of Capillary Non-Perfusion Determined From Fluorescein Angiography at Week 30 - Study Eye (LOCF Data)

ITT Population Week 30 Endpoints	Pegaptanib		
	0.3 mg	1 mg	Sham
	N=33	N=33	N=32
Mean Basline	0.0	0.1	0.3
Mean Change at Week 30	0.0	0.1	0.2
Change From Baseline (ANCOVA Model)[a]			
Up to Week 30			
N	21	24	24
Mean	0.04	0.12	0.24
LSMean (S.E)	0.04 (0.09)	0.10 (0.09)	0.18 (0.09)
Difference[b]	-0.14	-0.08	-
95% CI	(-0.39, 0.11)	(-0.32, 0.16)	-
p-value[c]	0.2630	0.4926	-

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; LOCF = Last Observation Carried Forward; LSMean = least square mean; N = number of subjects; S.E = standard error.

a. Adjusted for Baseline vision.
b. Difference in least square means between each dose group and sham.
c. P-values of pairwise comparisons, unadjusted for multiplicity.

- Change in Mean Center Point Retinal Thickness: The change in center point retinal thickness from Baseline to Week 30, as assessed by retinal vein occlusion grading, is summarized in Table 7 Week 30 Analysis. A greater proportion of subjects in the pegaptanib treatment arms experienced a decrease in retinal thickness of 2 degrees or more (19% in the 0.3 mg arm, 26% in the 1 mg arm and 10% in the sham arm). The difference was not statistically significant.

Table 7. Change in Center Point Retinal Thickening By RVO Grading[a] From Baseline to Week 30 (LOCF)

		Week 30 Degree (LOCF Data)					
Treatment	**Baseline Degree**	**Absent**	**Questionable**	**< 1x ref.**	**< 2x ref.**	**≥2x ref.**	**Total**
0.3 mg	Absent	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Questionable	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	< 1x reference	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
	< 2x reference	3 (10%)	1 (3%)	2 (6%)	16 (52%)	2 (6%)	24 (77%)
	≥2x reference	0 (0%)	0 (0%)	1 (3%)	4 (13%)	1 (3%)	6 (19%)
	Total	4 (13%)	1 (3%)	3 (10%)	20 (65%)	3 (10%)	31 (100%)
1 mg	Absent	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Questionable	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	< 1x reference	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	< 2x reference	3 (10%)	2 (6%)	2 (6%)	17 (55%)	0 (0%)	24 (77%)
	≥2x reference	0 (0%)	2 (6%)	1 (3%)	3 (10%)	1 (3%)	7 (23%)
	Total	3 (10%)	4 (13%)	3 (10%)	20 (65%)	1 (3%)	31 (100%)
Sham	Absent	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Questionable	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	< 1x reference	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	1 (3%)
	< 2x reference	3 (10%)	0 (0%)	1 (3%)	19 (61%)	4 (13%)	27 (87%)
	≥2x reference	0 (0%)	0 (0%)	0 (0%)	2 (6%)	1 (3%)	3 (10%)
	Total	3 (10%)	0 (0%)	1 (3%)	22 (71%)	5 (16%)	31 (100%)

Number of Subjects	**0.3 mg**	**1 mg**	**Sham**
	N=33	**N=33**	**N=32**
Subjects with ≥2 degrees decrease			
Yes	6 (19%)	8 (26%)	3 (10%)
No	25 (81%)	23 (74%)	28 (90%)

Estimates of the Odds Ratio and Cochran-Mantel-Haenszel (CMH) Test[b]

	Odds Ratio	**95% Confidence Interval**	**p-Value[c] (CMH)**
Subjects with ≥2 degrees decrease			
0.3 mg vs Sham	2.24	(0.51, 9.91)	0.2599
1 mg vs Sham	3.25	(0.77, 13.66)	0.1063

CMH = Cochran-Mantel-Haenszel; LOCF = Last Observation Carried Forward; N = number of subjects; ref = reference; RVO = retinal vein occlusion.

a. Data from University of Wisconsin Fundus Photograph Reading Center.
b. CMH test adjusted for baseline vision.
c. For pairwise comparison, not adjusted for multiple comparisons.

- PK Analysis: A comparison of plots from subjects receiving 0.3 and 1.0 mg doses indicated a dose dependent increase in plasma pegaptanib. While there was considerable variation among subjects, it appeared that the concentration profiles after the fourth dose were not consistently different from those after the first dose, suggesting little or no accumulation of pegaptanib with every 6 week dosing. The protocol-specified analyses were not performed.