CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-119

STATISTICAL REVIEW(S)

Statistical Review

NDA21-119
Name of Drug: VISUDYNE (BPD- MA Verteporfin for injection)
Applicant: QLT Phototherapeutics Inc.
Indication: For the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration
Documents Reviewed: Statistical sections of NDA
Reviewer: Qian Li, Sc.D.
Date of Review: September 1999-November 1999

I. Introduction:

Age-related macular degeneration (AMD) is a degenerative eye disease with increasing prevalence at older ages. The majority of patients have the nonneovascular form of the disease. However, most of the severe vision loss attributable to this disease is related to the neovascular form, characterized by chorodial neovascularization (CNV).

This NDA pursues market approval of photo-dynamic therapy (PDT) using intravenous injection of verteporfin. This therapy consists of two steps, intravenous injection of verteporfin and light irradiation. verteporfin 6 mg/m2 diluted in 30 mL of Dextrose 5% in water or placebo was administrated intravenously for 10 minutes followed by light application after 15 minutes of the start of infusion. Two types of light delivery device system were used, the Coherent Ocular Photoactivation Diode Laser system and the Zeiss VISULAS PDT Diode Laser system.

Evidence has shown that PDT with verteporfin leads to tumor death via occlusion of the vasculature feeding the tumor, as well as its direct cytotoxic effect on tumor cells. It is hypothesized in this NDA that the PDT with verteporfin will result in the occlusion of CNV, and the occlusion of CNV was directly associated with slowing deterioration of visual acuity for patients with CNV secondary to AMD. Therefore, the primary interest of this NDA is to show any difference in visual acuity after verteporfin therapy vs. placebo. The intended efficacy claim in label from sponsor is that verteporfin therapy is indicated for the treatment of age-related macular degeneration in patients with predominantly classic subfoveal chorodial neovascularization.

Two multi-center, randomized, double blinded, placebo controlled phase III studies, Studies BPD OCR 002 A and B (Referred to as Studies A and B), were conducted to test the treatment difference between verteporfin and placebo in visual acuity on patients with subfoveal CNV secondary to AMD. A health-related quality of life (HQL) study was amended to studies A and B to study the impact of verteporfin and placebo therapies using the National Eye Institute's Visual Functioning Questionnaire-25. In this statistical review, the two studies will be the focus of reviewing efficacy claim, followed by the review of HQL result.

II. Studies BPD OCR 002 A and B:

Both Studies A and B followed exact the same protocol. The primary objective was to demonstrate that verteporfin therapy to patients with subfoveal CNV secondary to AMD would significantly reduce vision loss compared to placebo.

Randomization was in a 2:1 ratio (verteporfin to placebo) and stratified by center and baseline visual acuity. There were 22 centers in total (10 in Study A and 12 in Study B), the VA stratification was 54-73 letters (approximately 20/40-20/80) and 34-53 letters (approximately 20/100-20/200). One eye per patient was treated. The total planned treatment duration was 24 months. Data at Month 12 was analyzed for this NDA submission. Patients received retreatment if evidence of CNV leakage was detected by fluorescein angiography in the intervals of 3 months.

Efficacy Variables:
The primary efficacy variable was the proportion of responders, which was defined as patients who loss less than 15 letters of BCVA from baseline.

The secondary efficacy variables were

- proportion of patients who loss less than 30 letters of BCVA from baseline,
- proportion of patients whose visual acuity score decrease to fewer than 34 letters in the study eye,
- time until a patient had a decrease from baseline of 15 or more letters of BCVA in the study eye,
- time until a patient had a decrease from baseline of 30 or more letters of BCVA in the study eye,
- Time until a patient's BCVA score decrease to fewer than 34 letters in the study eye,
- Change from baseline in the BCVA score in the study eye,
- The mean change from baseline for the number of letters scored from the Pelli-Robson chart for assessment of contrast sensitivity,
- Extent of fluorescein leakage from classic and occult CNV compared with baseline fluorescein angiography gradings as assessed by the photograph reading ceter,
- CNV lesion size compared with baseline was assessed for each of the three lesion size measurements: including natural scar and obscuring features, surrounding atrophy from treatment, greatest linear dimension of the leaking CNV.

Analysis population:
Two analysis populations were defined in analysis plan. Intent-to-treat (ITT) population included all randomized patients. Evaluable patients included all patients who received the treatments, meet the inclusion/exclusion criteria, and adhere to the protocol without significant deviation.

Statistical Analyses:

The primary efficacy analysis of response was based on the proportion of responders at the 12-month visit using ITT population with LOCF for missing data imputation. Comparison between treatment groups was made using a chi-square test.

Logistic regression analysis was also performed as a confirmatory analysis with covariates including treatment, baseline visual acuity, and other clinically significant baseline variables. Cox's proportional hazard model was used to analyze time to event data.

Fourteen variables were used independently to form many subgroups for further analyses. The variables were:

1) Study Center,
2) Age (<75 years vs. ≥75),
3) Gender (female vs. female),
4) Race (was not used because the majority was Caucasians),
5) Iris Color (dark, light, unknown),
6) Baseline visual acuity (stratum 1 vs. Stratum 2),
7) Size of lesion at Baseline in MPS disk areas,
8) percent of classic CNV at baseline (≥50%, <50%, questionable+no)
9) Presence of occult CNV at baseline (yes+questionable, no)
10) Presence of blood at baseline (yes+questionable, no)
11) Presence of fibrosis at baseline (0-25%, 26-50%, >50%)
12) Baseline hypertension (definite vs. all others)
13) cigarette smoking (non-smoker, current smoker, previous smoker)
14) Lesion (new vs. recurrent)

Results of Study A:

Study A included 10 centers (6 in North America and 4 in Europe) and a total of 311 patients. Patient disposition information was summarized in Table 1A.

The demographic information between the two treatment groups was balanced except gender. There was significantly higher proportion of female in placebo treatment group (p=0.005). For baseline disease and lesion characteristics assessed by Photograph Reading Center, there were more patients who had laser photocoagulation scar in placebo than in verteporfin treatment group (p=0.057). There were somewhat imbalances in medical history information, such as the body systems in gastrointestinal, head-ear-eyes-nose-throat and others.

<u>Patients who had fewer than 15 letters decrease from baseline:</u>

Overall, all the analyses on the primary efficacy variable have shown statistically significant treatment difference in favor of verteporfin therapy. The Chi-square test at Month 12 with LOCF yielded p-value 0.018 and 14% treatment difference in proportion.

Similar result was found without LOCF imputation (treatment difference=15.9%, p=0.010 at Month 12). Evaluable analysis also yielded the similar results by Chi-square test (difference=16.6%, p=0.011). Logistic regression analysis adjusting baseline visual acuity and gender showed treatment difference in odds ratio 1.901 with p-value 0.009 in favor of verteporfin treatment group. Survival analysis using Cox's proportional hazard model controlling baseline visual acuity and center also showed that verteporfin treatment group prolonged the occurrence of 15 letter decreasing as compared with placebo treatment group. The risk ratio between the two treatment groups (verteporfin vs. placebo) was 0.704 with p-value 0.036.

Patients who had fewer than 30 letters decrease from baseline:

The proportional difference was small and was not statistically significant by both ITT and evaluable analyses. The proportional difference between verteporfin and placebo was only 5.4% at Month 12 with p-value 0.232 by ITT analysis. However, survival analysis of time to 30 letter decrease did show statistical significant difference in favor of verteporfin therapy (risk ratio =0.568 p-value=0.022).

Other analyses:

The analysis of the majority secondary efficacy variables yielded results that supported the primary analyses, except that the analysis of the extent of fluorescein leakage from occult CNV did not show treatment benefit from verteporfin therapy. All the analyses on evaluable patients yielded very similar results to the ITT analyses.

Subgroup analyses:

Results of subgroup analyses for the primary variable on ITT population were summarized in Table 2A. The majority subgroups had shown positive trend of verteporfin therapy over placebo treatment except three subgroups – patients who had unknown iris color, recurrent lesion, and less than 50% classic component of CNV. The negative treatment differences were not statistically significant in the three subgroups The two subgroups, unknown iris color and recurrent lesion, had actually very small sample sizes.

Also from Table 2A, several subgroups have shown statistical significant (at level 0.05) treatment difference between verteporfin therapy and placebo. Those subgroups included worse stratum of baseline visual acuity, <75 years age group, men, light iris color, over 50% of classic CNV at baseline, no occult CNV at baseline, definite presence of hypertension at baseline, and new lesion.

Extended analyses were performed on predominantly classic CNV subgroup (86 in verteporfin and 41 in placebo) on the secondary efficacy variables as well. All the analyses showed larger treatment differences than that in whole group analyses.

Results of Study B:

Study B included 12 centers (7 in North America and 5 in Eroupe) and a total of 298 patients. Patient disposition information was summarized in Table 1B.

The verteporfin and placebo treatment groups were similar with regard to the demographic information, baseline disease and lesion characteristics. However, in medical history, there were more patients in verteporfin treatment group who had experienced dermatologic and pulmonary problems in the past.

Patients who had fewer than 15 letters decrease from baseline:

Overall, all the analyses on this primary variable were statistically significant in favor of verteporfin. Chi-square test with LOCF at Month 12 yielded p-value 0.010 and treatment difference 15.6%. Chi-square test without LOCF at Month 12 also yielded similar results (p=0.013 and treatment difference=15.7%). Chi-square test on evaluable population showed similar results as well (p=0.010, treatment difference=16.7%). Logistic regression analysis adjusted by baseline visual acuity stratum yielded p-value 0.009 and odds ratio 1.927 in favor of verteporfin treatment group. Survival analysis using Cox proportional hazard model controlling baseline visual acuity and center also showed statistically significant improvement of verteporfin treatment over placebo (p=0.007, risk ratio of verteprofin vs. placebo=0.624).

Patients who had fewer than 30 letters decrease from baseline:

Chi-square test on ITT population at Month 12 yielded p-value 0.007 and treatment difference 12.9% in favor of verteporfin treatment group. Survival analysis using Cox proportional hazard model also showed statistically significant improvement of verteporfin treatment group over placebo (p=0.007 and risk ratio=0.485).

Other analyses:

All the other secondary analyses on the secondary efficacy variables showed statistically significant improvement of verteporfin over placebo treatment at 0.05 level. The analyses on evaluable population yielded very similar results as the ITT analyses.

Subgroup analyses:

The results of subgroup analyses were summarized in Table 2B. In this table, several subgroups have shown statistical significant (at level 0.05) treatment difference in favor of verteporfin therapy. Those subgroups included light iris color, over 50% of classic CNV at baseline, no presence of occult CNV, no presence of blood at baseline, 0 to 25% of fibrosis at baseline, not definite presence of hypertension at baseline, previous smoker and new lesion.

Extended analyses were also performed on predominantly classic CNV subgroup (73 in verteprofin and 43 in placebo) on the secondary efficacy variables. These subgroup analyses also showed larger treatment differences than that in whole group analyses.

III. Comments and Conclusion:

Overall treatment effect assessed by 15 letter decrease:

The overall treatment effect of verteporfin group was consistent and robust in comparison with placebo treatment group. However, the size of treatment difference was not as large as it was expected. It was expected in the protocol that there was above 20% treatment difference in the proportion of patients who had less than 15 letters decrease from baseline at Month 12. The observed overall treatment difference was 14.8% with 95% CI [6.5%, 23.1%] combining both Studies A and B (14.0% in Study A and 15.6% in Study B).

Overall treatment effect assessed by 30 letter decrease:

The results based on 30 letter decrease were not consistent between the two studies. The estimated treatment difference in proportion was 5.4% percent in Study A, while 12.9% in Study B, at Month 12. Compared to the treatment difference in15 letter decrease, the treatment effect was smaller in 30 letter decrease than that assessed in 15 letter decrease. This result suggested there might be less treatment difference in severe visual acuity loss.

Subgroup analyses:

Since the results of the primary analyses were positive and supported the efficacy claim of verteporfin treatment, the purpose of subgroup analyses was to identify a set of subgroups that can benefit the most from the treatment. To facilitate the review, the integrated results of the subgroup analyses that combined Studies A & B were listed in Table 3.

As it was specified in the analysis plan, 14 variables were used independently to form subgroups. Excluding center and race subgroups, there were about 35 subgroups in total. Obviously, multiplicity adjustment was needed to fairly evaluate the subgroup results. Since no multiplicity adjustment was planned in the protocol and analysis plan, Bonferroni correction was used in this review. If the overall significance level is set at 0.05, the significance level of the individual integrated subgroup analysis becomes 0.0014 after Bonferroni correction.

In addition to the adjusted significance level, the results between the two studies had to be reasonably consistent. This is to avoid the case that one subgroup was very significant in one study while was not in the other study. The subgroup has to have reasonable sample size, neither too small to have valid results nor too large to present a subgroup.

Also there should be significant treatment by subgroup interaction. Significant subgroup by treatment interaction is another factor for assessing subgroup treatment effect.

By applying the aforementioned criteria, two subgroups were identified to have consistently larger treatment effects compared with the whole group. The two subgroups were patients who had predominantly classic CNV and who had no presence of occult CNV component. Note the subgroup that had no presence of occult CNV was a subset of predominantly classic CNV. From Table 3, the observed overall treatment difference in predominantly classic CNV subgroup was 28% in favor of verteporfin treatment with p-value <0.001. The observed overall treatment difference in no occult CNV subgroup was 46% with p-value <0.001. This suggests that the less occult component in CNV presented at baseline, the better treatment effect could be.

Gender imbalance in Study A:

In study A, gender was distributed unevenly between the two treatment groups. There was higher proportion of male in verteporfin treatment group than that in placebo group. However, gender was unlikely to be a confounding factor of treatment difference between treatment groups. As it was showed in Study B, there was a reasonable balance in gender and the treatment difference was replicated in Study B. It was observed in both studies, females had higher response rate regardless treatment groups in comparison with male patients. Such gender difference could reduce treatment difference since there were more females in placebo group in Study A.

Stratified analysis:

Since center and baseline visual acuity were stratification factors for randomization, a stratified analysis was also performed. The result was similar to the unstratified chi-square test.

Final conclusion:

The study results support the efficacy claim that patients who has predominant classic CNV secondary to AMD can benefit from verteprofin therapy, although the data indeed suggested that the less occult CNV component, the better the treatment effect could be. More information should be collected to confirm this observation.

IV. Health-Related Quality of Life (HQL): An amendment was added to the study protocol to incorporate the study of HQL on the AMD patients receiving the studied treatments. Only North American centers (12 of the 22 centers) were participated. With the assumption that verteporfin may slow down the deterioration of vision, it is therefore hoped that the treatment with verteporfin may also associate with the improvement of HQL compared to the treatment of placebo.

The HQL assessment consists of 30 questions, 25 of the questions from VFQ-25, three optional near-vision questions recommended by NEI for AMD studies, and two near-vision questions developed specifically for this study.

Only 126 patients had baseline HQL scores (82 in verteporfin and 44 in placebo), while 224 patients (146 in verteporfin and 78 in placebo) from HQL study sites did not participate HQL studies. No reason was recorded in study report. Among the 126 patients, only 89 patients (56 in verteporfin and 33 in placebo) completed HQL evaluation at Month 12, which were about 16% of the total number of patients (572).

Since there was only a small fraction of patients completed the HQL questionnaire, without valid sampling scheme from the original sample, the validity of the results based on such small sample is questionable. No conclusion should be drawn from the analysis no matter the results were positive or negative.

TABLE 1A. Disposition of Patients for Study A

	Number (%) of Patients		
	Verteporfin N=204	Placebo N=107	Total N=311
Randomized to masked treatment	204	107	311
Received treatment	204	107	311
Patients on study through:			
Month 0	204 (100.0)	107 (100.0)	311 (100.0)
Month 3	202 (99.0)	106 (99.1)	308 (99.0)
Month 6	200 (98.0)	104 (97.2)	304 (97.7)
Month 9	196 (96.1)	104 (97.2)	300 (96.5)
Month 12	196 (96.1)	102 (95.3)	298 (95.8)
Discontinued from study	15 (7.4)	7 (6.5)	22 (7.1)
Lost to follow-up	2 (1.0)	0 (0.0)	2 (0.6)
Patient request	8 (3.9)	1 (0.9)	9 (2.9)
Non-compliance	0 (0.0)	1 (0.9)	1 (0.3)
Inclusion/exclusion violation	1 (0.5)	1 (0.9)	2 (0.6)
Other	1 (0.5)	0 (0.0)	1 (0.3)
Death	3 (1.5)	4 (3.7)	7 (2.3)
Included in intent-to-treat analysis at:			
Month 0, 3, 6, 9, and 12	204 (100.0)	107 (100.0)	311 (100.0)
Included in evaluable-patients analysis at:			
Month 0	195 (95.6)	99 (92.5)	294 (94.5)
Month 3	186 (91.2)	97 (90.7)	283 (91.0)
Month 6	188 (92.2)	92 (86.0)	280 (90.0)
Month 9	177 (86.8)	91 (85.0)	268 (86.2)
Month 12	174 (85.3)	88 (82.2)	262 (84.2)

TABLE 2A. Subgroup Analyses for Study A

	Verteporfin		Placebo		Difference (Percent)	95% C.I. of Difference
	N	n (%)	N	n (%)		
Baseline Visual Acuity						
Stratum 1: 54 to 73 letters	109	58 (53.2)	55	25 (45.5)	(7.8)	[-8.4, 23.9]
Stratum 2: 34 to 53 letters	95	64 (67.4)	52	24 (46.2)	(21.2)	[4.7, 37.7]
Age at Baseline						
<75 years	107	69 (64.5)	44	16 (36.4)	(28.1)	[11.3, 45.0]
≥75 years	97	53 (54.6)	63	33 (52.4)	(2.3)	[-13.6, 18.1]
Gender						
Women	107	66 (61.7)	74	38 (51.4)	(10.3)	[-4.3, 25.0]
Men	97	56 (57.7)	33	11 (33.3)	(24.4)	[5.5, 43.2]
Iris Color						
Dark	67	35 (52.2)	28	10 (35.7)	(16.5)	[-4.9, 37.9]
Light	131	84 (64.1)	71	34 (47.9)	(16.2)	[2.0, 30.5]
Unknown	6	3 (50.0)	8	5 (62.5)	(-12.5)	[-64.7, 39.7]
Lesion Size (GLD)						
≤3	57	35 (61.4)	25	14 (56.0)	(5.4)	[-17.8, 28.6]
>3 to 6	80	47 (58.8)	50	21 (42.0)	(16.8)	[-0.7, 34.2]
>6 to 9	51	30 (58.8)	26	11 (42.3)	(16.5)	[-6.8, 39.8]
>9	12	6 (50.0)	5	2 (40.0)	(10.0)	[-41.4, 61.4]
Can't grade	4	4 (100.0)	1	1 (100.0)	N/A	N/A
Percent of Classic CNV at Baseline						
≥50%	86	58 (67.4)	41	14 (34.1)	(33.3)	[15.7, 50.9]
<50%	99	53 (53.5)	56	32 (57.1)	(-3.6)	[-19.9, 12.7]
None	19	11 (57.9)	10	3 (30.0)	(27.9)	[-8.2, 63.9]
Presence of Occult CNV at Baseline						
Yes	155	87 (56.1)	80	41 (51.3)	(4.9)	[-8.6, 18.3]
None	48	34 (70.8)	27	8 (29.6)	(41.2)	[19.7, 62.7]
Can't grade	1	1 (100.0)	0	N/A N/A	N/A	N/A
Presence of Blood at Base						
Yes	73	49 (67.1)	47	19 (40.4)	(26.7)	[9.0, 44.4]
None	130	72 (55.4)	60	30 (50.0)	(5.4)	[-9.9, 20.7]
Can't grade	1	1 (100.0)	0	N/A N/A	N/A	N/A
Percentage of Fibrosis at Baseline						
0 to 25%	154	90 (58.4)	79	37 (46.8)	(11.6)	[-1.9, 25.1]
26 to 50%	22	11 (50.0)	12	5 (41.7)	(8.3)	[-26.5, 43.2]
>50%	25	18 (72.0)	15	6 (40.0)	(32.0)	[1.6, 62.4]
Can't grade	3	3 (100.0)	1	1 (100.0)	N/A	N/A
Presence of Hypertension at Baseline						
Definite	95	56 (58.9)	43	16 (37.2)	(21.7)	[4.2, 39.2]
All Other	109	66 (60.6)	64	33 (51.6)	(9.0)	[-6.3, 24.3]
Cigarette Smoking						
Non-smoker (never)	63	35 (55.6)	47	20 (42.6)	(13.0)	[-5.7, 31.7]
Current smoker	31	22 (71.0)	12	8 (66.7)	(4.3)	[-26.8, 35.4]
Previous smoker	110	65 (59.1)	48	21 (43.8)	(15.3)	[-1.4, 32.1]
Lesion Status						
Recurrent	28	18 (64.3)	10[c]	8 (80.0)	(-15.7)	[-46.2, 14.8]
New	175	103 (58.9)	97	41 (42.3)	(16.6)	[4.4, 28.8]
Can't determine	1	1 (100.0)	0	N/A N/A	N/A	N/A

TABLE 1B. Disposition of Patients for Study B

Number (%) of Patients

	Verteporfin N=198	Placebo N=100	Total N=298
Randomized to masked treatment	198	100	298
Received treatment	198	100	298
Patients on study through:			
Month 0	198 (100.0)	100 (100.0)	298 (100.0)
Month 3	197 (99.5)	99 (99.0)	296 (99.3)
Month 6	194 (98.0)	99 (99.0)	293 (98.3)
Month 9	192 (97.0)	96 (96.0)	288 (96.6)
Month 12	192 (97.0)	96 (96.0)	288 (96.6)
Discontinued from study	7 (3.5)	4 (4.0)	11 (3.7)
Lost to follow-up	0 (0.0)	1 (1.0)	1 (0.3)
Patient request	4 (2.0)	3 (3.0)	7 (2.3)
Death	3 (1.5)	0 (0.0)	3 (1.0)
Included in intent-to-treat analysis at:			
Month 0, 3, 6, 9, and 12	198 (100.0)	100 (100.0)	298 (100.0)
Included in evaluable-patients analysis at:			
Month 0	191 (96.5)	95 (95.0)	286 (96.0)
Month 3	188 (94.9)	91 (91.0)	279 (93.6)
Month 6	183 (92.4)	91 (91.0)	274 (91.9)
Month 9	174 (87.9)	86 (86.0)	260 (87.2)
Month 12	179 (90.4)	85 (85.0)	264 (88.6)

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TABLE 2B. Subgroup Analyses for Study B

	Verteporfin		Placebo		Difference (Percent)	95% C.I. of Difference
	N	n (%)	N	n (%)		
Baseline Visual Acuity						
Stratum 1: 54 to 73 letters	94	53 (56.4)	46	18 (39.1)	(17.3)	[-0.1, 34.6]
Stratum 2: 34 to 53 letters	104	71 (68.3)	54	29 (53.7)	(14.6)	[-1.5, 30.6]
Age at Baseline						
<75 years	87	63 (72.4)	43	24 (55.8)	(16.6)	[-1.0, 34.2]
≥75 years	111	61 (55.0)	57	23 (40.4)	(14.6)	[-1.1, 30.3]
Gender						
Women	107	70 (65.4)	56	28 (50.0)	(15.4)	[-0.5, 31.3]
Men	91	54 (59.3)	44	19 (43.2)	(16.2)	[-1.6, 33.9]
Iris Color						
Dark	75	45 (60.0)	33	17 (51.5)	(8.5)	[-11.9, 28.8]
Light	116	73 (62.9)	65	29 (44.6)	(18.3)	[3.4, 33.3]
Unknown	7	6 (85.7)	2	1 (50.0)	(35.7)	[-38.3, 100.0]
Lesion Size (GLD)						
≤3	50	37 (74.0)	21	12 (57.1)	(16.9)	[-7.6, 41.3]
>3 to 6	72	48 (66.7)	47	23 (48.9)	(17.7)	[-0.2, 35.7]
>6 to 9	58	28 (48.3)	26	11 (42.3)	(6.0)	[-17.0, 28.9]
>9	13	8 (61.5)	3	0 (0.0)	(61.5)	[35.1, 88.0]
Can't grade	5	3 (60.0)	3	1 (33.3)	(26.7)	[-41.8, 95.1]
Percent of Classic CNV at Baseline						
≥50%	73	49 (67.1)	43	19 (44.2)	(22.9)	[4.6, 41.3]
<50%	103	60 (58.3)	47	25 (53.2)	(5.1)	[-12.1, 22.2]
None[e]	22	15 (68.2)	10	3 (30.0)	(38.2)	[3.8, 72.6]
Presence of Occult CNV at Baseline						
Yes	150	85 (56.7)	77	40 (51.9)	(4.7)	[-9.0, 18.4]
None	46	38 (82.6)	22	7 (31.8)	(50.8)	[28.5, 73.1]
Can't grade	2	1 (50.0)	1	0 (0.0)	(50.0)	[-19.3, 100]
Presence of Blood at Baseline						
Yes	60	36 (60.0)	40	18 (45.0)	(15.0)	[-4.8, 34.8]
None	136	87 (64.0)	60	29 (48.3)	(15.6)	[0.6, 30.6]
Can't grade	2	1 (50.0)	0	N/A N/A	N/A	N/A
Percentage of Fibrosis at Baseline						
0 to 25%	159	98 (61.6)	74	33 (44.6)	(17.0)	[3.4, 30.7]
26 to 50%	22	14 (63.6)	12	7 (58.3)	(5.3)	[-29.1, 39.7]
>50%	14	10 (71.4)	13	7 (53.8)	(17.6)	[-18.4, 53.6]
Can't grade	3	2 (66.7)	1	0 (0.0)	(66.7)	[13.3, 100.0]
Presence of Hypertension at Baseline						
Definite	75	47 (62.7)	34	16 (47.1)	(15.6)	[-4.4, 35.6]
All Other	123	77 (62.6)	66	31 (47.0)	(15.6)	[0.9, 30.4]
Cigarette Smoking						
Non-smoker (never)	72	49 (68.1)	43	24 (55.8)	(12.2)	[-6.1, 30.6]
Current smoker	31	18 (58.1)	11	5 (45.5)	(12.6)	[-21.6, 46.8]
Previous smoker	95	57 (60.0)	46	18 (39.1)	(20.9)	[3.7, 38.1]
Lesion Status						
Recurrent	31	17 (54.8)	13	5 (38.5)	(16.4)	[-15.3, 48.1]
New	166	106 (63.9)	87	42 (48.3)	(15.6)	[2.8, 28.4]
Can't determine	1	1 (100.0)	0	N/A-N/A	N/A	N/A

TABLE 3. Integrated Subgroup Analyses for Study A & B

	Verteporfin		Placebo		Difference (Percent)	95% C.I. of Difference
	N	n (%)	N	n (%)		
Baseline Visual Acuity						
Stratum 1: 54 to 73 letters	203	111 (54.7)	101	43 (42.6)	(12.1)	[0.3, 23.9]
Stratum 2: 34 to 53 letters	199	135 (67.8)	106	53 (50.0)	(17.8)	[6.3, 29.4]
Age at Baseline						
<75 years	194	132 (68.0)	87	40 (46.0)	(22.1)	[9.7, 34.4]
≥75 years	208	114 (54.8)	120	56 (46.7)	(8.1)	[-3.1, 19.3]
Gender						
Women	214	136 (63.6)	130	66 (50.8)	(12.8)	[2.0, 23.5]
Men	188	110 (58.5)	77	30 (39.0)	(19.5)	[6.6, 32.5]
Iris Color						
Dark	142	80 (56.3)	61	27 (44.3)	(12.1)	[-2.8, 27.0]
Light	247	157 (63.6)	136	63 (46.3)	(17.2)	[6.9, 27.5]
Unknown	13	9 (69.2)	10	6 (60.0)		
Lesion Size (GLD)						
≤3	107	72 (67.3)	46	26 (56.5)	(10.8)	[-6.1, 27.6]
>3 to 6	152	95 (62.5)	97	44 (45.4)	(17.1)	[4.6, 29.7]
>6 to 9	109	58 (53.2)	52	22 (42.3)	(10.9)	[-5.5, 27.3]
>9	25	14 (56.0)	8	2 (25.0)	(31.0)	[-4.8, 66.8]
Can't grade	9	7 (77.8)	4	2 (50.0)	(22.8)	
Percent of Classic CNV at Baseline						
≥50%	159	107 (67.3)	84	33 (39.3)	(28.0)	[15.3, 40.7]
<50%	202	113 (55.9)	103	57 (55.3)	(0.6)	[-11.2, 12.4]
None	41	26 (63.4)	20	6 (30.0)	(33.4)	[8.5, 58.3]
Presence of Occult CNV at Baseline						
Yes	305	172 (56.4)	157	81 (51.6)	(4.8)	[-4.8, 14.4]
None	94	72 (76.6)	49	15 (30.6)	(46.0)	[30.5, 61.5]
Can't grade	3	2 (66.7)	1	0 (0.0)		
Presence of Blood at Baseline						
Yes	133	85 (63.9)	87	37 (42.5)	(21.4)	[8.2, 34.6]
None	266	159 (59.8)	120	59 (49.2)	(10.6)	[-0.1, 21.3]
Can't grade	3	2 (66.70)	0	N/A N/A	N/A	N/A
Percentage of Fibrosis at Baseline						
0 to 25%	313	188 (60.1)	153	70 (45.8)	(14.3)	[4.7, 23.9]
26 to 50%	44	25 (56.8)	24	12 (50.0)	(6.8)	[-18.0, 31.6]
>50%	39	28 (71.8)	28	13 (46.4)	(25.4)	[2.1, 48.6]
Can't grade	6	5 (83.3)	2	1 (50.0)		
Presence of Hypertension at Baseline						
Definite	170	103 (60.6)	77	32 (41.6)	(19.0)	[5.8, 32.3]
All Other	232	143 (61.6)	130	64 (49.2)	(12.4)	[1.8, 23.0]
Cigarette Smoking						
Non-smoker (never)	135	84 (62.2)	90	44 (48.9)	(13.3)	[0.2, 26.5]
Current smoker	62	40 (64.5)	23	13 (56.5)	(8.0)	[-15.5, 31.5]
Previous smoker	205	122 (69.5)	94	39 (41.5)	(18.0)	[6.0, 30.0]
Lesion Status						
Recurrent	59	35 (59.3)	23	13 (56.5)	(2.8)	[-21.0, 26.6]
New	341	209 (61.3)	184	83 (45.1)	(16.2)	[7.3, 25.0]
Can't determine	2	2 (100.0)	0	N/A N/A	N/A	N/A

/S/

Qian Li, Sc.D
Mathematical Statistician

APPEARS THIS WAY
ON ORIGINAL

Concur:

/S/ 12/1/99

Stan Lin, Ph.D
Team Leader

CC:NDA 21-119
HFD-550/Div File
HFD-550/LGorski
HFD-550/WChambers
HFD-550/Kmidthun-

HFD-725/Div File
HFD-725/MHuque
HFD-725/SLin
HFD-725/QLi

APPEARS THIS WAY
ON ORIGINAL