

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**21-119/S-001**

**STATISTICAL REVIEW(S)**

## Statistical Review and Evaluation

sNDA#: 21-119SE1

Drug Name: Visudyne (verteporfin for injection)

Sponsor: QLT Inc.

Proposed Indication: Revision to add treatment for subfoveal choroidal neovascularization secondary to other macular diseases.

Date Submission: August 14, 2000

Documents Reviewed: Volumes 1, 26-38, and data submitted

Medical Reviewer: Wiley Chambers, MD

Statistical Reviewer: Stan Lin, Ph.D

It is gratefully acknowledged that my colleague, Suktae Choi, Ph.D., of HFD-725 helped with the re-analysis for this review.

### Background and Introduction

The sponsor has submitted a multipart supplemental application for components of a combination product consisting of visudyne, and specified lasers for use as light sources for the photoactivation of visudyne. The supplements propose a revision to the indication statement and adds treatment of patients with subfoveal choroidal neovascularization secondary to other macular diseases. Part I contains the supplemental new drug application and this part is being reviewed by CDER. Parts II and III are being reviewed by CDRH.

Verteoporfin photodynamic therapy (PDT) is approved for commercial use in predominantly classic choroidal neovascularization (CNV) (area of classic CNV at least 50% of entire lesion) secondary to age-related macular degeneration (AMD) in the USA, Canada, Switzerland, Malta, Brazil, and Argentina.

QLT Inc [redacted] propose to extend the commercial use of VISUDYNE™ (verteporfin) therapy to subfoveal CNV secondary to other diseases in addition to AMD. In support of the sponsor's current application, results from one randomized placebo-controlled study in CNV secondary to pathologic myopia (OCR-003-PM) and the interim data from an open-label study in CNV secondary to OHS have been submitted for review. This review will concentrate on the efficacy results from study OCR-003-PM.

### OCR-003-PM

This was a masked, multicenter, randomized, parallel, study of the treatment of new subfoveal choroidal neovascularization secondary to PM (pathologic myopia) using verteoporfin PDT treatment compared to placebo. Patients were required to have relatively good best-corrected visual acuity,  $\geq 50$  letters or approximately 20/100 or better on the ETDRS chart. Only one eye per patient was treated in the study. This multi-national, multicenter (26 centers) study planned to enroll approximately 110 PM patients. Patients who met eligibility criteria were randomized to verteoporfin or placebo in a 2:1 ratio. Randomization was stratified by investigative center.

Treatment consisted of an infusion over 10 minutes of either verteporfin (6 mg/m<sup>2</sup>) or dextrose placebo solution, followed by an application of 50 J/cm<sup>2</sup> of nonthermal red light (689 nm) initiated 15 minutes after the start of the infusion.

The primary analysis was prospectively planned after 12 months of follow-up data. The cutoff date for the 12-month analysis was October 29, 1999. The total study follow-up for each patient will be 24 months. The primary efficacy variable was defined as the proportion of patients who were classified as "responders" to treatment based on their best-corrected visual acuity (BCVA) score. Responders were patients who lost fewer than 8 letters (approximately <1.5 lines) of BCVA relative to baseline. For the statistical analysis, the agency requested that patients who lost fewer than 15 letters (approximately <3 lines) of BCVA be also analyzed. The basic statistical method for the primary variable was chi-square test. The intent-to-treat with LOCF was the primary analysis cohort, supplemented by the per-protocol evaluable patients analysis.

### **Study Results**

The results based on the ITT patients analysis are reviewed. Although the results based on per-protocol evaluable patients are not shown here, they were similar to those based on the ITT patients. Evaluable patients were those who met the protocol inclusion/exclusion criteria without significant deviation, and adhered to the protocol procedures without any significant deviation.

The patient disposition is listed in Table 1. Most patients completed the 12-month study and all patients were included in the ITT-LOCF analysis (all randomized patients). A follow-up visit was recorded for 96% of the patients at Month 12 and 83% of patients were included in the evaluable-patients analysis.

The study basically followed the protocol. There was a total of 120 PM patients, 81 randomized to verteporfin and 39 randomized to placebo. The first patient was randomized on February 26, 1998, and the last patient was randomized on September 25, 1998. The last Month 12 visit was completed on October 7, 1999.

Demographic and baseline characteristics are presented in Table 2. There were 70% women in the verteporfin group and 59% in the placebo group. The majority were Caucasian, representing 91 to 92% of patients in the two treatment groups. The mean age was 51.3 years for the verteporfin group and 47.3 years for the placebo group. The between-treatment difference in mean age approached statistical significance (P=.063). The mean baseline visual acuity score was 62 letters in the verteporfin group and 60 letters in the placebo group. The mean baseline contrast sensitivity was 27.2 letters and 28.9 letters for the verteporfin and placebo groups, respectively. The between-treatment differences for both visual acuity (P=.073) and contrast sensitivity (P=.053) also approached statistical significance.

### **Efficacy (Intent-to-Treat (ITT) Analyses)**

The primary efficacy variable was the proportion of patients who were considered responders to treatment. The protocol defined a responder as a patient who experienced a decrease from baseline of fewer than 8 letters of visual acuity. As mentioned above, patients who experienced a

decrease from baseline of fewer than 15 letters of visual acuity were also compared between treatment groups. This criterion is consistent with the definition of responder for the AMD studies and was considered as primary by the agency. The following table first summarizes the results on this criterion.

Patient Responder (<15-Letter Decrease in Visual Acuity) (Intent-to-Treat)							
Visit	Number (%) of Patients				Difference (Percent)	95% C.I. of Difference	P value
	Verteporfin N=81		Placebo N=39				
Month 3	76	(93.8)	31	(79.5)	(14.3)	[ 0.6, 28.1]	
Month 6	68	(84.0)	30	(76.9)	( 7.0)	[-8.4, 22.5]	
Month 9	71	(87.7)	26	(66.7)	(21.0)	[ 4.5, 37.4]	
Month 12	70	(86.4)	26	(66.7)	(19.8)	[ 3.2, 36.3]	.011

At Month 12 compared to baseline, 86.4% of the verteporfin-treated eyes were responders (<15 letters) compared to 66.7% of the placebo-treated eyes. This difference (19.8%) was statistically significant (P=.011).

Since the ITT analysis of the primary efficacy variable was done using the method of last observation carried forward, the same analysis was performed without LOCF, thus excluding those patients who did not complete the 12-month followup, to evaluate the effect of LOCF imputation on the results of the primary analysis. The analysis of the primary efficacy variable (without LOCF) showed results similar to the analysis with LOCF. At Month 12 compared to baseline, 87.3% of the verteporfin-treated eyes were responders versus 63.9% of the placebo-treated eyes. The difference between the treatment groups (23.5%) was statistically significant (P=.004).

The results (see Table 3) using the 8-letter criterion were consistent with the results using the 15-letter criterion although the percentages of responders in each treatment group were smaller for the 8-letter criterion than for the 15-letter criterion. The *difference* between treatments was larger for the 8-letter criterion than for the 15-letter criterion at each evaluation point and ranged from 19.1% to 30.5%. At Month 12 compared to baseline, 71.6% of the verteporfin-treated eyes were responders (<8 letters) compared to 43.6% of the placebo-treated eyes. This difference (28.0%) was statistically significant (P=.003). Again, completers analysis gave similar results (not shown).

COMMENT: As mentioned in the patient baseline and demographics above, age, visual acuity, and contrast sensitivity showed close to significant difference between treatment groups at baseline. Because age was dichotomized into <50 and ≥50 years, the numbers of responders at month 12 by age for the intent-to-treat patients are shown in Table 4. A logistic regression was used to evaluate the effect of these variables on the primary efficacy variable of patient responder status at 12 months. This analysis showed no significant treatment by variable interactions. In addition, a logistic regression was performed to evaluate responder status

adjusting for these potential baseline differences. Results of this logistic regression still showed a significant treatment effect with a p-value <0.01.

In addition to the primary endpoint of responder status, there were several secondary efficacy endpoints specified in the protocol and their results were presented in the study report (see summary Table 5). These analyses generally confirm and support the efficacy results based on the primary endpoint. Subgroup (gender, race, iris color, etc.) analyses were also specified. In all subgroups studied, the proportion of responders was generally higher for patients randomized to verteporfin than for patients randomized to placebo.

### **Summary and Conclusions**

This review evaluated a single controlled study (OCR-003-PM) comparing verteporfin PDT treatment to placebo in patients with subfoveal choroidal neovascularization (CNV) secondary to pathologic myopia (PM). (Verteporfin PDT was previously approved for classic-containing subfoveal CNV secondary to age-related macular degeneration.) Based on protocol specifications on endpoints and statistical analysis, study OCR-003-PM demonstrated a beneficial treatment effect.

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Concur: Dr. Huque

cc: NDA 21-119/SE001  
HFD-550/Div.  
HFD-550/Gorski  
HFD-550/Chambers  
HFD-550/Bull  
HFD-725/Huque  
HFD-725/Choi  
HFD-725/LinS  
Chron.

TABLE 1. Disposition of Patients by Treatment Group and Visit

	Number (%) of Patients		
	Verteporfin	Placebo	Total
Randomized to masked treatment	81	39	120
Received randomized treatment	80 <sup>a</sup>	39	119
Patients on study through <sup>b</sup> :			
Month 0	81 (100.0)	39 (100.0)	120 (100.0)
Month 3	81 (100.0)	39 (100.0)	120 (100.0)
Month 6	79 ( 97.5)	38 ( 97.4)	117 ( 97.5)
Month 9	79 ( 97.5)	37 ( 94.9)	116 ( 96.7)
Month 12	79 ( 97.5)	37 ( 94.9)	116 ( 96.7)
Month 15	21 ( 25.9)	9 ( 23.1)	30 ( 25.0)
Month 18	4 ( 4.9)	1 ( 2.6)	5 ( 4.2)
Discontinued from study <sup>d</sup>			
Lost to follow-up	1 ( 1.2)	0 ( 0.0)	1 ( 0.8)
Patient request	1 ( 1.2)	2 ( 5.1)	3 ( 2.5)
Included in intent-to-treat analysis at:			
Month 0, 3, 6, 9, and 12	81 (100.0)	39 (100.0)	120 (100.0)
Patients who had a follow-up visit <sup>c</sup> at:			
Month 3	81 (100.0)	39 (100.0)	120 (100.0)
Month 6	79 ( 97.5)	37 ( 94.9)	116 ( 96.7)
Month 9	78 ( 96.3)	37 ( 94.9)	115 ( 95.8)
Month 12	79 ( 97.5)	36 ( 92.3)	115 ( 95.8)
Included in evaluable-patient analysis:			
Month 0	70 ( 86.4)	34 ( 87.2)	104 ( 86.7)
Month 3	70 ( 86.4)	34 ( 87.2)	104 ( 86.7)
Month 6	69 ( 85.2)	32 ( 82.1)	101 ( 84.2)
Month 9	69 ( 85.2)	32 ( 82.1)	101 ( 84.2)
Month 12	69 ( 85.2)	31 ( 79.5)	100 ( 83.3)

- <sup>a</sup> Patient V28P53 did not receive full treatment at Month 0 due to dyspnea and flushing (allergic reaction) during infusion.
- <sup>b</sup> Includes missed visits if they occurred before patient's last recorded follow-up visit.
- <sup>c</sup> The visual acuity assessment was used to count the number (%) of patients with a follow-up visit.
- <sup>d</sup> Reason reported by investigator on CRF termination form.

TABLE 2. Demographic and Baseline Characteristics

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Characteristic	Number (%) of Patients					
	ITT Patients			Evaluable Patients at Month 12		
	Verteoporfin N=81	Placebo N=39	P value	Verteoporfin N=69	Placebo N=31	P value
<b>GENDER</b>			.223			.654
Women	57 (70.4)	23 (59.0)		46 (66.7)	19 (61.3)	
Men	24 (29.6)	16 (41.0)		23 (33.3)	12 (38.7)	
<b>RACE</b>			1.000			1.000
Caucasian	74 (91.4)	36 (92.3)		65 (94.2)	29 (93.5)	
Black	0 ( 0.0)	0 ( 0.0)		0 ( 0.0)	0 ( 0.0)	
Asian	3 ( 3.7)	2 ( 5.1)		2 ( 2.9)	1 ( 3.2)	
Hispanic	4 ( 4.9)	1 ( 2.6)		2 ( 2.9)	1 ( 3.2)	
<b>AGE (Years)<sup>a</sup></b>						
< 30	4 ( 4.9)	1 ( 2.6)		2 ( 2.9)	1 ( 3.2)	
30-39	10 (12.3)	12 (30.8)		9 (13.0)	9 (29.0)	
40-49	22 (27.2)	10 (25.6)		19 (27.5)	9 (29.0)	
50-59	25 (30.9)	12 (30.8)		21 (30.4)	9 (29.0)	
60-69	13 (16.0)	2 ( 5.1)		11 (15.9)	2 ( 6.5)	
≥70	7 ( 8.6)	2 ( 5.1)		7 (10.1)	1 ( 3.2)	
Mean	51.3	47.3	.063	52.3	46.7	.037
STD	12.7	12.7		12.6	11.9	
Median	51.0	46.0		51.0	45.0	
Minimum	19.0	27.0		19.0	27.0	
Maximum	77.0	84.0		77.0	78.0	
<b>DEFINITE HYPERTENSION</b>			.466			.788
Yes	14 (17.3)	9 (23.1)		13 (18.8)	7 (22.6)	
No	67 (82.7)	30 (76.9)		56 (81.2)	24 (77.4)	
<b>MEDICAL HISTORY</b>			.749			1.000
Yes	72 (88.9)	36 (92.3)		63 (91.3)	29 (93.5)	
No	9 (11.1)	3 ( 7.7)		6 ( 8.7)	2 ( 6.5)	
<b>IRIS COLOR (STUDY EYE)</b>			.150			.378
Dark	35 (43.2)	11 (28.2)		30 (43.5)	10 (32.3)	
Light	45 (55.6)	28 (71.8)		39 (56.5)	21 (67.7)	
Unknown	1 ( 1.2)	0 ( 0.0)		0 ( 0.0)	0 ( 0.0)	
<b>VISUAL ACUITY (STUDY EYE)<sup>a</sup></b>						
Mean	62.0	60.0	.073	62.3	60.8	.179
STD	6.6	8.6		6.3	9.1	
Median						
Minimum						
Maximum						

<sup>a</sup> Parameters are presented as number and percentage of patients. Age is also presented as mean and standard deviation. Visual acuity and contrast sensitivity are presented only as mean and standard deviation.

TABLE 2. Demographic and Baseline Characteristics

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Characteristic	Number (%) of Patients					
	ITT Patients			Evaluable Patients at Month 12		
	Verteporfin N=81	Placebo N=39	P value	Verteporfin N=69	Placebo N=31	P value
<b>CONTRAST SENSITIVITY (STUDY EYE)<sup>a</sup></b>						
Mean	27.2	28.9	.053	27.1	28.9	.067
STD	4.4	4.8		4.1	3.7	
Median						
Minimum						
Maximum						
<b>PRIOR TREATMENT FOR PM</b>						
			1.000			
No	63 (77.8)	31 (79.5)		55 (79.7)	23 (74.2)	.605
Yes						
Laser Photocoagulation <sup>b</sup>	9 (11.1)	6 (15.4)		9 (13.0)	6 (19.4)	
Interferon	1 ( 1.2)	0 ( 0.0)		1 ( 1.4)	0 ( 0.0)	
Other	9 (11.1)	3 ( 7.7)		5 ( 7.2)	3 ( 9.7)	
<b>SMOKING HISTORY</b>						
			.392			.452
Never smoked	43 (53.1)	26 (66.7)		37 (53.6)	21 (67.7)	
Current smoker	15 (18.5)	6 (15.4)		12 (17.4)	4 (12.9)	
Previous smoker	23 (28.4)	7 (17.9)		20 (29.0)	6 (19.4)	

<sup>a</sup> Parameters are presented as number and percentage of patients. Age is also presented as mean and standard deviation. Visual acuity and contrast sensitivity are presented only as mean and standard deviation.

<sup>b</sup> Denotes prior laser photocoagulation that was administered in the study eye, as reported by the Treating Center.

TABLE 3. Patient Responders\* (<8-Letter Decrease in Visual Acuity) (Intent-to-Treat)

Visit	Number (%) of Patients				
	Verteporfin N=81	Placebo N=39	Difference <sup>b</sup> (Percent)	95% C.I. of Difference	P value <sup>c</sup>
Month 3	62 (76.5)	22 (56.4)	(20.1)	[2.0, 38.2]	
Month 6	60 (74.1)	17 (43.6)	(30.5)	[12.2, 48.7]	
Month 9	57 (70.4)	20 (51.3)	(19.1)	[0.5, 37.7]	
Month 12	58 (71.6)	17 (43.6)	(28.0)	[9.6, 46.4]	.003

<sup>a</sup> A responder was a patient who had a decrease from baseline of <8 letters in VA.

<sup>b</sup> Proportion of verteporfin responders minus the proportion of placebo responders.

<sup>c</sup> Chi-square used to test significance between the proportion of patient responders for verteporfin treatment versus placebo at Month 12.

TABLE 4. Patient Responders<sup>a</sup> at Month 12 by Age at Baseline (Intent-to-Treat)

Age at Baseline	Number (%) of Patients				Difference <sup>b</sup> (Percent)	95% C.I. of Difference
	Verteporfin		Placebo			
	N	n (%)	N	n (%)		
<u>&lt;15 Letter Decrease in VA</u>						
<50 years	36	31 (86.1)	23	18 (78.3)	( 7.9)	[-12.4, 28.1]
≥50 years	45	39 (86.7)	16	8 (50.0)	(36.7)	[ 10.2, 63.1]
<u>&lt;8 Letter Decrease in VA</u>						
<50 years	36	28 (77.8)	23	12 (52.2)	(25.6)	[1.1, 50.1]
≥50 years	45	30 (66.7)	16	5 (31.3)	(35.4)	[8.9, 62.0]

TABLE 5. Results of Secondary Efficacy Variables at Month 12

Secondary Efficacy Variables	Verteporfin N=81	Placebo N=39	P value
Mean change in VA (letters) <sup>1</sup>	-2.3	-10.2	.009
Percentage of patients with VA <34 letters	6%	18%	.044
<i>Time to event analyses</i>			
Time to a ≥15 letter decrease	Hazard Ratio <sup>2</sup> 0.654	95% C.I. [0.480, 0.890]	.007
Time to a ≥8 letter decrease	0.685	[0.526, 0.892]	.005
Mean change in contrast sensitivity (letters) <sup>1</sup>	-0.3	-2.3	.106
Classic CNV progression (% of patients)	36%	54%	.206
Occult CNV progression (% of patients)	7%	10%	.320
Percentage of lesions ≤3 MPS	94%	69%	.001
Mean change in subjective vision score	4.8	-1.8	---