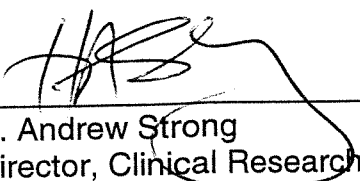**PROTOCOL No.:**   BPD OCR 002 AMENDMENT NO. 8, DATED November 20, 1998.

DRUG NAME: *BENZOPORPHYRIN DERIVATIVE MONO-ACID RING A (BPD-MA)*

TITLE AND NAME: *A Randomized, Placebo-Controlled, Masked, Multicenter, Phase 3 Study of the Treatment of Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD) Using Photodynamic Therapy (PDT) with Liposomal BPD-MA (verteporfin). Version: May 5, 1997.*

PREPARED BY:

_____   _Nov 20/98._____
H. Andrew Strong   Date
Director, Clinical Research

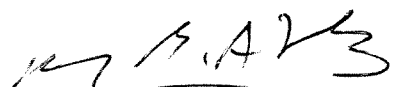_____   _____
John Koester   Date
Head, Biostatistics, Data Management
– CIBA Vision Inc.
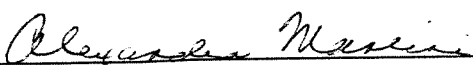

APPROVAL

The undersigned attest to the following:

　　1.　Reviewed the protocol Amendment
　　2.　Agree to its contents

_____   _November 23, 1998_____
Mohammad Azab   Date
Vice President, Clinical Research & Medical Affairs

_____   _November 23, 1998_____
Noel Buskard   Date
Medical & Safety Officer

_____   _November 24, 1998_____
Alexandra Mancini   Date
Vice President, Regulatory Affairs

PROTOCOL No.:   BPD OCR 002 AMENDMENT NO. 8, DATED November 20, 1998.

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PREPARED BY:

_____   _____

H. Andrew Strong   Date
Director, Clinical Research

John Koester _____   *November 24, 1998*

John Koester   Date
Head, Biostatistics, Data Management
– CIBA Vision Inc.

APPROVAL

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Mohammad Azab   Date
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REVISION NO. 1:

Reason for Revision: To append the detailed Statistical Analysis Plan to the protocol as Appendix 15. Administrative and non-substantial changes to the protocol cover sheet and Table of Contents are also included.

Amendment: Protocol Cover Sheet changes.

CLINICAL STUDY PROTOCOL

Benzoporphyrin Derivative Monoacid Ring A [BPD-MA (verteporfin)]

BPD OCR 002

A Randomized, Placebo-Controlled, Masked, Multicenter, Phase 3 Study of the Treatment of Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD) Using Photodynamic Therapy (PDT) with Liposomal BPD-MA (verteporfin)

SHORT TITLE: <u>T</u>reatment of <u>A</u>MD with <u>P</u>DT (TAP)

CONFIDENTIAL

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, British Columbia
Canada V5Z 4H5

Cibà Vision Ophthalmics AG, Hettlingen
Grenzstrasse 10
CH-8180 Bülach
Switzerland

Ciba Vision Ophthalmics Inc.
11460 Johns Creek Parkway
Duluth, Georgia 30155-1518

ORIGINAL PROTOCOL DATED OCTOBER 25, 1996.
THIS VERSION DATED MAY 5, 1997 INCORPORATES:
Amendment 1: Dated April 4, 1997

PROTOCOL No.:   **BPD OCR 002 AMENDMENT NO. 8, DATED November 20, 1998.**

DRUG NAME: *BENZOPORPHYRIN DERIVATIVE MONO-ACID RING A (BPD-MA)*

TITLE AND NAME: *A Randomized, Placebo-Controlled, Masked, Multicenter, Phase 3 Study of the Treatment of Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD) Using Photodynamic Therapy (PDT) with Liposomal BPD-MA (verteporfin). Version: May 5, 1997.*

Amendment 2:	**Dated April 28, 1997**
Amendment 3:	**Dated April 29, 1997**
Amendment 4:	**Dated May 2, 1997**
Amendment 5:	**Dated July 4, 1997**
Amendment 6:	**Dated August 5, 1997**
Amendment 7:	**Dated May 4, 1998**
Amendment 8:	***Dated November 20, 1998***

PROTOCOL No.: BPD OCR 002 AMENDMENT NO. 8, DATED November 20, 1998.

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Amendment: Table of Contents changes.

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Amendment: Page 27 Section 13.2, Statistical and Analytical Plan. Add following sentence after second paragraph.

A complete Statistical Analysis Plan dated September 25, 1998, is appended (Appendix 15)

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Amendment   :   **Addition of Appendix 15.**

APPENDIX 15

Benzoporphyrin Derivative Monoacid Ring A [BPD-MA (verteporfin)]

BPD OCR 002

A Randomized, Placebo-Controlled, Masked, Multicenter, Phase 3 Study of the Treatment of Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD) Using Photodynamic Therapy (PDT) with Liposomal BPD-MA (verteporfin)

SHORT TITLE: *Treatment of AMD with PDT (TAP)*

STATISTICAL ANALYSIS PLAN

[25-SEPTEMBER-98]

CONFIDENTIAL

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, British Columbia
Canada V5Z 4H5

CIBA Vision AG
Hettlingen
Grenzstrasse 10
CH-8180 Bülach
Switzerland

CIBA Vision Corporation
11460 Johns Creek Parkway
Duluth, Georgia   30097-1556

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STATISTICAL ANALYSIS PLAN
(DATED SEPTEMBER 25, 1998)
PDT - CLINICAL PROTOCOL BPD OCR OO2 (TAP TRIAL)

1. INTRODUCTION

Age-related macular degeneration (AMD) causes severe, irreversible vision loss and is the leading cause of blindness in individuals older than 50 years of age in the Western world. AMD is a degenerative eye disease with increasing prevalence at older ages. The majority of patients have the nonneovascular form of the disease, characterized by drusen and atrophic abnormalities in the retinal pigment epithelium. However, 80% of the severe vision loss attributable to this disease is related to the neovascular form, characterized by choroidal neovascularization (CNV). CNV leaks blood, lipid and fluid, and often leads to rapid loss of central vision.

Although the natural history of the disease is eventual quiescence and regression of the neovascularization process, this usually occurs at the cost of subretinal fibrosis and vision loss. Current treatment relies on destruction of the vessels using thermal laser photocoagulation. This procedure is quite non-selective, producing damage to the outer retina, including the photoreceptors, with an atrophic scar and corresponding visual scotoma. Although extensive studies have demonstrated a clinically significant advantage of laser treatment compared with observation in selected cases, the treatment benefit is problematic for subfoveal lesions.

Developing strategies have sought more selective treatment of the new vessels with preservation of the overlying neurosensory retina. One such strategy is photodynamic therapy (PDT), which relies on low intensity light exposure of tissues treated with photosensitizers to produce photochemical effects. Photodynamic therapy is a two-step process. The first step consists of intravenous injection of a photosensitizer. The second step is light irradiation. After exposure to light at an absorption peak of the dye, the activated dye interacts with oxygen and other compounds to form reactive intermediates which can then cause disruption of cellular structures and neovascular shutdown.

Study Objectives

The primary objective of this study is to determine if PDT treatment of patients with

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CNV secondary to AMD will, with an acceptable safety profile, significantly reduce vision loss compared with placebo (sham treatment). Secondary objectives include the comparison of the effects of PDT treatment with placebo on peak-contrast threshold, and the evaluation of the long-term safety of PDT treatment.

Study Design

This is a masked, multicenter, randomized, placebo-controlled, Phase 3 study of the treatment of subfoveal CNV secondary to AMD using photodynamic therapy. Two studies are being conducted under this protocol in North America and Europe. Approximately equal numbers of centers from each continent have been allocated into each study. The primary analysis of the efficacy data will be based on data obtained at the 12-month follow-up visit. Analysis of the results through the first 12 months will be used in regulatory submissions to international boards of health.

Patients, treating ophthalmologists, vision examiners and Photograph Reading Center graders are masked to the identity of the treatment. Sponsor personnel responsible for the conduct and monitoring of the trial are also masked to the identity of the treatment. The study coordinator from each center will remain unmasked, and is responsible for the randomization of patients using sealed treatment allocation codes, and for maintaining the masking of other center staff and the patient. Patients are randomized to PDT or placebo treatment in a ratio of 2-to-1, respectively. Patient randomization is stratified by center and by two levels of baseline visual acuity.

Outpatients with new or recurrent subfoveal CNV secondary to AMD are enrolled in the study. Only one eye per patient is being treated in the study. Efficacy will be assessed by comparing the effect of PDT with placebo on best-corrected visual acuity using modified ETDRS charts, on contrast threshold using Pelli-Robson charts, and on the extent of CNV closure as assessed by fluorescein angiography.

Study Procedures

Within 7 days before the initial treatment day, all patients are screened to determine if they conform to the inclusion and exclusion criteria. Baseline assessments include a laboratory profile, medical history, and a physical examination. All patients have an ophthalmic evaluation including manifest refraction using modified ETDRS visual acuity charts, contrast threshold assessment (using the Pelli-Robson chart), standardized color stereoscopic fundus photography and fluorescein angiography.

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At screening and every 3 months, all patients visit the clinic and undergo dilated ophthalmoscopy, assessments of visual acuity, contrast threshold, color fundus photography and fluorescein angiography. Best-corrected visual acuity and contrast threshold are determined by a masked vision examiner using a standardized protocol refraction and vision measurement. Retreatment will be conducted if evidence of CNV leakage is detected by fluorescein angiography.

Systemic safety is being assessed by laboratory evaluations at intervals of 6 months. A physical examination including an EKG is being conducted at intervals of 12 months. Adverse events and the patient's general health status is being assessed at each visit. Ocular safety is being assessed by the treating center's ophthalmoscopic examinations and the assessment of best-corrected visual acuity, and by the Photograph Reading Center's evaluation of the fundus photographs and fluorescein angiograms.

2. SAMPLE SIZE/POWER CONSIDERATIONS

In order to adequately assess the safety of PDT with respect to adverse events, a minimum of 300 patients on active treatment are required for the entire trial from both studies. For adverse events that have a true rate of occurrence during the treatment period of 1% or greater, 300 patients should provide a 95% chance of detecting at least one of these events during the trial. A 2-to-1 randomization is being used, so that a total sample size of 450 patients (300 on PDT and 150 on placebo) who complete two years of treatment is the minimum required.

The protocol is conducted and will be analyzed as two "separate" studies, referred to as studies "A" and "B." Each study is split by continent so that an approximate equal number of centers are in both Europe and North America. Within each study, a minimum sample size of 225 patients (150 on PDT and 75 on placebo) who complete 2 years is required. The data from both studies will also be combined in order to generate integrated summaries.

It is estimated that 50% of the placebo patients will be "responders" at the 1-year follow-up visit. A responder is defined as someone who loses less than 15 letters of visual acuity compared with baseline. Based on this estimate, a total sample size of 225 within each study will provide approximately 94% power to detect an absolute difference of 25% between PDT and placebo (Placebo=50% versus PDT=75%). In addition, this sample size will provide 80% power to detect an absolute difference

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from placebo of 20% (Placebo=50% versus PDT=70%). This assumes a two-sided significance level (α) of 0.050.

If it is assumed that up to 17% of the randomized patients will not have data available at the end of the trial because of death, loss to follow-up, and gross ineligibility, then a total of 540 patients (270 per study) need to be randomized to have 450 eligible patients (225 per study) complete the 2-year trial.

The patient randomization is stratified with respect to both study center and the patient's baseline vision level, based on their best-corrected visual acuity (BCVA). Two levels of vision are defined within each center, i.e., 54-73 letters scored on the ETDRS chart (approximately 20/40-20/80), and 34-53 letters scored on the ETDRS chart (approximately 20/100-20/200). The stratification of the randomization with respect to study center and baseline BCVA ensures a 2-to-1 balance between treatment groups within each center and within each level of baseline BCVA. The randomization is stratified on baseline vision level because of the high likelihood that the treatment response will be correlated with the baseline BCVA.

3. SCHEDULE OF ANALYSIS

The total planned study duration for each patient will be 24 months; however, the first analysis (primary analysis) of the efficacy data will be based on the data obtained after all patients have completed their 12-month follow-up visit. Analysis of the results through the first 12 months will be used in regulatory submissions to international boards of health. At the time of these submissions, many patients will have data beyond 12 months. For these regulatory submissions, available data from patients beyond the first 12 months will be included. The amount of data submitted to regulatory authorities will be based on the cut-off date (September 25, 1998) when all patients have completed their 12-month visit.

The second analysis will be performed after all patients have completed their 24-month follow-up visit. The purpose of this analysis will be to confirm the durability of effect and long-term safety of photodynamic therapy. All analyses will be performed using the same data sets and methods used for the 12-month analysis.

All statistical tests in this trial will be two-sided, and all p-values ≤ 0.050 will be considered statistically significant. All statistical analyses for this trial will be performed using the SAS® system.

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4. DATA SETS TO BE ANALYZED

4.1 Intent-to-Treat Data Set

The primary set of efficacy analyses will be performed on the intent-to-treat data set (for all randomized patients), which will include all available efficacy data collected during the trial, and data substituted for all missing values. These analyses will be referred to as the "intent-to-treat" analyses. For each patient, missing efficacy values will be substituted by carrying forward the last observed data point prior to the missing value. This method will be referred to as "last observation carried forward" or "LOCF". For the first analysis at Month 12, patients who were early dropouts will have their last value carried forward through Month 12, and through any additional visits that would have occurred as of the data cut-off date defined above. For the second analysis at Month 24, all patients who were early dropouts at any time during the study will have their last value carried forward through Month 24. The LOCF method will also be used for patients who have one or more missing values followed by an observed value. These missing "interim" value(s) will be replaced by carrying forward the observed value immediately prior to the missing value(s).

4.2 Evaluable-Patients Data Set

A secondary set of efficacy analyses will be performed on the "evaluable-patients" (i.e., "per-protocol") data set, which will include all efficacy data from patients who receive either of the two treatments, meet the inclusion/exclusion criteria without significant deviation, and adhere to the protocol procedures without any significant deviation. The data set will include only the "observed cases", i.e., only the data that was actually collected. No data will be substituted for missing values. These analyses will be referred to as the "evaluable-patients" analyses.

Patient Exclusions

Patients who deviate from the protocol in a significant manner during the course of the trial will have either all or part of their efficacy data excluded from the "evaluable-patients" analysis. Reasons for excluding data from these analyses follow; however, this list may not be exhaustive because of possible unforeseen protocol violations and/or deviations. If additional criteria are appended to the following list, it will be done prior to the unmasking of the treatment codes.

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1. *Patients whose CNV lesions deviate significantly from the protocol-defined inclusion criteria will have <u>all</u> of their efficacy data excluded. These deviations will include the following:*

   - *Extrafoveal CNV*
   - *CNV not due to AMD*
   - *CNV lesion larger than maximum linear dimension of 12 MPS disc area circle*
   - *Baseline visual acuity >73 letters or <34 letters (ETDRS)*

2. *Patients who have two visits with at least one of the following protocol deviations in the treatment administration will have <u>partial</u> data excluded. For these patients, any efficacy data collected following the second deviation will be excluded from all analyses.*

   - *Duration of light administration <50 seconds*
   - *Amount of drug given estimated to be <$4mg/m^2$*
   - *Light administration >30 minutes from the start of the infusion*

3. *Patients who drop out of the study and are no longer being treated according to the protocol, but who are still being followed for safety reasons, will have <u>partial</u> data excluded. Any efficacy data collected at the first visit after a patient's last scheduled treatment will be included in all analyses; however, additional measurements will be excluded.*

4. *Patients who deviate by more than 21 days from the intended treatment visit date will only have the efficacy data <u>at that visit</u> excluded.*

4.3 Safety Data Set

The analysis of the safety variables will be performed on all patients who receive at least one treatment and who have at least one safety variable recorded on the case report form following treatment. These analyses will be referred to as the "safety" analyses. No data will be excluded from these analyses because of protocol violations.

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5. BASELINE COMPARABILITY

Patient demographic and background characteristics (e.g., gender, age, race, smoking history, AMD disease history, vital signs, visual acuity, CNV location, lesion components, area of lesion) will be summarized and tested for treatment group comparability. These analyses will be performed on both the intent-to-treat and evaluable-patients data sets. Continuous-type variables (e.g., age) and ordered categorical variables (e.g., area of lesion) will be analyzed using a Wilcoxon rank sum test. Binary-response variables (e.g., gender) and unordered categorical variables (e.g., race) will be analyzed using a chi-square or Fisher's exact test.

6. EFFICACY ANALYSIS

6.1 Primary Efficacy Variable

The <u>primary</u> efficacy variable will be the proportion of patients who are classified as a "responder" to treatment, based on their BCVA, as measured using the ETDRS charts. Every letter that a patient identifies correctly on the ETDRS chart will be reflected in their BCVA score and thus factored into the determination of whether or not they are a responder. Patients who are not responders to treatment will be considered "non-responders" or "failures".

In the analyses, two separate definitions of a responder will be used which are based on the severity of vision loss:

(i) A decrease from baseline of less than <u>15 letters</u> of vision (approximately 3 lines) in the treated eye. A change of three lines of vision represents a doubling of the visual angle and is considered a <u>clinically significant</u> change.

(ii) A decrease from baseline of less than <u>30 letters</u> of vision (approximately 6 lines) in the treated eye.

The primary analysis for establishing efficacy will be based on the 15-letter responder rates at the 12-month visit. The 15-letter responder rates at the 24-month visit will be used for confirming the durability of effect. Therefore, if the difference in 15-letter responder rates at the 12-month visit is statistically significant between

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treatment groups favoring PDT at the 0.050 level (2-sided), then the study will be judged as having provided pivotal evidence of efficacy for the primary variable.

The corresponding null (H_0) and alternative (H_1) hypotheses to be tested for the primary efficacy variable are as follows:

H_0: The proportion of patient responders is the same for PDT and placebo.
H_1: The proportion of patient responders is different between PDT and placebo.

For the analysis of the responder rates at 12 and 24 months, comparisons between treatment groups will be made using a chi-square test. A 95% confidence interval around the difference in these proportions between groups will be calculated.

As a confirmatory analysis of patient responder rates, a logistic regression model will be used. This model will be used to examine the relationship between responder rates and a set of explanatory variables that will include treatment, baseline visual acuity, and other clinically significant baseline variables. An odds ratio with a 95% confidence interval will be calculated for the treatment effect.

Patient responder rates will also be analyzed using a repeated-measures analysis. For this analysis, the method of weighted-least squares will be used for parameter estimation and hypothesis testing. Factors in the model will include treatment, visit, and treatment-by-visit interaction, as well as other possible factors. For the 12-month analysis, the responder rates at 3, 6, 9, and 12 months will be included. For the 24-month analysis, the responder rates at 3, 6, 9, 12, 15, 18, 21, and 24 months will be included.

6.2 Secondary Efficacy Variables

Secondary efficacy variables will include the following:

a) *The time until a patient has a "moderate" loss of vision, i.e., a decrease from baseline of <u>15 or more letters</u> in the treated eye, based on the patient's BCVA.*

b) *The time until a patient has a "severe" loss of vision, i.e., a decrease from baseline of <u>30 or more letters</u> in the treated eye, based on the patient's BCVA.*

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c) *The proportion of patients whose visual acuity score in their treated eye becomes less than 34 letters (approximately 20/200).*

d) *The time until a patient's visual acuity score in their treated eye becomes less than 34 letters.*

e) *Visual acuity score (number of letters read on the ETDRS chart).*

f) *The number of letters scored from the Pelli-Robson chart for assessment of contrast sensitivity.*

g) *Evidence of increase/decrease in classic and occult CNV compared with baseline (fluorescein angiography gradings).*

For the analysis of the proportions in (c), the same methods will be used as will be done for the responder rates.

Time-to-Event Analysis

It is expected that normal fluctuations in visual acuity may show a patient initially losing 15 (or 30) letters of BCVA from baseline at various times early on in the study, and at later visits show less than a 15 (or 30) letter decrease or even improvement in BCVA. To adjust for this fluctuation, a treatment failure or "event" will be defined for the time-to-event analysis as a patient who demonstrates a 15 (or 30) letter loss of BCVA from baseline at two or more consecutive visits that are at least 45 days apart. Consecutive visits for the purpose of this analysis means consecutive completed visits by the patient, not necessarily protocol-specified visits. If a patient misses a visit, it is the consecutive visits that the patient completes that are used. Therefore, the time intervals in (a) and (b) will be calculated from the study entrance to the first of two consecutive losses of 15 (or 30) letters of BCVA from baseline.

If the first loss of 15 (or 30) letters occurs at the patient's last available measurement, then the time intervals in (a) and (b) will be calculated from the study entrance to this first loss. If the patient is lost to follow-up and the event has not yet occurred, then the observation will be considered censored at the time of loss to follow-up.

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TITLE AND NAME: *A Randomized, Placebo-Controlled, Masked, Multicenter, Phase 3 Study of the Treatment of Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD) Using Photodynamic Therapy (PDT) with Liposomal BPD-MA (verteporfin). Version: May 5, 1997.*

Life-table techniques and the associated methods for presentation of data (e.g., survival curves) will be used to describe the event-free distribution of the two treatment groups. The event-free distributions will be compared between the two treatment groups using a log-rank test. Life-table estimates of the hazard[1] and survival functions for each group will be plotted to assess the level to which the two hazards deviate from proportionality. In addition, a Cox proportional hazards model will be used to confirm the treatment effect and to adjust for predefined stratification variables, possible treatment-by-center interaction, and other clinically significant baseline variables.

If the hazards for the two treatment groups are shown to deviate significantly from proportionality, then either a Cox model with a time dependent covariate(s), or some other model may need to be evaluated.

For secondary variable (d), the time until a patient's visual acuity score in their treated eye becomes less than 34 letters, the same analysis methods will be used as described above (e.g., two or more consecutive visits with less than 34 letters, life-table analysis, etc.).

Visual Acuity Score

Visual acuity scores [secondary variable (e)] will be summarized descriptively at each visit and analyzed at Months 12 and 24 using an analysis of covariance (ANCOVA) model, with treatment and study center included as factors. The covariate will be the baseline visual acuity score. A treatment-by-center interaction term will be included to test for the homogeneity of treatment effects between centers. In addition, a treatment-by-baseline interaction term will be included to test for the homogeneity of regression slopes between treatments. The baseline lesion size (MPS disk areas) will also be investigated as a possible covariate.

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[1] The probability that an individual experiences a failure at time *t* conditional on that they have not experienced the event (failure) up until time *t*. The hazard represents an instantaneous failure rate for an individual not experiencing the event up until time *t*.

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Contrast Sensitivity

The number of letters read on the Pelli-Robson chart for the assessment of contrast sensitivity [secondary variable (f)] will be summarized descriptively and analyzed using an analysis of covariance model, as described above for visual acuity.

CNV Closure

The evidence of increase/decrease in classic and occult CNV compared with baseline [secondary variable (g)] will be based on the fluorescein angiography gradings as made by the Photograph Reading Center. The extent of closure is graded on a 4-point ordered categorical scale, with a fifth category for photographs that can't be graded:

A) No CNV or 100% Closed & No Recurrence
B) Partial Closure ≥50% to <100% Closed & No Recurrence
C) Less than 50% Closed & No Recurrence
D) Recurrence (New CNV)
E) Can't Grade

Frequency distributions of these closure grades will be summarized at each visit. Analyses comparing the two treatment groups will be made at Months 12 and 24 using a Mantel-Haenszel chi-square test. Photographs that can't be graded, i.e., category "E", will be counted as missing and will not be included in the tests. These summaries and statistical tests will be done separately for classic and occult CNV.

6.3 Subgroup Analyses

Subgroup analyses will be performed on the responder rates for visual acuity to determine if the response to treatment is consistent across the subgroup levels. Responder rates will be given by treatment group at each visit, with statistical tests provided at the 12- and 24-month visits. Analyses will be based on the following subgroups:

1. Study Center
2. Age (<75 Years vs. ≥75 Years)
3. Gender (Male vs. Female)

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4. *Race (Caucasian vs. Others)*
5. *Iris Color (Dark vs. Light)*
6. *Initial Visual Acuity (Stratum 1 vs. Stratum 2)*
7. *Size of Lesion at Baseline in MPS Disk Areas (≤ 3, >3 to ≤ 6, >6 to ≤ 9, >9)*
8. *Percent of Classic CNV at Baseline ($\geq 50\%$, $<50\%$, Questionable, No)*
9. *Presence of Occult CNV at Baseline (Yes + Questionable vs. No)*
10. *Presence of Blood at Baseline (Yes + Questionable vs. No)*
11. *Percent of Fibrosis at Baseline (0-25%, 26-50%, >50%)*
12. *Baseline Hypertension (Definite vs. All Others)*
13. *Cigarette Smoking (Past, Current, Never)*
14. *Lesion (New vs. Recurrent, as assessed by the Photograph Reading Center only)*

In #12, Definite Hypertension will be defined as:
- *Systolic BP $\geq$ 160 mmHg, or*
- *Diastolic BP $\geq$ 95 mmHg, or*
- *Systolic BP = 140-159 mmHg, and either history of hypertension, or currently on anti-hypertension medication, or*
- *Diastolic BP = 90-94 mmHg, and either history of hypertension, or currently on anti-hypertension medication.*

7. SAFETY ANALYSIS

Ocular safety will be assessed by evaluating ocular adverse events that occur during the trial, and by evaluating changes between the pre- and post-treatment ophthalmologic examinations. Systemic safety will be assessed by evaluating systemic adverse events that occur during the trial, and by evaluating changes in vital signs and laboratory parameters (hematology, serum chemistry and urinalysis).

7.1 Adverse Events

To help facilitate the summarizing of adverse events, reported adverse-event terms will be coded to a standardized set of "preferred terms" as defined in the COSTART dictionary. These preferred terms will then be categorized into one of twelve body systems as defined in the dictionary. Adverse events will be summarized in the following two sets of tables based on their relationship to the trial medication/

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procedure:

1) *All events regardless of their relationship to the trial medication/procedure.*
2) *Only events which are felt by the investigator to be <u>potentially related</u> to the trial medication/procedure (i.e., relationship listed as "possible," "probable," "definite," or "unknown").*

For each preferred term, summaries by treatment group will be made with respect to the proportion of patients having at least one occurrence of that event during the first year of the trial (plus during any additional visits that occur prior to the data cut-off date), and then again during the entire 2 years of the trial. In addition, the total number of occurrences of each adverse event will be reported for the same time periods. For differences between treatment groups that are felt to be clinically significant, statistical tests will be performed on the proportions using either a chi-square test or a Fisher's exact test.

7.2 Laboratory Data

For each laboratory variable measured every 6 months, both within- and between-group comparisons will be summarized and analyzed as follows:

<u>*Within-Group Changes from Baseline*</u>

A 2x2 square "shift table" will be created for each variable within each treatment group to summarize the distribution of clinically significant lab abnormalities, as indicated on the CRF:

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<u>Posttreatment Lab</u>
Clinically Significant
Abnormality?

		Yes	No
<u>**Baseline Lab**</u> **Clinically Significant Abnormality ?**	**Yes**	Y-Y	Y-N
	No	N-Y	N-N

Each cell of the table will include the frequency count and the corresponding percentage of the whole table, and each table will include marginal totals. To test for a significant shift in the distribution of values from baseline, a McNemar's test for matched pairs will be used. This test compares the "discordant pairs" which are counted in the two cells off the main diagonal (upper right and lower left corners of table).

Scatterplots of each variable comparing baseline to post-treatment will also be created. Since decentralized laboratories will result in different sets of normal ranges, each variable will be normalized as follows:

Relative Value = (Measured Value – Lower Limit) / (Upper Limit – Lower Limit),

where "Lower Limit" and "Upper Limit" refer to the lower and upper limits of the normal range. Thus, relative values less than 0 correspond to measured values below the normal range, relative values greater than 1 correspond to measured values above the normal range, and relative values between 0 and 1 correspond to measured values within the normal range. For each variable, a scatterplot of the baseline versus post-treatment values will be generated and visually assessed.

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Between-Group Changes From Baseline

For each variable assessed at each visit, a summary of the distribution of the changes from baseline will be made based on clinically significant abnormalities. The 4 categories of shifts, as defined above, will be summarized as follows:

Clinically Significant Lab Abnormality?
(Baseline:Posttreatment)

	No:Yes	No:No	Yes:Yes	Yes:No
PDT				
Placebo				

Direction of Shift:	NCS <----to---> CS	<-----No Change----->		CS <----to----> NCS

Each cell of the table will include the frequency count as well as the corresponding percentage within the treatment group, and each table will include marginal totals. A chi-square or Fisher's exact test will be used to test for differences in shifts between treatment groups.

8. REFERENCES

1) Allison P.D., *Survival Analysis Using the SAS® System: A Practical Guide*, Cary, NC: SAS Institute Inc., 1995. 292 pp.

2) Collett D., *Modelling Survival Data In Medical Research*, London: Chapman & Hall, 1994.

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3) Ferris F.L. III, Kassoff A., Bresnick G.H., Bailey I. "New visual acuity charts for clinical research," Am J Ophthalmol 1982; 94: 91-96.

4) Fleiss J.L., *Statistical Methods for Rates and Proportions*, New York: John Wiley & Sons, 1981.

5) Hosmer D.W., Lemeshow S., *Applied Logistic Regression*, New York: John Wiley & Sons, 1989.

6) SAS Institute Inc. *SAS® Procedures Guide, Version 6, Third Edition*, Cary, NC: SAS Institute Inc., 1990. 705 pp.

7) SAS Institute Inc. *SAS/STAT® User's Guide, Version 6, Forth Edition, Volume 1*, Cary, NC: SAS Institute Inc., 1989. 943 pp.

8) SAS Institute Inc. *SAS/STAT® User's Guide, Version 6, Forth Edition, Volume 2*, Cary, NC: SAS Institute Inc., 1989. 846 pp.

9) Stokes, M.E., Davis C.S., Koch G.G., *Categorical Data Analysis Using the SAS® System*, Cary, NC: SAS Institute Inc., 1995. 499 pp.

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REVISION NO. 2:

Reason for Revision: To extend the study in order to obtain additional long-term follow-up information after verteporfin treatment.

The first patients will be scheduled for their Month (M) 24 visit in the study in December 1998. We wish to continue to collect vision data beyond the M24 visit after continued PDT retreatment with verteporfin. There have been no safety concerns regarding retreatment with verteporfin raised by the Data and Safety Monitoring Committee (last data review on June 27 1998). Therefore, all patients on reaching the M24 visit will be offered active treatment in their study eye only (if patients meet the retreatment eligibility criteria in the TAP protocol and if the treating ophthalmologist considers that active treatment might provide some benefit). Neither the investigator nor the patient will be unmasked as to the identity of previous treatment assignment during the double masked randomized study. Laboratory testing, physical examination, vital signs and EKG will not be routinely obtained in this long-term extension. The patients' information on vision and any adverse events experienced will be collected in an abbreviated CRF. Photographs taken at visits beyond M24 must be kept in the study file with the patients records by the treating center but review of the photographs by the reading center is no longer required. No quality of life assessments will be obtained beyond M24.

Amendment: Addition of Appendix 16

APPENDIX 16
TAP Study Extension

Any patient reaching the Month 24 visit will be offered active treatment in their study eye if the patient meets the retreatment criteria in TAP and the treating

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ophthalmologist considers that there may be treatment benefit. Neither the investigator nor the patient will be unmasked. Active treatment will be provided every 3 months thereafter for an additional 24 months. A separate informed consent has to be signed for the study extension and the original informed consent document that the patient signed at the beginning of the TAP Investigation must be provided to, and reviewed with the patient. The flow chart below shows the study procedures that will be conducted at the 3-monthly follow up visit according to the detailed descriptions of the protocol dated May 5, 1997.

Study Procedures Flowchart

Procedure	Treatment Period (Months)								
	24	27	30	33	36	39	42	45	48
Informed Consent	x								
Assess Retreatment Criteria	x	x	x	x	x	x	x	x	x
Concomitant Medication	x	x	x	x	x	x	x	x	x
Best-Corrected Visual Acuity [a]	x	x	x	x	x	x	x	x	x
Peak Contrast Threshold [a]	x	x	x	x	x	x	x	x	x
Color Fundus Photography [a]	x	x	x	x	x	x	x	x	x
Fluorescein Angiography [a]	x	x	x	x	x	x	x	x	x
Dilated Ophthalmoscopy	x	x	x	x	x	x	x	x	x
PDT Treatment [b]	x	x	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x

[a]   *As per the TAP protocol only*
[b]   *If the CNV is leaking, treatment must be conducted within 7 days of fluorescein angiography*

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Information Letter For Patients Completing The 24-Month Follow-Up Visit Of TAP. An Invitation To Continue In The TAP Investigation.

Dear Patient:

During the past two years it has been our privilege to have you as a participant in the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) investigation. With this visit, you have completed the two-year commitment you originally made to the investigation. This letter has been prepared to tell you how much we appreciate your participation, to review the care you have received as a participant in the investigation and to clarify what you can expect from us in the future.

Your participation has enabled us to follow the condition of your eyes according to a fixed schedule. At each visit to the clinic your eyes have been examined, vision has been measured and photographs of the back of the eye have been taken. You may have been interviewed regarding your health status. You may have been retreated (after being given either sugar water or the investigational verteporfin) at your follow-up visits according to a protocol followed by your study ophthalmologist.

Your contribution has been invaluable in helping the ophthalmologists interested in macular diseases to evaluate the effects of photodynamic therapy with verteporfin for treating new blood vessels in the center of vision. More than 600 other patients are taking part in this investigation. The TAP physicians are still collecting data from patients who enrolled in the investigation after you and will be doing so until late 1999.

We do not yet know whether photodynamic therapy with verteporfin is beneficial for patients who have eye problems like yours. It is important for you to understand that this treatment is still experimental and may be associated with unknown adverse effects. However, an independent committee of retina experts has been monitoring the safety of the study and no safety concerns were raised in their last review of the data on June 27 1998. At the end of June 1998, more than half of the 600 patients had completed their 1-year follow-up. An analysis of all data collected from patients who have completed the first year of the TAP investigation will be conducted by the sponsors (QLT PhotoTherapeutics Inc. and CIBA Vision AG) in early 1999 and we will keep you informed as soon as these or any other results of

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the investigation are made available. We have no data at present regarding the safety or benefit of treatment with verteporfin at or beyond 2 years.

Since photodynamic therapy with verteporfin is an experimental treatment it cannot be made generally available until regulatory authorities have reviewed the data and given approval if it is found to be safe and effective. The sponsors are able to provide the active treatment to you if you are willing to continue to be assessed under a protocol. We would like you to consider continuing to be followed by us in an extension to the TAP investigation. This will enable us to obtain additional information on safety and effectiveness of treatment with the active verteporfin. You will be evaluated every 3 months and then if your ophthalmologist considers that there is any potential benefit to be gained by treatment, you will be offered active treatment for an additional period of 24 months whether or not you have been receiving active treatment or the placebo (sugar water) treatment. Neither you nor your ophthalmologist will know which treatment was given up until now, but both of you will be informed when all patients have completed the masked investigation in late 1999. If you do consent to continue in this study and receive verteporfin treatment, the procedures that will be followed at each of the 3 monthly clinic visits will be similar to those you have undergone in the masked TAP investigation, except that there will be no further requirement for routine laboratory testing (blood, urine, EKG), physical examinations and measurement of your blood pressure, heart rate and temperature.

If you are willing to continue in the extension of this TAP investigation, you will be given a copy of the information and consent that you reviewed and signed before entering the TAP investigation 2 years ago. This information will be reviewed with you to ensure that you fully understand the potential risks, discomforts and benefits, the availability of alternative treatments, that your identity will be kept confidential, that your participation is voluntary and you have the right to withdraw from the investigation at any time without affecting the quality of your care, what compensation will occur if you are injured as a direct result of this investigation, and your right to ask questions at any time about the investigation.

If you do not wish to receive verteporfin treatment, or do not wish to continue follow up with us, it is important to remember that you should continue to follow your doctor's advice with respect to monitoring the vision in each of your eyes. We want to make sure that you receive continuing care for your eyes. In the event that you return to the exclusive care of the eye doctor who referred you to us, a summary of

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the information about your eyes which we have collected in this clinic, will be made available to your doctor.

Regardless of where you choose to go for your future eye examinations, our interest in you, your eyes and your vision does not end with this visit. We may be in contact with you from time to time. We may want to tell you about findings from this investigation and any subsequent study, as these become available. We may want to examine your eyes again if there is any new information that may apply to you. Please continue to notify us of any changes in your address and telephone number, even if you plan to be away for only a few months.

We will discuss with you the current status of your eyes and your vision. We will be happy to answer any questions you have about the TAP investigation or about your future eye care.

All of us in the TAP investigation – doctors, nurses, scientists, technicians, photographers and secretaries – are sincerely grateful and appreciate your participation, cooperation and contribution to the TAP investigation.

Sincerely,

Dr. _____   *Phone:* _____
         TAP Ophthalmologist

_____   *Phone:* _____
         TAP Clinic Coordinator

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INFORMED CONSENT FORM FOR EXTENSION TO TAP INVESTIGATION

Consent:

I am aware that the protocol and this Informed Consent has been reviewed and approved by the recognized Institutional Review Board at _____.

I have read or have had read to me the above pages concerning the extension of the TAP investigation involving BPD-MA treatment of choroidal neovascularization. The purpose and procedures of this research project with its possible risks and benefits have been fully and adequately explained to me and I understand them. My questions have been answered, and I voluntarily agree to participate as a subject in the extension of the TAP research investigation. I have been given a copy of the following:

1. *The "Information Letter For Patients Completing The 24-Month Follow-Up Visit Of TAP. An Invitation To Continue In The TAP Investigation."*

2. *The information and consent form I signed at the start of the TAP investigation 2 years ago.*

3. *This consent form.*

_____ _____		_____
Date **Name of Subject**		**Signature of Subject**
_____ _____		_____
Date **Name of Witness**		**Signature of Witness**
_____ _____		_____
Date **Name of Investigator**		**Signature of Investigator**