Statistical Analysis Plan — BPD OCR 003

Verteporfin for Injection

A Randomized, Placebo-Controlled, Masked, Multicenter, Phase IIIB Study of the Treatment of New Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration or Pathologic Myopia using Photodynamic Therapy with Liposomal BPD-MA (verteporfin)

SHORT TITLE: Verteporfin in Photodynamic Therapy (VIP)

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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.

Pathologic myopia (PM) has been reported to be the seventh leading cause of blindness in the United States and is often associated with the development of choroidal neovascularization. The importance of CNV in pathologic myopia may be of even greater impact where pathologic myopia is endemic, such as in certain Asian populations in the United States, Canada, and Asia.

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

Primary:

To determine if verteporfin PDT of new subfoveal CNV will significantly improve or retain visual function compared to placebo (sham treatment); and to evaluate the safety of verporfin PDT.

Secondary:

(1) To determine if verteporfin PDT reduces the risk of developing classic CNV in lesions that present as occult CNV with no classic CNV.

(2) To determine if verteporfin PDT-induced improvements of visual function are associated with a better health-related quality of life compared to placebo (sham treatment).

Study Design

This is a masked, multicenter, randomized, placebo-controlled, Phase IIIB study of the treatment of new subfoveal CNV secondary to AMD or PM using photodynamic therapy. This study is being conducted in both North America and Europe. 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 may be used to support 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 verteporfin PDT or placebo treatment in a ratio of 2-to-1, respectively. Patient randomization is stratified by study center and by the etiology of their CNV (AMD or PM).

Outpatients with new subfoveal CNV secondary to AMD (aged 50 years or older) or any subfoveal CNV secondary to PM (aged 18 or older) 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 verteporfin PDT with placebo on visual acuity (best corrected), on contrast sensitivity, and on the extent of CNV closure as assessed by fluorescein angiography.

Study Procedures

Within 7 days prior to 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 also undergo an ophthalmic evaluation that includes manifest refraction using modified ETDRS visual acuity charts[1], contrast sensitivity using the Pelli-Robson chart, standardized color stereoscopic fundus photography and fluorescein angiography. Visual acuity and contrast sensitivity are determined by a masked vision examiner using a standardized protocol refraction and vision measurement.

Every 3 months following baseline, all patients visit the clinic to undergo dilated ophthalmoscopy, assessments of visual acuity, contrast sensitivity, color fundus photography and fluorescein angiography. Retreatment will occur if evidence of CNV leakage is detected by fluorescein angiography. Although performed at every visit, only the Month-12 and Month-24 fluorescein angiography data are being assessed by the Photograph Reading Center and will be available for analysis.

Adverse events and the patient's general health status (including vital signs) are assessed at each visit. Ocular safety is assessed through the treating center's ocular examinations and assessments of visual acuity, and by the Photograph Reading Center's evaluation of the fundus photographs and fluorescein angiograms.

2. SAMPLE SIZE / POWER CONSIDERATIONS

For the AMD patients, it is estimated that 60% of those who receive placebo will be “responders” (lose less than 15 letters of visual acuity compared with baseline) after one year. If approximately 270 patients (verteporfin PDT 180, Placebo 90) have data available for the analysis at one year, then this sample size will provide approximately 90% power to detect a difference between verteporfin PDT and placebo of 20% (Placebo 60% vs. verteporfin PDT 80%). It is assumed that up to 17% of the approximately 290 randomized AMD patients will not be eligible for the “evaluable-patients” efficacy analysis at one year, because of death, losses to follow-up, or significant protocol deviations resulting in exclusion of data. The remaining 240 patients (verteporfin PDT 160, Placebo 80) will provide approximately 86% power to detect a difference between verteporfin PDT and placebo of 20% (Placebo 60% vs. verteporfin PDT 80%). These calculations assume a two-sided significance level (α) of 0.050.

For the PM patients, it is estimated that 50% of those who receive placebo will be “responders” (lose less than 8 letters of visual acuity compared with baseline) after one

year. If approximately 102 patients (verteporfin PDT 68, Placebo 34) have data available for the analysis at one year, then this sample size will provide approximately 80% power to detect a difference between verteporfin PDT and placebo of 30% (Placebo 50% vs. verteporfin PDT 80%). If 17% of the approximately 110 randomized PM patients are not eligible for the "evaluable-patients" analysis at one year, then the remaining 90 patients (verteporfin PDT 60, Placebo 30) will provide approximately 80% power to detect a difference between verteporfin PDT and placebo of 32% (Placebo 50% vs. verteporfin PDT 82%).

The patient randomization is stratified with respect to study center and the patient's disease etiology (AMD or PM). This stratification will insure a 2-to-1 balance between treatment groups within each study center and within the AMD and PM patients.

3. SCHEDULE OF ANALYSIS

The total planned study duration for each patient will be 24 months; however, the first analysis (primary analysis) of efficacy and safety will be based on the data obtained after all patients have completed their 12-month follow-up visit. Results from this analysis may be used to support regulatory submissions to international boards of health. The database for this analysis will include data from all enrolled patients up to and including the 12-month follow-up visit. Additionally, data available from patient visits occurring after the first 12 months will also be included.

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 verteporfin PDT. All analyses will be performed using the same data sets and methods used for the 12-month analysis.

All statistical tests used in the analyses 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[2,3,4].

4. DATA SETS TO BE ANALYZED

All analyses described in the following sections will be conducted separately for the two CNV etiologies studied (i.e., separate analyses for the AMD and PM patient samples).

4.1 Intent-to-Treat Data Set

The primary set of efficacy analyses will be performed on the intent-to-treat (ITT) patient sample (for all randomized patients). These analyses will be referred to as the "intent-to-treat" analyses.

For the ITT analyses, missing efficacy data resulting from missed visits or premature discontinuations from the study will be handled as follows. For all analyses except the time-to-event analyses, data will be imputed for missing efficacy values by carrying forward the last observed data point prior to the missing value. This method will be referred to as “last observation carried forward” (LOCF).

For the first analysis at Month 12, LOCF will be used up through the 12-month follow-up for all patients; for the second analysis at Month 24, LOCF will be used up through the 24-month follow-up for all patients. For angiographic outcomes, "can't grade" will be considered a valid observation and will be carried forward to the next visit. For the time-to-event analyses, no data will be imputed for missing values since this would inappropriately extend the follow-up time for patients who prematurely discontinued from the study.

In addition, as confirmation of the primary ITT efficacy analysis with LOCF, the responder analysis (patients with a decrease from baseline of less than 15 letters [AMD] or 8 letters [PM] of visual acuity in the study eye) will be performed using the ITT patient sample without imputation for missing values (i.e., ITT without LOCF).

4.2 Evaluable-Patients Data Set

A secondary set of analyses on the primary efficacy variable (15-letter response for AMD patients or 8-letter response for PM patients) will be performed on the “evaluable-patients” data set. This data set 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. This data set will only include the “observed cases”, i.e., the data that were actually collected. No imputation for missing values will be done. 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 be excluded from the evaluable-patients analyses. The exclusions from the first year evaluable-patients analyses will be identified before the treatment codes are unmasked. Reasons for excluding patients from evaluable analyses follow; however, this list may not be exhaustive because of possible unforeseen protocol violations that may occur. If additional criteria are appended to the following list, they will be added prior to the unmasking of the treatment codes for the first year analyses.

1. Patients whose CNV lesions (as assessed by the Photograph Reading Center) or ETDRS visual acuity (as assessed by the Treating Center) deviate significantly from the protocol-defined inclusion criteria will be excluded. These baseline/screening deviations will include the following:

    - No CNV or <50% CNV
    - CNV not due to AMD or PM
    - Confirmed extrafoveal CNV
    - Greatest linear dimension of CNV lesion >6200 microns
    - Visual acuity <45 letters (only for PM patients and AMD patients without new classic CNV-containing lesions)
    - Visual acuity <65 letters (only for AMD patients with new classic CNV-containing lesions)

2. Patients who have two visits with at least one of the following protocol deviations in the treatment administration will be excluded.

    - Duration of light administration <50 seconds
    - Amount of drug given estimated to be <4mg/m^2 of body surface area
    - Light administration >30 minutes from the start of the infusion
    - Patient not retreated in violation of the protocol (i.e., CNV leakage was noted by the investigator but the patient was not retreated)
    - Patient missed a visit and was not evaluated for re-treatment

3. Patients who have cataract surgery or posterior capsulotomy in the study eye, or laser photocoagulation, external beam radiation or any experimental therapy applied to the CNV lesion of the study eye during the study, will be excluded.

4. Patients who have discontinued randomized treatment but are still on follow-up for visual acuity assessment will be excluded.

If a patient meets criteria 2, 3 or 4 prior to the Month 12 visit or meets criterion 1 then the patient will be excluded from all the evaluable patient analyses. If a patient meets criteria 2, 3 or 4 from Month 12 to Month 24 (not including the Month 24 visit) then the patient will be excluded from the second year analyses only.

4.3 Safety Data Set

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

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 comparability between treatment groups. 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. Unordered categorical variables (e.g., race) will be analyzed using a Fisher's exact test.

6. EFFICACY ANALYSIS

All efficacy analyses are for the treated (study) eyes.

6.1 Primary Efficacy Variable

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

In the analyses, the following definitions of a responder will be used:

(i) For PM patients: a decrease from baseline of less than 8 letters of visual acuity (approximately 1.5 lines). The ophthalmic community generally considers a visual acuity change in PM patients of 1.5 lines or more as clinically significant.

(ii) For AMD patients: a decrease from baseline of less than 15 letters of visual acuity (approximately 3 lines). A change of 3 lines of visual acuity represents a doubling of the visual angle and is considered a clinically significant change for AMD patients.

The primary analysis for establishing efficacy will be based on the 8-letter responder rate and the 15-letter responder rate at the 12-month visit for PM patients and AMD patients, respectively. The respective responder rates at the 24-month visit will be used for confirming the durability of effect. Therefore, if the difference in responder rates at the 12-month visit is statistically significant between treatment groups favoring verteporfin 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 in that population.

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

For the analysis of the proportion of responders at 12 and 24 months, comparisons between treatment groups will be made using a Pearson chi-square test[5] without continuity correction. A 95% confidence interval around the difference in these proportions between groups at each follow-up visit will be calculated.

To explore the relationships between the patient response and various baseline variables, and to adjust for these variables in assessing the treatment effect on the patient response, a logistic regression analysis[6] will be performed. This analysis will include treatment (verteporfin PDT vs. placebo), baseline visual acuity score, baseline classic lesion component [≥50% + <50% + Questionable (classic containing) vs. None (occult only)] for AMD patients, baseline lesion size (GLD), age at baseline, gender (male vs. female), race (Caucasian vs. others), iris color [dark (black, brown) vs. light (hazel, green, blue and gray)], presence of blood at baseline (Yes+Questionalble vs. No), laser type (Coherent vs Zeiss vs. mixed), pooled center (centers with ≥20 vs. <20 patients) and other unbalanced and clinically important baseline variables. Interactions between the treatment and each of the other variables in the logistic model will also be evaluated. Non-significant terms will be

removed from the model using a backward elimination procedure. Main effects, however, will not be removed from the model unless the interaction term involving the main effects was removed prior to the main effects (i.e., was not statistically significant). An odds ratio with a 95% confidence interval will be calculated for the treatment effect as well as for other variables in the final logistic model.

6.2 Secondary Efficacy Variables

Unless otherwise specified, the secondary efficacy variables listed below will be evaluated for both AMD and PM patients.

a) The change from baseline for visual acuity scores measured using the ETDRS charts.

b) The change from baseline for contrast sensitivity scores measured using the Pelli-Robson chart.

c) The proportion of patients with a decrease from baseline of less than 15 letters of visual acuity (approximately 3 lines). This endpoint will be analyzed as a secondary variable for PM patients only.

d) The proportion of patients with a decrease from baseline of less than 30 letters of visual acuity (approximately 6 lines). This endpoint will be analyzed as a secondary variable for AMD patients only.

e) The proportion of patients whose visual acuity score decreases to less than 34 letters (approximately 20/200).

f) The time until a patient has a decrease from baseline of 8 or more letters, based on the patient's visual acuity. This endpoint will be analyzed for PM patients only.

g) The time until a patient has a decrease from baseline of 15 or more letters, based on the patient's visual acuity.

h) The time until a patient has a decrease from baseline of 30 or more letters, based on the patient's visual acuity. This endpoint will be analyzed for AMD patients only.

i) The change from baseline in the level of classic CNV (separately for the level of occult CNV) as measured by the extent of fluorescein leakage by the Photograph Reading Center.

j) The proportion of AMD patients who had no classic CNV at baseline but later developed classic CNV during the course of the study.

k) The area of the lesion including CNV, natural scar and obscuring features.

l) The change from baseline in the subjective vision scores.

Visual Acuity Score

The change from baseline in the visual acuity score [secondary variable (a)] will be summarized descriptively (mean, standard deviation and frequency distribution) at each visit by treatment group and also evaluated using an analysis of covariance (ANCOVA) model at Months 12 and 24. Factors in the model will include treatment (verteporfin PDT vs. placebo), baseline classic lesion component (≥50% + <50% + Questionable vs. None) for AMD patients, gender (male vs. female) and the pooled study center [pooled according to number of patients (≥20 vs. <20) in each center]. Covariates will include baseline visual acuity score, baseline lesion size (GLD) and patient age at baseline. Other baseline variables, if unbalanced between the treatment groups and clinically important, may also be included in the model. Interactions between the treatment and each of the other variables in the analysis of covariance model will also be evaluated. Non-significant terms will be removed from the model using a backward elimination procedure. Main effects, however, will not be removed from the model unless the interaction term involving the main effects was removed prior to the main effects (i.e., was not statistically significant). Least squares means and the associated statistical tests will be provided for the variables in the final model.

Contrast Sensitivity

The change from baseline in the contrast sensitivity score [secondary variable (b)] will be summarized descriptively and analyzed using an analysis of covariance model, as described previously for visual acuity. In this analysis, the baseline contrast sensitivity score will be used as the covariate instead of baseline visual acuity score.

Analyses of Proportions

The proportions outlined in (c), (d), (e) and (j) of Section 6.2 will be analyzed using the same methods described for the primary analysis of the proportion of responders. For the secondary variable (j), patients who developed CNV during the course of study will be those

with the ratings of “partial closure”, “minimal closure” or “progression” as defined later in this section.

Time-to-Event Analysis

It is expected that normal fluctuation in visual acuity may show a patient initially losing a certain number of letters of visual acuity from baseline at various times early on in the study, and at later visits show less than the number of letters decrease or even improvement in visual acuity. To adjust for this possible variation, a treatment failure or “event” will be defined for the time-to-event analysis as an 8-, 15-, or 30-letter loss of visual acuity from baseline at *two or more consecutive visits that are at least 45 days apart*. Consecutive visits for the purpose of this analysis includes all visits completed by the patient, not only 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 (f), (g), and (h) will be calculated from initial treatment to the first of *two consecutive losses* of 8, 15, and 30 letters of visual acuity from baseline respectively.

If the first loss of 8, 15, or 30 letters occurs at the patient’s last available measurement, then the time intervals in (f), (g), and (h) will be calculated from initial treatment 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.

Kaplan-Meier techniques[7,8] 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. The logarithm of the negative logarithm of the Kaplan-Meier estimate of the survival function for each group will be plotted versus the logarithm of time to assess proportionality of the two hazards. A Cox proportional hazards model[7,8] will be used to assess the treatment effect while controlling for the significant variables and interactions identified in the logistic regression analysis. Non-significant variables and interactions will be further eliminated from the Cox model. In addition, the risk ratio (i.e., hazard ratio) of verteporfin relative to placebo also will be provided.

If the hazards for the two treatment groups deviate significantly from being proportional, then either a Cox model with a time dependent covariate, or some other model may need to be evaluated.

Extent of Fluorescein Leakage

Changes in the level of classic and occult CNV from baseline [secondary variable (i)] will be assessed using fluorescein angiography gradings as determined by the Photograph Reading Center. The change is graded on a 4-point ordered categorical scale, with a fifth category for photographs that can't be graded:

A)	Complete Closure:	No CNV or 100% closed & no progression
B)	Partial Closure:	≥50% to <100% closed & no progression
C)	Minimal Closure:	<50% closed & no progression
D)	Progression:	New CNV beyond the perimeter of the original overall lesion
E)	Can't Grade:	CNV grade cannot be determined

Frequency distributions of these grades will be summarized by treatment group at each visit where the measurements are available. Analyses comparing the two treatment groups will be made at Months 12 and 24 using a Mantel-Haenszel chi-square test[9] stratified by the baseline CNV lesion component (Yes+Questionable vs. No). 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.

Area of Lesion

The distribution of area of lesion [secondary variable (k)] will be tabulated for each treatment group at each visit. A Mantel-Haenszel chi-square test will be used to evaluate the difference in lesion area distributions between the two treatment groups at Months 12 and 24 stratified by the baseline lesion areas (≤3, >3 to ≤6, >6 to ≤9, and >9). Patients with the area of lesion equal to "Can't Grade" will be excluded from testing.

Patient's Subjective Vision Score

The mean change from baseline and the distribution of the change in the subjective vision score will be summarized by treatment group at each measurement point.

Health-Related Quality of Life (HQL) Analysis

HQL Statistical Analysis Plan will be a separate document. Results of HQL analyses will be summarized in a separate study report.

6.3 Subgroup Analyses

Subgroup analyses will be performed on the primary endpoints (8- and 15-letter responders for PM and AMD patients, respectively) for visual acuity if the treatment effect is inconsistent across the subgroup levels. The proportion of responders will be presented by treatment group at each visit (up to Month 12 and month 24 for the first and second analyses, respectively), with the between-group statistical tests provided at the 12- and 24-month visits. These analyses will only be performed on the ITT set of patients with LOCF used to impute for missing visual acuity scores. The possible variables to be included in the subgroup analyses and the levels of each variable are as follows:

1. Pooled center (centers with ≥20 patients vs. centers with <20 patients)
2. Gender (Male vs. Female)
3. Age (≥75 vs. <75 for AMD, ≥50 vs. <50 for PM)
4. Race (Caucasian vs. Others)
5. Iris Color [Dark (Black, Brown) vs. Light (Hazel, Green, Blue, Gray)]
6. Baseline visual acuity score (≥ 65 vs. < 65 for AMD and ≥ 60 vs. < 60 for PM)
7. Lesion size (GLD) at baseline (≥4000 vs. <4000 microns for AMD and ≥2000 vs. <2000 microns for PM) as determined by the Photograph Reading Center
8. Presence of classic CNV at Baseline (≥50% + <50% + Questionable vs. None) as determined by the Photograph Reading Center (for AMD only)
9. Presence of Blood at Baseline (Yes+Questionable vs. No) as determined by the Photograph Reading Center (for AMD only)
10. Laser type (Coherent vs. Zeiss vs. mixed) for treatments prior to Month 12 or Month 24

6.4 Additional Subgroup Analysis by Classic CNV Lesion Component for AMD Patients

Classic lesion component has been identified as an important factor affecting the outcome of the verteporfin PDT in two randomized, placebo controlled Phase III studies (BPD OCR 002A and B) in the treatment of subfoveal CNV secondary to AMD. The results of BPD OCR 002 suggest that for AMD patients the treatment effect is dependent on the proportion of classic CNV in the baseline lesion, and that the treatment is more efficacious when proportionally more classic CNV is present in the lesion at baseline. Since for AMD patients the presence of classic CNV in the lesion was determined to be an important predictor of the treatment effect, a detailed subgroup analysis (as described below) will be performed comparing AMD patients with classic CNV (≥50% + <50% + Questionable) versus those without classic CNV (None) as determined by the Photograph Reading Center.

Baseline comparability between the two treatment groups within each of the lesion component groups (with classic versus without classic) will be evaluated using the same methods as described in Section 5. The ITT analyses of all the primary and secondary variables will be repeated for the AMD patients with classic CNV and separately without classic CNV at baseline using the same methods as described in Sections 6.1 and 6.2.

6.5 Interim Evaluation in Pathologic Myopia

Since there was little known about the specific time-course of this disease, an interim evaluation of unmasked visual acuity data was planned in the protocol to assess the accuracy of the initial assumptions used in the sample size calculation. However, because the patient accrual was much faster than expected and the originally planned sample size was achieved by the time of the planned interim evaluation, the evaluation of unmasked visual acuity data was not performed.

7. SAFETY ANALYSIS

Ocular safety will be assessed by evaluating ocular adverse events that occur during the trial (i.e., treatment emergent), and by evaluating changes between the pre- and post-treatment ocular examinations. Ocular safety will also be assessed by tabulating the extent of fibrosis, and by tabulating changes from baseline for sub/intra retinal hemorrhage at each visit. These will both be determined from the fluorescein angiograms by the Photograph Reading Center.

Systemic safety will be assessed by evaluating systemic adverse events that occur during the trial, and by evaluating changes in vital signs (blood pressure and heart rate) using descriptive statistics (n, mean, standard deviation, minimum, maximum).

7.1 Adverse Events

For summarizing adverse events, each reported adverse event term will be coded to a preferred term and its corresponding body system using a modified Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) Dictionary (Fourth Edition, 1993). Sponsor-defined preferred terms have been added to the dictionary to allow more accurate coding of events that do not have a suitable COSTART term. The modified dictionary also includes an additional body system, called “Treatment Site — Ocular”, for study eye ocular events. Adverse events that occur in the non-study eye will be assigned to the standard COSTART body system Special Senses.

The Sponsor has also created two higher-level summary terms to group all patients who report injection site events, and all patients who report visual disturbance events (vision abnormal, vision decreased, and visual field defect). These two summary terms are called “Injection Site Adverse Events” and “Visual Disturbance”.

Summary tables by treatment group will be created for:

1. All adverse events combined.
2. All adverse events grouped by their recorded intensity.
3. All adverse events grouped by the number of treatment courses received prior to their occurrence.

For each of these three summaries, two sets of tables will be created based on the relationship of the adverse event to the study medication/procedure:

1. All events regardless of their relationship to the study medication/procedure.
2. Subset of events which are felt by the investigator to be associated with the study medication/procedure (i.e., relationship listed as “possible,” “probable” or “definite”).

For each summary table, the number and percentage of patients having at least one occurrence of each adverse event (based on the preferred term) will be summarized, along with the total number of occurrences of each adverse event. The first set of tables will be done for all events that occur prior to the 12-month data cut-off, and then later for all events that occur during the entire 24 months of the study.

For adverse events summarized by intensity, (mild, moderate, severe, life-threatening, or unknown), the most severe adverse event will be summarized for patients with more than one event coded to the same preferred term.

For adverse events summarized by course of treatment, the following conventions will be used:

- Adverse events that occur after Course 1 but before Course 2 will be counted as Course 1 events; adverse events that occur after Course 2 but before Course 3 will be counted as Course 2 events, etc.

- If an adverse event starts on the same day that treatment is administered, then the adverse event will be counted under the course of treatment given on that day.

- If an adverse event start date is missing, then the event will assume to have started prior to the visit at which it is reported.

For the AMD patients, all adverse event tables will also be generated for the two subgroups of patients described in Section 6.4. These subgroups will include AMD patients with classic CNV at baseline and those without classic CNV at baseline.

7.2 Concomitant Medications

For summarizing concomitant medications, each medication will be coded to a preferred term and a corresponding therapeutic drug class using the World Health Organization (WHO) Drug Dictionary. The “ATC Code” and “Level 3 Text” from the dictionary will be used for the preferred term and therapeutic drug class, respectively.

Summary tables by treatment group will be created for the number and percentage of patients receiving each medication (based on the preferred term) at least once during the given time period. The first set of tables will be done for all medications received prior to the 12-month data cut-off date, and then later for all medications received during the entire 24 months of the study.

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9. APPENDIX: MAJOR TABLE SHELLS

TABLE 1

DISPOSITION OF PATIENTS BY TREATMENT GROUP

	VERTEPORFIN PDT		PLACEBO		TOTAL	
NUMBER OF PATIENTS	N	(%)	N	(%)	N	(%)
RANDOMIZED TO MASKED TREATMENT	N =		N =		N =	
RECEIVED RANDOMIZED TREATMENT						
MONTH 0						
MONTH 3						
MONTH 6						
MONTH 9						
MONTH 12						
ON STUDY THROUGH[1]						
BASELINE						
MONTH 0						
MONTH 3						
MONTH 6						
MONTH 9						
MONTH 12						
HAD VA ASSESSMENT						
BASELINE						
MONTH 3						
MONTH 6						
MONTH 9						
MONTH 12						
DISCONTINUED FROM STUDY[2]						
LOST TO FOLLOW-UP						
PATIENT REQUEST						
NON-COMPLIANCE						
GROSS VIOLATION INC/EXC CRITERIA						
OTHER (OTHER THAN DEATH)						
DEATH						
** TOTAL **						
INCLUDED IN INTENT-TO-TREAT ANALYSIS (LOCF)						
BASELINE						
MONTH 0						
MONTH 3						
MONTH 6						
MONTH 9						
MONTH 12						
INCLUDED IN EVALUABLE-PATIENTS ANALYSIS (W/O LOCF)						
BASELINE						
MONTH 0						
MONTH 3						
MONTH 6						
MONTH 9						
MONTH 12						

[1] INCLUDES MISSED VISITS IF THEY OCCURRED BEFORE PATIENT'S LAST RECORDED FOLLOW-UP VISIT.
[2] REASON REPORTED BY INVESTIGATOR ON CRF TERMINATION FORM.

TABLE 2

CUMULATIVE DISTRIBUTION OF THE NUMBER OF TREATMENTS RECEIVED
OVER THE COURSE OF THE STUDY FOLLOW-UP BY TREATMENT GROUP

		TREATMENT GROUP					
		VERT. PDT		PLACEBO		TOTAL	
VISIT	NO. OF TREATMENTS	N	%	N	%	N	%
MONTH 0	1						
MONTH 3	1						
	2						
	» NO. TRT'D AT VISIT						
MONTH 6	1						
	2						
	3						
	» NO. TRT'D AT VISIT						
MONTH 9	1						
	2						
	3						
	4						
	» NO. TRT'D AT VISIT						
MONTH 12	1						
	2						
	3						
	4						
	5						
	» NO. TRT'D AT VISIT						

TABLE 3

DISTRIBUTION OF PATIENTS TREATED/NOT TREATED
BY TREATMENT GROUP, VISIT, AND REASONS FOR NON-TREATMENT

		VERTEPORFIN PDT		PLACEBO		TOTAL	
VISIT	TREATMENT RECEIVED?	N	(%)	N	(%)	N	(%)
MONTH 0	YES						
MONTH 3	YES						
	NO						
	NO CNV LEAKAGE						
	INELIGIBLE						
	ELIGIBLE, NOT TREATED						
	ON STUDY (MISSED VISIT)						
	ON STUDY (DISCONTINUED TRT)						
	DISCONTINUED FROM STUDY						
MONTH 6	YES						
	NO						
	NO CNV LEAKAGE						
	INELIGIBLE						
	ELIGIBLE, NOT TREATED						
	ON STUDY (MISSED VISIT)						
	ON STUDY (DISCONTINUED TRT)						
	DISCONTINUED FROM STUDY						
MONTH 9	YES						
	NO						
	NO CNV LEAKAGE						
	INELIGIBLE						
	ELIGIBLE, NOT TREATED						
	ON STUDY (MISSED VISIT)						
	ON STUDY (DISCONTINUED TRT)						
	DISCONTINUED FROM STUDY						
MONTH 12	YES						
	NO						
	NO CNV LEAKAGE						
	INELIGIBLE						
	ELIGIBLE, NOT TREATED						
	ON STUDY (MISSED VISIT)						
	ON STUDY (DISCONTINUED TRT)						
	DISCONTINUED FROM STUDY						

TABLE 4

SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS BY TREATMENT GROUP

	VERTEPORFIN PDT		PLACEBO		TOTAL		
	N	(%)	N	(%)	N	(%)	P-VALUE
NUMBER OF PATIENTS	N =		N =		N =		
GENDER							
FEMALE							
MALE							
RACE							
CAUCASIAN							
BLACK							
ASIAN							
HISPANIC							
OTHER							
AGE (YEARS)							
< 50							
50-64							
65-74							
75-84							
>= 85							
N							
MEAN							
STD							
MEDIAN							
MINIMUM							
MAXIMUM							
SYSTOLIC BP							
N							
MEAN							
STD							
MEDIAN							
MINIMUM							
MAXIMUM							
DIASTOLIC BP							
N							
MEAN							
STD							
MEDIAN							
MINIMUM							
MAXIMUM							
NOTABLE MEDICAL HISTORY?							
YES							
NO							
IRIS COLOR (STUDY EYE)							
DARK							
LIGHT							
UNKNOWN							

TABLE 4 (CONTINUED)

SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS BY TREATMENT GROUP

	VERTEPORFIN PDT		PLACEBO		TOTAL		
	N	(%)	N	(%)	N	(%)	P-VALUE
VISUAL ACUITY (#LETTERS) STUDY EYE							
N							
MEAN							
STD							
MEDIAN							
MINIMUM							
MAXIMUM							
VISUAL ACUITY (#LETTERS) FELLOW EYE							
N							
MEAN							
STD							
MEDIAN							
MINIMUM							
MAXIMUM							
CONTRAST SENSITIVITY (#LETTERS) STUDY EYE							
N							
MEAN							
STD							
MEDIAN							
MINIMUM							
MAXIMUM							
CONTRAST SENSITIVITY (#LETTERS) FELLOW EYE							
N							
MEAN							
STD							
MEDIAN							
MINIMUM							
MAXIMUM							
PRIOR TREATMENT FOR AMD?							
NO							
YES							
LASER PHOTOCOAG. (STUDY EYE)							
INTERFERON							
RETINOIC ACID							
THALIDOMIDE							
OTHER							
MICRONUTRIENT SUPPLEMENTS							
NO							
YES							
UNKNOWN							
SMOKING HISTORY							
NEVER SMOKED							
CURRENT SMOKER							
PREVIOUS SMOKER							

TABLE 5

SUMMARY OF BASELINE PHOTOGRAPH READING CENTER
DISEASE AND LESION CHARACTERISTICS BY TREATMENT GROUP

	VERTEPORFIN PDT N	(%)	PLACEBO N	(%)	TOTAL N	(%)	P-VALUE
NUMBER OF PATIENTS	N =		N =		N =		
EVIDENCE OF CNV							
>= 50% OF LESION							
< 50% OF LESION							
QUESTIONABLE							
NO EVIDENCE							
CAN'T GRADE							
CNV LOCATION							
SUBFOVEAL							
PROBABLY SUBFOVEAL							
NOT SUBFOVEAL							
CAN'T GRADE							
LESION COMPONENTS							
CLASSIC							
>= 50% OF LESION							
< 50% OF LESION							
QUESTIONABLE							
NO EVIDENCE							
CAN'T GRADE							
OCCULT							
NO							
YES							
QUESTIONABLE							
CAN'T GRADE							
LASER RX AREA							
NO							
YES							
QUESTIONABLE							
CAN'T GRADE							
BLOOD							
NO							
YES							
QUESTIONABLE							
CAN'T GRADE							
BLOCKED FLUORESCENCE							
NO							
YES							
QUESTIONABLE							
CAN'T GRADE							
SEROUS PED							
NO							
YES							
QUESTIONABLE							
CAN'T GRADE							

TABLE 5 (CONTINUED)

SUMMARY OF BASELINE PHOTOGRAPH READING CENTER
DISEASE AND LESION CHARACTERISTICS BY TREATMENT GROUP

	VERTEPORFIN PDT N	(%)	PLACEBO N	(%)	TOTAL N	(%)	P-VALUE
CNV SECONDARY TO:							
AMD ONLY							
PM ONLY							
AMD + OTHER							
PM + OTHER							
AMD + PM							
OTHER							
AREA OF LESION (MPS DA)							
<=3							
>3 to <=6							
>6 to <=9							
> 9							
CAN'T GRADE							
GREATEST LINEAR DIMENSION (MICRONS)							
N							
MEAN							
STD							
MEDIAN							
MINIMUM							
MAXIMUM							
MPS LASER ELIGIBLE							
NO							
YES							
NEW CNV <=2 MPS DA							
REC. CNV <=6 MPS DA							
CAN'T DETERMINE							

TABLE 6

ANALYSIS OF RESPONDERS (PATIENTS WHO LOST LESS THAN 15 LETTERS OF BCVA FROM BASELINE)
BY TREATMENT GROUP AND VISIT

	VERTEPORFIN PDT				PLACEBO				VERTEPORFIN PDT VS. PLACEBO		
	N	RESPONDERS			N	RESPONDERS			RESPONDERS		
VISIT	.	n	~(Ppdt)	95% CI	.	n	~(Ppla)	95% CI	~(Ppdt-Ppla)	95% CI	*P-VALUE
BASELINE											
MONTH 3											
MONTH 6											
MONTH 9											
MONTH 12											

* CHI-SQUARE TEST USED TO COMPARE THE PROPORTION OF PATIENT RESPONDERS (VERTEPORFIN PDT VS. PLACEBO)

~ P = PROPORTION OF RESPONDERS.

NOTE: THE SAME TABLE WILL BE PRODUCED FOR THE RESPONDER RATES BASED ON 8- AND 30-LETTER DECREASE IN BCVA FROM BASELINE.

TABLE 7

SUMMARY STATISTICS FOR VISUAL ACUITY SCORES BY TREATMENT GROUP AND VISIT

VISIT	VISUAL ACUITY (# LETTERS)	TREATMENT	N	MEAN	STD.	MIN.	MAX.
BASELINE	SCORE	VERTEPORFIN PDT					
		PLACEBO					
MONTH 3	SCORE	VERTEPORFIN PDT					
		PLACEBO					
	CHG. FROM BASELINE	VERTEPORFIN PDT					
		PLACEBO					
MONTH 6	SCORE	VERTEPORFIN PDT					
		PLACEBO					
	CHG. FROM BASELINE	VERTEPORFIN PDT					
		PLACEBO					
MONTH 9	SCORE	VERTEPORFIN PDT					
		PLACEBO					
	CHG. FROM BASELINE	VERTEPORFIN PDT					
		PLACEBO					
MONTH 12	SCORE	VERTEPORFIN PDT					
		PLACEBO					
	CHG. FROM BASELINE	VERTEPORFIN PDT					
		PLACEBO					

NOTE: THE SAME TABLE WILL BE PRODUCED FOR THE CONTRAST SENSITIVITY SCORES.

TABLE 8

CLOSURE OF CLASSIC CNV BY TREATMENT GROUP AND VISIT

		CNV CLOSURE GRADE													
		100%		50-<100%		<50%		RECURRENCE		CAN'T GRADE		MISSING		**TOTAL**	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
VISIT .	TREATMENT GROUP														
MONTH 3	VERT. PDT														
	PLACEBO														
MONTH 6	VERT. PDT														
	PLACEBO														
MONTH 9	VERT. PDT														
	PLACEBO														
MONTH 12	VERT. PDT														
	PLACEBO														

NOTE: THE SAME TABLE WILL BE PRODUCED FOR CLOSURE OF OCCULT CNV

TABLE 9

PHOTOGRAPH READING CENTER CONSENSUS GRADING OF CNV LESION SIZE (INCLUDING NATURAL SCAR AND OBSCURING FEATURES) BY TREATMENT GROUP AND VISIT

		LESION SIZE (MPS DA)																							
		<=1		<=2		<=3		<=4		<=5		<=6		<=9		<=12		<=16		>16		CAN'T GRADE		**TOTAL**	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
VISIT . .	TREATMENT GROUP																								
BASELINE	VERT. PDT																								
	PLACEBO																								
MONTH 3	VERT. PDT																								
	PLACEBO																								
MONTH 6	VERT. PDT																								
	PLACEBO																								
MONTH 9	VERT. PDT																								
	PLACEBO																								
MONTH 12	VERT. PDT																								
	PLACEBO																								

TABLE 10

SUMMARY OF ALL ADVERSE EVENTS BY TREATMENT GROUP, BODY SYSTEM AND PREFERRED TERM

		TREATMENT GROUP					
		VERTEPORFIN PDT			PLACEBO		
		PATIENTS		TOTAL EVENTS	PATIENTS		TOTAL EVENTS
		N	%	N	N	%	N
BODY SYSTEM	PREFERRED TERM						
-ALL-	- TOTAL PATIENTS EXPOSED TO TREATMENT						
	-ALL EVENTS						
BODY AS A WHOLE	-ALL EVENTS						
	ABDOMINAL PAIN						
	ABSCESS						
	ACCIDENTAL INJURY						
	ALLERGIC REACTION						
	ASTHENIA						
	BACK PAIN						
CARDIOVASCULAR	-ALL EVENTS						
	ANGINA PECTORIS						
	AORTIC STENOSIS						
	ARRHYTHMIA						
	ARTERIOSCLEROSIS						
	ATRIAL FIBRILLATION						
	ATRIAL FLUTTER						
DIGESTIVE	-ALL EVENTS						
	BLOODY DIARRHEA						
	CHOLECYSTITIS						
	CHOLELITHIASIS						
	COLITIS						
	CONSTIPATION						
	DIARRHEA						
	DRY MOUTH						
ENDOCRINE	-ALL EVENTS						
	HYPOTHYROIDISM						
HEMIC AND LYMPHATIC	-ALL EVENTS						
	ANEMIA						
	ECCHYMOSIS						

TABLE 11

SUMMARY OF VISUAL DISTURBANCE AND INJECTION SITE ADVERSE EVENTS
BY TREATMENT GROUP, SUMMARY TERM AND PREFERRED TERM

		TREATMENT GROUP					
		VERTEPORFIN PDT			PLACEBO		
		PATIENTS	TOTAL EVENTS		PATIENTS	TOTAL EVENTS	
		N	%	N	N	%	N
SUMMARY TERM	PREFERRED TERM						
-ALL-	- TOTAL PATIENTS						
	EXPOSED TO TREATMENT						
	-ALL EVENTS						
INJECTION SITE	-ALL EVENTS						
ADVERSE EVENT	INJECTION SITE EDEMA						
	INJECTION SITE						
	EXTRAVASATION						
	INJECTION SITE						
	FIBROSIS						
	INJECTION SITE						
	HEMORRHAGE						
	INJECTION SITE						
	HYPERSENSITIVITY						
	INJECTION SITE						
	INFLAMMATION						
	INJECTION SITE PAIN						
SPECIAL SENSES:	-ALL EVENTS						
VISUAL DISTURBANCE	VISION ABNORMAL						
	VISION DECREASED						
	VISUAL FIELD DEFECT						
TREATMENT SITE -	-ALL EVENTS						
OCULAR: VISUAL	VISION ABNORMAL						
DISTURBANCE	VISION DECREASED						
	VISUAL FIELD DEFECT						