STATISTICAL APPENDIX

Ocular Photodynamic Therapy with Verteporfin for Macular Degeneration

Centers for Medicare and Medicaid Services

Document Summary:

This document has been prepared for the Centers for Medicare and Medicaid Services (CMS) by Griswold Consulting. It is designed as a technical analysis, meant to augment the information regarding questions raised about Ocular Photodynamic Therapy with Verteporfin for Macular Degeneration. The background for the Verteporfin in Photodynamic Therapy (VIP) trial and the CMS questions therein may be found in the National Coverage Analysis of Ocular Photodynamic Therapy with Verteporfin for Macular Degeneration (#CAG-00066R1)

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PART I.

Primary Analyses Specified in TAP & VIP Protocols.

VIP Study

Primary Analyses from *Initial* Analytic Plan

Protocol BPD OCR 003
Dec 19, 1997 pg. 30-37

VIP Study

Initial Analytic Plan: Protocol BPD OCR 003; Dec 19, 1997 pg. 30-37

Protocol Page

Statistical and Analytic Plan (pg. 32)

DATA

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d. systemic hypertension
e. initial visual acuity
f. number of treatments performed
g. CNV lesion size
h. CNV lesion components
i. visual acuity in fellow eye
j. evidence of CNV in fellow eye
k. use of ICG
l. Recurrent vs. new CNV lesions

Efficacy Analysis (pg. 33)

Efficacy analyses based on patients' data ***at 12 months***

PRIMARY ANALYSES

Proportion of patients with a decrease from baseline of <3 lines of vision (<15 letters) in treated eye

Primary Hypothesis:

H_0: Proportion of patients with decrease is the same between PDT & Placebo
H_1: Proportion of patients with decrease is the different between PDT & Placebo

Cochran-Mantel-Haenszel Chi-Square: No adjustments specified

Logistic Regression:

- Covariates: Treatment, Center, Baseline VA, Treatment-by-Center (pg. 35)

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Proportion of patients with a decrease from baseline (pg. 33)
of <6 lines of vision (<30 letters) in treated eye

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10. CNV lesion closure grades
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DISCONTINUED TREATMENT:

Failures (>15 LL): Last Observation Carried Forward (LOCF) (pg. 36)
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PRIMARY ANALYSES 1

Proportion of patients with:

(i) A decrease from baseline of **<3 lines of vision (<15 letters)** in treated eye

Crude Data:

	VA Letters Lost < 15 Loss	VA Letters Lost ≥ 15 Loss	Total
Verteporfin	111 (49%)	114 (51%)	225
Placebo	52 (46%)	62 (54%)	114
Total	163	176	339

Cochran-Mantel-Haenszel Chi-sq:

Cochran-Mantel-Haenszel Statistics

Statistic	DF	Value	Prob
Cochran-Mantel-Haenszel	1	0.4180	0.5179

Estimate	Value	95% Confidence Limit	
Odds Ratio	1.1609	0.7389	1.8240

Logistic Regressions:

- Covariates: Treatment (VP), Center, Baseline VA, Treatment-by-Center

Analysis with all specified covariates:

LR Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	469.4551			
VP	469.0355	1	0.42	0.5171
Center	441.1634	27	27.87	0.4176
Baseline VA	438.9942	1	2.17	0.1408
VP*Center	404.5022	26	34.49	0.1231

(convergence is questionable)

Analysis without Treatment-by-Center interaction:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	469.4551			
VP	469.0355	1	0.42	0.5171
Center	441.1634	27	27.87	0.4176
Baseline VA	438.9942	1	2.17	0.1408

Analysis without Center:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	469.4551			
VP	469.0355	1	0.42	0.5171
Baseline VA	466.3322	1	2.70	0.1001

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.1847	0.7528	1.8700
Baseline VA	0.9789	0.9541	1.0041

Analysis without Baseline Visual Acuity:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	469.4551			
VP	469.0355	1	0.42	0.5171

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.1609	0.7394	1.8275

PRIMARY ANALYSES 2

Proportion of patients with:

(i) A decrease from baseline of **<6 lines of vision (<30 letters)** in treated eye

12 Month Crude Data:

:

	VA Letters Lost < 30 Loss	≥ 30 Loss	Total
Verteporfin	171 (76%)	54 (24%)	225
Placebo	78 (68%)	31 (32%)	114
Total	163	176	339

Cochran-Mantel-Haenszel Chi-sq:

Cochran-Mantel-Haenszel Statistics

Statistic	DF	Value	Prob
Cochran-Mantel-Haenszel	1	2.2222	0.1360

Estimate	Value	95% Confidence Limit	
Odds Ratio	1.4615	0.8869	2.4086

Logistic Regression:

- Covariates: Treatment (VP), Center, Baseline VA, Treatment-by-Center

Analysis with all specified covariates:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	392.3708			
VP	390.1793	1	2.19	0.1388
Center	351.8932	27	38.29	0.0735
Baseline VA	347.8257	1	4.07	0.0437
VP*center	317.3532	26	30.47	0.2485

(convergence is questionable)

Analysis without Treatment-by-Center interaction:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	392.3708			
VP	390.1793	1	2.19	0.1388
Center	351.8932	27	38.29	0.0735
Baseline VA	347.8257	1	4.07	0.0437

Analysis without Center:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	392.3708			
VP	390.1793	1	2.19	0.1388
Baseline VA	385.2004	1	4.98	0.0257

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.5161	0.9119	2.5085
Baseline VA	0.9674	0.9388	0.9960

Analysis without Baseline Visual Acuity:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	392.3708			
VP	390.1793	1	2.19	0.1388

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.4615	0.8832	2.4041

Subgroup Analyses 1

Proportion of patients with:

(i) A decrease from baseline of **<3 lines of vision (<15 letters)** in treated eye

a) Gender

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	469.4551			
VP	469.0355	1	0.42	0.5171
Baseline VA	466.3322	1	2.70	0.1001
Gender	460.9390	1	5.39	0.0202

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.1645	0.7367	1.8406
Baseline VA	0.9770	0.9522	1.0025
Gender=male	0.5945	0.3825	0.9239

b) Race

No data: 98% Caucasian

RACE	Frequency	Percent
Caucasian	334	98.53
Hispanic	5	1.47

c) Cigarette Smoking

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	469.4551			
VP	469.0355	1	0.42	0.5171
Baseline VA	466.3322	1	2.70	0.1001
Smoking Status	464.8077	2	1.52	0.4666

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.1812	0.7482	1.8651
Baseline VA	0.9788	0.9540	1.0042
Current Smoker	1.1678	0.5901	2.3112
Former Smoker	1.3381	0.8421	2.1260

d) Systemic Hypertension (Systolic BP > 160 mmHg)

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	469.4551			
VP	469.0355	1	0.42	0.5171
Baseline VA	466.3322	1	2.70	0.1001
HyperTension	466.2246	1	0.11	0.7429

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.1961	0.7566	1.8909
Baseline VA	0.9791	0.9544	1.0044
HyperTension	0.9032	0.4914	1.6601

e) Baseline VA

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	469.4551			
VP	469.0355	1	0.42	0.5171
Baseline VA	466.3322	1	2.70	0.1001
VP*Baseline VA	465.5663	1	0.77	0.3815

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	5.8551	0.1585	216.2489
Baseline VA	0.9952	0.9517	1.0406
VP*Baseline VA	0.9760	0.9242	1.0306

f) Number of Treatments Required

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	469.4551			
VP	469.0355	1	0.42	0.5171
Baseline VA	466.3322	1	2.70	0.1001
Treatment Number	444.9907	7	21.34	0.0033

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.1139	0.6888	1.8013
Baseline VA	0.9712	0.9454	0.9977
Trts=1	1.1549	0.4796	2.7810
Trts=2	2.4701	0.8754	6.9697
Trts=3	0.5983	0.2434	1.4709
Trts=4	0.7769	0.3599	1.6773
Trts=5	0.7933	0.3562	1.7667
Trts=6	0.5382	0.2562	1.1305
Trts=7	0.3086	0.1457	0.6540

g) CNV Baseline Lesion Size (LS)

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	387.2484			
VP	385.6364	1	1.61	0.2042
Baseline VA	381.2164	1	4.42	0.0355
Baseline LS	372.3746	5	8.84	0.1155

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.4702	0.8762	2.4671
Baseline VA	0.9717	0.9430	1.0012
LS <= 2	1.3047	0.5812	2.9286
LS <= 3	2.9155	1.2129	7.0082
LS <= 4	1.8742	0.8086	4.3441
LS <= 5	1.5537	0.6796	3.5521
LS <= 6	2.7126	1.0996	6.6915

h) CNV Baseline Lesion Components (LC)

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	466.5133			
VP	466.1908	1	0.32	0.5701
Baseline VA	463.6879	1	2.50	0.1136
Baseline LC	463.5213	1	0.17	0.6832

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.1560	0.7327	1.8240
Baseline VA	0.9793	0.9545	1.0047
Classic LC	0.8995	0.5408	1.4962

i) Visual Acuity in Fellow eye
j) Evidence of CNV in Fellow eye
k) Use of ICG
l) Recurrent vs. new CNV lesions

} Subgroups not analyzed (Data Obstacles)

Subgroup Analyses 2

Proportion of patients with:

(i) A decrease from baseline of **<6 lines of vision (<30 letters)** in treated eye

a) Gender

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	92.3708			
VP	90.1793	1	2.19	0.1388
Baseline VA	85.2004	1	4.98	0.0257
Gender	83.9786	1	1.22	0.2690

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.5316	0.9232	2.5409
Baseline VA	0.9681	0.9399	0.9972
Gender=male	1.3214	0.8069	2.1639

b) Race

No data: 98% Caucasian

RACE	Frequency	Percent
Caucasian	334	98.53
Hispanic	5	1.47

c) Cigarette Smoking

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	392.3708			
VP	390.1793	1	2.19	0.1388
Baseline VA	385.2004	1	4.98	0.0257
Smoking Status	380.9485	2	4.25	0.1193

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.4868	0.8932	2.4749
Baseline VA	0.9675	0.9391	0.9967
Current Smoker	1.8342	0.8045	4.1817
Former Smoker	1.6333	0.9707	2.7481

d) Systemic Hypertension (Systolic BP > 160 mmHg)

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	392.3708			
VP	390.1793	1	2.19	0.1388
Baseline VA	385.2004	1	4.98	0.0257
HyperTension	385.1836	1	0.02	0.8970

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.5095	0.9073	2.5114
Baseline VA	0.9673	0.9392	0.9963
HyperTension	1.0464	0.5275	2.0758

e) Baseline VA

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	392.3708			
VP	390.1793	1	2.19	0.1388
Baseline VA	385.2004	1	4.98	0.0257
VP*Baseline VA	384.8296	1	0.37	0.5426

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	0.4190	0.0063	27.6721
Baseline VA	0.9554	0.9083	1.0048
VP*Baseline VA	1.0194	0.9579	1.0849

f) Number of Treatments Required

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	392.3708			
VP	390.1793	1	2.19	0.1388
Baseline VA	385.2004	1	4.98	0.0257
Treatment Number	381.3876	7	3.81	0.8011

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.5077	0.8950	2.5396
Baseline VA	0.9658	0.9370	0.9954
Trts=1	1.0096	0.3610	2.8236
Trts=2	1.4221	0.4233	4.7781
Trts=3	0.9149	0.3139	2.6671
Trts=4	0.7273	0.3055	1.7313
Trts=5	0.7087	0.2884	1.7416
Trts=6	0.5760	0.2545	1.3037
Trts=7	0.6857	0.3075	1.5289

g) CNV Baseline Lesion Size (LS)

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	387.2484			
VP	385.6364	1	1.61	0.2042
Baseline VA	381.2164	1	4.42	0.0355
Baseline LS	372.3746	5	8.84	0.1155

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.4702	0.8762	2.4671
Baseline VA	0.9717	0.9430	1.0012
LS <= 2	1.3047	0.5812	2.9286
LS <= 3	2.9155	1.2129	7.0082
LS <= 4	1.8742	0.8086	4.3441
LS <= 5	1.5537	0.6796	3.5521
LS <= 6	2.7126	1.0996	6.6915

h) CNV Baseline Lesion Components (LC)

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	391.1323			
VP	389.0759	1	2.06	0.1516
Baseline VA	384.2581	1	4.82	0.0282
Baseline LC	383.9886	1	0.27	0.6037

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.5144	0.9123	2.5138
Baseline VA	0.9683	0.9401	0.9974
Classic LC	1.1629	0.6596	2.0502

m) Visual Acuity in Fellow eye
n) Evidence of CNV in Fellow eye
o) Use of ICG
p) Recurrent vs. new CNV lesions

} Subgroups not analyzed (Data Obstacles)

VIP Study

Primary Analyses from *Second* Analytic Plan

Protocol BPD OCR 003: CR-99009
Oct. 19, 1999

VIP Study

Second Analytic Plan: Protocol BPD OCR 003: CR-99009; Oct. 19, 1999

Protocol Page

PRIMARY ANALYSES

1. Efficacy and Safety will be based on the data obtained after all patients have completed their 12-month follow-up visit. (pg. 5)

2. The second analysis will be performed after all patients have completed their 24-month follow-up visit. (pg. 5)

DATA

Intent-To-Treat Data: (No exclusions from protocol violations): (pg. 5)

- Discontinued Treatment: Last Observation Carried Forward (LOCF)

PRIMARY OUTCOME

Proportion of patients with:

A decrease from baseline of <3 lines of vision (<15 letters) in treated eye (pg. 9)

Primary Hypothesis:

H_0: Proportion of patients with decrease is the same between PDT & Placebo

H_1: Proportion of patients with decrease is the different between PDT & Placebo

METHODS:

Pearson chi-square test without continuity correction. (pg. 9)

Follow-up Visit Rate Differences and 95% confidence intervals (pg. 9)

Logistic Regression: (pg. 9)

Covariates:

- Treatment,
- baseline visual acuity score,
- 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 + Questionable vs. No),
- laser type (Coherent vs Zeiss vs. mixed),
- pooled center (centers with =20 vs. <20 patients)
- other unbalanced and clinically important baseline variables

Procedure:

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.

PRIMARY ANALYSES 1

Data: **12 Month Data**

Outcome: Decrease from baseline of **<3 lines of vision (<15 letters)** in treated eye

Crude Data:

	VA Letters Lost < 15 Loss	≥ 15 Loss	Total
Verteporfin	111 (49%)	114 (51%)	225
Placebo	52 (46%)	62 (54%)	114
Total	163	176	339

Pearson Chi-sq:

Pearson Statistic

Statistic	DF	Value	P-Val
Chi-Square	1	0.42	0.52

Estimate	Value	95% Confidence Limits
Odds Ratio	1.16	(0.74, 1.82)

Rate Differences:

Rate Difference = Pr(< 15 Letters Lost | Verteporfin) – Pr(< 15 Letters Lost | Placebo)

Visit	Rate Difference	95% C.I.
Month 3	-0.038	(-0.13, 0.05)
Month 6	0.039	(-0.07, 0.15)
Month 9	0.064	(-0.05, 0.18)
Month 12	0.037	(-0.08, 0.15)

Logistic Regression:

Final Model from backward elimination procedure:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	469.4551			
VP	469.0355	1	0.42	0.5171
Baseline VA	466.3322	1	2.70	0.1001
Baseline AGE	448.1931	1	18.14	<.0001
Gender=Male	441.2516	1	6.94	0.0084

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.2427	0.7758	1.9994
Baseline VA	0.9643	0.9379	0.9908
Baseline AGE	0.9351	0.9058	0.9638
Gender=Male	1.8414	1.1684	2.9231

PRIMARY ANALYSES 2

Data: **24 Month Data**

Outcome: Decrease from baseline of **<3 lines of vision (<15 letters)** in treated eye

Crude Data:

	VA Letters Lost < 15 Loss	≥ 15 Loss	Total
Verteporfin	104 (46%)	121 (54%)	225
Placebo	38 (33%)	76 (67%)	114
Total	163	176	339

Pearson Chi-sq:

Pearson Statistic

Statistic	DF	Value	P-Val
Chi-Square	1	5.16	0.023

Estimate	Value	95% Confidence Limits
Odds Ratio	1.72	(1.08, 2.75)

Rate Differences:

Rate Difference = Pr(< 15 Letters Lost | Verteporfin) – Pr(< 15 Letters Lost | Placebo)

Visit	Rate Difference	95% C.I.
Month 3	-0.038	(-0.13, 0.05)
Month 6	0.039	(-0.07, 0.15)
Month 9	0.064	(-0.05, 0.18)
Month 12	0.037	(-0.08, 0.15)
Month 15	0.050	(-0.06, 0.16)
Month 18	0.138	(0.03, 0.25)
Month 21	0.151	(0.04, 0.26)
Month 24	0.129	(0.02, 0.24)

Logistic Regression:

Final Model from backward elimination procedure:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	460.9909			
VP	455.7558	1	5.24	0.0221
Baseline AGE	445.6926	1	10.06	0.0015

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.7999	1.1216	2.9244
Baseline AGE	0.9550	0.9271	0.9827

Other Models of interest (for comparison):

- Covariates: Treatment, Baseline VA, Age

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	460.9909			
VP	455.7558	1	5.24	0.0221
Baseline VA	455.4513	1	0.30	0.5811
Baseline AGE	444.3245	1	11.13	0.0009

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.8334	1.1402	2.9858
Baseline VA	0.9842	0.9582	1.0108
Baseline AGE	0.9518	0.9233	0.9800

- Covariates: Treatment, Baseline VA, Gender, Age

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	460.9909			
VP	455.7558	1	5.24	0.0221
Baseline VA	455.4513	1	0.30	0.5811
Baseline AGE	444.3245	1	11.13	0.0009
Gender=male	442.3296	1	1.99	0.1578

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.8199	1.1304	2.9673
Baseline VA	0.9831	0.9569	1.0097
Baseline AGE	0.9503	0.9217	0.9788
Gender=male	1.3857	0.8812	2.1835

VIP Study

Primary Analyses from *Third* Analytic Plan

Protocol BPD OCR 003: CR-99009
Jan. 11, 2001

VIP Study

Third Analytic Plan: Protocol BPD OCR 003: CR-99009; Jan 11, 2001

Protocol Page

PRIMARY ANALYSES

3. Efficacy and Safety will be based on the data obtained after all patients have completed their 12-month follow-up visit. (pg. 5)

4. The second analysis will be performed after all patients have completed their 24-month follow-up visit. (pg. 5)

DATA

Intent-To-Treat Data: (No exclusions from protocol violations): (pg. 6)

- Discontinued Treatment: Last Observation Carried Forward (LOCF)
- "Confirmatory Analyses" with Observed Cases

OUTCOME

Proportion of patients with:

A decrease from baseline of <3 lines of vision (<15 letters) in treated eye (pg. 9)

Primary Hypothesis:

H_0: Proportion of patients with decrease is the same between PDT & Placebo

H_1: Proportion of patients with decrease is the different between PDT & Placebo

METHODS:

Pearson chi-square test without continuity correction. (pg. 10)

Follow-up Visit Rate Differences and 95% confidence intervals (pg. 10)

Logistic Regression: (pg. 10)

Covariates:

- Treatment (Verteporfin vs Placebo),
- Baseline visual acuity score (<65 vs ≥ 65),
- Baseline Lesion Component (classic containing vs. occult only),
- Baseline Lesion Greatest Linear Dimension (<4000 vs ≥ 4000 microns),
- Baseline Lesion Size (≤4 vs > 4 MPS DA),
- Age at baseline (<75 vs ≥75),
- Gender (men vs women),
- Race (Caucasian vs. others),
- Iris color [dark (black, brown) vs. light (hazel, green, blue and gray)],
- Presence of blood at baseline (Yes + Questionable vs. No),
- Laser type (Coherent vs Zeiss vs. mixed),
- Pooled center (centers with =20 vs. <20 patients)
- Other unbalanced and clinically important baseline variables

Procedure:

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.

PRIMARY ANALYSES 1

Data: **12 Month Data**

Outcome: Decrease from baseline of **<3 lines of vision (<15 letters)** in treated eye

Crude Data:

	VA Letters Lost < 15 Loss	VA Letters Lost ≥ 15 Loss	Total
Verteporfin	111 (49%)	114 (51%)	225
Placebo	52 (46%)	62 (54%)	114
Total	163	176	339

Pearson Chi-sq:

Pearson Statistic

Statistic	DF	Value	P-Val
Chi-Square	1	0.42	0.52

Estimate	Value	95% Confidence Limits
Odds Ratio	1.16	(0.74, 1.82)

Rate Differences:

Rate Difference = Pr(< 15 Letters Lost | Verteporfin) – Pr(< 15 Letters Lost | Placebo)

Visit	Rate Difference	95% C.I.
Month 3	-0.038	(-0.13, 0.05)
Month 6	0.039	(-0.07, 0.15)
Month 9	0.064	(-0.05, 0.18)
Month 12	0.037	(-0.08, 0.15)

Logistic Regression:

Final Model from backward elimination procedure:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	469.4551			
VP	469.0355	1	0.42	0.5171
Baseline VA ≥ 65	463.3998	1	5.64	0.0176
Baseline AGE ≥ 75	451.6416	1	11.76	0.0006
Gender=Male	445.9582	1	5.68	0.0171

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.1318	0.7100	1.8082
Baseline VA ≥ 65	0.5264	0.3335	0.8245
Baseline AGE ≥ 75	0.4547	0.2889	0.7097
Gender=Male	1.7277	1.1018	2.7246

PRIMARY ANALYSES 2

Data: **24 Month Data**

Outcome: Decrease from baseline of **<3 lines of vision (<15 letters)** in treated eye

Crude Data:

	VA Letters Lost < 15 Loss	VA Letters Lost ≥ 15 Loss	Total
Verteporfin	104 (46%)	121 (54%)	225
Placebo	38 (33%)	76 (67%)	114
Total	163	176	339

Pearson Chi-sq:

Pearson Statistic

Statistic	DF	Value	P-Val
Chi-Square	1	5.16	0.023

Estimate	Value	95% Confidence Limits
Odds Ratio	1.72	(1.08, 2.75)

Rate Differences:

Rate Difference = Pr(< 15 Letters Lost | Verteporfin) – Pr(< 15 Letters Lost | Placebo)

Visit	Rate Difference	95% C.I.
Month 3	-0.038	(-0.13, 0.05)
Month 6	0.039	(-0.07, 0.15)
Month 9	0.064	(-0.05, 0.18)
Month 12	0.037	(-0.08, 0.15)
Month 15	0.050	(-0.06, 0.16)
Month 18	0.138	(0.03, 0.25)
Month 21	0.151	(0.04, 0.26)
Month 24	0.129	(0.02, 0.24)

Logistic Regression:

Final Model from backward elimination procedure:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	460.9909			
VP	455.7558	1	5.24	0.0221
Baseline VA ≥ 65	454.0512	1	1.70	0.1917
VP * (Baseline VA ≥ 65)	447.8039	1	6.25	0.0124

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	3.4776	1.6750	7.5707
Baseline VA ≥ 65	1.7308	0.7810	3.9606
VP * (Baseline VA ≥ 65)	0.2949	0.1103	0.7697

Odds Ratio Estimates: **Baseline VA < 65**

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals		Chi-Square	P-Value
VP	3.4776	1.6750	7.5707	10.61	0.0011

Odds Ratio Estimates: **Baseline VA ≥ 65**

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals		Chi-Square	P-Value
VP	1.0256	0.5574	1.9060	0.01	0.9355

TAP Study

Analyses from Initial Plan

Protocol BPD OCR 002
Oct 25, 1996 pg. 26-32

TAP Study

Initial Analytic Plan: Protocol BPD OCR 002; Oct 25, 1996 pg. 26-32

Protocol Page

Statistical and Analytic Plan (pg. 28)

DATA

Data Sets:

1. Intent-To-Treat Data: (No exclusions from protocol violations):
2. "Evaluable" patients Data: (adhere to protocol)

SUBGROUP ANALYSES

m. gender
n. race
o. number of treatments performed
p. CNV lesion size
q. CNV lesion components
r. Recurrent vs. new CNV lesions

Efficacy Analysis (pg. 29)

Efficacy analyses based on patients' data ***at 12 months***

PRIMARY ANALYSES

Proportion of patients with:

(i) A decrease from baseline of <3 lines of vision (<15 letters) in treated eye
(ii) A decrease from baseline of <6 lines of vision (<30 letters) in treated eye

Primary Hypothesis:

H_0: Proportion of patients with decrease is the same between PDT & Placebo
H_1: Proportion of patients with decrease is the different between PDT & Placebo

Cochran-Mantel-Haenszel Adjustments:

- Center & Baseline Visual Acuity (VA) category, (34-53 letters vs. 54-73 letters)
- Baseline VA category, (34-38, 39-43, 44-48, 49-53, 54-58, 59-63, 64-68, 69-73)

Logistic Regression:

- Covariates: Treatment, Center, Baseline VA, Treatment-by-Center (pg. 30)

SECONDARY ANALYSES

- Proportion with VA < 34 letters (pg. 29)
- Time until VA decrease $\geq$ 3 lines (15 letters)
- Time until VA decrease $\geq$ 6 lines (30 letters)
- Mean VA change from baseline (logMAR units) -- ANCOVA (pg. 30)
- Mean Contrast Sensitivity change from baseline -- ANCOVA
- CNV lesion closure grades

DISCONTINUED TREATMENT: Last Observation Carried Forward (LOCF) (pg. 32)

PRIMARY ANALYSES 1

Proportion of patients with:

(i) A decrease from baseline of **<3 lines of vision (<15 letters)** in treated eye

Cochran-Mantel-Haenszel Adjustments:

- Center & Baseline Visual Acuity (VA) category, (34-53 letters vs. 54-73 letters)

Cochran-Mantel-Haenszel Statistics

Statistic	DF	Value	Prob
Cochran-Mantel-Haenszel	1	12.0945	0.0005

Estimate	Value	95% Confidence Limit	
Odds Ratio	1.7869	1.2363	2.5827

- Baseline VA category, (34-38, 39-43, 44-48, 49-53, 54-58, 59-63, 64-68, 69-73)

Cochran-Mantel-Haenszel Statistics

Statistic	DF	Value	Prob
Cochran-Mantel-Haenszel	1	10.2832	0.0013

Estimate	Value	95% Confidence Limit	
Odds Ratio	1.7686	1.2493	2.5039

Logistic Regression:

- Covariates: Treatment (VP), Center, Baseline VA, Treatment-by-Center

Analysis with all specified covariates:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	834.9933			
VP	822.8443	1	12.15	0.0005
Center	797.1863	21	25.66	0.2198
Baseline VA	787.9243	1	9.26	0.0023
VP*center	766.3359	21	21.59	0.4235

(convergence is questionable)

Analysis without Treatment-by-Center interaction:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	834.9933			
VP	822.8443	1	12.15	0.0005
Center	797.1863	21	25.66	0.2198
Baseline VA	787.9243	1	9.26	0.0023

Analysis without Center:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	834.9933			
VP	822.8443	1	12.15	0.0005
Baseline VA	808.4136	1	14.43	0.0001

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.8664	1.3254	2.6351
Baseline VA	0.9698	0.9542	0.9854

PRIMARY ANALYSES 2

Proportion of patients with:

(i) A decrease from baseline of **<6 lines of vision (<30 letters)** in treated eye

Cochran-Mantel-Haenszel Adjustments:

- Center & Baseline Visual Acuity (VA) category, (34-53 letters vs. 54-73 letters)

Cochran-Mantel-Haenszel Statistics

Statistic	DF	Value	Prob
Cochran-Mantel-Haenszel	1	8.4449	0.0037

Estimate	Value	95% Confidence Limit	
Odds Ratio	1.9927	1.2618	3.1468

- Baseline VA category, (34-38, 39-43, 44-48, 49-53, 54-58, 59-63, 64-68, 69-73)

Cochran-Mantel-Haenszel Statistics

Statistic	DF	Value	Prob
Cochran-Mantel-Haenszel	1	7.2049	0.0073

Estimate	Value	95% Confidence Limit	
Odds Ratio	1.8512	1.1801	2.9040

Logistic Regression

- Covariates: Treatment (VP), Center, Baseline VA, Treatment-by-Center

Analysis with all specified covariates:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	569.2150			
VP	561.8821	1	7.33	0.0068
Center	530.4910	21	31.39	0.0674
Baseline VA	497.5581	1	32.93	<.0001
VP*Center	481.6375	21	15.92	0.7741

(convergence is questionable)

Analysis without Treatment-by-Center interaction:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	569.2150			
VP	561.8821	1	7.33	0.0068
Center	530.4910	21	31.39	0.0674
Baseline VA	497.5581	1	32.93	<.0001

Analysis without Center:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	569.2150			
VP	561.8821	1	7.33	0.0068
Baseline VA	524.3369	1	37.55	<.0001

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.9823	1.2742	3.0839
Baseline VA	0.9340	0.9120	0.9555

Subgroup Analyses 1

Proportion of patients with:

(i) A decrease from baseline of **<3 lines of vision (<15 letters)** in treated eye

a) Gender

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	834.9933			
VP	822.8443	1	12.15	0.0005
Baseline VA	808.4136	1	14.43	0.0001
Gender	804.9094	1	3.50	0.0612

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.9312	1.3653	2.7316
Baseline VA	0.9694	0.9540	0.9852
Gender=male	0.7281	0.5220	1.0157

b) Race

No data: 98% Caucasian

RACE	Frequency	Percent
Asian	1	0.16
Black	2	0.33
Caucasian	599	98.36
Hispanic	6	0.99
Other	1	0.16

c) Number of treatments performed

Data on number of treatments performed was not obtained from company.

d) CNV Baseline Lesion Size (LS)

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	834.9933			
VP	822.8443	1	12.15	0.0005
Baseline VA	808.4136	1	14.43	0.0001
Baseline LS	791.7094	6	16.70	0.0104

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.8235	1.2872	2.5833
Baseline VA	0.9688	0.9531	0.9848
LS <= 2	1.5379	0.4638	5.0997
LS <= 3	0.8052	0.2476	2.6183
LS <= 4	0.5899	0.1790	1.9438
LS <= 5	1.0264	0.3142	3.3524
LS <= 6	0.6642	0.2030	2.1738
LS <= 9	0.5513	0.1678	1.8113

c) CNV Baseline Lesion Components (LC)

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	834.9933			
VP	822.8443	1	12.15	0.0005
Baseline VA	808.4136	1	14.43	0.0001
Baseline LC	808.2896	2	0.12	0.9399

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.8675	1.3247	2.6326
Baseline VA	0.9698	0.9540	0.9858
≥ 50% Classic	1.0729	0.5992	1.9210
< 50% Classic	1.1042	0.6286	1.9398

Subgroup Analyses 2

Proportion of patients with:

(i) A decrease from baseline of **<6 lines of vision (<30 letters)** in treated eye

a) Gender

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	569.2150			
VP	561.8821	1	7.33	0.0068
Baseline VA	524.3369	1	37.55	<.0001
Gender	520.7344	1	3.60	0.0577

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	2.0574	1.3189	3.2093
Baseline VA	0.9333	0.9117	0.9554
Gender=male	1.5259	0.9861	2.3612

b) Race

No data: 98% Caucasian

RACE	Frequency	Percent
Asian	1	0.16
Black	2	0.33
Caucasian	599	98.36
Hispanic	6	0.99
Other	1	0.16

c) Number of treatments performed

Data on number of treatments performed was not obtained from company.

d) CNV Baseline Lesion Size (LS)

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	569.2150			
VP	561.8821	1	7.33	0.0068
Baseline VA	524.3369	1	37.55	<.0001
Baesline LS	514.5559	6	9.78	0.1342

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.9537	1.2507	3.0520
Baseline VA	0.9347	0.9130	0.9569
LS <= 2	1.4826	0.2849	7.7148
LS <= 3	1.2864	0.2501	6.6171
LS <= 4	0.7139	0.1408	3.6204
LS <= 5	1.4131	0.2724	7.3293
LS <= 6	1.1813	0.2297	6.0760
LS <= 9	0.6143	0.1225	3.0815

c) CNV Baseline Lesion Components (LC)

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	569.2150			
VP	561.8821	1	7.33	0.0068
Baseline VA	524.3369	1	37.55	<.0001
Baseline LC	519.0998	2	5.24	0.0729

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.9875	1.2759	3.0961
Baseline VA	0.9281	0.9059	0.9509
≥ 50% Classic	0.5276	0.2372	1.1736
< 50% Classic	0.8726	0.4012	1.8979

TAP Study

Analyses from Initial Plan
By Study (A/B)

Protocol BPD OCR 002
Oct 25, 1996 pg. 26-32

TAP Study

Initial Analytic Plan: Protocol BPD OCR 002; Oct 25, 1996 pg. 26-32

Protocol Page

Statistical and Analytic Plan (pg. 28)

DATA

Data Sets:

3. Intent-To-Treat Data: (No exclusions from protocol violations):
4. "Evaluable" patients Data: (adhere to protocol)

SUBGROUP ANALYSES

s. gender
t. race
u. number of treatments performed
v. CNV lesion size
w. CNV lesion components
x. Recurrent vs. new CNV lesions

Efficacy Analysis (pg. 29)

Efficacy analyses based on patients' data ***at 12 months***

PRIMARY ANALYSES

Proportion of patients with:

(i) A decrease from baseline of <3 lines of vision (<15 letters) in treated eye
(ii) A decrease from baseline of <6 lines of vision (<30 letters) in treated eye

Primary Hypothesis:

H_0: Proportion of patients with decrease is the same between PDT & Placebo
H_1: Proportion of patients with decrease is the different between PDT & Placebo

Cochran-Mantel-Haenszel Adjustments:

- Center & Baseline Visual Acuity (VA) category, (34-53 letters vs. 54-73 letters)
- Baseline VA category, (34-38, 39-43, 44-48, 49-53, 54-58, 59-63, 64-68, 69-73)

Logistic Regression:

- Covariates: Treatment, Center, Baseline VA, Treatment-by-Center (pg. 30)

SECONDARY ANALYSES

13. Proportion with VA < 34 letters (pg. 29)
14. Time until VA decrease $\geq$ 3 lines (15 letters)
15. Time until VA decrease $\geq$ 6 lines (30 letters)
16. Mean VA change from baseline (logMAR units) -- ANCOVA (pg. 30)
17. Mean Contrast Sensitivity change from baseline -- ANCOVA
18. CNV lesion closure grades

DISCONTINUED TREATMENT: Last Observation Carried Forward (LOCF) (pg. 32)

Sample Sizes by Center & Study

	Center	Number of Subjects
Study A	2	26
	3	15
	5	38
	7	17
	9	23
	10	30
	12	15
	14	25
	16	37
	19	21
	21	13
Study B	1	61
	4	21
	6	25
	8	18
	11	39
	13	31
	15	19
	17	24
	18	60
	20	39
	22	12

PRIMARY ANALYSES 1

Proportion of patients with:

(i) A decrease from baseline of **<3 lines of vision (<15 letters)** in treated eye

Cochran-Mantel-Haenszel Adjustments:

- Center & Baseline Visual Acuity (VA) category, (34-53 letters vs. 54-73 letters)

Study A:

Cochran-Mantel-Haenszel Statistics

Statistic	DF	Value	Prob
Cochran-Mantel-Haenszel	1	4.8731	0.0273

Estimate	Value	95% Confidence Limit	
Odds Ratio	1.6697	0.9387	2.9702

Study B:

Cochran-Mantel-Haenszel Statistics

Statistic	DF	Value	Prob
Cochran-Mantel-Haenszel	1	7.2236	0.0072

Estimate	Value	95% Confidence Limit	
Odds Ratio	1.8728	1.1598	3.0240

- Baseline VA category, (34-38, 39-43, 44-48, 49-53, 54-58, 59-63, 64-68, 69-73)

Study A:

Cochran-Mantel-Haenszel Statistics

Statistic	DF	Value	Prob
Cochran-Mantel-Haenszel	1	4.1710	0.0411

Estimate	Value	95% Confidence Limit	
Odds Ratio	1.6984	0.9653	2.9882

Study B:

Cochran-Mantel-Haenszel Statistics

Statistic	DF	Value	Prob
Cochran-Mantel-Haenszel	1	6.1808	0.0129

Estimate	Value	95% Confidence Limit	
Odds Ratio	1.7262	1.0800	2.7589

Logistic Regression:

- Covariates: Treatment (VP), Center, Baseline VA, Treatment-by-Center

Study A:

Final Analyses:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	352.9544			
VP	348.0833	1	4.87	0.0273
Baseline VA	344.1415	1	3.94	0.0471

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.8696	1.1034	3.1842
Baseline VA	0.9763	0.9529	0.9997

Study B:

Final Analyses:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	481.0595			
VP	473.8726	1	7.19	0.0073
Baseline VA	462.7735	1	11.10	0.0009

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.8466	1.1764	2.9132
Baseline VA	0.9643	0.9432	0.9853

PRIMARY ANALYSES 2

Proportion of patients with:

(i) A decrease from baseline of **<3 lines of vision (<30 letters)** in treated eye

Cochran-Mantel-Haenszel Adjustments:

- Center & Baseline Visual Acuity (VA) category, (34-53 letters vs. 54-73 letters)

Study A:

Cochran-Mantel-Haenszel Statistics

Statistic	DF	Value	Prob
Cochran-Mantel-Haenszel	1	7.7068	0.0055

Estimate	Value	95% Confidence Limit	
Odds Ratio	2.6224	1.3021	5.2811

Study B:

Cochran-Mantel-Haenszel Statistics

Statistic	DF	Value	Prob
Cochran-Mantel-Haenszel	1	2.0759	0.1496

Estimate	Value	95% Confidence Limit	
Odds Ratio	1.6253	0.8893	2.9706

- Baseline VA category, (34-38, 39-43, 44-48, 49-53, 54-58, 59-63, 64-68, 69-73)

Study A:

Cochran-Mantel-Haenszel Statistics

Statistic	DF	Value	Prob
Cochran-Mantel-Haenszel	1	5.9886	0.0144

Estimate	Value	95% Confidence Limit	
Odds Ratio	2.3803	1.1702	4.8416

Study B:

Cochran-Mantel-Haenszel Statistics

Statistic	DF	Value	Prob
Cochran-Mantel-Haenszel	1	2.0507	0.1521

Estimate	Value	95% Confidence Limit	
Odds Ratio	1.5616	0.8473	2.8780

Logistic Regression:

- Covariates: Treatment (VP), Center, Baseline VA, Treatment-by-Center

Study A:

Final Analyses:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	242.6817			
VP	235.7800	1	6.90	0.0086
Baseline VA	222.6758	1	13.10	0.0003

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	2.8419	1.4408	5.6796
Baseline VA	0.9404	0.9063	0.9730

Study B:

Final Analyses:

Likelihood Ratio Statistics For Type 1 Analysis

Source	Deviance	DF	Chi-Square	Pr > ChiSq
Intercept	326.5327			
VP	324.8137	1	1.72	0.1898
Baseline VA	299.0212	1	25.79	<.0001

Odds Ratio Estimates

Parameter	Estimate	Profile Likelihood 95% Confidence Intervals	
VP	1.4938	0.8271	2.6779
Baseline VA	0.9269	0.8970	0.9555

PART II.

Assessment of Treatment effect in VIP (Occult Subgroup)

Data from the VIP Study (Occult Subgroup):

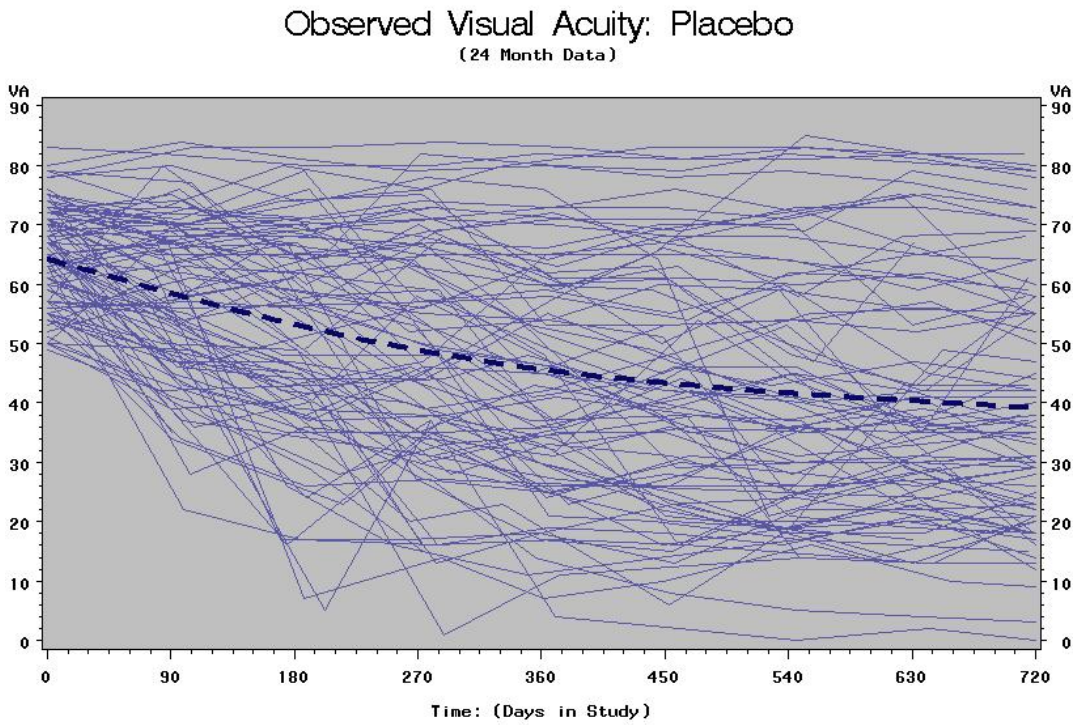


Figure 1. Individual and smoothed mean visual acuity trajectories over two years (~720 days) of the VIP study for occult subjects randomized to **Placebo**.

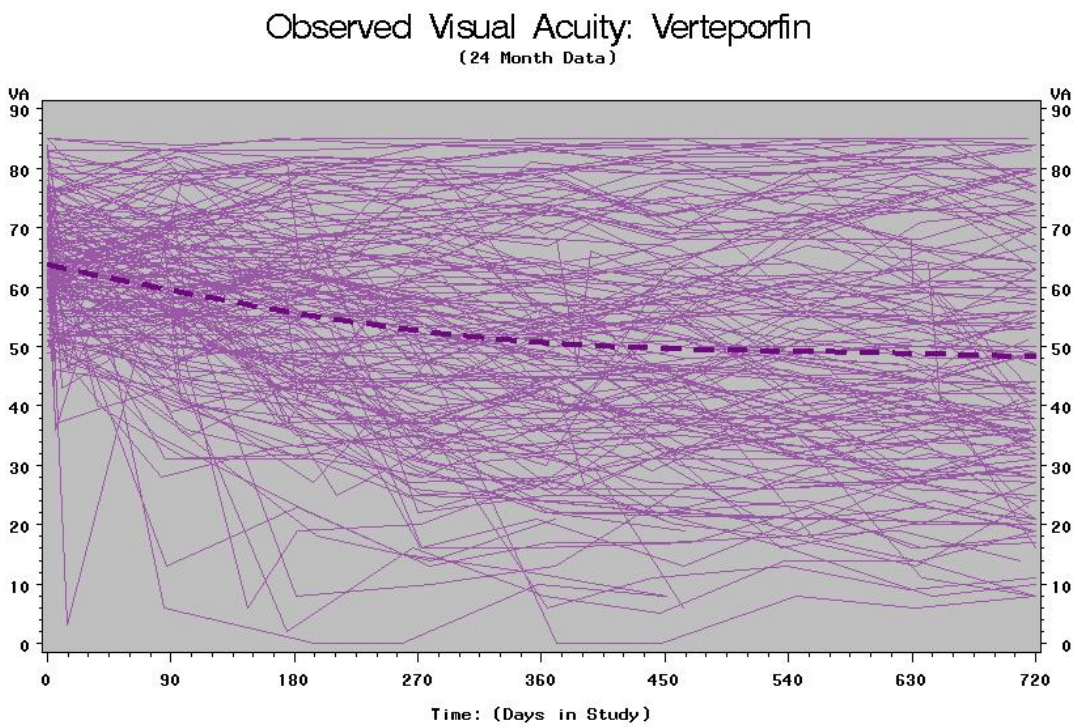


Figure 2. Individual and smoothed mean visual acuity trajectories over two years (~720 days) of the VIP study for occult subjects randomized to **Verteporfin**.

Figures 1 and 2 depict observed Visual Acuity profiles for each subject and the related average trajectories for the occult subgroup of the VIP study, (patients who presented at baseline with occult but no classic CNV on fluorescein angiogram). Both groups exhibit a non-linear (quadratic) decrease in their average Visual Acuity scores over time.

VIP Study

- Occult Data Subset -

GEE Analysis
(Quadratic Descent Model)

Analyses:

Basic Model:

1.) **VA** = $\beta_0 + \beta_1 \cdot I(\text{Trt=VP}) + \beta_2 \cdot \text{Month} + \beta_3 \cdot I(\text{Trt=VP}) \times \text{Month} + \beta_4 \cdot \text{Month}^2 + \beta_5 \cdot I(\text{Trt=VP}) \times \text{Month}^2 + \boldsymbol{\varepsilon}$

2.) $\boldsymbol{\varepsilon} \sim \text{MVN}(\mathbf{0}, \sigma^2\mathbf{R})$

3.) **R** modeled with unstructured correlations.

This model examines time-dependent differences between the Verteporfin and Placebo groups. The notation $I(\text{Trt=VP})$ represents an "indicator function" which takes on the value 0 if the statement "Trt=VP" is false (i.e. the subject received the Placebo treatment) and the value 1 if the statement "Trt=VP" is true (i.e. the subject received the Verteporfin treatment) Month is a variable measuring the passage of time in months. This model yields the following mean structures:

Table 1. Basic Model Average Trajectories: **Placebo** vs. **Verteporfin**

	Average Trajectory
Placebo	$\beta_0 + \beta_2 \cdot \text{Month} + \beta_4 \cdot \text{Month}^2$
Veretporfin	$(\beta_0 + \beta_1) + (\beta_2 + \beta_3) \cdot \text{Month} + (\beta_4 + \beta_5) \cdot \text{Month}^2$

We examine β_1 and, β_3 and β_5 to determine if there are systematic differences in the Verteporfin and Placebo groups over time. Additional explanatory variables, such as development of classic CNV, gender, baseline lesion size, etc., are used to enhance the basic model when appropriate.

We used a Generalized Estimating Equation (GEE) approach to obtain estimates and construct inferences for our models. To investigate the effects of covariance assumptions, the following covariance structures were examined: Independent, Compound Symmetric, Auto-Regressive, Toeplitz, and Unstructured. Results were robust to changes in the assumed covariance model and our final correlation structure was formulated via explorations of the residuals from the final mean model. The normality assumption did not appear to be considerably violated. Table 2 shows results from the basic mean model, fitted via GEE.

Results: Basic Model - 12 Month Data

Table 2. Basic Model Results: Mean Model - 12 Month Data

Parameter		Estimate	Standard Error	95% Confidence Limits		P-Value
β_0	Intercept	64.9375	0.9381	63.0989	66.7761	<.0001
β_1	VP	0.9974	1.1845	-1.3241	3.3189	0.3997
β_2	Month	-2.3636	0.4547	-3.2547	-1.4724	<.0001
β_3	VP*Month	0.1871	0.5583	-0.9072	1.2814	0.7376
β_4	Month^2	0.0506	0.0308	-0.0098	0.1110	0.1007
β_5	VP*Month^2	0.0200	0.0376	-0.0537	0.0937	0.5946

Both Table 2 and the observed data plots indicate that the quadratic trend is similar for the Placebo and Verteporfin groups. However, our main questions revolve around trajectory differences between the two groups and we thus maintain β_5 in our model to examine overall differences. Models assuming similar quadratic trends are investigated in subsequent documents.

Table 3. Basic Model Results: Overall Test for VP effects - 12 Month Data

H_0: $\beta_1 = 0$, $\beta_3 = 0$, $\beta_5 = 0$

Test	DF	Chi-Square	P-Value
Score Test	3	6.28	0.0985

Table 3 displays the overall hypothesis that Verteporfin has no effect on the average visual acuity trajectory, i.e. the hypothesis that all parameters associated with differences between Verteporfin and Placebo are zero.

Table 4. Basic Model Results: Alternative Tests for VP effects - 12 Month Data

H_0: $\beta_3 = 0$, $\beta_5 = 0$

Test	DF	Chi-Square	P-Value
Score Test	2	4.76	0.0923

H_0: $\beta_3 = 0$

Test	DF	Chi-Square	P-Value
Score Test	1	0.11	0.7354

Alternatively, the point might be raised that one does not need to include the baseline difference between the groups β_1 via randomization, or that, since the quadratic-descent terms appear similar, testing β_5 might also be unnecessary. Table 4 displays these alternative hypotheses for Verteporfin effects.

Table 5. Basic Model Results: VA Estimates at 12 Months

	Estimate	Standard Error	Confidence Limits	
Placebo Mean	43.8633	2.1627	39.6246	48.1020
VP Mean	49.9822	1.5291	46.9852	52.9793
Difference	6.1189	2.6486	0.9277	11.3102

Table 5 displays estimated 12-month average VA scores. The average VA score for subjects taking Placebo decreased to $64.9 - 2.36 \cdot (12) + 0.051 \cdot (12)^2 \cong$ **44 letters**, (95% C.I. [39.6, 48.1]), at the end of 12 months. Verteporfin subjects were estimated as decreasing to approximately **50 letters**, (95% C.I. [47.0, 53.0]), at the end of 12 months. Figure 3. displays the estimated mean trajectories and 95% confidence bands for the Verteporfin and Placebo groups.

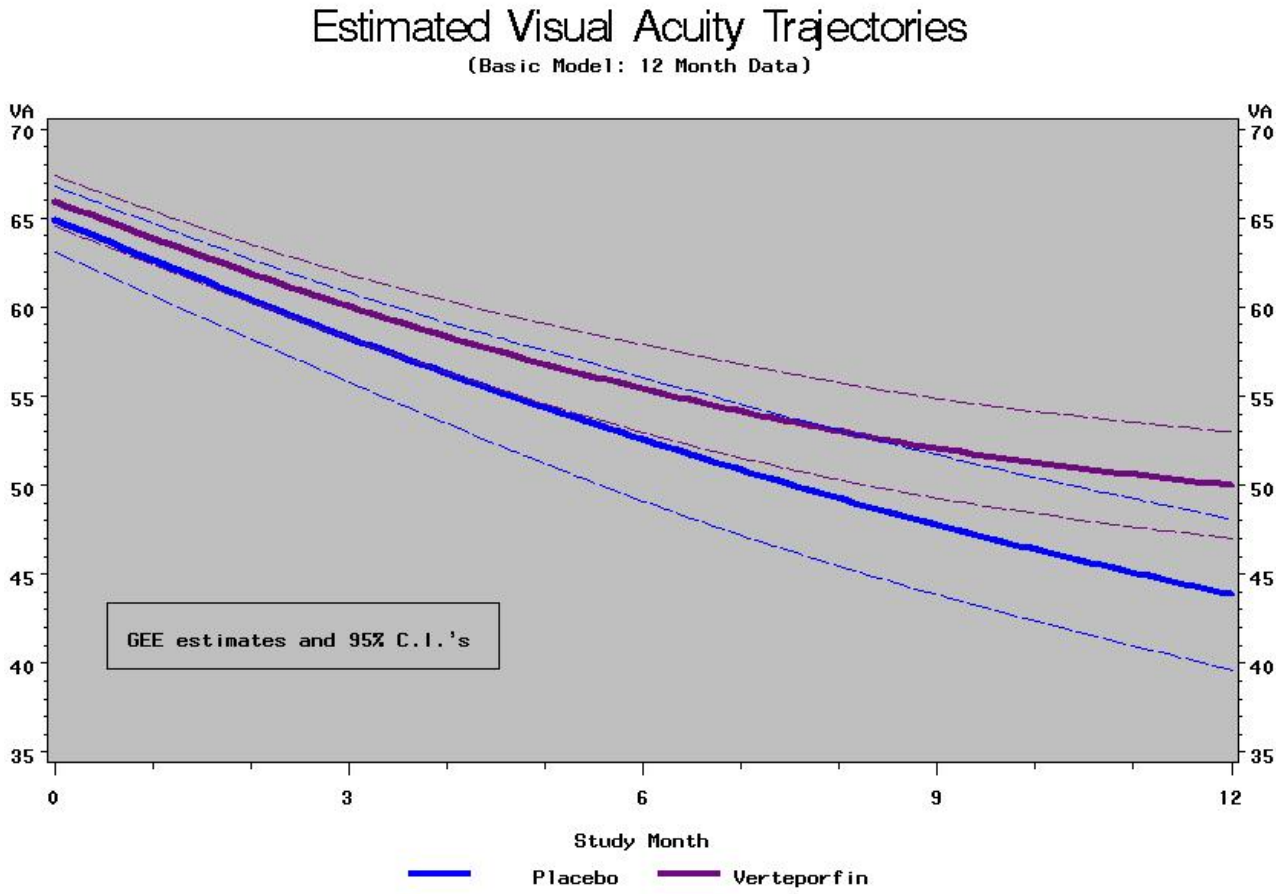


Figure 3. Verteporfin and Placebo Estimated Mean Visual Acuity Trajectories and 95% Confidence Bands for initial 12 months of VIP study.

After fitting the basic model, we examined the following covariates and their interactions with treatment to investigate the need for adjustments to the basic model, (similar to the VIP study protocols): baseline age, gender, smoking status, baseline lesion size, presence of hypertension, iris color, and large center size. The age of the subject played a significant role in explaining variations among subjects' baseline visual acuity scores, but had no perceivable effect on the trajectories of either the Placebo or VP group. We include the baseline adjustments for age in our adjusted mean model but note that it does not change the inferences concerning differences in the decline of Visual Acuity between the Verteporfin and Placebo groups, (see tables 6-8).

Results: Adjusted Model - 12 Month Data

Table 6. Adjusted Model Results: Mean Model -12 Month Data

Parameter	Estimate	Standard Error	95% Confidence Limits		P-Value
β_0 Intercept	95.6257	8.3177	79.3233	111.9281	<.0001
β_1 VP	1.0094	2.0005	-2.9114	4.9303	0.6138
β_2 Month	-2.3616	0.4324	-3.2091	-1.5141	<.0001
β_3 VP*Month	0.1798	0.5393	-0.8771	1.2367	0.7388
β_4 Month^2	0.0504	0.0275	-0.0036	0.1043	0.0673
β_5 VP*Month^2	0.0204	0.0343	-0.0467	0.0876	0.5506
β_6 Baseline Age	-0.4071	0.1083	-0.6193	-0.1949	0.0002

Table 7. Adjusted Model Results: Overall Test for VP effects - 12 Month Data

H_0: $\beta_1 = 0$, $\beta_3 = 0$, $\beta_5 = 0$

Test	DF	Chi-Square	P-Value
Score Test	3	6.51	0.0891

Table 8. Adjusted Model Results: VA Estimates at 12 Months*

	Estimate	Standard Error	Confidence Limits	
Placebo Mean	44.0072	2.1554	39.7826	48.2317
VP Mean	50.1184	1.4813	47.2150	53.0218
Difference	6.1112	2.6121	0.9917	11.2308

Table 9 gives the correlation matrix for observations made in the first 12 months of the study. Subjects' responses had an interesting association structure, with observations in the later months having a stronger relationship than in the earlier months. Since the focus of this investigation is on differences in Placebo and Verteporfin average trajectories, we report the correlation model simply for completion of our model specification and for reproduction of results.

Table 9. GEE Results: Correlation Model - 12 Month Data

GEE Working Correlation Matrix

	Baseline	Month 3	Month 6	Month 9	Month 12
Baseline	1.00000	0.51435	0.32663	0.29302	0.26441
Month 3	0.51435	1.00000	0.73623	0.66225	0.57180
Month 6	0.32663	0.73623	1.00000	0.81475	0.77050
Month 9	0.29302	0.66225	0.81475	1.00000	0.90010
Month 12	0.26441	0.57180	0.77050	0.90010	1.00000

Results: Basic Model - 24 Month Data

Table 10. Basic Model Results: Mean Model - 24 Month Data

Parameter	Estimate	Standard Error	95% Confidence Limits		P-Value
β_0 Intercept	64.1118	1.0862	61.9828	66.2408	<.0001
β_1 VP	0.0520	1.3404	-2.5752	2.6792	0.9691
β_2 Month	-2.1534	0.2680	-2.6786	-1.6281	<.0001
β_3 VP*Month	0.8061	0.3231	0.1728	1.4394	0.0126
β_4 Month^2	0.0466	0.0086	0.0297	0.0636	<.0001
β_5 VP*Month^2	-0.0200	0.0105	-0.0405	0.0005	0.0558

Table 10 and Figures 1 & 2 indicate that the quadratic trend may be similar for the Placebo and Verteporfin groups. We again maintain β_5 in our model to examine overall differences between the groups. Models assuming similar quadratic trends are investigated in subsequent documents.

Table 11. Basic Model Results: Overall Test for VP effects - 24 Month Data

H_0: $\beta_1 = 0$, $\beta_3 = 0$, $\beta_5 = 0$

Test	DF	Chi-Square	P-Value
Score Test	3	8.59	0.0352

Table 11 displays the overall hypothesis that Verteporfin has no effect on the average visual acuity trajectory, i.e. the hypothesis that all parameters associated with differences between Verteporfin and Placebo are zero.

Table 12. Basic Model Results: Alternative Tests for VP effects - 24 Month Data

H_0: $\beta_3 = 0$, $\beta_5 = 0$

Test	DF	Chi-Square	P-Value
Score Test	2	7.77	0.0205

H_0: $\beta_3 = 0$

Test	DF	Chi-Square	P-Value
Score Test	1	6.03	0.0140

Again, the point might be raised that one does not need to include the baseline difference between the groups β_1 via randomization, or that, since the quadratic-descent terms appear similar, testing β_5 might also be unnecessary. Table 12 displays these alternative hypotheses for Verteporfin effects.

Table 13. Basic Model Results: VA Estimates at 24 Months

	Estimate	Standard Error	Confidence Limits	
Placebo Mean	39.2914	2.2227	34.9349	43.6479
VP Mean	47.1681	1.6685	43.8979	50.4383
Difference	7.8767	2.7793	2.4294	13.3240

Table 13 displays estimated 12-month average VA scores. The average VA score for subjects taking Placebo decreased to $64.1 - 2.15 \cdot (24) + 0.047 \cdot (24)^2 \cong$ **39 letters**, (95% C.I. [34.9, 43.6]), at the end of 12 months. Verteporfin subjects were estimated as decreasing to approximately **47 letters**, (95% C.I. [43.9, 50.4]), at the end of 24 months. Figure 4 displays the estimated mean trajectories and 95% confidence bands for the Verteporfin and Placebo groups.

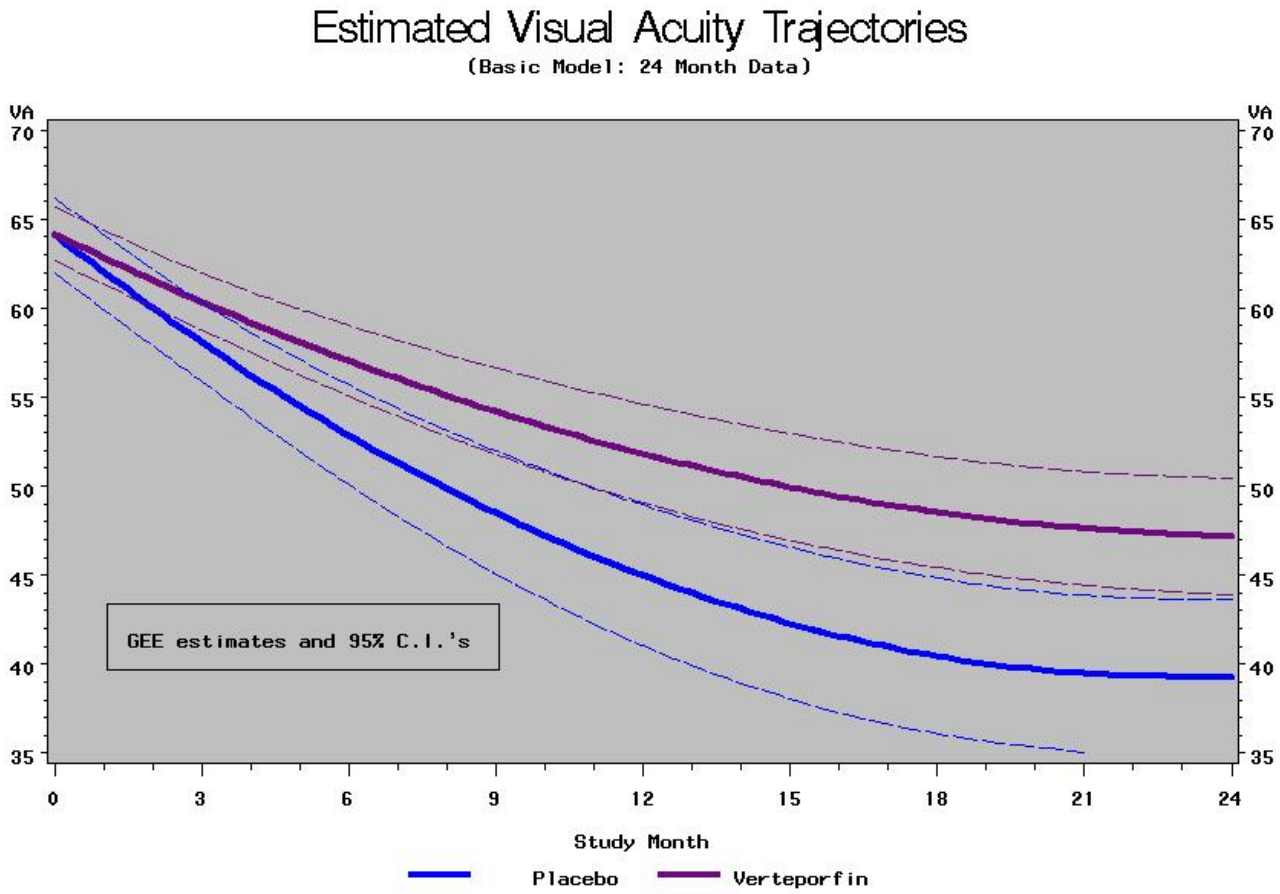


Figure 4. Verteporfin and Placebo Estimated Mean Visual Acuity Trajectories and 95% Confidence Bands for 24 months of the VIP study.

We examined necessary covariate adjustments similar to those reported above. Again only the age of the subject played a significant role in explaining variations among subjects' baseline visual acuity scores and had no effect on the trajectories of either the Placebo or VP group. We again include the baseline adjustments for age in our adjusted mean model noting that it does not change the inferences concerning differences in the decline of Visual Acuity between the Verteporfin and Placebo groups, (see tables 14-16).

Results: Adjusted Model - 24 Month Data

Table 14. Adjusted Model Results: Mean Model - 24 Month Data

Parameter		Estimate	Standard Error	95% Confidence Limits		P-Value
β_0	Intercept	95.2008	9.0600	77.4436	112.9580	<.0001
β_1	VP	0.0550	2.0474	-3.9577	4.0678	0.9786
β_2	Month	-2.1540	0.2363	-2.6171	-1.6910	<.0001
β_3	VP*Month	0.8047	0.2945	0.2275	1.3820	0.0063
β_4	Month^2	0.0466	0.0076	0.0317	0.0614	<.0001
β_5	VP*Month^2	-0.0199	0.0095	-0.0385	-0.0014	0.0349
β_6	Baseline Age	-0.4124	0.1182	-0.6441	-0.1808	0.0005

Table 15. Adjusted Model Results: Overall Test for VP effects - 24 Month Data

H_0: $\beta_1 = 0$, $\beta_3 = 0$, $\beta_5 = 0$

Test	DF	Chi-Square	P-Value
Score Test	3	8.74	0.0329

Table 16. Adjusted Model Results: VA Estimates at 24 Months*

	Estimate	Standard Error	Confidence Limits	
Placebo Mean	39.4088	2.2110	35.0753	43.7422
VP Mean	47.2931	1.6354	44.0878	50.4984
Difference	7.8844	2.7477	2.4990	13.2697

Table 17 gives the correlation matrix for observations made over the 24 months of the study. Subjects' responses again showed observations in the later months having stronger relationships than in the earlier months. Again, the focus of this investigation is on differences in Placebo and Verteporfin average trajectories, however, combining the quadratic-descents of the average Visual Acuity scores and the strong correlations at the later time points, it appears that subjects in this study tended to stabilize after approximately a year.

Table 17. GEE Results: Correlation Model - 12 Month Data

GEE Working Correlation Matrix

	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Baseline	1.0000	0.5143	0.3267	0.2928	0.2645	0.2383	0.2634	0.3171	0.2473
Month 3	0.5143	1.0000	0.7363	0.6623	0.5722	0.5109	0.4646	0.4827	0.4504
Month 6	0.3267	0.7363	1.0000	0.8147	0.7707	0.7300	0.6564	0.6573	0.6443
Month 9	0.2928	0.6623	0.8147	1.0000	0.9003	0.8549	0.7911	0.7686	0.7510
Month 12	0.2645	0.5722	0.7707	0.9003	1.0000	0.9281	0.8660	0.8394	0.8119
Month 15	0.2383	0.5109	0.7300	0.8549	0.9281	1.0000	0.9281	0.8992	0.8664
Month 18	0.2634	0.4646	0.6564	0.7911	0.8660	0.9281	1.0000	0.9466	0.9044
Month 21	0.3171	0.4827	0.6573	0.7686	0.8394	0.8992	0.9466	1.0000	0.9517
Month 24	0.2473	0.4504	0.6443	0.7510	0.8119	0.8664	0.9044	0.9517	1.0000

VIP Study

- Occult Data Subset -

Linear Mixed Model Analysis (Quadratic Descent Model)

Analyses:

Basic Model:

2.) $\mathbf{VA}_i \mid \mathbf{b}_i = \beta_0 + \beta_1 \cdot I(\text{Trt=VP}) + \beta_2 \cdot \text{Time} + \beta_3 \cdot I(\text{Trt=VP}) \times \text{Time} + \beta_4 \cdot \text{Time}^2 + \beta_5 \cdot I(\text{Trt=VP}) \times \text{Time}^2 + b_{0i} + b_{1i} \cdot \text{Time} + b_{2i} \cdot \text{Time}^2 + \boldsymbol{\varepsilon}$

4.) $\boldsymbol{\varepsilon} \sim \text{MVN}(\mathbf{0}, \sigma^2\mathbf{I})$

5.) $\mathbf{b}_i = \begin{pmatrix} b_{0i} \\ b_{1i} \\ b_{2i} \end{pmatrix} \sim \text{MVN}(\mathbf{0}, \boldsymbol{D})$

This model examines time-dependent differences between the Verteporfin and Placebo groups. The notation $I(\text{Trt=VP})$ represents an "indicator function" which takes on the value 0 if the statement "Trt=VP" is false (i.e. the subject received the Placebo treatment) and the value 1 if the statement "Trt=VP" is true (i.e. the subject received the Verteporfin treatment). "Time" is a variable measuring the passage of time, where the number of measurements and the dates at which they are taken are not necessarily identical for all subjects. The $\boldsymbol{\beta}$ parameters in the model are "population-specific", (i.e. pertain to all subjects) and are therefore often called "fixed effects", whereas the $\mathbf{b}_i$ parameters are "subject-specific" (i.e. pertain to an individual subject), are assumed to be random quantities and are often called "random effects". The inclusion of fixed and random effects in a linear model creates a Linear Mixed Effects model. This model yields the following mean structures for the population:

Table 1. Basic Model Average Trajectories: **Placebo** vs. **Verteporfin**

	Average Trajectory
Placebo	$\beta_0 + \beta_2 \cdot \text{Time} + \beta_4 \cdot \text{Time}^2$
Verteporfin	$(\beta_0 + \beta_1) + (\beta_2 + \beta_3) \cdot \text{Time} + (\beta_4 + \beta_5) \cdot \text{Time}^2$

We therefore examine β_1 and, β_3 and β_5 to determine if there are systematic differences in the Verteporfin and Placebo groups over time. Additional fixed effect explanatory variables, such as development of classic CNV, age at baseline, gender, baseline lesion size, etc., are used to enhance the basic model when appropriate.

Additionally, the model yields the following mean structures for the "i^{th}" and "j^{th}" individuals, conditional on the individuals' "random" effects:

Table 2. Basic Model Subject-Specific Trajectories:

	Conditional Average Trajectory
Placebo Subject i	$(\beta_0 + b_{0i}) + (\beta_2 + b_{1i}) \cdot \text{Time} + (\beta_4 + b_{2i}) \cdot \text{Time}^2$
Verteporfin Subject j	$(\beta_0 + \beta_1 + b_{0j}) + (\beta_2 + \beta_3 + b_{1j}) \cdot \text{Time} + (\beta_4 + \beta_5 + b_{2j}) \cdot \text{Time}^2$

Thus, individuals have their own "subject-specific" quadratic time-profile for their Visual Acuity measurements.

Only data from the full Two Year VIP study is considered here (i.e. no 12-month data subset results are shown.

Results: Basic Model - 24 Month Data

Table 3. Basic Model Results: Mean Model - 24 Month Data

Parameter	Estimate	Standard Error	95% Confidence Limits		P-Value
β_0 Intercept	65.0397	1.0073	63.0565	67.0230	<.0001
β_1 VP	-0.7812	1.2487	-3.2400	1.6776	0.5321
β_2 Month	-2.3894	0.2580	-2.8975	-1.8813	<.0001
β_3 VP*Month	0.7651	0.3211	0.1328	1.3974	0.0179
β_4 Month^2	0.05474	0.0087	0.0377	0.0718	<.0001
β_5 VP*Month^2	-0.01639	0.0108	0.0377	0.0049	0.1303

Both Table 3 and the observed data plots indicate that the quadratic trend is similar for the Placebo and Verteporfin groups. However, our main questions revolve around trajectory differences between the two groups and we thus maintain β_5 in our model to examine overall differences.

Table 3. Basic Model Results: Overall Test for VP effects - 24 Month Data

H_0: $\beta_1 = 0$, $\beta_3 = 0$, $\beta_5 = 0$

Test	Num DF	Den DF	F Value	P-Value
F-Test	3	245	3.35	0.0198

Table 3 displays the overall hypothesis that Verteporfin has no effect on the average visual acuity trajectory, i.e. the hypothesis that all parameters associated with differences between Verteporfin and Placebo are zero.

Table 4. Basic Model Results: Alternative Tests for VP effects - 24 Month Data

H_0: $\beta_3 = 0$, $\beta_5 = 0$

Test	Num DF	Den DF	F Value	P-Value
F-Test	2	239	5.01	0.0074

H_0: $\beta_3 = 0$

Test	Num DF	Den DF	F Value	P-Value
F-Test	1	251	5.68	0.0179

Alternatively, the point might be raised that one does not need to include the baseline difference between the groups β_1 via randomization, or that, since the quadratic-descent terms appear similar, testing β_5 might also be unnecessary. Table 4 displays these alternative hypotheses for Verteporfin effects.

Table 5. Basic Model Results: Visual Acuity Estimates at 24 Months

	Estimate	Standard Error	Confidence Limits	
Placebo Mean	39.2232	2.2488	34.7934	43.6530
VP Mean	47.3638	1.6812	44.0522	50.6755
Difference	8.1406	2.8078	2.6098	13.6714

Table 5 displays estimated 12-month average VA scores. The average VA score for subjects randomized to Placebo decreased to **39 letters**, (95% C.I. [34.8, 43.7]), at the end of 24 months. Verteporfin subjects were estimated as decreasing to approximately **47 letters**, (95% C.I. [44.0, 50.7]), at the end of 24 months. Figure 3. displays the estimated mean trajectories and 95% confidence bands for the Verteporfin and Placebo groups.

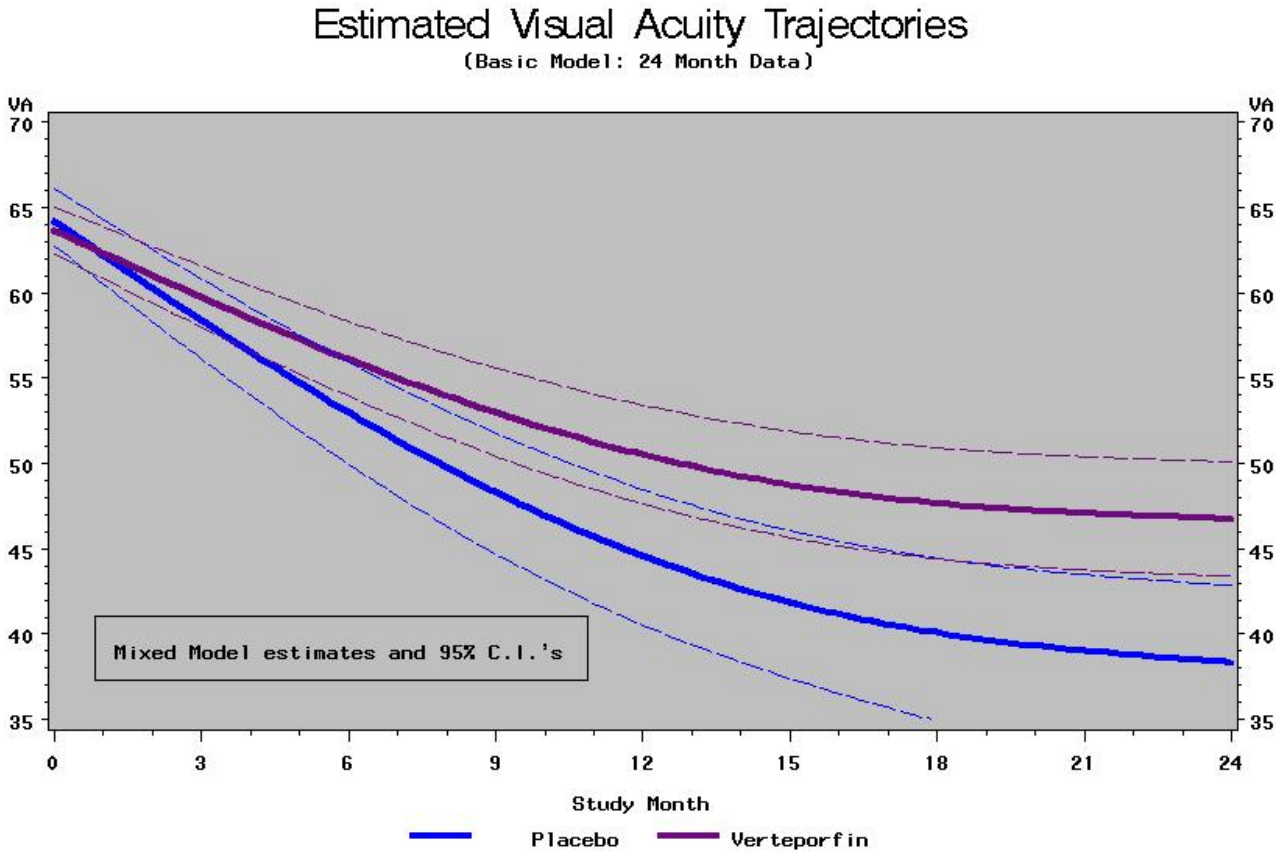


Figure 3. Verteporfin and Placebo Estimated Mean Visual Acuity Trajectories and 95% Confidence Bands for the 24 months of the VIP study.

We used an unstructured covariance model for ***D***, the covariance matrix of the random intercept, slope, and quadratic effects. Figure 4 compares the smoothed average trend of the squared residuals from an Ordinary Least Squares (OLS) fit, (the "empirical" variance function), with the fitted variance function obtained from our linear mixed model as a check on our assumed variance structure. The fitted variance function follows the trend of the empirical variance function quite closely.

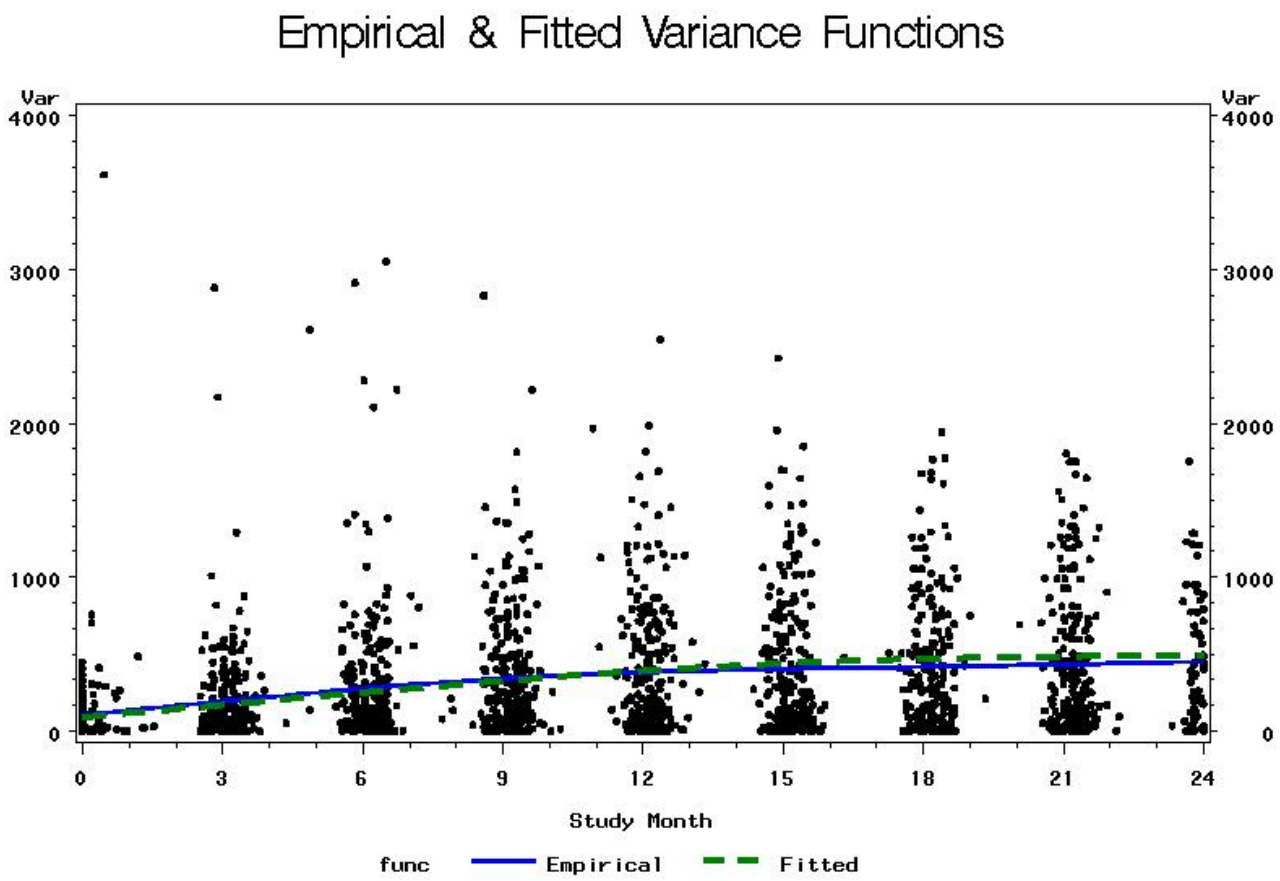


Figure 4. Empirical variance function, (smoothed average squared OLS residual), and linear mixed model fitted variance function for the VIP study.

VIP Study

- Occult Data Subset -

PHM Analysis
(Time to First 15 Letter Loss)

Time To First Loss of 15 Visual Acuity Letters:

We define our initial event of interest as the first recorded time that a subject's Visual Acuity score dropped at least 15 Letters from the subject's baseline value. We then use survival analysis techniques to examine differences between subjects randomized to Verteporfin and subjects randomized to Placebo in times until the event.

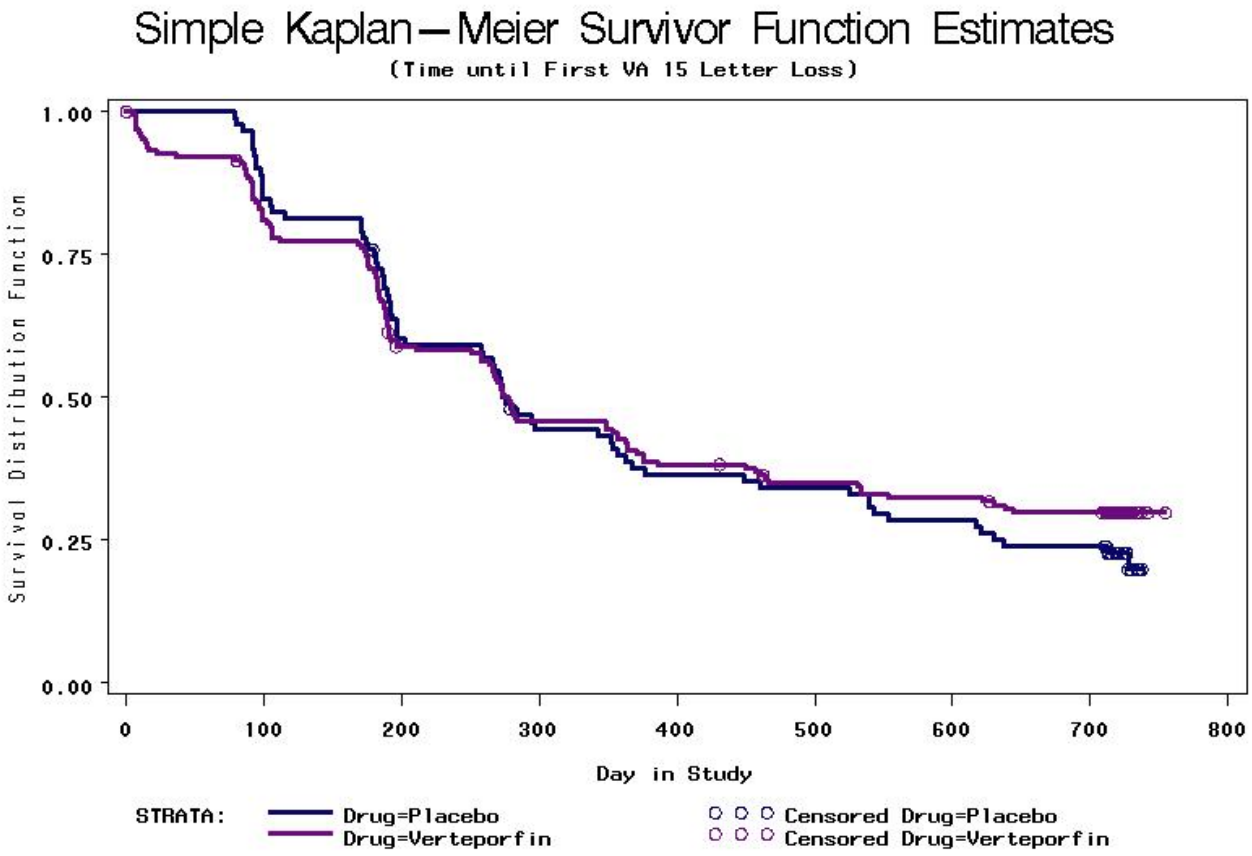


Figure 1. Kaplan-Meier survival function estimates for **Placebo** **vs** **Verteporfin** first Visual Acuity 15 letter loss .

The Kaplan-Meier Survival functions demonstrate a crossing at around 270 days (9 months), indicating that more VA scores in the Verteporfin group decreased by at least 15 letters in the initial period of the trial, and more VA scores in the Placebo group decreased by at least 15 letters in the later period of the trial. Overall the curves appear quite similar.

Table 1. Overall Log-Rank test for Verteporfin effects on the time to first VA 15 letter loss.

Test of Equality of VP & Placebo

Test	Chi-Square	DF	P-Value
Log-Rank	0.3547	1	0.5514

The overall log-rank test for differences between the Verteporfin and Placebo groups in their times to first 15 letter loss shows no diversity between the two groups, but we note again that the curves cross around the 9 month time point and thus an overall test may be misleading.

In terms of time until the decline of Visual Acuity, the median number of days to a 15 letter loss was 275 days (95% C.I. [202 days, 363 days]) for Placebo subjects and 278 days (95% C.I. [258 days, 363 days]) for Verteporfin subjects.

We can test for differences in the effects over time while adjusting for other covariates by using the workhorse of survival analyses, Cox's Proportional Hazards Model (PHM). We define the hazard $h(t)$ for an individual to have an event (VA 15 Letter Loss) at time t as:

$$\log\{h(t)\} = \log\{\lambda(t)\} + \beta_1 \cdot I(\text{Trt=VP}) + \beta_2 \cdot I(\text{Trt=VP}) \times I(t > 270 \text{ days})$$

or

$$h(t) = \lambda(t) \cdot \exp\{\beta_1 \cdot I(\text{Trt=VP}) + \beta_2 \cdot I(\text{Trt=VP}) \times I(t > 270 \text{ days}) \}$$

We examine β_1 for the difference between Verteporfin and Placebo hazards before 270 days (9 months) and $\beta_1 + \beta_2$ for the difference between Verteporfin and Placebo hazards after 9 months.

Table 2. PHM results for overall Verteporfin effects in increasing the time to VA 15 letter loss: adjusted for baseline age.

Proportional Hazards Model Results

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	P-value	Hazard Ratio
β_1 VP	1	1.86053	0.21356	75.8970	<.0001	6.427
β_2 VP*Day>270	1	-3.02488	0.25440	141.3753	<.0001	0.049
$\beta_1 + \beta_2$	1	-1.16435	0.20609	31.9208	<.0001	0.312

Thus, there appears to be a hazardous Verteporfin effect (the hazard of 15 letter loss is 6 times greater than Placebo) during the first 9 months and a beneficial Verteporfin effect (the hazard of 15 letter loss is 3 times less than Placebo) in the later stages of the study (post 9 months).

Time To First Loss of 30 Visual Acuity Letters:

We define our secondary event of interest as the first recorded time that a subject's Visual Acuity score dropped at least 30 Letters from the subject's baseline value. We again use survival analysis techniques to examine differences between subjects randomized to Verteporfin and subjects randomized to Placebo in their times until the event.

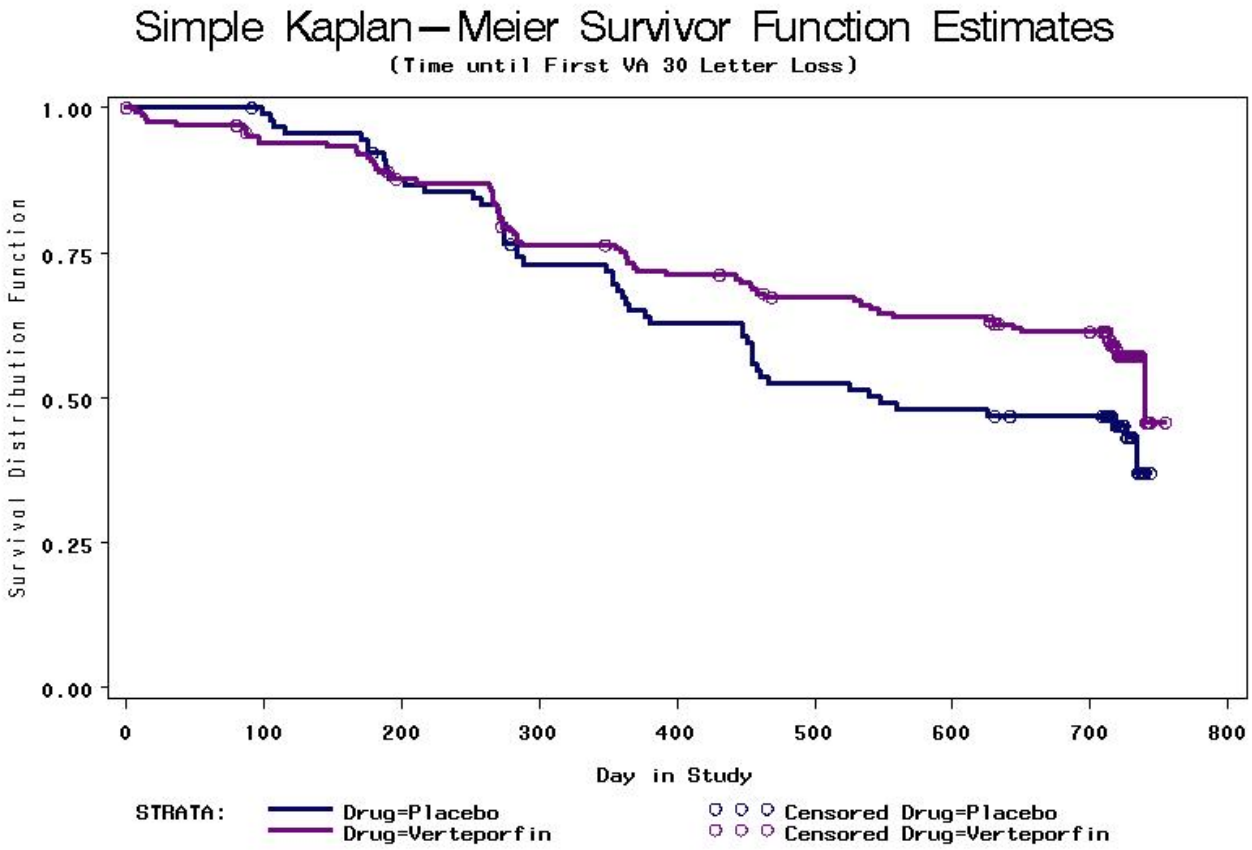


Figure 1. Kaplan-Meier survival function estimates for **Placebo** **vs** **Verteporfin** first Visual Acuity 15 letter loss .

The Kaplan-Meier Survival functions again demonstrate a crossing, this time at around 210 days (3 months), indicating that more VA scores in the Verteporfin group decreased by at least 30 letters in the initial period of the trial, and more VA scores in the Placebo group decreased by at least 30 letters in the later period of the trial. Differences at later times appear greater here.

Table 1. Overall Log-Rank test for Verteporfin effects on the time to first VA 15 letter loss.

Test of Equality of VP & Placebo			
Test	Chi-Square	DF	P-Value
Log-Rank	3.9912	1	0.0457

The overall log-rank test for differences between the Verteporfin and Placebo groups in their times to first 30 letter loss reflects the larger group differences in the later times outweighing the differences for earlier times.

In terms of time until the decline of Visual Acuity, the median number of days to a 30 letter loss was 548 days (95% C.I. [451 days, ∞ days]) for Placebo subjects and 740 days (95% C.I. [721 days, ∞ days]) for Verteporfin subjects.

We again test for differences in the effects over time while adjusting for other covariates such as baseline age by using Cox's Proportional Hazards Model (PHM). We define the hazard $h(t)$ for an individual to have an event (VA 30 Letter Loss) at time t as:

$$\log\{h(t)\} = \log\{\lambda(t)\} + \beta_1 \cdot I(\text{Trt=VP}) + \beta_2 \cdot I(\text{Trt=VP}) \times I(t > 210 \text{ days})$$

or

$$h(t) = \lambda(t) \cdot \exp\{\beta_1 \cdot I(\text{Trt=VP}) + \beta_2 \cdot I(\text{Trt=VP}) \times I(t > 210 \text{ days}) \}$$

We examine β_1 for the difference between Verteporfin and Placebo hazards before 210 days (7 months) and $\beta_1 + \beta_2$ for the difference between Verteporfin and Placebo hazards after 7 months.

Table 2. PHM results for overall Verteporfin effects in increasing the time to VA 15 letter loss: adjusted for baseline age.

Proportional Hazards Model Results

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	P-value	Hazard Ratio
β_1 VP	1	3.29999	0.39822	68.6737	<.0001	27.112
β_2 VP*Day>210	1	-4.04130	0.40472	99.7073	<.0001	0.018
$\beta_1 + \beta_2$	1	-0.74131	0.20355	13.2641	0.0003	0.477

Thus, there appears to be a hazardous Verteporfin effect (hazard is 27 times greater than Placebo) during the first 7 months and a beneficial Verteporfin effect (hazard is 2 times less than Placebo) in the later stages of the study (post 7 months).

In both the time to 15 letter loss analysis and the time to 30 letter loss PHM analysis, graphical methods were used to check proportionality assumptions (plots of the log-log survival function vs. time, the hazard vs. time and the survival function vs. time) and led to the choice of time cut points (270 days and 210 days) to better satisfy assumptions.

VIP Study

- Occult Data Subset -

Missing Data Discussion

Table 1 lists the numbers and percents of missing visual acuity measurements for each arm of the 24 month VIP study. Data listed is for the occult subgroup, (patients who presented at baseline with occult but no classic CNV on fluorescein angiogram). The amount of missingness appears similar between the two groups throughout the study.

VA Missingness by Visit and Treatment Group

Placebo

	VISIT								
	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Observed	92	91	89	89	83	81	81	81	81
%	100.00	98.91	96.74	96.74	90.22	88.04	88.04	88.04	88.04
Missing	0	1	3	3	9	11	11	11	11
%	0.00	1.09	3.26	3.26	9.78	11.96	11.96	11.96	11.96
Total	92	92	92	92	92	92	92	92	92

Verteporfin

	VISIT								
	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Observed	166	162	159	156	157	154	140	144	143
%	100.00	97.59	95.78	93.98	94.58	92.77	84.34	86.75	86.14
Missing	0	4	7	10	9	12	26	22	23
%	0.00	2.41	4.22	6.02	5.42	7.23	15.66	13.25	13.86
Total	166	166	166	166	166	166	166	166	166

Table 1. Number of missing Visual Acuity measurements for the two treatment groups over the 24 months of the VIP study (occult subgroup).

Missing Data Mechanisms:

We describe the standard classification system of missing value mechanisms as follows. Denoting $\boldsymbol{Y}^{*}$ as the complete set of measurements which would have been recorded if there were no missing data, we divide the complete set into, $\boldsymbol{Y}^{*} = (\boldsymbol{Y}^{o}, \boldsymbol{Y}^{m})$, where $\boldsymbol{Y}^{o}$ represents the observed measurements that were actually recorded and $\boldsymbol{Y}^{m}$ represents the measurements that would have been recorded if no values had been missing. In addition, let $\boldsymbol{R}$ represent the set of indicator variables denoting which values in $\boldsymbol{Y}^{*}$ are actually observed and are thus members of $\boldsymbol{Y}^{o}$.

The standard classification of missing data mechanisms is then:

- MCAR: Missing Completely At Random
  The missingness is independent of all measurements: $\boldsymbol{R} \perp$ of both $\boldsymbol{Y}^{\mathbf{o}}$ & $\boldsymbol{Y}^{\mathbf{m}}$.

- MAR: Missing At Random
  The missingness is independent of the unobserved (missing) measurements but depends on the observed measurements: $\boldsymbol{R} \mid \boldsymbol{Y}^{\mathbf{o}} \perp$ of $\boldsymbol{Y}^{\mathbf{m}}$.

- MNAR: Missing Not At Random (*Informative Missingness*)
  The missingness depends on the missing measurements and possibly the observed measurements also.

Common "Solutions" and Drawbacks Therein:

Last Observation Carried Forward (LOCF):

One of the most common methods of dealing with missing data is to extrapolate the last observed measurement for a given subject to all missing data points that follow that measurement for that subject. This is a simple form of missing data imputation (single) and suffers from the following drawbacks:

- If the imputation model is not correct, point estimates are biased.
- Even when the imputation model is correct, uncertainty is underestimated from filling in unknown values and treating them as if they were known.
- Severe biases can occur if the data are not MCAR

In addition, when LOCF is used, the very strong assumption must be made that a subject's measurement stayed at the same level from the moment the last observation was made. This assumption is highly suspect for the VIP trial, as evidenced in the quadratic-descent mean-trajectories observed earlier and via plots that follow this discussion.

Complete Case Analyses (CC):

Another commonly used missing data method is to use only those cases in which all measurements were actually observed in the analysis. This method can be seductive for its simplicity and for its common basis of inference, (all those who would complete the advised treatment), however, it too suffers some critical drawbacks:

- Loss of information and precision from the discarded data
- Severe biases can occur if the data are not MCAR

Likelihood Based Inference & Ignorability:

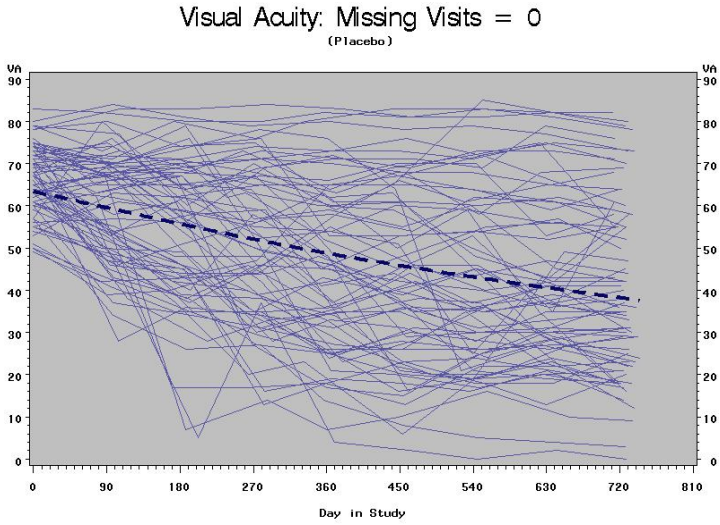
When using likelihood-based inference, the MCAR requirement is often relaxed to the less stringent MAR assumption. Under MAR, the likelihood function of the observable random variables ($\boldsymbol{Y}^{\mathbf{o}}$, $\boldsymbol{R}$), on which inference must be based, can often be separated into two terms, one involving the parameters of interest, the other containing no information about the distribution of the observed measurements. Inference using likelihood methods can therefore be based on the marginal density of the observed data alone and the missing data is often called "ignorable".

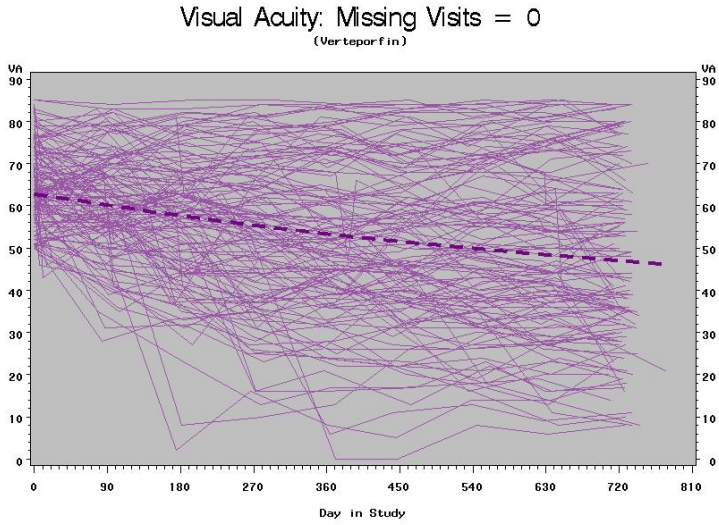
VIP Analyses:

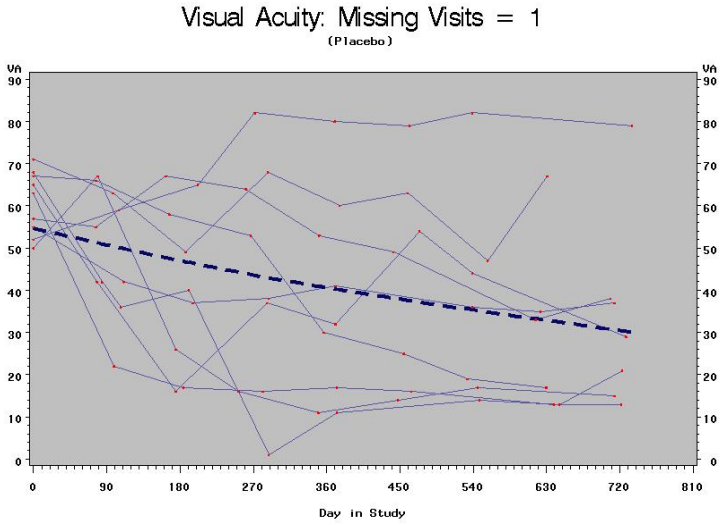
Mixed Models allow the fitting of ignorable models with likelihood-based methods. The models and inferences obtained under our Linear Mixed Model for the VIP occult group should therefore be valid under the MAR assumption, which is less restrictive than the MCAR requirements of the LOCF and CC analyses. Additionally, for Gaussian data, the Generalized Estimating Equations can be shown to be the score equations from a likelihood based analyses and therefore our GEE analyses of the VIP occult data should also hold under the MAR assumption. The question of missingness was one of the reasons we chose our analyses methods. It is also satisfying that although the models are based on different assumptions, results for the GEE and Mixed Model were exceedingly similar.

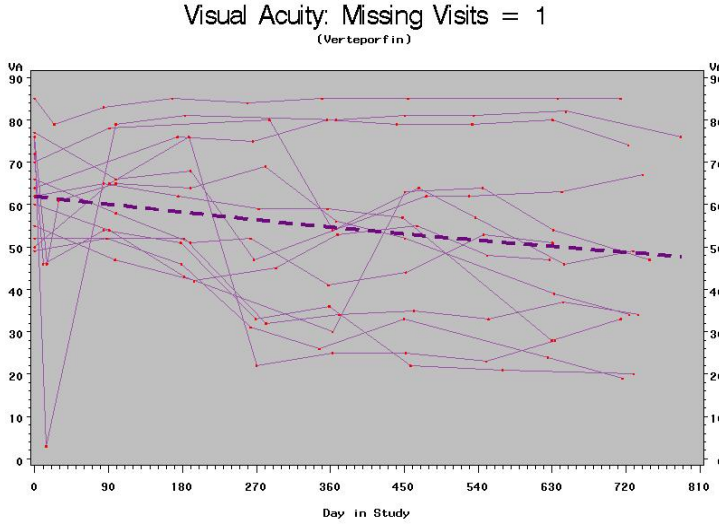
Visual Explorations:

The following represent the individual and smoothed mean visual acuity trajectories for subjects in the VIP trial (occult-subgroup), subset by the number of Visits for which missing values were recorded. For subjects with any missing data (subjects with number of Missing Visits > 0), red dots are added to record where the observed measurements were taken.

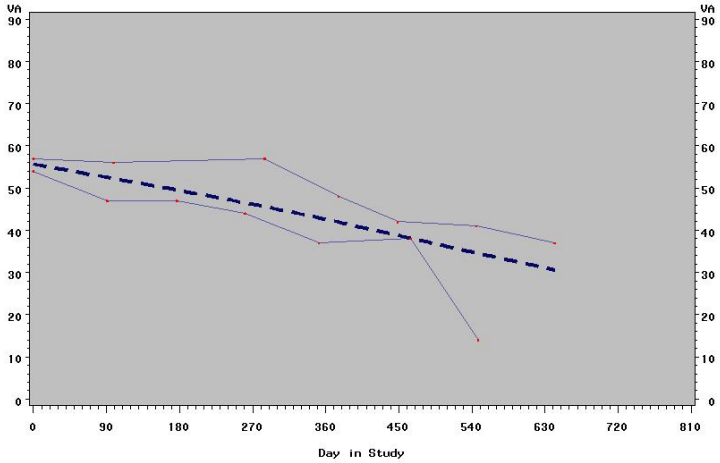






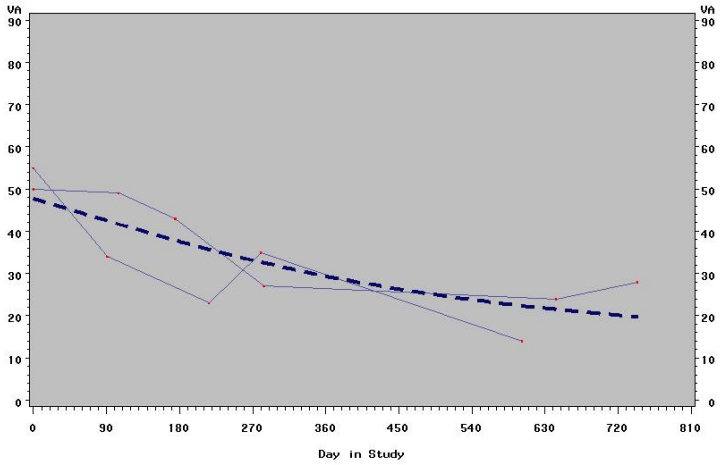


Visual Acuity: Missing Visits = 2
(Placebo)

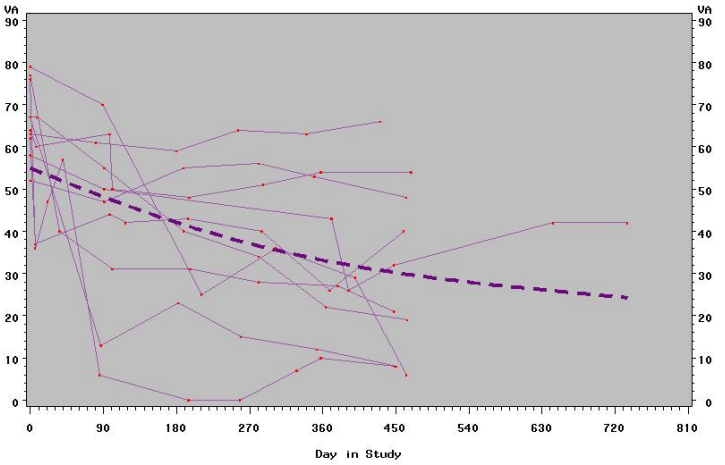


No VP subjects
with
2 Missing Values

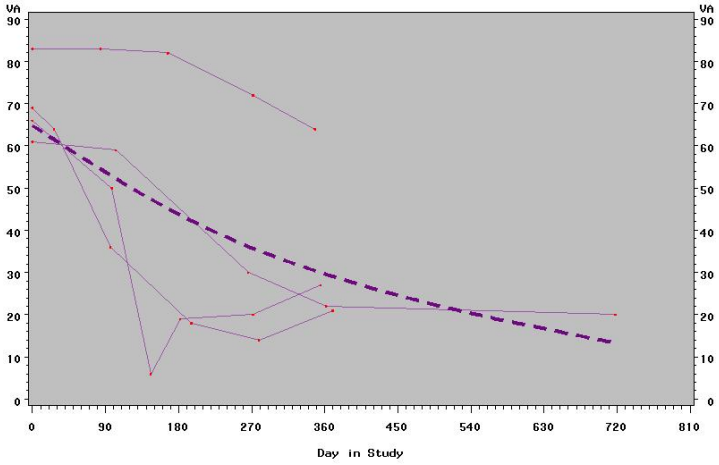
Visual Acuity: Missing Visits = 3
(Placebo)



Visual Acuity: Missing Visits = 3
(Verteporfin)

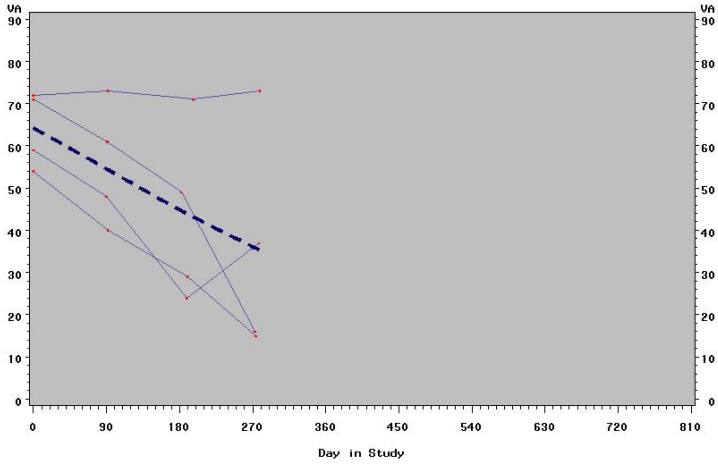


Visual Acuity: Missing Visits = 4
(Verteporfin)

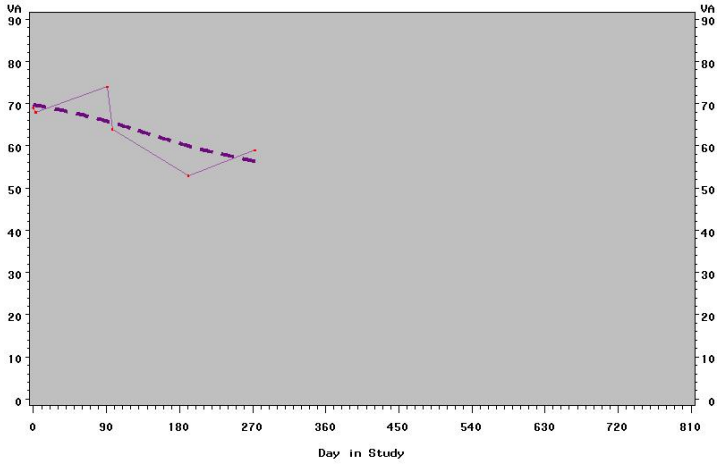


No Placebo subjects
with
4 Missing Values

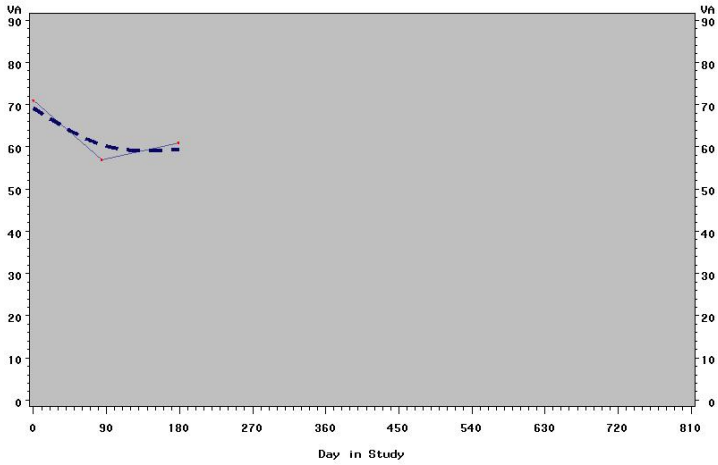
Visual Acuity: Missing Visits = 5
(Placebo)



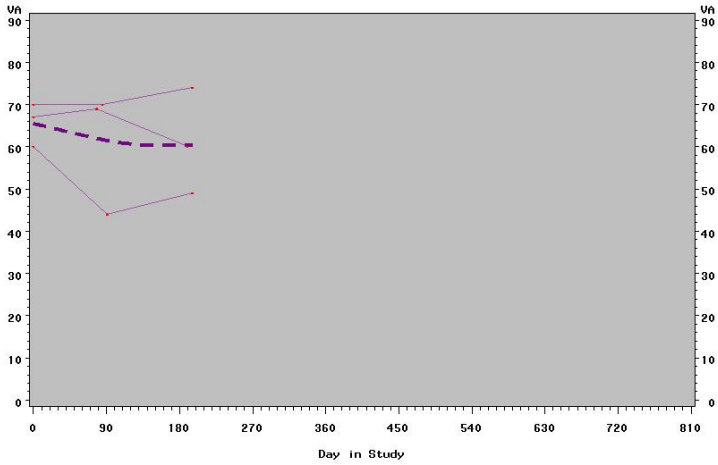
Visual Acuity: Missing Visits = 5
(Verteporfin)



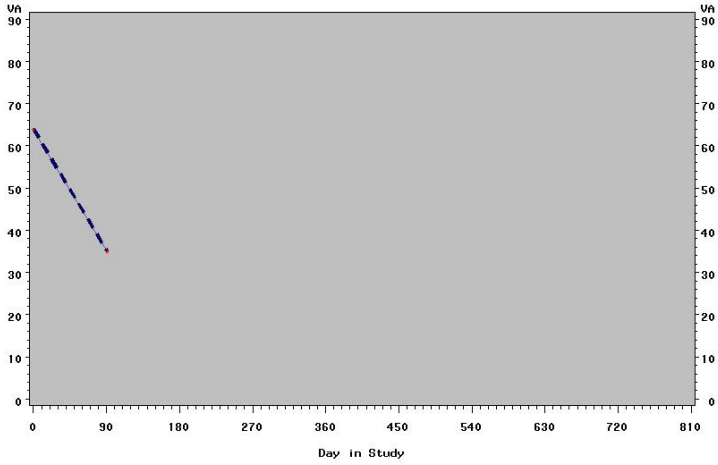
Visual Acuity: Missing Visits = 6
(Placebo)



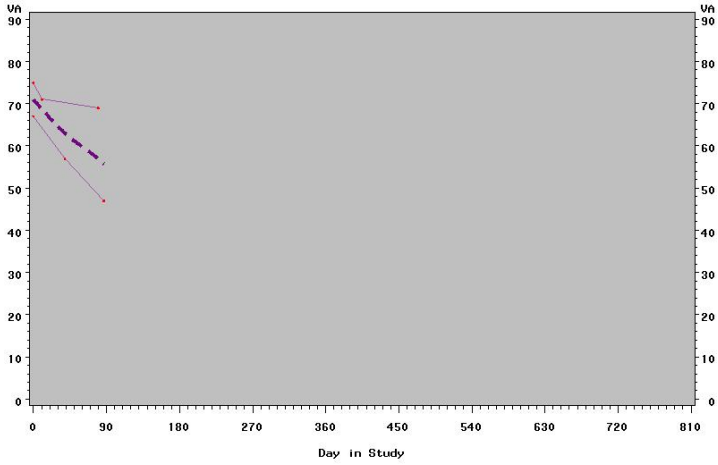
Visual Acuity: Missing Visits = 6
(Verteporfin)



Visual Acuity: Missing Visits = 7
(Placebo)



Visual Acuity: Missing Visits = 7
(Verteporfin)



VIP Study
- Occult Data Subset -

Occult-to-Classic CNV Conversions

Classic CNV development Analysis:

We split the data into three subsets, those who had no development of classic CNV throughout the 24 month study period (pure occult), those who developed classic CNV lesion components between baseline and 12 months and those who developed classic CNV lesion components between 12 and 24 months. We present individual and smoothed mean visual acuity trajectories over two years (~750 days) of the VIP study for subjects in these 3 subgroups for discussion. We additionally examine the probabilities of subjects falling into these categories.

Figures 1-3 show similarities in the smoothed mean trajectories of subjects randomized to Placebo and subjects randomized to Verteporfin. Hence, differences between the overall treatment groups may be due in part to less development of Classic CNV in the Verteporfin group.

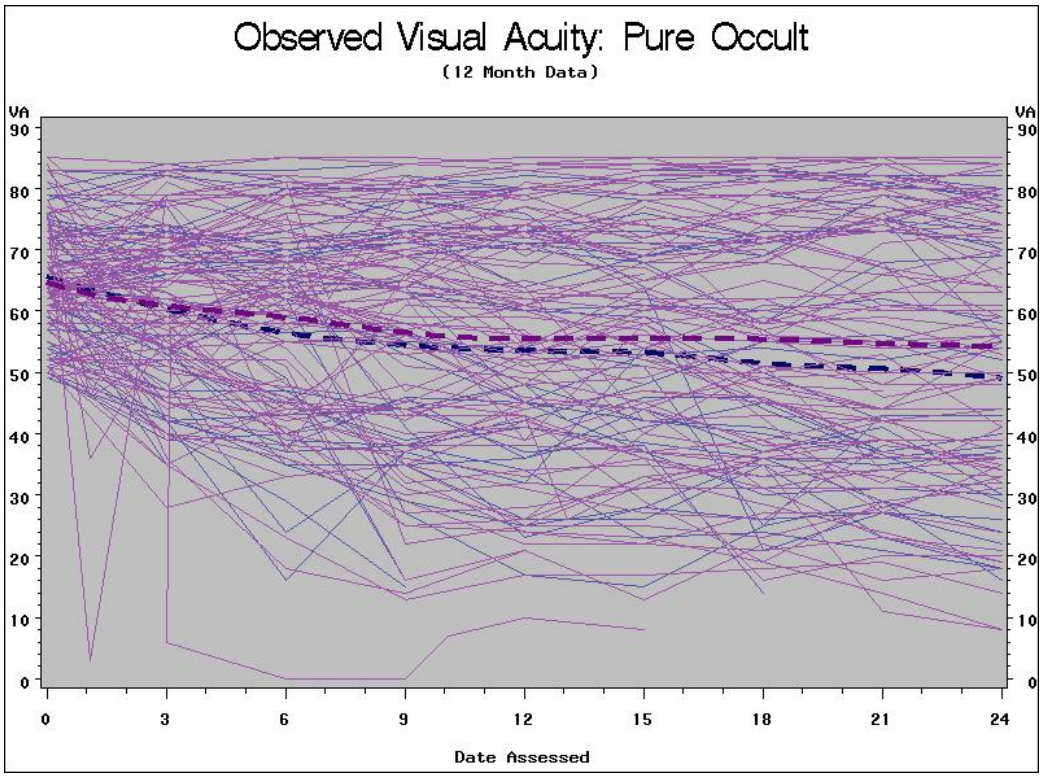


Figure 1. Individual and smoothed mean visual acuity trajectories over two years (~750 days) of the VIP study for subjects randomized to **Placebo** and **Verteporfin** who did not develop Classic CNV during the study.

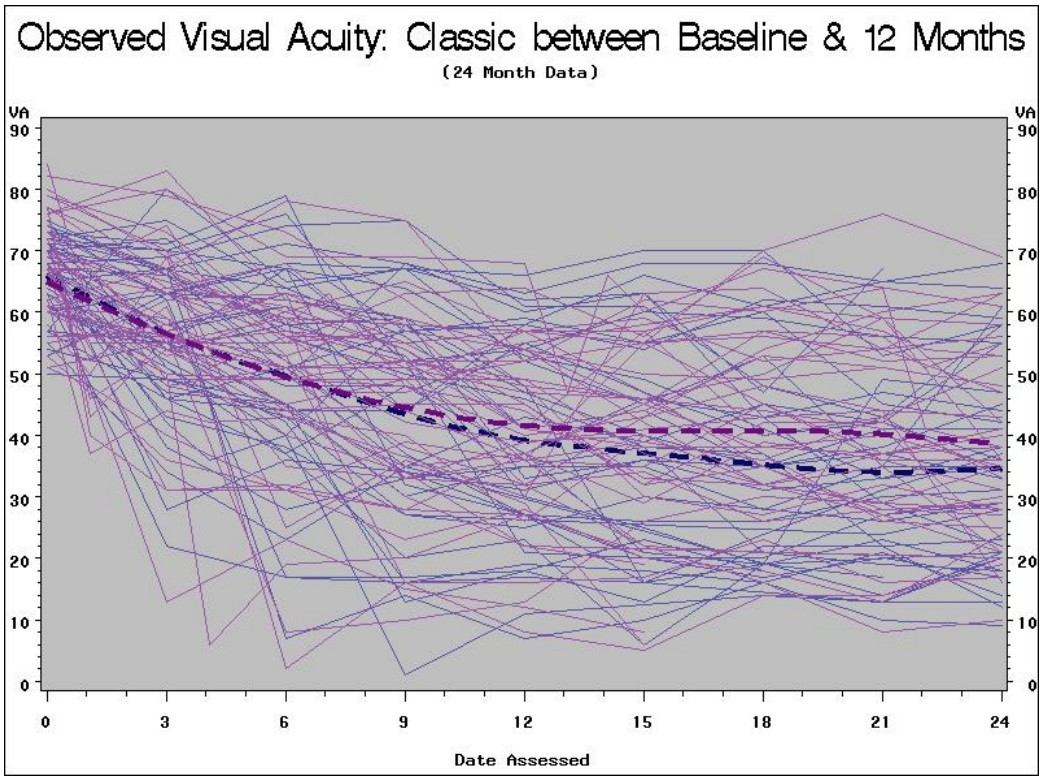


Figure 2. Individual and smoothed mean visual acuity trajectories over two years (~750 days) of the VIP study for subjects randomized to **Placebo** and **Verteporfin** who developed Classic CNV during the first year of the study.

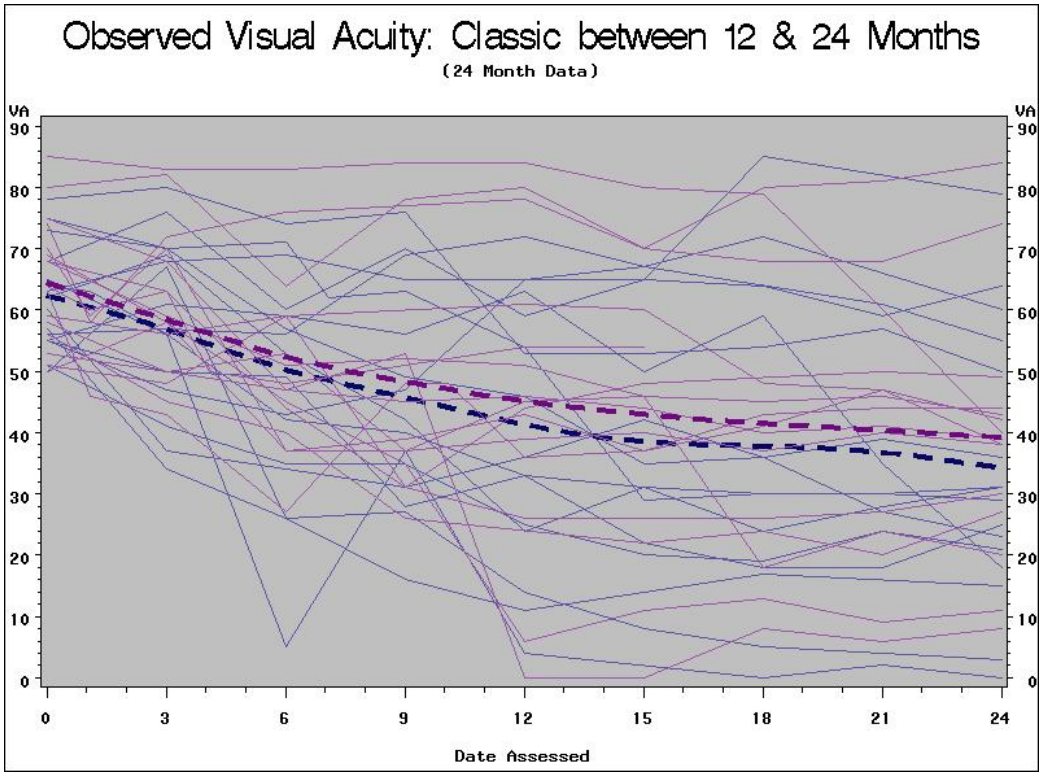


Figure 3. Individual and smoothed mean visual acuity trajectories over two years (~750 days) of the VIP study for subjects randomized to **Placebo** and **Verteporfin** who developed Classic CNV in the second year of the study.

Table 1. Crude Rates of Classic CNV Development by Treatment Status

	Classic CNV Development			
	Pure Occult	Classic 0-12 mo	Classic 12-24 mo	Total
Placebo	37	39	16	92
%	40.22	42.39	17.39	
Verteporfin	101	49	16	166
%	60.84	29.52	9.64	
Total	138	88	32	258

Table 2. General test of association of Verteporfin treatment and Classic CNV Development

Pearson Statistic			
Statistic	DF	Value	P-Val
Chi-Square	2	10.45	0.005

Tables 1 and 2 show an association between the Verteporfin treatment and development of classic CNV, with fewer subjects randomized to Verteporfin developing classic CNV than subjects randomized to Placebo.

VIP Study

- Occult Data Subset -

GEE Analysis 2
(Alternative Quadratic Descent Model)

Analyses:

Initial Model:

3.) **VA** = $\beta_0 + \beta_1 \cdot I(\text{Trt=VP}) + \beta_2 \cdot \text{Month} + \beta_3 \cdot I(\text{Trt=VP}) \times \text{Month} + \beta_4 \cdot \text{Month}^2 + \beta_5 \cdot I(\text{Trt=VP}) \times \text{Month}^2 + \boldsymbol{\varepsilon}$

6.) $\boldsymbol{\varepsilon} \sim \text{MVN}(\mathbf{0}, \sigma^2\mathbf{R})$

7.) **R** modeled with unstructured correlations.

This model examines time-dependent differences between the Verteporfin and Placebo groups. The notation I(Trt=VP) represents an "indicator function" which takes on the value 0 if the statement "Trt=VP" is false (i.e. the subject received the Placebo treatment) and the value 1 if the statement "Trt=VP" is true (i.e. the subject received the Verteporfin treatment) Month is a variable measuring the passage of time in months. We therefore have the following structure:

Table 1. Initial Model Average Trajectories: **Placebo** vs. **Verteporfin**

	Trajectory
Placebo	$\beta_0 + \beta_2 \cdot \text{Month} + \beta_4 \cdot \text{Month}^2$
Veretporfin	$(\beta_0 + \beta_1) + (\beta_2 + \beta_3) \cdot \text{Month} + (\beta_4 + \beta_5) \cdot \text{Month}^2$

We examine β_1 and, β_3 and β_5 to determine if there are systematic differences in the Verteporfin and Placebo groups over time. Additional explanatory variables, such as development of classic CNV, gender, baseline lesion size, etc., are used to enhance the *initial* model when appropriate.

We used a Generalized Estimating Equation (GEE) approach to obtain estimates and construct inferences for our models. To investigate the effects of covariance assumptions, the following covariance structures were examined: Independent, Compound Symmetric, Auto-Regressive, Toeplitz, and Unstructured. Results were robust to changes in the assumed covariance model and our final correlation structure was formulated via explorations of the residuals from the final mean model. The normality assumption did not appear to be considerably violated.

Results: Initial Model - 12 Month Data

Table 2. Initial 12 Month Model GEE Results: Mean Model

Parameter	Estimate	Standard Error	95% Confidence Limits		P-Value
β_0 Intercept	64.9375	0.9381	63.0989	66.7761	<.0001
β_1 VP	0.9974	1.1845	-1.3241	3.3189	0.3997
β_2 Month	-2.3636	0.4547	-3.2547	-1.4724	<.0001
β_3 VP*Month	0.1871	0.5583	-0.9072	1.2814	0.7376
β_4 Month^2	0.0506	0.0308	-0.0098	0.1110	0.1007
β_5 VP*Month^2	0.0200	0.0376	-0.0537	0.0937	0.5946

Both the observed data plots and the results for β_5 show that the quadratic trends for the Placebo and Verteporfin groups are similar. We therefore removed the quadratic-interaction term (β_5) and fit the simplified model. Results from the simplified model did not change after adjusting for gender, smoking status, baseline lesion size, and/or hypertension, and the simplified model thus represents our final model.

Table 3. Final Model Average Trajectories: **Placebo** vs. **Verteporfin**

	Trajectory
Placebo	$\beta_0 + \beta_2 \cdot \text{Month} + \beta_4 \cdot \text{Month}^2$
Veretporfin	$(\beta_0 + \beta_1) + (\beta_2 + \beta_3) \cdot \text{Month} + \beta_4 \cdot \text{Month}^2$

Results: Final Model - 12 Month Data

Table 4. Final 12 Month Model GEE Results: Mean Model

Parameter	Estimate	Standard Error	95% Confidence Limits		P-Value
β_0 Intercept	65.2373	1.0433	63.1925	67.2821	<.0001
β_1 VP	0.5315	1.3499	-2.1141	3.1772	0.6937
β_2 Month	-2.5551	0.2997	-3.1425	-1.9678	<.0001
β_3 VP*Month	0.4846	0.2190	0.0553	0.9139	0.0269
β_4 Month^2	0.0635	0.0177	0.0288	0.0982	0.0003

The average VA score for subjects taking Placebo was estimated to be 65.2 letters at baseline and decreased to $65.24 - 2.56 \cdot (12) + 0.064 \cdot (12)^2 \cong$ **44 letters**, (95% C.I. [39.5, 47.9]), at the end of 12 months. Verteporfin subjects were estimated as having an average baseline VA score of (65.2 + .5) = 65.7 letters, decreasing to $65.77 - 2.07 \cdot (12) + 0.064 \cdot (12)^2 \cong$ **50 letters**, (95% C.I. [47.1, 53.0]), at the end of 12 months. The difference between the Verteporfin and Placebo *rates of decline* was found to be statistically significant, ($p = 0.027$), but a difference of (50-44) = **6 letters**, (approximately 1 line), after 12 months does not appear substantial (see Figure 3).

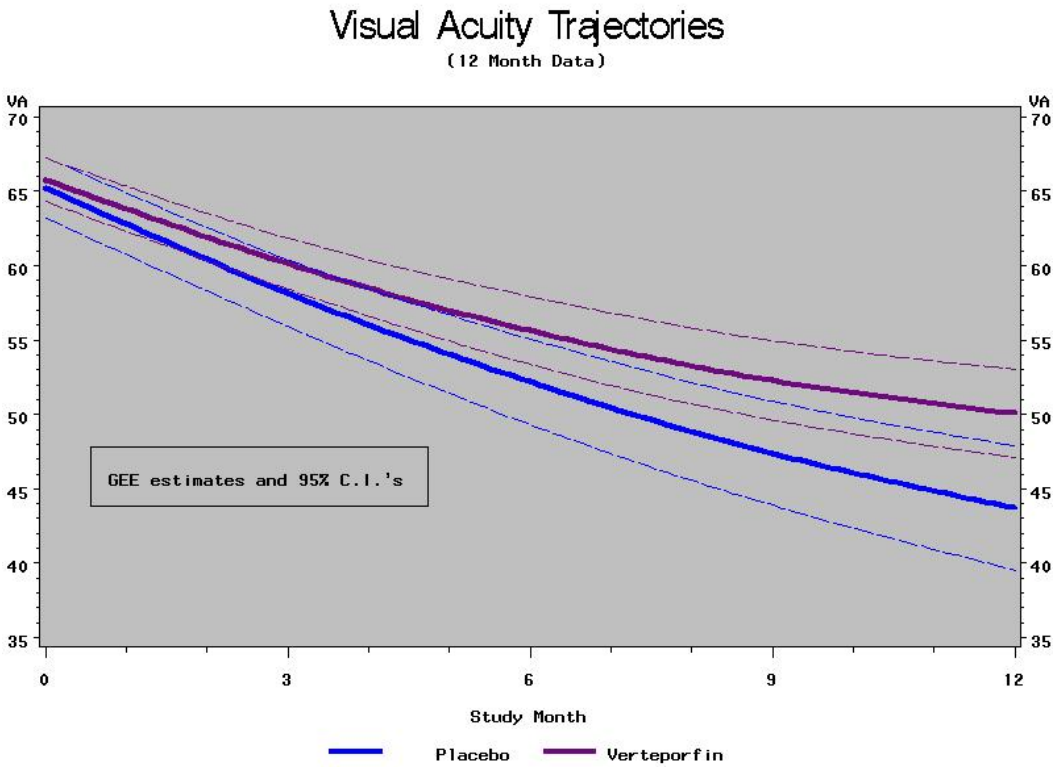


Figure 3. Verteporfin and Placebo Estimated Mean Trajectories and 95% Confidence Bands for initial 12 months of VIP study.

Table 5. Final 12 Month Model GEE Results: Correlation Model

GEE Working Correlation Matrix

	Baseline	Month 3	Month 6	Month 9	Month 12
Baseline	1.0000	0.5159	0.3285	0.2959	0.2693
Month 3	0.5159	1.0000	0.7374	0.6643	0.5760
Month 6	0.3285	0.7374	1.0000	0.8153	0.7722
Month 9	0.2959	0.6643	0.8153	1.0000	0.9016
Month 12	0.2693	0.5760	0.7722	0.9016	1.0000

Subjects' responses had an interesting association structure, with observations in the later months having a stronger relationship than in the earlier months. Since the focus of this investigation is on differences in Placebo and Verteporfin average trajectories, we report the correlation model simply for completion of our model specification and for reproduction of results.

Results: Initial Model - 24 Month Data

Table 6. Initial 24 Month Model GEE Results: Mean Model

Parameter	Estimate	Standard Error	95% Confidence Limits		P-Value
β_0 Intercept	64.1115	1.0858	61.9834	66.2397	<.0001
β_1 VP	0.0593	1.3396	-2.5663	2.6848	0.9647
β_2 Month	-2.1535	0.2680	-2.6788	-1.6281	<.0001
β_3 VP*Month	0.8048	0.3231	0.1715	1.4381	0.0127
β_4 Month^2	0.0466	0.0086	0.0297	0.0636	<.0001
β_5 VP*Month^2	-0.0200	0.0105	-0.0405	0.0005	0.0564

Examining data from the entire two-year study period, the preceding plots and the results for β_5 again show that the quadratic trends for the Placebo and Verteporfin groups are similar. We therefore removed the quadratic-interaction term (β_5) and fit the simplified model again for the 24 month data. Results from the simplified model for the 24 month data also did not change after adjusting for gender, smoking status, baseline lesion size, and/or hypertension, and this simplified model is again our final model.

Results: Final Model - 24 Month Data

Table 7. Final 24 Month Model GEE Results: Mean Model

Parameter	Estimate	Standard Error	95% Confidence Limits		P-Value
β_0 Intercept	63.0828	1.1163	60.8950	65.2706	<.0001
β_1 VP	1.6585	1.4118	-1.1086	4.4256	0.2401
β_2 Month	-1.7739	0.1675	-2.1021	-1.4456	<.0001
β_3 VP*Month	0.2146	0.1054	0.0079	0.4212	0.0418
β_4 Month^2	0.0338	0.0049	0.0242	0.0435	<.0001

The average VA score for subjects taking Placebo was estimated to be 63.1 letters at baseline and decreased to $63.08 - 1.77\cdot(24) + 0.034\cdot(24)^2 \cong$ **40 letters**, (95% C.I. [35.8, 44.2]), at the end of 24 months. Verteporfin subjects were estimated as having an average baseline VA score of (63.1+ 1.65) = 64.8 letters, decreasing to $64.74 - 1.56\cdot(24) + 0.034\cdot(24)^2 \cong$ **47 letters**, (95% C.I. [43.6, 50.0]), at the end of 24 months. The difference between the Verteporfin and Placebo rates of decline was found to be statistically significant, (p = 0.042), but a difference of (47-40) = **7 letters**, (approximately 1 line), after 24 months again does not appear substantial (see Figure 4).

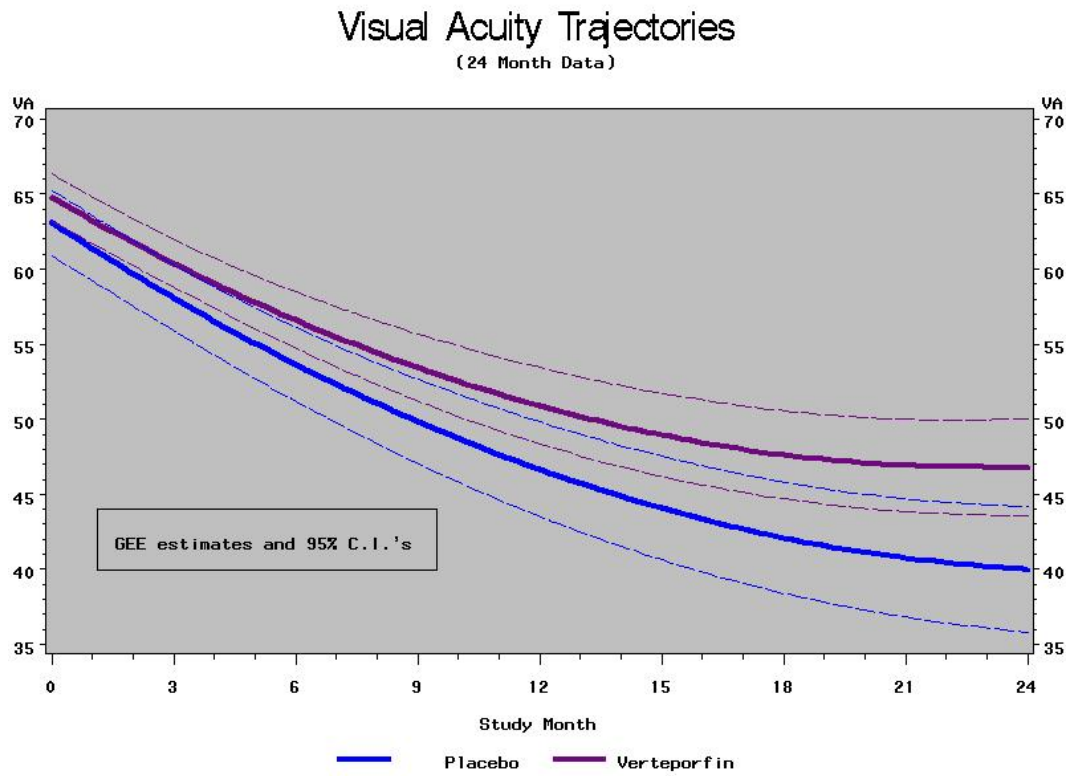


Figure 4. Verteporfin and Placebo Estimated Mean Trajectories and 95% Confidence Bands for initial 24 months of VIP study.

Table 8. Final 24 Month Model GEE Results: Correlation Model

GEE Working Correlation Matrix

	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Baseline	1.0000	0.5145	0.3265	0.2932	0.2644	0.2383	0.2625	0.3166	0.2478
Month 3	0.5145	1.0000	0.7362	0.6622	0.5719	0.5106	0.4644	0.4826	0.4502
Month 6	0.3265	0.7362	1.0000	0.8147	0.7706	0.7300	0.6564	0.6573	0.6435
Month 9	0.2932	0.6622	0.8147	1.0000	0.9003	0.8549	0.7912	0.7686	0.7503
Month 12	0.2644	0.5719	0.7706	0.9003	1.0000	0.9280	0.8661	0.8392	0.8108
Month 15	0.2383	0.5106	0.7300	0.8549	0.9280	1.0000	0.9282	0.8990	0.8656
Month 18	0.2625	0.4644	0.6564	0.7912	0.8661	0.9282	1.0000	0.9465	0.9038
Month 21	0.3166	0.4826	0.6573	0.7686	0.8392	0.8990	0.9465	1.0000	0.9514
Month 24	0.2478	0.4502	0.6435	0.7503	0.8108	0.8656	0.9038	0.9514	1.0000

Subjects' responses again showed observations in the later months having stronger relationships than in the earlier months. Again, the focus of this investigation is on differences in Placebo and Verteporfin average trajectories, however, combining the average quadratic-descents of the Visual Acuity scores and the strong correlations at the later time points, it appears that subjects in this study tended to stabilize after approximately a year.

VIP Study

- Occult Data Subset -

GEE Analysis 3
(Linear Descent Model)

Analyses:

Basic Model:

1.) **VA** = $\beta_0 + \beta_1 \cdot I(\text{Trt=VP}) + \beta_2 \cdot \text{Month} + \beta_3 \cdot I(\text{Trt=VP}) \times \text{Month} + \boldsymbol{\varepsilon}$

8.) $\boldsymbol{\varepsilon} \sim \text{MVN}(\mathbf{0}, \sigma^2\mathbf{R})$

9.) **R** modeled with an autoregressive (AR1) structure

This model examines simple time-dependent differences between the Verteporfin and Placebo groups. The notation I(Trt=VP) represents an "indicator function" which takes on the value 0 if the statement "Trt=VP" is false (i.e. the subject received the Placebo treatment) and the value 1 if the statement "Trt=VP" is true (i.e. the subject received the Verteporfin treatment) Month is a variable measuring the passage of time. We therefore have the following structure:

	Intercept (Baseline VA)	**Slope** (Change in VA per month)
Placebo	β_0	β_2
Veretporfin	$\beta_0 + \beta_1$	$\beta_2 + \beta_3$
Difference	β_1	β_3

Hence, we examine β_2 and β_3 to determine if there are systematic differences in the Verteporfin and Placebo groups over time. We use the above table to guide discussions on both statistical *and* clinical significance. Additional explanatory variables, such as development of classic CNV, gender, baseline lesion size, etc., are used to enhance the *basic* model above.

We used a Generalized Estimating Equation (GEE) approach to obtain estimates for the above model. Results were robust to changes in the assumed covariance model and the AR(1) structure was chosen as providing the most parsimonious fit. The normality assumption did not appear to be considerably violated.

12 Month Marginal Results

Parameter	Estimate	Standard Error	95% Confidence Limits		P-value
Intercept	64.6961	0.8757	62.9798	66.4124	<.0001
VP	-0.2085	1.1240	-2.4115	1.9945	0.8528
Month	-1.7684	0.1774	-2.1161	-1.4207	<.0001
VP*Month	0.5449	0.2146	0.1243	0.9655	0.0111

The average VA score for subjects taking Placebo was estimated to be 64.7 letters at baseline and decreased each month by 1.8 letters. At the end of 12 months Placebo patients were therefore estimated as having an average VA score of $64.7 - 1.8 \cdot (12) \cong$ **43 letters**. Verteporfin subjects were estimated as having an average baseline VA score of 64.5 letters, decreasing (-1.8 + .5) = -1.3 letters per month to an average VA score of **49 letters** in 12 months.

The difference between the Verteporfin and Placebo rates of decline was found to be statistically significant, (p = 0.0111), but a difference of (49-43) = 6 letters, (approximately 1 line), after 12 months does not appear to be substantial (see Figure 1). Results did not change after adjusting for gender, smoking status, baseline lesion size, and hypertension.

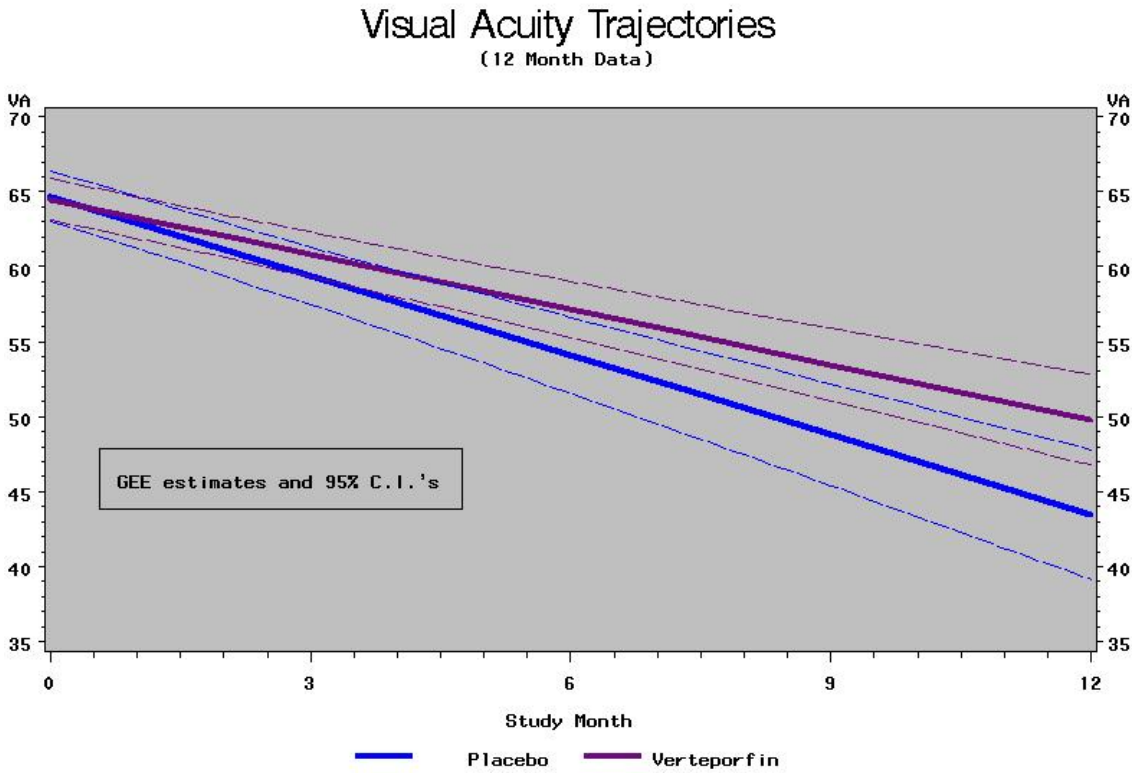


Figure 1. Verteporfin and Placebo Estimated Mean Trajectories and 95% Confidence Bands for initial 12 months of VIP study.

24 Month Marginal Results

Parameter	Estimate	Standard Error	95% Confidence Limits		P-value
Intercept	63.4436	0.8625	61.7530	65.1341	<.0001
VP	0.2317	1.1214	-1.9662	2.4295	0.8363
Month	-1.0962	0.0933	-1.2790	-0.9134	<.0001
VP*Month	0.3518	0.1170	0.1225	0.5811	0.0026

The average VA score for subjects taking Placebo was estimated to be 63.4 letters at baseline and decreased each month by 1.1 letters. At the end of 24 months Placebo patients were therefore estimated as having an average VA score of 63.4 – 1.1·(24) ≅ **37 letters**. Verteporfin subjects were estimated as having an average baseline VA score of 63.7 letters, decreasing (-1.1 + .35) = -0.75 letters per month to an average VA score of **46 letters** in 24 months. Results did not change after adjusting for gender, smoking status, baseline lesion size, and hypertension.

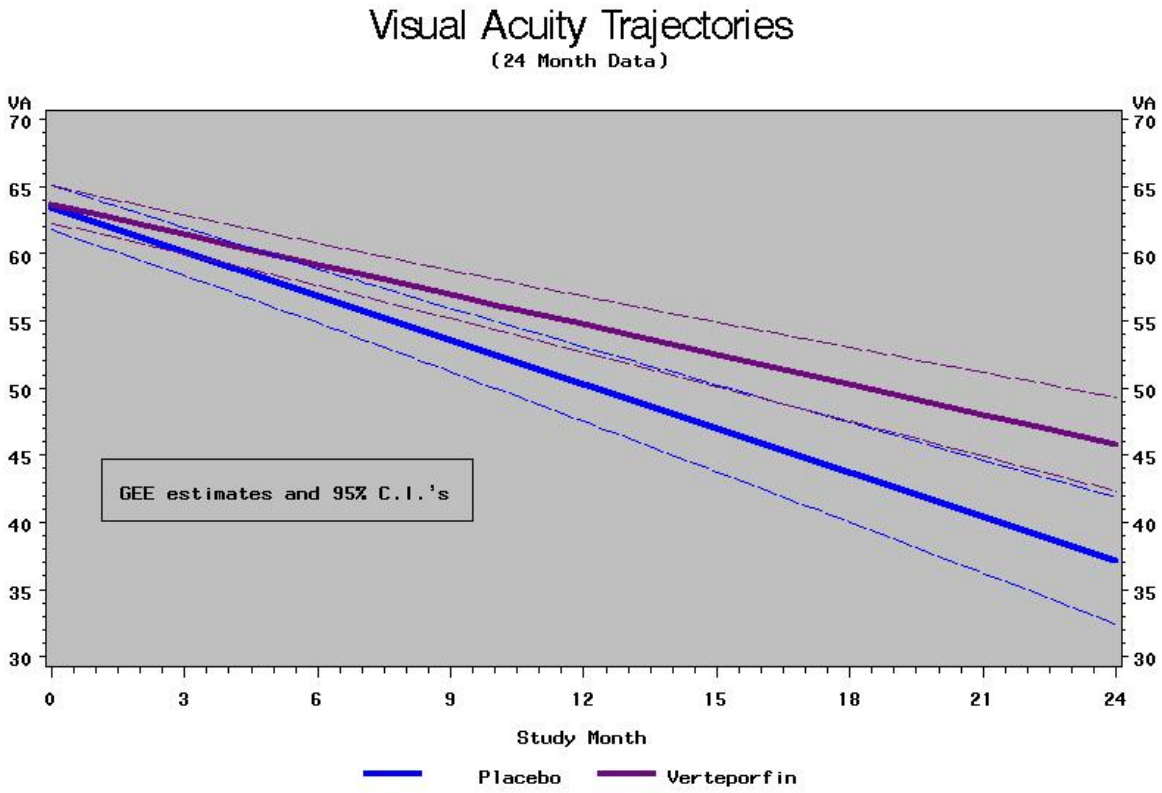


Figure 2. Verteporfin and Placebo Estimated Mean Trajectories and 95% Confidence Bands for initial 24 months of VIP study.