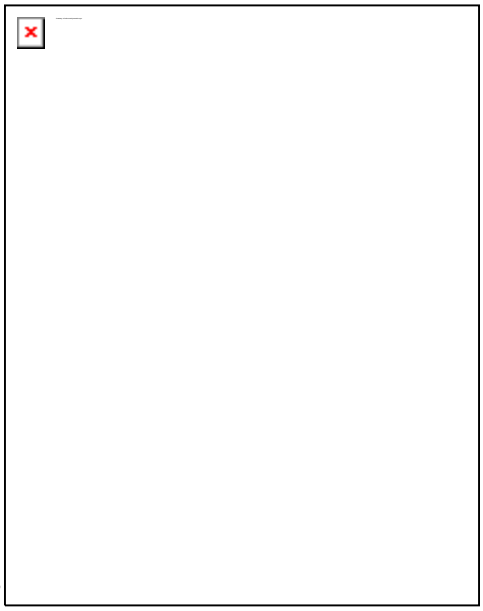
I. Clinical Background

Age-related macular degeneration (AMD) is the leading cause of legal blindness in Americans over the age of 65. The estimated prevalence of AMD in Americans 75 years of age or older is 7.1%.[1] While the exact etiology of AMD is not well understood, it is thought to be a multi-factorial disease. In addition to age, several other risk factors are associated with AMD. These include family history of AMD, smoking, and light eye color. Recent findings also suggest that low dietary intake of antioxidants may predispose people to AMD.

AMD involves the destruction of normal macular function. In AMD, acellular debris called drusen accumulates within Bruch's membrane. Bruch's membrane, as shown in Figure 1, is the layer between the outer edge of the retina and the choroid. This layer is important because it keeps the blood vessels of the choroid from leaking fluid into the retina.

Figure 1



The two basic types of AMD are dry and wet. Dry AMD is the most common type, accounting for 90% of all cases. In dry AMD, the accumulation of drusen and the resulting effect they have on macular function, leads to central vision deterioration. Wet AMD accounts for 10% of cases and poses a higher risk of severe central vision loss. In wet AMD, breaks in Bruch's membrane allow vessels from the choroid to grow, leak, and bleed into the subretinal space; this is termed choroidal neovascularization (CNV). CNV can cause large distortions of the macula and can progress quickly (over the course of days or weeks), effectively destroying central vision. While AMD is the most common condition associated with CNV, other retinal disorders such as pathologic myopia, ocular histoplasmosis syndrome, angioid streaks, and retinal hamartomas can be complicated by CNV formation. There is no definitive treatment for dry AMD. For patients with wet AMD, laser photocoagulation has been shown to help reduce the rate of vision loss in some patients.

Patients suspected of having wet AMD generally undergo flourescein angiography. Classic and occult are the two basic patterns of flourescein leakage in wet AMD. In pure classic CNV, the choriocapillaris plexuses that are involved can be seen distinctly. In pure occult lesions, the location of the offending vessels responsible for the leakage is not recognizable. Many CNV lesions are a combination of both occult and classic with a portion showing a defined site of leakage and another portion being obscured. CNV in AMD is further characterized by one of three locations: subfoveal, juxtafoveal and extrafoveal. Subfoveal, as the name implies, is CNV that lies directly below the fovea. Juxtafoveal and extrafoveal CNV lie progressively further away from the fovea (but still within the macula).

Laser photocoagulation has been shown to decrease vision loss by 50% in juxtafoveal and extrafoveal CNV. For subfoveal CNV, laser treatment has been shown to have some benefit, mainly in patients with classic CNV. Laser photocoagulation by itself destroys the retina overlying its area of application. When applied away from the foveal center (i.e., juxtafoveal or extrafoveal) the effect of the laser itself on vision is variable. When applied to the foveal center, as in cases of subfoveal CNV, the laser is almost certain to destroy some central vision. In addition, subfoveal CNV recurs approximately 50% of the time after "successful" laser therapy. Thus, while laser photocoagulation of subfoveal CNV theoretically maybe preferable to allowing the disease to progress naturally, that possible benefit carries potential risks.

Ocular Photodynamic Therapy (OPT) with Verteporfin: OPT for the treatment of CNV involves the intravenous injection of a photosensitive drug, verteporfin. A laser, which emits light only at verteporfin's absorption peak of 689 nm, is then directed into the eye. It is thought that the excitation of verteporfin generates singlet oxygen and other reactive intermediates that result in temporary closure of leaking blood vessels. The laser is non-thermal; thus it does not produce a heat effect on the retina and causes no damage to the retinal tissue. Verteporfin therapy is neither a cure nor a preventative for CNV in AMD; it is meant to slow progression of the disease. Indeed, its effect is generally not permanent. The closure of leaking blood vessels caused by OPT is often temporary. These vessels may re-open, requiring additional OPT treatments.

II. Studies of Ocular Photodynamic Therapy

The scientific evidence considering verteporfin OPT use with the aforementioned group of patients is concentrated on two studies: the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study (TAP) and the Verteporfin In Photodynamic Therapy Study (VIP). The information given here comes from published papers,[2-4] original and amended study protocols, and unpublished additional analyses of study data. TAP preceded VIP, and the two studies had similar designs and outcome measures.

The TAP investigation was a pair of multi-center, randomized, placebo-controlled clinical trials that were specifically conducted "to determine if photodynamic therapy with verteporfin…can safely reduce the risk of vision loss in patients with subfoveal CNV caused by AMD." The study enrolled 609 subjects in 22 ophthalmology practices in North America and Europe. Important inclusion criteria included:

- *CNV must be under the geometric center of the foveal avascular zone (subfoveal)*
- *Patients must have evidence of some classic CNV (with or without occult component) as determined by flourescein angiography*
- *Best-corrected visual acuity of 73 through 34 letters (approximate Snellen equivalent of 20/40 through 20/200)*
- *Patients must be ≥ 50 years of age*

The VIP study involved 339 patients from 28 clinical centers in North America and Europe. The study's purpose was to determine if OPT with verteporfin could safely reduce the rate of vision loss in patients with AMD-associated subfoveal CNV that were

not included in the TAP study. The VIP study enrolled patients who had (1) occult but no classic CNV on flourescein angiogram; or (2) presumed early-onset classic CNV with baseline visual acuity of 20/40 or better.

In both studies, patients were randomized to either the verteporfin treatment group or the placebo group at a ratio of 2:1 in favor of active treatment. Patients in the verteporfin group received an intravenous injection of 6 mg/m^2 body surface area of verteporfin in 30 cc of 5% Dextrose. The placebo group received 30 cc of 5% Dextrose intravenously. After the infusion, the patient's enrolled eye was exposed to a 689 nm wavelength nonthermal laser for 83 seconds. All patients were scheduled for regular three-month follow-up visits. At each regularly scheduled exam, the patients' vision was tested, a dilated fundus examination was performed and a fluorescein angiogram done. Physicians assessing the patients at each follow-up, as well as patients, were blinded to the treatment group. If there was any leakage seen on the fluorescein angiogram, the patient was retreated with the same agent to which they were randomized. Patients were followed for 24 months. To account for missing data points a "last observation carried forward" approach was used in the data analysis. To preserve randomization, guard against patient selection bias, and account for crossovers in the study groups, the protocols specified an "intent-to-treat" analysis as the primary analysis. The treatment protocols were maintained throughout the two-year time periods.

The primary efficacy outcome of the TAP study was the percentage of patients (eyes) that had fewer than 15 letters lost (approximately three lines of visual acuity lost) compared to baseline at 12 months. This value was chosen because a loss of three lines or more is indicative of moderate visual loss. Secondary efficacy outcomes included:

- *Proportion of eyes that had fewer than 30 letters lost (approximately six lines of visual acuity loss) compared to baseline—a measure of severe visual acuity loss*
- *Mean changes in numbers of letters read on a visual acuity chart*
- *Mean changes in numbers of letters read on a contrast sensitivity chart*
- *Angiographic outcomes (lesion size, leakage, and progression).*

These secondary efficacy outcome measures were included to validate any observed changes in the primary efficacy outcome within and between the two treatment groups.

Aggregate results of the 12 and 24 month examinations for the entire study population are given in Table 1A. At 12 months of follow-up (TAP report 1), the verteporfin group had an overall lower risk of visual acuity loss compared with placebo. In addition, mean contrast sensitivity was better in the verteporfin group compared with placebo. Differences in angiographic outcomes between the two groups at 12 months reinforced the observed treatment benefit of verteporfin. The verteporfin group showed greater reductions in lesion size, leakage, and progression than the placebo group. The results of the 24-month examination (TAP report 2) corroborated those of the 12-month examination. At two years of follow-up, visual acuity and mean contrast sensitivity remained significantly better for the verteporfin group compared with placebo. The angiographic outcomes at the 24-month follow-up also continued to show improvements in CNV lesion size, leakage, and progression in the verteporfin group.

Despite the significant improvements in angiographic outcome measures and the slowed rate of visual acuity loss observed in the verteporfin group, some leakage from the treated

subfoveal CNV lesion still occurred. Additional treatments were only administered to study participants if fluorescein angiography, which was performed every three months, revealed CNV leakage. If no leakage was detected, patients were not retreated. For the verteporfin group, patients were retreated an average of 3.4 times per participant during the first year of the study and 2.2 times during the second year of the study for a total of 5.6 treatments per participant over a two year period. In comparison, the placebo group was retreated an average of 3.7 times during the first year and 2.8 times during the second year for a total of 6.5 treatment per participant over two years. Neither TAP report 1 nor 2 addressed the issue of treatment cessation, an important concern given that an average patient received nearly six treatments over a two-year period. The appropriate frequency of treatment, the criteria needed to determine treatment failure, and the appropriate number of treatments needed beyond two years are questions that remain unanswered.

Table 1A: TAP Study - Analysis of Overall Treatment Effect

Outcome	Treatment Group	12-Month Endpoint	24-Month Endpoint
Loss of < 15 letters % of eyes	V	61.2	53.0
	P	46.4	38.0
		p<.001	p<.001
Loss of ≥ 30 letters % of eyes	V	14.7	18.2
	P	23.7	30.0
		p<.001	p<.001

V = verteporfin, P = placebo

In the VIP study, 258 subjects (76%) had occult with no classic CNV and 81 (24%) had early onset classic with good vision. The study's primary endpoint was the percentage of eyes that suffered moderate vision loss, as compared to baseline, at the 12-month follow-up. Moderate vision loss was defined as loss of 15 or more letters on a standardized eye chart. This corresponds to a loss of approximately three lines of vision from a standard Snellen eye chart. Of the 258 eyes in the occult with no classic subgroup, 166 eyes received treatment with verteporfin and 92 eyes received treatment with placebo. Of the 81 eyes with early classic and good vision CNV, 59 were treated with verteporfin and 22 were in the placebo group.

As stated above, the study's primary endpoint was moderate vision loss at 12 months. For the entire study group, the results did not achieve statistical significance at the primary endpoint (see Table 1B). By 24 months, the entire study group of all eyes treated with verteporfin did show a benefit in terms of moderate vision loss (Table 1B).

TABLE 1B: VIP Study - Moderate and Severe Vision Loss at 12 and 24 month Follow-Up, All Study patients

	12 month Follow-up		24 month Follow-up	
	Moderate loss	Severe loss	Moderate loss	Severe loss
Verteporfin	51% (114/225)	24% (54/225)	54% (121/225)	30% (67/225)
Placebo	54% (62/114)	32% (36/114)	67% (76/114)	47% (54/114)
	p=0.52	p=0.135	p=0.023	p=0.001

Subgroup analyses in both TAP reports, presented in Table 2A, suggested that the composition of the CNV lesion determines the extent of benefit from verteporfin therapy. At the 12-month follow-up, eyes that consisted of *predominantly classic* subfoveal CNV lesions at baseline (where the area of classic CNV occupies ≥ 50% of the area of the entire lesion) were the only subgroup of patients that appeared to benefit from verteporfin therapy. No treatment benefit was observed in eyes that consisted of *minimally classic* lesions at baseline (where the area of classic CNV occupies between 50% and 0% of the area of the entire lesion). At 24 months of follow-up, the treatment benefit continued to be limited to those with predominantly classic lesions; no benefit was observed in those patients with minimally classic lesions. The treatment effect was even stronger for the subgroup of lesions composed of entirely classic CNV with no occult CNV at baseline. However, it is important to note that, even when study eyes with 100% classic CNV were removed from the predominantly classic CNV subgroup, patients with predominantly classic CNV with some occult CNV still experienced a benefit from verteporfin treatment. Additional analyses suggested that the difference in observed effects might have been due to baseline differences in visual acuity and overall lesion size between the predominantly classic and minimally classic subgroups.

Table 2A: TAP Study - Subgroup Analysis by CNV Lesion Type

Outcome	Endpoint	Predominantly Classic Lesion (≥50% of lesion is classic)			Minimally Classic Lesion (>0% but <50% of lesion is classic)		
		V	P		V	P	
Loss of < 15 letters (primary efficacy outcome) % of eyes	12 month	67.3	39.3	p<.001	55.9	55.3	p=.92
	24 month	59.0	31.0	p<.001	47.5	44.2	p=.584

V = verteporfin, P = placebo

The VIP study reported several subgroup analyses. As Table 2B shows, the subgroup of occult with no classic CNV did not show a statistical benefit in terms of verteporfin treatment at the study's primary endpoint. In addition, there was no statistically significant benefit for verteporfin treatment in terms of severe vision loss at 12 months. Treatment with the drug did reach statistical significance for both moderate and severe vision loss at 24 months.

TABLE 2B: VIP Study - Moderate and Severe Vision Loss at 12 and 24 month Follow-Up, Occult with no Classic Subgroup

	12 month Follow-up		24 month Follow-up	
	Moderate loss	Severe loss	Moderate loss	Severe loss
Verteporfin	51% (84/166)	22% (36/166)	55% (91/166)	29% (48/166)
Placebo	55% (51/92)	33% (30/92)	68% (63/92)	47% (43/92)
	P=0.51	P=0.07	P=0.032	P=0.004

Mild adverse events, thought to be related to treatment, were noted in 43% (96/225) of the verteporfin group (both occult with no classic and early onset classic) and 18%

(21/114) of the placebo group. These adverse events consisted of slight visual disturbances unsubstantiated on exam, injection site related problems, infusion-related back pain, allergic reactions, and photosensitivity. None of these events were considered to be serious.

A more serious adverse event, severe vision loss, was noted in ten of the 225 verteporfin-treated patients (4.4%) within seven days of treatment. None of the placebo patients experienced severe vision loss. This vision loss was characterized as at least a 20-letter decrease in visual acuity as compared to pretreatment acuity. Eight of these 10 patients had occult with no classic CNV at baseline. Thus, severe vision loss was seen in 4.8% (8/166) of the occult with no classic subgroup. By three months after this event, five of the 10 patients recovered vision to less than 20 letters lost as compared to their pretreatment acuity. According to the study investigators, some of these five patients who regained vision were in the occult with no classic group. It should be noted that severe vision loss in the TAP study was noted in only 1% of verteporfin-treated patients. The reason for this elevated risk of severe vision loss in the VIP study is unclear.

Additional analyses are given in the Statistical Appendix.

III. Issues in Study Design

Clinical trials are scientific experiments. The scientific validity of information obtained in these studies can only be properly understood after a thorough assessment of their methodological quality. Careful examination of the protocols for both the TAP and VIP studies revealed important questions, particularly in the VIP study, that must influence the interpretation of the data.

Prespecification of the Analysis

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has written guidelines for the design of clinical trials.[5] The principal regulatory bodies in the United States, European Union and Japan have accepted these guidelines as standards for the evaluation of evidence.

The ICH guidelines emphasize the need for a thorough specification of the analysis before the trial begins:

- *"For each clinical trial … all important details of its design and conduct and the principal features of its proposed statistical analysis should be clearly specified in a protocol written before the trial begins." (p.2)*
- *"…the trial's primary objective, is always pre-defined, and is the hypothesis that is subsequently tested when the trial is complete." (p.4)*
- *"The primary analysis of the primary variable should be clearly distinguished from supporting analyses of the primary or secondary variables." (p.26)*
- *"Dichotomisation or other categorisation of continuous or ordinal variables may sometimes be desirable….The criteria for categorisation should be pre-defined and specified in the protocol, as knowledge of trial results could easily bias the choice of such criteria." (pp.7-8)*

Both the TAP and VIP studies come into conflict with these guidelines. Both studies had extensive revisions made to their statistical plans at a time when all subjects had already completed one year of treatment, the principal evaluation point (Tables 3A and 3B). The VIP analysis was revised again three months after the last subject had completed two years of treatment. In both studies, the criteria for categorization of variables were not specified in the initial plans.

Table 3A: TAP Study – Summary of Analysis Plans

	Initial	Revised
Primary Analyses	8	2
Secondary Analyses	7	7
Confirmatory Analyses	4	2
Subgroup Analyses	6	13
Subgroups Defined?	No	Yes
Total Month 12 Analyses	>420	520
Total Month 24 Analyses	?	520

Table 3B: VIP Study – Summary of Analysis Plans

	Initial	Revised
Primary Analyses	1	1
Secondary Analyses	14	11
Confirmatory Analyses	3	1
Subgroup Analyses	12	20
Subgroups Defined?	No	Yes
Total Month 12 Analyses	>864	70
Total Month 24 Analyses	?	70?

As stated above in the ICH guidelines, a study's pre-defined primary objective is the hypothesis that is tested at its completion. The results of that test form the conclusions that can be drawn from that experiment. Other analyses are useful in gathering insight into what factors may have contributed to the experimental results, generating hypotheses that could be tested in future experiments.

The TAP study was designed to consist of two separate simultaneous clinical trials under the same protocol. The original protocol described two primary outcome variables and two statistical tests for each variable. The result was eight different indicators of whether the null hypothesis (The proportion of patient responders for visual acuity is the same for verteporfin and placebo.) or the alternative hypothesis (The proportion of patient responders for visual acuity is different between verteporfin and placebo.) is the correct conclusion. The protocol gave no indication of how to account for multiple comparisons if these indicators were not in unanimous agreement. The revised analysis plan reduced the number of indicators to two (one for each trial) but again did not specify how to reconcile a difference in results between the trials. Since both indicators showed robust statistical significance ($p<0.02$), that issue became moot.

The published analyses from these trials differ substantially from those specified in the study protocols, particularly in their emphasis on subgroup analyses and the results at 24 months. The subgroup analyses cited in the papers were few among hundreds described in the initial analysis plans and were not given any special prominence in the study protocols. These analyses cannot be considered probative of the efficacy of OPT; they can only be considered to be sources of hypotheses for future clinical trials. The study protocols specify that the 24-month analyses were intended to confirm the durability of any effect seen at 12 months. In the VIP paper[2], as seen in Tables 1B and 2B, OPT with verteporfin did not reach statistical significance for preventing moderate (the primary outcome) or severe (a secondary outcome) vision loss at 12 months. According to the protocol the required conclusion is the null hypothesis, that the proportion of patient responders for visual acuity is the same for verteporfin and placebo. Unlike the TAP study, the 12-month results were not published until the 24-month results were available. Contrary to the analysis plan, the published VIP paper made little mention of the 12-month results and instead emphasized the results in a subgroup (subjects with only occult choroidal neovascularization) at 24 months as the principal findings of the study rather than as an exploratory examination of possible reasons for a negative result.

The analyses as specified in the study protocols are given in the Statistical Appendix.

Masking

The protocols for both studies specified that the treatment assignment, placebo or active drug, be masked from patients, treating ophthalmologists, and visual acuity examiners. However, the study design required repeated disclosure of treatment assignment on site. In order to prepare treatment the study coordinator or a designate needed to look up a subject's treatment arm every time the subject was treated (up to eight times) and follow a different process of preparation depending on treatment assignment. This process made it difficult to protect against excessive curiosity or inadvertent disclosure. These problems could have been avoided by creating vials of placebo that resembled verteporfin before reconstitution at an off-site location. From that location vials of placebo or verteporfin,

labeled only by assigned patient identification number could have been distributed to study locations.

Subject Population in the VIP Study

The TAP study excluded two groups of patients with AMD and CNV:

- *AMD with Occult CNV but No Evidence of Classic CNV*
  These patients were not included because "[v]isual acuity may deteriorate more in patients with lesions containing classic CNV than in patients with lesions containing occult with no classic CNV."[6] Inclusion of these patients might have delayed detection of a positive effect of treatment on classic CNV.
- *Classic CNV with visual acuity better than 20/40*
  "With limited safety data at the initiation of the TAP trial, the investigators were unwilling to apply this therapy to affected eyes with excellent visual acuity"[6]

The VIP study population consisted of these two groups that were excluded from the TAP trials. Despite differences in the characteristics of their disease and the reasons for exclusion, the VIP study protocol treated these two groups as entirely homogeneous: the primary hypothesis and power calculation for the study are based upon the entire population and there was no attempt to stratify treatment assignment. There was no particular interest in looking separately at the two groups through a subgroup analysis; the protocol states, "Additional subgroup analyses will be made to evaluate any effect on outcome of CNV lesion size, lesion components, visual acuity and evidence of CNV in fellow eye, used of ICG and recurrent versus new lesions." This is in contrast to the way the VIP study approached patients with CNV as a result not of AMD but of pathologic myopia. The pathologic myopia subjects were treated effectively as a separate trial: they had separate power calculations, randomization, primary hypothesis and analyses. The VIP study was not designed to look specifically at the efficacy of OPT for occult CNV in AMD; any analyses of such effects should be considered exploratory and not conclusive.

Approach to Missing Data

The analyses in both trials used "last observation carried forward" (LOCF) approach to account for missing patient data. This method of data analysis assumes that there is no further change in vision from the time the participant was lost to follow-up until the endpoint. This assumption does not seem valid given the natural history of progressive visual loss with subfoveal CNV and could bias the results of the study in favor of the group with more dropouts. This is likely to be the group receiving active treatment because of the greater likelihood of side effects and the lack of alternative therapies to attract patients in the placebo group who may be dissatisfied with their results. While it may be desirable to do an LOCF analysis for confirmatory purposes for submission to regulatory agencies, it should not be the basis for the primary analysis in this context. The most conservative test is to assume that subjects who are lost to the study as failures rather than successes. In the TAP study this did not influence the results. In the VIP study, if subjects lost to follow-up are considered treatment failures - a more reasonable assumption considering the progressive nature of the disease and the apparent need for ongoing maintenance therapy- the difference between treatments in the overall group at

24 months is no longer statistically significant (p=0.064) and the significance level for the occult only subgroup is marginal (p=0.043).

Choice of Primary Outcome

Another weakness in the design of both the TAP and VIP studies is the choice of primary outcome. Both studies used the loss of 15 or more letters of visual acuity after one year. This indicator limits the assessment of effect to a single threshold at a single point in time. In doing so much useful information is ignored and conclusions can be heavily influenced by random fluctuations about at the particular time or threshold. It does not give insight into vision preservation over the course of treatment and what this means in terms of actual vision.

The use of indicators that are based upon thresholds or single points in time can be justified if the threshold (such as death) or point in time is uniquely important. This is not the case for AMD. The thresholds are not unique. The loss in visual acuity from 14 to 16 letters cannot be considered more important than a loss from 6 to 14 letters or one from 16 to 25 letters. A treatment that led to inferior visual acuity for most of the year but a slight improvement at 12 months would not be considered superior. More information can be obtained by using measures of effect that do not rely on a fixed threshold or time point. Kaplan Meier survival curves, which were not presented in the published study, are useful in following data over time because they do not rely on predetermined intervals for looking at data. Indeed, in Kaplan Meier curves, events can be identified at the exact point in time at which they took place. Figure 2 shows the curves for time to moderate ($\geq$15 letter) vision loss comparing verteporfin and placebo occult with no classic groups in the VIP study. The time to $\geq$15 letter visual acuity loss curve shows that the placebo group did slightly better for the first six months while verteporfin showed a slight advantage after 18 months. On the whole, the difference between the curves is not statistically significant (p=0.551). Figure 3 shows the curves for time to severe ($\geq$30 letter) vision loss comparing verteporfin and placebo occult with no classic groups in the VIP study. The time to $\geq$30 letter visual acuity loss curve shows little difference in the first year of the study while verteporfin showed a some advantage after this point. On the whole, the difference between the curves has borderline statistical significance (p=0.046).

Alternatively, instead of looking at a specified threshold over time, visual acuity can be compared at a specified time point without specifying a threshold. Table 4A shows the results from the TAP study for average loss of visual acuity at 12 and 24 months. Table 4B shows the same figures for the VIP study for both the overall population and the occult only subgroup

Figure 2

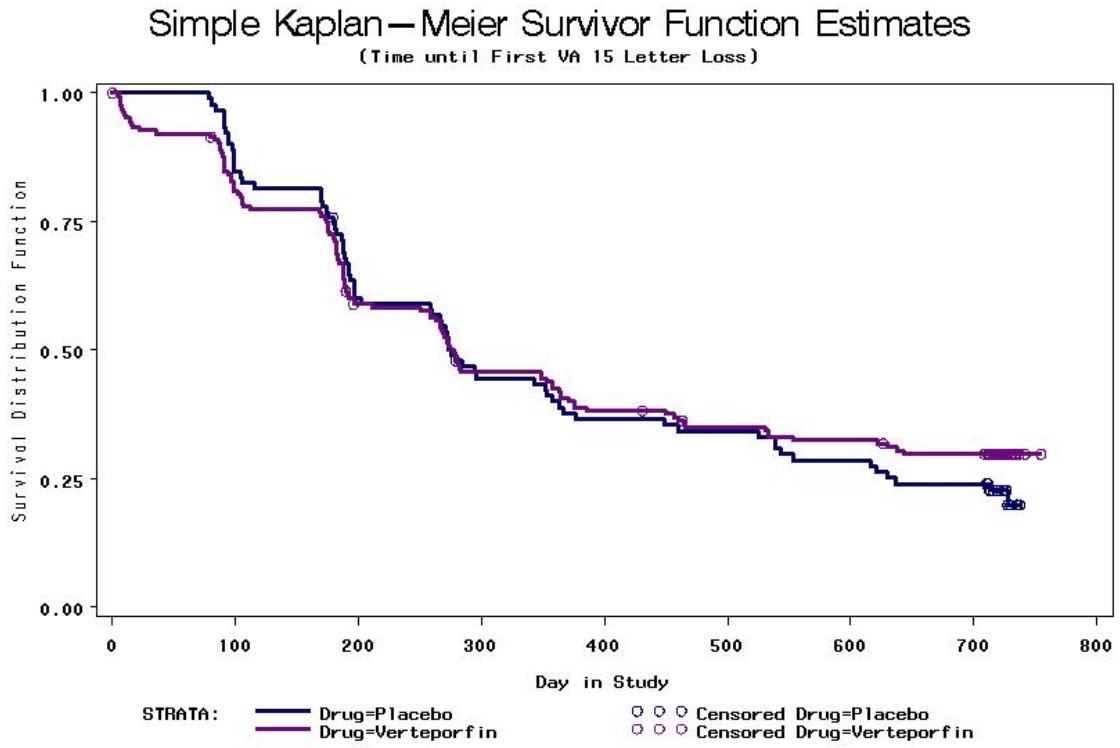


Figure 3

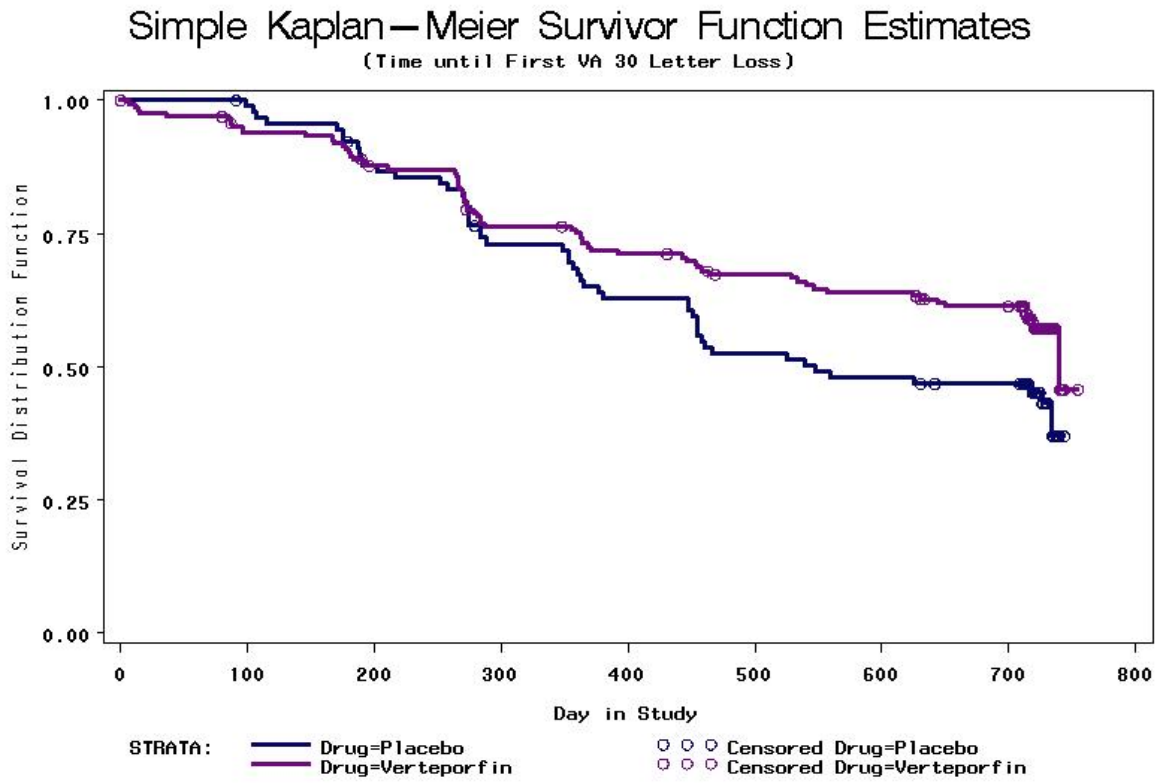


Table 4A: TAP Study – Average Loss of Visual Acuity (Letters)

Group	Treatment Group	12-Month Endpoint	24-Month Endpoint
All Subjects	V	11.3	13.4
	P	17.6	19.6
		p<0.0001	p<0.0001

V = verteporfin, P = placebo

Table 4B: VIP Study – Average Loss of Visual Acuity (Letters)

Group	Treatment Group	12-Month Endpoint	24-Month Endpoint
All Subjects	V	16.2	19.1
	P	20.0	25.1
		p=0.080	p=0.012
Occult CNV Only	V	15.7	19.0
	P	20.8	25.5
		p=0.045	p=.0.017

V = verteporfin, P = placebo

More sophisticated analyses that are not dependent on measurements restricted to a particular time or threshold are shown in the Statistical Appendix..

Interpretation of the VIP Control Group

Another issue was that any benefit seen in the occult CNV only subgroup might have been due to the development at some point during the trial of classic CNV. The TAP study showed that OPT with verteporfin was effective in treating classic CNV. A positive result from the VIP study may simply be a repetition of the TAP findings, with benefits comparable to the TAP findings occurring in subjects who, without treatment, would have developed classic CNV and negligible benefits occurring in subjects who would not have developed classic CNV. Analyzing treatment effect according to whether or not classic features developed could be misleading because the treatment itself could alter the natural course of development of classic CNV. It would be better to look at the control group, identify those subjects who developed classic CNV, and try to estimate the amount of visual acuity that might have been preserved if treatment were instituted at the time classic CNV was identified.

Flourescein angiography was performed every three months in the VIP study. With few exceptions, the results of the examinations are available only for the baseline, 12-month and 24-month visits. Among the 92 subjects in the control group who had occult only CNV at baseline, 39 (42%) had evidence of classic CNV recorded by the month 12 visit and 55 (60%) had classic CNV noted by the final examination. These figures should be considered minimums because evidence of classic CNV on other visits may have disappeared by the time of the recorded visits. (Bleeding, atrophy or fibrosis may obscure classic CNV lesions.)

To estimate the hypothetical impact of treatment for classic CNV among control group subjects we needed to estimate both when the classic CNV was identified and the effect of treatment on loss of visual acuity for the remainder of the two-year period. For the former we assumed an equal probability of finding classic CNV for the first time on every visit after the preceding negative angiogram until (and including) the visit on which classic CNV was first noted. To estimate treatment effect we used results from the TAP study (Table 5). As the table shows the proportionate reduction in loss of visual acuity due to treatment is fairly constant over time; the effect may diminish slightly in the second year.

Table 5: TAP Study – Loss of Visual Acuity by Treatment Group and Months of Treatment

Visit	M03	M06	M09	M12	M15	M18	M21	M24
Verteporfin	6.0	8.6	9.6	11.2	12.6	13.0	12.8	13.4
Placebo	9.7	13.5	15.5	17.4	18.3	17.8	19.2	19.6
Ratio	0.62	0.64	0.62	0.64	0.69	0.73	0.67	0.68

For every subject with baseline occult only CNV in the VIP control group for whom classic CNV was later recorded, we reduced the observed visual acuity loss subsequent to the estimated time of discovery of classic CNV by the treatment effect shown in Table 5 that corresponded to the remaining time in the trial. This resulted in an estimate of an average loss of 23.4 letters of visual acuity in the control group (instead of 25.5, see Table 4B); the difference from the treatment group would no longer be statistically significant (p=0.091). This estimate does not include the possibility of treatment of control group subjects who presented with classic CNV on other visits but did not have classic CNV detected on the 12 and 24 month visits which would further narrow the differences. It is plausible that if the control group were allowed treatment for classic CNV, there would have been no significant difference between the control group and the group treated for occult CNV.

Conclusions

While there are methodological problems with both the TAP and VIP studies, the issues with VIP are more serious and results are less robust. The evidence from the TAP trial that OPT with verteporfin is effective in the treatment of AMD with predominantly classic CNV is highly credible. OPT may also be effective in minimally classic CNV. While one exploratory analysis of the TAP data showed no effect, a second suggested that the effect re-emerges once corrections are made for baseline differences. Further studies would clarify this issue.

The VIP study does little to answer the question of whether OPT is effective in AMD with occult CNV. The trial was not designed to specifically examine the effect of OPT with verteporfin on occult CNV. The null hypothesis of no treatment effect was upheld at the study's primary endpoint. Exploratory data analyses do not consistently show a significant treatment effect. The nature of the control group makes it difficult to distinguish benefit from treatment of occult CNV from treatment of classic CNV.

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