Verteporfin Therapy of Subfoveal Minimally Classic Choroidal Neovascularization in Age-Related Macular Degeneration

2-Year Results of a Randomized Clinical Trial

Visudyne in Minimally Classic Choroidal Neovascularization Study Group*

Objective: To compare the treatment effect and safety of photodynamic therapy with verteporfin using a standard (SF) or reduced (RF) light fluence rate with that of placebo therapy in patients with subfoveal minimally classic choroidal neovascularization (CNV) with age-related macular degeneration.

Design: Phase 2, multicenter, double-masked, placebo-controlled, randomized clinical trial.

Setting: Nineteen ophthalmology practices in North America and Europe.

Participants: Patients with initial best-corrected visual acuity of at least 20/250 and a lesion size of no greater than 6 Macular Photocoagulation Study (MPS) disc areas.

Methods: We randomly assigned 117 patients (1:1:1) to verteporfin infusion (6 mg/m²) and light application with an RF rate (300 mW/cm²) for 83 seconds (light dose of 25 J/cm²) or an SF rate (600 mW/cm²) for 83 seconds (light dose of 50 J/cm²) or to placebo infusion with RF or SF. Treatment was repeated every 3 months if the treating physician noted fluorescein leakage from CNV on angiography. Patients in whom a predominantly classic lesion developed could receive open-label standard verteporfin treatment. Best-corrected visual acuity was measured every 3 months, and angiographic changes were assessed by the Photograph Reading Center through the 3-month examination unless an ocular adverse event or conversion to a predominantly classic lesion was identified by an investigator. Safety was assessed throughout the study. All outcomes were on an intent-to-treat basis.

Results: One hundred three (88%) of 117 patients completed the 24-month examination. Twelve (30%) of 40 patients assigned to placebo received open-label standard verteporfin treatment after confirmation of presence of predominantly classic CNV. At month 12, a loss of at least 3 lines of visual acuity occurred in 5 (14%) of 36 eyes assigned to RF and 10 (28%) of 36 eyes assigned to SF, compared with 18 (47%) of 38 eyes assigned to placebo (RF, P=.002; SF, P=.08; RF + SF, P=.004). At month 24, this loss occurred in 9 (26%) of 34 eyes assigned to RF and 17 (53%) of 32 assigned to SF, compared with 23 (62%) of 37 eyes assigned to placebo (RF, P=.003; SF, P=.45; RF + SF, P=.03). Progression to predominantly classic CNV by 24 months was more common in the placebo group (11 [28%] of 39 patients compared with 2 [5%] of 38 in the RF group [P=.007] and 1 [3%] of 37 in the SF group [P=.002]). No unexpected ocular or systemic adverse events were identified. Treatment-related, usually transient visual disturbances were 13% with SF, 10% with placebo, and 5% with RF.

Conclusions: Verteporfin therapy safely reduced the risks of losing at least 15 letters (≥3 lines) of visual acuity and progression to predominantly classic CNV for at least 2 years in individuals with subfoveal minimally classic lesions due to age-related macular degeneration measuring 6 MPS disc areas or less. Based on the overall evidence available on verteporfin therapy for these lesions, the VIM Study Group would consider recommending verteporfin therapy for relatively small minimally classic lesions similar to those enrolled in the VIM Trial.


*Authors: The Writing Committee served as author for the Visudyne in Minimally Classic Choroidal Neovascularization (VIM) Study Group.

Group Information: A list of the participants in the VIM Study Group appears on page 456.

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Photodynamic Therapy with Verteporfin (Visudyne; Novartis Pharma AG, Basel, Switzerland) (hereafter referred to as verteporfin therapy) decreases the risk of vision loss in selected patients with subfoveal choroidal neovascularization (CNV) caused by age-related macular degeneration (AMD). The strongest evidence from the Treatment of Age-related Macular Degeneration With Photodynamic Therapy (TAP) Investigation and Verteporfin in Photodynamic Therapy (VIP) Trial suggests that this benefit applies to patients with a predominantly classic lesion composition (in which the area of classic CNV was ≥50% of the area of the entire lesion) and those with an occult with no classic lesion composition with presumed re-
standardized definitions for these features. In contrast, visual acuity benefits owing to verteporfin therapy were not found in the subgroup of patients with minimally classic lesions (in which the area of classic CNV was <50% but >0% of the area of the entire lesion) in the TAP Investigation, although treatment effect in contrast sensitivity and several secondary angiographic outcomes, including a reduced risk of lesion growth, was observed.1-3 One possible explanation for the lack of a visual acuity treatment benefit among the subgroup of patients in the TAP Investigation with minimally classic lesions could be that an undetected imbalance in baseline lesion characteristics between the placebo and treatment groups created a bias against showing a treatment benefit for these lesions in that study. Another possible explanation is that patients with small (≤4 Macular Photocoagulation Study [MPS] disc areas) minimally classic lesions may benefit from the treatment in the same way as those with occult with no classic lesions did in the VIP Trial.

Retrospective exploratory analyses of data from the TAP Investigation and the VIP Trial demonstrated that smaller minimally classic lesions and smaller occult with no classic lesions were more likely to have a reduced risk of visual acuity loss with verteporfin therapy than were larger lesions.10 The apparent interaction between treatment group and baseline lesion size suggests that minimally classic lesions could benefit from verteporfin therapy if only smaller lesions are treated rather than lesions of up to 9 MPS disc areas, such as were evaluated in the TAP Investigation. The Visudyne in Minimally Classic CNV (VIM) Trial was designed, in part, to evaluate standard verteporfin therapy of smaller lesions of 6 MPS disc areas or less.

The VIM Trial also was designed to explore outcomes of a reduced fluence (RF) rate of 300 mW/cm² for 83 seconds, resulting in a decrease in the total light dose to 25 J/cm². This RF rate and light dose were used in a theoretical attempt to increase the selectivity of the photodynamic treatment effect and to minimize the inflammatory component of the photodynamic treatment reaction, as suggested by several recent publications.11-13 The potential benefits of the RF rate are based on a hypothesis that, with the standard light fluence (SF) rate, the tissue oxygen concentration determines the rate of the photochemical reaction within the area of light application. If oxygen is at similar concentrations in the CNV, choriocapillaries, and adjacent tissues, application of light when oxygen is rate determining would not result in selectivity of treatment, despite a preferential accumulation of verteporfin in the CNV. With RF, the delivery of light photons becomes the rate-determining step in the photochemical reaction, so selective accumulation of verteporfin in the CNV would result in selective treatment in the CNV and lessen effects in the choriocapillaries and pigment epithelial cells. No safety concerns were identified when an RF was used in a previous study.14 The present study compares the effects of verteporfin infusion or placebo infusion followed by exposure to SF or RF rates for all patients participating in the VIM Trial through 24 months of follow-up.

METHODS

This clinical study protocol BPD OCR 011 (originally dated November 30, 2000) and 5 protocol amendments through June 10, 2003, are on file with regulatory agencies in the United States, Canada, and Europe. The highlights of the protocol are described in this section.

PATIENT SELECTION

AND ENTRY EVALUATIONS

Nineteen clinical centers enrolled patients from April 2, 2001, through January 31, 2002, when the target sample size was approached. Vision testing, color photographs, fluorescein angiograms, indocyanine green angiography, medical histories, and physical examinations were completed within 7 days of study enrollment before patients were randomly assigned to treatment in the trial.

ELIGIBILITY CRITERIA

Ophthalmologists certified to enroll and treat study participants determined whether potential study candidates fulfilled the eligibility criteria. Key features of the eligibility criteria included a best-corrected visual acuity letter score (following the TAP vision protocol) of at least 30 (Snellen equivalent, approximately 20/250 or better) for lesions of 4 MPS disc areas or less and of 30 to 65 (approximate Snellen equivalent of 20/50) for lesions of greater than 4 but no greater than 6 MPS disc areas; fluorescent angiographic evidence of subfoveal CNV due to AMD in which at least 50% of the lesion was CNV; and a fluorescent pattern of some classic CNV (bright area of fluorescence in early-phase frames with leakage at the boundaries of this area through the middle- and late-phase frames) that was less than 50% of the entire area of the lesion using previously defined terms.8,9

VIM PHASE 2 STUDY DESIGN

The primary objective at the start of the study was to determine whether an RF rate of 300 mW/cm² delivered for 83 seconds (light dose of 25 J/cm²) compared with verteporfin therapy using the SF rate of 600 mW/cm² delivered for 83 seconds (light dose of 50 J/cm²) resulted in improved angiographic outcomes with an acceptable safety profile at 3 months. The study participants receiving the fluence rate determined to have the better angiographic outcome would then roll over with additional participants into a phase 3 trial comparing visual acuity outcomes of verteporfin therapy with those of placebo. However, before any unmasking of individual patient treatment assignments, the protocol was amended to remove the phase 3 part and to extend the phase 2 part for 12 months of follow-up with a primary outcome of at least 15 letters (3 lines) of visual acuity loss at 12 months. It was argued that longer follow-up would provide more clinically relevant visual acuity data. Subsequently, the study was further extended through 24 months of follow-up, again before any unmasking of individual patient treatment assignments.

VISION TESTING, PHOTOGRAPHS, AND STUDY ENTRY

After patients reviewed and signed a written informed consent form accompanied by an oral consent process with a certified investigator (ophthalmologist), best-corrected visual acuity testing, stereoscopic color fundus photography, film-based stereoscopic fluorescein angiography, and other procedures
as described in previous verteporfin trials.\textsuperscript{1,3} were undertaken. In addition, indocyanine green angiography was obtained at baseline and follow-up at some sites but was not analyzed for this report and will be reported separately. Patients who were judged by a VIM-certified enrolling ophthalmologist to satisfy all eligibility criteria were assigned randomly to verteporfin with the RF rate, verteporfin with the SF rate, placebo with the RF rate, and placebo with the SF rate in a 2:2:1:1 ratio, respectively.

**RANDOM ASSIGNMENTS AND MASKING**

Patients were randomly assigned to 1 of 2 fluence groups; at the same time, patients were randomly assigned to receive verteporfin therapy or placebo. The ratio of patients receiving the SF rate compared with the RF rate was maintained at 1:1, and the ratio of patients receiving verteporfin therapy compared with placebo was maintained at 2:1. All study participants and outcome assessors, including vision examiners, photographers, ophthalmologists, Photograph Reading Center personnel, and clinic monitors, were masked to the treatment assignment. The ophthalmologist responsible for applying the laser light was not masked to the fluence rate (RF or SF) because the treating ophthalmologist was responsible for the light fluence rate being applied to the study participant’s retina. Only the study coordinators and any other person who might assist in the setup of verteporfin or placebo solutions were aware of the treatment assignment with respect to verteporfin or placebo; these individuals were trained to make every reasonable attempt to maintain masking of participating patients and all other study personnel. However, treatment assignment was unmasked for a total of 3 patients. Investigators were unmasked to the treatment assignment of 2 patients. One patient was identified by the reading Center as having a predominantly classic lesion at the initial visit; the other was identified by the Reading Center as having a predominantly classic lesion at the 6-week examination. In both cases, the treating ophthalmologist believed that verteporfin therapy should not be delayed until the next scheduled visit. Therefore, the ophthalmologist for each patient wanted to know whether placebo or verteporfin had been given at the study visit just before identification of the predominantly classic CNV. If verteporfin had been given, then the ophthalmologist reasoned that no additional treatment would be considered until the next scheduled study visit. If placebo had been given, then the ophthalmologist reasoned that verteporfin therapy would be recommended promptly. A third patient inadvertently was unmasked to the sponsor by the study coordinator at the site where the patient was being treated because the coordinator asked the sponsor what the site should do if placebo had been given. However, treatment assignment was unmasked to the sponsor for the duration of the study; such patients were still analyzed within the treatment arm to which they were randomized.

**VERTEPORFIN THERAPY, PATIENT FOLLOW-UP, AND FLUORESCEIN AND INDOCYANINE GREEN ANGIOGRAPHIC ASSESSMENT AT FOLLOW-UP**

Verteporfin and placebo therapy were administered and patient follow-up was performed at all clinical centers according to a standard protocol. Fluorescein angiographic assessments at follow-up were graded by masked personnel at all treated centers 6 weeks and 3 months after the baseline treatment and at 3-month intervals thereafter. In addition, fluorescein angiography was performed 1 week after the baseline verteporfin therapy until 10 patients had been enrolled in each treatment group, but to maintain masking, the treating ophthalmologists did not assess these angiograms. The Photograph Reading Center evaluated all the angiograms performed during the first 3 months of the study and at any visit that a serious adverse event involving the retina in the study eye was identified by the treating ophthalmologist. If a treating ophthalmologist judged that a predominantly classic lesion had developed, and if this development was confirmed by the Photograph Reading Center, or if the Photograph Reading Center identified a predominantly classic lesion by the 3-month examination that was not first identified by the treating ophthalmologist, then the treating ophthalmologist could give verteporfin therapy in an unmasked fashion to the study participant for the duration of the study; such patients were still analyzed within the treatment arm to which they were randomized.

**STATISTICAL METHODS**

No formal power calculation was performed for this study. Forty patients per treatment group were judged to be adequate to generate descriptive statistics for fluorescein angiographic and visual acuity outcomes. When the phase 2 trial was extended to 24 months of follow-up with continuation of both verteporfin treatment groups, a statistical analysis plan was finalized by the sponsors in January 2003 before unmasking of individual patient assignments. The primary efficacy analyses were based on a strict intent-to-treat analysis; patients were analyzed within the group to which they were randomized, even if the Reading Center judged that the lesion was predominantly classic at baseline and even if a study participant originally assigned to placebo subsequently received open-label verteporfin therapy because of progression to a predominantly classic lesion. The primary efficacy outcome after the study’s extension to 24 months of follow-up was defined prospectively as the proportion of eyes that lost at least 15 letters from baseline at the 12-month examination. This end point was analyzed using a Pearson $\chi^2$ test.\textsuperscript{15(pp311-333)} Distribution of visual acuity scores and distribution of changes in scores from baseline were compared between groups using a Wilcoxon rank sum test.\textsuperscript{15(pp27.280-280-200)} Assessments of progression to a predominantly classic lesion were compared between groups using a Pearson $\chi^2$ test.\textsuperscript{15(pp311-333)}

The analysis chosen prospectively by the study group was an intent-to-treat analysis, including all patients who were randomized and who had measurements at specified follow-up examinations, without imputation for missing observations. The sponsor’s prospective statistical analysis plan was an intent-to-treat analysis with the last observation carried forward to impute missing visual acuity values. Outcomes by both methods were reported to regulatory authorities, although this report concentrates mainly on outcomes with the observed data that had no imputation for missing observations. The sponsor’s prospective analysis plan also described the pooling of data from the 2 verteporfin groups if a difference of no more than 5 letters (1 line) was noted between the mean visual acuity score changes of the 2 verteporfin groups from baseline to the 12-month examination using the last observation carried forward. The $P$ value for the primary comparison of the proportion of eyes that lost at least 15 letters from baseline at the 12-month examination was adjusted to .048 to account for the statistical testing performed on visual acuity outcome during the initial phase 2 part of the study. For all other analyses, $P> .05$ was deemed to be statistically insignificant.
DATA MONITORING AND REPORTING

Data monitoring was evaluated by an independent Data and Safety Monitoring Committee approximately every 6 months after enrollment began. No safety concerns were voiced by the committee at its reviews. On December 13, 2002, 6-month data analyzed by the sponsors were reviewed by the Data and Safety Monitoring Committee. Based on this review of the data and to comply with Securities and Exchange Commission policies in Canada and the United States, the topline results of this 6-month analysis were shared with the public via a news release from the sponsors on December 17, 2002, and did not result in any known unmasking of the study patients or assessors of outcomes for this trial. Subsequent 12- and 24-month data were reviewed by the Verteporfin Study Advisory Group and the VIM Study Group and are presented herein.

RESULTS

One hundred seventeen eyes in 117 patients were assigned randomly to verteporfin therapy (77 eyes) or placebo infusion with light exposure (40 eyes). Of the 77 eyes assigned to verteporfin therapy, 39 were assigned to the SF rate and 38 to the RF rate; of those assigned to placebo therapy, 19 were assigned to the SF rate and 21 to the RF rate. The baseline characteristics for these participants appeared balanced (Table 1 and Table 2) except for lesion size; the placebo group (Table 2) was more likely to have smaller lesions (<4 MPS disc areas). One patient in the placebo group and 2 patients in the SF treatment group had a lesion in the study eye with a predominantly classic composition at baseline, as judged by the Photograph Reading Center. The 12- and 24-month follow-up examinations were completed by 36 patients (95%) and 34 (89%), respectively, of the RF group; 36 (92%) and 32 (82%), respectively, of the SF group; and 38 (95%) and 37 (93%), respectively, of the placebo group (Figure 1). At each follow-up examination after month 3, the verteporfin-treated groups with RF or SF were less likely to receive an additional course of study treatment compared with the placebo group (Figure 2). Patients could receive a maximum possible 4 courses of treatment per year (8 courses in 2 years), including the initial course of study treatment at the baseline visit. Until the 12-month examination (including the application of verteporfin therapy at baseline and any subsequent therapy given at the 3-, 6-, and 9-month examinations), patients assigned to verteporfin therapy and the RF rate received an average of 3.1 treatments compared with 2.9 treatments for those assigned to the SF rate and 3.0 treatments for those assigned to placebo. In the time from the
12-month to the 24-month examinations, patients received an additional 1.5, 0.8, and 1.5 treatments on average, respectively, during the 12-, 15-, 18-, and 21-month examinations. Twelve patients (30%) assigned to the placebo group, 2 (5%) assigned to the RF group, and 2 (5%) assigned to the SF group received open-label verteporfin treatment in the study eye after the treating ophthalmologist confirmed the development of a predominantly classic lesion. Eight patients (20%) assigned to the placebo group, 1 (3%) assigned to the RF group, and 3 (8%) assigned to the SF group received verteporfin therapy to their fellow eye during follow-up within the trial. Overall, a total of 17 placebo-treated patients (42%) received verteporfin therapy in the study eye, the fellow eye, or both eyes during the study.

VISION OUTCOMES

For the primary outcome at the 12-month examination (without the last observation carried forward as chosen by the VIM Study Group), 18 (47%) of 38 study eyes assigned to placebo compared with 2 (14%) of 36 assigned to the RF rate ($P = .002$) and 10 (28%) of 36 assigned to the SF rate ($P = .08$) lost at least 15 letters or 3 lines on the Early Treatment of Diabetic Retinopathy Study visual acuity chart. The direction of these differences was maintained through the 24-month examination, when 23 (62%) of 37 eyes assigned to placebo compared with 9 (26%) of 34 assigned to the RF rate ($P = .003$) and 17 (53%) of 32 assigned to the SF rate ($P = .45$) lost at least 15 letters of visual acuity. When the RF and SF groups assigned to verteporfin were pooled, the combined verteporfin groups had a reduced risk of losing 15 or more letters at the 12- ($P = .004$) and 24-month examinations ($P = .03$), compared with the placebo group.

When the median change in visual acuity at each 3-month follow-up visit from baseline was examined (Figure 3), each group assigned to verteporfin treatment had a smaller median change in visual acuity through the 24-month examination than did the group assigned to placebo, with the RF group losing 2.0 letters (0.4 line; $P = .05$) and the SF group losing 16 letters (3.2 lines; $P = .12$) compared with the placebo group losing 21.0 letters (4.2 lines) at the 24-month examination. When the 2 verteporfin treatment groups were compared, the $P$ value was .03 in favor of the RF group at month 12 and .14 at month 24 (Table 3). The mean change in visual acuity from baseline showed a similar treatment benefit in favor of the verteporfin groups (Figure 4), but the difference between the RF and SF regimens was much smaller (a difference of 5 letters [1.0 line] at 12 months [$P = .08$] and 4 letters [0.8 line] at 24 months [$P = .45$]). With respect to the distribution of visual acuity letter scores (in Snellen equivalents) (Table 4), the visual acuity of eyes assigned to placebo compared with those assigned to verteporfin therapy with the RF rate or the SF rate favored the verteporfin groups at the 12- and 24-month examinations, ranging from 20/160$^{-1}$ to 20/200$^{+1}$ for the placebo group compared with 20/80$^{-2}$ to 20/160$^{+2}$ for the verteporfin groups. Similar trends were observed in the distribution of visual acuity changes at the 12- and 24-month examinations (Table 3), whether the eyes assigned to placebo were compared with those assigned to the RF rate with verteporfin ($P = .001$ at month 12 and $P = .004$ at month 24) or the SF rate with verteporfin ($P = .16$ at month 12 and $P = .08$ at month 24).

When these results were analyzed with the last observation carried forward for missing values, the prospective statistical analysis method for the primary outcome chosen by the sponsors, the results were similar, with 18 (45%) of 40 study eyes assigned to placebo compared with 7 (18%) of 38 assigned to the RF rate ($P = .01$) and 10 (26%) of 39 assigned to the SF rate ($P = .07$), losing at least 15 letters of visual acuity at the 12-month examination. Again, the direction of these differences between treatment arms, with the last observation carried forward, was maintained through the 24-month examination. Also, the distribution of visual acuity changes at the 12-month examination showed similar trends in favor of the verteporfin treatment groups when the results were analyzed with the last observation carried forward for missing values.

Because patients assigned to the placebo group were more likely to have smaller lesions, visual acuity out-
comes were also evaluated by lesion size, specifically for lesions of 4 MPS disc areas or less and greater than 4 MPS disc areas. Within both subgroups, those assigned to placebo were still more likely to lose 3 or more lines (assuming 5 letters per line) of visual acuity by the 24-month examination. In subjects with lesions of 4 MPS disc areas or less, these included 10 (53%) of 19 in the placebo, 4 (27%) of 15 in the RF, and 6 (50%) of 12 in the SF groups (2 placebo and 2 SF group patients had no 24-month examination); in subjects with lesions of greater than 4 MPS disc areas, 9 (64%) of 14 in the placebo, 2 (15%) of 13 in the RF, and 6 (43%) of 14 in the SF groups (1 placebo, 3 RF, and 4 SF group patients without a 24-month examination) lost 3 or more lines of visual acuity.

Similarly, within both subgroups, the median loss from baseline of lines of visual acuity was higher for patients assigned to placebo. Patients assigned to placebo with lesions of 4 MPS disc areas or less lost a median of 3.0 lines by the 24-month examination compared with 1.8 lines assigned to placebo. Patients assigned to placebo with lesions of greater than 4 MPS disc areas, 9 (64%) of 14 in the placebo, 2 (15%) of 13 in the RF, and 6 (43%) of 14 in the SF groups (1 placebo, 3 RF, and 4 SF group patients without a 24-month examination) lost 3 or more lines of visual acuity.

**FLUORESCEIN ANGIOGRAPHIC OUTCOMES**

As can be seen in **Figure 5**, and excluding 1 patient from the placebo group and 2 patients from the SF group judged by the Photograph Reading Center to have a predominantly classic lesion at baseline, angiographic progression to predominantly classic CNV confirmed by the Reading Center was more common in the placebo group, with 11 (28%) of 39 placebo group patients converting to predominantly classic CNV lesions by 24 months compared with 2 (5%) of 38 RF group patients (P = .007) and 1 (3%) of 37 SF group patients (P = .002).

**SAFETY**

Adverse events occurring by the 24-month examination that were judged to be clinically relevant and treatment related included visual disturbances in 4 (10%) of the patients assigned to placebo compared with 2 (5%) assigned to verteporfin with the RF rate and 5 (13%) assigned to verteporfin with the SF rate. The incidence of visual disturbances was similar between the pooled verteporfin-treated (9%)

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**Table 3. Frequency Distribution of Changes in Visual Acuity From Baseline by Treatment at the 12- and 24-Month Follow-up Examinations***

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>12-Month Examination</th>
<th>24-Month Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 38)</td>
<td>RF Verteporfin (n = 36)</td>
</tr>
<tr>
<td>Change from baseline in visual acuity†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3- to &lt;6-line increase</td>
<td>0</td>
<td>2 (6)</td>
</tr>
<tr>
<td>≥1- to &lt;3-line increase</td>
<td>3 (8)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>No change</td>
<td>9 (24)</td>
<td>14 (39)</td>
</tr>
<tr>
<td>≥1- to &lt;3-line decrease</td>
<td>8 (21)</td>
<td>9 (25)</td>
</tr>
<tr>
<td>≥3- to &lt;6-line decrease</td>
<td>12 (32)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>≥6-line decrease</td>
<td>6 (16)</td>
<td>0</td>
</tr>
<tr>
<td>P values vs placebo group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median change in letters</td>
<td>-13.5</td>
<td>-1.5</td>
</tr>
<tr>
<td>P values vs placebo group</td>
<td>.004‡</td>
<td>.16 §</td>
</tr>
<tr>
<td>P value between treatment groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo Group (n = 37 at 24 mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3- to &lt;6-line increase</td>
<td>0</td>
<td>2 (6)</td>
</tr>
<tr>
<td>≥1- to &lt;3-line increase</td>
<td>3 (8)</td>
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<td>5 (14)</td>
</tr>
<tr>
<td>≥6-line decrease</td>
<td>6 (16)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: RF, reduced fluence (300 mW/cm²); SF, standard fluence (600 mW/cm²).

*Includes observed data without last observation carried forward. Unless otherwise indicated, data are expressed as number (percentage) of patients.

†Values are approximate; there are 5 letters per line.

‡Calculated using the Wilcoxon rank sum test. The SF group had the better outcome compared with the placebo group.

§Calculated using the Wilcoxon rank sum test. The RF group had the better outcome compared with the placebo group.

*Calculated using the Wilcoxon rank sum test. The SF group had the better outcome compared with the placebo group.
and the placebo-treated (10%) groups. Acute severe visual acuity decrease was seen in 1 patient (3%) in the placebo group (after receiving a placebo, not open-label verteporfin), in no patients in the verteporfin group with RF rate, and in 1 patient (3%) in the verteporfin group with SF rate. In both cases, the acute severe visual acuity decrease occurred after the first baseline treatment. There were 4 patients (10%) assigned to placebo compared with 1 patient (3%) assigned to verteporfin with the RF rate and 2 patients (5%) assigned to verteporfin with the SF rate who had injection-site adverse events by the 24-month examination. One patient (3%) reported infusion-related pain in the group assigned to placebo (and had received open-label verteporfin therapy) compared with 3 patients (8%) in the group assigned to verteporfin with the RF rate and 6 patients (15%) in the group assigned to verteporfin with the SF rate. These events usually were graded as mild to moderate in intensity and self-limiting, resolving spontaneously by the end of the 10-minute infusion in most cases. No treatment-related allergic reactions were noted in any of the treatment arms, and no deaths occurred through the 24-month examination. With the protocol requiring protection from direct sunlight for up to 48 hours, no photosensitivity reactions were noted in any of the treatment arms, and no deaths occurred through the 24-month examination. With the protocol requiring protection from direct sunlight for up to 48 hours, no photosensitivity reactions were noted in any of the treatment arms, and no deaths occurred through the 24-month examination.

![Graph](https://via.placeholder.com/150)

Figure 5. Percentage of patients with minimally classic lesions at baseline (as judged by the enrolling ophthalmologist) who had predominantly classic lesions by the 24-month examination (as confirmed by the Photograph Reading Center), excluding 1 patient in the placebo group and 2 patients in the standard fluence (SF) group with lesions judged to be predominantly classic at baseline by the Photograph Reading Center. Limit lines represent 95% confidence intervals of the percentages. The reduced fluence (RF) group received light application at a rate of 300 mW/cm²; the SF group, a rate of 600 mW/cm².

![Table](https://via.placeholder.com/150)

Table 4. Visual Acuity Categories in Study Eyes by Treatment at the 12- and 24-Month Follow-up Examinations*

<table>
<thead>
<tr>
<th>Event</th>
<th>Treatment Group, No. (%) of Patients</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Placebo (n = 40)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 37)</td>
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<tr>
<td></td>
<td>Placebo (n = 38)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 39)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 38)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 38)</td>
</tr>
<tr>
<td>Acute severe visual acuity decrease</td>
<td>4 (10)</td>
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<tr>
<td>Infusion-related pain‡</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Injection-site event‡‡</td>
<td>4 (10)</td>
</tr>
</tbody>
</table>

*Includes observed data without last observation carried forward. Unless otherwise indicated, data are expressed as number (percentage) of patients.
†Calculated using the Wilcoxon rank sum test. The RF group had the better outcome compared with the placebo group. Compared with the distribution of change from baseline in visual acuity in the SF group, P = .32 at the 12-month examination and P = .19 at the 24-month examination.
‡Calculated using the Wilcoxon rank sum test. The SF group had the better outcome compared with the placebo group. Compared with the distribution of change from baseline in visual acuity in the RF group, P = .32 at the 12-month examination and P = .19 at the 24-month examination.
To our knowledge, this is the first randomized, controlled, double-masked trial studying efficacy and safety outcomes of verteporfin therapy in minimally classic CNV in patients with AMD. This randomized clinical trial showed outcomes in favor of reducing the risk of loss of at least 15 letters of visual acuity when 2 different verteporfin therapy fluence rates each were compared with placebo treatment through at least 2 years in patients with AMD and subfoveal minimally classic lesions measuring 6 MPS disc areas or less. When pooling the 2 verteporfin arms, the difference between the placebo and pooled verteporfin arms reached a significance level of $P = .004$ at the 12-month examination and $P = .03$ at the 24-month examination. These outcomes in favor of the verteporfin arms were supported by a reduction in the development of predominantly classic CNV in verteporfin-treated patients compared with placebo-treated patients ($P < .001$). Also, these outcomes in favor of the verteporfin arms were achieved despite the fact that 12 (30%) of 40 placebo-treated patients received open-label verteporfin treatment in the study eye at least once during the 24 months of follow-up for treatment of a predominantly classic lesion. These results suggest that treatment of relatively small minimally classic lesions before they convert to a predominantly classic lesion, as in the VIM Trial, will lead to a better outcome than if treatment is applied only after conversion to a predominantly classic lesion.

When the change from baseline in median visual acuity for the RF rate was compared with that for the SF group, the difference was almost 2 lines ($P = .03$) at 1 year and almost 3 lines ($P = .14$) at 2 years. However, this difference at the 15-, 18-, and 21-month examinations was smaller (approximately 1 line). In addition, the difference in the mean visual acuity score change between the fluence groups was approximately 1 line or less at the 12- and 24-month examinations.

With the recent decision of the US Centers for Medicare and Medicaid Services in January 2004 that “evidence is adequate to conclude that ocular photodynamic therapy (OPT) with verteporfin is reasonable and necessary” for treating relatively small subfoveal minimally classic lesions with recent disease progression, and with “small” defined as 4 MPS disc areas or less,17 the VIM Study Group believed it was reasonable to perform a retrospective analysis of VIM Trial results limited to lesions of 4 disc areas or less. The outcomes were in the same direction as that reported for the entire cohort, although there were only 21, 15, and 14 patients in the placebo, RF, and SF arms, respectively.

Although there were a limited number of participants in this study (approximately 40 in each group), the treatment benefit is unlikely to be due to chance because of the results in each of the 2 fluence groups and the confirmatory information on fluorescein angiography showing fewer instances of conversion to predominantly classic lesions (likely to have a more aggressive natural course than other lesion compositions) in the verteporfin-treated groups. This study confirms the results of retrospective analyses using the minimally classic lesion population from the TAP Investigation suggesting that lesions of 4 MPS disc areas or less with a Snellen equivalent visual acuity of 20/40 to 20/200 had better visual acuity outcomes with verteporfin therapy compared with placebo.10 Not all retrospective data completely support the VIM Trial results. Although fraught with many limitations, when minimally classic lesions as identified by the Photograph Reading Center in the TAP Investigation were limited to the lesion sizes and visual acuities eligible for the VIM Trial, there were only small differences between the verteporfin and placebo groups ($\geq 3$-line loss in 50% of 124 verteporfin-treated eyes compared with 59% of 63 placebo-treated eyes and $\geq 6$-line loss in 13% of verteporfin-treated eyes compared with 27% of placebo-treated eyes). As mentioned previously, a direct comparison of the VIM Trial with this retrospective analysis of a subgroup of the TAP Investigation has many limitations. For example, the patients were not entered concurrently, so there may be factors other than initial lesion size, lesion composition, and visual acuity that were not balanced in the absence of randomization to verteporfin or placebo. Also, a minimally classic case was defined by a central reading center in the TAP Investigation, in contrast to determination by the treating ophthalmologist in the VIM Trial. Although the VIM Trial had a relatively small number of patients, the results were consistent with the hypothesis generated by multiple logistic regression analysis showing a visual acuity outcome in favor of relatively small minimally classic lesions in the TAP Investigation10 and relatively small occult with no classic lesions in the VIP Trial. The data also was consistent with a decreased risk of visual acuity loss in the subgroup analysis of minimally classic lesions and occult with no classic lesions with a lesion size of 4 MPS disc areas or less.5,10

### CONCLUSIONS

Based on the totality of the evidence, the VIM Study Group would consider recommending verteporfin therapy for relatively small minimally classic lesions as were enrolled in the VIM Trial. Although no conclusive evidence of differences between the 2 verteporfin regimens was identified, the results warrant further evaluations of the RF rate in patients with AMD with different lesion compositions and sizes.
Clinical Centers

Includes participating clinics, investigators (principal investigators are listed first), clinic coordinators, vision examiners, and photographers in the VIM Study Group as of May 3, 2004.

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REFERENCES


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