

# Verteporfin therapy in occult with no classic CNV due to AMD: results of the Photodynamic Therapy in Occult-Only Lesions study

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## Abstract

**Purpose** To provide further information on verteporfin photodynamic therapy in occult with no classic choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

**Methods** Verteporfin therapy was administered at baseline and then at months 3, 6, and 9, if fluorescein leakage from CNV was evident on angiography.

**Results** Of 202 patients enrolled, 184 completed 12 months. Each patient was treated in one eye only. All study eyes received verteporfin therapy at baseline, with a progressive decrease in the number treated at subsequent visits (mean 2.5 treatments during 12 months). The mean change in visual acuity letter score from baseline to month 12 was  $-11.9$ . At month 12, 164 eyes (82.4%) had lost  $<30$  letters of visual acuity, 123 eyes (61.8%) had lost  $<15$  letters, 78 eyes (39.2%) had lost  $<5$  letters, 31 (15.6%) had  $>5$ -letter increase, and 7 (3.5%) had  $>15$ -letter improvement. The percentage of eyes with fluorescein leakage from CNV decreased from 75.5% at month 3 to 25.1% at month 12. Adverse events were documented for 54% patients. Few patients had treatment-associated adverse events (7%). Acute severe visual acuity decrease occurred in two eyes (1%), one of which had visual acuity that returned to baseline by the next follow-up visit.

**Conclusions** This study provides additional evidence that over 12 months, verteporfin is generally well tolerated and maintains or improves visual acuity in over one-third of eyes containing occult-only CNV. Verteporfin also improved anatomical outcomes by

reducing leakage from CNV in at least two-thirds of eyes.

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**Keywords:** age-related macular degeneration; occult-only lesions; photodynamic therapy; verteporfin

## Introduction

Age-related macular degeneration (AMD) is the most frequent cause of severe vision loss in the Western world in individuals older than 50 years.<sup>1–4</sup> Occult choroidal neovascularization (CNV) is probably the most frequent type of CNV seen in eyes with AMD. Although no formal studies are available on the prevalence of lesion subtypes, it is estimated that patients with occult, with no classic lesion compositions, represent 40–80% of all cases of subfoveal neovascular AMD.<sup>5,6</sup> Studies of the natural history of occult with no classic CNV indicate that it typically has a more benign prognosis than classic CNV.<sup>7–9</sup> However, data from randomized, controlled trials suggest that a significant proportion of eyes with occult, with no classic CNV, that have already lost vision will subsequently have severe decreases in visual acuity.<sup>10</sup> In one study, 32% eyes with occult with no classic CNV had lesions that more than doubled in size during 9–12 months of follow-up, there was a median decrease in visual acuity of 12.5 letters, and classic CNV developed in 52% eyes.<sup>11</sup> Furthermore, a recent meta-analysis showed that 70% eyes with occult with no classic CNV lost  $\geq 10$  letters of visual acuity and 47% lost  $\geq 30$  letters

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at 2–3 years.<sup>10</sup> In addition, classic CNV developed at 1 year in 46% eyes.

Verteporfin (Visudyne®; Novartis Pharma AG, Basel, Switzerland) is a light-activated agent used in photodynamic therapy that has been proven to safely reduce the risk of moderate and severe vision loss (loss of  $\geq 15$  and  $\geq 30$  letters of visual acuity, respectively) in a wide variety of eyes with subfoveal CNV due to AMD.<sup>12–14</sup> In the Treatment of AMD with Photodynamic Therapy (TAP) investigation, verteporfin therapy was shown to significantly reduce the risk of moderate and severe vision loss in eyes with predominantly classic lesions (lesions composed of  $\geq 50\%$  classic CNV).<sup>12</sup> The AMD arm of the Verteporfin in Photodynamic Therapy trial (VIP AMD trial) showed that verteporfin-treated eyes with subfoveal occult with no classic CNV were significantly more likely to lose  $< 15$  letters of visual acuity than eyes receiving placebo.<sup>13</sup> After 24 months of treatment and follow-up, significantly more verteporfin-treated eyes avoided at least moderate vision loss (45% of 166 eyes), compared with placebo recipients (32% of 92 eyes). Subgroup analysis showed that the greatest benefit was observed in the subgroup of eyes with either smaller lesions ( $\leq 4$  macular photocoagulation study disc areas (DAs)) or lower visual acuity ( $< 65$  letters), in which a significantly larger percentage of verteporfin-treated eyes (51%) lost  $< 15$  letters of visual acuity through 24 months, compared with placebo (25%;  $P < 0.001$ ).<sup>13</sup>

The Photodynamic Therapy in Occult-Only Lesions (POOL) study was conducted in European countries to evaluate the effect of verteporfin therapy on visual outcome over a 12-month period in subjects initially presenting with occult with no classic subfoveal CNV secondary to AMD.

On 26 April 2007, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency recommended that the indication for verteporfin in the treatment of occult subfoveal CNV secondary to AMD be removed from the drug's labeling in Europe. However, the results presented in the POOL study are relevant to treating clinicians, because efficacy is often observed in these patients.

## Materials and methods

### Study design and conduct

The POOL study was a non-controlled, open-label, multicentre, 12-month phase IV study conducted from September 2003 to June 2005 at 24 centres (Appendix) in 12 European countries where verteporfin therapy is approved for the treatment of occult lesions. The study was designed and reported in accordance with the guidelines for Good Clinical Practice, as described by the

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the ethical principles of the Declaration of Helsinki, and applicable local rules governing medicinal products in the European Community. The study protocol, the patient informed consent, and additional patient literature were reviewed and approved by Institutional Review Boards and Ethics Committees at each study centre before study initiation. All patients gave written informed consent to participate in the study.

### Patients

Patients were enrolled based on the investigator's assessment of eligibility and interpretation of baseline fluorescein angiograms. Adult patients ( $\geq 50$  years) with subfoveal occult with no classic CNV due to AMD were enrolled in the study if they had presumed recent disease progression in the study eye. The area of the occult CNV had to occupy  $\geq 50\%$  of the entire lesion area. Only one eye was treated in each patient. If both eyes were eligible for treatment, the patient and investigator jointly decided which one was to be treated as the study eye. Recent disease progression was defined as blood associated with the lesion at baseline or loss of  $\geq 6$  letters of visual acuity (Early Treatment of Diabetic Retinopathy study (ETDRS) equivalent) in the previous 3 months or at least a 10% increase in the greatest linear dimension (GLD) of the entire lesion on fluorescein angiography in the previous 3 months. In addition, eyes were required to have a baseline visual acuity letter score of  $\geq 34$  (approximate Snellen equivalent 20/200), and a lesion GLD not exceeding 5400  $\mu\text{m}$  (diameter of a 9 DA circle).

### Treatment and follow-up

Patients were treated at the baseline visit with a 10 min intravenous infusion of verteporfin ( $6 \text{ mg/m}^2$ ), with activating light applied to the study eye 15 min after the start of the infusion at a wavelength of 689 nm and a light dose of  $50 \text{ J/cm}^2$  ( $600 \text{ mW/cm}^2$  for 83 s). Additional verteporfin treatments were administered at months 3, 6, and 9 if angiography showed evidence of fluorescein leakage from CNV. No adjunctive treatments for AMD were permitted during the study. Patients were followed up at intervals of 3 months through month 12 (no treatment was administered at the month 12 visit).

### Visual acuity, angiographic, and safety assessments

Eyes were assessed at baseline and the month 3, 6, 9, and 12 follow-up visits by ophthalmic examination, measurement of ETDRS visual acuity letter score, colour

fundus photography, and fluorescein angiography. Study investigators assessed angiograms at baseline and all study visits to determine leakage from CNV. Fluorescein angiograms and colour fundus photographs from the baseline visit were also evaluated by a central photograph reading centre and were used to determine baseline lesion criteria for the subgroup analyses. Photograph reading centre evaluation of subsequent angiograms was only required if a serious ocular adverse event occurred. The primary outcome variable was the mean change from baseline to month 12 in the best-corrected visual acuity score. Secondary outcome variables included the percentages of eyes with an improvement in visual acuity from a baseline of  $\geq 5$  letters, decreases of  $< 5$ ,  $< 15$ , or  $< 30$  letters, or a final visual acuity letter score of  $< 34$  (approximate Snellen equivalent 20/200). Angiographic assessments included the investigator's assessment of the percentage of eyes with fluorescein leakage at each 3-monthly follow-up and the percentage that developed a classic component in the study eye. Safety was assessed by evaluating adverse events, concomitant medications, ophthalmic examinations, and monitoring vital signs throughout the study.

### Statistical analysis

The primary efficacy analyses were conducted within the intent-to-treat (ITT) population, which included all enrolled patients who received study medication, with the last observation carried forward in place of missing values. Safety analyses were conducted in all patients who received any treatment and performed at least one safety assessment after treatment. Planned analyses were also conducted within three subgroups of eyes categorized according to lesion size and visual acuity at baseline ( $\leq 4$  DAs and visual acuity letter score  $< 65$ ;  $\leq 4$  DAs and visual acuity letter score  $\geq 65$ ; and  $> 4$  DAs and visual acuity letter score  $< 65$ ), where a visual acuity letter score of 65 had an approximate Snellen equivalent of 20/50. A fourth unplanned subgroup analysis (lesion size  $> 4$  DAs and visual acuity letter score  $\geq 65$ ) was subsequently performed.

No formal statistical testing was performed. For primary and secondary efficacy variables, summary statistics and frequency tables were provided for each follow-up visit. Safety was evaluated by tabulating reports of ocular and non-ocular adverse events.

### Statement of ethics

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

## Results

### Patient disposition and baseline characteristics

A total of 202 patients were enrolled and received treatment with verteporfin therapy (Supplementary Figure 1). Eighteen patients (8.9%) discontinued from the study, most frequently because of withdrawal of consent (7 patients, 3.5%). Four patients (2.0%) discontinued because of adverse events (see the section Safety). All 202 patients were included in the ITT and safety populations. Baseline characteristics of these patients are summarized in Table 1. All patients were Caucasian, two-thirds were women, and 58% were  $> 75$  years of age. According to the photograph reading centre evaluation of baseline angiograms, which could differ from the study investigator's baseline assessment of eligibility, most lesions were subfoveal or probably subfoveal (85%) and the majority met the entry requirements of  $\geq 50\%$  occult CNV (80%) and no classic CNV (84%) (Table 1). There were seven cases of retinal choroidal anastomosis, as assessed by the reading centre.

### Study treatments

All patients received verteporfin treatment at baseline in their study eye. Treatment was administered at subsequent visits only if there was evidence of fluorescein leakage, resulting in a progressive decrease in the number of eyes treated from 140 (69.3%) at month 3 to 100 (49.5%) at month 6 and 72 (35.6%) at month 9. During the study, patients received a mean of 2.5 verteporfin treatments.

### Visual acuity outcomes

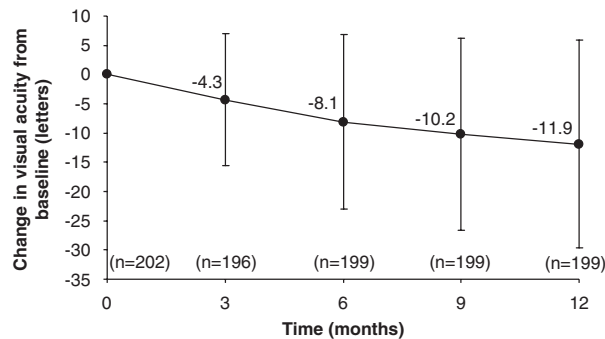
At month 12, the mean change in visual acuity from baseline (the primary outcome variable) was  $-11.9$  letters (Figure 1). Mean visual acuity scores decreased gradually in the course of the follow-up visits. At month 12, 164 eyes (82.4%) had lost  $< 30$  letters of visual acuity, 123 eyes (61.8%) had lost  $< 15$  letters, 78 eyes (39.2%) had maintained or gained visual acuity by having lost  $< 5$  letters, 31 (15.6%) had at least a 5-letter increase, and 7 eyes (3.5%) had at least a 15-letter improvement. Fifty-four eyes (27.1%) had visual acuity letter scores of  $< 34$  (approximate Snellen equivalent 20/200) at month 12. The distribution of changes from baseline in visual acuity at month 12 is shown in Figure 2.

Subgroup analyses showed no clear differences in mean change in visual acuity between eyes with differing baseline visual acuities and lesion sizes. Mean changes in visual acuity letter scores at month 12 were within approximately two letters of the value in the total study population in all four subgroups (Table 2), with absolute

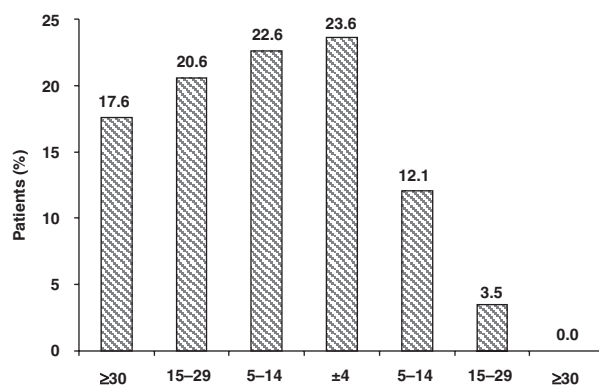
**Table 1** Baseline demographic and clinical characteristics (intent-to-treat population)

Characteristics	Patients (N = 202)
<b>Gender, n (%)</b>	
Men	68 (33.7)
Women	134 (66.3)
<b>Race, n (%)</b>	
Caucasian	202 (100)
<b>Age, years</b>	
Mean (SD)	76.4 (7.32)
Range	52.1–92.2
<b>Age distribution (years), n (%)</b>	
<55	1 (0.5)
55–64	12 (5.9)
65–74	72 (35.6)
75–84	96 (47.5)
≥85	21 (10.4)
<b>Evidence of CNV, n (%)</b>	
Yes	185 (91.6)
No	11 (5.4)
Questionable	3 (1.5)
Cannot grade	3 (1.5)
<b>CNV location, n (%)</b>	
Subfoveal	164 (81.2)
Probably subfoveal	8 (4.0)
Not subfoveal	16 (7.9)
Cannot grade	14 (6.9)
<b>Occult CNV ≥50% of lesions, n (%)</b>	
Yes	161 (79.7)
No	30 (14.9)
Questionable	8 (4.0)
Cannot grade	3 (1.5)
<b>Classic CNV, n (%)</b>	
Yes	22 (10.9)
No	170 (84.2)
Questionable	8 (4.0)
Cannot grade	2 (1.0)
<b>Blood</b>	
Yes	40 (19.8)
No	160 (79.2)
Cannot grade	2 (1.0)
<b>Area of lesion, mm<sup>2</sup></b>	
	(N = 187) <sup>a</sup>
Mean (SD)	8.0 (5.44)
Range	0.18–37.94
<b>Greatest linear dimension, μm</b>	
	(N = 187) <sup>a</sup>
Mean (SD)	3558.4 (1260.12)
Range	430–7779

<sup>a</sup>Ten eyes (5.0%) had no lesion and five eyes (2.5%) could not be graded. Data on lesion characteristics are from reading centre grading.



**Figure 1** Mean change (±SD) in visual acuity from baseline.



**Figure 2** Frequency distribution of change from baseline in visual acuity letter score at month 12.

*t*-score values lower than 1 for all pair-wise subgroup differences, indicating corresponding *P*-values of >0.3. Excluding 32 patients with classic CNV or questionable status regarding classic CNV from the analysis had little effect on the mean change in visual acuity letter scores at month 12, compared with the total study population (−11.9 ± 17.7 letters (total) vs −11.2 ± 18.2 letters).

### Angiographic outcomes

Evidence of fluorescein leakage from CNV was observed in a decreasing proportion of eyes at each subsequent visit over the 12-month period, with leakage observed in 75.5% eyes at month 3 and 25.1% at month 12. Development of classic CNV (based on the investigator’s assessment at baseline and during follow-up) was infrequent, occurring in <15% eyes at all study visits (Supplementary Table 1).

### Safety

Adverse events were reported in 109 patients (54%); most (73%) were of mild or moderate intensity with only 29

**Table 2** Change from baseline in visual acuity letter score in all patients and in the subgroups of patients divided according to baseline lesion size and visual acuity

	All patients	Subgroup			
		Lower VA and smaller lesions <sup>a</sup>	Higher VA and smaller lesions <sup>b</sup>	Lower VA and larger lesions <sup>c</sup>	Higher VA and larger lesions <sup>d</sup>
Patients, <i>n</i>	202	92	49	43	13
Mean (SD) baseline VA, letters	58.1 (11.64)	51.7 (8.84)	71.1 (4.54)	52.9 (7.99)	72.1 (5.59)
<i>Mean (SD) VA change from baseline, letters</i>					
Month 3	-4.3 (11.34)	-4.7 (11.58)	-4.6 (10.33)	-2.8 (11.82)	-7.9 (10.97)
Month 6	-8.1 (14.88)	-8.3 (14.44)	-7.9 (13.49)	-7.6 (16.95)	-9.7 (15.55)
Month 9	-10.2 (16.44)	-10.0 (16.15)	-10.7 (16.99)	-10.4 (16.90)	-10.3 (14.72)
Month 12 <sup>e</sup>	-11.9 (17.73)	-12.0 (16.99)	-13.4 (18.59)	-9.8 (17.87)	-14.1 (16.54)

VA, visual acuity.

<sup>a</sup>VA <65 letters, lesion ≤4 DA.<sup>b</sup>VA ≥65 letters, lesion ≤4 DA.<sup>c</sup>VA <65 letters, lesion >4 DA.<sup>d</sup>VA ≥65 letters, lesion >4 DA (this category was an unplanned analysis).<sup>e</sup>Absolute *t*-score values <1 for all pair-wise subgroup differences, indicating corresponding *P*-values of >0.3.

patients (14%) having severe adverse events (Table 3). The most frequent adverse events were abnormal vision (8.9%) and infection (5.4%; the term 'infection' refers to the body as a whole, and includes chest infection, cold symptoms, common cold, and toe infection), with all other adverse events occurring in <5% of patients. Fourteen patients (6.9%) had adverse events that were considered by the investigator to be associated with treatment. Ocular adverse events occurred in 43 patients (21.3%) and were mostly of mild (24 patients) or moderate (10 patients) intensity. The most frequent ocular adverse events were abnormal vision (18 patients, 8.9%), retinal disorder (6 patients, 3.0%), conjunctivitis (4 patients, 2.0%), and eye disorder (4 patients, 2.0%).

Thirty-one patients had serious adverse events (three of which were associated with treatment) and there were three deaths (none associated with treatment). The three deaths were those of one 86-year-old patient (coronary artery atheroma 4 weeks after completing the third visit), one 73-year-old patient (myocardial infarction 8 weeks after completing the first visit), and one 84-year-old patient (bowel cancer 12 weeks after completing the first visit). The serious adverse events judged to be associated with treatment included two cases of protocol-defined acute severe visual acuity decrease (loss of ≥20 letters of visual acuity within 7 days of treatment). The first patient had a baseline visual acuity letter score of 61 and experienced an acute severe decrease of 22 letters from baseline on day 5 after the first treatment with verteporfin therapy. The patient made a complete recovery (visual acuity letter score 75) by the month 3 visit and had stable vision through month 12 (visual acuity letter score 67). A second patient experienced a probable acute severe visual acuity decrease after the first

treatment. When he attended his month 3 visit, he reported experiencing acute severe visual acuity loss on the sixth day after initial treatment. The patient had not reported this vision loss to his physician until the next scheduled visit, so no visual acuity assessment was performed within 7 days that would confirm his vision loss as a protocol-defined severe visual acuity decrease event. His baseline visual acuity letter score was 70, whereas his visual acuity letter score at month 3 was 43, reflecting a loss of 27 letters; his vision remained stable for the remainder of the study through the month 12 visit (final visual acuity letter score 40). Another serious treatment-associated adverse event was an eye haemorrhage on day 10 after the second verteporfin treatment, resulting in the patient's discontinuation from the study. An ultrasound examination showed vitreous haemorrhage and subretinal haemorrhage temporal-inferior to the fovea. No retinal detachment was observed. A vitrectomy was performed and the patient was classified as having recovered with sequelae. Three patients discontinued because of adverse events that were not related to the study treatment (gastrointestinal carcinoma, dementia, and depression).

## Discussion

This study of eyes with occult with no classic CNV secondary to AMD with presumed recent disease progression showed that 61.8% of verteporfin-treated eyes lost <15 letters of visual acuity during 12 months. Additionally, 39.2% eyes lost <5 letters, 15.6% had at least minimal improvement (≥5-letter increase), and 3.5% had at least a 15-letter improvement. These visual acuity outcomes compare favourably with results from

**Table 3** Adverse events by coding symbols for a thesaurus of adverse reaction terms (COSTART); preferred terms occurred in at least 2.5% of the 202 patients studied

	Patients with at least one adverse event			
	All intensities n (%)	Mild <sup>a</sup> n	Moderate <sup>b</sup> n	Severe <sup>c</sup> n
Any adverse event	109 (54.0)	43	37	29
<i>Body as a whole</i>				
Back pain	9 (4.5)	5	3	1
Flu syndrome	5 (2.5)	3	2	0
Headache	8 (4.0)	5	3	0
Infection	11 (5.4)	8	3	0
Intentional injury	8 (4.0)	1	6	1
Pain	6 (3.0)	3	3	0
Injection-site reaction	2 (1.0)	2	0	0
<i>Digestive system</i>				
Gastrointestinal disorder	5 (2.5)	1	4	0
Nausea	5 (2.5)	3	2	0
<i>Musculoskeletal</i>				
Bone disorder	5 (2.5)	1	2	2
<i>Treatment-site ocular</i>				
Abnormal vision <sup>d</sup>	18 (8.9)	9	4	5
Retinal disorder <sup>e</sup>	6 (3.0)	1	3	2
Conjunctivitis	4 (2.0)	4	0	0
Retinal haemorrhage	3 (1.5)	1	0	2
Visual field defect	3 (1.5)	2	1	0
Eye disorder <sup>f</sup>	4 (2.0)	3	1	0
Chromatopsia	2 (1.0)	2	0	0
Lacrimation disorder	2 (1.0)	2	0	0
Cataract specified	1 (0.5)	1	0	0
Dry eyes	1 (0.5)	1	0	0
Eye haemorrhage	1 (0.5)	0	0	1
Eye pain	1 (0.5)	1	0	0
Eyelid disorder	1 (0.5)	1	0	0
Face oedema	1 (0.5)	1	0	0
Glaucoma	1 (0.5)	1	0	0
Retinal detachment	1 (0.5)	0	1	0
Vitreous disorder	1 (0.5)	0	1	0

<sup>a</sup>Events without impact on daily activities.

<sup>b</sup>Events interfering with daily activities.

<sup>c</sup>Events rendering daily activities impossible.

<sup>d</sup>Includes the other one of the two patients with acute severe visual acuity decrease. Adverse events are listed if they occurred in at least 2.5% patients, with the exception of events of special interest (injection-site reactions) and treatment-site ocular adverse events, which are listed in detail.

<sup>e</sup>Includes chorioretinal anastomosis (one case), tear in retinal pigment epithelium (RPE; three cases), rip in RPE (two cases) (includes one of the two patients with acute severe visual acuity decrease).

<sup>f</sup>Worsening occult CNV or AMD, possible tear at site of lesion.

the VIP AMD trial, in which 49% of 166 verteporfin-treated eyes with occult with no classic CNV lost <15 letters of visual acuity at month 12.<sup>13</sup> The lower mean changes in visual acuity between baseline and month 12

in the present study (−11.9 letters), compared with the VIP AMD trial (−15.6 letters), may reflect differences in baseline visual acuity letter scores (58 in the present study and 66 in the VIP AMD trial).

In the VIP AMD trial, the greatest visual acuity benefits were seen in eyes with occult with no classic CNV and either smaller lesions or lower levels of visual acuity at baseline. Visual acuity outcomes in the current study were similar across all subgroups of eyes with smaller or larger lesions and lower or higher levels of visual acuity at baseline. The planned subgroups together (≤4 DAs and visual acuity letter score <65; ≤4 DAs and visual acuity letter score ≥65; and >4 DAs and visual acuity letter score <65) represent the category (either smaller lesions or lower levels of visual acuity) that had the greatest visual acuity benefit in the VIP AMD trial. The mean visual acuity change from baseline for the three planned subgroups from the current study at month 12 (−12.0, −13.4, and −9.8 letters, respectively) was similar to that for the VIP AMD trial subgroup of smaller lesions or lower levels of visual acuity (−13.1 letters).<sup>13</sup> The mean visual acuity change from baseline for the unplanned subgroup in the current study (>4 DAs and visual acuity letter score ≥65) was also similar (−14.1 letters) to the planned subgroups, as well as to the VIP AMD subgroup that showed the greatest benefit. However, results are not directly comparable, because differences in outcomes between the VIP AMD trial and the present study may have been due to differences in lesion characteristics, treatment criteria, and duration of experience with verteporfin therapy in each study. Nevertheless, the similar outcomes across the subgroups in the present study indicate that baseline lesion size and visual acuity may not be as strong an influence on treatment outcomes as had been shown in previous analyses.

A recent retrospective, observational study of 277 patients with occult-only or predominantly classic CNV secondary to AMD investigated whether a difference in visual outcomes was detectable after treatment of these lesion subtypes with verteporfin therapy.<sup>15</sup> Patients with occult lesions lost an average of 8.7 letters (1.9 lines) from baseline over 12 months, compared with 10.0 letters (2 lines) in patients with predominantly classic lesions (difference of 1.3 letters). The mean letters lost at 12 months was not significantly different between the two groups ( $P=0.411$ ), and a minimal clinically important difference (set at 7.5 letters) was not detected.<sup>15</sup>

Eyes receiving verteporfin in this study also had improvements in angiographic outcomes between baseline and 12 months. At baseline, fluorescein leakage was present in 100% eyes according to the investigator's assessment and 91.6% eyes according to the reading centre. The percentage of eyes with evidence of

fluorescein leakage from CNV (investigator assessments) decreased progressively at each follow-up visit, from 75.5% at month 3 to 25.1% at month 12. The decreasing occurrence of leakage resulted in decreases in the number of eyes requiring verteporfin at each visit, from 69.3% at month 3 to 35.6% at month 9. During the study, patients received a mean of 2.5 verteporfin treatments in the study eye, which was lower than the mean of 3.1 treatments administered to eyes with occult with no classic CNV during the first 12 months of the VIP AMD trial.

Safety results in this study were consistent with the VIP AMD trial and TAP investigation, and there were no new safety concerns. Verteporfin was generally well tolerated and associated with a low incidence of adverse events. Acute severe visual acuity decreases were uncommon, occurring in two patients (1.0%), one of whose vision recovered at the next 3-monthly visit. This incidence is lower than that reported in the 2-year pooled data from the TAP investigation and VIP AMD trial (2.2%).<sup>16</sup>

Since the completion of this study, excellent results have been reported from two large-scale, randomized, controlled phase III trials—MARINA (minimally classic or occult-only) and ANCHOR (predominantly classic)—evaluating the anti-vascular endothelial growth factor (VEGF) antibody ranibizumab (Lucentis<sup>®</sup>; Genentech, San Francisco, CA, USA).<sup>17,18</sup> One-year data showed that patients receiving monthly intravitreal injections of ranibizumab (0.5 mg) had a mean increase in visual acuity of 7.2–11.3 letters, whereas approximately 95% patients lost <15 letters.<sup>17,18</sup> Benefits in visual acuity were maintained at 24 months, and ranibizumab also appeared to be generally safe and well tolerated.<sup>18,19</sup> Following the approval of ranibizumab, there has been a revolution in the treatment of neovascular AMD.<sup>20</sup> There have also been reports of the full-length, monoclonal anti-VEGF antibody bevacizumab (Avastin<sup>®</sup>; Genentech), which is approved for certain solid tumours (ie, metastatic colorectal cancer, non-small-cell lung cancer, breast cancer), administered as intravitreal injection in patients with neovascular AMD.<sup>21–28</sup> Findings from these small-scale, short-term, non-controlled, non-randomized studies or case series have shown improvements in visual acuity of 3.1–7.4 letters from baseline over 1–12 months follow-up, as well as anatomical benefits, following bevacizumab.<sup>21–25</sup> Although bevacizumab was generally well tolerated, adverse events included endophthalmitis, retinal pigment epithelial tears, and submacular haemorrhage.<sup>21,26,28</sup> The long-term efficacy and safety of bevacizumab in neovascular AMD have yet to be elucidated in large-scale, randomized, controlled trials.

Before the availability of anti-VEGF agents, there were reports of improved visual acuity from baseline in patients with neovascular AMD following treatment with verteporfin combined with anti-inflammatory steroids such as intravitreal triamcinolone acetonide.<sup>29,30</sup> There is now increasing interest in using verteporfin in combination with anti-VEGF therapies with or without concomitant anti-inflammatory agents.<sup>31–35</sup> Same-day administration of verteporfin combined with ranibizumab (0.5 mg) in an open-label, phase II study of 32 patients with occult ( $n = 19$ ) or predominantly classic ( $n = 13$ ) lesions was shown to be safe and improve visual acuity and anatomical outcomes over 9 months.<sup>36,37</sup> The hypothesis that the combination of therapies with different mechanisms of action, that is, verteporfin and ranibizumab, may lead to synergistic effects and improved clinical outcomes are being further investigated in the large-scale phase IIIb SUMMIT program. This comprises two prospective, randomized, controlled studies—DENALI (US and Canada) and MONT BLANC (Europe).<sup>38</sup>

The limitations of the present study should be noted. In particular, this was an open-label study with no comparator group, thereby limiting the conclusions that can be drawn. Additionally, the study included a number of patients who did not meet the eligibility criteria as determined by the photograph reading centre, including 7.9% whose CNV was not subfoveal, 14.1% who did not have occult CNV, 5.0% who had no lesion, 10.9% who had classic CNV present, and 5.4% who had no CNV. However, these patients were considered to meet the eligibility criteria by the enrolling investigator, and the overall study population therefore reflects the patients likely to be identified as having 'occult with no classic CNV' in clinical practice. The similar visual acuity findings in the total study population and in those with no classic CNV indicate that the inclusion of 32 patients with classic CNV or questionable status regarding classic CNV appears to not have an impact on vision outcomes.

In conclusion, the findings from this study provide additional data on verteporfin therapy in patients with occult CNV lesions and are consistent with the outcomes of the VIP AMD trial. Verteporfin therapy appeared to be safe and well tolerated, and no new safety concerns were raised in this study over 12 months. Visual acuity was maintained or improved in over one-third of eyes, and two-thirds of eyes showed reduced leakage from CNV.

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## Appendix

### Photodynamic Therapy in Occult-Only Lesions (POOL) study group clinical centres

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Bern Photographic Reading Center, Klinik und Poliklinik für Augenheilkunde, Inselspital, University Bern, Switzerland

The Rotterdam Eye Hospital, Rotterdam, The Netherlands  
St Paul's Clinical Eye Research Centre, Royal Liverpool & Broadgreen University, Liverpool, UK  
Wolverhampton and Midland Counties Eye Infirmary, West Midlands, UK  
Retina Division, Moorfields Eye Hospital, London, UK

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