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Photodynamic Therapy with Verteporfin for the Treatment of Neovascular Age-related Macular Degeneration: A Clinical Assessment

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Photodynamic Therapy with Verteporfin for the Treatment of Neovascular Age-related Macular Degeneration: A Clinical Assessment

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November, 2002

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Authorship

Donald Husereau led the development of the research protocol, supervised the literature review process and summarized results in the clinical draft document through to its final version. Donald Husereau and Vijay Shukla were responsible for judging relevance, assessing quality, and extracting data from the articles retrieved. Becky Skidmore was responsible for the design and execution of the electronic literature search strategies, for writing the methods section and associated appendix on literature searching, and for verifying and formatting bibliographic references. David Maberley assisted in developing the research protocol, provided clinical expertise, and contributed to the writing of the draft document and its subsequent revisions.

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Disclosure of Conflicts of Interest

Donald R. Husereau – none

Vijay Shukla – none

Becky Skidmore – none

David Maberley – none

REPORT *IN BRIEF*

November 2002

Photodynamic Therapy with Verteporfin for the Treatment of Neovascular Age-related Macular Degeneration

Technology Name

- Verteporfin photodynamic therapy

Disease/Condition

Age-related macular degeneration (AMD) is a disease that causes permanent central blindness. The macula, a small area of the retina responsible for central vision, deteriorates. In a small number of people, new blood vessels grow just beneath the retina, causing a more severe and rapid loss of vision called wet AMD.

An estimated more than 100,000 people in Canada had wet AMD in 2001; about 10% of all cases of AMD. The primary risk factor is age; others include family history, race (white), and cigarette smoking.

Technology Description

Photodynamic therapy (PDT) is the activation of a drug with light. The drug verteporfin is given intravenously and then light from a laser is applied to lesions below the retina. Free radicals that are created are believed to destroy and prevent further growth of blood vessels. Total costs for treatment and follow-up over two years range from $10,780 to $14,450.

The Issue

Currently there are no effective treatments for most people with AMD. Verteporfin PDT is a new treatment for wet AMD.

Assessment Objectives

1. To assess the clinical evidence reporting on the potential harms and benefits of verteporfin PDT
2. To discuss the economic implications

Methodology

Randomized controlled trials comparing verteporfin PDT with placebo or current therapy (e.g. laser photocoagulation) in adults with wet AMD were systematically reviewed. Outcome measures were the number of individuals with legal blindness or changed visual acuity, the impact on quality of life and the impacts on visual function and morbidity. The most frequent adverse events were also of interest. Two reports describing three high quality trials (TAP-A, TAP-B and VIP) met the eligibility criteria for analysis. Four cost-effectiveness analyses were identified.

Conclusions

Only a minority of individuals with wet AMD will likely be eligible for treatment after diagnosis and angiographic assessment. In these individuals, verteporfin PDT reduces the number of cases of legal central blindness after 24 months by slowing disease progression. However, the majority of treated individuals will continue to lose visual acuity. Long-term therapy can entail complications, more commonly sudden vision loss. Verteporfin PDT is reasonably well tolerated and appears unlikely to cause complications such as hospitalization or death.

The direct impact of this treatment on quality of life and ability to function with poor eyesight is not known. It is also not known what the impact of therapy is on those with poorer vision who may seek treatment.

Verteporfin PDT is likely to increase the need for angiographic screening. The cost-effectiveness studies reviewed suggest that verteporfin PDT will modestly increase patient quality-adjusted life-years but at a substantial cost.

This summary is based on a comprehensive health technology assessment report available from CCOHTA's web site (www.ccohta.ca): Husereau D, Shukla V, Skidmore B, Maberley D. **Photodynamic therapy with verteporfin for the treatment of neovascular age-related macular degeneration: a clinical assessment.**

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EXECUTIVE SUMMARY

The Issue

Age-related macular degeneration (AMD) is a disease that causes loss of vision and can lead to central blindness in some patients. Loss of vision from AMD is permanent and has a significant impact on an individual's functioning and quality of life. Currently, there are no effective treatments for the majority of individuals with AMD. Verteporfin photodynamic therapy (PDT) is a new treatment for "wet" AMD, the type of AMD responsible for more pronounced vision loss.

Objectives

To assess the clinical evidence on the potential harms and benefits of this new therapy by conducting a systematic review of the available evidence from randomized controlled trials.

Methods

Reports describing randomized controlled trials were identified systematically by cross-database searching of MEDLINE®, EMBASE®, HealthSTAR, PASCAL, SciSearch, and Toxline®, separate searches of PubMed and The Cochrane Library, by contacting experts in the field and contacting the drug manufacturer, bibliographic searches, and hand searches of reviews and conference abstracts. Relevant reports were independently identified by two reviewers using selection criteria developed *a priori.* They were then assessed for quality, and data were independently extracted and combined, if appropriate, by meta-analysis. The outcomes of interest were: (1) The number of individuals with legal blindness because of its societal impact; (2) the number of individuals with increased or decreased visual acuity to adequately assess the impact of the intervention on the population; (3) the impact on quality of life; (4) the impact on visual function; and (5) morbidity, in treated populations. For morbidity, serious (i.e. life-threatening) adverse events, withdrawals due to adverse events, patient adverse events, and laboratory-determined adverse events were of interest. Adverse events (serious or otherwise) reported to occur with the most frequency were also of interest. The degree of visual acuity lost (as measured by an eye chart) was a secondary outcome of interest.

Results

Of the 96 reports identified, two reports describing three high quality trials involving 948 participants met the eligibility criteria for analysis. One report describes two identical phase III trials (TAP-A and TAP-B) conducted in individuals with characteristics that included new or recurrent subfoveal lesions, evidence of classic features upon angiography, and a best-corrected visual acuity between 34 and 73 letters (20/200 to 20/40). A third trial (VIP) enrolled those not eligible for the TAP trials because they had better visual acuity or had no evidence of classic features upon angiography [but had a visual acuity of equal to or better than 50 letters (20/100)].

Compared to placebo (angiography plus sham therapy), the number of eyes requiring verteporfin PDT to result in one less case of legal blindness after 24 months was seven (95%CI: 5 to 18) in TAP trial participants and six (95% CI: 4 to 14) in VIP trial participants. The majority of participants [TAP trials: 70% (281/402) of verteporfin PDT recipients and 77% (160/207) of

placebo recipients; VIP trial: 74% (166/225) of verteporfin PDT recipients and 76% (87/114) of placebo recipients] lost visual acuity during that time. Compared to placebo, verteporfin PDT recipients lost 6.2 (95% CI: 3.2 to 9.3) and 6.0 (95% CI: 1.3 to 10.6) fewer letters on average in the TAP and VIP trials, respectively. No evidence was available to estimate the impact of these changes on visual function and quality of life.

A meta-analysis of potentially harmful outcomes from all trials was conducted using a random effects model. Compared to placebo, 1% (95% CI: -5% to 7%) fewer patients treated with verteporfin PDT experienced serious or life-threatening adverse events (including death). Four percent (95% CI: 2% to 6%) more patients were required to stop therapy because of an adverse event. An increased risk for developing an adverse event in the overall population was 3% (95% CI: -2% to 9%). Adverse events most commonly experienced were visual disturbances and injection site events.

Conclusions

Evidence from three high-quality RCTs suggests that, compared with placebo, verteporfin PDT treatment for two years reduces the number of cases of central blindness. However, these results apply to a study population with subfoveal neovascularization from AMD, and only a minority of these individuals is likely to qualify for treatment after diagnosis and angiographic assessment. Verteporfin PDT is likely to increase the need for angiographic screening.

Treatment is not aimed at restoring vision and the majority of treated individuals will continue to lose visual acuity. Compared to placebo (angiography and sham treatment), verteporfin did not cause an overall increase in serious adverse events and appears to be reasonably well tolerated. However, some adverse events, most commonly sudden vision loss, abnormal vision, visual defects, injection-site events and infusion-related back pain occurred with greater frequency in individuals undergoing verteporfin PDT.

The direct impact of this treatment on quality of life and visual function is not known. The two-year incremental costs for this procedure in Canada based on RCT evidence are estimated to be between $10,625 and $14,250.

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GLOSSARY

Amsler grid: a hand held chart featuring horizontal and vertical lines, usually white on black background, used to test for central visual field defects (distortions).

AMD (Age-related macular degeneration): destruction and loss of the photoreceptors in the macula region of the retina resulting in decreased central vision and, in advanced cases, central blindness. (See “Macular Degeneration”).

Central vision: the central part of the visual field responsible for high resolution vision. (See “Fovea”).

Classic: a well-defined pattern of leakage from abnormal choroidal blood vessels (neovascularization) seen by fluorescein angiography.

Fluorescein angiogram: a procedure for viewing and photographing the inner eye, involving injection of a dye into the bloodstream.

Fovea: the concave center of the retina, which is the region of highest visual acuity and cone cell density.

Laser photocoagulation: an outpatient treatment wherein blood vessels are cauterized by the heat from a fine-point laser beam.

Legal blindness: a standard of visual acuity set at 20/200. (See "Snellen chart").

Macula, Macula lutea ("yellow macula"): the centre of vision, characterized by yellow pigment permeating the retinal layers. Size is approximately 3-5 mm in diameter. It contains the fovea in its center, which is responsible for the highest visual acuity, contains no blood vessels except in its periphery, and receives nourishment from the choroid.

Macular degeneration: loss of central vision in one or both eyes as a result of malfunctioning cone cells in the retina. There are two types: "wet " (disciform) and "dry" (atrophic). This is also known as age-related macular degeneration (ARMD or AMD) and previously known as senile macular degeneration.

Myopia: also known as nearsightedness or shortsightedness. This is a condition in which rays of light from distant objects are focused in front of the retina, causing blurred vision.

Neovascularization: the formation of new blood vessels.

Occult: a poorly defined pattern of leakage from abnormal choroidal blood vessels (neovascularization) as distinguished from classic leakage.

Ophthalmoscopy: examination of the internal structures of the eye using an illumination and magnification system.

Peripheral vision: the outer part of the field of vision made possible by the rod cells.

Photodynamic therapy: an outpatient procedure which involves the systemic injection and activation of a light-sensitive drug to damage abnormal choroidal blood vessels.

RCT (Randomized controlled trial)**:** A trial designed to keep study groups as similar as possible, in order to isolate and quantify the effect of the intervention studied and control for other factors.

Snellen chart: the standard tool for the measurement of visual acuity, displaying letters of progressively smaller size. Normal vision is 20/20 which means that you are able to discriminate characters on the eye chart at 20 feet that a person with normal acuity can see at 20 feet. 20/30 vision means you are able to discriminate characters on an eye chart at 20 feet that a person with normal acuity can see at 30 feet, and so on.

Visual acuity: level of clarity, distinction, or sharpness.

Visual acuity test: use of an eye chart to measure accuracy of reading and perception at various distances. (See "Snellen chart").

Visual function: a measurement of the ability to perform everyday tasks that require vision.

1 INTRODUCTION

1.1 Background

Age-related macular degeneration (AMD) is a disease that causes central blindness. It is a deterioration of the macula (a small but important retinal area responsible for high resolution, central vision) hindering the ability to recognize faces, read, or drive. Loss of vision from AMD is permanent and has a significant impact on individual functioning and quality of life.[1] Currently, there are no effective treatments for the majority of individuals with AMD. The wet, or neovascular type of AMD is responsible for more pronounced vision loss. Verteporfin photodynamic therapy (PDT) is a new treatment for this type of AMD. Our review will attempt to assess the available evidence of this new technology and its potential clinical and economic impact on health services and patients.

1.1.1 Age-related macular degeneration

Age-related macular degeneration can be classified according to an early and a late stage of development. The early stage is associated with minimal visual impairment and is characterized by large (> 63 μm diameter) deposits of ingestible acellular debris, called drusen, and irregular pigmentation of the macula.[2] The deterioration of pigmented retinal epithelial (RPE) cells in the macula and the appearance of drusen without hemorrhage (observed by ophthalmoscopy and angiography) is referred to as dry, or atrophic AMD.[2,3]

Although most individuals with AMD manifest these characteristics only, a minority progress to more severe and rapid loss of vision when new blood vessels from the choroid begin to grow just beneath the retina, a process called choroidal neovascularization (CNV). Neovascularization may also cause detachment of the RPE, fibrovascular or disciform scarring, and vitreous hemorrhage.[2,4] This damage to the macula causes characteristic CNV lesions when observed by angiography. The location (extrafoveal, juxtafoveal, or subfoveal) and appearance (classic, occult, or both features) of the CNV lesions can be observed by fluorescein angiography[2-4] and other investigational visual techniques.[5]

Patients with neovascular AMD are left only with coarse peripheral vision hindering the ability to function well visually. Many of them lose enough vision to become legally blind (worse than 20/200). Changes in vision can be monitored by the use of visual tests, including visual acuity and contrast sensitivity charts.[2] Functional ability can be assessed with a visual function questionnaire or reading tests.

Table 1: Characteristics of different forms of late-stage age-related macular degeneration

Form	Dry	Wet
Other Names	Atrophic	Exudative, neovascular
Etiology	Accumulation of small deposits called "drusen" under the retina with deterioration of the retinal epithelium	Growth of new blood vessels from the choroid behind the retina that destroys the retinal pigment epithelium and sensory retina
Prevalence	80 - 90% of all AMD cases	10% of all AMD cases
Treatment(s)	A combination of antioxidants and zinc may slow progression	PDT, or laser photocoagulation for slowing neovascularization

1.1.2 Age-related macular degeneration in Canada

The prevalence of neovascular AMD in Canada in 2001 was estimated to be greater than 100,000 based on weighted prevalence figures, stratified by age from three population-based studies conducted outside of Canada.[6]

Because age is the primary risk factor for having the disease, the prevalence of the disease is expected to increase as the population ages.[2] Other established risk factors for the disease are family history, race (white), cigarette smoking, and a low dietary intake (or plasma concentration) of antioxidant vitamins and zinc. Some risk factors less consistently identified with the disease are sex (female), iris colour (light), cardiovascular disease and sunlight exposure.[2]

Verteporfin PDT is currently approved for use in individuals with predominantly classic subfoveal CNV secondary to AMD. Only a minority of individuals with neovascular AMD fit these treatment criteria. Estimates of the number of currently treatable cases from published and unpublished studies display a range from 3%[7] to 36%[8] of eyes with neovascular AMD (Table 2).

Table 2: Estimates of numbers eligible for verteporfin PDT treatment

Author (year) [Publication Status]	**Study Design (setting)**	**Neovascular AMD, Number of Eyes**	**Subfoveal CNV from AMD, Number of Eyes (%)**	**Number Eligible for Verteporfin Therapy (%)**
Baudo *et al.*[7] (2001) [Abstract]	Retrospective consecutive chart review of patients with newly diagnosed wet AMD (Maryland)	451	N.R.	14 (3)
Bermig *et al.*[9] (2001) [Abstract]	N.R.	191	N.R.	31 (16)
Gehrs *et al.*[10] (2001) [Abstract]	Retrospective consecutive chart review of patients with CNV from AMD (Iowa)	344	145 (42)	20 (6)
Haddad *et al.*[11] (2001) [Abstract]	Retrospective consecutive chart review of eyes examined within 15 days of diagnosis (Paris)	121	42 (35)	10 (8)
Margherio *et al.*[8] (2000) [Journal]	Retrospective consecutive chart review of patients with newly diagnosed AMD (Michigan)	474	392 (83)	171 (36)
Moisseiev *et al.*[12] (1995) [Journal]	Retrospective quasi-random chart review of patients with AMD Israel)	100	44 (44)	20 (20)

N.R. = not reported

1.1.3 Current practice

Patients typically present to their general ophthalmologist or optometrist with distorted or decreased central vision. They are subsequently referred to a retinal sub-specialist who evaluates their macular status. The final diagnostic process involves clinical evaluation of the macula with stereoscopic biomicroscopy, fluorescein angiography, and rarely, indocyanine green angiography.

Vision aids, such as reading magnifiers, are commonly employed in management of neovascular AMD. Evidence from one RCT suggests the psychosocial impact of the disease can be minimized through behavioural intervention and education at disease onset.[13]

Most interventions investigated in randomized controlled trials (RCTs) for managing neovascular AMD are aimed at slowing or stopping the neovascular process. These include laser photocoagulation[14] and external beam radiation therapy.[15] Other interventions, including submacular surgery, transpupillary thermotherapy, and other biological and chemical therapies are under investigation in human trials.[16]

Only laser photocoagulation, in a small proportion of patients with wet AMD, has been shown to minimize vision loss by slowing or stopping vascular leakage using a focused argon or krypton laser.[14] Laser photocoagulation has been shown to stabilize vision and prevent large decreases in visual acuity. When used for small or medium-sized subfoveal lesions (< 2 disc areas) in eyes with moderate to poor initial visual acuity, photocoagulation offers the possibility of preventing long-term vision loss at the cost of immediately decreasing visual acuity (average loss of three lines of vision).[17]

1.2 Technology Overview

PDT entails the activation of a drug with light.[18] Verteporfin PDT involves the intravenous administration of verteporfin followed by the application of light from a laser to CNV lesions below the retina. Unlike laser photocoagulation, PDT does not use light intense enough to cause thermal damage. Because of this, verteporfin PDT may offer fewer limitations than laser photocoagulation when CNV lesions are located under the fovea. Activation of the drug creates free radicals that are believed to facilitate the destruction of neovascular tissue and subsequently prevent further hemorrhage and leakage from new blood vessels.[19]

Verteporfin is reconstituted with sterile water from its original vial and then diluted with 5% dextrose for a total infusion volume of 30 mL. The drug is then administered intravenously over a ten minute period at a dose of 6mg/m^2 body surface area. Five minutes later, a laser with a wavelength of 689 ± 3 nm is set to deliver 50 J/cm^2 at an intensity of 600 mW/cm^2 for a period of 83 seconds using a corneal contact lens. The administered laser energy is modified to correct for the magnification of the corneal contact lens. The spot-size of the laser is set to cover the greatest linear diameter of the lesion with a 1000 micron border added to this dimension to ensure the entire lesion is covered. The diode laser generates free radicals following contact with the dye. Destruction of the choroidal neovascular lesion is thought to be secondary to these free radicals.

Patients are cautioned to avoid sunlight for 48 hours post treatment. Follow-up is arranged for repeat angiography and retinal evaluation three months post intervention, at which point further treatments can be considered. In trials subsequently described in this report, patients received an average of 5 and 5.5 treatments in the first 24 months of treatment respectively.

In May 2000, Health Canada approved verteporfin for use with PDT in patients with predominantly classic subfoveal CNV secondary to AMD. In July 2001, Health Canada approved verteporfin PDT for patients with predominantly classic subfoveal CNV secondary to pathologic myopia (PM).[20]

1.2.1 Economic impact

Costs associated with verteporfin PDT could involve physician consultations, a professional fee for performing the procedure, a facility fee, fluorescein angiography, fundus photography, and the acquisition cost of the drug, additional follow-up visits and retreatments. As fees billed for these services could vary between settings, a range of estimates of incremental costs for this treatment versus supportive therapy (one visit plus one follow-up visit plus one angiography in 24 months) in a Canadian setting can be calculated (Table 3).

Table 3: Total and incremental costs associated with two year average treatments with verteporfin PDT

Cost Item	**Cost**		**Units Consumed**		**Total Costs**	**Incremental Costs**
	Low Estimate	High Estimate	Low Estimate	High Estimate		
Consultations	$30	$50	9	9	$270-$450	$210-$350
Professional fee	$200	$350	5*	5.5‡	$1,000-$1,925	$1,000-$1,925
Fluroescein angiography	$95	$100	8	8	$760-$800	$665-$700
Facility/technical fee	$0	$250	5	5.5	$0-$1,375	$0-$1,735
Drug costs	$1,750	$1,800	5	5.5	$8,750-$9,900	$8,750-$9,900
Total costs (2 years)					**$10,780-$14,450**	**$10,625-$14,250**

*As seen in the VIP trial
‡ As seen in the TAP trials

2 OBJECTIVES

The purpose of this assessment was to:

1) assess the available evidence of verteporfin PDT and its potential clinical and economic impact on health services and patients;

2) evaluate the potential harms and benefits of verteporfin PDT in individuals diagnosed with neovascular AMD;

3) determine the influence of publication status and trial quality on these outcomes; and

4) assess the potential economic implications.

Potential harms were assessed from the observed impact of verteporfin PDT on serious and other adverse events, and adverse events causing patient withdrawals from treatment. Potential benefits were assessed from the observed impact of verteporfin PDT on the incidence of legal blindness (<34 letters or <20/200), and the impacts on visual acuity, functional outcomes (e.g. reading speed or visual function questionnaire scores), and quality of life.

3 METHODS

3.1 Clinical Assessment

3.1.1 Trial selection

The methods used to conduct this review follow guidance for conducting systematic reviews provided by the QUOROM statement.[21]

Search strategy:

a) Published literature was obtained by performing a cross-database search of MEDLINE®, EMBASE®, HealthSTAR, PASCAL, SciSearch: a Cited Reference Science Database, and Toxline® on the DIALOG® system (see Appendix 1). A parallel search was also run on PubMed.

b) Database alerts/updates were established on ADIS LMS Drug Alerts, Current Contents Search®, EMBASE® Alert, MEDLINE®, PASCAL, Pharmaceutical News Index (PNI®) and SciSearch. The Current Contents Search® and SciSearch updates were discontinued August 2001.

c) Searches were performed and updated on the CD ROM version of The Cochrane Library. Grey literature was obtained through searching the Web sites of regulatory agencies, health technology assessment and near-technology assessment agencies, as well as specialized databases, such as those of the University of York NHS Centre for Reviews and Dissemination and the Latin American and Caribbean Center on Health Sciences Information (LILACS). The Google™ search engine was used to search for a variety of Web-based information.

d) Economic information was obtained through searching PubMed, replacing the original clinical trial filter with an economic one. The CD ROM version of the Health Economic Evaluations Database (HEED) was also searched.

e) Drug approval information which was not available publicly from the U.S. Food and Drug Administration Web site was requested through the Freedom of Information Act; safety data were requested from the Adverse Drug Reaction Reporting Unit of Health Canada.

f) The bibliographies of narrative and systematic reviews and all retrieved reports were searched (by DH) for relevant trials.

g) Abstracts were obtained from a hand search (by DH) of the conference archives of the Association for Research in Vision and Ophthalmology (ARVO) 2000 and 2001 annual meetings.

h) The manufacturer of verteporfin PDT (Visudyne®), QLT Inc., was contacted in order to obtain an official copy of the Canadian product monograph. The company was invited to submit any relevant (published or unpublished) information and was asked to complete data abstraction forms.

i) Dr. David Maberley (DM) was also asked to identify any relevant reports.

Selection process: Two reviewers (DH and VS) systematically and independently screened the titles and abstracts of all citations captured in the initial search. If both reviewers determined a citation did not meet one of the eligibility criteria for review, it was excluded at this stage. In case of doubt on the part of either reviewer, the original report was retrieved for further assessment.

Inclusion and exclusion criteria were then applied to each retrieved report. Reports which could not be excluded at this point were considered potentially relevant and assessed by two reviewers (DH and VS). The full text of these reports was reviewed and assessed using a form that listed each report by an in-house reference number, title, and one question: "Include? Yes/No/ Unclear". If a report was rejected for inclusion or a decision for inclusion was unclear, further qualification by a written explanation on the form was required. Unclear decisions and disagreements were resolved by forced consensus between reviewers or by a third party.

Inclusion/exclusion criteria: Only randomized controlled trials (RCTs) were considered. Eligibility criteria were applied systematically to all reports captured by the literature search. A trial was eligible for inclusion if it met the criteria described in Table 4.

Table 4: RCT eligibility criteria

Trial Criterion	**Description**
General	No restrictions on publication status, year of publication, or language of publication
Study Design	RCTs
Participants	Adults (>18 yrs) diagnosed with neovascular age-related macular degeneration by study investigators
Intervention	Verteporfin photodynamic therapy: no restrictions on dose or dosing interval
Comparator	Placebo or current therapy (e.g. laser photocoagulation)

Outcomes: The outcomes of interest in treated populations were:

1) the number of individuals with legal blindness (due to societal impact);
2) the number of individuals with increased or decreased visual acuity (to adequately assess the impact of the intervention on the population);
3) the impact on quality of life;
4) the impact on visual function; and
5) morbidity.

For morbidity, serious (i.e. life-threatening) adverse events, withdrawals due to adverse events, patient adverse events, and laboratory-determined adverse events were of interest. Adverse events (serious or otherwise) reported to occur with the most frequency were also of interest. The degree of visual acuity lost (as measured by an eye chart) was a secondary outcome of interest.

3.1.2 Data abstraction strategy

Information on trial design, participant characteristics, and interventions was abstracted by two reviewers (DH and VS) independently onto a standard form for each relevant trial. Information was also abstracted by these reviewers independently on a standard form for each outcome. Disagreements were resolved by discussion and consensus. The use of an agreed-upon third party to resolve persisting differences was not required. Missing information was sought from the manufacturer. The authors and titles of the reports were not masked when performing data extraction.

3.1.3 Quality assessment strategy

The quality reporting of the included RCTs was assessed independently by two reviewers (DH and VS) using the three-item Jadad instrument (Appendix 2).[22] A calibration exercise was not conducted. Every attempt was made to assess the quality of the trials described in the studies by using supplemental information (i.e. duplicate reports, regulatory information, etc.). The adequacy of allocation concealment as an indicator of methodologic quality was also assessed independently by two reviewers as adequate, inadequate, or unclear (Appendix 2).[23]

3.1.4 Data synthesis and meta-analysis methods

Statistical analyses were performed on an intention-to-treat basis (ITT) whenever possible. Because the CCOHTA Guidelines for Authors[24] suggest meta-analysis is appropriate if a clinically homogeneous set of RCTs is found, it was felt that differences in angiographic and visual baseline characteristics would make a meta-analysis of potential benefits (i.e. visual outcomes) from therapy uninformative. However, meta-analysis is ideally suited to analyses of harm,[25] and we did not foresee differences in angiographic and visual baseline characteristics (the only difference between trials) rendering adverse event rate data uninformative, so we opted to meta-analyse these outcomes.

Cochrane Review Manager 4.0.4 software using MetaView 4.0 was used to calculate combined outcomes. DerSimonian and Laird random effects[26] and Mantel-Haenszel fixed effects models were used for combining dichotomous outcomes. DerSimonian and Laird random and inverse variance fixed effects models were used for combining continuous outcomes. Both random and fixed effects models were applied to all outcomes for comparison.

Statistical heterogeneity across trials was assessed by calculating a χ^2 statistic using MetaView. Publication bias was assessed by visual inspection of a funnel plot. Although both statistical heterogeneity and publication bias can compromise the validity of any meta-analysis, results from these statistical methods may be misleading, given the low number of RCTs.

A 95% confidence interval was calculated for each outcome measure if possible. Where appropriate, a number-needed-to-treat (NNT) or number-needed-to-harm (NNH) result for primary and secondary outcomes was calculated.

3.1.5 Sensitivity and subgroup analyses

Subgroup analyses were planned by dosage and dosing interval. Planned sensitivity analyses of primary outcome data to investigate heterogeneity included trial quality (defined by both the Jadad and Schulz methods), publication status, geographic location and language of publication. Given the low number of trials, results from these analyses were thought not likely to be informative and these analyses were not conducted.

4 RESULTS

4.1 Quantity and Quality of Research Available

Number of reports identified in total: Reports identified were abstracts, full trial reports, reviews, regulatory reviews, or commentaries. Appendix 3 shows the process of inclusion and exclusion. The original broad electronic search strategy identified 94 citations. Of these, two reviewers selected 41 citations by title/abstract that were retrieved for potential inclusion and further hand searching. Another 13 reports were identified from Internet searches (n=2), HTA databases (n=9), and regulatory bodies (n=2). A search of The Association for Research in Vision and Ophthalmology (ARVO) annual meeting abstracts from 2000 and 2001 and bibliographies of retrieved studies revealed another 42 unique citations. No unique, unpublished reports were identified through European or U.S. regulatory agencies.

Of the 96 identified reports, a total of 90 were excluded from further analysis because they were reviews (n=46), animal studies (n=2), duplicate reports (n=11), non-AMD trials (n=4), missing a comparator (n=15), non-randomized trials (n=8), overviews (n=1), case reports (n=2), or pharmacokinetic studies (n=1).

Potentially relevant trials: After exclusion of 90 reports, a total of six (five published and one unpublished) reports of potentially relevant trials were identified. Five of these were retrieved from the electronic searches of databases and one was identified from hand searching conference abstracts.

Of the six potentially relevant reports remaining, two described RCTs that met the criteria for evaluation.[27,28] Of the four excluded reports, two lacked a comparator,[29,30] one was considered a duplicate,[31] and one was judged to have an outcome not relevant to this review.[32]

Trials included for review: The two included reports[27,28] describe three trials: Treatment of Age-related Macular Degeneration with Photodynamic Investigation Using Verteporfin (two trials: TAP-A and TAP-B); and the Verteporfin in Photodynamic Therapy Report 2 (VIP). Excluded duplicate reports were used to supplement information missing from included reports. A list of all included and excluded reports can be found in Appendix 4.

A *kappa* statistic quantifying agreement (Yes/No/Unclear) between reviewers (DH and VS) for identifying included reports was 0.67 (95%CI: 0.07 to 1.2) indicating moderate agreement between reviewers. This reflects disagreement by one reviewer about whether the interim analysis report of the TAP trial should be included or considered a duplicate. Both reviewers agreed to consider it a duplicate but to use it for supplemental information.

Quality assessment of reports: The quality of selected reports is summarized in Appendix 5. In both publications, the number of screened and eligible participants prior to randomization was not reported. Treatment assignment was described as randomized in both reports. The method of randomization is not described in either but both refer the reader to a report [31] which describes the method of randomization in greater detail.

Both reports describe using a strict ITT analysis. The number of individuals completing the study arms of both reports is stated, but reasons for failing to complete are not specified. Missing information was subsequently provided by QLT Inc. Patients, investigators and assessors are described as being blinded to treatment in both trials and a reference for the complete description of this method is given in both studies.

A *kappa* (κ) statistic quantifying agreement between reviewers for assessing quality of the reports using the Jadad scale was 0.60 (95% CI: 0.104 to 1.096). Disagreement derived from judging quality strictly from a single report or relying on supplemental information (e.g. more methodological information was contained in the interim report of the TAP trial). Reviewers subsequently agreed to judge trials based on all information available. Reviewers were in complete agreement (κ =1) when assessing the reporting of treatment allocation.

4.1.1 Assessment of clinical effectiveness

Critical review and synthesis of information: All three trials included in this review are phase III trials investigating verteporfin PDT for subfoveal CNV related to AMD. Because of differences in visual and retinal baseline characteristics between TAP and VIP trial participants, only outcomes pertaining to harm were pooled by meta-analysis. A description of each trial is available in Appendix 6.

Differences between TAP and VIP patient groups: Most individuals with a visual acuity better than 70 letters or without classic features ineligible for the TAP trials would be eligible for the VIP trials. Differences in baseline characteristics for trial populations can be seen below. (Table 5)

Table 5: Baseline characteristics of patients in TAP-A, TAP-B, and VIP trials

Characteristic	TAP-A		TAP-B		VIP	
	Verteporfin %	Placebo %	Verteporfin %	Placebo %	Verteporfin %	Placebo %
Letter score (visual acuity*) in study eye						
>73 (>20/40)	0	0	0	0	20	16
73-53 (20/40-20/80)	53	51	47.5	46	72	77
52-34 (20/100-20/200)	47	49	52.5	54	8	7
Lesion area composed of classic CNV, %						
≥50	67	35	67	44	7	3
>0 to <50	33	65	33	56	17	16
0	0	0	0	0	67	70
Questionable or can't grade	0	0	0	0	9	11

*Snellen equivalent

4.1.2 Primary outcomes

Number of study eyes with legal blindness:

Table 6: Number of study eyes with legal blindness

	TAP (A and B)		VIP	
	Verteporfin	Placebo	Verteporfin	Placebo
Number of study eyes (ITT)	402	207	225	114
Baseline visual acuity in study eye, Snellen equivalent [letters] (range)	20/80-2 [52.8] (20/40-20/200)	20/80-2[52.6] (20/40-20/200)	20/50+1[66] (> 20/100)	20/50 [65] (> 20/100)
Number of study eyes with visual acuity less than 20/200 [34 letters] at two years (%)	165 (41.0%)	114 (55.1%)	59 (26.2%)	50 (43.9%)
Absolute Risk Difference, % number of study eyes (95% CI)	14.0 (6 to 22)		17.6 (7 to 28)	
NNT to prevent central blindness in study eye after two years (95% CI)	7 (5 to 18)		6 (4 to 14)	

TAP: The number of eyes with a visual acuity of 20/200 or less after 24 months was proportionally smaller [41% (165/402) vs. 55% (114/207), p=0.001] in verteporfin-treated compared with placebo-treated eyes. This represents a NNT of 7 (95% Confidence Interval (CI): 5 to 18) to prevent one extra case of legal blindness in an eye after 24 months.

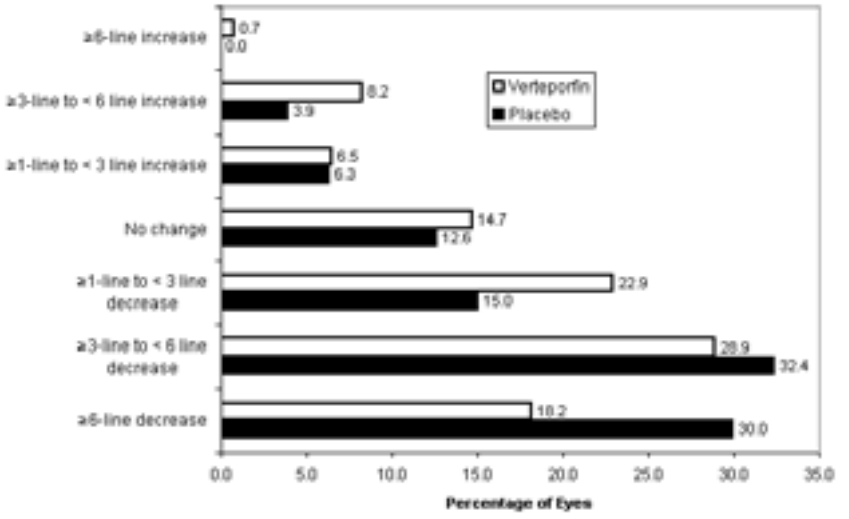
VIP: The number of eyes with a visual acuity of 20/200 or less after 24 months was proportionally smaller [26% (59/225) vs. 44% (50/114), p=0.001] in verteporfin-treated

compared with placebo-treated eyes. This represents a NNT of 6 (95% CI: 4 to 14) to prevent one extra case of legal blindness in an eye after 24 months.

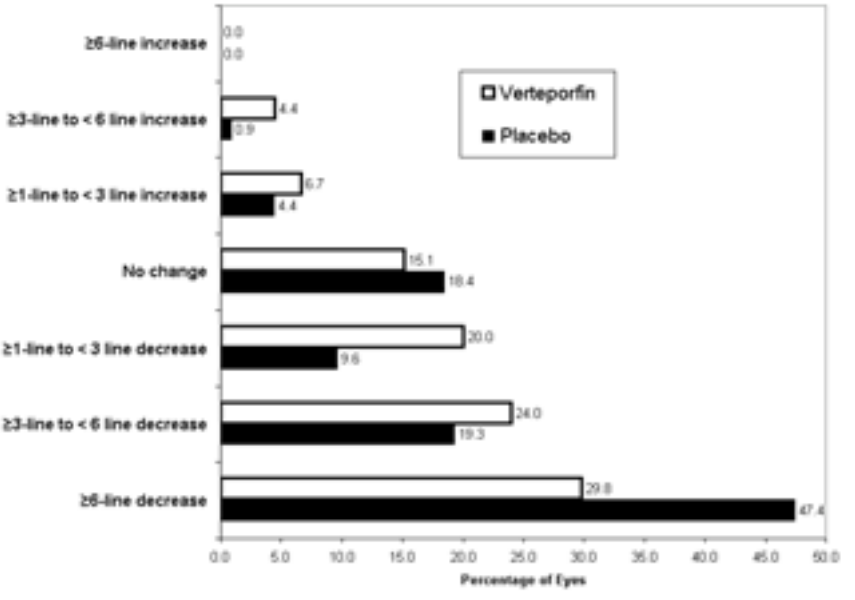
Number of study eyes with increased/decreased visual acuity from baseline:
TAP: Further vision loss based on eyechart performance after 24 months occurred in 70% (281/402) of verteporfin-treated eyes and 77% (160/207) of placebo-treated eyes. No change in vision was observed in 15% (59/402) of verteporfin-treated and 13% (26/207) of placebo-treated eyes. An increase in visual acuity was observed in 15% (62/402) of verteporfin-treated eyes and 10% (21/207) of placebo-treated eyes. A breakdown is seen in Figure 1.

Figure 1: Change in visual acuity from baseline

(a) TAP trials



(b) VIP trial



VIP: Further visual acuity loss after 24 months occurred in 74% (166/225) of verteporfin-treated eyes and 76% (87/114) of placebo-treated eyes. No change in vision was observed in 15% (34/225) of verteporfin-treated and 18% (21/114) of placebo-treated eyes. An increase in visual acuity was observed in 11% (25/225) of verteporfin-treated eyes and 5% (6/114) of placebo-treated eyes.

Quality of life measures[*]*:* These outcomes were not reported.

Functional measures: These outcomes were not reported**.**

4.1.3 Secondary outcomes

Mean difference in visual acuity from baseline:
TAP: Verteporfin-treated individuals lost an average of 13.4 letters (95% CI: 11.6 to 15.2) from baseline compared with an average of 19.6 (95% CI: 17.2 to 22.1) letters in the placebo-treated group. This resulted in a mean difference of 6.2 letters (95% CI: 3.2 to 9.3).

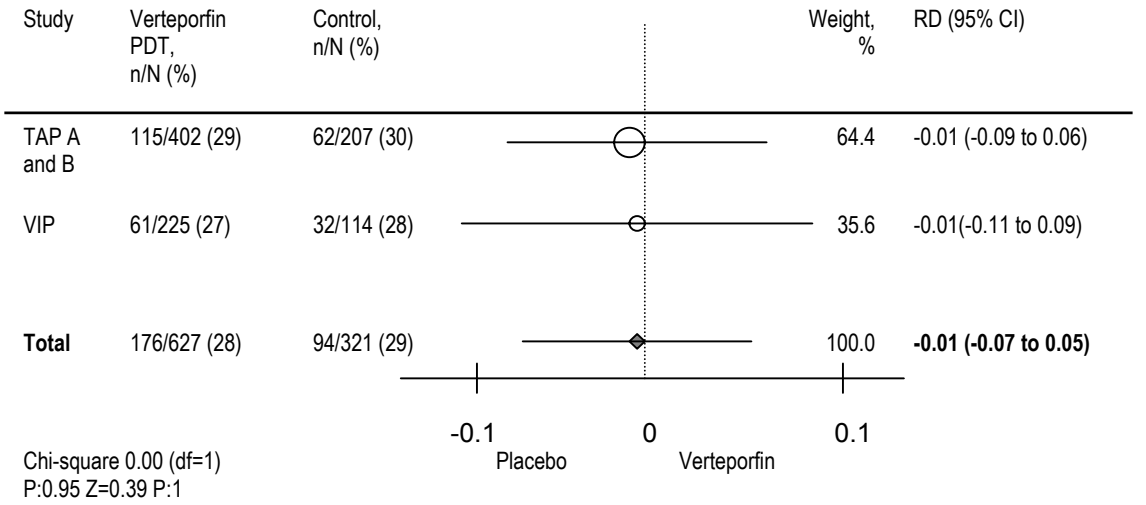
VIP: Verteporfin-treated individuals lost an average of 19.1 letters (95% CI: 16.4 to 21.8) from baseline compared with an average of 25.1 letters (95% CI: 21.2 to 28.9) in the placebo-treated group. The mean difference between verteporfin and placebo-treated groups was 6.0 letters (95% CI: 1.3 to 10.6).

4.1.4 Harm

Serious adverse events: We defined a serious adverse event as an event resulting in death; a life threatening event; an event resulting in hospitalization, prolongation of hospitalization or disability; or an event resulting in a birth defect/congenital anomaly. Serious adverse events occurred in 28% (176/627) of verteporfin-treated patients and 29% (94/321) of placebo-treated patients. A meta-analysis using a fixed effects model of results from all three trials shows the difference in percentage of patients experiencing a serious adverse event (including death) when treated with verteporfin decreases by 1% (95% CI: -5% to 7%), (see Figure 2). A random effects model was not applied due to the small number of trials.

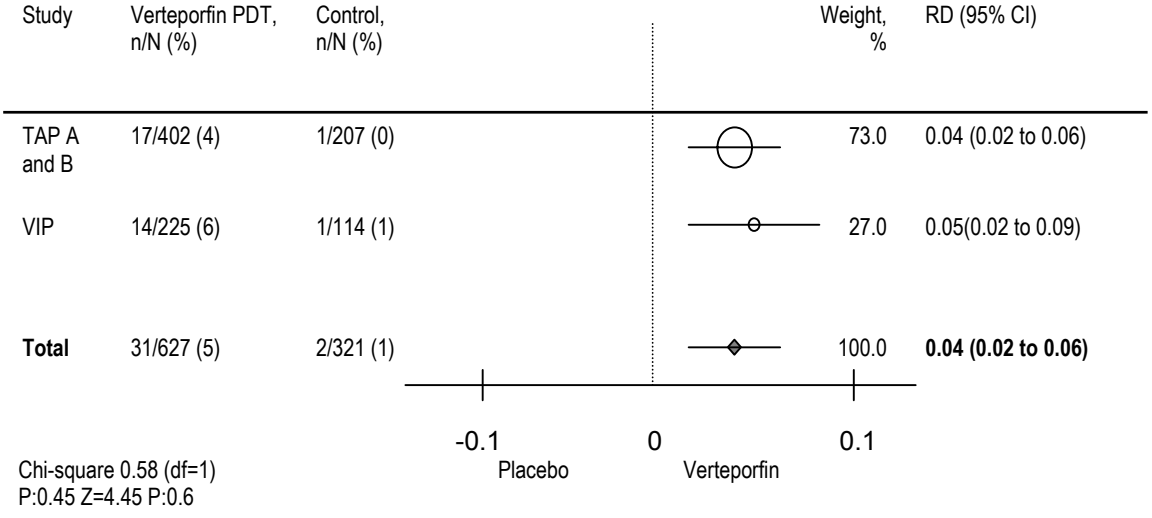
[*] A description of quality of life and functional outcomes data is available from the FDA statistical review document (Available: http://www.fda.gov/cder/foi/nda/2000/21-119_VISUDYNE_statr.pdf)

Figure 2: Serious adverse events



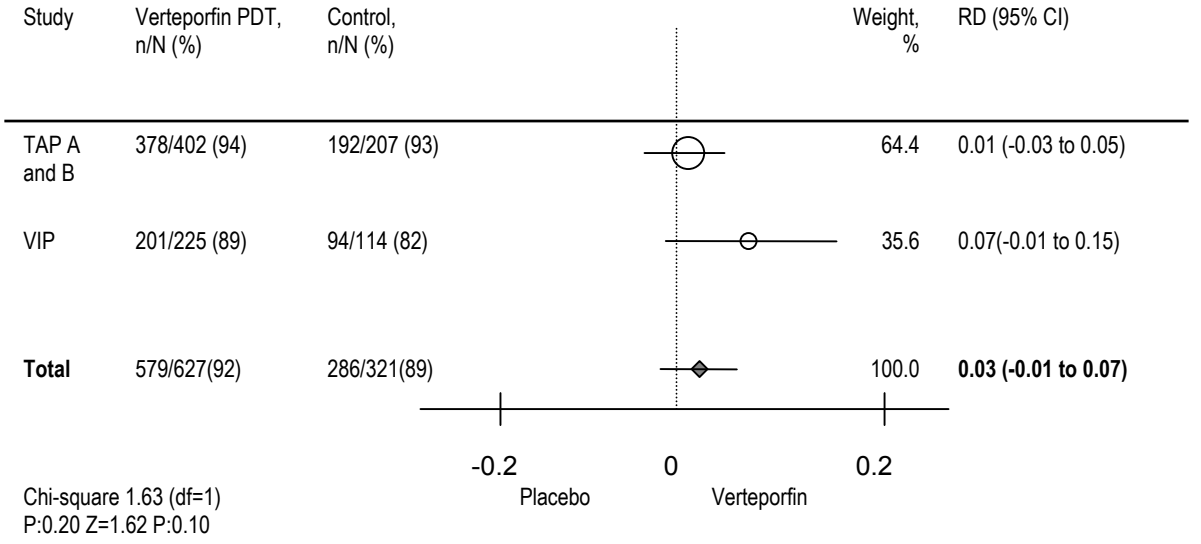
Withdrawals due to adverse events: Withdrawals due to adverse events occurred in 5% (31/627) of verteporfin-treated patients and 0.6% (2/321) of placebo-treated patients. A meta-analysis using a fixed effects model of results from all three trials show that 4% (95% CI: 2% to 6%) more patients withdrew due to an adverse event when treated with verteporfin versus placebo (Figure 3). A random effects model was not applied due to the small number of trials.

Figure 3: Withdrawals due to adverse events



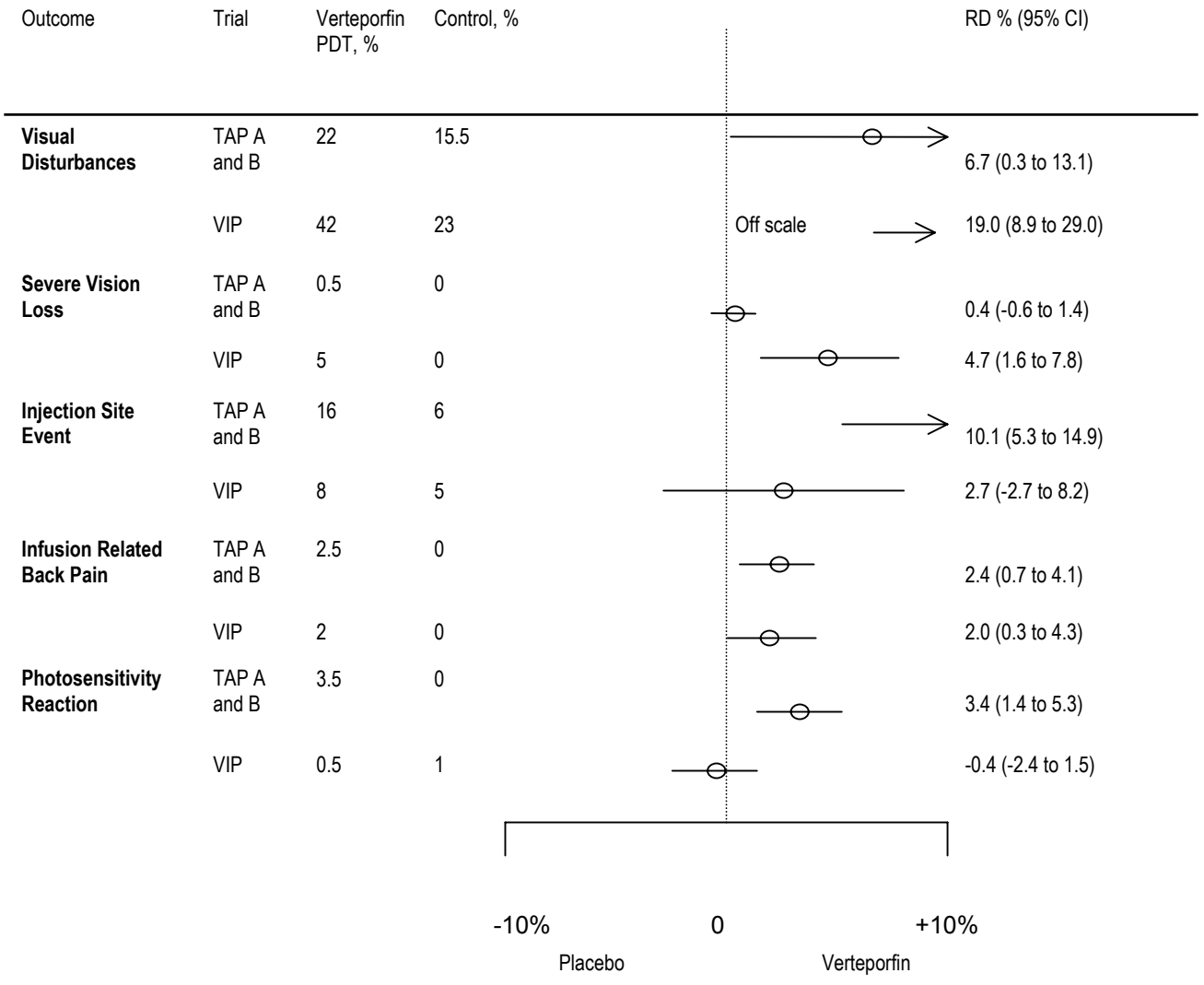
Patients with adverse events: An adverse event occurred in 92% (579/627) of verteporfin-treated individuals and 89% (286/321) of placebo-treated individuals. The risk difference for a patient developing an adverse event was 3% (95% CI: -2% to 9%) (Figure 4). A fixed effects analysis did not change this estimate.

Figure 4: Number of patients experiencing adverse events



Adverse events most commonly reported were (1) visual disturbances, including vision loss and severe vision loss (defined as a loss of at least 20 letters of visual acuity within seven days of treatment), abnormal vision and visual field defects; (2) injection site events, including discoloration, edema, extravasation, hemorrhage, hypersensitivity, inflammation, and pain; (3) infusion-related back pain; and (4) photosensitivity reactions. Significant statistical heterogeneity in all of these outcomes, with the exception of infusion-related back pain, and especially for severe vision loss and photosensitivity reactions, precluded meta-analysis. Figure 5 illustrates these data.

Figure 5: Patient adverse events



Frequency of adverse events: The frequency of occurrence of adverse events is shown in Appendix 6. (N.B. Some adverse events occurred more than once in individual patients)

Laboratory-determined adverse events: Laboratory-determined adverse events were reported for one trial (TAP).[33] Two abnormal lab tests were reported in verteporfin-treated patients (n=402) and four abnormal tests were reported in placebo-treated patients (n=207). The types of abnormal test are not known.

Sensitivity analyses: Sensitivity analyses of the effects of publication status or trial quality were not preformed as the small number of trials included in the analysis would make them uninformative.

5 DISCUSSION

Quantity and quality of research: The TAP and VIP reports[27,28] describe three trials; TAP-A, TAP-B, and VIP. These trials met a high level of methodological quality when rated by us using the Jadad scale[22] and by treatment allocation concealment.[23] Some methodological details not contained in the TAP reports were not available to us, including the trial protocol and amendments. These changes have been reported to be "not substantive" and "that there were no changes to the *a priori* determinants of the primary outcomes" in another well-conducted systematic review.[34]

Differences in baseline characteristics were observed in the TAP study.[31] A greater number of placebo recipients had never smoked (44% vs. 34%, p=0.045), were women (63% vs. 53%, p=0.02) and had a lesion that included blood leakage at baseline (42% vs. 33%, p=0.053). We assume this imbalance did not arise from predictable assignments to treatment allocation. A subgroup analysis conducted by trial investigators did not indicate that these variables contributed significantly to treatment response.[28]

Patients not completing a follow-up visit in month 24 are enumerated in each report but the reasons for lack of trial completion are not. A last-observation-carried-forward (LOCF) approach was used to conduct the analysis, a technique that can lead to over- and under-estimates of the treatment effect from patient discontinuation, withdrawal, and loss to follow-up (attrition bias). Both studies re-analyzed the data without the LOCF and stated (but did not report in detail) that similar conclusions were reached. Given the relatively low number of participants who failed to complete the trials and their reasons (reported in an unpublished analysis), we have assumed this is not a significant consideration.

Decisions to treat and retreat were determined by angiographic assessments performed by individual investigators. Recognizable angiographic patterns revealing prior verteporfin PDT would likely "unmask" a greater number of investigators than reported, leading to the possibility of bias from assessment and treatment (i.e. detection or performance bias). Angiographic readings and visual assessments independently performed by masked personnel who did not see retreatment angiograms in both trials would have standardized treatment outcomes and prevented this possibility.

5.1 Diagnostic Accuracy

Measures taken to enhance the internal validity of the TAP and VIP trials raise questions about external validity. Angiographic assessments using certified personnel under trial conditions were fairly accurate. In the TAP trials[28,31] for instance, study investigators were able to identify classic features approximately 91% of the time, subfoveal CNV roughly 95% of the time, and identify lesions composed of ≥ 50% CNV approximately 99% of the time. Accuracy of diagnosis in the VIP trial was similar.[27] Several other variables were considered before deciding to enroll trial participants.

Little is known about the reliability of diagnosis among retinal specialists in practice; many will not have received specific training under trial conditions to ensure the accuracy of their diagnoses. One report suggests only moderate agreement for both identifying relevant angiographic features and deciding whether or not to treat based on TAP criteria.[35] This report does not address the reliability of assessments by non-retinal specialists or the reliability of the assessments of angiograms for retreatment, which are likely to be even less accurate.

5.2 Patient Population

When considering the generalisability of results, it is important to consider that enrolled participants in the TAP trial had a best-corrected visual acuity (VA) between 34 and 73 letters. No evidence of a treatment effect in individuals with poorer vision is currently available.

Those with better visual acuity or only occult features were eligible for treatment in VIP. Specifically, two distinct groups were randomized together: those without classic features with a best-corrected VA of at least 70 letters and those with occult and no classic features (with evidence of disease progression within three months) who had a best-corrected VA of at least 50 letters. This scenario does not accurately represent those who would seek treatment in a clinical setting,[15] and, therefore, generalising the observed response in this trial to patients in practice may be imprudent. Because these results are not readily interpretable, results from an ongoing trial, the Verteporfin in Occult CNV (VIO) trial, may clarify these data.

Further to this, the VIP trial results are confounded by the development of classic features in those with occult CNV (that met the VIP inclusion criteria) at baseline. In the VIP trial, 34% and 53% of patients with occult (and no classic) features at baseline developed classic features by 12 months and 24 months, respectively. This is consistent with several RCTs and observational case series published previously.[15,36,37] The possibility that the effect of treatment is driven by those who develop classic features could reasonably explain the lack of any observed difference between verteporfin and placebo recipients in the first 12 months.

5.3 Clinical Effectiveness Results

5.3.1 Potential benefits

The identified TAP and VIP trials suggest that compared with placebo, verteporfin PDT can reduce by 14 to 18% the number of patients who become legally blind (20/200) after two years of treatment in eyes with subfoveal lesions from neovascular AMD that meet appropriate diagnostic criteria. As discussed, differences in patient characteristics prevented the pooling of potentially beneficial visual outcomes using meta-analysis.

It is clear from the observed outcomes that a majority of treated individuals will continue to lose vision. Those seeking and providing treatment should be made aware of this. In both trials, verteporfin recipients lost roughly six fewer letters (or one line) of visual acuity on average. The

clinical significance of this benefit and the impact of this difference on visual function and quality of life would be expected to vary from patient to patient.

Visual quality of life and visual function are not solely dependent on visual acuity results.[38,39] Data from the National Eye Institute 25-item visual function questionnaires (VF-25) were collected in both trials, however results from these analyses have not been published. These data, available from an FDA analysis, are uninterpretable because: (1) they are results from a small patient subgroup, not representative of the overall trial population who participated; and (2) assessments are based on the better-seeing eye, which was the study eye for less than half of the patients who participated in these assessments. Furthermore, only a fraction of better-seeing eyes were maintained as such throughout the entire study period.

Verteporfin PDT has been approved by Health Canada for the treatment of eyes with subfoveal CNV from AMD with predominantly (≥ 50%) classic angiographic features. It is worth noting that this subgroup, consisting of approximately 40% of study eyes (242/609) was identified in a subgroup analysis as having a treatment effect greater than that of the original ITT study population.

5.3.2 Potential harms

The trials did not reveal that compared with placebo, verteporfin PDT significantly increases serious or life-threatening adverse events. This is consistent with results from other ongoing open-label safety studies and pharmacovigilance data from Health Canada.[40] It should be noted that potential harm from fluorescein angiography is included in these analyses.[41-43] One case report has been published of a life-threatening adverse reaction where a 43-year old woman is described as experiencing loss of consciousness, grand mal seizure, and possible cardiopulmonary arrest two minutes after verteporfin infusion.[44]

Significant statistical heterogeneity was observed when adverse events were pooled by meta-analysis, with the exception of infusion-related back pain. This heterogeneity may have resulted from different population characteristics (e.g. visual disturbances and severe vision loss were observed with greater frequency in VIP participants) or from a learning curve in performing the procedure (e.g. photosensitivity and injection site reactions may have been reduced through proper education of treatment administrators).

Despite this, adverse events from treatment do occur, most commonly visual disturbances. Other significant adverse events include injection site events, infusion-related back pain, and photosensitivity reactions. These are consistent with randomized studies in other patient populations (e.g. pathologic myopia) and several ongoing open-label studies.[40-43,45] A single case report of a retinal pigment epithelial tear during treatment has been published but its clinical significance is not known.[46]

Severe vision loss, defined as a loss of 20 letters of visual acuity within seven days of treatment, is a significant drawback in treatment and was more commonly observed in verteporfin recipients [(TAP trials: 0.4% RD (95% CI –0.6 to 1.4); VIP trial: 4.7% RD (95% CI 1.6 to 7.8)].

This effect has been similarly observed in an ongoing open-label safety study.[43] The proportion of patients whose vision returns is unclear from these reports.

5.4 Economic Implications

As with the introduction of any new treatment, verteporfin PDT is likely to increase the number of physician visits and referrals for those with neovascular AMD. Visual acuity examinations might exclude some of those eligible for therapy, however, angiography will be necessary to determine which patients can benefit. Even the most optimistic estimates suggest that just over a third of those diagnosed with neovascular AMD will have an angiogram meeting the current criteria for treatment.[8] Costs, in part, will be incurred directly from the increased screening of potential candidates and indirectly from angiography-associated adverse events.[47] Increased accuracy of diagnosis through the interpretation of angiograms may improve overall effectiveness of the procedure by identifying those who will most benefit. Those trained to specifically recognize angiographic features of neovascular AMD may achieve better results.

Bilateral treatment, which can be performed using drug from the same injection, could arguably reduce costs of treatment. However, it would be rare for a patient to present with two eyes eligible for treatment. Because the occurrence of neovascular AMD in one eye is a risk factor for occurrence in the other eye, monitoring (and eventually treatment) is a more likely scenario. Indirect evidence from the bilateral treatment of cataracts (a procedure that, unlike verteporfin PDT, restores vision) implies this practice would be more cost-effective.[48] However, the potential for adverse reactions in both eyes (especially vision loss) suggests a clinically unacceptable risk.

We are aware of four separate cost-effectiveness analyses performed in various settings.[49-52] We have not, however, systematically reviewed the economic literature nor rated these studies for quality. All of them describe an increase in quality adjusted life years at a substantial third-party payer incremental cost.

It is evident that future research that attempts to assess the direct impact of verteporfin PDT on quality of life and visual function is needed. It is anticipated that the ongoing VIM (Verteporfin in Minimally Classic Choroidal Neovascularization due to Age-related Macular Degeneration Study) and VER (Verteporfin Early Retreatment in Predominantly Classic Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration Study) trials might assess these outcomes. The VIO (Verteporfin in Occult CNV) may also help clarify the role of verteporfin in treating those with purely occult features.[53]

6 CONCLUSION

Evidence from three high-quality RCTs suggests that, compared with placebo, verteporfin PDT treatment for two years reduces the number of cases of central blindness. However, these results apply to a study population with subfoveal neovascularization from AMD, and only a minority of these individuals is likely to qualify for treatment after diagnosis and angiographic assessment. Verteporfin PDT is likely to increase the need for angiographic screening.

Treatment is not aimed at restoring vision and the majority of treated individuals will continue to lose visual acuity. Compared to placebo (angiography and sham treatment), verteporfin did not cause an overall increase in serious adverse events and appears to be reasonably well tolerated. However, some adverse events, most commonly sudden vision loss, abnormal vision, visual defects, injection-site events and infusion-related back pain occurred with greater frequency in individuals undergoing verteporfin PDT.

The direct impact of this treatment on quality of life and visual function is not known. The two-year incremental costs for this procedure in Canada based on RCT evidence are estimated to be between $10,625 and $14,250.

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31. Arnold J, Blemenkranz M, Bressler NM, Bressler SB, Deslandes J, Donati G, et al. Photodynamic therapy of subfoveal choroidal neovascularization in age- related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials - TAP report 1 [published erratum appears in Arch Ophthalmol 2000;118:488]. **Arch Ophthalmol** 1999;117(10):1329-45.

32. Elsner H, Barbazetto I, Benecke A, Schmidt-Erfurth U. Evaluation of retinal sensitivity in photodynamic therapy using verteporfin: a two year follow-up [abstract]. AVRO Annual Meeting; 2000 Apr 30-May 5; Fort Lauderdale (FL).

33. Center for Drug Evaluation and Research, Food and Drug Administration. Medical review. In: **Visudyne (verteporfin) injection. Company: QLT Photo Therapeutics. Application no.: 21-119. Approval date: 4/12/2000**. Rockville (MD): The Center; 2001. Available: http://www.fda.gov/cder/foi/nda/2000/21-119_VISUDYNE_medr.pdf (accessed 2001 Dec 13).

34. Wormald R, Evans J, Smeeth L, Henshaw K. Photodynamic therapy for neovascular age-related macular degeneration. **Cochrane Database Syst Rev** 2001;(3):CD002030.

35. Harvey PT, Muni RH, Weaver B. Agreement among retina specialists in deciding which patients with age-related macular degeneration to treat with photodynamic therapy [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL). Program no 1642.

36. Bressler NM, Frost LA, Bressler SB, Murphy RP, Fine SL. Natural course of poorly defined choroidal neovascularization associated with macular degeneration. **Arch Ophthalmol** 1988;106(11):1537-42.

37. Stevens TS, Bressler NM, Maguire MG, Bressler SB, Fine SL, Alexander J, et al. Occult choroidal neovascularization in age-related macular degeneration. A natural history study. **Arch Ophthalmol** 1997;115(3):345-50.

38. Hazel CA, Petre KL, Armstrong RA, Benson MT, Frost NA. Visual function and subjective quality of life compared in subjects with acquired macular disease. **Invest Ophthalmol Vis Sci** 2000;41(6):1309-15.

39. McClure ME, Hart PM, Jackson AJ, Stevenson MR, Chakravarthy U. Macular degeneration: do conventional measurements of impaired visual function equate with visual disability? **Br J Ophthalmol** 2000;84(3):244-50.

40. Maestroni L, Ottochian M, Staurenghi G, Orzalesi N, VIT Study Group. Photodynamic therapy with verteporfin of predominantly classic subfoveal choroidal neovascularization secondary to age-related macular degeneration: evaluation of the efficacy and safety in the VIT study [abstract]. AVRO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL). Program no 2368.

41. Ho AC, VAM Study Group. Photodynamic therapy of subfoveal choroidal neovascularization (CNV) in age-related macular degeneration (AMD) using verteporfin: safety results from an expanded access study, the Verteporfin in Age-Related Macular Degeneration (VAM) Trial [abstract]. AVRO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL). Program no 1641.

42. Quaranta M, Bellemin B, Mauget-Faysse M, Vial T, Descotes J. Systemic adverse effects after photodynamic therapy with verteporfine [abstract]. AVRO Annual Meeting; 2002 May 5-10; Fort Lauderdale (FL).

43. Ho AC, VAM Study Group. The VAM Study: an open-label, multicenter, safety study of verteporfin therapy for predominantly classic subfoveal choroidal neovascularization (CNV) due to AMD [abstract]. AVRO Annual Meeting; 2002 May 5-10; Fort Lauderdale (FL).

44. Noffke AS, Jampol LM, Weinberg DV, Muñana A. A potentially life-threatening adverse reaction to verteporfin [letter]. **Arch Ophthalmol** 2001;119(1):143.

45. Schmidt-Erfurth U, Miller JW, Sickenberg M, Laqua H, Barbazetto I, Gragoudas ES, et al. Photodynamic therapy with verteporfin for choroidal neovascularization caused by age-related macular degeneration: results of retreatments in a phase 1 and 2 study [published erratum appears in Arch Ophthalmol 2000;118:488]. **Arch Ophthalmol** 1999;117(9):1177-87.

46. Gelisken F, Inhoffen W, Partsch M, Schneider U, Kreissig I. Retinal pigment epithelial tear after photodynamic therapy for choroidal neovascularization. **Am J Ophthalmol** 2001;131(4):518-20.

47. Kwiterovich KA, Maguire MG, Murphy RP, Schachat AP, Bressler NM, Bressler SB, et al. Frequency of adverse systemic reactions after fluorescein angiography. Results of a prospective study. **Ophthalmology** 1991;98(7):1139-42.

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49. Meads C, Moore D. **The clinical effectiveness and cost utility of photodynamic therapy for age-related macular degeneration. REP Committee draft report with amendments**. Birmingham (UK): Department of Public Health and Epidemiology, University of Birmingham; 2001. Available: www.publichealth.bham.ac.uk/wmhtac/pdf/Age_related_Macular_Degeneration.pdf.

50. Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C. **Clinical effectiveness and cost utility of photodynamic therapy for wet age-related macular degeneration**. Birmingham (UK): West Midlands Health Technology Assessment Group, University of Birmingham; 2002. Available: http://www.nice.org.uk/pdf/maculardegenerationassessmentreport.pdf.

51. Smith DH, Fenn P, Drummond M. Cost effectiveness of photodynamic therapy with verteporfin in the UK. **Value Health** 2002;5:247.

52. Sharma S, Brown GC, Brown MM, Hollands H, Shah GK. The cost-effectiveness of photodynamic therapy for fellow eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. **Ophthalmology** 2001;108(11):2051-9.

53. Securities and Exchange Commission. **Annual report persuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 for the fiscal year ended December 31, 2001. Commission File No. 0-17082: QLT Inc.** Washington: The Commission; 2002. Available: http://www.qltinc.com/Qltinc/_downloads/investment/10K-2001.pdf (accessed 2002 Nov 26).

Appendix 1: Literature Search Strategy

?	Truncation symbol, one character only
*	Truncation symbol, any number of characters
n	Near/next (i.e., terms are near/next to one another, any order)
" "	Phrase
l	Link (i.e., to subheading)
ti	Title
ab	Abstract
au	Author
de	Descriptor
dt	Publication type
tn	Trade name
mn	Manufacturer name
nd	Device name
md	Device manufacturer
rn	Registry number (i.e., CAS)
tw	Text word

DATABASES	**LIMITS**	**KEYWORDS/DESCRIPTORS**
DIALOG® EMBASE® HealthSTAR MEDLINE® PASCAL SciSearch Toxline®		EMBASE: photosensitizing agent/de OR photochemotherapy/de OR porphyrin/de OR porphyrin and porphyrin derivatives!/de OR photodynamic therapy/de OR tn=visudyne OR RN=129497-78-5 MEDLINE/HealthSTAR/Toxline: photosensitizing agents/de OR photochemotherapy/de OR porphyrins/de OR photodynamic therapy/de OR RN=129497-78-5 verteporfin OR visudyne* OR "benzoporphyrin derivative*" OR BDP/ti,ab OR BPD-MD/ti,ab OR "BPD MA"/ti,ab OR "photosensiti?ing agent*" OR photochemotherap* OR porphyrin* OR "photodynamic therap*" OR PDT/ti,ab *AND* EMBASE: subretinal neovascularization/de OR retina macula degeneration/de MEDLINE/HealthSTAR/Toxline: choroidal neovascularization/de OR macular degeneration/de "choroidal neovascularization" OR CNV/ti,ab OR "subretinal neovascularization" OR "macula? degeneration" OR AMD/ti,ab OR ARMD/ti,ab *AND* EMBASE: major clinical study/de OR prospective study/de OR controlled study!/de OR clinical trial!/de OR comparative study!/de OR

		evidence based medicine!/de OR dt=review or dt=short survey MEDLINE/HealthSTAR/Toxline: clinical trials!/de OR epidemiologic research design!/de OR evaluation studies/de OR comparative study/de OR follow-up studies/de OR prospective studies/de OR dt=review OR dt=meta-analysis OR dt=multicenter study OR dt=randomized controlled trial OR dt=controlled clinical trial OR dt=clinical trial, phase II OR dt=clinical trial, phase III OR dt=clinical trial, phase IV random* OR "single (blind* OR dumm* OR mask*)" OR "double (blind* OR dumm* OR mask*)" OR "triple (blind* OR dumm* OR mask*)" OR "treble (blind* OR dumm* OR mask*)" OR placebo* OR "meta analy*" OR metaanaly* OR "quantitative* (review* OR overview?*)" OR "systematic (review* OR overview*)" OR "methodologic* (review* OR overview*)" OR "control* clinical (study OR studies OR trial*)" OR RCT? OR "open label (study OR studies OR trial*)" OR "open-label (study OR studies OR trial*)" OR "comparative (study OR studies)" *AND* human OR people OR person? OR wom?n OR man OR men OR adult? OR elderly OR aged OR "middle(w)age?" OR middle-age? *Performed 12 June 2001* *94 unique hits* *EMBASE - 38 records* *HealthSTAR – 4 records* *MEDLINE – 46 records* *PASCAL – 5 records* *SciSearch – 1 record* *Toxline – 0 records*
PubMed		photosensitizing agents!/de OR photochemotherapy!/de OR porphyrins!/de OR photodynamic therapy!/de OR verteporfin/ti,ab OR visudyne/ti,ab OR RN=129497-78-5 *AND* macular degeneration!/de OR choroidal neovascularization!/de OR "subretinal neovascularization"/ti,ab OR "retinal macula degeneration"/ti,ab OR "macular degeneration"/ti,ab OR "choroidal neovascularization"/ti,ab OR ARMD/ti,ab OR AMD/ti,ab OR CNV/ti,ab *Performed 4 Feb 2002* *123 records*
PubMed		Economic Search: *Same MeSH and keywords as per MEDLINE, excluding clinical trial filter*

		AND economics!/de OR quality adjusted life years/de OR economic*/ti,ab OR cost/ti,ab OR costs/ti,ab OR price/ti,ab OR prices/ti,ab OR expenditure*/ti,ab OR budget*/ti,ab OR qaly*/ti,ab OR "willingness to pay*"/ti,ab *Performed 3 Apr 2002* *14 records*
The Cochrane Collaboration & Update Software Ltd. The Cochrane Library, 2002, Issue 1		*Same MeSH and keywords as per MEDLINE, excluding clinical trial filter* *The Cochrane Database of Systematic Reviews = 1 complete review; The Cochrane Controlled Trials Register = 6 references; 4 abstracts by INAHTA and other healthcare technology agencies*
OHE-IFPMA Database Ltd. HEED: Health Economic Evaluations Database May 2002		photosensiti* OR photochemotherap* OR porphyrin* OR photodynamic OR verteporfin OR visudyne OR macula* OR choroidal OR subretinal OR neovascularization OR retina OR ARMD OR AMD OR CNV *Performed 3 Apr 2002* *No records*
DIALOG® *Alerts:* ADIS LMS Drug Alerts Current Contents Search® EMBASE® Alert MEDLINE® PASCAL Pharmaceutical News Index (PNI®) SciSearch	Human *(MEDLINE only)*	*Same descriptors and keywords as per DIALOG search. Current Contents Search and SciSearch alerts discontinued 17 Aug 2001*
Websites of health technology assessment (HTA) and near-HTA agencies; clinical trial registries; other databases		NZHTA; AHRQ; National Research Register; University of York NHS Centre for Reviews and Dissemination – CRD databases; LILACS, etc.

Appendix 2: Instruments for Rating Reported Methodological Quality

Jadad Scale

RM # _____ Reviewer _____

Randomization: Total Points: ☐ 0 ☐ 1 ☐ 2

A trial reporting that it is "randomized" is to *receive one point.* Trials describing an appropriate method of randomization (table of random numbers, computer generated) *receive an additional point.* However, if the report describes the trial as randomized and uses an inappropriate method of randomization (date of birth, hospital numbers) *a point is deducted.*

Double-blinding: Total Points: ☐ 0 ☐ 1 ☐ 2

A trial reporting that is "double blind", it is to *receive one point.* Trials that describe an appropriate method of double blinding (identical placebo, active placebo) are to *receive an additional point.* However, if the report describes the trial as double blind and uses an inappropriate method (e.g., comparison of tablets versus injection with no double dummy), *a point is deducted.*

Withdrawals and dropouts: Total Points: ☐ 0 ☐ 1

A trial reporting the number and reason for withdrawals is to *receive one point*. If there is no statement, *no point* is given.

TOTAL Score ☐ Low (0-2 pts) ☐ Moderate (3-4 pts) ☐ High (5 pts)

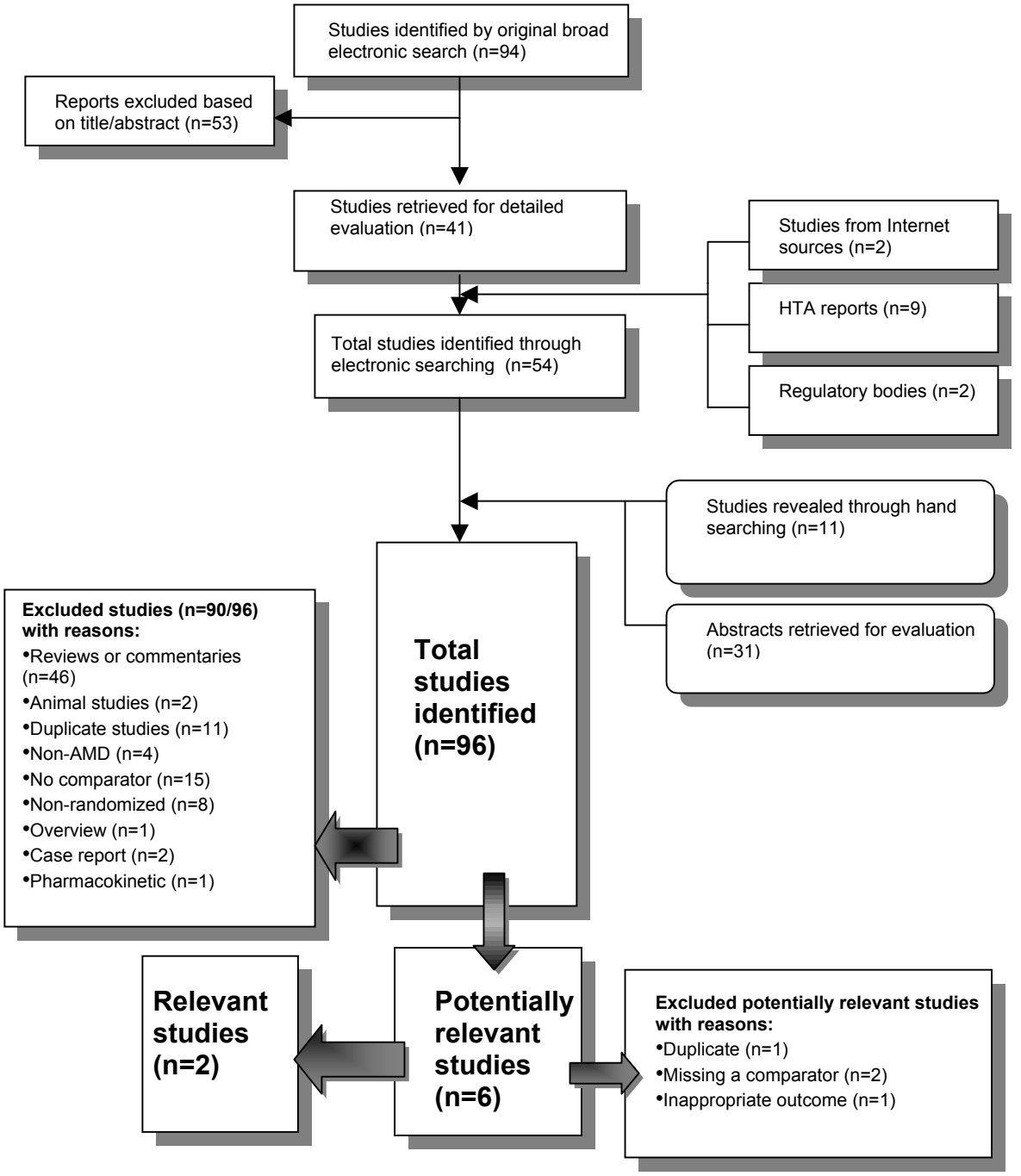
Allocation concealment

Adequate: Central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy, serially numbered, opaque, sealed envelopes, etc.
Inadequate: Alternation; reference to case record # or date of birth, etc.
Unclear: Allocation concealment approach is not reported or fits neither of the above categories.

Was treatment allocation concealed for:

Participants?	☐ Adequate	☐ Inadequate	☐ Unclear
Investigators?	☐ Adequate	☐ Inadequate	☐ Unclear
Assessors?	☐ Adequate	☐ Inadequate	☐ Unclear

Appendix 3: A Flowchart of the Inclusion/Exclusion Process



Appendix 4: Studies and Reviews Included and Excluded from Analysis with Reasons for Exclusion

Table 7: Potentially relevant studies

1	Arnold J, Barbezetto I, Birngruber R, Bressler NM, Bressler SB, Donati G, et al. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization--Verteporfin in photodynamic therapy report 2. **Am J Ophthalmol** 2001;131(5):541-60.
2	Arnold J, Blemenkranz M, Bressler NM, Bressler SB, Deslandes J, Donati G, et al. Photodynamic therapy of subfoveal choroidal neovascularization in age- related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials--TAP report 1. **Arch Ophthalmol** 1999;117(10):1329-45.
3	Arnold J, Barbazetto I, Birngruber R, Blumenkranz MS, Bressler SB, Bressler NM, et al. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials--TAP report 2. **Arch Ophthalmol** 2001;119(2):198-207.
4	Elsner H, Barbazetto I, Benecke A, Schmidt-Erfurth U. Evaluation of retinal sensitivity in photodynamic therapy using verteporfin: a two year follow-up [abstract]. ARVO Annual Meeting; 2000 Apr 30-May 5; Fort Lauderdale (FL).
5	Hager A, Schmidt-Erfurth U, Barbazetto I, Michels S, Laqua H. Photodynamische Therapie: ICG-angiographische Befunde. **Ophthalmologe** 1999;96(5):291-9.
6	Michels S, Barbazetto I, Schmidt-Erfurth U. Aderhautveränderungen nach photodynamischer Therapie (PDT). Verlaufsbeobachtungen über 2 jahre bei 38 patienten. **Klin Monatsbl Augenheilkd** 2000; 217(2):94-9.

Table 8: Studies excluded from review

1	Boyer DS, Thomas EL, Novack RL, Chu TG, Gallemore RP. Efficacy of verteporfin photodynamic therapy on laser induced choroidal neovascularizition [sic] and the ancillary effect on diabetic microvasculopathy [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	Case report
2	Bressler NM, TAP Research Group. Treatment of age-related macular degeneration with photodynamic therapy (TAP) investigation using verteporfin (BPD-MA): baseline characteristics and safety [abstract]. **Invest Ophthalmol Vis Sci** 1998; 39(4):S242.	Duplicate (TAP)
3	Bressler NM, Tap Study Group. Photodynamic therapy with verteporfin of subfoveal choroidal neovascularization in age-related macular degeneration (AMD): baseline characteristics and safety in the TAP randomized clinical trials [abstract]. **Invest Ophthalmol Vis Sci** 1999; 40(4):S401.	Duplicate (TAP)
4	Bressler NM, Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin: 1-year results of a randomized clinical trial--VIP report no. 1. **Ophthalmology** 2001;108(5):841-52.	Duplicate (VIP)
5	Bressler SB, Tap Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration using verteporfin (Visudyne): two-year results or 2 randomized clinical trials–TAP report #5 [abstract]. ARVO Annual Meeting; 2000 Apr 30-May 5; Fort Lauderdale (FL).	Duplicate (TAP)
6	Bunse A, Bock M, Lorenz B, Gabel VP. Photodynamic therapy in age-related macular degeneration: functional results [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	No comparator
7	Busbee BG, Sivalingam A, Abraham P, Reichel E. Photodynamic therapy after conversion from occult to classic choroidal neovascularization following transpupillary thermotherapy [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	Non-randomized

8	Busquets MA, Wickens J, Shah G, Blinder KJ, Burgess D, Grand MG, et al. Photodynamic therapy for subfoveal CNV in ocular histoplasmosis [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	Non-AMD
9	Copt RP, Zografos L. Retinal pigment epithelial tear after photodynamic therapy for choroidal neovascularization caused by age-related macular degeneration [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	Case Report
10	Coupland SG, Leonard BC, Kertes PJ. Effect of photodynamic therapy of subfoveal choroidal neovascularisation (CNV) on the multifocal electroretinogram [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	No comparator
11	Gelisken F, Inhoffen W, Partsch M, Schneider U, Kreissig I. Retinal pigment epithelial tear after photodynamic therapy for choroidal neovascularization. **Am J Ophthalmol** 2001;131(4):518-20.	Case Report
12	Gerosa F, Zanchi S, Ottochian M, Maestroni L, Massacesi AL, Orzalesi N. Microperimetry and reading performance after photodynamic therapy (PDT) for subfoveal choroidal neovascularization: short term results [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	No comparator
13	Greenberg PB, Rogers A, Martidis A, Duker JS, Puliafito CA. Photodynamic therapy with verteporfin for choroidal neovascularization due to angioid streaks [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	Non-AMD
14	Hassenstein AP, Schwartz R, Richard G. Follow-up of subfoveal classic choroidal neovascularization (CNV) after photodynamic therapy (PDT) by optical coherence tomography (OCT) [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	No comparator
15	Ho AC, VAM Study Group. Photodynamic therapy of subfoveal choroidal neovascularization (CNV) in age-related macular degeneration (AMD) using verteporfin: safety results from an expanded access study, the Verteporfin in Age-Related Macular Degeneration (VAM) Trial [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	No comparator
16	Houle J, Bain S, Azab M, Strong A. Clinical pharmacokinetics of verteporfin in healthy volunteers and patients with CNV [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	Pharmacokinetic Study
17	Husain D, Kramer M, Kenny AG, Michaud N, Flotte TJ, Gragoudas ES, et al. Effects of photodynamic therapy using verteporfin on experimental choroidal neovascularization and normal retina and choroid up to 7 weeks after treatment. **Invest Ophthalmol Vis Sci** 1999;40(10):2322-31.	Animal Study
18	Kallmark FP, Carle-Petrelius B. CNV-treatment with PDT [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	No comparator
19	Lewis H, Tap Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration using verteporfin (Visudyne): impact of lesion component on one-year visual outcomes--TAP report #2 [abstract]. ARVO Annual Meeting; 2000 Apr 30-May 5; Fort Lauderdale (FL).	Duplicate (TAP)
20	Lim JI, VIP Study Group. Photodynamic therapy of subfoveal choroidal neovascularization (CNV) in pathologic myopia using verteporfin: two-year results--VIP report #4 [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	Duplicate (VIP)
21	Lommatzsch A, Radermacher M, Spital G, Pauleikhoff D. Photodynamic therapy of pigment epithelium detachments in AMD [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	Non-randomized
22	Maestroni L, Ottochian M, Staurenghi G, Orzalesi N, VIT Study Group. Photodynamic therapy with verteporfin of predominantly classic subfoveal choroidal neovascularization secondary to age-related macular degeneration: evaluation of the efficacy and safety in the VIT study [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	No comparator
23	Meirelles RL, Nogueira R, Costa R, Oshima A, Belfort R, Farah ME. Assessing visual function and quality of life in patients with subfoveal choroidal neovascular membranes treated with photodynamic therapy with verteporfin [sic] [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	No comparator
24	Menchini U, Virgili G, Varano M, Pirracchio A, Stirpe M, Schmidt-Erfurth U. Photodynamic therapy of myopic macular degeneration: short term results in a clinical setting [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	Non-AMD

25	Meredith TA, VIP Study Group. Photodynamic therapy of subfoveal choroidal neovascularization (CNV) in age-related macular degeneration (AMD) using verteporfin: two-year results--VIP report #5 [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	Duplicate (VIP)
26	Michels SM, Schmidt-Erfurth U. Early vascular changes induced by photodynamic therapy using verteporfin [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	Non-randomized
27	Miller JW, Schmidt-Erfurth U, Sickenberg M, Pournaras CJ, Laqua H, Barbazetto I, et al. Photodynamic therapy with verteporfin for choroidal neovascularization caused by age-related macular degeneration: results of a single treatment in a phase 1 and 2 study. **Arch Ophthalmol** 1999; 117(9):1161-73.	Non-randomized
28	Mones J, VIP Study Group. Photodynamic therapy (PDT) with verteporfin of the subfoveal choroidal neovascularization in age-related macular degeneration: study design and baseline characteristics in the VIP randomized clinical trial [abstract]. **Invest Ophthalmol Vis Sci** 1999;40(4):S321.	Duplicate (VIP)
29	Noffke AS, Jampol LM, Weinberg DV, Muñana A. A potentially life-threatening adverse reaction to verteporfin [letter]. **Arch Ophthalmol** 2001;119(1):143.	Case Report
30	Palmowski AM, Allgayer R, Heinemann-Vernaleken B, Ruprecht KW. The influence of photodynamic therapy (PDT) in choroidal neovascularisation (CNV) on focal retinal function assessed with the multifocal-ERG (MF-ERG) and perimetry (Octopus d32) [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	No comparator
31	Piermarocchi S, Bertoja E, Giudice GL, Sartore M, Segato T, Midena E, et al. Photodynamic therapy (PDT) increases the eligibility for feeder vessel (FV) treatment of choroidal neovascularization (CNV) due to age-related macular degeneration (ARMD) [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	No comparator
32	Pruente C, Schroeder B, Frei J. Multifocal electroretinography after photodynamic therapy in age-related macular degeneration [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	No comparator
33	Rogers AH, Martidis A, Greenberg PB, Truong SN, Puliafito CA. Optical coherence tomography of subfoveal choroidal neovascularization treated with photodynamic therapy [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	Non-randomized
34	Schmidt-Erfurth U, Miller J, Sickenberg M, Strong A, Hoehne U, Fsadni M, et al. Photodynamic therapy of subfoveal choroidal neovascularization using benzoporphyrin derivative: first results of multicentre trial [abstract]. **Invest Ophthalmol Vis Sci** 1996;37(3):122.	No comparator
35	Schmidt-Erfurth U, Miller J, Sickenberg M, Bunse A, Laqua H, Gragoudas E, et al. Photodynamic therapy of subfoveal choroidal neovascularization: clinical and angiographic examples. **Graefes Arch Clin Exp Ophthalmol** 1998;236(5):365-74.	No comparator
36	Schmidt-Erfurth U, Miller JW, Sickenberg M, Laqua H, Barbazetto I, Gragoudas ES, et al. Photodynamic therapy with verteporfin for choroidal neovascularization caused by age-related macular degeneration: results of retreatments in a phase 1 and 2 study. **Arch Ophthalmol** 1999;117(9):1177-87.	Non-randomized
37	Schmidt-Erfurth UM, Niemeyer M, Michels S, Birngruber R, Laqua H. Three-dimensional imaging of dynamic and structural vascular changes induced by photodynamic therapy [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	No comparator
38	Sickenberg M, Schmidt-Erfurth U, Miller JW, Pournaras CJ, Zografos L, Piguet B, et al. A preliminary study of photodynamic therapy using verteporfin for choroidal neovascularization in pathologic myopia, ocular histoplasmosis syndrome, angioid streaks, and idiopathic causes. **Arch Ophthalmol** 2000;118(3):327-36.	Non-randomized
39	Singerman L, Tap Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration using verteporfin (Visudyne): exploratory analysis of good visual outcomes--TAP report #4 [abstract]. ARVO Annual Meeting; 2000 Apr 30-May 5; Fort Lauderdale (FL).	Duplicate (TAP)
40	Slakter J, VIP Research Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin: study design and baseline characteristics in the VIP randomized clinical trial [abstract]. **Invest Ophthalmol Vis Sci** 1999;40(4):S401.	Duplicate (VIP)

41	Stur M, VER Study Group. Rationale for and design of the Visudyne in Early Retreatment (VER) trial [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	Study Overview
42	Turnbull RG, Chen JC, Labow RS, Margaron P, Hsiang YN. Benzoporphyrin derivative monacid ring A (Verteporfin) alone has no inhibitory effect on intimal hyperplasia: in vitro and in vivo results. **J Invest Surg** 2000;13(3):153-9.	Animal Study
43	Wickens JC, Busquets MA, Shah G, Blinder KJ, Burgess D, Grand MG, et al. Photodynamic therapy for subfoveal CNV in myopic degeneration [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	Non-randomized
44	Zanchi S, Gerosa F, Massacesi AL, Staurenghi G, Orzalesi N. Early anatomical outcome in different types of subfoveal choroidal neovascularization treated with photodynamic therapy [abstract]. ARVO Annual Meeting; 2001 Apr 29-May 4; Fort Lauderdale (FL).	No comparator

Appendix 5: Quality Assessment of Included Studies

Study	Method of Randomization		Was Treatment Allocation Concealment Blinded for:			ITT* Analysis?	Jadad Score (Maximum = 5)
	Described?	Appropriate?	Participants?	Investigators?	Assessors?		
TAP-2	Yes†	Yes	Yes	Yes	Yes	Yes	5
VIP-2	Yes	Yes	Yes	Yes	Yes	Yes	5

* Intention-to-Treat

† Methods not described in the document but available from excluded, duplicate sources.

Appendix 6: Description of TAP and VIP Trials

Treatment of Age-related Macular Degeneration with Photodynamic (TAP) Investigation Using Verteporfin

The TAP investigation consisted of two concurrent randomized, placebo-controlled and double-blinded trials (TAP-A and TAP-B) that used identical protocols. These were designed to demonstrate the efficacy of verteporfin PDT compared to placebo (angiography plus sham therapy) in limiting the decrease in visual acuity in patients with subfoveal CNV due to AMD. Inclusion and exclusion criteria for participants in this trial are listed below (Table 9).

Table 9: Inclusion and exclusion criteria used in the TAP trials

Inclusion Criteria
Evidence of classic CNV on fluorescein angiography
New or recurrent subfoveal CNV lesions secondary to AMD Evidence of the extent of CNV under the geometric centre of the foveal avascular zone upon angiography
Male or female 50 years of age or older
The area of classic plus occult CNV must be at least 50% of the area of the total neovascular lesion
The greatest linear dimension of the entire lesion must be less than or equal to 5,400 μm
The best-corrected visual acuity in the study eye was 34 to 73 letters
The study participant must be willing and able to provide informed consent
Exclusion Criteria
Tear (rip) of retinal pigment epithelium
Any significant ocular disease (other than CNV) that has compromised or could compromise vision in the study eye and confound analysis of the primary outcome
Inability to obtain photographs to document CNV, including difficulty with venous access
History of treatment of CNV in study eye other than nonfoveal confluent laser photocoagulation
Participation in ophthalmic clinical trial or use of any other investigational new drugs within 12 weeks prior to the start of study treatment
Active hepatitis or clinically significant liver disease
Intraocular surgery within last two months or capsulotomy within last month in study eye

Participants (n=609) in Europe and North America were randomized to either verteporfin or placebo. They were telephoned within two to four days after treatment to determine if adverse events had occurred. Participants were scheduled to return approximately three months after each treatment where a protocol refraction, best-corrected visual acuity measurement, contrast threshold measurement, ophthalmoscopic examination, steroscopic color fundus photograph, and fluorescein angiography were performed in both eyes before retreatment. Retreatment was recommended to the participant if leakage was noted by the investigator.

The primary outcome for this study was the proportion of eyes that lost fewer than 15 letters compared with a baseline visual acuity examination using an EDTRS chart (approximately <3 lines of visual acuity loss). Secondary outcomes included the

proportion of eyes that lost fewer than 30 letters compared with a baseline visual acuity examination, the proportion of eyes with visual acuity less than 34 letters (i.e. <20/200), the time to moderate or severe decrease of visual acuity (i.e. ≥ 15 or 30 letters respectively), and the mean change from baseline of visual acuity. Other secondary efficacy outcomes were angiographic outcomes.

Information about these trials is available from two published reports,[27,30] several abstracts,[32-36] and regulatory information.[37,38]

Verteporfin in Photodynamic Therapy (VIP)

The VIP study was a randomized, placebo-controlled, double-blinded study of verteporfin PDT in 459 patients with a diagnosis of new subfoveal CNV secondary to AMD (n=339) or subfoveal CNV secondary to pathologic myopia (PM, n=120). The randomization was stratified by clinical population and separate reports of the impact on each disease state were subsequently published. For patients with new subfoveal CNV secondary to AMD, the inclusion and exclusion criteria described in Table 10 were used:

Table 10: Inclusion and exclusion criteria used in the VIP investigation

Inclusion Criteria
New subfoveal CNV lesions secondary to AMD with evidence of the extent of CNV under the geometric centre of the foveal avascular zone upon angiography
If evidence of occult CNV without classic CNV, then visual or anatomical evidence of disease progression within last three months
If evidence of classic CNV, then a best-corrected visual acuity letter score must be more than 70 letters
The area of occult plus classic features must be at least 50% of the area of the total neovascular lesion
The greatest linear dimension of the entire lesion must be less than or equal to 5,400 μm
The best-corrected visual acuity in the study eye was 50 letters or more
The study participant must be willing and able to provide informed consent
Exclusion Criteria
Tear (rip) of retinal pigment epithelium
Any significant ocular disease (other than CNV) that has compromised or could compromise vision in the study eye and confound analysis of the primary outcome
Inability to obtain photographs to document CNV, including difficulty with venous access
History of treatment of CNV in study eye other than nonfoveal confluent laser photocoagulation
Participation in ophthalmic clinical trial or use of any other investigational new drugs within 12 weeks prior to the start of study treatment
Active hepatitis or clinically significant liver disease
Intraocular surgery within last two months or capsulotomy within last month in study eye
Prior PDT for CNV
Features of any condition associated with CNV (other than AMD) in study eye
Porphyria or porphyrin sensitivity

Participants were randomized to either verteporfin or placebo treatment. They were telephoned within two to four days after treatment to determine if adverse events had occurred. Participants were scheduled to return approximately three months after each treatment where a best-corrected visual acuity measurement, contrast threshold measurement, ophthalmoscopic examination, steroscopic color fundus photograph, and fluorescein angiography were performed in both eyes before retreatment. Retreatment was recommended to the participant if leakage was noted by the investigator.

The primary outcome for this study was the proportion of eyes that had lost fewer than 15 letters. Secondary outcomes were the same as for the TAP investigation.

Information from this trial is available from two published reports,[26,42] regulatory information,[37] and several abstracts.[43]

Appendix 7: Frequency of Adverse Events

	TAP		VIP		Total	
	V n=402	P n=207	V n=225	P n=114	Verteporfin (n=627)	Placebo (n=321)
Visual Disturbance						
Visual Loss	41	13	67	15	108	28
Abnormal Vision	58	24	46	14	104	38
Visual Field Defect	24	7	34	8	58	15
Total	123	44	147	37	270/627 **(43.1%)**	81/321 **(25.2%)**
Injection Site Event						
Discoloration	2	0	2	0	4	0
Edema	26	1	7	0	33	1
Extravasation	25	6	12	4	37	10
Hemorrhage	9	4	1	0	10	4
Hypersensitivity	7	0	2	1	9	1
Inflammation	12	1	5	1	17	2
Pain	44	1	10	1	54	2
Total	125	13	39	7	164/627 **(26.2%)**	20/321 **(6.2%)**
Infusion related Back Pain	10	0	5	0	15/627 **(2.4%)**	0/321 **(0.0%)**
Severe Vision Loss	2	0	11	0	13/627 **(2.1%)**	0/321 **(0.0%)**
Photosensitivity Reaction	14	0	1	1	15/627 **(2.4%)**	1/321 **(0.3%)**