SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Visudyne. This scientific discussion has been updated until 1 December 2003. For information on changes after this date please refer to module 8B.

1. Introduction

Visudyne contains a new active substance, verteporfin INN, a benzoporphyrin derivative, which is a photosensitiser (i.e. light-activated) molecule developed for photodynamic therapy (PDT) with visible light. Visudyne was initially indicated for the treatment of patients with predominantly classic subfoveal choroidal neovascularisation due to age-related macular degeneration (AMD), which was later extended through a Type II variation to subfoveal choroidal neovascularisation secondary to pathological myopia (PM). A further Type II variation extended the indication to the treatment of patients with age-related macular degeneration with occult subfoveal choroidal neovascularisation with evidence of recent or ongoing disease progression.

Verteporfin has also been studied in other therapeutic areas (psoriasis and malignant cutaneous lesions), however, these indications are not claimed in this application.

AMD is a degenerative eye disease with increasing prevalence in old age. It causes severe loss of vision and is the most common cause of severe irreversible loss of vision in elderly subjects in industrialised countries. PM is a similar degenerative eye disease that occurs in myopic patients of younger age.

The central retina around the fovea has a very high metabolic turnover and in some patients the efficiency of recycling metabolic waste fails, with deposition of abnormal material in the retina and breakdown of tissue integrity. Two forms of AMD are known:

1. The "dry" form of the disease, which is the most frequent form, characterised by atrophic changes in the retinal pigment epithelium (RPE).
2. The “neovascular” form occurring in approximately 10 % of AMD patients. It is the more aggressive form of the disease responsible for 90 % of severe vision loss from AMD. Also known as the ‘wet’ or exudative form, this form is characterised by CNV when aberrant blood vessels grow into the fovea from the choroid beneath. These newly-formed blood vessels may leak fluid, lipid and blood, and may form a disciform scar which permanently damages the fovea. The neovascular type of AMD usually progresses in extent and character, from a localised submacular process consisting of delicate new vessels through an intermediate phase with serous exudation and haemorrhage to an end-stage with an involuted fibrous membrane underlying the entire macula with complete or near-complete loss of vision. Overall, it has been estimated that 70 % of eyes with CNV will have severe loss of vision within two years from diagnosis.

The general mechanism of PDT with porphyrins is the release of cytotoxic species (such as the highly reactive short-lived ‘singlet oxygen’). These species are generated in situ, on exposure to visible light energy. In this specific case in the context of CNV, the cytotoxic effect damages endothelial cells, ultimately resulting in localised vascular occlusion of the CNV. It is proposed that this selective occlusion of leaking blood vessels results in stabilisation of vision, or reduction in the rate of vision loss.

Current therapeutic strategies for neovascular AMD are few, and include Thermal Laser Photocoagulation, submacular surgery, radiotherapy or interferon alfa 2a. Of these, Laser photocoagulation is the only clinically-proven treatment available for the wet or exudative form of AMD characterised by CNV, but the prevalence of recurrence in the two main subgroups of CNV is in the region of 50 – 80% and furthermore only 15% of patients are considered eligible for laser treatment. Therefore, exudative AMD could be regarded as an intractable disease with a need for alternative treatments, which can control CNV whilst not affecting the surrounding and overlying tissues.

Visudyne is a lyophilised powder, which is reconstituted to a liposomal solution and given by intravenous infusion. The product has been co-developed by Novartis Ophtalmicis AG (formerly CibaVision AG), Switzerland and QLT Inc. (formerly QLT Phototherapeutics Inc.), Canada.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

The composition of this product is complex. Due to the very low solubility of the active substance, a lipid-based system is employed, consisting chiefly of phosphatidylglycerol (egg) and dimyristoylphosphatidylcholine, with antioxidants buylated hydroxytoluene and ascorbyl palmitate. Lactose is added to adjust osmolarity and to protect the system during the lyophilisation process.

The product is presented as a freeze-dried powder, 15 mg verteporfin per glass vial, to be reconstituted into solution as a concentrate, then diluted for infusion in accordance with the SPC to give a recommended dose of 6 mg/m^2 in 30 ml of infusion solution.

Active substance

Verteporfin INN is a semisynthetic mixture of porphyrins also known as Benzporphyrin Derivative Monoacid Ring A (BPD-MA). It consists of an equimolar mixture of the regioisomers BPD-MA$_C$ & BPD-MA$_D$ and each regioisomer is a racemate of two isomers. It exists as a dark green-to-black solid, insoluble in water, and is produced from porcine hemin as a starting material. The ability of the manufacturing process to remove or inactivate animal-derived pathogens has been investigated in a number of viral safety studies and the process has been shown to be acceptably safe from a virological point of view.

Verteporfin has been characterised by a range of physicochemical methods and the specification includes tests with satisfactory limits for assay, regioisomer ratio, related impurities etc, as well as microbiological tests including bacterial endotoxins.

A number of related impurities has been identified and quantified by means of HPLC. The pharmacodynamic activity of each is uncertain, but the impurity specification is considered justified with reference to material used in animal toxicology studies.

Stability of verteporfin has been shown by studies on 7 batches using validated stability-indicating methods. A photostability study according to the ICH guideline indicates that the storage containers give adequate protection, and in general the results support storage at –20^{o}C during the retest period following batch release.

Other ingredients

The composition includes a number of phospholipids, antioxidants and lactose PhEur.

Since some of these may have an animal origin, their microbiological status is important. Their potential to transmit animal-derived pathogens has been investigated in a number of viral safety studies, and they have been shown to be acceptably safe.

Product development and finished product

A lipid-based formulation is reasonable for this insoluble active substance. It is also proposed that lipid binding may be relevant with regard to this indication, as low-density lipoprotein (LDL) receptors are abundant in neovascular tissue. Unlike some liposomal systems, liposome size in this case does not appear to be critical with regard to specific ‘targetting’ and disposition. Selectivity in this indication (and PDT in general) is also related to the performance characteristics of the light irradiation system, shape of lesion vs. shape of light beam etc.

This complex formulation cannot be autoclaved, and sterilisation by means of filtration is reasonable in this case.

The manufacturing process involves mixing and evaporating the ingredients from dichloromethane to form an intermediate product (‘presomes’). Lactose is added in a hydration and size reduction process, followed by a pre-filtration step, two 0.22 micron sterile filtration steps, aseptic filling and lyophilisation. This process has been validated in a satisfactory way.

The specification includes tests for assay, related substances with limits slightly increased compared to the active substance, osmolality, antioxidant content, uniformity of content etc. The average size of the liposomes is less than 100nm and there are also tests for particulate matter above 10 microns, pyrogens and sterility.

Batch analyses (n=3) indicate satisfactory compliance with specification.

Stability of the product

Stability data have been generated from 6 small-scale batches, and no significant degradation has been observed during the conditions of study (25°C/60%RH, 30°C/60%RH, 40°C/75%RH.)

Temperature cycling and photostability studies have also been performed and no significant changes were recorded. The results indicate a stable product that needs no special storage requirements, although storage in the original outer carton is recommended (to protect from light), for the period defined in the SPC.

Stability studies after reconstitution of product one year old indicate a storage time of 4h would be acceptable for the reconstituted product.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

The general mechanism of PDT with porphyrins is the release of cytotoxic reactive oxygen species like free radicals and singlet oxygen. These molecules are generated in situ when certain porphyrins are exposed to visible light, in variable amounts depending on the quantum yield.

The quantum yield for singlet oxygen production from verteporfin is 0.78, i.e. 8 of 10 photons that are absorbed produce singlet oxygen. It can be calculated that 500,000 singlet oxygen molecules are produced by a verteporfin molecule in one second. Singlet oxygen can react directly with proteins, lipids and nucleic acids, generating products that can subsequently initiate the production of free radicals leading to auto-oxidation and breakdown of these molecules.

A photosensitizer can be activated with light at any wavelength within its absorption spectrum. The optical absorption spectrum of verteporfin is shown in Figure I. The action spectrum of verteporfin is known to follow its absorption spectrum in vitro, however in vivo, red light because of its deeper penetration, is more effective. Oxyhemoglobin has minimal absorption at the maximal absorption peak of verteporfin (689 nm), it will therefore interfere minimally with verteporfin activation at this wavelength. Therefore, 685-693 nm (red) light is the wavelength range of choice for applications in which hemoglobin could attenuate the effect. This wavelength range has been chosen for PDT in AMD and PM, and has been shown to be safe for the retina.

In vivo studies with animal tumour models demonstrated that the association of verteporfin with plasma lipoproteins enhances its photodynamic cytotoxicity. LDL receptors are present on tumour cells and endothelial cells and may be involved in the uptake of lipoprotein bound verteporfin by these cells. Moreover, morphological studies have shown the occurrence of early vascular damage consisting of congestion, stasis and haemorrhage in PDT-treated tumours and normal tissues.

A General Pharmacological Study of verteporfin was performed and did not show any effects on the CNS system in mice at doses up to 20 mg/kg. Furthermore, no marked changes were observed in the respiratory and cardiovascular system in anesthetized rabbits after intravenous administration of L-BPD-MA at 0.2, 2 and 20 mg/kg. Intravenous administration of L-BPD-MA at 0.2, 2 and 20 mg/kg did not induce any effects on the gastrointestinal or renal system in rats.

Pharmacokinetics

In vitro studies showed that verteporfin was metabolised to a ‘diacid’ metabolite by human liver S9 and human liver microsomes (HLM). The amounts of the diacid increased linearly with time, however, the formation of the diacid could only account for approximately 60% of the parent regioisomers in incubations with S9. The results suggest that the parent compound is metabolised further to unknown metabolites.

After iv administration the primary metabolic pathway is esterase hydrolysis. The end product of hydrolysing BPD-MA_C and BPD-MA_D is considered to be the same, a common diacid resulting from

the removal of the methyl group linked to C or D respectively. Excretion is mainly in the bile and with the faeces, as would be expected for highly lipophilic molecules with a relatively high molecular weight.

In rats given radiolabelled verteporfin, some 90% of the radioactivity is recovered in the faeces following i.v. administration, with approximately 3.5% of the radioactivity retained in the carcass on day 7 post dose. Since the proposed patient treatment is a single dose, the low level retained in the carcass for a period of days is not a cause for concern. Further identification of the composition of the 90% recovered radioactivity is difficult since endogenous porphyrins and their metabolites occur in faeces in both rat and man. The identification of porphyrin metabolites in faeces is further complicated by the action of bacterial flora, which can either synthesise various porphyrins de novo or metabolise porphyrins present in gut contents.

In summary, animal pharmacokinetic studies have demonstrated plasma lipoprotein affinity. The substance is primarily excreted in bile with a half-life below 5 hours in dogs and monkeys. The substance concentrates in dividing cells and tumors, however only very low levels of radioactivity were observed in the testes, indicating that this organ should not have a high potential for phototoxicity. Similarly low levels were found in the skin, although in pigs dermal phototoxicity appears to correlate with plasma levels rather than dermal tissue levels.

Toxicology

Single dose toxicity

The results of single dose toxicity studies in rats and dogs show that the primary findings were skin lesions, damage to subcutaneous tissue and muscles. The extent and severity was dose related to both verteporfin and light. The dog was the most sensitive species with a NOEL of 0.1 mg/kg at 50 J/cm^2

Repeated dose toxicity

Repeated administration i.v. to rats and dogs indicated similar findings to the above single dose studies.

Treatment resulted in dose-related damage to skin, subcutaneous tissue and muscle at the irradiation site in the absence of any indication of systemic effects. In the rat, where the dose levels of verteporfin were higher, the local effects at the irradation sites were accompanied by haematological changes. Haemolysis occurring at the higher dose levels was accompanied by increased spleen weight, moderate increase in extramedullary haematopoiesis in spleen, slight to moderate erythroid hyperplasia of bone marrow and minimal extramedullary haematopoiesis in the liver. In dogs daily administration in 2 weeks of 10 and 20 mg/kg resulted in perivascular neutrophilic infiltrate in the liver, interstitial nephritis and increased renal tubular basophilia together with increased erythropoiesis in bone marrow. Increased haematopoiesis in the spleen was observed in all groups except the sham injected control animals, i.e including the control animals receiving the placebo lipid based formulation. The classes of lipids used as excipients in Visudyne are known to be haemolytic at appropriate concentrations.

A 14-day study in rats in the absence of light irradiation resulted in mild extravascular haemolysis with increased bilirubin and enhanced haematopoietic response. High dose animals were dosed with undiluted lipid based verteporfin, while low dose groups received lipid based formulation which had been diluted with 5% dextrose. Control animals received 5% dextrose.

The toxicity observed in a 28-day study, without irradiation, in rats was qualitatively similar in nature to the findings in the 14-day study, but with pigment accumulation in the kidney and liver at the higher doses. The haemolysis and associated findings were related to the verteporfin dose and, as in the 14-day study, to the excipient concentration.

A major consistent finding in repeated dose studies of the formulation with or without verteporfin is haemolysis and regenerative haematopoesis.

Update arising from Type II Variation (II/01):

Anaesthetised pigs receiving a bolus injection of verteporfin have been found to show severe cardiovascular / haemodynamic effects with some fatalities after rapid or slow IV injection – a finding not observed in conscious pigs. These cardiovascular events were prevented by an antihistaminic drug (diphenhydramine) and were interpreted as an anaphylactoid reaction to verteporfin in conjunction with anaesthesia, possibly due to the rapid activation of Complement. In addition, a study in four young Landrace-Yorkshire pigs which received repeated IV injections of verteporfin at 2 mg/kg shows that two formulations of verteporfin and a placebo can all induce symptoms such as patchy red skin, decreased and weakened heartbeat, and problems with breathing culminating in apnoea which are consistent with those of an anaphylactic/anaphylactoid reaction caused by Complement activation. This study again suggests that pigs in particular are highly sensitive to this phenomenon. The study was performed under conditions of administration similar to those in humans but it may be regarded as a pilot study, which does not allow any firm quantitative conclusions. The clinical relevance of these results in humans is therefore not clear. An *in vitro* study carried out on human blood shows that verteporfin is able to activate the Complement system in humans (although no direct evidence of this was observed in the clinical studies).

Skin phototoxicity

Severe skin phototoxicity was demonstrated in mice exposed to whole-body light irradiation 3 hr after 10 or 20 mg/kg verteporfin, with no effect at a dose of 2 mg/kg. Whole-body irradiation 24 and 48 hr after verteporfin dosing did not elicit skin reactions.

In a study in pigs, the species usually considered to be the most appropriate model for human skin, the strongest skin reactions were observed within the first 45 minutes with 0.5 mg/kg lipid-based verteporfin and exposure to 100 J/cm^2 of light, at exposure to 50 J/cm^2 in the first 30 minutes and at 25 J/cm^2 only observed at 0 and 15 minute timepoints. The pharmacokinetic data from this study suggest that early development of phototoxicity correlates with plasma verteporfin levels.

In a study, which can be described as a phototoxicity tolerance study, albino rabbits were exposed to 14 PDT treatments at weekly intervals. The verteporfin dose was 0.5 mg/kg, which was followed with whole body exposure to 40% and 80% of the minimum erythematous light dose. Controls received no treatment or were treated with light only. The animals were sacrificed 16 weeks after the last PDT treatment. There were no significant differences between control and experimental groups in a wide range of parameters

Ocular Effects

The safety of single and multiple verteporfin and light treatments in the eye was investigated in studies in rabbits and monkeys in which laser light was used to activate verteporfin. These studies consistently and reproducibly demonstrated that the degree of damage caused by verteporfin PDT is dependent on drug dose, light dose and timing of photoactivation. Clearly the correct timing of infusion and light activation is very important in determining the necessary selectivity in therapy, whereby neovascular lesions are occluded but surrounding normal tissue is not damaged. The clinical timings involved in Visudyne PDT were based on the findings in these rabbit and monkey studies. In the rabbit studies, pigmented and albino strains were used. No differences were seen in the responses in pigmented and non-pigmented eyes. Sensitivity to light following verteporfin administration was investigated in dogs exposed to sunlight at 1 to 4 days after drug infusion. No evidence of retinal or other ocular toxicity was observed.

Genotoxicity

The mutagenic potential of verteporfin in the absence and presence of light irradiation was studied in four in vitro studies and one in vivo study. The source of light used in the in vitro studies was white fluorescent lighting. Due to the low solubility of the substance the actual exposure of the cells studied is not known. However, cytotoxicity taken as indicator of exposure was demonstrated at high doses.

In all bacterial strains without light irradiation and the Salmonella strains with light irradiation (1.04 J/M2) revertant frequencies were not increased over controls while in WP2uvrA, approximately 2 fold increases compared to control values were seen in the presence of light irradiation at doses of 15.4 and 46.1 µg/plate without S9.

In CHO cells 0.1μg/ml verteporfin with 0, 105, 210, 315, 420, 525 and 630 J/m^2 light exposures did not increase mutant frequency.

Cells treated with f 0.09μg/ml and 360 J/m^2 produced a 43% reduction in relative cell growth in the 36-hour harvest while the activated 3.7μg/ml irradiated with 300 J/m^2 produced a 54% reduction in cell growth in the 30-hour harvest. No statistically significant differences in chromosome aberrations were found between treated and control groups.

Control groups were not light activated.

In the in vivo micronucleus assay, mice that were irradiated with light were exposed to whole-body irradiation with simulated sunlight. The solvent for verteporfin in the *in vitro* assays was aqueous DMSO; verteporfin was administered as Visudyne in the micronucleus assay. All of the studies were GLP-compliant and, where appropriate, procedures were performed in subdued light.

Verteporfin (0.01 μg/ml with 0-5000 J/m^2) did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes.

A micronucleus study was performed in mice with a single i.v. dose of 2, 5 or 10 mg/kg verteporfin. The animals were maintained in subdued light for 3 hr and then treated with approximately 90 J/cm^2 of light irradiation. Animals, which received 10 mg/kg with light showed clear evidence of phototoxicity with loss of weight, dermal lesions and death.

At the 24-hr sampling, a marginally significant increase ($p=0.044$) was observed in the number of micronucleated PCEs in the verteporfin groups treated with light irradiation.

At the 48-hr sampling, the mid and high dose group values were statistically different in comparison to solvent control group values, as statistically significant dose trend was also observed. The number of micronucleated PCEs in the mid and high dose groups, however, was 1.0 per 1000 PCEs, a value within the range of concurrent solvent control group values.

At the 72-hr sampling there was no significant dose response trend and no statistically significant differences in the number of micronucleated PCEs in the treated groups versus the light-irradiated groups.

Concerning genotoxicity, it must be mentioned that a genotoxic effect may be expected in general, considering the mechanism of action of PDT itself and the generation of reactive oxygen species which are known to be genotoxic. However, this is a function of drug concentration and disposition and irradiation energy and time. Furthermore, verteporfin concentrates in the membrane and cytoplasm of cells rather than in the nucleus. Since the diffusion path length of singlet oxygen is extremely short, its effect on cellular structures is confined to the cytoplasmic region where verteporfin is localised. Therefore, a direct effect of verteporfin on DNA is not expected in this particular case.

Carcinogenicity

The CPMP accepts that verteporfin is essentially a single dose therapy in the context of this clinical indication, and it is not necessary to evaluate carcinogenic potential in life-span rodent studies.

Reproduction Toxicity

The effects of verteporfin on reproduction were evaluated in standard 3 segment, GLP-compliant studies. Animals were maintained in lighting conditions at intensities below 20 foot-candles.

In a fertility and general reproduction study in rats the dose levels were 1, 3 or 10 mg/kg/day of verteporfin as Visudyne.

In the rat teratogenicity study the dose levels of verteporfin were 2, 10 or 25 mg/kg/day. The developmental NOEL for verteporfin is 10 mg/kg/day. The 25 mg/kg/day dosage was associated with increases in malformations (anophthalmia/microphthalmia and bent/wavy ribs) that commonly occur at maternally toxic dosages. No other effects on embryo-foetal viability, growth or external, soft tissue or skeletal morphology were observed in litters of dams at doses as high as 25 mg/kg/day. Results from a placental transfer study indicated only a small amount (<1%) of verteporfin crossed the placental barrier. Hence, the effects observed may be attributed to maternal toxicity.

Following a dose-ranging study, verteporfin was administered to rabbits at dosages of 1, 3 or 10 mg/kg/day on days 6 through 18 of gestation. In the dose-finding study 25 mg/kg/day caused numerous clinical signs including death, and 10 mg/kg/day signs of anaemia. All surviving animals were killed on day 29 of gestation. There are no toxicokinetic data available for rabbits; however dosing at the maximum tolerated dose by the i.v.route means that maximum possible exposure of the foetuses was achieved. No adverse effects on embryo-foetal viability, growth or external, soft tissue or skeletal morphology were identified in litters of dams at doses as high as 10 mg/kg/day.

In general, at dose levels causing maternal haematological effects, no significant effects were seen in rats and rabbits on reproduction, apart from malformation commonly seen at maternally toxic doses.

Local tolerance

Not relevant in this case.

Other toxicity

A separate safety evaluation of the excipients in Visudyne was provided, as some of the placebo material used in the animal toxicity studies included the excipients. It was clear from some of the placebo results that effects seen may be attributed to the lipid constituents, possibly by dimyristoyl phosphatidylcholine (e.g. in a rat 14 day study - mild extravascular haemolysis accompanied by a compensatory haematopoeitic response in bone marrow, spleen and liver).

Ecotoxicity / Environmental risk assessment

No significant impact on the environment can be expected to arise from the use of the product in accordance with the SPC. However, occupational exposure during use and disposal needs to be considered as verteporfin is active in low concentrations when exposed to light, and this is addressed in the SPC.

Discussion on toxico-pharmacological aspects

All concerns raised by the CPMP during the evaluation process are now resolved for Part III:

The pharmacodynamic and pharmacokinetic profiles were correctly investigated. The pharmacodynamic data properly supported the conditions of use in humans. The lipid-base formulation, which is that tested in humans, is necessary to ensure a rapid distribution to the target organ (choroid) in patients. Evidence for selective accumulation of verteporfin in choroid neovascular endothelial cells has been demonstrated.

The systemic exposure to verteporfin was assessed in different animal models tested during the preclinical programme. Additional information on metabolites (especially their respective stereoisomers) profile observed in different animal models was provided. Esterase stereospecificity was shown in vitro, in the absence of lipoproteins, therefore there is no obvious relationship between stereospecific metabolism of verteporfin regioisomers and lipoprotein affinity. No other metabolites than the diacid were identified.

Tissue distribution was investigated in the main organs and no accumulation was observed.

The toxicological file is acceptable for the present indication i.e. one single i.v. injection which may be repeated at three month intervals. A satisfactory set of experiments was performed to demonstrate the safety of verteporfin after light irradiation, especially on skin and eye which can be directly exposed. All the excipients were presented as safe for use in the formulated product and the explanation given for the haematopoietic effects observed with high and repeated doses in the animal studies is that high concentrations of lipids lead to haematopoiesis, due to lysis of erythrocytes caused by membrane fluidity changes.

In the original dossier, no preclinical studies where verteporfin was repeatedly administrated indicated that the compound is immunogenic. However, updated toxicology information has confirmed the risk of severe cardiovascular/haemodynamic reactions in sedated/anaesthetised pigs - symptoms of patchy red skin, decreased and weakened heartbeat, and problems with breathing culminating in apnoea which are consistent with those of anaphylactic/anaphylactoid reaction caused by Complement activation. Verteporfin was also found to activate complement in an *in vitro* human blood study.

Taken together with a possible anaphyllactoid reaction in one patient, these pre-clinical findings support the statement on risk of allergic reactions, as mentioned in the SPC, sections 4.4 and 5.3.
Concerning genotoxicity, it is a consequence of PDT that any compound producing reactive oxygen species (ros) may be expected to be genotoxic because ros react with DNA and induce DNA single and double-strand breaks in genotoxicity studies. However, verteporfin concentrates in the cytoplasm rather than the nucleus and singlet oxygen has a very short half-life and diffusion path. Therefore DNA damage may not necessarily arise in this particular case. The test cell systems were exposed to verteporfin at appropriate concentrations, and therefore the observed results are valid.

It was clearly demonstrated that the degree of damage caused by verteporfin as well as its specificity for the targeted tissues is dependent on drug dose, i.e. blood level, light dose, and timing of activation.

The only remaining issue is the duration of the skin photosensitivity period. Assessed in an animal model, this duration has only little relevance to clinical situations, as the animal doses were several times higher than the proposed human doses. Based on the human data the applicant recommends that the patient avoids exposure to strong light for 48 hours.

The SPC has been adequately amended where necessary.

4. Part IV: Clinical aspects

The clinical development program comprises 3 pharmacokinetic studies in volunteers (total n = 73), an uncontrolled ocular study in patients with CNV (n = 142), two 'main' controlled ocular studies in patients who have CNV lesions secondary to AMD (n = 609), and one multicentre, double-blind placebo-controlled, randomised study in patients with subfoveal CNV caused by pathologic myopia (n=120 patients, 81 Visudyne, 39 placebo). (Another study in CNV secondary to Ocular Histoplasmosis Syndrome (BPD OCR 004, n=26) was reported but the CPMP considered that the evidence was not sufficient to support an indication in OHS).

Safety data were accumulated from the combined uncontrolled and controlled ocular clinical studies, together with supportive data from studies in a few dermatological indications.

Clinical pharmacology

Pharmacodynamics

No pharmacodynamic studies in healthy volunteers or patients were carried out.

Pharmacokinetics

Protocol number Study design	Population	Number of subjects	Route, regimen duration of therapy dosage	End points
BPD 004 Open-label Single-centre Non-randomised	Caucasian subjects with normal hepatic function versus subjects with mild hepatic function	Total: 17 -healthy: 8 -hepatic dysfunction: 9	IV infusion Single 45-minute infusion 0.3 mg/kg (i.e.12 mg/m^2) exposure to red light (2.5-50J/cm^2) on skin at baseline,days 1,5	Liver function tests C3a activation ECG Skin photosensitivity Adverse events
BPD PK 001A Open-label Non-randomised Parallel group	Caucasian	Total: 32 - 2X12 - 8	IV infusion or bolus - single 6 or 14 mg/m^2 as 10 minutes infusion - single 6 mg/m^2 as 1.5-2 minute bolus	Plasma and urine pharmacokinetics ECG Laboratory tests Adverse events
BPD PK 001B Open-label Non-randomised	Japanese	Total: 24 - 3X8	single IV infusion - 3 or 6 or 14 mg/m^2 as 10 minutes infusion	

Verteporfin is a 1:1 mixture of two structural isomers (regioisomers) of benzoporphyrin derivative mono acid A ring i.e. BDP-MA_C and BDP-MA_D. A HPLC method with ultraviolet detection was developed for plasma and urine to determine the concentrations of BDP-MA_C, BDP-MA_D, and their main metabolite benzoporphyrin derivative diacid (BPD-DA). Plasma concentrations of BDP-MA_C and BDP-MA_D were added to obtain verteporfin concentrations. This method has been properly validated with a limit of quantification of 2 or 5 ng/ml in plasma (according to the site of the study) and 0.5 ng/ml in urine. Capillary electrophoresis was used to determine the ratio of enantiomers of BPD-MA_C, BPD-MA_D and BPD-DA, which was also present as a pair of enantiomers. This method was satisfactorily validated with a limit of quantification of 2.5 ng/ml for BPD-MA_C, BPD-MA_D, and of 12.5 ng/ml for BPD-DA in plasma. The limit of quantification was 2.5 ng/ml for BPD-MA_C, BPD-MA_D and BPD-DA in urine.

Studies PK 001A & 001B:

The plasma concentration profiles of the verteporfin isomers BPD-MA_C and BPD-MA_D, and their sum, verteporfin, exhibited similar pharmacokinetic characteristics across the doses and rates of administration studied, and also in Caucasian compared with Japanese subjects. All plasma concentration profiles were bi-exponential, with a rapid distribution phase followed by a slower elimination phase.

The mean half-life of the regioisomer BPD-MA_C was similar to that of BPD-MA_D (5.3 – 6.2 hours). A small volume of distribution (Vss 0.6 l/kg) was found for BPD-MA_C, BPD-MA_D and verteporfin. Verteporfin is highly protein bound. In whole blood, 10 % of verteporfin is associated with red blood cells and 90% is found in plasma. 90 % of plasma verteporfin was found in lipoprotein owing to its high lipid solubility. It was not possible to determine the unbound fraction (see preclinical assessment). Inspection of the data shows that total body clearance of BDP-MA_C seemed slightly lower (80 – 108) ml/h/kg) than that of BDP-MA_D (89 – 127 ml/h/kg) resulting in slightly higher exposure (AUC) of BPD-MA_C. The determination of the enantiomeric ratios for each of the two regioisomers showed that the enantiomers of BDP-MA_C but not those of BDP-MA_D are subject to stereospecific disposal.

Mean verteporfin values for all elimination parameters were always very close to those reported for BDP-MA_C and BDP-MA_D. Cmax of verteporfin and its two regioisomers is an important parameter from an efficacy perspective when the photodynamic light is applied. For the dose group administered 6 mg/m² over 10 minutes, the mean Cmax was 1.2 – 1.3 mg/l for both Caucasian and Japanese groups.

When 6 mg/m² of verteporfin for injection was administered as a bolus, mean Cmax for BDP-MA_C, BDP-MA_D and verteporfin was 36 %, 13 % and 22 % higher compared with 6 mg/m² as a 10 minute infusion. None of these differences in Cmax was statistically significant, suggesting that the two dosing regimens provide adequate and rapid delivery of verteporfin into the bloodstream.

The interindividual variability of Cmax and AUC_{inf} expressed as coefficient of variation (CV) was moderate (CV ≤ 25 %).

The results of in vitro metabolism studies suggest that NADPH-dependent enzymes such as cytochrome P450 isozymes do not play a significant role in the disposition of verteporfin. Likewise, conjugation of either BDP-MA_C, BDP-MA_D or BDP-DA does not seem to occur. Metabolism is apparently carried out uniquely by plasma and hepatic esterases.

The cumulative urinary recovery of analytes was extremely low. Combined excretion of BDP-MA_C, BDP-MA_D and BDP-DA in urine was less than 0.004 % in Caucasian and Japanese subjects. These data strongly suggest that the majority of verteporfin (about 90 %) is eliminated by the liver.

Plasma concentrations of the metabolite, BDP-DA were near the limit of detection at all times following dosing. Based on the AUC ratio, the extent BPD-DA exposure represented 5 – 10 % of the verteporfin exposure.

Dose proportionality and linear pharmacokinetics were demonstrated only in Japanese subjects within the dose range studied i.e. 3 – 14 mg/m². No ethnic or gender effect was noted.

Pharmacokinetics in subjects with mild hepatic dysfunction. (study BPD-004)

Because preclinical studies as well as studies in healthy volunteers showed that verteporfin is cleared by the liver, the effect of hepatic dysfunction on the pharmacokinetics of verteporfin was investigated. Eight subjects with normal hepatic function and 9 subjects with mild hepatic dysfunction were enrolled and received an intravenous infusion of verteporfin (0.3 mg/kg) over a 45 minute period. This dose was approximately twice the usual recommended dose. Hepatic dysfunction was not graded according to the Child-Pugh classification. The extent of exposure in subjects with mild hepatic dysfunction was greater (≈ 40 %) but not statistically significant compared to normal subjects. The apparent volume of distribution indicated that the distribution was similar between the two groups. The maximal concentration values were very close in the two groups. The exposure ($AUC_{0\text{-}24h}$) of verteporfin, BDP-MA_C and BDP-MA_D was 1.42, 1.38 and 1.52 fold higher respectively in patients with abnormal function. The differences were not statistically significant. Only the half-lives of verteporfin and BDP-MA_D were significantly increased in the subjects with hepatic dysfunction (4.9 vs 5.9 h and 4.7 vs 6.5 h respectively). No information was gathered relating to BDP-DA.

It may be noted that in the clinical uncontrolled study BPD- OCR 001, pharmacokinetic data were gathered for 22 patients who had at least one cutaneous lesion caused by metastatic disease and who received single intravenous doses 0.15, 0.20, 0.375 or 0.50 mg/kg over 45 minutes. The pharmacokinetic characteristics of verteporfin and its regioisomers determined in these patients were similar to those found in healthy volunteers.

Clinical efficacy:

1. Studies relating to subfoveal CNV related to AMD

Uncontrolled ocular study in patients with CNV (Dose-response study)

Protocol number Study design	**Population**	**Number of subjects**	**Route, regimen duration of therapy dosage**	**End points**
BPD OCR 001 Non-controlled Open-label Multicenter	Patients with CNV of any cause	142 (total) 5 groups: 1 = 24 2 = 43 3 = 21 4 = 24 5 = 30	Doses of verteporfin: 6 and 12 mg/m^2 Light doses: 12.5, 25, 50, 75,100 and 150J/cm^2 Time of light application after start of VTP infusion: 10,15, 20 and 30minutes.	Drug plasma concentrations Dose-escalation Safety

Controlled ocular studies in patients with CNV

'STUDY A' BPD OCR 002A Placebo-controlled Masked Randomized Multicenter (10)	307 Caucasian 4 other with predominantly classic subfoveal CNV secondary to AMD	311	24 months 6 mg/m^2 10-min infusion followed 15-min after start of infusion by light at 50J/cm^2 Retreatment allowed every 3 months if CNV leakage	Efficacy: % of responders, i.e. VA < 15 letters (12 & 24 months analysis) Safety (*21 months analysis)
'STUDY B' BPD OCR 002B Placebo-controlled Masked Randomized Multicenter (12)	292 Caucasian 6 other with predominantly classic subfoveal CNV secondary to AMD	298		

* A global analysis for all patients at the 18 month time point was provided in the initial dossier, although some patients had progressed to 21 months.

The clinical programme includes one dose-response study BPD OCR 001, and two placebo-controlled ocular trials BPD OCR 002A & 002B. All studies where active drug is given have been performed with the formulation intended for marketing, and carried out according to current GCP standards.

The placebo given was 5% dextrose solution.

General principles

Irradiation sources
PDT studies have used a laser delivery system providing a uniform intensity narrow bandwidth red light at subthermal intensity, λ ~689 nm, applied over a circular area. Some degree of over-treatment is inevitable for linear lesions. Two different laser systems have been used, each complying with the relevant requirements of the Medical Devices legislation, and having comparable optical properties. There is no reason to suggest that the two systems differ significantly in their performance characteristics in a way that would compromise the study results.

CNV closure
CNV closure was a main indicator of efficacy in the dose evaluation study, and a secondary efficacy variable in the two controlled pivotal studies.

Four grades of CNV closure were predetermined: 100%, <100% to 50%, <50%, and 'progression'; they were evaluated by angiographic assessment of leakage of fluorescein from CNV lesions.

Visual Acuity (VA) Measurement
The other main indicator of efficacy in these studies was visual acuity changes, ideally the stabilisation of VA or more realistically a reduced decline in VA compared to placebo.

Measurement of VA was based on the procedure developed for the Early Treatment of Diabetic Retinopathy Study (ETDRS). A standard Snellen chart has been used for measuring the refraction. Charts 1 and 2 were used for testing the right eye and the left eye, respectively. The features of the charts are 14 lines of letters to be read at distance of 2 metres, and 3 lines of letters to be read at a distance of 1 meter for patients with reduced vision. Each line shows five high-contrast 'Sloan' letters and has a visual acuity equivalent recorded next to it. The lines are equally difficult and show a geometric progression of letter size (and thus, an arithmetic progression of the logarithm of the minimum angle of resolution) from line to line.

Dose-response studies and main clinical studies

Dose-response study BPD OCR 001

Design
The evaluation of the dosage regimen was carried out in one open-label study in 142 patients. The study results were checked by a Photograph Reading Center, an independent and central reading center.

Objectives
Dose escalation assessment was only one of the secondary objectives of the study. Protocol amendments were made to evaluate different dose regimens and to expand the number of patients treated from 20-30 to 142.The primary objective of the study was to assess ocular safety and to demonstrate preliminary efficacy of PDT using different drug-dose/light-dose regimens of verteporfin.

Inclusion criteria
Patients ≥ 21 years of age with subfoveal CNV from any cause and a best corrected VA <20/40.

Lesions should be characterised as following: presence of classic CNV in any proportion; evidence that the CNV involves the geometric centre of the foveal avascular zone (FAZ); a lesion size diameter ≤ 12 Macular Photocoagulation Study Disc Area units (MPS DA units) i.e. 5200μm.

Efficacy parameters
- The primary efficacy parameter was CNV closure determined by angiographic assessment of fluorescein leakage from CNV lesions.
- The secondary efficacy parameter was visual acuity (VA) measured using the ETDRS procedure.
- Assessments were made 1, 4 and 12 weeks after the first exposure to PDT with verteporfin.

Five treatment regimens were defined on the basis of both pre-clinical data in primates and clinical experience in oncology:

Treatment regimen	Number of AMD patients treated	Verteporfin dose[a] (mg/m^2)	Light doses (J/cm^2)	Time of light application after start of verteporfin infusion (minutes)
1	22	6	50, 75, 100, 150	30
2	37	6	50, 75, 100, 150	20
3	19	12	50, 75, 100, 150	30
4	**22**	**6**	**50, 75, 100**	**15**
5	28	6	12.5, 25, 50	10

[a] verteporfin infused at a rate of 3 ml/min (10-minute infusion) except in Regimen 5, which utilised a rate of 6 ml/min (5-minute infusion).

Retreatment for up to three courses was allowed.

Results

Demographic and baseline characteristics:

Of the 142 patients, 53 % were male and 47 % were female. All but one patient were Caucasian and the mean age was 72 years. Most of the patients had CNV secondary to AMD. 80 % of patients had a baseline visual acuity for the treated eye ≥ 20/200.

Classic CNV closure after the first course (number and percent of AMD patients [a]) is shown in the table below:

Dose (mg/m^2)	**Time[b] (minutes)**	**Light (J/cm^2)**	**Week 1**					**Week 4 [c]**				
			100%	**50 - 100%**	**< 50%**	**Prog.**	**n**	**100%**	**50 - 100%**	**< 50%**	**Prog.**	**n**
Regimen 1												
6	30	50-150	11(52)[d]	9(43)	1 (5)	0 (0)	**21**	2(10)	8(38)	7(33)	4(19)	**21**
Regimen 2												
6	20	50-150	27(82)	3 (9)	3 (9)	0 (0)	**33**	6(24)	9(36)	8(32)	2 (8)	**25**
Regimen 3												
12	30	50-150	16(84)	2(11)	1 (5)	0 (0)	**19**	2(11)	8(44)	4(22)	4(22)	**18**
Regimen 4												
6	**15**	**50-100**	**21(100)**	**0 (0)**	**0 (0)**	**0 (0)**	**21**	**6(29)**	**5(24)**	**7(33)**	**3(14)**	**21**
Regimen 5												
6	10	12.5-50	14(64)	5(23)	3(14)	0 (0)	**22**	0 (0)	6(27)	11(50)	5(23)	**22**

a excluding 10 patients due to no classic CNV at baseline. Sample sizes vary due to missing data.
b time of light application after start of 10-minute verteporfin infusion except for Regimen 5 which was after a 5-minute infusion.
c includes only patients who received a single course of PDT
d number (percentage)
Prog. = progression.

- Regarding the ability to produce classic CNV closure, Regimens 2 and 4 appeared to be the most effective of the five treatment strategies tested with a minor advantage for Regimen 4 at week 1. The incidence of complete closure range reaches a maximum of 100%, and by week 4 it continued to have the highest incidence of complete closure (29%).
- Conversely, Regimen 5 was the less effective regimen (week 4 = 0%).
- The results found in occult CNV closure after the first course did not match those seen in classic CNV closure: at week 1 the highest incidence of complete closure was observed in Regimens 1 and 3. Notable differences between regimens in complete closure were not seen at other visits.

- For all regimens, except Regimen 3, mean visual acuity after the first course increased from baseline at Weeks 1 and 4. Regimen 4 showed the highest and most persistent mean increases in VA at Week 4 (+1.1 line).
- No observable light-dose response was detected relative to classic or occult CNV closure.
- Non-selective closure of retinal arterioles at light doses of 150J/cm^2 administered either 20 minutes after 6mg/m^2 VTP or 30 minutes after 12mg/m^2 was found and thus, considered as a non tolerated light doses for these regimen.

On balance, Regimen 4 was selected to be used in clinical studies as it was considered the « lowest » drug dose and light combination producing classic CNV closure. This regimen corresponds to a 6 mg/m^2 10-minute infusion of verteporfin and a light dose of 50 J/cm^2 applied 15 minutes after the start of infusion.

Main Clinical studies BPD OCR 002A & 002B

Study objective
The primary objective was to demonstrate the long-term efficacy of PDT with verteporfin compared to placebo in limiting the decrease in visual acuity in patients with subfoveal CNV due to AMD.

Study design
Two identical placebo-controlled and randomised trials involving a total of 609 patients were conducted in Europe and North America under the same protocol: BPD OCR 002 A & 002 B

Both were planned for a two-year duration.

Selected patient population:

The selected inclusion criteria were:

- male and female patients over 50 years old ,
- with new or recurrent subfoveal CNV lesions secondary to AMD including a component of classic CNV and angiographic evidence of the extent of CNV under the geometric centre of the foveal avascular zone (FAZ),
- occult CNV lesions could also be included,
- area of classic plus occult CNV lesions were defined as ≥ 50% of the total lesion and the greatest linear dimension of the entire lesion were defined as ≤ 9 MPS disc area units (i.e 5400 μm),
- the specified best corrected visual acuity in the selected eye was 34 -73 letters.

Inclusion criteria comply with a frequently-encountered clinical situation. The selection criteria allow the possibility to eliminate isolated extra- or juxta-foveal CNVs, which are indications of laser treatment. 'Pure', isolated or predominantly occult CNV is also excluded, as the diagnosis is difficult and sometimes uncertain.

Primary efficacy parameter
The primary efficacy parameter was visual acuity response relative to baseline:

The responder rate was defined as the proportion of patients who lost less than 15 letters (i.e. 3 lines) of visual acuity at month 12; the sample size was calculated on this parameter.

The proportion of patients in whom VA decreased from baseline by less than 30 letters (i.e. 6 lines) was also selected as a primary efficacy parameter.

Secondary efficacy parameters

- Secondary efficacy parameters were the proportion of patients whose VA became less than 34 letters (i.e. <20/200), the time until a patient had moderate or severe decrease of visual acuity from baseline (i.e. ≥ 15 or 30 letters, respectively), the mean change from baseline in VA.
- Other secondary efficacy parameters were also employed, e.g. CNV closure determined by angiographic assessment of fluorescein leakage from classic & occult CNV lesions compared to baseline.
- Some secondary measures were defined post hoc, i.e. the time until a patient's VA score became less than 34 letters (not defined in the protocol), mean change from baseline in contrast sensitivity using the Pelli-Robson chart, lesion size measurement (not specified in the protocol).

Dose and duration of treatment

As indicated by the dose ranging study, the Regimen 4 was used in clinical studies, i.e. a single10-minute intravenous infusion of 6mg/m^2 body surface area of verteporfin (or placebo) was administered, followed by application of red light with a wavelength of 689 nm at a dose of 50 J/cm^2 delivered at a fluence of 600mW/cm^2 over 83 seconds, 15 minutes after the start of the infusion.

Only one eye per patient was allowed to be treated.

Retreatment was allowed every three months, up to a maximum of four treatments per year if necessary (i.e. if evidence of CNV leakage was detected by fluorescein angiography).

The total duration of treatment for each patient was 24 months.

Statistical analysis

Randomisation

Patients were randomised in a ratio of 2:1 (2 Visudyne for 1 placebo); a stratification by centre and baseline visual acuity was made and two classes were defined 54-73 letters and 34-53 letters.

Sample size

For each study, it was estimated that 50% of the placebo patients would loose less than 3 lines of visual acuity (i.e. 15 letters) compared to baseline after one year. Then a total sample size of 225 would provide approximately 94% power to detect a difference from placebo of 25% and 80% power to detect a difference from placebo of 20%. Statistical tests were 2-sided with significance level (α) of 0.05.

Efficacy analysis

The primary data set for efficacy analysis was the intent-to-treat (ITT). Analyses were performed on both intent-to-treat and evaluable-patient populations.

Between treatment comparisons of the proportion of responders were performed using a chi-square test and a logistic regression was made taking into account the gender, and the two states defined for baseline visual acuity, time interaction between these two variables and the treatment.

The time to a moderate or a severe decrease in visual acuity as well as the time to visual acuity <34 letters were analysed using a Cox model: the analysis comprises efficacy data for over 21 months.

Results

- Demographic and baseline characteristics

	BPD OCR 002 A n=311 10 centers		BPD OCR 002 B n=298 12 centers	
	Visudyne n=204	Placebo n=107	Visudyne n=198	Placebo n=100
Gender (female)	53%	69%	54%	56%
Age (years)	74	76	76	76
Iris color (light)	64%	68%	59%	65%
Visual acuity (nb of letters)				
54-73	53%	51%	47.5%	46%
34-53	47%	49%	52.5%	54%

Demographic data were well balanced between groups except for gender since there were significantly fewer women in the verteporfin group, compared to the placebo group (p = 0.005), in Study A.

Number of discontinued patients and number of courses administered through month 12:

	BPD OCR 002 A n=311		BPD OCR 002 B n=298	
	Visudyne n=204	Placebo n=107	Visudyne n=198	Placebo n=100
Discontinued from study (%)	4%	5%	3%	4%
Number of courses (%)				
1	9 (4%)	5 (5%)	13 (7%)	1 (1%)
2	19 (9%)	2 (2%)	21 (11%)	5 (5%)
3	20 (10%)	10 (9%)	31 (16%)	5 (5%)
4	44 (22%)	18 (17%)	36 (18%)	16 (16%)
5	112 (55%)	72 (67%)	97 (49%)	73 (73%)

The main reason for absence of retreatment was the absence of CNV leakage detected by fluorescein angiography.

Most of the patients were treated at least 3 times a year.

- Primary efficacy variables results in intent-to-treat analysis:

At the 12-month data point, the following results were recorded for number and percent of 'responders' i.e. patients in whom VA decreased < 15 letters compared to baseline:

	Study A		Study B		Study A + B	
	Verteporfin N=204	**Placebo N=107**	**Verteporfin N=198**	**Placebo N=100**	**Verteporfin N=402**	**Placebo N=207**
All patients	**N=122**	**N=49**	**N=124**	**N=47**	**N=246**	**N=96**
% responders*	60 %	46 %	63 %	47 %	61 %	46 %
Vert-Pbo	14 %		15.6 %		14.8 %	
P	0.018		< 0.01		<0.001	
Patients with predominantly classic CNV	**N=58**	**N=14**	**N=49**	**N=19**	**N=107**	**N=33**
% responders*	67 %	35 %	67 %	44 %	67 %	33 %
Vert-Pbo	32.4 %		22.9 %		27.5 %	
p	<0.001		0.015		<0.001	

At Month 12 compared to baseline, verteporfin was statistically significantly superior to placebo in both Study A and Study B. At 12 months, the difference in the proportion of responders was 14.8% in favour of verteporfin, for Studies A & B combined. For the subgroup of patients with predominantly classic CNV, the difference was 27.5% ($p<0.001$)

The results of the logistic regression model indicated that the odds of being a responder at month 12 for patients treated with verteporfin were approximately 1.9 times the odds of being a responder for patients treated with placebo. This risk is significantly different from 1 ($p=0.009$).

At the request of the CPMP the applicant provided the results of the 24 month analysis, summarised in the following table:

	Study A		Study B		Study A + B	
	Verteporfin N=204	**Placebo N=107**	**Verteporfin N=198**	**Placebo N=100**	**Verteporfin N=402**	**Placebo N=207**
All patients	**N=104**	**N=42**	**N=109**	**N=36**	**N=213**	**N=78**
% responders*	51 %	39 %	55 %	36 %	53 %	38 %
Difference, Vert - Pbo	12 %		19 %		15 %	
p	0.049		0.002		< 0.001	
% with a decrease < 30 letters	78 %	69 %	86 %	71 %	82 %	70 %
Difference, Vert - Pbo	9 %		15 %		12 %	
p	0.090		0.002		0.001	
VA < 34 letters	44 %	54 %	38 %	56 %	41 %	55 %
Difference, Vert-Pbo	-11 %		-18 %		-14 %	
p	0.076		0.004		0.001	
Patients with predominantly classic CNV	**N=51**	**N=13**	**N=43**	**N=13**	**N=94**	**N=26**
% responders*	59 %	33 %	59 %	30 %	59 %	31 %
Difference, Vert-Pbo	27 %		29 %		28 %	
p	0.005		0.003		< 0.001	
% with a decrease < 30 letters	84 %	63 %	86 %	65 %	85 %	64 %
Difference, Vert-Pbo	21 %		21 %		21 %	
p	0.008		0.007		< 0.001	
VA < 34 letters	45 %	68 %	43 %	67 %	44 %	68 %
Difference, Vert-Pbo	-22 %		-25 %		-23 %	
p	0.021		0.009		0.001	

* decrease from baseline of < 15 letters in VA, N= number of patients.

The second analysis at Month 24 confirmed the treatment effect seen at Month 12, indicating that the treatment benefit continues through 24 months of follow-up. At Month 24, the difference between the verteporfin and placebo groups, favouring verteporfin, was 15.3% for all patients in studies A+B ($p<0.001$). This difference at Month 24 was statistically significant in both Study A (11.7%, $p=.049$) and Study B (19.1%, $p= 0.002$).

Concerning those patients with predominantly classic CNV, the difference calculated from the combined studies is 28% ($p<0.001$)

Considering the elderly patient population and the long duration of the study, a high percentage of patients had visual acuity assessments. Approximately 94% at month 12 (i.e. verteporfin n=379 and placebo n= 194; and 87% at month 24 (i.e. verteporfin n=351 and placebo n= 178), for all patients in studies A+B. A similar high percentage of patients had acuity assessments in the predominantly classic CNV subgroup in studies A+B (i.e. verteporfin 87% and placebo 88%).

- Secondary efficacy variables results in intent-to-treat analysis

Time-to-event analysis (month 0 - through month 21 inclusive):

For both studies (A&B respectively), treatments were statistically significant compared to placebo for the time to a moderate decrease in visual acuity as well as for the time to severe decrease with a decrease in risk by 30% and 38% (≤15 letters) and by 43% and 51% (≤30 letters).

Conversely, treatment was not statistically significant for the time for visual acuity to become less than 34 letters in study A (p=0.246) but statistically significant in study B (p=0.024) with a decrease in risk of 33%.

Change from baseline in visual acuity scores at month 12:

For both studies (A&B respectively): the adjusted means showed a 13.3 and 10.6-letter decrease in verteporfin-treated patients compared to a decrease of 19.2 and 17.7 letters in the placebo group. The differences between the two groups were significant (5.9 letters – p=0.004 and 7.1 letters – p=0.001).

Angiography results at month 12:

Angiography results at month 12	BPD OCR 002 A		BPD OCR 002 B	
Percentage of patients with:	Visudyne N=204	Placebo N=107	Visudyne N=198	Placebo N=100
complete + partial closure of classic CNV*	28%	15%	42%	21%
complete + partial closure of occult CNV **	20%	22%	28%	16%
progression of classic CNV	44%	66%	41%	72%
progression of occult CNV.	71%	71%	63%	78%

* for all patients including those who did not have classic CNV at baseline.
** for all patients including those who did not have occult CNV at baseline.

At month 12, the angiography results of both studies A&B were significantly in favour of verteporfin patients either on complete plus partial classic CNV closure or in slowing down classic CNV progression compared to placebo.

No conclusion could be raised for occult CNV. The efficacy that was shown is due to the effect on "classic" CNV.

Various sub-group analyses were realised. Overall, results were consistent with the previous results showing a higher percentage of 12-month responders in verteporfin groups compared to placebo groups. The only main difference was observed between predominantly classic CNV (i.e. classic CNV ≥ 50% compared to occult CNV (i.e classic CNV <50%) at the inclusion. The results show a difference in favour of the classic CNV group.

1. Study in subfoveal CNV related to Pathologic Myopia (PM).

Study BPD OCR 003: After the original authorisation of Visudyne, this study was later submitted as a Type II variation to extend the indication (See 'Steps taken after granting the authorisation'). It is a placebo-controlled, double-masked, randomised study on a total of 459 patients with new subfoveal CNV secondary to AMD (n=339) or subfoveal CNV secondary to Pathologic Myopia, i.e. PM (n=120). The study was stratified by pathologies and thus, separate reports for the AMD and PM populations were presented. The following table summarises the findings for the 120 PM patients:-

BPD OCR 003 PM **26 centers** **Start:** 26 February 98 **Enrolment end:** 25 September 1998	**Design, goal & population:** randomised, placebo-controlled, double-masked, multicentre, study in patients with : Early AMD or Pathologic Myopia (PM) **Evaluations:** visual acuity, contrast sensitivity, fluorescein leakage, laboratory tests, AE.	**Total:** 120 PM patients **Age:** 19-84 (mean: 50 years) **Verteporfin:** 81 (24 men, 57 women) **Placebo:** 39 (16 men, 23 women)	**PM patients'results** At Month 12, 86.4% of verteporfin eyes had a loss of less than 15 letters to treatment versus 66.7% of placebo eyes (p = 0.011). At Month 12, 71.6% of verteporfin eyes had a loss of less than 8 letters to treatment versus 43.6% of placebo eyes (p = 0.003). All AE: 50 patients (62%) on verteporfin, 24 (62%) on placebo. SAE: 3 patients (4%) on verteporfin, 2 patients (5%) on placebo No severe vision decrease in PM verteporfin-treated patients

The posology, visual acuity assessments etc. were the same as in the AMD studies BPD OCR 002 A and B reported above.

Primary efficacy parameter
The primary efficacy parameter was the proportion of patients who were classified as responders to the treatment, based on the visual acuity response at Month 12 relative to baseline.
The responder rate was originally defined prospectively in the protocol as the proportion of patients who lost less than 1.5 lines of visual acuity (i.e. 8 letters) in the treated eye. However, following an FDA recommendation, responders were re- defined as the proportion of patients who lost less than 3 lines of visual acuity (i.e. 15 letters) in the treated eye.

Secondary efficacy parameter
Secondary criteria were the same as those selected for BPD OCR 002 A and B studies.
i.e. the proportion of patients whose VA became less than 34 letters (i.e. < 20/200), the time until a patient had moderate or severe decrease of visual acuity from baseline (i.e. ≥ 15 or 30 letters decrease respectively).

Results
Primary efficacy variables results in intent-to-treat analysis regarding the two definitions of responders:

Patient Responders[a] (<15-letter Decrease in Visual Acuity,Intent-to-Treat) - *as recommended by the Food and Drug Administration.*

Visit	Verteporfin N=81	Placebo N=39	Difference[b] (Percent)	95% C.I. of Difference	P value[c]
Month 3	76 (93.8)	31 (79.5)	(14.3)	[0,6, 28.1]	
Month 6	68 (84.0)	30 (76.9)	(7.0)	[-8.4, 22.5]	
Month 9	71 (87.7)	26 (66.7)	(21.0)	[4.5, 37.4]	
Month 12	70 (86.4)	26 (66.7)	(19.8)	[3.2, 36.3]	.011

[a] A responder was a patient who had a decrease from baseline of < 15 letters in VA.
[b] Proportion of verteporfin responders minus the proportion of placebo responders.
[c] Chi-square used to test significance between the proportion of patient responders for verteporfin treatment versus placebo at Month 12.

Logistic Regression Analysis of Response[a] (<15-letter Decrease in Visual Acuity) at Month 12 (Intent-to-Treat)[b]

Parameter	Parameter Estimate	S.E. of Estimate	P. value[c]	Odds Ratio[d]	95% C.I. of Odds Ratio[e]
Treatment	1.158	0.470	.014	3.182	[1.267, 7.988]

[a] A responder was a patient who had a decrease from baseline of < 15 letters in VA.
[b] At month 12, the sample sizes were 81 and 39 for the verteporfin and placebo groups, respectively.
[c] Wald Chi-square used to test significance.
[d] Odds Ratio : verteporfin treatment group compared to placebo group ; a ratio higher than 1 indicates a greater odds of response with verteporfin.
[e] Wald 95% Confidence Interval for Odds Ratio.

Patient Responders[a] (<8-Letter Decrease in Visual Acuity) (Intent-to-Treat) as at first defined in the protocol.

Number (%) of Patients

Visit	Verteporfin N=81	Placebo N=39	Difference[b] (Percent)	95% C.I. of Difference	P value[c]
Month 3	62 (76.5)	22 (56.4)	(20.1)	[2.0, 38.2]	
Month 6	60 (74.1)	17 (43.6)	(30.5)	[12.2, 48.7]	
Month 9	57 (70.4)	20 (51.3)	(19.1)	[0.5, 37.7]	
Month 12	58 (71.6)	17 (43.6)	(28.0)	[9.6, 46.4]	.003

[a] A responder was a patient who had a drecrease from baseline of <8 letters in VA.
[b] Proportion of verteporfin responders minus the proportion of placebo responders.
[C] Chi-square used to test significance between the proportion of patient responders for verteporfin treatment versus placebo at Month 12.

Logistic Regression Analysis of Response[a] (<8-Letter decrease in Visual Acuity) at Month 12 (Intent-to-Treat)[b]

Parameter	Parameter Estimate	S.E. of Estimate	P value[c]	Odds Ratio[d]	95% C.I. of Odds Ratio[e]
Treatment	1.183	0.406	.004	3.263	[1.472, 7.235]

[a] A responder was a patient who had a decrease from baseline of <8 letters in VA.
[b] At Month 12, the sample sizes were 81 and 39 for the verteporfin and placebo groups, respectively.
[c] Wald Chi-square used to test significance.
[d] Odds Ratio : verteporfin treatment group compared to placebo group ; a ratio higher than 1 indicates a greater odds of response with verteporfin.
[e] Wald 95% Confidence Interval for Odds Ratio.

Secondary Efficacy Variables:

Change from baseline in visual acuity scores at month 12:
The decrease means adjusted on age and on VA baseline showed a decrease of 2.3 letters in verteporfin-treated patients compared to a decrease of 10.2-letter in the placebo group. The difference between the two groups was significant (7.8 letters – p=0.009).

Patients with visual acuity less than 34 letters (severe decrease in Visual Acuity) (Intent-to-Treat)

Number (%) of Patients

Visit	Verteporfin N=81	Placebo N=39	Difference[a] (Percent)	95% C.I. of Difference	P value[b]
Month 12	5 (6.2)	7 (17.9)	(-11.8)	[-24.9, 1.4]	.044

[a] Proportion of verteporfin responders minus the proportion of placebo responders.
[b] Chi-square test used to compare the proportion of patient with visual acuity <34 letters for verteporfin versus placebo at month 12.

In general, based on the one-year results from this trial, the efficacy of PDT with verteporfin has been demonstrated in the treatment of 120 patients with pathologic myopia.

The loss in visual acuity was significantly lower in patients receiving verteporfin. Moderate and severe decreases in visual acuity were significantly reduced by the treatment. The treatment brings a moderate benefit but of clinical importance in slowing down the loss of visual acuity and also in some cases, in improving vision, which was not obtained up to now by other therapy.

The extension of the indication for the treatment of subfoveal choroidal neovascularisation secondary to pathological myopia (PM) was authorised in March 2001 on the basis of the 1-year results. It was concluded that the benefit/risk at 1-year was acceptable for patients with pathological Myopia.

The CPMP, however, requested the complete two-year results as a follow-up commitment for the variation, in order to confirm the long-term benefit/risk balance in patients with subfoveal choroidal neovascularisation secondary to pathological myopia. The complete two-year results were provided by the MAH in July 2001. It was concluded that the results of the 2-year follow up no longer reached statistical significance and suggested that the clinical benefit may decrease over time. However, results showed more variability than a clear temporal trend and were numerically still in favour of verteporfin. No additional safety concerns were raised from the safety data in PM patients.

The CPMP recommended to update the section 5.1 of the SPC to reflect the clinical results of study BPD OCR 003 PM at 24 months and to add that the clinical benefit may diminish over time. These changes were introduced to the SPC through a Type II variation.

Extension of indication to include the indication of occult subfoveal choroidal neovascularisation due to age-related macular degeneration

Visudyne was initially approved for the treatment of patients with predominantly classic subfoveal choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD), and through a Type II varition also to patients with subfoveal choroidal neovascularisation secondary to pathologic myopia (PM).

The Marketing Authorisation Holder applied for a Type II variation, to extend the current use of verteporfin to a broader AMD patient population who have **occult** subfoveal choroidal neovascularisation. The study supporting the MAH's request is Study BPD OCR 003. The study is a placebo-controlled, double-masked, randomised study involving a total of 339 patients, 225 were randomised to verteporfin and 114 to placebo. Clinical studies procedures and measurement tools used in the additional clinical study were the same as they were in the original file for AMD patients (studies OCR 002 A & B). The exclusion criteria were the same as those selected for AMD patients previously analysed.

The primary efficacy parameter was the proportion of patients who were classified as responders to the treatment, based on the visual acuity response at Month 12 relative to baseline.
The responder rate was defined prospectively in the protocol as the proportion of patients who lost less than 3 lines of visual acuity (i.e.15 letters) in the treated eye.
A change of 15 letters is a moderate decrease in visual acuity and represents a doubling in the visual angle. This is of clinical significance and is consistent with the definition previously used in BPD OCR 002 A and 002 B studies for AMD patients.

Secondary efficacy criteria were: change from baseline of mean visual acuity scores, proportion of patients with a decrease from baseline of less than 30 letters, the proportion of patients whose visual acuity decreased to less than 34 letters, time until a patient had a decrease from baseline in BCVA of 15 letters or more and of 30 letters or more, the change from baseline in the level of classic and occult CNV, the proportion of patients who had no classic CNV at baseline but developed classic CNV during the study, lesion size measurements, the change from baseline in the mean subjective visual performance scores and assessment of change in contrast sensitivity.

The primary analysis of efficacy was when all patients had completed 12 months of follow-up (cut-off date: October 29, 1999). A second analysis was planned when all patients had completed 24 months of follow-up.

Between treatment comparisons of the proportion of responders at one year were performed using a chi-square test and a logistic regression was made taking into account the demographic and lesion characteristics, the two strata defined for baseline visual acuity, time interaction between these variables and the treatment.

The time to a moderate decrease (≥ 15 letters) or a severe decrease (≥30 letters) in visual acuity were analysed using a Cox model. The baseline visual acuity was included in the model.

The intent-to-treat analysis was the primary set of efficacy analyses, which included all available data from patients who have evidence of CNV in their lesion at baseline as assessed by the photograph reading centre. For ITT analysis, data were imputed for all missing values by a last observation carried forward (LOCF) method. The evaluable-patients analysis included all available data from patients who follow the protocol without significant deviation.

Three data sets were analysed as intent-to-treat samples:

- The first was the overall study patient sample (n=339).
- The second was comprised of patients who had occult with no classic CNV lesions at baseline (n=258, i.e. 76% of the overall population).
- The third included patients who had occult with no classic CNV lesions and either a smaller lesion (™4 MPS DA i.e. Macular Photocoagulation Study Disc Area) or a poorer visual acuity score (™65 letters) at baseline (n=187, i.e. 55% of the overall population).

The two first data sets were defined prospectively, the third presented as explanatory. For each of these data sets, missing efficacy values were imputed by the method of LOCF except for the time-to-event analyses.

At baseline, the mean visual acuity scores were comparable: verteporfin 66.3 and placebo 65.4 letters. Lesion characteristics were for verteporfin group and placebo group, respectively: 97.8% and 97.4% of patients showed evidence of CNV in ≥ 50% of the treatable lesion, subfoveal in 84.9% and 80.7% of the lesions, a classic component documented in 24% and 18.4% and an occult CNV was seen in 92.9 and 95.6% of patients.

Overall, demographic and lesion characteristics were well balanced between the two treatment groups except for contrast sensitivity (p=0.017).

The number (percentage) of Patient Responders[a] (<15-letter Decrease in Visual Acuity) at Months 12 and 24 for the overall population (n=339) are shown below:

Visit	Verteporfin N=225	Placebo N=114	Difference[b] (Percent)	95% C.I. of Difference	P value[c]
Month 3	175 (77.8)	93 (81.6)	(-3.8)	[-12,8, 5.2]	
Month 6	147 (65.3)	70 (61.4)	(3.9)	[-7.0, 14.8]	
Month 9	127 (56.4)	57 (50.0)	(6.4)	[-4.8, 17.7]	
Month 12	**111 (49.3)**	**52 (45.6)**	**(3.7)**	**[-7.5, 15.0]**	**0.517**
Month 15	108 (48.0)	49 (43.0)	(5.0)	[-6.2, 16.2]	
Month 18	112 (49.8)	41 (36.0)	(13.8)	[2.8, 24.8]	
Month 21	109 (48.4)	38 (33.3)	(15.1)	[4.3, 26.0]	
Month 24	**104 (46.2)**	**38 (33.3)**	**(12.9)**	**[2.1, 23.7]**	**0.023**

[a] A responder was a patient who had a decrease from baseline of < 15 letters in VA.
[b] Proportion of verteporfin responders minus the proportion of placebo responders.
[c] Chi-square used to test significance between the proportion of patient responders for verteporfin treatment versus placebo at Month 12 and Month 24.

The Logistic Regression Analysis of Response[a] (<15-letter Decrease in Visual Acuity) at Month 12 and Month 24 (Intent-to-Treat)[b] is given in the table below:

Treatment effect	Parameter Estimate	S.E. of Estimate	P. value[c]	Odds Ratio	95% C.I. of Odds Ratio[d]
Month 12	**0.1238**	**0.238**	**0.603**	**1.132**	**[0.710, 1.805]**
Month 24	**1.208**	**0.385**	**0.002**	**3.346**	**[1.574, 7.113]**
Factors[f]					
Visual acuity	0.460	0.416	0.270	1.583	[0.700, 3.580]
Age	-0.440	0.228	0.054	0.644	[0412, 1.007]
Interaction terms [g]					
Treatment by VA Stratum	-1.155	0.498	0.020	0.315	[0.119, 0.836]

[a] A responder was a patient who had a decrease from baseline of < 15 letters in VA.
[b] At month 12, the sample sizes were 225 and 114 for the verteporfin and placebo groups, respectively. [b] At month 24, the sample sizes were 225 and 114 for the verteporfin and placebo groups, respectively.
[c] Wald Chi-square used to test significance.
[d] Wald 95% Confidence Interval for Odds Ratio.
[e] Odds Ratio : verteporfin treatment group compared to placebo group ; a ratio higher than 1 indicates a greater odds of response with verteporfin.
[f] For visual acuity, <65 vs≥65 letters ; For age <75 vs ≥75 years.
[g] For treatment by visual acuity interaction, patients with worse visual acuity (< 65 letters) generally had a better treatment effect than patients with better visual acuity (≥65 letters).

At Month 12, the ITT analysis shows 49.3% of verteporfin eyes had a loss of less than 15 letters to treatment versus 45.6% of placebo eyes. The difference in favour of verteporfin was not statistically significant (3.7%; (p = 0.517). The results of the evaluable patients also show a non significant difference p=0.948).

The analysis using the logistic regression as well as the analysis performed in the evaluable-patients data set (p=0.948) yields to similar results.

At Month 24, the difference in responder rate increases to 12.9% and becomes statistically significant (p=0.023). A secondary confirmatory analysis performed without LOCF shows a difference between groups no longer statistically significant (11.2%; p=0.065).

Analysis using the logistic regression shows that the overall treatment effect was confounded by a significant interaction between treatment and Visual acuity stratum. This interaction indicates that the treatment effect is inconsistent across the two VA strata: patients with worse visual acuity (< 65 letters) generally had a better treatment effect than patients with better visual acuity (≥65 letters) (p=0.020).
Results from the evaluable data show a difference of 9.8% in favour of verteporfin but did not reach statistical significance (p=0.146).

The differences in the subgroup of patients with occult CNV and no classical lesions (n=258, 76% of the population), as well as the level of significance, are similar to those observed in the overall study population (4.2%; p=0.515 and 13.7%; p=0.032 at Months 12 and 24 respectively). In the subgroup of patients with occult CNV, the results of the analysis performed without LOCF showed at 24 months a non significant difference (13.9%, p=0.41).

The subgroup of patients with classic-containing CNV was small and no statistical difference between groups was observed.

Analysis using the logistic regression showed at month 12, a significant interaction between treatment and baseline visual score (p=0.041) and at month 24, a significant interaction between treatment and baseline visual score (p=0.003) and baseline lesion size (p=0.024).

The results of the secondary efficacy endpoints (ITT population) are given in the table below:

		Verteporfin n = 225	Placebo n = 114	Difference	p[a]
30-letter responder					
At Month 12	% of patients	76.0	68.4	7.6	0.136
At Month 24	% of patients	70.2	52.6	17.6	0.001
Mean visual acuity changes					
At Month 12	mean # letters	-16.1	-20.0	3.9	0.027
At Month 24	mean # letters	-19.1	-25.1	6.0	0.003
Less than 34 letters (< 20/200 Snellen equivalent)					
At Month 12	% of patients	21.8	30.7	-8.9	0.072
At Month 24	% of patients	26.2	43.9	-17.6	0.001
Time to event					
Moderate VA decrease[b]	median # days	367	293	74	0.109
Severe VA decrease[c]	median # days	Not reached	724	-	0.024
Mean contrast sensitivity changes					
At Month 12	mean # letters	-3.6	-4.7	1.1	0.037
At Month 24	mean # letters	-3.8	-6.3	2.5	< 0.001
Progression of classic CNV					
At Month 12	% of patients	23.1	33.3	-10.2	0.019
At Month 24	% of patients	23.1	42.1	-19.0	0.001
Progression of occult CNV					
At Month 12	% of patients	56.4	69.3	-12.9	0.010
At Month 24	% of patients	45.8	54.4	-8.6	0.065
Lesion ≤ 6 MPS DA					
At Month 12	% of patients	58.2	42.1	16.1	0.001
At Month 24	% of patients	52.4	35.1	17.3	0.001
Mean GLD of leaking CNV					
At Month 12	microns	4076	4953	-877	0.001
At Month 24	microns	3179	4285	-1107	0.001

a Chi square test, log rank test, ANCOVA, Cochran-Mantel-Haenszel test, Wicoxon rank sum test

b Moderate VA decrease: 15 or more letters lost from baseline

c Severe VA decrease: 30 or more letters lost from baseline

At Month 12, the negative results are confirmed for decrease from baseline of less than 6 lines of visual acuity (i.e. 30 letters) and severe decrease in visual acuity to less than 34 letters, which is an important criterion as it corresponds to the threshold of severe visual handicap. For mean visual acuity decrease a difference between groups of only 3.9 letters is observed. The results of analysis of variance show a significant difference in adjusted mean change of 4.6 letters (i.e 1 line) in favour of verteporfin (p=0.027); however, this result is not clinically relevant (i.e. =1 line).
Results on classic or occult CNV progression, contrast sensitivity and and lesion size are statistically in favour of verteporfin.

At Month 24, all secondary efficacy variables except progression of occult CNV showed a statistical difference. These differences increased from Month 12 to Month 24. The difference in mean visual acuity decrease reaches 6 letters.

Fewer verteporfin-treated occult patients developed progression of classic CNV compared with placebo-treated patients (23.1% vs. 33.3% and 42.1% at Months 12 and 24, respectively) over the course of the study.

Results Secondary Efficacy Endpoints for subpopulation with no classical lesions or with classic-containing lesions

For patients who had occult only CNV, most secondary efficacy variables were favourable to verteporfin at Month 12. At Month 24, results for all secondary visual acuity and angiographic variables become statistically significantly different from placebo except for progression of occult CNV.

Visual acuity scores show a mean decrease between groups in favour of verteporfin of 5.2 letters (p=0.024) at Month 12 and of 6.5 letters at Month 24 (p=-.002).

At Months 12 and 24, respectively only 29.5% and 27.1% of verteporfin-treated patients compared with 42.4% and 48.9% of placebo-treated patients developed a classic CNV component in the Lesion.

Exploratory subgroup analysis for patients with occult but no classic CNV lesions with either baseline lesion size 4 MPS DA* or poorer baseline visual acuity <65 letters

(*4 MPS DA : Macular Photocoagulation Study Disc Area)

Univariate subgroup analyses and multivariable logistic regression analyses were performed for the primary efficacy variable. These analyses were conducted in the overall patient population but also in the occult with no classic CNV patient population.

For patient population who had occult with no classic lesions at baseline, these analyses revealed statistically significant interactions between the treatment effect and:

a) baseline lesion size,

b) baseline visual acuity scores.

They also indicated that:

a) smaller lesions at baseline (4 MPS DA) had significantly better treatment benefit than larger lesions (≥4 MPS DA);

b) patients with poorer visual acuity at baseline (<65 letters) had significantly better treatment benefit than patients with better visual acuity score (≥65 letters).

Thus, unplanned exploratory analyses based on baseline lesion size and visual acuity were repeated by the MAH for primary and secondary variables on a subgroup of patients "with occult but no classic CNV lesions with either baseline lesion size 4 MPS DA or poorer baseline visual acuity <65 letters." This subgroup contains 187 patients, 123 in the verteporfin group and 64 in the placebo group (i.e. 55% of the total population).

Primary efficacy variable results:

At month 12, the difference between verteporfin and placebo is not statistically significant for ITT analysis (14.6%, p=0.058). At month 24, that difference becomes statistically significant (26.2% in favour of verteporfin; p<0.001).

Secondary efficacy variables results:

Overall, the differences between treatments were in favour of verteporfin. Generally, a statistically significant effect is reached either at month 12 or at month 24.

This is particularly true for visual acuity scores, which show in addition a clinically relevant benefit at month 24 (10.8 letters; p<0.001) but a lower effect at month 12 (7.7 letters; p=0.003). These findings are confirmed for decrease from baseline of less than 6 lines of visual acuity (i.e. 30 letters) and severe decrease in visual acuity to less than 34 letters.

Angiographic criteria follow the same trend. At 2-year, angiographic results in this subgroup suggest that verteporfin treatment could reduce the development and the progression of classic CNV. This finding is of great clinical interest as the development of classic CNV is a sign of a severe progression of the disease.

The CPMP questioned the negative results for the primary endpoint in the Request for Supplementary Information and the lack of robustness in the 24 month results in the global population and in several subgroups of patients. The MAH responded that the 12-month time point was selected in the analysis plan of Study BPD OCR 002 to allow for the earliest possible submission if a benefit was shown. In Study BPD OCR 003, the 12-month time point was also selected as the primary analysis time point for consistency with Study BPD OCR 002. When the protocol for Study BPD OCR 003 was designed, limited information was available on occult choroidal neovascularisation (CNV) progression and there was no evidence to contradict the choice of the 12-month time point (based on the classic-containing CNV studied in Study BPD OCR 002).

The MAH further argued that the robustness of the results of Study BPD OCR 003 is confirmed by the logistic regression analysis (odds ratio = 3.35, p = 0.002) and the fact that the results were consistent over time in the second year. The difference in the responder rate was in favour of verteporfin at Months 18, 21, and 24 with a 95% confidence interval not containing 0 at each of the last 3 time points. In the AMD study population of Study BPD OCR 003, results of the 15-letter responder rate at 24 months are very similar in terms of treatment benefit with verteporfin in both analyses with LOCF (12.9%, p = 0.023), without LOCF (11.2%, p = 0.065) and also, for evaluable patients (9.8%, p = 0.146) without LOCF. The changes in p-value were due to the smaller sample size of the considered populations and not to an unbalanced effect between treatment groups of carrying forward the last observation or excluding protocol deviators. In this context, the differences between the different analyses are too small to conclude that they invalidate the observed treatment effect.
Moreover, the logistic regression analysis of the primary efficacy variable (15-letter responder rate) in evaluable patients confirmed the treatment effect observed in the ITT population (odds ratio in evaluable patients = 3.17 in favor of verteporfin, p = 0.010). Also, the analysis of the 30-letter responder rate with and without LOCF (p = 0.001 and 0.005, respectively) and for the evaluable patients (p = 0.014) was statistically significant at 24 months. These results support the robustness of a treatment effect on vision outcomes at Month 24.

Following the oral explanation the majority of the CPMP found that it is acceptable to interpret the reported difference in the primary efficacy parameter between verteporfin treatment and placebo treatment of 3.7 % (p=0.517) at 12 months, with a responder rate of 49.3 % and 45.6 % in the two groups, respectively, in connection with the corresponding 24 months results of a difference of 12.9 % (p=0.023), with 46.2 % versus 33.3 % responders in the two groups, respectively. The observed benefit occurs later than anticipated, but this may reflect the slow progression of the decrease in vision in this population.

As for the secondary efficacy parameters: The proportion of patients who lost fewer than 30 letters in VA, the mean VA change from baseline, the proportion of patients whose VA decreased to fewer than 34 letters, mean contrast sensitivity changes, progression of classic and occult CNV, all results were statistically different from those observed with sham treatment in favour of verteporfin at 24 months, except for progression of occult CNV. For contrast sensitivity and progression of classic CNV statistically significant differences were obtained also at 12 months.

In the Request for Supplementary Information the CPMP also asked the MAH to comment on the clinical relevance of the positive results observed on the total and occult populations at 24 months. The MAH responded that the clinical relevance of the results at 24 months is dependent on the clinical importance of vision and other outcomes that were prospectively planned efficacy variables. The MAH focused on five efficacy variables (15-letter responder rate, 30-letter responder rate, percentage of patients with < 34 letters, The development of classic CNV and mean visual acuity) as clinically important and in terms of all of them evidence of benefit was suggested at Month 12 and was conclusive at Month 24 time points with the exception of the 15- and 30-letter responder rates where the evidence of benefit was only confirmed at the 24 month time point.

At the oral explanation the MAH presented calculations of the number patient to be treated to have a 3-line responder (7.8 patients), a 6-line responder or to avoid legal blindness VA<20/200 (5.7 patients). The MAH also argued by comparing the percentage of 3-line and 6-line responders, the percentage of patients with VA<20/200 and the mean VA decrease that the disease progression was delayed by a year or more.

The majority of the CPMP concluded that although the total numerical benefits obtained may seem moderate the results should be considered in the perspective of the poor prognosis for the population, acknowledging that even a modest amelioration in the visual capacity may be of significance to these patients. Also in the application of low visus aids/optics even a slightly better visual capacity is of significance in the daily life of the patient. Apart from the VA results and the proportion of patients with a visual acuity below 34 letters, the parameter contrast sensitivity is of major importance, indicating a better paracentral visus, which is helpful for the patient. The majority of the CPMP felt that there is a need for an additional study in this indication and the MAH agreed to perform and report the requested additional study as a Follow-Up Measure.

After 24 months of follow-up, the percentage of patients who reported at least one adverse event (AE) considered as related by the investigator was higher in VTP group compared to the placebo group (43 % vs 18 %).

The incidence of visual disturbances (vision decreased, vision abnormal, visual field defect) in the BPD OCR 003 was higher than in the controlled BPD OCR 002 A and B studies.

Visual disturbances in the study eye occurred with a higher incidence in the treated group than in the placebo group (42 % vs 23 % for all AE / 30 % vs 8 % for related AE). Blepharitis is the other AE, which occurred with a difference in incidence between VTP and placebo ≥5 % (6 % vs 1 %).

Most of visual disturbances related to VTP :

- were considered as mild or moderate (74 patients of 94) ;
- occurred in the first 2 courses of treatment and within the first week after the treatment (about 65 % of visual disturbances were reported from 3 to 7 days after each treatment) ;
- seemed to resolve within a few days to a few weeks. However, about 50 % of the visual field defects were ongoing at the end of the 24 months follow-up;

In contrast, the majority of visual disturbances in the placebo group started a long time after any treatment and most did not resolve.

Among the 20 serious cases of visual disturbances, 11 (no placebo patient) were cases of severe vision decrease (a severe decrease in vision was defined as a decrease in visual acuity of at least 20 letters relative to pre-treatment and confirmed clinically within 7 days of treatment), i.e. 4.9 % of patients in this study:

- most of cases occurred after the first course of treatment (9 of 11 patients), and mostly within the first 2 days (7 of 9 patients). It is to be noted that one case occurred during the second year of treatment (course 7);
- for most of patients, vision decrease was still severe 3 months after the initial event and was comprised between –18 letters to –70 letters (average = - 28 letters). Independently, only one patient had gained 3 letters at the 3 month follow-up visit.
- the mechanism evoked by the MAH may be an increase in sub/intraretinal hemorrhage or neurosensory detachment.

Other serious ocular AE reported were mostly vitreous or subretinal hemorrhages (6 cases).

The incidence of visual disturbance events seems to be higher in patients with baseline VA ≥ 65 VA score than in patients with VA score < 65 letters except for vision abnormal in placebo-treated patients. However, it is to be noted that the difference is not statistically significant (p=0,09 ; Fisher test).

The adverse event, visual disturbance, is defined as the combination of three individual events: Vision abnormal, vision decreased and visual field defect. The incidence of this adverse event is higher in the present study (BPD OCR 003 AMD), namely between 10.7 % and 18.7 %, as opposed to 4.2 to 8.5 % in the classic-containing study (BPD OCR 002). The argumentation from the MAH that the higher incidence can be subscribed to the better baseline visual acuity and therefore with correspondingly more to loose in VA was accepted by the CPMP.

A partial or complete recovery vision baseline values has been observed for most of patients with severe vision decrease. No risk factor (treatment anomalies, predisposing medical history or concomitant medication) for developing severe vision decrease can be evidenced. The risk of experiencing severe decrease of vision is described in section 4.4 and section 4.8 of the SPC and the MAH agreed to add the percentage of patients with severe vision decrease to the SPC as requested by the CPMP.

Clinical studies in special populations

No specific clinical data in patients with impaired renal function were provided in the file but these patients were not excluded from the studies. In any case, no effect of renal dysfunction is expected in view of the pharmacokinetic data.

The effect of hepatic dysfunction on the pharmacokinetics of verteporfin was investigated in subjects with mild hepatic dysfunction and compared with subjects with normal hepatic function showing a significant increase in half-lives of verteporfin in subjects with mild hepatic dysfunction (4.9 vs 5.9 h and 4.7 vs 6.5 h respectively).

The SPC clearly reflects that there are no data related to renal impairment and mentions a contraindication in patients with severe hepatic impairment.

Studies were carried out with a large proportion of elderly patients (mean age approximately 75 years), which is the target population for AMD. No studies have been performed in children, since the specific form of macular degeneration cited in the indications is age-related.

Clinical safety

Patient exposure

The clinical development programme has involved a total of 878 subjects:

- Study BPD OCR 001 142
- Study BPD OCR 002 A 311
- Study BPD OCR 002 B 298
- Study BPD OCR 003 459
- Study BPD OCR 004 26
- Study BPD 004 17
- Study BPD 002 21
- Study BPD PSI 001 6
- Study BPD 001 35
- Study BPD PK 001 A 24
- Study BPD PK 002 B 24

The safety data were collected from two sources:

1. Ocular studies, 751 elderly patients participated in ocular studies, the posologies used were the following:

- BPD OCR 001, dose escalation study: light and drug doses were variable, 6 to 12 mg/m^2 for Verteporfin dose and 12.5-150 J/cm^2 for light dose.

- BPD OCR 002 A and B, two identical placebo controlled studies: as defined in dose escalation study and as reflected in the SPC, light and drug doses were 6 mg/m^2 for verteporfin and 50 J/cm2 for light dose. These studies were planned for two years. A global analysis of all patients up to at least 12 months was provided in the original Integrated Safety Summary. A Safety Update was provided later for all patients up to at least 18 months.

In the two main ocular studies A & B, a total of 2164 verteporfin treatment courses were administered to 402 patients, giving an average number of 5.4 verteporfin courses per patient. (These figures are derived from an 18-month Safety Update report, and include data at the 21-month point for a limited number of patients).

2. Extra ocular studies

The exposure to verteporfin was higher (6-20 mg/m^2 + light 40.5-150 J/cm^2) and the mean age of patient population was lower (58 years) than in ocular studies. Thus, these trials are of interest to study systemic adverse events:

BPD 004: comparative study between subjects with normal hepatic function and subjects with mild hepatic impairment.

BPD 002 and BPD PSI 001: in psoriasis.

BPD 001: in cutaneous malignancies.

Adverse events and serious adverse events/deaths

Original Integrated Safety Study results (12m):

1 Overview of results from three ocular studies (001, 002A, 002B):

	VERTEPORFIN N = 544	**PLACEBO** N = 207
AGE	74,2 years	76 years
SEX	Female : 52% Male : 48%	Female : 63% Male : 37%
RACE	Caucasian : 98.7 % Other : 1.3 %	Caucasian : 98.1 % Other : 1.9 %
Number of adverse events (AE)	1774	729
Related AE	534	117
Treatment discontinued due to AE	12	1
Death	11	6
Death related	0	0
Serious AE	180	91
Related SAE	22	4

The target population is elderly patients (mean age: 74.2 years for verteporfin and 76 years for placebo). The medical history of these elderly patients explain the observed frequent use of concomitant medications, and this in turn may explain some of the adverse events (AEs) encountered during the studies. From the safety point of view, no drug-interactions were detected from the clinical studies.

In the Verteporfin group (544), 396 patients reported at least one adverse event and, in the placebo group (207), 178 patients reported at least one adverse event (72,8 % versus 86 %).

Body systems	VERTEPORFIN N=544	PLACEBO N=207
Body as a whole	38.2 %	42.0 %
Cardiovascular	16.7 %	17.4 %
Digestive	14.3 %	17.9 %
Endocrinologic	0.4 %	1.0 %

Blood and lymphatic	6.6 %	4.3 %
Metabolic and nutritional	13.6 %	20.8 %
Musculoskeletal	8.1 %	14.5 %
Nervous	15.1 %	15.5 %
Respiratory	13.2%	16.9 %
Skin	10.1 %	12.1 %
Special Senses	16.2 %	23.7 %
Ocular	35.5 %	30.9 %
Uro-genital	8.3 %	13.5 %

Two body systems (ocular system and blood and lymphatic system) show clearly more frequent AEs in the Verteporfin group than in placebo treated patients.

- Ocular system AEs :

ALL	VERTEPORFIN N=544	PLACEBO N=207
Vision abnormal	9.6 %	9.2 %
Vision decreased	6.1 %	4.3 %
Visual field defect	3.7 %	2.4 %

- Back pain:

Back pain was reported by 21 patients (3.9 %) in the Verteporfin group (11 cases (2 %) including low back pain. In the placebo group, back pain was reported in 6 patients (2.9 %). In one case, low back pain was responsible of the discontinuation of the treatment.

- Local reaction:

Injection site adverse events in studies BPD OCR 002 A&B:

6 adverse events were reported more frequently in the verteporfin treated group versus the placebo group.

- Blood and Lymphatic System:

Verteporfin was involved in 36 cases (6.6 %) and placebo in nine (4.3%). 16 anaemias were reported: 2.9 % versus 1.9 % for the placebo group. The erythrocyte count was altered: 6 patients at 6 months and 5 at 12 months. At the same date: 2 patients of the placebo group had a change in the erythrocyte count.

Deaths in the two controlled studies 002A & 002B:

12 deaths were reported in controlled studies: 8 in the Verteporfin group (2 %), and 4 in the placebo group (2 %) in studies BPDOCR 002 A and B. The causes were:

Cardiopulmonary disease: 8
Malignancies: 3
Pancreas: 1.

10 deaths were considered as not related to treatment and only 2 were considered as unlikely related to treatment: a necrotizing pancreatitis in the verteporfin group and arrhythmia in the placebo group.

In such an elderly population, some reports of death are not unexpected.

Serious Adverse Events
Serious adverse events were reported in the two controlled studies (BPD OCR 002 A and B):

- 66 in the Verteporfin group (16 %),
- 36 in the placebo group (17 %).

These concerned mainly cardiopulmonary events and malignancies.

In the verteporfin group, 60 were quoted as unlikely or not related to treatment.

6 patients of the Verteporfin group exhibited adverse events, which were quoted as 'possibly' or 'probably' or 'definitely' related to the treatment:

- 3 ocular reactions:

  large subretinal pigmented epithelium haematoma
  visual acuity decrease,
  decrease in reading and distant vision.

  The symptoms started from a few hours to two days after treatment and these cases were quoted possibly for the first and probably related for the two others.

- 2 local reactions:

  2 paravenous infusions with, in one case, photosensitivity following exposition to sunlight. The site of these adverse events make these reactions « definitely related ».

- 1 anaemia:

  The patient was hospitalised but had previous iron deficiency anaemia.

Patients withdrawn from treatment due to adverse events
12 patients discontinued treatment because of adverse events in studies BPD OCR 002 A and B, 11 from Verteporfin group (2.7 %), and 1 from the placebo group (0.5 %).

3 vitreous haemorhage, 1 retinal detachment, 1 suprachoroidal haemorrhage and 1 extensive subretinal haemorrhage were encountered in 3 patients, one of them being a placebo treated patient.

These events were considered as « possibly » related to treatment, but 2 vitreous haemorrhages were considered as unlikely related to treatment.

Site injection
1 pain at injection site 'definitely' related to treatment.

Others
3 allergic reactions: one with shortness of breath and increase of blood pressure, and an other with a skin rash attributed to fluorescein, were considered as possibly related. Another case was an allergic reaction to mydriatics and was considered as not related to treatment.

Laboratory findings

Slighly higher incidences were reported for change in serum creatinine in the verteporfin group : in the studies BPDOCR 002 A and B, 5 patients exhibited an increase in serum creatinine at month 6 and 10 patients at month 12.

Hypercholesterolemia: 22 patients group (5,4 %) were reported with hypercholesteremia in the Verteporfin and 14 in the placebo group (6,7 %).

Safety Update (18 months)

The Safety Update (representing an additional 6 months of data in the ongoing trials) confirms the ocular adverse event and systemic safety profile for verteporfin as originally presented in the Integrated Safety Summary, ISS:

The overall incidence of ocular adverse events was slightly higher in the Safety Update (43% and 37% for verteporfin and placebo, respectively) than in the ISS (37% and 31% for verteporfin and placebo, respectively) and this difference was mainly due to a slightly higher incidence of visual disturbance events (21% and 16% in the verteporfin group and the placebo group, respectively).

Subretinal haemorrhage incidence in verteporfin group was slightly higher for verteporfin in the Safety Update (2.2%) than in the ISS (1.5%) while the incidence in the placebo remains the same (1.0%).

Both sets of data are consistent in showing that a higher percentage of verteporfin–treated patients than placebo-treated patients had study eye adverse events.

The occurrences of injection site pain have decreased with more experience in the study.

Only one additional patient experienced photosensitivity reaction and one another experienced infusion-related back pain, these two reactions occurred on the day of treatment and resolved quickly (within one day).

In the supportive ongoing masked Study OCR 003, most patients had completed their 6-month follow-up. The data show similar results for AMD population than in studies OCR 002 A and B except for the incidence of visual disturbance and severe vision decrease that appeared at higher incidence. This was already pointed out in ISS. No further severe vision decrease was reported in the Safety Update.

Non ocular studies: additional serious adverse events and deaths were not related to the treatment.

The likelihood of a continuously acceptable safety profile is acknowledged. There is little reason to be concerned about ocular safety, however, because of the poor prognosis for subfoveal classical neovascularisation.

Apart from the specific AE profile, a general safety issue common to both the ISS and the Update is that some degree of light sensitivity may be expected considering the mechanism of action of PDT itself. Therefore a recommendation has been added to the SPC to the effect that the patient should avoid strong light for 48h after the therapy.

Safety Update following the Type II Variation (II/01), authorised 2001

i.e. includes the 1-year results from Study BPD OCR 003 in PM patients and Study BPD OCR 004 in OHS patients :

In addition to the safety data from studies BPD OCR 002A & 002B in an AMD population whose mean age was 75 years and in whom the medical history explained the frequent use of concomitant medications, the more recent ocular studies BPD OCR 003 PM and BPD OCR 004 give information related to a younger patient population of around 50 years of age with Pathologic Myopia or Ocular Histoplasmosis Syndrome (this last indication was not authorised).

The comparison of the analysis of the safety data by body systems for the OCR 002 A&B-studies at two years and the OCR 003-study at one year with that of the additional studies confirms that a higher incidence of adverse events could be related to Visudyne than to placebo for some of the body systems, but do not indicate additional verteporfin toxicity on a specific organ system, or any difference with the verteporfin safety profile of the AMD population as previously analysed.

However, arising from BPD OCR 003, at the cut-off date of June 15, 2000, two serious adverse events in 2 verteporfin PM patients led to study discontinuation:

- colon cancer with liver metastasis diagnosed two months after the last treatment, in a 60-year-old Asian woman who received two courses of VTP treatment (patient V13P51),
- allergic reaction with dyspnoea during the verteporfin infusion in a 41-year-old caucasian woman

The allergic reaction was considered related to Visudyne (the colon cancer was not).
No death was reported in either Study BPD OCR 003 PM or Study BPD OCR 004.
This suggests that case reports of suspected allergic reactions occurring in Visudyne-treated patients should be closely documented, especially as this is supported by the results of pre-clinical studies (In sedated or anaesthetised pigs, a Visudyne dose significantly higher than the recommended dose in patients given as a bolus injection caused severe haemodynamic effects including death, probably as a result of complement activation). The SPC section 4.4 highlights this allergic risk.

Safety in special populations

All data relate to adult patients. No studies have been performed in children since the specific form of macular degeneration cited in the indication is age-related.

Safety Update following the first and second PSUR

In the assessment report for the first PSUR, the MAH was asked to provide a cumulative safety review on cardiovascular events.

The data provided from the placebo-controlled studies including 627 AMD patients showed that the incidence of serious cardiovascular adverse events is similar in VTP and placebo groups. However, data from post-marketing surveillance showed that clinical symptoms indicative of vasospastic angina could occur in patients, with or with no cardiovascular medical history (occurrence during VTP infusion, outcome rapidly favourable after trinitrine treatment, normal cardiac evaluation). The physiopathologic mechanism is still unknown.

The occurrence of chest pain was already mentioned in section 4.8. of the SPC, however, the CPMP requested that the term "chest pain" was added to section 4.4. of the SmPC, which was introduced through a Type II variation.

Three cases of vaso-vagal attacks, which occurred during the verteporfin infusion were notified during the period covered by the second PSUR: one serious case of asystolic cardiac arrest, syncope, and vasovagal reaction, one serious case of collapse associated with back pain and one non serious vaso-vagal episode. Moreover, follow-up information received for a case described in the first PSUR led to reclassification of a case of cardiac event as serious vaso-vagal reaction associated with syncope, and grand mal seizure, 2 minutes into the verteporfin infusion, in a patient considered as "extremely tense before the procedure".

Two serious cases of hypersensitivity were reported during the period covered by the second PSUR :
In both cases, the outcome was favourable on stopping verteporfin infusion and single treatment with a histamin-1 receptor blocking drug. Additionally, four non-serious cases of allergic reaction were reported.

The occurrence of serious hypersensitivity reactions and vaso-vagal reactions during the infusion of verteporfin were added to the SPC (section 4.4 and 4.8) and to the Package Leaflet through a Type II variation. |It was also added to section 4.4. of the SPC that patients should be under close medical supervision during the Visudyne infusion.

5. Overall conclusions and benefit/risk assessment

Quality

The applicant has developed a product of satisfactory quality in relation to the clinical use, i.e. a stable, sterile powder suitable for solution for injection. The manufacturing process has been validated and provides a satisfactory assurance that the product will be sterile when opened for the first time. Methods used for batch control and stability studies have been validated and should ensure a product of reproducible quality.

Pre-clinical pharmacology and toxicology

The toxicological file is acceptable for the present indication i.e. one single i.v. injection which may be repeated at three month intervals. A satisfactory set of experiments was performed to demonstrate the safety of verteporfin after light irradiation, especially on skin and eye, which can be directly exposed. All the excipients were presented as safe for use in the formulated product and the explanation given for the haematopoietic effects observed with high and repeated doses in the animal studies is that high concentrations of lipids lead to increased extramedullary haematopoiesis, due to lysis of erythrocytes caused by membrane fluidity changes.

No preclinical studies where verteporfin was repeatedly administrated indicated that the compound is immunogenic. In genotoxicity studies the test cell systems were exposed to verteporfin at appropriate concentrations, and therefore the observed results are valid.

It was clearly demonstrated that the degree of damage caused by verteporfin as well as its specificity for the targeted tissues is dependent on drug dose, i.e. blood level, light dose, and timing of activation.

Clinical efficacy

Full ADME studies were not performed, however, trials were properly designed, realised and analysed. The CPMP considered that the kinetic data provided were not sufficient to define a light protection period for the patient after PDT with verteporfin; this was defined on the basis of the safety data generated in the controlled clinical trials.

As sample sizes in the dose evaluation study were small, further optimisation of the treatment regimen may be possible. The observed results in both controlled trials were consistent for both primary and secondary efficacy parameters. Overall, compared to placebo group, the loss in visual acuity was lower in patients receiving Visudyne. Moderate and severe decreases in visual acuity were significantly reduced by the treatment.

The combined one-year main efficacy results have shown acceptable efficacy (+14.8% of responders in verteporfin group as compared to placebo) in slowing down the vision loss in the two placebo-controlled trials (BPD OCR 002 A and 002 B) in which a total of 609 patients were enrolled.

Concerning the subgroup of patients with predominantly classic CNV, the difference at one year was 27.5% favouring verteporfin (combined studies A & B).

Considering the elderly patient population and the long duration of the study, the majority were actually followed up and had visual acuity assessments.

The combined two years main efficacy results (studies A & B) show that verteporfin efficacy is maintained in the entire population studied (+15.3% of responders in verteporfin group as compared to placebo) as well as in the prospectively determined subgroup 'predominantly classic CNV' (+28% of responders in verteporfin group as compared to placebo).

Concerning Pathologic Myopia, and considering :

- the clinical importance of the benefit in relatively young patients,
- the degree of the observed improvement of visual acuity which appears more pronounced than in AMD patients,
- the two-year experience of verteporfin in AMD,

The CPMP considered that PDT of CNV related to pathological myopia could be recommended.

The majority of the CPMP considered that the indication of occult subfoveal choroidal neovascularisation due to age-related macular degeneration was acceptable. Although the total numerical benefits obtained may seem moderate the results should be considered in the perspective of the poor prognosis for the population, acknowledging that even a modest amelioration in the visual capacity may be of significance to these patients. Also in the application of low visus aids/optics even a slightly better visual capacity is of significance in the daily life of the patient.

Retreatment is allowed every 3 months if necessary, and up to four times a year.

Clinical safety

There is no major safety concern arising from the analysis of the safety data, which rests on the main ocular efficacy studies plus additional supportive dermatological studies.

The safety analysis as expected indicates that adverse events were observed at the injection site and in the eye, which are target organs due to the route of administration and modality of PDT for AMD & PM. However, there also appears to be a high rate of back pains observed during the studies, and this is also reflected in the SPC. Arising from a Type II Variation (II/01) to extend the indication, and preclinical studes, the case reports of Visudyne patients with allergic reactions should be closely documented. This is related to the case observed in a PM patient and to pre-clinical data related to the activation of Complement in anaesthetised pigs although no clinically relevant complement activation was reported in clinical trials. The SPC section 4.4 highlights the allergic risk.

The incidence of visual disturbances (vision decreased, vision abnormal, visual field defect) is higher in the study BPD OCR 003 AMD, namely between 10.7 % and 18.7 %, as opposed to 4.2 to 8.5 % in the classic-containing study (BPD OCR 002). Visual disturbances in the study eye occurred with a higher incidence in the treated group than in the placebo group (42 % vs 23 % for all AE / 30 % vs 8 % for related AE).

A partial or complete recovery vision baseline values has been observed for most of patients with severe vision decrease. No risk factor (treatment anomalies, predisposing medical history or concomitant medication) could be determined. The risk of experiencing severe decrease of vision is described in section 4.4 and section 4.8 of the SPC as well as the percentage of patients with severe vision decrease.

One of the general safety concerns of PDT therapy is the duration of the period for light protection to be recommended. In this case, the CPMP considered that the period for light protection should be 48 hours, which is that studied in controlled ocular clinical trials for AMD.

Benefit/risk assessment

Considering that there appears to be no major safety concern arising from the use of Visudyne, and the efficacy data are satisfactory in the indication as defined in Section 4.1 of the SPC, the benefit/risk analysis for this product is positive.

It is clear from the 2-year efficacy results in CNV related to AMD that the treatment slows down the loss of visual acuity rather than improves vision. The treatment has been shown effective in CNV closure. However, most of the patients (80%) required repeated treatments at least 3 times a year because of early recurrences. The efficacy of PDT with verteporfin has been demonstrated from the two-year results of both clinical trials in the treatment of age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularisation.

Concerning the 1-year efficacy results in CNV related to PM, the CPMP expected that the benefit could be maintained similarly to the experience of PDT in AMD. As there are no alternative treatments in patients with subfoveal CNV in myopic eyes, the CPMP therefore considered that the two-year results could be provided as a post-authorisation measure. . The two-year results were submitted in April and July 2001. The results no longer reached statistical significance and suggested that the clinical benefit may decrease over time. However, the CPMP concluded that the results showed more variability than a clear temporal trend and were numerically still in favour of verteporfin.

The majority of the CPMP considered that the indication of occult subfoveal choroidal neovascularisation due to age-related macular degeneration was acceptable. Although the total numerical benefits obtained may seem moderate the results should be considered in the perspective of the poor prognosis for the population, acknowledging that even a modest amelioration in the visual capacity may be of significance to these patients. Also in the application of low visus aids/optics even a slightly better visual capacity is of significance in the daily life of the patient.

Thus, in total, the indication in the SPC reflects the patient population in which efficacy has been demonstrated.

Concerning safety, an 18 months analysis was available at the time of the original opinion, later supplemented by the full 24-months analysis as for efficacy.

Therefore, based on the CPMP review of data on quality, safety and efficacy, the CPMP considered that the benefit /risk profile of Visudyne was favourable in the following indication:

for the treatment of patients with age-related macular degeneration with

- Predominantly classic subfoveal choroidal neovascularisation
- Occult subfoveal choroidal neovascularisation with evidence of recent or ongoing disease progression

or

patients with subfoveal choroidal neovascularisation secondary to pathological myopia.