SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of PhotoBarr. For information on changes after approval please refer to module 8.

1. Introduction

Barrett's Oesophagus (BO) is a metaplastic disorder in which normal squamous epithelium of the oesophagus is replaced by a specialised columnar epithelium. It is an acquired condition, secondary to chronic, severe, and long-standing gastroesophageal reflux and the subsequent damage of the mucosa.

It is estimated that BO is found (depending on the inclusion of so-called "short segment" Barrett) in approximately 6-12% of patients undergoing endoscopy for symptoms of gastro-oesophageal reflux disease and in 1% or less of unselected patient populations.

The diagnosis of BO is established if the squamocolumnar junction is displaced proximal to the gastroesophageal junction, and intestinal metaplasia is histologically detected after the performance of biopsies.

BO is associated with an increased incidence of oesophageal adenocarcinoma. Adenocarcinoma of the oesophagus has been recognised as one of the malignancies with the fastest increasing numbers since the 70s in the Western world. However, the absolute incidence of this cancer still remains low (in comparison with the incidence rates of e.g. colorectal or lung cancer).

Whereas the dysplasia-carcinoma sequence in BO is widely uncontroversial, the issue of the precise incidence of adenocarcinoma in patients with BO in general is uncertain. Recent findings revealed that the actual cancer risk has been overestimated in the previous years and will amount, in the general BO population, to 0.5% or less annually.

Screening and surveillance programs have been developed for BO based on the poor 5-years survival rate of 11% for oesophageal cancer. Goal of surveillance in patients with BO is to detect cancer at an early stage. Therapy at an early stage of cancer can dramatically improve 5-years survival rates. However, no clinical trials have been performed to link the performance of rigorous surveillance programs with increased survival.

Surveillance is primarily directed to the detection of dysplasia which itself is classified according to a 5-grades system ranging from negative for dysplasia, indefinite dysplasia, low-grade dysplasia, high-grade dysplasia (HGD) to carcinoma. Recommendations for surveillance intervals range according to these stages for those without dysplasia from 2-3 (even 5) years to intervals for those with HGD of 3 months.

These intervals and programs have been recommended although the actual incidence of adenocarcinoma in HGD has been a matter of dispute:

Studies performed during the 90s have revealed that carcinoma is detected at oesophagectomy in approximately 40% of the patients with (preoperative) high-grade dysplasia, with a range of 0-73%. Also, studies investigating surveillance without surgery in patients with HGD found discrepant results in the rate of cancer incidence from "only" 20% of patients developing cancer after 7 years up to 60% within 5 years.

Currently, therapy of BO and HGD in BO consists of a basic therapy of acid suppression with high-dose proton pump inhibitors. This therapy, however, results either in no or in modest regression of the Barrett's segment at best. Proton pump inhibitors typically increase squamous islands in the Barrett's mucosa with intestinal metaplasia persisting underneath. As observation times have been short and the clinical significance of the modest regression of BO observed is uncertain, the value of acid suppressive therapy in BO and in HGD in BO remains uncertain. The same problems apply to anti-reflux surgery which can be performed as an alternative to pharmacological acid suppression.

Therefore, many clinicians recommend the performance of oesophagectomy once the diagnosis of HGD has been established. However, morbidity and even mortality after surgical resection is high, ranging from 18%-48% for morbidity and a 3-5% mortality rate at experienced centres and up to 10%

in less experienced centres. These results have also to be seen in the light of the fact that a certain proportion of these patients would never have developed invasive cancer.

Thus, the need for alternative, less invasive and less dangerous methods specifically for HGD is obvious.

The search for alternatives is reflected in the reports of a growing number of ablative methods used in HGD in BO. These range from the use of photodynamic therapy (PDT) with substances other than porfimer sodium (most widely used 5-aminolevulinic acid), different laser thermal coagulation/ablation techniques, thermal ablation including argon plasma coagulation, to endoscopic mucosal resection. None of these forms of therapy can be regarded as an established treatment and for none of these techniques convincing documentation is available that goes beyond the performance of mostly small, short-term and uncontrolled, pilot studies.

About the product

PDT with porfimer sodium in general is an established procedure and the product Photofrin has marketing authorisations in most member states for longer than a decade, albeit for different therapeutic indications. The general principle of PDT with porfimer sodium is the specific enrichment, or better delayed clearance, of haematoporfimer derivates in, or from, dysplastic, metaplastic or malignant transformed epithelia compared to surrounding not transformed epithelia. It is assumed that differences in vascularisation of transformed and non transformed epithelium play the major role in the specific enrichment in, or delayed clearance from, transformed epithelia of photodynamic substances although the exact mechanism is not fully understood. Accordingly, administration of laser light (in the case of porfimer sodium light of the wave length of 630 nm) is performed with a delay after administration of the photodynamic active substance. Both the dose of 2 mg/kg porfimer sodium and the time interval of 40 to 50 h between porfimer and laser light administration have been found more or less empirically (most of the work was done with Photofrin in obstructive lung and oesophageal cancer). It is assumed that after the time interval of 40 to 50 hours and the administration of 2 mg/kg body weight the ratio of the concentration of photodynamic active substances in transformed vs. the surrounding not transformed epithelium is optimal. This means also that the peak concentration in the transformed lesions may just have passed at the time point of the PDT. The photodynamic reaction caused by the illumination with the light of the wavelength of 630 nm is thought to be due to the formation of singlet oxygen (requiring the presence of oxygen) being toxic for cells and thus causing cell death and (specific) eradication of illuminated (malignant) transformed epithelia. For a better understanding it should be noted that PDT uses, in comparison to thermal ablation with e.g. a Neodym/YAG laser, light of low energy. The photodynamic effect is not directly seen during the endoscopic procedure but requires time (typically 1 to 3 days).

A clear advantage of ablation of a transformed epithelium using the photodynamic effect vs. ablation based more on direct thermal or even mechanical effects on the lesion is a priori not evident. However, none of the ablative alternatives have the range of being standard therapy of HGD of BO.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

PhotoBarr is formulated as a powder for solution for injection containing 15 mg or 75 mg of porfimer sodium, as active substance. It is to be reconstituted with a 5% dextrose solution (final concentration 2.5 mg/ml).

The other ingredients include nitrogen contained in the headspace of the vial, sodium hydroxide and hydrochloric acid.

PhotoBarr is supplied in type I clear glass vials, which are closed with a butyl rubber stopper and an aluminium seal.

Active substance

Porfimer sodium is not a new chemical entity and is already registered in Europe. It is not a single chemical entity but a complex mixture of oligomers of porphyrin units joined by either ether or ester

linkage, ranging from dimers to octomers, and four related monomeric impurities. These latter do not contribute to the phototherapeutic effect of the product.

The active substance is a dark red to reddish brown cake or crystalline powder, sensitive to high temperatures and light. It is soluble in water and like other large organic anions it exhibits dynamic aggregation/desegregation equilibrium in aqueous solution. Porfimer sodium is prepared through a two-step synthesis from commercially available hematoporphyrin dihydrochloride derived from porcine hemin. Acceptable specifications and associated methods have been provided for the starting materials, key intermediate, reagents and solvents.

Two synthesis processes (process I and IR) were used during development phase, before commercial process II was established. Changes introduced in the second step have permitted to obtain lower monomer content, higher oligomer content and to improve the stability of the bulk concentrate.Satisfactorty viral safety data have been provided in support of hematoporphyrin dihydrochloride starting material derived from porcine hemin.

Specification

The active substance specification include test for description, identification (UV/Vis - HPLC), assay (HPLC), impurities, concentration, pH (PhEur), bacterial endotoxins (PhEur) and microbial limits (PhEur).Porfirmer sodium being chemically complex, it has not been feasible to fully characterise it. No single oligomeric or individual component of porfimer sodium (other than the related monomers) has been isolated and identified so far by standard physical/analytical methods. As a consequence, the active substance is identified by comparison to a reference standard which has been satisfactorily characterised. The HPLC method used for the assay and purity tests is capable of separating the active substance from its process-related impurities and degradation products. All the specification limits have been adequately justified by analytical, stability and toxicity data.

Batch analysis data have been provided for 83 batches (51 produced using the commercial synthetic process II) synthesised by the 3 processes and confirm satisfactory compliance and uniformity with the proposed specification.

Stability

Stability data are available for three full-scale batches produced by the commercial synthetic process II and stored under long-term conditions. Under accelerated conditions 1-month data is available. A photostability study has been performed and indicates that the active substance is light sensitive, as expected.

These data support the proposed retest period of 3-month at -20ºC and of 8 days at 2-8ºC in polycarbonate bottles with polypropylene closure protected from light. The active substance is tested prior to use to ensure conformity to specification.

Other ingredients

The other ingredients that may theorically be present i.e. sodium hydroxide, hydrochloric acid are of PhEur quality. Nitrogen is present in the headspace of the vials (see Product development).

Regarding the TSE risk, PhotoBarr includes no component of ruminant origin. The conventional viral safety risk has been satisfactorily addressed (see active substance).

The type I glass vials and the butyl rubber cap used as primary packaging material for the finished product meet the general Ph Eur requirements. Compatibility of the finished product with the primary packaging material has been addressed.

Product development and finished product

For stability reasons and ease of use, a freeze-dried formulation has been chosen over the frozen liquid formulation initially developed (final concentration of porfimer sodium for both formulations: 2.5 mg/ml). Due to incompatibilities of the active substance with common lyophilisation excipients, porfimer sodium is formulated without excipients apart from sodium hydroxide and hydrochloric acid used to adjust the pH before lyophilisation. The presence of nitrogen in the composition of the finished product is due to its use at the end of the lyophilisation step to release the vacuum and is not used for

stability reasons. The choice of a 5% dextrose solution for reconstitution has been adequately justified by compatibility studies.

The instability of porfimer sodium at high temperatures precluded a terminal sterilisation of the finished product. Therefore, a sterilising filtration followed by an aseptic process is performed.

The filling overages prior to freeze-drying and the recommended volume of 5% dextrose solution to be used for reconstitution are suitable to allow withdrawal and administration of the labeled content.

The method of manufacture involves the following operations: weighing and mixing of different batches of refrigerated or frozen bulk concentrate of porfimer sodium, pH adjustment, calculation of the target vial fill, sterile filtration, filling into vials and freeze-drying under aseptic conditions, sealing of the stoppered vials with an aluminium seal and packaging. Satisfactory in-process controls have been established. The entire manufacturing process, including all the critical steps i.e. sterile filtration, aseptic filling and lyophilisation process, has been satisfactorily validated at commercial scale.

Specification

The product specification include tests for appearance, identity (UV/VIS, HPLC), assay (HPLC), impurities (HPLC), ester content (HPLC), reconstituted solution (reconstitution time, appearance and degree of coloration, pH (PhEur), particulate matter (PhEur)), water content (PhEur), uniformity of content (PhEur), bacterial endotoxins (PhEur), sterility (PhEur), biological assay, oligomer characterisation, osmolarity of the reconstituted solution.

Batch analysis data provided for production-scale batches comply with the specifications and indicate consistent and reproducible manufacture.

Stability of the product

Stability of the Product before reconstitution

36-month data are available under long-term conditions in packaging intended for commercialisation. Up to 6-month data under accelerated conditions are available.

The results presented support the proposed shelf life and storage conditions defined in the SPC.

In-use stability of the reconstituted solution

In use stability of the reconstituted solution was tested either directly after reconstitution with dextrose 5% or after storage at 3ºC or 25ºC for 24h.

The results presented support the proposed shelf life and storage conditions defined in the SPC

Discussion on chemical, pharmaceutical and biological aspects

The active substance is well characterised and documented. The pharmaceutical form selected is adequate taken into account the properties and stability of the active substance. The excipients are commonly used in this kind of formulation and the packaging material is well documented. The manufacturing process enhances to obtain reproducible finished product batches. Stability tests indicate that the product is stable for the proposed shelf life.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

The efficacy of Photofrin as an anti-tumour agent is dependent upon light activation at an appropriate wavelength. A number of laser light sources may be used for PDT with Photofrin, all of which can be coupled to optical fibres that are easily positioned for maximal effect and can also be used with an endoscope. The recommended laser light dosimetry is based on the most efficient delivery system for producing necrosis at appropriate tissue depths for tumour destruction while sparing surrounding normal tissue.

Most evidence for the efficacy of HPD and Photofrin with light activation as anticancer agents has come from clinical trials in patients. However, preclincal studies using different species (mouse, rat,

dog, cat) and tumour models (either spontaneous or transplanted) including myosarcoma, mammary, bladder, lung, ocular, glioma and kidney, have been carried out under a number of experimental conditions. In general, beneficial responses have been reported.

It is well established that the efficacy of PDT is dependent on oxygen levels, and that singlet oxygen and/or free radicals are likely to be the major toxic products of the photodynamic action both *in vivo* and *in vitro.* Studies conducted in mice with transplanted Lewis lung carcinoma and a study conducted in dogs with transplanted squamous cell carcinoma have shown that PDT with HPD effectively produced tumour necrosis and regression in animal models of lung cancer during short-term follow-up. Local efficacious PDT doses to a tumour that develops reproducible lung metastases did not enhance distal tumour dissemination and in fact resulted in comparable or lower numbers of pulmonary metastases than those seen following surgery alone (studies conducted in mice with transplanted Lewis lung carcinoma). Other models showing positive responses include bladder cancers in mice, rats and dogs, melanomas in mice, rhabdomyosarcoma in rats, and solid head and neck cancers in dogs. Depending upon the precise conditions used, tumour regression and necrosis are often preceded by shutdown of the tumour microvasculature.

Within the cell, the major sites of Photofrin binding have been noted as the membranes, particularly the cellular and mitochondrial membranes. Recent experiments with Photofrin using human embryonic epithelium cells provide evidence that the monomeric components of Photofrin are rapidly taken up by cells whereas oligomeric components have a slower uptake and release. Furthermore, the oligomeric elements of the mixture binds more strongly than monomeric to cellular and subcellular membrane structures owing to their greater lipophilicity.

A variety of morphologic changes have been noted in cells exposed to photodynamic treatment with Photofrin. Mitochondrial and cellular swelling preceding cell lysis thought to be associated with alterations in membrane permeability. Cross-linking of membrane proteins was observed prior to the onset of photoactivated protoporphyrin IX induced haemolysis.

In prostate tumour tissues treated with PDT *ex vivo*, cell damage was widespread and included mitochondrial and endoplasmic swelling as well as nuclear and cellular disintegration

Many changes at the molecular level have been associated with Photofrin PDT. Diminution of the activity of a number of enzymes involved in membrane biosynthesis, particularly acyltransferases. Mitochondria are a significant intracellular target for Photofrin, and inhibition of the associated respiratory processes produces cell death. Human bladder transitional cell carcinoma cells, following sublethal PDT treatment, were found to release arachidonic acid metabolites, mainly thromboxane B2 and prostaglandin E2 in a biphasic manner. Photocytotoxicity can be partially mitigated by agents such as indomethacin which block the action of PGE, suggesting a relationship between PGE and photodynamic cell damage. PDT treatment of macrophages *in vitro* stimulates the production of TNF (tumour necrosis factor), a cytokine known to induce haemorrhagic necrosis of tumours. The urine of bladder cancer patients following Photofrin PDT has been shown to contain elevated levels of the cytokines interleukin-1 (IL-1), interleukin-2 (IL-2) and TNF. It is not known whether this is a direct or indirect effect of PDT.

Mitomycin C, which blocks cells at G_2/M, enhances the effects of PDT. In a human colon adenocarcinoma cell line mitomycin C treated cells were shown to take up significantly higher levels of Photofrin than untreated controls.

PDT with Photofrin or HPD is dependent on oxygen for efficacy, and the generation of active oxygen species, namely singlet oxygen or free radicals, is responsible for the photodynamic effects seen on cells. Quenching of these species under experimental conditions has been shown to mitigate the effects of PDT . Treatment of TA-3 mouse mammary carcinoma cells with diphenylisobenzofuran (DPF) protected cells from the effects of Photofrin followed by light exposure. Similarly, DPF prevented cytotoxicity induced by PDT with HPD in human gastric cells. HPD-induced cell lysis was moderately inhibited by dimethylsulfoxide, ethanol, formate, and mannitol, all of which react with hvdroxyl radicals, indicating a possible role for free hydroxyl radicals in the photodynamic effect on cells. Etanidazole, rnisonidazole and trifluoro-misonidazole were all found to be photoprotective against Photofrin when cells were incubated for 24 hours with Photofrin under aerobic and lirnited oxygen (0.3%) conditions.

- *Secondary pharmacodynamics*

General pharmacology studies were performed in mice, rats, guinea pigs and dogs under conditions of weak light for 12 hours a day. For general conditions in mice no effect was observed in 25 or 50 mg/kg porfimer sodium administered intravenously. At 100 mg/kg and 200 mg/kg there were some disorders in general condition and at 200 mg/kg all animals died at least within 3 days which is not surprising because this is within the range of the LD50. With regard to the central nervous system, porfimer sodium administered intravenously at doses of 50 mg/kg and above resulted in decreased movement, lengthened thiopental-induced sleep, and inhibition of strychnine–induced convulsions.

A transient lowering of body temperature at 50 mg/kg in rats was observed which returned to normal three hours later. Movement of isolated guinea pig ileum was inhibited by porfimer sodium at 10 µg/ml, a plasma level which may be equivalent to 5 mg/kg administered intravenously to mice. In heart and circulatory system there was no effect on blood pressure, pulse rate and electrocardiogram when tested in dogs up to the highest dose of 16 mg/kg. There was no influence on lung function. For liver function the effect on elimination of sulphobromophtalein sodium was tested in rats. At doses of 6.3 mg/kg and above administered intravenously there was a delayed elimination of BSP from the plasma in a dose-dependent manner.

- *Safety pharmacology*

Safety pharmacology studies were only performed without illumination and with Photofrin® used at the human therapeutic dose of 2 mg/kg for cardiovascular system investigation. No significant effects were observed on the CNS, pulmonary function, cardiovascular system including renal vascular blood flow, gastric acid secretion, and ethanol-induced gastric lesions. Photofrin® also did not have histamine-like effects on blood pressure in anaesthetized cats.

- *Pharmacodynamic drug interactions*

The effects of PDT with porfimer sodium combined with thiotepa, adriamycin, mitomycin or BCG on tumor growth were studied with subcutaneously injected MTB 2 murine transitional cell carcinoma in mice. All drugs except BCG were given intraperitoneally 48 hours before light application. The efficacy of PDT was markedly increased by adriamycin, mitomycin and BCG but not by thiotepa. Important was the sequence of the combination because no potentiation was noted when the cytostatics were administered after PDT (28).

On the contrary, glucocorticoids combined with PDT with hematoporphyrin derivate show only an increasing effect on tumor growth in a transplantable mouse tumor model when given after PDT (29).

Pharmacokinetics

The pharmacokinetics of porfimer sodium have been studied in male and female Sprague Dawley rats and in male beagle dogs. In rats, dogs, and humans the results of the pharmacokinetic investigations are basically very similar and are always the same for both genders.

- *Absorption- Bioavailability*

Intravenous or intraperitoneal single dose (5 mg/kg) pharmacokinetics in mice indicated a long half-life for plasma elimination of residual [^{14}C]-radioactivity associated with the porphyrins in porfimer sodium or with metabolites : triexpontentially decrease with elimination half-lives of about 0.75 (α), 10 (β) and 220 (γ) hours, following i.v dosing, and biexponentially after i.p. with elimination half-lives of 4 and 220 hours.

- *Distribution*

In mice and rats, the results showed that, although most of an i.v. dose was removed from circulation by the liver, spleen and kidney, potentially useful concentrations were retained for long periods in other tissues, including implanted human tumours.

The protein binding in rat, dog and human was comparable within the species between 80 and 90 % and was not dependent on the concentration of porfimer sodium.

It could be shown that porfimer sodium has a strong affinity to lipoprotein, especially to LDL. In plasma, lipoproteins may be porphyrin carriers to the tumor tissue and its corresponding receptors .

- *Metabolism*

Biotransformation is difficult to interpret with complex mixtures such as Photofrin, and metabolism studies per se were not conducted with Photofrin. However in a biliary excretion study in the rat, the amount of haematoporphyrin (HP monomer) excreted in the bile within 48 hours after dosing was twice the amount of HP injected in the dosing preparation. This indicates that some of ester/ether linkages in the PHE dimer/oligomer fraction were hydrolysed *in vivo*.

- *Excretion*

There is only one investigation for the elimination profile of the ^{14}C porfimer. Urine and feces of rats were collected each 24 hours for 7 days. The major route (42 %) of elimination of ^{14}C porfimer sodium was via the feces, whereas only 4% of the dose was excreted in the urine.

It is suggested that the fecal route is mainly via bile excretion because 23 % of porfimer were excreted into bile within 48 hours in rats. Also this is in accordance with human data where excretion data have shown that the major route of elimination is fecal suggesting biliary excretion of 28 % of the i.v. dose over 72 hours.

- *Other pharmacokinetic studies*

In an animal model (hamster) bearing a pancreatic-tumor it could be shown that porfimer has a high affinity to tumor tissue and was retained for a long time in this tumor tissue. In other similar studies in mice it was shown that the amount of labelled hematoporphyrin derivate in tumor tissue was in fact higher than in muscle and skin but lower than in liver, spleen and kidney which were the favoured organs for distribution.

The placental transfer of Photofrin® was studied in pregnant rats (N=5) following a single 20 mg/kg i.v. dose of Photofrin® given on Day 18 of gestation. No porphyrin derivatives were detected in amniotic fluid or foetuses at times when placenta concentration of PIE ranged from 48 - 62 mg/g. The transfer of porfimer sodium into breast milk was studied in lactating rats (n=5) following a single 20 mg/kg i.v. dose on Day 9 after delivery. Trace concentrations of PHE were found in breast milk between 6 and 48 hours after dosing with a maximum concentration of 7.4 µg/ml at 24 hours post-dose.

Toxicology

- *Single dose toxicity*

Studies were performed in the absence and in the presence of light activation.

Without light activation, at lethal doses in rodents, signs of intravascular haemolysis, lymphoid depletion, necrosis of the lymph nodes, spleen and thymus are reported. Signs of partial recovery are noted in rats that survived (haemosiderin pigment increase, extramedullary erythropoiesis). At lethal doses in dogs, increase in white blood cell counts (WBC) and decrease in red blood cell counts (RBC), bilirubin and alanine aminotransferase (ALT) increases are reported.

With light activation, animals were exposed to two hours of fluorescent light irradiation (160 footcandles for rats in study 0586/48 and 120 footcandles for mice) and then maintained in ambient lighting conditions (< 20 footcandles within the cages for 12 hours on / 12 hours off) for the remainder of the 14-day observation period. Signs of toxicity are represented by phototoxicity processed to necrosis and scab formation at various sites (ears, head, feet, eyelids, nose…). The no-effect illuminance level after 60 mg/kg of Photofrin was greater than ambient animal room but less than 30 footcandles (study 0686/50). The duration of the photosensitivity in rats after a single dose of Photofrin is comprised between 12 and 16 weeks (study 0586/49).

- *Repeat dose toxicity*

Repeated-dose toxicity studies have been studied in rats (a 6 weeks study under normal light conditions of <20 footcandles, and a 13-week toxicity study Sprague Dawley rats at < 14 footcandles) and in dogs (a 13 weeks study at < 30 footcandles, and a 13 weeks study at < 12 footcandles). The main findings were similar in both species. The repeated injection with porfimer sodium was associated with a brown pigment originated by porfimer sodium which is deposited in macrophages in the reticuloendothelial system. The clearance of the pigment from the macrophages appeared to be very slow as also seen in the pharmacokinetics but the deposition is suggested to be reversible. Changes in hematological parameters lead to the suggestion that there might still be a slight hemolytic effect which was fatal in previous tests with very high doses in rodents.

- *Genotoxicity*

The assessment of the genotoxic potential of porfimer is based on findings of a standard battery of genotoxicity tests and a considerable number of published data from a wide variety of genotoxicity assays. Although the studies of the standard testing battery gave negative results both in the presence and absence of ambient light there is sufficient evidence from literature data demonstrating that porfimer in the presence of light has the potential to damage the DNA. Such effects are considered to be directly related to the pharmacodynamic mode of action of porfimer, i.e. the generation of cytotoxic and potentially mutagenic singlet oxygen or other free radicals after irradiation with light of appropriate wavelength. The available data suggest that in most cell types cytotoxicity exceeds DNA damage (preventing detection of photogenotoxic effects in several experiments) but the latter cannot be entirely excluded and should therefore be carefully considered in the safety assessment. Possible genotoxic effects associated with the intended clinical use of porfimer are not confined to the deliberately irradiated tumors but due to the systemic distribution and the very slow clearance of porfimer from the body the surface tissues would be also at risk if exposed to light. Increased photosensitivity of patients was found to remain for up to 90 days and more, also suggesting a sustained photomutagenic hazard. The exposure of patients to direct sunlight or bright indoor light should therefore be avoided for an appropriate duration of time after treatment

- *Carcinogenicity*

No conventional, rodent life-time, assays for increased tumour incidence have been conducted with porfimer sodium. No carcinogenicity study of any porphyrin-containing product is known.

- *Reproductive and developmental studies*

Studies using conventional protocols for detecting effects on male and female fertility, embryo/fetal development, parturition, rearing, postnatal and behavioral development, and second generation reproductive performance were conducted. No effects on male and female fertility were detected at doses up to 4 mg/kg/d in rats. Embryo/fetal development was not affected at doses up to 2 mg/kg/d in rats and rabbits. In rats no effects on parturition and lactation were seen in F_0-dams at doses up to 4 mg/kg/d. Effects on the F_1-generation were observed at the high dose (4mg/kg/day) which also exhibited toxic properties for the dams.

- *Local tolerance (if applicable)*

Relevant examinations have been conducted for local tolerance. There were no abnormal changes when porfimer sodium was administered strictly intravenously. No test regarding the paravenous tissue has been performed. In a study with 1.5 ml porfimer sodium administered to rabbits in a single intramuscular injection under subdued lighting conditions, degenerative and necrotic changes with inflammatory cellular infiltration and hemorrhage could be observed after 2 days. Similar changes but with a beginning regeneration and fibrosis could be seen seven days after the injection.

- *Other toxicity studies*

Studies in sensitised mice, and rats, showed no passive cutaneous anaphylaxis reactions derived from Photofrin, indicating no antigenicity under the reported experimental conditions. There was no antibody production in mice to Photofrin alone, suggesting that Photofrin did not raise antibody production in mice under the reported experimental conditions.

4. Part IV: Clinical aspects

Clinical pharmacology

Pharmacodynamics

Three pharmacokinetic studies were provided . The most comprehensive and recent kinetic study was PHO PK 001 in which a single i.v. dose of 2 mg/kg porfimer sodium was given to 24 healthy volunteers (12 females, 12 males). The serum decay was bi-exponential, with a slow distribution phase and a very long elimination phase that started approximately 24 hours after injection. The t½ was a mean of 415 hours (range of 45 to 646 hours). C_{max} was determined to be 40 mcg/ml and the area under the curve to infinity (AUC(inf)) was 2400 mcg·hour/mL. Peak porfimer sodium concentration after drug administration was attained at a later time in women (1.5 hours) compared with men (0.17 hours). This difference was statistically significant, but judged as not clinically relevant to therapeutic porfimer sodium PDT since light administration occurs much later in the elimination phase (40-50 hours) when the profiles of men and women are similar.

The description of the distribution of the "haematophorphyine derivates" showed that the monomers distribute in plasma primarily to albumin while di- and oligomers are transported by the HDL fraction of the lipoproteins. Distribution to tissue, and in particular relative distribution into e.g. healthy skin vs. healthy oesophageal mucosa vs. mucosa of BO, has not been investigated. The extremely long elimination half times in the range of 2 to 3 weeks clearly indicates that deeper compartments, from which elimination is slow, exist for oligomers. Such a "deep compartment" appears to be skin as trial PHO PK 001 reveals a long lasting accumulation of photosensitizer (or photosensitivity respectively) in the skin.

Metabolism of the mono-, di- and oligomeric mixture product PhotoBarr takes place (also just in the product itself in particular after reconstitution) in the sense of dimerisation, hydrolysis, transformation of ether- into ester bonds, and so forth. Further sources of metabolism can be the sun exposed skin of patients, the Barrett's oesophagus of the patient treated with PDT, and the liver.

The pathways of elimination have, however, not been further characterised. The most plausible elimination way appears to be hepatic/biliary metabolism and excretion.

Two old kinetic studies provided consistent data. A pharmacokinetic study was conducted in 12 endobronchial cancer patients given 2 mg/kg of porfimer sodium intravenously. Samples of plasma were obtained out to 50 days post injection and total monomeric porphyrins determined. The average peak plasma concentration (C_{max}) immediately following injection was 79.6 µg/mL (C.V.61%, range 39-222); the mean elimination half-life (t½) was 515 hours, i.e. 21.5 days (C.V. 26%, range 264-672). Thus, porfimer sodium is slowly cleared from the body, with a mean clearance (CL) of 0.0143 mL/min/kg (C.V. 53%). Another pharmacokinetic study was performed at the same dose in four patients with bladder cancer. Total hematoporphyrin equivalents were measured, but plasma samples were only collected over 48 hours and thus the sampling schedule was insufficient to allow determination of the terminal elimination phase. Initial plasma levels of approximately 15 µg/mL were maintained for at least 1 hour, after which the rate of disappearance was consistent with an initial half-life of 22 hours, which would represent the distribution phase of the drug within the whole body.

- *Interaction studies*

No formal interaction studies have been performed with PhotoBarr investigating pharmacokinetic drug-drug interactions, although in amendment 4 and 5 of trial D73 P503 and in trial PHO PK 001 almost all patients have received concomitant drug therapy.

- *Special populations*

Trial PHO PK 001 was planned to investigate effect of gender, and major gender effects on PK can be excluded although a trend to a higher AUC in females exists which does, however, not translate into a higher but a lower photosensitivity rate in female patients. No data on PK in children, elderly patients and patients with renal or hepatic impairment are available.

Pharmacokinetics

The dose of PhotoBarr used in all clinical studies (2 mg/kg body weight via the intravenous route), and timing of the light in relation to (single) dose administered, were determined empirically, taking into account the recommended dose of the product Photofrin.

In trial TCSC 93-07 the effect of a range of light doses from 175 up to 300 J/cm was evaluated. The small number of patients in each light dose level and the overlap of doses make the interpretation of the study results difficult. However, it seems that efficacy/safety results with the lowest dose of 175 J/cm were similar to that of higher doses of 250 and 300 J/cm. Based on these data, the applicant has finally recommended a light dose of 130 J/cm.

A white light reflector investigational product ("TOTAL BLOCK SPF 75"), as well as prophylactic corticosteroids were used in pharmacodynamic drug-drug interactions studies to investigate the potential reduction of side effects. These drug-drug interactions studies showed that the experimental product TOTAL BLOCK SPF 75 protected against skin toxicity but prophylactic corticosteroids have no or even detrimental effects on overall outcome.

Discussion on clinical pharmacology

The results of the 3 pharmacokinetic studies are consistent and adequately reflected in the SPC. The most significant PK property of PhotoBarr is the very slow elimination, with $t_{1/2}$ in the range of 2 to 3 weeks. Further investigations are necessary to clarify if hepatic impairment has an effect on elimination half life and exposure. The applicant has committed to investigate the PK in patients with hepatic insufficiency as a post-marketing commitment.

Tumour and dysplastic tissue selectivity in treatment may occur partly through selective retention of PhotoBarr but mainly through a selective delivery of light. Further investigations are necessary to clarify what is the optimal dose of photoBarr, of light, and what is the optimal timing of the light for the treatment of HGD in BO. The applicant committed to a post-marketing study to investigate this aspect.

In an open label pharmacokinetic study with healthy subjects, all subjects experienced photosensitivity reactions, which were characteristically represented by erythematous rash and oedema and were mild to moderate in intensity (data not shown). The photosensitivity reactions occurred primarily on the face, hands, and neck regions, which are the areas of the skin that are most susceptible to accidental sunlight exposure. Other less common skin manifestations were reported in areas where photosensitivity reactions had occurred, such as increased hair growth, skin discolouration, skin nodules, skin wrinkling and skin fragility. These manifestations may be attributable to a pseudoporphyria state (temporary drug-induced cutaneous porphyria). The frequency and nature of the photosensitivity reactions experienced in this study are unlike the documented incidence seen in previous clinical studies in cancer patients (approx. 20%) or the spontaneously reported incidence from commercial use of PhotoBarr (< 20%). It is possible that prolonged exposure to light at the clinical research unit or accidental sunlight exposure after discharge may be responsible for the high frequency of photosensitivity reactions. The more active lifestyle of the healthy and relatively younger subjects compared with cancer patients may have been a contributing factor to these photosensitivity reactions. This experience is adequately described in the SPC.

Concerning TOTAL BLOCK SPF 75 to prevent skin toxicity, its use cannot be recommended currently, as this experimental product is not available on the market. An appropriate warning for prophylctic use of corticosteroids has been introduced into the SPC. No evidence for further interactions between PhotoBarr and other medicinal products was detected in the clinical programme, although the number of patients was small.

Potential interaction, or additive photosensitising respectively, can be expected to occur with the concomitant use of other medications known to produce photosensitivity or cutaneous phototoxicity. It is possible that concomitant use of other photosensitising agents (e.g., tetracyclines, sulphonamides, phenothiazines, sulphonylurea hypoglycaemic agents, thiazide diuretics, griseofulvin and fluoroquinolones) could increase the photosensitivity reaction. These potential pharmacodynamic interactions are adequately reflected in the SPC.

Clinical efficacy

Dose-response studies and main clinical studies

The clinical programme in support of the PhotoBarr indication in BO with HGD consists of one main, multicentre, randomised, controlled and partially blinded study (PHO BAR 01) and two supportive, single centre, uncontrolled studies (TCSC 93-07 and TCSC 96-01). The supportive studies recruited patients with adenocarcinoma, HGD and low grade dysplasia (LGD). Only the sub-group with HGD are analysed in this application. 208 patients were randomised in PHO BAR 01 and the minimum follow up was 2 years. The HGD subpopulations in TCSC 93-07 and TCSC 96-01 were 44 and 42 patients respectively, with a majority of patients followed up to 12 months. In TCSC 93-07, laser light intensity varied to determine the optimum light dose. The effect of prednisone on the incidence of oesophageal stricture was evaluated in TCSC 96-01.

Main study PHO BAR 01

Methods

Overall Study Design and Plan

PHO BAR 01 was a multicentre, partially blinded, randomised study in patient with high-grade dysplasia (HGD) in Barrett's oesophagus (BO). Eligible patients were randomised to receive PHOTOBARR PDT plus OM therapy or OM Only therapy. Patients and study physicians were aware of the treatment each patient received; however, the pathologists who read the biopsies from each oesophageal endoscopy were blinded to the patients' treatment.

Patients were centrally randomised in a 2:1 design to receive PhotoBarr PDT plus omeprazole therapy or omeprazole therapy alone. All histological assessments were carried out at a central reference laboratory (Dr R. Haggitt, University of Washington, Seattle). A study to assess the inter-rater agreement on histological diagnoses assigned to sets of endoscopic biopsy samples was completed by this reference laboratory prior to the start of the pivotal trial. The results indicated a high rater agreement on the histological diagnoses between readers of 88% (95%-CI: 78%-94%) for HGD and 96% for adenocarcinoma. The study planned the enrolment of at least 200 patients with HGD in BO at 30 clinical trial sites mostly in North-America.

All patients were followed every three months until four consecutive quarterly follow-up endoscopic biopsy results were negative for HGD, and then biannually until the last enrolled patient had completed a minimum of 24 months of follow-up evaluations after randomisation. Endoscopic surveillance was no longer required after treatment failure unless the patient received PhotoBarr PDT at the time of the treatment failure. Patients were assessed for efficacy (histological assessment of biopsies) and safety (adverse experiences, laboratory results and physical exams). An evaluation committee (DSMC) reviewed safety data every six months. There was no interim analysis planned in the study.

Study Participants

Two hundred patients with BE and HGD on biopsy were to be included in this trial. The main inclusion criteria were biopsy-proven HGD in BO, as assessed by the central reference pathology laboratory; four quadrant jumbo biopsies at every 2 cm of the entire Barrett's mucosa had to be obtained within 4 weeks of randomisation (biopsy sampling was to start at the upper limit of the gastric folds); absence of invasive cancer confirmed by endoscopic ultrasonography and thorax computed tomography (CT); age $\geq$ 18 years.

Treatments

PhotoBarr was to be administered at a dose of 2.0 mg/kg with light application 48 hours following injection. The light dose administered was 130 J/cm of diffuser length using the centering balloon. Applications of laser light could be repeated 96-120 hours post PhotoBarr injection for residual lesions. In such case, a 2.5 cm fiber optic diffuser at the light dose of 50 J/cm of the diffuser length was to be used. A maximum of 7 cm of BO was treated during one course of PDT; one course of PDT consisted of an intravenous injection of PhotoBarr followed by one or two laser light applications. The second light application could be given two days after the first light application, and was only given to

one under-treated ("skip") area that occurred during the first light application. If a patient had more than 7 cm of Barrett's mucosa, a second course of PDT was needed to treat the segment not treated in the previous course. It was required that the entire length of Barrett's mucosa be treated with PDT therefore, up to three PDT courses could be given. Course of PDT had to be separated by at least three months. If a previous course of treatment resulted in residual areas of dysplasia, Barrett metaplasia, or any remaining "skip" areas, an additional course of PDT was to be given. Patients in both treatment groups received omeprazole therapy (20 mg BID) to reduce reflux oesophagitis.

Objectives

The primary objective was to assess the efficacy of PDT with PhotoBarr for injection plus omeprazole [PDT + PhotoBarr + OM] compared to omeprazole alone [OM Only] in the complete ablation of HGD in patients with BO, in conjunction with a strict endoscopic surveillance and biopsy protocol. Secondary objectives included to assess the safety and efficacy of PDT + PhotoBarr + OM and systematic endoscopic surveillance compared to OM Only therapy plus systematic endoscopic surveillance in terms of quality of complete response, duration of complete response, delaying progression to cancer (time to progression to cancer), delaying the need for esophagectomy or other intervening therapy (time to treatment failure) and survival time.

Outcomes/endpoints

The primary efficacy variable was complete response (complete ablation of HGD at any endoscopic assessment) which was evaluated using a biopsy protocol and defined by the occurrence of any of the following three categories:

- complete response 1 (CR1): complete replacement of all Barrett's metaplasia and dysplasia with normal squamous cell epithelium.

- complete response 2 (CR2): ablation of all histological grades of dysplasia, including patients with indefinite grade of dysplasia, but some areas of Barrett's metaplastic epithelium still remain, or

- complete response 3 (CR3): ablation of all areas of HGD but some areas of LGD with or without areas, which are definite for dysplasia or areas of Barrett's metaplastic epithelium sill remain.

Secondary efficacy endpoints were quality of complete response (CR1; CR1 or CR2); duration of complete response; time to progression to adenocarcinoma; time to treatment failure; survival time.

Sample size

The sample size of 200 patients was chosen based on power considerations for the primary efficacy parameter of CR and the secondary efficacy parameter of time to progression to cancer(TTP). It was estimated that the rate of complete ablation of HGD would be no more than 27% in the control arm and at least 60% in the PHOTOFRIN PDT arm at the time of the planned primary analysis (minimum of 6 months with an approximate median follow-up of 17 months). These estimates for the control arm and PHOTOFRIN PDT arm were based on results in the literature reported after a median follow-up of 26 and 19 months, respectively. Based on these estimates, 117 patients, 78 in the study treatment arm and 39 in the control arm, would provide 90% power to detect a difference between rates of 60% versus 27% in a two-sided test of proportions at a significant level of 5% .

For time to progression to cancer, a sample size of 191 patients was required to provide at least 80% power to detect an increase in time to progression to cancer of 24 months in a two-sided test at a significance level of 5%, assuming a median time to progression of 24 months in the control arm. It was assumed that the enrolment period would not be 15 months and the minimum follow-up period would be 24 months. The sample size was increased to 200 patients to account for up to 5% ineligible or untreated patients.

Patients were randomised in a 2.1 ratio to receive either PhotoBarr PDT + OM or OM Only, respectively. The patient randomisation was stratified with respect to study centre. No other stratification of patients took place.

Randomisation

Biopsies taken at screening were sent to the central reference pathology laboratory for histological confirmation of the diagnosis of HGD. Random assignment in a 2.1 design to PhotoBarr PDT plus OM or OM only treatment was performed through a central randomisation office. Randomisation was stratified by centre only.

Statistical methods

No interim analyses were planned. The planned overall study duration was 24 months. Statistical analyses were planned at two different time points:

a. The primary analysis of complete response was based on data collected up to a minimum of 6 months of follow-up after the last patient was enrolled in the study, and
b. A final response analysis was planned after the last patient enrolled in the study has completed 24 months of follow-up to confirm the durability of effect and to provide long-term safety results. The final analyses was to be performed using the same data sets and methods as defined for the primary analyses. The primary analysis of the secondary time to event variables was to be based on 24 months of data.

With the exception of additional analyses, all efficacy variables were to be analysed for the intent-to-treat (ITT) and evaluable populations. Additional analyses of the primary efficacy variable were considered exploratory and performed only on the ITT data set. The ITT population consisted of all randomised patients. The evaluable population was defined as those patients with confirmed histological diagnosis, exclusion of oesophageal cancer at baseline, and that have received at least one complete course of PhotoBarr PDT (2.0 mg/kg injection of PhotoBarr followed by one or two laser light sessions applied to the oesophageal segment) or omeprazole for at least one week. Additional reasons for excluding patients from the Evaluable population analyses were to be identified and documented prior to the database close. The safety population was defined as all randomized patients who received either an injection of PhotoBarr or a single dose of omeprazole, according to treatment received.

Statistical analysis

For the primary analysis, the proportion of responders between the two arms was to be compared using a Fisher's exact test. A patient was to be classified as a responder if the patient achieved complete ablation of HGD defined as any response of CR1, CR2 or CR3 at any one of the evaluations prior to the date of data cut-off (minimum of 6 months of follow up after the last patient was enrolled in the study) for the analysis. For each patient who received intervening therapy, the assessment for primary efficacy was to be considered as treatment failure from the day that the intervening therapy began. The CR rates and the 95% CIs using a normal approximation to the binomial distribution were to be calculated. The difference between treatment arms in CR rates was to be provided with 95% CIs.

In addition, the CR rates (CR1, CR2 or CR3) at follow-up visits Month 6, Month 12, Month 18 and Month 24 were to be calculated for each treatment arm.

The analysis of duration of CR was to be restricted to complete responders. For all time to event endpoints, the primary analysis of the secondary efficacy variables was to be considered as a preliminary analysis. The final analysis was to be based on the 24-month data.

The duration of CR1 or CR2 or CR3 response was defined as the period in days from the day of first documentation of a CR3 or better response until the day of first documentation of either recurrence of HGD or progression to cancer. The duration of CR1 or CR2 response was defined as the period in days from the day of first documentation of a CR2 or better response until the day of first documentation of either recurrence of dysplasia (indefinite, LGD, or HGD) or progression to cancer. The duration of CR1 response was defined as the period in days from the day of first documentation of a CR1 response until the day of first documentation of metaplasia, any dysplasia (indefinite, LGD, or HGD) or progression to cancer. The duration of CR was to be censored at last follow-up or on the day that the intervening therapy began (oesophagectomy or an alternative method of endoscopic ablation) whichever first. Time to progression to cancer was defined as the period in days from the date of randomisation until the date of the first documented progression to cancer or censoring at last follow-up or intervening therapy began, whichever first. Time to treatment failure was defined as the time in days from the date of randomisation until the date of the first documentation of progression of HGD to

cancer or the start of any intervening therapy for HGD other than the randomised study treatment or censoring at the last efficacy assessment. Survival was defined as the period in days beginning on the date of randomisation to the date of death or censoring at the last date that the patient was known to be alive. The Kaplan-Meier method was used for estimating the distribution of time-to-event endpoints, and the log rank test was to be used to compare the distribution of events between treatment arms.

Additional analyses were performed to evaluate the effect of various baseline and demographic factors on the primary efficacy variable,(complete response.) using a logistic regression analysis.

Results

Patient disposition

A total of 486 patients were screened for inclusion. Of those, 278 patients were excluded during screening, mostly because HGD was not confirmed by the central reference pathology laboratory. Of the 486 patients screened, a total of 208 patients were enrolled in the study. According to a 2.1 ratio, 138 patients were randomised to receive PhotoBarr PDT + OM (treatment arm) and 70 patients were randomised to receive OM Only (control arm). A summary of patient disposition is provided in Table 1.

Table 1. Summary of patient disposition (6 month follow-up and the 24 months follow-up)

	Study treatment groups			
	Photofrin PDT + OM		OM Only	
	6 months	24 months	6 months	24 months
No. of pat. Randomized (%)	138		70	
No. of pat. Receiving study therapy (%)	132		69	
No. of patients included in the				
ITT population[2]	138 (100)		70 (100%)	
Safety population[2]	133 (96.4)		69 (98.6%)	
Evaluable population[2]	130 (94.2)		69 (98.6%)	
No. of patients completing follow-up[1]	124 (93.9)	78 (56.5)	55 (79.7)	26 (37.1)
No. of patients discontinued from study[2]	36 (26.0)	57 (41.3)	28 (40.0)	49 (70.0)
AE	3 (2.2)	4 (2.8)	0 (-)	1 (1.4)
Progression of disease	14 (10.1)	18 (13.0)	14 (20.0)	22 (31.4)
Death	2 (1.4)	2 (1.4)	1 (1.4)	1 (1.4)
Other	9 (6.5)	22 (15.8)	13 (18.6)	19 (27.2)
Administrative reasons	8 (5.8)	11 (7.9)	1 (1.4)	6 (8.6)

[1] Percentages are based on the number of patients who received study therapy in each group
[2] Percentages are based on the number of patients randomized in each group.

Recruitment

The first patients were enrolled in January 1998 The study was completed 07 November 2001. At the time of submission of the application a report displaying an analysis on a minimum follow-up of 6 months with a cut-off date of August 2000 for the data sets was presented. At that time the study was still in progress. A final analysis with the 24 month follow-up data sets, signed January 2003, was presented by March 2003.

Conduct of the study

Study PHO BAR 01 was performed in compliance with GCP. Protocol amendments and patient informed consent were reviewed by IRBs. An independent Data and Safety Monitoring Board was appointed to oversee the conduct of the study.

Baseline data

Demographic of age, gender, height, race and smoking history were well balanced between the two groups.

The mean age of the patients enrolled in the PhotoBarr PDT + OM group was 66.1 (SD=10.7) years with the age ranging from 38.4 to 88.5 years. The mean age of the patients enrolled in the OM Only group was 67.3 (SD=11.1) years with the age ranging from 36.1 to 87.6 years. The total study

population was predominantly male (85%), Caucasian (99%), and former smokers (64%). There was no statistical difference between the two treatment groups.

At baseline, 63% of the patients in the Photobarr PDT + OM group had a history of BO for over a year as compared to 59% of the patients in the OM Only group (p=0.6498), for the ITT population. The median duration of BE was 20.27 months (ranging from 1.3 to 216.7 months) and 19.22 months (ranging from 0.9 to 141.7 months) in the PhotoBarr PDT + OM group and OM Only group, respectively. The duration of HGD was 6 months or less in 71% and 73% of the patients in the PhotoBarr PDT + OM group and OM Only group, respectively –(p=0.8689), for the ITT population. The median duration of HGD was 3.55 months (ranging from 0.1 to 40.7 months) and 4.11 months (ranging from 0.4 to 72.4 months) in the PhotoBarr PDT + OM group and OM Only group, respectively. There was no statistical difference between the two arms (p=0.9280).

The length of BO as determined by endoscopy was categorized as $\leq$ 6 cm and > 6 cm. Patients in the OM Only group were evenly distributed between the two categories while the proportion of patients in the PhotoBarr PDT + OM group was slightly higher in the > 6 cm category. There was no statistical difference between the two arms (p=0.5605). The length of BO as determined by histology was also categorized as $\leq$ 6 cm and > 6 cm. Results showed a higher proportion of patients in the $\leq$ 6 cm category in both groups: 54% of the patients in the PhotoBarr PDT + OM versus 60% of the patients in the OM Only group (p=0.4603). In most patients, HGD extended over multiple levels: 63% of patients in the PhotoBarr PDT + OM group as compared to 61% of patients in the OM Only group (p=0.7639). Extent of HGD did not differ between the two groups and between the ITT and Evaluable population.

In the ITT group, 134 of the 138 patients who received PhotoBarr PDT + OM reported prior therapy for BO. Most patients (97%) reported prior medical therapy, 4% of patients reported prior surgery, and 4% of patients reported other types of therapy. Sixty-six of the 70 patients who received OM Only reported prior therapy for BO: 94% of patients reported other types of therapy. Other types of therapy consisted of oesophageal dilations and blood transfusion. Endocopic ablation was not reported in either group. Although there was no statistical difference between the two groups with regards to prior therapy for BO, a higher proportion of patients randomised to the OM Only arm had prior surgery as compared to the PhotoBarr PDT + OM group (p=0.0767 for the ITT population and p=0.0657 for the Evaluable population).

Outcomes and estimation

A summary of efficacy result for primary and secondary endpoints is shown in Tables 2 and 3. For time-related secondary efficacy endpoints the data were not mature to estimate median time to event. In particular, median duration of response could not be calculated, and median time to progression to cancer, could not be estimated. However, in an exploratory analysis with 24 months minimum follow-up, 18 (13%) patients with progression to cancer were observed in the PDT group, compared to 20 (29%) in the Ome only group (P=0.006). At the end of follow up 39 patients (28%) in the PDT group had failed treatment, compared to 44 patients (63%) in the Ome only group (P<0.001).

Table 2. Efficacy results (primary endpoints)

	ITT-population (138/70)				Evaluable population (130/69)			
	PDT		Ome only		PDT		Ome only	
	6 mo.	24 mo.	6 mo.	24 mo.	6 mo.	24 mo.	6 mo.	24 mo.
CR 1 or 2 or 3 (=no HGD)	**71.7%**	**76.8%** (0.70-0.84)	**31.4%**	**38.6%** (0.27-0.50)	**76.2%**	**81.5%**	**31.9%**	**39.1%**
	P<0.0001*		P<0.0001		P<0.0001		P<0.0001	
CR 1 (normal epithelium)	**41.3%**	**52.2%** (0.44-0.61)	**4.3%**	**7.1%** (0.01-0.13)	**43.8%**	**55.4%**	**4.3%**	**7.2%**
	P<0.0001		P<0.0001		P<0.0001		P<0.0001	
CR 1 or 2 (=no dysplasia)	**48.6%**	**58.7%** (0.51-0.67)	**5.7%**	**14.3%** (0.06-0.23)	**51.1%**	**62.3%**	**5.8%**	**14.5%**
	P<0.0001		P<0.0001		P<0.0001		P<0.0001	

*p-values in the white columns are comparing the 6 months data, whereas grey columns represent comparisons of the 24 months data.

Table 3. Efficacy (secondary endpoints)

	ITT-population (138/70)				Evaluable population (130/69)			
	PDT		Ome only		PDT		Ome only	
Rates of	6 months	24 months	6 months	24 months	6 months	24 months	6 months	24 months
Progression to cancer	**14 (10.1%)**	**18 (13.0%)**	**13 (18.5%)**	**20 (28.6%)**	**12 (9.2%)**	**16 (12.3%)**	**13 (18.8%)**	**20 (29.0%)**
	P=0.0875*		P=0.0062		P=0.0516		P=0.0036	
Treatment failure	**23 (16.7%)**	**39 (28.3%)**	**26 (37.1%)**	**44 (62.8%)**	**21 (16.2%)**	**36 (20.0%)**	**26 (37.7%)**	**43 (62.3%)**
	P=0.001		P<0.001		P<0.001		P<0.001	

*p-values in the white columns are comparing the 6 months data, whereas grey columns represent comparisons of the 24 months data.

Ancillary analyses

Additional analyses showed that treatment (PhotoBarr PDT + OM *v*. OM Only, p<0.0001), HGD foci (single *v*. multiple, p<0.0001) prior omeprazole intake of at least three months (yes *v*. no, p=0.0005), and age (<65 years old *v*. ≥ 65 years old, p=0.0219) were covariates influencing the CR rate (CR1 or CR2 or CR3). HGD duration, BO length, nodular conditions, gender, smoking history, and centre's size did not influence the CR rate. A significant treatment × age interaction (p=0.0047) was observed. The logistic regression analysis showed that the PhotoBarr PDT + OM treatment was more likely to provide CR (OR=9.7094, 95% Cl=4.129, 22.829). Complete response was more likely to be observed in patients with single foci HGD (OR=11.8416, 95% Cl=4.431, 31.643) and in patients having taken omeprazole for more than three months prior to study entry (OR=4.0072, 95% Cl=1.835, 8.749). In addition, age was identified as being an important influential factor. Patients of less than 65 years old were more likely to achieve CR than older patients regardless of the treatment received (OR=2.4664, 95%, 1.140, 5.337). In the <65 years old and ≥ 65 years old categories, patients on PhotoBarr PDT + OM treatment were more likely to achieve CR than patients on OM Only treatment (OR=40.6260, 95% Cl=9.706, 170.042 and OR=4.2053, 95% Cl=1.586, 11.150, respectively). Clinician's experience with PDT did not influence study outcome (p=0.6895). Progression to cancer was associated with the number of PDT courses administered. Patients who received one course of PDT had a greater risk of progression to cancer than patients who received two or three courses of PDT (50% vs. 39% and 11% respectively).

Discussion on clinical efficacy

PhotoBarr effectiveness in the ablation of HGD in patients with BO has been shown in a single controlled study Pho Bar 01. A central randomisation scheme was used. Patient characteristics were well balanced in the two groups indicating an appropriate randomisation. The method for acquisition of biopsies was compliant with the accepted standards. The definition of complete response used as primary efficacy end-points is clinically relevant.

The most impressive and obviously most relevant (single) result concerning this (combined)/these primary endpoint(s) is the high proportion of patients in the PDT+Ome showing complete replacement of all Barrett's metaplasia, including dysplasia. The data were generally not mature for estimation of time-related secondary efficacy endpoints.

PHO BAR 01 is the largest and the only randomised trial performed so far in this setting. The development program did not comprise a comparison with oesophagectomy. As this surgical technique, and alternative conservative ablative treatment options, cannot be considered as standard treatment options in HGD of BO as of today, the development program is adequate, although not fully devoid from deficits.

The main criticisms to PHO BAR 01 relate to questions on the validity of the primary endpoint complete response rate as a surrogate endpoint for progression to cancer. Despite this weakness, PHO BAR 01 shows that PDT with PhotoBarr is feasible in HGD of BO, and that this method can achieve a clinically relevant number of complete ablation of HGD, complete re-epithelialisation of BO by normal squamous epithelium. In addition, the frequency of progression to cancer was significantly in

favour of PDT compared to Ome alone, and a significantly lower proportion of treatment failure was observed in the PDT group compared to the Ome only group. Thus, one can assume that the observed effect in terms of complete response translates to a clinically relevant effect in terms of progression to cancer as well.

Supportive studies

Study 93-07 was a single centre, uncontrolled Phase II study. The objectives of the study were to evaluate the safety and efficacy of PhotoBarr PDT in patients being treated for dysplasia or early adenocarcinoma in BO and to determine the required light dose to produce effective results. A total of 99 patients were enrolled in the study, 44 with a diagnosis of HGD. The other non-pivotal Study 96-01 was a single centre, partially blinded, randomised, Phase II parallel-group study. The study objective was to compare the incidence and severity of oesophageal strictures between patients with BO who received steroid therapy after PhotoBarr PDT and patients who received steroid-free PDT for treatment of dysplasia and/or early adenocarcinoma of the oesophagus. A total of 87 patients were enrolled in the study, 42 with a diagnosis of HGD. Both studies included patients with adenocarcinoma, HGD and low-grade dysplasia (LGD). They were retrospectively analysed with only the HGD subgroup to ensure consistency with the main study. The patient populations of HGD treated were different than those in the pivotal study since they enrolled only patients who refused, or were ineligible for surgery. While study information included 12-month data, 6-month data formed the primary analysis and the 12-month data was the basis of secondary efficacy parameters. The overall clinical response in these non-pivotal studies was consistent with that seen in the main study.

Clinical safety

Patient exposure

The Integrated Summary of Safety puts together the safety information derived from study PHO BAR 01 and from the two non-pivotal studies TCSC 93-07 and TCSC 96-01. The report comprises the 138 patients from PHO BAR 01 and 42 plus 44 patients from the non-pivotal studies who have received PDT in HGD of BO, 70 patients of the OME only group in the pivotal study and 99 patients who received PDT for other indications. This sums up to a total of 324 patients receiving PDT of which 224 had the indication under evaluation. The duration on study amounted to a median duration 15.8 months in total, of which the patients with HGD in BO receiving PDT had a median study time of 19.3 months (of which the group from study PHO BAR 01 had a median of 26 months), the OME only group of 21.2. months, and the other PDT patients of 13.0 months.Of the total of 219 patients receiving PDT for HGD in BO, 115 received two courses of PDT, and 45 received three courses. In the other indications, of the 99 patients only 10 received two courses and 3 received three courses. All patients who received at least one dose of porfimer sodium or omeprazole are included in the safety analysis. Baseline characteristics of the different groups were comparable.

Adverse events and serious adverse events/deaths

A total of three patients died during the study, two patients of the PDT (metastatic breast cancer, cardiac arrest following complications after bypass-graft surgery) group and one in the omeprazole (massive stroke attack) only group. All three deaths were not considered to be associated with treatment. A total of 118 serious AEs occurred in 40 patients in the PDT group and 36 serious AEs in 12 patients in the omeprazole only group.

Of the serious adverse events (SAEs) in the PhotoBarr PDT + OM group, 44 (23.1%) were considered associated with the treatment. The most commonly reported treatment associated SAE was dehydration (4%) experienced by 5 patients. The majority of the SAEs experienced by 11 patients were gastrointestinal disorders (8%), specifically nausea (3% - 4 patients), vomiting (3% - 4 patients) and upper abdominal pain (2%) experienced by two patients. No cases of anaphylaxis have been reported although occasionally rashes have been observed.

Three serious adverse events led to patient withdrawal from the study which all occurred in the PDT group. One patient produced an anxiety crisis before the first laser light application, one was diagnosed with lung cancer (which undermined the eligibility of the patient), and the third patient

underwent esophagectomy after a perforation of the esophagus related to a dilation procedure following a PDT associated stricture formation.

Laboratory findings

Laboratory data were collected at baseline and at month 3 after each PDT course in the PDT group and at baseline and month 3 in the omeprazole only group. There was only one grade 4 toxicity (neutrophil cell counts in the PDT group), only one grade 3 toxicity (white blood cell counts in the PDT group), 2 grade 2 toxicities (total bilirubin and ALT, both in the PDT group), and 32 grade 1 toxicities (9 (13%) in the omeprazole only group and 23 (17%) in the PDT group).

Safety in special populations

Additional analyses of safety were performed for patients of old age (>75 years) as opposed to the younger patients as well as for patients with a history of or with a current cardiac or pulmonary disease/condition. These analyses revealed additional increased risks for certain adverse events (cardiac and pulmonary events as well as dehydration) that warrant the inclusion as warnings in the SPC.

5. Overall conclusions and benefit/risk assessment

Benefit/risk assessment

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of PhotoBarr was favourable in the treatment of "Ablation of high-grade dysplasia (HGD) in patients with Barrett's Oesophagus".