

CENTER FOR DRUG EVALUATION AND RESEARCH

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NDA 20-451/S-012**

Medical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

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Sponsor: Axcan Scandipharm Inc.

Drug name: Photofrin (porfimer sodium)

Pharmacological category: Photosensitizing agent, polyporphyrin oligomer

Indication: Ablation of high-grade dysplasia in Barrett's esophagus

Route of administration: Intravenous injection

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LIST OF ABBREVIATIONS

AE	Adverse event
BE	Barrett's Esophagus
BID	Twice daily
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
CR	Complete Response
CRF	Case report form
CT	Computerized tomography
DSMC	Data and Safety Monitoring Committee
EUS	Endoscopic ultrasound
GERD	Gastroesophageal reflux disease
HGD	High-grade dysplasia
IEC	Independent Ethics Committee
INR	International Normalized ratio
ITT	Intent-to-Treat
IV	Intravenous
J/cm	Joules/cm
KTP	Potassium-Titanyl-Phosphate (laser)
LGD	Low-grade dysplasia
OM	Omeprazole
PDT	Photodynamic therapy
PT	Prothrombin time
PTG	Polymer Technology Group
QLT	Quadralogic Technologies, Inc.
RBC	Red blood cells
SAE	Serious adverse event
SD	Standard deviation
TE	Treatment emergent
TEAE	Treatment emergent adverse events
TTF	Time to treatment failure
TTP	Time to progression to cancer
WBC	White blood cells
WHO	World Health Organization

Executive Summary

I. Recommendations

A. Recommendation on Approvability

1. Approval of a new indication for PHOTOFRIN® (porfimer sodium) for Injection (75 mg vial).

PHOTOFRIN® (porfimer sodium) is a photosensitizing agent, used in conjunction with photodynamic therapy, that is approved for treatment of patients with completely obstructing esophageal cancer, of patients with obstructing endobronchial non-small cell lung cancer, or of patients with micro-invasive endobronchial non-small cell lung cancer. The proposed new indication, as stated in the cover letter and in the Proposed Package Insert of the original NDA supplement submission (May 31, 2002) reads as follows: Under **INDICATIONS AND USAGE**, "Photodynamic therapy with PHOTOFRIN® is indicated for:...the ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE) among patients who are not considered to be candidates for esophagectomy." In the April 4, 2003 Proposed Package Insert draft the new indication was changed to read: "for:...the ablation of HGD in BE among patients who refuse esophagectomy and who are in overall good health."

In support of the new indication, the Sponsor submitted the results of a multi-center, randomized, controlled, partially blinded, 2-arm trial, in which 130 patients with Barrett's esophagus and high-grade dysplasia were treated with PHOTOFRIN® photodynamic therapy (PDT) and 69 patients underwent aggressive surveillance. Patients in both arms of the trial were treated with omeprazole (OM) 20 mg BID to suppress acid reflux. The length of follow-up was at least 2 years, with some patients followed for up to 3.6 years.

The primary efficacy endpoint, assessed after a minimum follow-up of 24 months, was the complete ablation of high-grade dysplasia with re-growth of normal squamous cell epithelium, termed Complete Response. PHOTOFRIN® photodynamic therapy resulted in a Complete Response in 81.5% of treated patients, while treatment with only omeprazole resulted in a Complete Response in 39.1% of patients. The difference between the two groups was significant, with $p < 0.0001$.

Secondary efficacy endpoint analyses showed that

- the most common type of Complete Response was re-growth of completely normal squamous cell epithelium in the PHOTOFRIN® PDT group and re-growth of normal squamous cell epithelium with areas of metaplasia, indefinite dysplasia, and low-grade dysplasia in the OM Only group,
- the median duration of Complete Response was 987 days in the PHOTOFRIN PDT group and 98 days in OM Only group ($p < 0.001$),
- the proportion of patients who progressed to cancer was about twice as high in the OM Only group compared to PHOTOFRIN® PDT group,

- failure to achieve a Complete Response was associated with approximately ten-fold increased risk of progression to cancer in both PHOTOFRIN® PDT group and in the OM Only group (in evaluable populations, which included patients who had completed at least one course of treatment),
- a greater proportion of patients had not progressed to cancer or had another therapeutic intervention in the PHOTOFRIN® PDT group than in the OM Only group (only 16% of the OM Only group remained in follow-up at the end of the study compared to 62% of the PHOTOFRIN PDT group), and
- survival time could not be estimated for either group.

In addition, the Sponsor submitted the results from two open-label, uncontrolled, single-center studies, in which 86 patients with Barrett's Esophagus and high-grade dysplasia were treated with PHOTOFRIN® PDT and omeprazole, and followed for a minimum of 12 months. The efficacy results in these supporting studies were consistent with the results of the principal multi-center trial. The principal efficacy endpoint, the Complete Response rate, in the two studies was 94%.

PHOTOFRIN® photodynamic therapy was relatively safe and well tolerated. Few patients withdrew from the studies because of treatment related-adverse events. The major side-effects were acute effects related to laser light treatment of the esophagus, skin photosensitivity reactions due to PHOTOFRIN®, and treatment-related esophageal strictures requiring dilations (in about 38% of patients). There were no deaths related to treatment. Two patients (of 318) had esophageal perforations, one requiring an emergency esophagectomy.

Areas of concern regarding PHOTOFRIN® photodynamic therapy in patients with Barrett's Esophagus and high-grade dysplasia are as follows:

- Ablation of high-grade dysplasia should result in a clinically meaningful outcome, which is long-term reduction of the risk of adenocarcinoma of the esophagus. The length of follow-up (a minimum of 2 years) in the Sponsor's studies is not long enough to demonstrate such a long-term clinical outcome, although failure to achieve a Complete Response appears to be associated with progression to cancer.
- The diagnosis of high-grade dysplasia should be confirmed by experts before therapy is undertaken. About 50% of patients referred to the pivotal trial with the diagnosis of high-grade dysplasia were not enrolled because the diagnosis was not confirmed by the expert panel of pathologists, who were blinded to patients' diagnoses.
- Patients with high-grade dysplasia should be treated for a minimum of 90 days with vigorous gastric acid suppression and the diagnosis of high-grade dysplasia then re-confirmed before treatment is undertaken. Omeprazole intake of at least 3 months was associated with a Complete Response ($p=0.0026$).
- Patients treated with only omeprazole had a relatively high Complete Response rate (39%). This finding emphasizes the therapeutic value of vigorous gastric acid secretion suppression in the management of high-grade dysplasia, even though the benefits of such treatment were relatively short-term.
- Patients diagnosed with high-grade dysplasia should be made fully aware of the uncertainties in the natural history of high-grade dysplasia, of the estimated risks of

progression of high-grade dysplasia to cancer, and of alternatives in the management of high-grade dysplasia.

PHOTOFRIN® photodynamic therapy provides a new therapeutic alternative for the management of high-grade dysplasia (in addition to “watchful waiting” or esophagectomy) and for that reason was granted priority review status.

From a clinical perspective, PHOTOFRIN® photodynamic therapy should be approved for the ablation of high-grade dysplasia in Barrett’s esophagus patients who do not undergo esophagectomy.

2. Reviewer’s recommendations for PHOTOFRIN® labeling are stated in Recommendations (Section X).

B. Recommendation on Phase 4 Studies an/or Risk Management Steps

1. The sponsor has made a commitment to a ~year follow up of the pivotal study. This study, entitled PHO BAR 02, is on-going.
2. The sponsor has made a commitment to perform a pharmacokinetic study in patients with hepatic impairment (IX. Section D).

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The drug under review is PHOTOFRIN (porfimer sodium) for Injection, which is a photosensitizing agent used in conjunction with a laser light delivery system. PHOTOFRIN is a polyporphyrin oligomer derived from hemoglobin. After intravenous injection, PHOTOFRIN, is widely distributed throughout tissues, and is preferentially concentrated in tumors, reticuloendothelial system and skin. A laser light at 630 nm wavelength applied to a tumor results in necrosis due to free radical reactions and to anoxia resulting from occlusion of blood vessels. PHOTOFRIN is approved for treatment of patients with

- completely obstructing esophageal cancer,
- obstructing endobronchial non-small cell lung cancer, and with
- micro-invasive endobronchial non-small cell lung cancer.

The indication of the present submission is ablation of high-grade dysplasia in patients with Barrett’s Esophagus who are not candidates for esophagectomy. Barrett’s Esophagus is a rare complication of a very common disorder, gastroesophageal reflux disease. High-grade dysplasia is a rare complication of Barrett’s Esophagus, and is a pre-malignant lesion. About 25% to 30% of high-grade dysplasia patients develop adenocarcinoma over a 3 to 7 year follow-up. Esophageal adenocarcinoma carries a very poor prognosis.

There is no agreement on the best treatment for high-grade dysplasia. Some experts advise esophagectomy, others, intensive surveillance, reserving esophagectomy for patients who develop adenocarcinoma. A third option is mucosal ablation therapy in which the dysplastic

epithelium is destroyed and, with suppression of acid production during healing, squamous cell epithelium re-grows. This is an out-patient procedure, it is minimally invasive, and it may eliminate the need for major surgery, especially in elderly poor-risk patients.

Supporting the indication are the results of three trials:

- PHO BAR 01, a multi-center, partially blinded, randomized, controlled trial in which 208 patients with high-grade dysplasia were enrolled; 138 were randomized to be treated with PHOTOFRIN photodynamic therapy (PDT) plus omeprazole, and 70 were randomized to be treated with omeprazole alone. This is the pivotal trial.
- TCSC 93-07, a single center, open-label, investigator-sponsored uncontrolled Phase II study, in which 99 patients were treated with PHOTOFRIN PDT plus omeprazole and with two different light doses and light delivery systems. Forty-four of these patients had high-grade dysplasia. This is one of the supportive trials.
- TCSC 96-01, a single center, randomized study of the effect of steroid therapy on the incidence of esophageal strictures in patients treated with PHOTOFRIN PDT plus omeprazole, in which 87 patients were enrolled, 42 of whom had high-grade dysplasia. This is the other supportive trial.

The data of TCSC 93-07 and TCSC 96-01 trials were obtained by the sponsor, and the efficacy results were analyzed in high-grade dysplasia patients by the same methodology as in PHO BAR 01 trial. The entire patient population treated with PHOTOFRIN PDT was used for safety analysis.

Patients in these studies were predominantly male (85%), white (99%), and former or current smokers (71%). The mean age was about 66 years (range, 38 to 88 years). The patient population enrolled in these studies is representative of the general population with Barrett's esophagus and high-grade dysplasia. Characteristics of Barrett's esophagus at baseline (duration of Barrett's esophagus, duration of high-grade dysplasia, endoscopic length of Barrett's esophagus, extent of high-grade dysplasia, presence of hiatal hernias, esophageal nodules, ulcers and strictures, and prior treatment) were similar in the group randomized to PHOTOFRIN PDT and in the group randomized to OM Only treatment.

Histopathologic diagnoses were performed at a central pathology laboratory by three pathologists, who were blinded to patients' identity, treatment arm assignment, study phase, or clinical trial site. A sub-study of rater agreement on histological diagnosis showed a high percent of intra-rater and inter-rater agreement. These results add to the quality of the submitted data.

Treatment in the PHOTOFRIN PDT group consisted of an intravenous injection of 2 mg/kg of PHOTOFRIN (the standard dose for all indications) and laser light administration 40 to 50 hours later. A second light treatment was administered to some patients 2 days afterwards to treat skip areas. Both treatments constituted one course. A total of three courses could be administered, separated by intervals of at least 3 months. Patients in both the PHOTOFRIN PDT group and in the OM Only group were treated with omeprazole 20 mg orally twice a day.

B. Efficacy

The primary efficacy endpoint was Complete Response, defined as complete ablation of high grade dysplasia and re-growth of normal squamous cell epithelium (CR1), or of normal epithelium with some areas of Barrett's metaplasia (CR2), or of normal epithelium with some areas of low-grade dysplasia, metaplasia, or indefinite dysplasia (CR3) after a minimum of 24 months of follow-up. In the PHO BAR 01 trial, 77% of PHOTOFRIN PDT patients and 39% of OM Only patients had a Complete Response (ITT populations; the respective percentages in the Evaluable populations were 82% and 39%). The difference between treatment arms was significant, with $p < 0.0001$. In the two supporting uncontrolled trials 88% of patients (ITT population; 94% in the Evaluable population) had a Complete Response.

The secondary efficacy endpoints addressed the quality of response (CR1 vs. CR2 vs. CR3), the duration of the response, the time to treatment failure, the time to progression to cancer, and survival time.

- The quality of response was significantly better ($p < 0.0001$) in the PHOTOFRIN PDT patients than in OM Only patients. Re-growth of normal epithelium (CR1) occurred in 52% of PHOTOFRIN PDT patients and in only 7% of OM Only patients ($p < 0.0001$). Re-growth of normal epithelium with some areas of metaplasia (CR1 + CR2) occurred in 59% of PHOTOFRIN PDT patients and in only 14% of Omeprazole Only patients ($p < 0.0001$).
- Duration of response was analyzed at each response level. By the end of the 24-month follow-up period, the probability of maintaining a CR3 or better response was 53% in the PHOTOFRIN PDT patients and only 13% in OM Only patients.
- Rate of progression to cancer was lower in the PHOTOFRIN PDT group. By the end of the minimum follow-up of 24 months, 13% of PHOTOFRIN PDT patients had progressed to cancer as compared to 28% of OM Only patients ($p = 0.006$).
- By the end of the follow-up period patients in the PHOTOFRIN PDT group had an 83% chance of being cancer-free as compared to 53% chance for patients in the OM Only group. The difference in the time to progression to cancer was significant with $p = 0.0014$.
- Treatment failure was defined as a combination of progression to cancer and of use of other interventional therapy. By the end of the minimum follow-up of 24 months, 25% of patients in the PHOTOFRIN PDT group and 53% of patients in the OM Only group had failed treatment.
- Difference in survival times was not significant as very few patients had died in either group. No patient died because of esophageal adenocarcinoma.

These secondary endpoints are important, because Complete Response, i.e. ablation of high-grade dysplasia, is important only as a means of preventing the development of adenocarcinoma. Analysis of the outcomes in patients who did not have a Complete Response showed that the risk of progression to cancer was about ten-fold higher in these patients compared to patients who had a Complete Response.

The results of the PHO BAR 01 controlled trial are important in that two approaches to the management of high-grade dysplasia, mucosal ablation using PHOTOFRIN PDT and surveillance, were directly compared in the two arms of the study. There was no esophagectomy arm in the study, therefore the three approaches to the management of high-grade dysplasia could not be directly compared. Surveillance appeared to be an ineffective method of

management, because about 85% of the patients in the surveillance arm either progressed to cancer, or chose another therapeutic modality, or were discontinued from the trial for other reasons.

C. Safety

Adequacy of safety testing. A total of 318 patients were treated with PHOTOFRIN PDT in the three studies. The median follow-up was 12 months. The patients were followed at least every 3 months, and esphagoscopy data indicate a high degree of patient compliance with the outlined follow-up surveillance program.

Serious side-effects. The side-effect profile of a control group with the same diagnosis provides a very useful benchmark for evaluation of side-effects of PHOTOFRIN PDT therapy. There appears to be an acute PDT syndrome consisting of chest pain, odynophagia, dysphagia, abdominal pain, fever, nausea and vomiting that afflicted about a third of the PDT patients and that was absent in the control group. These acute side effects abated in about 4 weeks. Following the injection of PHOTOFRIN all the patients became photosensitive, and the photosensitivity of the skin continued for at least 30 days and sometimes longer. Patients were given elaborate and detailed instructions on avoiding bright light; nevertheless, about one-half to two-thirds of patients had photosensitivity reactions, which were severe in about 10% of patients. All photosensitivity reactions resolved with time.

The main safety issue with photodynamic therapy is the development of esophageal strictures during the healing process. Strictures, defined as esophageal narrowing that required dilation, developed in about 38% of patients. Severity of strictures was graded as mild (in 44% of patients), moderate (in 43% of patients), or severe (in 12% of patients). There is no known method to prevent strictures at the present time. According to the results of the TCSC 96-01 trial, treatment with corticosteroids did not reduce the incidence of strictures. Areas of esophagus that had a mucosal segment treated twice appear to be predisposed to stricture formation.

The only treatment for strictures at present is esophageal dilation. About 35% of patients with strictures received 1 to 2 dilations, about 29% received 3 to 5 dilations, about 22% received 6 to 10 dilations, and about 15% received more than 10 dilations. There was only one patient with a stricture in the OM Only group of patients, and the stricture was successfully treated with only one dilation.

Common side-effects. Almost all (98%) of patients in the PHOTOFRIN PDT group reported adverse events, as compared to 68% of patients in the OM Only group. Furthermore, the total number of adverse events was more than three times as high in the PHOTOFRIN PDT group as in OM Only group (1,245 vs. 206 events). In the PHOTOFRIN PDT group the most common side effects were related to the gastrointestinal system, body as a whole (chest pain, fever, pain), photosensitivity reactions, and dehydration. There no predominant side effects in the OM Only group; the most common were related to the gastrointestinal system, body as a whole, nervous system, and metabolic and nutritional system.

Deaths and SAEs. There were 6 deaths in the three studies, none of which were treatment-related. Twenty-five percent of patients in the PHOTOFRIN PDT group reported SAEs, most commonly related to gastrointestinal, cardiovascular, metabolic, nutritional, and nervous systems. Most treatment-related SAEs (80 events) were reported as gastrointestinal disorders and dehydration. Twenty-eight percent of patients in the OM Only group reported SAEs; four SAEs were treatment-related.

Withdrawals because of adverse events. Seven patients (2.2%) in the PHOTOFRIN PDT group and one patient (1.4%) in the OM Only group withdrew from studies because of adverse events. Two such events were treatment-related; they were esophageal perforations, one requiring an esophagectomy.

Drug-drug interactions. The Sponsor raised possibilities of interactions of PHOTOFRIN with other photosensitizing drugs and with drugs degraded by cytochrome P450 enzymes, but these possible interactions have not been studied. There is no basis for suspecting an interaction with omeprazole. In terms of other drugs increasing or decreasing photosensitivity, it is important to remember that the photosensitivity after PHOTOFRIN injection is massive and dwarfs the effects of any other drugs increasing or decreasing photosensitivity.

Exposure in trials versus probable marketing exposure. The PHOTOFRIN PDT protocols have been applied consistently, and no changes are expected after marketing.

Effect of trial exclusions on safety profile vs. expected marketed population. The main reason for excluding patients from the pivotal trial was failure to confirm the presence of high-grade dysplasia (86% of excluded patients). Since these patients were referred with this diagnosis for inclusion in the trial, the possibility is very real that patients without high-grade dysplasia may undergo PHOTOFRIN PDT therapy.

Recommended warnings. Patients diagnosed with high-grade dysplasia in Barrett's esophagus should be treated with aggressive gastric acid suppression therapy for at least 90 days and their diagnosis confirmed by an expert pathologist. Other warnings should include the risks of acute PDT symptomatology as described above, of photosensitivity reactions, and of strictures.

Relationship of safety to other drugs available for indication. No other drugs are available for this indication.

Unresolved safety issues. Stricture formation may go hand in hand with the treatment, since shallower ablation may not be effective for high-grade dysplasia.

D. Dosing

The same dosing of PHOTOFRIN (2 mg/kg intravenously) has been used for over 10 years in over 3,000 applications. The drug in PDT is not the active therapeutic agent, the light is. The drug is given in a sufficient dose to achieve photosensitivity.

E. Special Populations

Gender differences. None found in pharmacology, safety, or effectiveness.

Ethnic and racial studies. Small-scale Japanese studies have been reported, but differences in trial design, dosing and efficacy endpoints do not permit drawing of any definite conclusions.

Elderly. The Complete Response rates decreased progressively with age, from 85.7% in the 30- to 49-year age group to 70.0% in the 80- to 89-year age group. On initial analysis, PHOTOFRIN PDT appeared to be more effective in patients less than 65 years of age than in patients more than 65 years of age ($p = 0.0219$). However, when the patients were grouped as <70 and ≥ 70 years of age, the differences between groups were not statistically significant ($p = 0.1584$, Fisher's Exact Test).

Status of pediatric studies and pediatric plan. A waiver for pediatric studies in children is requested on the basis that PHOTOFRIN is designated as an Orphan Drug. This waiver should be granted, especially as Barrett's esophagus with high-grade dysplasia is not known to occur in the pediatric population.

Pregnancy use information. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. PHOTOFRIN should be used during pregnancy only if the potential benefit justifies the potential risk to fetus. Animal toxicity studies showed increased resorptions, decreased litter size, delayed ossification, and reduced fetal weight, as tested in rats and rabbits.

Nursing mothers. It is not known whether PHOTOFRIN is excreted in human milk. Women receiving PHOTOFRIN must not breast feed, because of potential for serious reactions in nursing infants.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Drug established trade name: PHOTOFRIN® (porfimer sodium)

Drug class: Photosensitizing agent

Approved indications (under NDA 20-451):

- Palliation of patients with completely obstructing esophageal cancer,
- Palliation of patients with obstructing endobronchial non-small cell lung cancer, and
- Treatment of patients with micro-invasive endobronchial non-small cell lung cancer for whom surgery and radiotherapy are not indicated.

Proposed indication: Ablation of high-grade dysplasia in patients with Barrett's Esophagus who are not candidates for esophagectomy (May 31, 2002 submission), or "among patients who refuse esophagectomy and who are in overall good health" (April 4, 2003 Proposed Package Insert).

Dose: Intravenous infusion of 2 mg/kg body weight.

Regimens: PHOTOFRIN is approved as a drug-device combination for photodynamic therapy (PDT). The devices are endoscopically placed fiber optics devices with cylindrical diffusers and with inflatable centering balloons of various lengths (3, 5, and 7 cm). Light activation, using red light laser of 630 nm wavelength, is performed 40 to 50 hours after PHOTOFRIN injection and, if required for a second session, 5 days after PHOTOFRIN injection.

Age groups: Most of the patients who may be candidates for PHOTOFRIN PDT therapy will be >50 years of age, since both high-grade dysplasia in Barrett's Esophagus (BE), a pre-malignant condition, and adenocarcinoma of the esophagus increase with age. Sponsor's Table 3.7-1 shows the incidence of esophageal adenocarcinoma in BE patients of various ages.

Sponsor's Table 3.7-1: Adenocarcinoma Incidence with Age in BE

Age range	Incidence/100,000
30-39	0.01
40-49	0.06
50-59	1.8
60-69	3
70-79	3.9

Gender: Most of the candidates for PHOTOFRIN therapy will be males, since

- BE is 2 to 5 times more common in men than in women, and since
- most of the patients (about 86%) with esophageal carcinoma are male (Cameron *in* Tilanus & Attwood, pp. 281 – 290).

B. State of Armamentarium (Treatment Options) for the Indication

In order to put high-grade dysplasia (HGD) in Barrett's Esophagus (BE) into perspective, this section contains discussions of gastroesophageal reflux disease (GERD), Barrett's esophagus, pathogenesis of esophageal adenocarcinoma, natural history of HGD, and management options for HGD.

1. Gastroesophageal reflux disease and Barrett's Esophagus. GERD, defined as abnormal reflux of gastric contents into the esophagus accompanied by chronic symptoms and, in some cases, by mucosal damage, is very common in the adult population. Prevalence estimates are as high as 10% to 20% of the population in the U.S. (Shaheen & Ransohoff, Cameron *in* Tilanus & Attwood, p. 281).
2. Barrett's Esophagus (BE) is a complication that develops in a minority (about 6% - 12%) of patients with GERD, or in about 1% of persons over the age of 60, or in about 0.4% of

persons in the general population including all ages (Cameron, op.cit.). BE is clearly associated with

- severe and long-lasting gastroesophageal reflux,
- the presence of a hiatal hernia,
- a lower basal esophageal sphincter pressure, and
- abnormal epithelial repair resulting in replacement of squamous cell by columnar cell epithelium.

The diagnosis of BE is established if the squamocolumnar junction is displaced proximal to the gastroesophageal junction, and the normal squamous cell epithelium of the esophagus is replaced by a specialized or intestinal-type columnar cell lining containing acid mucin-containing goblet cells (Falk, Shaheen & Ransohoff). The origin of the columnar cells composing the Barrett's esophagus is unclear; they are not gastric cells, since they differ histologically from cells of the gastric cardia.

3. Pathogenesis of adenocarcinoma of the esophagus. The importance of BE and of GERD is their association with the development of adenocarcinoma of the esophagus, a highly lethal disease with a 5-year survival of 11% in the early 1990s. Adenocarcinoma of the esophagus is, for unknown reasons, increasing in incidence in the United States and other countries. Population-based cohort studies suggest a 300% to 500% increase throughout the last 30 to 40 years. The pathogenesis of adenocarcinoma of the esophagus is thought to progress through several stages.

Severe, frequent and long-lasting reflux leads to a metaplastic change from squamous to intestinal-type columnar lining (i.e. BE). This process involves the destruction of the squamous mucosa as a result of acid reflux and subsequent re-epithelialization. The specialized columnar epithelium progresses to:

- low-grade dysplasia, then to
- high-grade dysplasia, then to
- adenocarcinoma.

4. Prevention of adenocarcinoma of the esophagus. A number of approaches have been described for prevention of adenocarcinoma; however, at the present time there is no consensus on which one is best. Below are the options under consideration.

a. Screening patients for BE. The subjects for endoscopic screening would be those at highest risk for BE: white men, 50 years of age and older, with long-standing reflux symptoms. No clinical trials have been carried out to support such a strategy. Because the number of Americans with reflux symptoms is so high and because the incidence of esophageal carcinoma is so low, by necessity the absolute risk to the average person with reflux is low. Shaheen & Ransohoff calculated that there are about 10 million individuals in the U.S. who are older than 50 years and who experience reflux weekly. Of these 10 million individuals, approximately 6500 a year will develop esophageal adenocarcinoma. Thus, the cancer risk to any given older individual with reflux is 0.00065 per year, an extraordinarily low figure.

If BE is diagnosed, symptoms can be relieved by proton pump inhibitors and esophagitis can be healed, but intestinal metaplasia is not reversed. Moreover, the vast majority of BE patients never develop cancer. Most recent studies suggest that the annual incidence of adenocarcinoma in BE patients is about 0.5% or less (Shaheen & Ransohoff; Falk). Furthermore, approximately 94% to 98% of adenocarcinomas are diagnosed in patients without a prior diagnosis of Barrett's esophagus. These findings may be explained in part by the absence of reflux symptoms in an estimated 40% of patients with BE. In five published series of patients with adenocarcinoma and BE found simultaneously, a history of preceding reflux symptoms was obtained in 52% to 65% of cases (Cameron). Nevertheless, the only hope for improved survival of patients with esophageal carcinoma is detection of cancer at an early and potentially curable stage.

- b. Surveillance of BE patients to detect cancer at an early and potentially curable stage. Several retrospective studies clearly suggest that BE patients in whom adenocarcinoma was detected in a surveillance program had dramatically improved 5-year survival compared to similar patients not undergoing routine endoscopic surveillance. A recent decision-analysis study of the optimal surveillance strategy for BE with an endpoint of esophagectomy for high-grade dysplasia concluded that surveillance every 5 years was the most effective strategy to increase both length and quality of life (Provenzale et al.).

The aim of surveillance is the detection of dysplasia. Surveillance guidelines recommend obtaining systematic 4-quadrant biopsy specimens at 2-cm intervals along the entire length of BE. An even more comprehensive "Seattle protocol" specifies jumbo forceps and biopsies at 1-cm intervals. Results from surveillance programs have shown that dysplasia and superficial adenocarcinoma may be extraordinarily focal. Reid BJ et al. reported that among 45 patients with high-grade dysplasia who eventually developed cancer, 82% had cancer in a single 1-cm segment and 69% had cancer in a single biopsy specimen. On the other hand, only 39% of patients with cancer diagnosed by endoscopic biopsy had cancer found at surgery.

Surveillance every 2-3 years is recommended as adequate in patients without dysplasia, once a year in patients with low-grade dysplasia, and every 3 months in patients with high-grade dysplasia, if esophagectomy is not performed (American College of Gastroenterology Guidelines for the Diagnosis and Surveillance of Barrett Esophagus, Am J Gastroenterol 1998; 93:1028-32). These intervals are arbitrary and have never been subject to a clinical trial. Other authors argue that because most patients with BE will not die from esophageal cancer, endoscopic surveillance is not warranted until substantiated by prospective studies (Van der Burgh A et al.; MacDonald CE et al.). A randomized controlled trial of surveillance vs. no surveillance in BE has not been performed.

- c. Natural history and management of low-grade dysplasia. The natural history of low-grade dysplasia is poorly understood. Results of recent studies suggest that approximately 10% - 28% of low-grade dysplasia patients go on to develop high-grade dysplasia or adenocarcinoma, about 60% - 65% of patients show a regression, and the remainder continue to have low-grade dysplasia. American College of Gastroenterology recommends continued surveillance.

d. Natural history and management of high-grade dysplasia. Patients with high-grade dysplasia have a risk of subsequent adenocarcinoma exceeding 25%. Additionally, because endoscopic biopsies of BE are taken at random locations, the sampling error in individuals with high-grade dysplasia is great. When those with high-grade dysplasia undergo resection, up to 50% of the resected specimens demonstrate previously unrecognized adenocarcinoma (cited in Shaheen & Ransohoff). Recent studies report development of cancer in 16% to 59% of high-grade dysplasia patients who were followed with endoscopic surveillance for 3 to 7 years (Buttar NA et al.; Reid BJ et al.; Schnell TG et al.).

The options available to the patient with BE and high-grade dysplasia are shown in the Reviewer's Table below.

Reviewer's Table. Treatment Options in HGD Patients

Intervention
1. Esophageal resection
2. Intensive endoscopic surveillance, with esophagectomy reserved only for patients who develop adenocarcinoma
3. Mucosal ablation therapy to areas of BE, including <ul style="list-style-type: none"> a) Thermal therapy, such as: <ul style="list-style-type: none"> • Multipolar electrocoagulation • Heater probe • Argon plasma coagulator • Nd:YAG laser • Argon laser • KTP (potassium titanyl phosphate) laser b) Photodynamic therapy, using as photosensitizers: <ul style="list-style-type: none"> • porfimer sodium (PHOTOFRIN) • hematoporphyrin • 5-delta-amino-levulinic acid
4. Endoscopic mucosal resection

e. Issues in Management of HGD. Esophageal resection will not be discussed. Intensive endoscopic surveillance was discussed above.

1) The rationale of mucosal ablation therapy is that the metaplastic epithelium is destroyed and, with vigorous suppression of acid production during healing, squamous cell epithelium re-grows. Ablation therapy has tremendous appeal to both patients and physicians. It is minimally invasive, "high-tech", and may eliminate the need for major surgery, especially in elderly poor-risk patients. However, several difficult issues need to be kept in mind.

- The reversion to squamous epithelium may be incomplete, leaving islands of metaplastic (Barrett's) mucosa in the treated area.

- Barrett's mucosa may underlie what appears to be normal squamous epithelium; there have been reports of adenocarcinoma developing beneath squamous epithelium. The risk of cancer in areas of Barrett's esophagus treated with ablative therapy is not defined.
- Techniques are not standardized and esophageal movement makes accurate and complete targeting difficult.
- Risks, including strictures, perforation, and incurable cancer developing in otherwise curable patients.
- Endoscopic surveillance is still warranted in these patients, but previous landmarks are now obscured, making targeting of biopsies problematic.
- Persistent biomarker abnormalities have been described in the new squamous epithelium that replaced high-grade dysplasia.

2) Thermal ablation. Experience with various types of lasers has been documented, but lasers are no longer widely available. Multipolar electrocoagulation has been shown to result in histologic reversal of BE in about 80% of patients, as has argon plasma coagulation therapy. Both techniques have significant adverse events, including chest pain, odynophagia, fever, pleural effusion, perforations, strictures, and pneumomediastinum.

3) Photodynamic therapy is based on the systemic administration of certain photosensitizing agents that are retained with some selectivity in rapidly proliferating and malignant tissues. When the target tissues are exposed to appropriate wavelength laser light, oxygen radicals are generated causing cellular destruction. The choice of photosensitizer is crucial to achieve the depth of necrosis that is required. Oral 5-aminolevulinic acid used to generate protoporphyrin IX will produce necrosis to a depth of 2 mm. PHOTOFRIN (porfimer sodium) or any derivative of di-hematoporphyrin ester/ether will produce necrosis up to a depth of 6 mm. Of the photosensitizing agents, only PHOTOFRIN is available in the United States for use in photodynamic therapy. The main complication of this therapy is the development of strictures.

4) Endoscopic mucosal resection has been used in BE with adenocarcinoma or high-grade dysplasia. It is most effective in low-risk lesions (diameter <2cm, limited to mucosa, well or moderately differentiated histology); less effective in high-risk lesions (diameter >2cm, extending into submucosa or ulcerated, poorly differentiated histology). During a 1-year follow-up, 17% of the low-risk group and 14% of the high-risk group developed high-grade dysplasia or cancer (Ell C et al.). The applicability of this technique to invisible lesions or multi-focal lesions is questionable at present.

C. Important Milestones in Product Development

PHOTOFIN for Injection was studied under IND 42,313 for ablation of high-grade dysplasia in Barrett's esophagus and superficial esophageal cancer (studies TCSC 93-07 and TCSC 96-01, which are reviewed in this submission).

The PHO BAR 01 study protocol was submitted to the Division of Oncology Drug Products (IND 25,064) on November 13, 1997 by QuadraLogics Technologies (QLT) and the study was initiated in January of 1998. QLT conducted the study until June of 2000, when Axcan Pharma

acquired the product and took over clinical monitoring of the product. On June 21, 2000 the Agency requested that this study be re-filed with the Division of Gastrointestinal and Coagulation Drug Products, which the new sponsor (Axcen Scandipharm, Inc.) did on September 26, 2000 (IND 61,011).

The Agency clearly enunciated key elements to be provided in the submission. In an Advice Letter dated January 25, 2001 after the completion of the review of IND 61,011 describing the pivotal study, the Agency specified that:

- To qualify as a pivotal trial the primary response variable must reflect an improvement in the long-term clinical outcome. Partial histopathological responses to photodynamic therapy (PDT) might not reflect clinically meaningful long-term outcomes. In addition, the current standard of care which includes esophagectomy in individuals who are surgical candidates should be included in the definition of an appropriate population for whom PDT therapy might be indicated.
- The sponsor should provide an analysis of clinical outcomes of individuals associated with treatment failure in conjunction with the outcomes associated with treatment success. Such outcomes should be compared to those associated with other modes of treatment such as esophagectomy.
- The sponsor should provide information about the timing and severity of strictures associated with PDT.
- The sponsor should clearly define the treatment of nodules before therapy. For example, the protocol should provide details how carcinoma underlying nodules will be excluded prior to PDT.
- The sponsor should provide an up-to-date model informed consent form to the Agency.

A teleconference with the sponsor on March 5, 2001 clarified the above concerns in greater detail, namely that:

- Six months' follow-up may be inadequate to assess the impact of the treatment. A follow-up time frame of 5 years or more was recommended, but follow-up of at least 2 to 3 years would be acceptable
- The Agency is concerned that the use of histopathological effects for measuring clinical benefit might be a surrogate endpoint. The appropriateness of this endpoint is questionable considering the differences in the natural course of high-grade dysplasia from low-grade dysplasia in the occurrence of cancer. The measurement should be linked to a clinically meaningful outcome.
- The Agency is concerned that PDT might be a cosmetic effect of treatment rather than changing the course of disease. The Agency is most interested in assessing whether there is a long-term sustained response to therapy.

The sponsor stated that the response to therapy is sustained.

As related in the above communications, the importance of PDT with PHOTOFRIN is prevention of adenocarcinoma of the esophagus, and the trials must provide evidence that this is an effective and relatively safe therapy for this purpose.

D. Other Relevant Information

PHOTOFRIN for Injection was first approved in Canada. Reviewer's Table below describes the indications approved, the countries in which the indication was approved, and the date of approval. Following tables describe Rejections, and Submissions (adapted from Tables 3.2-1, 3.2-2, and 3.2-3, vol. 1, pp. 135-9). The indications have been abbreviated by the reviewer; the wording of indications differs between countries.

Reviewer's Table on Regulatory History in Other Countries - Approvals

Indication	Countries where approved and year of approval
Recurrent superficial papillary bladder cancer: second-line treatment for those who have failed standard intravesical therapy	Canada (1993)
Obstructing esophageal cancer	Canada (1995), The Netherlands (1994), France (1996), United Kingdom (1998), Finland (1999), Iceland (1999), Denmark (1999), Portugal (1999), Norway (1999), Luxembourg (1999), Ireland (2000), Austria (2000), Italy (2000), Sweden (2000), Belgium (2001), Greece (2001), Poland (2001)
Obstructing endobronchial non-small cell lung cancer	Canada (1999), The Netherlands (1994), France (1996), Germany (1997), United Kingdom (1998), Finland (1999), Iceland (1999), Denmark (1999), Portugal (1999), Norway (1999), Luxembourg (1999), Ireland (2000), Austria (2000), Italy (2000), Sweden (2000), Belgium (2001), Greece (2001), Poland (2001)
Superficial endobronchial non-small cell lung cancer in patients for whom surgery and radiotherapy are not indicated	Canada (1999), The Netherlands (1994), France (1996), Iceland (1999), Greece (2001)
In patients for whom curative therapy is impossible and there is no therapy except PDT: Early lung cancer (stage 0 and I) Superficial esophageal cancer Superficial gastric cancer Early cervical cancer and dysplasia	Japan (1994)
Ablation of high-grade dysplasia in Barrett's	Canada (March, 2003)

esophagus patients who are ineligible for or who have refused esophagectomy	
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Reviewer's Table on Regulatory History in Other Countries - Rejections

Indication	Country where rejected
[]	

Reviewer's Table on Regulatory History in Other Countries – Submissions neither Approved nor Rejected at the Time of this Submission

Indication	Country where submitted and date of submission
[]	
]]

E. Important Issues with Pharmacologically Related Agents

PHOTOFRIN is the only photosensitizing agent approved for use in photodynamic therapy. The drug is innocuous until activated by light. Other photosensitizing agents share this property. The duration of photosensitivity varies by agent.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Chemistry. PHOTOFRIN (porfimer sodium) for Injection is a complex mixture of porphyrin oligomers, porphyrin monomers, [

] In the oligomers, porphyrin units are joined by ether [] and ester [] linkages. The active ingredient, porfimer sodium, consists of oligomeric species, ranging from dimers to octamers, the majority of which are dimers and trimers. []

The chemical complexity of the oligomeric mixture is further complicated by the dynamic aggregation/disaggregation exhibited by porphyrins in aqueous solution. These characteristics have precluded resolution of the oligomers present in PHOTOFRIN by conventional analytical methods. All fractions resulting from attempts to fractionate PHOTOFRIN by multiple gel chromatography or HPLC consisted of mixtures of oligomers. All such fractions were biologically active in a tumoricidal assay. Thus, single components of PHOTOFRIN cannot be isolated, and structure-function relationships cannot be determined for the complex components of PHOTOFRIN.

Manufacture. Porfimer sodium bulk concentrate is manufactured by [] in [] which uses [] is prepared [] by [] which obtains [] from []

The molecular weight of the oligomeric components of porfimer sodium ranges from 1178 to 4659 daltons, depending on the number of porphyrin units per oligomer and the extent of dehydration occurring at hydroxyethyl end groups.

Porfimer sodium is manufactured as a dark red liquid or freeze-dried powder, which is soluble in water. It is formulated without excipients. Bulk concentrate of PHOTOFRIN is stable up to 3 months when stored frozen.

Degradation Products. Degradation of porfimer sodium in solution occurs primarily through hydrolysis. The degradation products are []

Nonclinical pharmacology studies.

- Study TX-96005: A Pilot Study to Measure and Compare the Amount of Light from Black and White Balloon Catheters on the Dog Esophagus. No drug, light only. Mucosal light doses for white and black balloons measured.
- Study TX-96003: To assess the "new" white balloon catheters in the dog esophagus.
- Study TX-97005: A study of light delivered by balloon catheters by two different manufacturers.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

There are no new pharmacokinetic or other Phase I studies conducted by the sponsor that are included in this supplemental NDA. Human pharmacokinetics has been studied in three clinical trials in cancer patients who were undergoing photodynamic therapy (PDT) and in one clinical trial in healthy volunteers (a post-marketing study that was submitted in an Annual Report to the NDA).

1. Absorption. PHOTOFRIN is given intravenously, and the absorption of PHOTOFRIN from the GI tract has never been studied. Animal studies have shown that after I.V. administration of ³H-hematoporphyrin derivative (an unpurified form of porfimer sodium), maximum radioactivity concentrations in the digestive tract were about 5% of those in the liver. Radioactivity concentrations in the digestive tract were greatest in the small intestine, followed by the gastric antrum, esophagus, gastric fundus, and colon. Three days after drug administration, radioactivity in the GI tract was present at 44% - 75% of that observed at 1 - 4 hours post-dose (Vol. 27, p. 1).

PHOTOFRIN maximum plasma concentrations (T_{max}) were seen between 5 min and 60 min after the start of the 3-5 min I.V. injection. The cause of this variability is unknown. C_{max} values after injection of 2mg/kg PHOTOFRIN were in the range of 15 to 80 mg/mL.

The percentage of PHOTOFRIN-related porphyrins bound to serum proteins was about 90% and was independent of concentration. The predominant site for total porphyrin binding was to high density lipoproteins. Porphyrin monomers were primarily bound to albumin; dimers/oligomer fraction was associated with lipoproteins. The elimination of albumin-bound porphyrins was faster than of lipoprotein-bound porphyrins (Vol. 32, p. 200).

2. Distribution. Distribution of PHOTOFRIN into tissues occurs in the first 24 hours after dosing, and, once in tissues, the clearance of PHOTOFRIN is slow. Due to extensive distribution of PHOTOFRIN into tissues, serum concentrations may not be the best indicator of the concentration of PHOTOFRIN at the site of action, and may also be a poor indicator for the potential of adverse photosensitivity reactions.

3. Metabolism. Due to the complexity of the mixture of porphyrins in PHOTOFRIN, the metabolism of PHOTOFRIN has not been adequately studied. Results from animal studies suggest that the ester and ether linkages holding multimeric structures are likely to be hydrolyzed to monomeric porphyrin units. The pathways of porphyrin and of heme degradation are well known. The catabolism of heme is carried out by heme oxygenase I and cytochrome P450, which cleave porphyrin into biliverdin. Biliverdin is oxidized to bilirubin, which is excreted by the liver into bile.

Another important aspect of the breakdown of PHOTOFRIN is photo-bleaching. Reduction in photosensitivity after PHOTOFRIN injection appears to be best achieved through gradual exposure to low levels of light, which allow for the gradual breakdown of PHOTOFRIN within the skin. It is not known to what extent photo-bleaching contributes to the overall clearance of PHOTOFRIN; however, it is an important process for reducing risks associated with photosensitivity.

The sponsor states that direct competition between PHOTOFRIN and other drug products for cytochrome P450 enzymes is not expected to occur, and that genetic variation in cytochrome P450 isozymes within the human population is not expected to influence the metabolism of PHOTOFRIN (vol. 1, p. 167).

4. Excretion. PHOTOFRIN is excreted from the body mainly unchanged (61%); 35% is excreted in the form of metabolites (Vol. 27, p.8). Elimination appears to be biphasic, with the

first phase having a half-life of about 220 hours (about 9 days) and the second phase, a half-life of about 870 hours (about 36 days). The first phase may represent tissue distribution, and the second phase, metabolism and excretion. PHOTOFRIN-related materials are excreted mainly through the bile/feces (59%), and only minimally through the urine (6%) when measured in samples collected over the first 192 hours (8 days) after dosing. These data are consistent with metabolism of PHOTOFRIN monomeric units into bilirubin.

5. Variations in Special Populations

a. Gender differences. In PHO PK 001 (Table 3.5-1), the pharmacokinetics of PHOTOFRIN in healthy male and female volunteers were compared after a single dose. A bi-exponential serum decay was observed, with a slow distribution phase and a very long elimination phase that started approximately 24 hours after injection and had a $T_{1/2}$ of 415 hours (17 days). Pharmacokinetic parameters were not affected by gender, except for T_{max} , which was longer in women (vol. 7, p. 112).

b. Race differences. PHOTOFRIN has been studied in Caucasian and Japanese cancer patients. However, due to the differences in the sampling times between studies, and small numbers of patients involved, it is difficult to draw any conclusions about variation in PHOTOFRIN pharmacokinetics between these populations (vol. 31, p. 14).

c. Differences between patients and healthy volunteers. Three studies were conducted in patients, and one in healthy volunteers. The mean C_{max} values from these studies ranged from 14.2 mcg/mL to 79.6 mcg/mL, and the mean $T_{1/2}$ ranged from 22 hours to 515 hours. The sponsor states that the two shorter estimates of PHOTOFRIN half-life are an artifact of reduced sampling in these studies. The long half-life in Report 1 (515 hours) in patients is consistent with that of PHO PK 001 study (415 hours) in normal volunteers.

d. Potential for drug-drug interactions. In the treatment of high-grade dysplasia PHOTOFRIN is given by single injection with repeat doses being at least 90 days apart. There have been no formal interaction studies of PHOTOFRIN and any other drugs. However, it is possible that concomitant use of other photosensitizing agents, such as tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide diuretics and griseofulvin could increase the photosensitivity reaction. In addition, there exists a theoretical possibility that there may be interactions with other drugs with significant biliary excretion, such as erythromycin, azithromycin and lansoprazole.

Compounds that quench active oxygen species or scavenge radicals, such as dimethylsulfoxide, beta-carotene, ethanol, formate and mannitol would be expected to decrease PDT effectiveness. Pre-clinical data suggest that tissue ischemia, allopurinol, calcium channel blockers and some prostaglandin synthesis inhibitors could interfere with PHOTOFRIN PDT. Drugs that decrease clotting, vasoconstriction or platelet aggregation, such as thromboxane A2 inhibitors, could decrease the efficacy of PDT. Glucocorticoids given before or concomitant with PDT may decrease the efficacy of the treatment (*Reviewer's note*: TCSC 96-01 trial does not support this possibility, as noted below).

Omeprazole or other proton pump inhibitors are most likely to be used in conjunction with PDT in the treatment of high-grade dysplasia. PHOTOFRIN and omeprazole differ significantly in their absorption, distribution, metabolism and excretion properties, and pharmacokinetic interaction between these agents is not expected to be of clinical concern.

B. Pharmacodynamics

1. Mechanism of cytotoxic action. PHOTOFRIN is a photosensitizing agent that is used in photodynamic therapy for cancer. Tumor selectivity in treatment occurs through a combination of 1) selective retention of PHOTOFRIN and 2) selective delivery of light. By 40-50 hours after I.V. injection PHOTOFRIN has largely cleared from a variety of normal tissues, and has been retained by neoplastic tissues, skin, and organs of the reticuloendothelial system. At this time light activation is performed with red light at 630 nm wavelength. This is the longest wavelength that can adequately activate PHOTOFRIN and provide the greatest tissue penetration. Also, at this wavelength, the absorption of activating light by hemoglobin is minimal. The activation of PHOTOFRIN results in a generation of reactive oxygen species including singlet oxygen. Tumor necrosis occurs as a result of direct cytotoxicity to tumor cells, and also as a result of ischemia because of the sensitivity of tumor vasculature to PDT. Thrombogenic agents appear to be liberated locally and result in occlusion of tumor capillaries within 20 minutes of photoactivation.

2. Dosage of PHOTOFRIN and of light. The dose of PHOTOFRIN used in all studies (2 mg/kg of body weight, given I.V.) was determined empirically. This dose has been used for more than 3,000 treatments as the standard dose for all indications. The 40- to 50-hour interval between PHOTOFRIN injection and light treatment is also standard. This timing is based on the clearance of PHOTOFRIN from most tissues except skin and tumors. The total light dose delivered to tumor or dysplastic tissue is a key factor in efficacy and safety. The light doses recommended for use in high-grade dysplasia in BE are the lowest that achieved consistent efficacy and an acceptable safety profile.

3. Light delivery systems. The delivery of light is accomplished using laser light passed through endoscopically placed fiber optics tipped with cylindrical diffusers. Because the normal esophagus does not behave as a cylindrical tube, but tends to collapse when empty, an inflatable centering balloon was developed. The centering balloon helped achieve a PDT response that was circumferential and uniform. The balloon designs underwent progressive developments: from an optically transparent to "black-capped" with black ends and a 360° central transparent window and, finally, to "white-capped" balloons with a reflective inner coating at the ends allowing for a more uniform output from the balloon. The "black-capped" balloons had a non-linear light output across the window, resulting in a peak at the mid-point of the window. This peak in light intensity appeared to correspond to the position of stricture development in at least some patients.

IV. Description of Clinical Data and Sources

A. Overall Data

Sources of data used in the review are from a clinical trial program as described below.

B. Tables Listing the Clinical Trials

Clinical trial no.	Clinical trial title
PHO BAR 01	A multicenter, partially blinded, randomized Phase III study of the efficacy and safety of photodynamic therapy (PDT) using PHOTOFRIN (porfimer sodium) for Injection for the ablation of high-grade dysplasia in Barrett's Esophagus.
TCSC 93-07	A Phase I/II Study of the Safety and Efficacy of Photodynamic Therapy (PDT) Utilizing PHOTOFRIN for Treatment of Dysplasia or Early Adenocarcinoma of the Esophagus in Barrett's Esophagus.
TCSC 96-01	Photodynamic Therapy of Dysplasia or Early Adenocarcinoma in Barrett's Esophagus: A Randomized Study of the Effect of Steroid Therapy on the Incidence of Esophageal Stricture

The Sponsor conducted the pivotal trial PHO BAR 01. Trials TCSC 93-07 and 96-01 were individual investigator-sponsored trials by Bergein F. Overholt, M.D., Thompson Cancer Survival Center, Knoxville, TN. PHO BAR 01 enrolled patients only with BE and high-grade dysplasia. TCSC 93-07 and 96-01 enrolled patients with high-grade dysplasia, with low-grade dysplasia, and with superficial adenocarcinoma of the esophagus. The Sponsor obtained access to the data in the TCSC 93-07 and 96-01 trials, selected high-grade dysplasia patients, and re-analyzed the data according to PHO BAR 01 efficacy endpoints. All the TCSC 93-07 and 96-01 enrollees, irrespective of diagnosis, served as safety population.

C. Postmarketing Experience

The sponsor recognizes the importance of long-term follow-up data in the treatment of high-grade dysplasia in Barrett's esophagus. Axcan has committed to this follow-up with the new protocol, PHO BAR 02, submitted to IND 61,011 on November 26, 2001. The purpose of this study is to assess the 5-year efficacy of PDT with PHOTOFRIN plus omeprazole compared to omeprazole alone in the complete ablation of high-grade dysplasia in patients with BE, in conjunction with a strict endoscopic surveillance and biopsy protocol. PHO BAR 02 is a continuation of PHO BAR 01, the pivotal trial in this submission. Patients will remain in their assigned treatment groups. The secondary efficacy analyses are the same as in PHO BAR 01. Patients are eligible for additional courses of PDT, up to a maximum of three (cumulative with those administered during the PHO BAR 01 study). Patients will be followed for a maximum of

60 months after their individual randomization date. PHO BAR 02 was initiated in December of 2001, and has an estimated duration of 3 years.

D Literature Review

The sponsor summarized the most important literature and provided copies of publications, including those derived from the supporting studies (vols. 9 – 12). The Reviewer retrieved the following articles and used them in describing various portions of this review. Some of the articles had not been published when the sponsor submitted this NDA.

Falk GW	Barrett's Esophagus. Gastroenterology 2002; 122:1569-1591
Shaheen N & Ransohoff DF	Gastroesophageal Reflux, Barrett Esophagus, and Esophageal Cancer. Scientific Review. Clinical Applications. JAMA 2002; 287:1972-81, 1982-6
Tilanus HW & Attwood SEA	Barrett's Esophagus. Kluwer Academic Publishers. 2001, pp. 159 – 280
Provenzale D, Schmitt C & Wong JB	Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. Am J Gastroenterol 1999;94:2043-53
Reid BJ, Blount PL, Feng Z & Levine DS	Optimizing endoscopic biopsy detection of early cancers in Barrett's high-grade dysplasia. Am J Gastroenterol 2000; 95:3089-96
Van der Burgh A, Dees J, Hop WC & van Blankenstein M	Oesophageal cancer is an uncommon cause of death in patients with Barrett's oesophagus. Gut 1996; 39:5-8
MacDonald CE, Wicks AC & Playford RJ	Final results from 10 year cohort of patients undergoing surveillance for Barrett's oesophagus: observational study. Br Med J 2000; 321:1252-5
Buttar NS et al.	Extent of high-grade dysplasia in Barrett's esophagus correlates with risk of adenocarcinoma. Gastroenterology 2001; 120:1630-9
Reid BJ et al.	Predictors of progression to cancer in Barrett's esophagus: baseline histology and flow cytometry identify low- and high-risk patient subsets. Am J Gastroenterol 2000; 95:1669-76
Schnell TG et al.	Long-term non-surgical management of Barrett's esophagus with high-grade dysplasia. Gastroenterology 2001; 120:1607-19
American College of Gastroenterology	Guidelines for the Diagnosis and Surveillance of Barrett Esophagus. Am J Gastroenterol 1998; 93:1028-32

V. Clinical Review Methods

A. How the Review was Conducted

The original review followed this sequence:

- A survey of current literature on Barrett's esophagus, adenocarcinoma of the esophagus, photodynamic therapy, surgery of the esophagus
- Volume 1, 2 – summary of information PHOTOFRIN, PHOTOFRIN label, and proposed label
- Volume 6 – human pharmacokinetics and bioavailability
- Volume 8 - a summary of the Clinical section
- Volumes 13, 42, 47 describing the 3 trials
- Volumes describing chemistry, pharmacokinetics and pharmacodynamics of PHOTOFRIN
- Tables and listings of the trials, vols. 13 – 51, and 57 - 95
- Statistical section, vol. 52
- Financial disclosure forms, vol. 100.

Subsequent reviews included:

- Volumes 1 to 27 of the September 26, 2002 submission containing the minimum 24-month efficacy data
- N-000 SU submission of October 23, 2002 containing safety update
- N-000 AZ submission of February 3, 2003 containing data requested at the time of completion of the review of the original submission
- Division of Scientific Investigations report.

B. Overview of Materials Consulted in Review

Summarized in **I B. State of Armamentarium for Indication**, and in Materials Reviewed (below).

Materials reviewed:

NDA 21-525/20-451	Vol.1-100
IND 61,011	Medical Officer's review (January 4, 2001)
IND 61,011	Meeting Minutes, Industry Meeting – Type B, Pre-NDA (June 1, 2001)
IND 61,011	Advice letter (January 24, 2001)
IND 61,011	Memorandum of Teleconference (dated March 21, 2001)
NDA 21-525	Statistical Review and Evaluation
NDA 21-525	Pharmacology and Biopharmaceutics Review
NDA 21-525	Clinical Inspection Summary by Division of Scientific Investigations, dated November 22, 2002

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The sponsor was requested to clarify the following:

- Clarify which patients were enrolled in which centers. The Sponsor provided this information in the February 3, 2003 submission.
- Provide the response rate for the primary efficacy endpoint if Dr. Overholt's patients were excluded. [Dr. Overholt's center enrolled 37/208 (17.8%) patients in the pivotal trial and 86 high-grade dysplasia patients in the supporting trials, a total of 123/294 (41.8%) patients.] This information was provided in the February 3, 2003 submission.
- Clarify if updated follow-up data will be provided (and if so, when) to allow calculation of a more complete value for duration of response. [The original submission contained the 6-month data (preliminary) for primary efficacy endpoint, rather than 24-month data that were to be the final data for the trial]. This information was provided in the September 26, 2002 and February 3, 2003 submissions.

DSI reviewed Dr. Overholt's data, because a high proportion of patients were enrolled at his center (51 of 208 subjects [24.5%] in the PHO BAR 01 trial and 86 HGD patients in the TCSC 93-07 and the TCSC 96-01 trials). DSI concluded that the data submitted in support of NDA 21-525 appeared to be acceptable.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor presented sufficient documentation of conduct of trials in accordance with accepted ethical standards, including

- An Independent Ethics Committee or Institutional Review Board review of protocol and the informed consent form
- The study was to be performed in accordance with the rules of Good Clinical Practice. The conditions were to be in compliance with the Declaration of Helsinki, the recommendations of the WHO, the recommendations of the Health Protection Branch, Ottawa, Canada, and the recommendations of the FDA as published in General Considerations for the Clinical Evaluation of Drugs (1977), and the recommendations as published in the Federal Register and in the Code of Federal Regulations (21 CFR 312.60-69) and applicable state laws.
- Each patient reviewed and signed a written approved informed consent form prior to any study procedures. The consent form complied with U.S. 21 CFR 50, Canadian or ICH guidelines (Section 0) and local Institutional Review Board or Ethics Committee requirements. A sample consent form is provided in the submission.

E. Evaluation of Financial Disclosure

Vol. 100 of the original submission contains Financial Disclosure Forms from Clinical Investigators. The following three investigators admitted a proprietary or financial interest in the test product:

- Masoud Panjehpour, Ph.D. indicated that he is a co-inventor of esophageal PDT balloon owned by Thompson Cancer Survival Center.

- Bergein F. Overholt, M.D. indicated that he is a co-inventor and co-patent holder for esophageal centering balloon.
- Thomas J. Dougherty, Ph.D. indicated that he is a “co-inventor of PHOTOFRIN patent”.

All the other investigators denied any financial interests or arrangements. The Financial Disclosure Form is adequate.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

1. Primary endpoint: Percentage of patients with complete response (complete ablation of HGD). The results of the pivotal PHO BAR 01 study, based on a minimum of 24-month follow-up, indicated that photodynamic therapy using PHOTOFRIN and omeprazole (PHOTOFRIN PDT + OM) was significantly more effective than control treatment (OM Only) in causing complete ablation of high-grade dysplasia in Barrett's esophagus and replacement with normal squamous epithelium with or without some areas of Barrett's metaplasia, areas of indefinite dysplasia or low-grade dysplasia (76.8% vs. 38.6%, $p < 0.0001$, in the ITT population, and 81.5% vs. 39.1%, $p < 0.0001$, in the evaluable [treated] population). The results in supporting trials were consistent with the above results in the pivotal trial: complete response rates after 12-month follow-up periods were 93.2% in the TCSC 93-07 trial and 95.2% in the TCSC 96-01 trial (results for evaluable populations).
2. Secondary endpoint: Quality of complete response. PHOTOFRIN PDT resulted in higher quality response than OM Only treatment. Replacement of high-grade dysplasia by normal epithelium, the best quality of response (CR1), was common in patients (ITT population) treated with PHOTOFRIN PDT + OM (52.2%) and rare (7.1%) in patients treated with OM Only ($p < 0.0001$). In most patients in the OM Only group, high-grade dysplasia was replaced by normal squamous cell epithelium with areas of metaplasia, indefinite dysplasia, and low-grade dysplasia (CR3). CR1 response rates after 12-month follow-up periods were 56.8% in the TCSC 93-07 trial and 59.5% in the TCSC 96-01 trial.
3. Secondary endpoint: Duration of complete response. Complete responses lasted longer in patients treated with PHOTOFRIN PDT than with omeprazole only. Duration of complete response was a median of 987 days in the PHOTOFRIN PDT + OM group, and 98 days in the OM Only group. The respective median durations of CR1 response were 316 days and 84 days.
4. Secondary endpoint: Rate of progression to cancer. By the end of the minimum 24-month follow-up period, a smaller percentage of patients progressed to cancer in the PHOTOFRIN PDT group (13%) than in the OM Only treatment group (28%). The difference between the two groups was significant ($p = 0.006$).
5. Secondary endpoint: Time to progression to cancer. By the end of the minimum 24-month follow-up period, patients in the PHOTOFRIN + OM group had an 82.8% chance of being cancer-free as compared to 52.6% chance for patients in the OM Only group. The

comparison between the survival curves of the two treatment arms using the log rank test showed a statistically significant difference between the curves of the two groups in the ITT population ($p=0.0014$) and in the evaluable population ($p=0.0005$).

6. Secondary endpoint: Time to treatment failure. A smaller proportion of patients experienced treatment failure in the PHOTOFRIN PDT group than in omeprazole only treatment group. Treatment failure occurred when patients either progressed to cancer or were treated for HGD with other therapy. By the end of the minimum 24-month follow-up period, 28.3% of patients in the PHOTOFRIN PDT + OM group and 62.8% of patients in the OM Only group failed treatment. At the 24-month (730 day) time point, the probability of treatment success was 75.0% of patients in the PHOTOFRIN + OM group and 46.8% of patients in the OM Only group. By the end of 3.5 years (1280 days) of follow-up, the probability of treatment success was 51.8% in the PHOTOFRIN PDT + OM group and 19.4% in the OM Only group.
7. Secondary endpoint: Survival time. Median survival time could not be estimated for either group.
8. Other efficacy analyses: Complete Response was influenced by treatment with PHOTOFRIN PDT (vs. OM Only), by single focus of HGD (vs. multiple foci), and by prior omeprazole intake of at least 3 months (vs. no such intake).

B. General Approach to Review of the Efficacy of the Drug

PHO BAR 01, TCSC 93-07 (high-grade dysplasia patients only), and TCSC 96-01 (high-grade dysplasia patients only) were all reviewed in detail. The original submission (review filed in DFS on January 9, 2003) contained the preliminary (a minimum of 6 months) data of the PHO BAR 01 study and the final data of the TCSC studies. The September 26, 2002 submission contained the minimum of 24 months' data of the PHO BAR 01 study. The February 3, 2003 submission contained revisions and clarifications of the September 26, 2002 data, as well as responses to issues raised in the Agency's "Approvable" letter. Summaries, supporting tables, narratives and case reports were consulted as needed. Especially important in the review were the patient outcome listings in the February 3, 2003 submission.

C. Detailed Review of Trials by Indication

1. PIVOTAL STUDY:

a. Study Title: PHO BAR 01, A Multicenter, Partially Blinded, Randomized Phase III Study of the Efficacy and Safety of Photodynamic Therapy (PDT) Using PHOTOFRIN (porfimer sodium) for Injection for the Ablation of High-Grade Dysplasia in Barrett's Esophagus.

b. Introduction and Background:

The protocol for the pivotal study (PHO BAR 01) was submitted for review to the Division of the Oncology Drug Products (IND 25,064) by QLT (the sponsor at that time) on November 13, 1997, and the study was started on January 15, 1998. It was a multicenter, controlled, randomized, partially blinded trial comparing PDT with PHOTOFRIN and omeprazole to a surveillance arm consisting of omeprazole only. Two hundred eight (208) patients with high-grade dysplasia in BE were randomized in a 2:1 (PDT: surveillance) proportion. The omeprazole control group was included to allow assessment of the natural history of untreated high-grade dysplasia in BE. Since there was no esophagectomy arm in the trial, the Division of Gastrointestinal and Coagulation Drug Products in a pre-NDA meeting with the Sponsor (Axcan Scandipharm Inc.) concluded that the data from this trial and the supporting trials could only support the indication of PDT with PHOTOFRIN for those patients with high-grade dysplasia in BE who are not candidates for esophagectomy.

Timelines:

Date of Study Initiation: January 15, 1998

Date of Study Completion: November 7, 2001

Date of Submission of NDA: May 31, 2002

Date of the 24-month Follow-up Efficacy Data submission: September 26, 2002

Date of the 24-month Follow-up Safety Data submission: October 23, 2002

Date of the Agency's Approvable Letter: November 29, 2002

Date of Response to Approvable Letter: January 28, 2003

Previous review: This reviewer reviewed the original NDA submission, which contained the minimum of 6 months of follow-up data (the review was filed in DFS on January 9, 2003). The present review will not reiterate those findings, and will focus only on the minimum of 24 months' of follow-up findings.

c. Study Objectives:

- 1) **Primary Objective:** To assess the efficacy of PDT with PHOTOFRIN for Injection plus omeprazole (PHOTOFRIN PDT + OM) compared to omeprazole alone (OM Only) in the complete ablation of high-grade dysplasia in patients with BE, in conjunction with a strict endoscopic surveillance and biopsy protocol.
- 2) **Secondary Objectives:** To assess the safety and efficacy of PDT with PHOTOFRIN plus omeprazole and systematic endoscopic surveillance compared to omeprazole only therapy plus systematic endoscopic surveillance in terms of :
 - a) quality of complete response
 - b) duration of complete response
 - c) delaying progression to cancer (time to progression to cancer)
 - d) delaying the need for esophagectomy or other intervening therapy for HGD [included together with c) in "time to treatment failure"], and
 - e) survival time.

d. Study Design and Study Plan:

This was a multicenter, partially blinded, randomized, Phase III study in patients with high-grade dysplasia in BE. Eligible patients were randomized to receive PHOTOFRIN PDT plus OM therapy or OM Only therapy.

1) Blinding: Patients and study physicians were aware of the treatment each patient received; however, the pathologists who read the biopsies from each esophageal endoscopy were blinded to the patients' treatment. All histological assessments were carried out at a central reference laboratory.

2) Randomization: Patients were centrally randomized in a 2:1 design to receive PHOTOFRIN PDT plus OM therapy or OM therapy alone. The study planned the enrollment of at least 200 patients with high-grade dysplasia in BE at approximately 40 clinical trial sites in North America and Europe.

3) Treatment: Photodynamic therapy (PDT) with PHOTOFRIN is a 2-stage process. The first stage is the intravenous injection of PHOTOFRIN at a dose of 2.0 mg/kg of body weight over 3 to 5 minutes 40 to 50 hours prior to the light treatment. The second stage of treatment is the illumination of the area of treatment with a laser light.

The maximum length of BE treated during one course of PDT (I.V. PHOTOFRIN followed by 1 or 2 laser light applications) was 7 cm. A second light application could be given 2 days after the first application, and was only given to one under-treated ("skip") area that occurred during the first light application.

If Barrett's mucosa was greater than 7 cm in length, a second course of PDT was needed to treat the segment not treated in the first course. The entire length of Barrett's mucosa was to be treated; therefore up to three courses could be given. Courses of PDT had to be separated by at least 3 months. If a previous course of treatment resulted in residual areas of dysplasia, Barrett's metaplasia, or any remaining "skip areas", an additional course of PDT was to be given.

Patients in both treatment groups received omeprazole (20 mg BID) to reduce acid reflux.

4) Follow-up: All patients were to be followed every 3 months until four consecutive, quarterly follow-up endoscopic biopsy results were negative for high-grade dysplasia, and then semi-annually until the last enrolled patient had completed at least 24 months of follow-up evaluation after randomization. Patients were to be assessed for efficacy (by histological assessment of biopsies), and safety (adverse events, laboratory results and physical examinations).

5) Treatment response: Defined as the complete ablation of high-grade dysplasia at any one of endoscopic assessment time points. The quality and duration of the complete response were also to be assessed. Secondary treatment responses included: time to progression to cancer, time to treatment failure, and survival time.

The majority of patients with high-grade dysplasia do not progress to cancer over a period of observation of several years. Therefore, the efficacy of photodynamic therapy of high-grade dysplasia in cancer prevention was assessed by comparing the persistence and re-occurrence of high-grade dysplasia in PDT-treated patients and in OM Only-treated patients, who were the control patients exhibiting the natural history of high-grade dysplasia. Final analysis was to be performed after 24 months from the date of randomization of the last patient.

Additional analyses were to be performed to evaluate the effect of various baseline and demographic factors on the primary efficacy variable, i.e. complete response. The factors included the following:

- High-grade dysplasia duration (6 months or less vs. more than 6 months)
- BE length as a continuous variable
- High-grade dysplasia foci, single vs. multiple
- Nodular vs. non-nodular disease
- Prior omeprazole for at least 3 months (yes, no)
- Size of center enrollment (>10 patients vs. 1-9 patients), pooled data
- Gender (male vs. female)
- Age (<65 vs. >65 years old)
- Smoking history (smoker vs. non-smoker)
- Physician's experience with PHOTOFRIN PDT (first 3 patients in the study arm from each center vs. all other patients)

6) Safety monitoring. An evaluation committee (Data Safety Monitoring Committee) was to review the safety data every six months. An interim analysis was not planned in the study.

7) Study Population:

a) Inclusion Criteria:

1. High-grade dysplasia in BE, as assessed by the central reference laboratory
2. 18 years of age or older
3. Not pregnant
4. If female of childbearing potential, practicing reliable birth control
5. Signed Informed Consent

b) Exclusion Criteria:

1. Invasive cancer of the esophagus, or patients in whom invasive cancer, lymph node involvement or metastases could not be ruled out by endoscopic ultrasonography or by CT scan
2. History of cancer within 5 years before screening, other than non-melanoma skin cancer
3. Prior PDT to esophagus
4. Esophageal strictures unresponsive to dilation
5. Known contra-indications to analgesia or endoscopy
6. Significant acute or chronic illness beside BE (in the judgement of the investigator)
7. Contra-indication to omeprazole

8. Porphyria or known hypersensitivity to porphyrins
9. WBC <2.5/cu.mm; platelets <50,000/cu.mm; Hgb <9.0 g/dL; PT/INR >1.5
10. Serum creatinine >1.5 times the upper limit of normal; total bilirubin >1.5 times the upper limit of normal; AST, ALT, alkaline phosphatase >2.5 times the upper limit of normal
11. Unable or unwilling to complete the follow-up evaluations required for the study
12. Unstable heart disease (NYHA Class III and IV)
13. Esophageal ulcers >1 cm in diameter
14. Esophageal or gastric varices

c) Removal of Patients from Therapy or Assessment:

Patients were to be removed from the study because of

- disease progression,
- unacceptable adverse events,
- refusal to continue, or
- at the investigator's discretion if it is in the patient's best interest.

d) Screening and Selection:

The plan was to include 200 patients in the study. A total of 485 patients were screened for inclusion at 30 centers in the United States, Canada and Europe, and a total of 208 patients were enrolled. The reasons for patient exclusion are shown in the table below.

Reviewer's Table. Reasons for Patient Exclusion from Enrollment

Total screened	485
Total randomized to treatment	208 (42.9%)
Total not randomized	277 (57.1%)
• no high-grade dysplasia	237 (85.60% of 277) (48.9% of 485)
• other screening criteria not met	13 (4.7% of 277)
• declined participation	25 (9.0% of 277)
• other	2 (0.7% of 277)

The predominant reason for patient exclusion was the failure to confirm the diagnosis of high-grade dysplasia in 48.9% of screened patients. This is an important finding suggesting the possibility that patients without HGD may be treated unnecessarily with PHOTOFRIN PDT.

One center (Thompson Cancer Survival Center, Knoxville, TN) enrolled 51 patients into the study (24.5%), four centers (Columbia-Presbyterian Hospital, NYC; Mayo Clinic, Rochester, MN; Johns Hopkins Hospital, Baltimore, MD; and Parkland Memorial Hospital, Dallas, TX) enrolled 13-14 patients each. Other centers enrolled between 1 and 9 patients. The majority of the patients were enrolled in American institutions (196 or 94.2%). Five patients were enrolled in Canada, six in UK and one in France.

The preponderance of the Thompson Cancer Survival Center may be due to the presence of acknowledged expertise in this area. Dr. Overholt and colleagues at the Thompson Center

developed many of the techniques and instruments used in PDT, and published the two largest series of BE patients treated with PDT (TCSC 93-07 and TCSC 96-01). These two studies are supporting studies in this application. Patient screening and selection appeared not to differ at the Thompson Center from the overall statistics [113 patients screened, 51 randomized (45.1%)].

e) Patient characteristics:

1) Demographic characteristics. The demographic and other baseline characteristics are shown in the table below for the Evaluable population (from Sponsor's Panel 11.4, vol. 2, p. 97). The characteristics in the ITT population were similar.

Reviewer's Table. Patient Demographic and Baseline Characteristics (Evaluable Population)

Characteristics	PHOTOFRIN PDT + OM N = 130	OM Only N = 69
Age (years), mean (range)	65.98 (38.4 – 88.5)	67 (36.1 – 87.6)
Gender		
-Male	110 (85%)	58 (84%)
-Female	20 (15%)	11 (16%)
Race		
-Caucasian	129 (>99%)	67 (97%)
-Black	0	1 (1%)
-Asian	1 (<1%)	1 (1%)
-Hispanic	0	0
-Other	0	0
Height (cm), mean (range)	172.77 (147.3 – 193.0)	173.06 (147.4 – 190.5)
Smoking history		
-Current smoker	8 (6%)	8 (12%)
-Former smoker	80 (62%)	46 (67%)
-Never smoked	(32%)	15 (22%)

The differences between the two treatment groups were not statistically significant.

The total study population was predominantly male (85%), white (Caucasian) (99%), and former or current smokers (71%). The patient population enrolled in this study is representative of the general BE population affected by high-grade dysplasia. Male to female ratio is 7:1 in this population (Sharma & Sampliner 2001).

2) Medical history, physical examination, and laboratory values. Patients in the two treatment groups reported mostly gastrointestinal (79%), cardiovascular (68%) and musculoskeletal (63%) medical history. Three patients had prior radiotherapy to thorax. One patient had radiotherapy to head and neck 4 years before randomization. One patient had radiotherapy for breast tumor 3 years before randomization. One patient had radiotherapy to the distal esophagus and upper abdomen 2.5 years before randomization. Baseline CT scan of the thorax showed abnormalities in 86% - 87% of patients in both groups; 7% of these abnormalities in both groups were considered clinically significant. Chest X-ray abnormalities were detected in 60% of patients in the PHOTOFRIN PDT + OM group and in 56% of patients in the OM Only group. These

included reticular infiltrates, increased interstitial markings, and calcified granulomas in the PHOTOFRIN PDT group, and heart enlargement, pleural thickening, and spondylosis of the thoracic spine in the OM Only group. There were no statistical differences between the two treatment groups with regards to medical history, physical findings, and routine laboratory values.

3) Characteristics of BE at baseline. The BE characteristics are shown below in Reviewer's Table (data from Sponsor's Panel 11.5). The two treatment groups were well matched in

- duration of BE,
- duration of high-grade dysplasia,
- endoscopic length of BE,
- histological length of BE,
- endoscopic characteristics of high-grade dysplasia including the presence of hiatal hernias, esophageal ulcers, nodules and strictures, and
- prior treatment (medical, surgical, esophageal dilations and blood transfusion; there were no cases of endoscopic ablation).

Reviewer's Table. Barrett's Esophagus at Baseline (Evaluable population)

Characteristic	PHOTOFRIN PDT + OM N = 130	OM Only N = 69
Duration of BE in months, Mean (range)	36.19 (1.3 – 216.7)	35.30 (0.9 – 141.7)
Duration of high-grade dysplasia in months, Mean (range)	6.08 (0.1 – 40.7)	6.54 (0.4 – 72.4)
Endoscopic length of BE		
- < 6 cm (%)	58 (44.6%)	35 (50.7%)
- > 6 cm (%)	72 (55.4%)	34 (49.3%)
Histological length of BE		
- < 6 cm (%)	67 (51.5%)	42 (60.9%)
- > 6 cm (%)	63 (48.5%)	27 (39.1%)
Extent of high-grade dysplasia		
- Single biopsy	33 (25.4%)	17 (24.6%)
- Single level	47 (36.2%)	27 (39.1%)
- Multiple levels	83 (63.8%)	42 (60.9%)
Endoscopic condition		
- Hiatal hernia	120 (92.3%)	57 (82.6%)
- Nodules	40 (30.8%)	19 (27.5%)
- Ulcers	7 (5.4%)	3 (4.3%)
- Strictures	7 (5.4%)	3 (4.3%)
Prior treatment		
- Surgery	5 (4%)	8 (12%)
- Medical therapy	127 (98%)	65 (94%)
- Other	6 (5%)	2 (3%)

Source: Panel 11.5, vol. 13, p. 94

Other clarifications of the above table:

- HGD: HGD extended over multiple levels in both groups. The extent of HGD did not differ between the two groups. Hiatal hernias were somewhat more frequent in the PHOTOFRIN PDT + OM group than in the OM Only group. Nodules, ulcers, and strictures occurred at the same frequency in both groups.
- Prior therapy: Most patients in both groups had received medical therapy. Few patients received prior surgery. "Other therapy" consisted of blood transfusions and esophageal dilations.

f) Rater Agreement on Histological Diagnosis for Patients in Study PHO BAR 01:

Since the primary efficacy endpoint depended on histopathologic diagnosis, a study was carried out by the Sponsor to assess the inter-rater and intra-rater percent agreement on histologic diagnoses assigned to sets of endoscopic biopsy samples in the screening and trial phases of the PHO BAR 01 clinical trial (vol. 41).

Secondary objectives included: 1) assessment of the intra-rater and inter-rater percent agreement on a per biopsy basis, 2) assessment of pre-PDT-treatment rater agreement vs. post-PDT-treatment rater agreement, and 3) assessment as to whether the following factors may affect rater agreement: presence of inflammation, presence of ulcers/erosions, and endoscopy/treatment site.

Study design. The rater reliability study was conducted in parallel with PHO BAR 01. Three pathologists (the central reference pathology laboratory) at the University of Washington Medical Center participated in the study. Two rounds of readings were performed for the slides, i.e. each pathologist read each endoscopic slide set twice.

Study procedures. Readings for the rater agreement study were performed by the pathologists in a blinded fashion. Pathologists had no knowledge of the patient's identity, randomization arm, study phase or clinical trial site. Rater agreement slides were inserted into the stream of PHO BAR 01 study slides that were read by the pathologist-on-call. The order of reading by the second and third pathologist was randomized.

Sample size. There were 26 sets of slides, from an equal number of pre- and post-treatment biopsies, for a total of 437 biopsies with 6 repetitions of the reading on each biopsy. There were a total of 2622 individual biopsy readings.

Outcomes to be analyzed: presence of 1) high-grade dysplasia, 2) cancer, 3) high-grade dysplasia or cancer, 4) dysplasia (low-grade or high-grade), and 5) metaplasia (Barrett's esophagus). Two raters were to agree on the outcome of high-grade dysplasia (both agreed it was absent or present) and similarly on the other outcomes.

Results. Reviewer's Tables below (from Table 2, vol. 41, p. 15 and Table 5, vol.41, p. 20) show inter-rater agreement and intra-rater agreement on the five diagnoses tested.

Reviewer's Table. Percent Inter-Rater Agreement on Endoscopy Diagnoses

Diagnosis	Mean % agreement (range of percentages)
High-grade dysplasia	88 % (78% - 94%)
Cancer	96 % (85% - 99%)
High-grade dysplasia or cancer	92 % (83% - 97%)
Dysplasia (low-grade and high-grade)	86% (74% - 92%)
Barrett's esophagus	99% (98% - 100%)

Reviewer's Table. Percent Intra-Rater Agreement on Endoscopy Diagnoses

Diagnosis	Intra-rater agreement, % (range)
High-grade dysplasia	94% (87% - 97%)
Cancer	99 % (92% - 99.8%)
High-grade dysplasia or cancer	96% (77% - 99.5%)
Dysplasia (low-grade and high-grade)	92% (83% - 97%)
Barrett's esophagus	99% (92% - 99.8%)

Source: Table 5, vol. 41, p.15.

Factors that had the greatest impact on inter-rater agreement on the endoscopy diagnosis of high-grade dysplasia were the presence of obscuring inflammation (81% when inflammation was present vs. 94% when inflammation was not present), when high-grade dysplasia was not excluded (77% vs. 93%), and the number of biopsies (with >16 it was 82% vs. 95% with 16 or fewer).

Factors that had the greatest impact on agreement were:

- On the diagnosis of cancer: "high-grade dysplasia not excluded", erosions, and inflammation.
- On the diagnosis of high-grade dysplasia and cancer, there was no disagreement that it was either high-grade dysplasia or cancer.
- On the diagnosis of dysplasia: the presence of inflammation, "high-grade dysplasia not excluded", number of biopsies over 16, and the presence of erosions.

Intra-rater agreement on the endoscopy diagnosis was very high (average 96%; range, 92% - 99%). The main factors influencing intra-rater agreement were post-treatment samples and the presence of erosion.

Overall Conclusion. The primary conclusion of this study is that rater agreement on the endoscopic diagnosis is generally high. These high rates of agreement (88% for high-grade dysplasia, 96% for cancer, 92% for high-grade dysplasia or cancer, 85% for dysplasia, and 99% for Barrett's esophagus) suggest that the effect of rater disagreement on the reproducibility of PHO BAR 01 will be minimal.

However, an incidental finding of this study was that of the 13 screening (pre-enrollment) endoscopies in the study, only 7 were given the diagnosis of high-grade dysplasia. All the patients entering the screening phase of the trial had a diagnosis of high-grade dysplasia by another pathologist determined from biopsy samples taken from a different endoscopy in the

recent past. The failure to verify the diagnosis of high-grade dysplasia in 6 of the 13 cases indicates that variability in the diagnoses across time and across raters from different institutions may be higher than the inter-rater variability seen in this study, where rater variability estimates were restricted to 3 pathologists in a single institution and the raters read slides from the same endoscopy. The above noted failure to confirm the diagnosis of high-grade dysplasia in 49.2% of patients during screening for the study reinforces this concern.

g) Treatment assignment and disposition:

Of the 208 enrolled patients (ITT population), 138 were assigned to the PHOTOFRIN PDT + OM group and 70, to OM Only group. Six (6) of the PHOTOFRIN PDT + OM patients did not receive at least one course of study therapy for the following reasons: one patient had low-grade dysplasia and was randomized by error, one patient was found to have an adenocarcinoma and was randomized by error, three patients withdrew consent, and one patient received the PHOTOFRIN injection, but did not undergo PDT because of procedure-related anxiety. In addition, two patients received the first course of treatment, but esophageal invasive cancer could not be excluded by esophageal ultrasound, and the patients' participation in the study was administratively terminated. Thus, the evaluable population consisted of 130 patients. The safety population consisted of 133 patients (all patients who had at least one PHOTOFRIN injection).

In the OM Only group, one patient chose to undergo an esophagectomy instead of taking omeprazole. Thus, the evaluable and safety populations consisted of 69 patients.

Reviewer's Table. Treatment assignment and disposition of patients

Patient population	PHOTOFRIN + OM	OM only
Number of patients (%)		
Intent-to-treat (number of patients randomized)	N = 138 (100%)	N = 70 (100%)
Evaluable (number of patients receiving at least one course of study therapy)	N = 130 (94%)	N = 69 (99%)
Safety	N = 133 (96%)	N = 69 (99%)
Completed study	N = 81 (60.9%)	N = 11 (15.7%)

h) Protocol Deviations:

Protocol deviations that led to exclusion from the analyses:

- **ITT population.** No patients were excluded from the data set for the ITT analysis.
- **Safety population.** Six patients, five from the PHOTOFRIN PDT treatment group and one from the OM Only treatment group were excluded from the Safety analysis data set, because PHOTOFRIN PDT or omeprazole had not been administered.
- **Evaluable population.** Three additional patients from the PHOTOFRIN PDT group were excluded from the Evaluable population data set, because cancer could not be excluded by esophageal ultrasound in two patients, and light application was not administered following PHOTOFRIN injection in one patient.

Protocol deviations that did not lead to exclusion from the analyses:

- Inclusion/exclusion criteria. At randomization, no patients violated inclusion criteria, nine patients violated exclusion criteria (history of cancer in 8 patients, history of stable anemia in one patient, and increased BUN/creatinine values in one patient).
- Randomization scheduling. Randomization was to be scheduled within 4 weeks of the baseline biopsy. Overall, 27 patients, 18 in the PHOTOFRIN PDT group and 9 in the OM Only group, were randomized outside the window period allowed by the protocol. The deviation varied by less than 8 days in 19/27 patients; the longest delay in the others was 26 days.
- Study Day 1 scheduling. According to the protocol, Study Day 1 (the date of the first PHOTOFRIN injection in the PHOTOFRIN PDT + OM arm, or the first day of omeprazole administration in the OM Only arm), was to be scheduled within 7 days of the randomization date. Deviation occurred in 35/202 (17%) patients: Day 1 was scheduled between 8 and 27 days after randomization in 34 patients, and one patient received the first PHOTOFRIN injection 3 days before being randomized in the study.
- Dose of PHOTOFRIN. Six out of 133 (4.5%) patients received less than 2.0 ± 0.02 mg/kg dose (range, 1.4970 – 1.9108 mg/kg). No patients received a dose greater than 2.0195 mg/kg.
- Dose of PDT. According to protocol, laser light was to be applied at a dose of 130 J/cm. Overall, 22% of patients (29/133) received the wrong laser light dose at any one treatment courses. Most (22/29) received more than 130 J/cm, ranging from 131 to 174 J/cm, but only three patients received more than 140 J/cm. Of the 7 patients who received less than 130 J/cm, four received less than 120 J/cm.
- Time between treatment courses and/or follow-up visits. Two patients received a second treatment course before a 90-day period had elapsed. Follow-up visits were to be scheduled at 3 months \pm 10 days apart (80 – 100 days). This standard was not met by any of the patients, because of difficulty in visit scheduling. Overall, 65.2% of patients were scheduled at 3 months \pm 20 days apart. During follow-up visits, any additional courses of PDT were to be repeated within 4 weeks of the biopsy results. Deviation occurred in 28 patients; in 9/28 patients (32.1%) repeat PDT courses deviated by more than 2 weeks.

i) PDT Treatment:

PHOTOFRIN was administered intravenously at a dose of 2 mg/kg. Laser light at 630 nm was administered using light delivery systems described in the Safety Section 40 to 50 hours after drug administration. A Summary Table of the Extent of PDT in the Evaluable Group is shown in the Reviewer's Table below (from Panel 12.3, vol. 2, p. 136).

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Reviewer's Table. Photodynamic Therapy Treatment

Laser light sessions Number of patients (%)	Course 1 N = 130 (100%)	Course 2 N = 89 (100%)	Course 3 N = 42 (100%)
First laser light session			
Pre-treatment of nodules	35 (26.9%)	27 (30.3%)	12 (28.6%)
Balloon light treatment	129 (99.2%)*	89 (100%)	41 (97.6%)*
Second laser light session			
Treatment of skip areas	60 (46.2%)	49 (55.1%)	21 (50%)

*Excludes patients who received PDT without balloon.

j) Concomitant Medication and Adjunctive Therapy:

During the study, 133 (100%) patients in the PHOTOFRIN PDT + OM group and 65 (94%) patients in the OM Only group took at least one concomitant medication. PHOTOFRIN PDT + OM group took many more medications than the OM Only group. Especially impressive is the very high usage of analgesics, anti-emetics, antacids, gastrointestinal agents, glucocorticoids and cytoprotective agents (described in Safety section below).

k) Patients' Duration on Study:

This submission contains data on patients who have completed at least 24 months of follow-up. The Reviewer's Table below shows the patients' duration on study (from Panel 12.1, vol. 2, p. 134).

Reviewer's Table on Patients' Duration on Study

Patient Duration on Study	PHOTOFRIN PDT + OM Evaluable population, N = 130		OM Only Evaluable population, N = 69	
≤ 3 months	2	(1.5%)	3	(9%)
3 – 6 months	3	(2.3%)	10	(14.5%)
6 – 9 months	9	(6.9%)	7	(10.1%)
9 – 12 months	5	(3.8%)	4	(5.8%)
12 – 15 months	7	(5.4%)	3	(4.3%)
15 – 18 months	5	(3.8%)	3	(4.3%)
18 – 21 months	4	(3.1%)	3	(4.3%)
21 – 24 months	17	(13.1%)	10	(14.1%)
24 – 27 months	13	(10.0%)	9	(13.0%)
27 – 30 months	11	(8.5%)	5	(7.2%)
30 – 33 months	19	(14.6%)	1	(1.4%)
33 – 36 months	17	(13.1%)	5	(7.2%)
36 – 39 months	7	(5.4%)	3	(4.3%)
39 – 42 months	8	(6.2%)	3	(4.3%)

42 – 45 months	3	(2.3%)	0
Mean no. of months	25.5		18.9

Seventy-eight of 138 patients (59%) in the PHOTOFRIN + OM group and 26 of 70 patients in the OM Only group provided a minimum of 24-month follow-up data. The most frequent reasons for not completing the 24-month follow-up once enrolled into the study were progression to cancer (13% on the PHOTOFRIN PDT group and 28% in the OM Only group) and other intervening therapy for HGD (13% in the PHOTOFRIN PDT group and 27% in the OM Only group).

l) Measurements of Treatment Compliance:

PHOTOFRIN PDT treatments were administered at the site and recorded in the patient file. Omeprazole was self-administered by the patient, but compliance could not be confirmed, because drug supplies were not provided to all patients by the sites. Some patients had their own drug supply. Therefore, CRF drug accountability may not be an accurate representation of patient compliance.

m) Efficacy Results:

1) Primary efficacy endpoint: Complete Ablation of High-grade Dysplasia

Patients with complete ablation of high-grade dysplasia included:

- 1) patients who had complete replacement of all Barrett's metaplasia and dysplasia with normal squamous cell epithelium (Complete Response 1 or CR1),
- 2) patients who had ablation of all grades of dysplasia, but had some areas of Barrett's metaplasia remaining (Complete Response 2 or CR2), and
- 3) patients who had ablation of all areas of high-grade dysplasia, but had some areas of low-grade dysplasia, or areas indefinite for dysplasia, or areas of metaplasia (Complete Response 3 or CR3).

The primary efficacy analysis was based on the CR rate at any one of the evaluations during the follow-up of a minimum of 24 months.

As shown in the Reviewer's Table below, the proportion of responders (CR1 + CR2 + CR3) was significantly higher in the PHOTOFRIN + OM group than in OM Only group (81.5% vs. 39.1% in the Evaluable population, $p < 0.0001$; 76.8% vs. 38.6% in the ITT population, $p < 0.0001$). More than twice the percentage of patients had a complete ablation of HGD in the PHOTOFRIN PDT + OM group than in the OM Only group, an impressive difference of 42% in the treated population.

Reviewer's Table on Primary Efficacy – Overall Clinical Response

Response	PHOTOFRIN PDT + OM	OM Only
CR1 + CR2 + CR3		
Evaluable population	106/130 (81.5%)	27/69 (39.1%)
ITT population	106/138 [76.8%]	27/70 [38.6%]

Source: Panel 11.6, vol. 2 of the 9.26.2002 submission, p. 103.

Reviewer's Note: Many authors state that HGD does not respond to omeprazole, that histologic changes only indicate subsidence of inflammation due to GERD. The 39% response in this careful study is surprisingly high.

2) Secondary efficacy endpoint: Complete response of CR3 or better at 6, 12, 18, and 24 months of follow-up

The numbers and percentages of patients who showed a CR3 or better response during the four 6-month intervals of follow-up are shown in the table below (from Sponsor's Panel 11.8). The percentages in parentheses are for the Evaluable Population, and in brackets, for the ITT population.

Reviewer's Table. Complete Responses at 6-month Follow-up Intervals

Months of follow-up	PHOTOFRIN PDT + OM		OM Only	
	N=130	[N=138]	N=69	[N=70]
6 months	73 (56.2%)	[52.9%]	18 (26.1%)	[25.7%]
12 months	98 (75.4%)	[71.0%]	21 (30.4%)	[30.0%]
18 months	104 (80.0%)	[75.4%]	25 (36.2%)	[35.7%]
24 months	106 (81.5%)	[76.8%]	27 (39.1%)	[38.6%]

The increasing numbers of complete responses in the PHOTOFRIN PDT + OM group indicates the number of patients who have completed the entire PDT program, which may last from 9 to 12 months, if 3 cycles of therapy are administered. Prolonged omeprazole treatment also appears to increase response rates.

3) Secondary Efficacy Endpoint: Quality of Complete Response

The quality of responses in the PHOTOFRIN PDT + OM group were much better than in the OM Only group, as measured by the percentages of CR1 and CR2 responses. Reviewer's Table below depicts the data from Panel 11.7 (vol. 2, p. 104). The percentages of patients with CR in the Evaluable Population are shown in parentheses, and in the ITT Population, in brackets. The most common result in the PHOTOFRIN PDT group was a CR1 response (in 55.4% of patients). The most common result in the OM Only group was a failure of response, followed in frequency, by a CR3 response. The following Reviewer's Table depicts the relative frequencies of responses in the two populations.

Reviewer's Table on the Quality of Complete Response in Evaluable Populations

Quality of response	PHOTOFRIN PDT + OM		OM Only	
	N = 130	[N=138]	N = 69	[N=70]
CR1	72 (55.4%)	[52.2%]	5 (7.2%)	[7.1%]
CR1 + CR2	81 (62.3%)	[58.7%]	10 (14.5%)	[14.3%]
CR1 + CR2 + CR3	106 (81.5%)	[76.8%]	27 (39.1%)	[38.6%]

Reviewer's Table on the Relative Frequencies of Responses in the Evaluable Populations

Quality of response	PHOTOFRIN PDT + OM	OM Only
CR1	55.4%	7.2%
CR2	6.9%	7.3%
CR3	19.2%	24.6%
No response	18.5%	60.9%

Most of the responses in both arms of the study were consistent from one evaluation to the next, except as response failures occurred.

4) Secondary Efficacy Endpoint: Duration of Response

The duration of response to PHOTOFRIN PDT or OM were analyzed separately at each response level (CR1, CR2 or better, and CR3 or better). Duration of response was censored for patients with no data that indicated an end to response, as follows:

- for patients who had not received any intervening therapy for HGD, censor occurred at the date the patient was last known to be participating in the study,
- for patients who did receive intervening therapy, censor occurred on the day that the intervening therapy (esophagectomy or alternative method of endoscopic ablation) began.

The Kaplan-Meier method was used to present the distribution of duration of response. The median duration of response (the day 50.0% of the patients had experienced the failure event) data are shown below (from Sponsor's Panel 11.9).

Reviewer's Table. Median Duration months of Response after a Minimum follow-up of 24 months

Complete response levels	PHOTOFRIN PDT + OM Median (days)	OM Only Median (days)
CR1	316	84
CR1 + CR2	478	184
CR1 + CR2 + CR3	987	98

The Sponsor claims, in the revision submitted on January 28, 2003, the following probabilities of maintaining complete responses by the end of the 24-month follow-up (730 days):

CR level	PHOTOFRIN PDT + OM Probability of maintaining CR by 24 months	OM Only Probability of maintaining CR by 24 months
CR 1 + CR2 + CR3	52.7%	12.8%
CR1 + CR2	47.5%	42.9%
CR1	45.8%	33.3%

5) Secondary Efficacy Endpoint: Time to Progression to Cancer

Characteristics of patients who progressed to cancer (adenocarcinoma, intra-mucosal carcinoma, or invasive carcinoma) are shown below in the Reviewer's Table, which contains information from Sponsor's Panels 11.10 and 11.11.

- In the PHOTOFRIN PDT + OM group, 18 (13.0%) patients in the ITT population and 18 (13.8%) patients in the Evaluable population had progressed to cancer. Patients #1102 and #1204 were excluded at days 48 and 311, respectively, from the Evaluable population, because there were suspicions of cancer at baseline.
 - Fifteen were males and 3 were females.
 - The average age was 67.9 years; the range was 44 to 79 years.
 - Nine patients had had 1 course of PDT; 7 patients had had 2 courses; and 2 patients had had 3 courses.
 - The Days on which the cancer was diagnosed are shown below in a table.
- In the OM Only group, 20 patients (29%) in the ITT population or the Evaluable population had progressed to cancer.
 - Seventeen were males, and 3 were females.
 - The average age was 66.5; the range was 36 to 87 years.
 - The Days on which the cancer was diagnosed is shown in the table below.

Reviewer's Table of Time to Progression to Cancer

Time to Progression Interval, in days (Day 1 is first day of 1 st course)	PHOTOFRIN PDT + OM Day cancer was diagnosed	OM Only Day cancer was diagnosed
0 – 180	42, 80, 86, 93, 94.	64, 93, 94, 101, 102, 103, 118, 130, 131.
181 – 360	197, 220, 225, 226, 226, 256, 304, 339.	179, 186, 203, 222, 278.
361 – 540	372.	652, 660, 664, 669.
541 – 730	618.	
>731	784, 803, 1039.	803, 859.
Total	18 (13%)	20 (29%)

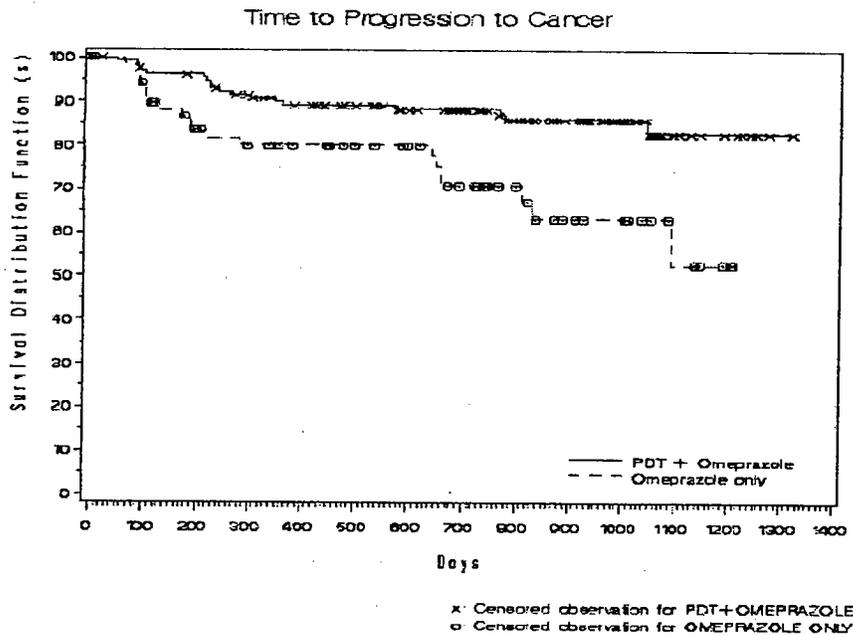
In the PHOTOFRIN PDT group, 5 out of 18 cases (28%) were diagnosed during the first 6 months, and 8 (44%) were diagnosed during the second 6 months from the start of treatment. Thereafter, cancer continued to occur at infrequent intervals (2 cases in the second year, and 3 cases in the third year of follow-up).

In the OM Only group, 9 cases out of 20 (45%) were diagnosed during the first 6 months, 5 (25%) during the second 6 months, and 4 (20%) during the third 6 months. Two cases were diagnosed in the third year of follow-up.

Reviewer's Note:

The Progression to Cancer data are key efficacy data, without which the Primary Efficacy Endpoint is of little importance. More than twice as many patients in the surveillance OM Only arm progressed to cancer as in the PHOTOFRIN PDT + OM arm.

Revised Figure 11.4
Comparison by Treatment Group of the Time to Progression to Cancer Over Time
(ITT population)



Data source: Revised Table 1.25

6) Secondary Efficacy Endpoint: Time to Treatment Failure

Time to Treatment Failure (TTF) was defined as the period in days from the date of randomization until the date of the first documentation of 1) progression of high-grade dysplasia to cancer or 2) the start of any intervening therapy for high-grade dysplasia other than the randomized study treatment.

Reviewer's Table below (from Sponsor's Panels 11.12 and 11.13, revised in January 28, 2003 submission, pp. 115-118) show the two main reasons for treatment failure, either progression to cancer or persistence of HGD.

Reviewer's Note:

- Persistence of HGD has different implications in the two arms. In the PHOTOFRIN PDT + OM arm, it indicated a failure of treatment and called for an alternative form of treatment. In the OM Only arm, it did not indicate a failure of treatment, as this was the surveillance arm. The choice to terminate the enrollment and undergo some form of active treatment meant that at some time during the follow-up patients became dissatisfied staying in the surveillance arm.

Reviewer's Table. Reasons for Treatment Failure

Nature of Treatment Failure	PHOTOFRIN PDT + OM Evaluable Population, N = 130	OM Only Evaluable Population N = 69
Persistence of HGD	18 (13.8%)	21 (30.4%)
Progression to cancer	18 (13.8%)	20 (29.0%)
TOTAL	36 (27.7%)	41 (59.4%)

The Days on which patients chose another form of treatment for HGD and were discharged from the study are shown below in Reviewer's Table (data from Sponsor's Listing S. 3.0 in Appendix 3, January 28, 2003 submission). In the PHOTOFRIN PDT group one-half of the patients chose another intervening therapy in the first six months of the second year, probably because many of the treatment failures occurred in the second six months of the first year. In the OM Only group, patients chose an interventional therapy at a fairly constant time intervals.

Reviewer's Table of Time to Choice of Other Intervening Therapy for HGD

Time to Other Intervening Therapy, in days (Day 1 – first day of 1 st course)	PHOTOFRIN PDT + OM Day of disenrollment or of intervening therapy	OM Only Day of disenrollment or of intervening therapy
0 – 180	0	80, 106, 112
181 – 360	338	185, 190, 209, 336, 353
361 – 540	384, 418, 425, 439, 472, 478, 479, 499, 537	445, 459, 476, 497
541 – 730	600, 678, 692	566, 581, 664, 668
> 730	895, 1021, 1026, 1064, 1243	741, 745, 919, 1052, 1101

Other Intervening Therapies were:

- In PHOTOFRIN PDT group diagnosed with cancer, esophagectomy was the most common procedure. Other procedures were PDT bare fiber, EMR with or without PDT, and radiation therapy with or without chemotherapy.

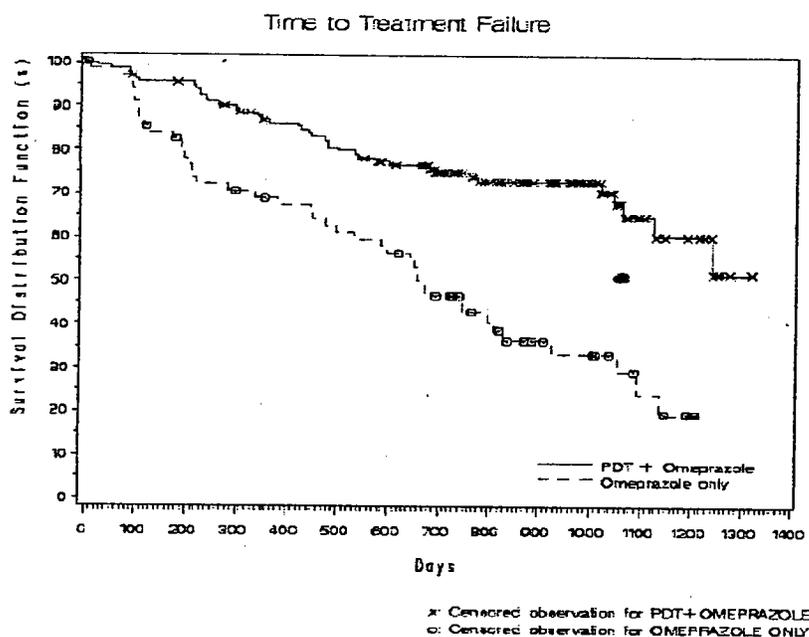
- In PHOTOFRIN PDT group with persistent HGD, esophagectomy was the most common procedure, followed by contact YAG laser, an additional course of PDT, plasma coagulator, Nd:YAG laser, heater probe ablation, mucosal resection, argon beam, and electrocautery.
- In OM Only group diagnosed with cancer, PHOTOFRIN PDT and esophagectomy were the most commonly used therapeutic procedures. The other therapies were as listed above for the PHOTOFRIN PDT group.
- In OM Only group diagnosed with persistent HGD, PHOTOFRIN PDT was used in 75% of patients and esophagectomy in the rest.

The Kaplan-Meier method was used to present the distribution of Time to Treatment Failure (TTF). Median TTF could not be estimated for the PHOTOFRIN PDT + OM group, because fewer than 50% of the patients had documented TTF by the end of follow-up. Median TTF was estimated at 670.0 days (95% CI=497.0, 827.0) for the OM Only group. Comparison between the two treatment arms using the log rank test showed that esophagectomy or other intervening therapy was significantly postponed in the PHOTOFRIN PDT + OM group as compared to the OM Only group in the ITT and the Evaluable populations ($p < 0.0001$).

According to the Kaplan-Meier plot (shown below), by the end of the minimum follow-up of 2 years (730 days), the probability of treatment success was 75.0% in the PHOTOFRIN PDT + OM group compared to 46.8% in the OM Only group. By the end of 3.5 years of follow-up (1280 days), the probability of treatment success was 51.8% in the PHOTOFRIN PDT + OM group compared to 19.4% in the OM Only group.

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Revised Figure 11.5
Comparison by Treatment Group of the Time to Treatment Failure
Over Time (ITT population)



Data source: Revised Table 1.26

Reviewer's Notes:

- Treatment success is defined as 1) no progression to cancer and 2) no other therapy for HGD other than randomized study treatment. This definition is acceptable for the PHOTOFRIN PDT group, but is inappropriate for the OM Only group. The use of other therapy in the OM Only group is not because of treatment failure, but because of study subjects' anxiety to continue in the surveillance arm.
- Treatment success may be more appropriately reflected by the Time to Progression to Cancer Kaplan-Meier plot (above, Revised Figure 11.4, p. 113). By the end of the 2-year follow-up period (730 days), the probability of cancer was 11.75% in the PHOTOFRIN PDT group and 29.15% in the OM Only group.

Reviewer's Note on Patient Disposition by the end of the study:

Non-responders, PHOTOFRIN PDT. Of the 130 patients who had been treated with PHOTOFRIN PDT (Evaluable population), there were 24 patients (18.5%) who did not show a response to treatment (Primary Efficacy endpoint, above). After destruction of HGD by PDT, HGD epithelium re-grew. Of these 24 patients, 12 continued to have HGD during the follow up period, and 12 progressed to cancer. Thus, these patients appear to have a very high risk (50%) of developing cancer.

Responders, PHOTOFRIN PDT. Of the 106 patients in the PHOTOFRIN PDT + OM group who showed a complete response, 81 remained in complete response (CR3 or better) by the end of

follow-up, 10 had a recurrence of HGD and had other form of treatment, 6 progressed to cancer, 2 died from causes unrelated to HGD, 2 were discontinued from the study because of adverse events, and 3 were discontinued for administrative reasons (outcomes in 2 patients not stated in Listings S-1.0, S-2.0, and S-3.0, and Panels 11.12 and 11.13).

Non-responders, OM Only. Of the 42 patients who did not show a response to omeprazole, 15 continued to have HGD, 19 progressed to cancer, 2 probably had HGD, one died, one was discontinued because of adverse event, and 4 were discontinued because of administrative reasons. Thus, about one-half of the control group developed cancer within the 24-month follow-up period.

Responders, OM Only. Of the 27 patients who had a CR3 or better during treatment with omeprazole, 11 continued in CR3 or better status at the end of the study, 7 developed HGD, only one progressed to cancer, and one was discontinued because of administrative reasons (outcomes uncertain in 7 patients from the Sponsor's listings).

Quality of response and outcomes. The quality of response was related to outcome. In the PHOTOFRIN PDT group, all of CR1 responders and all but one of CR2 responders continued in CR3 or better response at the end of the study. CR3 responders were equally likely to continue in CR3 or develop HGD; the only progressions to cancer occurred in CR3 responders. In the OM Only group, only one CR3 patient progressed to cancer. Thus, progression to cancer or regression to HGD occurred almost completely in the CR3 response group, as would be expected in patients with BE and low-grade dysplasia.

Conclusions:

- Responders in either PHOTOFRIN PDT group or in OM Only group were far less likely to progress to cancer than non-responders.
- CR1 or CR2 responders were far less likely to progress to cancer or to HGD than CR3 responders in either the PHOTOFRIN PDT or in the OM Only group.

Reviewer's Table below summarizes some of the above findings:

Reviewer's Table. Progression to Cancer Among Responders and Non-Responders in the Evaluable Populations with a Minimum Follow-up of 24 Months

Patient group*	Total number of patients	Total number who progressed to cancer
PHOTOFRIN PDT	130	18 (13.8%)
• CR1+CR2+CR3	106	6 (5.7%)
• No response	24	12 (50%)
OM Only	69	20 (29.0%)
• CR1+CR2+CR3	27	1 (3.7%)
• No response	42	19 (45.2%)

*Evaluable populations.

7) Secondary Efficacy Endpoint: Survival Time

Survival Time was defined as the period in days from the date of randomization to the date of the patient's death. Median survival time could not be estimated for either treatment group. Two patients died in the PHOTOFRIN PDT + OM group (on days 631 and 643) and 1 patient died in the OM Only group (on day 25). None of the deaths were attributable to adenocarcinoma of the esophagus or to treatment. One resulted from cardiac arrest after CABG surgery, one from cancer of the male breast, and one from a stroke.

8) Other analyses

Additional analyses showed that Complete Response (CR1 + CR2 + CR3) rate was influenced by the following factors (vol. 3, Table 1.30, p. 130):

- treatment with PHOTOFRIN PDT (vs. OM Only, $p < 0.0001$)
- single high-grade dysplasia focus vs. multiple foci ($p < 0.0001$)
- prior omeprazole intake of at least 3 months (yes vs. no, $p = 0.0026$. Odds ratio 3.05 [95% CI: 1.475, 6.309])

Complete Response rate was not influenced by:

- duration of high-grade dysplasia (incident < 6 months vs. prevalent > 6 months)
- length of BE
- nodular conditions (nodular vs. non-nodular)
- gender
- age (see Section IX. B)
- smoking history (smoker vs. non-smoker)
- study center's size (< 10 patients vs. > 10 patients enrolled)

2. SUPPORTING STUDIES:

The results of supporting studies will be described together, since both are very similar in study design, treatments administered, and endpoints evaluated.

a.1. Study Title: TCSC 93-07. A Phase I/II Study of the Safety and Efficacy of Photodynamic Therapy (PDT) Utilizing PHOTOFRIN for Treatment of Dysplasia or Early Adenocarcinoma of the Esophagus in Barrett's Esophagus.

- **Study Objectives:** Study TCSC 93-07 was a single center, investigator-sponsored (Dr. Bergein Overholt), uncontrolled Phase II study. The objectives of the study were to evaluate the safety and efficacy of PHOTOFRIN PDT in patients being treated for dysplasia or early adenocarcinoma in BE and to determine the required light dose to produce effective results.
- **Study Plan:** This was an open-label study in which patients were divided into 2 treatment groups. All patients were treated with PHOTOFRIN and omeprazole (20mg BID). About

one-half of the entire study population, including 14 high-grade dysplasia patients, were treated with a 175 – 225 Joules/cm light dose and a 5 or 7 cm PTG balloon at first treatment. The other half of the study population were treated with a light dose of 150 – 300 J/cm light dose and a 2, 3, 5, or 7 cm PTG balloon at first treatment.

- **Study Patients:** A total of 99 patients were enrolled in the study. Of these patients, 44 had BE with HGD. Criteria for patient selection were similar to those in the PHO BAR 01 study, although much less extensive.

a.2. Study Title: TCSC 96-01. Photodynamic Therapy of Dysplasia or Early Adenocarcinoma in Barrett's Esophagus: A Randomized Study of the Effect of Steroid Therapy on the Incidence of Esophageal Stricture.

- Study TCSC 96-01 was a follow-up to study TCSC 93-07, which had demonstrated that PHOTOFRIN PDT was an effective treatment for destroying dysplasia and early cancer in BE patients. However, a serious side effect of PHOTOFRIN PDT was the formation of esophageal strictures due to fibrosis and scar formation during the healing process after treatment. Steroid therapy had been reported to reduce fibrosis in a variety of conditions, including corrosive burns of the esophagus.
- **Study Objectives:** Study TCSC 96-01 was a single center, investigator-sponsored (Dr. Bergein Overholt), partially blinded, randomized, Phase II parallel-group study. The study objective was to compare the incidence and severity of esophageal strictures between patients with BE who received steroid therapy after PHOTOFRIN PDT and patients who received PHOTOFRIN PDT, without post-treatment steroids, for treatment of dysplasia and/or early adenocarcinoma of the esophagus.
- **Study Plan:** The study was partially blinded. All patients received PHOTOFRIN PDT and omeprazole 20 mg BID, and were randomized to steroid treatment or no steroid treatment. Patients and investigators were aware of the treatments administered. Only the endoscopists, who were responsible for evaluating esophageal stricture formation in the patients during the study, were blinded to whether the patient was in the steroid treatment group or not.
- **Study Patients:** A total of 87 patients were enrolled in the study. Forty-two (42) of these patients had BE with HGD, 30 patients had BE with low-grade dysplasia, 4 patients had adenocarcinoma, and 10 patients had other conditions, including patients with BE without dysplasia or carcinoma.

b. Reanalysis of Phase II study data by the sponsor:

The data from the Phase II studies were reanalyzed by the sponsor in accordance with the analysis of the pivotal study, including

- 1) revised patient inclusion criteria (only patients with high-grade dysplasia),
- 2) revised objectives, and
- 3) revised outcome endpoints (primary efficacy endpoint data at 6 months of follow-up, and secondary efficacy endpoints and safety endpoints at 12 months of follow-up).

Thus, these analyses included data on 44 patients out of 99 in the TCSC 93-07 study, and on 42 patients out of 87 in the TCSC 96-01 study.

c. Demographic Characteristics

Baseline demographic characteristics of high-grade dysplasia patients in the uncontrolled studies are shown in the Reviewer's Table below.

Reviewer's Note: The Sponsor divides the patients in TCSC 93-07 into two treatment groups. Since neither the baseline characteristics (vol. 42, p. 203; vol. 47, p. 166) nor the overall clinical response (primary efficacy endpoint) (vol. 42, p. 206; vol. 47, p. 170) differed between the two groups, the results of both groups are combined in the Reviewer's tables below.

Reviewer's Table. Demographic Characteristics of High-Grade Dysplasia Patients in the Uncontrolled Studies

Characteristic	PHOTOFRIN PDT TCSC 93-07, N = 44	PHOTOFRIN PDT TCSC 96-01, N = 42
Age in years, mean (range)	65.4 (39.1 – 81.1)	67.3 (48.0 – 82.0)
Sex – Male, number (%)	39 (88.6%)	34 (81%)
Female number (%)	5 (11.4%)	8 (19%)
Race – White (Caucasian)	44 (100%)	40 (95.2%)
- Black (African-American)	0	1 (2.4%)
- Asian	0	1 (2.4%)

Sources: vol. 42, p. 203; vol. 47, p. 166.

The characteristics of Barrett's Esophagus at baseline are shown in the Reviewer's Table below (from Panel 11.2 in vol. 42, p. 204 for study TCSC 93-07, and Panel 11.2 in vol. 47, p. 168 for study TCSC 96-01).

Reviewer's Table on the Characteristics of Barrett's Esophagus at Baseline

Characteristic	PHOTOFRIN PDT TCSC 93-07, N = 44	PHOTOFRIN PDT TCSC 96-01, N = 42
Duration of BE in months, median (range)	24.2 (1.1 – 102.3)	10.9 (2.5 – 328.8)
Endoscopic length of BE		
< 6 cm	in 9 patients	In 9 patients
> 6 cm	in 27 patients	In 19 patients
Prior treatment		
- Medical therapy	in 40 patients	In 39 patients
- Surgery	in 9 patients	In 7 patients
- Endoscopic Ablation	in 1 patient	0
- Other	in 2 patients	0

The Inclusion Criteria were as follows:

1. Biopsy-proven dysplasia or early adenocarcinoma of the esophagus in BE, without ultrasound evidence of tumor extension through the muscularis (stage T₂N₀M₀ or less).
2. Ineligible or refused standard methods of treatment including esophageal resection.
3. No contraindications to endoscopy
4. Male or female, 18 years of age or older. Females with adequate precautions against pregnancy.
5. Signed informed consent, or consent by next of kin or legal representative.
6. Karnofsky Performance status >30.

The Exclusion Criteria were as follows:

1. Tumor extension beyond muscularis
2. Porphyria or sensitivity to porphyrins
3. WBC <2,000, platelets <50,000, PT >1.5 times normal
4. Impaired renal or hepatic function
5. Received radiation or chemotherapy within 4 weeks before the admission to this study

Removal of Patients from Therapy or Assessment:

1. If no tumor response after 2 courses of PHOTOFRIN PDT (visual or biopsy evidence)
2. Unacceptable toxicity
3. Patient refused to continue treatment

Patients who were removed from the study less than 30 days after receiving PHOTOFRIN were cautioned against sunlight or strong light.

d. Treatment of Patients with PHOTOFRIN and Photodynamic Therapy

1) Study TCSC 93-07

All patients received 2.0 mg/kg of PHOTOFRIN I.V., and the first laser light treatment was administered to the esophageal segment 40 to 50 hours later. A second laser light treatment, if indicated, occurred 4 - 9 days after injection of PHOTOFRIN. Patients were divided into two equal groups. Patients in one group were treated with a light dose of 175-225 J/cm and 5 cm or 7 cm balloon at first treatment. Patients in the other group were treated with a light dose of 150 - 300 J/cm and a 2, 3, 5, or 7 cm balloon at first treatment. All patients received omeprazole 20 mg BID.

Patient follow-up and assessments were as described below for study TCSC 96-01.

2) Study TCSC 96-01

All patients received 2.0 mg/kg of PHOTOFRIN I.V., and the first laser light treatment was administered to the esophageal segment 40 to 50 hours later. A second laser light treatment, if indicated, occurred 4 to 9 days after injection of PHOTOFRIN. A 5 or 7 cm balloon was selected

to treat, when possible, the entire length of HGD with at least 0.5 cm of normal tissue margins. Most patients received a light dose of 175 or 200 Joules/cm. The predominant balloon type used in this study was the second generation Polymer Technology Group (PTG) balloon; toward the end of the study the 3rd generation Wilson Cook balloons ("Oreo balloons") began to be used. Light doses of 175 and 200 J/cm with a PTG balloon are approximately equivalent to a Wilson Cook balloon used at 130 J/cm, which is the light dose/balloon combination that was used in the pivotal PHO BAR 01 study.

Patients, who were randomized to receive steroid therapy, received tapering doses of oral prednisone. Prednisone was started on the light treatment day at 60 mg daily and was tapered every 2 days according to the following dose schedule: 50 mg, 40 mg, 30 mg, 20 mg, and 10 mg (the total prednisone treatment period was 12 days).

All patients underwent efficacy evaluation by biopsy (4 quadrant) at each treatment session and at 6 and 12 months after first treatment. Debridement of necrotic tissue via endoscopy was performed if indicated 4 - 9 days after PHOTOFRIN injection. Treatment in some patients included Nd:YAG laser thermal ablation, if indicated. Patients could be treated with up to 2 additional courses of PHOTOFRIN PDT, providing at least 30 days or more had elapsed since the previous PHOTOFRIN injection. The goal of each treatment session was to destroy the entire segment of Barrett's mucosa with HGD.

The duration of each patient's participation was 12 months; thereafter, patients were followed for survival time. Follow-up included telephone contact once a week for the first 2 months and then monthly for the following 4 months after treatment to determine if patients developed dysphagia.

Reviewer's Table on Photodynamic Therapy in Patients

Courses of treatment	PHOTOFRIN PDT TCSC 93-07, N = 44 patients	PHOTOFRIN PDT TCSC 96-01, N = 42 patients
Course 1	44 patients - 1 st laser Rx 25 patients - 2 nd laser Rx	42 patients - 1 st laser Rx 15 patients - 2 nd laser Rx 1 patient - 3 rd laser Rx
Course 2	13 patients - 1 st laser Rx 7 patients - 2 nd laser Rx	12 patients - 1 st laser Rx 2 patients - 2 nd laser Rx
Course 3	2 patients	1 patient - 1 st laser Rx

Description of PDT treatments is from Tables 1.13 and 3.1 in vol. 42, p. 270, 297 for study TCSC 93-07 and from Table 1.13 in vol. 47, p.261 for study TCSC 96-01.

Thirty-five (35) of 44 patients (80%) completed study TCSC 93-07, and 36 of 42 patients (86%) completed study TCSC 96-01. The reasons for discontinuation of patients from both studies are shown in the Reviewer's Table below.

Reviewer's Table on Patient Disposition in the Uncontrolled Studies

Causes of patients' discontinuations from the study	PHOTOFRIN PDT TCSC 93-07 N = 44	PHOTOFRIN PDT TCSC 96-01 N = 42
Death	2 (1 cardiac arrest, 1 meningitis)	1 (cause unknown, 19 days after Course 3)
Patient withdrew	1	
Other	1 dehydration, 1 bladder cancer & hematuria, 1 thrombocytopenia, 1 atrial fibrillation, 1 renal failure & bilateral pleural effusion, 1 ventricular fibrillation	1 esophagectomy, 1 lung transplant disrupting schedule, 1 different follow-up schedule, 2 missing records
Total	9 (20%)	6 (14.3%)

Sources: vol. 42, pp. 199,200, 232; vol. 47, pp.199, 162, 315.

Patient follow-up after treatment is shown in the Reviewer's Table below.

Reviewer's Table of Patient Duration in the Uncontrolled Studies

Patient Duration on Study	PHOTOFRIN PDT TCSC 93-07, N = 44	PHOTOFRIN PDT TCSC 96-01, N = 42
< 3 months	1	0
3 – 6 months	1	1
6 – 9 months	2	0
9 – 12 months	3	3
12 months (patients censored at 12 months)	35	36
> 12 months	2	2
Mean (range)	10.89 (2.2 – 27.5)	11.82 (3.0 – 16.0)

4. Efficacy Results:

a) Primary efficacy endpoint: Overall Clinical Response after first Six Months

The primary efficacy endpoint was the Clinical Response (as defined in the PHO BAR 01 study, namely complete ablation of HGD and re-growth of normal squamous epithelium with or without various degrees of metaplasia and LGD) as measured at 6 months of follow-up after the first day of PHOTOFRIN PDT. The response rates are shown in Reviewer's Table below (data from vol. 86, p. 206 for TCSC 93-07; vol. 47, p. 171 for TCSC 91-01).

In TCSC 93-07 the responses to 2 different laser treatments were about the same: 12 out of 14 (86%) patients responded after treatment with 175 – 225 J/cm, and 27 out of 30 (90%) patients responded after treatment with 150 – 300 J/cm. Therefore, the results of both treatment arms are combined.

In study TCSC 96-01 the responses were about the same in patients treated with steroids and in patients not treated with steroids, 18/21 (86%) and 19/21 (91%), respectively. The results of both treatment arms are combined.

**Reviewer's Table on Primary Efficacy – Overall Clinical Response
(First Six Months of Follow-up)**

Responders	PHOTOFRIN PDT TCSC 93-07 N = 44	PHOTOFRIN PDT TCSC 96-01 N = 42
CR1 + CR2 + CR3	39 (89%)	37 (88%)

b) Secondary efficacy endpoints: Overall Clinical Response (Complete, i.e. Twelve-month, Follow-up) and Quality of Response

Initially, both uncontrolled trials had Overall Clinical Response at 12 months of follow-up as the primary endpoint. When the data were analyzed by the Sponsor, the 12-month complete response data were presented as a Secondary Efficacy Endpoint. The 12-month follow-up data together with the quality of response data are shown in the Reviewer's Table below.

**Reviewer's Table on Secondary Efficacy Endpoints – Overall Clinical Response and
Quality of Response
(Complete, i.e. Twelve-month, Follow-up)**

Responders	PHOTOFRIN PDT TCSC 93-07, N = 44 patients	PHOTOFRIN PDT TCSC 96-01, N = 42
CR1	25 patients (57%)	25 (60%)
CR1 or CR2	36 patients (81%)	38 (91%)
CR1 or CR2 or CR3	41 patients (93%)	40 (95%)

Sources: vol.41, pp. 207, 208, 210; vol. 47, pp.171-2.

The 12-month complete response data are better than the 6-month response data, as patients continued to complete full courses of PHOTOFRIN PDT. Five patients who had been classified as response failures at the 6-month follow-up were reclassified as responders at the 12-month follow-up.

c. Secondary efficacy endpoint: Duration of response

Responders and Duration (median, in days)	PHOTOFRIN PDT TCSC 93-07, N = 44 patients	PHOTOFRIN PDT TCSC 96-01, N = 42
CR1	Median duration 105 days	Median duration 98 days
CR1 or CR2	Median duration 192 days	Median duration 273 days
CR1 or CR2 or CR3	Median duration 391 days	Value cannot be estimated

Sources: vol. 42, p. 210, Panel 11.6 for TCSC 93-07; vol. 47, p. 173.

The relatively short (12-month) follow-up period permits only tentative estimates of duration of responses; the sponsor was unable to establish 95% confidence intervals for the above response data. The sponsor presented Kaplan-Meier plots (vol. 42, p. 211; vol. 47, p. 174) of the durations of responses stretching out to over 1,000 days, but the small number of patients followed beyond 12 months raise the issue of reliability of these plots. They are not reproduced in this review. The Duration of Response data is inconsistent with the 12-month complete response data in TCSC 93-07. According to the sponsor, most failures appeared to occur within the first 4 months after randomization and treatment. The reviewer examined the data listings for times of failure, which are presented in the Reviewer's Table below. The times of failures are grouped by 3 month intervals. The sponsor's conclusions on the time of most failures are not well-supported by these data, especially in study TCSC 96-01.

Reviewer's Table of Response Failures During 12-month Follow-up

Months after first treatment	PHOTOFRIN PDT TCSC 93-07, N = 44	PHOTOFRIN PDT TCSC 96-01, N = 42
0 – 3 months	8 (days 55, 56, 75, 79, 88 x 2, 90, 91)	3 (days 2, 68, 86)
3 – 6 months	6 (days 100, 120, 137, 139, 167, 174)	3 (days 96, 97, 102)
6 – 9 months	1 (day 215)	3 (days 195, 196, 259)
9 – 12 months +	2 (days 310, 322)	3 (days 341, 361, 430)
12-month total	17 (36.8%)	11 or 12 (28.6%)

Sources: Table 3.7.3, vol. 86, p. 286 for TCSC 93-07; Table 3.7.3, vol. 47, p. 250 for TCSC 96-01.

c. Secondary Efficacy Endpoint: Time to Progression to Cancer

The Time to Progression to Cancer (TTP) was defined as the period in days from the date of first treatment with PHOTOFRIN PDT until the date the progression to cancer was first documented. Median TTP could not be estimated because fewer than 50% of patients had a documented TTP by the end of the 12-month follow-up period.

The reviewer examined the data listings to find out how many patients had progressed to cancer and when the progression to cancer was noted. Eight patients (18%) progressed to cancer in TCSC 93-07 during the 12-month follow-up. Reviewer's Table below shows the time periods when progression to cancer was first noted. Two patients (5%) progressed to cancer in TCSC 96-01 within 12 months and one in the subsequent follow-up.

Reviewer's Table on Time to Progression to Cancer

Months after first treatment	PHOTOFRIN PDT TCSC 93-07, N = 44	PHOTOFRIN PDT TCSC 96-01, N = 42
0 – 3 months	2 patients (days 2 & 25)	0
3 – 6 months	3 patients (days 93, 99 & 176)	1 patient (day 106)
6 – 9 months	3 patients (days 194, 227 & 232)	1 patient (day 186)
9 – 12 months +	0 patients	1 patient (day 491)
Total for 12 months	8 (18%)	3 (7%)

Sources: Table 3.9.1, vol. 42, p. 293; Table 3.9.1, vol. 47, p. 255.

d. Secondary Efficacy Endpoint: Survival Time

Survival Time was defined as the period in days from the date of first treatment with PHOTOFRIN PDT to the date of patient's death.

In study TCSC 93-07 only one patient died within 12 months of follow-up at day 281 (cause: cardiac arrest). Four patients died at days 430 (cause: meningitis), 933, 1079, and 1337.

The sponsor states that in study TCSC 96-01 no patient had a documented death by the end of the follow-up (Efficacy Summary, vol. 8, p. 101). Table 3.10.1 showing Comparison by Group of the Survival Time is missing in vol. 47, but there is a death report among adverse events narratives in vol. 47, p. 315. An 83-year old female patient received 3 courses of PHOTOFRIN PDT over an eighteen-month period. Seventeen days after the third course she died; no information as to cause of death is available.

The Secondary Endpoint: Survival Times could not be estimated in either study, because there were very few deaths and all were not related either to esophageal carcinoma or to PHOTOFRIN PDT treatment. Thus, this was not a useful endpoint.

D. Efficacy Conclusions

1. The primary endpoint efficacy data in the controlled trial are impressive: the Complete Response (CR), complete ablation of high-grade dysplasia with re-epithelialization with normal epithelium, or normal epithelium with some areas of metaplasia, low-grade dysplasia or indefinite dysplasia was found in 77% of PHOTOFRIN PDT patients (ITT population) and in 39% of control patients, a 38% difference that is highly significant ($p < 0.0001$). These results in the PHO BAR 01 trial are supported by the results in the two uncontrolled trials, in which the 12-month follow-up Complete Response rates were 93% in TCSC 93-07 and 95% in TCSC 96-01.
2. The secondary efficacy endpoint Quality of Complete Response demonstrated that most of the responders the PHOTOFRIN PDT group had a CR1 (re-epithelialization with normal squamous cell epithelium only) response (68% of 106), while most of the

- responders in the OM Only group (63% of 27) had a CR3 (re-epithelialization with areas of low-grade or indefinite dysplasia) response. These findings are important, because CR1 responders did not progress to cancer, while CR3 responders did, as described below.
3. The secondary efficacy endpoint Duration of Response showed a significantly longer duration of complete responses in the PHOTOFRIN PDT group than in OM Only group. By the end of minimum 24-month follow-up period the probability of maintaining a CR3 of better response was 52.7% in the PHOTOFRIN PDT group and 12.8% in the OM Only group.
 4. The secondary efficacy endpoint Time to Progression to Cancer could not be evaluated as originally specified (time period in days when 50% of patients in each study arm had progressed to cancer). However, about 13% of patients in the PHOTOFRIN PDT group and 28% of patients in the OM Only group had progressed to cancer during the follow-up period. Patients in the PHOTOFRIN PDT group had a greater chance of being cancer-free than patients in the OM Only group (83% vs. 53%).
 5. The secondary efficacy endpoint Time to Treatment Failure could not be evaluated for the PHOTOFRIN PDT group as originally specified (time period in days when 50% of patients had treatment failure). This endpoint is a composite endpoint of 1) progression to cancer and 2) the start of any interventional therapy for high-grade dysplasia other than the randomized study treatment. In the PHOTOFRIN PDT arm 26% of patients (ITT population) had treatment failure during the follow-up period compared to 59% of patients in the OM Only arm. Comparison between the two treatment arms by log rank test showed that other intervening therapy, such as esophagectomy, was significantly postponed in the PHOTOFRIN PDT group as compared to OM Only group ($p < 0.0001$).
 6. Secondary efficacy endpoint Survival Time, defined as the period in days from the date of randomization to the date of the patient's death, could not be estimated for either treatment group, because there were very few deaths (3) in this study. None of the deaths in the PHOTOFRIN PDT trial or in the supporting trials were related to adenocarcinoma of the esophagus or to treatment.
 7. Other analyses by the sponsor showed that Complete Response rate was influenced by 1) single HGD focus vs. multiple foci ($p < 0.0001$) and 2) prior omeprazole intake of at least 3 months ($p = 0.0026$). Complete response rate was not influenced by 1) duration of HGD, 2) length of Barrett's esophagus, 3) nodular conditions, 4) gender, 5) age, 6) smoking history, and 7) study center size (<10 patients vs. >10 patients).
 8. Other analyses by this reviewer showed that 1) complete responders had about a ten-fold lower probability of progressing to cancer than non-responders (6% vs. 50% in the PHOTOFRIN PDT group and 4% vs. 45% in the OM Only group – in the Evaluable population), and 2) most of the complete responders who progressed to cancer had a CR3 response (6/7). None of the responders with a CR1 progressed to cancer.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety data appear to be adequately presented. The major drawback of these studies is the small number of patients, a total of 318. An important contribution of the pivotal trial is that it is a controlled study; thus, the control arm provides a background of adverse event frequency in this population.

The major side-effects of photodynamic therapy, using PHOTOFRIN as photosensitizing agent, are acute events related to the light treatment itself and longer lasting effects relating to the healing of esophagus and the extended period of photosensitivity of the skin.

- The acute effects were dysphagia, odynophagia, vomiting, nausea, abdominal pain, chest pain and fever. These symptoms were reported by about 25 % to 35% of patients.
- The most important sub-acute effects were esophageal strictures and photosensitivity reactions. A stricture was defined as esophageal narrowing requiring dilation.
- Strictures affected about 38% of patients. Their treatment required repeated dilations, probably because PHOTOFRIN PDT injury results in deep (up to 6 mm) tissue necrosis, involving not only the esophageal mucosa but also the muscularis, and healing results in tight bands of fibrous tissue.
- Skin photosensitivity reactions were common (67% of patients in the pivotal study), in spite of documented warnings about exposure to sunlight and bright lights for 30 days.

Almost all (98%) of patients in the PHOTOFRIN PDT group reported adverse events, compared to 68% in the Omeprazole Only group. The total number of adverse events was more than three times as high in the PHOTOFRIN PDT group as in omeprazole only group (1,245 vs. 206 events). In the PHOTOFRIN PDT group the most common adverse events were related to the gastrointestinal system, body as a whole (chest pain, fever, pain), photosensitivity reactions, and dehydration. The most common adverse events in the OM Only group were related to the gastrointestinal system, body as a whole, nervous system, and metabolic and nutritional system.

There were 6 deaths in the three studies, none of which were treatment-related. Twenty-five percent of patients in the PHOTOFRIN PDT group reported SAEs, most commonly related to gastrointestinal, cardiovascular, metabolic, nutritional, and nervous systems. Most treatment-related SAEs (80 events) were reported as gastrointestinal disorders and dehydration. Twenty-eight percent of patients in the OM Only group reported SAEs; four SAEs were treatment-related.

Seven patients (2.2%) in the PHOTOFRIN PDT group and one patient (1.4%) in the OM Only group withdrew from studies because of adverse events. Two such events were treatment-related; they were esophageal perforations, one resulting in esophagectomy.

Interactions of PHOTOFRIN with other photosensitizing drugs and with drugs degraded by cytochrome P450 enzymes have not been studied. However, photosensitivity after PHOTOFRIN injection is massive and dwarfs the effects of any other drugs increasing or decreasing photosensitivity. There is no basis for suspecting an interaction with omeprazole.

B. Description of Patient Exposure

The present NDA contains the results of three studies in patients with BE who had high-grade dysplasia, a pre-malignant condition. The pivotal PHO BAR 01 study compared PDT with PHOTOFRIN plus omeprazole (PHOTOFRIN + OM) to a surveillance arm consisting of omeprazole only (OM Only). In this study, 208 patients were enrolled in 2:1 ratio, 138 patients were randomized to receive PHOTOFRIN + OM (treatment arm) and 70 patients were randomized to receive OM Only (control arm). Of those, 133 patients (96%) received at least one injection of PHOTOFRIN and 132 out of 133 received at least one complete course of PHOTOFRIN PDT. Seventy patients were randomized into the OM Only treatment group, of whom 69 (99%) received at least one omeprazole dose.

In addition, this NDA includes data from 2 open-label clinical trials (TCSC 93-07 and TCSC 96-01) conducted under a physician-sponsored IND of PDT with PHOTOFRIN in BE (Dr. B.F. Overholt, Thompson Cancer Survival Center, Knoxville, TN; IND 42,313). Study 93-07 was an open-label study in 99 patients, 44 of whom met the criteria for high-grade dysplasia. These patients were divided into 2 treatment groups, which received different laser light treatments. Study 96-01 was a randomized, partially blinded study of the effect of steroid treatment on the development and severity of esophageal strictures associated with PDT. Forty-two (42) BE patients with high-grade dysplasia were randomized into two equal groups, one that was treated for 12 days with tapering doses of prednisone following the light exposure and one that was not treated with prednisone. All the patients in studies TCSC 93-07 and TCSC 96-01 were treated with omeprazole (20 mg twice daily).

Extent of Exposure. Photodynamic therapy (PDT) consists of 2 modalities: administration of photosensitizing agent PHOTOFRIN, and administration of laser light, which results in tissue damage. Each of these modalities (PHOTOFRIN and laser light) poses distinct safety issues.

- PHOTOFRIN. Treatment with PHOTOFRIN is by intravenous injection and consists of a 2 mg/kg dose, followed by 630 nm laser-light treatment 48-72 hours after drug administration. Additional injection of PHOTOFRIN is not performed until 90 days has passed, and only if follow-up endoscopy reveals new areas of dysplasia in need of treatment. The specified PHOTOFRIN dose was the same in all the patients in all 3 studies. The majority of patients in the Safety Population received the recommended PHOTOFRIN dose of 2 ± 0.005 mg/kg: 74.8% (237/317 patients) in Course 1, 83.2% (104/125 patients) in Course 2, and 93.7% (45/48 patients) in Course 3.
- Laser light at 630 nm. In contrast to the standardized PHOTOFRIN treatment, light delivery methods and doses changed during the individual studies and between the studies. Laser light is passed through endoscopically placed fiber optics tipped with cylindrical diffusers. In normal esophagus, as well as BE, an inflatable centering balloon is needed to improve light dosimetry in an organ that tends to collapse, with the result that internal mucosal folds create a "hill and valley" effect. Pre-clinical and necropsy data demonstrated that with the diffuser/balloon combination the PDT response is circumferential and uniform, while with

the diffuser alone the effect varied from minimal to severe. Reviewer's Table below summarizes the types of balloons and the 630 nm light dosages used in the three trials.

Reviewer's Table Summarizing Light Delivery Systems in the PHOTOFRIN Trials

Study ID	Equipment and Light Doses	Comments
TCSC 93-07	"Black-capped" (black at ends, transparent in the center) 3 cm balloons, later 5 cm and 7 cm balloons.	Multiple light sessions were required to treat segments > 3 cm. Overlap areas received more than one light treatment. These areas were particularly prone to development of esophageal strictures. Longer balloons of 5 cm and 7 cm length were then developed. A peak of light in the middle of the 5 cm window may have led to strictures. Fifteen (15) courses were administered with 3 cm balloons, 13 courses with 5 cm balloons, 6 courses with 7 cm balloons, and 2 courses with 2 cm balloons.
TCSC 96-01	"White capped" (reflective inner coating at ends), 5 cm and 7 cm. Light doses 175 J/cm and 200 J/cm.	Sixteen (16) courses were administered with 5 cm balloons, and 38 courses were administered with 7 cm balloons.
PHO BAR 01	Fiber optic diffusers of 9 cm, 7 cm, and 5 cm. Wilson Cook white-capped balloons, window sizes of 7 cm, 5 cm, and 3 cm. Light dose 130 J/cm of diffuser length. Treatment time was 480 sec.	Short fiber optic diffusers (<2.5 cm) were used to pre-treat nodules with 50 J/cm diffuser length (86 treatments in 35 patients) prior to regular balloon treatment in the first laser light session. Thirty-nine (39) courses were administered with 3 cm balloons, 57 courses with 5 cm balloons, and 170 courses with 7 cm balloons.

Sources: vol. 3, p.50; vol. 11, p. 151; vol. 48, p. 25; vol. 13, p. 35.

A summary of the extent of photodynamic therapy treatment is shown below in Reviewer's table (data from Sponsor's Panel 6.3, N-000 SU, p. 27).

Reviewer's Table. Extent of Photodynamic Therapy Treatment in PHO BAR 01, TCSC 93-07, and TCSC 96-01 Studies

Laser light sessions	Course 1 318 patients	Course 2 125 patients	Course 3 48 patients
Use of balloon in % of patients treated	93.0%	92.0%	89.6%
Length of balloon window used in % of treatments			
-2 cm	2.5%	0.8%	0
-3cm	19.8%	12.1%	25.5%
-5cm	22.6%	22.4%	36.2%
-7cm	54.8%	64.7%	38.3%
Light dose delivered in % of treatments			
<129 J/cm	5.7%	6.0%	1.8%
129 – 131 J/cm	31.3%	60.2%	66.0%
>131 J/cm	62.9%	38.8%	39.3%

In PHO BAR 01 22% of patients (29/133) received the wrong laser light dose (not the prescribed 130 J/cm). Most patients (22/29) received more than 130 J/cm, but only 3 patients received more than 140 J/cm. Of the 7 patients who received less than 130 J/cm, 4 received less than 120 J/cm.

Precautions taken during the studies. All patients injected with PHOTOFRIN were photosensitive and had to observe precautions to avoid exposure of eyes and skin to direct sunlight or bright indoor light (e.g. examination lamp, dental lamps, operating room lamps, unshaded light bulbs at close proximity) for at least 30 days. Some patients remained photosensitive for up to 90 days or more. Therefore, patients were asked to avoid darkened rooms after 30 days, and were encouraged to expose their skin to ambient indoor light to allow gradual inactivation of the remaining drug through photobleaching. The level of photosensitivity varied for different areas of the body, depending on the extent of previous exposure to light. Before exposing any area of the skin to direct sunlight or bright indoor light, patients were asked to test the skin for residual photosensitivity by exposing a small area of the skin to sunlight for 10 minutes. If no photosensitivity reaction (erythema, edema, blistering) occurred within 24 hours, patients could gradually resume normal outdoor activities. If some photosensitivity reaction occurred, patients had to continue precautions for another week before re-testing. Skin around the eyes may be more sensitive to light; patients were asked not to use the face for testing residual photosensitivity.

Ocular discomfort, commonly described as sensitivity to sun, bright light, or car headlights, has been reported. Patients were asked to wear dark sunglasses (average white light transmittance of <4%) when outdoors for a period of 30 days.

Precautions must be taken to prevent extravasation of PHOTOFRIN at the injection site. If extravasation occurred, the area had to be protected from light.

As a result of PDT treatment, some patients complained of substernal chest pain and nausea because of inflammatory responses within the area of treatment. Such pain may be of sufficient intensity to warrant the short-term prescription of opiate analgesics.

Durations of follow-up in the three studies are described in Reviewer's Tables in the Efficacy section.

B. Methods and Specific Findings of Safety Review

1. Summary of Patient Disposition

Reviewer's table describes the populations in the 3 studies (data from Sponsor's table in N—000 SU, Panel 5.2, p. 22).

Reviewer's Table. Summary of Patient Disposition in the PHOTOFRIN PDT Studies

Number of Patients (%)	HGD PHOTOFRIN PDT + OM	HGD OM Only	Other* PHOTOFRIN PDT + OM	Total PHOTOFRIN PDT
ITT Population†	224	70	100	324
-PHO BAR 01	138	70	N/A	138
-TCSC 93-07	44	N/A	55	99
-TCSC 96-01	42	N/A	45	87
Safety population (n, %)‡	219 (97.8%)	69 (98.6%)	99 (99%)	318 (98.1%)
-PHO BAR 01	133 (96.4%)	69 (98.6%)	N/A	133 (96.4%)
-TCSC 93-07	44 (100%)	N/A	55 (100%)	99 (100%)
-TCSC 96-01	42 (100%)	N/A	44 (97.7%)	86 (98.9%)
Completed study (n, %)‡	152 (69.4%)	21 (30.4%)	87 (87.9%)	239 (75.2%)
-PHO BAR 01	81 (60.9%)	21 (30.4%)	N/A	81 (60.9%)
-TCSC 93-07	35 (79.5%)	N/A	48 (87.3%)	83 (83.8%)
-TCSC 96-01	36 (85.7%)	N/A	39 (88.6%)	75 (86.2%)
Discontinued from study (n, %)	72 (32.1%)	49 (70%)	13 (13.0%)	85 (26.2%)
---Adverse event (AE)	5 (2.2%)	1 (1.4%)	2 (2.0%)	7 (2.2%)
---Death	4 (1.8%)	1 (1.4%)	0	4 (1.2%)
---Moved away	0	1 (1.4%)	2 (2.0%)	2 (0.6%)
---Uncooperative patient	1 (0.4%)	1 (1.4%)	0	1 (0.3%)
---Patient withdrawal	7 (3.1%)	1 (1.4%)	2 (2.0%)	9 (2.8%)
---Progression of disease	18 (8.0%)	22 (31.4%)	0	18 (5.6%)
---Other therapy	22 (9.8%)	19 (27.1%)	0	22 (6.8%)
---Other reasons	15 (6.7%)	3 (4.3%)	7 (7.0%)	22 (6.8%)

*Includes patients with adenocarcinoma, indefinite dysplasia, LGD, or metaplasia at baseline from TCSC 93-07 and TCSC 96-01 studies.

†Percentages are based on the number of patients randomized to each group (ITT population).

‡Percentages are based on the number of patients who received study therapy in each group (Evaluable population).

2. Summary of Patient Exposure

Patient exposure to PHOTOFRIN and photodynamic therapy is described above under B.

Exposure to concomitant medications is described under PHO BAR 01 study and was similar in the supporting studies. PHOTOFRIN PDT patients used more concomitant medications than OM Only patients in the following categories: alimentary tract and metabolism (97.8% vs. 59.4%), nervous system (94.3% vs. 66.7%), systemic hormonal preparations (45.6% vs. 24.6%), and blood and blood-forming organs (39.3% vs. 24.6%). OM Only patients commonly used more concomitant medications than PHOTOFRIN PDT patients in the following categories: cardiovascular (72.5% vs. 64.2%) and musculoskeletal (37.7% vs. 26.4%) systems. All (100%) PHOTOFRIN PDT patients took at least one concomitant medication, as did almost all (97.1%) OM Only patients.

A more informative analysis is by the percentage of patients who took medications in more specific categories rather than by organ system indications. The following table describes the use of concomitant medications in the two treatment groups in the PHO BAR 01 study. PHOTOFRIN PDT + OM group took many more medications than the OM Only group. Especially impressive is the very high usage of opioid and non-opioid analgesics, local anesthetics, anti-nausea agents and anti-emetics, anxiolytics, antacids, gastrointestinal agents, glucocorticoids, and cytoprotective agents.

Drug group	PHOTOFRIN PDT + OM % of patients using	OM Only % of patients using
Opioid analgesics	90%	23%
Non-opioid analgesics	83%	32%
Phenothiazines	62%	4%
Antacids	56%	9%
Local anesthetics	55%	1%
Glucocorticoids	39%	10%
Benzodiazepenes	28%	14%
Gastrointestinal agents	26%	1%
Ethanolamines	20%	4%
Glucagon	20%	1%
Cytoprotective agents	14%	7%
Stimulant laxatives	11%	3%
Aminoglycosides	1%	6%

3. Demographics and Other Characteristics of Study Population

Patient demographic and baseline characteristics for the Safety population are shown in Reviewer's Table below (data from Sponsor's Panel 7.1, N-000 SU, p. 30).

Reviewer's Table. Patient demographic and baseline characteristics

Characteristics	Total PHOTOFRIN PDT N = 318	OM Only N = 69
Age (years)		
• <60	83 (26.1%)	18 (25.6%)
• 60 – 75	164 (51.6%)	31 (44.9%)
• >75	70 (22.0%)	20 (29.0%)
Mean	66.0	67.2
Gender		
• Male	257 (80.8%)	58 (84.1%)
• Female	61 (19.2%)	11 (15.9%)
Race		
• Caucasian	314 (98.7%)	67 (97.1%)
• African American	2 (0.6%)	1 (1.4%)
• Asian	2 (0.6%)	1 (1.4%)

Barrett's esophagus characteristics are described under individual studies. Total PHOTOFRIN PDT population did not differ from the OM Only population in

- Duration of BE
- Endoscopic length and histological length of BE
- Single vs. multiple levels of HGD, and
- Frequency of nodules, ulcers, and strictures.

The presence of hiatal hernia was more frequent in the OM Only group than in the PHOTOFRIN PDT group, as described in the PHO BAR 01 study.

4. Adverse Events

Almost all the patients treated with PHOTOFRIN PDT + OM experienced at least one treatment-emergent adverse event (TEAE). For the sake of clarity the frequencies of events will be summarized for all three PHOTOFRIN PDT trials and contrasted with the frequency of TEAE's in the OM Only arm of the PHO BAR 01 trial. Differences in the frequencies of TEAEs among the three PHOTOFRIN trials will be noted. An updated integrated safety summary of PHO BAR 01 24-month follow-up study was submitted on October 23, 2002 (N-000 SU). The submission also included safety data from TCSC 93-07 and TCSC 96-01 supporting studies, which had not changed from the original NDA submission.

Reviewer's Table. Treatment Emergent Adverse Events in More Than 2.0% of High-grade Dysplasia Patients in PHO BAR 01, TCSC 93-07, and TCSC 96-01 Studies

Body System and Preferred Term	All 3 PHOTOFRIN PDT studies, N = 318	PHO BAR 01	
		PHOTOFRIN PDT N = 133	OM Only N = 69
Number of patients (%) with Any Event	316 (99.4%)	130 (97.7%)	51 (74%)
Gastrointestinal	267 (84%)	97 (73%)	25 (36%)
Nausea	124 (39%)	17 (13%)	5 (7%)
Dysphagia	77 (24.2%)	26 (20%)	1 (1%)
Esophageal stricture	95 (29.9%)	48 (36%)	1 (1%)
Vomiting	107 (34%)	46 (35%)	4 (6%)
Odynophagia	48 (15.1%)	16 (12%)	0
Abdominal pain	34 (10.4%)	15 (11%)	3 (4%)
Hiccup	24 (7.5%)	13 (10%)	0
Constipation	44 (13.8%)	34 (26%)	5 (7%)
Diarrhea	16 (5.0%)	16 (12%)	7 (10%)
Body as a Whole	221 (69.5%)	74 (56%)	21 (30%)
Chest pain	151 (47.5%)	36 (27%)	8 (12%)
Fever	70 (22.0%)	30 (23%)	3 (4%)
Pain	62 (19.4%)		
Skin and Appendages	157 (49.4%)	100 (75%)	8 (12%)
Photosensitivity reaction	140 (44.0%)	89 (67%)	0
Skin disorder	14 (4.4%)	13 (10%)	1 (1%)
Metabolic and Nutritional	55 (17.3%)	37 (28%)	9 (13%)
Dehydration	29 (9.2%)	16 (12%)	2 (3%)
Weight decrease	9 (2.8%)		
Central Nervous System	30 (9.4%)	30 (23%)	11 (16%)
Headache	14 (4.4%)	14 (11%)	5 (7%)
Heart rate/ Rhythm disturbances	12 (3.8%)		
Psychiatric	26 (8.2%)		
Anorexia	16 (4.7%)		

While the frequencies of many adverse events were similar among the three PHOTOFRIN groups, there were some differences, such as

- Treatment-related esophageal strictures (Endoscopy data) occurred in 42% of TCSC 93-07 patients (vol.8, p.141), in 36% of TCSC 96-01 patients (vol. 8, p. 148), and in 36.5% of PHO BAR 01 patients (vol.8, p.121). In a composite Table on Strictures in all 3 studies (vol.8, p.115) the percentages of patients with esophageal strictures are 31%, 14%, and 36%, respectively. The table specifies that esophageal stricture category "includes all esophageal narrowing regardless of dilation needs." However, this statement is not correct. In study TCSC 93-07 28.3% of all PHOTOFRIN patients group developed an esophageal narrowing

not requiring dilations, while 42.4% developed an esophageal stricture (vol.8, p.140). The percentage of patients in study 96-01 who developed an esophageal narrowing not requiring dilations is not stated. In PHO BAR 01 study, 18% of patients in the PHOTOFRIN PDT group and 6% of patients in the control group developed an esophageal narrowing not requiring dilations. In general, the percentages of esophageal strictures are lower in the Adverse Event data than in the Endoscopy data. For that reason the above table underestimates the incidence of strictures.

- Nausea was less frequent in PHO BAR 01 patients (13%) than in the two TCSC trials (56% and 61%).
- Chest pain was less frequent in PHO BAR 01 patients (27%) than in the two TCSC trials (69% and 55%).
- Pain was not listed as occurring in PHO BAR 01 patients, but was present in 12% and 55% in TCSC 93-07 and TCSC 96-01, respectively.
- Pleural effusions were not noted in the PHO BAR 01 trial, but occurred in 20% and 14% of patients in TCSC 93-07 and 96-01 trials, respectively.
- Photosensitivity reactions were present in 67% of PHO BAR 01 patients, but in only 27% of TCSC 93-07 or TCSC 96-01 patients.

The adverse events profile of the OM Only group was strikingly different from the PHOTOFRIN PDT groups, and brings into focus adverse events that accompany PDT. In particular, PDT appears to be characterized by acute adverse events at the time or shortly after PDT, and by more chronic adverse events that develop over weeks following PDT, as shown below:

- Acute gastrointestinal adverse events following therapy: nausea, vomiting, dysphagia, odynophagia.
- Acute chest and abdominal adverse events: chest pain, abdominal pain, fever, pleural effusions.
- Sub-acute adverse events: esophageal stricture, photosensitivity reactions.

Not only a greater percentage of patients in the PHOTOFRIN PDT group experienced adverse events than patients in the OM Only group; they experienced about twice number of adverse events, as shown in the Reviewer's Table below (data from vol. 13, p. 124).

Reviewer's Table. Treatment Emergent Adverse Events in >10% of the Patients in the PHO BAR 01 Study

	PHOTOFRIN PDT + OM	OM Only
Total number of patients with TEAEs, (%)	130 (98%)	47 (68%)
Total number of events	1,245	206
Life threatening	10	1
Severe	212	33
Moderate	387	64
Mild	636	108
Number of events/number of patients	9.6	4.4

Photosensitivity reactions. Photosensitivity of the skin is a known side effect of PHOTOFRIN treatment. Most of the photosensitivity reactions occurred within 90 days after PHOTOFRIN injection. Most of the reactions were mild (68%) or moderate (26%), and 97% were considered associated with treatment. Exposed areas (face, hands and neck) were affected the most. Severe reactions occurred in 12 (9.2%) patients in the PHO BAR 01 study and were characterized by swelling, pruritus, erythema, blisters, itching, burning sensation and heat. All resolved over time.

Esophageal stricture. Esophageal strictures are the most important of treatment-related adverse events. All esophageal narrowing data were collected using the term "esophageal stricture", regardless of subsequent management. Later, only esophageal narrowing that required dilation was considered a stricture. The following composite table presents a summary of esophageal strictures from the endoscopy data in the three trials. The sponsor characterizes the strictures as mild in about 51.4% of patients, moderate in 38.8%, and severe in 9.7%.

Reviewer's Table. Esophageal Strictures Following PHOTOFRIN Photodynamic Therapy in PHO BAR 01, TCSC 93-07, and TCSC 96-01 Patients (Endoscopy Data)

	TCSC 93-07	TCSC 96-01	PHO BAR 01	Total (%)
Numbers of patients in trial (Safety populations)	99	86	133	318
Patients with strictures following treatment	42 (42.4%)	31 (36.0%)	48 (36.1%)	121 (38.1%)
Course 1		26 (30.2%)	18 (13%)	
Course 2		5 (5.8%)	29 (21%)	
Course 3		0	1 (1%)	

Sources: vol. 13, p. 127; vol. 42, p. 227; vol. 47, p. 186.

Esophageal strictures were sufficiently severe requiring multiple dilations. Two of the patients developed esophageal perforations during dilations (described below). The Reviewer's Table below presents the composite data on esophageal dilations.

Reviewer's Table . Esophageal Dilations in Patients with Treatment-related Strictures

	TCSC 93-07 N = 99	TCSC 96-01 N = 86	PHO BAR 01 N = 133	Total N = 318
Number of patients with strictures	42	31	48	121
1 -2 dilations	12 (28.6%)*	14 (45.2%)*	16 (33.3%)*	42 (34.7%)*
3 - 5 dilations	13 (31.0%)*	12 (38.7%)*	10 (20.8%)*	35 (28.9%)*
6 - 10 dilations	7 (16.7%)*	5 (16.1%)*	14 (29.2%)*	26 (21.5%)*
>10 dilations	10 (23.8%)*	0	8 (16.7%)*	18 (14.9%)*

*Percentage of the number of patients with strictures.

Sources: vol. 13, p. 127; vol. 42, p. 228; vol. 47, p. 188.

Re-treatment of a mucosal segment with PDT was associated with development of esophageal strictures. Strictures developed in 44.2% of patients who had a mucosal segment treated twice and in 23.5% of patients who did not have a same segment re-treated.

Chest Pain. The number of patients reporting chest pain increased shortly after PDT and then declined over a 4-week period. About 12% of patients reported severe chest pain, 34-41% reported moderate chest pain, and the 19-30% mild chest pain.

Odynophagia and dysphagia. About 5% of patients reported severe odynophagia, about 15-18% moderate odynophagia, and 11-19% mild odynophagia. Approximately the same percentages of patients reported dysphagia. Odynophagia remitted over 4 weeks following PDT, and dysphagia, over 6 months.

5. Deaths and SAEs.

Deaths. There were 3 deaths in PHO BAR 01 study during the minimum 24-month follow-up. Two female subjects, 74 and 82 years of age, died in the PHOTOFRIN group. One died from metastatic breast cancer, aortic valve stenosis, deep vein thrombosis, pulmonary embolism and renal failure; the other died from cardiac arrest, following CABG and cardiac tamponade. One 68-year old male died from a massive stroke in the OM Only group.

Two patients died in the TCSC 93-07 study. A 75-year old male with a history of cardiac arrhythmias died from cardiac arrest, and a 77-year old male died from enterococcal meningitis. One patient died in the TCSC 96-01 study, an 83-year old female with CAD. Death was unexpected and cause of death was not ascertained.

None of the deaths in the 3 studies were thought to be related to treatment.

SAEs. In the total PHOTOFRIN PDT patient group, 80 patients (25%) reported 240 SAEs. Most SAEs were reported by only one or two patients in each instance. Most common SAEs were gastrointestinal (28 patients, 9%), cardiac (18 patients, 6%), general disorders (16 patients, 5%), neoplasms (11 patients, 3%), metabolism and nutrition disorders (10 patients, 3%), vascular disorders (9 patients, 3%), and nervous system disorders (6 patients, 2%). The majority of SAEs were of severe/very severe (118 events, 49% of total) or moderate (84 events, 35%) intensity. Seventy-two (72) SAEs were considered to be associated with treatment, most were of severe (38 events) or moderate (28 events) intensity. Most of SAEs associated with treatment were reported as gastrointestinal disorders; the most common SAE was dehydration.

Patients in the OM Only group had a similar incidence of SAEs (19 patients, 28%). Only 4 SAEs were considered associated with treatment. They were single instances of nausea, melena, ulcerative esophagitis and anemia.

6. Withdrawals Due to Adverse Events. In the PHO BAR 01 study, 4 patients in the PHOTOFRIN group had adverse events that led to withdrawal from the study. One patient underwent an esophagectomy following perforation of the esophagus that occurred during an esophageal dilation for an esophageal stricture. One patient developed an anxiety reaction during

the period between PHOTOFRIN injection and laser light treatment; she refused the light treatment. One patient was diagnosed with non-small cell lung cancer. One patient had stroke-related mental status changes. One patient in the OM Only group had a stroke and was withdrawn from the study.

Two patients were discontinued from study 93-07 due to adverse events, both were in the low-grade dysplasia group. A 66 year old male patient suffered an esophageal perforation with sepsis after Nd:YAG laser treatment. A 70-year old male patient was diagnosed with pulmonary carcinoma; the event was definitely not related to treatment. One patient was discontinued from study 96-01, a 76-year old male patient with worsening heart disease, an event not related to treatment.

7. Clinical Laboratory Evaluations. In the PHO BAR 01 study, laboratory data were collected at baseline and at Month 3 follow-up. Most (95% to 100%) abnormalities in hematology and clinical chemistry parameters were not clinically significant. None of the hematologic abnormalities shifted from "not clinically significant" to "clinically significant". Shifts from not clinically significant at baseline to clinically significant at Month 3 occurred in 4 parameters: ALT (2%), total bilirubin (1%), and potassium (5%) in the PHOTOFRIN group and creatinine (4%) in the OM Only group. Clinical laboratory evaluations were not performed in the 2 supportive studies.

D. Adequacy of Safety Testing

Overall, safety testing appears to have been adequate. The collection and analyses of safety data in the 3 trials were relatively straightforward. Variations in the frequencies of the most common adverse events between the 3 trials that were noted above may have been due to the relatively small numbers of patients. They may have also been influenced by local variations in care among the centers. It should be noted that one center (Dr. Overholt's Thompson Cancer Survival Center in Knoxville, TN) contributed about 69% of the total safety population. Patients' experiences at that one center may have influenced the relative frequencies of some adverse events. For example, photosensitivity reactions were reported in 28% of patients in the TCSC studies and in 68% of patients in the PHO BAR 01 study.

E. Summary of Critical Safety Findings and Limitations of Data

The main safety issue with photodynamic therapy is the development of esophageal strictures. The incidence of strictures may have decreased with improvements of the light delivery system, but the incidence of 36% in the PHO BAR 01 study is still very high. The number of dilations for strictures is also impressive: 35% of patients with strictures had to have only 1 to 2 dilations; 29% of patients, 3 to 5 dilations; 22% of patients, 6 to 10 dilations; and 15%, more than 10 dilations. The single patient in the OM Only group with a stricture needed only one dilation.

The main limitation of the safety data is the relatively small number of patients in the three studies, and the short (12-month) follow-up in the supportive studies.

VIII. Dosing, Regimen, and Administration Issues

Dosing of PHOTOFRIN has been standard for in all the studies, and does not need to be modified. Light administration underwent considerable development during the decade during which the three studies were conducted.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Approximately 15% of all study patients were female (Reviewer's Table below). This 6:1 male/female ratio is consistent with the published data on the gender ratios in esophageal adenocarcinoma and in BE. Neither efficacy nor safety gender analyses were carried out by the sponsor. The statistical reviewer carried out complete response (CR1 + CR2 + CR3) analysis by gender in the PHO BAR 01 trial. There appeared to be no gender differences. About 70% (82/117) of males and about 81% (17/21) of females had complete responses in the PHOTOFRIN PDT + OM group. About 30% (18/59) of males and about 36% (4/11) of females had complete responses in the OM Only group.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

1. Age. A preliminary analysis by the sponsor suggested an age effect in the complete response (CR1 + CR2 + CR3) rate in the PHOTOFRIN + OM group, as shown below.

Age	PHOTOFRIN + OM	OM Only
< 65 years	51/61 (84%)	6/25 (24%)
> 65 years	48/77 (62%)	16/45 (36%)
	p = 0.0219	

However, a more detailed analysis failed to confirm such an age effect (January 28, 2003 submission, p.7). When the patients were grouped into a 30- to 69-year old group and a 70- to 89-year old group (which showed a 10% response difference), the differences between groups were found not to be statistically significant ($p = 0.1584$, Fisher's Exact test). Baseline demographic and other characteristics, PHOTOFRIN and PDT exposure, GERD symptom profile, stricture incidence, and duration of response did not reveal any differences between the groups.

Reviewer's Table. CR3 or Better Responses by Age Category

Age (years)	PHOTOFRIN PDT + OM N = 138 (ITT population) Responders/total (%)	OM Only N = 70 (ITT population) Responders/total (%)
30 - 49	12/14 (85.7%)	2/8 (25%)
50 - 59	19/23 (82.6%)	1/9 (11.1)
60 - 69	34/43 (79.1%)	9/18 (50%)
70 - 79	34/48 (70.8%)	12/30 (40%)
80 - 89	7/10 (70%)	3/5 (60%)

2. Race. White (Caucasian) race predominated overwhelmingly in the studies, as can be justified by the high incidence rates of both BE and esophageal adenocarcinoma in this race. Thus, no analyses by racial background are possible. As noted above in Variations in Special Populations, PHOTOFRIN has been studied in Japanese cancer patients, but because of different sampling times and small numbers of patients involved no conclusions could be drawn about variation in PHOTOFRIN pharmacokinetics between Caucasians and Japanese.

3. Ethnic backgrounds were not described in the study populations in this submission.

C. Evaluation of Pediatric Program

Axcan Scandipharm, Inc. is requesting a waiver for pediatric studies in children. The reason for this request is that PHOTOFRIN has obtained Orphan Drug Designation, in accordance with Title 21 CFR 314.55 (d) (vol.1, p.259).

D. Comments on Data Available or Needed in Other Populations

The sponsor has an OCPB Phase IV commitment (No. 2) under previous NDA 20-451 as follows:

“Conduct Phase IV studies to gather further pharmacokinetic (PK) data in patients with hepatic impairment and in patients who have received more than one course of therapy.”

As noted above, PHOTOFRIN is excreted in the form of metabolites (about 35%), primarily through bile/feces, and minimally through the urine (6%). Exclusion criteria in the pivotal trial specify hepatic or renal impairment. Patients with BE with high-grade dysplasia and with mild hepatic impairment may be candidates for PHOTOFRIN PDT, although the incidence of BE and esophageal adenocarcinoma appears not to be increased in alcohol abuse patients.

X. Conclusions and Recommendations

A. Conclusions

1. The results of the pivotal multi-center, partially blinded, controlled PHO BAR 01 trial with a minimum follow-up of 2 years demonstrated that PHOTOFRIN PDT plus omeprazole is an effective method of ablating HGD in Barrett's esophagus. PHOTOFRIN PDT plus omeprazole was compared to treatment with omeprazole alone, which was the active surveillance arm. Effectiveness of PHOTOFRIN PDT compared to esophagectomy is not known, since an esophagectomy arm was not included in the trial.
2. PHOTOFRIN PDT was effective in reducing the risk of adenocarcinoma of the esophagus in patients with HGD during the period of the follow-up.
3. Long-term effectiveness of PHOTOFRIN PDT in cancer risk reduction requires a longer follow-up, at least 5 years.

4. PHOTOFRIN PDT was relatively safe and well tolerated, since only very few patients left the trials because of treatment-related adverse effects.
5. Benefit/risk of PHOTOFRIN PDT is difficult to evaluate because its long-term effectiveness in cancer risk reduction is not known.
6. A surveillance program (Omeprazole Only arm of the study) was not an effective option for most patients, who left this arm of the study because they progressed to cancer or because they chose active treatment for high-grade dysplasia.
7. Prior omeprazole intake of at least 3 months was associated with Complete Response, suggesting that patients with HGD should be treated with omeprazole before undergoing PHOTOFRIN PDT.
8. The diagnosis of HGD should be confirmed by a reference laboratory with special expertise in Barrett's esophagus, since about one-half of patients referred to the study with the diagnosis of HGD did not have this diagnosis confirmed.
9. Complete Response consisting of complete ablation of HGD and re-epithelialization by normal squamous cell epithelium was associated with lower probability of progression to cancer than failure to achieve a Complete Response.
10. PDT with PHOTOFRIN should be administered by physicians trained in the endoscopic use of PDT with PHOTOFRIN, and only in those facilities properly equipped for the procedure.

B. Recommendations

1. Photodynamic therapy with PHOTOFRIN® should be approved for the indication of "... ablation of high-grade dysplasia in Barrett's esophagus patients who do not undergo esophagectomy." The sponsor's request for the indication "...the ablation of HGD in BE among patients who refuse esophagectomy and who are in overall good health." is also acceptable to this reviewer.
2. The Proposed labeling Text should be amended as follows:
 - Under **CLINICAL STUDIES**, reasons for failure to enroll patients into the pivotal trial should be stated
 - Under **CLINICAL STUDIES**, results of secondary efficacy endpoints should be presented in greater detail, such as with the Kaplan-Meier plot of time to progression to cancer
 - Under **CLINICAL STUDIES**, cancer risk reduction within the follow-up period, but not beyond it, should be stated
 - Under **CLINICAL STUDIES**, the association between failure to achieve a complete response and progression to cancer should be stated
 - Under **CLINICAL STUDIES**, the association between low quality of complete response (CR3) and progression to cancer should be stated
 - Under **CLINICAL STUDIES**, association of prior omeprazole treatment and complete response should be stated
 - Under **CLINICAL STUDIES**, description of supporting studies should be abbreviated to data that support the conclusions of the pivotal trial
 - Under **INDICATIONS AND USAGE**, indication for use in ablation of high-grade dysplasia should be condensed as noted in the Executive Summary

- Under **WARNINGS**, continued endoscopic surveillance after PHOTOFRIN PDT should be recommended
- Under **PRECAUTIONS**, section subtitle Esophageal Strictures should be retained, strictures defined as endoscopically detected esophageal narrowing requiring dilation, and a table on the frequency of dilations should be inserted
- Under **ADVERSE REACTIONS**, adverse event data should be combined for the three trials as they are presented in Table 9 of the label, and SAEs and deaths should be described
- Under **DOSAGE AND ADMINISTRATION**, description of light delivery devices should be reviewed by the CDRH reviewer.

cc.:

NDA 21-525

HFD-180/Division File

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A Secondary Review by Dr. Hugo E. Gallo-Torres, the
GI Medical Team Leader, will be completed in
the near future. This review includes multidisciplinary considerations, and
recommendations for regulatory action from all disciplines.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS**

MEDICAL OFFICER'S REVIEW

NDA: 21-525

Related NDAs/INDs/PMA: NDA 20-451; IND 61,011; IND 42,313; IND 25,064; PMA P990021; PMA P940010

Sponsor: Axcan Scandipharm Inc.

Drug name: Photofrin (porfimer sodium)

Pharmacological category: Photosensitizing agent, polyporphyrin oligomer

Indication: Ablation of high-grade dysplasia in Barrett's esophagus

Route of administration: Intravenous injection

Date submitted: May 31, 2002

Date assigned: July 2, 2002

Date review completed: November 14, 2002

Date filed into DFS: November 14, 2002

Medical reviewer: Edvardas Kaminskas, M.D.

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CLINICAL REVIEW

Executive Summary Section

Clinical Review for NDA 21-525

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Approval is sought for PHOTOFRIN, a photosensitizing agent, and for a special laser light delivery system to be used in photodynamic therapy (PDT) for ablation of high-grade dysplasia in Barrett's Esophagus patients who are not candidates for esophagectomy. Barrett's Esophagus is an uncommon complication of patients with gastroesophageal reflux disease, and consists of replacement of normal squamous cell epithelium by metaplastic, intestinal-type epithelium. High-grade dysplasia is a rare complication in Barrett's Esophagus, in which metaplastic epithelium is replaced by highly dysplastic epithelium.

High-grade dysplasia is a pre-malignant lesion; approximately 25% to 30% of patients with high-grade dysplasia will develop adenocarcinoma of the esophagus, a highly lethal malignancy with a 5-year survival of 11%. Patients with high-grade dysplasia are mainly managed by esophageal resection, or by intensive endoscopic surveillance with esophagectomy reserved only for those who develop adenocarcinoma. A third approach is mucosal ablation of high-grade dysplasia, with re-epithelialization of the treated area by normal squamous cell epithelium. The feasibility of this approach has been demonstrated in uncontrolled trials.

The present submission contains the preliminary results of a controlled trial, in which high-grade dysplasia patients were randomized to be treated by PHOTOFRIN PDT plus oral omeprazole or by oral omeprazole alone (control arm). The benefit of PHOTOFRIN PDT, as shown in the 6-month follow-up data from the controlled trial (all the patients had 6 months of follow-up; the median length of follow-up was 12 months), is a high complete response rate (72% of treated patients compared to 31% of control patients). Complete response is defined as ablation of high-grade dysplasia and re-epithelialization of the treated area by normal squamous cell epithelium with or without areas of metaplasia, low grade dysplasia, or indeterminate dysplasia. Because of the short follow-up, duration of this response is not certain. Endpoints, such as time to treatment failure, time to progression to cancer, and survival time, could not be estimated reliably. The major risk of PHOTOFRIN PDT is formation of esophageal strictures that require repeated dilations, probably because photodynamic damage to the esophagus is deep and healing results in scarring. Strictures requiring dilations occur in about 35% of patients. Other side-effects are less debilitating. An acute PDT syndrome with chest pain, fever, odynophagia, dysphagia occurs in about one-third of patients. Skin photosensitivity is common, but is self-limited. If the complete response to therapy is durable, then the benefits of therapy appear to outweigh risks. The results of two uncontrolled trials are submitted in support of the pivotal controlled trial.

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The sponsor has submitted the final report of this trial, which contains data on 24 months of follow-up. These data may clarify both efficacy and safety issues raised by the 6 month follow-up data.

PHOTOFRIN is approvable for this indication. The Conclusions and Recommendations section (Section X) contains specific requirements for approval.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

1. The sponsor has made a commitment to a 5-year follow up of the pivotal study. This study, entitled PHO BAR 02, has been started.
2. The sponsor has made a commitment to perform a pharmacokinetic study in patients with hepatic impairment (IX. Section D).

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The drug under review is PHOTOFRIN (porfimer sodium) for Injection, which is a photosensitizing agent used in conjunction with a laser light delivery system. PHOTOFRIN is approved for treatment of patients with completely obstructing esophageal cancer, with obstructing endobronchial non-small cell lung cancer, and with micro-invasive endobronchial non-small cell lung cancer. After intravenous injection, PHOTOFRIN, which is a polyporphyrin oligomer derived from hemoglobin, is widely distributed throughout tissues, and is preferentially concentrated in tumors, reticuloendothelial system and skin. A laser light at 630 nm wavelength applied to a tumor results in necrosis due to free radical reactions and to anoxia resulting from occlusion of blood vessels.

The indication of the present submission is ablation of high-grade dysplasia in patients with Barrett's Esophagus who are not candidates for esophagectomy. Barrett's Esophagus is a rare complication of a very common disorder, gastroesophageal reflux disease. High-grade dysplasia is a rare complication of Barrett's Esophagus, and is a pre-malignant lesion. About 25% to 30% of high-grade dysplasia patients develop adenocarcinoma, which carries a very poor prognosis. There is no agreement on the best treatment for high-grade dysplasia. Some experts advise esophagectomy, others, intensive surveillance, reserving esophagectomy for patients who develop adenocarcinoma. A third option is mucosal ablation therapy in which the dysplastic epithelium is destroyed and, with suppression of acid production during healing, squamous epithelium regrows. This is an out-patient procedure, it is minimally invasive, and it may eliminate the need for major surgery, especially in elderly poor-risk patients.

Supporting the indication are the results of three trials:

- PHO BAR 01, a multicenter, partially blinded, randomized, controlled trial in which 208 patients with high-grade dysplasia were enrolled; 138 were randomized to be treated with PHOTOFRIN photodynamic therapy (PDT) plus omeprazole, and 70 were randomized to be treated with omeprazole alone. This is the pivotal trial.

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- TCSC 93-07, a single center, open-label, investigator-sponsored uncontrolled Phase II study, in which 99 patients were treated with different light doses and light delivery systems. Of these patients, 44 patients had high-grade dysplasia.
- TCSC 96-01, a single center, randomized study of the effect of steroid therapy on the incidence of esophageal stricture in patients treated with PDT, in which 87 patients were enrolled, 42 of whom had high-grade dysplasia.

The data of TCSC 93-07 and TCSC 96-01 trials were obtained by the sponsor, and the efficacy results were analyzed in high-grade dysplasia patients by the same methodology as in PHO BAR 01 trial. The entire patient population treated with PHOTOFRIN PDT was used for safety analysis.

Patients in these studies were predominantly male (85%), white (99%), and former or current smokers (71%). The mean age was about 66 years (range, 38 to 88 years). The patient population enrolled in these studies is representative of the general population with Barrett's Esophagus and high-grade dysplasia. Characteristics of Barrett's Esophagus at baseline, including duration of Barrett's esophagus, duration of high-grade dysplasia, endoscopic length of Barrett's esophagus, extent of high-grade dysplasia, presence of hiatal hernia, nodules, ulcers and strictures, and prior treatment, were similar in the group randomized to PHOTOFRIN PDT and in the group randomized to OM Only treatment.

Histopathologic diagnoses were performed at a central pathology laboratory by three pathologists, who were blinded to patients' identity, treatment arm assignment, study phase, or clinical trial site. A sub-study of rater agreement on histological diagnosis showed a high percent of intra-rater and inter-rater agreement. These results add to the quality of the submitted data.

Treatment in the PHOTOFRIN PDT group consisted of an intravenous injection of 2 mg/kg of PHOTOFRIN (this is the standard dose for all indications), followed by laser light administration 40-50 hours later. A second light treatment was administered 2 days later, both treatments constituting one course. Up to a total of three courses could be given; courses had to be separated by at least 3 months. Patients in the PHOTOFRIN PDT group and in the OM Only group were treated with omeprazole 20 mg orally twice a day.

B. Efficacy

The primary efficacy endpoint was complete ablation of high grade dysplasia and re-growth of normal squamous cell epithelium, or of normal epithelium with some areas of Barrett's metaplasia, or of normal epithelium with some areas of low-grade dysplasia, metaplasia, or indefinite for dysplasia. In the PHO BAR 01 trial, 72% of PHOTOFRIN PDT patients had a complete response as defined above; only 31% of Omeprazole Only patients had a complete response (the difference between treatment arms was significant with $p < 0.0001$). In the two supporting uncontrolled trials 88% of patients had a complete response.

The secondary efficacy endpoints addressed the quality of response (re-growth of normal epithelium versus re-growth of normal epithelium with some areas of metaplasia or dysplasia),

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the duration of the response, the time to treatment failure, the time to progression to cancer, and survival time. The quality of response was significantly better ($p < 0.0001$) in the PHOTOFRIN PDT patients than in Omeprazole Only patients. However, the other secondary efficacy endpoints could not be evaluated, because at 12 months of follow-up 50% of patients had not reached any of the above endpoints (the exception being that duration of response in the Omeprazole Only group was estimated at 98 days). Secondary endpoints could not be evaluated in the supporting trials either.

These secondary endpoints are important, because ablation of high-grade dysplasia is only important as a means of preventing the development of adenocarcinoma. The sponsor has submitted 24 month-follow-up data, which will be reviewed. It should be pointed out that the Agency had previously expressed concern that the results of therapy should reflect an improvement in the long-term clinical outcome and that 6 months of follow-up is too short and therefore inadequate to demonstrate such an improvement.

The results of the PHO BAR 01 controlled trial are important in that mucosal ablation using PHOTOFRIN PDT was directly compared to surveillance. There was no esophagectomy arm in the study, therefore the three approaches to the management of high-grade dysplasia could not be directly compared.

The results of the trials could be presented in a manner that is more useful to the clinician and the patient. The important clinical issue is not only how effective PHOTOFRIN PDT is in ablating high-grade dysplasia but how effective it is in prevention of adenocarcinoma. Therefore, the available data in the follow-up period should be presented in terms of probabilities of developing adenocarcinoma at various time intervals after treatment.

C. Safety

Adequacy of safety testing. A total of 318 patients were treated with PHOTOFRIN PDT in the three studies. The median follow-up was 12 months. The patients were followed at least every 3 months, and esphagoscopy data indicate a high degree of patient compliance with the outlined follow-up surveillance program.

Serious side-effects. The side-effect profile of the control group with the same diagnosis provides a very useful benchmark for evaluation of side-effects of PHOTOFRIN PDT therapy. There appears to be an acute PDT syndrome consisting of chest pain, odynophagia, dysphagia, abdominal pain, fever, nausea and vomiting that afflicted about a third of the PDT patients and that was absent in the control group. These acute side-effects abated within about a week, except for dysphagia, which remitted in about 4 weeks. Following the injection of PHOTOFRIN all the patients became photosensitive, and the photosensitivity of the skin continued for at least 30 days and sometimes longer. Patients were given elaborate and detailed instructions on avoiding bright light; nevertheless, about one-half to two-thirds of patients had photosensitivity reactions, which were severe in about 10% of patients. All photosensitivity reactions resolved with time.

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The main safety issue with photodynamic therapy is the development of esophageal strictures during the healing process. Even in the pivotal trial, with latest light delivery systems, strictures developed in 35% of patients. (It should be noted that a stricture was defined as esophageal narrowing that required dilation.) Severity of strictures was graded as mild (in 44% of patients), moderate (in 43% of patients), or severe (in 12% of patients). Treatment of strictures consisted of 1 - 2 dilations in 35% of patients with strictures, of 3 - 5 dilations in 29% of patients, of 6 - 10 dilations in 21% of patients, and of more than 10 dilations, in 15% of patients. There was only one stricture in the OM Only group of patients and that required only one dilation.

Common side-effects. Almost all (98%) of patients in the PHOTOFRIN PDT group reported adverse events, as compared to 68% in the Omeprazole Only group. Furthermore, the total number of adverse events was more than three times as high in the PHOTOFRIN PDT group as in omeprazole only group (1,245 vs. 206 events). In the PHOTOFRIN PDT group the most common side effects were related to the gastrointestinal system, body as a whole (chest pain, fever, pain), photosensitivity reactions, and dehydration. There no predominant side effects in the OM Only group; the most common were related to the gastrointestinal system, body as a whole, nervous system, and metabolic and nutritional system.

Drug-drug interactions. The sponsor raised possibilities of interactions of PHOTOFRIN with other photosensitizing drugs and with drugs degraded by cytochrome P450 enzymes, but these possible interactions have not been studied. There is no basis for suspecting an interaction with omeprazole. In terms of other drugs increasing or decreasing photosensitivity, it is important to remember that the photosensitivity after PHOTOFRIN injection is massive and dwarfs the effects of any other drugs increasing or decreasing photosensistivity.

Exposure in trials versus probable marketing exposure. The PHOTOFRIN PDT protocols have been applied consistently, and no changes are expected after marketing.

Effect of trial exclusions on safety profile vs. expected marketed population. The main reason for excluding patients from the pivotal trial is the absence of high-grade dysplasia (86% of patients excluded). Since these patients were referred with this diagnosis for inclusion in the trial, the possiblity is very real that patients without high-grade dysplasia may undergo PHOTOFRIN PDT therapy.

Recommended warnings. Acute PDT symptomatology as described above, photosensitivity precautions, and risk of strictures.

Relationship of safety to other drugs available for indication. No other drugs are available for this indication.

Unresolved safety issues. Stricture formation, which may never be resolved, because it goes hand in hand with the treatment.

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D. Dosing

The same dosing of PHOTOFRIN (2 mg/kg intravenously) has been used for over 10 years in over 3,000 applications. The drug in PDT is not the active therapeutic agent, the light is. The drug is given in a sufficient dose to achieve photosensitivity.

E. Special Populations

Gender differences. None found in pharmacology, safety, or effectiveness.

Ethnic and racial studies. Small-scale Japanese studies have been reported, but differences in trial design, dosing and efficacy endpoints do not permit any conclusions to be drawn.

Elderly. PHOTOFRIN PDT appears to be more effective in patients less than 65 years of age than in patients more than 65 years of age ($p = 0.0219$).

Status of pediatric studies and pediatric plan. A waiver for pediatric studies in children is requested on the basis that PHOTOFRIN has Orphan Drug Designation.

Pregnancy use information. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. PHOTOFRIN should be used during pregnancy only if the potential benefit justifies the potential risk to fetus. Animal toxicity studies showed increased resorptions, decreased litter size, delayed ossification, and reduced fetal weight, as tested in rats and rabbits.

Nursing mothers. It is not known whether PHOTOFRIN is excreted in human milk. Women receiving PHOTOFRIN must not breast feed, because of potential for serious reactions in nursing infants.

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I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

PHOTOFRIN® (porfimer sodium) for injection is a photosensitizing agent that is approved under NDA 20-451

- for palliation of patients with completely obstructing esophageal cancer,
- for palliation of patients with obstructing endobronchial non-small cell lung cancer, and
- for treatment of patients with micro-invasive endobronchial non-small cell lung cancer for whom surgery and radiotherapy are not indicated.

The sponsor's proposed indication is **ablation of high-grade dysplasia in patients with Barrett's Esophagus who are not candidates for esophagectomy.**

PHOTOFRIN is approved as a drug-device combination for photodynamic therapy (PDT) and is used with a laser light passed through endoscopically placed fiber optics tipped with cylindrical diffusers and with inflatable centering balloons of various lengths (3, 5 and 7 cm). PHOTOFRIN is infused intravenously at a dose of 2 mg/kg body weight. Light activation, using red light at 630 nm, is performed 40-50 hours after PHOTOFRIN injection.

Patients who may be candidates for PHOTOFRIN therapy will be 50 years or older, since both dysplasia in Barrett's Esophagus (BE), a pre-malignant condition, and adenocarcinoma of the esophagus increase with age. Sponsor's Table 3.7-1 shows the incidence of esophageal adenocarcinoma in BE patients of various ages. Most of the candidates for PHOTOFRIN therapy will be males, since BE is 2 to 5 times more common in men than in women, and since most of the patients (about 86%) with esophageal carcinoma are male (Cameron *in* Tilanus & Attwood, pp. 281 – 290).

Sponsor's Table 3.7-1: Adenocarcinoma Incidence with Age in BE

Age range	Incidence/100,000
30-39	0.01
40-49	0.06
50-59	1.8
60-69	3
70-79	3.9

B. State of Armamentarium (Treatment Options) for Indication

Gastroesophageal reflux disease (GERD), defined as abnormal reflux of gastric contents into the esophagus and resulting in chronic symptoms and, in some cases, in mucosal damage, is very

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common in the adult population. Prevalence estimates are as high as 10% to 20% of the population in the U.S. (Shaheen & Ransohoff, Cameron *in* Tilanus & Attwood, p. 281). Barrett's Esophagus (BE) is a complication that develops in a minority (about 6% - 12%) of patients with GERD, or in about 1% of persons over the age of 60, or in about 0.4% of persons in the general population including all ages (Cameron, op.cit.).

BE is clearly associated with severe and long-lasting gastroesophageal reflux, the presence of a hiatal hernia, a lower basal esophageal sphincter pressure, and abnormal epithelial repair resulting in replacement of squamous by columnar epithelium. The diagnosis is established if the squamocolumnar junction is displaced proximal to the gastroesophageal junction, and the normal squamous epithelium of the esophagus is replaced by a specialized or intestinal-type columnar lining containing acid mucin-containing goblet cells (Falk, Shaheen & Ransohoff). The origin of the columnar cells composing the Barrett's esophagus is unclear; they are not gastric cells, since they differ histologically from cells of the gastric cardia.

The importance of BE and of GERD is their association with the development of adenocarcinoma of the esophagus, a highly lethal disease with a 5-year survival of 11% in the early 1990s. Adenocarcinoma of the esophagus is, for unknown reasons, increasing in incidence in the United States and other countries. Population-based cohort studies suggest a 300% to 500% increase throughout the last 30 to 40 years. The pathogenesis of adenocarcinoma of the esophagus is thought to progress through several stages:

- Severe, frequent and long-lasting reflux leads to a metaplastic change from squamous to intestinal-type columnar lining (i.e. BE). This process involves the destruction of the squamous mucosa as a result of acid reflux and subsequent re-epithelialization. The specialized columnar epithelium progresses to:
 - low-grade dysplasia, then to
 - high-grade dysplasia, then to
 - adenocarcinoma.

A number of approaches have been developed for prevention of adenocarcinoma; however, at the present time there is no consensus on which one is best. Below are the options under consideration.

- Screening patients for BE. The subjects for endoscopic screening would be those at highest risk for BE: white men, 50 years of age and older, with long-standing reflux symptoms. No clinical trials have been carried out to support such a strategy. Because the number of Americans with reflux symptoms is so high and because the incidence of esophageal carcinoma is so low, by necessity the absolute risk to the average person with reflux is low. Shaheen & Ransohoff (JAMA 2000) calculated that there are about 10 million individuals in the U.S. who are older than 50 years and who experience reflux weekly. Of these 10 million individuals, approximately 6500 a year will develop esophageal adenocarcinoma. Thus, the cancer risk to any given older individual with reflux is 0.00065 per year, an extraordinarily low figure.

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If BE is diagnosed, symptoms can be relieved by proton pump inhibitors and esophagitis can be healed, but intestinal metaplasia is not reversed. Moreover, the vast majority of BE patients never develop cancer; most recent studies suggest that the annual incidence of adenocarcinoma in BE patients is about 0.5% or less (Shaheen & Ransohoff; Falk).

Furthermore, approximately 94% to 98% of adenocarcinomas are diagnosed in patients without a prior diagnosis of Barrett's esophagus. These findings may be explained in part by the absence of reflux symptoms in an estimated 40% of patients with BE. In 5 series of patients with adenocarcinoma and BE found simultaneously, a history of preceding reflux symptoms was obtained in 52%, 54%, 59%, 61%, 62%, and 65% of cases (Cameron, op. cit.). Nevertheless, the only hope for improved survival of patients with esophageal carcinoma is detection of cancer at an early and potentially curable stage.

- Surveillance of BE patients to detect cancer at an early and potentially curable stage. Several retrospective studies clearly suggest that BE patients in whom adenocarcinoma was detected in a surveillance program had dramatically improved 5-year survival compared to similar patients not undergoing routine endoscopic surveillance. A recent decision-analysis study of the optimal surveillance strategy for BE with an endpoint of esophagectomy for high-grade dysplasia found that surveillance every 5 years was the most effective strategy to increase both length and quality of life (Provenzale et al.). The aim of surveillance is the detection of dysplasia. Surveillance guidelines recommend obtaining systematic 4-quadrant biopsy specimens at 2-cm intervals along the entire length of BE. An even more comprehensive "Seattle protocol" specifies jumbo forceps and biopsies at 1-cm intervals. Results from surveillance programs have shown that dysplasia and superficial adenocarcinoma may be extraordinarily focal. In one study (Reid BJ et al.) among 45 patients with high-grade dysplasia who eventually developed cancer, 82% had cancer in a single 1-cm segment and 69% had cancer in a single biopsy specimen. Furthermore, only 39% of patients with cancer diagnosed by endoscopic biopsy had cancer found at surgery. Surveillance every 2-3 years is recommended as adequate in patients without dysplasia, every year with low-grade dysplasia, and every 3 months in patients with high-grade dysplasia if esophagectomy is not performed (American College of Gastroenterology Guidelines for the Diagnosis and Surveillance of Barrett Esophagus, Am J Gastroenterol 1998; 93:1028-32). These intervals are arbitrary and have never been subject to a clinical trial. Esophagectomy is recommended for high-grade dysplasia by some authors, and continuous rigorous surveillance by others. Still others argue that because most patients with BE will not die from esophageal cancer, endoscopic surveillance is not warranted until substantiated by prospective studies (Van der Burgh A et al.; MacDonald CE et al.). A randomized controlled trial of surveillance vs. no surveillance in BE has not been performed.
- Management of low-grade dysplasia. The natural history of low-grade dysplasia is poorly understood. Results of recent studies suggest that approximately 10% - 28% of low-grade dysplasia patients go on to develop high-grade dysplasia or adenocarcinoma, about 60% - 65% of patients show a regression, and the remainder continue to have low-grade dysplasia. Continued surveillance is recommended by the American College of Gastroenterology.

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- Management of high-grade dysplasia. Patients with high-grade dysplasia demonstrate a risk of subsequent adenocarcinoma exceeding 25%. Additionally, because endoscopic biopsies of BE are taken at random locations, sampling error in individuals with high-grade dysplasia is great. When those with high-grade dysplasia undergo resection, up to 50% of the resected specimens demonstrate previously unrecognized adenocarcinoma (cited in Shaheen & Ransohoff). Recent studies report development of cancer in 16% - 59% of high-grade dysplasia patients followed with endoscopic surveillance for 3 – 7 years (Buttar NA et al.; Reid BJ et al.; Schnell TG et al.). What are the options offered to the patient with BE and high-grade dysplasia?
 - Esophageal resection
 - Intensive endoscopic surveillance, with esophagectomy reserved only for those who develop adenocarcinoma
 - Mucosal ablation therapy to areas of Barrett's esophagus, including
 - Thermal
 - Multipolar electrocoagulation
 - Heater probe
 - Argon plasma coagulator
 - Nd:YAG laser
 - Argon laser
 - KTP (potassium titanyl phosphate) laser
 - Photodynamic therapy
 - 5-delta-amino-levulinic acid
 - Porfimer sodium (the drug being reviewed in NDA 20-525)
 - Hematoporphyrin
 - Endoscopic mucosal resection

The rationale of mucosal ablation therapy is that the metaplastic epithelium is destroyed and, with vigorous suppression of acid production during healing, squamous cell epithelium regrows. Ablation therapy has tremendous appeal to both patients and physicians. It is minimally invasive, "high-tech", and may eliminate the need for major surgery, especially in elderly poor-risk patients. However, several difficult issues need to be kept in mind.

- 1) The reversion to squamous epithelium may be incomplete, leaving islands of Barrett mucosa in the treated area.
- 2) Barrett mucosa may underlie what appears to be normal squamous epithelium; there have been reports of adenocarcinoma developing beneath squamous epithelium. The risk of cancer in areas of Barrett's esophagus treated with ablative therapy is not defined.
- 3) Techniques are not standardized and esophageal movement makes accurate and complete targeting difficult.
- 4) Risks, including strictures, perforation, and incurable cancer developing in otherwise curable patients.
- 5) Endoscopic surveillance is still warranted in these patients, but previous landmarks are now obscured, making targeting of biopsies problematic.
- 6) Persistent biomarker abnormalities have been described in the new squamous epithelium that replaced high-grade dysplasia.

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Experience with various types of lasers has been documented, but lasers are no longer widely available. Multipolar electrocoagulation has been shown to result in histologic reversal of BE in about 80% of patients, as has argon plasma coagulation therapy. Both techniques have significant adverse events, including chest pain, odynophagia, fever, pleural effusion, perforations, strictures, and pneumomediastinum.

Photodynamic therapy is based on the systemic administration of certain photosensitizing agents that are retained with some selectivity in rapidly proliferating and malignant tissues. When the target tissues are exposed to appropriate wavelength laser light, oxygen radicals are generated causing cellular destruction. The choice of photosensitizer is crucial to achieve the depth of necrosis that is required. Oral 5-aminolevulinic acid used to generate protoporphyrin IX will produce necrosis to a depth of 2 mm. PHOTOFRIN (porfimer sodium) or any derivative of di-hematoporphyrin ester/ether will produce necrosis up to a depth of 6 mm. Of the photosensitizing agents, only PHOTOFRIN is available in the United States for use in photodynamic therapy. The main complication of this therapy is the development of strictures.

Endoscopic mucosal resection has been used in BE with adenocarcinoma or high-grade dysplasia. It is most effective in low-risk lesions (diameter <2cm, limited to mucosa, well or moderately differentiated histology); less in high-risk lesions (diameter >2cm, extending into submucosa or ulcerated, poorly differentiated histology). During the 1-year follow-up 17% of the low-risk group and 14% of the high-risk group developed high-grade dysplasia or cancer (Ell C et al. 221). The applicability of this technique to invisible lesions or multifocal lesions is questionable at present.

C. Important Milestones in Product Development

PHOTOFIN for Injection has been studied under IND 42,313 for ablation of high-grade dysplasia in Barrett's esophagus and superficial esophageal cancer (studies TCSC 93-07 and TCSC 96-01 reviewed in this submission). The PHO BAR 01 study protocol was submitted to the Division of Oncology Drug Products (IND 25,064) on November 13, 1997 by QuadraLogics Technologies (QLT) and the study was initiated in January, 1998. QLT conducted the study until June, 2000, when Axcan Pharma acquired the product and took over clinical monitoring of the product. On June 21, 2000 the Agency requested that this study be re-filed with the Division of Gastrointestinal and Coagulation Drug Products, which the new sponsor (Axcan Scandipharm, Inc.) did on September 26, 2000 (IND 61,011).

The Agency clearly enunciated key elements to be provided in the submission, as described below.

In an Advice Letter dated January 25, 2001 after the completion of the review of IND 61,011 describing the pivotal study, the Agency specified that:

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- To qualify as a pivotal trial the primary response variable must reflect an improvement in the long-term clinical outcome. Partial histopathological responses to photodynamic therapy (PDT) might not reflect clinically meaningful long-term outcomes. In addition, the current standard of care which includes esophagectomy in individuals who are surgical candidates should be included in the definition of an appropriate population for whom PDT therapy might be indicated.
- The sponsor should provide an analysis of clinical outcomes of individuals associated with treatment failure in conjunction with the outcomes associated with treatment success. Such outcomes should be compared to those associated with other modes of treatment such as esophagectomy.
- The sponsor should provide information about the timing and severity of strictures associated with PDT.
- The sponsor should clearly define the treatment of nodules before therapy. For example, the protocol should provide details how carcinoma underlying nodules will be excluded prior to PDT.
- The sponsor should provide an up-to-date model informed consent form to the Agency.

A teleconference with the sponsor on March 5, 2001 clarified the above concerns in greater detail, namely that:

- 6 months follow-up may be inadequate to assess the impact of the treatment. A follow-up time frame of 5 years or more was recommended, but follow-up of at least 2 to 3 years would be acceptable
- The Agency is concerned that the use of histopathological effects for measuring clinical benefit might be a surrogate endpoint. The appropriateness of this endpoint is questionable considering the differences in the natural course of high-grade dysplasia from low-grade dysplasia in the occurrence of cancer. The measurement should be linked to a clinically meaningful outcome.
- The Agency is concerned that PDT might be a cosmetic effect of treatment rather than changing the course of disease. The Agency is most interested in assessing whether there is a long-term sustained response to therapy.

The sponsor stated that the response to therapy is sustained.

As related in the above communications, the importance of PDT with PHOTOFRIN is prevention of adenocarcinoma of the esophagus, and the trials must provide evidence that this is an effective and relatively safe therapy for this purpose.

C. Other Relevant Information

PHOTOFRIN for Injection was first approved in Canada. Reviewer's Table below describes the indications approved, the countries in which the indication was approved, and the date of approval. Following tables describe Rejections, and Submissions (adapted from Tables 3.2-1, 3.2-2, and 3.2-3, vol. 1, pp. 135-9). The indications have been abbreviated by the reviewer; their wording differs between countries.

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Reviewer's Table on Regulatory History in Other Countries - Approvals

Indication	Countries where approved and year of approval
Recurrent superficial papillary bladder cancer: second-line treatment for those who have failed standard intravesical therapy	Canada (1993)
Obstructing esophageal cancer	Canada (1995), The Netherlands (1994), France (1996), United Kingdom (1998), Finland (1999), Iceland (1999), Denmark (1999), Portugal (1999), Norway (1999), Luxembourg (1999), Ireland (2000), Austria (2000), Italy (2000), Sweden (2000), Belgium (2001), Greece (2001), Poland (2001)
Obstructing endobronchial non-small cell lung cancer	Canada (1999), The Netherlands (1994), France (1996), Germany (1997), United Kingdom (1998), Finland (1999), Iceland (1999), Denmark (1999), Portugal (1999), Norway (1999), Luxembourg (1999), Ireland (2000), Austria (2000), Italy (2000), Sweden (2000), Belgium (2001), Greece (2001), Poland (2001)
Superficial endobronchial non-small cell lung cancer in patients for whom surgery and radiotherapy are not indicated	Canada (1999), The Netherlands (1994), France (1996), Iceland (1999), Greece (2001)
In patients for whom curative therapy is impossible and there is no therapy except PDT: Early lung cancer (stage 0 and I) Superficial esophageal cancer Superficial gastric cancer Early cervical cancer and dysplasia	Japan (1994)

Reviewer's Table on Regulatory History in Other Countries - Rejections

Indication	Country where rejected
[]	[]

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Reviewer's Table on Regulatory History in Other Countries – Submissions neither Approved nor Rejected at the Time of this Submission

Indication	Country where submitted and date of submission
[]
[]

E. Important Issues with Pharmacologically Related Agents

PHOTOFRIN is the only photosensitizing agent approved for use in photodynamic therapy. The drug is innocuous until activated by light. Other photosensitizing agents share this property. The duration of photosensitivity varies by agent.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

PHOTOFRIN (porfimer sodium) for Injection is a complex mixture of porphyrin oligomers, porphyrin monomers, [] In the oligomers, porphyrin units are joined by ether [] and ester [] linkages. The active ingredient, porfimer sodium, consists of oligomeric species, ranging from dimers to octamers, the majority of which are dimers and trimers. []

The chemical complexity of the oligomeric mixture is further complicated by the dynamic aggregation/disaggregation exhibited by porphyrins in aqueous solution. These characteristics have precluded resolution of the oligomers present in PHOTOFRIN by conventional analytical methods. All fractions resulting from attempts to fractionate PHOTOFRIN by multiple gel chromatography or HPLC consisted of mixtures of oligomers. All such fractions were biologically active in a tumoricidal assay. Thus, single components of PHOTOFRIN cannot be isolated, and structure-function relationships cannot be determined for the complex components of PHOTOFRIN.

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Porfimer sodium bulk concentrate is manufactured by [] in []
[] which uses []
[] is prepared [] by [] which
obtains [] from []
[]

The molecular weight of the oligomeric components of porfimer sodium ranges from 1178 to 4659 daltons, depending on the number of porphyrin units per oligomer and the extent of dehydration occurring at hydroxyethyl end groups.

Porfimer sodium is manufactured as a dark red liquid or freeze-dried powder, which is soluble in water. It is formulated without excipients. Bulk concentrate of PHOTOFRIN is stable up to 3 months when stored frozen. Degradation of porfimer sodium in solution occurs primarily [] The degradation products are []
[]

Nonclinical pharmacology studies.

- Study TX-96005: A Pilot Study to Measure and Compare the Amount of Light from Black and White Balloon Catheters on the Dog Esophagus. No drug, light only. Mucosal light doses for white and black balloons measured.
- Study TX-96003: To assess the 'new' white balloon catheters in the dog esophagus.
- Study TX-97005: A study of light delivered by balloon catheters by two different manufacturers.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

There are no new pharmacokinetic or other Phase I studies conducted by the sponsor that are included in this supplemental NDA. A summary of previous studies was requested by the Division of Gastrointestinal and Coagulation Drug Products at the pre-NDA meeting held on June 1, 2001. Human pharmacokinetics has been studied in three clinical trials in cancer patients who were undergoing photodynamic therapy (PDT) and in one clinical trial in healthy volunteers (a post-marketing study that was submitted in an Annual Report to the NDA). The key results are shown below in sponsor's Table 3.5-1.

Absorption and Distribution

PHOTOFIN is given intravenously, and the absorption of PHOTOFRIN from the GI tract has never been studied. Animal studies have shown that after I.V. administration of ³H-hematoporphyrin derivative (an unpurified form of porfimer sodium), maximum radioactivity concentrations in the digestive tract were about 5% of those in the liver. Radioactivity concentrations in the digestive tract were greatest in the small intestine, followed by the gastric antrum, esophagus, gastric fundus, and colon. Three days after drug administration, radioactivity

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in the GI tract was present at 44% - 75% of that observed at 1 - 4 hours postdose [Original NDA, vol. 27, p. 1].

PHOTOFRIN maximum plasma concentrations (T_{max}) were seen between 5 min and 60 min after the start of the 3-5 min I.V. injection (Table 3.5-1). The cause of this variability is unknown. C_{max} values after injection of 2mg/kg PHOTOFRIN were in the range of 15 to 80 mg/mL.

The percentage of PHOTOFRIN-related porphyrins bound to serum proteins was about 90% and was independent of concentration. The predominant site for total porphyrin binding was to high density lipoproteins. Porphyrin monomers were primarily bound to albumin; dimers/oligomer fraction was associated with lipoproteins. The elimination of albumin-bound porphyrins was faster than of lipoprotein-bound porphyrins [Original NDA, vol. 32, p. 200].

Distribution of PHOTOFRIN into tissues occurs in the first 24 hours after dosing, and, once in tissues, the clearance of PHOTOFRIN is slow. Due to extensive distribution of PHOTOFRIN into tissues, serum concentrations may not be the best indicator of the concentration of PHOTOFRIN at the site of action, and may also be a poor indicator for the potential of adverse photosensitivity reactions.

Metabolism

Due to the complexity of the mixture of porphyrins in PHOTOFRIN, the metabolism of PHOTOFRIN has not been adequately studied. Results from animal studies suggest that the ester and ether linkages holding multimeric structures are likely to hydrolyzed to monomeric porphyrin units. The pathways of porphyrin and of heme degradation are well known. The catabolism of heme is carried out by heme oxygenase I and cytochrome P450, which cleave porphyrin into biliverdin. Biliverdin is oxidized to bilirubin, which is excreted by the liver into bile. Another important aspect of the breakdown of PHOTOFRIN is photo-bleaching. Reduction in photosensitivity after PHOTOFRIN injection appears to be best achieved through gradual exposure to low levels of light, which allow for the gradual breakdown of PHOTOFRIN within the skin. It is not known to what extent photo-bleaching contributes to the overall clearance of PHOTOFRIN; however, it is an important process for reducing risks associated with photosensitivity.

The sponsor states that direct competition between PHOTOFRIN and other drug products for cytochrome P450 enzymes is not expected to occur, and that genetic variation in cytochrome P450 isozymes within the human population is not expected to influence the metabolism of PHOTOFRIN [vol. 1, p. 167]. The sponsor does not support these statements with a rationale and/or evidence.

Excretion

PHOTOFRIN is excreted from the body mainly unchanged (61%); 35% is excreted in the form of metabolites [Original NDA, v. 27, p.8]. Elimination appears to be biphasic, with the first phase having a half-life of about 220 hours (9.17 days) and the second phase, a half-life of about

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870 hours (36.25 days). The first phase may represent tissue distribution, and the second phase, metabolism and excretion. PHOTOFRIN-related materials are excreted mainly through the bile/feces (59%), and only minimally through the urine (6%) when measured in samples collected over the first 192 hours (8 days) after dosing. These data are consistent with metabolism of PHOTOFRIN monomeric units into bilirubin.

Variations in Special Populations

Gender differences. In PHO PK 001 (Table 3.5-1), the pharmacokinetics of PHOTOFRIN in healthy male and female volunteers were compared after a single dose. A bi-exponential serum decay was observed, with a slow distribution phase and a very long elimination phase that started approximately 24 hours after injection and had a $T_{1/2}$ of 415 hours (17 days). Pharmacokinetic parameters were not affected by gender, except for T_{max} , which was longer in women [vol. 7, p. 112].

Race differences. PHOTOFRIN has been studied in Caucasian and Japanese cancer patients. However, due to the differences in the sampling times between studies, and small numbers of patients involved, it is difficult to make any conclusions about variation in PHOTOFRIN pharmacokinetics between these populations [Original NDA, vol. 31, p. 14].

Differences between patients and healthy volunteers. Three studies were conducted in patients, and one in healthy volunteers (Table 3.5-1). The mean C_{max} values from these studies ranged from 14.2 mcg/mL to 79.6 mcg/mL, and the mean $T_{1/2}$ ranged from 22 hours to 515 hours. The sponsor states that the two shorter estimates of PHOTOFRIN half-life are an artifact of reduced sampling in these studies. The long half-life in Report 1 (515 hours) in patients is consistent with that of PHO PK 001 study (415 hours) in normal volunteers.

Potential for drug-drug interactions. In the treatment of high-grade dysplasia PHOTOFRIN is given by single injection with repeat doses being at least 90 days apart. There have been no formal interaction studies of PHOTOFRIN and any other drugs. However, it is possible that concomitant use of other photosensitizing agents, such as tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide diuretics and griseofulvin could increase the photosensitivity reaction. In addition, there exists a theoretical possibility that there may be interactions with other drugs with significant biliary excretion, such as erythromycin, azithromycin and lansoprazole.

Compounds that quench active oxygen species or scavenge radicals, such as dimethylsulfoxide, beta-carotene, ethanol, formate and mannitol would be expected to decrease PDT effectiveness. Preclinical data suggest that tissue ischemia, allopurinol, calcium channel blockers and some prostaglandin synthesis inhibitors could interfere with PHOTOFRIN PDT. Drugs that decrease clotting, vasoconstriction or platelet aggregation, such as thromboxane A2 inhibitors, could decrease the efficacy of PDT. Glucocorticoids given before or concomitant with PDT may decrease the efficacy of the treatment.

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Omeprazole or other proton pump inhibitors are most likely to be used in conjunction with PDT in the treatment of high-grade dysplasia. PHOTOFRIN and omeprazole differ significantly in their absorption, distribution, metabolism and excretion properties, and pharmacokinetic interaction between these agents is not expected to be of clinical concern.

B. Pharmacodynamics

PHOTOFRIN is a photosensitizing agent that is used in photodynamic therapy for cancer. Tumor selectivity in treatment occurs through a combination of selective retention of PHOTOFRIN and selective delivery of light. By 40-50 hours after I.V. injection PHOTOFRIN has largely cleared from a variety of normal tissues, and has been retained by neoplastic tissues, skin, and organs of the reticuloendothelial system. At this time light activation is performed with red light at 630 nm wavelength. This is the longest wavelength that can adequately activate PHOTOFRIN and provide the greatest tissue penetration. Also, at this wavelength, the absorption of activating light by hemoglobin is minimal. The activation of PHOTOFRIN results in a generation of reactive oxygen species including singlet oxygen. Tumor necrosis occurs as a result of direct cytotoxicity to tumor cells, and also as a result of ischemia because of the sensitivity of tumor vasculature to PDT. Thrombogenic agents appear to be liberated locally and result in occlusion of tumor capillaries within 20 minutes of photoactivation.

The dose of PHOTOFRIN used in all studies (2 mg/kg of body weight, given I.V.) was determined empirically. This dose has been used for more than 3,000 treatments as the standard dose for all indications. The 40-50 hour interval between PHOTOFRIN injection and light treatment is also standard. This timing is based on the clearance of PHOTOFRIN from most tissues except skin and tumors. The total light dose delivered to tumor or dysplastic tissue is a key factor in efficacy and safety. The light doses recommended for use in high-grade dysplasia in BE are the lowest that achieved consistent efficacy and an acceptable safety profile.

The delivery of light is accomplished using laser light passed through endoscopically placed fiber optics tipped with cylindrical diffusers. Because the normal esophagus does not behave as a cylindrical tube, but tends to collapse when empty, an inflatable centering balloon was developed. The centering balloon helped achieve a PDT response that was circumferential and uniform. The balloon designs underwent progressive developments: from an optically transparent to "black-capped" with black ends and a 360 degree central transparent window and, finally, to "white-capped" balloons with a reflective inner coating at the ends allowing for a more uniform output from the balloon. The "black-capped" balloons had a non-linear light output across the window, resulting in a peak at the mid-point of the window. This peak in light intensity appeared to correspond to the position of stricture development in at least some patients.

IV. Description of Clinical Data and Sources

A. Overall Data

Sources of data used in the review are from a clinical trial program as described below.

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B. Tables Listing the Clinical Trials

Clinical trial no.	Clinical trial title
PHO BAR 01	A multicenter, partially blinded, randomized Phase III study of the efficacy and safety of photodynamic therapy (PDT) using PHOTOFRIN (porfimer sodium) for Injection for the ablation of high-grade dysplasia in Barrett's Esophagus.
TCSC 93-07	A Phase I/II Study of the Safety and Efficacy of Photodynamic Therapy (PDT) Utilizing PHOTOFRIN for Treatment of Dysplasia or Early Adenocarcinoma of the Esophagus in Barrett's Esophagus.
TCSC 96-01	Photodynamic Therapy of Dysplasia or Early Adenocarcinoma in Barrett's Esophagus: A Randomized Study of the Effect of Steroid Therapy on the Incidence of Esophageal Stricture

The sponsor conducted the pivotal trial PHO BAR 01. Trials TCSC 93-07 and 96-01 were individual investigator-sponsored trials (by Bergein F. Overholt, M.D., Thompson Cancer Survival Center, Knoxville, TN). PHO BAR 01 enrolled patients only with BE and high-grade dysplasia. TCSC 93-07 and 96-01 enrolled BE patients with high-grade dysplasia and with low-grade dysplasia, and patients with superficial adenocarcinoma of the esophagus. The sponsor obtained access to the data in the 93-07 and 96-01 trials, selected high-grade dysplasia patients, and re-analyzed the data according to PHO BAR 01 efficacy endpoints. All the 93-07 and 96-01 enrollees served as safety population.

C. Postmarketing Experience

The sponsor recognizes the importance of long-term follow-up data in the treatment of high-grade dysplasia in Barrett's esophagus. Axcan has committed to this follow-up with the new protocol, PHO BAR 02, submitted to IND 61,011 on November 26, 2001. The purpose of this study is to assess the 5-year efficacy of PDT with PHOTOFRIN plus omeprazole compared to omeprazole alone in the complete ablation of high-grade dysplasia in patients with BE, in conjunction with a strict endoscopic surveillance and biopsy protocol. PHO BAR 02 is a continuation of PHO BAR 01, the pivotal trial in this submission. Patients will remain in their assigned treatment group. The secondary efficacy analyses are the same as in PHO BAR 01. Patients are eligible for additional courses of PDT, up to a maximum of three (cumulative with those administered during the PHO BAR 01 study). Patients will be followed for a maximum of 60 months after their individual randomization date. PHO BAR 02 was initiated in December, 2001, and has an estimated duration of 3 years.

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D. Literature Review

The sponsor summarized the most important literature and provided copies of publications, including those derived from the supporting studies (vols. 9 – 12). The Reviewer retrieved the following articles and used them in describing various portions of this review. Some of the articles had not been published when the sponsor submitted this NDA.

Falk GW	Barrett's Esophagus. Gastroenterology 2002; 122:1569-1591
Shaheen N & Ransohoff DF	Gastroesophageal Reflux, Barrett Esophagus, and Esophageal Cancer. Scientific Review. Clinical Applications. JAMA 2002; 287:1972-81, 1982-6
Tilanus HW & Attwood SEA	Barrett's Esophagus. Kluwer Academic Publishers. 2001, pp. 159 – 280
Provenzale D, Schmitt C & Wong JB	Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. Am J Gastroenterol 1999;94:2043-53
Reid BJ, Blount PL, Feng Z & Levine DS	Optimizing endoscopic biopsy detection of early cancers in Barrett's high-grade dysplasia. Am J Gastroenterol 2000; 95:3089-96
Van der Burgh A, Dees J, Hop WC & van Blankenstein M	Oesophageal cancer is an uncommon cause of death in patients with Barrett's oesophagus. Gut 1996; 39:5-8
MacDonald CE, Wicks AC & Playford RJ	Final results from 10 year cohort of patients undergoing surveillance for Barrett's oesophagus: observational study. Br Med J 2000; 321:1252-5
Buttar NS et al.	Extent of high-grade dysplasia in Barrett's esophagus correlates with risk of adenocarcinoma. Gastroenterology 2001; 120:1630-9
Reid BJ et al.	Predictors of progression to cancer in Barrett's esophagus: baseline histology and flow cytometry identify low- and high-risk patient subsets. Am J Gastroenterol 2000; 95:1669-76
Schnell TG et al.	Long-term non-surgical management of Barrett's esophagus with high-grade dysplasia. Gastroenterology 2001; 120:1607-19
American College of Gastroenterology	Guidelines for the Diagnosis and Surveillance of Barrett Esophagus. Am J Gastroenterol 1998; 93:1028-32

V. Clinical Review Methods

A. How the Review was Conducted

The review followed this sequence:

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- A survey of current literature on Barrett's esophagus, adenocarcinoma of the esophagus, photodynamic therapy, surgery of the esophagus
- Volume 1, 2 – summary of information PHOTOFRIN, PHOTOFRIN label, and proposed label
- Volume 6 – human pharmacokinetics and bioavailability
- Volume 8 - a summary of the Clinical section
- Volumes 13, 42, 47 describing the 3 trials
- Volumes describing chemistry, pharmacokinetics and pharmacodynamics of PHOTOFRIN
- Tables and listings of the trials, vols. 13 – 51, and 57 - 95
- Statistical section, vol. 52
- Financial disclosure forms, vol. 100.

B. Overview of Materials Consulted in Review

Summarized in I B. State of Armamentarium for Indication, and in Materials Reviewed (below).

Materials reviewed:

NDA 21-525/20-451	Vol.1-100
IND 61,011	Medical Officer's review (January 4, 2001)
IND 61,011	Meeting Minutes, Industry Meeting – Type B, Pre-NDA (June 1, 2001)
IND 61,011	Advice letter (January 24, 2001)
IND 61,011	Memorandum of Telecon (dated March 21, 2001)
NDA 21-525	Statistical Review and Evaluation
NDA 21-525	Pharmacology and Biopharmaceutics Review

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The sponsor was requested to clarify the following:

- Clarify which patients were enrolled in which centers
- Provide the response rate for the primary efficacy endpoint if Dr. Overholt's patients were excluded. [Dr. Overholt's center enrolled 37/208 (17.8%) patients in the pivotal trial and 86 high-grade dysplasia patients in the supporting trials, a total of 123/294 (41.8%) patients.]
- Clarify if updated follow-up data will be provided (and if so, when) to allow calculation of a more complete value for duration of response. [The submission contains the 6-month data (preliminary) for primary efficacy endpoint, rather than 24-month data that were to be the final data for the trial].

DSI was consulted to review Dr. Overholt's data, because such a high proportion of patients were enrolled at his center.

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D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor presented sufficient documentation of conduct of trials in accordance with accepted ethical standards, including

- An Independent Ethics Committee or Institutional Review Board review of protocol and the informed consent form
- The study was to be performed in accordance with the rules of Good Clinical Practice. The conditions were to be in compliance with the Declaration of Helsinki, the recommendations of the WHO, the recommendations of the Health Protection Branch, Ottawa, Canada, and the recommendations of the FDA as published in *General Considerations for the Clinical Evaluation of Drugs (1977)*, and the recommendations as published in the Federal Register and in the Code of Federal Regulations (21 CFR 312.60-69) and applicable state laws.
- Each patient reviewed and signed a written approved informed consent form prior to any study procedures. The consent form complied with U.S. 21 CFR 50, Canadian or ICH guidelines (Section 0) and local Institutional Review Board or Ethics Committee requirements. A sample consent form is provided in the submission.

E. Evaluation of Financial Disclosure

Vol. 100 of the submission contains Financial Disclosure Forms from Clinical Investigators. The following three investigators admitted a proprietary or financial interest in the test product:

- Masoud Panjehpour, Ph.D. indicated that he is a co-inventor of esophageal PDT balloon owned by Thompson Cancer Survival Center.
- Bergein F. Overholt, M.D. indicated that he is a co-inventor and co-patent holder for esophageal centering balloon.
- Thomas J. Dougherty, Ph.D. indicated that he is a "co-inventor of PHOTOFRIN patent".

All the other investigators denied any financial interests or arrangements. The Financial Disclosure Form is adequate.

The Thompson Cancer Survival Center, where Drs. Overholt and Panjehpour were investigators, had higher complete response rates in the primary efficacy endpoint (30/34 or 88.2%) than all other sites (76/104 or 73.1%) (NDA 21-525 N-000BM, submitted on 9.26.2002). Dr. Overholt's results in the 2 uncontrolled trials also showed complete response rates of 88-89%. These superior results may indicate much greater expertise than in other centers, in that Drs. Overholt and Panjehpour developed the instruments and performed both pre-clinical and clinical trials prior to the pivotal trial. This reviewer would be reluctant to cast doubt on their results without any other evidence.

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VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Preliminary analysis of the pivotal PHO BAR 01 study, based on 6 months of follow-up (too short, therefore inadequate), indicates that photodynamic therapy using PHOTOFRIN and omeprazole was significantly more effective than control treatment (omeprazole) in causing complete ablation of high-grade dysplasia in Barrett's esophagus and replacement with normal squamous epithelium with or without some areas of Barrett's metaplasia, areas of indefinite dysplasia or low-grade dysplasia (72% vs. 31%, $p < 0.0001$). Replacement of high-grade dysplasia by normal epithelium, the best quality of response, was common in patients treated with PHOTOFRIN PDT plus omeprazole (41%) and rare (4%) in patients treated with omeprazole alone ($p < 0.0001$). Responses in the omeprazole alone group were generally not of the same quality, since high-grade dysplasia was replaced by normal squamous cell epithelium with areas of metaplasia, indefinite dysplasia, and low-grade dysplasia.

The short follow-up (a mean of 12 months) did not permit estimates of the duration of response, time to progression to cancer, time to treatment failure, or survival time. These secondary efficacy endpoints are of great importance, since the purpose of ablation of high-grade dysplasia is the prevention of adenocarcinoma.

The results in the two uncontrolled studies, based on a median follow-up of 6 months, indicated complete responses (complete ablation of high-grade dysplasia and replacement by normal squamous epithelium with or without some areas of metaplasia, indefinite dysplasia, or low-grade dysplasia) in about 88% of patients treated with PHOTOFRIN PDT. Results of a longer follow-up, median of 12 months, indicated a complete response rate of 93% - 95%. The duration of response, time to progression to cancer, time to treatment failure, or survival time could not be reliably estimated because of the short follow-up time.

The sponsor states (vol. 1, p. 251) that the primary analysis of the pivotal PHO BAR 01 study was to be done after a minimum of 6 months of follow-up. The results from this primary analysis form the basis of this submission, "as agreed with the Division" (vol. 7, p. 64, which contain Axcan Scandifarm Inc. Minutes of the pre-NDA meeting held on June 1, 2001). The statement by the Agency recorded in those minutes reads in its entirety "Additional information is required to determine the acceptability of this approach". In this reviewer's opinion, efficacy of PDT cannot be adequately assessed until sufficient follow-up has documented the duration of response. The sponsor's statement that "most failures occurred during the first 4 months" after treatment is not supported by the sponsor's data, which are described in the clinical review below.

B. General Approach to Review of the Efficacy of the Drug

PHO BAR 01, TCSC 93-07 (high-grade dysplasia patients only), and TCSC 96-01 (high-grade dysplasia patients only) were all reviewed in detail. The results are summarized above in A. as well as in Detailed Review of Trials and in Efficacy Conclusions below.

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B. Detailed Review of Trials by Indication

PIVOTAL STUDY:

Study Title: PHO BAR 01, A Multicenter, Partially Blinded, Randomized Phase III Study of the Efficacy and Safety of Photodynamic Therapy (PDT) Using PHOTOFRIN (porfimer sodium) for Injection for the Ablation of High-Grade Dysplasia in Barrett's Esophagus.

The protocol for the pivotal study (PHO BAR 01) was submitted for review to the Division of the Oncology Drug Products (IND 25,064) by QLT (the sponsor at that time) on November 13, 1997, and the study was started on January 15, 1998. It was a multicenter, controlled, randomized, partially blinded trial comparing PDT with PHOTOFRIN and omeprazole to a surveillance arm consisting of omeprazole only. Two hundred eight (208) patients with high-grade dysplasia in BE were randomized in a 2:1 (PDT:surveillance) proportion. The omeprazole control group was included to allow assessment of the natural history of untreated high-grade dysplasia in BE. Since there was no esophagectomy arm in the trial, the Division of Gastrointestinal and Coagulation Drug Products in a pre-NDA meeting with the then-sponsor (Axcan Scandipharm Inc.) concluded that the data from this trial and the supporting trials could only support the PDT with PHOTOFRIN for those patients with high-grade dysplasia in BE who are not candidates for esophagectomy.

Date of Study Initiation: January 15, 1998

Date of Study Completion: November 7, 2001

Date of the Present Submission (Preliminary Findings): May 31, 2002

Date of the 24-month Follow-up Efficacy Data submission by the Sponsor: September 30, 2002

Date of the 24-month Follow-up Safety Data submission by the Sponsor: October 23, 2002

Study Objectives:

1. **Primary Objective:** To assess the efficacy of PDT with PHOTOFRIN for Injection plus omeprazole compared to omeprazole alone in the complete ablation of high-grade dysplasia in patients with BE, in conjunction with a strict endoscopic surveillance and biopsy protocol.
2. **Secondary Objectives:** To assess the safety and efficacy of PDT with PHOTOFRIN plus omeprazole and systematic endoscopic surveillance compared to omeprazole only therapy plus systematic endoscopic surveillance in terms of :
 - a) quality of complete response
 - b) duration of complete response

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- c) delaying progression to cancer (time to progression to cancer)
- d) delaying the need for esophagectomy or other intervening therapy (included together with c) in time to treatment failure), and
- e) survival time.

Study Design and Study Plan:

This was a multicenter, partially blinded, randomized, Phase III study in patients with high-grade dysplasia in BE. Eligible patients were randomized to receive PHOTOFRIN plus omeprazole (OM) therapy or OM only therapy.

Blinding: Patients and study physicians were aware of the treatment each patients received; however, the pathologists who read the biopsies from each esophageal endoscopy were blinded to the patients' treatment. All histological assessments were carried out at a central reference laboratory.

Randomization: Patients were centrally randomized in a 2:1 design to receive PHOTOFRIN PDT plus OM therapy or OM therapy alone. The study planned the enrollment of at least 200 patients with high-grade dysplasia in BE at approximately 40 clinical trial sites in North America and Europe.

Treatment: Photodynamic therapy (PDT) with PHOTOFRIN is a 2-stage process. The first stage is the intravenous injection of PHOTOFRIN at a dose of 2.0 mg/kg of body weight over 3-5 minutes 2 days (40-50 hours) prior to the light treatment. The second stage of treatment is the illumination of the area of treatment with a laser light.

A maximum of 7 cm of BE was treated during one course of PDT (I.V. PHOTOFRIN followed by 1 or 2 laser light applications). The second light application could be given 2 days after the first 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. The entire length of Barrett's mucosa was to be treated; therefore up to three courses could be given. Courses of PDT had to be separated by at least 3 months. If a previous course of treatment resulted in residual areas of dysplasia, Barrett's metaplasia, or any remaining "skip areas", an additional course of PDT was to be given. Patients in both treatment groups received omeprazole (20 mg BID) to reduce reflux esophagitis.

Follow-up: All patients were to be followed every 3 months until four consecutive, quarterly follow-up endoscopic biopsy results were negative for high-grade dysplasia, and then biannually until the last enrolled patient had completed at least 24 months of follow-up evaluation after randomization. Patients were to be assessed for efficacy (by histological assessment of biopsies), and safety (adverse events, laboratory results and physical examinations).

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Treatment response: Defined as the complete ablation of high-grade dysplasia at any one of endoscopic assessment time points. The quality and duration of the complete response were also to be assessed. Secondary treatment responses included: time to progression to cancer, time to treatment failure, and survival time.

The majority of patients with high-grade dysplasia do not progress to cancer over a period of observation of several years. Therefore, the efficacy of photodynamic therapy of high-grade dysplasia in cancer prevention was assessed by comparing the persistence and re-occurrence of high-grade dysplasia in PDT-treated patients and in omeprazole only-treated patients, who were the control patients exhibiting the natural history of high-grade dysplasia. Primary analysis was to be performed after 6 months, and final analysis after 24 months from the date of randomization of the last patient.

Additional analyses were to be performed to evaluate the effect of various baseline and demographic factors on the primary efficacy variable, i.e. complete response. The factors included the following:

- High-grade dysplasia duration (6 months or less vs. more than 6 months)
- BE length as a continuous variable
- High-grade dysplasia foci, single vs. multiple
- Nodular vs. non-nodular disease
- Prior omeprazole for at least 3 months (yes, no)
- Size of center enrollment (>10 patients vs. 1-9 patients), pooled data
- Gender (male vs. female)
- Age (<65 vs. >65 years old)
- Smoking history (smoker vs. non-smoker)
- Physician's experience with PHOTOFRIN PDT (first 3 patients in the study arm from each center vs. all other patients)

Safety monitoring. An evaluation committee (Data Safety Monitoring Committee) was to review the safety data every six months. An interim analysis was not planned in the study.

Sponsor's Figure 9.1 shows the Schematic of Study Design and Figure 9.2 shows the Schematic of Schedule of Procedures (in Appendix A. Other Relevant Materials).

Study Population:

Inclusion Criteria:

1. High-grade dysplasia in BE, as assessed by the central reference laboratory
2. 18 years of age or older
3. Not pregnant
4. If female of childbearing potential, practicing reliable birth control
5. Signed Informed Consent

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Exclusion Criteria:

1. Invasive cancer of the esophagus, or patients in whom invasive cancer, lymph node involvement or metastases could not be ruled out by endoscopic ultrasonography or by CT scan
2. History of cancer within 5 years before screening, other than non-melanoma skin cancer
3. Prior PDT to esophagus
4. Esophageal strictures unresponsive to dilation
5. Known contraindications to analgesia or endoscopy
6. Significant acute or chronic illness beside BE (in the judgement of the investigator)
7. Contra-indication to omeprazole
8. Porphyria or known hypersensitivity to porphyrins
9. WBC <2.5/cu.mm; platelets <50,000/cu.mm; Hgb <9.0 g/dL; PT/INR >1.5
10. Serum creatinine >1.5 times the upper limit of normal; total bilirubin >1.5 times the upper limit of normal; AST, ALT, alk.phosphatase >2.5 times the upper limit of normal
11. Unable or unwilling to complete the follow-up evaluations required for the study
12. Unstable heart disease (NYHA Class III and IV)
13. Esophageal ulcers >1 cm in diameter
14. Esophageal or gastric varices

Removal of Patients from Therapy or Assessment: Patients were to be removed from the study because of

- disease progression,
- unacceptable adverse events,
- refusal to continue, or
- at the investigator's discretion if it is in the patient's best interest.

Screening and Selection: The plan was to include 200 patients in the study. A total of 486 patients were screened for inclusion at 30 centers in the United States, Canada and Europe, and a total of 208 patients were enrolled. The reasons for patient exclusion are shown in the table below.

Total screened	486
Total randomized to treatment	208 (42.8%)
Total not randomized	278 (57.2%)
--no high-grade dysplasia	239 (86.0% of 278) (49.2% of 486)
--other screening criteria not met	14 (5.0% of 278)
--declined participation	25 (9.0% of 278)

The predominant reason for patient exclusion was the failure to confirm the diagnosis of high-grade dysplasia in 49.2% of screened patients. This is an important finding that suggests a potential misuse of PHOTOFRIN PDT in patients without high-grade dysplasia.

One center (Thompson Cancer Survival Center, Knoxville, TN) enrolled 51 patients into the study (24.5%), four centers (Columbia-Presbyterian Hospital, NYC; Mayo Clinic, Rochester,

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MN; Johns Hopkins Hospital, Baltimore, MD; and Parkland Memorial Hospital, Dallas, TX) enrolled 13-14 patients each. Other centers enrolled between 1 and 9 patients. A great majority of the patients were enrolled in American institutions (196 or 94.2%). Five patients were enrolled in Canada, six in UK and one in France.

The preponderance of the Thompson Cancer Survival Center is presumably due to the presence of acknowledged expertise in this area. Dr. Overholt and colleagues at the Thompson Center developed many of the techniques and instruments used in PDT, and published the two largest series of BE patients treated with PDT. These two studies are supporting studies in this application. Patient screening and selection appeared not to differ at the Thompson Center from the overall statistics (113 patients screened, 51 randomized (45.1%)).

Patient characteristics:

The mean age of patients enrolled in the PHOTOFRIN PDT + OM group was 66.13 with a range from 38.4 to 88.5 years. The mean age of patients in the OM Only group was 67.27, with a range from 36.1 to 87.6 years. The mean height was 173 cm. The total study population was predominantly male (85%), white (Caucasian) (99%), and former or current smokers (71%). Reviewer's Table in the Safety section of this review contains a table of the demographic characteristics of enrolled patients in PHO BAR 01 as well as the two uncontrolled studies.

The patient population enrolled in this study is representative of the general BE population affected by high-grade dysplasia. Male to female ratio is 7:1 in this population (Sharma & Sampliner 2001).

Patients in the two treatment groups reported mostly gastrointestinal (79%), cardiovascular (68%) and musculoskeletal (63%) medical history. There were no statistical differences between the two treatment groups with regards to medical history.

Characteristics of BE at baseline are shown below in sponsor's Panel 11.5 (vol.13, p.94). The two treatment groups were well-matched in

- duration of BE (mean and median values of about 36 months and of about 20 months, respectively),
- duration of high-grade dysplasia (mean and median values of about 6 months and of about 4 months, respectively),
- endoscopic length of BE (about one-half shorter and one-half longer than 6 cm),
- histological length of BE,
- endoscopic characteristics of high-grade dysplasia including the presence of hiatal hernia, esophageal ulcers, nodules and strictures, and
- prior treatment (medical, surgical, esophageal dilations and blood transfusion; there were no cases of endoscopic ablation).

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Barrett's Esophagus at Baseline

Characteristic	PHOTOFRIN PDT + OM N = 138	OM Only N = 70
Duration of BE in months, Median (range)	20.27 (1.3 – 216.7)	19.22 (0.9 – 141.7)
Duration of high-grade dysplasia in months, Median (range)	3.55 (0.1 – 40.7)	4.11 (0.4 – 72.4)
Endoscopic length of BE		
- < 6 cm (%)	63 (46%)	35 (50%)
- > 6 cm (%)	75 (54%)	35 (50%)
Histological length of BE		
- < 6 cm (%)	74 (54%)	42 (60%)
- > 6 cm (%)	64 (46%)	28 (40%)
Extent of high-grade dysplasia		
- Single biopsy	34 (25%)	17 (24%)
- Single level	50 (36%)	27 (39%)
- Multiple levels	87 (63%)	43 (61%)
Endoscopic condition		
- Hiatal hernia	125 (91%)	58 (83%)
- Nodules	45 (33%)	19 (27%)
- Ulcers	8 (6%)	3 (4%)
- Strictures	6 (4%)	2 (3%)
Prior treatment		
- Surgery	6 (4%)	8 (11%)
- Medical therapy	134 (97%)	66 (94%)
- Other	6 (4%)	2 (3%)

Source: Panel 11.5, vol. 13, p. 94.

Sub-study: Rater Agreement on Histological Diagnosis for Patients in study PHO BAR 01

A study was carried out by the sponsor to assess the inter-rater and intra-rater percent agreement on histologic diagnoses assigned to sets of endoscopic biopsy samples in the screening and trial phases of the PHO BAR 01 clinical trial (vol. 41).

Secondary objectives included: 1) assessment of the intra-rater and inter-rater percent agreement on a per biopsy basis, 2) assessment of pre-PDT-treatment rater agreement vs. post-PDT-treatment rater agreement, and 3) assessment as to whether the following factors may affect rater agreement: presence of inflammation, presence of ulcers/erosions, and endoscopy/treatment site.

Study design. The rater reliability study was conducted in parallel with PHO BAR 01. Three pathologists at [redacted] (the central reference pathology laboratory) at the University of Washington Medical Center participated in the study. Two rounds of readings were

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performed for the slides, i.e. each pathologist read each endoscopic slide set in the rater agreement study twice.

Study procedures. Readings for the rater agreement study were performed by the pathologists in a blinded fashion. Pathologists had no knowledge of the patient identity, randomization arm, study phase or clinical trial site. Rater agreement slides were inserted into the stream of PHO BAR 01 study read by the pathologist on call. The order of reading by the second and third pathologist was randomized.

Sample size. There were 26 sets of slides, from an equal number of pre- and post treatment biopsies, for a total of 437 biopsies with 6 repetitions of the reading on each biopsy. There were a total of 2622 individual biopsy readings.

Outcomes to be analyzed: presence of 1) high-grade dysplasia, 2) cancer, 3) high-grade dysplasia of cancer, 4) dysplasia (low-grade or high-grade), and 5) Barrett's esophagus. Two raters were defined to agree on the outcome of high-grade dysplasia (both agreed it was absent or present) and similarly on the other outcomes.

Results. Reviewer's Tables below (from Table 2, vol. 41, p. 15 and Table 5, vol.41, p. 20) show inter-rater agreement and intra-rater agreement on the five diagnoses tested.

Reviewer's Table: Percent Inter-Rater Agreement on Endoscopy Diagnoses

Diagnosis	Mean % agreement (range of percentages)
High-grade dysplasia	88 % (78% - 94%)
Cancer	96 % (85% - 99%)
High-grade dysplasia or cancer	92 % (83% - 97%)
Dysplasia (low-grade and high-grade)	86% (74% - 92%)
Barrett's esophagus	99% (98% - 100%)

Reviewer's Table: Percent Intra-Rater Agreement on Endoscopy Diagnoses

Diagnosis	Intra-rater agreement, % (range)
High-grade dysplasia	94% (87% - 97%)
Cancer	99 % (92% - 99.8%)
High-grade dysplasia or cancer	96% (77% - 99.5%)
Dysplasia (low-grade and high-grade)	92% (83% - 97%)
Barrett's esophagus	99% (92% - 99.8%)

Source: Table 5, vol. 41, p.15.

Factors that had the greatest impact on inter-rater agreement on the endoscopy diagnosis of high-grade dysplasia were the presence of obscuring inflammation (81% when inflammation was present vs. 94% when inflammation was not present), when high-grade dysplasia was not

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excluded (77% vs. 93%), and the number of biopsies (with >16 it was 82% vs. 95% with 16 or fewer).

Factors that had the greatest impact on agreement on cancer were high-grade dysplasia not excluded, erosions, and inflammation. For high-grade dysplasia and cancer, while there was disagreement on the presence of cancer, there was no disagreement that it was either high-grade dysplasia or cancer. Diagnosis of dysplasia was influenced by the presence of inflammation, high-grade dysplasia not excluded, number of biopsies over 16, and the presence of erosions.

Intra-rater agreement on the endoscopy diagnosis was very high (average 96%; range, 92% - 99%). The main factors influencing intra-rater agreement were post-treatment samples and the presence of erosion.

Overall Conclusion. The primary conclusion of this study is that rater agreement on the endoscopic diagnosis is generally high. These high rates of agreement (88% for high-grade dysplasia, 96% for cancer, 92% for high-grade dysplasia or cancer, 85% for dysplasia, and 99% for Barrett's esophagus) suggest that the effect of rater disagreement on the reproducibility of PHO BAR 01 will be minimal.

However, an incidental finding of this study was that of the 13 screening endoscopies in the study, only 7 were given the diagnosis of high-grade dysplasia. All the patients entering the screening phase of the trial had a diagnosis of high-grade dysplasia by another pathologist determined from biopsy samples taken from a different endoscopy in the recent past. The failure to verify the diagnosis of high-grade dysplasia in 6 of the 13 cases indicates that variability in the diagnoses across time and across raters from different institutions may be higher than the inter-rater variability seen in this study, where rater variability estimates were restricted to 3 pathologists in a single institution and the raters read slides from the same endoscopy. The above noted failure to confirm the diagnosis of high-grade dysplasia in 49.2% of patients during screening reinforces this concern.

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Treatment assignment and disposition:

Number of patients randomized	PHOTOFRIN + OM N = 138	OM only N = 70
Number of patients receiving at least one course of study Therapy	N = 132 N = 6 not. Reasons: (1) low-grade dysplasia; (1) adenocarcinoma; (3) declined participation; (1) received PHOTOFRIN but no light because of anxiety	N = 69 N = 1 not. Reason: esophagectomy
Follow-up of at least 6 months	N = 126 (95% of 132) N = 8 not. Reasons: (5) progression of disease; (1) lung cancer; (2) missing data	N = 55 (79.7% of 69) N = 14 not. Reasons: (8) progression of disease; (1) died from stroke; (1) esophagectomy; (2) PHOTOFRIN PDT; (2) missed 6-month assessments or uncooperative

Source: vol. 13, p.65

Number of patients included in the:	PHOTOFRIN + PDT	OM only
ITT population	138 (100%)	70 (100%)
Safety population	133 (96%)	69 (99%)
Evaluable population	130 (94%)	69 (99%)
Number of patients randomized	138	70
Number of patients receiving study therapy	132	69
Number of patients completing 6-mo follow-up	124	55
Number of patients discontinued from the Study:	37 (27%)	29 (41%)
Adverse event	3 (2%)	0
Progression of disease:	15 (11%)	14 (20%)
confirmed by histopathology	14 (10%)	13 (19%)
unconfirmed by histopathology	1 (<1%)	1 (1%)
Death	2 (1%)	1 (1%)
Other therapy	9 (6%)	13 (19%)
Administrative reasons	8 (6%)	1 (1%)

Source: Panel 10.2, vol. 13, p. 66; Listing 36.0, vol. 83, pp. 151-168

Reviewer's note: The above sponsor's Panel 10.2 is somewhat difficult to follow, but the following explanations should be made:

1. 132/138 patients in the PHOTOFRIN PDT arm received at least one complete course of therapy. Of the six who did not, three withdrew consent before therapy, one withdrew

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consent after PHOTOFRIN infusion but before the light treatment, one was found to have an adenocarcinoma and one was found to have a low-grade dysplasia.

124/132 patients in the PHOTOFRIN PDT arm provided 6-month follow-up data. Of the eight patients who did not, five had a progression of the disease, one had a newly diagnosed lung cancer and two had missing data.

2. 79/138 patients in the PHOTOFRIN PDT arm received one course of treatment; 52/138 received two courses; and 29/138 received three courses (Panel 10.3, vol. 13, p. 68).
3. It appears that only a few patients in the PHOTOFRIN PDT arm had completed 24 months of follow-up (sponsor's Panel 10.3, vol. 13, p. 68 is shown below). The protocol called for all the patients to complete at least 24 months of follow-up.
4. 69/70 patients in the OM arm received at least one omeprazole dose. One did not, because he had an esophagectomy.
5. Patient follow-up data in the OM arm are incomplete after the 6-month time point. Only a few patients in the OM arm had completed the planned 24 months of follow-up.
6. The number of patients discontinued from the Study, 37 in the PHOTOFRIN PDT group and 29 in the OM Only group, must have been after a variable follow-up (see below in Reviewer's Table on Patient's Duration on Study).

Protocol Deviations:

No patients were excluded from the data set for the ITT analysis. Six patients, five from the PHOTOFRIN PDT treatment group and one from the OM Only treatment group were excluded from the Safety analysis data set, because neither PHOTOFRIN PDT nor omeprazole had been administered. Three additional patients from the PHOTOFRIN PDT group were excluded from the Evaluable population data set, because in two patients cancer could not be excluded by esophageal ultrasound and one patient did not receive the light application following PHOTOFRIN treatment.

At randomization, no patients violated inclusion criteria, nine patients violated exclusion criteria (history of cancer in 8 patients, history of stable anemia in one, and increased BUN/creatinine values in one). Randomization was to be scheduled with 4 weeks of the baseline biopsy; 27 patients (18 in the PHOTOFRIN PDT group and 9 in the OM Only group) violated this directive.

PDT Treatment:

PHOTOFRIN was administered intravenously at a dose of 2 mg/kg. Laser light at 630 nm was administered using light delivery systems described in the Safety Section 40 - 50 hours after drug administration. A Summary Table of the Extent of PDT in the Evaluable Group is shown in the Reviewer's Table below (from Table 8.8 - 3, vol. 8, p. 110).

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Reviewer's Table: Photodynamic Therapy Treatment

Laser light sessions	Course 1 N = 130 (%)	Course 2 N = 81 (%)	Course 3 N = 29 (%)
First laser light session			
Pre-treatment of nodules	33 (25%)	24 (30%)	9 (31%)
Balloon light treatment	129 (99%)	81 (100%)	28 (97%)
Second laser light session			
Treatment of skip areas	60 (46%)	46 (57%)	14 (48%)

Concomitant Medication and Adjunctive Therapy

During the study, 133 (100%) patients in the PHOTOFRIN PDT + OM group and 65 (94%) patients in the OM Only group took at least one concomitant medication. The following table describes the use of concomitant medications in the two treatment groups. PHOTOFRIN PDT + OM group took many more medications than the OM Only group. Especially impressive is the very high usage of analgesics, anti-emetics, antacids, gastrointestinal agents, glucocorticoids and cytoprotective agents.

Drug group	PHOTOFRIN PDT + OM % of patients using	OM Only % of patients using
Opioid analgesics	90%	23%
Non-opioid analgesics	83%	32%
Phenothiazines	62%	4%
Antacids	56%	9%
Local anesthetics	55%	1%
Glucocorticoids	39%	10%
Benzodiazepenes	28%	14%
Gastrointestinal agents	26%	1%
Ethanolamines	20%	4%
Glucagon	20%	1%
Cytoprotective agents	14%	7%
Stimulant laxatives	11%	3%
Aminoglycosides	1%	6%

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Patients' Duration on Study

This submission contains data on patients who have completed at least 6 months of follow-up, and this data is used for a preliminary analysis of the study. The Reviewer's Table below shows the patients' duration on study (from Table 1.10, vol. 14, p. 113, data compiled on December 11, 2000). This information provides the reason for the preliminary nature of the results. At the time of this data collection very few patients had completed at least 24 months of follow-up. The final analysis of the study will be performed with data on patients who will have completed at least 24 months of follow-up.

Reviewer's Table on Patients' Duration on Study

Patient Duration on Study	PHOTOFRIN PDT + OM ITT population, N = 138	OM Only – ITT population N = 70
< 3 months	10 (7%)	6 (9%)
3 – 6 months	3 (2%)	14 (20%)
6 – 9 months	35 (25%)	15 (21%)
9 – 12 months	22 (16%)	9 (13%)
12 – 15 months	23 (17%)	8 (11%)
15 – 18 months	20 (14%)	7 (10%)
18 – 21 months	14 (10%)	5 (7%)
21 – 24 months	8 (6%)	5 (7%)
>24 months	3 (2%)	1 (1%)
Mean no. of months	12.1	10.3

RESULTS:

Primary efficacy endpoint: Complete Ablation of High-grade Dysplasia

Patients with complete ablation of high-grade dysplasia included:

- 1) those who had complete replacement of all Barrett's metaplasia and dysplasia with normal squamous cell epithelium (Complete Response 1 - CR1),
- 2) those who had ablation of all grades of dysplasia, but had some areas of Barrett's metaplasia remaining (Complete Response 2 – CR2), and
- 3) those who had ablation of all areas of high-grade dysplasia, but had some areas of low-grade dysplasia, or areas indefinite for dysplasia, or areas of metaplasia (Complete Response 3 – CR3).

The proportion of responders (CR1 + CR2 + CR3) was significantly higher in the PHOTOFRIN + OM group than in OM Only group (72% vs. 31%, $p < 0.0001$), as shown in Reviewer's Table below (from Panel 11.6, vol. 13, p. 98). More than twice the percentage of patients had a response to PHOTOFRIN PDT + OM than to OM Only, an impressive difference of 41%.

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Reviewer's Table on Primary Efficacy – Overall Clinical Response

Response	PHOTOFRIN PDT + OM N = 138	OM Only N = 70
CR1 + CR2 + CR3	99 (72%)	22 (31%)

Reviewer's Note: With a 6-month follow-up, the difference in results between the two treatments is impressive. It should be pointed out that most of the literature maintains that high-grade dysplasia does not respond to omeprazole at all, and the response seen in this study may be due, at least in part, by control and subsidence of inflammation due to GERD.

It is important to note the reasons of failures of the Primary efficacy endpoint. Reviewer's Table below (from Data listings) show the reasons for response failures, the patients who at 6-month follow-up did not have a complete response.

Reviewer's Table on Response Failures and Patient Discontinuations from the Study

Reason for discontinuation from study	PHOTOFRIN PDT + OM N = 37 (27% OF 138)	OM Only N = 29 (41%)
Progression of disease (further therapy mainly not stated)	15 (11%)	14 (20%)
Other therapy (these patients are not included under Progression of disease)	9 (7%) Esophagectomy – 3 YAG laser – 3 Heater probe mucosal ablation – 1 4 th PHOTOFRIN PDT – 1 Other - 1	13 (19%) PHOTOFRIN PDT – 9 Esophagectomy – 3 Not specified - 1
Patient withdrew	5 (4%)	
Adverse event	3 (2%)	
Death	2 (1%)	1
Uncooperative/unreliable patient	1	1
Other administrative	2	

Reviewer's Note: Patients did not have a minimum of 24 months follow-up in either group and therefore the data on response failures (see Reviewer's Table above) can be regarded only as preliminary. Nevertheless, during the minimum of 6 months' follow-up, 20% of patients in the OM Only group had progression of disease and another 19% had other therapy (a total of 39%) versus 11% and 7%, respectively, (a total of 18%) in the PHOTOFRIN PDT + OM group - more than twice the number.

The Kaplan-Meier plot shows that all Omeprazole Only patients relapsed, progressed or had other therapy within 180 days, while about 75% of PHOTOFRIN PDT + OM patients

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maintained the response at that time. Inadequate follow-up data need to be kept in mind in assessing response maintenance after 360 days.

Secondary Efficacy Endpoint: Quality of Complete Response

The quality of response in the PHOTOFRIN PDT + OM group was significantly better than in the OM Only group, as measured by the percentages of CR1 and CR2 responses. Reviewer's Table below depicts the data from Panel 11.7 (vol. 13, p. 99). There was a ten-fold difference in CR1 between treatments, and an eight-fold difference in CR1 + CR2.

Reviewer's Table on the Quality of Complete Response

Number of patients – ITT population	PHOTOFRIN PDT + OM N = 138	OM Only N = 70
CR1	57 (41%)	3 (4%)
CR1 + CR2	67 (49%)	4 (6%)

Secondary Efficacy Endpoint: Duration of Response

Duration of response was defined as the day 50% of the patients had experienced the failure event for the response category. Median duration of response (CR1, or CR1 + CR2, or CR1 + CR2 + CR3) in the PHOTOFRIN PDT + OM group could not be estimated. In the OM Only group the median duration of CR1 was 81 days and of CR1 + CR2 + CR3, 98 days.

A Kaplan-Meier plot showing the probability of maintaining a CR3 or better is not reproduced because the small number of patients followed for longer than 12 months make these estimates unreliable (see Statistical Review).

Secondary Efficacy Endpoint: Time to Progression to Cancer

This endpoint was defined as the day 50% of the patients in a treatment group had documented progression to cancer. Median Time to Progression to Cancer could not be estimated for either group. According to the sponsor, most treatment failures occurred within 4 months after the first course of treatment. Patients in the PHOTOFRIN PDT + OM group had 96% chance of being cancer-free after 4 months as compared to a 90% chance for patients in the OM Only group.

Reviewer's note: The above conclusions appear premature in view of the duration of patient follow-up. Most treatment failures could be predicted to occur early, if the follow up is short. Fifteen (15) patients (11%) in the PHOTOFRIN PDT + OM group had progressed to cancer from days 65 to 373. Fourteen (14) patients (20%) in the OM Only group had progressed to cancer

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from days 63 to 642. Reviewer's Table below shows the Time to Progression to Cancer in days in the two arms (Listing 36.0, vol. 83, pp. 151-156).

Reviewer's Table of Time to Progression to Cancer

Time to Progression Interval in days	PHOTOFRIN PDT + OM Day progression diagnosed (number of courses)	OM Only Day progression diagnosed
0 – 120	43 (1 course); 81 (1 course); 87 (1 course); 94 (1 course); 95 (1 course); 100 (2 courses) 101 (2 courses); 102 (2 courses); 108 (2 courses); 115 (2 courses)	64; 93; 94; 101; 102; 103
121 – 240	186 (2 courses); 198 (1 course); 221 (1 course)	130; 131; 179; 186; 203; 222
> 241	361 (1 course); 373 (1 course)	278; 664
Total	15 (11%)	14 (20%)

Secondary Efficacy Endpoint: Time to Treatment Failure

Time to Treatment Failure (TTF) was defined as the period in days from the date of randomization until the date of the first documentation of 1) progression of high-grade dysplasia to cancer or 2) the start of any intervening therapy for high-grade dysplasia other than the randomized study treatment.

Median TTF could not be estimated for the PHOTOFRIN PDT + OM group, because fewer than 50% of the patients had documented TTF by the end of the follow-up: 23 patients (17%) had failed treatment from days 65 to 499. Median TTF was 642 days in the OM Only group: 26 patients (37%) had failed treatment from days 7 to 644. The last patient was censored at day 499 in the PHOTOFRIN PDT + OM group and at day 642 in the OM Only group.

According to the sponsor, the probability of treatment success in the PHOTOFRIN PDT + OM group was 96% after 4 months as compared to 84% in the OM Only group (vol.13, p.105). The data presented above on Response Failures contradict this statement by the sponsor. Kaplan-Meier plot supporting this conclusion by the sponsor (vol.13, p.106) is not reproduced.

Secondary Efficacy Endpoint: Survival Time

Survival Time was defined as the period in days from the date of randomization to the date of the patient's death. Median survival time was the day 50% of the patients had died.

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Median survival time could not be estimated for either treatment group: 2 patients died in the PHOTOFRIN PDT + OM group (on days 631 and 643) and 1 patient died in the OM Only group (on day 25).

Reviewer's Note: None of the deaths were attributable to adenocarcinoma of esophagus (one cardiac arrest after CABG surgery, one cancer of male breast, one stroke). Thus, this endpoint is not useful.

Other analyses

Additional analyses showed that Complete Response (CR1 + CR2 + BR3) rate was influenced by the following factors:

- treatment with PHOTOFRIN PDT (vs. OM Only, $p < 0.0001$)
- single high-grade dysplasia focus vs. multiple foci ($p < 0.0001$)
- prior omeprazole intake of at least 3 months ($p = 0.0005$), and
- age, < 65 years old vs. > 65 years old ($p = 0.0219$).

Complete Response rate was not influenced by:

- duration of high-grade dysplasia
- length of BE
- nodular conditions
- gender
- smoking history
- study center's size (< 10 patients vs. > 10 patients)
- clinician's experience with PDT ($p = 0.06895$).

SUPPORTING STUDIES:

Study Title: TCSC 93-07. A Phase I/II Study of the Safety and Efficacy of Photodynamic Therapy (PDT) Utilizing PHOTOFRIN for Treatment of Dysplasia or Early Adenocarcinoma of the Esophagus in Barrett's Esophagus.

Study TCSC 93-07 was a single center, investigator-sponsored (Dr. Bergein Overholt), uncontrolled Phase II study. The objectives of the study were to evaluate the safety and efficacy of PHOTOFRIN PDT in patients being treated for dysplasia or early adenocarcinoma in BE and to determine the required light dose to produce effective results. A total of 99 patients were enrolled in the study. Of these patients, 44 had BE with high-grade dysplasia.

This was an open-label study in which patients were divided into 2 treatment groups. About one-half of the entire study population, including 14 high-grade dysplasia patients, were treated with a 175 – 225 Joules/cm light dose and a 5 or 7 cm PTG balloon at first treatment. The other half

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of the study population were treated with a light dose of 150 – 300 J/cm light dose and a 2, 3, 5, or 7 cm PTG balloon at first treatment.

Criteria for patient selection were similar to those in the PHO BAR 01 study, although much less extensive.

The Inclusion Criteria were as follows:

1. Biopsy-proven dysplasia or early adenocarcinoma of the esophagus in BE, without ultrasound evidence of tumor extension through the muscularis (stage T₂N₀M₀ or less).
2. Ineligible or refused standard methods of treatment including esophageal resection.
3. No contraindications to endoscopy
4. Male or female, 18 years of age or older. Females with adequate precautions against pregnancy.
5. Signed informed consent, or consent by next of kin or legal representative.
6. Karnofsky Performance status >30.

The Exclusion Criteria were as follows:

1. Tumor extension beyond muscularis
2. Porphyria or sensitivity to porphyrins
3. WBC <2,000, platelets <50,000, PT >1.5 times normal
4. Impaired renal or hepatic function
5. Received radiation or chemotherapy within 4 weeks before the admission to this study

Removal of Patients from Therapy or Assessment:

1. If no tumor response after 2 courses of PHOTOFRIN PDT (visual or biopsy evidence)
2. Unacceptable toxicity
3. Patient refused to continue treatment

Patients who were removed from the study less than 30 days after receiving PHOTOFRIN were cautioned against sunlight or strong light.

Study Title: TCSC 96-01. Photodynamic Therapy of Dysplasia or Early Adenocarcinoma in Barrett's Esophagus: A Randomized Study of the Effect of Steroid Therapy on the Incidence of Esophageal Stricture.

Study TCSC 96-01 was a single center, investigator-sponsored (Dr. Bergein Overholt), partially blinded, randomized, Phase II parallel-group study. The study objective was to compare the incidence and severity of esophageal strictures between patients with BE who received steroid therapy after PHOTOFRIN PDT and patients who received PHOTOFRIN PDT alone for treatment of dysplasia and/or early adenocarcinoma of the esophagus. A total of 87 patients were enrolled in the study. Forty-two (42) of these patients had BE with high-grade dysplasia, 30 patients had BE with low-grade dysplasia, 4 patients had adenocarcinoma, and 10 patients had other conditions, including patients with BE without dysplasia or carcinoma.

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Study TCSC 96-01 was a follow-up to study TCSC 93-07, which had demonstrated that PHOTOFRIN PDT was an effective treatment for destroying dysplasia and early cancer in BE patients. However, a serious side effect of PHOTOFRIN PDT was the formation of esophageal strictures due to fibrosis and scar formation during the healing process after treatment. Steroid therapy had been reported to reduce fibrosis in a variety of conditions, including corrosive burns of the esophagus.

The study was partially blinded. All patients received PHOTOFRIN PDT and omeprazole, and were randomized to steroid treatment or no steroid treatment. Patients and investigators were aware of the treatments administered. Only the endoscopists, who were responsible for evaluating esophageal stricture formation in the patients during the study, were blinded to whether the patient was in the steroid treatment group or not.

Reanalysis of Phase II study data by the sponsor

The data from the Phase II studies were reanalyzed by the sponsor in accordance with the analysis of the pivotal study, including

- 1) revised patient inclusion criteria (only patients with high-grade dysplasia),
- 2) revised objectives, and
- 3) revised outcome endpoints (primary efficacy endpoint data at 6 months of follow-up, and secondary efficacy endpoints and safety endpoints at 12 months of follow-up).

Thus, these analyses included data on 44 patients out of 99 in the TCSC 93-07 study, and on 42 patients out of 87 in the TCSC 96-01 study. Omeprazole was administered to all the patients in both trials.

Demographic Characteristics

Baseline demographic characteristics of high-grade dysplasia patients in the uncontrolled studies are shown in the Reviewer's Table below.

Note: the sponsor divides the patients in TCSC 93-07 into 2 groups: a group in which the patients were treated with a light dose of 175-225 J/cm and a 5 or 7 cm balloon at first treatment, and a second group in which the patients were treated with a light dose of 150 – 300 J/cm and a 2, 3, 5, or 7 cm balloon at first treatment. Since neither the baseline characteristics (vol. 42, p. 203; vol. 47, p. 166) nor the overall clinical response (primary efficacy endpoint) (vol. 42, p. 206; vol. 47, p. 170) differed between the two groups, the results of both groups are combined in the reviewer's tables below.

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Reviewer's Table on the Demographic Characteristics of High-Grade Dysplasia Patients in the Uncontrolled Studies

Characteristic	PHOTOFRIN PDT TCSC 93-07, N = 44	PHOTOFRIN PDT TCSC 96-01, N = 42
Age in years, mean (range)	65.4 (39.1 – 81.1)	67.3 (48.0 – 82.0)
Sex – Male, number (%)	39 (88.6%)	34 (81%)
Female number (%)	5 (11.4%)	8 (19%)
Race – White (Caucasian)	44 (100%)	40 (95.2%)
- Black (African-American)	0	1 (2.4%)
-Asian	0	1 (2.4%)

Sources: vol. 42, p. 203; vol. 47, p. 166.

The characteristics of Barrett's Esophagus at baseline are shown in the Reviewer's Table below (from Panel 11.2 in vol. 42, p. 204 for study TCSC 93-07, and Panel 11.2 in vol. 47, p. 168 for study TCSC 96-01)

Reviewer's Table on the Characteristics of Barrett's Esophagus at Baseline

Characteristic	PHOTOFRIN PDT TCSC 93-07, N = 44	PHOTOFRIN PDT TCSC 96-01, N = 42
Duration of BE in months, median (range)	24.2 (1.1 – 102.3)	10.9 (2.5 – 328.8)
Endoscopic length of BE		
< 6 cm	in 9 patients	In 9 patients
> 6 cm	in 27 patients	In 19 patients
Prior treatment		
- Medical therapy	in 40 patients	In 39 patients
- Surgery	in 9 patients	In 7 patients
- Endoscopic Ablation	in 1 patient	0
- Other	in 2 patients	0

Treatment of Patients with PHOTOFRIN and Photodynamic Therapy

1) Study TCSC 93-07

All patients received 2.0 mg/kg of PHOTOFRIN I.V., and the first laser light treatment was administered to the esophageal segment 40-50 hours later. A second laser light treatment, if indicated, occurred 4 - 9 days after injection of PHOTOFRIN. One-half of the patients were treated with a light dose of 175-225 J/cm and 5 cm or 7 cm balloon at first treatment; the other half of the patients were treated with a light dose of 150 - 300 J/cm and a 2, 3, 5, or 7 cm balloon at first treatment.

Follow-up and assessments were as described below for study TCSC 96-01.

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2) Study TCSC 96-01

All patients received 2.0 mg/kg of PHOTOFRIN I.V., and the first laser light treatment was administered to the esophageal segment 40-50 hours later. A second laser light treatment, if indicated, occurred 4 - 9 days after injection of PHOTOFRIN. A 5 or 7 cm balloon was selected to treat, when possible, the entire length of Barrett's mucosa that was biopsy positive for high-grade dysplasia with at least 0.5 cm of normal tissue margins. Most patients received a light dose of 175 or 200 Joules/cm. The predominant balloon type used in this study was the second generation Polymer Technology Group (PTG) balloon; toward the end of the study the 3rd generation Wilson Cook balloons ("Oreo balloons") began to be used. Light doses of 175 and 200 J/cm with a PTG balloon are approximately equivalent to a Wilson Cook balloon used at 130 J/cm, which is the light dose/balloon combination that was used in the pivotal PHO BAR 01 study.

Patients, who were randomized to receive steroid therapy, received descending oral doses of prednisone, starting on the treatment day at a dose of 60 mg daily for 2 days, followed by 50 mg daily for 2 days, 40 mg daily for 2 days, 30 mg daily for 2 days, 20 mg daily for 2 days, and 10 mg daily for 2 days (a total of 12 days).

All patients underwent efficacy evaluation by biopsy (4 quadrant) at each treatment session and at 6 and 12 months after first treatment. Debridement of necrotic tissue via endoscopy was performed if indicated 4 - 9 days after PHOTOFRIN injection. Treatment in some patients included Nd:YAG laser thermal ablation, if indicated. Patients could be treated with up to 2 additional courses of PHOTOFRIN PDT, providing at least 30 days or more had elapsed since the previous PHOTOFRIN injection. The goal of each treatment session was to destroy the entire segment of Barrett's mucosa with high-grade dysplasia.

The duration of each patient's participation was 12 months; thereafter, patients were followed for survival time. Follow-up included telephone contact once a week for the first 2 months and then monthly for the following 4 months after treatment to determine if patients developed dysphagia.

Reviewer's Table on Photodynamic Therapy in Patients

Description of PDT treatments is from Tables 1.13 and 3.1 in vol. 42, p. 270, 297 for study TCSC 93-07 and from Table 1.13 in vol. 47, p.261 for study TCSC 96-01.

Courses of treatment	PHOTOFRIN PDT TCSC 93-07, N = 44 patients	PHOTOFRIN PDT TCSC 96-01, N = 42 patients
Course 1	44 patients - 1 st laser Rx 25 patients - 2 nd laser Rx	42 patients - 1 st laser Rx 15 patients - 2 nd laser Rx 1 patient - 3 rd laser Rx
Course 2	13 patients - 1 st laser Rx 7 patients - 2 nd laser Rx	12 patients - 1 st laser Rx 2 patients - 2 nd laser Rx
Course 3	2 patients	1 patient - 1 st laser Rx

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Thirty-five (35) of 44 patients (80%) completed study TCSC 93-07. The reasons for discontinuation of 9 patients from the study are shown in the Reviewer's Table below (sources: vol. 42, pp. 199,200, 232).

Thirty-six (36) of 42 patients (85.7%) completed study TCSC 96-01. The reasons for discontinuation of 6 patients from the study are shown in the Reviewer's Table below (sources: Table 1.1, vol. 47, pp.199, 162, 315).

Reviewer's Table on Patient Disposition in the Uncontrolled Studies

Causes of patients' discontinuations from the study	PHOTOFRIN PDT TCSC 93-07 N = 44	PHOTOFRIN PDT TCSC 96-01 N = 42
Death	2 (1 cardiac arrest, 1 meningitis)	1 (cause unknown, 19 days after Course 3)
Patient withdrew	1	
Other	1 dehydration, 1 bladder cancer & hematuria, 1 thrombocytopenia, 1 atrial fibrillation, 1 renal failure & bilateral pleural effusion, 1 ventricular fibrillation	1 esophagectomy, 1 lung transplant disrupting schedule, 1 different follow-up schedule, 2 missing records
Total	9 (20%)	6 (14.3%)

Patient follow-up after treatment is shown in the Reviewer's Table below. In study TCSC 93-07 84% of patients completed 12 months of follow-up (data source: Panel 10.1, Tables 1.1 and 1.10 in vol. 42, pp. 200, 240, 243).

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Reviewer's Table of Patient Duration in the Uncontrolled Studies

Duration on Study	PHOTOFRIN PDT TCSC 93-07 N = 44	PHOTOFRIN PDT TCSC 96-01 N = 42
< 3 months	1	0
3 – 6 months	1	1
6 – 9 months	2	0
9 – 12 months	3	3
= 12 months (patients censored at 12 months)	35	36
> 12 months	2	2
Mean (range)	10.89 (2.2 – 27.5)	11.82 (3.0 – 16.0)

Primary Efficacy Endpoint: Overall Clinical Response

The response rates are shown in Reviewer's Table below (data from vol. 86, p. 206 for TCSC 93-07; In TCSC 93-07 the responses to different laser treatments were about the same: 12 out of 14 (85.7%) patients responded after treatment with 175 – 225 J/cm, and 27 out of 30 (90%) patients responded after treatment with 150 – 300 J/cm. Therefore, the results of both treatment arms are combined.

In study TCSC 96-01 the responses were about the same in patients treated with steroids and in patients not treated with steroids, 18/21 (85.7%) and 19/21 (90.5%), respectively. Patients in the steroids arm were treated with tapering doses of oral prednisone (described above) for 12 days after PHOTOFRIN PDT. The results of both treatment arms are combined.

Reviewer's Table on Primary Efficacy – Overall Clinical Response (First Six Months of Follow-up)

Responders	PHOTOFRIN PDT TCSC 93-07 N = 44	PHOTOFRIN PDT TCSC 96-01 N = 42
CR1 or CR2 or CR3	39 (88.6%)	37 (88.1%)

These results support the complete response data in the controlled study.

Secondary Efficacy Endpoints: Overall Clinical Response (Complete, i.e. Twelve-month, Follow-up) and Quality of Response

Both uncontrolled trials had Overall Clinical Response at 12 months of follow-up as the primary endpoint. The sponsor presents the 6-month follow-up results as the Primary Efficacy Endpoint for comparison with the same endpoint in the controlled trial. The 12-month complete response

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data is presented as a Secondary Efficacy Endpoint. These data together with the quality of response data are shown in the Reviewer's Table below.

Reviewer's Table on Secondary Efficacy Endpoints – Overall Clinical Response and Quality of Response (Complete, i.e. Twelve-month, Follow-up)

Responders	PHOTOFRIN PDT TCSC 93-07, N = 44 patients	PHOTOFRIN PDT TCSC 96-01, N = 42
CR1	25 patients (56.8%)	25 (59.5%)
CR1 or CR2	36 patients (81.2%)	38 (90.5%)
CR1 or CR2 or CR3	41 patients (93.2%)	40 (95.2%)

Sources: vol.41, pp. 207, 208, 210; vol. 47, pp.171-2.

The 12-month complete response data are even better than the 6-month response data. That is puzzling. Not only there appear to be no failures in the second 6 months, but 5 patients who had been response failures at 6 months were responders at 12 months.

Secondary Efficacy Endpoint – Duration of Response

Responders and Duration (median, in days)	PHOTOFRIN PDT TCSC 93-07, N = 44 patients	PHOTOFRIN PDT TCSC 96-01, N = 42
CR1	Median duration 105 days	Median duration 98 days
CR1 or CR2	Median duration 192 days	Median duration 273 days
CR1 or CR2 or CR3	Median duration 391 days	Value cannot be estimated

Sources: vol. 42, p. 210, Panel 11.6 for TCSC 93-07; vol. 47, p. 173.

The relatively short (12-month) follow-up period permits only tentative estimates of duration of responses; the sponsor was unable to establish 95% confidence intervals for the above response data. The sponsor presented Kaplan-Meier plots (vol. 42, p. 211; vol. 47, p. 174) of the durations of responses stretching out to over 1,000 days, but the small number of patients followed beyond 12 months raise the issue of reliability of these plots. They are not reproduced in this review.

The Duration of Response data is inconsistent with the 12-month complete response data in TCSC 93-07. If median duration of complete response was 391 days, then nearly half of the patients had failed after 12 months of follow-up, not 7% as shown in the previous table.

According to the sponsor, most failures appeared to occur within the first 4 months after randomization and treatment. The reviewer examined the data listings for times of failure, which are presented in the Reviewer's Table below. The times of failures are grouped by 3 month intervals. The sponsor's conclusions on the time of most failures are not well-supported by these data, especially in study TCSC 96-01.

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Reviewer's Table of Response Failures During 12-month Follow-up

Months after first treatment	PHOTOFRIN PDT TCSC 93-07, N = 44	PHOTOFRIN PDT TCSC 96-01, N = 42
0 – 3 months	8 (days 55, 56, 75, 79, 88 x 2, 90, 91)	3 (days 2, 68, 86)
3 – 6 months	6 (days 100, 120, 137, 139, 167, 174)	3 (days 96, 97, 102)
6 – 9 months	1 (day 215)	3 (days 195, 196, 259)
9 – 12 months +	2 (days 310, 322)	3 (days 341, 361, 430)
12-month total	17 (36.8%)	11 or 12 (28.6%)

Sources: Table 3.7.3, vol. 86, p. 286 for TCSC 93-07; Table 3.7.3, vol. 47, p. 250 for TCSC 96-01.

The above data are not consistent with the 12-month Complete Response data and may not be consistent with the Duration of Response estimates.

Secondary Efficacy Endpoint: Time to Progression to Cancer

The Time to Progression to Cancer (TTP) was defined as the period in days from the date of first treatment with PHOTOFRIN PDT until the date the progression to cancer was first documented. Median TTP could not be estimated because fewer than 50% of patients had a documented TTP by the end of the 12-month follow-up period.

The reviewer examined the data listings to find out how many patients had progressed to cancer and when the progression to cancer was noted. Eight patients (18.2%) progressed to cancer in TCSC 93-07 during the 12-month follow-up. Reviewer's Table below shows the time periods when progression to cancer was first noted. Two patients (4.8%) progressed to cancer in TCSC 96-01 within 12 months and one in the subsequent follow-up.

Reviewer's Table on Time to Progression to Cancer

Months after first treatment	PHOTOFRIN PDT TCSC 93-07, N = 44	PHOTOFRIN PDT TCSC 96-01, N = 42
0 – 3 months	2 patients (days 2 & 25)	0
3 – 6 months	3 patients (days 93, 99 & 176)	1 patient (day 106)
6 – 9 months	3 patients (days 194, 227 & 232)	1 patient (day 186)
9 – 12 months +	0 patients	1 patient (day 491)
Total for 12 months	8 (18.2%)	3 (7.1%)

Sources: Table 3.9.1, vol. 42, p. 293; Table 3.9.1, vol. 47, p. 255.

Reviewer's Note: The sponsor appears to separate response failures (Tables 3.7.3) from progression to cancer (Tables 3.9.1), as the different days of occurrence indicate. Patient

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identification numbers are not provided in these two sets of tables. Presumably response failures represent patients who underwent other forms of therapy. Both patients who progressed to cancer and patients who received other forms of therapy should be considered treatment failures. The sponsor will be asked to clarify these discrepancies.

If the number of patients in study TCSC 93-07 whose Complete Responses failed (17) and those who Progressed to Cancer (8) are added (25), then such patients comprise 56.8% of the patients treated and followed for 12 months. Patients in study TCSC 96-01 whose Complete Responses failed (12) and those who Progression to Cancer (3) together (15) comprise 35.7% of the treated population followed for 12 months.

Secondary Efficacy Endpoint: Survival Time

Survival Time was defined as the period in days from the date of first treatment with PHOTOFRIN PDT to the date of patient's death.

In study TCSC 93-07 only one patient died within 12 months of follow-up at day 281 (cause: cardiac arrest). Four patients died at days 430 (cause: meningitis), 933, 1079, and 1337.

The sponsor states that in study TCSC 96-01 no patient had a documented death by the end of the follow-up (Efficacy Summary, vol. 8, p. 101). Table 3.10.1 showing Comparison by Group of the Survival Time is missing in vol. 47, but there is a death report among adverse events narratives in vol. 47, p. 315. This 83 year old female patient received 3 courses of PHOTOFRIN PDT over an eighteen-month period. Seventeen days after the third course she died; no information as to cause of death is available.

The Secondary Endpoint: Survival Times could not be estimated in either study. With the short follow-up this is not a useful endpoint.

D. Efficacy Conclusions

Treatment of high-grade dysplasia as surrogate endpoint for prevention of adenocarcinoma. High-grade dysplasia does not need to be treated except for one reason: 25% to 30% of high-grade dysplasia patients develop adenocarcinoma of the esophagus over a period of 3 to 7 years. The corollary is that 70% - 75% do not, and any treatment of high-grade dysplasia has to be evaluated with these statistics in mind. Because esophageal carcinoma carries a very dismal prognosis, some gastroenterologists recommend esophagectomy as treatment of choice for high-grade dysplasia, while others recommend an aggressive surveillance protocol. Photodynamic therapy with PHOTOFRIN offers a third choice.

The primary endpoint efficacy data in the controlled trial are impressive: the initial response, complete ablation of high-grade dysplasia with re-epithelialization with normal squamous epithelium, was found in 41% of PHOTOFRIN PDT patients and in only 4% of control arm patients. Complete ablation followed by re-epithelialization with normal squamous epithelium or with normal epithelium and some areas of Barrett's metaplasia was found in 49% of

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PHOTOFRIN PDT patients and in only 6% of control patients. And, finally, re-epithelialization with normal epithelium, or normal epithelium with some areas of metaplasia, low-grade dysplasia or indefinite dysplasia was found in 72% of PHOTOFRIN PDT patients and in 31% of control patients, a 41% difference that is highly significant.

However, the response to PDT has little meaning if it is not sustained. Within 12 months from enrollment 27% of PHOTOFRIN PDT were discontinued from the study, 11% because of progression of disease (adenocarcinoma) and 7% because they had other therapy. The statistics were worse in the control group, 41% were discontinued from the study, 20% because of progression of disease (adenocarcinoma), 19% because they had other therapy, including PHOTOFRIN PDT. Median duration of response could not be reliably estimated during this length of follow-up, and 24 month follow-up data are required to better assess the efficacy of PHOTOFRIN PDT.

Other secondary efficacy endpoints: median time to progression to cancer, median time to treatment failure, and survival time could not be estimated during the short follow-up and insufficient number of patients studied. None of the patients developed metastatic adenocarcinoma of the esophagus, and none died from adenocarcinoma of the esophagus.

The single-center uncontrolled trials appear to provide outcome data that support the results of the primary controlled trial, but there are inconsistencies in these data that require clarification.

Thus, the sponsor has provided data showing that PHOTOFRIN PDT is effective in ablation of high-grade dysplasia, but has not shown that is sustained and is effective in preventing deaths due to adenocarcinoma of the esophagus. The Agency had noted in the March 5, 2001 teleconference that "6-month follow-up data may be inadequate to assess the impact of treatment." The Advice Letter after the review of PHO BAR 01 protocol (January 25, 2001) communicated to the sponsor that "the primary response variable must reflect an improvement in the long-term clinical outcome."

In addition, the January 25, 2001 Advice Letter requested "an analysis of clinical outcomes of individuals associated with treatment failure in conjunction with outcomes associated with treatment success. Such outcomes should be compared to those associated with other modes of treatment such as esophagectomy." The sponsor did not provide this analysis with this submission.

The review of the efficacy section was made difficult by lack of composite outcomes analyses, incorporating the following:

- Patient ID number
- Length of follow-up
- Outcome (continuing in CR, or Progression of cancer [and treatment for it], or Other Therapy [specified], Discontinued from Study [reasons])
- Percentages of patients remaining in CR as a function of time
- Percentages of patients progressing to cancer as a function of time
- Percentages of patients treated with Other Therapies as a function of time

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These pieces of information are scattered, and some conclusions have to be inferred from dates of treatment failure or of progression to cancer.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety data appears to be adequately presented. The major drawback of these studies is the small number of patients, a total of 318. The pivotal trial is a controlled study; the control arm provides a background of adverse event frequency in this population.

The major side-effects of photodynamic therapy, using PHOTOFRIN as photosensitizing agent, are acute events related to the light treatment itself and longer lasting effects relating to the healing of esophagus and the extended period of photosensitivity of the skin. The acute effects were dysphagia, odynophagia, vomiting, nausea, abdominal pain, chest pain and fever. These symptoms were reported by about 25 % to 35% of patients. The most important sub-acute effects were esophageal strictures and photosensitivity reactions. A stricture was defined as esophageal narrowing requiring dilation. Strictures affected about 35% of patients. Their treatment required repeated dilations, probably because PHOTOFRIN PDT results in deep (up to 6 mm) necrosis, involving not only the esophageal mucosa but also the muscularis, and healing results in tight bands of fibrous tissue. Skin photosensitivity reactions were common (67% of patients in the pivotal study), in spite of documented warnings about exposure to sunlight and bright lights for 30 days.

The relatively good safety record of PHOTOFRIN PDT is reflected in 1) few withdrawals from the study (4 %), and in 2) high percentage of study completion.

B. Description of Patient Exposure

The present NDA contains the results of three studies in patients with BE who had high-grade dysplasia, a pre-malignant condition. The pivotal PHO BAR 01 study compared PDT with PHOTOFRIN plus omeprazole (PHOTOFRIN + OM) to a surveillance arm consisting of omeprazole only (OM Only). In this study, 208 patients were enrolled in 2:1 ratio, 138 patients were randomized to receive PHOTOFRIN + OM (treatment arm) and 70 patients were randomized to receive OM Only (control arm). Of those, 133 patients (96%) received at least one injection of PHOTOFRIN and 132 out of 133 received at least one complete course of PHOTOFRIN PDT. Seventy patients were randomized into the OM Only treatment group, of which 69 (99%) received at least one omeprazole dose.

In addition, this NDA includes data from 2 open-label clinical trials (TCSC 93-07 and TCSC 96-01) conducted under a physician-sponsored IND of PDT with PHOTOFRIN in BE (Dr. B.F. Overholt, Thompson Cancer Survival Center, Knoxville, TN; IND 42,313). Study 93-07 was an open-label study in 99 patients, 44 of whom met the criteria for high-grade dysplasia. These

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patients were divided into 2 treatment groups, which received different laser light treatments. Study 96-01 was a randomized, partially blinded study of the effect of steroid treatment on the development and severity of esophageal strictures associated with PDT. Forty-two (42) BE patients with high-grade dysplasia were randomized in 1:1 ratio into 2 groups, one that will be treated for 12 days with tapering doses of prednisone following the light exposure and one that will not be treated. All the patients in studies TCSC 93-07 and TCSC 96-01 were treated with omeprazole (20 mg twice daily).

Extent of Exposure. Photodynamic therapy (PDT) consists of 2 modalities: administration of a photosensitizing agent, in this case PHOTOFRIN, and administration of light, which results in tissue damage. Each of these modalities poses distinct safety issues.

Treatment with PHOTOFRIN is by intravenous injection and consists of a 2 mg/kg dose, followed by 630 nm laser-light treatment 48-72 hours after drug administration. Additional injection of PHOTOFRIN is not performed until 90 days has passed, and only if follow-up endoscopy reveals new areas of dysplasia in need of treatment. The PHOTOFRIN dose was the same in all the patients in these 3 studies, and had been the standard dose in all the previous studies for other indications.

In contrast to PHOTOFRIN treatment, light delivery methods and doses changed during the individual studies and between the studies. Laser light is passed through endoscopically placed fiber optics tipped with cylindrical diffusers. In normal esophagus, as well as BE, an inflatable centering balloon is needed to improve light dosimetry in an organ that tends to collapse, with the result that internal mucosal folds create a "hill and valley" effect. Pre-clinical and necropsy data demonstrated that with the diffuser/balloon combination the PDT response is circumferential and uniform, while with the diffuser alone the effect varied from minimal to severe. Reviewer's Table below summarizes the types of balloons and the 630 nm light dosages used in the three trials.

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Reviewer's Table Summarizing Light Delivery Systems in the PHOTOFRIN Trials

Study ID	Equipment and Light Doses	Comments
TCSC 93-07	"Black-capped" (black at ends, transparent in the center) 3 cm balloons, later 5 cm and 7 cm balloons.	Multiple light sessions were required to treat segments > 3 cm. Overlap areas received more than one light treatment; these areas were particularly prone to development of esophageal strictures. Balloons of 5 and 7 cm developed. Peak of light in the middle of 5 cm window may have led to strictures. Fifteen (15) courses were administered with 3 cm balloons, 13 courses with 5 cm balloons, 6 courses with 7 cm balloons, and 2 courses with 2 cm balloons.
TCSC 96-01	"White capped" (reflective inner coating at ends), 5 cm and 7 cm. Light doses 175 J/cm and 200 J/cm.	Sixteen (16) courses were administered with 5 cm balloons, and 38 courses were administered with 7 cm balloons.
PHO BAR 01	Fiber optic diffusers of 9 cm, 7 cm, and 5 cm. Wilson Cook white-capped balloons, window sizes of 7 cm, 5 cm, and 3 cm. Light dose 130 J/cm of diffuser length. Treatment time 480 sec.	Short fiber optic diffusers (<2.5 cm) were used to pre-treat nodules with 50 J/cm diffuser length (86 treatments in 35 patients) prior to regular balloon treatment in the first laser light session. Thirty-nine (39) courses were administered with 3 cm balloons, 57 courses with 5 cm balloons, and 170 courses with 7 cm balloons.

Sources: vol. 3, p.50; vol. 11, p. 151; vol. 48, p. 25; vol. 13, p. 35.

Precautions taken during the studies. All patients injected with PHOTOFRIN were photosensitive and had to observe precautions to avoid exposure of eyes and skin to direct sunlight or bright indoor light (e.g. examination lamp, dental lamps, operating room lamps, unshaded light bulbs at close proximity) for at least 30 days. Some patients remained photosensitive for up to 90 days or more. Therefore, patients were asked to avoid darkened room after 30 days, and were encouraged to expose their skin to ambient indoor light to allow gradual inactivation of the remaining drug through photobleaching. The level of photosensitivity varies for different areas of the body, depending on the extent of previous exposure to light. Before exposing any area of the skin to direct sunlight or bright indoor light, patients were asked to test the skin for residual photosensitivity by exposing a small area of the skin to sunlight for 10 minutes. If no photosensitivity reaction (erythema, edema, blistering) occurred within 24 hours, patients could gradually resume normal outdoor activities. If some photosensitivity reaction occurred, patients had to continue precautions for another week before re-testing. Skin around the eyes may be more sensitive to light; patients were asked not to use the face for testing residual photosensitivity.

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Ocular discomfort, commonly described as sensitivity to sun, bright light, or car headlights, has been reported. Patients were asked to wear dark sunglasses (average white light transmittance of <4%) when outdoors for a period of 30 days.

Precautions must be taken to prevent extravasation of PHOTOFRIN at the injection site. If extravasation occurs, the area had to be protected from light.

As a result of PDT treatment, some patients complained of substernal chest pain and nausea because of inflammatory responses within the area of treatment. Such pain may be of sufficient intensity to warrant the short-term prescription of opiate analgesics.

Durations of follow-up in the 3 studies are described in Reviewer's Tables in the Efficacy section.

C. Methods and Specific Findings of Safety Review

Almost all the patients treated with PHOTOFRIN PDT + OM experienced at least one treatment-emergent adverse event (TEAE). For the sake of clarity the frequencies of events will be summarized for all three PHOTOFRIN PDT trials and contrasted with the frequency of TEAE's in the OM Only arm of the PHO BAR 01 trial. Differences in the frequencies of TEAEs among the three PHOTOFRIN trials will be noted.

Reviewer's Table: Treatment Emergent Adverse Events in >2.0% of High-grade Dysplasia Patients in TCSC 93-07, TCSC 96-01 and PHO BAR 01 Studies

Body System and Preferred Term	All 3 PHOTOFRIN PDT studies, N = 318	PHO BAR 01	
		PHOTOFRIN PDT N = 133	OM Only N = 69
Number of patients (%) with Any Event	313 (98.4%)	130 (98%)	47 (68%)
Gastrointestinal	259 (81.4%)	97 (73%)	22 (32%)
Nausea	124 (38.9%)	17 (13%)	6 (9%)
Dysphagia	62 (19.5%)	26 (20%)	0
Esophageal stricture	91 (28.6%)	48 (36%)	1 (<1%)
Vomiting	102 (32.1%)	46 (35%)	4 (6%)
Odynophagia	48 (15.1%)	16 (12%)	0
Abdominal pain	34 (10.4%)	15 (11%)	3 (4%)
Hiccup	24 (7.5%)	13 (10%)	0
Constipation	44 (13.8%)	34 (26%)	5 (7%)
Diarrhea	16 (5.0%)	16 (12%)	5 (7%)
Body as a Whole	221 (69.5%)	74 (56%)	21 (30%)
Chest pain	151 (47.5%)	36 (27%)	5 (7%)
Fever	70 (22.0%)	30 (23%)	2 (3%)
Pain	62 (19.4%)		

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Skin and Appendages	157 (49.4%)	100 (75%)	4 (6%)
Photosensitivity reaction	140 (44.0%)	89 (67%)	0
Skin disorder	14 (4.4%)	13 (10%)	1 (1%)
Metabolic and Nutritional	55 (17.3%)	37 (28%)	9 (13%)
Dehydration	29 (9.2%)	16 (12%)	2 (3%)
Weight decrease	9 (2.8%)		
Central Nervous System	30 (9.4%)	30 (23%)	11 (16%)
Headache	14 (4.4%)	14 (11%)	5 (7%)
Heart rate/ Rhythm disturbances	12 (3.8%)		
Psychiatric	26 (8.2%)		
Anorexia	16 (4.7%)		

While the frequencies of many adverse events were similar among the three PHOTOFRIN groups, there were some differences, such as

- Treatment-related esophageal strictures (Endoscopy data) occurred in 42% of TCSC 93-07 patients (vol.8, p.141), in 36% of TCSC 96-01 patients (vol. 8, p. 148), and in 35% of PHO BAR 01 patients (vol.8, p.121). In a composite Table on Strictures in all 3 studies (vol.8, p.115) the percentages of patients with esophageal strictures are 31%, 14%, and 36%, respectively. The table specifies that esophageal stricture category “includes all esophageal narrowing regardless of dilation needs.” However, this statement is not correct. In study 93-07 28.3% of all PHOTOFRIN patients group developed an esophageal narrowing not requiring dilations, while 42.4% developed an esophageal stricture (vol.8, p.140). The percentage of patients in study 96-01 who developed an esophageal narrowing not requiring dilations is not stated. In PHO BAR 01 study, 18% of patients in the PHOTOFRIN PDT group and 6% of patients in the control group developed an esophageal narrowing not requiring dilations. In general, the percentages of esophageal strictures are lower in the Adverse Event data than in the Endoscopy data. For that reason the above table underestimates the incidence of strictures.
- Nausea was less frequent in PHO BAR 01 patients (13%) than in the two TCSC trials (56% and 61%).
- Chest pain was less frequent in PHO BAR 01 patients (27%) than in the two TCSC trials (69% and 55%).
- Pain was not listed as occurring in PHO BAR 01 patients, but was present in 12% and 55% in TCSC 93-07 and 96-01, respectively.
- Pleural effusions were not noted in the PHO BAR 01 trial, but occurred in 20% and 14% of patients in TCSC 93-07 and 96-01 trials, respectively.
- Photosensitivity reactions were present in 67% of PHO BAR 01 patients, but in only 27% of TCSC 93-07 or TCSC 96-01 patients.

The adverse events profile of the OM Only group was strikingly different from the PHOTOFRIN PDT groups, and brings into focus adverse events that accompany PDT. In particular, PDT appears to be characterized by acute adverse events at the time or shortly after PDT, and by more chronic adverse events that develop over weeks following PDT, as shown below:

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- Acute gastrointestinal adverse events following therapy: nausea, vomiting, dysphagia, odynophagia
- Acute chest and abdominal adverse events: chest pain, abdominal pain, fever, pleural effusions
- Sub-acute adverse events: esophageal stricture, photosensitivity reactions

Not only a greater percentage of patients in the PHOTOFRIN PDT group experienced adverse events than patients in the OM Only group; they experienced about twice number of adverse events, as shown in the Reviewer's Table below (data from vol. 13, p. 124).

Reviewer's Table: Treatment Emergent Adverse Events in >10% of the Patients in the PHO BAR 01 Study

	PHOTOFRIN PDT + OM	OM Only /
Total number of patients with TEAEs, (%)	130 (98%)	47 (68%)
Total number of events	1,245	206
Life threatening	10	1
Severe	212	33
Moderate	387	64
Mild	636	108
Number of events/number of patients	9.6	4.4

Photosensitivity reactions. Photosensitivity of the skin is a known side effect of PHOTOFRIN treatment. Most of the photosensitivity reactions occurred within 90 days after PHOTOFRIN injection. Most of the reactions were mild (68%) or moderate (26%), and 97% were considered associated with treatment. Exposed areas (face, hands and neck) were affected the most. Severe reactions occurred in 12 (9.2%) patients in the PHO BAR 01 study and were characterized by swelling, pruritus, erythema, blisters, itching, burning sensation and heat. All resolved over time.

Esophageal stricture. Esophageal strictures are the most important of treatment-related adverse events. All esophageal narrowing data were collected using the term "esophageal stricture", regardless of subsequent management. Later, only esophageal narrowing that required dilation was considered a stricture. The following composite table presents a summary of esophageal strictures from the endoscopy data in the three trials. The sponsor characterizes the strictures as mild in about 44% of patients, moderate in 43%, and severe in 12%.

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**Reviewer's Table: Esophageal Strictures in PHO BAR 01, 93-07 and 96-01 Patients
(Endoscopy Data)**

	TCSC 93-07 N = 99	TCSC 96-01 N = 86	PHO BAR 01, PDT, N = 138	OM Only N = 70
Patients with baseline strictures		1 (2.4%)	2 (1%)	2 (3%)
Strictures following treatment	42 (42.4%)	31 (36.0%)	48 (35%)	1 (1%)
Course 1		26 (30.2%)	18 (13%)	
Course 2		5 (5.8%)	29 (21%)	
Course 3		0	1 (1%)	

Sources: vol. 13, p. 127; vol. 42, p. 227; vol. 47, p. 186.

Esophageal strictures were sufficiently severe requiring multiple dilations. Two of the patients developed esophageal perforations during dilations (described below). The Reviewer's Table below presents the composite data on esophageal dilations.

Reviewer's Table: Esophageal Dilations in Patients Treated with PHOTOFRIN PDT

Number of Dilations	TCSC 93-07, N = 99	TCSC 96-01, N = 86	PHO BAR 01 N = 138
1-2	12(12.1%)	14 (16.3%)	16 (12%)
3-5	13(13.1%)	12 (14.0%)	10 (7%)
6-10	7 (7.1%)	5 (5.8%)	14 (10%)
>10	10 (10.1%)	0	8 (6%)

Sources: vol. 13, p. 127; vol. 42, p. 228; vol. 47, p. 188.

Reviewer's Table: Distribution of Frequency of Dilations

Number of Dilations	Total Number of Patients in the Three PHOTOFRIN PDT Trials Undergoing Dilations	Percentages of Frequencies of Dilations
1-2	42	34.7%
3-5	35	28.9%
6-10	26	21.5%
>10	18	14.9%

Chest Pain. The number of patients reporting chest pain increased shortly after PDT and then declined over a 4-week period. About 12% of patients reported severe chest pain, 34-41% reported moderate chest pain, and the 19-30% mild chest pain.

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Odynophagia and dysphagia. About 5% of patients reported severe odynophagia, about 15-18% moderate odynophagia, and 11-19% mild odynophagia. Approximately the same percentages of patients reported dysphagia. Odynophagia remitted over 4 weeks following PDT, and dysphagia, over 6 months.

Deaths. There were 3 deaths in PHO BAR 01 study during the 12-month follow-up; none related to treatment. Two female subjects, 74 and 82 years of age, died in the PHOTOFRIN group, one from breast cancer, deep vein thrombosis, pulmonary embolism and renal failure, the other from a cardiac arrest, following CABG and cardiac tamponade. One 68 year old male died in the OM Only group, from a massive stroke.

Two patients died in the 93-07 study. A 75 year old male with a history of cardiac arrhythmias died from cardiac arrest, and a 77 year old male died from enterococcal meningitis. One patient died in the 96-01 study, an 83 year old female with CAD. Death was unexpected and cause of death was not ascertained. None of the deaths in either study were thought to be related to treatment.

Withdrawals Due to Adverse Events. In the PHO BAR 01 study, three patients in the PHOTOFRIN group had adverse events that led to withdrawal from the study. One patient underwent an esophagectomy following perforation of the esophagus that occurred during an esophageal dilation for an esophageal stricture. One patient developed an anxiety reaction during the period between PHOTOFRIN injection and laser light treatment; she refused the light treatment. One patient was diagnosed with non-small cell lung cancer.

Two patients were discontinued from study 93-07 due to adverse events, both were in the low-grade dysplasia group. A 66 year old male patient suffered an esophageal perforation during Course 1 of treatment; the event was probably related to treatment. A 70 year old male patient was diagnosed with pulmonary carcinoma; the event was definitely not related to treatment. One patient was discontinued from study 96-01, a 76 year old male patient with worsening heart disease, an event not related to treatment.

Other Serious Adverse Events. Forty (30%) of patients PHOTOFRIN PDT + OM group in the PHO BAR 01 study reported 118 SAEs, of which 36 were considered to be treatment-associated. Most related to the gastrointestinal system, followed by chest pain, abdominal pain, dehydration. The OM Only group had a lower incidence of SAEs (12 patients, 17%). None of the SAEs were considered to be associated with treatment.

Clinical Laboratory Evaluations. In the PHO BAR 01 study, laboratory data were collected at baseline and at Month 3 follow-up. Most (95% to 100%) abnormalities in hematology and clinical chemistry parameters were not clinically significant. None of the hematologic abnormalities shifted from not clinically significant to clinically significant. Shifts from not clinically significant at baseline to clinically significant at Month 3 occurred in 4 parameters: ALT (2%), total bilirubin (1%), and potassium (5%) in the PHOTOFRIN group and creatinine

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(4%) in the OM Only group. Clinical laboratory evaluations were not performed in the 2 supportive studies.

D. Adequacy of Safety Testing

The collection and analyses of safety data in the 3 trials were relatively straightforward, as compared to efficacy results and analyses. Variations in the frequencies of the most common adverse events between the 3 trials that were noted above may have been due to the relatively small numbers of patients. They may have also been influenced by local variations in care among the centers. It should be noted that one center (Dr. Overholt's Thompson Cancer Survival Center in Knoxville, TN) contributed about 69% of the total safety population. Patients' experiences at that one center may have influenced the relative frequencies of some adverse events.

Overall, safety testing appears to have been adequate.

E. Summary of Critical Safety Findings and Limitations of Data

The main safety issue with photodynamic therapy is the development of esophageal strictures. The incidence of strictures may have decreased with the development of light delivery systems, but at 35% in the PHO BAR 01 study it is still very high. The number of dilations for strictures is also impressive: 33% of patients with strictures had to have only 1-2 dilations, 21% of patients, 3-5 dilations, 29% of patients, 6-10 dilations, and 17%, more than 10 dilations. The single patient in the Omeprazole Only group with a stricture needed only 1 dilation.

The main limitation of the safety data is the relatively small number of patients in the three studies, and the very short follow-up.

VIII. Dosing, Regimen, and Administration Issues

Dosing of PHOTOFRIN has been standard for in all the studies, and does not need to be modified. Light administration underwent considerable development during the decade during which the three studies were conducted.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Approximately 15% of all study patients were female (Reviewer's Table below). This 6:1 male/female ratio is consistent with the published data on the gender ratios in esophageal adenocarcinoma and in BE. Neither efficacy nor safety gender analyses were carried out by the sponsor. The statistical reviewer carried out complete response (CR1 + CR2 + CR3) analysis by gender in the PHO BAR 01 trial. There appeared to be no gender differences. About 70%

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(82/117) of males and about 81% (17/21) of females had complete responses in the PHOTOFRIN PDT + OM group. About 30% (18/59) of males and about 36% (4/11) of females had complete responses in the OM Only group.

Demographic Characteristics of all BE with high-grade dysplasia patients in the three studies are shown in sponsor's table below, as condensed by the reviewer.

Reviewer's Table: Demographic Characteristics of BE with High-grade Dysplasia Patients

Study	PHOTOFRIN PDT + OM (PHO BAR 01, TCSC 93-07, TCSC 96-01)	OM Only	All study patients
Number of patients receiving study therapy	224	70	294
Age in years, mean (range)	66.95 (38.4 – 88.5)	67.27 (36.1 – 87.6)	66.26 (36.1 – 88.5)
Gender			
-Male	190 (84.8%)	59 (84%)	249 (84.7%)
-Female	34 (15.2%)	11 (16%)	45 (15.3%)
Race			
White (Caucasian)	221 (98.7%)	68 (97%)	289 (98.3%)
African-American	1	1 (1%)	2 (0.7%)
Asian	2	1 (1%)	3 (1.0)
Hispanic	0	0	0
Other	0	0	0

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

There appears to be an age effect in the complete response (CR1 + CR2 + CR3) rate in the PHOTOFRIN + OM group, as shown below.

Age	PHOTOFRIN + OM	OM Only
< 65 years	51/61 (84%)	6/25 (24%)
> 65 years	48/77 (62%)	16/45 (36%)
P	P = 0.0219	

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The other effects influencing complete response rates were treatment (PHOTOFRIN + OM vs. OM Only, $p < 0.0001$), high-grade dysplasia foci (single vs. multiple, $p < 0.0001$), and prior omeprazole intake of at least 3 months (yes vs. no, $p = 0.0005$).

White (Caucasian) race predominated overwhelmingly in the studies, as can be justified by the high incidence rates of both BE and esophageal adenocarcinoma in this race. Thus, no analyses by racial background are possible. As noted above in **Variations in Special Populations**, PHOTOFRIN has been studied in Japanese cancer patients, but because of different sampling times and small numbers of patients involved no conclusions could be drawn about variation in PHOTOFRIN pharmacokinetics between Caucasians and Japanese. Ethnic backgrounds were not described in the study populations in this submission.

C. Evaluation of Pediatric Program

Axcan Scandipharm, Inc. is requesting a waiver for pediatric studies in children. The reason for this request is that PHOTOFRIN has obtained Orphan Drug Designation, in accordance with Title 21 CFR 314.55 (d). (Volume 1, p. 259 of the submission).

D. Comments on Data Available or Needed in Other Populations

The sponsor has an OCPB Phase IV commitment (No. 2) under previous NDA 20-451 as follows:

“Conduct Phase IV studies to gather further pharmacokinetic (PK) data in patients with hepatic impairment and in patients who have received more than one course of therapy.”

As noted above, about 35% of PHOTOFRIN is excreted in the form of metabolites, primarily through bile/feces and minimally through the urine (6%). Exclusion criteria in the pivotal trial specify hepatic or renal impairment. Patients with BE with high-grade dysplasia and with mild hepatic impairment may be candidates for PHOTOFRIN PDT, although the incidence of BE and esophageal adenocarcinoma appears not to be increased in alcohol abuse patients.

X. Conclusions and Recommendations

A. Conclusions

The sponsor has presented preliminary findings of a controlled trial of photodynamic therapy using PHOTOFRIN for high-grade dysplasia in Barrett's Esophagus. The 6-month primary efficacy endpoint documents a complete response rate of 72% in the PHOTOFRIN PDT group versus a complete response rate of 31% in the control group. The complete responses consisted of complete ablation of high-grade dysplasia and re-epithelialization with normal epithelium as well as some metaplastic, low-grade dysplastic and indefinite epithelium. Re-epithelialization with completely normal squamous epithelium was ten times more common in the PHOTOFRIN PDT group than in the control group.

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Duration of the response, time to progression to cancer, time to treatment failure, and survival time could not be estimated, because these endpoints were defined as the day 50% of the patients had failure of complete response, progression to cancer, treatment failure, or survival. With a 12-month follow-up none of these secondary endpoints could be estimated. Yet, even at 6 months of follow-up there were marked advantages in outcomes favoring the PDT arm when compared to the control arm. The percentages of patients having progression of disease (11% in the PDT arm, 20% in the control arm), and the percentages of patients opting for other therapy (7% in the PDT arm, 19% in the control arm) clearly indicated the superiority of PHOTOFRIN PDT over active surveillance.

The superior early results of PHOTOFRIN PDT therapy have to be balanced by the far more frequent adverse events than in control group. Even then, it should be emphasized that there were no treatment-related deaths and that most SAEs were not treatment-related. The major safety issue is the common occurrence (35%) of esophageal strictures, which in some patients have posed major therapeutic challenges necessitating multiple dilations. There were two esophageal perforations as complications of the dilations.

A convincing risk-benefit requires a longer follow-up than the 12-month data provide.

B. Recommendations

1. The application for PHOTOFRIN for Injection for use in photodynamic therapy for high-grade dysplasia in Barrett's Esophagus is approvable.
2. Approval will depend on the review of the final study report of the pivotal, controlled trial, which contains a minimum of 24-month follow-up efficacy and safety data. As noted in the Advice Letter to the sponsor on January 25, 2001, "the primary response variable must reflect an improvement in the long-term clinical outcome." In addition the January 25, 2001 Advice Letter requested "an analysis of clinical outcomes of individuals associated with treatment failure in conjunction with outcomes associated with treatment success. Such outcomes should be compared to those associated with other modes of treatment such as esophagectomy."
3. Please provide a listing of patients who remained in complete response at the end of the follow up period in the 24-months follow-up in PHO BAR 01 study listing by patient the ID number and the length of follow-up. Similarly, please provide listings of patients who progressed to cancer, who received Other Treatment (specify), and who were discontinued from the study (specify reasons).
4. Please clarify the following. In the supporting Trials TCSC 93-07 and 96-01 patient ID numbers are not provided in Tables 3.7.3 and in Tables 3.9.1 in vols. 42 and 47. These Tables document Response Failures and Times to Progression to Cancer. The latter should be subsumed in the former, but the days of failure are different. This raises the question, were patients who Progressed to Cancer included among those who were Response Failures, as they should have been?

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5. Please clarify the following. The Complete Response rates in the supporting trials (93% and 95% at 12 months of follow-up, vol. 41, pp. 207, 208, 210; vol. 47, pp. 171-2) are not consistent with 12-month response failures of 36.8% and 28.6% (vol. Tables 3.7.3, vol. 86, p. 286; vol. 47, p. 250) or with time to Progression to Cancer (Table 3.9.1, vol. 42, p. 293).
6. Please perform a more detailed analysis of the poorer response rate to PHOTOFRIN PDT in older patients. Is there an age group in which PHOTOFRIN PDT is contra-indicated?
7. The Proposed Package Insert will need to be changed as dictated by the results of the minimum 24-month data.

XI. Appendix

A. Other Relevant Materials

The sponsor's Proposed Package Insert is not appended.

B. Individual More Detailed Study Reviews (If performed)

Not applicable.

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/s/

Edvardas Kaminskas
12/6/02 09:27:13 AM
MEDICAL OFFICER

Minor corrections of the November 14, 2002 review.

Hugo Gallo Torres
1/9/03 02:40:00 PM
MEDICAL OFFICER

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS**

MEDICAL OFFICER'S REVIEW

NDA: 21-525

Related NDAs/INDs/PMAs: NDA 20-451; IND 61,011; IND 42,313; IND 25,064; PMA P990021; PMA P940010

Sponsor: Axcan Scandipharm Inc.

Drug name: Photofrin (porfimer sodium)

Pharmacological category: Photosensitizing agent, polyporphyrin oligomer

Indication: Ablation of high-grade dysplasia in Barrett's esophagus

Route of administration: Intravenous injection

Date submitted: May 31, 2002

Date assigned: July 2, 2002

Date review completed: November 14, 2002

Date filed into DFS: November 14, 2002

Medical reviewer: Edvardas Kaminskas, M.D.

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Clinical Review for NDA 21-525

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Approval is sought for PHOTOFRIN, a photosensitizing agent, and for a special laser light delivery system to be used in photodynamic therapy (PDT) for ablation of high-grade dysplasia in Barrett's Esophagus patients who are not candidates for esophagectomy. Barrett's Esophagus is an uncommon complication of patients with gastroesophageal reflux disease, and consists of replacement of normal squamous cell epithelium by metaplastic, intestinal-type epithelium. High-grade dysplasia is a rare complication in Barrett's Esophagus, in which metaplastic epithelium is replaced by highly dysplastic epithelium.

High-grade dysplasia is a pre-malignant lesion; approximately 25% to 30% of patients with high-grade dysplasia will develop adenocarcinoma of the esophagus, a highly lethal malignancy with a 5-year survival of 11%. Patients with high-grade dysplasia are mainly managed by esophageal resection, or by intensive endoscopic surveillance with esophagectomy reserved only for those who develop adenocarcinoma. A third approach is mucosal ablation of high-grade dysplasia, with re-epithelialization of the treated area by normal squamous cell epithelium. The feasibility of this approach has been demonstrated in uncontrolled trials.

The present submission contains the preliminary results of a controlled trial, in which high-grade dysplasia patients were randomized to be treated by PHOTOFRIN PDT plus oral omeprazole or by oral omeprazole alone (control arm). The benefit of PHOTOFRIN PDT, as shown in the 6-month follow-up data from the controlled trial (all the patients had 6 months of follow-up; the median length of follow-up was 12 months), is a high complete response rate (72% of treated patients compared to 31% of control patients). Complete response is defined as ablation of high-grade dysplasia and re-epithelialization of the treated area by normal squamous cell epithelium with or without areas of metaplasia, low grade dysplasia, or indeterminate dysplasia. Because of the short follow-up, duration of this response is not certain. Endpoints, such as time to treatment failure, time to progression to cancer, and survival time, could not be estimated reliably. The major risk of PHOTOFRIN PDT is formation of esophageal strictures that require repeated dilations, probably because photodynamic damage to the esophagus is deep and healing results in scarring. Strictures requiring dilations occur in about 35% of patients. Other side-effects are less debilitating. An acute PDT syndrome with chest pain, fever, odynophagia, dysphagia occurs in about one-third of patients. Skin photosensitivity is common, but is self-limited. If the complete response to therapy is durable, then the benefits of therapy appear to outweigh risks. The results of two uncontrolled trials are submitted in support of the pivotal controlled trial.

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The sponsor has submitted the final report of this trial, which contains data on 24 months of follow-up. These data may clarify both efficacy and safety issues raised by the 6 month follow-up data.

PHOTOFRIN is approvable for this indication. The Conclusions and Recommendations section (Section X) contains specific requirements for approval.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

1. The sponsor has made a commitment to a 5-year follow up of the pivotal study. This study, entitled PHO BAR 02, has been started.
2. The sponsor has made a commitment to perform a pharmacokinetic study in patients with hepatic impairment (IX. Section D).

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The drug under review is PHOTOFRIN (porfimer sodium) for Injection, which is a photosensitizing agent used in conjunction with a laser light delivery system. PHOTOFRIN is approved for treatment of patients with completely obstructing esophageal cancer, with obstructing endobronchial non-small cell lung cancer, and with micro-invasive endobronchial non-small cell lung cancer. After intravenous injection, PHOTOFRIN, which is a polyporphyrin oligomer derived from hemoglobin, is widely distributed throughout tissues, and is preferentially concentrated in tumors, reticuloendothelial system and skin. A laser light at 630 nm wavelength applied to a tumor results in necrosis due to free radical reactions and to anoxia resulting from occlusion of blood vessels.

The indication of the present submission is ablation of high-grade dysplasia in patients with Barrett's Esophagus who are not candidates for esophagectomy. Barrett's Esophagus is a rare complication of a very common disorder, gastroesophageal reflux disease. High-grade dysplasia is a rare complication of Barrett's Esophagus, and is a pre-malignant lesion. About 25% to 30% of high-grade dysplasia patients develop adenocarcinoma, which carries a very poor prognosis. There is no agreement on the best treatment for high-grade dysplasia. Some experts advise esophagectomy, others, intensive surveillance, reserving esophagectomy for patients who develop adenocarcinoma. A third option is mucosal ablation therapy in which the dysplastic epithelium is destroyed and, with suppression of acid production during healing, squamous epithelium regrows. This is an out-patient procedure, it is minimally invasive, and it may eliminate the need for major surgery, especially in elderly poor-risk patients.

Supporting the indication are the results of three trials:

- PHO BAR 01, a multicenter, partially blinded, randomized, controlled trial in which 208 patients with high-grade dysplasia were enrolled; 138 were randomized to be treated with PHOTOFRIN photodynamic therapy (PDT) plus omeprazole, and 70 were randomized to be treated with omeprazole alone. This is the pivotal trial.

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- TCSC 93-07, a single center, open-label, investigator-sponsored uncontrolled Phase II study, in which 99 patients were treated with different light doses and light delivery systems. Of these patients, 44 patients had high-grade dysplasia.
- TCSC 96-01, a single center, randomized study of the effect of steroid therapy on the incidence of esophageal stricture in patients treated with PDT, in which 87 patients were enrolled, 42 of whom had high-grade dysplasia.

The data of TCSC 93-07 and TCSC 96-01 trials were obtained by the sponsor, and the efficacy results were analyzed in high-grade dysplasia patients by the same methodology as in PHO BAR 01 trial. The entire patient population treated with PHOTOFRIN PDT was used for safety analysis.

Patients in these studies were predominantly male (85%), white (99%), and former or current smokers (71%). The mean age was about 66 years (range, 38 to 88 years). The patient population enrolled in these studies is representative of the general population with Barrett's Esophagus and high-grade dysplasia. Characteristics of Barrett's Esophagus at baseline, including duration of Barrett's esophagus, duration of high-grade dysplasia, endoscopic length of Barrett's esophagus, extent of high-grade dysplasia, presence of hiatal hernia, nodules, ulcers and strictures, and prior treatment, were similar in the group randomized to PHOTOFRIN PDT and in the group randomized to OM Only treatment.

Histopathologic diagnoses were performed at a central pathology laboratory by three pathologists, who were blinded to patients' identity, treatment arm assignment, study phase, or clinical trial site. A sub-study of rater agreement on histological diagnosis showed a high percent of intra-rater and inter-rater agreement. These results add to the quality of the submitted data.

Treatment in the PHOTOFRIN PDT group consisted of an intravenous injection of 2 mg/kg of PHOTOFRIN (this is the standard dose for all indications), followed by laser light administration 40-50 hours later. A second light treatment was administered 2 days later, both treatments constituting one course. Up to a total of three courses could be given; courses had to be separated by at least 3 months. Patients in the PHOTOFRIN PDT group and in the OM Only group were treated with omeprazole 20 mg orally twice a day.

B. Efficacy

The primary efficacy endpoint was complete ablation of high grade dysplasia and re-growth of normal squamous cell epithelium, or of normal epithelium with some areas of Barrett's metaplasia, or of normal epithelium with some areas of low-grade dysplasia, metaplasia, or indefinite for dysplasia. In the PHO BAR 01 trial, 72% of PHOTOFRIN PDT patients had a complete response as defined above; only 31% of Omeprazole Only patients had a complete response (the difference between treatment arms was significant with $p < 0.0001$). In the two supporting uncontrolled trials 88% of patients had a complete response.

The secondary efficacy endpoints addressed the quality of response (re-growth of normal epithelium versus re-growth of normal epithelium with some areas of metaplasia or dysplasia),

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the duration of the response, the time to treatment failure, the time to progression to cancer, and survival time. The quality of response was significantly better ($p < 0.0001$) in the PHOTOFRIN PDT patients than in Omeprazole Only patients. However, the other secondary efficacy endpoints could not be evaluated, because at 12 months of follow-up 50% of patients had not reached any of the above endpoints (the exception being that duration of response in the Omeprazole Only group was estimated at 98 days). Secondary endpoints could not be evaluated in the supporting trials either.

These secondary endpoints are important, because ablation of high-grade dysplasia is only important as a means of preventing the development of adenocarcinoma. The sponsor has submitted 24 month-follow-up data, which will be reviewed. It should be pointed out that the Agency had previously expressed concern that the results of therapy should reflect an improvement in the long-term clinical outcome and that 6 months of follow-up is too short and therefore inadequate to demonstrate such an improvement.

The results of the PHO BAR 01 controlled trial are important in that mucosal ablation using PHOTOFRIN PDT was directly compared to surveillance. There was no esophagectomy arm in the study, therefore the three approaches to the management of high-grade dysplasia could not be directly compared.

The results of the trials could be presented in a manner that is more useful to the clinician and the patient. The important clinical issue is not only how effective PHOTOFRIN PDT is in ablating high-grade dysplasia but how effective it is in prevention of adenocarcinoma. Therefore, the available data in the follow-up period should be presented in terms of probabilities of developing adenocarcinoma at various time intervals after treatment.

C. Safety

Adequacy of safety testing. A total of 318 patients were treated with PHOTOFRIN PDT in the three studies. The median follow-up was 12 months. The patients were followed at least every 3 months, and esphagoscopy data indicate a high degree of patient compliance with the outlined follow-up surveillance program.

Serious side-effects. The side-effect profile of the control group with the same diagnosis provides a very useful benchmark for evaluation of side-effects of PHOTOFRIN PDT therapy. There appears to be an acute PDT syndrome consisting of chest pain, odynophagia, dysphagia, abdominal pain, fever, nausea and vomiting that afflicted about a third of the PDT patients and that was absent in the control group. These acute side-effects abated within about a week, except for dysphagia, which remitted in about 4 weeks. Following the injection of PHOTOFRIN all the patients became photosensitive, and the photosensitivity of the skin continued for at least 30 days and sometimes longer. Patients were given elaborate and detailed instructions on avoiding bright light; nevertheless, about one-half to two-thirds of patients had photosensitivity reactions, which were severe in about 10% of patients. All photosensitivity reactions resolved with time.

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The main safety issue with photodynamic therapy is the development of esophageal strictures during the healing process. Even in the pivotal trial, with latest light delivery systems, strictures developed in 35% of patients. (It should be noted that a stricture was defined as esophageal narrowing that required dilation.) Severity of strictures was graded as mild (in 44% of patients), moderate (in 43% of patients), or severe (in 12% of patients). Treatment of strictures consisted of 1 - 2 dilations in 35% of patients with strictures, of 3 - 5 dilations in 29% of patients, of 6 - 10 dilations in 21% of patients, and of more than 10 dilations, in 15% of patients. There was only one stricture in the OM Only group of patients and that required only one dilation.

Common side-effects. Almost all (98%) of patients in the PHOTOFRIN PDT group reported adverse events, as compared to 68% in the Omeprazole Only group. Furthermore, the total number of adverse events was more than three times as high in the PHOTOFRIN PDT group as in omeprazole only group (1,245 vs. 206 events). In the PHOTOFRIN PDT group the most common side effects were related to the gastrointestinal system, body as a whole (chest pain, fever, pain), photosensitivity reactions, and dehydration. There no predominant side effects in the OM Only group; the most common were related to the gastrointestinal system, body as a whole, nervous system, and metabolic and nutritional system.

Drug-drug interactions. The sponsor raised possibilities of interactions of PHOTOFRIN with other photosensitizing drugs and with drugs degraded by cytochrome P450 enzymes, but these possible interactions have not been studied. There is no basis for suspecting an interaction with omeprazole. In terms of other drugs increasing or decreasing photosensitivity, it is important to remember that the photosensitivity after PHOTOFRIN injection is massive and dwarfs the effects of any other drugs increasing or decreasing photosensistivity.

Exposure in trials versus probable marketing exposure. The PHOTOFRIN PDT protocols have been applied consistently, and no changes are expected after marketing.

Effect of trial exclusions on safety profile vs. expected marketed population. The main reason for excluding patients from the pivotal trial is the absence of high-grade dysplasia (86% of patients excluded). Since these patients were referred with this diagnosis for inclusion in the trial, the possiblity is very real that patients without high-grade dysplasia may undergo PHOTOFRIN PDT therapy.

Recommended warnings. Acute PDT symptomatology as described above, photosensitivity precautions, and risk of strictures.

Relationship of safety to other drugs available for indication. No other drugs are available for this indication.

Unresolved safety issues. Stricture formation, which may never be resolved, because it goes hand in hand with the treatment.

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D. Dosing

The same dosing of PHOTOFRIN (2 mg/kg intravenously) has been used for over 10 years in over 3,000 applications. The drug in PDT is not the active therapeutic agent, the light is. The drug is given in a sufficient dose to achieve photosensitivity.

E. Special Populations

Gender differences. None found in pharmacology, safety, or effectiveness.

Ethnic and racial studies. Small-scale Japanese studies have been reported, but differences in trial design, dosing and efficacy endpoints do not permit any conclusions to be drawn.

Elderly. PHOTOFRIN PDT appears to be more effective in patients less than 65 years of age than in patients more than 65 years of age ($p = 0.0219$).

Status of pediatric studies and pediatric plan. A waiver for pediatric studies in children is requested on the basis that PHOTOFRIN has Orphan Drug Designation.

Pregnancy use information. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. PHOTOFRIN should be used during pregnancy only if the potential benefit justifies the potential risk to fetus. Animal toxicity studies showed increased resorptions, decreased litter size, delayed ossification, and reduced fetal weight, as tested in rats and rabbits.

Nursing mothers. It is not known whether PHOTOFRIN is excreted in human milk. Women receiving PHOTOFRIN must not breast feed, because of potential for serious reactions in nursing infants.

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I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

PHOTOFRIN® (porfimer sodium) for injection is a photosensitizing agent that is approved under NDA 20-451

- for palliation of patients with completely obstructing esophageal cancer,
- for palliation of patients with obstructing endobronchial non-small cell lung cancer, and
- for treatment of patients with micro-invasive endobronchial non-small cell lung cancer for whom surgery and radiotherapy are not indicated.

The sponsor's proposed indication is ablation of high-grade dysplasia in patients with Barrett's Esophagus who are not candidates for esophagectomy.

PHOTOFRIN is approved as a drug-device combination for photodynamic therapy (PDT) and is used with a laser light passed through endoscopically placed fiber optics tipped with cylindrical diffusers and with inflatable centering balloons of various lengths (3, 5 and 7 cm). PHOTOFRIN is infused intravenously at a dose of 2 mg/kg body weight. Light activation, using red light at 630 nm, is performed 40-50 hours after PHOTOFRIN injection.

Patients who may be candidates for PHOTOFRIN therapy will be 50 years or older, since both dysplasia in Barrett's Esophagus (BE), a pre-malignant condition, and adenocarcinoma of the esophagus increase with age. Sponsor's Table 3.7-1 shows the incidence of esophageal adenocarcinoma in BE patients of various ages. Most of the candidates for PHOTOFRIN therapy will be males, since BE is 2 to 5 times more common in men than in women, and since most of the patients (about 86%) with esophageal carcinoma are male (Cameron *in* Tilanus & Attwood, pp. 281 - 290).

Sponsor's Table 3.7-1: Adenocarcinoma Incidence with Age in BE

Age range	Incidence/100,000
30-39	0.01
40-49	0.06
50-59	1.8
60-69	3
70-79	3.9

B. State of Armamentarium (Treatment Options) for Indication

Gastroesophageal reflux disease (GERD), defined as abnormal reflux of gastric contents into the esophagus and resulting in chronic symptoms and, in some cases, in mucosal damage, is very

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common in the adult population. Prevalence estimates are as high as 10% to 20% of the population in the U.S. (Shaheen & Ransohoff, Cameron *in* Tilanus & Attwood, p. 281). Barrett's Esophagus (BE) is a complication that develops in a minority (about 6% - 12%) of patients with GERD, or in about 1% of persons over the age of 60, or in about 0.4% of persons in the general population including all ages (Cameron, op.cit.).

BE is clearly associated with severe and long-lasting gastroesophageal reflux, the presence of a hiatal hernia, a lower basal esophageal sphincter pressure, and abnormal epithelial repair resulting in replacement of squamous by columnar epithelium. The diagnosis is established if the squamocolumnar junction is displaced proximal to the gastroesophageal junction, and the normal squamous epithelium of the esophagus is replaced by a specialized or intestinal-type columnar lining containing acid mucin-containing goblet cells (Falk, Shaheen & Ransohoff). The origin of the columnar cells composing the Barrett's esophagus is unclear; they are not gastric cells, since they differ histologically from cells of the gastric cardia.

The importance of BE and of GERD is their association with the development of adenocarcinoma of the esophagus, a highly lethal disease with a 5-year survival of 11% in the early 1990s. Adenocarcinoma of the esophagus is, for unknown reasons, increasing in incidence in the United States and other countries. Population-based cohort studies suggest a 300% to 500% increase throughout the last 30 to 40 years. The pathogenesis of adenocarcinoma of the esophagus is thought to progress through several stages:

- Severe, frequent and long-lasting reflux leads to a metaplastic change from squamous to intestinal-type columnar lining (i.e. BE). This process involves the destruction of the squamous mucosa as a result of acid reflux and subsequent re-epithelialization. The specialized columnar epithelium progresses to:
 - low-grade dysplasia, then to
 - high-grade dysplasia, then to
 - adenocarcinoma.

A number of approaches have been developed for prevention of adenocarcinoma; however, at the present time there is no consensus on which one is best. Below are the options under consideration.

- Screening patients for BE. The subjects for endoscopic screening would be those at highest risk for BE: white men, 50 years of age and older, with long-standing reflux symptoms. No clinical trials have been carried out to support such a strategy. Because the number of Americans with reflux symptoms is so high and because the incidence of esophageal carcinoma is so low, by necessity the absolute risk to the average person with reflux is low. Shaheen & Ransohoff (JAMA 2000) calculated that there are about 10 million individuals in the U.S. who are older than 50 years and who experience reflux weekly. Of these 10 million individuals, approximately 6500 a year will develop esophageal adenocarcinoma. Thus, the cancer risk to any given older individual with reflux is 0.00065 per year, an extraordinarily low figure.

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If BE is diagnosed, symptoms can be relieved by proton pump inhibitors and esophagitis can be healed, but intestinal metaplasia is not reversed. Moreover, the vast majority of BE patients never develop cancer; most recent studies suggest that the annual incidence of adenocarcinoma in BE patients is about 0.5% or less (Shaheen & Ransohoff; Falk). Furthermore, approximately 94% to 98% of adenocarcinomas are diagnosed in patients without a prior diagnosis of Barrett's esophagus. These findings may be explained in part by the absence of reflux symptoms in an estimated 40% of patients with BE. In 5 series of patients with adenocarcinoma and BE found simultaneously, a history of preceding reflux symptoms was obtained in 52%, 54%, 59%, 61%, 62%, and 65% of cases (Cameron, op. cit.). Nevertheless, the only hope for improved survival of patients with esophageal carcinoma is detection of cancer at an early and potentially curable stage.

- Surveillance of BE patients to detect cancer at an early and potentially curable stage. Several retrospective studies clearly suggest that BE patients in whom adenocarcinoma was detected in a surveillance program had dramatically improved 5-year survival compared to similar patients not undergoing routine endoscopic surveillance. A recent decision-analysis study of the optimal surveillance strategy for BE with an endpoint of esophagectomy for high-grade dysplasia found that surveillance every 5 years was the most effective strategy to increase both length and quality of life (Provenzale et al.). The aim of surveillance is the detection of dysplasia. Surveillance guidelines recommend obtaining systematic 4-quadrant biopsy specimens at 2-cm intervals along the entire length of BE. An even more comprehensive "Seattle protocol" specifies jumbo forceps and biopsies at 1-cm intervals. Results from surveillance programs have shown that dysplasia and superficial adenocarcinoma may be extraordinarily focal. In one study (Reid BJ et al.) among 45 patients with high-grade dysplasia who eventually developed cancer, 82% had cancer in a single 1-cm segment and 69% had cancer in a single biopsy specimen. Furthermore, only 39% of patients with cancer diagnosed by endoscopic biopsy had cancer found at surgery. Surveillance every 2-3 years is recommended as adequate in patients without dysplasia, every year with low-grade dysplasia, and every 3 months in patients with high-grade dysplasia if esophagectomy is not performed (American College of Gastroenterology Guidelines for the Diagnosis and Surveillance of Barrett Esophagus, Am J Gastroenterol 1998; 93:1028-32). These intervals are arbitrary and have never been subject to a clinical trial. Esophagectomy is recommended for high-grade dysplasia by some authors, and continuous rigorous surveillance by others. Still others argue that because most patients with BE will not die from esophageal cancer, endoscopic surveillance is not warranted until substantiated by prospective studies (Van der Burgh A et al.; MacDonald CE et al.). A randomized controlled trial of surveillance vs. no surveillance in BE has not been performed.
- Management of low-grade dysplasia. The natural history of low-grade dysplasia is poorly understood. Results of recent studies suggest that approximately 10% - 28% of low-grade dysplasia patients go on to develop high-grade dysplasia or adenocarcinoma, about 60% - 65% of patients show a regression, and the remainder continue to have low-grade dysplasia. Continued surveillance is recommended by the American College of Gastroenterology.

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- Management of high-grade dysplasia. Patients with high-grade dysplasia demonstrate a risk of subsequent adenocarcinoma exceeding 25%. Additionally, because endoscopic biopsies of BE are taken at random locations, sampling error in individuals with high-grade dysplasia is great. When those with high-grade dysplasia undergo resection, up to 50% of the resected specimens demonstrate previously unrecognized adenocarcinoma (cited in Shaheen & Ransohoff). Recent studies report development of cancer in 16% - 59% of high-grade dysplasia patients followed with endoscopic surveillance for 3 – 7 years (Buttar NA et al.; Reid BJ et al.; Schnell TG et al.). What are the options offered to the patient with BE and high-grade dysplasia?
 - Esophageal resection
 - Intensive endoscopic surveillance, with esophagectomy reserved only for those who develop adenocarcinoma
 - Mucosal ablation therapy to areas of Barrett's esophagus, including
 - Thermal
 - Multipolar electrocoagulation
 - Heater probe
 - Argon plasma coagulator
 - Nd:YAG laser
 - Argon laser
 - KTP (potassium titanyl phosphate) laser
 - Photodynamic therapy
 - 5-delta-amino-levulinic acid
 - Porfimer sodium (the drug being reviewed in NDA 20-525)
 - Hematoporphyrin
 - Endoscopic mucosal resection

The rationale of mucosal ablation therapy is that the metaplastic epithelium is destroyed and, with vigorous suppression of acid production during healing, squamous cell epithelium regrows. Ablation therapy has tremendous appeal to both patients and physicians. It is minimally invasive, "high-tech", and may eliminate the need for major surgery, especially in elderly poor-risk patients. However, several difficult issues need to be kept in mind.

- 1) The reversion to squamous epithelium may be incomplete, leaving islands of Barrett mucosa in the treated area.
- 2) Barrett mucosa may underlie what appears to be normal squamous epithelium; there have been reports of adenocarcinoma developing beneath squamous epithelium. The risk of cancer in areas of Barrett's esophagus treated with ablative therapy is not defined.
- 3) Techniques are not standardized and esophageal movement makes accurate and complete targeting difficult.
- 4) Risks, including strictures, perforation, and incurable cancer developing in otherwise curable patients.
- 5) Endoscopic surveillance is still warranted in these patients, but previous landmarks are now obscured, making targeting of biopsies problematic.
- 6) Persistent biomarker abnormalities have been described in the new squamous epithelium that replaced high-grade dysplasia.

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Experience with various types of lasers has been documented, but lasers are no longer widely available. Multipolar electrocoagulation has been shown to result in histologic reversal of BE in about 80% of patients, as has argon plasma coagulation therapy. Both techniques have significant adverse events, including chest pain, odynophagia, fever, pleural effusion, perforations, strictures, and pneumomediastinum.

Photodynamic therapy is based on the systemic administration of certain photosensitizing agents that are retained with some selectivity in rapidly proliferating and malignant tissues. When the target tissues are exposed to appropriate wavelength laser light, oxygen radicals are generated causing cellular destruction. The choice of photosensitizer is crucial to achieve the depth of necrosis that is required. Oral 5-aminolevulinic acid used to generate protoporphyrin IX will produce necrosis to a depth of 2 mm. PHOTOFRIN (porfimer sodium) or any derivative of di-hematoporphyrin ester/ether will produce necrosis up to a depth of 6 mm. Of the photosensitizing agents, only PHOTOFRIN is available in the United States for use in photodynamic therapy. The main complication of this therapy is the development of strictures.

Endoscopic mucosal resection has been used in BE with adenocarcinoma or high-grade dysplasia. It is most effective in low-risk lesions (diameter <2cm, limited to mucosa, well or moderately differentiated histology); less in high-risk lesions (diameter >2cm, extending into submucosa or ulcerated, poorly differentiated histology). During the 1-year follow-up 17% of the low-risk group and 14% of the high-risk group developed high-grade dysplasia or cancer (Ell C et al. 221). The applicability of this technique to invisible lesions or multifocal lesions is questionable at present.

C. Important Milestones in Product Development

PHOTOFIN for Injection has been studied under IND 42,313 for ablation of high-grade dysplasia in Barrett's esophagus and superficial esophageal cancer (studies TCSC 93-07 and TCSC 96-01 reviewed in this submission). The PHO BAR 01 study protocol was submitted to the Division of Oncology Drug Products (IND 25,064) on November 13, 1997 by QuadraLogics Technologies (QLT) and the study was initiated in January, 1998. QLT conducted the study until June, 2000, when Axcan Pharma acquired the product and took over clinical monitoring of the product. On June 21, 2000 the Agency requested that this study be re-filed with the Division of Gastrointestinal and Coagulation Drug Products, which the new sponsor (Axcan Scandipharm, Inc.) did on September 26, 2000 (IND 61,011).

The Agency clearly enunciated key elements to be provided in the submission, as described below.

In an Advice Letter dated January 25, 2001 after the completion of the review of IND 61,011 describing the pivotal study, the Agency specified that:

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- To qualify as a pivotal trial the primary response variable must reflect an improvement in the long-term clinical outcome. Partial histopathological responses to photodynamic therapy (PDT) might not reflect clinically meaningful long-term outcomes. In addition, the current standard of care which includes esophagectomy in individuals who are surgical candidates should be included in the definition of an appropriate population for whom PDT therapy might be indicated.
- The sponsor should provide an analysis of clinical outcomes of individuals associated with treatment failure in conjunction with the outcomes associated with treatment success. Such outcomes should be compared to those associated with other modes of treatment such as esophagectomy.
- The sponsor should provide information about the timing and severity of strictures associated with PDT.
- The sponsor should clearly define the treatment of nodules before therapy. For example, the protocol should provide details how carcinoma underlying nodules will be excluded prior to PDT.
- The sponsor should provide an up-to-date model informed consent form to the Agency.

A teleconference with the sponsor on March 5, 2001 clarified the above concerns in greater detail, namely that:

- 6 months follow-up may be inadequate to assess the impact of the treatment. A follow-up time frame of 5 years or more was recommended, but follow-up of at least 2 to 3 years would be acceptable
- The Agency is concerned that the use of histopathological effects for measuring clinical benefit might be a surrogate endpoint. The appropriateness of this endpoint is questionable considering the differences in the natural course of high-grade dysplasia from low-grade dysplasia in the occurrence of cancer. The measurement should be linked to a clinically meaningful outcome.
- The Agency is concerned that PDT might be a cosmetic effect of treatment rather than changing the course of disease. The Agency is most interested in assessing whether there is a long-term sustained response to therapy.

The sponsor stated that the response to therapy is sustained.

As related in the above communications, the importance of PDT with PHOTOFRIN is prevention of adenocarcinoma of the esophagus, and the trials must provide evidence that this is an effective and relatively safe therapy for this purpose.

C. Other Relevant Information

PHOTOFRIN for Injection was first approved in Canada. Reviewer's Table below describes the indications approved, the countries in which the indication was approved, and the date of approval. Following tables describe Rejections, and Submissions (adapted from Tables 3.2-1, 3.2-2, and 3.2-3, vol. 1, pp. 135-9). The indications have been abbreviated by the reviewer; their wording differs between countries.

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Reviewer's Table on Regulatory History in Other Countries - Approvals

Indication	Countries where approved and year of approval
Recurrent superficial papillary bladder cancer: second-line treatment for those who have failed standard intravesical therapy	Canada (1993)
Obstructing esophageal cancer	Canada (1995), The Netherlands (1994), France (1996), United Kingdom (1998), Finland (1999), Iceland (1999), Denmark (1999), Portugal (1999), Norway (1999), Luxembourg (1999), Ireland (2000), Austria (2000), Italy (2000), Sweden (2000), Belgium (2001), Greece (2001), Poland (2001)
Obstructing endobronchial non-small cell lung cancer	Canada (1999), The Netherlands (1994), France (1996), Germany (1997), United Kingdom (1998), Finland (1999), Iceland (1999), Denmark (1999), Portugal (1999), Norway (1999), Luxembourg (1999), Ireland (2000), Austria (2000), Italy (2000), Sweden (2000), Belgium (2001), Greece (2001), Poland (2001)
Superficial endobronchial non-small cell lung cancer in patients for whom surgery and radiotherapy are not indicated	Canada (1999), The Netherlands (1994), France (1996), Iceland (1999), Greece (2001)
In patients for whom curative therapy is impossible and there is no therapy except PDT: Early lung cancer (stage 0 and I) Superficial esophageal cancer Superficial gastric cancer Early cervical cancer and dysplasia	Japan (1994)

Reviewer's Table on Regulatory History in Other Countries - Rejections

Indication	Country where rejected
[

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Reviewer's Table on Regulatory History in Other Countries – Submissions neither Approved nor Rejected at the Time of this Submission

Indication	Country where submitted and date of submission
[J

E. Important Issues with Pharmacologically Related Agents

PHOTOFRIN is the only photosensitizing agent approved for use in photodynamic therapy. The drug is innocuous until activated by light. Other photosensitizing agents share this property. The duration of photosensitivity varies by agent.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

PHOTOFRIN (porfimer sodium) for Injection is a complex mixture of porphyrin oligomers, porphyrin monomers. [] In the oligomers, porphyrin units are joined by ether [] and ester [] linkages. The active ingredient, porfimer sodium, consists of oligomeric species, ranging from dimers to octamers, the majority of which are dimers and trimers. []

[] The chemical complexity of the oligomeric mixture is further complicated by the dynamic aggregation/disaggregation exhibited by porphyrins in aqueous solution. These characteristics have precluded resolution of the oligomers present in PHOTOFRIN by conventional analytical methods. All fractions resulting from attempts to fractionate PHOTOFRIN by multiple gel chromatography or HPLC consisted of mixtures of oligomers. All such fractions were biologically active in a tumoricidal assay. Thus, single components of PHOTOFRIN cannot be isolated, and structure-function relationships cannot be determined for the complex components of PHOTOFRIN.

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Porfimer sodium bulk concentrate is manufactured by [redacted] in [redacted] process, which uses [redacted] [redacted] is prepared [redacted] by [redacted] which obtains [redacted] from [redacted]

The molecular weight of the oligomeric components of porfimer sodium ranges from 1178 to 4659 daltons, depending on the number of porphyrin units per oligomer and the extent of dehydration occurring at hydroxyethyl end groups.

Porfimer sodium is manufactured as a dark red liquid or freeze-dried powder, which is soluble in water. It is formulated without excipients. Bulk concentrate of PHOTOFRIN is stable up to 3 months when stored frozen. Degradation of porfimer sodium in solution occurs primarily [redacted] The degradation products are [redacted]

Nonclinical pharmacology studies.

- Study TX-96005: A Pilot Study to Measure and Compare the Amount of Light from Black and White Balloon Catheters on the Dog Esophagus. No drug, light only. Mucosal light doses for white and black balloons measured.
- Study TX-96003: To assess the 'new' white balloon catheters in the dog esophagus.
- Study TX-97005: A study of light delivered by balloon catheters by two different manufacturers.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

There are no new pharmacokinetic or other Phase I studies conducted by the sponsor that are included in this supplemental NDA. A summary of previous studies was requested by the Division of Gastrointestinal and Coagulation Drug Products at the pre-NDA meeting held on June 1, 2001. Human pharmacokinetics has been studied in three clinical trials in cancer patients who were undergoing photodynamic therapy (PDT) and in one clinical trial in healthy volunteers (a post-marketing study that was submitted in an Annual Report to the NDA). The key results are shown below in sponsor's Table 3.5-1.

Absorption and Distribution

PHOTOFIN is given intravenously, and the absorption of PHOTOFRIN from the GI tract has never been studied. Animal studies have shown that after I.V. administration of ³H-hematoporphyrin derivative (an unpurified form of porfimer sodium), maximum radioactivity concentrations in the digestive tract were about 5% of those in the liver. Radioactivity concentrations in the digestive tract were greatest in the small intestine, followed by the gastric antrum, esophagus, gastric fundus, and colon. Three days after drug administration, radioactivity

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in the GI tract was present at 44% - 75% of that observed at 1 - 4 hours postdose [Original NDA, vol. 27, p. 1].

PHOTOFRIN maximum plasma concentrations (T_{max}) were seen between 5 min and 60 min after the start of the 3-5 min I.V. injection (Table 3.5-1). The cause of this variability is unknown. C_{max} values after injection of 2mg/kg PHOTOFRIN were in the range of 15 to 80 mg/mL.

The percentage of PHOTOFRIN-related porphyrins bound to serum proteins was about 90% and was independent of concentration. The predominant site for total porphyrin binding was to high density lipoproteins. Porphyrin monomers were primarily bound to albumin; dimers/oligomer fraction was associated with lipoproteins. The elimination of albumin-bound porphyrins was faster than of lipoprotein-bound porphyrins [Original NDA, vol. 32, p. 200].

Distribution of PHOTOFRIN into tissues occurs in the first 24 hours after dosing, and, once in tissues, the clearance of PHOTOFRIN is slow. Due to extensive distribution of PHOTOFRIN into tissues, serum concentrations may not be the best indicator of the concentration of PHOTOFRIN at the site of action, and may also be a poor indicator for the potential of adverse photosensitivity reactions.

Metabolism

Due to the complexity of the mixture of porphyrins in PHOTOFRIN, the metabolism of PHOTOFRIN has not been adequately studied. Results from animal studies suggest that the ester and ether linkages holding multimeric structures are likely to hydrolyzed to monomeric porphyrin units. The pathways of porphyrin and of heme degradation are well known. The catabolism of heme is carried out by heme oxygenase I and cytochrome P450, which cleave porphyrin into biliverdin. Biliverdin is oxidized to bilirubin, which is excreted by the liver into bile. Another important aspect of the breakdown of PHOTOFRIN is photo-bleaching. Reduction in photosensitivity after PHOTOFRIN injection appears to be best achieved through gradual exposure to low levels of light, which allow for the gradual breakdown of PHOTOFRIN within the skin. It is not known to what extent photo-bleaching contributes to the overall clearance of PHOTOFRIN; however, it is an important process for reducing risks associated with photosensitivity.

The sponsor states that direct competition between PHOTOFRIN and other drug products for cytochrome P450 enzymes is not expected to occur, and that genetic variation in cytochrome P450 isozymes within the human population is not expected to influence the metabolism of PHOTOFRIN [vol. 1, p. 167]. The sponsor does not support these statements with a rationale and/or evidence.

Excretion

PHOTOFRIN is excreted from the body mainly unchanged (61%); 35% is excreted in the form of metabolites [Original NDA, v. 27, p.8]. Elimination appears to be biphasic, with the first phase having a half-life of about 220 hours (9.17 days) and the second phase, a half-life of about

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870 hours (36.25 days). The first phase may represent tissue distribution, and the second phase, metabolism and excretion. PHOTOFRIN-related materials are excreted mainly through the bile/feces (59%), and only minimally through the urine (6%) when measured in samples collected over the first 192 hours (8 days) after dosing. These data are consistent with metabolism of PHOTOFRIN monomeric units into bilirubin.

Variations in Special Populations

Gender differences. In PHO PK 001 (Table 3.5-1), the pharmacokinetics of PHOTOFRIN in healthy male and female volunteers were compared after a single dose. A bi-exponential serum decay was observed, with a slow distribution phase and a very long elimination phase that started approximately 24 hours after injection and had a $T_{1/2}$ of 415 hours (17 days). Pharmacokinetic parameters were not affected by gender, except for T_{max} , which was longer in women [vol. 7, p. 112].

Race differences. PHOTOFRIN has been studied in Caucasian and Japanese cancer patients. However, due to the differences in the sampling times between studies, and small numbers of patients involved, it is difficult to make any conclusions about variation in PHOTOFRIN pharmacokinetics between these populations [Original NDA, vol. 31, p. 14].

Differences between patients and healthy volunteers. Three studies were conducted in patients, and one in healthy volunteers (Table 3.5-1). The mean C_{max} values from these studies ranged from 14.2 mcg/mL to 79.6 mcg/mL, and the mean $T_{1/2}$ ranged from 22 hours to 515 hours. The sponsor states that the two shorter estimates of PHOTOFRIN half-life are an artifact of reduced sampling in these studies. The long half-life in Report 1 (515 hours) in patients is consistent with that of PHO PK 001 study (415 hours) in normal volunteers.

Potential for drug-drug interactions. In the treatment of high-grade dysplasia PHOTOFRIN is given by single injection with repeat doses being at least 90 days apart. There have been no formal interaction studies of PHOTOFRIN and any other drugs. However, it is possible that concomitant use of other photosensitizing agents, such as tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide diuretics and griseofulvin could increase the photosensitivity reaction. In addition, there exists a theoretical possibility that there may be interactions with other drugs with significant biliary excretion, such as erythromycin, azithromycin and lansoprazole.

Compounds that quench active oxygen species or scavenge radicals, such as dimethylsulfoxide, beta-carotene, ethanol, formate and mannitol would be expected to decrease PDT effectiveness. Preclinical data suggest that tissue ischemia, allopurinol, calcium channel blockers and some prostaglandin synthesis inhibitors could interfere with PHOTOFRIN PDT. Drugs that decrease clotting, vasoconstriction or platelet aggregation, such as thromboxane A2 inhibitors, could decrease the efficacy of PDT. Glucocorticoids given before or concomitant with PDT may decrease the efficacy of the treatment.

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Omeprazole or other proton pump inhibitors are most likely to be used in conjunction with PDT in the treatment of high-grade dysplasia. PHOTOFRIN and omeprazole differ significantly in their absorption, distribution, metabolism and excretion properties, and pharmacokinetic interaction between these agents is not expected to be of clinical concern.

B. Pharmacodynamics

PHOTOFRIN is a photosensitizing agent that is used in photodynamic therapy for cancer. Tumor selectivity in treatment occurs through a combination of selective retention of PHOTOFRIN and selective delivery of light. By 40-50 hours after I.V. injection PHOTOFRIN has largely cleared from a variety of normal tissues, and has been retained by neoplastic tissues, skin, and organs of the reticuloendothelial system. At this time light activation is performed with red light at 630 nm wavelength. This is the longest wavelength that can adequately activate PHOTOFRIN and provide the greatest tissue penetration. Also, at this wavelength, the absorption of activating light by hemoglobin is minimal. The activation of PHOTOFRIN results in a generation of reactive oxygen species including singlet oxygen. Tumor necrosis occurs as a result of direct cytotoxicity to tumor cells, and also as a result of ischemia because of the sensitivity of tumor vasculature to PDT. Thrombogenic agents appear to be liberated locally and result in occlusion of tumor capillaries within 20 minutes of photoactivation.

The dose of PHOTOFRIN used in all studies (2 mg/kg of body weight, given I.V.) was determined empirically. This dose has been used for more than 3,000 treatments as the standard dose for all indications. The 40-50 hour interval between PHOTOFRIN injection and light treatment is also standard. This timing is based on the clearance of PHOTOFRIN from most tissues except skin and tumors. The total light dose delivered to tumor or dysplastic tissue is a key factor in efficacy and safety. The light doses recommended for use in high-grade dysplasia in BE are the lowest that achieved consistent efficacy and an acceptable safety profile.

The delivery of light is accomplished using laser light passed through endoscopically placed fiber optics tipped with cylindrical diffusers. Because the normal esophagus does not behave as a cylindrical tube, but tends to collapse when empty, an inflatable centering balloon was developed. The centering balloon helped achieve a PDT response that was circumferential and uniform. The balloon designs underwent progressive developments: from an optically transparent to "black-capped" with black ends and a 360 degree central transparent window and, finally, to "white-capped" balloons with a reflective inner coating at the ends allowing for a more uniform output from the balloon. The "black-capped" balloons had a non-linear light output across the window, resulting in a peak at the mid-point of the window. This peak in light intensity appeared to correspond to the position of stricture development in at least some patients.

IV. Description of Clinical Data and Sources

A. Overall Data

Sources of data used in the review are from a clinical trial program as described below.

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B. Tables Listing the Clinical Trials

Clinical trial no.	Clinical trial title
PHO BAR 01	A multicenter, partially blinded, randomized Phase III study of the efficacy and safety of photodynamic therapy (PDT) using PHOTOFRIN (porfimer sodium) for Injection for the ablation of high-grade dysplasia in Barrett's Esophagus.
TCSC 93-07	A Phase I/II Study of the Safety and Efficacy of Photodynamic Therapy (PDT) Utilizing PHOTOFRIN for Treatment of Dysplasia or Early Adenocarcinoma of the Esophagus in Barrett's Esophagus.
TCSC 96-01	Photodynamic Therapy of Dysplasia or Early Adenocarcinoma in Barrett's Esophagus: A Randomized Study of the Effect of Steroid Therapy on the Incidence of Esophageal Stricture

The sponsor conducted the pivotal trial PHO BAR 01. Trials TCSC 93-07 and 96-01 were individual investigator-sponsored trials (by Bergein F. Overholt, M.D., Thompson Cancer Survival Center, Knoxville, TN). PHO BAR 01 enrolled patients only with BE and high-grade dysplasia. TCSC 93-07 and 96-01 enrolled BE patients with high-grade dysplasia and with low-grade dysplasia, and patients with superficial adenocarcinoma of the esophagus. The sponsor obtained access to the data in the 93-07 and 96-01 trials, selected high-grade dysplasia patients, and re-analyzed the data according to PHO BAR 01 efficacy endpoints. All the 93-07 and 96-01 enrollees served as safety population.

C. Postmarketing Experience

The sponsor recognizes the importance of long-term follow-up data in the treatment of high-grade dysplasia in Barrett's esophagus. Axcan has committed to this follow-up with the new protocol, PHO BAR 02, submitted to IND 61,011 on November 26, 2001. The purpose of this study is to assess the 5-year efficacy of PDT with PHOTOFRIN plus omeprazole compared to omeprazole alone in the complete ablation of high-grade dysplasia in patients with BE, in conjunction with a strict endoscopic surveillance and biopsy protocol. PHO BAR 02 is a continuation of PHO BAR 01, the pivotal trial in this submission. Patients will remain in their assigned treatment group. The secondary efficacy analyses are the same as in PHO BAR 01. Patients are eligible for additional courses of PDT, up to a maximum of three (cumulative with those administered during the PHO BAR 01 study). Patients will be followed for a maximum of 60 months after their individual randomization date. PHO BAR 02 was initiated in December, 2001, and has an estimated duration of 3 years.

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D. Literature Review

The sponsor summarized the most important literature and provided copies of publications, including those derived from the supporting studies (vols. 9 – 12). The Reviewer retrieved the following articles and used them in describing various portions of this review. Some of the articles had not been published when the sponsor submitted this NDA.

Falk GW	Barrett's Esophagus. Gastroenterology 2002; 122:1569-1591
Shaheen N & Ransohoff DF	Gastroesophageal Reflux, Barrett Esophagus, and Esophageal Cancer. Scientific Review. Clinical Applications. JAMA 2002; 287:1972-81, 1982-6
Tilanus HW & Attwood SEA	Barrett's Esophagus. Kluwer Academic Publishers. 2001, pp. 159 – 280
Provenzale D, Schmitt C & Wong JB	Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. Am J Gastroenterol 1999;94:2043-53
Reid BJ, Blount PL, Feng Z & Levine DS	Optimizing endoscopic biopsy detection of early cancers in Barrett's high-grade dysplasia. Am J Gastroenterol 2000; 95:3089-96
Van der Burgh A, Dees J, Hop WC & van Blankenstein M	Oesophageal cancer is an uncommon cause of death in patients with Barrett's oesophagus. Gut 1996; 39:5-8
MacDonald CE, Wicks AC & Playford RJ	Final results from 10 year cohort of patients undergoing surveillance for Barrett's oesophagus: observational study. Br Med J 2000; 321:1252-5
Buttar NS et al.	Extent of high-grade dysplasia in Barrett's esophagus correlates with risk of adenocarcinoma. Gastroenterology 2001; 120:1630-9
Reid BJ et al.	Predictors of progression to cancer in Barrett's esophagus: baseline histology and flow cytometry identify low- and high-risk patient subsets. Am J Gastroenterol 2000; 95:1669-76
Schnell TG et al.	Long-term non-surgical management of Barrett's esophagus with high-grade dysplasia. Gastroenterology 2001; 120:1607-19
American College of Gastroenterology	Guidelines for the Diagnosis and Surveillance of Barrett Esophagus. Am J Gastroenterol 1998; 93:1028-32

V. Clinical Review Methods

A. How the Review was Conducted

The review followed this sequence:

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- A survey of current literature on Barrett's esophagus, adenocarcinoma of the esophagus, photodynamic therapy, surgery of the esophagus
- Volume 1, 2 – summary of information PHOTOFRIN, PHOTOFRIN label, and proposed label
- Volume 6 – human pharmacokinetics and bioavailability
- Volume 8 - a summary of the Clinical section
- Volumes 13, 42, 47 describing the 3 trials
- Volumes describing chemistry, pharmacokinetics and pharmacodynamics of PHOTOFRIN
- Tables and listings of the trials, vols. 13 – 51, and 57 - 95
- Statistical section, vol. 52
- Financial disclosure forms, vol. 100.

B. Overview of Materials Consulted in Review

Summarized in I B. State of Armamentarium for Indication, and in Materials Reviewed (below).

Materials reviewed:

NDA 21-525/20-451	Vol.1-100
IND 61,011	Medical Officer's review (January 4, 2001)
IND 61,011	Meeting Minutes, Industry Meeting – Type B, Pre-NDA (June 1, 2001)
IND 61,011	Advice letter (January 24, 2001)
IND 61,011	Memorandum of Telecon (dated March 21, 2001)
NDA 21-525	Statistical Review and Evaluation
NDA 21-525	Pharmacology and Biopharmaceutics Review

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The sponsor was requested to clarify the following:

- Clarify which patients were enrolled in which centers
- Provide the response rate for the primary efficacy endpoint if Dr. Overholt's patients were excluded. [Dr. Overholt's center enrolled 37/208 (17.8%) patients in the pivotal trial and 86 high-grade dysplasia patients in the supporting trials, a total of 123/294 (41.8%) patients.]
- Clarify if updated follow-up data will be provided (and if so, when) to allow calculation of a more complete value for duration of response. [The submission contains the 6-month data (preliminary) for primary efficacy endpoint, rather than 24-month data that were to be the final data for the trial].

DSI was consulted to review Dr. Overholt's data, because such a high proportion of patients were enrolled at his center.

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D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor presented sufficient documentation of conduct of trials in accordance with accepted ethical standards, including

- An Independent Ethics Committee or Institutional Review Board review of protocol and the informed consent form
- The study was to be performed in accordance with the rules of Good Clinical Practice. The conditions were to be in compliance with the Declaration of Helsinki, the recommendations of the WHO, the recommendations of the Health Protection Branch, Ottawa, Canada, and the recommendations of the FDA as published in General Considerations for the Clinical Evaluation of Drugs (1977), and the recommendations as published in the Federal Register and in the Code of Federal Regulations (21 CFR 312.60-69) and applicable state laws.
- Each patient reviewed and signed a written approved informed consent form prior to any study procedures. The consent form complied with U.S. 21 CFR 50, Canadian or ICH guidelines (Section 0) and local Institutional Review Board or Ethics Committee requirements. A sample consent form is provided in the submission.

E. Evaluation of Financial Disclosure

Vol. 100 of the submission contains Financial Disclosure Forms from Clinical Investigators. The following three investigators admitted a proprietary or financial interest in the test product:

- Masoud Panjehpour, Ph.D. indicated that he is a co-inventor of esophageal PDT balloon owned by Thompson Cancer Survival Center.
- Bergein F. Overholt, M.D. indicated that he is a co-inventor and co-patent holder for esophageal centering balloon.
- Thomas J. Dougherty, Ph.D. indicated that he is a "co-inventor of PHOTOFRIN patent".

All the other investigators denied any financial interests or arrangements. The Financial Disclosure Form is adequate.

The Thompson Cancer Survival Center, where Drs. Overholt and Panjehpour were investigators, had higher complete response rates in the primary efficacy endpoint (30/34 or 88.2%) than all other sites (76/104 or 73.1%) (NDA 21-525 N-000BM, submitted on 9.26.2002). Dr. Overholt's results in the 2 uncontrolled trials also showed complete response rates of 88-89%. These superior results may indicate much greater expertise than in other centers, in that Drs. Overholt and Panjehpour developed the instruments and performed both pre-clinical and clinical trials prior to the pivotal trial. This reviewer would be reluctant to cast doubt on their results without any other evidence.

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VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Preliminary analysis of the pivotal PHO BAR 01 study, based on 6 months of follow-up (too short, therefore inadequate), indicates that photodynamic therapy using PHOTOFRIN and omeprazole was significantly more effective than control treatment (omeprazole) in causing complete ablation of high-grade dysplasia in Barrett's esophagus and replacement with normal squamous epithelium with or without some areas of Barrett's metaplasia, areas of indefinite dysplasia or low-grade dysplasia (72% vs. 31%, $p < 0.0001$). Replacement of high-grade dysplasia by normal epithelium, the best quality of response, was common in patients treated with PHOTOFRIN PDT plus omeprazole (41%) and rare (4%) in patients treated with omeprazole alone ($p < 0.0001$). Responses in the omeprazole alone group were generally not of the same quality, since high-grade dysplasia was replaced by normal squamous cell epithelium with areas of metaplasia, indefinite dysplasia, and low-grade dysplasia.

The short follow-up (a mean of 12 months) did not permit estimates of the duration of response, time to progression to cancer, time to treatment failure, or survival time. These secondary efficacy endpoints are of great importance, since the purpose of ablation of high-grade dysplasia is the prevention of adenocarcinoma.

The results in the two uncontrolled studies, based on a median follow-up of 6 months, indicated complete responses (complete ablation of high-grade dysplasia and replacement by normal squamous epithelium with or without some areas of metaplasia, indefinite dysplasia, or low-grade dysplasia) in about 88% of patients treated with PHOTOFRIN PDT. Results of a longer follow-up, median of 12 months, indicated a complete response rate of 93% - 95%. The duration of response, time to progression to cancer, time to treatment failure, or survival time could not be reliably estimated because of the short follow-up time.

The sponsor states (vol. 1, p. 251) that the primary analysis of the pivotal PHO BAR 01 study was to be done after a minimum of 6 months of follow-up. The results from this primary analysis form the basis of this submission, "as agreed with the Division" (vol. 7, p. 64, which contain Axcen Scandifarm Inc. Minutes of the pre-NDA meeting held on June 1, 2001). The statement by the Agency recorded in those minutes reads in its entirety "Additional information is required to determine the acceptability of this approach". In this reviewer's opinion, efficacy of PDT cannot be adequately assessed until sufficient follow-up has documented the duration of response. The sponsor's statement that "most failures occurred during the first 4 months" after treatment is not supported by the sponsor's data, which are described in the clinical review below.

B. General Approach to Review of the Efficacy of the Drug

PHO BAR 01, TCSC 93-07 (high-grade dysplasia patients only), and TCSC 96-01 (high-grade dysplasia patients only) were all reviewed in detail. The results are summarized above in A. as well as in Detailed Review of Trials and in Efficacy Conclusions below.

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B. Detailed Review of Trials by Indication

PIVOTAL STUDY:

Study Title: PHO BAR 01, A Multicenter, Partially Blinded, Randomized Phase III Study of the Efficacy and Safety of Photodynamic Therapy (PDT) Using PHOTOFRIN (porfimer sodium) for Injection for the Ablation of High-Grade Dysplasia in Barrett's Esophagus.

The protocol for the pivotal study (PHO BAR 01) was submitted for review to the Division of the Oncology Drug Products (IND 25,064) by QLT (the sponsor at that time) on November 13, 1997, and the study was started on January 15, 1998. It was a multicenter, controlled, randomized, partially blinded trial comparing PDT with PHOTOFRIN and omeprazole to a surveillance arm consisting of omeprazole only. Two hundred eight (208) patients with high-grade dysplasia in BE were randomized in a 2:1 (PDT:surveillance) proportion. The omeprazole control group was included to allow assessment of the natural history of untreated high-grade dysplasia in BE. Since there was no esophagectomy arm in the trial, the Division of Gastrointestinal and Coagulation Drug Products in a pre-NDA meeting with the then-sponsor (Axcan Scandipharm Inc.) concluded that the data from this trial and the supporting trials could only support the PDT with PHOTOFRIN for those patients with high-grade dysplasia in BE who are not candidates for esophagectomy.

Date of Study Initiation: January 15, 1998

Date of Study Completion: November 7, 2001

Date of the Present Submission (Preliminary Findings): May 31, 2002

Date of the 24-month Follow-up Efficacy Data submission by the Sponsor: September 30, 2002

Date of the 24-month Follow-up Safety Data submission by the Sponsor: October 23, 2002

Study Objectives:

1. **Primary Objective:** To assess the efficacy of PDT with PHOTOFRIN for Injection plus omeprazole compared to omeprazole alone in the complete ablation of high-grade dysplasia in patients with BE, in conjunction with a strict endoscopic surveillance and biopsy protocol.
2. **Secondary Objectives:** To assess the safety and efficacy of PDT with PHOTOFRIN plus omeprazole and systematic endoscopic surveillance compared to omeprazole only therapy plus systematic endoscopic surveillance in terms of :
 - a) quality of complete response
 - b) duration of complete response

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- c) delaying progression to cancer (time to progression to cancer)
- d) delaying the need for esophagectomy or other intervening therapy (included together with c) in time to treatment failure), and
- e) survival time:

Study Design and Study Plan:

This was a multicenter, partially blinded, randomized, Phase III study in patients with high-grade dysplasia in BE. Eligible patients were randomized to receive PHOTOFRIN plus omeprazole (OM) therapy or OM only therapy.

Blinding: Patients and study physicians were aware of the treatment each patients received; however, the pathologists who read the biopsies from each esophageal endoscopy were blinded to the patients' treatment. All histological assessments were carried out at a central reference laboratory.

Randomization: Patients were centrally randomized in a 2:1 design to receive PHOTOFRIN PDT plus OM therapy or OM therapy alone. The study planned the enrollment of at least 200 patients with high-grade dysplasia in BE at approximately 40 clinical trial sites in North America and Europe.

Treatment: Photodynamic therapy (PDT) with PHOTOFRIN is a 2-stage process. The first stage is the intravenous injection of PHOTOFRIN at a dose of 2.0 mg/kg of body weight over 3-5 minutes 2 days (40-50 hours) prior to the light treatment. The second stage of treatment is the illumination of the area of treatment with a laser light.

A maximum of 7 cm of BE was treated during one course of PDT (I.V. PHOTOFRIN followed by 1 or 2 laser light applications). The second light application could be given 2 days after the first 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. The entire length of Barrett's mucosa was to be treated; therefore up to three courses could be given. Courses of PDT had to be separated by at least 3 months. If a previous course of treatment resulted in residual areas of dysplasia, Barrett's metaplasia, or any remaining "skip areas", an additional course of PDT was to be given. Patients in both treatment groups received omeprazole (20 mg BID) to reduce reflux esophagitis.

Follow-up: All patients were to be followed every 3 months until four consecutive, quarterly follow-up endoscopic biopsy results were negative for high-grade dysplasia, and then biannually until the last enrolled patient had completed at least 24 months of follow-up evaluation after randomization. Patients were to be assessed for efficacy (by histological assessment of biopsies), and safety (adverse events, laboratory results and physical examinations).

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Treatment response: Defined as the complete ablation of high-grade dysplasia at any one of endoscopic assessment time points. The quality and duration of the complete response were also to be assessed. Secondary treatment responses included: time to progression to cancer, time to treatment failure, and survival time.

The majority of patients with high-grade dysplasia do not progress to cancer over a period of observation of several years. Therefore, the efficacy of photodynamic therapy of high-grade dysplasia in cancer prevention was assessed by comparing the persistence and re-occurrence of high-grade dysplasia in PDT-treated patients and in omeprazole only-treated patients, who were the control patients exhibiting the natural history of high-grade dysplasia. Primary analysis was to be performed after 6 months, and final analysis after 24 months from the date of randomization of the last patient.

Additional analyses were to be performed to evaluate the effect of various baseline and demographic factors on the primary efficacy variable, i.e. complete response. The factors included the following:

- High-grade dysplasia duration (6 months or less vs. more than 6 months)
- BE length as a continuous variable
- High-grade dysplasia foci, single vs. multiple
- Nodular vs. non-nodular disease
- Prior omeprazole for at least 3 months (yes, no)
- Size of center enrollment (>10 patients vs. 1-9 patients), pooled data
- Gender (male vs. female)
- Age (<65 vs. >65 years old)
- Smoking history (smoker vs. non-smoker)
- Physician's experience with PHOTOFRIN PDT (first 3 patients in the study arm from each center vs. all other patients)

Safety monitoring. An evaluation committee (Data Safety Monitoring Committee) was to review the safety data every six months. An interim analysis was not planned in the study.

Sponsor's Figure 9.1 shows the Schematic of Study Design and Figure 9.2 shows the Schematic of Schedule of Procedures (in Appendix A. Other Relevant Materials).

Study Population:

Inclusion Criteria:

1. High-grade dysplasia in BE, as assessed by the central reference laboratory
2. 18 years of age or older
3. Not pregnant
4. If female of childbearing potential, practicing reliable birth control
5. Signed Informed Consent

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Exclusion Criteria:

1. Invasive cancer of the esophagus, or patients in whom invasive cancer, lymph node involvement or metastases could not be ruled out by endoscopic ultrasonography or by CT scan
2. History of cancer within 5 years before screening, other than non-melanoma skin cancer
3. Prior PDT to esophagus
4. Esophageal strictures unresponsive to dilation
5. Known contraindications to analgesia or endoscopy
6. Significant acute or chronic illness beside BE (in the judgement of the investigator)
7. Contra-indication to omeprazole
8. Porphyria or known hypersensitivity to porphyrins
9. WBC <2.5/cu.mm; platelets <50,000/cu.mm; Hgb <9.0 g/dL; PT/INR >1.5
10. Serum creatinine >1.5 times the upper limit of normal; total bilirubin >1.5 times the upper limit of normal; AST, ALT, alk.phosphatase >2.5 times the upper limit of normal
11. Unable or unwilling to complete the follow-up evaluations required for the study
12. Unstable heart disease (NYHA Class III and IV)
13. Esophageal ulcers >1 cm in diameter
14. Esophageal or gastric varices

Removal of Patients from Therapy or Assessment: Patients were to be removed from the study because of

- disease progression,
- unacceptable adverse events,
- refusal to continue, or
- at the investigator's discretion if it is in the patient's best interest.

Screening and Selection: The plan was to include 200 patients in the study. A total of 486 patients were screened for inclusion at 30 centers in the United States, Canada and Europe, and a total of 208 patients were enrolled. The reasons for patient exclusion are shown in the table below.

Total screened	486
Total randomized to treatment	208 (42.8%)
Total not randomized	278 (57.2%)
--no high-grade dysplasia	239 (86.0% of 278) (49.2% of 486)
--other screening criteria not met	14 (5.0% of 278)
--declined participation	25 (9.0% of 278)

The predominant reason for patient exclusion was the failure to confirm the diagnosis of high-grade dysplasia in 49.2% of screened patients. This is an important finding that suggests a potential misuse of PHOTOFRIN PDT in patients without high-grade dysplasia.

One center (Thompson Cancer Survival Center, Knoxville, TN) enrolled 51 patients into the study (24.5%), four centers (Columbia-Presbyterian Hospital, NYC; Mayo Clinic, Rochester,

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MN; Johns Hopkins Hospital, Baltimore, MD; and Parkland Memorial Hospital, Dallas, TX) enrolled 13-14 patients each. Other centers enrolled between 1 and 9 patients. A great majority of the patients were enrolled in American institutions (196 or 94.2%). Five patients were enrolled in Canada, six in UK and one in France.

The preponderance of the Thompson Cancer Survival Center is presumably due to the presence of acknowledged expertise in this area. Dr. Overholt and colleagues at the Thompson Center developed many of the techniques and instruments used in PDT, and published the two largest series of BE patients treated with PDT. These two studies are supporting studies in this application. Patient screening and selection appeared not to differ at the Thompson Center from the overall statistics (113 patients screened, 51 randomized (45.1%).

Patient characteristics:

The mean age of patients enrolled in the PHOTOFRIN PDT + OM group was 66.13 with a range from 38.4 to 88.5 years. The mean age of patients in the OM Only group was 67.27, with a range from 36.1 to 87.6 years. The mean height was 173 cm. The total study population was predominantly male (85%), white (Caucasian) (99%), and former or current smokers (71%). Reviewer's Table in the Safety section of this review contains a table of the demographic characteristics of enrolled patients in PHO BAR 01 as well as the two uncontrolled studies.

The patient population enrolled in this study is representative of the general BE population affected by high-grade dysplasia. Male to female ratio is 7:1 in this population (Sharma & Sampliner 2001).

Patients in the two treatment groups reported mostly gastrointestinal (79%), cardiovascular (68%) and musculoskeletal (63%) medical history. There were no statistical differences between the two treatment groups with regards to medical history.

Characteristics of BE at baseline are shown below in sponsor's Panel 11.5 (vol.13, p.94). The two treatment groups were well-matched in

- duration of BE (mean and median values of about 36 months and of about 20 months, respectively),
- duration of high-grade dysplasia (mean and median values of about 6 months and of about 4 months, respectively),
- endoscopic length of BE (about one-half shorter and one-half longer than 6 cm),
- histological length of BE,
- endoscopic characteristics of high-grade dysplasia including the presence of hiatal hernia, esophageal ulcers, nodules and strictures, and
- prior treatment (medical, surgical, esophageal dilations and blood transfusion; there were no cases of endoscopic ablation).

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Barrett's Esophagus at Baseline

Characteristic	PHOTOFRIN PDT + OM N = 138	OM Only N = 70
Duration of BE in months, Median (range)	20.27 (1.3 – 216.7)	19.22 (0.9 – 141.7)
Duration of high-grade dysplasia in months, Median (range)	3.55 (0.1 – 40.7)	4.11 (0.4 – 72.4)
Endoscopic length of BE		
- < 6 cm (%)	63 (46%)	35 (50%)
- > 6 cm (%)	75 (54%)	35 (50%)
Histological length of BE		
- < 6 cm (%)	74 (54%)	42 (60%)
- > 6 cm (%)	64 (46%)	28 (40%)
Extent of high-grade dysplasia		
- Single biopsy	34 (25%)	17 (24%)
- Single level	50 (36%)	27 (39%)
- Multiple levels	87 (63%)	43 (61%)
Endoscopic condition		
- Hiatal hernia	125 (91%)	58 (83%)
- Nodules	45 (33%)	19 (27%)
- Ulcers	8 (6%)	3 (4%)
- Strictures	6 (4%)	2 (3%)
Prior treatment		
- Surgery	6 (4%)	8 (11%)
- Medical therapy	134 (97%)	66 (94%)
- Other	6 (4%)	2 (3%)

Source: Panel 11.5, vol. 13, p. 94.

Sub-study: Rater Agreement on Histological Diagnosis for Patients in study PHO BAR 01

A study was carried out by the sponsor to assess the inter-rater and intra-rater percent agreement on histologic diagnoses assigned to sets of endoscopic biopsy samples in the screening and trial phases of the PHO BAR 01 clinical trial (vol. 41).

Secondary objectives included: 1) assessment of the intra-rater and inter-rater percent agreement on a per biopsy basis, 2) assessment of pre-PDT-treatment rater agreement vs. post-PDT-treatment rater agreement, and 3) assessment as to whether the following factors may affect rater agreement: presence of inflammation, presence of ulcers/erosions, and endoscopy/treatment site.

Study design. The rater reliability study was conducted in parallel with PHO BAR 01. Three pathologists at [redacted] (the central reference pathology laboratory) at the University of Washington Medical Center participated in the study. Two rounds of readings were

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performed for the slides, i.e. each pathologist read each endoscopic slide set in the rater agreement study twice.

Study procedures. Readings for the rater agreement study were performed by the pathologists in a blinded fashion. Pathologists had no knowledge of the patient identity, randomization arm, study phase or clinical trial site. Rater agreement slides were inserted into the stream of PHO BAR 01 study read by the pathologist on call. The order of reading by the second and third pathologist was randomized.

Sample size. There were 26 sets of slides, from an equal number of pre- and post treatment biopsies, for a total of 437 biopsies with 6 repetitions of the reading on each biopsy. There were a total of 2622 individual biopsy readings.

Outcomes to be analyzed: presence of 1) high-grade dysplasia, 2) cancer, 3) high-grade dysplasia of cancer, 4) dysplasia (low-grade or high-grade), and 5) Barrett's esophagus. Two raters were defined to agree on the outcome of high-grade dysplasia (both agreed it was absent or present) and similarly on the other outcomes.

Results. Reviewer's Tables below (from Table 2, vol. 41, p. 15 and Table 5, vol.41, p. 20) show inter-rater agreement and intra-rater agreement on the five diagnoses tested.

Reviewer's Table: Percent Inter-Rater Agreement on Endoscopy Diagnoses

Diagnosis	Mean % agreement (range of percentages)
High-grade dysplasia	88 % (78% - 94%)
Cancer	96 % (85% - 99%)
High-grade dysplasia or cancer	92 % (83% - 97%)
Dysplasia (low-grade and high-grade)	86% (74% - 92%)
Barrett's esophagus	99% (98% - 100%)

Reviewer's Table: Percent Intra-Rater Agreement on Endoscopy Diagnoses

Diagnosis	Intra-rater agreement, % (range)
High-grade dysplasia	94% (87% - 97%)
Cancer	99 % (92% - 99.8%)
High-grade dysplasia or cancer	96% (77% - 99.5%)
Dysplasia (low-grade and high-grade)	92% (83% - 97%)
Barrett's esophagus	99% (92% - 99.8%)

Source: Table 5, vol. 41, p.15.

Factors that had the greatest impact on inter-rater agreement on the endoscopy diagnosis of high-grade dysplasia were the presence of obscuring inflammation (81% when inflammation was present vs. 94% when inflammation was not present), when high-grade dysplasia was not

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excluded (77% vs. 93%), and the number of biopsies (with >16 it was 82% vs. 95% with 16 or fewer).

Factors that had the greatest impact on agreement on cancer were high-grade dysplasia not excluded, erosions, and inflammation. For high-grade dysplasia and cancer, while there was disagreement on the presence of cancer, there was no disagreement that it was either high-grade dysplasia or cancer. Diagnosis of dysplasia was influenced by the presence of inflammation, high-grade dysplasia not excluded, number of biopsies over 16, and the presence of erosions.

Intra-rater agreement on the endoscopy diagnosis was very high (average 96%; range, 92% - 99%). The main factors influencing intra-rater agreement were post-treatment samples and the presence of erosion.

Overall Conclusion. The primary conclusion of this study is that rater agreement on the endoscopic diagnosis is generally high. These high rates of agreement (88% for high-grade dysplasia, 96% for cancer, 92% for high-grade dysplasia or cancer, 85% for dysplasia, and 99% for Barrett's esophagus) suggest that the effect of rater disagreement on the reproducibility of PHO BAR 01 will be minimal.

However, an incidental finding of this study was that of the 13 screening endoscopies in the study, only 7 were given the diagnosis of high-grade dysplasia. All the patients entering the screening phase of the trial had a diagnosis of high-grade dysplasia by another pathologist determined from biopsy samples taken from a different endoscopy in the recent past. The failure to verify the diagnosis of high-grade dysplasia in 6 of the 13 cases indicates that variability in the diagnoses across time and across raters from different institutions may be higher than the inter-rater variability seen in this study, where rater variability estimates were restricted to 3 pathologists in a single institution and the raters read slides from the same endoscopy. The above noted failure to confirm the diagnosis of high-grade dysplasia in 49.2% of patients during screening reinforces this concern.

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Treatment assignment and disposition:

Number of patients randomized	PHOTOFRIN + OM N = 138	OM only N = 70
Number of patients receiving at least one course of study Therapy	N = 132 N = 6 not. Reasons: (1) low-grade dysplasia; (1) adenocarcinoma; (3) declined participation; (1) received PHOTOFRIN but no light because of anxiety	N = 69 N = 1 not. Reason: esophagectomy
Follow-up of at least 6 months	N = 126 (95% of 132) N = 8 not. Reasons: (5) progression of disease; (1) lung cancer; (2) missing data	N = 55 (79.7% of 69) N = 14 not. Reasons: (8) progression of disease; (1) died from stroke; (1) esophagectomy; (2) PHOTOFRIN PDT; (2) missed 6-month assessments or uncooperative

Source: vol. 13, p.65

Number of patients included in the:	PHOTOFRIN + PDT	OM only
ITT population	138 (100%)	70 (100%)
Safety population	133 (96%)	69 (99%)
Evaluable population	130 (94%)	69 (99%)
Number of patients randomized	138	70
Number of patients receiving study therapy	132	69
Number of patients completing 6-mo follow-up	124	55
Number of patients discontinued from the Study:	37 (27%)	29 (41%)
Adverse event	3 (2%)	0
Progression of disease:	15 (11%)	14 (20%)
confirmed by histopathology	14 (10%)	13 (19%)
unconfirmed by histopathology	1 (<1%)	1 (1%)
Death	2 (1%)	1 (1%)
Other therapy	9 (6%)	13 (19%)
Administrative reasons	8 (6%)	1 (1%)

Source: Panel 10.2, vol. 13, p. 66; Listing 36.0, vol. 83, pp. 151-168

Reviewer's note: The above sponsor's Panel 10.2 is somewhat difficult to follow, but the following explanations should be made:

1. 132/138 patients in the PHOTOFRIN PDT arm received at least one complete course of therapy. Of the six who did not, three withdrew consent before therapy, one withdrew

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consent after PHOTOFRIN infusion but before the light treatment, one was found to have an adenocarcinoma and one was found to have a low-grade dysplasia.

124/132 patients in the PHOTOFRIN PDT arm provided 6-month follow-up data. Of the eight patients who did not, five had a progression of the disease, one had a newly diagnosed lung cancer and two had missing data.

2. 79/138 patients in the PHOTOFRIN PDT arm received one course of treatment; 52/138 received two courses; and 29/138 received three courses (Panel 10.3, vol. 13, p. 68).
3. It appears that only a few patients in the PHOTOFRIN PDT arm had completed 24 months of follow-up (sponsor's Panel 10.3, vol. 13, p. 68 is shown below). The protocol called for all the patients to complete at least 24 months of follow-up.
4. 69/70 patients in the OM arm received at least one omeprazole dose. One did not, because he had an esophagectomy.
5. Patient follow-up data in the OM arm are incomplete after the 6-month time point. Only a few patients in the OM arm had completed the planned 24 months of follow-up.
6. The number of patients discontinued from the Study, 37 in the PHOTOFRIN PDT group and 29 in the OM Only group, must have been after a variable follow-up (see below in Reviewer's Table on Patient's Duration on Study).

Protocol Deviations:

No patients were excluded from the data set for the ITT analysis. Six patients, five from the PHOTOFRIN PDT treatment group and one from the OM Only treatment group were excluded from the Safety analysis data set, because neither PHOTOFRIN PDT nor omeprazole had been administered. Three additional patients from the PHOTOFRIN PDT group were excluded from the Evaluable population data set, because in two patients cancer could not be excluded by esophageal ultrasound and one patient did not receive the light application following PHOTOFRIN treatment.

At randomization, no patients violated inclusion criteria, nine patients violated exclusion criteria (history of cancer in 8 patients, history of stable anemia in one, and increased BUN/creatinine values in one). Randomization was to be scheduled with 4 weeks of the baseline biopsy; 27 patients (18 in the PHOTOFRIN PDT group and 9 in the OM Only group) violated this directive.

PDT Treatment:

PHOTOFRIN was administered intravenously at a dose of 2 mg/kg. Laser light at 630 nm was administered using light delivery systems described in the Safety Section 40 - 50 hours after drug administration. A Summary Table of the Extent of PDT in the Evaluable Group is shown in the Reviewer's Table below (from Table 8.8 - 3, vol. 8, p. 110).

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Reviewer's Table: Photodynamic Therapy Treatment

Laser light sessions	Course 1 N = 130 (%)	Course 2 N = 81 (%)	Course 3 N = 29 (%)
First laser light session			
Pre-treatment of nodules	33 (25%)	24 (30%)	9 (31%)
Balloon light treatment	129 (99%)	81 (100%)	28 (97%)
Second laser light session			
Treatment of skip areas	60 (46%)	46 (57%)	14 (48%)

Concomitant Medication and Adjunctive Therapy

During the study, 133 (100%) patients in the PHOTOFRIN PDT + OM group and 65 (94%) patients in the OM Only group took at least one concomitant medication. The following table describes the use of concomitant medications in the two treatment groups. PHOTOFRIN PDT + OM group took many more medications than the OM Only group. Especially impressive is the very high usage of analgesics, anti-emetics, antacids, gastrointestinal agents, glucocorticoids and cytoprotective agents.

Drug group	PHOTOFRIN PDT + OM % of patients using	OM Only % of patients using
Opioid analgesics	90%	23%
Non-opioid analgesics	83%	32%
Phenothiazines	62%	4%
Antacids	56%	9%
Local anesthetics	55%	1%
Glucocorticoids	39%	10%
Benzodiazepenes	28%	14%
Gastrointestinal agents	26%	1%
Ethanolamines	20%	4%
Glucagon	20%	1%
Cytoprotective agents	14%	7%
Stimulant laxatives	11%	3%
Aminoglycosides	1%	6%

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Patients' Duration on Study

This submission contains data on patients who have completed at least 6 months of follow-up, and this data is used for a preliminary analysis of the study. The Reviewer's Table below shows the patients' duration on study (from Table 1.10, vol. 14, p. 113, data compiled on December 11, 2000). This information provides the reason for the preliminary nature of the results. At the time of this data collection very few patients had completed at least 24 months of follow-up. The final analysis of the study will be performed with data on patients who will have completed at least 24 months of follow-up.

Reviewer's Table on Patients' Duration on Study

Patient Duration on Study	PHOTOFRIN PDT + OM ITT population, N = 138	OM Only – ITT population N = 70
< 3 months	10 (7%)	6 (9%)
3 – 6 months	3 (2%)	14 (20%)
6 – 9 months	35 (25%)	15 (21%)
9 – 12 months	22 (16%)	9 (13%)
12 – 15 months	23 (17%)	8 (11%)
15 – 18 months	20 (14%)	7 (10%)
18 – 21 months	14 (10%)	5 (7%)
21 – 24 months	8 (6%)	5 (7%)
>24 months	3 (2%)	1 (1%)
Mean no. of months	12.1	10.3

RESULTS:

Primary efficacy endpoint: Complete Ablation of High-grade Dysplasia

Patients with complete ablation of high-grade dysplasia included:

- 1) those who had complete replacement of all Barrett's metaplasia and dysplasia with normal squamous cell epithelium (Complete Response 1 - CR1),
- 2) those who had ablation of all grades of dysplasia, but had some areas of Barrett's metaplasia remaining (Complete Response 2 – CR2), and
- 3) those who had ablation of all areas of high-grade dysplasia, but had some areas of low-grade dysplasia, or areas indefinite for dysplasia, or areas of metaplasia (Complete Response 3 – CR3).

The proportion of responders (CR1 + CR2 + CR3) was significantly higher in the PHOTOFRIN + OM group than in OM Only group (72% vs. 31%, $p < 0.0001$), as shown in Reviewer's Table below (from Panel 11.6, vol. 13, p. 98). More than twice the percentage of patients had a response to PHOTOFRIN PDT + OM than to OM Only, an impressive difference of 41%.

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Reviewer's Table on Primary Efficacy – Overall Clinical Response

Response	PHOTOFRIN PDT + OM N = 138	OM Only N = 70
CR1 + CR2 + CR3	99 (72%)	22 (31%)

Reviewer's Note: With a 6-month follow-up, the difference in results between the two treatments is impressive. It should be pointed out that most of the literature maintains that high-grade dysplasia does not respond to omeprazole at all, and the response seen in this study may be due, at least in part, by control and subsidence of inflammation due to GERD.

It is important to note the reasons of failures of the Primary efficacy endpoint. Reviewer's Table below (from Data listings) show the reasons for response failures, the patients who at 6-month follow-up did not have a complete response.

Reviewer's Table on Response Failures and Patient Discontinuations from the Study

Reason for discontinuation from study	PHOTOFRIN PDT + OM N = 37 (27% OF 138)	OM Only N = 29 (41%)
Progression of disease (further therapy mainly not stated)	15 (11%)	14 (20%)
Other therapy (these patients are not included under Progression of disease)	9 (7%) Esophagectomy – 3 YAG laser – 3 Heater probe mucosal ablation – 1 4 th PHOTOFRIN PDT – 1 Other - 1	13 (19%) PHOTOFRIN PDT – 9 Esophagectomy – 3 Not specified - 1
Patient withdrew	5 (4%)	
Adverse event	3 (2%)	
Death	2 (1%)	1
Uncooperative/unreliable patient	1	1
Other administrative	2	

Reviewer's Note: Patients did not have a minimum of 24 months follow-up in either group and therefore the data on response failures (see Reviewer's Table above) can be regarded only as preliminary. Nevertheless, during the minimum of 6 months' follow-up, 20% of patients in the OM Only group had progression of disease and another 19% had other therapy (a total of 39%) versus 11% and 7%, respectively, (a total of 18%) in the PHOTOFRIN PDT + OM group - more than twice the number.

The Kaplan-Meier plot shows that all Omeprazole Only patients relapsed, progressed or had other therapy within 180 days, while about 75% of PHOTOFRIN PDT + OM patients

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maintained the response at that time. Inadequate follow-up data need to be kept in mind in assessing response maintenance after 360 days.

Secondary Efficacy Endpoint: Quality of Complete Response

The quality of response in the PHOTOFRIN PDT + OM group was significantly better than in the OM Only group, as measured by the percentages of CR1 and CR2 responses. Reviewer's Table below depicts the data from Panel 11.7 (vol. 13, p. 99). There was a ten-fold difference in CR1 between treatments, and an eight-fold difference in CR1 + CR2.

Reviewer's Table on the Quality of Complete Response

Number of patients – ITT population	PHOTOFRIN PDT + OM N = 138	OM Only N = 70
CR1	57 (41%)	3 (4%)
CR1 + CR2	67 (49%)	4 (6%)

Secondary Efficacy Endpoint: Duration of Response

Duration of response was defined as the day 50% of the patients had experienced the failure event for the response category. Median duration of response (CR1, or CR1 + CR2, or CR1 + CR2 + CR3) in the PHOTOFRIN PDT + OM group could not be estimated. In the OM Only group the median duration of CR1 was 81 days and of CR1 + CR2 + CR3, 98 days.

A Kaplan-Meier plot showing the probability of maintaining a CR3 or better is not reproduced because the small number of patients followed for longer than 12 months make these estimates unreliable (see Statistical Review).

Secondary Efficacy Endpoint: Time to Progression to Cancer

This endpoint was defined as the day 50% of the patients in a treatment group had documented progression to cancer. Median Time to Progression to Cancer could not be estimated for either group. According to the sponsor, most treatment failures occurred within 4 months after the first course of treatment. Patients in the PHOTOFRIN PDT + OM group had 96% chance of being cancer-free after 4 months as compared to a 90% chance for patients in the OM Only group.

Reviewer's note: The above conclusions appear premature in view of the duration of patient follow-up. Most treatment failures could be predicted to occur early, if the follow up is short. Fifteen (15) patients (11%) in the PHOTOFRIN PDT + OM group had progressed to cancer from days 65 to 373. Fourteen (14) patients (20%) in the OM Only group had progressed to cancer

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from days 63 to 642. Reviewer's Table below shows the Time to Progression to Cancer in days in the two arms (Listing 36.0, vol. 83, pp. 151-156).

Reviewer's Table of Time to Progression to Cancer

Time to Progression Interval in days	PHOTOFRIN PDT + OM Day progression diagnosed (number of courses)	OM Only Day progression diagnosed
0 – 120	43 (1 course); 81 (1 course); 87 (1 course); 94 (1 course); 95 (1 course); 100 (2 courses) 101 (2 courses); 102 (2 courses); 108 (2 courses); 115 (2 courses)	64; 93; 94; 101; 102; 103
121 – 240	186 (2 courses); 198 (1 course); 221 (1 course)	130; 131; 179; 186; 203; 222
> 241	361 (1 course); 373 (1 course)	278; 664
Total	15 (11%)	14 (20%)

Secondary Efficacy Endpoint: Time to Treatment Failure

Time to Treatment Failure (TTF) was defined as the period in days from the date of randomization until the date of the first documentation of 1) progression of high-grade dysplasia to cancer or 2) the start of any intervening therapy for high-grade dysplasia other than the randomized study treatment.

Median TTF could not be estimated for the PHOTOFRIN PDT + OM group, because fewer than 50% of the patients had documented TTF by the end of the follow-up: 23 patients (17%) had failed treatment from days 65 to 499. Median TTF was 642 days in the OM Only group: 26 patients (37%) had failed treatment from days 7 to 644. The last patient was censored at day 499 in the PHOTOFRIN PDT + OM group and at day 642 in the OM Only group.

According to the sponsor, the probability of treatment success in the PHOTOFRIN PDT + OM group was 96% after 4 months as compared to 84% in the OM Only group (vol.13, p.105). The data presented above on Response Failures contradict this statement by the sponsor. Kaplan-Meier plot supporting this conclusion by the sponsor (vol.13, p.106) is not reproduced.

Secondary Efficacy Endpoint: Survival Time

Survival Time was defined as the period in days from the date of randomization to the date of the patient's death. Median survival time was the day 50% of the patients had died.

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Median survival time could not be estimated for either treatment group: 2 patients died in the PHOTOFRIN PDT + OM group (on days 631 and 643) and 1 patient died in the OM Only group (on day 25).

Reviewer's Note: None of the deaths were attributable to adenocarcinoma of esophagus (one cardiac arrest after CABG surgery, one cancer of male breast, one stroke). Thus, this endpoint is not useful.

Other analyses

Additional analyses showed that Complete Response (CR1 + CR2 + BR3) rate was influenced by the following factors:

- treatment with PHOTOFRIN PDT (vs. OM Only, $p < 0.0001$)
- single high-grade dysplasia focus vs. multiple foci ($p < 0.0001$)
- prior omeprazole intake of at least 3 months ($p = 0.0005$), and
- age, < 65 years old vs. > 65 years old ($p = 0.0219$).

Complete Response rate was not influenced by:

- duration of high-grade dysplasia
- length of BE
- nodular conditions
- gender
- smoking history
- study center's size (< 10 patients vs. > 10 patients)
- clinician's experience with PDT ($p = 0.06895$).

SUPPORTING STUDIES:

Study Title: TCSC 93-7. A Phase I/II Study of the Safety and Efficacy of Photodynamic Therapy (PDT) Utilizing PHOTOFRIN for Treatment of Dysplasia or Early Adenocarcinoma of the Esophagus in Barrett's Esophagus.

Study TCSC 93-07 was a single center, investigator-sponsored (Dr. Bergein Overholt), uncontrolled Phase II study. The objectives of the study were to evaluate the safety and efficacy of PHOTOFRIN PDT in patients being treated for dysplasia or early adenocarcinoma in BE and to determine the required light dose to produce effective results. A total of 99 patients were enrolled in the study. Of these patients, 44 had BE with high-grade dysplasia.

This was an open-label study in which patients were divided into 2 treatment groups. About one-half of the entire study population, including 14 high-grade dysplasia patients, were treated with a 175 – 225 Joules/cm light dose and a 5 or 7 cm PTG balloon at first treatment. The other half

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of the study population were treated with a light dose of 150 – 300 J/cm light dose and a 2, 3, 5, or 7 cm PTG balloon at first treatment.

Criteria for patient selection were similar to those in the PHO BAR 01 study, although much less extensive.

The Inclusion Criteria were as follows:

1. Biopsy-proven dysplasia or early adenocarcinoma of the esophagus in BE, without ultrasound evidence of tumor extension through the muscularis (stage T₂N₀M₀ or less).
2. Ineligible or refused standard methods of treatment including esophageal resection.
3. No contraindications to endoscopy
4. Male or female, 18 years of age or older. Females with adequate precautions against pregnancy.
5. Signed informed consent, or consent by next of kin or legal representative.
6. Karnofsky Performance status >30.

The Exclusion Criteria were as follows:

1. Tumor extension beyond muscularis
2. Porphyria or sensitivity to porphyrins
3. WBC <2,000, platelets <50,000, PT >1.5 times normal
4. Impaired renal or hepatic function
5. Received radiation or chemotherapy within 4 weeks before the admission to this study

Removal of Patients from Therapy or Assessment:

1. If no tumor response after 2 courses of PHOTOFRIN PDT (visual or biopsy evidence)
2. Unacceptable toxicity
3. Patient refused to continue treatment

Patients who were removed from the study less than 30 days after receiving PHOTOFRIN were cautioned against sunlight or strong light.

Study Title: TCSC 96-01. Photodynamic Therapy of Dysplasia or Early Adenocarcinoma in Barrett's Esophagus: A Randomized Study of the Effect of Steroid Therapy on the Incidence of Esophageal Stricture.

Study TCSC 96-01 was a single center, investigator-sponsored (Dr. Bergein Overholt), partially blinded, randomized, Phase II parallel-group study. The study objective was to compare the incidence and severity of esophageal strictures between patients with BE who received steroid therapy after PHOTOFRIN PDT and patients who received PHOTOFRIN PDT alone for treatment of dysplasia and/or early adenocarcinoma of the esophagus. A total of 87 patients were enrolled in the study. Forty-two (42) of these patients had BE with high-grade dysplasia, 30 patients had BE with low-grade dysplasia, 4 patients had adenocarcinoma, and 10 patients had other conditions, including patients with BE without dysplasia or carcinoma.

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Study TCSC 96-01 was a follow-up to study TCSC 93-07, which had demonstrated that PHOTOFRIN PDT was an effective treatment for destroying dysplasia and early cancer in BE patients. However, a serious side effect of PHOTOFRIN PDT was the formation of esophageal strictures due to fibrosis and scar formation during the healing process after treatment. Steroid therapy had been reported to reduce fibrosis in a variety of conditions, including corrosive burns of the esophagus.

The study was partially blinded. All patients received PHOTOFRIN PDT and omeprazole, and were randomized to steroid treatment or no steroid treatment. Patients and investigators were aware of the treatments administered. Only the endoscopists, who were responsible for evaluating esophageal stricture formation in the patients during the study, were blinded to whether the patient was in the steroid treatment group or not.

Reanalysis of Phase II study data by the sponsor

The data from the Phase II studies were reanalyzed by the sponsor in accordance with the analysis of the pivotal study, including

- 1) revised patient inclusion criteria (only patients with high-grade dysplasia),
- 2) revised objectives, and
- 3) revised outcome endpoints (primary efficacy endpoint data at 6 months of follow-up, and secondary efficacy endpoints and safety endpoints at 12 months of follow-up).

Thus, these analyses included data on 44 patients out of 99 in the TCSC 93-07 study, and on 42 patients out of 87 in the TCSC 96-01 study. Omeprazole was administered to all the patients in both trials.

Demographic Characteristics

Baseline demographic characteristics of high-grade dysplasia patients in the uncontrolled studies are shown in the Reviewer's Table below.

Note: the sponsor divides the patients in TCSC 93-07 into 2 groups: a group in which the patients were treated with a light dose of 175-225 J/cm and a 5 or 7 cm balloon at first treatment, and a second group in which the patients were treated with a light dose of 150 – 300 J/cm and a 2, 3, 5, or 7 cm balloon at first treatment. Since neither the baseline characteristics (vol. 42, p. 203; vol. 47, p. 166) nor the overall clinical response (primary efficacy endpoint) (vol. 42, p. 206; vol. 47, p. 170) differed between the two groups, the results of both groups are combined in the reviewer's tables below.

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Reviewer's Table on the Demographic Characteristics of High-Grade Dysplasia Patients in the Uncontrolled Studies

Characteristic	PHOTOFRIN PDT TCSC 93-07, N = 44	PHOTOFRIN PDT TCSC 96-01, N = 42
Age in years, mean (range)	65.4 (39.1 – 81.1)	67.3 (48.0 – 82.0)
Sex – Male, number (%)	39 (88.6%)	34 (81%)
Female number (%)	5 (11.4%)	8 (19%)
Race – White (Caucasian)	44 (100%)	40 (95.2%)
- Black (African-American)	0	1 (2.4%)
-Asian	0	1 (2.4%)

Sources: vol. 42, p. 203; vol. 47, p. 166.

The characteristics of Barrett's Esophagus at baseline are shown in the Reviewer's Table below (from Panel 11.2 in vol. 42, p. 204 for study TCSC 93-07, and Panel 11.2 in vol. 47, p. 168 for study TCSC 96-01)

Reviewer's Table on the Characteristics of Barrett's Esophagus at Baseline

Characteristic	PHOTOFRIN PDT TCSC 93-07, N = 44	PHOTOFRIN PDT TCSC 96-01, N = 42
Duration of BE in months, median (range)	24.2 (1.1 – 102.3)	10.9 (2.5 – 328.8)
Endoscopic length of BE		
< 6 cm	in 9 patients	In 9 patients
> 6 cm	in 27 patients	In 19 patients
Prior treatment		
- Medical therapy	in 40 patients	In 39 patients
- Surgery	in 9 patients	In 7 patients
- Endoscopic Ablation	in 1 patient	0
- Other	in 2 patients	0

Treatment of Patients with PHOTOFRIN and Photodynamic Therapy

1) Study TCSC 93-01

All patients received 2.0 mg/kg of PHOTOFRIN I.V., and the first laser light treatment was administered to the esophageal segment 40-50 hours later. A second laser light treatment, if indicated, occurred 4 - 9 days after injection of PHOTOFRIN. One-half of the patients were treated with a light dose of 175-225 J/cm and 5 cm or 7 cm balloon at first treatment; the other half of the patients were treated with a light dose of 150 - 300 J/cm and a 2, 3, 5, or 7 cm balloon at first treatment.

Follow-up and assessments were as described below for study TCSC 96-01.

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2) Study TCSC 96-07

All patients received 2.0 mg/kg of PHOTOFRIN I.V., and the first laser light treatment was administered to the esophageal segment 40-50 hours later. A second laser light treatment, if indicated, occurred 4 - 9 days after injection of PHOTOFRIN. A 5 or 7 cm balloon was selected to treat, when possible, the entire length of Barrett's mucosa that was biopsy positive for high-grade dysplasia with at least 0.5 cm of normal tissue margins. Most patients received a light dose of 175 or 200 Joules/cm. The predominant balloon type used in this study was the second generation Polymer Technology Group (PTG) balloon; toward the end of the study the 3rd generation Wilson Cook balloons ("Oreo balloons") began to be used. Light doses of 175 and 200 J/cm with a PTG balloon are approximately equivalent to a Wilson Cook balloon used at 130 J/cm, which is the light dose/balloon combination that was used in the pivotal PHO BAR 01 study.

Patients, who were randomized to receive steroid therapy, received descending oral doses of prednisone, starting on the treatment day at a dose of 60 mg daily for 2 days, followed by 50 mg daily for 2 days, 40 mg daily for 2 days, 30 mg daily for 2 days, 20 mg daily for 2 days, and 10 mg daily for 2 days (a total of 12 days).

All patients underwent efficacy evaluation by biopsy (4 quadrant) at each treatment session and at 6 and 12 months after first treatment. Debridement of necrotic tissue via endoscopy was performed if indicated 4 - 9 days after PHOTOFRIN injection. Treatment in some patients included Nd:YAG laser thermal ablation, if indicated. Patients could be treated with up to 2 additional courses of PHOTOFRIN PDT, providing at least 30 days or more had elapsed since the previous PHOTOFRIN injection. The goal of each treatment session was to destroy the entire segment of Barrett's mucosa with high-grade dysplasia.

The duration of each patient's participation was 12 months; thereafter, patients were followed for survival time. Follow-up included telephone contact once a week for the first 2 months and then monthly for the following 4 months after treatment to determine if patients developed dysphagia.

Reviewer's Table on Photodynamic Therapy in Patients

Description of PDT treatments is from Tables 1.13 and 3.1 in vol. 42, p. 270, 297 for study TCSC 93-07 and from Table 1.13 in vol. 47, p.261 for study TCSC 96-01.

Courses of treatment	PHOTOFRIN PDT TCSC 93-07, N = 44 patients	PHOTOFRIN PDT TCSC 96-01, N = 42 patients
Course 1	44 patients - 1 st laser Rx 25 patients - 2 nd laser Rx	42 patients - 1 st laser Rx 15 patients - 2 nd laser Rx 1 patient - 3 rd laser Rx
Course 2	13 patients - 1 st laser Rx 7 patients - 2 nd laser Rx	12 patients - 1 st laser Rx 2 patients - 2 nd laser Rx
Course 3	2 patients	1 patient - 1 st laser Rx

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Thirty-five (35) of 44 patients (80%) completed study TCSC 93-07. The reasons for discontinuation of 9 patients from the study are shown in the Reviewer's Table below (sources: vol. 42, pp. 199,200, 232).

Thirty-six (36) of 42 patients (85.7%) completed study TCSC 96-01. The reasons for discontinuation of 6 patients from the study are shown in the Reviewer's Table below (sources: Table 1.1, vol. 47, pp.199, 162, 315).

Reviewer's Table on Patient Disposition in the Uncontrolled Studies

Causes of patients' discontinuations from the study	PHOTOFRIN PDT TCSC 93-07 N = 44	PHOTOFRIN PDT TCSC 96-01 N = 42
Death	2 (1 cardiac arrest, 1 meningitis)	1 (cause unknown, 19 days after Course 3)
Patient withdrew	1	
Other	1 dehydration, 1 bladder cancer & hematuria, 1 thrombocytopenia, 1 atrial fibrillation, 1 renal failure & bilateral pleural effusion, 1 ventricular fibrillation	1 esophagectomy, 1 lung transplant disrupting schedule, 1 different follow-up schedule, 2 missing records
Total	9 (20%)	6 (14.3%)

Patient follow-up after treatment is shown in the Reviewer's Table below. In study TCSC 93-07 84% of patients completed 12 months of follow-up (data source: Panel 10.1, Tables 1.1 and 1.10 in vol. 42, pp. 200, 240, 243).

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Reviewer's Table of Patient Duration in the Uncontrolled Studies

Duration on Study	PHOTOFRIN PDT TCSC 93-07 N = 44	PHOTOFRIN PDT TCSC 96-01 N = 42
< 3 months	1	0
3 – 6 months	1	1
6 – 9 months	2	0
9 – 12 months	3	3
= 12 months (patients censored at 12 months)	35	36
> 12 months	2	2
Mean (range)	10.89 (2.2 – 27.5)	11.82 (3.0 – 16.0)

Primary Efficacy Endpoint: Overall Clinical Response

The response rates are shown in Reviewer's Table below (data from vol. 86, p. 206 for TCSC 93-07; In TCSC 93-07 the responses to different laser treatments were about the same: 12 out of 14 (85.7%) patients responded after treatment with 175 – 225 J/cm, and 27 out of 30 (90%) patients responded after treatment with 150 – 300 J/cm. Therefore, the results of both treatment arms are combined.

In study TCSC 96-01 the responses were about the same in patients treated with steroids and in patients not treated with steroids, 18/21 (85.7%) and 19/21 (90.5%), respectively. Patients in the steroids arm were treated with tapering doses of oral prednisone (described above) for 12 days after PHOTOFRIN PDT. The results of both treatment arms are combined.

Reviewer's Table on Primary Efficacy – Overall Clinical Response (First Six Months of Follow-up)

Responders	PHOTOFRIN PDT TCSC 93-07 N = 44	PHOTOFRIN PDT TCSC 96-01 N = 42
CR1 or CR2 or CR3	39 (88.6%)	37 (88.1%)

These results support the complete response data in the controlled study.

Secondary Efficacy Endpoints: Overall Clinical Response (Complete, i.e. Twelve-month, Follow-up) and Quality of Response

Both uncontrolled trials had Overall Clinical Response at 12 months of follow-up as the primary endpoint. The sponsor presents the 6-month follow-up results as the Primary Efficacy Endpoint for comparison with the same endpoint in the controlled trial. The 12-month complete response

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data is presented as a Secondary Efficacy Endpoint. These data together with the quality of response data are shown in the Reviewer's Table below.

Reviewer's Table on Secondary Efficacy Endpoints – Overall Clinical Response and Quality of Response (Complete, i.e. Twelve-month, Follow-up)

Responders	PHOTOFRIN PDT TCSC 93-07, N = 44 patients	PHOTOFRIN PDT TCSC 96-01, N = 42
CR1	25 patients (56.8%)	25 (59.5%)
CR1 or CR2	36 patients (81.2%)	38 (90.5%)
CR1 or CR2 or CR3	41 patients (93.2%)	40 (95.2%)

Sources: vol.41, pp. 207, 208, 210; vol. 47, pp.171-2.

The 12-month complete response data are even better than the 6-month response data. That is puzzling. Not only there appear to be no failures in the second 6 months, but 5 patients who had been response failures at 6 months were responders at 12 months.

Secondary Efficacy Endpoint – Duration of Response

Responders and Duration (median, in days)	PHOTOFRIN PDT TCSC 93-07, N = 44 patients	PHOTOFRIN PDT TCSC 96-01, N = 42
CR1	Median duration 105 days	Median duration 98 days
CR1 or CR2	Median duration 192 days	Median duration 273 days
CR1 or CR2 or CR3	Median duration 391 days	Value cannot be estimated

Sources: vol. 42, p. 210, Panel 11.6 for TCSC 93-07; vol. 47, p. 173.

The relatively short (12-month) follow-up period permits only tentative estimates of duration of responses; the sponsor was unable to establish 95% confidence intervals for the above response data. The sponsor presented Kaplan-Meier plots (vol. 42, p. 211; vol. 47, p. 174) of the durations of responses stretching out to over 1,000 days, but the small number of patients followed beyond 12 months raise the issue of reliability of these plots. They are not reproduced in this review.

The Duration of Response data is inconsistent with the 12-month complete response data in TCSC 93-07. If median duration of complete response was 391 days, then nearly half of the patients had failed after 12 months of follow-up, not 7% as shown in the previous table.

According to the sponsor, most failures appeared to occur within the first 4 months after randomization and treatment. The reviewer examined the data listings for times of failure, which are presented in the Reviewer's Table below. The times of failures are grouped by 3 month intervals. The sponsor's conclusions on the time of most failures are not well-supported by these data, especially in study TCSC 96-07.

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Reviewer's Table of Response Failures During 12-month Follow-up

Months after first treatment	PHOTOFRIN PDT TCSC 93-01, N = 44	PHOTOFRIN PDT TCSC 96-07, N = 42
0 – 3 months	8 (days 55, 56, 75, 79, 88 x 2, 90, 91)	3 (days 2, 68, 86)
3 – 6 months	6 (days 100, 120, 137, 139, 167, 174)	3 (days 96, 97, 102)
6 – 9 months	1 (day 215)	3 (days 195, 196, 259)
9 – 12 months +	2 (days 310, 322)	3 (days 341, 361, 430)
12-month total	17 (36.8%)	11 or 12 (28.6%)

Sources: Table 3.7.3, vol. 86, p. 286 for TCSC 93-07; Table 3.7.3, vol. 47, p. 250 for TCSC 96-01.

The above data are not consistent with the 12-month Complete Response data and may not be consistent with the Duration of Response estimates.

Secondary Efficacy Endpoint: Time to Progression to Cancer

The Time to Progression to Cancer (TTP) was defined as the period in days from the date of first treatment with PHOTOFRIN PDT until the date the progression to cancer was first documented. Median TTP could not be estimated because fewer than 50% of patients had a documented TTP by the end of the 12-month follow-up period.

The reviewer examined the data listings to find out how many patients had progressed to cancer and when the progression to cancer was noted. Eight patients (18.2%) progressed to cancer in TCSC 93-07 during the 12-month follow-up. Reviewer's Table below shows the time periods when progression to cancer was first noted. Two patients (4.8%) progressed to cancer in TCSC 96-01 within 12 months and one in the subsequent follow-up.

Reviewer's Table on Time to Progression to Cancer

Months after first treatment	PHOTOFRIN PDT TCSC 93-07, N = 44	PHOTOFRIN PDT TCSC 96-01, N = 42
0 – 3 months	2 patients (days 2 & 25)	0
3 – 6 months	3 patients (days 93, 99 & 176)	1 patient (day 106)
6 – 9 months	3 patients (days 194, 227 & 232)	1 patient (day 186)
9 – 12 months +	0 patients	1 patient (day 491)
Total for 12 months	8 (18.2%)	3 (7.1%)

Sources: Table 3.9.1, vol. 42, p. 293; Table 3.9.1, vol. 47, p. 255.

Reviewer's Note: The sponsor appears to separate response failures (Tables 3.7.3) from progression to cancer (Tables 3.9.1), as the different days of occurrence indicate. Patient

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identification numbers are not provided in these two sets of tables. Presumably response failures represent patients who underwent other forms of therapy. Both patients who progressed to cancer and patients who received other forms of therapy should be considered treatment failures. The sponsor will be asked to clarify these discrepancies.

If the number of patients in study TCSC 93-07 whose Complete Responses failed (17) and those who Progressed to Cancer (8) are added (25), then such patients comprise 56.8% of the patients treated and followed for 12 months. Patients in study TCSC 96-01 whose Complete Responses failed (12) and those who Progression to Cancer (3) together (15) comprise 35.7% of the treated population followed for 12 months.

Secondary Efficacy Endpoint: Survival Time

Survival Time was defined as the period in days from the date of first treatment with PHOTOFRIN PDT to the date of patient's death.

In study TCSC 93-07 only one patient died within 12 months of follow-up at day 281 (cause: cardiac arrest). Four patients died at days 430 (cause: meningitis), 933, 1079, and 1337.

The sponsor states that in study TCSC 96-01 no patient had a documented death by the end of the follow-up (Efficacy Summary, vol. 8, p. 101). Table 3.10.1 showing Comparison by Group of the Survival Time is missing in vol. 47, but there is a death report among adverse events narratives in vol. 47, p. 315. This 83 year old female patient received 3 courses of PHOTOFRIN PDT over an eighteen-month period. Seventeen days after the third course she died; no information as to cause of death is available.

The Secondary Endpoint: Survival Times could not be estimated in either study. With the short follow-up this is not a useful endpoint.

D. Efficacy Conclusions

Treatment of high-grade dysplasia as surrogate endpoint for prevention of adenocarcinoma. High-grade dysplasia does not need to be treated except for one reason: 25% to 30% of high-grade dysplasia patients develop adenocarcinoma of the esophagus over a period of 3 to 7 years. The corollary is that 70% - 75% do not, and any treatment of high-grade dysplasia has to be evaluated with these statistics in mind. Because esophageal carcinoma carries a very dismal prognosis, some gastroenterologists recommend esophagectomy as treatment of choice for high-grade dysplasia, while others recommend an aggressive surveillance protocol. Photodynamic therapy with PHOTOFRIN offers a third choice.

The primary endpoint efficacy data in the controlled trial are impressive: the initial response, complete ablation of high-grade dysplasia with re-epithelialization with normal squamous epithelium, was found in 41% of PHOTOFRIN PDT patients and in only 4% of control arm patients. Complete ablation followed by re-epithelialization with normal squamous epithelium or with normal epithelium and some areas of Barrett's metaplasia was found in 49% of

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PHOTOFRIN PDT patients and in only 6% of control patients. And, finally, re-epithelialization with normal epithelium, or normal epithelium with some areas of metaplasia, low-grade dysplasia or indefinite dysplasia was found in 72% of PHOTOFRIN PDT patients and in 31% of control patients, a 41% difference that is highly significant.

However, the response to PDT has little meaning if it is not sustained. Within 12 months from enrollment 27% of PHOTOFRIN PDT were discontinued from the study, 11% because of progression of disease (adenocarcinoma) and 7% because they had other therapy. The statistics were worse in the control group, 41% were discontinued from the study, 20% because of progression of disease (adenocarcinoma), 19% because they had other therapy, including PHOTOFRIN PDT. Median duration of response could not be reliably estimated during this length of follow-up, and 24 month follow-up data are required to better assess the efficacy of PHOTOFRIN PDT.

Other secondary efficacy endpoints: median time to progression to cancer, median time to treatment failure, and survival time could not be estimated during the short follow-up and insufficient number of patients studied. None of the patients developed metastatic adenocarcinoma of the esophagus, and none died from adenocarcinoma of the esophagus.

The single-center uncontrolled trials appear to provide outcome data that support the results of the primary controlled trial, but there are inconsistencies in these data that require clarification.

Thus, the sponsor has provided data showing that PHOTOFRIN PDT is effective in ablation of high-grade dysplasia, but has not shown that is sustained and is effective in preventing deaths due to adenocarcinoma of the esophagus. The Agency had noted in the March 5, 2001 teleconference that "6-month follow-up data may be inadequate to assess the impact of treatment." The Advice Letter after the review of PHO BAR 01 protocol (January 25, 2001) communicated to the sponsor that "the primary response variable must reflect an improvement in the long-term clinical outcome."

In addition, the January 25, 2001 Advice Letter requested "an analysis of clinical outcomes of individuals associated with treatment failure in conjunction with outcomes associated with treatment success. Such outcomes should be compared to those associated with other modes of treatment such as esophagectomy." The sponsor did not provide this analysis with this submission.

The review of the efficacy section was made difficult by lack of composite outcomes analyses, incorporating the following:

- Patient ID number
- Length of follow-up
- Outcome (continuing in CR, or Progression of cancer [and treatment for it], or Other Therapy [specified], Discontinued from Study [reasons])
- Percentages of patients remaining in CR as a function of time
- Percentages of patients progressing to cancer as a function of time
- Percentages of patients treated with Other Therapies as a function of time

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These pieces of information are scattered, and some conclusions have to be inferred from dates of treatment failure or of progression to cancer.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety data appears to be adequately presented. The major drawback of these studies is the small number of patients, a total of 318. The pivotal trial is a controlled study; the control arm provides a background of adverse event frequency in this population.

The major side-effects of photodynamic therapy, using PHOTOFRIN as photosensitizing agent, are acute events related to the light treatment itself and longer lasting effects relating to the healing of esophagus and the extended period of photosensitivity of the skin. The acute effects were dysphagia, odynophagia, vomiting, nausea, abdominal pain, chest pain and fever. These symptoms were reported by about 25 % to 35% of patients. The most important sub-acute effects were esophageal strictures and photosensitivity reactions. A stricture was defined as esophageal narrowing requiring dilation. Strictures affected about 35% of patients. Their treatment required repeated dilations, probably because PHOTOFRIN PDT results in deep (up to 6 mm) necrosis, involving not only the esophageal mucosa but also the muscularis, and healing results in tight bands of fibrous tissue. Skin photosensitivity reactions were common (67% of patients in the pivotal study), in spite of documented warnings about exposure to sunlight and bright lights for 30 days.

The relatively good safety record of PHOTOFRIN PDT is reflected in 1) few withdrawals from the study (4 %), and in 2) high percentage of study completion.

B. Description of Patient Exposure

The present NDA contains the results of three studies in patients with BE who had high-grade dysplasia, a pre-malignant condition. The pivotal PHO BAR 01 study compared PDT with PHOTOFRIN plus omeprazole (PHOTOFRIN + OM) to a surveillance arm consisting of omeprazole only (OM Only). In this study, 208 patients were enrolled in 2:1 ratio, 138 patients were randomized to receive PHOTOFRIN + OM (treatment arm) and 70 patients were randomized to receive OM Only (control arm). Of those, 133 patients (96%) received at least one injection of PHOTOFRIN and 132 out of 133 received at least one complete course of PHOTOFRIN PDT. Seventy patients were randomized into the OM Only treatment group, of which 69 (99%) received at least one omeprazole dose.

In addition, this NDA includes data from 2 open-label clinical trials (TCSC 93-07 and TCSC 96-01) conducted under a physician-sponsored IND of PDT with PHOTOFRIN in BE (Dr. B.F. Overholt, Thompson Cancer Survival Center, Knoxville, TN; IND 42,313). Study 93-07 was an open-label study in 99 patients, 44 of whom met the criteria for high-grade dysplasia. These

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patients were divided into 2 treatment groups, which received different laser light treatments. Study 96-01 was a randomized, partially blinded study of the effect of steroid treatment on the development and severity of esophageal strictures associated with PDT. Forty-two (42) BE patients with high-grade dysplasia were randomized in 1:1 ratio into 2 groups, one that will be treated for 12 days with tapering doses of prednisone following the light exposure and one that will not be treated. All the patients in studies TCSC 93-07 and TCSC 96-01 were treated with omeprazole (20 mg twice daily).

Extent of Exposure. Photodynamic therapy (PDT) consists of 2 modalities: administration of a photosensitizing agent, in this case PHOTOFRIN, and administration of light, which results in tissue damage. Each of these modalities poses distinct safety issues.

Treatment with PHOTOFRIN is by intravenous injection and consists of a 2 mg/kg dose, followed by 630 nm laser-light treatment 48-72 hours after drug administration. Additional injection of PHOTOFRIN is not performed until 90 days has passed, and only if follow-up endoscopy reveals new areas of dysplasia in need of treatment. The PHOTOFRIN dose was the same in all the patients in these 3 studies, and had been the standard dose in all the previous studies for other indications.

In contrast to PHOTOFRIN treatment, light delivery methods and doses changed during the individual studies and between the studies. Laser light is passed through endoscopically placed fiber optics tipped with cylindrical diffusers. In normal esophagus, as well as BE, an inflatable centering balloon is needed to improve light dosimetry in an organ that tends to collapse, with the result that internal mucosal folds create a "hill and valley" effect. Pre-clinical and necropsy data demonstrated that with the diffuser/balloon combination the PDT response is circumferential and uniform, while with the diffuser alone the effect varied from minimal to severe. Reviewer's Table below summarizes the types of balloons and the 630 nm light dosages used in the three trials.

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Reviewer's Table Summarizing Light Delivery Systems in the PHOTOFRIN Trials

Study ID	Equipment and Light Doses	Comments
TCSC 93-07	"Black-capped" (black at ends, transparent in the center) 3 cm balloons, later 5 cm and 7 cm balloons.	Multiple light sessions were required to treat segments > 3 cm. Overlap areas received more than one light treatment; these areas were particularly prone to development of esophageal strictures. Balloons of 5 and 7 cm developed. Peak of light in the middle of 5 cm window may have led to strictures. Fifteen (15) courses were administered with 3 cm balloons, 13 courses with 5 cm balloons, 6 courses with 7 cm balloons, and 2 courses with 2 cm balloons.
TCSC 96-01	"White capped" (reflective inner coating at ends), 5 cm and 7 cm. Light doses 175 J/cm and 200 J/cm.	Sixteen (16) courses were administered with 5 cm balloons, and 38 courses were administered with 7 cm balloons.
PHO BAR 01	Fiber optic diffusers of 9 cm, 7 cm, and 5 cm. Wilson Cook white-capped balloons, window sizes of 7 cm, 5 cm, and 3 cm. Light dose 130 J/cm of diffuser length. Treatment time 480 sec.	Short fiber optic diffusers (<2.5 cm) were used to pre-treat nodules with 50 J/cm diffuser length (86 treatments in 35 patients) prior to regular balloon treatment in the first laser light session. Thirty-nine (39) courses were administered with 3 cm balloons, 57 courses with 5 cm balloons, and 170 courses with 7 cm balloons.

Sources: vol. 3, p.50; vol. 11, p. 151; vol. 48, p. 25; vol. 13, p. 35.

Precautions taken during the studies. All patients injected with PHOTOFRIN were photosensitive and had to observe precautions to avoid exposure of eyes and skin to direct sunlight or bright indoor light (e.g. examination lamp, dental lamps, operating room lamps, unshaded light bulbs at close proximity) for at least 30 days. Some patients remained photosensitive for up to 90 days or more. Therefore, patients were asked to avoid darkened room after 30 days, and were encouraged to expose their skin to ambient indoor light to allow gradual inactivation of the remaining drug through photobleaching. The level of photosensitivity varies for different areas of the body, depending on the extent of previous exposure to light. Before exposing any area of the skin to direct sunlight or bright indoor light, patients were asked to test the skin for residual photosensitivity by exposing a small area of the skin to sunlight for 10 minutes. If no photosensitivity reaction (erythema, edema, blistering) occurred within 24 hours, patients could gradually resume normal outdoor activities. If some photosensitivity reaction occurred, patients had to continue precautions for another week before re-testing. Skin around the eyes may be more sensitive to light; patients were asked not to use the face for testing residual photosensitivity.

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Ocular discomfort, commonly described as sensitivity to sun, bright light, or car headlights, has been reported. Patients were asked to wear dark sunglasses (average white light transmittance of <4%) when outdoors for a period of 30 days.

Precautions must be taken to prevent extravasation of PHOTOFRIN at the injection site. If extravasation occurs, the area had to be protected from light.

As a result of PDT treatment, some patients complained of substernal chest pain and nausea because of inflammatory responses within the area of treatment. Such pain may be of sufficient intensity to warrant the short-term prescription of opiate analgesics.

Durations of follow-up in the 3 studies are described in Reviewer's Tables in the Efficacy section.

C. Methods and Specific Findings of Safety Review

Almost all the patients treated with PHOTOFRIN PDT + OM experienced at least one treatment-emergent adverse event (TEAE). For the sake of clarity the frequencies of events will be summarized for all three PHOTOFRIN PDT trials and contrasted with the frequency of TEAE's in the OM Only arm of the PHO BAR 01 trial. Differences in the frequencies of TEAEs among the three PHOTOFRIN trials will be noted.

Reviewer's Table: Treatment Emergent Adverse Events in >2.0% of High-grade Dysplasia Patients in TCSC 93-07, TCSC 96-01 and PHO BAR 01 Studies

Body System and Preferred Term	All 3 PHOTOFRIN PDT studies, N = 318	PHO BAR 01	
		PHOTOFRIN PDT N = 133	OM Only N = 69
Number of patients (%) with Any Event	313 (98.4%)	130 (98%)	47 (68%)
Gastrointestinal	259 (81.4%)	97 (73%)	22 (32%)
Nausea	124 (38.9%)	17 (13%)	6 (9%)
Dysphagia	62 (19.5%)	26 (20%)	0
Esophageal stricture	91 (28.6%)	48 (36%)	1 (<1%)
Vomiting	102 (32.1%)	46 (35%)	4 (6%)
Odynophagia	48 (15.1%)	16 (12%)	0
Abdominal pain	34 (10.4%)	15 (11%)	3 (4%)
Hiccup	24 (7.5%)	13 (10%)	0
Constipation	44 (13.8%)	34 (26%)	5 (7%)
Diarrhea	16 (5.0%)	16 (12%)	5 (7%)
Body as a Whole	221 (69.5%)	74 (56%)	21 (30%)
Chest pain	151 (47.5%)	36 (27%)	5 (7%)
Fever	70 (22.0%)	30 (23%)	2 (3%)
Pain	62 (19.4%)		

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Skin and Appendages	157 (49.4%)	100 (75%)	4 (6%)
Photosensitivity reaction	140 (44.0%)	89 (67%)	0
Skin disorder	14 (4.4%)	13 (10%)	1 (1%)
Metabolic and Nutritional	55 (17.3%)	37 (28%)	9 (13%)
Dehydration	29 (9.2%)	16 (12%)	2 (3%)
Weight decrease	9 (2.8%)		
Central Nervous System	30 (9.4%)	30 (23%)	11 (16%)
Headache	14 (4.4%)	14 (11%)	5 (7%)
Heart rate/ Rhythm disturbances	12 (3.8%)		
Psychiatric	26 (8.2%)		
Anorexia	16 (4.7%)		

While the frequencies of many adverse events were similar among the three PHOTOFRIN groups, there were some differences, such as

- Treatment-related esophageal strictures (Endoscopy data) occurred in 42% of TCSC 93-07 patients (vol.8, p.141), in 36% of TCSC 96-01 patients (vol. 8, p. 148), and in 35% of PHO BAR 01 patients (vol.8, p.121). In a composite Table on Strictures in all 3 studies (vol.8, p.115) the percentages of patients with esophageal strictures are 31%, 14%, and 36%, respectively. The table specifies that esophageal stricture category “includes all esophageal narrowing regardless of dilation needs.” However, this statement is not correct. In study 93-07 28.3% of all PHOTOFRIN patients group developed an esophageal narrowing not requiring dilations, while 42.4% developed an esophageal stricture (vol.8, p.140). The percentage of patients in study 96-01 who developed an esophageal narrowing not requiring dilations is not stated. In PHO BAR 01 study, 18% of patients in the PHOTOFRIN PDT group and 6% of patients in the control group developed an esophageal narrowing not requiring dilations. In general, the percentages of esophageal strictures are lower in the Adverse Event data than in the Endoscopy data. For that reason the above table underestimates the incidence of strictures.
- Nausea was less frequent in PHO BAR 01 patients (13%) than in the two TCSC trials (56% and 61%).
- Chest pain was less frequent in PHO BAR 01 patients (27%) than in the two TCSC trials (69% and 55%).
- Pain was not listed as occurring in PHO BAR 01 patients, but was present in 12% and 55% in TCSC 93-07 and 96-01, respectively.
- Pleural effusions were not noted in the PHO BAR 01 trial, but occurred in 20% and 14% of patients in TCSC 93-07 and 96-01 trials, respectively.
- Photosensitivity reactions were present in 67% of PHO BAR 01 patients, but in only 27% of TCSC 93-07 or TCSC 96-01 patients.

The adverse events profile of the OM Only group was strikingly different from the PHOTOFRIN PDT groups, and brings into focus adverse events that accompany PDT. In particular, PDT appears to be characterized by acute adverse events at the time or shortly after PDT, and by more chronic adverse events that develop over weeks following PDT, as shown below:

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- Acute gastrointestinal adverse events following therapy: nausea, vomiting, dysphagia, odynophagia
- Acute chest and abdominal adverse events: chest pain, abdominal pain, fever, pleural effusions
- Sub-acute adverse events: esophageal stricture, photosensitivity reactions

Not only a greater percentage of patients in the PHOTOFRIN PDT group experienced adverse events than patients in the OM Only group; they experienced about twice number of adverse events, as shown in the Reviewer's Table below (data from vol. 13, p. 124).

Reviewer's Table: Treatment Emergent Adverse Events in >10% of the Patients in the PHO BAR 01 Study

	PHOTOFRIN PDT + OM	OM Only
Total number of patients with TEAEs, (%)	130 (98%)	47 (68%)
Total number of events	1,245	206
Life threatening	10	1
Severe	212	33
Moderate	387	64
Mild	636	108
Number of events/number of patients	9.6	4.4

Photosensitivity reactions. Photosensitivity of the skin is a known side effect of PHOTOFRIN treatment. Most of the photosensitivity reactions occurred within 90 days after PHOTOFRIN injection. Most of the reactions were mild (68%) or moderate (26%), and 97% were considered associated with treatment. Exposed areas (face, hands and neck) were affected the most. Severe reactions occurred in 12 (9.2%) patients in the PHO BAR 01 study and were characterized by swelling, pruritus, erythema, blisters, itching, burning sensation and heat. All resolved over time.

Esophageal stricture. Esophageal strictures are the most important of treatment-related adverse events. All esophageal narrowing data were collected using the term "esophageal stricture", regardless of subsequent management. Later, only esophageal narrowing that required dilation was considered a stricture. The following composite table presents a summary of esophageal strictures from the endoscopy data in the three trials. The sponsor characterizes the strictures as mild in about 44% of patients, moderate in 43%, and severe in 12%.

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Reviewer's Table: Esophageal Strictures in PHO BAR 01, 93-07 and 96-01 Patients (Endoscopy Data)

	93-07 N = 99	96-01 N = 86	PHO BAR 01, PDT, N = 138	OM Only N = 70
Patients with baseline strictures		1 (2.4%)	2 (1%)	2 (3%)
Strictures following treatment	42 (42.4%)	31 (36.0%)	48 (35%)	1 (1%)
Course 1		26 (30.2%)	18 (13%)	
Course 2		5 (5.8%)	29 (21%)	
Course 3		0	1 (1%)	

Sources: vol. 13, p. 127; vol. 42, p. 227; vol. 47, p. 186.

Esophageal strictures were sufficiently severe requiring multiple dilations. Two of the patients developed esophageal perforations during dilations (described below). The Reviewer's Table below presents the composite data on esophageal dilations.

Reviewer's Table: Esophageal Dilations in Patients Treated with PHOTOFRIN PDT

Number of Dilations	TCSC 93-07 N = 99	TCSC 96-01, N = 86	PHO BAR 01 N = 138
1-2	12(12.1%)	14 (16.3%)	16 (12%)
3-5	13(13.1%)	12 (14.0%)	10 (7%)
6-10	7 (7.1%)	5 (5.8%)	14 (10%)
>10	10 (10.1%)	0	8 (6%)

Sources: vol. 13, p. 127; vol. 42, p. 228; vol. 47, p. 188.

Reviewer's Table: Distribution of Frequency of Dilations

Number of Dilations	Total Number of Patients in the Three PHOTOFRIN PDT Trials Undergoing Dilations	Percentages of Frequencies of Dilations
1-2	42	34.7%
3-5	35	28.9%
6-10	26	21.5%
>10	18	14.9%

Chest Pain. The number of patients reporting chest pain increased shortly after PDT and then declined over a 4-week period. About 12% of patients reported severe chest pain, 34-41% reported moderate chest pain, and the 19-30% mild chest pain.

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Odynophagia and dysphagia. About 5% of patients reported severe odynophagia, about 15-18% moderate odynophagia, and 11-19% mild odynophagia. Approximately the same percentages of patients reported dysphagia. Odynophagia remitted over 4 weeks following PDT, and dysphagia, over 6 months.

Deaths. There were 3 deaths in PHO BAR 01 study during the 12-month follow-up; none related to treatment. Two female subjects, 74 and 82 years of age, died in the PHOTOFRIN group, one from breast cancer, deep vein thrombosis, pulmonary embolism and renal failure, the other from a cardiac arrest, following CABG and cardiac tamponade. One 68 year old male died in the OM Only group, from a massive stroke.

Two patients died in the 93-07 study. A 75 year old male with a history of cardiac arrhythmias died from cardiac arrest, and a 77 year old male died from enterococcal meningitis. One patient died in the 96-01 study, an 83 year old female with CAD. Death was unexpected and cause of death was not ascertained. None of the deaths in either study were thought to be related to treatment.

Withdrawals Due to Adverse Events. In the PHO BAR 01 study, three patients in the PHOTOFRIN group had adverse events that led to withdrawal from the study. One patient underwent an esophagectomy following perforation of the esophagus that occurred during an esophageal dilation for an esophageal stricture. One patient developed an anxiety reaction during the period between PHOTOFRIN injection and laser light treatment; she refused the light treatment. One patient was diagnosed with non-small cell lung cancer.

Two patients were discontinued from study 93-07 due to adverse events, both were in the low-grade dysplasia group. A 66 year old male patient suffered an esophageal perforation during Course 1 of treatment; the event was probably related to treatment. A 70 year old male patient was diagnosed with pulmonary carcinoma; the event was definitely not related to treatment. One patient was discontinued from study 96-01, a 76 year old male patient with worsening heart disease, an event not related to treatment.

Other Serious Adverse Events. Forty (30%) of patients PHOTOFRIN PDT + OM group in the PHO BAR 01 study reported 118 SAEs, of which 36 were considered to be treatment-associated. Most related to the gastrointestinal system, followed by chest pain, abdominal pain, dehydration. The OM Only group had a lower incidence of SAEs (12 patients, 17%). None of the SAEs were considered to be associated with treatment.

Clinical Laboratory Evaluations. In the PHO BAR 01 study, laboratory data were collected at baseline and at Month 3 follow-up. Most (95% to 100%) abnormalities in hematology and clinical chemistry parameters were not clinically significant. None of the hematologic abnormalities shifted from not clinically significant to clinically significant. Shifts from not clinically significant at baseline to clinically significant at Month 3 occurred in 4 parameters: ALT (2%), total bilirubin (1%), and potassium (5%) in the PHOTOFRIN group and creatinine

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(4%) in the OM Only group. Clinical laboratory evaluations were not performed in the 2 supportive studies.

D. Adequacy of Safety Testing

The collection and analyses of safety data in the 3 trials were relatively straightforward, as compared to efficacy results and analyses. Variations in the frequencies of the most common adverse events between the 3 trials that were noted above may have been due to the relatively small numbers of patients. They may have also been influenced by local variations in care among the centers. It should be noted that one center (Dr. Overholt's Thompson Cancer Survival Center in Knoxville, TN) contributed about 69% of the total safety population. Patients' experiences at that one center may have influenced the relative frequencies of some adverse events.

Overall, safety testing appears to have been adequate.

E. Summary of Critical Safety Findings and Limitations of Data

The main safety issue with photodynamic therapy is the development of esophageal strictures. The incidence of strictures may have decreased with the development of light delivery systems, but at 35% in the PHO BAR 01 study it is still very high. The number of dilations for strictures is also impressive: 33% of patients with strictures had to have only 1-2 dilations, 21% of patients, 3-5 dilations, 29% of patients, 6-10 dilations, and 17%, more than 10 dilations. The single patient in the Omeprazole Only group with a stricture needed only 1 dilation.

The main limitation of the safety data is the relatively small number of patients in the three studies, and the very short follow-up.

VIII. Dosing, Regimen, and Administration Issues

Dosing of PHOTOFRIN has been standard for in all the studies, and does not need to be modified. Light administration underwent considerable development during the decade during which the three studies were conducted.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Approximately 15% of all study patients were female (Reviewer's Table below). This 6:1 male/female ratio is consistent with the published data on the gender ratios in esophageal adenocarcinoma and in BE. Neither efficacy nor safety gender analyses were carried out by the sponsor. The statistical reviewer carried out complete response (CR1 + CR2 + CR3) analysis by gender in the PHO BAR 01 trial. There appeared to be no gender differences. About 70%

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(82/117) of males and about 81% (17/21) of females had complete responses in the PHOTOFRIN PDT + OM group. About 30% (18/59) of males and about 36% (4/11) of females had complete responses in the OM Only group.

Demographic Characteristics of all BE with high-grade dysplasia patients in the three studies are shown in sponsor's table below, as condensed by the reviewer.

Reviewer's Table: Demographic Characteristics of BE with High-grade Dysplasia Patients

Study	PHOTOFRIN PDT + OM (PHO BAR 01, TCSC 93-07, TCSC 96-01)	OM Only	All study patients
Number of patients receiving study therapy	224	70	294
Age in years, mean (range)	66.95 (38.4 – 88.5)	67.27 (36.1 – 87.6)	66.26 (36.1 – 88.5)
Gender			
-Male	190 (84.8%)	59 (84%)	249 (84.7%)
-Female	34 (15.2%)	11 (16%)	45 (15.3%)
Race			
White (Caucasian)	221 (98.7%)	68 (97%)	289 (98.3%)
African-American	1	1 (1%)	2 (0.7%)
Asian	2	1 (1%)	3 (1.0)
Hispanic	0	0	0
Other	0	0	0

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

There appears to be an age effect in the complete response (CR1 + CR2 + CR3) rate in the PHOTOFRIN + OM group, as shown below.

Age	PHOTOFRIN + OM	OM Only
< 65 years	51/61 (84%)	6/25 (24%)
> 65 years	48/77 (62%)	16/45 (36%)
P	P = 0.0219	

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The other effects influencing complete response rates were treatment (PHOTOFRIN + OM vs. OM Only, $p < 0.0001$), high-grade dysplasia foci (single vs. multiple, $p < 0.0001$), and prior omeprazole intake of at least 3 months (yes vs. no, $p = 0.0005$).

White (Caucasian) race predominated overwhelmingly in the studies, as can be justified by the high incidence rates of both BE and esophageal adenocarcinoma in this race. Thus, no analyses by racial background are possible. As noted above in **Variations in Special Populations**, PHOTOFRIN has been studied in Japanese cancer patients, but because of different sampling times and small numbers of patients involved no conclusions could be drawn about variation in PHOTOFRIN pharmacokinetics between Caucasians and Japanese. Ethnic backgrounds were not described in the study populations in this submission.

C. Evaluation of Pediatric Program

Axcan Scandipharm, Inc. is requesting a **waiver for pediatric studies in children**. The reason for this request is that PHOTOFRIN has obtained Orphan Drug Designation, in accordance with Title 21 CFR 314.55 (d). (Volume 1, p. 259 of the submission).

D. Comments on Data Available or Needed in Other Populations

The sponsor has an OCPB Phase IV commitment (No. 2) under previous NDA 20-451 as follows:

“Conduct Phase IV studies to gather further pharmacokinetic (PK) data in patients with hepatic impairment and in patients who have received more than one course of therapy.”

As noted above, about 35% of PHOTOFRIN is excreted in the form of metabolites, primarily through bile/feces and minimally through the urine (6%). Exclusion criteria in the pivotal trial specify hepatic or renal impairment. Patients with BE with high-grade dysplasia and with mild hepatic impairment may be candidates for PHOTOFRIN PDT, although the incidence of BE and esophageal adenocarcinoma appears not to be increased in alcohol abuse patients.

X. Conclusions and Recommendations

A. Conclusions

The sponsor has presented preliminary findings of a controlled trial of photodynamic therapy using PHOTOFRIN for high-grade dysplasia in Barrett's Esophagus. The 6-month primary efficacy endpoint documents a complete response rate of 72% in the PHOTOFRIN PDT group versus a complete response rate of 31% in the control group. The complete responses consisted of complete ablation of high-grade dysplasia and re-epithelialization with normal epithelium as well as some metaplastic, low-grade dysplastic and indefinite epithelium. Re-epithelialization with completely normal squamous epithelium was ten times more common in the PHOTOFRIN PDT group than in the control group.

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Duration of the response, time to progression to cancer, time to treatment failure, and survival time could not be estimated, because these endpoints were defined as the day 50% of the patients had failure of complete response, progression to cancer, treatment failure, or survival. With a 12-month follow-up none of these secondary endpoints could be estimated. Yet, even at 6 months of follow-up there were marked advantages in outcomes favoring the PDT arm when compared to the control arm. The percentages of patients having progression of disease (11% in the PDT arm, 20% in the control arm), and the percentages of patients opting for other therapy (7% in the PDT arm, 19% in the control arm) clearly indicated the superiority of PHOTOFRIN PDT over active surveillance.

The superior early results of PHOTOFRIN PDT therapy have to be balanced by the far more frequent adverse events than in control group. Even then, it should be emphasized that there were no treatment-related deaths and that most SAEs were not treatment-related. The major safety issue is the common occurrence (35%) of esophageal strictures, which in some patients have posed major therapeutic challenges necessitating multiple dilations. There were two esophageal perforations as complications of the dilations.

A convincing risk-benefit requires a longer follow-up than the 12-month data provide.

B. Recommendations

1. The application for PHOTOFRIN for Injection for use in photodynamic therapy for high-grade dysplasia in Barrett's Esophagus is approvable.
2. Approval will depend on the review of the final study report of the pivotal, controlled trial, which contains a minimum of 24-month follow-up efficacy and safety data. As noted in the Advice Letter to the sponsor on January 25, 2001, "the primary response variable must reflect an improvement in the long-term clinical outcome." In addition the January 25, 2001 Advice Letter requested "an analysis of clinical outcomes of individuals associated with treatment failure in conjunction with outcomes associated with treatment success. Such outcomes should be compared to those associated with other modes of treatment such as esophagectomy."
3. Please provide a listing of patients who remained in complete response at the end of the follow up period in the 24-months follow-up in PHO BAR 01 study listing by patient the ID number and the length of follow-up. Similarly, please provide listings of patients who progressed to cancer, who received Other Treatment (specify), and who were discontinued from the study (specify reasons).
4. Please clarify the following. In the supporting Trials TCSC 93-07 and 96-01 patient ID numbers are not provided in Tables 3.7.3 and in Tables 3.9.1 in vols. 42 and 47. These Tables document Response Failures and Times to Progression to Cancer. The latter should be subsumed in the former, but the days of failure are different. This raises the question, were patients who Progressed to Cancer included among those who were Response Failures, as they should have been?

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5. Please clarify the following. The Complete Response rates in the supporting trials (93% and 95% at 12 months of follow-up, vol. 41, pp. 207, 208, 210; vol. 47, pp. 171-2) are not consistent with 12-month response failures of 36.8% and 28.6% (vol. Tables 3.7.3, vol. 86, p. 286; vol. 47, p. 250) or with time to Progression to Cancer (Table 3.9.1, vol. 42, p. 293).
6. Please perform a more detailed analysis of the poorer response rate to PHOTOFRIN PDT in older patients. Is there an age group in which PHOTOFRIN PDT is contra-indicated?
7. The Proposed Package Insert will need to be changed as dictated by the results of the minimum 24-month data.

XI. Appendix

A. Other Relevant Materials

The sponsor's Proposed Package Insert is not appended.

B. Individual More Detailed Study Reviews (If performed)

Not applicable.

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/s/

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