MEMORANDUM

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

DATE: May 30, 2003

FROM: Brian Strongin, R.Ph., M.B.A., Project Manager, *for*
Robert L. Justice, M.D., M.S., Director
Division of Gastrointestinal and Coagulation Drug Products,
HFD-180

SUBJECT: Briefing Document for the June 26, 2003 Meeting of the Gastrointestinal Drugs Advisory Committee on Photofrin® (porfimer sodium) for ablation of high-grade dysplasia in Barrett's Esophagus with Photodynamic Therapy

MEETING TIME: 8:30AM – 5:00PM

MEETING LOCATION: Marriott Washingtonian Center, The Ballrooms,
9751 Washingtonian Blvd., Gaithersburg, MD

Please find enclosed the following items:

Attachment One: Medical Officer's Summary

Attachment Two: Medical Device Reviewer's Summary

Thank you for your willingness to participate in the June 26, 2003 Gastrointestinal Drugs Advisory Committee meeting regarding Photofrin? [porfimer sodium for injection] for the "ablation of high-grade dysplasia in Barrett's esophagus among patients who are not considered candidates for esophagectomy".

You have been provided the draft reviews of the NDA from the Food and Drug Administration (FDA) medical and device reviewers. The FDA background package often includes initial reviews and/or preliminary conclusions and recommendations written by individual FDA reviewers. These conclusions and recommendations do not necessarily represent the final position of the individual reviewer, nor do they necessarily represent the final position of the FDA. The FDA will not take a final action on the application until input from the advisory committee process has been considered and all reviews have been finalized.

In order to aid your review of the documents provided by the FDA as well as Axcan Scandipharm Inc., we would like you to focus on the following topics:

- The exclusion of approximately 50% of the patients who were determined not to have a diagnosis of high-grade dysplasia by the central histopathology laboratory and its relationship to the target population;
- The number of patients who later went on to esophagectomy;
- The adequacy of a 2-year follow up period for the claim of cancer risk reduction in high-grade dysplasia patients;
- The safety of Photofrin® and photodynamic therapy in this population.
- The contribution of proton pump inhibitors.

The final Advisory Committee questions will be given to you prior to the actual meeting.

We look forward to your participation and seeing you on June 26, 2003.

ATTACHMENT ONE

MEDICAL OFFICER'S SUMMARY

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Briefing Document for Gastrointestinal Drug Advisory Committee

NDA:	21-525, N-000
Related NDAs/INDs/PMAs:	NDA 20-451; IND 61,011; IND 42,313; IND 25,064; PMA P990021; PMA P940010.
Sponsor:	Axcan Scandifarm Inc.
Drug name:	Photofrin® (porfimer sodium)
Pharmacological category:	Photosensitizing agent, polyporphyrin oligomer
Proposed indication:	Ablation of high-grade dysplasia in Barrett's Esophagus with Photodynamic Therapy
Route of administration:	Intravenous injection
Dates submitted:	May 31, 2002; September 30, 2002; October 28, 2002; February 3, 2003.
Action date:	August 1, 2003
Medical Reviewer:	Edvardas Kaminskas, M.D.
Statistical Reviewer:	Milton Fan, Ph.D.

Executive Summary

1. Brief Overview of Clinical Program

Patients with Barrett's Esophagus and high-grade dysplasia have a high risk of developing adenocarcinoma of the esophagus. Three approaches to management of high-grade dysplasia have been described: esophagectomy, aggressive surveillance, and mucosal ablation therapy. There have not been any prospective randomized trials comparing these approaches, and currently there is no agreement as to which is the best approach.

The Sponsor has submitted the results of three clinical trials in which photodynamic therapy with Photofrin® was used for mucosal ablation of high-grade dysplasia. Photofrin® is an approved photosensitizing agent that is administered intravenously and is innocuous until activated by light. When target tissues are exposed to laser light at 630 nm, tissue necrosis occurs by at least two mechanisms, oxygen radical damage and anoxia due to thrombosis of capillaries. Photodynamic therapy with Photofrin® is approved for esophageal cancer patients and endobronchial lung cancer patients.

The principal findings, supporting the indication for photodynamic therapy with Photofrin® in patients with Barrett's Esophagus and high-grade dysplasia in patients who refuse esophagectomy and who are in overall good health, come from a multi-center, randomized, controlled, partially blinded, 2-arm trial, in which 130 patients were treated with photodynamic therapy with Photofrin® and 69 patients underwent aggressive surveillance. Both groups received omeprazole to reduce acid reflux. Patients in the photodynamic therapy arm underwent up to three treatment courses, separated by at least 90 days, either because of the extent of high-grade dysplasia (the longest segment that could be treated was 7 cm) or lack of response. The dose of Photofrin® was standard in this trial, as in all other Photofrin® trials. Light delivery systems consisted of endoscopically placed fiber-optic filaments tipped with cylindrical diffusers and of centering balloons of various lengths and types. Patients were followed every 3 months until four consecutive endoscopic 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. The length of follow-up ranged from 2 to 3.6 years.

The two open-label, uncontrolled, single-center studies provided efficacy results on 86 patients with high-grade dysplasia who had been followed for a minimum of 12 months after randomization. In addition, these studies provided safety results on 99 additional patients who did not have high-grade dysplasia, and who were treated with Photophrin® photodynamic therapy for low-grade dysplasia, metaplasia, or superficial adenocarcinoma.

The average age of patients in the three trials was 66 years, 81% were males, 99% were of the Caucasian race, and 71% were former or current smokers. These characteristics are typical of patients with Barrett's Esophagus with high-grade dysplasia and of patients with esophageal adenocarcinoma.

2. Efficacy

The primary efficacy endpoint, assessed after a minimum follow-up of 24 months, was the complete ablation of high-grade dysplasia with regrowth of normal squamous epithelium (Complete Response or CR1), of squamous epithelium with some areas of metaplasia (CR2), or of squamous epithelium with some areas of low grade dysplasia, indefinite dysplasia, or metaplasia (CR3). Photofrin® photodynamic therapy resulted in a Complete Response in 81.5% of treated patients, while omeprazole alone resulted in 39.1% Complete Response (difference between groups was significant, with $p<0.0001$).

Secondary efficacy endpoint analyses showed that 1) the most common type of Complete Response was CR1 in the Photofrin® photodynamic therapy group and CR3 in the omeprazole only group, 2) the median duration of Complete Response was 987 days in the Photofrin photodynamic therapy group and 98 days in omeprazole only group (difference significant, with $p<0.001$), 3) while the median time to progression to cancer could not be assessed, the percentage of patients who progressed to cancer was about twice as high in the omeprazole only group compared to Photofrin® photodynamic therapy group, and 4) a greater percentage of patients had not progressed to cancer or had another therapeutic intervention in the Photofrin® photodynamic therapy group than in the omeprazole only group (only 16% of the omeprazole only group remained in follow-up at the end of the study compared to 62% of the Photofrin photodynamic therapy group). Survival time could not be estimated for either group.

Additional analyses showed that patients who failed to achieve a Complete Response in either group of patients had about a ten-fold higher risk of progression to cancer than patients who achieved a Complete Response.

The results of the supporting studies were consistent with the results of the primary trial.

3. Safety

The major side-effects of Photofrin photodynamic therapy were acute effects related to the light treatment (such as chest pain, abdominal pain, fever, nausea, vomiting, odynophagia and dysphagia), skin photosensitivity reactions, and treatment-related esophageal strictures requiring dilations (in about 38% of patients).

None of the deaths were related to treatment and none was due to adenocarcinoma of the esophagus. Most common serious adverse events were gastrointestinal disorders and dehydration. There were two patients who had esophageal perforations, one of whom underwent an emergency esophagectomy. One patient withdrew from the study because of an anxiety reaction before photodynamic therapy. Other withdrawals were not related to high-grade dysplasia or to treatment.

4. Dosing

The standard dose of Photofrin® was 2 mg/kg, and this dose was administered to over 95% of patients. The prescribed 630nm laser light dose was 130 J/cm, and 92% of patients received this dose.

5. Special Populations

Differences in pharmacology, safety, or effectiveness have not been found with respect to gender, race (Caucasians vs. Asians), or age. A waiver for pediatric studies was requested on the basis that Photofrin® is designated as an Orphan Drug. There are no adequate and well-controlled studies in pregnant women or nursing mothers.

Clinical Review

1. Background

High-grade dysplasia (HGD) in Barrett's Esophagus may progress to adenocarcinoma of the esophagus, a neoplasm that carries a poor prognosis and that has been dramatically increasing in incidence. Risk of adenocarcinoma in HGD patients is broadly stated as 25%, but different studies have reported development of cancer in 16% to 59% of HGD patients who were followed with endoscopic surveillance for 3 to 7 years. At the present time, there is no consensus on the best management of HGD.

- ?? An esophagectomy is advocated by some, as up to 50% of the resected specimens demonstrate previously unrecognized adenocarcinoma.
- ?? Aggressive surveillance every 3 months, if esophagectomy is not performed, is recommended by the American College of Gastroenterology. The purpose of surveillance is to detect cancer at an early and potentially curable stage. The endpoint of surveillance is esophagectomy for cancer. Several retrospective studies clearly suggest that Barrett's esophagus patients in whom adenocarcinoma was detected in a surveillance program had a dramatically improved 5-year survival compared to similar patients who did not undergo routine endoscopic surveillance. Surveillance consists of four-quadrant biopsy specimens at 2-cm intervals along the entire length of Barrett's esophagus.
- ?? A third option is mucosal ablation therapy by photodynamic therapy, thermal therapy or endoscopic mucosal resection.
- ?? There have not been any prospective randomized trials comparing the efficacies and the benefit/risk ratios of these approaches.

The Sponsor is seeking the following indication for photodynamic therapy (PDT) with Photofrin®: "the ablation of HGD in Barrett's Esophagus among patients who refuse esophagectomy and who are in overall good health." In support of this indication the Sponsor has presented the results of three clinical trials. The principal findings are from a multi-center, randomized, controlled, 2-arm,

partially blinded study (PHO BAR 01) in which 130 HGD patients in one arm were treated with PDT using Photofrin® as a photosensitizing agent and an endoscopically administered laser light as the therapeutic agent causing the destruction of HGD, while 69 HGD patients in the other arm underwent a rigorous surveillance program. Patients in both arms were treated with omeprazole to reduce acid reflux. The two arms will be referred to as PHOTOFRIN PDT + OM arm, and OM Only arm, respectively.

The results of the principal study are supported by the results of two single-center, partially blinded, uncontrolled studies (TCSC 93-07 and TCSC 96-01) in which patients with HGD, as well as patients with low-grade dysplasia, localized adenocarcinoma, and BE without dysplasia or carcinoma, were treated with PHOTOFRIN PDT and omeprazole. In the supporting studies efficacy endpoints were assessed in patients with HGD, and safety aspects were assessed in all treated patients irrespective of the diagnosis.

2. Photodynamic therapy: Photofrin® and light delivery systems

Photodynamic therapy (PDT) is based on systemic administration of photosensitizing agents that are retained with some selectivity in rapidly proliferating and malignant tissues. When target tissues are exposed to appropriate wavelength laser light, the resulting tissue necrosis is thought to occur by two mechanisms, direct cytotoxicity by oxygen radicals and anoxia resulting from thrombosis of tumor capillaries.

Photofrin®: The only approved photosensitizing agent for PDT is Photofrin® (porfimer sodium) for Injection. Photofrin is a complex mixture of porphyrin oligomers joined by ether and ester linkages, primarily dimers and trimers, but including molecular species as big as octamers. Oligomer aggregation/disaggregation reactions occur spontaneously in aqueous solution and result in mixtures of oligomers, all of which are active as photosensitizing agents. Molecular weights of oligomers in porfimer sodium range from 1178 to 4659 daltons. The starting material for porfimer sodium is hemin, which is prepared from porcine hemoglobin solution.

Photofrin® is administered intravenously. It is 90%-bound to serum proteins, distributed in tissues within 24 hours, and excreted very slowly, with a first-phase half-life of about 9 days and a second-phase half-life of about 36 days. Photofrin® monomers are degraded to bilirubin and excreted into bile. An important aspect of Photofrin® breakdown is photo-bleaching, which reduces the risks of skin photosensitivity. Photofrin® is innocuous until activated by light.

Present indications: Photofrin® PDT is approved for treatment of patients with completely obstructing esophageal cancer, patients with obstructing endobronchial non-small lung cancer, and patients with micro-invasive endobronchial non-small lung cancer. The standard dose of Photofrin® is 2 mg/kg of body weight.

There appear to be no gender differences, race differences (Photofrin® has been studied in Caucasian and Japanese patients, but the numbers of patients were small), or differences between

volunteers and patients. There are no known drug-drug interactions, except with concomitant use of other photosensitizing agents, or drugs that are excreted in bile. However, photosensivity due to Photofrin® is so overwhelming that it dwarfs the effects of any other photosensitizers. There are no known interactions with omeprazole.

PDT: In photodynamic therapy, light activation is performed with red light at 630 nm wavelength 40 to 50 hours after Photofrin® injection, at which time Photofrin® has largely cleared from a variety of normal tissues, but has been retained by neoplastic tissues, skin, and organs of the reticuloendothelial system. Because the normal esophagus tends to collapse when empty, light delivery systems have been developed that consist of endoscopically placed fiber-optic filaments tipped with cylindrical diffusers and of centering balloons of various lengths and types. Regular light laser sessions were performed using balloons with window lengths of 3 cm, 5 cm, and 7 cm. HGD areas longer than 7 cm required additional courses of treatment. The specified light dose was 130 J/cm. Nodules within HGD were pre-treated with short-fiber optic diffusers (<2.5 cm) with a light dose of 50 J/cm.

3. Study population

In the pivotal PHO BAR 01 study, a total of 485 patients with HGD were screened at 30 centers in the United States, Canada, and Europe. The plan was to enroll 200 patients; 208 patients were enrolled. The reasons for exclusion are shown in Reviewer's Table 1. It should be noted that 237 patients were excluded because the diagnosis of HGD was not confirmed by the Central Reference Laboratory. The excluded patients had metaplasia, indefinite dysplasia, low-grade dysplasia or carcinoma; all had been diagnosed with HGD and referred for Photofrin PDT. This is an important finding that raises the possibility that patients without HGD may be treated unnecessarily with Photofrin® PDT. The methods used in diagnosis of HGD will be described in the next section.

Reviewer's Table 1. 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 (85.6% of 277)**
?? **Other screening criteria not met**	**13 (4.7% of 277)**
?? **Declined participation**	**25 (9.0% of 277)**
?? **Other**	**2 (0.7% of 277)**

Inclusion criteria were few: HGD as assessed by the central reference laboratory, at least 18 years of age, not pregnant, practicing birth control if of childbearing potential, and signed informed consent. Exclusion criteria were more extensive: cancer of the esophagus, history of any cancer within 5 years, prior PDT to esophagus, esophageal strictures unresponsive to dilation, acute or severe chronic illness, contraindications to analgesia, esophagoscopy or omeprazole, porphyria, esophageal ulcers or varices, and abnormal renal, hepatic or hematologic laboratory values.

The average age of patients was 66 years (range, 36 to 88 years), 85% were males, 99% were Caucasians, and 71% were former or current smokers. The composition of study patient population was similar to that of patients with Barrett's Esophagus with HGD, and of patients with adenocarcinoma of the esophagus. Mean duration of BE was about 3 years and mean duration of HGD was 6 months. Most patients had hiatal hernias, about 30% had nodules, about 5% had strictures, and about 5% had ulcers. Almost all patients had previous medical therapy; a few patients had prior surgery.

4. Diagnosis of HGD

Since the primary efficacy endpoint of the study depended on histological diagnoses, all biopsy slides were read by three pathologists at the Central Reference Laboratory, which was the GI Biopsy Laboratory at the University of Washington Medical Center. As part of the PHO BAR 01 study, a sub-study was carried out to assess the intra-rater and inter-rater percent agreement on histologic diagnoses. The intra-rater agreement was very high (average 96%; range, 92% to 99%). The inter-rater agreement was generally high: 88% for high-grade dysplasia, 96% for cancer, 92% for high-grade dysplasia or cancer, 85% for dysplasia (low-grade or high-grade), and 99% for Barrett's esophagus (metaplasia). Obscuring inflammation due to acid reflux had the greatest impact on inter-rater agreement of HGD.

5. Treatment assignment and disposition

Of the 208 patients enrolled in the PHO BAR 01 study (ITT population), 138 were randomized to the PHOTOFRIN + OM group and 70 to the OM Only group. The Evaluable population consisted of 130 patients in the PHOTOFRIN + OM group and of 69 patients in the OM Only

group. The reasons for exclusion of eight patients from the ITT PHOTOFRIN + OM group were: 1) one patient had low grade dysplasia at baseline and was randomized by error, 2) one patient had was found to have an adenocarcinoma at baseline and was randomized by error, 3) three patients withdrew consent, 4) one patient received the Photofrin® injection but did not undergo PDT because of procedure-related anxiety, and 5) two patients received the first course of treatment but were discontinued because invasive esophageal cancer could not be excluded by esophageal ultrasound. One patient in the ITT OM Only group was excluded from the Evaluable population because the patient chose to undergo an esophagectomy instead of taking omeprazole.

The efficacy results will be presented for the Evaluable population rather than for the ITT population, because the inclusion of untreated patients as non-responders in a relatively small population base will serve to confuse rather than to clarify the effect of PHOTOFRIN PDT. The results, as recalculated for the ITT population, are presented in the Appendix. The Safety population consisted of all the ITT patients who had at least one Photofrin injection in the PHOTOFRIN + OM group and one week of omeprazole treatment in the OM Only group. Treatment assignment and patient disposition is shown in Reviewer's Table 2.

Reviewer's Table 2. Treatment assignment and disposition of patients

Patient population	PHOTOFRIN PDT + OM Number of patients (%)	OM Only Number of patients (%)
Intent-to-treat (number of patients randomized)	N = 138 (100%)	N = 70 (100%)
Evaluable	N = 130 (94%)	N = 69 (99%)
Safety	N = 133 (96%)	N = 69 (99%)
Completed study (minimum 24 months)	N = 81 (60.9%)	N = 11 (15.7%)

The reasons for the low percentages of patients completing the study will be described below under efficacy endpoints and outcomes.

6. PDT Treatment

Photofrin® was administered I.V. at a dose of 2.0 ± 0.02 mg/kg to over 95% of patients. Laser light at 630 nm was administered 40 to 50 hours after drug administration. The prescribed dose was 130 J/cm; 92% of patients received doses between 130 and 140 J/cm at any one of the treatment courses. The remainder received lower or higher doses.

Each course consisted of one or two laser light sessions. The first session included a balloon light treatment in all patients and pre-treatment of nodules in some patients. A second laser light session 2 days later treated skip areas. Patients were permitted to receive at most 3 courses of treatment separated by no less than 90 days. The reasons for additional courses of treatment were the length of HGD (a maximum of 7 cm could be treated in one course) and unsatisfactory

response. Reviewer's Table 3 (below) shows the number of courses and the number of sessions administered to the Evaluable population.

Reviewer's Table 3. Photodynamic Therapy Treatment in Evaluable Population in PHO BAR 01 Study

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			
?? **Pretreatment 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.**

All patients in both arms of the study received omeprazole 20 mg twice daily.

7. Follow-up

All patients were to be followed every 3 months until 4 consecutive quarterly follow-up endoscopic results were negative for HGD, and then semi-annually until the last enrolled patient had completed at least 24 months of follow-up evaluation after randomization. The length of follow-up ranged from 2 to 3.6 years.

8. Efficacy results

Efficacy analysis in the PHO BAR 01 study was performed after a minimum follow-up of 24 months after the last patient was randomized.

?? The primary efficacy endpoint was the complete ablation of HGD, with re-growth of only normal squamous epithelium (complete response 1 or CR1), of squamous epithelium with some areas of metaplasia (CR2 response), or of squamous epithelium with some areas of low-grade dysplasia, indefinite dysplasia, or metaplasia (CR3 response).

?? The primary efficacy analysis was based on the clinical response (CR) rate at any one of the evaluations during the 24-month follow-up periods. The percentages of responding patients in the two treatment arms are shown in Reviewer's Table 4.

Reviewer's Table 4. Clinical Response After a Minimum Follow-up of 24 Months

Response	PHOTOFRIN PDT + OM	OM Only
CR1 + CR2 + CR3 **Intent-To-Treat population**	**106/138 (76.8%)***	**27/70 (38.6%)***
CR1 + CR2 + CR3 **Evaluable population**	**106/130 (81.5%)***	**27/69 (39.1%)***

***Differences between PHOTOFRIN PDT and OM Only groups are significant with p<0.0001.**

?? Further analysis during the review showed that Complete Response was not only an improvement in the anatomy of the esophageal mucosa but appeared to correlate with a decreased risk of development of carcinoma. Reviewer's Table 5 demonstrates the following findings:

1) Non-responders in both PHOTOFRIN + OM and OM Only groups had a very high percentage of patients who progressed to cancer, about 45% to 50%.
2) Responders in both groups had a much lower percentage of patients who progressed to cancer, about 4% to 6%.
3) The percentages of patients who progressed to cancer were about twice as high in the control group (OM Only) as in the PHOTOFRIN PDT + OM group.

Reviewer's Table 5. 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.**

The above results should be considered as preliminary, since the numbers of patients are small and the follow-up periods are relatively short.

?? Secondary efficacy endpoint: The Quality of CR. Most of the responders in the PHOTOFRIN PDT + OM group had a CR1 response, while most of the responders in the OM Only group had a CR3 response (as shown in Reviewer's Table 6). Most of the responses in both arms were consistent from one evaluation to the next, except as response failure occurred. It was not possible to determine whether the quality of CR correlated with failure to progress to cancer because of the small number of responders who progressed to cancer.

Reviewer's Table 6. Relative Frequencies of Responses in the Evaluable Populations

Quality of response	PHOTOFRIN PDT + OM N = 130	OM Only N = 69
CR1	72 (55.4%)	5 (7.2%)
CR2	9 (6.9%)	5 (7.2%)
CR3	25 (19.2%)	17 (24.6%)
No response	24 (18.5%)	42 (60.9%)

?? Secondary efficacy endpoint: Duration of Response. Kaplan-Meier method was used for estimation of duration of response. Median durations are shown in Reviewer's Table 7.

Reviewer's Table 7. Median Duration months of Response after a Minimum follow-up of 24 months

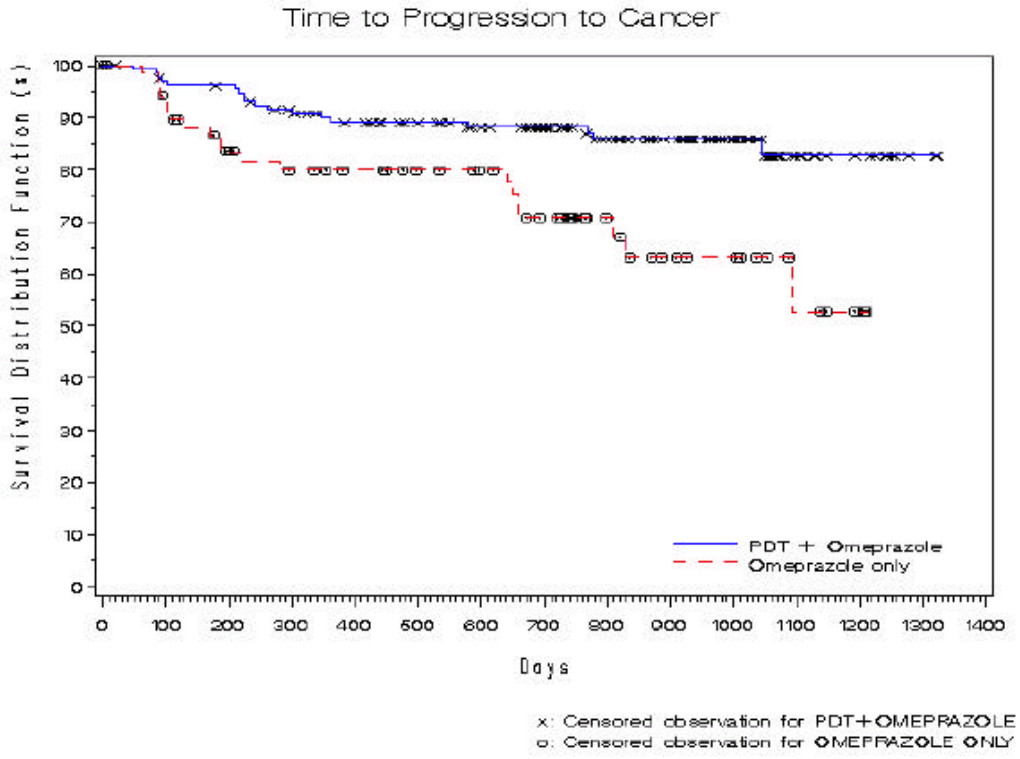
Complete response	PHOTOFRIN PDT + OM Median (days)	OM Only Median (days)	Log-rank p-value
CR1	316	84	0.1905
CR1 + CR2	478	184	0.5182
CR1 + CR2 + CR3	987	98	<0.001

?? Secondary efficacy endpoint: Time to progression to cancer. This endpoint was defined as the day 50% of the patients had documented progression to cancer. Since 50% of patients in either group had not progressed to cancer, this endpoint could not be assessed. About 70% of patients who progressed to cancer in both the PHOTOFRIN PDT group and in the OM Only group did so within 12 months from the start of treatment. A Kaplan-Meier plot of the time to progression to cancer is shown below.

N

F

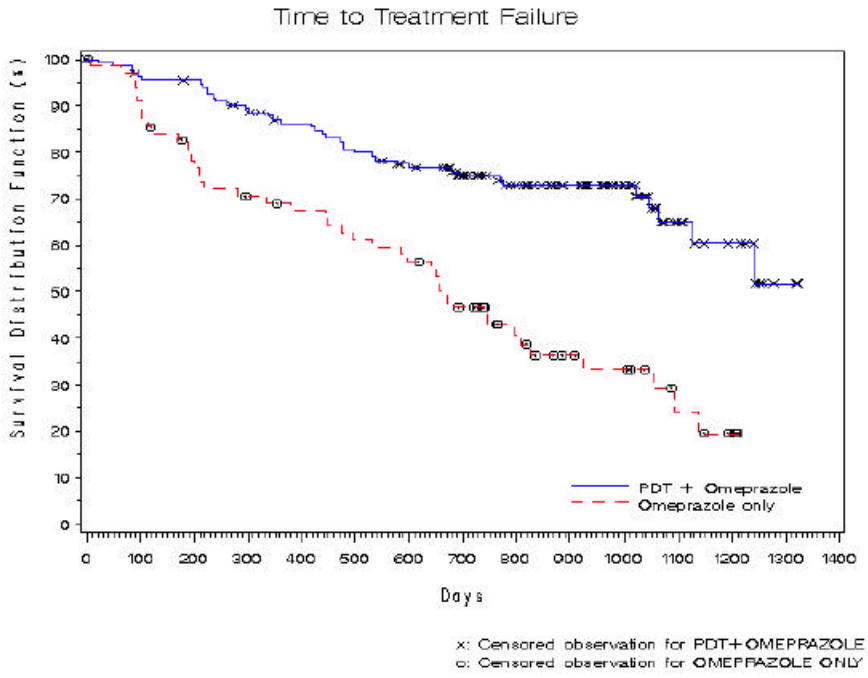
Revised Figure 11.4
Comparison by Treatment Group of the Time to Progression to Cancer Over Time
(ITT population)



Data source: **Revised** Table 1.25

?? Secondary efficacy endpoint: Time to Treatment Failure. This endpoint was a composite of 1) progression to cancer, and 2) any intervening therapy other than the randomized study treatment. A Kaplan-Meier plot of this endpoint is shown below. The median Time to Treatment Failure could not be estimated for the PHOTOFRIN PDT group, and was 670.0 days for the OM Only group.

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 Table 8 shows an accounting of the numbers of patients during the study that may help understanding the above Kaplan-Meier plot.

Reviewer's Table 8. Patient Outcomes in Evaluable Populations

Patients	PHOTOFRIN PDT + OM	OM Only
Evaluable population	130	69
Progressed to cancer	18	20
Had another therapeutic intervention	18	21
Deaths, AEs, discontinued for administrative reasons	13	17
Total discontinued (%)	49 (37.7%)	58 (84.1%)
Total remaining at end of follow-up (%)	81 (62.3%)	11 (15.9%)

?? In the PHOTOFRIN PDT group, 18 patients had progressed to cancer, and another 18 had another therapeutic intervention because of persistence or recurrence of HGD. Thus, 36 patients were discontinued because they had failed PHOTOFRIN PDT (27.7% of the evaluable population).

- In the OM Only group, 20 patients had progressed to cancer, and 21 had a therapeutic intervention for HGD. Since this was the surveillance group, the latter patients did not experience treatment failure but decided to undergo some form of active treatment. Anxiety was stated to be the motivational force in some cases. A total of 41 patients were discontinued from the study for these reasons (59.4% of the evaluable population).
- Administrative discontinuations, deaths, and adverse events accounted for discontinuation of additional 13 patients in the PHOTOFRIN PDT group and of additional 17 patients in the OM Only group.
- By the end of the follow-up period the two patient populations were far more out of balance than the 2:1 ratio at the start of the study.

There are several implications of these statistics:

- At least in this study, it was difficult to maintain patients in a control treatment arm, as patients opted for active treatment.
- Treatment failure due to intervening therapy in the control arm is different from that in the PHOTOFRIN PDT arm, because it is not a failure of treatment, but the choice to undergo active treatment instead of continuing surveillance. By contrast, the intervening therapy in the PHOTOFRIN PDT arm was for recurrence of HGD. In the PHOTOFRIN PDT group, 9 of the 18 patients had intervening therapy in the 12 – 18 month period after the start of therapy, 3 had in the 18 – 24 month period, and the rest between 2 and 3 years after the start of therapy. In the OM Only group approximately equal groups of patients had intervening therapy in each successive 6-month period.
- Combining the two types of events into one endpoint of Treatment Failure makes the Kaplan-Meier plots of the two patient groups difficult to understand.

Secondary endpoint: Survival Time. This endpoint could not be estimated. There were only 3 deaths in both treatment groups during this period, and none of them were due to adenocarcinoma of the esophagus or to treatment.

9. Efficacy results in Supporting Studies

Two open-label, uncontrolled, single-center studies provided results on 86 patients with HGD treated with PHOTOFRIN PDT and omeprazole, and followed for a minimum of 12 months. The results of the supporting studies were consistent with the results of the principal trial.

- The overall complete response (CR1 + CR2+ CR3) in the two studies was 94.2%.
- The median duration of complete response was 391 days in one study, and could not be estimated in the second one.
- Progression to cancer occurred in 11 (12.8%) of patients during a 12-month follow-up.
- Response failures (includes patients who progressed to cancer and patients who had other intervening therapy) occurred in 28/86 (32.6%) of patients during a minimum follow-up of 12

months.

?? Survival time could not be estimated in either study. Six patients died in the two studies. None of the deaths were related to adenocarcinoma of the esophagus or to treatment.

10. Other Intervening Therapies (in Treatment Failure patients) in the PHO BAR 01 trial were as follows:

?? 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.

11. Safety

The Safety population consisted of 318 patients treated with PHOTOFRIN PDT from the principal multi-center, controlled study and the two single-center, uncontrolled studies. The latter studies included 100 patients with superficial adenocarcinoma, low-grade dysplasia, and metaplasia, in addition to 86 patients with high-grade dysplasia.

The major side-effects of PHOTOFRIN PDT were acute events related to the light treatment, longer lasting effects relating to the healing of the esophagus, and the extended period of photosensitivity of the skin.

?? The acute effects were chest pain (in 47% of patients), abdominal pain (in 10%), fever (in 22%), nausea (in 39%), vomiting (in 34%), odynophagia (in 15%), and dysphagia (in 24%). Acute symptoms abated gradually, generally over about 4 weeks.
?? Skin photosensitivity reactions were common (in 44% of patients), in spite of detailed warnings about exposure to sunlight and bright lights for 30 days. Most of the photosensitivity reactions occurred within 90 days after PHOTOFRIN injection. Most were mild (68%) or moderate (26%). Severe reactions (6%) were characterized by swelling, erythema, blisters, itching, burning sensation, and heat. All resolved over time.
?? The most important sub-acute effects were esophageal strictures. Their treatment required repeated dilations, 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.

The incidence of esophageal strictures depends on whether the data were collected from adverse event reports or from endoscopy reports. According to adverse event reports, symptoms of strictures occurred in 29.9% of patients. Endoscopy data were first collected using the term "esophageal stricture" regardless of subsequent management. Later on, only esophageal narrowing that required dilation was considered a stricture (incidence of 38.1%).

Reviewer's Table 9 shows the incidence of strictures in the three trials, according to endoscopy data. Most of the strictures were noted after the first PDT course in the TCSC 96-01 trial, and after the second course in PHO BAR 01 (randomized) trial. In the randomized trial two patients had baseline strictures in the PHOTOFRIN PDT + OM arm and two patients, in the OM Only arm.

Reviewer's Table 9. 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 **Course 2** **Course 3**		**26 (30.2%)** **5 (5.8%)** **0**	**18 (13%)** **29 (21%)** **1 (1%)**	

There is no known method to prevent strictures at the present time. TCSC 96-01 trial tested the hypothesis that post-PDT corticosteroids may decrease the incidence of strictures, and randomized patients to receive corticosteroids or placebo. Treatment with corticosteroids did not reduce the incidence of strictures. Recent analyses suggest that areas of esophagus, which had received overlapping light exposure or had been treated a second time, appear to be predisposed to stricture formation (44% of such patients developed strictures compared to 24% of patients who did not have a mucosal segment treated twice).

The only treatment for strictures at present is esophageal dilation. Patients with baseline strictures in the OM Only arm needed only one dilation. Most of the PDT-treated patients underwent multiple dilations, as shown in Reviewer's Table 10. The Sponsor characterized PHOTOFRIN PDT-related strictures as mild in 51.4% of patients, moderate in 38.8%, and severe in 9.7%. The data on esophageal dilations suggest that strictures require considerable medical attention and some risk. About 65% of patients with strictures required more than 2 dilations, about 36% required more than 5 dilations, and about 15% required more than 10 dilations.

Reviewer's Table 10. 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.**

Other safety indicators were the following:

- There were six deaths in the three studies. None were related to treatment.
- Serious adverse events were reported by 25% of patients treated by PHOTOFRIN PDT. Most common treatment-related SAEs were reported as gastrointestinal disorders and dehydration.
- Adverse events that led to patient withdrawal from the studies included two patients who had esophageal perforations, one after esophageal dilation, the other after Nd:YAG laser treatment. One of these two patients underwent esophagectomy. One patient developed an anxiety reaction after PHOTOFRIN injection and before laser light treatment. Two patients had strokes, two were diagnosed with lung cancer, and one had worsening heart disease.

12. Ethical Standards and Financial Disclosure

- The clinical trials were conducted in accordance with accepted ethical standards, including reviews of the protocols by Institutional Review Boards or Independent Ethics committees, and compliance with the Declaration of Helsinki, recommendations of the World Health Organization, Health Protection Branch (Canada), and the FDA, and with applicable state laws. Each patient reviewed and signed a written approved informed consent.
- 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.

13. Summary and Conclusions

?? PHOTOFRIN PDT appears to be an effective method of cancer risk reduction. The following findings lend support to this possibility: 1) cancer developed at about one-half the rate in the PHOTOFRIN PDT group as compared to the rate in the surveillance group, 2) PHOTOFRIN PDT was very effective in ablating HGD and leading to a Complete Response, and 3) patients with a Complete Response had a much lower probability of development of cancer than patients who failed to achieve a Complete Response. However, it is not possible to assess the long-term effectiveness of PHOTOFRIN PDT in cancer risk reduction using 2-year follow-up results. The Sponsor is continuing to follow PHO BAR 01 patients in PHO BAR 02 study that is expected to last 3 years.

?? PHOTOFRIN PDT was relatively well-tolerated, since very few patients left the trials because of treatment-related adverse effects. Nevertheless, the benefit/risk ratio is difficult to evaluate because long-term effectiveness in cancer risk reduction is not known at this time.

?? There was no esophagectomy arm in the Sponsor's studies, and patients who chose to undergo esophagectomy were not followed in any of the three studies. Thus, the efficacy (in cancer risk reduction) and safety of PHOTOFRIN PDT could not be compared to that of esophagectomy.

?? A surveillance program for patients with Barrett's Esophagus and HGD was an ineffective option for most patients. Over a follow-up period of at least 2 years, 84% of patients either developed cancer, chose an active form of treatment, or left the trial because of adverse events and administrative dismissals.

?? HGD in Barrett's Esophagus is the only known lesion that progresses to adenocarcinoma of the esophagus. Even though 94% to 98% of esophageal adenocarcinomas are diagnosed in patients without a prior diagnosis of Barrett's esophagus, ablation of HGD offers a method of reducing the risk of this highly lethal disease in this select group of patients.

A P P E N D I X

Reviewer's Tables 5 and 6 for ITT populations.

Reviewer's Table 5. Progression to Cancer Among Responders and Non-Responders in the Intent-to-Treat Populations with a Minimum Follow-up of 24 Months

Patient group	Total number of patients	Total number who progressed to cancer
PHOTOFRIN PDT	**138**	**18 (13.0%)**
?? **CR1+CR2+CR3**	**106**	**6 (5.7%)**
?? **No response**	**32**	**12 (37.5%)**
OM Only	**70**	**20 (28.6%)**
?? **CR1+CR2+CR3**	**27**	**1 (3.7%)**
?? **No response**	**43**	**19 (44.2%)**

Reviewer's Table 6. Relative Frequencies of Responses in ITT Populations

Quality of response	PHOTOFRIN PDT + OM, N = 138	OM Only N = 70	Fisher's exact P value
CR1	**72 (52.2%)**	**5 (7.1%)**	**<0.0001**
CR2	**9 (6.5%)**	**5 (7.1%)**	**1.000**
CR3	**25 (18.1%)**	**17 (24.3%)**	**0.3609**
No response	**32 (23.2%)**	**43 (61.4%)**	**<0.0001**

ATTACHMENT TWO

MEDICAL DEVICE REVIEWER'S SUMMARY

Briefing document for devices for use with Photofrin in the treatment of Barrett's Esophagus.

There are three specific devices that are used in combination to deliver the required optical radiation to the treatment site for the activation of the drug Photofrin for the treatment of high- grade dysplasia in Barrett's Esophagus. The devices that make up this total system are:

1. The Diomed 630 PDT Laser Model T2USA is a diode laser with an output wavelength of 630 ± 3 nm which has been shown in past studies to be effective in the activation of the drug Photofrin. The Diomed 630 PDT Laser is capable of delivering 2000 mW of laser energy at the delivery fiber tip. This laser system has been shown to be compatible with the OPTIGUIDE Diffusing Fiber Optics used in this study as the light delivery systems. When using the Diomed laser to activate Photofrin for treatment of Barrett's Esophagus, the physician will specify the diffuser length to be used in the treatment and the laser software will calculate the laser on time to produce the required 130 J/cm of diffuser length required for treatment. The package insert for the OPTIGUIDE Diffusing Fiber Optics contains specific tables for each diffuser length, corresponding laser setting and required on time for the required fluence for treatment.

2. The OPTIGUIDE Fiber Optic Diffusers, like the Diomed 630 PDT Laser have been shown in previous studies to be capable of delivering the required 630 nm light to target sites for the activation of Photofrin. These diffusing fibers are used in the treatment of Barrett's Esophagus in two different methods. Diffusing fibers of 1.0 to 2.5 cm are used to either pretreat nodular areas prior to treatment of the total dysplastic area or can be used following treatment at follow-up to treat skipped areas. The second use for these diffusing fibers is to deliver the required activating light to the Wizard Balloon Diffuser for the treatment of the total dysplastic area of Barrett's. Fibers having lengths of 5.0, 7.0, and 9.0 cm are used with the corresponding window size of Wizard Balloon. The OPTIGUIDE diffusers are designed to allow exposure of tissue in a circumferential pattern 90^{o} to the fiber shaft in a 360^{o} pattern with no forward or reverse exposure. The package insert for the fibers comes with tables for each length of fiber and required laser output in mW and recommended time for treatment.

3. For the actual treatment of the dysplastic Barrett's area, a third device is required. This device is the Wizard X-Cell which is a combination device consisting of a balloon with a 360^{o} window for total exposure of the intended treatment site. As with the OPTIGUIDE diffusers, the Wizard X-Cell incorporates reflective mirrors to prevent both forward or reverse exposure with the added advantaged that this internally reflected light enhances the light energy available for treatment. The actual treatment light is delivered through the windows by use of the appropriate length OPTIGUIDE Fiber Optic Diffuser. In actual use

the diffuser used to deliver the light to the Wizard is longer than the Wizard window to insure total exposure. The Wizard windows are 3, 5, and 7 cm in length thus the corresponding diffuser length would be 5, 7, and 9 cm. The balloon feature of the Wizard X-Cell provides some stability to device positioning and also provides some smoothing of the esophageal folds to allow for a more uniform light exposure.