

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

**NDA 21-525
NDA 20-451/S-012**

Statistical Review(s)

**STATISTICAL REVIEW AND EVALUATION -- NDA
CLINICAL STUDIES**

Medical Division: Gastrointestinal and Coagulant Drug Products (HFD-180)

Biometrics Division: Division of Biometrics II (HFD-715)

STATISTICAL KEY WORD:

NDA #: 21-525

SERIAL NUMBER:

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DRUG NAME: Photofrin (porfimer sodium) Injection

INDICATION: Ablation of high-grade dysplasia in Barrett's Esophagus

SPONSOR: Axcan Scandipharm Inc.

DOCUMENTS REVIEWED: Amendment #2 Vol. 1 - 27 Dated September 26, 2002

Response to Clinical Questions

Amendment #7 Dated January 28, 2003

Response to Approvable Letter dated Nov. 29, 2002

Amendment #9 Dated February 18, 2003

Information Amendment Response to Request for
Statistical Information

Amendment #11- Response to Clinical and Statistical
Information Requests Dated May 13, 2003

Amendment #12 SAS datasets Dated June 3, 2003

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1. EXECUTIVE SUMMARY OF STATISTICAL FINDING

1.1 Conclusion and Recommendation

The results of the 24-month data from the PHO BAR 01 study confirmed those reported in the 6-month study report.

For the 24-month data, statistically significant percentage of patients in the Photofrin PDT + OM group demonstrated a response at level CR1 or CR2 or CR3, 77% for the ITT population, as compared to the OM only group, 39% for ITT population.

For a more stringent definition of "complete response" (a patient was considered as a responder if patient met the response criteria for CR1 during the entire endoscopic monitoring period) in ITT population, the proportion of responders was numerically higher in the Photofrin PDT + OM than in the OM only group. But, the treatment difference did not achieve statistical significance.

There were statistically significant differences between treatment groups in terms of time to progression to cancer and time to treatment failure. However, there was no statistical difference in survival time.

Furthermore, from the reviewer's exploratory analysis it revealed that most of patients who had progression to cancer used intervening therapy. More than a third of non-responders for CR3 or better had progression to cancer and more than a half of non-responders for CR3 or better had treatment failure or underwent intervening therapy.

1.2 Overall of the Clinical Program and Studies Reviewed

Photofrin injection was approved on December 27, 1995 as part of a drug-device combination-product for use in photodynamic therapy with specified device for palliation of esophageal cancer.

In the current NDA, the sponsor seeks approval of Photofrin injection (75 mg vial) in photodynamic therapy for the ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE) among patients who are not considered to be candidates for esophagectomy. The sponsor has submitted one pivotal clinical study (protocol PHO BAR 01) with 6-month data. Statistical Review and Evaluation for this original NDA was performed and documented October 30, 2002.

Recently, the sponsor submitted an original NDA amendment 2 dated September 26, 2002 and amendment 7 dated January 28, 2003, containing clinical study report and its addendum with follow-up (24-month) data for protocol PHO BAR 01.

This review will address on 24-month data provided in the original NDA amendment and Amendments #7, #9, #11 and #12.

1.2.1 Brief Description for Study Design for PHO BAR 01

This was a parallel, omeprazole-single therapy controlled study. Patients were followed by a strict endoscopic surveillance and biopsy protocol for a minimum of 24 months.

All patients were followed every three months until four consecutive, quarterly follow-up endoscopic biopsy results were negative for HGD and then semiannually until the last enrolled patient had completed a minimum of 24 months of follow-up evaluation after randomization.

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

The primary analyses were performed after a minimum follow-up of 24 months from the date of randomization of the last patient (expected median follow-up of 24 months). All patients on study were followed for a minimum of 24 months after randomization of the last patient.

1.3 Principal Finding

In both ITT and Evaluable populations, the proportion of responders (CR1 or CR2 or CR3) was statistically significantly higher in the Photofrin PDT + OM than in the OM only group.

As suggested by Medical Officer, Mark Avigan, a more stringent definition of "complete response" was considered that a patient was classified as a responder if patient met the response criteria for CR1 during the entire endoscopic monitoring period.

Even for a more stringent definition of "complete response" in ITT population, the proportion of responders was numerically higher in the Photofrin PDT + OM group than in the OM only group (8.0% vs. 1.4%). But, the treatment difference did not achieve statistical significance.

There were statistically significant differences between treatment groups in terms of time to progression to cancer and time to treatment failure. However, there was no statistical difference in survival time.

2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Background

Photofrin injection was approved on December 27, 1995 as part of a drug-device combination-product for use in photodynamic therapy with specified device for palliation of esophageal cancer.

In the current NDA, the sponsor seeks approval of Photofrin injection (75 mg vial) in photodynamic therapy for the ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE) among patients who are not considered to be candidates for esophagectomy. The sponsor has submitted one pivotal clinical study (protocol PHO BAR 01) with 6-month data. Statistical Review and Evaluation for this original NDA was performed and documented October 30, 2002.

Recently, the sponsor submitted an original NDA amendment 2 dated September 26, 2002 and amendment 7 dated January 28, 2003, containing clinical study report and its addendum with follow-up (24-month) data for protocol PHO BAR 01.

This review will address on 24-month data provided in the original NDA amendment and Amendments #7, #9, #11 and #12.

2.2 Protocol PHO BAR 01

This was a parallel, omeprazole-single therapy controlled study. Patients were followed by a strict endoscopic surveillance and biopsy protocol for a minimum of 24 months.

All patients were followed every three months until four consecutive, quarterly follow-up endoscopic biopsy results were negative for HGD and then semiannually until the last enrolled patient had completed a minimum of 24 months of follow-up evaluation after randomization.

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

The primary analyses were performed after a minimum follow-up of 24 months from the date of randomization of the last patient (expected median follow-up of 24 months). All patients on study were followed for a minimum of 24 months after randomization of the last patient.

2.2.1 Sponsor's Analysis

Of the 485 patients screened for inclusion, a total of 208 patients were enrolled in the study. 138 patients were randomized to received Photofrin PDT + omeprazole and 70 patients were randomized to receive omeprazole only. Of these, 132 patients received Photofrin PDT + omeprazole and 69 patients received omeprazole only.

Of the 138 patients enrolled in the treatment arm of the study, 133 (96%) patients received a full course 1; 90 patients out of 133 (68%) went onto Course 2, while 42 patients out of 90 (47%) underwent a third course.

There were 78 (59%) patients in Photofrin PDT + omeprazole group and 26 (38%) patients in omeprazole group provided a minimum of 2-year (730 days) follow-up data. Overall, the most frequent reasons for not completing the 2-year follow-up once enrolled into the study included disease progression (13% in the Photofrin PDT + OM treatment group vs. 31% in the OM only treatment group) and requirement of other therapy (16% in the Photofrin PDT + OM treatment group vs. 27% in the OM only treatment group).

Overall, 16 patients in the Photofrin PDT + omeprazole treatment group underwent an esophagectomy (11.6%). Most patients in the omeprazole group received a Photofrin PDT treatment (34.3%).

There were 57 patients in Photofrin PDT + omeprazole group and 49 in omeprazole group discontinued from the study.

2.2.1.1 Sponsor's Analysis of Primary Efficacy Variable

The primary analysis consisted of the analysis of the complete response based on data collected up to a minimum of 24 months of follow-up after the last patient was enrolled in the study.

Complete response was the primary efficacy endpoint. Complete response rate was determined using the following definitions:

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

Complete Response 2 (CR2) - ablation of all histological grades of dysplasia, including patients with indefinite grade of dysplasia, but some areas of Barrett's metaplastic epithelium still remain.

Complete Response 3 (CR3) - ablation of all areas of HGD but some areas of LGD with or without areas which are indefinite for dysplasia, or areas of Barrett's metaplastic epithelium.

A patient was classified as a responder for the primary efficacy analysis if he or she met the response criteria for CR1 or CR2 or CR3 at any time.

The overall clinical response for both treatment groups in ITT and Evaluable populations whose response was at CR1 or CR2 or CR3 at any one of the evaluation time points is given below.

**Overall Clinical Response
(ITT Population[†])**

Treatment	Rate	95% C.I.	p-value
Photofrin PDT + OM	106/138 (76.8%)	(69.8%, 83.9%)	<0.0001
OM only	27/70 (38.6%)	(27.2%, 50.0%)	

[†]Six patients in the Photofrin PDT + Om group and three patients in the OM only group without post-baseline biopsy data are considered as non-responders.

Copied from Panel 11.6, page 103, Vol. 2.

**Overall Clinical Response
(Evaluable Population[†])**

Treatment	Rate	95% C.I.	p-value
Photofrin PDT + OM	106/130 (81.5%)	(74.9%, 88.2%)	<0.0001
OM only	27/69 (39.1%)	(27.6%, 50.6%)	

[†]three patients in the OM only group without post-baseline biopsy data are considered as non-responders.

Copied from Panel 11.6, page 103, Vol. 2.

As seen from table above, in both ITT and Evaluable populations, the proportion of responders was statistically significantly higher in the Photofrin PDT + OM than in the OM only group.

2.2.1.2 Sponsor's Analysis of Secondary Efficacy Variables

2.2.1.2.1 Quality of Complete Response

The results of the analysis of responders for both treatment groups in ITT population to Photofrin PDT or omeprazole at CR1 and at CR1 or CR2 at any one of the follow-up evaluations are given below.

**Quality of Response
(ITT Population)**

Responders	Photofrin PDT + OM		OM only		p-value
	Rate	95% C.I.	Rate	95% C.I.	
CR1	72/138 (52.2%)	(43.8%, 60.5%)	5/70 (7.1%)	(1.1%, 13.2%)	<0.0001
CR1 or CR2	81/138 (58.7%)	(50.5%, 66.9%)	10/70 (14.3%)	(6.1%, 22.5%)	<0.0001

Copied from Panel 11.7, page 104, Vol. 2.

As seen from table above, the quality of response in the Photofrin PDT + OM group was statistically significantly better than that in the OM only group in ITT population.

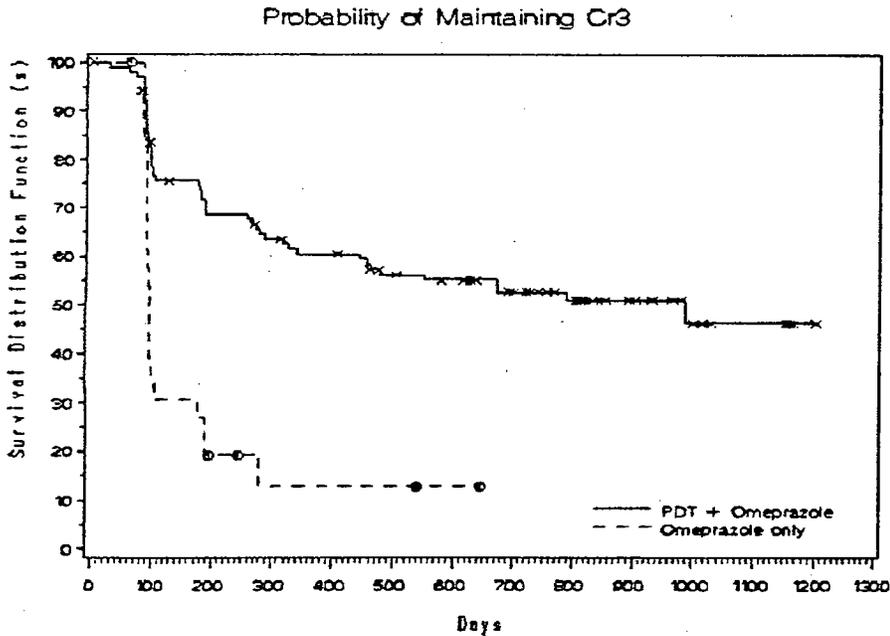
2.2.1.2.2 Duration of Response

The duration of response to Photofrin PDT or omeprazole in the ITT population was analyzed separately at each response level (CR1, CR1 or CR2, and CR1 or CR2 or CR3. Duration of response was censored for patients with no data indicating an end to response as follows:

For patients who received no intervening therapy, censoring occurred at the date the patient was last known to be participating in the study; or

For patients who received 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 probability of maintaining a CR3 or better response over time by treatment in the ITT population is displayed below.



x: Censored observation for PDT+OMEPRAZOLE
o: Censored observation for OMEPRAZOLE ONLY

By the end of the 2-year follow-up period (730 days), the probability of maintaining the CR3 or better criteria was 52.7% in the Photofrin PDT + OM group as compared to 12.8% in the OM only group. At the CR2 or better response level, the probability of maintaining the criteria after two years was 47.5% in the Photofrin PDT + OM group as compared to 42.9% in the OM only group. At the CR1 Response level, the probability of maintaining the criteria after two years was 45.8% in the Photofrin PDT + OM group as compared to 33.3% in the OM only group.

2.2.1.2.3 Progression to Cancer

2.2.1.2.3.1 Rate of Progression to Cancer

This secondary endpoint of rate of progression to cancer was not pre-specified in the protocol.

In the Photofrin PDT + OM group, a total of 18 patients (13%) had progressed to cancer in the ITT population by the end of the minimum follow-up of 2 years. By the end of the minimum follow-up of 2 years, a total of 20 patients (28%) in OM only group had progressed to cancer in the ITT population.

The rate of patients who progressed to cancer in the Photofrin PDT + OM group was statistically lower than those in the OM only group in the ITT population ($p=0.0060$).

2.2.1.2.3.2 Time to Progression to Cancer (TTP)

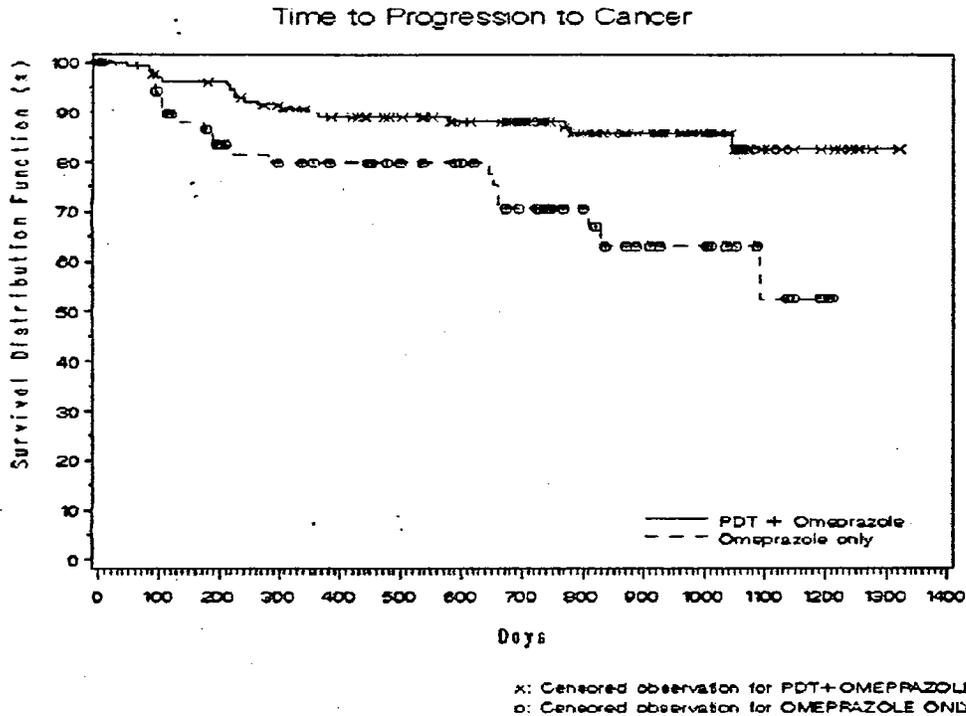
The TTP was defined as the period in days from the date of randomization until the date the progression to cancer was first documented.

The TTP was censored for patients with no data indicating progression to cancer as follows:

1. For patients with no intervening therapy, TTP was censored at the last known day on study.
2. For patients who received intervening therapy, TTP was censored on the day that any Intervening therapy began.

The distribution of the TTP was summarized by treatment group using the Kaplan-Meier method and compared between the two treatment groups using the log-rank test.

The probability that a patient was cancer-free over time by treatment group in the ITT population is displayed below.



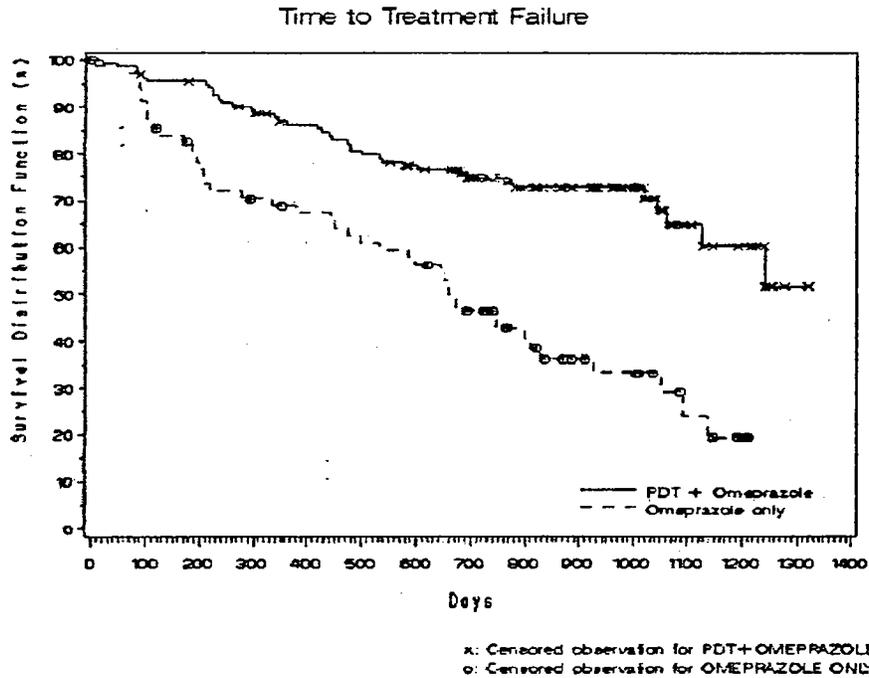
By the end of the entire follow-up period, patients in the Photofrin PDT +OM group had a 82.8% chance of being cancer-free as compared to 52.6% chance for patients in the OM only group. Comparison between the two treatment groups using the log rank test showed a statistically marginally significant delay in the progression to cancer in the Photofrin PDT + OM group as compared to the OM only group in the ITT population ($p=0.0014$).

2.2.1.2.4 Time to Treatment Failure (TTF)

The TTF was originally defined as the period in days from the date of randomization until the date of the first documentation of progression of HGD to cancer or the start of any intervening therapy for HGD other than the randomized study treatment. However, such definition excluded patients with no documented start date of intervening therapy and included patients who received intervening therapy for reasons other than HGD. To ensure inclusion of patients who prematurely discontinued from the study due to treatment failure (progression of disease or use of other therapy for HGD), the sponsor re-defined TTF as the period in days from the date of randomization until the date of the first documentation of progression of HGD to cancer or the patient's termination of study for use of other therapy for HGD. For patients with no documented event of treatment failure, TTF was censored at the last efficacy assessment.

The distribution of the TTF was summarized by treatment group using the Kaplan-Meier method and compared between the two treatment groups using the log-rank test.

The probability of treatment success over time by treatment group in the ITT population is displayed 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. Comparison between the two treatment groups using the log rank test showed that the need for esophagectomy or other intervening therapy was significantly postponed in the Photofrin PDT + OM group as compared to the OM only group in the ITT ($p < 0.0001$).

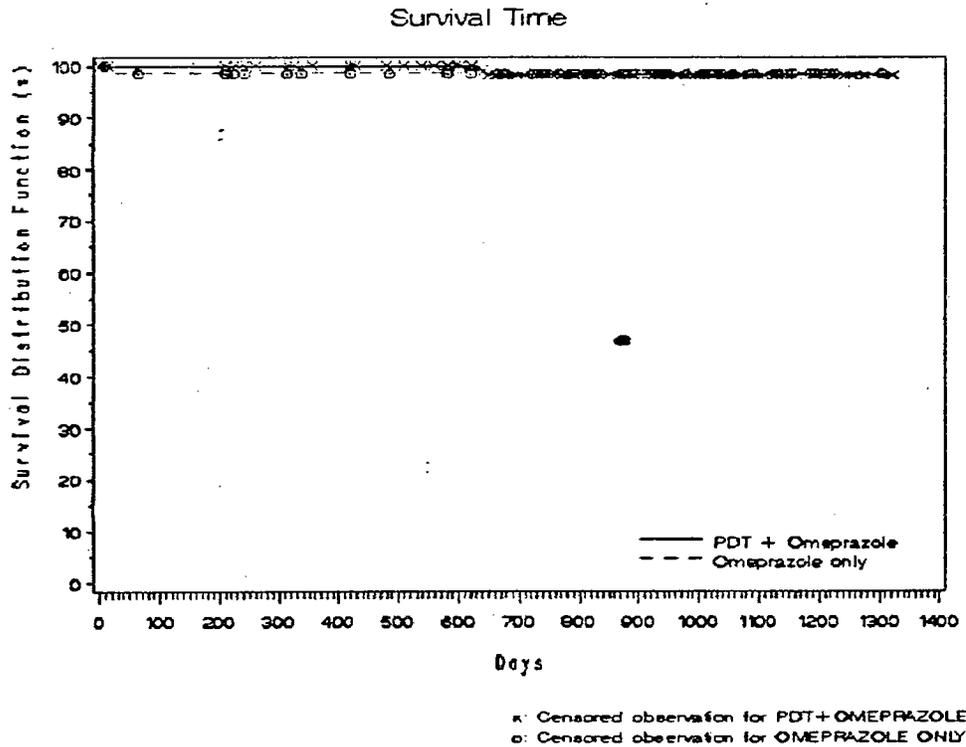
2.2.1.2.5 Survival Time

Survival time was defined as the period in days from the date of randomization to the date of the patient's death. For patients who had no documented date of death, survival data was censored at the last date that the patient was known to be alive.

The Kaplan-Meier method was used to estimate the survival curves for each treatment group and the log rank test was used to compare the survival curves between the two treatment groups.

The comparison between the two treatment groups showed no statistical difference between two treatment groups ($p = 0.9880$).

The probability of survival over time by treatment group in the ITT population is displayed below.



2.2.1.3 Safety

The Photofrin PDT + OM group had a much higher incidence of SAE (38%) than OM only group (28%). Two patients in Photofrin PDT + OM group and one patient in the OM only group experienced treatment emergent AE that led to death.

In the Photofrin PDT + OM group, 132 (99%) patients experienced treatment emergent AEs, 50 (38%) patients experienced SAEs, and 4 (3%) patients withdraw from the study due to treatment emergent AEs. The most commonly reported treatment emergent AEs were photosensitivity reaction (68%), esophageal strictures (40%), vomiting (38%), constipation (27%), chest pain (25%), and pyrexia (24%).

In the OM only group, 51 (74%) patients experienced treatment emergent AEs, 19 (28%) patients experienced SAEs, and one (1%) patient withdrew from the study due to an AE. The most commonly reported treatment emergent AEs were chest pain (12%) and diarrhea (10%).

2.3 Reviewer's Evaluation

2.3.1 Reviewer's Comments on Sponsor's Revised Efficacy Data

In the sponsor's Clinical Study Report – Addendum dated January 6, 2003, it stated that the secondary efficacy parameters: time to progression to cancer (TTP); time to treatment failure (TTF); and survival time (SURVIV) had been revised.

Recently, the sponsor submitted SAS datasets containing the changes. This reviewer found that there were 70 patients (35 photofrin + OM and 35 OM only) whose secondary efficacy parameters were revised. Listings of changes for time to progression to cancer, time to treatment failure, survival time, and intervening therapy are given Attachments 1 to 4, respectively.

For time to progression to cancer (TTP), a total of 24 patients (16 photofrin + OM and 8 OM only) had time to event revised. The changes were minor and did not affect the results.

For survival time (SURVIV), a total of 26 patients (9 photofrin + OM and 17 OM only) had time to event revised. All patients with revised time to event were censored. The changes did not affect the results.

For time to treatment failure (TTF), a total of 41 patients (22 photofrin + OM and 19 OM only) had either censored flag or time to treatment failure revised. The number of patients who were considered treatment failure were revised from 26 to 40 for photofrin + OM group (3 from treatment failure to non-treatment failure and 17 from non-treatment failure to treatment failure) and from 36 to 42 for OM only group (1 from treatment failure to non-treatment failure and 7 from non-treatment failure to treatment failure) from the original submission. But, the changes in time to event were minor. The changes did not affect the results.

This reviewer also found that a total of 47 patients (27 photofrin + OM and 20 OM only) had intervening therapy revised from missing.

2.3.2 Reviewer's Comments

Medical officer, Mark Avigan, stated "Use of PDT in these individuals with consequent delay of surgery may lead to dramatic improvement in histopathologic findings that is only temporary" in his protocol review dated January 4, 2001.

2.3.2.1 Disproportionate Number of Patients Discontinued from the Study

There was statistically significantly disproportionate number of patients discontinued from the study between treatment groups (41% for Photofrin vs. 70% for omeprazole, $p < 0.0001$).

2.3.2.2 Disproportionate Number of Patients Completing the 24-month Follow-UP

There was statistically significantly disproportionate number of patients completing the 24-month follow-up (59% for Photofrin vs. 38% for omeprazole, $p=0.0039$).

2.3.2.3 Disproportionate Exposure to Concomitant Medication and Adjunctive Therapy

Patients in the Photofrin PDT + OM commonly used significantly more concomitant medications in the following therapeutic class than patients in the OM only group: nervous system (99% vs. 67%); alimentary tract and metabolism (95% vs. 59%); systemic hormonal preparations excluding sex hormones and insulins (62% vs. 25%); respiratory systems (59% vs. 42%), antiinfectives for systemic use (46% vs. 35%); blood and blood-forming products (29% vs. 25%); dermatologicals (20% vs. 10%), and antineoplastic and immunomodulating agents (5% vs. 15%).

During the study, 119 (86%) patients in the Photofrin PDT + OM group and 34 (49%) patients in the OM only group used at least one adjunctive therapy.

2.3.3 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable

Medical Officer, Mark Avigan M.D., pointed out that "to be score as complete responder, the patient needs only to demonstrate complete disappearance of high-grade dysplasia in only one of the study's three monthly endoscopic biopsy assessment visits during the monitoring phase prior to any intervening therapy. Such a limited response may not clinically correlate with the long term outcome."

He also pointed out that "the sponsor had avoided a more stringent definition of "complete response" to only include ablation all histologic grades of dysplasia including low grade and indefinite dysplasia and complete replacement of all sites of Barrett' metaplasia and dysplasia with normal squamous epithelium during the entire endoscopic monitoring period. Such a response may be more directly linked to favorable clinical outcomes."

So, the sponsor's highly statistical significant results on the overall clinical response (CR3 or better) might not be clinical meaningful.

The overall clinical response by center is displayed in Attached Table 1. This reviewer performed an alternative analysis of primary efficacy variable using Mantel-Haenszel method adjusted for center. The resulting p-value was <0.0001 . No statistical significant interaction between treatment and center was observed (Breslow-Day p-value 0.5599). The result was not driven by the largest center (Center 7). If center 7 would be excluded, the statistical significance still holds.

2.3.3.1 Subgroup Analysis

This reviewer performed subgroup analyses of the overall clinical response by gender and age. The results of subgroup analyses are given below.

Subgroup Analysis			
Subgroup	Photofrin PDT + OM	OM only	Fisher's Exact p-value
Male	88/117 (75.2%)	22/59 (37.3%)	<0.0001
Female	18/21 (85.7%)	5/11 (45.4%)	0.0350
Age<65	51/61 (83.6%)	7/25 (28.0%)	<0.0001
Age≥65	55/77 (71.4%)	20/45 (44.4%)	0.0040

Compiled by this reviewer.

As seen from table above, there was a consistent trend in favor of Photofrin PDT +OM in subgroups of gender and age.

Because most patients were Caucasian (98%), subgroup analysis of the overall clinical response by race was not performed.

2.3.3.2 Reviewer's Analysis of Reviewer's Modified Primary Efficacy Variable

A patient was classified as a responder for the primary efficacy analysis if he or she met the response criteria for CR1 or CR2 or CR3 at any time.

As suggested by Medical Officer, Mark Avigan, M.D., a more stringent definition of "complete response" was considered that a patient was classified as a responder if patient met the response criteria for CR1 during the entire endoscopic monitoring period. For both treatment group, a more stringent definition of "complete response" in ITT population defined as patients whose response was CR1 at all evaluation time points is given below.

More Stringent Definition of "Complete Response" (ITT Population)

Treatment	Rate	95% C.I.	Fisher's exact p-value
Photofrin PDT + OM	11/138 (8.0%)	(4.0%, 13.8%)	0.0638
OM only	1/70 (1.4%)	(0.0%, 7.7%)	

Compiled by this reviewer.

As seen from table above, for a more stringent definition of "complete response" in ITT population, the proportion of responders was numerically higher in the Photofrin PDT + OM than in the OM only group. But, the treatment difference did not achieve statistical significance.

2.3.4 Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Variable

The Medical Officer, Mark Avigan M.D., stated that for sponsor's secondary efficacy variables including time to progression to cancer and time to treatment failure, "Because of the pre-malignant nature of high-grade dysplasia these endpoints were of relatively little importance. Therefore, the long-term survival rate which correlates with the cure rate for high-grade dysplasia is more relevant."

With printouts submitted by the sponsor, this reviewer could verify the sponsor's results for 24-month data by reproducing the sponsor's results using the sponsor's provided datasets.

There were statistically significant differences between treatment groups in terms of time to progression to cancer and time to treatment failure. However, there was no statistical difference in survival time.

2.3.5 Reviewer's Exploratory Analyses

For medical officer's presentation for Advisory Committee, this reviewer performed some exploratory analyses for progression to cancer, treatment failure, and intervening therapy using the SAS datasets provided by the sponsor.

2.3.5.1 Intervening Therapy

The tabulation of patients who received intervening therapy by treatment group is given below.

Intervening Therapy		
	Photofrin PDT + OM (n=39)	OM only (n=40)
Esophagectomy	16 (41%)	11 (28%)
Photofrin PDT	6 (15%)	24 (60%)
Other	17 (44%)	5 (13%)

Other included resection, YAG laser, chemoradiotherapy, and other ablation.

As seen from the table above, 16 patients (41%) in the Photofrin PDT + omeprazole treatment group underwent an esophagectomy. 24 patients in the omeprazole group received a Photofrin PDT treatment (60%).

2.3.5.2 Progression to Cancer by Intervening Therapy

The tabulation of patients who had progression to cancer by intervening therapy and treatment group is given below.

Progression to Cancer

	Photofrin PDT + OM (n=18)	OM only (n=20)
No intervening therapy	3 (17%)	4 (20%)
Intervening therapy	15 (83%)	16 (80%)
Esophagectomy	8 (44%)	7 (35%)
Photofrin PDT	3 (17%)	5 (25%)
Other	4 (22%)	4 (20%)

Other included resection, YAG laser, chemoradiotherapy, and other ablation.

As seen from the table above, most of patients who had progression to cancer used intervening therapy. There was no treatment difference with regard to intervening therapy for patients who had progression to cancer.

2.3.5.3 Treatment Failure by Intervening Therapy

The tabulation of patients who had treatment failure by intervening therapy by treatment group is given below.

Treatment Failure

	Photofrin PDT + OM (n=40)	OM only (n=42)
No intervening therapy	3 (8%)	4 (10%)
Intervening therapy	37 (93%)	38 (91%)
Esophagectomy	14 (35%)	11 (26%)
Photofrin PDT	6 (15%)	22 (52%)
Other	17 (43%)	5 (12%)

Other included resection, YAG laser, chemoradiotherapy, and other ablation.

As seen from table above, there were more patients in photofrin PDT + OM group underwent other intervening therapy (e.g. resection, other ablation) as compared to patients in OM only group. 14 patients (35%) in the Photofrin PDT + omeprazole treatment group underwent an esophagectomy. 6 patients (15%) in the Photofrin PDT + omeprazole treatment group underwent the 4-th course of Photofrin PDT. 22 patients in the omeprazole group underwent a Photofrin PDT treatment (52%).

2.3.5.4 Complete Response by Treatment Failure, Progression to Cancer, and Intervening Therapy.

The tabulations of responders for both treatment groups in ITT population to Photofrin PDT or omeprazole at CR1, at CR1 or CR2 and at CR1 or CR2 or CR3 at any one of the follow-up evaluations by progression to cancer, treatment failure, and intervening therapy are given below.

CR1

	Photofrin PDT + OM		OM only	
	Responder (n=72)	Non-responder (n=66)	Responder (n=5)	Non-responder (n=65)
Progression of Cancer	0 (0%)	18 (27%)	0 (0%)	20 (31%)
Treatment Failure	5 (7%)	35 (53%)	0 (0%)	42 (65%)
Intervening Therapy	5 (7%)	34 (52%)	0 (0%)	40 (62%)

CR1 or CR2

	Photofrin PDT + OM		OM only	
	Responder (n=81)	Non-responder (n=57)	Responder (n=10)	Non-responder (n=60)
Progression of Cancer	1 (1%)	17 (30%)	0 (0%)	20 (33%)
Treatment Failure	7 (8%)	33 (58%)	1 (10%)	41 (68%)
Intervening Therapy	7 (9%)	32 (56%)	1 (10%)	39 (65%)

CR1 or CR2 or CR3

	Photofrin PDT + OM		OM only	
	Responder (n=106)	Non-responder (n=32)	Responder (n=27)	Non-responder (n=43)
Progression of Cancer	6 (6%)	12 (38%)	1 (4%)	19 (44%)
Treatment Failure	17 (16%)	23 (72%)	8 (30%)	34 (79%)
Intervening Therapy	17 (16%)	22 (69%)	8 (30%)	32 (74%)

Compiled by this reviewer.

As seen from tables above, more than a third of non-responders for CR3 or better had progression to cancer and more than a half of non-responders for CR3 or better had treatment failure or underwent intervening therapy. There was no treatment difference.

3. Overall Summary and Recommendation

3.1 Summary and Conclusion

The results of the 24-month data from the PHO BAR 01 study confirmed those reported in the 6-month study report.

For the 24-month data, statistically significant percentage of patients in the Photofrin PDT + OM group demonstrated a response at level CR1 or CR2 or CR3, 77% for the ITT population, as compared to the OM only group, 39% for ITT population.

For a more stringent definition of "complete response" (a patient was considered as a responder if patient met the response criteria for CR1 during the entire endoscopic monitoring period) in ITT population, the proportion of responders was numerically higher in the Photofrin PDT + OM than in the OM only group. But, the treatment difference did not achieve statistical significance.

There were statistically significant differences between treatment groups in terms of time to progression to cancer and time to treatment failure. However, there was no statistical difference in survival time.

Furthermore, from the reviewer's exploratory analysis it revealed that most of patients who had progression to cancer used intervening therapy. More than a third of non-responders for CR3 or better had progression to cancer and more than a half of non-responders for CR3 or better had treatment failure or underwent intervening therapy.

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Attachment 1: Changes of Time to Progression to Cancer

Obs	PTNO	TMTGR	CENS_TTP	C_TTP3	TTP	TTP3
1	503	1	1	1	612	692
2	713	2	1	1	1028	1052
3	715	1	1	1	439	472
4	721	1	1	1	418	439
5	723	2	1	1	572	671
6	725	1	1	1	1018	1061
7	727	1	1	1	390	425
8	742	2	1	1	445	448
9	747	2	1	1	571	597
10	749	1	1	1	376	418
11	801	1	1	1	596	678
12	1504	1	1	1	516	537
13	1806	1	1	1	350	384
14	1810	2	1	1	645	741
15	1903	1	1	1	456	479
16	2202	1	1	1	1037	1064
17	2205	1	1	1	567	600
18	2303	1	1	1	885	916
19	2305	1	1	1	924	1021
20	2403	1	1	1	199	338
21	2502	2	1	1	665	798
22	2706	2	1	1	447	585
23	2801	2	1	1	640	745
24	3201	1	1	1	1280	1224

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Attachment 2: Changes of Time to Failure

Obs	PTNO	TMTGR	CENS_TTF	C_TTF3	C_TTF_1	C_TTF_3	TTF	TTF3	TTF_3
1	503	1	1	0	0	0	612	692	692
2	504	2	0	0	0	0	112	112	106
3	602	1	0	0	1	1	443	443	377
4	703	2	0	0	0	0	93	93	80
5	705	2	0	0	0	0	380	380	353
6	713	2	1	0	0	0	1028	1052	1052
7	715	1	1	0	0	0	439	472	472
8	718	2	0	0	0	0	670	670	644
9	721	1	1	0	0	0	418	439	439
10	723	2	1	0	0	0	572	671	668
11	725	1	1	1	0	0	1018	1018	1026
12	727	1	1	0	0	0	390	425	425
13	742	2	1	0	0	0	445	448	445
14	747	2	1	0	0	0	571	597	581
15	749	1	1	0	0	0	376	418	418
16	801	1	1	0	0	0	596	678	678
17	1101	2	0	0	0	0	1136	1136	1110
18	1203	2	0	0	0	0	195	195	185
19	1504	1	1	0	0	0	516	537	537
20	1806	1	1	1	0	0	350	350	384
21	1810	2	1	0	0	0	645	741	741
22	1903	1	1	0	0	0	456	479	479
23	2202	1	1	0	0	0	1037	1064	1064
24	2205	1	1	0	0	0	567	600	600
25	2301	2	0	0	0	0	207	207	190
26	2303	1	1	1	0	0	885	885	895
27	2304	2	0	0	0	0	532	532	459
28	2305	1	1	0	0	0	924	1021	1021
29	2403	1	1	0	0	0	199	338	338
30	2501	1	1	0	0	0	296	296	296
31	2502	2	1	0	1	1	665	798	665
32	2705	1	1	0	0	0	1126	1126	1126
33	2706	2	1	0	0	0	447	585	566
34	2801	2	1	0	0	0	640	745	745
35	3004	2	0	0	0	0	925	925	919
36	3201	1	0	1	1	1	1280	1224	1224
37	3305	2	0	0	1	1	444	444	376
38	4201	1	0	0	0	0	531	531	201
39	4203	2	0	0	0	0	200	200	112
40	7901	1	0	0	0	0	234	234	203
41	7904	1	0	0	1	1	20	20	0

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Attachment 3: Changes of Survival Time

Obs	PTNO	TMTGR	CENS_SUR	C_SURV3	SURVIV	SURVIV3
1	306	2	1	1	545	818
2	709	2	1	1	103	740
3	715	1	1	1	472	662
4	718	2	1	1	694	1129
5	721	1	1	1	439	620
6	723	2	1	1	668	1132
7	725	1	1	1	1026	1091
8	727	1	1	1	425	559
9	735	2	1	1	327	482
10	742	2	1	1	445	811
11	747	2	1	1	581	788
12	1101	2	1	1	1164	1304
13	1203	2	1	1	790	979
14	2001	1	1	1	18	581
15	2303	1	1	1	895	945
16	2602	1	1	1	41	210
17	2706	2	1	1	566	826
18	3001	1	1	1	364	648
19	3004	2	1	1	953	1014
20	3205	2	1	1	279	311
21	3206	2	1	1	651	793
22	3301	2	1	1	130	577
23	3801	2	1	1	178	417
24	4101	1	1	1	266	509
25	4203	2	1	1	515	676
26	7101	2	1	1	102	334

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Attachment 4: Changes of Intervening Therapy

Obs	PTNO	TMTGR	THERA1	THERA3	THERADT1	THERADT3
1	314	2	.	1	.	12/27/1999
2	502	2	.	3	.	10/01/1998
3	503	1	.	6	.	06/05/2000
4	505	1	.	2	.	06/05/2000
5	604	1	.	3	.	08/18/1999
6	607	2	.	3	.	07/06/1999
7	609	1	.	3	.	12/15/1999
8	709	2	.	2	.	07/09/1998
9	713	2	.	2	.	03/31/2001
10	715	1	.	4	.	09/20/1999
11	720	2	.	3	.	05/08/2000
12	721	1	.	4	.	09/29/1999
13	723	2	.	2	.	06/15/2000
14	725	1	.	2	.	07/31/2001
15	727	1	.	4	.	11/15/1999
16	739	2	.	3	.	11/14/2000
17	742	2	.	2	.	06/15/2000
18	747	2	.	2	.	03/31/2001
19	749	1	.	4	.	11/07/2000
20	801	1	.	6	.	01/02/2001
21	1102	1	.	2	.	09/25/1998
22	1504	1	.	3	.	08/01/2000
23	1806	1	.	2	.	09/27/1999
24	1807	2	.	1	.	02/20/2001
25	1810	2	.	5	.	05/08/2001
26	1903	1	.	6	.	11/09/2000
27	2002	2	.	2	.	10/25/1999
28	2202	1	.	4	.	08/14/2001
29	2205	1	.	4	.	06/11/2001
30	2303	1	.	2	.	05/07/2001
31	2305	1	.	1	.	10/25/2001
32	2403	1	.	1	.	01/06/2000
33	2409	2	.	1	.	09/10/2001
34	2501	1	.	6	.	12/03/1999
35	2502	2	.	2	.	06/04/2001
36	2705	1	.	3	.	10/10/2001
37	2706	2	.	2	.	05/08/2000
38	2707	1	.	3	.	04/11/2001
39	2801	2	.	1	.	02/08/2001
40	3201	1	6	.	11/19/2001	.
41	3205	2	.	2	.	12/15/1999
42	3206	2	.	2	.	02/05/2001
43	3304	1	.	1	.	04/02/2001
44	3306	1	.	2	.	08/15/1999
45	3801	2	.	2	.	03/29/1999
46	3803	1	.	5	.	06/01/1999
47	3807	1	.	1	.	08/09/2001

Table 1 Overall Clinical Response by Center

Overall Clinical Response (ITT Population)			
Center	Photofrin PDT + OM	OM only	Fisher's Exact p-value
3	5/9 (55.6%)	2/5 (40%)	1.0000
5	4/5 (80%)	0/2 (0.0%)	0.1429
6	8/10 (80%)	3/4 (75%)	1.0000
7	30/34 (88.2%)	7/17 (41.2%)	0.0008
8	1/1 (100%)	0/0	
11	2/3 (66.7%)	1/1 (100%)	1.0000
12	0/3 (0%)	0/1 (0%)	
15	2/2 (100%)	0/2 (0%)	0.3333
16	2/2 (100%)	0/0	
18	7/9 (77.8%)	2/4 (50%)	0.5301
19	2/3 (66.7%)	0/0	
20	0/1 (0%)	1/2 (50%)	1.0000
22	2/4 (50%)	0/2 (0%)	0.4667
23	3/4 (75%)	0/2 (0%)	0.4000
24	5/6 (83.3%)	1/3 (33.3%)	0.2262
25	1/1 (100%)	1/1 (100%)	
26	1/2 (50%)	0/1 (0%)	1.0000
27	4/5 (80%)	2/2 (100%)	1.0000
28	4/4 (100%)	1/3 (33.3%)	0.1429
29	2/2 (100%)	0/0 (0%)	
30	3/3 (100%)	1/2 (50%)	0.4000
32	4/5 (80%)	0/2 (0%)	0.1429
33	5/6 (83.3%)	1/3 (33.3%)	0.2262

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Table 1 Overall Clinical Response by Center (Continued)

Overall Clinical Response
(ITT Population)

Center	Photofrin PDT + OM	OM only	Fisher's Exact p-value
38	6/8 (75%)	3/5 (60%)	1.0000
41	1/1 (100%)	0/0	
42	1/2 (50%)	0/1 (0%)	1.0000
43	0/0	0/1 (0%)	
71	0/0	0/1 (0%)	
79	1/3 (33.3%)	0/2 (0%)	1.0000
82	0/0	1/1 (100%)	
Total	106/138 (76.8%)	27/70 (38.6%)	<0.0001
Total (Ex Center 7)	76/104 (73.1%)	20/53 (37.7%)	<0.0001

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/s/

Milton Fan
6/23/03 11:16:09 AM
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Please signoff

Thomas Permutt
6/23/03 11:46:03 AM
BIOMETRICS
concur

**STATISTICAL REVIEW AND EVALUATION — NDA
CLINICAL STUDIES**

Medical Division: Gastrointestinal and Coagulant Drug Products (HFD-180)
Biometrics Division: Division of Biometrics II (HFD-715)

STATISTICAL KEY WORD:

NDA #: 21-525

SERIAL NUMBER:

DATE RECEIVED BY CENTER: May 31, 2002

DRUG NAME: Photofrin (porfimer sodium) Injection

INDICATION: Ablation of high-grade dysplasia in Barrett's Esophagus

SPONSOR: Canreg Inc.

DOCUMENTS REVIEWED: Vol. 1, Vol. 52-95 Dated May 24, 2002

SAS data set Dated July 25, 2002

STATISTICAL REVIEWER: Milton C. Fan, Ph.D. (HFD-715)

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1. EXECUTIVE SUMMARY OF STATISTICAL FINDING

1.1 Conclusion and Recommendation

Data with minimum of 6-month might not long enough to assess the clinical impact of the treatment in all patients in high-grade dysplasia in Barrett's esophagus.

A statistically significant percentage of patients in the Photofrin PDT + OM group demonstrated a response at level CR1 or CR2 or CR3, 72% for the ITT population, as compared to the OM only group, 31% for ITT population.

However, for secondary endpoints, duration of response, time to progression to cancer, time to treatment failure, and survival time, sponsor's results based on 6-month data were inconclusive.

1.2 Overall of the Clinical Program and Studies Reviewed

Photofrin injection was approved on December 27, 1995 as part of a drug-device combination-product for use in photodynamic therapy with specified device for palliation of esophageal cancer.

In the current NDA, the sponsor seeks approval of Photofrin injection (75 mg vial) in photodynamic therapy for the ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE) among patients who are not considered to be candidates for esophagectomy. The sponsor has submitted one clinical study (protocol PHO BAR 01) with 6-month data. The sponsor recently submitted an original NDA amendment containing follow-up (24-month) data for protocol PHO BAR 01.

1.2.1 Brief Description for Study Design for Study

This study was a multicenter (30 sites), partially blinded, randomized phase III study of the efficacy and safety of photodynamic therapy (PDT) using Photofrin for injection for the ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE). This study was conducted in North America and Europe.

Patients were randomized to receive either Photofrin PDT +omeprazole or omeprazole alone in a 2-1 proportion. All patients underwent rigorous systematic quarterly endoscopic biopsy surveillance.

Patients randomized to the Photofrin PDT + OM arm received 2.0 mg/kg Photofrin as a slow intravenous injection followed two days later by intraluminal laser light (630 nm wavelength) applied to the esophageal segment with HGD. A light dose of 130 J/cm of fiber optic diffuser length was delivered using a centering balloon. Two days after the first laser light session, the esophagus was assessed for initial PDT-induced injury; an optional second light dose might be given at this time to treat under-treated ("skip") areas

only. Additional courses of PDT might be administered and had to be separated by at least three months. One course of PDT consisted of a Photofrin injection followed by up to 2 laser light sessions 2 days apart. Patients in both arms received omeprazole 20 mg BID for the duration of the study.

Efficacy was assessed by rigorous systematic endoscopic biopsy surveillance every 3 months including mapping of Barrett's mucosa and 4-quadrant jumbo biopsies for every 2 cm of the length of BE. All patients were followed quarterly until treatment failure or until 4 consecutive quarterly follow-up biopsies were negative for HGD and then bi-annually until the last enrolled patient had completed a minimum of 24 months of follow-up after randomization. All histological assessments were carried out at a central reference laboratory. Other assessments included a baseline CT scan of the thorax and esophageal ultrasound (EUS), which might be repeated at any time for accurate staging if a biopsy was found to be positive or suspicious for cancer. The pathologists examining the biopsies were blinded to the treatment administered.

The primary analyses were performed after a minimum follow-up of 6 months from the date of randomization of the last patient (expected median follow-up of 12 months). All patients on study were followed for a minimum of 24 months after randomization of the last patient.

Complete response rate was determined using the following definitions:

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

Complete Response 2 (CR2) - ablation of all histological grades of dysplasia, including patients with indefinite grade of dysplasia, but some areas of Barrett's metaplastic epithelium still remain.

Complete Response 3 (CR3) - ablation of all areas of HGD but some areas of LGD with or without areas which are indefinite for dysplasia, or areas of Barrett's metaplastic epithelium.

The primary endpoint was the rate of patients who achieved complete ablation of HGD, i.e., a CR3 or better (CR3+CR2+CR1).

1.3 Principal Finding

A statistically significant percentage of patients in the Photofrin PDT + OM group demonstrated a response at level CR1 or CR2 or CR3, 72% for the ITT population, as compared to the OM only group, 31% for ITT population.

As suggested by Medical Officer, Edvardas Kaminskas, a more stringent definition of "complete response" was considered that a patient was classified as a responder if patient met the response criteria for CR1 during the entire endoscopic monitoring period.

Even for a more stringent definition of “complete response” in ITT population, the proportion of responders was statistically significantly higher in the Photofrin PDT + OM than in the OM only group (10% vs. 1%).

However, for secondary endpoints, duration of response, time to progression to cancer, time to treatment failure, and survival time, sponsor’s results based on 6-month data were inconclusive.

Furthermore, contrary to sponsor’s findings, this reviewer found that there were no statistically significant difference for time to progression to cancer and time to treatment failure (logrank test p-value=0.8201 and 0.2703, respectively).

2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1. Background

Photofrin injection was approved on December 27, 1995 as part of a drug-device combination-product for use in photodynamic therapy with specified device for palliation of esophageal cancer.

In the current NDA, the sponsor seeks approval of Photofrin injection (75 mg vial) in photodynamic therapy for the ablation of high-grade dysplasia (HGD) in Barrett’s esophagus (BE) among patients who are not considered to be candidates for esophagectomy. The sponsor has submitted one clinical study (protocol PHO BAR 01) with 6-month data. The sponsor recently submitted an original NDA amendment containing follow-up (24-month) data for protocol PHO BAR 01.

The sponsor has also submitted two phase II studies (TCSC 93-07 and TCSC 96-01).

Study TCSC 93-07 was a single center, investigator-sponsored, uncontrolled phase II study. Study TCSC 96-01 was a single center, investigator-sponsored, partially blinded, randomized, phase II parallel-group study.

Studies TCSC 93-07 and TCSC 96-01, phase II study, will not be evaluated in this review because both studies were uncontrolled.

The NDA amendment will not be assessed in this review because of later submission. This review will address on 6-month data provided in the original NDA submission.

2.2. Protocol PHO BAR 01

2.2.1 Study Design

This study was a multicenter (30 sites), partially blinded, randomized phase III study of the efficacy and safety of photodynamic therapy (PDT) using Photofrin for injection for

the ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE). This study was conducted in North America and Europe.

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.

Patients were randomized to receive either Photofrin PDT +omeprazole or omeprazole alone in a 2-1 proportion. All patients underwent rigorous systematic quarterly endoscopic biopsy surveillance.

Patients randomized to the Photofrin PDT + OM arm received 2.0 mg/kg Photofrin as a slow intravenous injection followed two days later by intraluminal laser light (630 nm wavelength) applied to the esophageal segment with HGD. A light dose of 130 J/cm of fiber optic diffuser length was delivered using a centering balloon. Two days after the first laser light session, the esophagus was assessed for initial PDT-induced injury; an optional second light dose might be given at this time to treat under-treated ("skip") areas only. Additional courses of PDT might be administered and had to be separated by at least three months. One course of PDT consisted of a Photofrin injection followed by up to 2 laser light sessions 2 days apart. Patients in both arms received omeprazole 20 mg BID for the duration of the study.

Efficacy was assessed by rigorous systematic endoscopic biopsy surveillance every 3 months including mapping of Barrett's mucosa and 4-quadrant jumbo biopsies for every 2 cm of the length of BE. All patients were followed quarterly until treatment failure or until 4 consecutive quarterly follow-up biopsies were negative for HGD and then bi-annually until the last enrolled patient had completed a minimum of 24 months of follow-up after randomization. All histological assessments were carried out at a central reference laboratory. Other assessments included a baseline CT scan of the thorax and esophageal ultrasound (EUS), which might be repeated at any time for accurate staging if a biopsy was found to be positive or suspicious for cancer. The pathologists examining the biopsies were blinded to the treatment administered.

The Data and Safety Monitoring Committee (DSMC) was formed to review summaries of data (demography, efficacy, and safety). In addition, the committee was mandated to recommend change to the conduct of trial for safety reasons and to review the primary and final statistical analysis.

The primary analyses were performed after a minimum follow-up of 6 months from the date of randomization of the last patient (expected median follow-up of 12 months). All patients on study were followed for a minimum of 24 months after randomization of the last patient.

Complete response rate was determined using the following definitions:

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

Complete Response 2 (CR2) - ablation of all histological grades of dysplasia, including patients with indefinite grade of dysplasia, but some areas of Barrett's metaplastic epithelium still remain.

Complete Response 3 (CR3) - ablation of all areas of HGD but some areas of LGD with or without areas which are indefinite for dysplasia, or areas of Barrett's metaplastic epithelium.

The primary endpoint was the rate of patients who achieved complete ablation of HGD, i.e., a CR3 or better (CR3+CR2+CR1).

The complete response rate for patients with CR3 or better was compared between the treatment groups using Fisher's exact test as the primary analysis.

The secondary efficacy endpoints were quality of complete response, duration of complete response, time to progression to cancer, time to treatment failure, and survival.

Quality of complete response was characterized by the rate of patients who achieved a response level of CR2 or better (CR2+CR1), or who achieve a CR1.

Duration of complete response was analyzed separately for patients who achieved a CR3 or better, CR2 or better, or CR1 only. The durations were defined as the time from the first documented response at the appropriate level until the time of first documented recurrence or progression to cancer in responding patients.

Time to progression to cancer was defined as the time from the date of randomization until the first documented evidence of cancer.

Time to treatment failure was defined as the time from the date of randomization until the first documented evidence of any of the following: progression to cancer, esophagectomy, or the start of any intervening therapy for HGD other than the randomized study treatment.

Survival was defined as the duration from the date of randomization until death or until the last date on which the patient is known to be alive.

These complete response rates were compared between treatment groups using Fisher's exact test, as for the primary endpoint.

For all time to event parameters, Kaplan-Meier plots were presented. Estimates of median time to event and 95% CI was calculated using the Kaplan-Meier techniques. The difference between the treatment arms was analyzed using the log rank test.

The sample size was based on power consideration involving the primary efficacy parameter (complete response defined as the complete ablation of HGD at any endoscopic assessment timepoint), as well as the secondary efficacy outcome time to progression (TTP). A minimum response rate of 60% is expected in patients receiving Photofrin PDT. It was assumed that true proportion of responders is 60% in Photofrin PDT treatment group and 27% in the omeprazole group, a total of 117 patients (78 in PDT arm and 39 patients in the control arm) would provide 90% power to detect a significant difference using a two-sided test comparing proportions at a significance level of 5%.

The sample size was also selected to provide sufficient power to detect treatment group difference in time to progression (TTP). A total of 191 patients would provide at least 80% power to detect an improvement in TTP of 24 months in a two-sided test at the 5% significance level, assuming a median time to progression of 24 months on the control arm, an enrollment period of 15 months and a minimum follow-up period of 24 months.

2.2.2 Sponsor's Analysis

Of the 485 patients screened for inclusion, a total of 208 patients were enrolled in the study. 138 patients were randomized to received Photofrin PDT + omeprazole and 70 patients were randomized to receive omeprazole only. Of these, 132 patients received Photofrin PDT + omeprazole and 69 patients received omeprazole only.

There were 124 patients in Photoferin PDT + omeprazole group and 55 patients in omeprazole group completing the 6-monthly follow-up. There were 36 patients in Photoferin PDT + omeprazole group and 29 in omeprazole group discontinued from the study.

2.2.2.1 Treatment Group Comparability

The summary of results of comparability of treatment groups at baseline for Intent-to-Treat population is given in Attached Table 1.

As seen from Attached Table 1, there was no statistically significant difference in demographics between the two treatment groups.

There was no statistically significant difference between two treatment groups for history of BE, median duration of BE, duration of HGD \leq 6 months, and median duration of HGD.

2.2.2.2 Sponsor's Analysis of Primary Efficacy Variable

The primary analysis consisted of the analysis of the complete response based on data collected up to a minimum of six months of follow-up after the last patient was enrolled in the study.

Complete response was the primary efficacy endpoint. Complete response rate was determined using the following definitions:

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

Complete Response 2 (CR2) - ablation of all histological grades of dysplasia, including patients with indefinite grade of dysplasia, but some areas of Barrett's metaplastic epithelium still remain.

Complete Response 3 (CR3) - ablation of all areas of HGD but some areas of LGD with or without areas which are indefinite for dysplasia, or areas of Barrett's metaplastic epithelium.

A patient was classified as a responder for the primary efficacy analysis if he or she met the response criteria for CR1 or CR2 or CR3 at any time.

The overall clinical response for both treatment groups in ITT and Evaluable populations whose response was at CR1 or CR2 or CR3 at any one of the evaluation time points is given below.

**Overall Clinical Response
(ITT Population)**

Treatment	Rate	95% C.I.	p-value
Photofrin PDT + OM	99/138 (72%)	(64.2%, 79%)	<0.0001
OM only	22/70 (31%)	(20.6%, 42%)	

Copied from Panel 11.6, page 98, Vol. 57.

**Overall Clinical Response
(Evaluable Population)**

Treatment	Rate	95% C.I.	p-value
Photofrin PDT + OM	99/130 (76%)	(68.8%, 83.5%)	<0.0001
OM only	22/69 (32%)	(20.9%, 42.9%)	

Copied from Panel 11.6, page 98, Vol. 57.

As seen from table above, in both ITT and Evaluable populations, the proportion of responders was statistically significantly higher in the Photofrin PDT + OM than in the OM only group.

2.2.2.3 Sponsor's Analysis of Secondary Efficacy Variables

2.2.2.3.1 Quality of Complete Response

The results of the analysis of responders for both treatment groups in ITT population to Photofrin PDT or omeprazole at CR1 and at CR1 or CR2 at any one of the follow-up evaluations are given below.

Quality of Response (ITT Population)

Responders	Photofrin PDT + OM		OM only		p-value
	Rate	95% C.I.	Rate	95% C.I.	
CR1	57/138 (41%)	(33.1%, 49.5%)	3/70 (4%)	(0%, 9.0%)	<0.0001
CR1 or CR2	67/138 (49%)	(40.2%, 56.9%)	4/70 (5%)	(0.3%, 11.3%)	<0.0001

Copied from Panel 11.7, page 99, Vol. 57.

As seen from table above, the quality of response in the Photofrin PDT + OM group was statistically significantly better than that in the OM only group in ITT population.

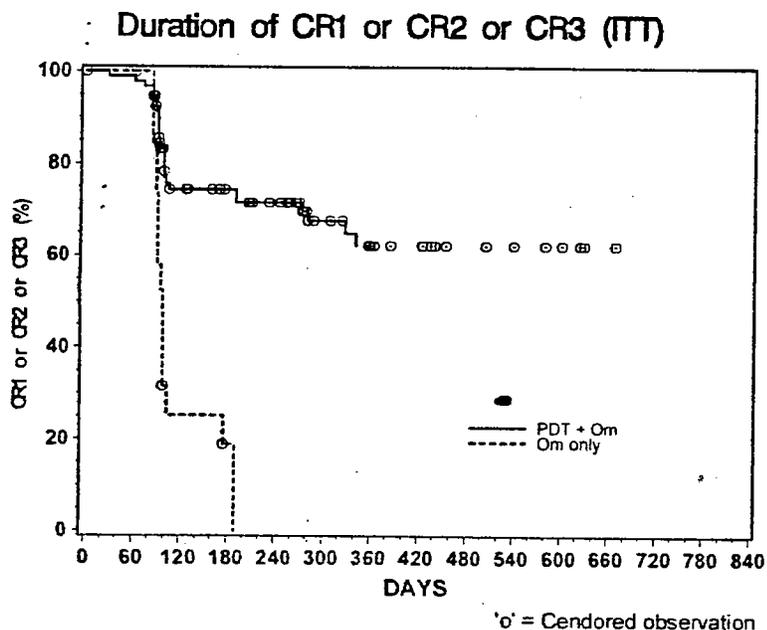
2.2.2.3.2 Duration of Response

The duration of response to the Photofrin PDT + OM or the OM only in the ITT population was analyzed separately at each response level (CR1, CR1 or CR2, and CR1 or CR2 or CR3. Duration of response was censored for patients with no data indicating an end to response as follows:

For patients who received no intervening therapy, censor occurred at the date the patient was last known to be participating in the study; or

For patients who received intervening therapy, censoring occurred on the day that the intervening therapy (esophagectomy or alternative method of endoscopic ablation) began.

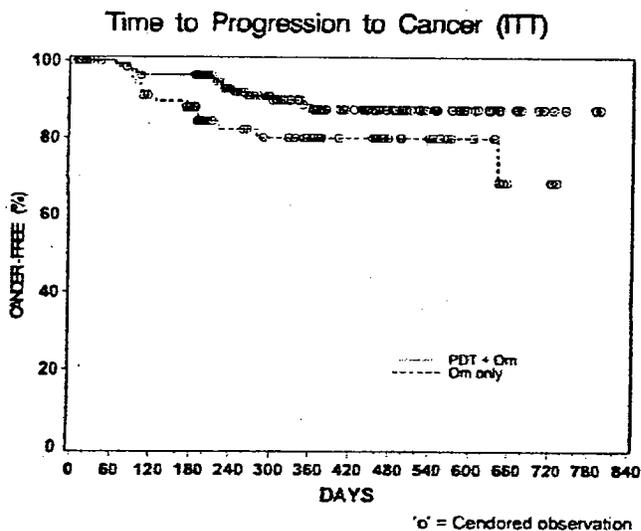
The Kaplan-Meier method was used to present the distribution of duration of response. The probability of maintaining a CR3 or better response over time by treatment in the ITT population is displayed below.



2.2.2.3.3 Time to Progression to Cancer (TTP)

The TTP was defined as the period in days from the date of randomization until the date the progression to cancer was first documented.

The probability that a patient was cancer-free over time by treatment group in the ITT population is displayed below.

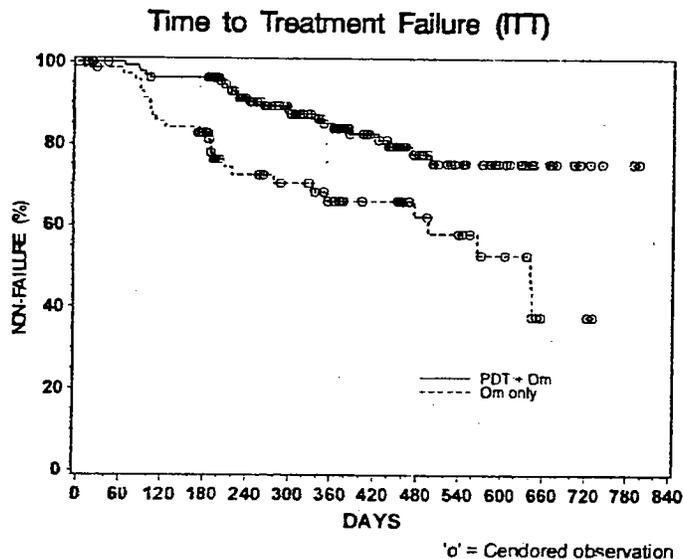


Comparison between the two treatment groups using the log rank test showed a statistically marginally significant delay in the progression to cancer in the Photofrin PDT + OM group as compared to the OM only group in the ITT population ($p=0.0453$).

2.2.2.3.4 Time to Treatment Failure (TTF)

The TTF was defined as the period in days from the date of randomization until the date of the first documentation of progression of HGD to cancer or the start of any intervening therapy for HGD other than the randomized study treatment.

The probability of treatment success over time by treatment group in the ITT population is displayed below.



Comparison between the two treatment groups using the log rank test showed that the need for esophagectomy or other intervening therapy was significantly postponed the Photofrin PDT + OM group as compared to the OM only group in the ITT ($p=0.0005$).

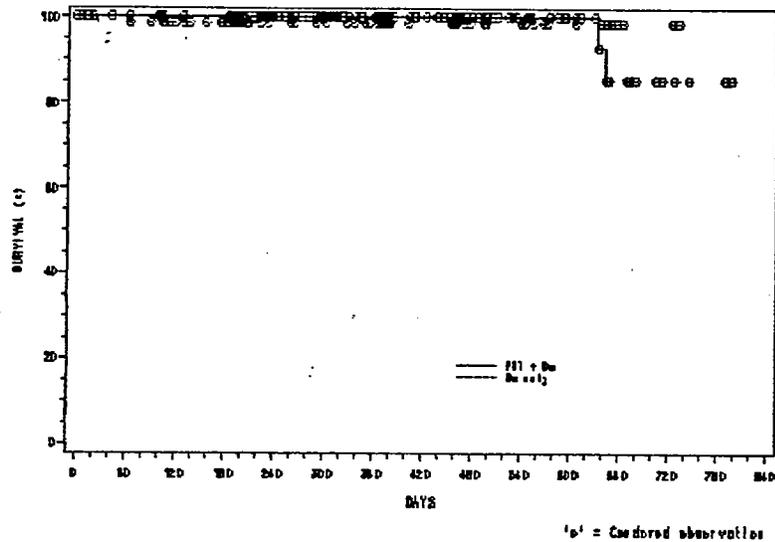
2.2.2.3.5 Survival Time

Survival time was defined as the period in days from the date of randomization to the date of the patient's death.

The comparison between the two treatment groups showed no statistical difference between two treatment groups ($p=0.9293$).

The probability of survival over time by treatment group in the ITT population is displayed below.

SURVIVAL TIME



2.2.3 Safety

The Photofrin PDT + OM group had a much higher incidence of SAE (30%) than the OM only group (17%). Two patients in the Photofrin PDT + OM group and one patient in the OM only group experienced treatment emergent AE that led to death.

In the Photofrin PDT + OM group, 130 (98%) patients experienced treatment emergent AEs, 40 (30%) patients experienced serious adverse events. The most commonly reported treatment emergent AEs were photosensitivity reaction (67%), esophageal strictures (36%), vomiting (35%), chest pain (27%), constipation (26%), and fever (23%).

In the OM only group, 47 (68%) patients experienced treatment emergent AEs, 12 (17%) patients experienced SAEs. The most commonly reported treatment emergent AEs were nausea (9%), chest pain (7%), coughing (7%), and headache (7%).

73% of the events reported as being severe in the Photofrin PDT + OM group were considered to be associated with treatment as compared to none in the OM only group.

2.2.4 Reviewer's Evaluation

2.2.4.1 Reviewer's Comments

Medical officer, Mark Avigan, stated "Use of PDT in these individuals with consequent delay of surgery may lead to dramatic improvement in histopathologic findings that is only temporary" in his protocol review dated January 4, 2001.

2.2.4.1.1 Disproportionate Number of Patients Discontinued from the Study

There was statistically significantly disproportionate number of patients discontinued from the study between treatment groups (26% for Photofrin vs. 41% for omeprazole, $p=0.0241$).

2.2.4.1.2 Disproportionate Number of Patients Completing the 6-month Follow-UP

There was statistically significantly disproportionate number of patients completing the 6-month follow-up (94% for Photofrin vs. 80% for omeprazole, $p=0.0022$).

2.2.4.1.3 Disproportionate Exposure to Concomitant Medication and Adjunctive Therapy

Patients in the Photofrin PDT + OM used more of the following concomitant medications than patients in the OM only group: opioid analgesics (90% vs. 23%); non-opioid analgesics (83% vs. 32%); phenothiazines (62% vs. 4%); antacids (56% vs. 9%), local anesthetics (55% vs. 1%); glucocorticoids (39% vs. 10%); benzodiazepines (28% vs. 14%), gastrointestinal agents (26% vs. 1%); ethanolamines (20% vs. 4%); glucagon (20% vs. 1%); cytoprotective agents (14% vs. 7%); and stimulant laxatives (11% vs. 3%).

During the study, 101 (76%) patients in the Photofrin PDT + OM group and 25 (36%) patients in the OM only group used at least one adjunctive therapy.

2.2.4.2 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable

Medical Officer, Mark Avigan, pointed out that "to be scored as complete responder, the patient needs only to demonstrate complete disappearance of high-grade dysplasia in only one of the study's three monthly endoscopic biopsy assessment visits during the monitoring phase prior to any intervening therapy. Such a limited response may not clinically correlate with the long term outcome."

He also pointed out that "the sponsor had avoided a more stringent definition of "complete response" to only include ablation all histologic grades of dysplasia including low grade and indefinite dysplasia and complete replacement of all sites of Barrett's metaplasia and dysplasia with normal squamous cell epithelium during the entire endoscopic monitoring period. Such a response may be more directly linked to favorable clinical outcomes."

Data with minimum of 6-month and median of 11.9 month might not be long enough to assess the clinical impact of the treatment in all patients in high-grade dysplasia in Barrent's esophagus.

So, the sponsor's highly statistically significant results on the overall clinical response (CR3 or better) might not be clinical meaningful.

The overall clinical response by center is displayed in Attached Table 2. This reviewer performed an alternative analysis of primary efficacy variable using Mantel-Haenszel method adjusted for center. The resulting p-value was less than 0.0001. No statistically significant interaction between treatment and center was observed (Breslow-Day p-value 0.5159). The result was not driven by the largest center (Center 7). If center 7 would be excluded, the statistical significance still holds.

2.2.4.2.1 Subgroup Analysis

This reviewer performed subgroup analyses of the overall clinical response by gender and age. The results of subgroup analyses are given below.

Subgroup Analysis

Subgroup	Photofrin PDT + OM	OM only	Fisher's Exact p-value
Male	82/117 (70%)	18/59 (30%)	<0.0001
Female	17/21 (81%)	4/11 (36%)	0.0198
Age<65	51/61 (84%)	6/25 (24%)	<0.0001
Age≥65	48/77 (62%)	16/45 (36%)	0.0051

Compiled by this reviewer.

As seen from table above, there was a consistent trend in favor of the Photofrin PDT +OM in subgroups of gender and age.

2.2.4.2.2 Reviewer's Analysis of Reviewer's Modified Primary Efficacy Variable

In the sponsor's analysis of primary efficacy variable, a patient was classified as a responder for the primary efficacy analysis if he or she met the complete response criteria for CR1 or CR2 or CR3 at any time.

As suggested by Medical Officer, Edvardas Kaminskas, a more stringent definition of "complete response" was considered that a patient was classified as a responder if patient met the complete response criteria for CR1 during the entire endoscopic monitoring period.

For both treatment group, a more stringent definition of "complete response" in ITT population defined as patients whose response was CR1 at all evaluation time points is given below.

**More Stringent Definition of “Complete Response”
(ITT Population)**

Treatment	Rate	95% C.I.	Fisher’s exact p-value
Photofrin PDT + OM	14/138 (10.1%)	(5.66%, 16.44 %)	0.0224
OM only	1/70 (1.4%)	(0.04%, 7.70%)	

Compiled by this reviewer.

As seen from table above, even for a more stringent definition of “complete response” in ITT population, the proportion of responders was statistically significantly higher in the Photofrin PDT + OM than in the OM only group.

2.2.4.3 Reviewer’s Comments on Sponsor’s Analysis of Secondary Efficacy Variable

The Medical Officer, Mark Avigan, stated that for sponsor’s secondary efficacy variables including time to progression to cancer and time to treatment failure, “Because of the pre-malignant nature of high-grade dysplasia these endpoints were of relatively little importance. Therefore, the long-term survival rate which correlates with the curve rate for high-grade dysplasia is more relevant.”

According to the protocol, all patients on study were followed for a minimum of 24 months after randomization of the last patient. But, this reviewer found that there were only 27 patients (13%) (22 in Photofrin PDT + OM and 5 in OM) who had study duration more than or equal to 24 months.

Based on 6-month efficacy data, the sponsor’s results on secondary endpoints were inconclusive.

Furthermore, the plots provided by the sponsor for duration of response, time to progression to cancer, time to treatment failure, and survival time are misleading. The vertical axis (Y-axis) should be survival distribution function obtained from the Kaplan-Meier method.

This reviewer failed to reproduce the sponsor’s results using the sponsor’s provided dataset. With limited printouts submitted and no information about the statistical software used, this reviewer could not verify the sponsor’s results. This reviewer performed an alternative analyses of secondary efficacy variables using PROC LIFETEST in SAS version 8.2. Contrary to sponsor’s findings, there were no statistically significant difference between treatment groups for time to progression to cancer and time to treatment failure (logrank test p-value=0.8201 and 0.2703, respectively).

3. Overall Summary and Recommendation

3.1 Summary and Conclusion

Data with minimum of 6-month might not long enough to assess the clinical impact of the treatment in all patients in high-grade dysplasia in Barrett's esophagus.

A statistically significant percentage of patients in the Photofrin PDT + OM group demonstrated a response at level CR1 or CR2 or CR3, 72% for the ITT population, as compared to the OM only group, 31% for ITT population.

However, for secondary endpoints, duration of response, time to progression to cancer, time to treatment failure, and survival time, sponsor's results based on 6-month data were inconclusive.

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Table 1 Summary of Demographic and Baseline Characteristics ---
Protocol PHO BAR 01

Characteristics	(ITT Population)		Between Treatment p-value
	Photofrin + OM (n=138)	OM only (n=70)	
Sex			1.000
Male	117 (85%)	59 (84%)	
Female	21 (15%)	11 (16%)	
Race			0.4117
Caucasian	137 (99%)	68 (97%)	
Black		1 (1%)	
Asian	1 (1%)	1 (1%)	
Other			
Age (yr)			0.3467
Mean (SD)	66.13 (10.68)	67.27 (11.0%)	
Height (cm)			0.6980
Mean (SD)	172.61 (9.61)	173.13 (9.50)	
Smoking history			0.1384
Current user	8 (6%)	8 (11%)	
Former user	85 (62%)	47 (67%)	
Never user	44 (32%)	15 (21%)	
History of BE	(63%)	(59%)	0.6498
Duration of BE (mo)			0.8676
Mean (SD)	36.34 (40.82)	35.07 (38.24)	
Duration of HGD (mo)			0.9280
Mean (SD)	6.08 (7.14)	6.51 (10.09)	
Endoscopic length of BE			0.5605
≤6 cm	63 (46%)	35 (50%)	
>6 cm	75 (54%)	35 (50%)	
Histological length of BE			0.4603
≤6 cm	74 (54%)	42 (60%)	
>6 cm	64 (46%)	28 (40%)	
Extent of HGD			0.7639
Single level	50 (36%)	27 (39%)	
Multiple levels	87 (63%)	43 (61%)	

Copied from Panels 11.4 and 11.5, pages 92 and 93, vol. 57

p-value generated using Wilcoxon rank sum test for continuous variables and Fisher's Exact test for categorical variables.

Table 1 Summary of Demographic and Baseline Characteristics ---
 Protocol PHO BAR 01 (Continued)

Characteristics	(ITT Population)		Between Treatment p-value
	Photofrin + OM (n=138)	OM only (n=70)	
Prior therapy for BE	(97%)	(94%)	
Endoscopic condition			
Hiatal hernia	125(91%)	58 (83%)	0.1179
Nodules	45 (33%)	19 (27%)	0.5250
Ulcers	8 (6%)	3 (4%)	0.7539
Strictures	6 (4%)	2 (3%)	0.7202
Prior treatment			
Surgery	6 (4%)	8 (11%)	0.0767
Medical therapy	134 (97%)	66 (94%)	0.4465
Other	6 (4%)	2 (3%)	0.7202

Copied from Panels 11.4 and 11.5, pages 92 and 93, vol. 57

p-value generated using Wilcoxon rank sum test for continuous variables and Fisher's Exact test for categorical variables.

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Table 2 Overall Clinical Response by Center

Overall Clinical Response (ITT Population)			
Center	Photofrin PDT + OM	OM only	Fisher's Exact p-value
3	5/9 (55.6%)	2/5 (40%)	1.0000
5	4/5 (80%)	0/2 (0.0%)	0.1429
6	8/10 (80%)	1/4 (25%)	0.0949
7	28/34 (82.4%)	7/17 (41.2%)	0.0045
8	1/1 (100%)	0/0	
11	2/3 (66.7%)	1/1 (100%)	1.0000
12	0/3 (0%)	0/1 (0%)	
15	2/2 (100%)	0/2 (0%)	0.3333
16	2/2 (100%)	0/0	
18	7/9 (77.8%)	1/4 (25%)	0.2168
19	2/3 (66.7%)	0/0	
20	0/1 (0%)	1/2 (50%)	1.0000
22	2/4 (50%)	0/2 (0%)	0.4667
23	3/4 (75%)	0/2 (0%)	0.4000
24	5/6 (83.3%)	1/3 (33.3%)	0.2262
25	1/1 (100%)	1/1 (100%)	
26	0/2 (0%)	0/1 (0%)	
27	3/5 (60%)	2/2 (100%)	1.0000
28	4/4 (100%)	1/3 (33.3%)	0.1429
29	2/2 (100%)	0/0 (0%)	
30	3/3 (100%)	1/2 (50%)	0.4000
32	4/5 (80%)	0/2 (0%)	0.1429
33	4/6 (66.7%)	1/3 (33.3%)	0.5238

Compiled by this reviewer.

Table 2 Overall Clinical Response by Center (Continued)

Overall Clinical Response (ITT Population)			
Center	Photofrin PDT + OM	OM only	Fisher's Exact p-value
38	4/8 (50%)	1/5 (20%)	0.5649
41	1/1 (100%)	0/0	
42	1/2 (50%)	0/1 (0%)	1.0000
43	0/0	0/1 (0%)	
71	0/0	0/1 (0%)	
79	1/3 (33.3%)	0/2 (0%)	1.0000
82	0/0	1/1 (100%)	
Total	99/138 (71.7%)	22/70 (31.4%)	<0.0001
Total (Ex Center 7)	71/104 (68.3%)	15/53 (28.3%)	<0.0001

Compiled by this reviewer.

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/s/

Milton Fan
10/30/02 10:53:58 AM
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Please sign it off.

Thomas Permutt
11/1/02 10:27:24 AM
BIOMETRICS
concur