PHOTOFRIN® PDT + OM
Fewer Patients Progressed to Cancer

Time to progression to cancer was significantly longer for PHOTOFRIN® PDT + OM patients (P=0.0014).

- At 2 years, patients receiving PHOTOFRIN® PDT + OM had an 83% (N=138) chance of being cancer-free vs 53% (N=70) chance among the OM-only group.

[Graph showing percentage of patients who progressed to cancer—end of minimum 3-year follow-up]

- Risk reduction beyond 2 years has not been demonstrated.

STUDY DESIGN:
A multicenter, partially blinded, randomized Phase III study to assess the efficacy and safety of PDT using PHOTOFRIN® for the ablation of HGD in patients with BE randomized to receive either PHOTOFRIN® administered (2 mg/kg) as a slow IV injection over 3-5 minutes or OM only. Patients were monitored for 3 years. The long-term effect of PDT on HGD in BE is unknown.

PHOTOFRIN® is indicated for the ablation of HGD in Barrett's esophagus patients who do not undergo esophagectomy.

PHOTOFRIN® is contraindicated in patients with porphyria or in patients with known allergies to porphyrins. PDT is contraindicated in patients with tumors eroding into a major blood vessel. PDT is contraindicated in patients with an existing esophageal stricture.

Esophageal strictures as a result of PDT in HGD in BE are a common adverse event. Esophageal strictures may be required. Special care should be taken during dilations to avoid perforation of the esophagus.

There is always a risk of leaving cancerous cells behind or leaving residual abnormal epithelium beneath the new squamous cell epithelium; these facts emphasize the risk of overlooking cancer in such patients and the need for continued monitoring as recommended by physician.

Secondary efficacy endpoints:
- CR: Complete replacement of all Barrett’s metaplasia and dysplasia with normal squamous cell epithelium
- CR2: Ablation of all histological grades of dysplasia, including indefinite-grade dysplasia, but with some areas of Barrett’s epithilium still remaining
- CR3: Ablation of all areas of HGD but with some areas of low-grade dysplasia or without areas which are indefinite for dysplasia, or areas of Barrett’s metaplastic epithilium

Duration of complete response:
- Time to progression to cancer
- Time to treatment failure

Results reported are for the intent-to-treat (ITT) population.
Complete Ablation of HGD in BE with PHOTOFRIN®

Results

- Approximately 3 out of 4 patients (77%, n=106) experienced complete ablation of HGD with PHOTOFRIN® PDT + OM (CR3)

![Graph showing complete ablation of HGD with PHOTOFRIN®](image)

- Complete ablation of HGD at any assessment point.

PHOTOFRIN® is indicated for the ablation of HGD in Barrett's esophagus patients who do not undergo esophagectomy.

PHOTOFRIN® is contraindicated in patients with porphyria or in patients with known allergies to porphyrins. PDT is contraindicated in patients with tumors eroding into a major blood vessel. PDT is contraindicated in patients with an existing tracheoesophageal or bronchoesophageal fistula. PDT is not suitable for patients with esophageal varices, or patients with esophageal ulcers >1 cm in diameter.

The long-term effect of PDT on HGD in BE is unknown. The follow-up of the pivotal study at the time of analysis was a minimum of 2 years (ranging from 2 to 3.6 years).

Esophageal strictures as a result of PDT in HGD in BE are a common adverse event. Multiple dilations of esophageal strictures may be required. Special care should be taken during dilations to avoid perforation of the esophagus.

There is always a risk of leaving cancerous cells behind or leaving normal abnormal epithelium beneath the new squamous cell epithelium. These facts emphasize the risk of esophageal cancer in such patients and the need for rigorous continuing surveillance despite the histologic appearance of complete squamous reepithelialization.

Please see accompanying full Prescribing Information.
Fewer Patients Progressed to Cancer

Proportion of patients

- At 2 years, patients receiving PHOTOFRIN® PDT + OM had an 83% (N=138) chance of being cancer-free vs 53% (N=70) chance among the OM-only group.

Time to progression to cancer was significantly longer for PHOTOFRIN® PDT + OM patients (\(p<0.0001\)) compared to the OM-only group.

PHOTOFRIN® is indicated for the ablation of HGD in Barrett’s esophagus patients who do not undergo esophagectomy.

Patients with endobronchial lesions must be closely monitored between the laser light therapy and the commencing radiotherapy. If PDT is to be given after radiotherapy, it is recommended that 4 weeks be allowed before the start of radiotherapy.

PHOTOFRIN® administered (2 mg/kg) as a slow IV injection over 3-5 minutes.

PHOTOFRIN® is manufactured by Wyeth-Ayerst Lederle, Inc. for Axcan Pharma (Ireland) Ltd. and distributed by Axcan Scandipharm Inc.

AXCAN SCANDIPHARM INC.
Birmingham, Alabama 35242
www.photofrin.com
Fax (205) 991-8426

Photodynamic therapy is not suitable for emergency treatment of patients with severe acute respiratory distress caused by an obstructing endobronchial lesion because 40 to 50 hours are required between injection with PHOTOFRIN® and laser light treatment.

Photodynamic therapy (PDT) for the ablation of high-grade dysplasia (HGD) in Barrett’s esophagus (BE) is a minimally invasive and office-based treatment option.

Barrett’s Esophagus HGD

PHOTOFRIN® PDT Administration

Day 1
ADMINISTERED IN OFFICE
PHOTOFRIN® administered (2 mg/kg) as a slow IV injection over 3-5 minutes.

Day 3
PDT TREATED ENDOSCOPY PERFORMS PROCEDURE
Placement of nodule. Short fiber optic diffuser (2.25 cm) with a light dose of 50 J/cm delivered without a centering balloon. Treatment: Activation with red laser light—a light dose of 130 J/cm² delivered using a centering balloon (2.25 cm²).

Day 5
FOLLOW-UP ENDOSCOPY
Optional second red laser light application. A 4.5 cm fiber optic diffuser length at a reduced light dose of 50 J/cm delivered without a centering balloon.

FOLLOW-UP VISITS
Continued monitoring as recommended by physician.

- Each course consists of one injection of PHOTOFRIN® followed by up to 2 red laser light applications—first, 40 to 50 hours after injection; the second, if needed, 96 to 120 hours after injection.
- Up to 3 courses of PDT with PHOTOFRIN® can be given, each separated by a minimum of 90 days.

Please consult full prescribing information for complete dosage and administration instructions.

PDT therapy should be used in conjunction with follow-up endoscopy with biopsies every 1-2 years and 3 years if laser light therapy is used but no positive response is observed. If endobronchial lesions are resected, biopsies should be performed at 1 year after resection.

Women of childbearing potential should practice an effective method of contraception during therapy.

Contraindications to PDT:
- PDT therapy is contraindicated in patients with multiple systemic diseases causing an obstructing endobronchial lesion because 40 to 50 hours are required between injection with PHOTOFRIN® and laser light treatment.
- PDT therapy is contraindicated in patients with severe acute respiratory distress caused by an obstructing endobronchial lesion because 40 to 50 hours are required between injection with PHOTOFRIN® and laser light treatment.
- PDT therapy is contraindicated in patients with tumors eroding into a major blood vessel. PDT is contraindicated in patients with an existing tracheoesophageal or bronchoesophageal fistula. PDT is not suitable for patients with esophageal or gastric varices, or with areas which are indefinite for dysplasia, or areas of Barrett’s malpighian epithelium.

Duration of complete response:
- Time to progression to cancer
- Time to treatment failure

Results reported were for the intent-to-treat (ITT) population.

Comparators
• PHOTOFRIN® PDT plus omeprazole (OM) 20 mg bid (N=138) vs OM 20 mg bid only (N=70)

Primary efficacy endpoint:
- Complete ablation of HGD at any assessment point (CR3) or better

Secondary efficacy endpoints:
- Quality of complete response:
  • CR1: Complete ablation of all Barrett’s metaplasia and dysplasia with normal squamous cell epithelium
  • CR2: Ablation of all histological grades of dysplasia, including indefinite-grade dysplasia, but with some areas of Barrett’s epithilum still remaining
  • CR3: Ablation of all areas of HGD but with some areas of low-grade dysplasia with or without areas which are indefinite for dysplasia, or areas of Barrett’s malpighian epithelium
- Duration of complete response
- Time to progression to cancer
- Time to treatment failure

Photodynamic therapy (PDT) for the ablation of high-grade dysplasia (HGD) in Barrett’s esophagus (BE) patients who do not undergo esophagectomy.

The Pivotal Study

Design
- Multicenter, partially blinded, randomized Phase III study

Duration of follow-up
- Minimum 2 years
- Maximum 3.6 years
- Risk beyond 2 years has not been established

Patient population
- 208 patients with biopsy-confirmed HGD in Barrett’s metaplasia

Comparators
• PHOTOFRIN® PDT + OMEPRAZOLE
• PHOTOFRIN® PDT ± omeprazole (OM) 20 mg bid (N=138) vs OM 20 mg bid only (N=70)

Primary efficacy endpoint:
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- Duration of complete response
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Results reported were for the intent-to-treat (ITT) population.

Photodynamic therapy (PDT) for the ablation of high-grade dysplasia (HGD) in Barrett’s esophagus (BE) patients who do not undergo esophagectomy.
Quality of Response to PHOTOFRIN® PDT

Results

• Half (52%, n=72) of PHOTOFRIN® + OM patients had a complete replacement of Barrett's metaplasia and all grades of dysplasia with normal squamous cell epithelium (CR1)
• 59% (n=81) of patients had complete replacement of all grades of dysplasia for the PHOTOFRIN® + OM group vs 14% (n=10) for the OM-only group (CR2)

Quality of response included all secondary endpoints

• Quality of response in the PHOTOFRIN® + OM group was better than that measured in the OM-only group at all response levels (P<0.0001)

Adverse Events

Most common adverse events (AEs) that occurred more frequently in the PHOTOFRIN® PDT + OM group vs OM-only group

<table>
<thead>
<tr>
<th>Event</th>
<th>In PHOTOFRIN® PDT + OM (%)</th>
<th>In OM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photosensitivity Reaction</td>
<td>44%</td>
<td>21%</td>
</tr>
<tr>
<td>Esophageal Stricture</td>
<td>36%</td>
<td>21%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>33%</td>
<td>15%</td>
</tr>
<tr>
<td>Chest Pain of Non-cardiac Origin</td>
<td>32%</td>
<td>11%</td>
</tr>
<tr>
<td>Nausea</td>
<td>28%</td>
<td>11%</td>
</tr>
<tr>
<td>Esophageal Narrowing</td>
<td>25%</td>
<td>10%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>19%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Photosensitivity reaction was defined as a flare lasting more than 72 hours in any location that was not treated with PHOTOFRIN®.

**Esophageal stricture was defined as a fixed lumen narrowing with solid food dysphagia which required dilatation.

IIEsophageal narrowing was defined as any undilated esophageal stenosis.

§Esophageal stricture occurred within 6 months following PDT and was manageable through dilatation.

Conventional UV (ultraviolet) sunscreens are of no value in protecting against photosensitivity reactions because photoactivation is caused by visible light.

Patients may complain of substernal chest pain because of inflammatory responses within the area of treatment. Such pain may be of severe intensity to warrant the short-term prescription of opiate analgesics.

Patients must observe precautions to avoid exposure of skin and eyes to direct sunlight or bright indoor light from examination lamps, including dental lamps, operating room lamps, unfiltered light bulbs at close proximity, and for at least 30 days.
Quality of Response to PHOTOFRIN® PDT

Results

• Half (52%, n=72) of PHOTOFRIN® + OM patients had a complete replacement of Barrett’s metaplasia and all grades of dysplasia with normal squamous cell epithelium (CR1)

• 59% (n=81) of patients had complete replacement of all grades of dysplasia for the PHOTOFRIN® + OM group vs 14% (n=10) for the OM-only group (CR2)

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Adverse Events

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<tr>
<th>Event</th>
<th>PHOTOFRIN® PDT + OM</th>
<th>OM-only group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photosensitivity Reaction</td>
<td>46%</td>
<td>21%</td>
</tr>
<tr>
<td>Esophageal Stricture</td>
<td>35%</td>
<td>21%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>35%</td>
<td>15%</td>
</tr>
<tr>
<td>Chest Pain of Non-cardiac Origin</td>
<td>12%</td>
<td>15%</td>
</tr>
<tr>
<td>Nausea</td>
<td>13%</td>
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</tr>
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</table>

Photosensitivity reaction occurred in approximately 46% of patients with HGD or BE in clinical studies. Typically, these reactions were mild to moderate erythema, but they also included edema, itching, redness, burning, and/or pain. In a clinical study of 466 subjects, complete resolution of photosensitivity reactions occurred in all subjects. Other less common skin manifestations were also reported in areas where photosensitivity reactions had occurred, such as increased skin pigmentation, skin thickening, and/or increased skin turgor. These manifestations may be attributable to a pseudoporphyric state (temporary drug-induced cutaneous porphyria). Occular discomfort (sensitivity to sun, bright lights, or car headlights) has also been reported.

Conventional UV (ultraviolet) sunscreens are of no value in protecting against photosensitivity reactions because photostimulation is caused by visible light. Patients should be educated about the importance of avoiding exposure of skin and eyes to direct sunlight or bright indoor light from examination lamps, including dental lamps, operating room lamps, unfiltered light bulbs at close proximity, and for at least 30 days.

Quality of Response to PHOTOFRIN® PDT

![Quality of Response to PHOTOFRIN® PDT](image)
PHOTOFRIN® PDT + OM
Fewer Patients Progressed to Cancer

- At 2 years, patients receiving PHOTOFRIN® PDT + OM had an 83% (N=138) chance of being cancer-free vs 53% (N=70) chance among the OM-only group

Primary efficacy endpoint
- Complete response rate defined as complete ablation of HGD at any assessment point (CR3) or better

Secondary efficacy endpoints
- Time to treatment failure
- Duration of complete response
- Time to treatment failure

Comparators
- PHOTOFRIN® PDT plus omeprazole (OM) 20 mg bid (N=138) vs OM 20 mg bid only (N=70)

Patient population
- All patients with biopsy-confirmed HGD in Barrett’s metaplasia

The follow-up of the pivotal study at the time of analysis was a minimum of 2 years (ranging from 2 to 3.6 years).

Esophageal strictures as a result of PDT in HGD in BE are a common adverse event. Special care should be taken during dilations to avoid perforation of the esophagus.

Continuous monitoring as recommended by physician
- Physicians should continue to monitor patients with a history of HGD in BE for signs of recurrence or other potential issues after the completion of treatment.
- Endoscopy should be performed periodically to monitor for any signs of progression or recurrence.

FOLLOW-UP VISITS
- Continued monitoring as recommended by physician
- Follow-up visits should be scheduled at regular intervals to assess for potential recurrence or other adverse events.

FOLLOW-UP ENDOSCOPY
- For patients with evidence of regression or persistence of dysplasia, endoscopy should be performed to confirm the status of the lesion.

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PHOTOFRIN® PDT Administration

Day 1
ADMINISTERED IN OFFICE
PHOTOFRIN® injected (2 mg/kg) as a slow IV injection over 3-5 minutes

Day 3
PDT-TREATED ENDOSCOPY PERFORMS PROCEDURE
Preparation of nodule. Short fiber optic diffuser (2.5 cm) with a light dose of 50 J/cm² delivered without a centering balloon. Treatment: Activation with red laser light—a light dose of 130 J/cm² delivered using a centering balloon (1 cm²)

Day 5
FOLLOW-UP ENDOSCOPY
Optimal second red laser light application: A 2.5 cm fiber optic diffuser length at a reduced light dose of 50 J/cm² delivered without a centering balloon

PHOTOFRIN® PDT + OM

Complete Ablation of HGD in BE

PHOTOFRIN® is indicated for the ablation of high-grade dysplasia (HGD) in Barrett’s esophagus (BE) patients who do not undergo esophagectomy.

PHOTOFRIN® + OM

Please see accompanying full Prescribing Information.