

# CLINICAL STUDY PROTOCOL

## A MULTICENTER, PROSPECTIVE, OPEN-LABEL, NON-RANDOMIZED SINGLE-ARM CLINICAL STUDY OF THE SAFETY AND TISSUE RESPONSE TO PHOTODYNAMIC THERAPY USING PORFIMER SODIUM FOR INJECTION AS TREATMENT FOR SOLID LUNG TUMOR PRIOR TO SURGICAL RESECTION

**Protocol Number:** CLI-PHO1701

**Type of Study:** Phase Ib

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**Date Amended**

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## PROTOCOL/PROTOCOL AMENDMENT APPROVAL PAGE

**Protocol Number:** CLI-PHO1701

A Multicenter, Prospective, Open-Label, Non-Randomized Single-Arm Clinical Study of the Safety and Tissue Response to Photodynamic Therapy using Porfimer Sodium for Injection as Treatment for Solid Lung Tumor prior to Surgical Resection

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## INVESTIGATOR'S AGREEMENT

I have read the study protocol titled “*A multicenter, prospective, open-label, non-randomized single-arm clinical study of the safety and tissue response to photodynamic therapy using porfimer sodium for injection as treatment for solid lung tumor prior to surgical resection*”, and agree to:

- Conduct this study in accordance with the design and provisions of this protocol.
- Await IRB approval for the protocol and informed consent before initiating enrollment into the study.
- Ensure that the requirements for obtaining informed consent are met according to FDA requirements of 21 CFR 50.20 and to obtain informed consent from subjects before their enrollment into the study.
- Provide sufficient and accurate financial disclosure and update information if any relevant changes occur during the investigation and for one year following the completion of the study.
- Collect and record data as required by this protocol into the case report form.
- Maintain the confidentiality of all information received or developed in connection with this protocol.
- Conduct this study in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the Declaration of Helsinki, and applicable regulatory requirements.
- Permit study-related monitoring, audits, Institutional Review Board (IRB) review, and regulatory inspection(s) by providing direct access to source data/documents.
- Prepare annual, final, and adverse event reports as required by this protocol.
- Maintain study documentation for the period of time required.
- Report all adverse events within the specified timeframe to Concordia Laboratories Inc.
- Report all serious adverse events/incidents within 24 hours after becoming aware of the event to Concordia Laboratories Inc. third party, Mapi Group, and enter the data into the Electronic Data Capture (EDC) system.
- Adhere to the publication policy of Concordia Laboratories Inc. for data collected during this study.

I acknowledge the study protocol contains all necessary details for me and my staff to conduct the study as described. I will conduct this study in compliance with all applicable regulations and guidelines as stated in the protocol and other information supplied to me.

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**Signature of Principal Investigator**

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**Date (dd/mmm/yyyy)**

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**Print Name**

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**Site Number**

## STUDY SYNOPSIS

<b>NAME OF SPONSOR:</b> Concordia Laboratories Inc.	
<b>PROTOCOL NUMBER:</b> CLI-PHO1701	<b>IND NUMBER:</b> 25,064
<b>NAME OF FINISHED PRODUCT:</b> Photofrin® (PHO)	
<b>LIST OF ACTIVE INGREDIENTS:</b> Porfimer sodium	
<b>TITLE OF STUDY:</b> A multicenter, prospective, open-label, non-randomized single-arm clinical study of the safety and tissue response to photodynamic therapy using porfimer sodium for injection as treatment for solid lung tumor prior to surgical resection	
<b>DEVELOPMENT PHASE:</b> Phase Ib	
<b>INDICATION:</b> Solid tumor in peripheral lung	
<b>NUMBER OF PLANNED SUBJECTS AND SITES:</b> Approximately 10 subjects from approximately 5 sites in the United States (US).	
<b>STUDY DESIGN:</b> Prospective, non-randomized, non-controlled study.	
<b>STUDY POPULATION:</b> Subjects with histological or cytological confirmation of peripherally located primary lung cancer or metastatic cancer to the lung parenchyma. Solid lung tumors will have a maximal tumor of < 5 cm along any axis. All subjects will undergo surgery for the resection of the tumor.	
<b>OBJECTIVES:</b> <b>Primary Objective:</b> To assess the safety of photodynamic therapy (PDT) in subjects with solid tumors in peripheral lung prior to surgical resection. <b>Secondary Objective:</b> To assess the lung tumor and healthy tissue response to PDT.	
<b>STUDY PROCEDURES:</b> Eligible subjects will undergo screening evaluation conducted during the 30 days prior to enrollment. This phase will involve medical evaluation and eligibility assessment. Upon successful baseline evaluations, subject will be enrolled to receive PHO 2 mg/kg as a slow intravenous injection over 3 to 5 minutes. Forty to 50 hours after the injection, a laser light at a dose of 200 J/cm (630 nm wavelength) of diffuser length will be delivered to the tumor through navigational and or peripheral ultrasound guided bronchoscopy. Subjects will be hospitalized for 48-72 hours after PDT for safety monitoring. Ten to 15 days after PDT, all subjects will undergo surgery as per standard of care. Macroscopic and microscopic examinations of the tumor and surrounding healthy lung tissue will be evaluated to determine the effect of PDT on the tumor and the healthy/non-tumor lung tissue. Macroscopic examinations will be performed at the local institution. Microscopic examinations will be performed by a central reader. Follow-up assessments will include some or all the following procedures: physical exam; vital signs evaluation; body weight measurement; chest CT; chest X-ray; performance status; and clinical laboratory testing. All subjects will be asked general questions about the occurrence of adverse events, concurrent medical conditions, use of adjunctive therapy/procedure, and intake of concomitant medication.	
<b>PLANNED STUDY ENROLLMENT DATES:</b> Q2 2017 to Q1 2018.	
<b>TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION:</b> Porfimer sodium (Photofrin®) 2.0 mg/kg delivered intravenously.	
<b>DURATION OF TREATMENT:</b> This study is a one-time administration of Photofrin® and one-time use of navigational with or without radial ultrasound bronchoscopy-PDT. <b>Duration of Follow-Up:</b> Subjects will be followed for 3 months post-surgery.	
<b>MAIN CRITERIA FOR INCLUSION:</b> <ol style="list-style-type: none"> <li>1. Male or female subject is eighteen years of age and older (but less than 80 years of age).</li> <li>2. Subject is diagnosed with primary or metastatic tumor &lt; 5 cm located in peripheral lung that can be completely resectable (R0).</li> </ol>	

3. Subject is a candidate for surgical resection.
4. Subject is a candidate for bronchoscopy.
5. The tumor is accessible for unrestricted illumination of PDT.
6. Subject is deemed likely to survive for at least 3 months.
7. Non-menopausal or non-sterile female subject of childbearing potential has a negative serum  $\beta$ -HCG at the time of entry into the study.
8. Non-menopausal or non-surgically sterilized female subject of childbearing potential uses a medically acceptable form of birth control.
9. Subject is able and willing to provide written informed consent to participate in the study, which must comply with the *International Council for Harmonisation (ICH)* guidelines and local requirements.

**MAIN CRITERIA FOR EXCLUSION:**

1. Subject diagnosed with small cell lung cancers or carcinoid tumors.
2. Subject has a primary or metastatic lung tumor located within 2 cm of the proximal bronchial tree or within 2 cm of a major structure (e.g., aorta, heart, trachea, pericardium, superior vena cava, pulmonary artery, pulmonary vein, esophagus, spine).
3. Subject has a primary or metastatic lung tumor near the vertebral body.
4. The tumor invades a major blood vessel.
5. Subject with concurrent non-solid malignancy.
6. Subject has had previous direct radiation treatment (other than mediastinal radiation) on the tumor scheduled for resection.
7. Subject has had chemotherapy in the last four weeks.
8. Subject has received prior PDT on the tumor scheduled for resection during 3 months prior to the date of the ICF signature.
9. Subject with blood parameters of Grade 3 or higher on the Common Terminology Criteria for Adverse Events (CTCAE) 5-point scale; parameters of Grade 2 will be excluded if judged clinically significant by the investigator.
10. Subject with known porphyria or known hypersensitivity to Photofrin<sup>®</sup> or porphyrin-like compounds or to any of its excipients.
11. Subject with a coexisting ophthalmic disease likely to require slit-lamp examination within the next 90 days.
12. Subject with any acute or chronic medical or psychological illnesses as judged clinically significant by the investigator to preclude bronchoscopy procedures.
13. Female subject who is breastfeeding or intends to breastfeed during the study.
14. Subject who participates or intends to participate in another investigational study (other than observational studies) during the study.

**CRITERIA FOR EVALUATION:**

**Primary Endpoint:**

Safety evaluation will include incidence of adverse events. Overall safety evaluation will include adverse events, serious adverse events, laboratory data, physical examination, vital signs, and concomitant medication.

**Secondary Endpoints:**

- Tumor destruction and cell death in area of the PDT (0.75 cm radius if the laser fiber is eccentrically placed, or 1.5 cm diameter if the laser fiber is centrally placed) as defined by cytological and pathological evaluation.
- Effect of PDT on the non-cancerous lung tissue surrounding the targeted tumor.

**DATE OF PROTOCOL:** 01 March 2017 (Version 1)

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## ABBREVIATIONS

<b>Abbreviation or Term</b>	<b>Definition</b>
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRX	Chest X-ray
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
EBUS	Endobronchial ultrasonography
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ENB	Electromagnetic navigation bronchoscopy
EVF	Eligibility Verification Form
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HPFB	Health Products and Food Branch
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ILP	Interstitial laser photocoagulation
IRB	Institutional Review Board
IV	Intravenous
J/cm	Joules/centimeter
Kg	Kilogram
LLN	Lower limit of normal
mg	Milligram
NCCN	National Comprehensive Cancer Network
NOS	Not otherwise specified
NSCLC	Non-small-cell-lung cancer
PDT	Photodynamic therapy
PET	Positron Emission Tomography
PT	Preferred term
R0	No cancerous cells seen microscopically
REBUS	Radial probe endobronchial ultrasonography
RFA	Radiofrequency ablation
RP	Radiation pneumonitis
SABR	Stereotactic ablative radiation therapy

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SAE	Serious adverse event
SBRT	Stereotactic body radiation therapy
SoC	Standard of Care
SOC	System organ class
TBNA	Transbronchial needle aspiration
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
WHO	World Health Organization

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## 1. INTRODUCTION

### 1.1. Current Treatment Approaches for Solid Tumor in the Lung

#### 1.1.1. Current Treatment Approaches for Non-Small Cell Lung Cancer

Lung cancer accounts for almost one-third of cancer deaths. Cancer screening strategies have the potential to achieve a 20% reduction in death rates. Screening for lung cancer with low dose computerized tomography (CT) will result in the identification of an increasing number of peripherally located lung cancers with the majority being stage I (Detterbeck *et al.*, 2013). Early stage (T1-2 N0) primary non-small cell lung cancer (NSCLC) has been traditionally managed with surgical resection.

The use of stereotactic ablative radiation (SABR) therapy as primary treatment for early stage NSCLC or for ablation of metastases has increased rapidly in the past decade. Published series using SABR have reported local recurrence ranging from 10% to 30% (similar to that reported with limited surgical resection) with most recurrence occurring within the first year after treatment. Tissue diagnosis was not obtained in several SABR studies and benefits of SABR thus may have been slightly overestimated (Howington *et al.*, 2013). Nevertheless, previous studies in subjects with early-stage NSCLC in the Western European population have shown that the risk of finding benign lesions during surgery is less than 4.3% (Lagerwaard *et al.*, 2012). Radiation pneumonitis (RP), while less common than with conventional radiation, can occur after SABR and is a limitation of this treatment modality. In a multicenter prospective single-arm study of subjects with inoperable stage I NSCLC receiving SABR, the rate of grade 3 or 4 pulmonary or respiratory tract-specific toxicity was 16%, and the rate of protocol-specified hypoxia or pneumonitis was 8% (Timmerman *et al.*, 2010). This risk was even higher (26%) in subjects with interstitial lung disease (Takeda *et al.*, 2014). Symptomatic RP is characterized by cough or dyspnea, often accompanied with fever, chest discomfort, and pleuritic pain, occasionally requiring oxygen supplementation or hospitalization. Other SABR-induced acute or sub-acute adverse effects can include skin toxicity, chest wall pain, and nausea, whereas late effects can include chronic chest wall pain, rib fracture, and less commonly, injury to the mediastinal structures when SABR is delivered to centrally located tumors including obliterative bronchitis and “vanishing airway” syndrome. In addition, three randomized trials comparing lobectomy or wedge resection to SABR have prematurely closed because of a lack of accrual. As a result, randomized comparisons with surgery will unlikely be available in the near future.

Percutaneous radiofrequency ablation (RFA) of peripheral cancers is the most studied of the ablative modalities which has been used in medically inoperable patients with small (< 3 cm) peripheral stage I NSCLC (Howington *et al.*, 2013). Although, there is currently no comparative studies, the local control rates seem lower than those reported with SABR or sublobar resection (Howington *et al.*, 2013; Donington *et al.*, 2012). Tumors larger than 3 cm had the highest local recurrence rate (50%) and thus ideal lesions for this treatment should include lesions less than 3 cm in size (Lanuti *et al.*, 2009). Studies show a consistent local control rate of 60%, with a 30% to 40% overall survival at 3 years and a cancer-specific survival of 30% to 40% at 5 years. These

outcomes are better than those seen in untreated patients with clinical stage I NSCLC but worse than those reported with SABR or sublobar resection. In the studies specifically addressing the inoperable stage I NSCLC, the primary tumor relapse rate after percutaneous RFA ranges from 8% to 43% (Donington *et al.*, 2012). The most common reported complications were pneumothorax (18%-62%), pleural effusion (7%-21%), and hemoptysis (4%-11%). Chest tube drainage was required in 5%-25% of subjects. There are also reports of bronchopleural fistula and massive hemoptysis.

### 1.1.2. Current Treatment Approaches for Metastatic Lung Lesions

Although metastasis is responsible for up to 90% of all cancer-associated mortality it is still poorly understood (Chaffer and Weinberg, 2011). The lung is one of the primary targets of several cancers. Twenty to 50% of primary extrapulmonary solid malignancies demonstrate pulmonary metastases. Solid metastatic tumors of the endobronchial area are most commonly from breast, kidney, and colon-rectum. Other primary tumors such as prostate cancer, melanoma, thyroid cancer, account for less than 5% of lung metastasis (Marchioni *et al.*, 2014). Generally, distant metastasis from breast cancer remains common and incurable (Kennecke *et al.*, 2010) with bone metastases being the most common site and lung as the next most common site for metastases. The exception is the basal-type tumor which has a high rate of lung metastasis of 18.5% (Berman *et al.*, 2013). Metastasis to the lung occurs in 50-60% of patients with renal cell carcinoma (NCCN Guidelines<sup>®</sup>, Kidney Cancer, V2.2017, 2016) while approximately 4-9% of patients with colon or rectal cancer will have lung metastases (NCCN Guidelines<sup>®</sup>, Colon cancer, V1.2017, 2016). Because more colorectal cancer patients are surviving longer, lung metastasis is more frequent. It increased from 8.9% between 1990 and 1999 to 11.9% between 2000 and 2009. It is assumed it will continue to increase (Nozawa *et al.*, 2012).

Most lung lesions are recommended to be treated with resection when possible. First line treatment for metastatic disease has traditionally been systemic therapy (Lischalk *et al.*, 2016). Although chemotherapy is typically first-line treatment for metastatic disease it is unlikely to provide durable local control for such lung metastases (Okunieff *et al.*, 2006). When resection is not feasible, image guided ablation or stereotactic body radiation therapy (SBRT) are considered reasonable options (NCCN Guidelines<sup>®</sup>, Colon cancer, V1.2017, 2016). Tumor ablation therapy is also used when there are lung oligometastases (NCCN Guidelines<sup>®</sup>, Rectal cancer, V2.2017, 2016). Lischalk and colleagues (Lischalk *et al.*, 2016) retrospectively examined 20 consecutive patients with a median age of 66 years (range, 24 to 82 years) treated with SBRT from November 2008 to November 2011. All patients presented with inoperable metastatic lung lesions localized to the central pulmonary tree. Most metastatic lesions (35%) were adenocarcinoma, with squamous cell accounting for 20%, renal cell for 15% and the remaining tumor sites accounted for 10% each (sarcoma, carcinoid, other). At a median follow up of 19 months, the 1- and 2-year Kaplan-Meier local control was 70.1 and 57.4 %, respectively. Acute grade 2 or higher toxicity was noted in one patient who developed medically manageable esophagitis (grade 2). Late grade 2 or higher radiation toxicity occurred in 30 % of treated patients and included the following: grade 2 atelectasis (3), grade 2 bronchitis (1), grade 3 pneumonitis (1), and grade 4 atelectasis (1).

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## 1.2. Newly Developed Bronchoscopic Technologies

Newly developed bronchoscopic technologies such as navigational bronchoscopy, including the electromagnetic navigation bronchoscopy (ENB) system, and radial endobronchial ultrasonography (REBUS) have shown that reaching peripheral lung lesions and obtaining diagnosis in humans is both feasible and safe (Eberhardt et al., 2007; Wang Memoli et al., 2012; Brownback et al., 2102; Jensen et al., 2012; Loo et al., 2014; Al-Jaghbeer et al., 2016). In a retrospective chart review of 98 ENB procedures in 92 patients, the diagnostic yield was 60% with a 6% pneumothorax rate (Al-Jaghbeer *et al.*, 2016).

The results of a meta-analysis that included 19 studies totalizing 1,106 patients with peripheral lung nodules reported a total of 40 (6%) pneumothoraces that occurred in 681 procedures, in which two cases were induced using transbronchial biopsy, otherwise, no pneumothorax was ENB procedure-related (Zhang *et al.* 2015). In addition, minor or moderate bleeding was reported in seven cases, and two post-procedure respiratory failure cases were recorded, none of them requiring specific treatment. Other adverse events included two of chest drainage, five of chest pain, three of fever, seven of sore throat, four of hemoptysis, and four of emesis, attributed to sedation or biopsy procedure.

## 1.3. Navigational Bronchoscopy Photodynamic Therapy

Photodynamic therapy (PDT) is a technique for local destruction of tissue with light after prior administration of a photosensitizing agent. Complete response rates of 85% can be achieved in non-surgical candidates with early (microinvasive, superficial) central airway lung cancer (Furuse *et al.*, 1993; Kato *et al.*, 2003). Photodynamic therapy can reduce the degree of central airway obstruction, often leading to better respiratory function. In addition, PDT may help resolve acute hemoptysis and post-obstructive pneumonia and improve performance status (Kato *et al.*, 2012; Wisnivesky *et al.*, 2013).

The approved treatment with PDT in lung cancer involves the systemic administration of a photoreactive drug known as a photosensitizer, which is inert until activated by the light of a specific wavelength. The only approved photosensitizer agent for treatment of lung cancer in US is porfimer sodium (Photofrin®). Photodynamic therapy with Photofrin® is indicated for 1) the treatment of microinvasive endobronchial NSCLC in patients for whom surgery and radiotherapy are not indicated, and 2) for the reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial NSCLC. Treatment selectivity is achieved by directed light delivery obtained by the placement of optical fibers at the tumor site for intraluminal activation or by interstitial fiber placement to produce better efficacy with less exposure of the normal bronchial mucosa to light (US Package Insert). Light activation of the photosensitizer leads to the production of reactive oxygen species, direct tumor cell death, and vascular shutdown.

The biological effect of this treatment is photochemical rather than thermal and thus normal tissue injury is less than with thermal ablative techniques (Fielding *et al.*, 2001). There is remarkably little effect on connective tissue like collagen, hence maintaining the basic mechanical integrity of

organs. The PDT-necrotized areas heal well with less scarring than most other forms of localized necrosis and without cumulative toxicity (Fielding *et al.*, 2001). Photofrin<sup>®</sup> followed by PDT can cause treatment-induced inflammation and obstruct the main airway. In patients with superficial endobronchial tumors, the most common reaction to therapy was a mucositis reaction in one-fifth of the patients, which manifested as edema, exudate, and obstruction. The obstruction (mucus plug) was easily removed with suction or forceps. Mucositis can be minimized by avoiding exposure of normal tissue to excessive light. Stent placement was required in 3% of the patients due to endobronchial stricture.

Although PDT was initially considered a local treatment, several studies have indicated that local PDT can result in systemic neutrophilia, induction of acute phase proteins, increased circulating levels of complement proteins, and systemic release of proinflammatory cytokines, all of which indicate the presence of a systemic inflammatory response with T-cell mediated anti-tumor immune response. Studies demonstrate that local PDT of murine tumors could lead to the induction of anti-tumor immunity, which may control distant, untreated disease sites (Gollnick and Brackett, 2010). Friedberg and collaborators reported an increased survival for subjects with NSCLC with malignant pleural disease who receive surgery and PDT when compared to historical controls of subjects receiving surgery alone (Friedberg *et al.*, 2004). These results suggest that local PDT of tumors may lead to induction of an anti-tumor immune response capable of controlling the growth of tumors outside the treatment field and indicate that this modality has potential in the treatment of distant disease sites (Kabingu *et al.*, 2007; Pizova *et al.*, 2012).

Musani and collaborators explored the safety of Photofrin<sup>®</sup>-PDT via navigational bronchoscopy to treat peripheral lung cancers in 3 dogs (Musani *et al.*, submitted). One week after PDT, the tumors and involved lung lobe were surgically excised and evaluated histologically. PDT was found to be successful in all 3 dogs and was associated with tolerable and manageable adverse effects. One dog experienced pneumothorax due to pre-existing fibrosis which necessitated more extensive surgical resection. Tissue sections from within PDT-treated tumors showed regions of coagulative central necrosis admixed with small numbers of inflammatory cells, and arterial thrombosis consistent with local necrosis without damage to adjacent areas by accurate placement of the optical fiber.

In the last decade, two pulmonary procedures have been used with PDT to treat peripheral early-stage lung cancer: transthoracic robotic needle PDT and navigational bronchoscopy PDT (Kato *et al.*, 2012). To date, several subjects have been treated with transthoracic robotic needle PDT (Kato *et al.*, 2012). The tumors in these subjects were on average larger than those treated in the RFA studies (range 1.2 to 8.0 cm *versus* 0.7-5.0 cm, respectively) (Fanucchi *et al.*, 2016). Partial response was obtained in 78% of these subjects (Kato *et al.*, 2012). The efficacy of RFA is limited by tumor size as it is commonly difficult to achieve complete ablation of cancerous lesions in tumors with diameter larger than 3 cm (Hataji *et al.*, 2005). The transthoracic approach *via* CT guidance using 19 gauge needles has been reported to result in partial remission in 7/9 (78%) subjects. Partial response was defined as a reduction in tumor volume greater than 50% but with the cancer still recognizable on biopsy or brushing for at least 4 weeks after therapy. There were

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two cases of pneumothorax (Okunaka *et al.*, 2004). Furthermore, an animal study in nine normal pigs suggests that interstitial PDT (iPDT) necrosis lesions, large enough to cover a small tumor similar to those found in humans, can be made safely in the lung parenchyma (Fielding *et al.*, 2001). The authors compared interstitial laser photocoagulation (ILP) where the laser energy heats the tissue *versus* iPDT performed at a light dose of 100 J/cm at 50-100 W. On Day 3 post injection of the photosensitizer, well-defined, localized treated areas, typically 3.5 x 2 x 2 cm, were observed. Histology showed hemorrhagic necrosis after iPDT but no late cavitation as seen after ILP. The PDT treated lung areas healed with preservation of larger arteries and bronchi. The few small pneumothoraces resolved spontaneously and were probably related to the chest wall puncture used for the placement of the fibers (Fielding *et al.*, 2001).

#### 1.4. Rationale

Considering the advances in bronchoscopic technologies, PDT applied *via* navigational bronchoscopy may be a reasonable alternative to RFA and SABR for solid lung tumors. Although PDT has been used to treat endobronchial tumors there is limited information about its effects on metastatic lung tumor and on surrounding healthy lung tissue. Consequently, this study is designed to assess the safety of PDT delivered through navigational bronchoscopy on the parenchymal lung tumors of primary and metastatic nature that warrant surgical resection to permit macroscopic and microscopic examination of the tissue effect post PDT.

## 2. STUDY OBJECTIVES

### 2.1. Primary Objective

The primary objective of this study is to assess the safety of photodynamic therapy (PDT) in subjects with solid tumors in peripheral lung prior to surgical resection

### 2.2. Secondary Objective

The secondary objective to assess the lung tumor and healthy tissue response to PDT.

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### 3. STUDY DESCRIPTION

#### 3.1. Over all Study Description

This is a prospective, multicenter, uncontrolled, non-randomized, open-label, clinical study with the primary objective to assess safety of PDT in subjects with peripherally located malignant tumors in lung parenchyma prior to surgical resection. A Time and Procedures Schedule for the overall conduct of the study is outlined in Appendix 13-1.

The primary diagnosis will be performed as per standard of care no more than 60 days prior to consent signature. Upon signing consent, subjects will be assigned a unique participation number and will undergo screening evaluation conducted during the 30 days prior to enrollment. This phase will involve medical evaluations and thorough review of all reports that led to the primary diagnosis. Upon successful screening evaluations, subjects will be enrolled into the study.

Treatment Procedures will consist of one PDT-Photofrin<sup>®</sup> course performed through navigational bronchoscopy or peripheral ultrasound guided bronchoscopy. One course will consist of an intravenous (IV) injection of Photofrin<sup>®</sup> 2 mg/kg over 3-5 minutes followed by one laser light application. The end of injection will be Study Hour 0. Photodynamic laser therapy will be performed on Study Hour 40-50. Laser light (630 nm wavelength) will be applied at a dose of 200 J/cm of the diffuser length.

Ten to 15 days after PDT, subjects will undergo surgery as per standard of care. Macroscopic and microscopic examinations of the tumor and surrounding healthy lung tissue will be evaluated to determine the effect of PDT on the tumor and the healthy/non-tumor lung tissue. Macroscopic examinations will be performed at the local institution. Microscopic examinations will be performed by a central reader pathologist.

Follow-up assessments will include some or all the following procedures: physical exam; vital signs evaluation; body weight measurement; chest CT; chest X-ray; performance status; and clinical laboratory testing. All subjects will be asked general questions about the occurrence of adverse events, concurrent medical conditions, use of adjunctive therapy/procedure, and intake of concomitant medication.

Data will be analyzed to evaluate the safety of the modality up to 90 days.

#### 3.2. Scheduling of Visits

Pretreatment assessments will be performed during the 30 days prior to enrollment. After enrollment, study visits will be as follows:

- Study Day 0 will be the day the subject is enrolled.
- Study Day 1 will be the day of the PHO injection. Study Hour 0 will be the time of the end of PHO injection.
- Study Day 3 will be the day of PDT. Study Hour 40-50 will be calculated from Study Hour 0.
- Study Day 13 to Day 18 will be the time-period where the surgery will be performed post PDT.

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- Study Day 20 to Day 25 ( $\pm 2$  days) will be the 7-day post-surgery visit.
  - Study Day 43 to Day 48 ( $\pm 3$  days) will be the 30-day post-surgery visit.
  - Study Day 103 to Day 108 ( $\pm 7$  days) will be the 90-day post-surgery last study visit.

### 3.3. Estimated Duration of the Study

Time permitted for enrollment will be 9 months. Therefore, this study has an estimated duration of approximately 15 months.

Enrollment at all sites will be reviewed on an ongoing basis. After six months, if enrollment at any site falls below 50% of the projected total, the sponsor can exercise the right to terminate the study at that site.

The end of the clinical part of the study at any sites will be defined as the date of the last visit of the last active subject at that site. The official end of the clinical part of the study at all sites will be defined as the date of the last visit of the last active subject in the study. At the end of the clinical part of the study, subjects will be treated as per the investigator's judgment.

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## 4. STUDY POPULATION

### 4.1. Primary Diagnosis

This study plans to enroll subjects with histologically or cytologically confirmation of peripherally located solid tumor in lung parenchyma. When applicable, subjects will be staged with chest CT and positron emission tomography (PET) scanning or as per local practice. Ideally subjects should have undergone an initial integrated whole body PET CT scan as part of their standard of care (SoC) staging protocol.

All procedures performed to confirm the primary diagnosis will be considered SoC and not research-related activities and will be performed no more than 60 days prior to ICF signature. Primary diagnosis will be based on the following assessments as per local practice and physician's clinical judgement to avoid unneeded procedures.

1. Confirmed solid tumor.
2. Either biopsy- or cytology-proven confirmation of primary or metastatic lung tumor of any subtype (e.g., adenocarcinoma, carcinoids, squamous cell carcinoma, large cell carcinoma, NOS [not otherwise specified], etc.).
3. Peripheral tumor location as defined by the Radiation Therapy Oncology Group protocols as the primary tumor not touching a 2-cm volume in all directions around the proximal bronchial tree (distal 2 cm of the trachea, main stem bronchi, and lobar bronchi). Tumors beyond the 3<sup>rd</sup> generation airways are included.
4. Tumor < 5 cm along any axis based on official radiology report.
5. Candidate for surgery.

### 4.2. Number of Subjects

This study plans to enroll up to approximately 10 subjects from about five US clinical research sites experienced in navigational bronchoscopy.

### 4.3. Eligibility Criteria

#### 4.3.1. Inclusion Criteria

In order to be eligible to participate in the study, potential subjects must meet all of the following inclusion criteria.

1. Male or female subject is eighteen years of age and older (but less than 80 years of age).
2. Subject is diagnosed with primary or metastatic tumor < 5 cm located in peripheral lung that can be completely resectable (R0).
3. Subject is a candidate for surgical resection.
4. Subject is a candidate for bronchoscopy.
5. The tumor is accessible for unrestricted illumination of PDT.

6. Subject is deemed likely to survive for at least 3 months.
7. Non-menopausal or non-sterile female subject of childbearing potential has a negative serum  $\beta$ -HCG at the time of entry into the study.
8. Non-menopausal or non-surgically sterilized female subject of childbearing potential uses a medically acceptable form of birth control.
9. Subject is able and willing to provide written informed consent to participate in the study, which must comply with the International Council for Harmonisation (ICH) guidelines and local requirements.

#### 4.3.2. Exclusion Criteria

Potential subjects who meet any of the exclusion criteria will not be allowed to enroll into the study.

1. Subject diagnosed with small cell lung cancers or carcinoid tumors.
2. Subject has a primary or metastatic lung tumor located within 2 cm of the proximal bronchial tree or within 2 cm of a major structure (e.g., aorta, heart, trachea, pericardium, superior vena cava, pulmonary artery, pulmonary vein, esophagus, spine).
3. Subject has a primary or metastatic lung tumor near the vertebral body.
4. The tumor invades a major blood vessel.
5. Subject with concurrent non-solid malignancy.
6. Subject has had previous direct radiation treatment (other than mediastinal radiation) on the tumor scheduled for resection.
7. Subject has had chemotherapy in the last four weeks.
8. Subject has received prior PDT on the tumor scheduled for resection during 3 months prior to the date of the ICF signature.
9. Subject with blood parameters of Grade 3 or higher on the Common Terminology Criteria for Adverse Events (CTCAE) 5-point scale; parameters of Grade 2 will be excluded if judged clinically significant by the investigator.
10. Subject with known porphyria or known hypersensitivity to Photofrin<sup>®</sup> or porphyrin-like compounds or to any of its excipients.
11. Subject with a coexisting ophthalmic disease likely to require slit-lamp examination within the next 90 days.
12. Subject with any acute or chronic medical or psychological illnesses as judged clinically significant by the investigator to preclude bronchoscopy procedures.
13. Female subject who is breastfeeding or intends to breastfeed during the study.
14. Subject who participated within the last 30 days, participates or intends to participate in another investigational study (other than observational studies) during the study.

#### 4.4. Concomitant Medication

Subjects may receive medication that is clinically indicated, such as pain prophylaxis, as per the investigator's clinical judgement. The brand name (or, if unknown, the generic name), dose, dose unit (or dosage form if compound), frequency, route of administration, duration of use (start date

and, if applicable, stop date) and indication for all previous medications (taken 30 days prior to the date of the ICF signature) and concomitant medications (taken at the time of the ICF signature and during the course of the study) must be documented altogether in the concomitant medication record section of the case report form (CRF). Concomitant medications include intravenous fluids, herbal products, vitamins, and any over-the-counter medicines.

#### 4.5. Adjunctive Therapy/Procedure

An adjunctive therapy/procedure is defined as any procedure or intervention (e.g., psychotherapy, surgery, dental work, acupuncture, physiotherapy, chiropractic, osteopathy) used to treat an illness. Diagnostic tests or procedures (e.g., chest X-rays, ECG) are not considered as a therapy. These will not be recorded unless the test or procedure may have played a role in the occurrence of an adverse event or was performed to assess an adverse event.

The adjunctive therapy/procedure (type, duration of use [start date and, if applicable, stop date], and indication) received during 30 days prior to the date of the ICF signature and throughout the study must be recorded in the adjunctive therapy record of the CRF.

#### 4.6. Acceptable Contraceptive Regimens

Current regulations and guidelines pertaining to pharmaceutical industry require properly documenting and monitoring exposure to any drugs, whether investigational or not, under clinical research during pregnancy of study human subjects and/or their partner.

##### 4.6.1. Female Study Subjects

During the study, it is expected that females of childbearing potential will have to take appropriate measures to prevent pregnancy for 3 months after PDT, such as the use of medically acceptable contraceptive regimens namely:

- systemic contraceptives (e.g., transdermal patch, birth control pills, injectable or implantable or insertable hormonal birth control products);
- double-barrier method (e.g., diaphragm with intravaginal spermicide, cervical cap with intravaginal spermicide, condom with intravaginal spermicide, condom with diaphragm);  
or
- Intrauterine or intravaginal methods (e.g., vaginal contraceptive ring, intrauterine system with hormone release, copper intrauterine device).

Female subjects will be instructed to inform the investigator should a change in the contraceptive regimen occur during the study. Females of childbearing potential will be informed about this requirement in the ICF. Abstinence will not be considered as a medically acceptable contraceptive method.

Females who do not use an acceptable contraceptive regimen will be allowed to participate in this study only if they are not considered to be of childbearing potential: female who has had a hysterectomy, bilateral ovariectomy, or tubal ligation (performed during at least six months prior

to enrollment), is clinically diagnosed infertile, or is in a menopausal state (minimum of one year without menses). A female subject engaged with a vasectomized partner will not require an additional contraceptive method.

Should a case of pregnancy in female subject occur during the course of the study, the female subject will be monitored for the pregnancy outcome at birth, 6 months and 12 months following birth.

#### 4.6.2. Male Study Subjects

Contraceptive methods will be required for the male subject in the study as well as for the partner of the male subject in the study for 3 months after PDT. Contraceptive methods will not be required if the male subject in the study is vasectomized or if the partner of the male subject in the study is not considered to be of childbearing potential.

Cases of pregnancy in partner of male subject in the study will be monitored during the course of the study. Should a case of pregnancy in the partner of the male subject occur during the course of the study, the male subject will remain in the study and the partner of the male subject will be monitored for the pregnancy outcome (at birth, 6 months and 12 months following birth) after giving consent.

#### 4.7. Early Discontinuation Criteria

Early discontinuation from study will not, on its own, invalidate a subject for the safety analyses.

An investigator may choose to remove a subject from the study for any variety of reasons. Below is a list of possible reasons for removal of a subject; however, it does not include all possible justifiable reasons for removing a subject from the study.

1. The subject has been included in violation of the inclusion / exclusion criteria (as described under Section 4.3).
2. The subject chooses to discontinue participation for personal reasons (e.g., moving away, no time).
3. The subject chooses to discontinue, or is discontinued by the investigator or the sponsor due to intolerable, serious or unexpected adverse event or laboratory values judged to be clinically significant.
4. The investigator or the sponsor discontinues the subject for a significant protocol violation (e.g., pregnancy, current participation in another clinical study, etc.).
5. An illness newly develops as determined by the physician in charge that compromises continued participation.
6. The subject is uncooperative or does not comply with the protocol requirements (e.g., failure to return for scheduled visits at the enrolling study site, failure to complete study evaluation tools, failure to follow instructions).

7. In the investigator's or sponsor's judgment, withdrawal from the study would be in the subject's best interest (e.g., an immediate medical or surgical procedure is required that would compromise the subject's continued participation, lack of adequate therapeutic response resulting in intolerable symptoms or unacceptable risk).
8. The study is terminated by the sponsor.

For any subject who leaves the study, the investigator must complete the CRF up to the time study participation is terminated. Every effort should be made to ascertain the reason for discontinuation and to perform the early discontinuation procedures (Section 5.3.2). All reasonable effort must be made to contact subjects who fail to return for scheduled visits and to encourage them to comply with the procedure. All attempts to contact subjects must be clearly documented. The investigator will advise the sponsor immediately of every dropout by telephone, facsimile, or E-mail.

In case of withdrawal of consent, the date of and the reason for withdrawing consent will be collected. No additional data will be collected from the time of consent withdrawal.

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## 5. STUDY PROCEDURES

A detailed description of the time and events schedule of planned study assessments and visit procedures is outlined in Appendix 13-1.

### 5.1. Pretreatment Procedures

Pretreatment procedures (ICF and screening) will be performed during 30 days prior to enrollment. All procedures performed to confirm the primary diagnosis must be performed no more than 60 days prior to ICF signature.

#### 5.1.1. Informed Consent

Before a subject is enrolled in this study and prior to any evaluation performed for the study, the investigator or designee must explain the study to the subject in sufficient detail to allow for her/his informed decision to participate. Availability of alternative treatment must be fully explained to the subjects and documented in the Patient Information Sheet (PIS)/Informed Consent Form (ICF). If the subject understands the requirements of the study and agrees to participate, the subject will sign the ICF. This form must also be signed by the investigator or designee. All signatures must be dated. If the investigator chooses to alter a medical regimen of the subject for the purpose of enrolling the subject in this study, the informed consent for the study should be signed at that time and prior to any alteration in the subject's ongoing therapeutic regimen. A copy of the signed and dated consent form must be given to the subject before the start of the study. The signed ICF must be available for the sponsor monitor or designee for on-site review. Upon willingness and meeting requirements to participate in the study, each subject will be enrolled in the study by assignment of a unique sequential enrollment number for each study site.

#### 5.1.2. Screening Procedures

Before any study-specific procedures are performed, informed consent will be obtained (Section 5.1.1). All subjects will undergo the following evaluations at the screening visit:

1. Review of eligibility criteria (including primary diagnosis);
2. Collection of demographic data;
3. Collection of medical and oncological history, including concurrent medical conditions;
4. Comprehensive physical examination as per SoC (excluding genital/gynecologic and urogenital unless indicated);
5. ECOG Performance Status (Appendix 13-2);
6. Skin phototype according to Fitzpatrick Classification (Appendix 13-3);
7. Vital signs (pulse, blood pressure, temperature, and respiration rate), body weight (SoC), and height assessment;
8. Chest X-ray if has not been performed up to 90 days prior to ICF signature;

9. A 5-minute resting 12-lead ECG if has not been performed up to 30 days prior to ICF signature;
10. Clinical laboratory (Appendix 13-4);
11. Serum  $\beta$ -HCG (only for female subjects of childbearing potential);
12. Collection of all adjunctive therapies/procedures and medication information including over-the-counter and phytomedicinal products currently taken by the subject as well as up to 30 days prior to the date of the ICF signature;
13. Collection of adverse events.

### 5.1.3. Enrollment Procedure

Along with the reports confirming the subject's primary diagnosis (Section 4.1), the investigator will check all the eligibility criteria (Section 4.3) of the subject based on all screening procedure results. This requires the availability and evaluation of the results of all screening procedures (Section 5.1.2). The investigator will then submit the Eligibility Verification Form (EVF) to the sponsor's medical monitor to approve the enrollment of the subject. Subjects will be provided with instructions on how to manage light exposure upon enrollment (Study Day 0).

### 5.2. Treatment Procedures

Treatment procedures will consist of three periods: Period I – PDT Course; Period II – Surgery; and Period III – Follow-up.

#### 5.2.1. Period I – PDT Course

##### *5.2.1.1. Study Day 1 (Photofrin® Injection)*

At the Study Day 1 visit, Photofrin® injection will be administered and the following assessments will be performed.

##### ***Prior to Photofrin® injection***

1. Reevaluate eligibility criteria.
2. Vital signs (pulse, blood pressure, temperature, and respiration rate).
3. Body weight.
4. Review instructions on how to manage light exposure.
5. Record concomitant medications and adverse events.

##### ***Photofrin® injection***

1. Subjects will receive Photofrin® at a dose of 2 mg/kg as a single, slow IV injection lasting 3–5 minutes corresponding to approximately 5 mL every 15 seconds. It may be administered through the “Y” tube of an IV administration set. It cannot be mixed with other drugs. Precautions should be taken to prevent extravasation at the injection site. If

extravasation occurs, care must be taken to protect the area from light. There is no known benefit from injecting the extravasation site with another substance. Further information on reconstitution and administration of PHO can be found in Section 6.1.3 and in the Pharmacy Manual.

2. Vital signs (pulse, blood pressure, temperature, and respiration rate) at 15 minutes, 30 minutes, 1, 2, 4, and 8 hours after the injection.
3. After the injection, subjects will be asked general questions about how they feel. Any occurrence of adverse events and need of concomitant medication will be recorded.

#### *5.2.1.2. PDT Bronchoscopy (Study Day 3, 40-50 Hours post Photofrin<sup>®</sup> injection)*

Subjects will return to the institution on Study Day 3 (40-50 hours post Photofrin<sup>®</sup> injection) for the PDT bronchoscopy procedure. The following assessments will be performed.

1. Vital signs (pulse, blood pressure, temperature, and respiration rate).
2. ECOG Performance Status.
3. Under general anesthesia or deep sedation
  - a. Subjects will undergo a flexible bronchoscopy with navigation guidance to confirm the location and the size of the lesion with the use of radial probe endobronchial ultrasonography (REBUS). This will be captured by video.
  - b. The investigator will select the optical fiber diffuser length to match the tumor length.
  - c. Once the desired placement of the probe is confirmed by REBUS, the investigator will remove the REBUS probe and will insert the selected optical fiber in the lesion under fluoroscopy guidance. This will be captured by video. Exceptionally, the placement of the diffuser adjacent to the tumor for intraluminal activation will be acceptable only if the placement of the optical diffuser in the lesion has been unsuccessful. For larger lesions than 1.5 cm the placement of multiple fibers from different directions will be allowed if feasible.
  - d. After the placement of the optical fiber in the lesion, the 630 nm PDT laser will be turned on and will deliver a light dose of 200 J/cm of diffuser length for an exposure time of 8 minutes and 20 seconds using a pre-set total power output. Subjects presenting multiple metastases, only one lesion would be treated.
4. Re-educate the subject on how to manage light exposure.
5. Record concomitant medications and adverse events.
6. Admit subject for a 48-hour hospitalization period.

#### *5.2.1.3. Study Day 5 (Hospital Discharge Evaluation)*

Approximately 48 hours after PDT bronchoscopy, the following safety evaluations will be performed to determine if subjects are medically stable to be discharged from the hospital.

1. Vital signs (pulse, blood pressure, temperature, and respiration rate).

2. Clinical labs (Appendix 13-4).
3. Chest X-ray.
4. Record concomitant medications and adverse events.

*5.2.1.3.1. Subject medically stable*

Discharge subject and provide instructions on how to manage light exposure.

*5.2.1.3.2. Subject non-medically stable (Day 6 to Day 10 -Extended hospitalization as required)*

The subject's 48-hour hospitalization can be extended to 72 hours (or longer) at the discretion of the investigator if the subject is deemed medically unstable. During this extended hospitalization, the following assessments should be performed daily until the subject is considered stable and able to be discharged.

1. Vital signs (pulse, blood pressure, temperature, and respiration rate).
2. Record concomitant medications and adverse events.

The day of the discharge, the following assessments should be performed.

1. Clinical labs (Appendix 13-4).
2. Chest X-ray.

The prolongation of hospitalization after 72 hours due to subject being medically unstable is to be reported to the sponsor as a serious adverse event. If a subject is still hospitalized at Day 10, the sponsor should be notified promptly.

*5.2.2. Period II - Surgery (Study Day 13 to Day 18)*

All subjects will undergo surgery as per standard of care 10 to 15 days after PDT. The following assessments will be performed.

***Prior to surgery***

1. Vital signs (pulse, blood pressure, temperature, and respiration rate).
2. ECOG Performance Status.
3. Chest CT scan.
4. Record concomitant medications and adverse events.

***Surgery and post-surgery care***

1. Surgery and post-surgery care as per standard of care.
2. Reduced light settings and subject draping will be used to avoid potential problems from bright surgical lights:
  - from the moment the subject enters the hospital and will continue while the subject is in the surgical suite and on the surgical care units;

- surgery will be performed with room lights which are modified by amber filters that block wavelength below 550 nm;
- incisions will be shielded from inadvertent light exposure (e.g., sterile blue towels);
- remainder of the subject's skin will be draped in the usual surgical manner.

In addition, measuring oxygen saturation with pulse oximetry (pulse ox) will expose the skin to red light, which may cause skin burns if left in one place too long. Continuous monitoring can be carried out by setting up multiple monitors and rotating on and off status of the fixed sensors, or by moving a single sensor to different pulsating arteriolar bed, such as the finger, great toe, nose, or earlobe.

3. Record concomitant medications and adverse events.
4. Macroscopic and microscopic examinations of lung tumor tissue and lung healthy tissue. Lung tissue following surgical resection will be sent to the local pathology lab for macroscopic examination. Slides for microscopic examination will be prepared by the local pathology lab and sent to an independent expert pathologist (ARUP Laboratories, Salt Lake City, UT, USA) for central reading. The central assessor will interpret all histology samples obtained through surgery across all sites. Procedures for slide preparation and shipment will be performed as per laboratory instructions provided to participating sites.
5. Re-educate the subject on how to manage light exposure.

### 5.2.3. Period III - Follow-Up

#### 5.2.3.1. 7-Day Post-Surgery Visit (Study Day 20 to Day 25 [ $\pm 2$ days])

Subjects will undergo the following evaluations.

1. Vital signs (pulse, blood pressure, temperature, and respiration rate).
2. ECOG Performance Status.
3. Chest X-ray.
4. Re-educate the subject on how to manage light exposure and train the subject on how to perform the Light Challenge procedures at home the day before the next visit (Section 7.1).
5. Record concomitant medications and adverse events.

#### 5.2.3.2. 30-Day Post-Surgery Visit (Study Day 43 to Day 48 [ $\pm 3$ days])

Subjects will undergo the following evaluations.

1. Vital signs (pulse, blood pressure, temperature, and respiration rate).
2. ECOG Performance Status.
3. Chest CT scan.
4. Serum  $\beta$ -HCG (only for female subjects of childbearing potential).
5. Record the result of the Light Challenge.

6. Re-educate the subject on how to manage light exposure based on the result of the Light Challenge.
  - If the subject passes the Light Challenge, the subject will be instructed to gradually resume normal outdoor activities, initially continuing to exercise caution and gradually allowing increased exposure.
  - If the subject does not pass the Light Challenge, the subject will be instructed to continue adhering to light restrictions and repeat the Light Challenge in 14 days. The Light Challenge should be repeated every 14 days until passed.
7. Record concomitant medications and adverse events.

#### *5.2.3.3. 90-Day Post-Surgery Last Study Visit (Study Day 103 to Day 108 [ $\pm 7$ days])*

Subjects will undergo the following evaluations.

1. Vital signs (pulse, blood pressure, temperature, and respiration rate).
2. Comprehensive Physical Examination.
3. ECOG Performance Status.
4. CT scan and evaluation.
5. Clinical labs (Appendix 13-4).
6. Serum  $\beta$ -HCG (only for female subjects of childbearing potential).
7. Re-educate the subject on how to manage light exposure, if needed.
8. Record concomitant medications and adverse events.

### 5.3. End-of-Study Procedures

#### 5.3.1. Subjects who completed the study

For subjects who complete this study, no additional post-treatment follow-up visits are required.

Any subject with a clinically significant abnormal laboratory value, a continuing adverse event judged to be associated with treatment, or a continuing serious adverse events will be followed according to accepted medical standards until all parameters, including laboratory values, have either returned to normal or to the baseline value or are otherwise explained or judged acceptable by the investigator. Subjects with continuing abnormalities/events should be discussed with the sponsor to ensure appropriate management and follow-up.

#### 5.3.2. Subjects who prematurely discontinued the study

##### *5.3.2.1. Early discontinuation due to consent withdrawal*

In case of withdrawal of consent, the date of withdrawing consent will be collected. If possible, the reason for withdrawing consent will be collected to exclude safety reason. No additional data will be collected from the time of consent withdrawal.

*5.3.2.2. Early discontinuation for reason other than withdrawing consent*

The investigator will make every effort to complete the following at the time of study discontinuation.

1. Reason for early discontinuation.
2. Comprehensive Physical Examination.
3. Vital signs (pulse, blood pressure, temperature, and respiration rate).
4. ECOG Performance Status.
5. Clinical labs (Appendix 13-4).
6. Serum  $\beta$ -HCG (only for female subjects of childbearing potential).
7. Concomitant medications and adverse events.

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## 6. MATERIALS

### 6.1. Photofrin®

#### 6.1.1. Supply

Photofrin® 75 mg (porfimer sodium) for injection will be supplied by Concordia Laboratories Inc. (St. Michael, Barbados).

#### 6.1.2. Packaging and Labelling

##### 6.1.2.1. Primary Packaging (Vial)

A label will be affixed to each vial. The label will comply with local regulations and will reflect the following, but not be limited to, pertinent study information: pharmaceutical dosage form, route of administration, the name/identifier and strength/potency, protocol number, lot number, re-assay/expiry date, subject number (or space provided), investigator name (or space provided), sponsor identification, storage conditions.

##### 6.1.2.2. Secondary Packaging (Carton)

A label will be affixed to each carton. The label will comply with local regulations and will reflect the following, but not be limited to, pertinent study information: pharmaceutical dosage form, route of administration, the name/identifier and strength/potency, protocol number, lot number, re-assay/expiry date, subject number (or space provided), investigator name (or space provided), sponsor identification, storage conditions, caution statement, direction for use.

#### 6.1.3. Reconstitution and Administration of Photofrin®

##### 6.1.3.1. Reconstitution

Reconstitute each 75-mg vial of Photofrin® with 31.8 mL of 5% Dextrose Injection (USP) which will result in a final concentration of 2.5 mg/mL. Shake well until dissolved. Do not mix Photofrin® with other drugs in the same solution. Porfimer sodium, reconstituted with 5% Dextrose Injection, has a pH in the range of 7 to 8 and has been formulated with an overage to deliver the 75 mg labeled quantity.

The reconstituted product should be protected from bright light and used immediately. Reconstituted Photofrin® is an opaque solution, in which detection of particulate matter by visual inspection is extremely difficult. Reconstituted Photofrin®, however, like all parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

##### 6.1.3.2. Administration

Photofrin® dose will be 2 mg/kg body weight.

For conversion from subject's weight in pounds to kilograms multiply by 0.454 (e.g., 200 lbs x 0.454 = 91 kg).

The “mg/kg” will be converted in “mL” to be administered as follows:

$$\text{Total volume of Photofrin}^{\text{®}} \text{ (mL)} = \frac{\text{Subject's weight (kg)} \times 2 \text{ mg/kg}}{2.5 \text{ mg/mL}}$$

#### **6.1.3.3. Spillage and Disposal**

Any spillage of Photofrin<sup>®</sup> should be wiped up with a damp cloth. Contact to the skin and eyes should be avoided due to the potential of photosensitivity reactions upon exposure to light. It is recommended that rubber gloves and eye protection be used. All contaminated materials should be disposed of in a polyethylene bag in compliance with local regulations.

#### **6.1.3.4. Study Drug Dosing Compliance**

Assessment of compliance with the dosing regimen is not applicable as Photofrin<sup>®</sup> will not be provided to subjects for self-administration. Any variance of administration with the intended dose will be recorded.

#### **6.1.3.5. Storage, Dispensing and Reconciliation**

Prior to reconstitution, vials must be stored at controlled room temperature of 20°C-25°C (68-77°F) in a secure, locked facility accessible only to the investigator or authorized personnel. The vial must be kept in the carton until its used. Reconstituted solutions must be protected from bright light and used immediately. The storage area must be free of environmental extremes. Prior to the study start, the drug storage area will be inspected by a Concordia Laboratories Inc. monitor or designee.

A qualified individual (pharmacist or authorized study personnel) designated by the investigator will dispense Photofrin<sup>®</sup> only to subjects enrolled in this study. Photofrin<sup>®</sup> supplies must not be loaned or dispensed by the investigator to another investigator or site or used for any purpose other than the study.

Upon receiving Photofrin<sup>®</sup> supplies, the qualified individual must complete, sign and return to the sponsor the form acknowledging the receipt of Photofrin<sup>®</sup>. Each box will be identified by a reference number, which will be recorded in the inventory/dispensing record to document its use per subject. It is the responsibility of the qualified individual designated by the investigator to maintain and keep current the inventory/dispensing record for all drugs withdrawn and dispensed. A copy of the Photofrin<sup>®</sup> inventory/dispensing record must be kept at the investigator's site and be available to the sponsor's monitor or designee who will visit the site. Any discrepancy and deficiency are to be recorded and explained.

## **6.2. Optical Fibers**

### **6.2.1. Supply**

Sterile Optiguide™ cylindrical diffusers (DCYL700 series) manufactured for Concordia Laboratories Inc. are available in several lengths for single use and will be supplied in sufficient quantities to allow for the treatment of subjects on the study. The choice of the diffuser length

will depend on the length of the tumor to avoid exposure of nonmalignant tissue to light and to minimize overlapping of previously treated malignant tissue.

#### 6.2.2. Packaging and Labelling

Labeling of the primary and secondary packaging will comply with all local regulations of the receiving country.

Optical fibers will be mechanically protected in a dispenser tray. The primary packaging will consist of a sealed pouch. The loaded tray will be placed into the pouch. The secondary packaging will consist of an individual box and will contain the primary packaging and the instructions for use. A label will be affixed to the primary and secondary packaging. The label will comply with local regulations and will reflect the following, but not be limited to, pertinent study information: device name/identifier, protocol number, subject number (or space provided), investigator name (or space provided), lot number, re-assay/expiry date, caution statement as per local regulations, manufacturer or manufactured for identification, storage conditions.

#### 6.2.3. Storage, Dispensing, and Reconciliation

Optical fibers must be stored in its original individual box and in a secure, dry location, away from temperature extremes, accessible only to authorized study personnel.

Upon receiving the optical fibers, the authorized study personnel will complete, sign and return to the sponsor the form acknowledging the receipt of the optical fibers. Each optical fiber will be identified by a reference number, which will be recorded in the inventory/dispensing record to document its use per subject. A copy of the device inventory/dispensing record must be kept at the study site and be available to the sponsor's monitor or designee who will visit the site. Any discrepancies and deficiencies are to be recorded.

Optical fibers must not be loaned or dispensed by the investigator to another investigator or site or used for any purpose other than the study.

#### 6.2.4. Inspection of Optical Fibers

Fiber optic diffusers must be checked for gross defects, proper functioning and power output prior to use. Optical fibers should visually be inspected by placing the optical fiber into the laser calibration port. Using the trace light emitted during about 10-20 sec when the laser is preparing for calibration, the fiber can be inspected for irregularities such as "hotspots" or nicks in the cylinder or coating on the fiber itself, which would interfere with the proper administration of the light dose. If such defects are detected a new fiber should replace the defective fiber. Likewise, the new fiber must be tested for defects prior to use. In the event of damage, the damaged optical fiber diffuser must be returned to the sponsor using the provided event form.

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### 6.3. Disposition of Photofrin<sup>®</sup> and Optical Fibers

During the study, the sponsor's monitor or designee will periodically check the inventory/dispensing record for the complete accountability of Photofrin<sup>®</sup> vials and optical fibers. At the end of the study, the sponsor's monitor or designee will perform a last check of the inventory/dispensing record. Any discrepancies will be explored and documented.

#### 6.3.1. Disposition of Unused Photofrin<sup>®</sup> and Optical Fibers

At the end of the study, all unused Photofrin<sup>®</sup> vials and optical fibers, along with the inventory/dispensing records, will be returned to the sponsor or designee who will perform the final reconciliation; any discrepancies will be explored and documented.

The sponsor may grant permission for the destruction of unused Photofrin<sup>®</sup> vials on site. In such case, Photofrin<sup>®</sup> vials shall be disposed as per institution's guidelines for biohazard medical waste with written documentation. The record shall include the following:

- A copy of the institution's Standard Operating Procedures;
- The name and signature of the person who destroyed the supplies;
- The identity and quantity of destroyed product;
- Method and date of destruction.

A copy of the destruction record will be provided to the sponsor.

#### 6.3.2. Disposition of Used Photofrin<sup>®</sup> and Optical Fibers

All used Photofrin<sup>®</sup> vials and optical fibers shall be disposed as per institution's guidelines for biohazard medical waste with written documentation. The record shall include the following:

- A copy of the institution's Standard Operating Procedures;
- The name and signature of the person who destroyed the supplies;
- The identity and quantity of destroyed product;
- Method and date of destruction.

A copy of the destruction record will be provided to the sponsor.

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## 7. WARNINGS AND PRECAUTIONS

### 7.1. Phototoxicity Reactions

All subjects who receive Photofrin® will be photosensitive and must observe precautions to avoid exposure of eyes and skin to direct sunlight or bright indoor light (from examination lamps, including dental lamps, operating room lamps, unshaded light bulbs at close proximity, etc.) for at least 30 days or longer as per local labelling.

The level of phototoxicity will vary for different areas of the body, depending on the extent of previous exposure to light. Before exposing any area of skin to direct sunlight or bright indoor light, the subject should perform the Light Challenge to test the skin for residual phototoxicity. A small area of skin (e.g., hand) should be exposed to sunlight for 10 minutes. If no phototoxicity reaction (erythema, edema, blistering) occurs within 24 hours, the subject can gradually resume normal outdoor activities, initially continuing to exercise caution and gradually allowing increased exposure. If a phototoxicity reaction occurs with the limited skin test, the subject should continue the existing precautions for another 2 weeks before re-testing. As the tissue surrounding the eyes may be more sensitive, it is therefore not recommended that the face be used for testing. If subjects travel to a different geographical area with greater sunshine, they should retest their level of phototoxicity. Ultraviolet (UV) sunscreens are of no value in protecting against phototoxicity reactions because photoactivation is caused by visible light.

Some subjects may remain photosensitive for up to 90 days or more. The photosensitivity is due to residual drug, which will be present in all parts of the skin. Exposure of the largest possible area of skin to ambient indoor light is, however, beneficial because the remaining drug will be inactivated gradually and safely through a photobleaching reaction. Therefore, subjects should not stay in a darkened room during this period and should be encouraged to expose their skin to ambient indoor light.

### 7.2. Ocular Sensitivity

Ocular discomfort, commonly described as sensitivity to sun, bright lights, or car headlights, has been reported in subjects who received Photofrin®. Subjects should wear dark sunglasses when outdoors, which have an average white light transmittance of < 4% for at least 30 days or longer as per local labelling. Subject should be advised to consult their ophthalmologist if they notice any change in vision after PDT.

### 7.3. Training and Instructions

Members at each site will be trained by the sponsor-designated representatives to ensure knowledge of subject safety issues prior to recruitment of the first subject. All subjects will be seen in clinic prior to scheduling the procedure and will be educated on the risks and benefits of the intervention and educated on the preventive measures to avoid cutaneous phototoxicity. Subjects will also be given a "Patient Kit", which includes gloves, sunglasses, hat with neck protection, and instructions on how to manage light exposure. Subjects will be encouraged to

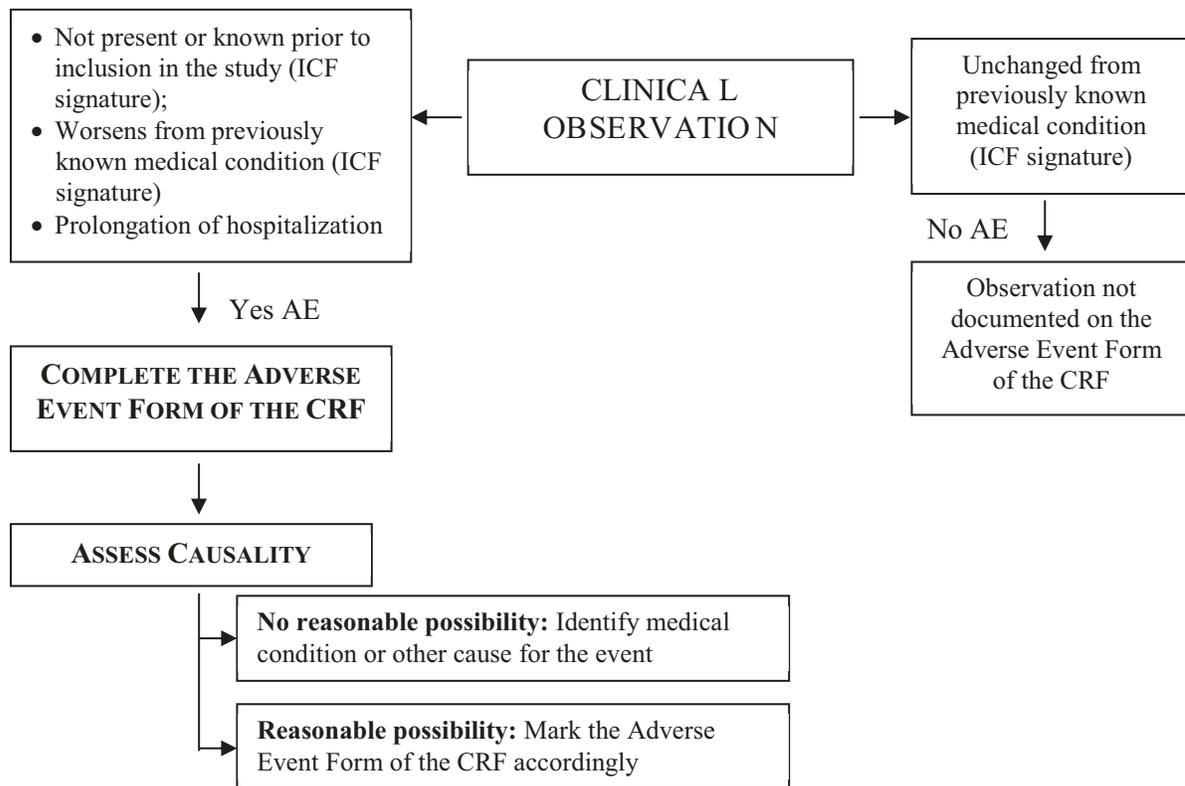
expose their skin to ambient indoor light. Subjects will not be considered for the study if the clinician deems that the subject is not mentally capable of following instructions to prevent phototoxicity.

## 8. ASSESSMENT OF SAFETY

Any adverse event/concurrent illness experienced by a subject during any portion of the study must be described in detail and be fully evaluated by the investigator. The investigator is responsible for recording and reporting all adverse events observed or reported during the study from informed consent signature until date of completion/discontinuation, regardless of drug-related assessment and/or clinical significance. Any pertinent information must be recorded in the Case Report Form (CRF) and additional comments describing the course and outcome of these events should be provided as appropriate.

### 8.1. Definitions

An **Adverse Event (AE)** is defined as any untoward medical occurrence in a subject or clinical investigation subject during the course of a clinical study regardless of the causal relationship. The following flow chart illustrates the decision-making process the investigator should follow in determining how to document an AE in the study.



An **Unexpected Adverse Event** is defined as an adverse drug event, the nature or incidence of which is not consistent with the Investigator Brochure.

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A **Serious Adverse Event (SAE)** is defined as any untoward medical occurrence that at any drug dose:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization excepting hospital admissions due to administrative reasons (e.g., the subject has no transportation home) or hospitalization for elective treatment of a pre-existing condition that did not worsen during the study unless a complication occurs during the hospitalization;
- Results in permanent or significant disability/incapacity; or
- Results in congenital anomaly/birth defect.

Other important medical adverse events may also be considered serious, depending on the judgment of the investigator or the sponsor (e.g., from ICH guidelines, intensive treatment in an emergency room or at home to prevent one of the outcomes listed in this definition, blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse). In addition, suspected transmission of infectious agents should always be considered as a SAE.

Note that as defined, serious events (expected or not) are not necessarily causally associated with the study treatment.

## 8.2. Pre-existing Medical Conditions

Any pre-existing medical condition (including findings from physical examination), which does not worsen in duration, intensity or frequency during the study, is not an AE. These pre-existing medical conditions should be adequately documented in the medical history/current illnesses of the CRF and any other appropriate ancillary documents. Pre-existing medical conditions which worsen after ICF signature will be recorded as an AE on the Adverse Event Form of the CRF.

## 8.3. Laboratory Abnormalities

During the course of the study, the investigator will be required to comment on any laboratory values outside the normal reference range. A laboratory abnormality should be regarded as an AE and recorded on the Adverse Event Form of the CRF if, per the investigator's judgment, the value is significantly worse than at pretreatment (where "significantly worse" is defined as Grade 3 or 4 by the CTCAE) and has been confirmed by repeat testing, when applicable. In addition, a clinically significant abnormal laboratory test value discovered after ICF signature and that was not previously known should be considered as an AE.

## 8.4. Guidelines and Evaluation

To promote consistency between assessments, the following guidelines should be taken into consideration along with good clinical judgment when documenting and recording AEs.

#### 8.4.1. Assessment and Recording

An AE, whether or not considered to be causally related to the treatment, must be promptly documented and recorded. At each study visit, after the subject has had an opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking the appropriate open questions. In addition to straightforward subject observation (e.g., headache, nausea, etc.), AEs will also be documented from any data collected in the CRF (e.g., laboratory values, physical examination findings, ECG changes, etc.) or other documents that are relevant to the safety of the subject.

At each follow-up visit or assessment by phone or otherwise, all AEs, whether observed by the investigator or other professional collaborators, or reported by the subject spontaneously or in response to an open question, will be recorded on the Adverse Event Form included in the CRF with the following information.

- Name of the AE: Name should be a medical term. When possible, the investigator should differentiate an illness entity from isolated symptoms or signs. For instance, the term “flu” should be recorded instead of listing all the flu-related symptoms. Where a differentiation is not possible, symptoms and signs should be separately recorded and evaluated as adverse events.
- Date of onset of the AE.
- Intensity: Event intensity will be assessed according to the CTCAE. If not described in the CTCAE, the intensity should be assessed according to the following categories: *Mild* (noticeable to the subject, does not interfere with the subject’s daily activities, usually does not require additional therapy, dose reduction, or discontinuation of the study); *Moderate* (interferes with the subject’s daily activities, possibly requires additional therapy, but does not require discontinuation of the study); *Severe* (severely limits the subject’s daily activities and may require discontinuation of the study); *Life-threatening*; *Death*.
- Date of resolution (or statement that the event is continuing).
- Action taken (e.g., concomitant medication or adjunctive therapy given will be recorded on the Concomitant Medications Form or the Adjunctive Therapy Form of the CRF, respectively).
- Outcome defined as resolved, resolving, ongoing, worsening, death, or unknown.
- Whether the event meets the definition of a SAE (see Section 8.1).

Wherever possible, all AEs, regardless of the seriousness, must be followed through resolution. The completeness and accuracy of the Adverse Event Form will be checked by the study monitor who visits the site.

#### 8.4.2. Causality Assessment

Part of the adverse event documentation will involve the investigator making a causality assessment. To promote consistency between investigators, the following guidelines should be taken into consideration along with good clinical judgment when determining the relationship of Photorin<sup>®</sup>, devices and laser light application to adverse event.

The following criteria can be used to evaluate the causal relationship between PDT-Photofrin<sup>®</sup> and the AE.

#### NO REASONABLE POSSIBILITY

- The AE is definitely not associated with PDT-Photofrin<sup>®</sup>;
- The AE does not follow a reasonable temporal sequence from PDT-Photofrin<sup>®</sup> administration;
- The AE does not disappear or decrease on discontinuation of PDT-Photofrin<sup>®</sup> (dechallenge) and/or does not reappear or increase on repeated exposure (rechallenge);
- The AE is reasonably explained by known characteristics of the subject's clinical state, history, environment, other therapy administered to the subject (drug or non-drug); and/or
- The AE may be caused by reasons other than administration of PDT-Photofrin<sup>®</sup>.

#### REASONABLE POSSIBILITY

- The AE follows or may follow a reasonable temporal sequence from PDT-Photofrin<sup>®</sup> administration;
- The AE disappears or abates upon discontinuation of PDT-Photofrin<sup>®</sup> (dechallenge) and/or reappears or worsens on repeated exposure (rechallenge);
- The AE cannot be reasonably explained by known characteristics of the subject's clinical state, history, environment, other therapy administered to the subject (drug or non-drug); and/or
- The AE is a known effect of PDT-Photofrin<sup>®</sup>.

### 8.4.3. Reporting Requirements

#### **8.4.3.1. Serious Adverse Events**

All SAEs, regardless of relationship to study treatment, must be reported by the investigator to the sponsor-designated third party drug safety group (Mapi Group, UK), by completing the SAE form within 24 hours of awareness. This includes SAEs occurring as soon as the subject signs the informed consent (i.e., pre-treatment SAEs). Serious Adverse Events which could be associated with the study procedures and which could modify the conduct of the study are reportable within 24 hours. In addition, any spontaneously reported SAE that occurs within 30 days after the last study procedure for subjects who completed the study protocol or within 90 days after the Photofrin<sup>®</sup> injection for subjects who prematurely discontinued study treatment should be reported using the SAE form.

The SAE form should be completed as thoroughly as possible, given the information available and time constraints. Upon completion, the SAE form should be signed by the investigator or sub-investigator and faxed or emailed to the designated drug safety group.

Conventional paper-based SAE Form will be provided in the Investigator Study File (ISF). The form will also be electronically available.

Death and surgery should not be reported as an event. Death and surgery are viewed as an outcome of an event, rather than the event itself. In cases where the cause of death is unknown, death may be initially reported as an event. Every attempt should be made to submit a follow-up report identifying the cause of death.

All SAEs will be monitored by Concordia Laboratories Inc. or designee in real time throughout the study.

#### **8.4.3.2. Adverse Events**

All AEs will be reported on the Adverse Events Form of the CRF.

#### **8.4.3.3. Pregnancy**

Pregnancy will be recorded and reported within 24 hours to the sponsor designee. Any pregnancy that occurs to study subjects or their partners during the study should be recorded and reported using the appropriate pregnancy surveillance form provided in the ISF. Pregnancy's outcome should also be reported. When the newborn is healthy, additional follow-up is not needed. In case of health problem in the newborn, follow-up must be performed and the investigator will provide follow-up information concerning the outcome of pregnancy within 24 hours of awareness.

#### **8.4.3.4. Other Reportable Events**

The following should be recorded and reported on the appropriate form provided in the ISF:

- Drug abuse and overdose with or without AEs. An overdose is a dose higher than that prescribed by a health care professional for clinical reasons. It is up to the participating investigator to decide whether a dose was an overdose;
- Inadvertent or accidental exposure to Photofrin<sup>®</sup> with or without an AE;
- Any other medication errors (including dispensing errors such as inadvertent use of expired medication and dosing errors) with or without an AE;
- Suspected transmission of an infectious agent.

### **8.5. Follow-Up and Final reports**

The clinical condition of subjects who have had a SAE must be followed until all parameters, including laboratory values, have either returned to normal or to baseline value or are otherwise explained or judged acceptable by the investigator. Follow-up and/or Final Reports, including information on the action taken and the outcome, must be sent to the sponsor.

In the event of death, any post-mortem findings (including histopathology and an autopsy report) must be provided to the sponsor.

If the follow-up information is received after the last study procedure or last Photofrin<sup>®</sup> administration, this information will not be recorded in the CRF but should be provided to the sponsor using the SAE form provided in the ISF.

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#### 8.6. Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be formed of three experts (two clinicians and one statistician) all of whom are independent of the sponsor and the investigators conducting the study. The DSMB will independently review safety data and, if needed, recommend any changes to the conduct of the study for safety reasons. The DSMB will also review the final analyses.

#### 8.7. Regulatory Aspects

Concordia Laboratories Inc. has a legal responsibility to notify the Health Products and Food Branch (HPFB) of Canada, the FDA of the USA, European Medicines Agency (EMA), National Competent Authorities and Central Ethics Committees of European Union, and all other foreign regulatory agencies as well as all study sites about the safety of Photofrin®.

The investigator has the responsibility to notify the local Ethics Committee about SAEs. Copies of the notification to the ethics committee must be sent to the sponsor.

## 9. UNANTICIPATED PROBLEMS

### 9.1. Definition

An unanticipated problem is defined as any occurrence that may negatively affect the subject and/or the study conduct and that is not in accordance with the approved study documents. The unanticipated problem can be related to a specific subject or to the whole site.

### 9.2. Categories of Unanticipated Problems

Unanticipated problems should be classified in at least one of these categories:

Categories of Unanticipated problems

Risk	Definition	Example
Physical risk	Unanticipated problem that may jeopardize the physical health of the subject.	Potential physical hazard associated with the participation of subject(s) to the study such as building refection and/or use of dysfunctional medical material.
Psychological risk	Unanticipated problem that may jeopardize the psychological health of the subject.	Pressure coming from another health professional and/or subject(s) relative regarding the participation of subject(s) to the study.
Economic risk	Unanticipated problem that may negatively impair the economic status of the subject.	Unplanned financial burden for subject(s) due to loss of income or expenses related to the study conduct (e.g., travelling to another site for a study procedure, etc.)
Social risk	Unanticipated problem that may negatively impair the social behavior of the subject.	More frequent and/or unplanned follow-up visit(s) and/or procedure(s) affecting subject(s) social life.
Other	Unanticipated problem that may represent a risk to the subject (other than physical, psychological, economic and/or social) or that may jeopardize the study conduct.	Partial or total loss of subject(s) confidential information.

### 9.3. Reporting of Unanticipated Problems

Unanticipated problems identified during the course of the clinical study should be reported to the sponsor within 24 hours of awareness using the appropriate form of the CRF. Occurrences meeting the definition of adverse event (see Section 8.1) should be reported as an adverse event (Adverse Event form of the CRF) and not as unanticipated problem. For site-related unanticipated problem, the data will be entered under only one subject and will be identified as site-specific on the unanticipated problem form of the CRF.

## 10. DATA MANAGEMENT AND STATISTICS

### 10.1. Sample Size/Power Considerations

This study is designed to assess the safety of PDT in subjects with solid lung tumors prior to surgical resection and to assess the lung tumor and healthy tissue response to PDT. The intent of this study is to enroll 10 subjects. This sample size has the following precision for estimation of rates of AE's of special interest (AESI). The following table shows historical AE rates for RFA ranging from <1 to ~50%.

AESI	Rate observed with RFA
Pneumothorax	11-52%
Pleural effusion	6-19%
Hemorrhage	6-18%
Pulmonary artery pseudoaneurysm	0.2%
Needle tract seeding	0.3-0.7%
Cavitation	14%
Bronchopleural fistula	0.6%
Pneumonitis	0.4%

The sample size of N=10 has precision for estimation of AE rates for estimates ranging from <0.01 to ~0.5 as shown in the following list. Precision is measured by 1-sided 95% upper confidence limit (CL) on the estimated AE rate *via* exact binomial distribution. PDT is expected to have lower AE rates than RFA, so, for example, for a RFA historical rate of 0.27 (27%), if no such AE's are observed on PDT, then the TRUE underlying PDT rate is lower than 0.27 with 95% confidence since the upper 95% CL is 0.26 - indicated by "\*" in the list below.

No. of AESIs	Rate	Upper 1-sided 95% confidence limit
0	0.00	0.26*
1	0.10	0.39
2	0.20	0.51
3	0.30	0.61
4	0.40	0.70
5	0.50	0.78

The study will be suspended and re-evaluated from a safety standpoint if 20% of the subjects experience a serious adverse event that is related to PDT.

### 10.2. Data Collection and Case Report Form Monitoring

Prior to CRF and chart review, the study monitor will confirm that each subject has signed a Health Insurance Portability and Accountability Act (HIPAA)-compliant consent form or a HIPAA supplement to the consent form.

All data will be collected using ProtocolFirst (P1) Electronic Data Capture (EDC) system. The

set-up of the Web-based system will be executed by P1. A completion guideline will be developed to provide guidance to study site personnel on how to record data in the electronic case report form (eCRF).

A detailed monitoring plan will be developed to ensure the quality of the data. The progress of the study will be monitored by on-site and telephone communications between the investigator and personnel from the sponsor and/or designee. On-site visits would be performed at intervals deemed necessary to ensure compliance with the study protocol, to review the subject CRFs against the source documents as described below, to ensure that adequate records of clinical study supplies are maintained and to assess the continued suitability of the site. The investigator will permit direct access to paper/electronic source data/documents. If access to electronic Medical Records not granted due to institution's policy, the investigator will print and provide paper source bounded and signed.

The eCRFs must be kept up-to-date, always reflecting the latest observations on the subjects enrolled in the study.

### 10.3. Study Files and Source Documents

The investigator must maintain adequate and accurate clinical study documentation to ensure protocol procedures were adequately performed and provide documentation that study data was appropriately collected and accurately entered into the eCRF. The investigator will ensure that all study files are maintained, including IRB-approved study protocol and amendments, IRB-approved consent forms, inventory records, and all other required regulatory documents.

All individual entries in the source need signature and date by the authors. All typed or dictated documents and computer printouts must be signed and dated by the investigator to confirm review. Preliminary and/or fax copies of laboratory reports must be initialed and dated, and need to be retained. Final laboratory reports should be signed and dated by the investigator to confirm review. Original laboratory reports should be kept in file.

The following are considered to be source documents, but not limited to:

- Medical charts, clinic charts, nurses' notes, medical correspondence regarding the subject;
- Subject progress notes;
- ECG tracing, X-ray reports, CT scans;
- Pathology reports;
- Quality of life questionnaires;
- Laboratory reports;
- Study worksheets; and/or
- Electronic (paperless) hospital reporting systems – the investigator must sign and date a hard copy of this data for this to be considered a source document.

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#### 10.4. Data Validation

A detailed validation plan will be developed to ensure the quality of the data. The Web-based system will integrate data discrepancy management and resolution with audit trails. The CRF will be validated through extensive data checking and query processing capabilities. Capabilities will include generating open queries and routing answers.

#### 10.5. Data Analysis

##### 10.5.1. Samples for Analysis

###### *10.5.1.1. Intent-to-Treat Population*

The Intent-to-Treat (ITT) Population will be defined as all enrolled subjects.

###### *10.5.1.2. Safety Population*

The Safety Population will be defined as all enrolled subjects who received the Photofrin<sup>®</sup> injection.

##### 10.5.2. Analysis of Baseline, Disposition, and Demographic Data

Baseline and subject demographic information will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum) for quantitative variables (e.g., weight) and counts and percentages for categorical variables (e.g., sex). Subject demographics and selected baseline information will be summarized for the Safety Population.

The frequency and percent of subjects who enroll in the study, complete the study, or discontinue the study prior to completion will be summarized.

##### 10.5.3. Safety Analysis

Safety analysis will be performed on the Safety Population.

The number and percentage of subjects with normal and abnormal findings will be provided for each physical examination in a shift table comparing screening and the end of study evaluation.

Vital signs will be summarized descriptively (mean, standard deviation, median, minimum and maximum). Change from baseline will also be summarized.

Skin photosensitivity is an adverse event of special interest and will be summarized separately from other adverse events at each safety assessment. Changes in skin will be assessed by grade of erythema, edema and blistering. The data will be tabulated by CTCAE grade in the Dermatology/Skin category.

Descriptive statistics for each clinical laboratory test will be presented for the baseline and the end of study assessment. Change from baseline will also be summarized. According to the laboratory normal ranges, laboratory test results will be categorized as low (< lower limit of normal, LLN), normal (within normal range), and high (> ULN). Shift tables, comparing the distributions of these three categories at baseline versus the end of study assessment, will be presented.

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Concomitant medications will be coded using the WHO Drug dictionary. Medications initiated prior to start of treatment and maintained during the study, or taken during the course of the study will be considered as concomitant medications. Concomitant medications will be summarized according to the preferred terms only.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects who experienced any AEs as well as serious AEs will be presented by system organ class (SOC) and by preferred term (PT) within SOC. All AEs will be similarly presented by intensity (mild, moderate, severe or using the CTCAE grading system) and by relationship to treatment (reasonable possibility/no reasonable possibility). One-sided 95% confidence limit will be computed for each AE percentage via exact binomial method (Clopper-Pearson, 1934).

#### 10.5.4. Tissue Response Analysis

The secondary efficacy endpoints will involve the assessment of the tissue response. Macroscopic and microscopic examinations will be tabulated and summarized for tumor tissue and healthy tissue.

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## 11. ADMINISTRATIVE PROCEDURES AND ETHICAL CONSIDERATIONS

### 11.1. Ethical Conduct of the Study and Quality Assurance

This study will be conducted in compliance with Institutional Review Board (IRB), *International Council for Harmonisation* (ICH) Good Clinical Practice (GCP) Guidelines; United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR § 50, 56, 312); the Declaration of Helsinki, and with ICH guidelines regarding scientific integrity (E4, E8, E9, and E10). This study will also adhere to the US Food and Drug Administration (FDA) and applicable local laws and regulations, as well as requirements for data protection. The investigator must adhere to these principles, in addition to any applicable or local requirements.

To ensure compliance with GCP and all applicable regulatory requirements, a quality assurance audit may be conducted by the sponsor, sponsor's designee, and/or other representatives (e.g., site representatives, etc.). Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

The investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by Concordia Laboratories Inc., its designees, and/or auditor/inspector. In signing this protocol, the investigator understands and agrees to give access to the necessary documentation and files.

### 11.2. Medical Care

Subjects will be informed that their right to medical care will not be affected in any way by their agreement or refusal to participate in this study and that they are free to withdraw from the study at any time without compromising their relationship with their clinician.

### 11.3. Subject Information and Informed Consent

Information in simple terms will be provided to explain the risks and the benefits of the subject's participation in the study, the procedures involved and other relevant details. Written informed consent must be obtained from the subject by the investigator (or designee) before the subject takes part in the study or before altering the medical regimen of the subject for the purpose of enrolling the subject in the study. The investigator must adopt a standardized approach for obtaining informed consent from each subject. The following items must be described fully to each subject prior to obtaining consent.

1. A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the subject's participation, a description of the procedures involved and the identification of any procedures which are experimental.
2. A description of any foreseeable risk or discomfort to the subject.
3. A description of the benefits for the subject, which may reasonably be expected.

4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing to what extent, if any, the confidentiality of records identifying the subject will be maintained and noting the possibility that the records will be inspected by the sponsor and/or other representatives.
6. An explanation of whom to contact for answers to pertinent questions about the research and subject's rights, and whom to contact in the event of a research-related injury to the subject.
7. A statement that participation is voluntary, that refusal to participate will not involve any penalty or loss of benefits to which the subject is otherwise entitled and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
8. Any anticipated circumstances under which the subject's participation may be terminated by the investigator without the need of the subject's consent.
9. Any additional costs to the subject that may result from participation in the research.
10. The consequences of a subject's decision to withdraw from the research and the procedures for orderly termination of participation by the subject.
11. A statement explaining that significant new findings developed during the course of the research which may influence the subject's willingness to continue participation will be provided to the subject.
12. The approximate number of subjects involved in the study.
13. Any other country-specific and ICH/GCP requirements.

Should the investigator decide to modify the Informed Consent document, the modified version must be approved by the sponsor or designee prior to its submission to the IRB. Should the IRB request modifications, the IRB's version must be submitted to the sponsor or designee for approval prior to study initiation. The original signed Informed Consent document is to be maintained with the source documents. The subject should receive a copy of the signed Informed Consent document. All signed and dated Informed Consent documents will be inspected by the study monitor or designee.

#### 11.4. Ethics Committee Review

Before study initiation, the investigator and institution must have written and dated approval from the IRB for the study protocol/amendment(s), written ICF, any consent form updates, subject recruitment procedures (e.g., advertisements), and any written information to be provided to subjects. Appropriate reports on the progress of the study will be made to the IRB and the sponsor by the investigator in accordance with applicable regulatory regulations. When necessary, an extension or renewal of the IRB approval must be obtained and copy forwarded to the sponsor. Upon approval and before the study start, the following IRB approval documentation must be sent to the sponsor:

- A letter documenting the IRB approval of the protocol and the ICF (indicating its title, protocol number and version).
- A letter documenting the IRB approval of amendment(s) to the protocol and/or the ICF, if applicable (indicating its title, protocol number and version).
- A list of the IRB members, their representative capacities, and their affiliations. Should this list be unavailable due to local regulations of the institution, a letter to this effect must be provided to the sponsor with a copy remaining in the study file.

The ICH guidelines for GCP specify that the committee should include persons of varying backgrounds (including peers of the responsible investigator and lay people) and must exclude the responsible investigator as a voting member.

#### 11.5. Standards

The study will be conducted according to the principles of the Declaration of Helsinki (Fortaleza, October 2013) and the ICH guidelines for the Good Clinical Practice. The sponsor will ensure that the study complies with all local, federal or national regulatory requirements as applicable.

#### 11.6. Confidentiality

Subjects will only be identified by unique identification code. Their names will not be disclosed in any publication or presentation of results.

#### 11.7. Investigator Responsibilities

The investigator undertakes to perform the study in accordance with ICH Guidelines per GCPs and the applicable regulatory requirements. It is the investigator's responsibility to ensure that adequate time and appropriate resources are available at the investigational site prior to commitment to participate in this study. The investigator should also be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks. An up-to-date copy of the curriculum vitae for the investigator and sub-investigator(s) will be provided to the sponsor (or its designee) before starting the study.

Before study initiation, each investigator must provide the protocol signature page and a fully executed and signed Form FDA 1572 to the sponsor or their representative. Financial Disclosure Forms must be completed by all investigators and sub-investigators who will be directly involved in the treatment or evaluation of research subjects in this study. The investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study following information; any significant payments of other sorts from Concordia Laboratories Inc. such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria; any proprietary interest in Photofrin®; any significant equity interest in Concordia Laboratories Inc. as

defined in the US Code of Federal Regulations (21 CFR 54 2(b)).

In consideration of participation in the study, Concordia Laboratories Inc. will pay the investigator, or nominated payee the sums set out in the payment schedule attached to the Investigator Agreement.

#### 11.8. Protocol Adherence and Investigator Agreement

The investigator must adhere to the protocol as detailed in this document. The investigator will be responsible for enrolling only those subjects who have met protocol eligibility criteria. The investigators will be required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

At each visit, subjects failing to comply with treatment will be assessed to determine whether the lack of adherence to study treatment is related to safety. The investigator should make every effort to ensure that visits occur at the appropriate intervals. The reason for any deviation in the visit schedule must be documented in the eCRFs.

It is the investigator's responsibility to communicate with their local IRB to ensure accurate and timely information is provided at all phases during the study. The appropriate approvals must be in place prior to recruitment, notification of any SAEs during the study must take place and the IRB must be informed of study completion. The reason for any deviation in the visit schedule must be documented in the eCRFs.

The study will be administered by and monitored by employees or representatives of Concordia Laboratories Inc. The study monitor or Clinical Research Associate (CRA) will visit each site on a periodic basis and perform verification of source documentation for each subject.

#### 11.9. Protocol Amendments and Other Changes in Study Conduct

Any substantial changes, other than strictly administrative changes that do not affect the management and the safety of the subject, clinical procedures, or outcomes assessment, will be made as formal amendments to the protocol and will be submitted to each participating site for appropriate review by the IRB and to regulatory authorities.

Any change or addition to this protocol requires a written protocol amendment that must be approved by the sponsor and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study, require additional approval by the IRB of all centers and by the regulatory authority. A copy of the written approval of the IRB, which becomes part of the protocol, must be provided to Concordia Laboratories Inc. Examples of amendments requiring such approval are:

- Any increase in study drug dosage or duration of exposure of subjects to the study drug beyond that in the current protocol;
- Any significant increase in the number of subjects under study;
- Any significant change in the design of the protocol (such as the addition or dropping of a control group);

- 
- Addition or deletion of a test procedure for safety monitoring;
  - An increase in the number of invasive procedures to which subjects are exposed.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Concordia Laboratories Inc. in the interests of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented by him/her for safety reasons, Concordia Laboratories Inc. should be notified and the IRB at the center should be informed within 10 working days.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB of each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval that can be treated as administrative amendments include:

- Changes in the staff used to monitor studies (e.g., the sponsor staff versus Contract Research Organization [CRO] staff);
- Minor changes in the packaging or labeling of the study drug.

Changes in study conduct as defined in this protocol are not permitted. Any planned deviation from the specific requirements of the protocol must be discussed in advance with the study monitor and will require prior approval. Any unforeseen changes in study conduct will be recorded in the clinical study report.

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## 12. PUBLICATION POLICY

All information concerning the study and related to Concordia Laboratories Inc. operations, such as patent applications, manufacturing processes, basic scientific data, assay methods, and formulation information supplied by Concordia Laboratories Inc. and not previously published, is considered confidential by Concordia Laboratories Inc. and shall remain the sole property of Concordia Laboratories Inc. The investigator agrees to only use this information for the purpose of undertaking this study and will not use it for any other purpose without prior written consent from Concordia Laboratories Inc.

Concordia Laboratories Inc. is committed to ensure that publications of all its clinical study results in biomedical journals are done in a timely manner, regardless of the Results. Publications should follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals (<http://www.icmje.org>). Concordia Laboratories Inc. is committed to ensuring that authorship for all publications comply with the criteria defined by the ICMJE.

Since this is a multicenter study, a study publication group composed of different investigators with a key involvement in the Study and representatives of Concordia Laboratories Inc.'s Clinical Department (the "Study Publication Group"), will be created and it will be the Study Publication Group's responsibility to identify the individuals who accept direct responsibility for the primary abstract and/or manuscript (the "Primary Manuscript"). These individuals should fully meet the criteria for authorship referred to above. Other members of the Study Publication Group should be listed in the acknowledgments if and as appropriate. The development, review and submission of the Primary Manuscript will be done in accordance with Concordia Laboratories Inc.'s Standard Operating Procedure. Presentation or publication of data subsets from individual institutions participating in the multicenter studies ("Individual Manuscripts") should not precede the Primary Manuscript, without Concordia Laboratories Inc.'s prior written consent, unless the Primary Manuscript is not published within twenty-four (24) months after the Site close-out visit. All proposed Individual Manuscripts will be submitted to Concordia Laboratories Inc. at least sixty (60) days prior to submission, for prior review by Concordia Laboratories Inc.

- to allow Concordia Laboratories Inc. to identify any Confidential Information, excluding Results, which must be removed from the Individual Manuscript prior to publication or presentation;
- to ensure accuracy of the data and analyses being published or presented, and
- to allow Concordia Laboratories Inc. to identify any information requiring intellectual property protection prior to publication or presentation.

In the event Concordia Laboratories Inc. identifies any information requiring intellectual property protection, Institution and/or Principal Investigator agrees to delay publication or presentation of the Individual Manuscript for an additional period not to exceed ninety (90) days for Concordia Laboratories Inc. to secure appropriate intellectual property protection. Except as otherwise provided under this Section, the Principal Investigator will be under no obligation to modify the

Individual Manuscript and will retain full control over its publication, including where it is published. Concordia Laboratories Inc. is authorized to freely use and distribute the Primary Manuscript and Individual Manuscripts as needed, after their publication, without any other obligation. Insofar as required, Concordia Laboratories Inc. is therefore granted a free license for an unlimited duration and territory.

### 13. APPENDICES

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### Appendix 13-1 Time and Procedures Schedule

Procedures/Examinations	STUDY TIME								
	S	E	Period I - PDT Course			Period II - Surgery	Period III - Follow-up		
	Days -30 to -1	Day 0	Injection Day 1	PDT Day 3 40-50 H	Hospital Discharge <sup>g</sup> Day 5	Day 13-18	Day 20-25 (±2 days)	Day 43-48 (±3 days)	Study Exit Day 103-108 (±7 days)
Informed Consent	X								
Eligibility criteria	X <sup>a</sup>		X						
Demography	X								
Medical and oncologic history and current medical conditions	X								
Skin phototype	X								
Vital signs <sup>b</sup>	X		X	X	X	X	X	X	X
Height	X								
Body weight	X		X						
Comprehensive physical examination	X								X
ECOG Status	X			X		X	X	X	X
Chest X-ray	X <sup>c</sup>				X		X		
12-lead ECG	X <sup>d</sup>								
CT scan and evaluation						X		X	X
Clinical labs <sup>e</sup>	X				X				X
Serum β-HCG <sup>f</sup>	X							X	X
Enrolment		X							
Photofrin <sup>®</sup> injection			X						
Instructions to subjects		X	X	X	X	X	X	X	X
PDT & 48-hour hospitalization				X					
Macroscopic/microscopic tissue examination						X			
Light Challenge								X	
Record Adverse Events <sup>h</sup>	X		X	X	X	X	X	X	X
Medication/Therapy Assessment <sup>i</sup>	X		X	X	X	X	X	X	X

S=Screening; E=Enrolment; <sup>a</sup> Will include radiology/pathology reports confirming primary or metastatic solid tumor in peripheral lung and thoracic surgeon confirming the tumor resectability; <sup>b</sup> On Day 1, vital signs (pulse, blood pressure, temperature, and respiration rate) to be performed prior to Photofrin<sup>®</sup> injection and repeated at 15 and 30 minutes, 1, 2, 4, and 8 hours after injection. Afterwards, vital signs to be assessed once, prior to all other procedures being performed; <sup>c</sup> If not done up to 90 days prior to ICF signature; <sup>d</sup> If not done up to 30 days prior to ICF signature; <sup>e</sup> Clinical labs to include hematology and chemistry as specified in Appendix 13-4; <sup>f</sup> For females of childbearing potential only, who must agree to use acceptable contraceptive method for 90 days post Photofrin<sup>®</sup> injection; <sup>g</sup> Subject to be discharged from the 48-hour hospital stay after the Chest X-ray and other safety evaluations indicating that the subject is stable and able to be discharged; otherwise, the subject's hospital stay may be extended to 72 hours or until the subject is stable for discharge; <sup>h</sup> All AEs to be recorded from the time of ICF signature; <sup>i</sup> All medications and adjunctive therapies/procedures to be recorded 30 days prior to screening and throughout the study.

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**Appendix 13-2      ECOG Performance Status**

<b>GRADE</b>	<b>ECOG PERFORMANCE STATUS</b>
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

**Appendix 13-3 Fitzpatrick Skin Type Classification**

<b>FITZPATRICK SKIN TYPE</b>	<b>COLOR</b>	<b>SKIN DESCRIPTION</b>
I	Caucasian; blond or red hair, freckles, fair skin, blue eyes	Extremely fair skin Always burns, never tans
II	Caucasian; blond or red hair, freckles, fair skin, blue or green eyes	Fair skin Always burns, sometimes tans
III	Darker Caucasian, light Asian	Medium skin Sometimes burns, always tans
IV	Mediterranean, Asian, Hispanic	Olive skin Rarely burns, always tans
V	Middle Eastern, Latin, light-skinned black, Indian	Moderately pigmented brown skin Never burns, always tans
VI	Dark-skinned black	Markedly pigmented black skin Never burns, always tans

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**Appendix 13-4 Clinical Laboratory**

<b>HEMATOLOGY</b>	<b>CHEMISTRY</b>
Hemoglobin (Hb)	Glucose (random)
Hematocrit (Hct)	Blood urea nitrogen (BUN)
White blood cell (WBC)	Electrolytes: sodium, potassium, chloride
Red blood cell (RBC)	Creatinine
Platelet count	Alkaline Phosphatase (ALP)
Prothrombin time (ProT)	Aspartate Aminotransferase (AST)
	Alanine Aminotransferase (ALT)
	Total bilirubin
	Albumin
	Total protein

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