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A Phase II Study of Photodynamic Therapy (PDT) with Photofrin® (IND 104,613) for Recurrent High-Grade Gliomas in Adults

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FDA IND Number: 104,613
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PROTOCOL SYNOPSIS

Protocol Identifiers.	**ClinicalTrials.gov ID**: NCT01966809 **IND No.:** 104,613 **MCW/FH IRB:** PRO00023580 **MCW GC:** FP00005327
Title	A Phase II Study of Photodynamic Therapy (PDT) with Photofrin® (IND 104,613) for Recurrent High-Grade Gliomas in Adults
Principal Investigator	**Harry T. Whelan, MD**
Protocol Investigators	Please refer to page 4 of the protocol.
Sponsor(s) & Collaborators	**Sponsor-Investigator:** Harry T. Whelan, MD **Industry Collaborator:** Pinnacle Biologics Inc.
Institution(s)	Medical College of Wisconsin/Froedtert Hospital
IND Number(s)	
Name of Approved Investigational Drug(s)	Hematoporphyrin Derivatives (HPDs) Photofrin® (porfimber sodium, 75 mg) for Injection
Name of Approved Investigational Devices(s)	Angiodynamics DIOMED 630 PDT Laser Laserscope KTP/532® Surgical Laser System(Series 800) [A] Laserscope KTP YAG® Surgical Laser System (Series 800) [A] [A] Pending FDA Approval
Dose of Investigational Drug	2.5 mg kg^{-1} Photofrin® (porfimer sodium, 75 mg) for Injection 240 J cm^{-2} Laser light (630 nm)
Route of Administration	Investigational Drug: Intravenous Injection (IV), over 3 to 5 minutes Photodynamic Therapy: Intraoperative Photoillumination
Study Population/ Treatment Group(s)	Single Arm, adult patients with recurrent high-grade gliomas will receive one dose of Photofrin® and PDT during the time of clinically indicated tumor resection surgery.
Sample Size	30 Adult patients
Selection of Study Patients	30 adult patients with high-grade recurrent gliomas will be referred to and/or screened at the MCW/FH Cancer Center. Patients will be reviewed by the Neuro-Oncology Brain Tumor Board and determine if tumor resection will be part of their clinically indicated plan of care. An investigative team member and a neuro-oncologist will determine if potential patients meet the inclusion and exclusion eligibility criteria as defined in the protocol.

Inclusions Eligibility Criteria	1. Age: ≥ 18 years 2. Disease: Patients with relapsed or refractory high-grade glioma are eligible. Patients must have had histologic verification of malignancy at original diagnosis or relapse. Tumors must be supratentorial in location. 3. Disease Status: Patients must have potentially resectable disease. 4. Therapeutic Options: Patients' current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life. 5. Performance Level: Karnofsky ≥ 50% **Note:** Neurologic deficits in patients with CNS tumors must have been relatively stable for at least 7 days prior to study enrollment. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score. 6. Predictable Life Expectancy: > 8 weeks 7. Prior Therapy: Patients must have fully recovered from the acute toxic effects of all prior anti–cancer chemotherapy. At least three weeks from previous chemotherapy and 4 weeks from prior radiation therapy **Note:** Although clinical determination of true progression vs. pseudoprogression may be difficult within the first 12 weeks following radiation and/or chemotherapy, qualified candidates need only be 4 weeks out from prior radiation and/or chemotherapy, a common standard of other recurrent glioma trials. 8. Organ Function: a. Adequate bone marrow function i. Absolute neutrophil count ≥ 1,000 ii. Platelet count ≥ 100,000 (may transfuse to meet requirement) b. Adequate renal function i. Creatinine clearance or radioisotope GFR ≥ ~~70~~ 60 mL/min/1.73 m^2 c. Adequate liver function i. Bilirubin (direct) ≤ 3X upper limit of normal (ULN) for age ii. SGPT (ALT) ≤ 10X ULN 1. For the purpose of this study, the ULN for SGPT is 45 U/L iii. Serum albumin ≥ 2 g/dL d. Adequate coagulation i. PT and INR ≤ 2X ULN , per institutional guidelines 9. Central Nervous System Function: Patients with seizure disorder may be enrolled if receiving non– enzyme inducing anticonvulsants and well controlled. 10. Informed Consent: All patients or legally authorized representatives must sign a written informed consent according to institutional guidelines. 11. All available archival tumor tissue slides disease evaluations should be reviewed by a Froedtert Health-MCW neuropathologist prior to study enrollment.

Exclusion Eligibility Criteria	1. Disseminated disease 2. Pregnancy or Breast–Feeding: Pregnant or breast–feeding women will not be entered on this study, as risks of fetal and teratogenic adverse effects of Photofrin® are not known. 3. Other concurrent tumor therapy 4. Subjects with porphyria 5. Subjects taking potentially photosensitizing drugs (Appendix 3) 6. The presence of adverse events of neurologic function, photosensitivity, or photophobia Grade 4 or higher (CTCAE Version 4.0)[47] 7. Allergy to eggs, soybean oil, or safflower oil (due to potential allergy against intralipids) 8. Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.
Estimated Length of Study	Patients will be followed up for 3 years following their PDT treatment. Accrual Period is projected to take 3 years with an average of 10 patients enrolling annually.
Regimen	Patients will be give one regimen of the investigational drug for PDT at the time of normal tumor resection for recurrent, high-grade gliomas
Design	Single Arm, Phase II Study
Multicenter	No
Blinding	None
Randomization	None
Primary Objective(s)	**1.1.1** To estimate the six-month relapse-free survival (RFS) distribution in adults with recurrent gliomas
Secondary Objective(s)	**1.2.1** To further explore and report descriptively the safety and tolerability of photodynamic therapy (PDT) in adults with recurrent glioma tumors **1.2.2** To obtain preliminary data toward determining whether this combination results in higher remission rate when compared to historical data **1.2.3** To further explore and report progression-free survival and overall survival for three years post PDT treatment **1.2.4** To measure complete response, partial response, stable disease or progressive disease using the response assessment for Neuro-Oncology (RANO) criteria with the follow-up medical imaging, which specifically incorporates volumetric measurements of brain tumor enhancement and clinical measures of neurological decline and to compare these outcomes to historical controls
Other Outcomes of Interest	None at the time

PROTOCOL REVISION HISTORY

Version No.	Revision Date	Summary of Changes
1.0	**01/15/2013**	**Version of the Original Submission (OS)**
1.1	**05/10/2013**	**Changes Requested by the MCW/FH IRB, Letter Dated 11/07/2013** ▪ Removed References to Avastin from the protocol ▪ Administrative Changes/Updates
2.0	**07/14/2014**	**Protocol Reformatting Overhaul for the Cancer Center CTO** ▪ Addition of the following protocol sections: ➢ Title page ➢ Table of Contents ➢ Study Committee page ➢ Protocol Synopsis ➢ List of Abbreviations ➢ 7.0 Investigational Drug and Device Information ➢ 10.0 Statistical Considerations ➢ 11.0 Evaluation Criteria ➢ 12.0 Adverse Event Reporting Requirements ➢ 13.0 Study Data Collection and Safety Monitoring ➢ 14.0 Conduct of Study ➢ Appendix 4 Overview of Published Literature: Photodynamic Therapy ▪ Reformatted Sections from Letters (A, B, C,.. etc.) to Numbers (1, 2, 3, … etc.) ▪ Target Accrual updated from 12-18 patients to 30 patients
2.0	**08/08/2014**	**Changes Requested by the FRC on 07/22/2014 and 08/04/2014** **Changes Requested by the SRC on 06/16/2014** ▪ Administrative Updates were made to the following sections ➢ Section 1.0: Reformatted Primary and Secondary Objectives ➢ Section 2.6: Titles were provide for subsections 2.6.1, 2.6.2, 2.6.3 ➢ Section 3.4: Updated to clarify screening and eligibility process ➢ Section 6.7: Clarification of use of other investigational agents ➢ References: Reference numbered 59 to 73 were added ▪ Section 3.2 ➢ Clarification of Protocol Screening Process to avoid treatment of necrosis and/or pseudoprogression ▪ Section 5.7.1 ➢ Clarification of Study Endpoints, Tests and Procedures ▪ Section 6.2 ➢ Included specifications for monitoring pulse oximetry ▪ Appendix 1 ➢ Updates were made to clarify protocol specific procedures, observations, and EHR data collection of the patients' standard of care

Version No.	Revision Date	Summary of Changes
2.0	**08/29/2014**	**Changes Requested by the SRC on 08/21/2014** ▪ Section 2.3: Additional background added to clarify the dose of Photofrin® ▪ Section 5.1.1: Table of Study Specific Procedures added for Clarification ▪ Section 5.1.3: Updated to clarify that patients will receive Photofrin® in the Adult Translational Research Unit ▪ Section 5.1.6: Administrative update for clarification ▪ Section 5.1.7: Administrative update to account for the occurrence of weekends and holidays ▪ References: : Addition of reference number 73
2.0	**10/30/2014**	**Addition of Data Safety Monitoring Plan for DSMC Review** ▪ Title page: Clarification of clinical trial funding and support ▪ Title page: Change to MCW/FH IRB protocol number ▪ Table of Contents: Administrative updates ▪ Study Committee: Administrative updates to Nonemergency Contact ▪ Study Committee: Administrative updates to Collaborators Information ▪ Protocol Synopsis: Update to new MCW/FH IRB protocol number ▪ Protocol Synopsis: Clarification to Selection of Study Patients ▪ Section 7.1.7: Administrative updates to Collaborators Information ▪ Section 12.3: Administrative change to section title ▪ Section 12.6.1: Clarification provided for Reporting to the MCW/FH IRB ▪ Section 12.6.2: Clarification provided to guide reader where to look for expedited reporting to the DSMC ▪ Section 13.3.2: Addition/Clarification Expedited Reporting in the Data Safety Monitoring Plan ▪ Section 13.3.3: Interim Analysis and Stopping Guidelines section added to the Data Safety Monitoring Plan ▪ Section 13.3.3: Safety Monitoring and Stopping Guidelines section added to the Data Safety Monitoring Plan ▪ Section 13.4.1: Administrative formatting update ▪ Section 13.4.2: Administrative formatting update ▪ Section 13.5: Study records will be retained for 10 years per the MCW/FH IRB SOP
2.0	**12/01/2014**	**Administrative Update for MCW/FH IRB and FDA Review** ▪ Section: Protocol Revision History Added/Completed ▪ ICF: Replaced ‘Clinical Cancer Center’ with ‘Hope Clinic’ ▪ ICF: Update Information regarding blood clotting risks

LIST OF ABBREVIATIONS

AE	adverse event
ALT	Alanine Aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration time curve
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
CNS	central nervous system
CR	complete remission
CrCl	creatinine clearance calculator
CRF	case report forms
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trials Management System
CTO	Clinical Trials Office
DFS	disease free survival
DLT	dose limiting toxicity
DSMC	data safety monitoring committee
DSMP	data safety monitoring plan
ECHO	echocardiogram
EFS	event free survival
EP	European Pharmacopeia
FISH	fluorescence in situ hybridization
FRC	Faculty Review Committee
GFR	glomerular filtration rate
HgB	hemoglobin
HpD	hematoporphyrin derivative
HSV	herpes simplex virus
IRB	Institutional Review Board
LDH	lactate dehydrogenase
MCW	Medical College of Wisconsin
MFC	multiparameter flow cytometry
MRD	minimal residual disease
MTD	maximum tolerated dose
MRI	magnetic resonance imaging
MUGA	multi gated acquisition scan

NOS	not otherwise specified
NRM	non-relapse mortality
NS	normal saline
OnCore™	Online Enterprise Research Management Environment
ORR	overall response rate
OS	overall survival
PCP	pneumocystis carinii pneumonia
PCR	polymerase chain reaction
PDT	photodynamic therapy
PFS	progression free survival
PI	principal investigator
PR	partial response
PS	photosensitizer
RFS	recurrence free survival
SAE	serious adverse event
SIRS	systemic inflammatory response
SRC	Scientific Review Committee
ULN	upper limit of normal
UPIRSO	unanticipated problems involving risks to subjects or others
USP	United States Pharmacopeia
WBC	white blood count

1.0 GOALS AND OBJECTIVES/SCIENTIFIC AIMSPrimary Objectives/Aims

1.1.1 To estimate the six month relapse-free survival (RFS) distribution in adults with recurrent gliomas

1.2 Secondary Objectives/Aims

1.2.1 To further explore and report descriptively the safety and tolerability of photodynamic therapy (PDT) in adults with recurrent glioma tumors

1.2.2 To obtain preliminary data toward determining whether this combination results in higher remission rate when compared to historical data

1.2.3 To further explore and report progression-free survival and overall survival for three years post PDT treatment

1.2.4 To measure complete response, partial response, stable disease or progressive disease using the response assessment for Neuro-Oncology (RANO) criteria with the follow-up medical imaging, which specifically incorporates volumetric measurements of brain tumor enhancement and clinical measures of neurological decline and to compare these outcomes to historical controls

2.0 BACKGROUNDIntroduction/Purpose

High-grade gliomas are highly vascular tumors with tendency to infiltrate. Tumor growth results in breakdown of the blood-brain barrier via secretion of vascular endothelial growth factor, which simulates angiogenesis and increases endothelial cell permeability.[57] Even with standard treatment of surgery, radiation and chemotherapy, these tumors almost always recur. Despite extensive research, little advancement has been made in the treatment changing overall survival. Treatment challenges exist, given the inherent nature of malignant tumor cells to migrate among the normal architecture of the brain, creating an intricate neuronal network. Even successful surgeries as evident by gross total resections are plagued with tumor recurrence nearly 100% of the time due to microscopic infiltrative disease. The presence of the blood-brain barrier limits the ability of systemically administered medications in reaching the target of action.

Studies have shown that a majority of malignant gliomas recur within 2 cm of the original tumor location and only a small number of patients achieve a long-term survival.[53, 54] New therapies to reduce local recurrence rate and late morbidities are urgently needed.

2.2 Photodynamic Therapy

Photodynamic therapy (PDT) is a paradigm shift from standard treatment for brain tumors. The principle behind PDT is light-mediated activation of a photosensitizer (PS) that is selectively accumulated in tumor cells resulting in tumor cell destruction through singlet oxygen production.[56] The PS agent is systemically administered and 24 hours later the tumor is surgically resected. Retained PS in tumor cells in the resection cavity is then activated using a laser light of appropriate wavelength resulting in tumor cell death. This approach has been used successfully in preclinical models of brain tumors[2,5,7] and in a small number of patients including some children[3,4]. The type of PS agent, the dose of PS and the light source have all shown to influence outcomes[3,4]. Optimizing the PS agent and laser light combination have not been performed and will be important to maximize efficacy and minimize toxicity of this novel therapeutic approach[41].

2.3 Hematoporphyrin Derivative and Photofrin®

Photofrin® is a second-generation hematoporphyrin derivative (HpD) that is selectively accumulated in tumor tissue compared with normal brain in preclinical models[32] and in human subjects[3,4]. Photofrin® targets tumor cells in addition to vascular structures providing a biologic advantage over others that primarily target tumor vasculature for disease control. Importantly,

the level of uptake of Photofrin® by normal brain cells in previous studies would be predicted to leave normal brain relatively unaffected by the photo-illumination.

A study from Australia using PDT in adult and a few adolescents with high-grade gliomas demonstrated 3 year survival overall survival rates of 37-56% [4], much greater than historical controls. Stylli, Kaye and colleagues found that the type of laser for photo-illumination was not important to patient outcome. They did show that higher laser light doses were associated with statistically improved long-term survival in patients with primary or recurrent high-grade gliomas. Importantly, their approach was associated with minimal immediate or late toxicities. Stylli, Kaye and colleagues used HpD (5 mg kg^{-1}) and Photofrin® (2.5 mg kg^{-1}) as the PS agent[4]. In 1981, Dougherty[73] separated HpD by gel exclusion chromatography and identified the component of the mixture responsible for the tumor photosensitizing ability. This component represented approximately 45% of the mixture and is the basis for the currently available commercial drug Photofrin®. The Stylli and Kaye et. al group has since revised his protocol to use 2.5 mg kg^{-1} of Photofrin® as the equivalent of the original 5.0 mg kg^{-1} of HpD (Stanley Stylli, MD, e-mail communication, April 2008).

2.4 Significance

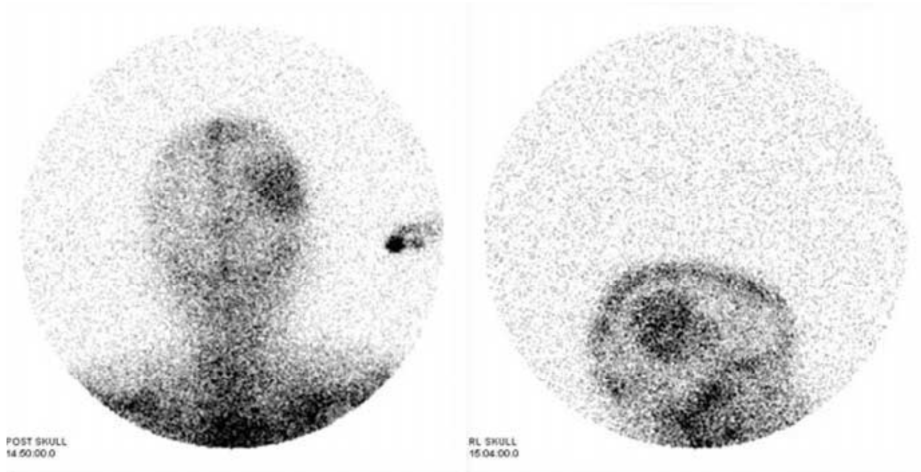
Brain and other nervous system cancers affect a substantial number of people, with 22,910 estimated new cases in the U.S. for the year 2012, and estimated deaths for 2012 of 13,700.[8] Migration of malignant brain tumor cells is a particular problem in the treatment of primary brain tumors, as few treatment options are available, and recurrent growth often occurs for most malignant tumors. Ultimately, blocking or controlling the infiltration of these cells may allow the prevention or amelioration of brain tumor dispersal. The development of a treatment that targets tumor cells dispersed in the surrounding cellular tissue would be a powerful tool in fighting the reoccurrence of brain tumors after primary interventions. Photodynamic therapy (PDT) is one such possible treatment.

PDT is a cancer treatment modality that involves a localized PS agent, which upon activation with light destroys tumors.[9-19] This tumor destruction is achieved by a selective retention of the PS in tumor cells, effecting cell destruction via the production of singlet oxygen upon localized illumination by light set at the appropriate wavelength.

For PDT to work effectively, it must be shown that the PS chosen is taken up by the targeted tumor cells in larger quantities than normal cells, and does so when using practical and safe dosage levels. Large molecules are normally prevented from entering the brain by the presence of the blood-brain barrier. An effective PS therefore must be able to pass this barrier, and be detected in tumor cells in amounts beyond that attributable to any physical breakdown of this

barrier. Uptake and biodistribution of PS agents such as hematoporphyrin derivative (HpD), its major component dihematoporphyrin (DHE), and the second generation HpD derivative Photofrin® have been investigated in several studies, using a variety of normal tissues and tumor models, and fluorescence, ^{3}H, ^{14}C, and ^{111}In detection.[20-32] For our studies, Photofrin® was labeled with Indium-111. Labeling yield of ^{111}In-Photofrin® was > 95%, as determined by chromatographic analysis.[32] In animal and human studies, the bio-distribution of conjugated ^{111}In-Photofrin® was determined using external imaging and quantitation with a gamma camera (Figure 1). ^{99m}TC-DTPA was used as a control for nonspecific uptake. Specific tumor uptake of the ^{111}In-Photofrin® occurred well beyond that resulting from blood-brain-barrier breakdown. Tissue levels of Photofrin® were seven times greater in tumor tissue than in the surrounding normal brain tissue, with the greatest concentration occurring at 24 hrs.[32] In our initial clinical study using doses from 0.75 mg kg^{-1} to 2.0 mg kg^{-1}, preferential tumor uptake was documented in humans. Overall, our studies indicate[7] that there is preferential uptake/retention of Photofrin® labeled with ^{111}In in tumor cells as compared to normal cells. Normal cells, therefore, should be relatively unaffected by the photoillumination.

Figure 1: 24 hour image of ^{111}In-labeled Photofrin® before tumor resection. The pictures demonstrate intense uptake of ^{111}In-labeled Photofrin® as shown by the darker areas visible in the anteroposterior and lateral views of a patient with an anaplastic ependymoma.[3]



A number of clinical studies have published updates on the use of HpD-PDT in human brain tumors.[17,19,34-38] HpD doses range from 2.0 - 10.0 mg kg^{-1}, with fluences ranging from 0.9 - 68 J cm^{-2}. In some studies, fluences are not given, but total radiant energy doses of 658 - 2028 J are reported. Overall, complications of PDT, such as skin photosensitization and cerebral edema, are within acceptable limits and many malignant gliomas showed a response to PDT which translated into prolonged survival.[16] However, these responses do not show the dramatic improvement in survival rates seen in the Australian study.[4] Development of a treatment protocol

matching these survival rates in the U.S. could provide a substantial improvement in domestic cancer treatments. In addition, most of the studies using Photofrin® have been done on adults and on supratentorial brain tumors.

2.5 Innovation

Since Photofrin® will preferentially accumulate in tumor cells in quantities beyond that due solely to diffusion or break down of the blood-brain barrier; these cells should selectively experience destruction upon exposure to light of the appropriate wavelength and of sufficient energy. Light in the near infrared range (NIR) can penetrate some distance through tissue, allowing it to reach cells containing PS, and will energize the PS with production of cell destructive singlet oxygen. Specifically, the attenuation depth (defined as 37% loss) in brain tissue, with 1.5 W of red light available, has been measured *in vivo* in the range of 2–4 mm,[19] with effective tumor necrosis to three times this distance.[39] With light generated at up to 2W the Multidiode PDT 4G laser available from Intermedic (Intermedic Arfran S.A., Spain), necrosis of tumor cells at a depth of 2 cm or beyond is not unreasonable. The majority of high-grade gliomas recurs within 2 cm of the original tumor location.[40] Photo-illumination commencing at the center of the tumor resection cavity, and falling on the tissue nearest the original tumor, should penetrate far enough into the tissue to reach tumor cells that have migrated away from the original site. In this manner, it is hoped to destroy any migrating brain tumor cells within 2 cm from the original tumor location, without harming the healthy cells in which they are dispersed.

The excellent results of the Australian group were obtained with a 4 W KTP laser.[4] The Multidiode PDT 4G laser is able to deliver the light at the power levels needed for effective tumor cell destruction. If we were to choose to use a much weaker light source than this, we would give the tumor cells a much better chance to repair photodynamic damage. As a result, we could end up with much reduced anti-tumor effect, even if we prolonged illumination times to compensate for the low fluence rate of the other light sources. In other words, photodynamic damage needs to be delivered at a rate that overwhelms tumor cell repair mechanisms. Optimal light and PS dosing regimens are necessary for effective PDT treatment of glioma patients. Up to now, light and PS dosing regimens have proven to be less than optimal, and there is need for further work in this area to optimize results.[41]

The use of the Multidiode PDT 4G laser to activate PDT agents in a short period of time also enhances patient safety. PDT will be delivered to the cavity left following tumor resection. Since patients will already be under general anesthesia for several hours for the preceding resection procedure, shortening the duration of the subsequent PDT stage, which may last up to 45 minutes, will certainly be advantageous.

2.6 Relevant Clinical Data

2.6.1 Photoillumination and Postoperative Intracranial Pressure

Muller and Wilson have reported that using photoillumination of the tumor cavity had increased intracranial pressure in the immediate postoperative period, but this was easily controlled with steroid therapy.[16,19] The PS used was either HpD or DHE, and fluences were 8-175 J cm^{-1}. As patients will typically be on steroid therapy, we do not anticipate problems with increased intracranial pressure; we will be paying special attention however to any increased steroid requirements. Muller also reported on 50 cases of malignant glioma treated with cavitary photoillumination and suggested that greater light doses resulted in increased survival.[16]

2.6.2 PDT Laser Light Dosing

Powers *et al*.[36] recently reported the results of 7 patients with recurrent gliomas treated with stereo tactically implanted optical fibers. Two of the 7 patients remained free of tumor more than 15 months after treatment. However, the other 5 patients had tumor recurrence within 2 months of their treatment that appeared at the border of the PDT-induced area of tumor necrosis and was located in the brain adjacent to tumor (BAT) medially adjacent to the solid tumor. Photofrin® levels were measured from surgical tissue specimens in all patients and showed adequate levels of PS in tumor and BAT for photosensitization. From this study it was concluded that tumor recurrence occurs as a result of insufficient light dose (658-2028 J) to the BAT and lack of photosensitization of tumor cells invading this region. These reports show the necessity for increased PS levels and greater light doses for activation in order to improve outcomes.

2.6.3 Stylli and Kaye et. al.: PDT 3 Year Survival Analysis

Clinical studies by Stylli and Kaye *et al*. [4] report on hematoporphyrin derivative (HpD) mediated–PDT that had been investigated as an adjuvant treatment for cerebral high-grade glioma. The study recorded the survival of patients at the Royal Melbourne Hospital, utilizing the Victorian Cancer Registry database for patients treated with adjuvant PDT following surgical resection of the tumor. For primary (newly diagnosed) tumors, median survival from initial diagnosis was 76.5 months for anaplastic astrocytoma (AA) and 14.3 months for glioblastoma multiforme (GBM). 73% of patients with AA and 25% with GBM survived longer than 36 months. For recurrent tumors, median survival from the time of surgery was 66.6 months for AA and 13.5 months for GBM. 57% of patients with recurrent AA and 37% of patients with recurrent GBM survived longer than 36 months. Younger patients (< 40) had even better survival. These survival data for high–grade glioma patients are superior to the current published survival rates in adult as well as pediatric studies. Laser light doses above the sample median of 230 J cm^{-2} were associated with better prognosis in the 136 patients studied. There was no mortality directly associated with the therapy; three

patients had increased cerebral edema thought to be related to PDT that was controlled with conventional therapies. No patients had permanent neurological deficit. Of the 29 patients who received chemotherapy, no association between the use of chemotherapy and prognosis following PDT was found.

2.6.4 Previous Phase 1 Clinical Data

We conducted a human brain tumor PDT study in 2004 that evaluated the toxicity of PDT based on both light– emitting diode (LED) and laser technology in selected patients with brain tumors [3]. Complete results are presented below in Table 1.

Table 1: Patient characteristic and tumor location in relation to PDT– exposed eloquent brain regions [3]

PT	Age (Yrs.)	Location of Tumor	Histology	Eloquency	Photosensitizer	Light Source	Neurotoxicity	Relapse Free Survival
1	14	Right parietal	Anaplastic ependymoma	Visual cortex	Photofrin® 2.0 mg kg^{-1}	Laser – balloon	None	11 months (treatment one)
	16	Right parietal	Ependymoma	Visual cortex	Photofrin® 2.0 mg kg^{-1}	Laser – balloon	None	3 months (treatment two)
	20	Left occipital	Ependymoma		Photofrin® 2.0 mg kg^{-1}	LED – balloon	None	9 months (treatment three)
2	21	Right temporal	Anaplastic oligoastrocytoma	Cerebral peduncle	Photofrin® 2.0 mg kg^{-1}	Laser – balloon	None	7 years 7 months (to date)
3	36	Left frontal	Anaplastic oligoastrocytoma	None	Photofrin® 2.0 mg kg^{-1}	Laser – balloon	None	1 year 5 months
4	17	Right frontal	Medulloblastoma	Thalamus	Photofrin® 2.0 mg kg^{-1}	Laser – fiber	None	10 months
5	14	Right frontal lobe	Central neuroblastoma	Speech	Photofrin® 2.0 mg kg^{-1}	Laser – balloon	None	8 weeks
6	1	Left parietal	Rhabdoid tumor	Speech	Photofrin® 2.0 mg kg^{-1}	Laser – balloon	None	10 weeks
7	19	Cerebellar vermis	Anaplastic astrocytoma	Floor of the 4^{th} ventricle	Photofrin® 2.0 mg kg^{-1}	Laser – fiber	severe truncal ataxia, bilateral facial weakness, dysphagia	3 years 10 months
8	48	Right occipital	Glioblastoma multiforme	Visual cortex	Photofrin® 2.0 mg kg^{-1}	Laser – balloon	None	9 months
9	1	4^{th} ventricle	Ependymoma	Floor of the 4^{th} ventricle	Photofrin® 2.0 mg kg^{-1}	Laser – balloon	None	4 months
10	51	Left frontal	Anaplastic oligoastrocytoma	None	Photofrin® 2.0 mg kg^{-1}	Laser – balloon	None	3 months

PT	Age (Yrs.)	Location of Tumor	Histology	Eloquency	Photosensitizer	Light Source	Neurotoxicity	Relapse Free Survival
11	45	Right temporal	Glioblastoma multiforme	Cerebral peduncle	Photofrin® 2.0 mg kg^{-1}	Laser – balloon	right facial nerve palsy	6 months
12	11	Brain stem & Left cerebellum	Pilocytic astrocytoma	Infratentorial	Photofrin® 2.0 mg kg^{-1}	Laser – balloon	None	6 months
13	12	Right frontal	Central neuroblastoma	None	Photofrin® 2.0 mg kg^{-1}	Laser – balloon	None	4 years 5 months (to date)
14	39	Right frontal	Astrocytoma	None	Photofrin® 2.0 mg kg^{-1}	Laser – balloon	None	4 years (to date)
15	20	Left frontal	Glioblastoma multiforme	None	Photofrin® 2.0 mg kg^{-1}	LED – balloon	None	4 months
16	18	Brain stem	Astrocytoma	Infratentorial, med. oblong.	Photofrin® 2.0 mg kg^{-1}	LED – balloon	None	2 months
17	15	Right temporal	Glioblastoma multiforme	Cerebral peduncle	Photofrin® 2.0 mg kg^{-1}	LED – balloon	None	2.5 months
18	51	Left posterior frontal	Glioblastoma multiforme	Motor cortex	Photofrin® 2.0 mg kg^{-1}	LED – balloon	None	2 months
19	59	Right temporal	Adenocarcinoma	None	BPD 0.25 mg kg^{-1}	LED – balloon	None	5 months
20	53	Left front temporal	Malignant meningioma	Speech	BPD 0.25 mg kg^{-1}	LED – balloon	None	5 months

Twenty patients (eight pediatric) with recurrent malignant brain tumors received 22 treatments with PDT and Photofrin® or Visudyn®. Sixteen tumors were supratentorial and four tumors were infratentorial. Eighteen patients received IV Photofrin® 24 hours prior to light exposure starting at 0.75 mg kg^{-1}. Two patients received LED light with 0.25 mg kg^{-1} of Visudyne®, a benzoporphyrin derivative (BPD, QLT, Vancouver, BC, Canada). Laser and LED arrays were used to deliver 100 J cm^{-2} of light to the sensitized tumors. Of the 22 PDT treatments, 15 treatments were performed with laser (13 by balloon adapter and two by fiber optic with 1.5 cm cylinder diffuser tip) and seven treatments by LED using a balloon adapter. At the maximum Photofrin® dose of 2.0 mg kg^{-1} five patients received laser–balloon adapter light exposure and five patients received LED light. Quantitative analysis of toxicity and time to progression was performed.

Only two patients displayed neurotoxicity, one after laser treatment using an interstitial fiber directly inserted into the tumor, and one with the laser–balloon adapter combination. Escalating doses of Photofrin® were tolerated to the maximum dose of 2.0 mg kg^{-1}. PDT in the posterior fossa or near eloquent brain was tolerated using the LED or laser–balloon adapter.

All patients had tumor responses as documented by MRI scan and the mean time to tumor progression after PDT was 67 weeks.

Eight of the patients were pediatric patients, all of whom received Photofrin®, who exhibited relapse–free survival times ranging from 8 weeks to 4 years 5 months (to date as of publication of the study) with a mean value of 12.6 months. None showed neurotoxicity. Of the 20 patients, four had tumors in the posterior fossa area, with one developing a significant neurological deficit. This patient was one of the two using interstitial fiber illumination.

The pediatric patients did not have any photosensitivity. Only one adult in the study had photosensitivity due to the use of the fiber optic involving the cerebellar peduncle near the brain stem and this was because the fiber optic catheter was next to brain tissue. None of the patients had any skin or eye photosensitivity.

This pilot data shows that PDT with LED or laser balloon–adapters (also tunable dye laser) has acceptable toxicity in brain tumor patients, and can be successfully used in both pediatric patients and in those with infratentorial tumors.

2.6.5 Pediatric Phase I Clinical Data

The pediatric phase I study CHW 13-31 is a dose–escalation study of Photofrin® in pediatric and adolescent patients with recurrent or refractory brain tumors. The primary objectives of this study are to identify a maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) and characterize the toxicity profile of Photofrin® in pediatric and adolescent patients with recurrent/refractory brain tumors.

Patients ranging in age from 6 months to 18 years with recurrent/refractory brain tumors will be eligible. Supratentorial and infratentorial (posterior fossa) brain tumors that are potentially resectable are eligible. Diagnoses include PNET (primitive neuro–ectodermal tumor), medulloblastoma, ependymoma, high–grade glioma, germ–cell tumor, and/or ATRT (atypical teratoid/rhabdoid tumor). Disease evaluation will be completed after completion of PDT, and at 1, 3, 6, 9, 12, 18, 24, 30 and 36 months thereafter. Dosing of Photofrin® will be based on body weight (kg). The trial started with a dose of 0.5 mg kg^{-1}. At this does level three patients were enrolled and there were no dose limiting toxicities (DLTs). (Phase I Dose Level 1 Toxicity Review Study Progress Report, December 2013) Doses will be escalated to 1.3 mg kg^{-1}, 2 mg kg^{-1} and 3 mg kg^{-1} in subsequent cohorts using a rolling three design [50]. The trial is currently open and accruing.

2.6.6 Correlative Nonclinical Studies

In addition to the 2004 clinical trial discussed above, our team has performed studies in PDT

using a canine glioma model, both *in vivo* and *in vitro*, [2, 6, 7] and human glioma cells *in vitro* [5, 7]. Also studied were radiolabeled PS uptake, [3, 7, 32] and alternate light sources and PS choices [3, 5–7]. This work provides a depth of background and experience encompassing nearly 20 years.

2.7 Rationale For The Adult Phase II Study

The survival of adult patients with recurrent brain tumors is measured in months with few long-term survivors. The methodology utilized by Stylli, Kaye and colleagues has shown impressive survival rates in adults and adolescents with high–grade gliomas with minimal acute or late toxicities. We believe the demonstrated efficacy and safety profile of the Stylli and Kaye methodology in adults warrants further study with recurrent/refractory high-grade gliomas. Medical College of Wisconsin is one of the few centers in the country with experience utilizing PDT technology for the treatment of brain tumors.[4] As a result we are uniquely poised to apply the methods used by Stylli, Kaye and colleagues. In addition, we also believe that we can further improve their encouraging results by partaking in a Phase II trial with Photofrin® at set dose of 2.5 mg/kg body weight and set light dose of 240 J cm^{-2} with wavelength at 630 nm.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

3.1 Regulatory IRB Approval

All institutional and FDA requirements for human studies must be met. Local IRB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit IRB continuing review and amendment approvals to the sponsor-investigator.

3.2 Patient Screening Process and Eligibility Assessment

3.2.1 Neuro-Oncology Tumor Board Patient Assessment

Potentially eligible patients will be screened by the Neuro-oncology Tumor Board, which is a group of MCW Neurosurgeons, Neuro-oncologists, a Pathologist, and a Radiologist. This group meets on a weekly basis to review cases. The team's review of the medical history, laboratory, pathology, and imaging results for each case is part of the standard clinical practice. Indication for tumor resection will be determined by evaluating all available imaging studies. This includes variety of specialized MRIs, which are completed on a case-by-case basis with prior insurance approval. If there is not enough evidence to reasonably rule out false positive MRIs, or pseudoprogression by the Neuro-oncology Tumor Board, the patient will not meet eligibility criteria. This is because patients must be clinically indicated for gross tumor resection as part of their standard of care plan for their disease status. Refer to Section 4.

3.2.2. PDT Protocol Specific Eligibility Assessment

An Investigator member of the study team and neuro-oncologist will screen and approve patient eligibility specifically for this protocol. The Screening and Eligibility Check List Case Report Form must be prepared by a member of the study team and signed by an investigator member of the study team. A copy of this documentation will be sent to the TRU Nurse to verify prior the administration of Photofrin®.

3.3 Informed Consent

All potential study participants will be given a copy of the IRB-approved consent to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the consent document. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

3.4 Patient Registration

After completion of the screening evaluation, an investigator member of the study team will document inclusion and exclusion eligibility confirmation. Written informed consent must be obtained prior to patient registration. Eligible patients will be registered by the Cancer Center Clinical Trials Office (CTO) using OnCore™ Clinical Trials Management System (CTMS).

3.5 Patients Who Do Not Begin Study Treatment

If a patient is registered on the study, and is later found not able to begin the planned study treatment, for whatever reason, the patient will be removed from study and treated at the physician's discretion. Study data will be collected until the time of study removal. The reason for removal from study will be clearly indicated on the case report forms.

If a patient begins treatment, and then is discontinued for whatever reason, the patient must be followed for 3 months for toxicity review.

4.0 PATIENT ELIGIBILITY

All clinical, imaging and laboratory studies to determine eligibility must be performed within 30 days prior to enrollment.

The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical or research record, which will serve as the source document for verification.

4.1 Inclusion Eligibility Criteria

1. Age: ≥ 18 years
2. Disease: Patients with relapsed or refractory high-grade glioma are eligible. Patients must have had histologic verification of malignancy at original diagnosis or relapse. Tumors must be supratentorial in location.
3. Disease Status: Patients must have potentially resectable disease.
4. Therapeutic Options: Patients' current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.
5. Performance Level: Karnofsky Score ≥ 50%.

   Note: Neurologic deficits in patients with CNS tumors must have been relatively stable for at least 7 days prior to study enrollment. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.
6. Predictable Life Expectancy: > 8 weeks
7. Prior Therapy: Patients must have fully recovered from the acute toxic effects of all prior anti–cancer chemotherapy. At least three weeks from previous chemotherapy and 4 weeks from prior radiation therapy

   Note: Although clinical determination of true progression vs. pseudoprogression may be difficult within the first 12 weeks following radiation and/or chemotherapy, qualified candidates need only be 4 weeks out from prior radiation and/or chemotherapy, a common standard of other recurrent glioma trials.
8. Organ Function:
   a. Adequate bone marrow function
      i. Absolute neutrophil count ≥ 1,000
      ii. Platelet count ≥ 100,000 (may transfuse to meet requirement)
   b. Adequate renal function

i. Creatinine clearance or radioisotope GFR ≥ 60~~70~~ mL/min/1.73 m^2

c. Adequate liver function
   i. Bilirubin (direct) ≤ 3X upper limit of normal (ULN) for age
   ii. SGPT (ALT) ≤ 10X ULN
      1. For the purpose of this study, the ULN for SGPT is 45 U/L
   iii. Serum albumin ≥ 2 g/dL

d. Adequate coagulation
   i. PT and INR ≤ 2X ULN , per institutional guidelines

9. Central Nervous System Function: Patients with seizure disorder may be enrolled if receiving non– enzyme inducing anticonvulsants and well controlled.
10. Informed Consent: All patients or legally authorized representatives must sign a written informed consent according to institutional guidelines.
11. All available archival tumor tissue slides disease evaluations should be reviewed by a Froedtert Health-MCW neuropathologist prior to study enrollment.

4.2 Exclusion Eligibility Criteria

1. Disseminated disease
2. Pregnancy or Breast–Feeding: Pregnant or breast–feeding women will not be entered on this study, as risks of fetal and teratogenic adverse effects of Photofrin® are not known.
3. Other concurrent tumor therapy
4. Subjects with porphyria
5. Subjects taking potentially photosensitizing drugs (Appendix 3)
6. The presence of adverse events of neurologic function, photosensitivity, or photophobia Grade 4 or higher (CTCAE Version 4.0)[47]
7. Allergy to eggs, soybean oil, or safflower oil (due to potential allergy against intralipids)
8. Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

5.0 TREATMENT PLAN

5.1 Overview of the Treatment Plan

5.1.1 Study Procedures

The study specific procedures include infusion of Photofrin® intra–operative laser activation of Photofrin®, 4 weekly history and physical assessments for toxicity review, and 2 week lab assessments for toxicity review. A table has been provide below for your reference. All other testing including laboratory, radiology as well as the schedule for follow–up will be performed as part of standard of care for patients with brain tumors undergoing therapy.

Study Specific Procedures	Study Calendar Time Frame	Requires A Study Specific Hospital Visit?
Informed Consent	Before Day 0	No
PDT Protocol Specific Screening & Eligibility Assessment	Day -30 to Day 0	No
HIPAA for Medical Record Follow-Up	Before Week +5	No
Preoperative Administration of Photofrin®	Day 0	Yes
Intraoperative Photodynamic Therapy Photoillumination	Day 1	No
History and Physical Assessments for Toxicity Review	1st Month Follow-up	No
Lab Assessments for Toxicity Review ▪ Complete blood count ▪ Renal function studies (BUN, creatinine) ▪ Hepatic function studies (ALT, AST, T bilirubin, alkaline phosphatase)	2 Week Postoperative Assessment	No
Medical Record Review & Prospective Follow-up*	Up to 3 Years Post PDT	No

- *A complete of Assessments collected from your medical record for this study is delineated in Appendix 1.*

5.1.2 Pre–Treatment Evaluation (Evaluation Table Appendix 1)

These must be obtained within 30 days of enrollment.

1. Complete history and physical examination (including a skin exam)
2. Karnofsky functional status

3. Complete neurological examination including visual acuity when possible
4. Laboratory assessment:
    a. Complete blood count
    b. Renal function studies (BUN, creatinine)
    c. Hepatic function studies (ALT, AST, T bilirubin, alkaline phosphatase)
    d. Endocrine function studies (TSH, Free T4, IGF–1, IGF–BP3, cortisol) as clinically warranted
5. MRI scan of the brain
6. MRI scan of the spine, only if clinically warranted

5.1.3 Preoperative Administration of Photofrin®

The subjects entering the study will receive a prescribed dose of 2.5 mg kg^{-1} of Photofrin® (supplied by Pinnacle Biologics, Inc., Bannockburn, IL), given intravenously over 3-5 minutes during an outpatient clinic visit, scheduled 24 hours prior to the planned surgical resection. Research participants will report to the Adult Translatoinal Research Unit (TRU) to receive the injection by a TRU nurse. Prior to the administration of Photofrin® the TRU nurse will assess the patient and ensure the patient has adequate protective gear and clothing for the patient's journey home and back to the hospital for tumor resection the following day. Subjects will have already received a PDT Patient Kit and instructions for protection from sunlight. Subjects will be advised to remain out of direct sunlight and bright artificial lighting for at least 30 days and up to 90 days after Photofrin® injection and PDT. (Appendix 2) If a photosensitivity reaction occurs, subjects are instructed to contact their physician immediately for guidance in the treatment of the reaction.

5.1.4 Surgical Treatment for Tumors – Craniotomy and Resection

Craniotomy and tumor resection will be carried out in the standard fashion in order to achieve the maximum tumor resection compatible with preservation of neurological function.

5.1.5 Operative Treatment and Intraoperative PDT of the Tumor

After tumor resection, room temperature Intralipid (Fresineus Kabi) will be infused into the open craniotomy and maintained for approximately 45-90 minutes, while PDT will be performed. The rational for the time frame listed includes the time it would take to drape the photosensitive patient, calibrate the optical fiber(s) verify the dose calculations, place the optical fibers in the tumor cavity, administer PDT laser light dose of 240 J cm^{-2}, and remove the optical fiber(s). All efforts will be made to minimize additional time in the OR. Up to a combination of 2 lasers may be used to supply the prescribed light dose of 240 J cm^{-2}.

The Intralipid will diffuse the light and ensure uniformity of light delivery, and will be replenished as needed at the discretion of the surgeon. The temperature of the tumor cavity can

be monitored by use of the Licox probe and should be maintained at normal body temperature (37°C).

Photoactivation of Photofrin® is controlled by the total light dose delivered over the treatment time. PDT lasers are equipped with a calibration unit to calibrate the fibers and yield the required power density output (mW) necessary to deliver a light dose of 240 J cm^{-2}. The illumination time will be calculated from the power density (mW) emitted by the laser through the fiber, and the radius (r) of the resection cavity to deliver a total light dose (energy) of 240 J cm^{-2} at a wavelength of 630 ± 3 nm using the following formula:

$$\text{Treatment Time (sec)} = \frac{\text{Light Dose (J cm}^{-2}) \times \text{Cavity Surface (cm}^2) \times 1000}{\text{Power Density (mW)}}$$

$$\text{Where, Cavity Surface (cm}^2) = 4 \cdot \pi \cdot r^2$$

The optic fiber or fibers output will be calibrated to the appropriate power density setting using the FDA approved laser calibration unit or units according to the procedure described in the laser manufacturer's instructions, or using a suitable external calibration unit.

The subject's head will be positioned on the operating table such that the tumor resection cavity is uppermost. The optical fiber will be placed in the approximate center of the surgical cavity and photoillumination will commence. The laser light exposure time will be calculated as above. An optic fiber probe may be used at the time of photoillumination to measure the light flux in the brain or brain tumor in order to ensure that no fall off of light penetration into the cavity surface occurs during treatment.

After PDT, the intralipid solution will be removed and the wound will be closed. The subject will be extubated, recovered from anesthesia, and then sent to the intensive care area for appropriate observation.

5.1.6 Acute Postoperative Care

1. When clinically indicated, subjects will be monitored in the Neurosurgical Intensive Care Unit for approximately 72 hours postoperatively or as long as deemed clinically appropriate by the care team.
2. When clinically indicated, subjects will have continuous intracranial pressure monitoring for approximately 48 postoperative hours or as long as deemed clinically appropriate.
3. When clinically indicated, subjects will receive postoperative dexamethasone at a dose

and for a time period dictated by their clinical condition. The dose and duration steroid administration will be recorded.

4. Subjects will receive anticonvulsants as deemed clinically appropriate.
5. Subjects will get an MRI of the resection site 1–3 days following PDT to assess the degree of resection
6. Subjects will receive any additional laboratory and imaging evaluations as clinically indicated.
7. Subjects will continue to be reminded and educated regarding PDT, the precautions in place to prevent phototoxicities by minimizing exposure to intense light and avoiding other phototoxic medications.

5.1.7 Follow–Up

- **Required Standard of Care MRI Evaluations:** Patients will have a post-operative MRI of brain on Day +2 (± 1 day), 1st-Month/Week +4 (± 3 days)follow-up, and 6-Month/Week +24 follow-up with and without gadolinium pending scan results, patient's clinical exam and healing of incision site.
- **First Month:** Patient will be followed in the neurosciences clinic at Froedtert Health-MCW Cancer Care Center for a minimum of once a week for four weeks following PDT as part of their postoperative standard of care for brain tumor resection. During these clinic visits, patients will have a history and physical exam including thorough neurological exam and documentation of medicines and doses administered. Interval history and physical exams will focus on identifying toxicities related to Photofrin® or the PDT procedure. Additional laboratory and imaging studies will be performed as clinically indicated.
- **After the First Month:** Many study participants will go on to receive additional anti-cancer therapy following recovery of neurosurgery during this time. Therapy dosing and schedule will also be recorded for study purposes as outlined in this protocol. Patients will be followed at a schedule to be determined by their respective treating physicians. For study purposes and as part of their routine care, patients will be evaluated from Week +1 to Year +3, as clinically indicated, without study specific follow-up time points. During this time, the study coordinator will report survival status when required for DSMC review, study progress reports, as well as FDA and IRB annual reports. This is outlined in Appendix 1. Evaluation will include a thorough history and physical, MRI of the resection area, medications and doses and laboratory evaluations deemed clinically appropriate.

5.2 Concomitant Therapy Restrictions

5.2.1 Concomitant Medications

Subjects should not receive other photsensitizing drugs while on protocol therapy or in toxicity review. Appendix 3 lists the commonly prescribed drugs that are known photosensitizers. Subjects must use precaution if receiving potentially photosensitizing drugs for the first three months following administration of Photofrin®. The patient and family will be instructed to call the Phase II team prior to starting any new medications in the first three months (until Week + 13, of Day + 90) after Photofrin® administration.

5.2.2 Post PDT Anticancer Therapy

Many of these patients will receive additional therapy for their recurrent cancer. Therapy dosing and schedule must be recorded for study purposes. Patients may begin other anticancer therapy regimens as early 1 month after PDT. Anticancer therapy starting before 3 months (90 days) after PDT should proceed with caution if the regimen contains any possible phototoxic agents.

5.3 Modifications For Toxicities

There will be no dose modifications for the administration of Photofrin®. All enrolled patients will receive 2.5 mg kg^{-1}. If the enrolled patient does not receive the full investigation drug dose or complete the intraoperative photodynamic therapy for any reason, the patient should be evaluated for toxicities for 90 days. The patient must follow the precautions and consideration of Photofrin® risks.

6.0 SUPPORTIVE CARE GUIDELINES AND OTHER CONCOMITANT THERAPY

6.1 Standard Surgical Risks

Supportive care and treatment for reported operative and postoperative adverse events associated with standard care craniotomy and resection will be given as appropriate to each patient (anti-emetics, antibiotics, transfusions, oxygen therapy, nutritional support, palliative treatment for pain etc.) according to institutional guidelines.

A. General postoperative complications
   1. Reversal agents for anesthetic complications—as needed if a preoperative level of consciousness is not obtained
   2. Respiratory complications
      a. Decreased level of consciousness and inability to protect airway following surgery
      b. Development of edema in and around the brain stem
   3. Cardiovascular complications
      a. Hypovolemic shock
      b. Blood pressure—usually normotensive state is maintained
      c. Cardiac arrhythmias
   4. Gastrointestinal complications—gastric stress ulceration and hemorrhage
   5. Endocrine complications
      a. Diabetes insipidus
      b. Syndrome of inappropriate antidiuretic hormone (SIADH)
      c. Cerebral salt wasting
   6. Infectious complications
      a. Meningitis
      b. Brain abscess
      c. Intracranial epidural abscesses
   7. Hematological complications
      a. Deep vein thrombosis (DVT)
   8. Pain

B. Specific neurologic complications
   1. Hemorrhage
   2. Increased intracranial pressure
   3. Peritumoral edema
   4. Cerebral infarction

5. Pneumocephalus
6. Hydrocephalus
7. Seizures
8. Cerebrospinal fluid leak
9. Cranial nerve deficits
10. Wound infection

6.2 Supportive Care for Intraoperative PDT Risks

Increased surgical risk due to the PDT procedure is expected to be minimal, as the subject will be undergoing a standard care tumor resection.

6.2.1 Photoillumination of the Tumor Resection Cavity

The addition of an illumination stage results in minor additional risk limited to increased temperature due to light energy. An Intralipid bath will be utilized to control for this possibility. Intralipid has micron-sized lipid droplets that efficiently scatter the light. By placing the distal end of the laser fiberoptic directly in this lipid droplet suspension the 630 nm laser light is evenly distributed within the tumor resection cavity, thus activating Photofrin® evenly over the entire exposed tumor inner surface area. This reduces risk of any areas of over- or under-exposure to light, controlling the photodynamic effect, and avoiding "spotty" overdose or under-dose.

6.2.2 Intraoperative Photosensitivity Precautions

Reduced light settings and patient draping will be used to avoid potential problems from bright surgical lights, whenever possible. In addition, measuring oxygen saturation with pulse oximetry (pulse ox) exposes the skin to red light, which may cause skin burns if left in one place too long. When a pulse ox is used during neurosurgery, acute postoperative care and after approximately 30 days have elapsed (or as long as photosensitivity is experienced), care should be taken to have the photo detector/sensor device moved to a new location every few minutes. Use different fingers and toes if necessary. Continuous monitoring can 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.

6.3 Photofrin® Risks and Guidelines

6.3.1 Photosensitivity

The major risk of Photofrin® skin photosensitivity sensitivity, which will persist for some time after the procedure. Risks of photosensitivity can be avoided by taking light exposure

precautions. As such, all patients who receive Photofrin® will be instructed to avoid exposure of skin and eyes to direct sunlight or bright indoor light (from examination lamps, including dental lamps, operating room lamps, un-shaded light bulbs at close proximity, etc.) for at least 30 days. Some patients 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.

6.3.2 Ocular Sensitivity

Ocular sensitivity to sun, bright lights, or car headlights, causing ocular discomfort, can occur in patients who receive Photofrin®. For at least 30 days and until ocular sensitivity resolves, patients will be instructed, to wear dark sunglasses when outdoors. Sunglasses have an average white light transmittance of < 4% and will reduce risk of ocular sensitivity.

6.3.3 Photobleaching Precautions

Exposure of the skin to ambient indoor light is, however, beneficial because the remaining drug will be inactivated gradually and safely through a photobleaching reaction. Therefore, patients should not stay in a darkened room during this period and should be encouraged to expose their skin to ambient indoor light. The level of photosensitivity 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 patient should test it for residual photosensitivity. A small area of skin should be exposed to sunlight for 10 minutes. If no photosensitivity reaction (erythema, edema, blistering) occurs within 24 hours, the patient can gradually resume normal outdoor activities, initially continuing to exercise caution and gradually allowing increased exposure. If some photosensitivity reaction occurs with the limited skin test, the patient should continue precautions for another 2 weeks before retesting. The tissue around the eyes may be more sensitive, and therefore, it is not recommended that the face be used for testing. If patients travel to a different geographical area with greater sunshine, they should retest their level of photosensitivity. Conventional ultraviolet (UV) sunscreens will only protect against UV light-related photosensitivity and will be of no value in protecting against induced photosensitivity reactions caused by visible light.

6.3.4 Use Before or After Radiotherapy

If PDT is to be used before or after radiotherapy, sufficient time should be allotted between the two therapies to ensure that the inflammatory response produced by the first treatment has subsided before commencing the second treatment. The inflammatory response from PDT will depend on tumor size and extent of surrounding normal tissue that receives light. It is recommended that 2 to 4 weeks be allowed after PDT before commencing radiotherapy. Similarly, if PDT is to be given after radiotherapy, the acute inflammatory reaction from radiotherapy usually subsides within 4 weeks after completing radiotherapy, after which PDT may be given.

6.3.5 Hepatic and Renal Impairment

Hepatic or Renal impairment will likely prolong the elimination of porfimer sodium leading to higher rates of toxicity. Patients with severe renal impairment or mild to severe hepatic impairment should be clearly informed that the period requiring the precautionary measures for photosensitivity may be longer than 90 days.

6.3.6 Thromboembolism

Thromboembolic events can occur following photodynamic therapy with Photofrin®. Most reported events occurred in patients with other risk factors for thromboembolism including advanced cancer, following major surgery, prolonged immobilization, or cardiovascular disease.

6.3.7 Pulse Oximetry Use Precautions

In addition, the use of pulse oximetry (pulse ox) exposes the skin to red light, which may cause skin burns if left in one place too long. Up to 30 days or as long as photosensitivity is experienced, after receive Photofrin®, care should be taken to have the photo detector/sensor device moved to a new location every few minutes. Use different fingers and toes if necessary. Continuous monitoring can 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.

6.4 Overall Adverse Reaction Profile

Systemically induced effects of photodynamic therapy (PDT) with Photofrin® consist of photosensitivity and mild constipation. All patients who receive Photofrin® will be photosensitive and must observe precautions to avoid sunlight and bright indoor light. Photosensitivity reactions occurred in approximately 20% of cancer patients and in 69% of high-grade dysplasia (HGD) in Barrett's esophagus (BE) patients treated with Photofrin®. Typically these reactions were mostly mild to moderate erythema but they also included swelling, pruritus, burning sensation, feeling hot, or blisters. In a single study of 24 healthy subjects, some evidence of photosensitivity reactions occurred in all subjects. Other less common skin manifestations were also reported in areas where photosensitivity reactions had occurred, such as increased hair growth, skin discoloration, skin nodule, skin wrinkling and increased skin fragility. These manifestations may be attributable to a pseudoporphyria state (temporary drug-induced cutaneous porphyria).

In the Australian study conducted in 136 adult patients, there were no direct serious complications from the PDT itself. One patient died from acute myocardial infarction and another suffered a hemiplegia (total paralysis of the arm, leg, and trunk on the same side of the

body) after tumor resection. Three patients had increasing drowsiness (somnolence) and hemiparesis (muscle weakness on only one side of the body) associated with cerebral edema (excess accumulation of water in the brain) despite usual doses of steroid. All three cases resolved after the use of steroids and diuretics.

In the US pediatric and adult study, two out 20 patients developed complications. Immediately postoperatively, one patient developed severe truncal ataxia (lack of muscle coordination), bilateral facial weakness as well as dysphagia (difficulty swallowing). The other patient who underwent an extensive reoperation followed by laser light PDT, had a right facial nerve palsy (paralysis), which improved in 3 months, but did not completely resolve.

6.5 Phlebotomy Risks

Inserting a needle for blood sampling can be associated with some discomfort and bruising and, although very rarely, inflammation of the arm veins or possible infection.

Infusion reactions: Infusion reactions including urticaria, bradycardia, hypotension, dizziness, and hypertension

6.6 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of Photofrin® with PDT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

6.7 Concurrent Anticancer Therapy

Concurrent anticancer therapy not defined within this protocol, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug (from Day –30 to Day +30). If anticancer therapeutics are administered to the patient during this time he or she may (1) not be permitted to begin protocol therapy, (2) be removed from protocol therapy, (3) be considered inevaluable for toxicity review and/or survival analyses.

6.8 Other Investigational Agents

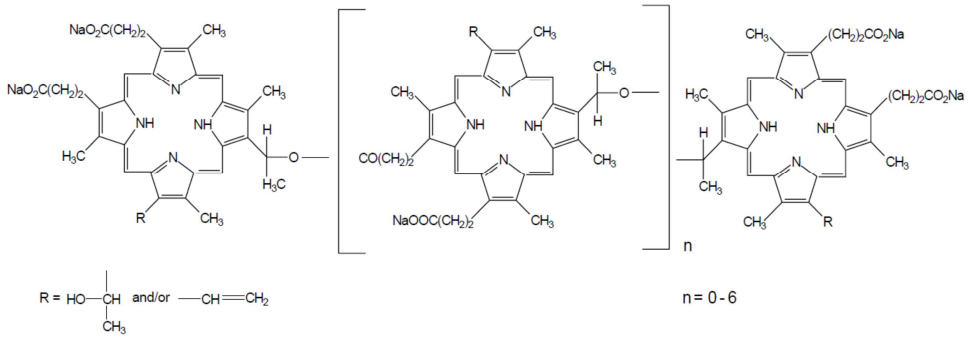
Other investigational agents not specified in this protocol may NOT be given while the patient is on protocol therapy, or during the first month follow-up for toxicity review.

7.0 INVESTIGATIONAL DRUG AND DEVICE INFORMATION

7.1 Photofrin ® (porfimer sodium, 75 mg) for Injection

7.1.1 Description

Photofrin® (porfimer sodium) for Injection is a photosensitizing agent used in the photodynamic therapy (PDT) of tumors and of high-grade dysplasia (HGD) in Barrett's esophagus (BE). Following reconstitution of the freeze-dried product with 5% Dextrose Injection (USP) or 0.9% Sodium Chloride Injection (USP), it is injected intravenously. This is followed 40–50 hours later by illumination of the tumor or HGD in BE with laser light (630 nm wavelength). Photofrin® is not a single chemical entity; it is a mixture of oligomers formed by ether and ester linkages of up to eight porphyrin units. It is a dark red to reddish brown cake or powder. Each vial of Photofrin® contains 75 mg of porfimer sodium as a sterile freeze-dried cake or powder. Hydrochloric Acid and/or Sodium Hydroxide may be added during manufacture to adjust the pH to within 7.2 – 7.9. There are no preservatives or other additives. The structural formula below is representative of the components present in Photofrin®



7.1.2 Pharmacology

The cytotoxic and antitumor actions of Photofrin® are light and oxygen dependent. Photodynamic therapy with Photofrin® is a two-stage process. The first stage is the intravenous injection of Photofrin®. Clearance from a variety of tissues occurs over 40-72 hours, but tumors, skin, and organs of the reticuloendothelial system (including liver and spleen) retain Photofrin® for a longer period. Illumination with 630 nm wavelength laser light constitutes the second stage of therapy. Tumor selectivity in treatment occurs through a combination of selective retention of Photofrin® and selective delivery of light. Cellular damage caused by Photofrin® PDT is a consequence of the propagation of radical reactions. Radical initiation may occur after Photofrin® absorbs light to form a porphyrin excited state. Spin transfer from Photofrin® to molecular oxygen may then generate singlet oxygen. Subsequent radical reactions can form superoxide and hydroxyl radicals. Tumor death also occurs through ischemic necrosis secondary

to vascular occlusion that appears to be partly mediated by thromboxane A2 release. The laser treatment induces a photochemical, not a thermal, effect. The necrotic reaction and associated inflammatory responses may evolve over several days.

7.1.3 Pharmacokinetics

Following a 2 mg kg^{-1} dose of porfimer sodium to 4 male cancer patients, the average peak plasma concentration was 15 ± 3 mcg/mL, the elimination half-life was 250 ± 285 hours, the steady-state volume of distribution was 0.49 ± 0.28 L kg^{-1}, and the total plasma clearance was 0.051 ± 0.035 mL min^{-1} kg^{-1}. The mean plasma concentration at 48 hours was 2.6 ± 0.4 mcg mL^{-1}. The influence of impaired hepatic function on Photofrin® disposition has not been evaluated.

Photofrin® was approximately 90% protein bound in human serum, studied in vitro. The binding was independent of concentration over the concentration range of 20–100 mcg mL^{-1}.

The pharmacokinetics of Photofrin® was also studied in 24 healthy subjects (12 men and 12 women) who received a single dose of 2 mg kg^{-1} Photofrin® given via the intravenous route. The serum decay was bi-exponential, with a slow distribution phase and a very long elimination phase. The elimination half-life was 415 ± 104 hours (17 ± 4.3 days). C_{max} was determined to be 40 ± 11.6 mcg/mL and AUC_{inf} was 2400 ± 552 mcg × hourmL^{-1}. Women had a lower C_{max} and a higher AUC. The clinical significance of these differences is unknown. T_{max} was approximately 1.5 hours in women and 0.17 hours in men. At the time of intended photoactivation 40-50 hours after injection, the pharmacokinetic profiles of Photofrin® in men and women were similar.

7.1.4 Drug Interactions

There have been no formal interaction studies of Photofrin® and any other drugs. However, it is possible that concomitant use of other photosensitizing agents (e.g., tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide diuretics, griseofulvin, and fluoroquinolones) could increase the risk of photosensitivity reaction.

Photofrin® PDT causes direct intracellular damage by initiating radical chain reactions that damage intracellular membranes and mitochondria. Tissue damage also results from ischemia secondary to vasoconstriction, platelet activation and aggregation and clotting. Research in animals and in cell culture has suggested that many drugs could influence the effects of PDT, possible examples of which are described below. There are no human data that support or rebut these possibilities.

Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulfoxide, β-carotene, ethanol, formate and mannitol would be expected to decrease PDT activity. Preclinical data also suggest that tissue ischemia, allopurinol, calcium channel blockers and some

prostaglandin synthesis inhibitors could interfere with Photofrin® PDT. Drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A_2 inhibitors, could decrease the efficacy of PDT. Glucocorticoid hormones given before or concomitant with PDT may decrease the efficacy of the treatment.

7.1.5 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been conducted to evaluate the carcinogenic potential of Photofrin®. In vitro, Photofrin® PDT did not cause mutations in the Ames test, nor did it cause chromosome aberrations or mutations (HGPRT locus) in Chinese hamster ovary (CHO) cells. Photofrin® caused < 2-fold, but significant, increases in sister chromatid exchange in CHO cells irradiated with visible light and a 3-fold increase in Chinese hamster lung fibroblasts irradiated with near UV light, Photofrin® PDT caused an increase in thymidine kinase mutants and DNA-protein cross-links in mouse L5178Y cells, but not mouse LYR83 cells. Photofrin® PDT

Pregnancy Category C: Porfirmer sodium has been shown to have an embryocidal effect in rats and rabbits when given in doses 0.64 times the recommended human dose on a [mg m^{-2}] basis. Porfimer sodium given to rat dams during fetal organogenesis intravenously at 0.64 times the clinical dose on a [mg m^{-2}] basis for 10 days caused no major malformations or developmental changes. This dose caused maternal and fetal toxicity resulting in increased resorptions, decreased litter size, delayed ossification, and reduced fetal weight. Porfimer sodium caused no major malformations when given to rabbits intravenously during organogenesis at 0.65 times the clinical dose on a [mg m^{-2}] basis for 13 days. This dose caused maternal toxicity resulting in increased resorptions, decreased litter size, and reduced fetal body weight.

Porfirmer sodium given to rats during late pregnancy through lactation intravenously at 4 [mg m^{-2} per day] (0.32 times the clinical dose on a [mg m^{-2}] basis) for at least 42 days caused a reversible decrease in growth of offspring. Parturition was unaffected.

There are no adequate and well-controlled studies in pregnant women. Photofrin® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Photofrin® women receiving Photofrin® must not breast feed.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Approximately 70% of the patients treated with PDT using Photofrin®

in clinical trials were over 60 years of age. There was no apparent difference in effectiveness or safety in these patients compared to younger people. Dose modification based upon age is not required.

7.1.6 Photofrin® Administration

Photofrin® should be administered as a single slow intravenous injection over 3 to 5 minutes at 2.5 mg kg^{-1} body weight. Reconstitute each vial of Photofrin® with 31.8 mL of either 5% Dextrose Injection (USP) or 0.9% Sodium Chloride Injection (USP), resulting in a final concentration of 2.5 mg mL^{-1}. Shake well until dissolved. Do not mix Photofrin® with other drugs in the same solution. Photofrin® reconstituted with 5% Dextrose Injection (USP) or with 0.9% Sodium Chloride Injection (USP), has a pH in the range of 7 to 8. Photofrin® 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. 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.

7.1.7 Supplying/Order, Storage, and Handling

Supplied: Photofrin® (porfimer sodium) for Injection is supplied as a freeze-dried cake or powder as follows: NDC 76128-155-75, 75 mg vial

Supplier: Pinnacle Biologics, Inc., as subsidiary of Concordia Laboratories Inc.

Agent Ordering: The study site's investigational pharmacy will place orders with Pinnacle Biologics using their trial specific order form.

Storage: Photofrin® freeze-dried cake or powder should be stored at Controlled Room Temperature 20-25 °C (68-77 °F) [

Spills and Disposal: Spills of Photofrin® should be wiped up with a damp cloth. Skin and eye contact should be avoided due to the potential for photosensitivity reactions upon exposure to light; use of rubber gloves and eye protection is recommended. All contaminated materials should be disposed of in a polyethylene bag in a manner consistent with local regulations.

Accidental Exposure: Photofrin® is neither a primary ocular irritant nor a primary dermal irritant. However, because of its potential to induce photosensitivity, Photofrin® might be an eye

and/or skin irritant in the presence of bright light. It is important to avoid contact with the eyes and skin during preparation and/or administration. As with therapeutic over dosage, any overexposed person must be protected from bright light.

7.2 Photodynamic Therapy (PDT) Lasers

The following PDT Lasers may be used to administer the prescribed light dose of 240 J cm^{-2}, with the output laser power at the fiber tip ranging from 1.0 to 4.0 watts. One or two lasers may be used at a time to administer the PDT. When utilizing two lasers any combination of the laser listed or two of the same can be used. Please notify the Sponsor Investigator and the Industry Collaborator, Pinnacle Biologics, Inc. to ensure availability and approval of the PDT Laser for each enrolled case.

- Angiodynamics DIOMED 630 PDT Laser
- Laserscope KTP/532® Surgical Laser System (Series 800)
- Laserscope KTP/YAG® Surgical Laser System (Series 800)

7.3 Photodynamic Therapy (PDT) Light Diffusers: Optical Fibers

Optical fibers serve to diffuse the laser light in the brain tumor cavity. One optical fiber will be needed for each laser. Optical fibers must be sterilized one time use only. Currently, the protocol is using a spherical light diffuser manufactured by MedLightSA, Model SD200.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical and Laboratory and Disease Evaluations

A list of the required clinical and laboratories has been provided in Appendix 1. This includes a table of the study specific and standard of care events and evaluations necessary to answer the primary and secondary aims as well as additional evaluations of the patient's medical records, which should be reported in the patients study record for the overall survival analysis and data safety monitoring.

8.2 Follow-up

Data from the subjects' medical records will be collected up to three years following completion of the protocol therapy. Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule. This long-term follow-up from Week +5 to Week +156 (3-Year follow-up) will be evaluated as clinically indicated, and/or according to their Anti—cancer therapy follow-up schedule up to Year +3. During this time, the study coordinator will report data from the medical record on study specific CRFs periodically. Current follow-up data must be reported for all required and routine semiannual DSMC reviews, study progress reports, including the FDA and IRB Annual Reports.

9.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

9.1 Criteria for Removal from Protocol Therapy

1. Refusal of further protocol therapy by patient/legally authorized representative
2. Physician determines it is in patient's best interest.
3. Patient becomes pregnant while on study.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

9.2 Off Study Criteria

1. Death
2. Lost to follow-up
3. Withdrawal of consent for any further data submission
4. The third anniversary of the date the patient was enrolled on this study

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design

This Phase II study includes adults with recurrent high-grade gliomas refractory to first line treatment (concurrent radiation and Temodar followed by maintenance Temodar). Eligible patients will consist of individuals with supratentorial recurrent high-grade gliomas that are surgically amenable, are not multi-focal and are without leptomeningeal spread. Eligible patients will have injection of Photofrin® at 2.5 mg kg^{-1}, followed by surgical resection of the tumor 24 hours later. Craniotomy and tumor resection will be carried out in the standard fashion in order to achieve the maximum tumor resection compatible with preservation of neurological function. Tissue sample will be evaluated via frozen technique and discussed with the neurosurgeon before proceeding with Photofrin® activation. Patient must have dx of a high-grade glioma before the surgery to be a candidate. Activation of residual Photofrin® in the tumor bed, after resection, will be performed using an intra-operative laser with set light dose of 240 J cm^{-2} and wavelength at 630 nm. Patients will receive standard post-operative care including observation in the post-anesthesiology recovery unit followed by post-operative computerized tomography (CT) of the brain and close monitoring in the neuro-intensive care unit (NICU). Magnetic resonance imaging (MRI) of the brain will be obtained on Day +2 (± 1 day) following the surgery. An MRI will be obtained again at 4 weeks after surgery. Patient will be closely monitored at Froedtert Health-MCW for toxicities associated with Photofrin®.

This is a single arm Phase II study of Photofrin® with set dosing of 2.5 mg kg^{-1} body weight in adult patients with recurrent or refractory high-grade glioma. The primary objective of this study is to evaluate antitumor activity of Photofrin® and laser light activation by evaluating 6 month relapse-free as well as overall survival for three years post PDT treatment We will follow progression-free survival and overall survival for three years post PDT treatment.

Any individual over the age of 18 with a recurrent/refractory high-grade glioma meeting the criteria for the study will be considered a candidate. Photofrin® will be dosed at 2.5 mg kg^{-1}.

10.2 Sample Size and Study Duration

The sample size is based on a single-arm phase II study designed to detect an increase in the 6-month relapse-free survival rate from the historical value of 35% (treated as fixed) to 55%. With 29 subjects with known 6-month outcome, the study will have 80% power to detect such an increase at a one-sided 10% significance level. This calculation is slightly conservative, because

it does not incorporate the increase in the estimated survival rate from censored observations, thus the actual power might be slightly higher. A censoring rate of less than 5% is expected, so 30 patients will be enrolled in the study. The following table shows the estimated power of the study under various hypothetical values of 6-month relapse-free survival.

6-month RFS	Power
45%	43%
50%	64%
55%	**82%**
60%	93%
65%	98%

10.3 Methods of Analysis

Survival probabilities will be estimated by using the product limit estimate technique. Overall survival and Relapse-free survival will be visualized using Kaplan-Meier plots. Greenwood's formula will be used to estimate the variance. The 6-month relapse free survival will be compared to the historical control value of 35% via a one-sided z-test at a 10% significance level.

10.4 Methods of Analyses for Secondary Objectives

In this single arm phase II trial, the secondary objectives are considered exploratory and will be reported descriptively based on appropriate statistical methods and accounting for patients who may undergo additional anticancer therapy post documentation of a sustained objective response. It is not possible to determine how many patients will provide data that may be used to address each of the secondary objectives. Central review histological diagnoses will be compared with diagnoses reported by the treating site. We will assess the potential impact of any differences on primary conclusions of this study. Considerations will be accounted for when making comparisons of survival and disease free survival for recurrent glioma patients. Refer to Appendix 4

10.5 Inclusion of Genders and Minorities

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities

to such studies. The small number of patients entered into this trial will obviate any analysis of variation in response rate with gender or ethnicity.

11.0 EVALUATION CRITERIA

11.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website. Additionally, toxicities are to be reported on the appropriate case report forms. Refer to sections 12 and 13 for details.

Please note: 'CTCAE v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (ie, v4.02 and all subsequent iterations prior to version 5.0).

11.2 Methodology to Determine Tumor Measurement

Radiographic response should be determined in comparison to the tumor measurement obtained at pretreatment baseline for determination of response, and the smallest tumor measurement at either pretreatment baseline or after initiation of therapy should be used for determination of progression. In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, observe the patient closely, for example at 4-week intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the date of the scan at which this issue was first raised. The determination of radiographic response after treatment with agents, such as antiangiogenic therapies, that affect vascular permeability is particularly difficult. In these patients, consideration should be given to performing a second scan at 4 weeks to confirm the presence of response or stable disease. All measurable and nonmeasurable lesions should be assessed using the same techniques as at baseline. Ideally, patients should be imaged on the same MRI scanner, or at least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

11.3 Response Criteria

Secondary outcomes will be measured using the response assessment for Neuro-oncology (RANO) criteria[58] applied to follow-up medical imaging. Specifically, complete response, partial response, stable disease or progressive disease will be determined using volumetric measurements of brain tumor enhancement and clinical measures of neurological decline.

1. Complete response requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
2. Partial response requires all of the following: > 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
3. Stable disease will require all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
4. Progression will be defined by any of the following: > 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

These criteria are published and currently accepted in the neuro-oncology community[58]. The imaging interpretation will be completed by a board certified neuro-radiologist, while the neurological outcome/status will be assessed by a board certified neurologist/neuro-oncologist.

12.0 ADVERSE EVENT REPORTING REQUIREMENTS

12.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

12.2 Expedited Reporting Requirements

See Next Page…

12.2.1 Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the Sponsor-Investigator within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs.	10 Calendar Days	Initial Report: 24-Hours Full Report: 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs.	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention if they occur within 90 days after the last administration of investigational agent/intervention.

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

12.3 Expedited Reporting the Sponsor Investigator Examples

12.3.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Events (SAEs) occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours. Any SAE occurring ***greater than 30 and up to 90 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

12.3.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported to the sponsor if it occurs at any time following treatment with an agent under an IND/IDE since these are considered serious AEs.

12.3.3 Death

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours. Any death occurring ***greater than 30 and up to 90 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

Reportable Categories of Death

- Death attributable to a CTCAE term
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5
- Death NOS : A cessation of life that cannot be attributed to a CTCAE term associated with grade 5
- Death due to progressive disease should be reported as ***Grade 5 "Neoplasms benign, malignant and unspecified (includes cysts and polyps) - Other (Progressive Disease)"*** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

12.4 Reporting Methods for SAEs

Steps to Determine if an Adverse Event Related to DRUG or the Regimen as a Whole is to be Reported in an Expedited Manner

Step 1: Identify the event type using the NCI Common Toxicity Criteria (CTC), version 4.0.
The CTC provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTC can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, if assistance is needed, the NCI has an Index to the CTC that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTC.

Step 2: Grade the event using the NCI CTCAE.
This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website. Additionally, toxicities are to be reported on the appropriate case report forms.

Step 3: Determine whether the adverse event is related to the protocol therapy.
The investigator will assess the causal relationship between the investigational product and the adverse event. The investigator will use his/her clinical expertise and judgment to select the attribution category below that best fits the circumstances of the AE.

Attribution Categories:

❖Unrelated❖	❖Unlikely❖	❖Possible❖	❖Probable❖	❖Definite❖

Unrelated:
- The adverse event is clearly unrelated to the investigational agent(s).
- Does not follow a known response pattern to the suspect investigational product (if response pattern is previously known)
- Can be explained by the known characteristics of the patient's clinical state or therapy administered to the patient

Unlikely:
a. The adverse event is doubtfully related to the investigational agent(s).
b. May or may not follow a reasonable temporal sequence from administration of the investigational product.
c. Likely explained by the known characteristics of the patient's clinical state

or other therapy administered to the patient

Possibly Related:

a. The adverse event may be related to the investigational agent(s).
b. Follows a reasonable temporal sequence from administration of the investigational product
c. May also be reasonably explained by the patient's clinical state or therapy administered to the patient.
d. May follow a known response pattern to the investigational product (if response pattern is previously known)

Probably Related:

a. The adverse event is likely related to the investigational agent(s).
b. Follows a reasonable temporal sequence from administration of the investigational product
c. May follow a known response pattern to the investigational product (if response pattern is previously known)
d. Could not be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient, if applicable;

Definitely Related:

a. The adverse event is clearly related to the investigational agent(s).
b. Follows the temporal sequence from administration of the investigational product
c. Follows a known response pattern to the investigational product
d. Cannot be explained by the known characteristics of the patient's clinical state or other therapy administered to the patient
e. Is confirmed by improvement of symptoms on stopping or slowing administration of the investigational product and re-emergence of symptoms on restarting administration of the investigational product, (if applicable)

Step 4: Determine the prior experience of the adverse event.

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the toxicities listed in the drug information section of the protocol.

Step 5: Report the adverse events as outlined in the protocol.

12.5 Reporting Requirements – Investigator Responsibilities

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.
Note: All expedited AEs must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

12.6.1 Additional Protocol Specific Reporting Requirements

12.6.1 Reporting to the Medical College of Wisconsin/Froedtert Hospital IRB

The Principal Investigator will submit timely reports to the MCW/FH IRB including any unanticipated problems, serious adverse device and drug events occurring during the investigation, and any deviation from the investigational plan, either unintentional or made to protect the life or physical wellbeing of a subject in an emergency. Any UPIRSO's, Internal Adverse Events, Adverse Device or Drug Effects, or other events meeting the MCW/FH IRB prompt reporting criteria will be reported no later than 5 calendar days after the study team becomes aware of the problem, event or information. All other adverse events will be reported at time of continuing review in accordance with MCW/FH IRB policy. Non–serious Adverse Events (collected from Day 0 to Day +30/1-Month follow-up) and non-serious/administrative protocol deviations will be collected and reported on an annual basis as per MCW/FH IRB policy. SAEs (collected from Day 0 to Day +90) that are unrelated to the study will be reported to the IRB on an annual basis via the DSMC Study progress reports. Refer to section 13.3 for details. SAEs require DSMC expedited review will be reported to the IRB within 5 calendar days.

12.6.2 Reporting to Pinnacle Biologics, Inc.

The industry collaborator, Pinnacle Biologics, Inc. is an international company with obligations in several European countries to quickly report all SAEs from all ongoing clinical trials using Photofrin®. We have developed a reporting plan that will facilitate Pinnacle's reporting requirements while safeguarding patient's confidentiality.

Reporting Serious AEs:
The investigator will report each SAE, regardless of causality, within 24 hours of awareness by

e–mail, or fax to the Pinnacle Biologics, Inc. third party Drug Safety delegate. This includes SAEs occurring as soon as the patient or patient's legally representative signs the informed consent (i.e., pre–treatment SAEs). The SAE form provided by Pinnacle Biologics, Inc. should be completed as thoroughly as possible, given the information available and time constraints.
A full initial report accompanied by additional relevant information documenting the occurrence of the event should be forwarded to the Drug Safety delegate within 4 calendar days (in case of death or life–threatening events) or 7 calendar days (for other SAEs) respectively. Follow up report should be forwarded within the next 5 calendar days (in case of death or life–threatening events) or as soon as this information is available (for other type of events).

In addition, any spontaneously reported SAE that occurs within 30 days after the last study procedure for patient who completed the study protocol or within 90 days after the Photofrin® injection for patients who prematurely discontinued study treatment should be recorded and reported.

Other Events Requiring Expedited Reporting:
The following events should be also reported to the Drug Safety delegate within 24 hours of awareness:

- Any pregnancy that occurs to study patients. Drug exposure during pregnancy should be reported on the "Pregnancy Exposure form" provided by Pinnacle Biologics, Inc.
- Drug or light dose overdose with or without adverse events
- Inadvertent or accidental exposure to the study drug with or without adverse events
- All other medication errors (use of expired medication, dosing errors, etc.) with or without adverse events
- Suspected transmission of an infectious agent
- SAEs that meet the criteria for expedited reporting to the Data Safety Monitoring Committee for this clinical trial. Refer to section 13.3.

Reporting Non–Serious AEs
Non–serious Adverse Events should be collected by the Investigator, but do not require expedited report to Pinnacle Biologics, Inc. Because this protocol is a FDA IND study, these events are to be reported periodically (as per FDA regulations) by Pinnacle Biologics, Inc. and listed in the final study report. Listings will be provided to Pinnacle Biologics, Inc. periodically.

12.6.3 Reporting to the Data Safety Monitoring Committee
Please refer to section 13.3.

12.7 Routine Adverse Event Reporting

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all expedited reportable events and Grade 3 and higher Adverse Events.

13.0 STUDY DATA COLLECTION AND SAFETY MONITORING

13.1 Data Management

This Cancer Center CTO will report clinical trial data using The Online Enterprise Research Management Environment (OnCore™), a web based Oracle® database utilizing study specific trial management tracking forms. Key study personnel are trained on the use of OnCore™ and will comply with protocol specific instructions embedded within the OnCore™ forms. Patient demographics, patient specific study treatment calendars, adverse events, reporting of deaths, and other information required for annual reporting will be placed in OnCore™ and other research databases maintained by MCW IT.

13.2 Case Report Forms

Initial Plans: Participant data will be collected using protocol specific case report forms developed by the sponsor. The CRFs will be approved by the study's Principal Investigator and the Biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the patient at time of study entry, completing CRFs based on the patient specific calendar or roadmap, and updating the patient record until the end of required study participation.

Implementation of REDCap Database: Participant data will be collected using protocol specific electronic case report forms (e-CRFs) developed within REDCap based on its library of standardized forms. The e-CRF will be approved by the study's Principal Investigator and the Biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the patient into REDCap at time of study entry, completing e-CRFs based on the patient specific calendar, and updating the patient record until the end of required study participation.

REDCap (Research Electronic Data Capture) is a secure web application for building and managing online surveys and databases hosted by the Medical College of Wisconsin (MCW), a CTSA consortia partner, who manages and maintains the IT infrastructure and environment in which REDCap functions. This includes the web server and database server, the communication

between those two servers, and the communication of the web server with the REDCap end–user. MCW hosts REDCap according to typical best practices with the web server and database server function two separate servers located securely behind a firewall, as required by institutional policy. Secure access requires a username/password and a Secure Sockets Layer Certificate (SSL) is in order to maintain secure communication with the end–user to login to REDCap.

This secure, web–based application designed to support data capture for research studies, providing:

1. An intuitive interface for validated data entry
2. Audit trails for tracking data manipulation and user activity
3. Automated data export and de–identification procedures for seamless data downloads to common statistical packages
4. Built–in project calendar, a scheduling module, ad hoc reporting tools
5. Advanced features – branching logic, file uploading, and calculated fields

Monitors, auditors, and other authorized agents of the United States Food and Drug Administration, as well as that of any other applicable government agencies, will be granted direct access to the study subjects' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

13.3 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will comply with the Medical College of Wisconsin Cancer Center's Data & Safety Monitoring Plan (DSMP). For the purposes of data and safety monitoring, this study is classified as moderate risk. Therefore, the following requirements will be fulfilled:

13.3.1 Routine Reporting to the Data Safety Monitoring Committee

Study Progress Reports: The PI and Study Statistician will complete and submit a Semi-Annual Study Progress Report, every 6 months, to the MCW Cancer Center Data and Safety Monitoring Committee (DSMC) with the understanding the MCW DSMC may require more frequent reporting. Contents of the Study Progress Reports will include the information provided in the following provided table:

Table:	**Content of Routine Study Progress Reports to the DSMC**

Table: Content of Routine Study Progress Reports to the DSMC	
Section 1: Protocol Administration	▪ Number ▪ title ▪ PI ▪ Dates of IRB approval and activation ▪ Listing of agents, dose level, route, schedule
Section 2: Demographics	▪ Number of patients enrolled ▪ M/F ▪ ages ▪ diagnoses ▪ prior treatment ▪ performance status ▪ disease status
Section 3: Phase II [per arm]	▪ Dose ▪ number of patients ▪ number of courses ▪ Adverse event table with frequency and severity ▪ DLT's observed ▪ SAE's encountered ▪ Efficacy parameters: response, and biomarkers, if applicable
Section 4: SAE's	▪ All SAE reports
Section 5: Patient Listing	▪ Date enrolled ▪ dose level ▪ # courses ▪ maximum AE severity ▪ presence or absence of DLTs observed ▪ SAEs ▪ overall response ▪ overall outcome ▪ survival status

13.3.2 Expedited Reporting to the Data Safety Monitoring Committee

SAEs that will be assessed for trial monitoring/stopping are defined as any of the following events with possible attribution to the experimental intervention(s) (the investigational drug,

investigational device, and/or investigational therapy). This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website. Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (ie, v4.02 and all subsequent iterations prior to version 5.0).
The DSMC will be notified within 5 calendars days of all serious adverse events occurring within 30 days after receipt of protocol therapy, which meets the criteria of one or more of the following:

Monitoring of Serious Adverse Events for Stopping Guidelines

1. Photosensitivity:
Skin changes of Grade 4 or higher occurring within 4 weeks of Photofrin® injection.

2. Ocular Sensitivity:
Photophobia of Grade 4 or greater occurring within 4 weeks of Photofrin® injection.

3. Neurotoxicity:
Attributing a measured decline in neurologic status to either resection or PDT will be difficult as many patients have deficits from surgical resection alone. In addition, many patients have significant neurological changes immediately post–op that improve with time and steroids. These transient neurological deficits are believed to be secondary to acute tissue injury followed by inflammation. Most transient neurological deficits improve within the first month post–op, while fixed deficits do not. Fixed deficits have a greater impact on overall quality of life. For the purposes of this study neurotoxicity will be defined as persistent neurological deficits measured at 4 weeks of Grade 4 or greater, or a decline of 2 levels (i.e. 1 to 3) when compared to pre–operative testing, recorded baseline toxicities. The study team will attempt to localize deficiencies using MRI, clinical exams and other testing (i.e. EEG) to the brain outside of the resection, but within the penumbra of the photodynamic effect (within 2 cm of the surgical field) to help with attribution (surgery versus PDT) when possible.

4. Any other hematologic or non–hematologic toxicity Grade 4 or higher.

Both progression free survival (PFS) and overall survival (OS) will be tracked.

13.3.3 Interim Analysis and Stopping Guidelines

There will be no interim analysis for efficacy (i.e., overall survival endpoint). Monitoring for the safety endpoint of SAE occurrence related to Photofrin®, as determined by the PI, will be conducted as described in the next section. If rates significantly exceed pre-set thresholds, the Data and Safety Monitoring Committee (DSMC) will be consulted. The stopping guidelines serve as a trigger for consultation with DSMC for additional review, and are not formal "stopping rules" that would mandate automatic closure of study enrollment.

13.3.4 Safety Monitoring and Stopping Guidelines

To ensure the safety of patients on study, SAEs will be reported by 4 Weeks post PDT as defined in section 13.3.1 or section 13.3.2. The 6-month relapse free survival status will be determined based on radiological assessment as defined by section 11 and standard of care medical exam carried out at Week +24. Expected enrollment is 30 patients over the course of 3 years. The stopping guidelines are summarized in the table below.

Table: Stopping Guideline for Dose Limiting Toxicities or 6-month Relapse Free Survival

Number of patients (n)	Stopping boundary (x)
1-6	2
7-12	3
13-18	4
19-30	5

** Stopping guideline is triggered if ≥ x patients out of n experience a SAE with attribution to the protocol*

13.4 Monitoring

The investigator will permit study-related monitoring, audits, and inspections by the applicable compliance groups/regulatory bodies. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

13.4.1 Clinical Site Monitoring

This protocol will be monitored by an individual or group of individuals from the MCW Cancer Center who are not directly or indirectly responsible for the supervision of this trial. Monitoring

will occur at a minimum of once per year to ensure all regulatory aspects of this study comply with the FDA and any other applicable regulatory boards/bodies.

13.4.2 Supervision of Clinical Trial Reporting

The Sponsor-Investigator will oversee the submission of all reportable events per the definition of reportable in Section 13 to the MCW Cancer Center's DSMC. The PI will oversee the submission of all reportable events to the FDA, MCW/FH IRB, Industry Collaborators, and other required regulatory agencies as outlined in section 12 of the protocol.

13.5 Record Retention

The investigator will retain study records including source data, copies of case report forms, consent forms, and all study correspondence in a secured facility for at least 10 years after the study file is closed with the IRB and FDA.

In addition, the Cancer Center Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient. Please contact the CTO before destroying any study related records.

14.0 CONDUCT OF STUDY

14.1 Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

14.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, informed consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

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APPENDIX 1: PHOTODYNAMIC THERAPY (PDT) EVALUATION TABLE

STANDARD OF CARE & STUDY SPECIFIC EVENTS & EVALUATIONS	PRE–STUDY	TREATMENT PHASE			POST-OP FOLLOW–UP				LONG–TERM FOLLOW–UP		
	Day –30 To Day 0	Day 0: Photofrin®	Day +1: PDT Photoillumination	Day +2 To Discharge: Post–Op Care	Week 1 To 4 (Week No.): 1	2	3	4	Week 5 to 13: (Patient SOC Plan)	Week 24: (6 Months Post PDT)	Week 52 to 156: (Patient SOC Plan)
SCREENING											
Neuro-Oncology Eligibility Review	**X**	**X**									
ENROLLMENT & REGISTRATION											
Informed Consent	**X²**		**X**								
HIPAA Authorizations for Follow-Up Reports	**X²**										
Eligibility Checklist & Registration CRFs	**X²**										
TREATMENT											
Photofrin® Dose Calculation, Preparation, & Duration (Start & Stop Time)		**X²**									
Tumor Resection			**X**								
PDT Photoillumination Dose Calculation, Preparation, & Duration (Start & Stop Time)			**X²**								
ACUTE POST–OP CARE											
Dexamethasone Dose			X[1]	X[1]	X[1]	X[1]	X[1]	X[1]			
Intracranial Pressure Monitoring			X[1]	X[1]							
LABS											
CBC	**X**			X[1]	X[1]	**X²**	X[1]	X[1]	X[1]		
BUN	**X²**			X[1]	X[1]	**X²**	X[1]	X[1]	X[1]		
Creatinine	**X²**			X[1]	X[1]	**X²**	X[1]	X[1]	X[1]		
ALT	**X²**			X[1]	X[1]	**X²**	X[1]	X[1]	X[1]		
AST	**X²**			X[1]	X[1]	**X²**	X[1]	X[1]	X[1]		
Total Bili	**X²**			X[1]	X[1]	**X²**	X[1]	X[1]	X[1]		
ALK	**X²**			X[1]	X[1]	**X²**	X[1]	X[1]	X[1]		
PT	**X²**			X[1]	X[1]	**X²**	X[1]	X[1]	X[1]		
PTT	**X²**			X[1]	X[1]	**X²**	X[1]	X[1]	X[1]		
Other[1]	X[1]			X[1]	X[1]	X[1]	X[1]	X[1]	X[1]		
EVALUATIONS											
H & P	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Skin Exam	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X[1]		
Karnofsky Score	**X**			**X**	**X**	**X**	**X**	**X**	X[1]	**X**	X[1]
Neurologic Exam	**X**		**X**	**X**	**X**	**X**	**X**	**X**	X[1]	**X**	X[1]
MRI Brain	**X**			**X**	X[1]	X[1]	X[1]	**X**	X[1]	**X**	X[1]
MRI Total Spine	X[1]			X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Required CTCAE Reporting [Grade(s)]		**1–5**	**1–5**	**1–5**	**1–5**	**1–5**	**1–5**	**1–5**	**3 – 5**		
All Concomitant Medications		**X**	**X**	**X**	**X**	**X**	**X**	**X**	X[1]		
Anti-Cancer Therapy: Chemo/XRT/Surgery									**X**	**X**	**X**
Disease Evaluations									X[1]	**X**	X[1]
Survival Status/Cause of Death (if applicable)		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

X Required Reporting & SOC for the Patient X[1] **Recorded IFF Clinically Indicated According to the Patient's SOC** **X² Required Study Event; Not SOC**

APPENDIX 2: PATIENT INFORMATION SHEET

What is photodynamic therapy?

Photodynamic therapy (PDT) is an experimental treatment for brain tumors in adults. PDT has been used successfully in adults with high-risk, brain tumors that recurred after treatment with chemotherapy or radiation therapy. PDT uses a medicine called Photofrin® given into a vein that accumulates in tumor cells more than normal cells. The brain tumor is surgically removed and then Photofrin® in the remaining tumor cells is activated by light delivered by a laser at the time of surgery. Light-activated Photofrin® then kills the tumor cells.

How is this medicine given, and what are its side effects?

Photofrin® is given intravenously (IV), or into a catheter in a vein, the day before surgery. Medicines that are given IV may affect cells in many parts of the body. As a result, it is important for you to know that this medicine will make your skin and eyes very sensitive to bright light for at least 30 days and up to 90 days after it is given. You need to follow special precautions to protect yourself from serious side effects from exposure to bright light during this time. Sunburn-like reactions, including redness, itching, a burning sensation, a feeling of warmth, and discomfort on exposed skin, can occur. In severe reactions, blisters and swelling develop. When these reactions are seen, it is called **phototoxicity**.

On the day you receive Photofrin® , it is important to take the following actions:

- Close your window shades at home before you come to the hospital
- Wear the following protective items, or bring them to the hospital to wear home:
  - Dark sunglasses (light transmittance of less than 4%)
  - Gloves (canvas or leather, not knit)
  - Wide-brimmed hat (not straw)
  - Long-sleeved shirt (tightly woven fabric that does not allow light to penetrate)
  - Scarf, pants, socks and shoes
- For individuals who drive, please note that dark sunglasses may impact your ability to drive or use machinery. As a result, be sure you have transportation home from the hospital.

Are there any special precautions while on this medication?

For at least the first 30 days after receiving Photofrin®, it is important to take the following actions:

- Avoid bright light. Examples of bright light include the following:
  - Direct sunlight, including direct light from skylights
  - Neon lights
  - Halogen and spotlights
  - Un-shaded light bulbs at close proximity
  - Exam lights used by health care providers, including a dentist or an eye doctor
  - Tanning salon lights
  - Make-up lights
- Wear protective items, as described above, if you must be exposed to bright light. Avoid bright light and going outdoors during the day, if at all possible.
- Wear dark sunglasses when outdoors.
- If you travel to a different geographic area, be sure to retest your skin's level of sensitivity to light in the new location.
- Watching TV or using a computer is fine.
- Remember that some individuals may remain sensitive to light for up to 90 days or more.

In addition, there are additional guidelines based on the number of days since Photofrin® was given:

- On Days 1-3 after Photofrin® is given: dim the lights indoors and keep the curtains and blinds closed.
- On Days 4-14 after Photofrin® is given: keep the curtains and blinds closed, but you no longer need to dim the lights indoors. Once you have reached the fourth day, exposure to normal indoor light is helpful, since it assists the body to inactivate the Photofrin® that has reached the skin.
- On Days 14-30 after Photofrin® is given, keep curtains and blinds closed if the sun is coming into the room.
- On Day 31 after Photofrin® is given, test different areas of skin to determine the level of phototoxicity still remaining.

How do I test my skin's level of sensitivity to light?

The level of sensitivity to light will vary for different areas of the body. Before exposing any area of skin to direct sun or bright indoor light, you should test that area's sensitivity to light. See an example of how to test your skin's level of sensitivity to light listed below.

Test Instructions:

- Cut a 2-inch hole in a paper bag and put your hand in the bag.
- Expose only this area to sunlight for 10 minutes. Keep the rest of your skin covered.

- The next day, check if your skin shows a reaction. If you do not get a red area, swelling, or blisters, you can then gradually resume normal outdoor activities. At first, use great caution and gradually increase your exposure to light. Try not to go outside during the middle of the day when the sun is brightest.
- If a phototoxicity reaction occurs with the skin test, you should continue precautions for another 2 weeks before retesting this area of skin again.
- The skin around the eyes is sensitive, so do not use the fact to test the skin's sensitivity to light.

Will sunscreen prevent phototoxicity?

Sunscreen will **NOT** protect your skin or eyes from phototoxicity. Sunscreen bought in drugstores or in supermarkets is not sufficient because it only protects against ultraviolet light and will not protect your skin from visible light.

When should I call a doctor?

- Call the study doctor before taking any new medicines.
- Call the study doctor if you experience any signs of phototoxicity.

APPENDIX 3: COMMONLY PRESCRIBED PHOTOTOXIC DRUGS

This is NOT intended to be a comprehensive list of all Phototoxic medications, but a list of medications that are commonly taken by cancer patients. You should consult your physician before taking any new medications, prescribed by a doctor or over the counter, in the first three months of the study to determine if these medications could contribute to phototoxicity (skin or eye changes).

Antibiotics/Antifungals

- Quinolones (ciprofloxacin, levofloxacin)
- Tetracyclines (tetracycline, doxycycline)
- Sulfonamides (sulfamethoxazole/trimethoprim, clotrimazole)
- Azoles (voriconazole, itraconazole, terbinafine, griseofulvin)
- Dapsone

Antihistamines

- Diphenhydramine

Cancer Chemotherapy Drugs

- 5-fluorouracil (5-FU, Efudex, Carac, Fluoroplex)
- Vinblastine (Velban, Velsar)
- Dacarbazine (DTIC-Dome)
- Paclitaxel

Cardiac Drugs

- Amiodarone (Cordarone)
- Nifedipine (Procardia)
- Quinidine (Quinaglute, Quinidex)
- Diltiazem (Cardizem, Dilacor, Tiazac)

Diabetic Drugs

- Sulfonylureas (chlorpropamide, glyburide, glipizide)

Diuretics

- Loop diuretics (furosemide, bumetanide)
- Thiazides (hydrochlorothiazie)

Epidermal Growth Factor Receptors

- Cetuximab
- Erlotinib
- Panitumumab
- Lapatinib

Malaria Medications

- Quinine (Quinerva, Quinite, QM-260)
- Chloroquine (Aralen)
- Hydroxychloroquine (Plaquenil)

Painkillers

- Nonsteroidal anti-inflammatory drugs (naproxen, aleve, piroxicam, ibuprofen)

Psychiatric Drugs

- Phenothiazines (Chlorpromazine)
- Tricyclic antidepressants (desipramine, imipramine)

Retinoids

- Isotretinoin (Accutane)
- Acitretin (Soriatane)

Skin Medications

- Photodynamic therapy for skin cancer (ALA or 5-aminolevulinic acid (Levulan), Methyl-5-aminolevulinic acid)

APPENDIX 4: OVERVIEW OF PUBLISHED LITERATURE: PHOTODYNAMIC THERAPY

Reference [Study Phase] ▪ Approach	N	Type of Brain Tumor GBM	AA	Other	Photosensitizer [Dose]	Light Density [J/cm^2]	Median Overall (Progression Free) Survival [months] Group ID	Primary	Recurrent
Stupp[59] [phase 3] ▪ TMZ	573	Control 287					Control	**12.1 (5.0)**	
		TMZ 286					TMZ	**14.6 (6.9)**	
Akimoto[60] [case series] ▪ i/o cavitary spot	14	10		4	Talaporfin sodium [40 mg m^{-3}]	27		**26 (23)**	**9 (3)**
Muragaki[61] [case series] ▪ i/o cavitary spot	22	13	3	6	Talaporfin sodium [40 mg m^{-3}]	27	**27.9 (20)**	**24.8 (12)**	
Stylli[62] [case series] ▪ i/o cavitary Intralipid pool	136	78	58		Hematoporphorin derivative (HpD) [5 mg kg^{-1}]	70-240	GBM	**14.3**	**13.5**
							AA	**76.5**	**66.6**
Rosenthal[63] [phase 1] ▪ i/o cavitary Intralipid pool	28	16	8		Boronated porphyrin (BOPP) [0.25-8 mg kg^{-1}]	25-100	GBM	**5**	**11**
							AA		**18**
Schmidtl[3] [phase 1] ▪ i/o cavitary balloon	20	5	3	12	Photofrin® [0.75 - 2.0 mg kg^{-1}]	100			
Stummer[64] [phase 3] ▪ FGR	243	Control 115		Control 16	5-ALA [20 mg kg^{-1}]		Control	**13.5 (3.6)**	
		FGR 122		FGR 17			FGR	**15.2 (5.1)**	
Beck[65] [case series] ▪ interstitial	10	10			5-ALA [20 mg kg^{-1}]				**15**
Kostron[66] [case series] ▪ i/o cavitary superficial &interstitial	58	50			HpD [2.5 mg kg^{-1}]	250		**19**	**7**
Kostron[67] [phase 3] ▪ i/o cavitary balloon or diffusor	52	Control 26			Foscan (mTHPC) [0.15 mg kg^{-1}]	20		**3.5**	
		PDT 26						**8.5**	
Eljamel[68] [phase 3] ▪ FGR post-operative cavitary	27	Control 14			5-ALA FGR Photofrin® PDT [20 mg kg^{-1} 2 mg kg^{-1}]	100	Control	**5.6 (4.8)**	
		PDT 13					PDT	**12.2 (8.6)**	
Lyons[69] [phase 2] ▪ FGR post-operative cavitary ▪ repetitive balloon ▪ IORT	73	ST 25			5-ALA FGR Photofrin® PDT [20 mg kg^{-1} 2 mg kg^{-1}]	100	ST	**4.6**	
		ST+ PDT 13					ST+PDT	**9.2**	
		ST+IORT 18					ST+IORT	**11.2**	
		ST+PDT+IORT 17					ST+PDT+IORT	**18.2**	
Muller[71, 70] [phase 3] ▪ unknown	77	Control 34			Photofrin® [2 mg kg^{-1}]	120	Control	**8**	
		PDT 43					PDT	**11**	
Muller[72] [case series] ▪ i/o cavitary balloon & fiber	96	49	24	26	Photofrin® [2 mg kg^{-1}]	58 ± 17	GBM	**7.6**	**6.7**
							Non-GBM	**15.5**	**13.8**