Clinical Protocol

Title:	**An International, Multi-Center, Randomized, Double Blind Placebo Controlled Phase II Study to Evaluate the Safety and Efficacy of Lucanthone Administered as an Adjunct to Radiation and Temozolomide for Primary Therapy of Glioblastoma Multiforme**
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1 LIST OF ABBREVIATIONS

Table 1 Abbreviations and specialist terms

Abbreviation or specialist term	Explanation
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
C_{max}	Maximum Serum Concentration
CR	Complete Response
CRF	Case Report Form
CRA	Clinical Research Associate
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum Vitae
dL	Deciliter
DLT	Dose Limiting Toxicity
ECG	Electro Cardiogram
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GBM	Glioblastoma multiforme
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
mg	Milligram
mL	Milliliter
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NOAEL	No Adverse Effect Level
PFS	Progression Free Survival
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RANO	Criteria for Response Assessment Incorporating MRI and Clinical Factors
ORR	Objective Response Rate
SAE	Serious Adverse Event
SEC	Securities and Exchange Commission

t½	Half-life
TID	Three times daily
TMZ	Temozolomide
US	United States of America

2 SYNOPSIS

Title	An International, Multi-Center, Randomized, Double Blind Placebo Controlled Phase II Study to Evaluate the Safety and Efficacy of Lucanthone Administered as an Adjunct to Radiation and Temozolomide for Primary Therapy of Glioblastoma Multiforme
Phase	II
Study sites	Approx. 12 sites in US and India
Planned number of patients	140
Investigational Product	Lucanthone
Dose	10-15 mg/kg/day
Route of administration	Oral
Primary Objective	To determine the efficacy of lucanthone when given along with temozolomide (TMZ) and radiation in the primary treatment of glioblastoma multiforme (GBM) due for radiation and TMZ treatment.
Secondary Objective	To evaluate the safety and toxicity of lucanthone when used in combination with temozolomide (TMZ) and radiation in primary treatment of GBM due for radiation and TMZ treatment.
Primary end-point	Progression free survival at 9 months
Secondary end-point	• ORR at months 2, 4, 6, 9 and 12 • PFS at one year • Overall survival at one year • Safety profile of Lucanthone at 10-15 mg/kg/day
Patient Population	Male or female patients between 18 and 70 years of age with bidimensional measurable GBM eligible for radiation and TMZ treatment
Study Design	This is an international, multicenter, randomized, double blind placebo controlled phase II study to evaluate the safety and efficacy of lucanthone administered as an adjunct to patients receiving primary treatment of GBM with temozolomide and radiation. Eligible patients will be randomized to lucanthone or placebo arm in ratio of 1:1. The treatment period will be in two phases ; an initial six weeks of concomitant therapy with temozolomide and radiation, followed by a maintenance phase of six cycles of temozolomide given on Days 1 to 5 of a 28-day cycle. Lucanthone / placebo will be given as an add on in both concomitant and maintenance phases.
Study Duration	The total treatment period for a patient is approximately 7 ½ months, and the total duration of the study for a patient is one year.
Randomization	Patients will be randomized in 1:1 fashion to one of two groups. • Radiation + TMZ + Lucanthone • Radiation +TMZ + Placebo
Efficacy evaluation	MRI – head. The size of the enhancing tumor will be defined as the product of the largest perpendicular diameters of enhancement.
Data Monitoring Committee	Data Monitoring Committee (DMC) will be constituted to review the safety data generated by the study. The committee will be responsible for reviewing and monitoring safety of the clinical trial on a regular basis. The data monitoring committee will provide recommendations concerning the safety of the patients and suggest any interventions if deemed necessary.
Safety evaluation	AEs, ECG, CBC, Blood chemistry and Urinalysis
Adverse Event Reporting	Adverse events will be captured from the first dose of study drug until 9-month

Period	follow-up visit.

3 INTRODUCTION

Over the past two decades, virtually no progress has been made in the treatment of recurrent brain tumors. Treatment of malignant brain tumors with conventional approaches is largely unsuccessful because curative therapeutic doses generally cannot be delivered without excessive toxicity to normal brain (Zalutsky 1). Primary brain tumors are traditionally treated with a combination of surgery, chemotherapy and radiation (NCI 20).

Brain tumors account for 85% to 90% of all primary central nervous system (CNS) tumors (CBTRUS 2). Available registry data from the Surveillance, Epidemiology, and End Results (CBTRUS 2, SEER 3) (database for 1996 to 2000) indicate that the combined incidence of primary invasive brain tumors in the United States is 6.6 per 100,000 persons per year with an estimated mortality of 4.7 per 100,000 per year (CBTRUS 2, SEER 3). Worldwide, approximately 176,000 new cases of brain and other CNS tumors were diagnosed in the year 2000, with an estimated mortality of 128,000 (CBTRUS 2). With such a high mortality rate, much attention of brain tumor treatment has been focused on novel therapies (Milker-Zabel 4).

Anaplastic astrocytoma and glioblastoma account for approximately 38% of primary brain tumors; meningiomas and other mesenchymal tumors account for approximately 27% (CBTRUS, Levin 5). Other less common primary brain tumors include pituitary tumors, schwannomas, CNS lymphomas, oligodendrogliomas, ependymomas, low grade astrocytomas and medulloblastomas in decreasing order of frequency. The clinical presentation of these brain tumors varies with their location (CBTRUS, Levin 5). General signs and symptoms include headaches; gastrointestinal symptoms such as nausea, loss of appetite and vomiting; and changes in personality, mood, mental capacity, and concentration. Other clinical presentations of brain tumors include focal cerebral syndromes such as seizures (CBTRUS 2, Levin 5).

While overall mortality remains high, recent work leading to an understanding of the molecular mechanisms and gene mutations combined with clinical trials have led to more promising and tailored therapeutic approaches. Multiple challenges remain, including tumor heterogeneity, tumor location in a region where it is beyond the reach of local control, and rapid, aggressive tumor relapse. The treatment of most malignant brain tumors still remains palliative and includes surgery, radiation therapy and chemotherapy (Bruce 6) Radiation therapy in addition to surgery or surgery combined with chemotherapy has shown to prolong survival in patients with malignant brain tumors (Bruce 6). Temozolomide is an orally active alkylating agent that is used for malignant glioma patients. It was approved by the United States Food and Drug Administration (FDA) in March 2005. Temozolomide is 100 % orally bioavailable, enters cerebrospinal space , does not require hepatic metabolism for activation, demonstrates reproducible linear pharmacokinetics, and has non cumulative myelosuppression that is rapidly reversible (Friedman 37).Studies have shown that this drug is well tolerated and provides a survival benefit. Temozolomide with radiation was associated with significantly improved median progression-free survival (6.9 versus 5 months), overall survival (14.6 versus 12.1 months), and the likelihood of being alive 2 years

(26% versus 10%) (Bruce 6). The American Association of Neurological Surgeons (AANS)/ Congress of Neurological Surgeons (CNS) guidelines for treatment of newly diagnosed GBM recommend chemotherapy with temozolomide both during and after radiation (Fadul 38).There are no standard therapies for a patient when a tumor recurs (Vredenburgh 7).

Currently, temozolomide is the standard of care for primary treatment of GBM. Temozolomide is an alkylating agent that causes methylation of guanine on the N7 and O6 atoms and methylation of adenine on the N3 atom (Tentori 8). The guanine lesion O6-MeG is repaired by O6- methylguanine-DNA methyltransferase (Wood 9). More than 80% of the temozolomide-induced DNA lesions are substrates for the base excision repair (BER) pathway (Tentori 8, Wood 9, Sobol 10).

BER is the predominant DNA repair system in mammalian cells for eliminating small DNA base lesions (Lindahl 11). Damaged base residues are removed by a lesion-specific DNA glycosylase. The resulting abasic site is recognized by an apurinic/apyrimidinic endonuclease, APE1, which incises the damaged strand, leaving 3V-OH and 5Vdeoxyribose phosphate (5VdRP) groups at the margins. A DNA polymerase h (pol-h)–mediated DNA synthesis step fills the single nucleotide gap (Sobol 10, Wilson 12).

Hegi, et al 13 have recently shown that resistance to temozolomide is associated with activity of the methylguanine methyltransferase (MGMT) repair gene (Hegi). However, even in patients in whom this gene has been silenced, gliomas eventually escape the antineoplastic effects of temozolomide through other DNA repair mechanisms. Lucanthone inhibits apurinic endonuclease 1 (APE1) repair activity and this is the proposed mechanism through which lucanthone may enhance the cell-killing effect of alkylating agents such as temozolomide (Luo 14).

Lucanthone is a thiaxenthenone, formerly used as an antiparasitic that inhibits post-radiation DNA repair in HeLa cells. Lucanthone is hypothesized to work synergistically with temozolomide and radiation by inhibiting DNA repair.

3.1 Mechanism of Action

Lucanthone was initially developed as treatment for schistosomiasis. It was given orally to patients usually at a dose of 15 mg/kg/day for seven days. In the 1950’s and 1960’s, lucanthone had been used to treat approximately 200,000 patients (Blair 15).

In a review article by Blair 15 the safety of lucanthone hydrochloride was described. In a study of 23 patients receiving 15-18 mg/kg/day with a total dose of 130 mg/kg, the most common side effects were anorexia and vomiting each experienced by 39% of the patients. The second most common side effect was insomnia experienced by 22% of these patients (Blair 15).

Side effects are less frequent in children due to more efficient metabolism and more rapid excretion. In 1964, Einhorn 16 reported the effect of lucanthone hydrochloride in 46 children referred to the Bronx Medical Center. In this sample of children aged 7-15 years, 12 of the children had no adverse effects. In the remainder, the most common were nausea 60%, vomiting 54%, abdominal pain 41% and anorexia 39%.

More recently lucanthone was found to inhibit post-radiation repair in HeLa cells. The clonigenic potential of irradiated cells is abnormally sensitive to lucanthone during the first

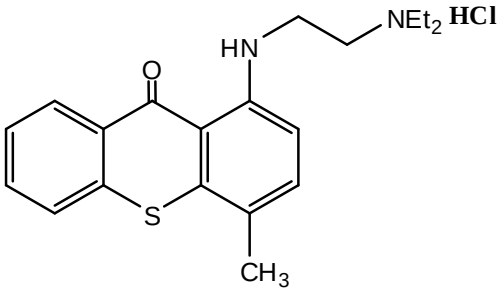
few hours after ionizing radiation. Irradiated cells destined to repair DNA damage and survive are prevented from doing so by lucanthone (Bases 17). Lucanthone's ability to inhibit topisomerase II (Bases 18) and AP endonuclease (Mendez 19**)** probably account for the special interference with DNA repair in irradiated cells.

3.2 Lucanthone API

Chemical Name

1-((2-(diethylamino)ethyl)amino)-4-methyl-9H-thioxanthen-9-one hydrochloride

Structural Formula



Molecular Formula

$C_{20}H_{24}N_2OS \bullet HCl$

Molecular Weight

376.94 (340.48 as free base)

Physical Properties

Physical Form	A yellow-orange, nearly odorless powder that readily stains the skin.
Taste	Bitter
Melting point	195-196°C
Chirality	Lucanthone is not a chiral molecule
Solubility	Diethyl ether: insoluble Acetone: insoluble Ethyl Alcohol: 1g dissolves in 85 mL Water: 1 g dissolves in 110 mL Chloroform: 1 g dissolves in 20 mL

3.3 Lucanthone Clinical Product

Lucanthone HCl is formulated for oral administration as enteric tablets with 2 strengths, 25 mg and 100 mg, which are calculated on a free base content basis. Additional excipients include microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate and methacrylic acid copolymer type C (Acryl-Eze). A matching placebo for each dose group is formulated without the active ingredient. The tablets are stored in bulk sealed plastic bottles, in a controlled room temperature.

3.4 Lucanthone Preclinical Studies

Lucanthone has been shown to have antitumor, radiation sensitizer and chemo-sensitizer activities *in vitro* and *in vivo*. These studies are briefly summarized here.

3.4.1 In vitro pharmacology

3.4.1.1 Antitumor activity

Lucanthone was tested at the NCI for in vitro anti-tumor activity against the entire panel of 60 cell lines following standard published procedures. The data is available at the NCI Developmental Therapeutics Program website (NCI 20**)**. The results of the study showed that lucanthone had in vitro anti-tumor activity against all the cell lines tested, at µM concentrations. The ranges of GI_{50}, TGI and LC_{50} are relatively narrow indicating that the sensitivity of the cell lines to lucanthone does not vary widely.

3.4.1.2 Radiation sensitizer activity

Lucanthone, at concentrations of 3-5 µg /mL, was shown to enhance radiation damage in HeLa cells (Bases 17), CHO cells (Leeper 21) and Chinese Hamster V-79 cells (Durand 22) probably by inhibiting postradiation repair process. The radiation sensitizing effect of lucanthone was dependent on exposure time and was reversible.

3.4.1.3 Chemosensitizer activity

Lucanthone, at a concentration of 4 µM, was shown to enhance the cytotoxic activity of the alkylating agent Temozolamide against MDA-MB231 breast cancer cells by two folds (Luo 14).

3.4.2 In vivo pharmacology

3.4.2.1 Antitumor activity

Antitumor activity of lucanthone against a variety of tumors was studied by a number of investigators using mouse, rat and hamster models. In these studies, reviewed by Hirschberg 23, lucanthone was shown to inhibit the growth of about half of the tumors tested. Lucanthone was also tested at NCI against a number of tumors in mouse models. Results of these studies are available at the NCI Developmental Therapeutic Program website (NCI 20). In these studies, lucanthone showed antitumor activity against approximately 30% of the tumors tested.

3.4.2.2 Radiation sensitizer activity

Lucanthone, administered at sublethal doses, was shown to enhance the sensitivity of mice (Bases 24) and Chinese hamsters (Milligan 25). Milligan *et al* also found that lucathone reduced the radiation tolerance of the small intestine but had little or no effect on radiation tolerance of bone marrow.

Lucanthone was shown to cause radiosensitization of C3H mammary tumors (Pittock 26). In contrast, Rao 27 did not find radiosensitization of Ehrlich ascites tumor, grown in mice as ascites or solid tumor, when mice were administered with lucanthone (70 mg/kg, ip). The

reasons for the negative observation are not clear. It is possible that Ehrlich ascites tumor is not sensitive to lucanthone or the dose administered is not adequate.

3.4.2.3 Chemosensitizer activity

Lucanthone, administered at sublethal doses (100 mg/kg, ip), was shown to enhance the sensitivity of Chinese hamsters to the alkylating anticancer agent cyclophosphamide in a time dependent and reversible manner (Milligan 28). As in the case of radiation sensitization, lucanthone enhanced the sensitivity of gastrointestinal but not bone marrow stem cells to cyclophosphamide.

Lucanthone, administered orally (2 x 50 mg/kg/day with an interval of 8 hours), was shown to synergistically enhance the antitumor activity of mitoxantrone (Topoisomerase II inhibitor) against L 1210 and P 388 leukemia cells grown as ascites in mice (Osswald 29).

3.4.3 Safety pharmacology

Wood 30 in 1947 reported safety pharmacology studies with lucanthone. These studies showed that lucanthone, when administered intravenously to anaesthetized rabbits or cats, had no effect on the cardiovascular system at low doses but caused depression of the heart and dilation of the peripheral vessels at doses greater than 5 mg/kg. Other investigations on isolated organs had shown no significant pharmacological actions except a mild spasmolytic action on intestinal muscle.

3.4.4 Toxicology

Based on two-week non-GLP dose-range finding studies, 5, 10 and 20 mg/kg doses were chosen for the subsequent six-week GLP toxicity study in rats as well as dogs to support clinical studies in humans. Groups of 15 rats or 6 dogs of each sex were administered lucanthone orally once daily for six weeks. Reversibility of toxicity was evaluated during a four-week recovery period following the final dose of the test article. The results of these studies, detailed below, showed that lucanthone is well tolerated when administered orally once daily for six weeks at doses up to 10mg/kg in rats and at least up to 20mg/kg in dogs.

3.4.4.1 Hematologic Toxicity

In the rat study, increase in white blood cell, absolute neutrophil and absolute monocyte counts was observed at a 20 mg/kg dose (but not at a 5 or 10 mg/kg dose). Decrease in spleenic and thymic weights with associated lymphoid depletion was also observed at 20 mg/kg dose. These alterations are likely related to the GI tract inflammation observed in rats. In addition, increase in parameters related to erythron mass, such as red blood cell counts, hemoglobin, hematocrit, and mean cell hemoglobin concentration, and decrease in reticulocyte counts observed at the 20-mg/kg dose were probably secondary to dehydratation observed in rats. All the changes in hematological parameters were found to be reversible in the recovery animals.

In the dog study, there were statistically significant or trending decreases in some white cell and red cell hematologic parameters at the 10 and 20 mg/kg doses (but not at the 5 mg/kg dose). However, all changes were within normal reference ranges, and were biologically insignificant. Decreases in thymic weights and bone marrow hypocellularity were also

observed at the 20 mg/kg dose. As in the case of rats, the hematological changes observed in dogs were also found to be reversible.

3.4.4.2 Non-Hematologic Toxicities

Non-hematological toxicities observed in the rat study were as follows:

1. Mortality (60% in males and 24% in females) at the high dose of 20 mg/kg/day, mostly during the last two weeks of dosing.
2. Dose-dependent fecal abnormalities including discolored feces, soft feces, and mucoid to watery diarrhea. High incidences of dehydration, emaciation, and unkempt appearance at the 20 mg/kg dose.
3. Reduction in food consumption, body weight and body weight gain in a dose dependent manner.
4. Decrease in total protein, albumin and globulin and an increased albumin globulin ratio at the 20 mg/kg dose.
5. GI tract inflammation at the 20 mg/kg dose.

All non-lethal toxic effects observed above were found to be reversible in the recovery animals. The No Observed Adverse Effect Level (NOAEL) was the low dose of 5 mg/kg. The dose of 10 mg/kg was the highest dose that caused non-life threatening reversible adverse effects.

Non-hematological toxicities observed in the dog study were as follows:

1. No mortality at any dose level during the study.
2. Clinical observations associated with the GI tract, such as fecal changes and emesis, in a dose related manner.
3. Reduced food consumption and reduced body weight gain or weight loss in a dose-dependent manner.
4. Yellowish discoloration of the intestinal mucosa, and pale liver.
5. Organ weight changes considered directly related to lucanthone administration were limited to increased liver weights in both males and females administered 20 mg/kg.
6. Slower heart rate, longer RR interval, prolonged PR interval, and prolonged QT interval on administration for 37 days (but not 12 days) at the 20 mg/kg dose. However, the prolongation of the QT interval was not statistically significant after correction for the slower heart rate.
7. Vacuolation of seminiferous tubules at the 10 and 20 mg/kg doses.

All toxic effects observed above were found to be reversible in the recovery animals. The Lowest Observed Adverse Effect Level (LOAEL) was the low dose of 5 mg/kg. The dose of 20 mg/kg was the highest dose that caused non-life threatening reversible adverse effects.

3.4.5 Pharmacokinetics

The pharmacokinetics of lucanthone administered orally to monkeys at doses ranging from 10 mg/kg to 0.4 g/kg were reported by Hawking and Ross 31.

In a Spectrum sponsored study, the toxicokinetics of lucanthone administered to dogs orally once a day for six weeks in a GLP toxicology study were analyzed on Day 1 and Day 41.

These studies, briefly described in the following sections, show that:

1. Lucanthone is absorbed on oral administration.
2. Plasma concentration levels of lucanthone increase with an increase in dose but not in a dose proportional manner.
3. There is no accumulation of lucanthone on repeated oral administration.
4. Plasma concentrations reached at a given dose on repeated administration for six weeks appear to be lower than those obtained initially.
5. There were no gender differences in the pharmacokinetics of lucanthone.
6. Half-life values estimated approximately in individual dogs ranged from 3 to 7 hours.
7. The concentrations of hycanthone, a metabolite of lucanthone, in dog plasma were negligible when compared to those of lucanthone.

3.4.5.1 Literature review

Hawking and Ross 31 reported absorption distribution and excretion studies following oral administration of lucanthone to monkeys. In this study, lucanthone present in body fluids or tissues was quantified by spectrophotometry, following alkalinzation and extraction, first into ether and then into dilute hydrochloric acid.

Absorption of lucanthone was found to be rapid following oral administration to monkeys. After a single dose of 0.4 g/kg, the concentration of lucanthone in blood reached a maximal level of 0.8 mg/L within 2.5 hours, and the level was sustained for at least 21 hours. On oral administration of 10 or 20 mg/kg of lucanthone to different monkeys, the maximum concentration reached in blood varied from <0.1mg/L (detection limit) to 0.45 mg/L.

On oral administration of lucanthone at doses ranging from 0.1 to 0.4 g/kg to three monkeys, daily or every other day, the concentrations of lucanthone in the blood were not found to be proportional to the dosage administered. In a monkey that received 20 doses of lucanthone (0.2 g/kg per dose) over a period of 30 days, lucanthone was barely detectable (0.1mg/L) in the blood 3 days after the last dose.

3.4.5.2 Toxicokinetics from six-week oral GLP toxicology study in dogs

Toxicokinetics of lucanthone administered to dogs orally once a day for six weeks in a GLP toxicology study were analyzed on Day 1 and Day 41. Lucanthone was dosed by oral capsules in four groups of six male and six female beagle dogs at 0, 5, 10 or 20 mg/kg/day for 42 consecutive days (Groups 1 to 4, respectively). Blood samples were collected prior to dosing and at 10 and 30 minutes and 1, 3, 8 and 24 hours post-dose on Days 1 and 41 from each animal. The harvested plasma was assayed for lucanthone and hycanthone, a metabolite

of lucanthone, by a validated HPLC-MS/MS assay. Standard non-compartmental analyses were employed to determine the toxicokinetic parameters in dogs.

The absorption of lucanthone administered orally at dose levels of 5 to 20 mg/kg/day was demonstrated in male and female dogs during a 6-week toxicity study. Very sporadic and low plasma concentrations of the metabolite hycanthone were observed in a majority of dogs following lucanthone administration. Dose-related increases in lucanthone mean C_{max} and $AUC_{(0-24)}$ were observed. Increases were generally more than dose-proportional between the 5 and 10 mg/kg doses and less than dose-proportional between 10 and 20 mg/kg. The highest exposure of lucanthone was seen in female dogs in the 20 mg/kg dose group on Day 1 with a C_{max} of 630 ng/mL and $AUC_{(0-24)}$ of 6010 ng·h/mL. Following once daily dosing with lucanthone for 41 consecutive days, no accumulation of lucanthone was observed, and in fact, decreases in Day 41 mean C_{max} and $AUC_{(0-24)}$ as compared to Day 1 values were seen. The Day 41 to Day 1 ratio of mean $AUC_{(0-24)}$ values ranged from 0.32 to 0.90 in male and female dogs after lucanthone doses of 5, 10 and 20 mg/kg. There was no apparent gender difference in the toxicokinetics of lucanthone after single or multiple doses. The half-life values could not be determined accurately as the post C_{max} time points were inadequate. However, half-life values estimated approximately for individual animals with at least 3 time points post C_{max} ranged from 3 to 7 hours.

3.5 Clinical Studies with Lucanthone

3.5.1 Clinical Pharmacology

3.5.1.1 Pharmacokinetics in healthy volunteers

Hawking and Ross 31 studied pharmacokinetics of lucanthone in six healthy volunteers. In this study, lucanthone was administered orally at doses ranging from 0.05 to 0.3 g once, twice or thrice daily for one to six days and the concentration of lucanthone in blood, urine and feces was determined by absorption spectrophotometry. The results of the study can be summarized as follows:

1. Lucanthone was absorbed rapidly, reaching maximum concentration in blood in 2 to 3 hours.
2. There were considerable individual differences with respect to the maximum concentrations reached in the blood (0.1 to 1.2 µg/mL) and the rate of elimination from blood.
3. On repeated dosing, lucanthone did not accumulate in blood beyond Day 2 and disappeared from blood in two to three days once drug administration was stopped.
4. Absorption of lucanthone appeared to be complete, as only a small fraction (about 3%) appeared in the feces.
5. Only about 7% of lucanthone was excreted in urine suggesting that much of the drug is metabolized in the body.

3.5.1.2 Pharmacokinetics in cancer patients

Del Rowe et al 32 administered repeated doses of lucanthone (10 mg/kg/day in three divided doses) orally to a group of 9 cancer patients with brain metastases and determined serum

concentrations of lucanthone by spectrophotometry, at around 3 hours post morning dose over a period of 7 days. The study showed that the concentrations of lucanthone gradually increased over a period of 4 to 5 days, reaching a maximum of 3-4 µg/mL, the concentrations at which lucanthone was shown to be effective as a radiation sensitizer and chemosensitizer (Luo 14, Bases 17).

3.5.2 Phase I Clinical Studies

3.5.2.1 Study 1

A Phase I study of lucanthone to determine a tolerable dose schedule was conducted on 12 patients with Glioblastoma multiforme (GBM) at Montefiore Hospital Bronx, NY from 1999-2002. See Table 2.

Table 2 Phase I study of lucanthone to determine a tolerable dose schedule

Study	Investigator/ Location	Treatment Schedule	Dose	No. pts.
Phase I	Dr. Robert Bases/Montefiore Hospital, Bronx, NY	2, 4 or 6 weeks concomitant with radiation therapy (60Gy/30 fractions (6 wks))	10 mg/kg/day ($370\ mg/m^2$) 5 days/week	12

The results from this trial are anecdotal, there were no case report forms created or completed. Adverse events have been extracted directly from the patients' charts. Therefore, no causality assessment is given.

Survival results from the Phase I trial in patients with GBM were based on personal communication with Dr. Bases and are summarized in Table 3.

Table 3 Summary of Patient Information from Phase I study in patients with GBM

Patient Initials and Age	Lucanthone Duration of treatment	Radiation Therapy	Patient survival from study start
R.O.-52y	2 weeks	6 weeks	33 months

Patient Initials and Age	**Lucanthone** **Duration of treatment**	**Radiation Therapy**	**Patient survival from study start**
A.R.-44y	2 weeks	6 weeks	7 months
K.R.-52y	2 weeks	6 weeks	6 ½ months
L.M.	4 weeks	4 weeks	4 weeks
T.M.-80y	2 weeks	6 weeks	7 months
C.H.-50y	3 weeks	6 weeks	2 ½ months
D.L.-81y	2 weeks	6 weeks	9 months
W.E.-77y	3 weeks	6 weeks	6 months
M.D.-54y	4 weeks	7 weeks	7 months
S.S.-15y	2 weeks	6 weeks	11 months
A.G.-19y	4 weeks	6 weeks	7 months
L.L.	4 weeks	6 weeks	1 ½ months

3.5.2.1.1 Phase I Adverse Events

Nine patients (75%) reported 75 adverse events in this Phase I study in patients with GBM. The most commonly recorded AEs occurred in the CNS and GI body systems. Eighty-nine percent (89%) of patients experienced CNS Adverse Events while fifty-five percent (55%) of patients experienced gastrointestinal adverse events.

The most commonly recorded neurological adverse event was fatigue. There was a 50% incidence in these patients. The second most commonly recorded neurological adverse events were headaches and seizures. There was an incidence of 33% of both seizures and headaches in these patients.

The most commonly recorded gastrointestinal adverse events were nausea and vomiting. There was an incidence of 16% of both nausea and vomiting in these patients.

Other neurological adverse events were limb tremors, mental confusion, depressed state, double vision, numbness, papilledema, aphasia, swallowing difficulty, ataxia, confusion, anxiety, unsteady gait, muscle weakness and dizziness.

Other gastrointestinal adverse events were abdominal tenderness, swallowing difficulty, dry mouth, decreased appetite, abdominal pain, and constipation.

Many of these adverse events are common in patients with GBM undergoing radiation therapy. Since there were no CRFs for this study, AEs were extracted directly from patients' charts. Thus, no causality assessment is given.

For a complete list of adverse events, see the current Lucanthone Investigator's Brochure.

3.5.2.2 Study 2

Study SPI-LUC-07-01 was a dose escalation study of safety and tolerability of lucanthone in combination with temozolomide in patients with recurrent brain tumors. The study planned to enroll approximately 24 patients to receive 21 days of lucanthone concurrently with temozolomide. Lucanthone was administered orally in tablets of 25 mg and 100 mg strength. The design was dose escalation with four lucanthone total daily dose levels of 75 mg, 300 mg, 675 mg and 975 mg.

Three patients were enrolled into the first dose level of 75 mg before the study was closed due to lack of patient accrual. One patient withdrew consent after 13 days of therapy. The patient was experiencing headache and was subsequently diagnosed to have developed cerebral edema.

Adverse events reported in this study included nausea, vomiting, lymphopenia, thrombocytopenia, hypercoagulbility state, irritability, intertrigo candida, dermatitis acneform, cellulites, dehydration, headache, hypertension and benign neoplasm of the thyroid gland, gravitational edema and dyspnea.

One patient experienced serious adverse event (SAE) of cerebral edema. A second patient was hospitalized for SAE of deep vein thrombosis (DVT). Two days after admission to hospital, the patient with DVT developed pulmonary embolism. Both events were deemed to be unrelated to the study drug by the investigators.

3.5.3 Phase II Clinical Studies

3.5.3.1 Study 1

A Phase II study was completed and published in 1975 by Dr. Turner to determine whether lucanthone affects radiation-induced regression in measurable pulmonary metastases and advanced squamous-cell oral and pharyngeal tumors. The study showed that the time required for 50% tumor regression was decreased by approximately 50% in those patients who received lucanthone in addition to irradiation compared with patients who received radiation therapy alone (Turner 33).

3.5.3.2 Study 2

A Phase II study was completed and published in 1999 by Dr. Bases and his team at Montefiore Hospital in the Bronx. The study was done to compare patients with brain

metastases receiving lucanthone and radiation therapy versus patients with brain metastases receiving radiation alone. Dr. Bases noticed in his previous studies that inhibition of post radiation repair and inhibition of topoisomerase II would be expected if serum levels of 3µg/ml lucanthone could be attained (Bases 18, Kingma 34). Therefore patients in this trial were given lucanthone in three divided doses to maintain blood and tissue levels. The total daily dose of 10 mg/kg per day for ten days was well tolerated.

This Phase II study by Dr. Bases showed accelerated tumor regression in five patients who received lucanthone and 30 Gy compared with three patients who received 30 Gy alone (Del Rowe 32**)**.

3.5.3.3 Study 3

Another Phase II study was conducted by Dr. Bases and his team at Montefiore in 2004 and 2005 and investigated the addition of lucanthone to radiation therapy in five patients with brain metastases. All of these patients received a dose of 10 mg/kg/day of lucanthone for ten days concomitant with radiation therapy (30 Gy in 10 fractions in 2 weeks). These results are anecdotal and were not published.

Five patients were enrolled in this study; four patients with large cell carcinoma of the lung and one with thyroid cancer.

The outcomes for these five patients were as follows:

Pt #1: treated 6/30/2004-7/14/2004, large cell carcinoma of the lung with brain mets, died 4/20/2005 from progressive disease ten months after completing therapy.

Pt #2: treated 11/24/2004-12/7/2004, large cell carcinoma of the lung with brain mets, died 2/19/2006 from progressive disease fourteen months after completing therapy.

Pt #3: treated 1/11/2005-1/21/2005, thyroid cancer metastatic to the brain, patient did not complete treatment, died 1/21/2005 from progressive disease.

Pt #4: treated 2/18/2005-unknown, large cell carcinoma of the lung with brain mets, patient did not complete radiation treatment, died 10/3/2005 from progressive disease.

Pt #5: treated 3/14/2005-4/1/2005, large cell carcinoma of the lung with brain mets, died 7/20/2006 from progressive disease sixteen months after completing therapy.

Four patients (80%) reported adverse events in this study. The most commonly reported adverse events occurred in the CNS, GI, musculoskeletal and respiratory body systems. The most commonly reported adverse event was weakness experienced by 60% of patients. The next most commonly reported adverse event was headache, dizziness, fatigue, nausea, GI upset, shortness of breath and back pain experienced by 40% of the patients. Other neurological adverse events were dysequilibrium and anxiety. Other GI adverse events were vomiting, dysphagia, burping stomach pain, decreased appetite and constipation. Other respiratory body systems adverse events experienced by the patients were chest tightness, chest pain (non-cardiac), COPD exacerbation and cough. Adverse events that affected the vascular system were coughing up blood and lower extremity thrombus. Other adverse events experienced by patients were skin hyperpigmentation, waking difficulty, oral thrush, pruritic rash, insomnia, leg pain, alopecia and swelling of legs.

The CNS adverse events in this study are also experienced by patients with brain tumors so causality assessment is difficult to determine. Since there were no CRFs for these studies, AEs were extracted directly from patients' charts. Thus, no causality assessment is given.

For a complete list of adverse events, see the current Lucanthone Investigator's Brochure.

3.6 Summary of Risks and Benefits

3.6.1 Potential Risks

Lucanthone has been used formerly for the treatment of schistosomiasis in Africa in well over 200,000 patients (Blair 15). The most common side effects of lucanthone seen in this population were nausea, anorexia, vomiting, insomnia, dizziness and vertigo. Other neurological side effects included reports of lack of depth perception, psychosis and seizures.

The side effects of lucanthone appear to be less frequent in children due to their more efficient metabolism and rapid excretion of the drug. Einhorn 16 reported the effect of lucanthone at a dose of 15-20 mg/kg/day for seven days in 46 children referred to the Bronx Medical Center. In this sample of children aged 7-15 years, 12 of the children had no adverse effects. In the remainder, the most common were nausea (28), vomiting (25), abdominal pain (19) and anorexia (18). One patient had a convulsive seizure and a post-treatment encephalogram was normal.

Birch 35 reported the effect of lucanthone at a dose of 15 mg/kg/day for a total of seven days in 38 patients aged 9-50 years living in Chicago. Thirteen patients were unable to complete therapy due to intolerance. The most common side effects were headache, nausea, vomiting and malaise.

Adults given lucanthone for *Schistosoma mansoni* infection at a total dose of 150 mg/kg over nine days experienced mostly neurological disturbances. These included mental depression, anxiety, confusion, hallucinations, insomnia and hysteria (Einhorn 16).

It is clear from these reports that the majority of side effects seen in patients taking lucanthone are neurological and gastrointestinal. The most common side effects associated with temozolomide are nausea, vomiting, alopecia, headaches, fatigue, convulsions, weakness, constipation and thrombocytopenia . Since the drugs have not been used in combination, it is possible that the addition of lucanthone to temozolomide may exacerbate some of the side effects, especially the gastrointestinal side effects, malaise and fatigue.

3.6.2 Potential Benefits

Patients with malignant brain tumors receive various treatments depending on their tumor type and the location of the tumor. In 286 patients of Glioblastoma multiforme primary therapy of with radiation alone resulted in progression free survival of 5 months and median overall survival of 12.1 months in comparison with 287 patients who received temozolomide in addition to radiation and had a PFS of 6.9 month and overall survival of 14.6 months ; a survival advantage of approx 8 weeks (Stupp 36). Lucanthome has the potential of enhancing the anti cancer effect of both radiation and temozolomide and could further increase the progression free and overall survival.

3.7 Justification of the Dose of Lucanthone

In vitro studies have demonstrated that lucanthone acts as a radiosensitizer (Bases 17) and chemosensitizer (Luo 14).

In an *in vitro* study it was noticed that inhibition of post radiation repair and inhibition of topoisomerase II can be achieved if serum levels of 3µg/mL lucanthone are attained (Bases 18, Kingma 34).

The clinical studies (phase I and phase II) conducted to date with an indication of efficacy have used lucanthone at doses of 10-15 mg/kg/day.

In one phase II study conducted in patients with metastatic pulmonary nodules, two patients -- one with 2 nodules and the other with 3 nodules of similar size -- were treated with radiotherapy and lucanthone. Different nodules were treated with radiation or radiation and lucanthone in the same patient. There was 50% less time for 50% reduction in the size of the nodules when lucanthone was given with radiation. In this study the patients were given lucanthone in dose of 15mg/kg/day in divided doses concomitant with radiation therapy(Turner 33).

In another study, 8 patients with brain metastasis were divided into 2 groups. One group received only radiation for 2 weeks, and the other group received radiation and lucanthone (10 mg/kg) for 2 weeks. The group receiving lucanthone and radiation had an accelerated tumor regression as compared to the group that received radiation alone. The daily dose in this trial was 10mg/kg/day given as three divided doses and was well tolerated (Del Rowe 32).

The dose of 10-15 mg/kg/day helps in attaining the serum level of 3-4 µg/mL and is the dose which has been used in clinical studies conducted with lucanthone. Therefore the dose of 10 to 15 mg/kg/day was chosen for the study.

4 TRIAL OBJECTIVES AND PURPOSE

4.1 Primary Objective

To determine the efficacy of lucanthone when given along with temozolomide (TMZ) and radiation in the primary treatment of GBM due for radiation and TMZ treatment.

4.2 Secondary Objective

To evaluate the safety and toxicity of lucanthone when used in combination with temozolomide (TMZ) and radiation in primary treatment of GBM due for radiation and TMZ treatment.

4.3 End Points

4.3.1 Primary endpoint

1. Progression free survival (PFS) at 9 months

4.3.2 Secondary endpoint

1. Objective response rate (ORR) at months 2, 4, 6, 9 and 12

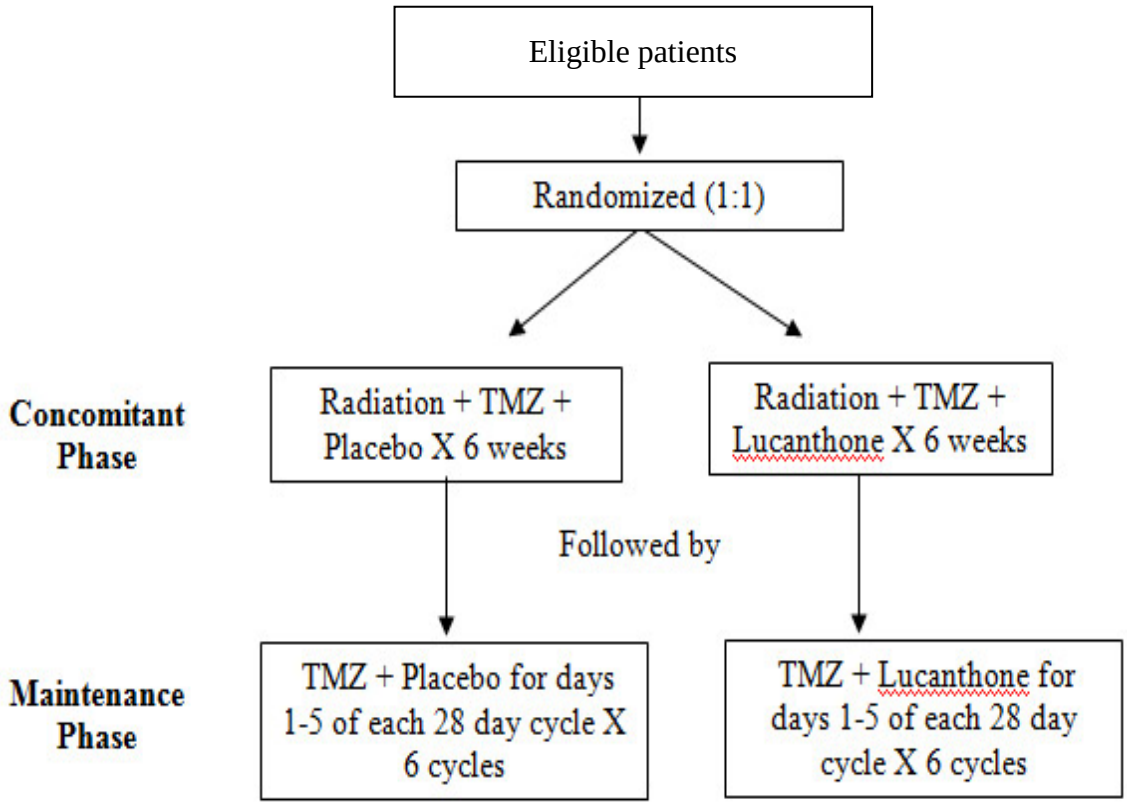
2. PFS at one year
3. Overall survival at (OS) one year
4. Safety of Lucanthone given as add on to radiation and TMZ.

5 INVESTIGATIONAL PLAN : OVERALL STUDY DESIGN

5.1 Overview

This is an international, multicenter, randomized, double blind placebo controlled phase II study to evaluate safety and efficacy of lucanthone administered as an adjunct to patients receiving primary treatment of GBM with temozolomide and radiation. Eligible patients will be randomized to lucanthone or placebo arm in ratio of 1:1. The treatment period will be in two phases -- an initial six weeks of concomitant therapy with temozolomide and radiation, followed by a maintenance phase of six cycles of temozolomide given on Days 1 to 5 of a 28-day cycle. Lucanthone / placebo will be given as an adjunct to temozolomide in both of the concomitant and maintenance phases.

Study arm	**Control arm**
Lucanthone + TMZ + Radiation	TMZ + Radiation + Placebo



In the concomitant phase, eligible patients will receive lucanthone/placebo for 6 weeks along with focal radiation and TMZ. In the maintenance phase, lucanthone/placebo will be administered along with TMZ on days 1-5 of a 28-day cycle for 6 cycles. In both phases, the lucanthone dose will be administered in three divided doses. (Refer to Section 7.1 for the lucanthone/placebo doses and Section 7.2.1 for the TMZ doses.)

The primary study endpoint is progression free survival at 6 months. The secondary endpoint include ORR at 2.4.6.9 and 12 months, PFS at one year, OS and safety. Tumor assessments for response will be made according to Criteria for Response Assessment Incorporating MRI and Clinical Factors (RANO) criteria and will be made by radiologic imaging using MRI – Head. Radiological assessments on tumor will be made at baseline and at months 2, 4, 6, 9, and 12. (Refer to Section 12.3.2 for efficacy assessment.) The radiological assessments will be discontinued at the time of tumor progression or initiation of new anticancer therapy, after which the patient will be followed up for survival. Safety will be evaluated during the study period of one year, and survival data will be collected subsequently. Adverse events and abnormal laboratory parameters will be graded according to NCI-CTCAE version 4.

The study will enroll a total of 140 patients from approximately 12 centers in the USA and India. The total treatment period for a patient is approximately 7 ½ months, and the total duration of the study for a patient is one year.

6 SELECTION AND WITHDRAWL OF SUBJECTS

6.1 Inclusion Criteria

A patient will be eligible for study participation only if all of the following criteria apply:

1. The patient has given informed consent*.
   *A signed consent form that has been approved by an IRB/IEC is required prior to the performance of any protocol-related procedures or assessments.
2. The patient is willing and able to abide by the protocol.
3. The patient is between age 18 and 70 (both included).
4. The patient has histologically proven GBM who
   a. May or may not have undergone surgery
   b. Has at least one well demarcated bidimensional measurable lesion; and
   c. Is scheduled to receive treatment with temozolomide and radiation.
5. If the patient is of childbearing potential, he/she is using an acceptable/effective method of contraception.
6. If the patient is a female of childbearing potential, she has a negative serum pregnancy test.
7. The patient's Karnofsky score is $\geq$ 70%.

6.2 Exclusion Criteria

A patient will not be eligible for study participation if any of the following criteria apply:

1. Patient has a diagnosis of recurrent brain tumor.
2. The patient has received temozolomide previously.
3. The patient has an absolute neutrophil count less than or equal to 1.5 X 10^9/L.
4. The patient has a screening platelet count less than 100 K/uL.
5. The patient has a screening bilirubin greater than 1.6 mg/dL.
6. The patient has a screening creatinine greater than 2.25 mg/dL in men and 1.8 mg/dL in women.
7. The patient has a screening alanine aminotransferase (ALT), or aspartate aminotransferase (AST) greater than 2.5 times the upper limit of the laboratory reference range.
8. The patient has an unstable medical condition or significant comorbid pathophysiology (e.g. active infection, poorly controlled diabetes, unstable angina, severe heart failure) that would interfere with his/her participation in the study.
9. The patient is enrolled, or plans to enroll, in a concurrent treatment protocol with another investigational product.

10. The patient is receiving, or plans to receive, an anti-cancer therapy other than temozolomide during the study.
11. The patient has received prior chemotherapy or radiation therapy within four weeks of enrollment.

6.3 Withdrawal Criteria

Participation in this study includes:

1. Study drug treatment.
2. Study-related procedures including laboratory studies and radiologic scans.
3. Follow-up for toxicity, tumor assessments, and survival.

Patients, at their own request or at the request of their legally acceptable representative, may withdraw from the study at any time for any reason. Should a patient decide to withdraw consent, the reason for withdrawal must be noted and end of study evaluations should be carried out. The patient should be followed up for survival information.

Patients are to be withdrawn from study drug treatment for any of the following reasons:

1. Progression of disease.
2. Unacceptable or recurrent toxicity despite optimal prophylaxis and appropriate dose.
3. Substantial non-compliance with the requirements of the study.
4. Positive pregnancy test.
5. Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable risk of contributing to toxicity or otherwise skewing results.
6. Development of an intercurrent illness or situation which would, in the opinion of the investigator, affect assessments of clinical status and study endpoints to a significant degree.
7. Noncompliance after repeated counseling.

Patients who are withdrawn from study drug treatment will undergo an end of study visit and will be followed for survival.

The investigator also has the right to withdraw patients from study if in the investigator's opinion, continuation would be detrimental to the patient's well-being.

If a patient is withdrawn prematurely from study treatment, end of study evaluations should be carried out, and the reason for withdrawal must be recorded in the case report form.

7 TREATMENT OF SUBJECTS

7.1 Description of Study Drug:Lucanthone / Placebo

The Sponsor will supply Lucanthone or identical placebo tablets for use in the study. Lucanthone / identical placebo will be supplied as 25 mg and 100 mg tablets. The tablets should be swallowed intact and should not be broken in half or chewed.

Along with temozolomide, lucanthone will be administered at a dose of 10-15 mg/kg/day in three divided doses for 6 weeks during the concomitant phase and then for Days 1-5 of each 28 day cycle for 6 such cycles during the maintenance phase.

Lucanthone will be administered according to the weight of the patients as per the table given below:

Patient Weight	**Dose of Lucanthone**
< 45 kg	150 mg TID*
45- 60 kg	200 mg TID
> 60 kg	250 mg TID
* TID = three times a day	

The study drug will always be given as an adjunct to temozolomide. Any interruption or discontinuation of temozolomide will necessitate the identical interruption or discontinuation of the study drug. The dose of lucanthone will be based on the weight of the patient at baseline. Any dose changes in temozolomide will not influence the dose of study drug.

Temozolomide for the study will be supplied by the sponsor.

7.2 Concomitant Therapy

7.2.1 Temozolomide

7.2.1.1 Concomitant Phase

TMZ is administered at 75mg/m^2 daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions). No dose reductions are recommended during the concomitant phase; however, dose interruptions or discontinuation may occur based on toxicity. The TMZ dose should be continued throughout the 42-day concomitant period up to 49 days if all of the following conditions are met:

1. Absolute neutrophil count $\geq 1.5 \times 10^9$/L
2. Platelet count $\geq 100 \times 10^9$/L
3. Common toxicity criteria (CTC) nonhematological toxicity $\leq$ Grade 1(except for alopecia, nausea, and vomiting).

During treatment a complete blood count should be obtained weekly. Temozolomide dosing should be interrupted or discontinued during concomitant phase according to the hematological and non-hematological toxicity criteria as noted in Table 4.

Table 4 Temozolomide Dosing Interruption or Discontinuation During Concomitant Radiotherapy and Temozolomide

Toxicity	TMZ Interruption	TMZ Discontinuation
Absolute Neutrophil Count	≥0.5 and <1.5 x 10^9/L	<0.5 x 10^9/L
Platelet Count	≥10 and <100 x 10^9/L	<10 x 10^9/L
CTC Nonhematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

TMZ=temozolomide; CTC=Common Toxicity Criteria.

7.2.1.2 Maintenance Phase

Cycle 1: Four weeks after completing the TMZ+RT phase, TMZ is administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment.

Cycles 2-6: At the start of Cycle 2, the dose can be escalated to 200 mg/m^2, if the CTC non-hematologic toxicity for Cycle 1 is Grade ≤2 (except for alopecia, nausea, and vomiting), absolute neutrophil count (ANC) is ≥1.5 x 10^9/L, and the platelet count is ≥100 x 10^9/L. The dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs.

If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles.

Dose Reduction or Discontinuation during Maintenance:

Dose reductions during the maintenance phase should be applied according to Table 5 and Table 6.

During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose of temozolomide) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1500/μL) and the platelet count exceeds 100 x 10^9/L (100,000/μL). The next cycle of TMZ should not be started until the ANC and platelet count exceed these levels. Dose reductions during the next cycle should be based on the lowest blood counts and worst non-hematologic toxicity during the previous cycle. Dose reductions or discontinuations during the maintenance phase should be applied according to Table 5 and Table 6.

Table 5 Temozolomide Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m^2/day)	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Table 6 Temozolomide Dose Reduction or Discontinuation during Maintenance Treatment

Toxicity	Reduce TMZ by 1 Dose Level*	Discontinue TMZ
Absolute Neutrophil Count	<1.0 x 10^9/L	See footnote†
Platelet Count	<50 x 10^9/L	See footnote†
CTC Nonhematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4†

* TMZ dose levels are listed in Table 5.

† TMZ is to be discontinued if dose reduction to <100 mg/m^2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

7.2.2 Radiation

During the concomitant phase RT will be administered as focal 60Gy/ 30 fractions to the tumor bed or resection (surgery) site with 2-3 cm margin. Adequate immobilization masks are required to ensure reproducibility.

7.3 Randomization and Blinding

Eligible patients will be randomized to lucanthone or placebo in a blinded fashion and in a 1:1 ratio. Randomization will be done in blocks of four patients. Sites will be supplied drug in blocks each containing four randomization kits (1 block = 4 patient specific kits). On confirmation of eligibility the patient will be randomized into the study. The randomization

or kit number will be on the patient specific study drug kit supplied to the site. The randomized kit will be assigned to the patients in sequential order starting with the lowest available number.

8 STUDY DRUG MANGEMENT

8.1 Study drug composition

Lucanthone or a matching placebo is supplied as round, white tablets for oral administration. Each tablet contains either 25 mg or 100 mg of lucanthone base; the 25 mg tablet being much smaller than the 100 mg tablet. The inactive ingredients are microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate and methacrylic acid copolymer type C (Acryl-Eze). Each tablet is enteric-coated to delay dissolution of the tablet until it reaches the intestine. Lucanthone tablets should be swallowed intact and should not be broken in half or chewed.

8.2 Packaging and Dispensing

Lucanthone or identical placebo will be packaged in patient specific kits. Lucanthone will be packaged in 2 different strengths: 100 mg and 25 mg. Each kit will contain 14 bottles each of two strengths viz. 25 mg and 100 mg. Dispensing and administration

Each bottle will contain 42 tablets.

During the concomitant phase weekly supplies of lucanthone or placebo will be dispensed at each visit for six weeks. At each visit, an additional one-week supply will be provided in the event that a patient misses a scheduled visit. In this event, he/she will be instructed to continue taking the tablets from the extra supplies.

During the maintenance phase, drug will be dispensed prior to each cycle. The patient will be instructed to consume the drug for five days along with Temozolomide.

The dose of Lucanthone to be administered will be calculated based on the patient's body weight at the screening visit as per Table 7.

Table 7 Dose of Lucanthone to be administered

Patient Weight	Dose	Weekly Dispensation	Daily dose
< 45 kg	150 mg TID	25 mg : 1 bottle 100 mg : 1 bottle	25 mg : 2 tablets TID 100 mg : 1 tablet TID
45- 60 kg	200 mg TID	100 mg : 1 bottle	100 mg : 2 tablet TID
> 60 kg	250 mg TID	25 mg : 1 bottle 100 mg : 1 bottle	25 mg : 2 tablets TID 100 mg : 2 tablet TID

8.3 Labeling

The labeling on the individual drug kits and individual bottles of 25 mg and 100 mg are reproduced below.

Carton Label

STUDY # SPI -LUC-11-01
PATIENT RANDOMIZATION / KIT NUMBER:_____
Store at 20 - 25°C
Lucanthone 25 mg and 100 mg Tablets or Placebo Tablets
14 bottles of each strength in each kit
Caution : FOR CLINICAL TRIAL USE ONLY. New Drug Limited by U.S. Federal Law to Investigational Use
Spectrum Pharmaceuticals, Inc., 157 Technology Dr., Irvine, CA 92618 USA
Tel: 001-949-743-9229
OncoRx Pharma Pvt Ltd, 85 Mittal Chambers, Nariman Point, Mumbai 400021, India
Tel: 022-32092464

Bottle Label of 25 mg

STUDY # **SPI -LUC-11-01**
PATIENT RANDOMIZATION / KIT NUMBER: _____
Store at 20 - 25°C
Lucanthone 25 mg or Placebo Tablet
1 bottle contains 42 tablets
Lot: XXXXXX Retest Date: DD-MMM-YYYY
Caution: FOR CLINICAL TRIAL USE ONLY. New Drug Limited by U.S. Federal Law to Investigational Use
Spectrum Pharmaceuticals, Inc., 157 Technology Dr., Irvine, CA 92618 USA
Tel: 001-949-743-9229
OncoRx Pharma Pvt Ltd, 85 Mittal Chambers, Nariman Point, Mumbai 400021, India
Tel: 022-32092464

Bottle Label of 100 mg

STUDY # **SPI -LUC-11-01**
PATIENT RANDOMIZATION/ KIT NUMBER: _____
Store at 20 - 25°C
Lucanthone 100 mg or Placebo Tablet
1 bottle contains 42 tablets
Lot: XXXXXX Retest Date: DD-MMM-YYYY
Caution: FOR CLINICAL TRIAL USE ONLY. New Drug Limited by U.S. Federal Law to Investigational Use
Spectrum Pharmaceuticals, Inc., 157 Technology Dr., Irvine, CA 92618 USA
Tel: 001-949-743-9229
OncoRx Pharma Pvt Ltd, 85 Mittal Chambers, Nariman Point, Mumbai 400021, India
Tel: 022-32092464

8.4 Storage

Lucanthone Tablets and Placebo Tablets are stored at controlled room temperature (20°C - 25°C) with excursions permitted to 15°C to 30°C [59° - 86°F]) and away from bright light.

8.5 Accountability and disposal

The Investigator must maintain accurate accounting of study drug supplied by the Sponsor. During the study, the following information must be recorded:

1. Date of receipt, quantity and identification(randomization / kit number) of the study drug received from the Sponsor.
2. The date(s) and quantity of the product dispensed.
3. Dates and quantity of product returned, lost or accidentally or deliberately destroyed.

Accountability Record Forms will be provided by the Sponsor. They must be kept current and must be readily available for inspection.

All Lucanthone tablets returned by the patients or expired tablets of lucanthone and placebo should be retained. The CRA will periodically conduct an accountability of thestudy drug including returned or expired bottles (product) and authorize and organize their return .

8.6 Concomitant and Prohibited Medications

8.6.1 Concomitant Medications

Patients may use non-prescription analgesics or antipyretics to manage systemic side effects associated with the administration of lucanthone. If patients are also taking antinausea or other medications to relieve the side effects associated with temozolomide, the patients are advised to take these medications 30 minutes before they take temozolomide.During the concomitant phase metoclopramide may be given to control nausea and during the maintenance phase antiemetic prophylaxis with 5HT3 antagonist may be given.

Steroids should be used only if clinically indicated and lowest effective dose should be used.Steroids should be preferably administered in the mornings to avoid insomnia.If steroids are discontinued during the study period and if they have been administered for over two weeks, they should be tapered off gradually and not discontinued abruptly.

Patients should receive PCP (*Pneumocystis carinii pneumonia*) prophylaxis during the concomitant phase and should continue until recovery of lymphocytopenia (CTC grade < / = 1).

Anticonvulsants should be administered only if clinically indicated and if patient has experienced seizures. If anticonvulsants are administered for brain surgery, they should be tapered off after the first week post surgery and prior to randomization into the study. If anti-convulsants are needed, non –enzyme inducing anticonvulsants like Levetiracetam are preferred.

Concomitant medications used by patients during their participation in this study should be recorded on the Concomitant Medication CRF.

8.6.2 Prohibited Medications

Patients may not receive other chemotherapy treatments or investigational products while enrolled in this study. Patients should be withdrawn from the study before receiving a new treatment for their cancer, such as chemotherapy, surgery or investigational therapy.

9 STUDY ASSESSMENTS AND VISITS

Patients will be treated until there is disease progression or unmanageable treatment-related toxicities or until both concomitant and maintenance phases are completed.

The patient assessment will consist of:

1. Screening and Eligibility
2. Baseline assessment
3. Concomitant phase assessments
4. Maintenance phase assessments
5. Follow-up period assessments
6. Survival data

For details of schedule of assessments, see Schedule of Events in Appendix 3.

9.1 Screening and Pre-Study Assessments

Prior to the performance of any protocol-specific procedures, written informed consent must be obtained. After signing the informed consent, the patient will be assigned a screening number which will be composed of seven digits. The first three digits will be the site ID, and the next four digits will be allocated sequentially, starting with 9001. No subject will be enrolled twice in the study. Once the identification number has been assigned to a subject, no attempt should be made to use that number again. The investigational site personnel must maintain a log of screened patients.

The following screening assessments should be performed in order to determine whether the patient is eligible for this study and must be completed within 21 days prior to randomisation:

9.1.1 Screening Assessments:

1. Informed consent
2. Demographic information
3. A complete medical history, including review of systems, cancer history and history of previous treatment for cancer, must be performed. Copies of pathology reports confirming diagnosis should be obtained and reviewed.
4. Physical examination (heart, lungs, abdomen and neurological examination)
5. Weight, height, vital signs (temperature, blood pressure, and pulse).
6. Karnofsky performance status (refer to Appendix 1)
7. MRI- Head.

8. Laboratory tests
    a. Complete blood count (CBC) with differential and platelet count
    b. Prothrombin time (PT) and partial thromboplastin time (PTT)
    c. Serum chemistry, including electrolytes, blood-urea-nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), ALT and AST
    d. Urinalysis (dipstick) including albumin, glucose, ketones and blood (microscopic analysis if abnormal dipstick and clinical symptoms)
    e. Serum pregnancy test for females of childbearing potential
9. 12 lead Electrocardiogram (ECG) with QTc quantitation
10. Concomitant medication

9.2 Study Entry and Randomization

After performing all screening procedures, the site will assess the eligibility of the patient and if eligible, the patient will be randomized into the study.

The site will assign the randomization number. This number will be the next available number on the patient specific kits supplied to the site, starting with the lowest number available.

9.2.1 Concomitant phase

The concomitant phase constitutes 6 weeks of treatment with radiation and daily oral Temozolomide and study drug. During this period there will be weekly study visits.

9.2.1.1 Baseline / Visit 1

1. Physical examination.
2. Weight, vital signs (temperature, blood pressure, pulse, and height)
3. Karnofsky performance status
4. MRI-Head (if > 3 days from screen MRI)
5. Laboratory tests
    a. Complete blood count (CBC) with differential and platelet count
    b. Prothrombin time (PT) and partial thromboplastin time (PTT)
    c. Serum chemistry, including electrolytes, blood-urea-nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), ALT and AST
    d. Serum pregnancy test for females of childbearing potential
6. 12 lead ECG with QTc quantitative
7. Concomitant medications

8. Dispense drug for one week from the patient specific randomized kit.

9.2.1.2 Visit 2- Visit 6 (six weekly visits including baseline)

1. Physical exam
2. Weight, vital signs (temperature, blood pressure, pulse, and height)
3. Karnofsky performance status
4. Laboratory tests
    a. Complete blood count (CBC) with differential and platelet count
    b. Serum chemistry, including electrolytes, blood-urea-nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), ALT and AST
5. Concomitant medications
6. Adverse events
7. Dispense drug for one week.

9.2.1.3 Visit 7 / End of concomitant phase

1. Physical exam
2. Weight, vital signs (temperature, blood pressure, pulse, and height)
3. Karnofsky performance status
4. Laboratory tests
    a. Complete blood count (CBC) with differential and platelet count
    b. Prothrombin time (PT) and partial thromboplastin time (PTT)
    c. Serum chemistry, including electrolytes, blood-urea-nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), ALT and AST
5. 12 lead ECG with QTc quantitative
6. Concomitant medications
7. Adverse events

9.2.2 Maintenance Phase

The maintenance phase starts 4 weeks after completion of the concomitant phase. It will consist of six 28-day cycles during which the patient will receive temozolomide and study drug on Days 1 to 5 of each 28-day cycle.

Visits will be as follows for each cycle:

9.2.2.1 Cycle 1 – 6 : Day -7

The patient will be instructed to come 7 days in advance of day 1 of each cycle.

1. Vital signs
2. Physical exam
3. Karnofsky performance status
4. Concomitant medications
5. Adverse events
6. Laboratory tests
    a. Complete blood count (CBC) with differential and platelet count
    b. Serum chemistry, including electrolytes, blood-urea-nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), ALT and AST
7. Dispense drug after review of laboratory report.

If the hematology parameters fail to reach the required counts (refer section 7.2.1.2) , the hematology evaluation should be repeated every 4-7 days till such time that the required levels are achieved prior to start of next cycle.

9.2.2.2 End of treatment period assessments: Day 5 , Cycle 6 (EOT: End of treatment)

1. Vital signs
2. Physical exam
3. Karnofsky performance status
4. 12 lead ECG with QTc quantitative
5. Adverse events
6. Concomitant medications
7. Laboratory tests
    a. Complete blood count (CBC) with differential and platelet count
    b. Prothrombin time (PT) and partial thromboplastin time (PTT)
    c. Serum chemistry, including electrolytes, blood-urea-nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), ALT and AST
    d. Urinanalysis

9.2.3 Visits for conducting radiological investigations during the treatment period

During the treatment period, the patient will receive a MRI-Head at 2, 4, and 6 months from the baseline date.

9.3 Follow-up period assessment

9.3.1 Follow-up Visit: Month 9

1. Vital signs
2. Physical exam
3. Karnosfky performance status
4. 12 lead ECG with QTc quantitative
5. Adverse events
6. Concomitant medications
7. Laboratory tests
    a. Complete blood count (CBC) with differential and platelet count
    b. Serum chemistry, including electrolytes, blood-urea-nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), ALT and AST
8. MRI-Head

9.3.2 End of study visit: Month 12 (EOS)

1. Vital signs
2. Physical exam
3. Karnofsky performance status
4. 12 lead ECG with QTc quantitative
5. Adverse events will be captured if related to study drug
6. Laboratory tests
    a. Complete blood count (CBC) with differential and platelet count
    b. Prothrombin time (PT) and partial thromboplastin time (PTT)
    c. Serum chemistry, including electrolytes, blood-urea-nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), ALT and AST
7. MRI-Head

During the follow up period if the patients returns with progressive disease the end of study evaluations should be conducted prior to starting the patient on alternative therapy.

Following the EOS, patient survival data will be recorded.The patient will be contacted telephonically once a quarter for a period of three years.In the event of death of the patient; the date and cause of death will be recorded.

10 ASSESSMENT OF EFFICACY

The primary assessment will be to evaluate the efficacy of lucanthone when given along with temozolomide (TMZ) and radiation in the primary treatment of malignant gliomas due for radiation and TMZ treatment. Progression free survival at 6 months and one year, ORR at months 2, 4, 6, 9 and 12, overall survival at one year will be evaluated. MRI-Head scans will be performed baseline and months 2, 4, 6, 9 and 12.. Copies of all scans will be centrally reviewed by an expert panel of radiologists. The size of the enhancing tumor will be defined as the product of the largest perpendicular diameters of enhancement. Objective assessments of overall response will be based on tumor assessments from MRI scans interpreted using the RANO criteria.

11 ASSESSMENT OF SAFETY

11.1 Definitions

11.1.1 Definition: Adverse Event

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease experienced by a study participant while in a clinical study, whether or not considered related to the investigational product. Examples include: reactions or side effects, a pre-existing condition that worsens in severity or frequency, a concurrent illness, an injury, or a clinically significant laboratory abnormality.

11.1.2 Definition: Serious Adverse Event

A serious adverse event is an AE that meets at least one of the following criteria:

1. Is fatal
2. Is life-threatening (A life-threatening AE is an AE that places the patient at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.)
3. Requires inpatient hospitalization or prolongs an existing hospitalization (excluding emergency room visits)
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect in the offspring of an exposed patient
6. Other important medical events that may not result in death, be life-threatening or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The onset date of an SAE is defined as the date on which it met the criteria for an SAE; e.g., the date of admission to a hospital. The end date is the date on which the event no longer met the criteria for an SAE, e.g., the date that the patient was discharged from a hospital.

11.2 Relationship to Study Drug

In this study, the investigational product consists of lucanthone. The relationship of an adverse event to the investigational product should be classified by the Investigator using the following guidelines:

Definite: Experience follows a reasonable temporal association and could not have been explained by the patients underlying condition or is confirmed with a positive re-challenge.

Probable: Experience follows a reasonable temporal association, is confirmed by improvement upon discontinuation of investigational product, and is not reasonably explained by the patient's clinical state, environment, or other factors.

Possible: Experience follows a reasonable temporal association, but may have been produced by the patient's clinical state, environment, or other factors.

Unlikely: Experience does not follow a clear temporal association, and is probably produced by the patient's clinical state, environment, or other factors.

Unrelated: No relationship between the experience and administration of the investigational product.

For this study, adverse events that are considered by the Investigator to have a Possible, Probable, or Definite relationship to the investigational product are considered to be related to the investigational product.

11.3 Severity of Adverse Events

The severity of an AE should be defined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. AEs that are **not** listed in the CTCAE should be evaluated using the following guidelines:

1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.(ADL = Activities of Daily Living)

3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**

4 = Life threatening consequences; urgent intervention indicated.

5 = Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.4 Recording Adverse Events

All AEs should be recorded on the Adverse Event CRF from the first dose of lucanthone until the 9-month follow-up visit. However, any AE or death that the Investigator suspects

may be related to lucanthone should be reported regardless of the time elapsed from the final dose in this study. At each visit, patients should be asked in an open-ended manner about the occurrence of AEs. All AEs, regardless of whether or not ascribed to the investigational product, should be recorded in the CRF.

It is generally not necessary to record both a diagnosis and its associated symptoms and laboratory abnormalities. For example, if "acute renal failure" is recorded as an AE, "creatinine 5 mg/dL" need not be recorded.

If an AE necessitates a procedure, the description of the event (e.g., appendicitis) rather than the procedure (appendectomy) should be listed as the AE. However, if a procedure is performed for a reason other than an AE, the name of the procedure should be used as the name of the event.

If an AE was caused by the patient's cancer, that fact should be clear from the name of the event, e.g., "seizures due to brain metastases" or "jaundice due to liver metastases".

11.5 Reporting Serious Adverse Events

11.5.1 Reporting Serious Adverse Events to the Sponsor

The Investigator must notify the Sponsor of any event that meets one of the criteria for an SAE within one working day of learning of the event. The investigator will complete the SAE form provided and fax the information to Central Safety group at +1-949-861-6599 or email the form to drugsafety@sppirx.com.

Each SAE should be followed until resolution, or until such time as the Investigator determines its cause or determines that it has become stable. Information pertaining to follow-up of SAEs should be sent immediately in the same manner as initial information.

11.5.2 Reporting Serious Adverse Events to the IRB/IEC

It is the Investigator's responsibility to report serious adverse events to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) according to the requirements of the IRB/IEC.

11.6 Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC) will be constituted to review the safety . The committee will be responsible for reviewing and monitoring safety data of the clinical trial.

DMC will consist of independent experts not involved in the trial, including at least one pharmacologist and one oncologists.

The committee will review unblinded serious adverse event data on regular basis. DMC will provide recommendations concerning the safety of the patients and suggest interventions if deemed necessary.

The work of the DMC is described in a separate document; Charter for the independent Data Monitoring Committee (DMC).

12 STATISTICS

The section contains an overview of the statistical design and analysis plan for this study.

12.1 Sample Size

Eligible patients will be randomly assigned, 1:1, to receive radiotherapy and temozolomide (TMZ), with either lucanthone or placebo, as primary therapy of Glioblastoma multiforme (GBM). GBM patients treated with radiation and TMZ have achieved a median progression-free survival (PFS) time of 6.9 months, which conforms to a 40% PFS rate at 9 months. Adding lucanthone and extending the median PFS time by 5.1 months, to 12 months (i.e. a 9-month PFS rate of about 60%) will be of major clinical benefit to the patients. With these assumptions, a sample size of 70 patients per treatment group (total 140 patients) has 75% power to detect a difference in the 9-month PFS rate of patients treated with lucanthone versus those receiving placebo, at a two-sided 10% significance level.

12.2 Study Endpoints

12.2.1 Efficacy Endpoint

The primary efficacy endpoint is the progression free survival rate at 9 months.

Other efficacy endpoints are:

- Objective response rate(ORR) at months 2, 4, 6 , 9 and 12
- PFS at one year
- Overall survival (OS) at one year

12.2.2 Safety Endpoints

- Worst grade adverse events
- Deaths and other serious adverse events
- Worst grade laboratory abnormalities

12.3 Analysis Methods

12.3.1 Analysis Populations

Intention-to-Treat (ITT): all patients classified according to the treatment arms into which they were randomly assigned, regardless of the actual treatment received.

Safety Population (SAF): all patients who receive any study treatment, classified according to the treatment received.

12.3.2 Analysis of Efficacy

Analysis of efficacy will be in the ITT population.

Distributions of PFS and OS times will be estimated using the Kaplan-Meier product-limit method, and com. The 9-month PFS rate and the 12-month PFS and OS rates will be determined from Kaplan-Meier estimates.

The following will be summarized by treatment group:

- Number of events/number of patients (%)
- Estimates of the median and the corresponding two-sided 95% confidence intervals
- Log-rank p-value for treatment effect
- Hazard ratio and the corresponding two-sided 95% confidence interval
- Estimated 9-month (PFS only) and 12-month survival rates
- z-test for comparing 9- and 12-month rates

The best overall response to protocol treatment will be classified by RANO's criteria as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE). The objective response rate (ORR) is the proportion of patients who achieve either a CR or a PR.

The objective response rate (ORR) in each treatment arm, with corresponding exact 95% confidence intervals, will be computed at months 2, 4, 6, 9 and 12. In addition, the difference in response rates, along with a 95% confidence interval, will be calculated. The primary test of treatment effect between the two treatment arms will be a Fisher's exact test.

The following will be summarized by treatment group at each time-point:

- Best overall response: Number and % of patients with CR, PR, SD, PD, or NE
- Objective response rate: Number of patients, percent, and the corresponding exact 95% confidence intervals
- Difference in response rates with the two-sided 95% confidence interval
- Fisher's exact test p-value
- Odds ratio with the two-sided 95% confidence interval

12.3.3 Analysis of Safety

Analysis of safety will be in the safety population.

Treatment emergent adverse events will be graded by CTCAE version 4, and grouped by the MedDRA preferred term, and summarized by worst grade severity per patient and by treatment group.

Deaths, other serious adverse events, and other adverse events leading to discontinuation of study treatment will be summarized by treatment group.

All laboratory abnormalities will be classified according to the CTCAE version 4, and summarized by worst grade severity per patient and by treatment group.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Protocol and Regulatory Compliance

The Investigator must conduct the study according to this protocol. The investigator is responsible for appropriate medical care of subjects during the study.

The study must be conducted by all Investigators in compliance with Good Clinical Practices (GCP) as defined in the U.S. FDA Code of Federal Regulations 21 CFR 312 (Investigational New Drug Application), 21 CFR 50 (Protection of Human Subjects), 21 CFR 54 (Financial Disclosure by Clinical Investigators), 21 CFR 56 (Institutional Review Boards) and ICH guidelines (Guideline to Good Clinical Practice).

13.2 Protocol Amendments

Any changes to this protocol will be initiated by the Sponsor as a protocol amendment. The Investigator must submit the amendment to the IRB/IEC, with a revised Informed Consent Document if applicable. The Investigator must receive written approval from the IRB/IEC before the amendment may take effect.

13.3 Regulatory Binder

To be in compliance with GCPs, the Investigator must maintain accurate, complete, and organized documentation supporting the conduct of the study. This documentation includes, but is not limited to, the following: study personnel's qualifications and training, IRB/IEC approvals and communications, communications with the Sponsor, Site Signature & Responsibility Log, Form FDA 1572s, and Informed Consent Documents (copies of IRB/IEC-approved versions, signed/dated originals, or copies for all enrolled patients).

13.4 Informed Consent

Prior to the performance of any protocol-specific procedures, informed consent must be obtained and documented by the use of a written Informed Consent Document approved by the Sponsor and the IRB/IEC. The Informed Consent Document must be signed and dated by the patient or by the patient's legally authorized representative and by the person conducting the informed consent discussion. The Informed Consent Document must fulfill the requirements as contained in the U.S. Code of Federal Regulations (21 CFR 50.25), the ICH guidelines (Section 4.8), and the Declaration of Helsinki. In addition to these requirements, the Informed Consent Document must contain wording whereby the patient permits the review of his/her relevant medical records by representatives of Spectrum Pharmaceuticals, OncoRx representatives, and by representatives of the U.S. Food and Drug Administration (FDA) or other applicable national or local regulatory or health authorities. The Informed Consent Document must be written in a language understandable to the patient or to the patient's representative.

A signed and dated copy of the Informed Consent Document must be given to the person signing the document. The original must be retained by the Investigator with the study documentation and be available for inspection by persons conducting an audit of the study (e.g., regulatory authorities, Spectrum Pharmaceuticals representatives, OncoRx representatives).

The Sponsor will provide a template Informed Consent Document to the study sites. Modifications to this template may be made by study site personnel to be in compliance with national, regional (e.g., state) or local laws and/or institutional requirements. All versions of the Informed Consent Document should be reviewed and approved by Spectrum Pharmaceuticals and OncoRx prior to the submission of the Informed Consent Document for IRB/IEC approval.

13.5 Institutional Review Boards and Independent Ethics Committees

The protocol, Informed Consent Document, patient recruitment procedures (e.g., advertisements), information about payments and compensation available to patients, and any amendments must be approved by a properly constituted IRB or IEC in compliance with current regulations of the U.S. FDA, ICH guidelines, and any country-specific regulations. Specifically, the study must not be initiated until the Investigator has provided Spectrum Pharmaceuticals with documentation of IRB/IEC approval of the protocol, the Informed Consent Document, and all recruiting materials. In addition, prior to their implementation or use, there must be documented IRB/IEC approval for the following: protocol amendments, revised Informed Consent Documents, patient recruitment materials (e.g., advertisements), and study-related supplements that are provided to study patients.

13.6 IRB/IEC Communications

The Investigator must make timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding one year, as well as satisfying any other local IRB/IEC regulations regarding reporting, including reporting on safety aspects of the study (e.g., SAEs, safety letters). The study must receive documented IRB/IEC approval annually. Furthermore, at the completion or early termination of the study, a final report must be made to the IRB/IEC by the Investigator within the applicable IRB/IEC timeframes.

It is the Investigator's obligation to maintain an IRB/IEC correspondence file and to make this available for review by Spectrum Pharmaceuticals representatives as part of the study monitoring process. Copies of all correspondence between the Investigator and the IRB/IEC (including all attachments to any correspondence) must be provided for the Spectrum Pharmaceuticals internal file.

13.7 Curriculum Vitae and Medical Licenses

The Principal Investigator is responsible for ensuring that the study is conducted by qualified personnel. Documentation of these qualifications must be maintained within the Regulatory Binder, and includes the following:

Curriculum Vitae (CV): CVs for the Principal Investigator and all Sub-investigators listed on the Form FDA 1572 must be signed and dated. These CVs must show affiliation with the institution conducting the study and be current within two years of the personnel initiating their participation in the study.

Medical Licenses: Medical licenses (physicians, physician assistants, nurses) listed on the Form FDA 1572 must be kept current, and copies must be maintained in the Regulatory Binder.

13.8 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. Patient medical information obtained for the purposes of this study is confidential, and disclosure to third parties, other than those noted below, is prohibited. Patients should not be identified by name, social security number or medical record number on any documents or materials (samples, slides) sent to Spectrum Pharmaceuticals or its representatives (e.g., data management organization) or during verbal communications. Patients should be identified only by their initials and protocol-assigned patient ID number.

For clinical sites in the US, study personnel should follow the requirements of the Health Insurance Portability and Accountability Act (HIPAA) and the Personal Information Protection and Electronic Documents Act (PIPEDA), respectively.

For clinical sites in India, study personnel should follow the requirements of the MOH (DCGI) and applicable Ethics Committee.

All clinical information is confidential, but data generated for this study must be available for inspection on request to representatives of the U.S. FDA, other national or local regulatory or health authorities, Spectrum Pharmaceuticals and OncoRx representatives, and the associated IRB/IEC.

All records must be kept in a secured area.

13.9 Financial Disclosure

Documentation of each Investigator's proprietary or financial interest in Spectrum Pharmaceuticals, Inc. is required by the U.S. Code of Federal Regulations (21 CFR 54). A financial disclosure form provided by the Sponsor must be completed, signed, and dated by the Principal Investigator and each Sub-investigator listed on the Form FDA 1572. This form must be executed prior to the personnel's participation in the study. The original form will be retained by the Sponsor. Each Investigator must inform the Sponsor of any change in his/her financial interest in the Sponsor for up to one year after the end of the study.

The U.S. Securities and Exchange Commission (SEC) prohibits any person who has material, non-public information concerning Spectrum Pharmaceuticals or a possible transaction involving Spectrum Pharmaceuticals from purchasing or selling securities in reliance upon such information or from communicating such information to any other person or entity under circumstances in which it is reasonably foreseeable that such person or entity is likely to purchase or sell such securities in reliance upon such information.

14 QUALITY ASSURANCE

14.1 Routine Clinical Site Monitoring

Spectrum Pharmaceuticals CRAs or OncoRx representatives will make a pre-study site visit (if deemed necessary) to determine the qualifications of the Investigator, inspect the clinical facilities, and fully inform the Investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the course of the study, a Spectrum Pharmaceuticals CRA or an OncoRx CRA will make routine contacts (e.g., telephone communications and site visits) at appropriate intervals to review protocol compliance; to

examine CRFs and individual patient's medical records, the Regulatory Binder, the investigational product handling and accountability procedures, and data recording practices; and to ensure that the study is being conducted in compliance with applicable requirements. CRF entries will be verified against source documentation.

The Investigator and the site personnel are expected to cooperate with Spectrum Pharmaceuticals CRAs or OncoRx CRAs and to provide, upon request, all relevant study documentation that is requested at each site visit.

14.2 Site Audits

The Investigator must permit inspection of the study files (e.g., source documentation such as clinic notes, nurses' notes, radiological and laboratory records, CRFs, Regulatory Binder) by a Sponsor representative and by authorized representatives of the U.S. FDA or other applicable country regulatory agencies. If the site is informed of an inspection by any regulatory authority, the Investigator should notify Spectrum Pharmaceuticals or OncoRx immediately.

15 DATA HANDLING AND RECORD KEEPING

15.1 CRF Completion and Transmittal

The study will have CRF in electronic format. CRFs should be completed in a timely manner and must be available for review during routine monitoring visits. All CRFs should be completed on-line via Electronic Data Capture (EDC) system. All references to specific patients must be made by use of initials and by patient ID number, not by name. Patient confidentiality should be maintained by obscuring all names, social security numbers or patient record numbers (using a black marker) in any reports or records sent to the Sponsor or its representatives. The Principal Investigator is responsible for reviewing each page of the CRF and for signing the appropriate forms. The Investigator will attest to the accuracy and completeness of the information contained in the CRFs.

CRFs will be completed no more than seven days from the patient visit. At the completion or termination of the study, each site will be provided with electronic copies of all patients' CRFs.

15.2 Data Corrections

All corrections to source documents must be initialed and dated by the individual making the correction. Corrections to the source documents must be made by drawing a single line through the incorrect entry and recording the correct entry nearby. Incorrect entries should not be obliterated; the original text should remain legible. Use of opaque correction fluid, correction tape, or highlighters is prohibited.

15.3 Record Retention

Records that individually or collectively permit the evaluation of the conduct of the study and the quality of the data produced with this study must be maintained for review by the Sponsor's representatives and by U.S. and non-U.S. regulatory authorities. The Investigator must retain these records minimally for a period of two years following the date of the last marketing application in an ICH region and until there are no pending or contemplated

marketing applications in an ICH region, or for at least two years following the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

The Sponsor will inform the Investigator in writing when the study-related records are no longer needed. The Investigator must notify the Sponsor in writing at least 30 days prior to the intended date of disposal of any study records related to this protocol. If the Investigator leaves the institution where the study was conducted, the Investigator must inform the Sponsor in writing where the records associated with this protocol are archived and who is responsible for their security.

16 COMPENSATION, INSURANCE AND INDEMNITY

Information regarding compensation, insurance and indemnity will be provided to the Investigator in the Clinical Trial Agreement.

17 USE OR PUBLICATION OF STUDY-RELATED INFORMATION

All information obtained as a result of this study should be regarded as confidential.

Information regarding use or publication of study-related information will be provided to the Investigator in the Clinical Trial Agreement.

18 INVESTIGATOR AGREEMENT

An International, Multi-Center, Randomized, Double Blind Placebo Controlled Phase II Study to Evaluate the Safety and Efficacy of Lucanthone Administered as an Adjunct to Radiation and Temozolomide for Primary Therapy of Malignant Gliomas

I understand that all information concerning this study supplied to me by Spectrum Pharmaceuticals, Inc. is confidential information. I have read this protocol and agree to conduct the study according to Good Clinical Practice Guidelines and in accordance with the Clinical Trial Agreement.

I understand that this protocol and all amendments must be submitted to the appropriate IRB/IEC.

Investigator Name (PLEASE PRINT): _____

Signature: _____ _____
Date

Please sign and return this agreement to:

US sites
George Tidmarsh, MD, PhD
Chief Scientific Officer
Spectrum Pharmaceuticals Inc.
157 Technology Drive
Irvine, CA 92618

India Sites
Sunita Rajadhyaksha, MD
Medical Director
OncoRx Pharma Pvt Ltd
85 Mittal Chambers
228 Nariman Point, Mumbai 400021

Please keep a copy for your records.

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Appendix 1 **Karnofsky Score**

A Karnofsky performance status score should be assigned in conjunction with the physical examination. The following criteria will be applied.

100	Normal, no complaints or evidence of disease
90	Able to perform normal activity; minor signs and symptoms of disease
80	Able to perform normal activity with effort; some signs and symptoms of disease
70	Cares for self, unable to perform normal activity or to do active work
60	Requires occasional assistance but is able to care for most of own needs
50	Requires considerable assistance and frequent medical care
40	Requires special care and assistance; disabled
30	Hospitalization indicated, although death not imminent; severely disabled
20	Hospitalization necessary; active supportive treatment required, very sick
10	Fatal processes progressing rapidly; moribund
0	Dead

Appendix 2 Criteria for Response Assessment Incorporating MRI and Clinical Factors (RANO Criteria)

1. **Complete response (CR):** Requires all of the following : complete disappearance of all enhancing measurable and non measurable disease sustained for at least 4 weeks; no new lesions; stable or improved non enhancing (T2/FLAIR) lesions; patient 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 (PR):** - Requires all of the following : >/= 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing disease sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved non enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the the corticosteroid dose at time of scan evaluation should be no less than at the time of baseline scan; and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease

3. **Stable disease (SD):** - Requires all of the following : does not qualify for complete response, partial response or progression; stable non enhancing (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 that this increase in corticosteroids was required because of disease progression , the last scan considered to show stable disease will be scan obtained when the corticosteroid dose was equivalent to the baseline dose.

4. **Progression :-** Defined by any of the following : >/= 25% increase in the sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at the baseline(if no decrease) or best response, on stable or increasing doses of corticosteroids (stable dose of corticosteroids include patients not on corticosteroids); significant increase in T2/FLAIR non-enhancing lesion on stable or increasing dose of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by comorbid events(eg 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(eg 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 non measurable disease.

Source: Updated Response Assessment Criteria for High Grade Glioms:Response Assessment in Neuro-Oncology Working Group. PYWen et al. Journal of Clinical Oncology March15,2010.

Response Criteria (RANO criteria):

	T1 contrast enhancement (CE)	FLAIR images	Steroids	Neurologic exam
Complete Response (CR)	No residual CE (complete disappearance of all enhancing measurable disease for at least 4 weeks; 4-week confirmation required to score as CR) and no new lesions.	Stable or reduced area of FLAIR signal abnormality	No steroids	Stable or improved from prior evaluation
Partial Response (PR)	>50% reduction in sum of products of the perpendicular diameters of all measureable enhancing lesions sustained for at least 4 weeks and no new lesions or progression of non-measurable lesions	Stable or reduced area of FLAIR signal abnormality	Stable or reduced glucocorticoids from baseline MRI	Stable or improved from prior evaluation
Minor response (MR)	>25% reduction in sum of products of the perpendicular diameters of all measureable enhancing lesions sustained for at least 4 weeks and no new lesions or progression of non-measurable lesions	Stable or reduced area of FLAIR signal abnormality	Stable or reduced glucocorticoids from baseline MRI	Stable or improved from prior evaluation
Stable Disease (SD)	<25% reduction in area of CE maintained for at least 4 weeks duration. Does not qualify for CR, PR or progression	Stable or reduced area of FLAIR signal abnormality	Stable or reduced glucocorticoids from baseline MRI	Stable or improved from prior evaluation
Progressive Disease	>25% in the sum of products of the perpendicular diameters of CE lesions; evidence of new lesion(s).	Measurable increase* in the sum of products of the perpendicular diameters of FLAIR signal abnormality from the baseline scan or the scan representing the best response (if there was a response) following therapy and not attributable to other co-morbid events (seizure, radiation, injury, infection, ischemia, etc.) OR presence of a new focus of FLAIR signal abnormality that cannot be explained by any other pathologic process.	Stable or increased dose of glucocorticoids	Stable or worsening neurologic symptoms

Appendix 3 **Schedule of Events**

		Concomitant Phase							**Maintenance Phase**						**EOT**	**FU Month 9**	**FU Month 12**
	Screening Day -21to Baseline	**Baseline Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**EOCP Visit 7**	**Day -7 Cycle 1**	**Day -7 Cycle 2**	**Day -7 Cycle 3**	**Day -7 Cycle 4**	**Day -7 Cycle 5**	**Day -7 Cycle 6**	Day 5 Cycle 6		
Informed Consent	X																
Medical history	X																
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight, Height, Temp	X	X	X	X	X	X	X	X									
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Karnofsky Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test	X																
PT and PTT	X	X						X							X		X
Urinalysis	X														X		
ECG	X	X						X							X	X	X
Concomitant medications review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X(study drug related)
MRI-Tumor assessment	X	Tumor assessments (see below)							Tumor assessments (see below)							X	X
Radiation		Radiation Exposure (see below)															
Timozolomide		X	X	X	X	X			X	X	X	X	X	X			
Study drug		**X**	**X**	**X**	**X**	**X**			**X**	**X**	**X**	**X**	**X**	**X**			

Tumor assessment : MRI head will be done at screen , baseline, months 2,4,6,9 and 12

Radiation : During the concomintant phase patient will receive focal radiation 60Gy/30 for 5 days a week for 6 weeks.