PROTOCOL SUBMISSION FORM	PROTOCOL NO.	PRINCIPAL INVESTIGATOR (NIH Employee Name, Inst/Br, Telephone and e-mail):
Amendment Form	00C0080-H	William Dahut NCI MOB 301.435.8183 dahutw@mail.nih.gov

PROTOCOL TITLE: A Double-Blinded Randomized Crossover Phase III Study of Oral Thalidomide versus Placebo in Patients with Stage D0 Androgen Dependent Prostate Cancer Following Limited Hormonal Ablation

ABBREVIATED TITLE: Not Applicable

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Amendment Version Date: 04/30/2009 Amendment Letter: I

The Following revisions were incorporated into this protocol and approved by:

☒ Expedited Review (risk/ benefit ratio not changed)
☐ Full Board Review (meeting date)

Amendment includes changes required by:

☐ N/A
☐ NCI IRB
☐ CTEP
☐ Other Sponsor
☐ FDA
☒ Other

If Other, list:

OPS

Amendment required Scientific Review?

☐ Yes ☒ No

ADMINISTRATIVE CHANGES

☐ Protocol Title/ Abbreviated Title
☐ New Principal Investigator
☐ NIH Personnel Change
☐ Non-NIH Personnel Change
☐ Converting to multi-institutional trial

DEC clearance required? ☐ Yes ☒ No

Date submitted to IC DEC: N/A Date cleared by IC DEC: N/A

PROTOCOL CONTENT CHANGES

☐ Precis
☐ Study Objectives
☐ Background and Rationale
☐ Eligibility Assessment and Enrollment
☐ Implementation of Study Design
☐ Supportive Care
☐ Accrual Ceiling Changed to: N/A
☐ Data Collection/Evaluation
☐ Human Subject Protections
☐ Data Reporting
☐ IND/IDE Information
☐ Pharmaceutical Information
☐ Appendices

Does the amendment impact the risk/benefit assessment?

☐ Yes ☒ No

INFORMED CONSENT DOCUMENTATION

☐ Text Revisions to Consent(s)
☐ Investigator Contact Information on Consent(s)
☒ No Changes to Consent Form

SIGNATURE

William Dahut - applied signature on 05/13/2009 1:07 PM EDT
New and Old Principal Investigators - electronic signature and date

APPROVALS

Giuseppe Giaccone - applied signature on 05/20/2009 5:38 AM EDT
Branch Chief - electronic signature and date

Carvn Steakley - applied signature on 05/21/2009 11:27 AM EDT
Clinical Director- electronic signature and date

Wanda Salzer - applied signature on 05/20/2009 3:18 PM EDT
Chair, IRB Review - electronic signature and date

William Dahut 6/10/09 Am I

IRB Meeting Date:

A Double Blind Randomized Crossover Phase III Study of Oral Thalidomide versus Placebo in Patients with Stage D0 Androgen Dependent Prostate Cancer Following Limited Hormonal Ablation

MB-419
NCI # T99-0053

Principal Investigator: William Dahut, M.D., MB/DCS/NCI
<dahutw@mail.nih.gov>

Protocol Chairperson: William D. Figg, Pharm.D., MB/DCS/NCI
<wdfigg@helix.nih.gov>

Associate Investigators:
David Kohler, Pharm.D., Pharmacy Dept/NIHCC
Seth Steinberg, Ph.D., BDMS/CCR//NCI
James Gulley, M.D., MB/CCR/NCI
Phil Arlen, M.D., Volunteer

CTEP Study Monitor: Howard Streicher, IDB/CTEP/NCI
MultiCenter Collaborators: Dan Petrylak, M.D., Columbia Hospital, New York, NY
Ulka Vaishampayan, M.D., Wayne State University, Detroit, MI
Joseph Fontana, M.D., Wayne State University, Detroit, MI
Gurkamal Chatta, MD., University of Pittsburgh, Pittsburgh, PA
Celestia Higano, M.D., University of Washington, Seattle, WA
Arkadiusz Dudek, M.D.,, University of Minnesota, Minneapolis, MN
Leonard Seigel, M.D., Holy Cross Hospital, Fort Lauderdale, FL
Jon L. Hopkins, M.D., Portsmouth Naval Medical Center, Portsmouth, VA

Study Conducted by: Medical Oncology Clinical Research Unit (MOCRU)
Center for Cancer Research
National Cancer Institute
Warren G. Magnuson Clinical Center (Bldg 10)
National Institutes of Health
Bethesda, MD 20892
Tel: (301) -402-3622
Fax:(301) -402-8606

Columbia Hospital, New York, NY MPA #M-1356
LSU, New Orleans, LA MPA #M-1130
Wayne State, Detroit, MI MPA #M-1261
University of Washington, WA MPA #M-1183
University of Pittsburgh, Pittsburgh, PA MPA #: M-1259
University of Minnesota, Minneapolis, MN: IORG0000261
Holy Cross Hospital, Fort Lauderdale, FL: #T-3393
Portsmouth Naval Medical Center, Portsmouth, VA

Columbia University

Principal Investigator:	Daniel P. Petrylak, M.D.
Complete address:	Columbia Presbyterian Medical Center 161 Fort Washington Avenue Atchley Pavilion, Rm. 919 New York, NY 10032
Phone number:	(212) 305-1731
Email address:	dpp5@columbia.edu
IRB contact:	Donald Kornfield, M.D., Chairman
IRB address:	Columbia Presbyterian Medical Center Institutional Review Board 630 West 168th Street P&S 3-460 New York, NY 10032
IRB phone number:	(212) 305-5883
IRB contact email:	This information is not available.
Pharmacy contact:	Robert B. MacArthur, Pharm. D., Director
Complete address:	Research Pharmacy Columbia Presbyterian Medical Center 710 West 168th Street Neurological Institute, Rm. B-9 New York, NY 10032
Pharmacy phone number:	(212) 305-3589

Pharmacy fax number:	(212) 305-0397
Pharmacy email:	macartr@cuadmin.cis.columbia.edu

LSU

Principal Investigator:	Oliver Sartor, M.D.
Complete address:	Louisiana State University Health Sciences Center Stanley S. Scott Cancer Center Clinical Sciences Research Building 533 Bolivar Street, 4th Floor New Orleans, LA 70122
Phone number:	(504) 568-5148 or 5151
Email address:	osarto@lsumc.edu
IRB contact:	Kenneth Kratz, Ph.D., Chairman
IRB address:	Louisiana State University Health Sciences Center Institutional Review Board 433 Bolivar Street, Room 206 New Orleans, LA 70122
IRB phone number:	(504) 568-4060
IRB contact email:	kkratz@lsumc.edu
Pharmacy contact:	Oliver Sartor, M.D.
Complete address:	Louisiana State University Health Sciences Center Stanley S. Scott Cancer Center Clinical Sciences Research Building 533 Bolivar Street, 4th Floor New Orleans, LA 70122
Pharmacy phone number:	(504) 568-5148
Pharmacy fax number:	(504) 568-6888
Pharmacy email:	osarto@lsumc.edu

Wayne State University

Principal Investigator:	Ulka Vaishampayan, M.D.
Complete address:	Harper Hospital 3990 John R, 5-Hudson Detroit, MI 48201
Phone number:	(313) 745-2749
Email address:	vaishamu@karmanos.org
IRB contact:	Francis LeVeque, M.D.
IRB address:	University Health Center, 6G 4201 St. Antoine Detroit, MI 48201
IRB phone number:	(313) 577-1628
IRB contact email:	fleveque@med.wayne.edu
Pharmacy contact:	Barb Manica, Pharm.D.
Complete address:	3990 John R Detroit, MI 48201
Pharmacy phone number:	(313) 745-8216
Pharmacy fax number:	Not available.
Pharmacy email:	bmanica@dmc.org

University of Washington

Principal Investigator:	Celestia Higano, M.D.
Complete address:	Seattle Cancer Center Care Alliance Clinic 825 Eastlake Avenue East Seattle, WA 98109-1023

Phone number:	(206) 288-2048
Email address:	thigano@u.washington.edu
IRB contact:	Michael Donahue, Committee A
IRB address:	University of Washington Human Subjects Division 3935 University Way NE Seattle, WA 98105-6613
IRB phone number:	(206) 543-0098
IRB contact email:	hsd@u.washington.edu
Pharmacy contact:	Sherre Miller, R.Ph., PharmD.
Complete address:	University of Washington Medical Center Investigational Drug Services Box 356015 1959 NE Pacific Street, Room EA-151 Seattle, WA 98195-6015
Pharmacy phone number:	(206) 598-6054
Pharmacy fax number:	(206) 598-4901
Pharmacy email:	uwmcids@u.washington.edu

University of Minnesota

Principal Investigator:	Hikaru Nakajima, M.D.
Complete address:	NMC 480 420 Delaware Street, S..E. Minneapolis, MN 55455
Phone number:	(612) 624-5109
Email address:	naka0053@umn.edu
IRB contact:	Moira Keane
IRB address:	420 Delaware Street, S.E. Room D528 Mayo Building Minneapolis, MN 55455
IRB phone number:	(612) 626-6061

IRB contact email:	keane002@umn.edu
Pharmacy contact:	Shelly Oliverson
Complete address:	Fairview-University Medical Center Phillips-Wangensteen Building Room 2-350 516 Delaware Street, S.E. Minneapolis, MN 55455
Pharmacy phone number:	(612) 626-2828
Pharmacy fax number:	(612) 625-3235
Pharmacy email:	soliver1@FAIRVIEW.ORG

University of Pittsburgh

Principal Investigator:	Gurkamal Chatta, M.D.
Complete address:	UPMC Cancer Pavillion Division of Hematology/Oncology 5150 Centre Ave. 5th Floor Room 560 Pittsburgh, PA 15232
Phone number:	(412) 692-4673
Email address:	chattags@msx.upmc.edu
IRB contact:	Janie Hofacker, RN, BSN Program Leader, Regulatory Affairs
IRB address:	University of Pittsburgh Institutional Review Board 3500 Fifth Avenue Ground Level Pittsburgh, PA 15213
IRB phone number:	(412) 578-3424
IRB contact email:	hofackerjk@msx.upmc.edu

Pharmacy contact:	Carol Matthews, RPh, PharmD
Complete address:	UPCI Outpatient Pharmacy William Cooper Ambulatory Care Pavillion Hillman Cancer Center 5115 Centre Ave, 2nd Floor Pittsburgh, PA 15232
Pharmacy phone number:	(412) 623-3464
Pharmacy fax number:	(412) 692-2416
Pharmacy email:	matthewsc@msx.upmc.edu

Holy Cross Hospital

Principal Investigator:	Leonard Seigel, M.D.
Complete address:	Michael & Dianne Bienes Comprehensive Cancer Center Holy Cross Hospital 4725 North Federal Highway, Fort Lauderdale, Florida 33308
Phone number:	(954) 267-7700
Email address:	Leonard.seigel@holy-cross.com
IRB contact:	Richard M. Luceri, MD Chairman, Human Protection Committee
IRB address:	Holy Cross Hospital Institutional Review Board 4725 North Federal Highway Ft. Lauderdale, FL 33308
IRB phone number:	(954) 772-1080
IRB contact email:	richard.luceri@holy-cross.com
Pharmacy contact:	Eddie Chong R.Ph., BCNSP
Complete address:	Michael & Dianne Bienes Comprehensive Cancer Center Holy Cross Hospital 4725 North Federal Highway Fort Lauderdale, Florida 33308
Pharmacy phone number:	(954) 267-7747
Pharmacy fax number:	(954) 267-7799
Pharmacy email:	etwchong@hotmail.com

Portsmouth Naval Medical Center

Principal Investigator:	Jon L. Hopkins, M.D.
Complete Address:	Naval Medical Center 620 John Paul Jones Circle Portsmouth, VA 23708-2197
Phone number:	(757) 953-1043
Email address:	jlhopkins@mar.med.navy.mil
IRB contact:	Charles W. Morgan, Ph.D. Research Program Administrator/ Chief, Research Subject Protection
IRB address:	Naval Medical Center 620 John Paul Jones Circle Attn.: Clinical Investigation and Research Department Code 00J2 Portsmouth, VA 23708-2197
IRB phone number:	(757) 953-5939
IRB contact email:	cwmorgan@mar.med.navy.mil
Pharmacy contact:	Tim Gendron, R.Ph.
Complete address:	Pharmacy Department Charette Health Care Center Naval Medical Center 620 John Paul Jones Circle Portsmouth, VA 23708-2197
Pharmacy phone number:	(757) 953-0252
Pharmacy FAX number:	(757) 953-0863
Pharmacy email:	rtgendron@mar.med.navy.mil

Table of Contents

A Double Blind Randomized Crossover Phase III Study of Oral Thalidomide versus Placebo in Patients with Stage D0 Androgen Dependent Prostate Cancer Following Limited Hormonal Ablation

I. Precis

This is a double-blind randomized phase III study designed to determine if thalidomide can improve the efficacy of the LHRH agonist (leuprolide or goserelin) in hormone-responsive patients with a rising PSA after primary definitive therapy for prostate cancer. Patients with only a rising PSA will be randomized to LHRH agonist for six months followed by oral thalidomide 200 mg per day or placebo (Phase A). At the time of PSA progression, an LHRH agonist will be restarted for six additional months. After six months, patients originally treated with thalidomide will be crossed over to placebo and patients originally treated with placebo will be crossed over to thalidomide and followed until PSA progression or the development of metastatic disease, whichever occurs first (Phase B). Additional information will be obtained on changes in the circulating levels of the following growth factors: bFGF, TNF, VEGF, and TGFβ. Likewise we will monitor changes in testosterone and DHT throughout the study. Neurological complications are the primary dose-limiting toxicity anticipated with chronic thalidomide administration.

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II. Treatment Scheme:

Prior to Day 1	Evidence of a rising PSA over at least 2 weeks (outside laboratory values are acceptable) Bone Scan (within 8 weeks prior to day 1) CT Scan (within 8 weeks prior to day 1) Laboratory Evaluation (within 2 weeks prior to day 1) Tumor Markers (within 2 weeks prior to day 1) History and Physical Exam (prior to day 1) Neurological Exam (prior to starting)
Day 1	Randomization to Placebo versus Treatment Arms Leuprolide 7.5 mg IM - 30 day Depot formulation OR 22.5 mg-3 month formulation (both arms) OR goserelin 3.6 SQ-30 day formulation OR goserelin 10.8mg SQ-3 month formulation
Day 28 (1 mo)	History and Physical Examination Leuprolide 7.5 mg IM - 30 day Depot formulation - for those who didn't receive the 3 month formulation (both arms) OR goserelin 3.6 SQ-30 day formulation Laboratory Evaluation Tumor Markers Neurological Exam This visit is not necessary if the patient received the 3-month formulation.
Day 56 (2 mo)	History and Physical Examination Leuprolide 7.5 mg IM - 30 day Depot formulation OR goserelin 3.6 SQ-30 day formulation - for those who didn't receive the 3 month formulation (both arms) Laboratory Evaluation Tumor Markers Neurological Exam This visit is not necessary if the patient received the 3-month formulation.
Day 84 (3 mo)	History and Physical Examination Leuprolide 7.5 mg IM - 30 day Depot formulation OR 22.5 mg-3 month formulation (both arms) OR goserelin 3.6 SQ-30 day formulation OR goserelin 10.8mg SQ-3 month formulation Laboratory Evaluation Tumor Markers Neurological Exam

Day 112 (4 mo)	History and Physical Examination Leuprolide 7.5 mg IM - 30 day Depot formulation - for those who didn't receive the 3 month formulation (both arms) OR goserelin 3.6 SQ-30 day formulation Laboratory Evaluation Tumor Markers Neurological Exam This visit is not necessary if the patient received the 3-month formulation.
Day 140 (5 mo)	History and Physical Examination Leuprolide 7.5 mg IM - 30 day Depot formulation - for those who didn't receive the 3 month formulation (both arms) OR goserelin 3.6 SQ-30 day formulation Laboratory Evaluation Tumor Markers Neurological Exam This visit is not necessary if the patient received the 3-month formulation.
Day 168 (6 mo)	History and Physical Examination Laboratory Evaluation Tumor Markers Neurological Exam Begin thalidomide or placebo q month till progression History and Physical Exam Neurological Exam Laboratory Evaluation Tumor Markers

q month till progression … (1) collect all "old" bottles [i.e., empty bottle(s), partial bottle(s), full bottle(s)] of thalidomide / placebo capsules from the patient; (2) perform a capsule count and record the results on the bottom portion of the "old" Pill Count Case Report Form [i.e., the Pill Count Case Report Form started at the previous clinic visit] (see Appendix C); (3) determine the total number of capsules remaining in all "old" bottle(s) of thalidomide / placebo capsules and subtract that number from 140 … round up to the next even "100" to determine how many "new" bottle(s) of thalidomide / placebo capsules will be needed until the next clinic visit … note that the minimum number of capsules dispensed at each clinic visit should be 140 and the maximum number of capsules dispensed at each clinic visit should be 239 [Example 1: 60 capsules remaining from "old" bottle(s) … 140 – 60 = 80 … round up to 100 … dispense 60 capsules from "old" bottle plus 100 capsules from "new" bottle for a total of 160 capsules / Example 2: 20 capsules remaining from "old" bottle … 140 – 20 = 120 … round up to 200 … dispense 20 capsules from "old" bottle and 200 capsules from two "new" bottles for a total of 220 capsules]; (4) complete the upper portion of a "new" Pill Count Case Report Form and affix

the tear-off label(s) from any "new" bottle(s) of thalidomide / placebo capsules; (5) dispense the partial and full bottles of thalidomide / placebo capsules to the patient.

At time of progression repeat CT scan, bone scan, and/or imaging study.

Patients whose PSA returns to baseline (as defined by PSA prior to LHRH agonist) or increases to 5 ng/mL (whichever is lower) or who experience side effects of Grade 3 or greater will be switched over to the other treatment arm. The whole process repeats again from Day 1.

The thalidomide dose is 200 mg per day taken orally. Patients will be blinded to thalidomide versus placebo and thus will simply take four capsules every evening about 9:00 pm after their six months of LHRH agonist treatment has been completed.

If a patient develops objective metastasis or if the PSA rises while on an LHRH agonist, the patient will be removed from the study and placed on total androgen blockade.

A Double Blind Randomized Crossover Phase III Study of Oral Thalidomide versus Placebo in Patients with Stage D0 Androgen Dependent Prostate Cancer Following Limited Hormonal Ablation

1.0 Introduction

1.1 Study Objectives

1.1.1 To determine the potential clinical activity of thalidomide in patients with Stage D0 androgen dependent prostate cancer (time to progression).

1.1.2 To evaluate all toxicities related to thalidomide in patients with stage D0 androgen dependent prostate cancer following definitive therapy.

1.1.3 To determine whether there are changes in molecular markers of angiogenesis.

1.1.4 Monitor for changes in testosterone, DHT, and/or other endocrine endpoints.

1.1.5 Attempt to make pharmacodynamic correlations between activity and toxicity.

1.2 Background of Stage D0 Androgen Dependent Prostate Cancer

Carcinoma of the prostate is currently the most commonly diagnosed cancer in American men, after skin cancer, and the number two cause of cancer mortality (Sartor et al). Definitive therapy for localized disease consists of either surgery, radiation therapy with external beam or brachytherapy, or cryosurgery. The widespread monitoring of PSA following definitive therapy has resulted in a large cohort of patients initially recurring with Stage D0 disease (i.e., PSA only disease). In fact, approximately 50% of patients will develop a rising PSA after definitive therapy, indicating the presence of recurrent or persistent disease. Options for those treated with definitive therapy include radiation, hormonal therapy, intermittent androgen ablation, potency sparing androgen ablation, or watchful waiting. All patients presenting with a rising PSA will ultimately develop metastatic disease; however, there is tremendous debate about when to initiate hormonal ablation (Figg et al, 1997).

1.3 Background on Intermittent Androgen Ablation

Although continuous androgen ablation therapy is the current standard of care for advanced metastatic prostate cancer patients, there is mounting support for treatments, which manipulate the selection pressure of total androgen withdrawal in an attempt to delay the onset of hormone-independence, especially in the PSA only patient. Treatment options such as intermittent androgen deprivation have demonstrated the ability to induce recurrent responses to treatment. In several studies, it has been reported that intermittent androgen suppression is a safe alternative to continuous androgen blockade with an improved quality of life for patients while off treatment (Cude et al).

Goldenberg evaluated 30 patients that had locally advancing prostate cancer (failed definitive therapy and experienced recurrent PSA only disease, stage D0 following definitive therapy) (Goldenberg et al). Combined androgen blockade was initiated and those patients with a normal PSA between 24 and 32 weeks after starting therapy were eligible. Androgen blockade was discontinued and PSA was monitored. Patients with a pretreatment PSA >20 ng/ml were started with a second cycle of combined androgen blockade when the PSA increased to 10-20 ng/mL, patients with an initial PSA between 10 and 20 ng/ml resumed therapy when the PSA increased to between 5 and 15 ng/mL. The mean duration of cycle was 73 weeks with an mean time off therapy of 30 weeks (range 9 to 108 weeks).

1.4 Background of Angiogenesis

Angiogenesis is the process by which new blood vessels invade a tissue (Folkman et al 1971, Figg et al 1998). It occurs normally during wound healing, menstruation, and the development of an embryo. Vessel growth is normally controlled by a balance of endogenous inhibitors and stimulators. Elevated levels of stimulators of angiogenesis such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) have been demonstrated in association with ocular angiogenesis. Basic fibroblast growth factor is an extremely potent endothelial mitogen.

Tumor angiogenesis is the process of new blood vessel formation within a malignancy. It is more extensive than the growth of capillaries associated with wound healing. It has been shown that tumor cells stimulate the proliferation of endothelial cells and new capillaries, allowing enlargement of the tumor mass via increased nutritional supply to the cells (Folkman, 1971). The inhibition of this phenomenon has been the center of much work as a potential therapeutic modality. Judah Folkman has proposed that inhibiting tumor recruitment of new blood vessels would most likely isolate a tumor to a local primary site and limit its growth to only a few millimeters in diameter (Folkman, 1971).

Epithelial tumors have the ability to grow to a finite size in the absence of vascularization as a result of passive diffusion of nutrients and passive elimination of waste products. Most solid tumors begin as avascularized malignant cells. These lesions are usually thin, flat collections of cells; however, they can extend to as much as 2 mm in size during this period. Some tumors can remain in this avascular state for years: skin, pharynx, gastrointestinal tract, respiratory tract, genitourinary (bladder), and uterine cervix (carcinoma in situ). During this time the tumor is in a non-proliferative state, and metastases are rare (Folkman, 1993).

Angiogenesis allows the tumor to increase in size and increases the probability of metastasis. The blood vessels themselves may stimulate tumor growth via the

production of growth factors (i.e., bFGF, PDGF, IGF-1) and cytokines (i.e. IL-1, IL-6). Gimbrone et al. reported that a tumor implanted near the iris vessel of a rabbit will become vascularized within 5 days and then increase in volume 16,000 times over the next 2 weeks (Gimbrone, 1972). Numerous other reports have shown similar results with other model systems.

Demonstration of the potential clinical importance of angiogenesis has been presented for breast cancer (Weidner, 1993a), prostate cancer (Weidner, 1993b), and other malignancies. Weidner et al. recently showed a correlation between microvessel count and metastatic prostate cancer. The mean microvessel count for the metastatic group was 76.8 vessels per field, as compared to 39.2 for those without metastasis ($p<0.0001$) (Weidner, 1993b). This study appears to support the theory that the degree of angiogenesis is an important predictor of disease progression.

At least eight polypeptide molecules have been shown to stimulate angiogenesis. Fibroblast growth factors (FGF), basic FGF and acidic FGF, are two of the most potent endothelial mitogens. Several other FGF's have been identified including three oncogenes: kFGF from Kaposi's sarcoma, FGF-5 from bladder cancer, and hst from gastric cancer. bFGF levels are easily monitored in the urine of patients with rapid growing tumors (i.e. newborns with hemangiomas will have large quantities of bFGF, as well as patients with bladder cancer and renal carcinoma). Other possible regulators of angiogenesis include: angiogenin, transforming growth factor-alpha, transforming growth factor-beta, tumor necrosis factor-alpha, platelet-derived endothelial cell growth factor, angiotropin, vascular endothelial growth factor, and low molecular weight non-peptide angiogenic factors (Folkman, 1993).

The inhibition of angiogenesis has been proposed as a potential means for selectively impairing tumor growth. The first compound identified as an angioinhibin was collagenase inhibitors found in cartilage. Other agents with activity include: steroid combined with heparin acting as an angiostatic combination, protamine, platelet factor 4, sulfated polysaccharide-peptidoglycan complex derived from the bacterial wall of Arthobactor, pentosan, D-penicillamine, TNP-470, gold thiomalate, suramin, thrombospondin, and analogues of vitamin D3 (Folkman, 1993, Masiero et al). One of the first clinical reports was by White et al. who observed, in a child, the regression of pulmonary capillary hemangiomatosis, a disease characterized by active angiogenesis, following the administration of alpha interferon (White, 1989).

The NCI Metastatic Prostate Cancer Clinic has had a long history of evaluating agents from this class. In fact, this clinic has conducted more clinical trials with angiogenesis inhibitors than any other solid tumor group. To date we have clinically evaluated or are currently evaluating: suramin, somatuline, pentosan, thalidomide, CAI, and COL-3. In addition, we have collaborated on the early trials with TNP-470.

1.5 Background of Thalidomide

Thalidomide is a potent teratogen that causes dysmelia (stunted limb growth) in humans (Kruger et al, Figg et al 1999). Thalidomide was marketed as a sedative, but was withdrawn from the European market 30 years ago because of its teratogenic effects. The compound was later discovered to be extremely effective in lepromatous leprosy (and received FDA approval in 1998 for the treatment of leprosy (Bauer et al 1998a)) and is presently used as an experimental drug in the treatment of a variety of diseases with an autoimmune character, including recurrent aphthosis of non-viral and non-fungal origin in human immunodeficiency patients. Recently, in vitro data has suggested that thalidomide has antiangiogenic activity (D'Amato, et al). Figg and colleagues demonstrated that a metabolite of thalidomide was responsible for the antiangiogenesis properties (Bauer et al 1998b). Thalidomide's safety in non-pregnant humans was initially established in a study of graft versus host disease (GVHD) conducted at the Johns Hopkins University School of Medicine. Its known side effects (at dosages above that to be used in this trial) include sedation, constipation, and sensory peripheral neuropathy, occurring in 3% of subjects. More recently, four anticancer phase II trials were conducted: Androgen Independent Prostate cancer conducted at the National Cancer Institute, Kaposi's Sarcoma trial conducted at the National Cancer Institute, Glioblastoma trial conducted at Dana Farber Cancer Center, and a Breast Cancer trial conducted at Georgetown University.

It has been postulated that limb defects seen with thalidomide were secondary to an inhibition of blood vessel growth in the developing fetal limb bud. The limb bud is unique in requiring a complex interaction within angiogenesis. Since angiogenesis is the formation of new blood vessels from sprouts of preexisting vessels, the limb bud would be a particularly vulnerable target to a teratogen that inhibited vascular endothelial growth. It was recently demonstrated that orally administered thalidomide is an inhibitor of angiogenesis when using the rabbit cornea micropocket assay (D'Amato, et al). Based on this in vivo animal model, it is suggested that thalidomide might be useful in the treatment of angiogenesis of solid tumors.

Thalidomide, a glutamic acid derivative, was first described in 1953 by the Swiss pharmaceutical company Ciba. Ciba discontinued research on the compound and a German company Chemie Grunenthal undertook development in 1954. It was later marketed as a sleeping pill, and was subsequently blamed for nearly 12,000 birth defects between the late 1950s and early 1960s.

Shortly after the withdrawal of thalidomide from the market, a pronounced effectiveness of the substance against inflammation associated with leprosy was noted. Despite its teratogenic potential, it has been used in the treatment of leprosy for more than 20 years. Additionally, thalidomide was reported to inhibit

the graft versus host reactions following bone marrow transplantation. Recently, in vitro data has suggested that thalidomide has antiangiogenic activity.

1.5.1 Physical, Chemical and Pharmaceutical Properties

Thalidomide (N-Phthalidoglutarimide; C13O4N2H9) is a racemate. The S(-)/l and R(+)/d forms represent derivatives of l- and d-glutamic acid, respectively (Simmons et al). The maximal solubility of racemic thalidomide in water is approximately 2 x 104 mol/L (45 to 60 mg/L) [Schumacher et al.]. The ultraviolet spectrum of thalidomide is characterized by an absorbance maximum at 300nm, which is dependent on an intact phthalimide moiety. All 4 amide bonds present in the molecule are susceptible to hydrolytic cleavage in vitro at pH values higher than 6 (Schumacher et al., Luzzio et al).

General: CAS registry No.50-35-1
Molecular formula = C13 H9 N2 O4
Molecular weight = 258.23 daltons

Non-enzymatic cleavage of 1 or more of the amide bonds in the thalidomide molecule produces hydrolysis products which contain at least 1 carboxyl group (Schumacher et al.). They are thus more polar and can be expected to cross biological membranes less efficiently than the parent compound.
Thalidomide constitutes a transport form for its hydrolysis products; the non polar parent compound enters cells or tissues and is converted to polar derivatives which have been shown to accumulate in erythrocytes and in the embryo (Fabro et al. 1967a).

1.5.2 Preclinical Experience

Thalidomide has recently been shown to inhibit angiogenesis (30-51% reduction in vascularization) induced by FGF in the rabbit cornea micropocket model. It appears the antiangiogenic activity in this model is the result of one of the epoxide active metabolites; thalidomide did not have activity in the chicken chorioallantoic membrane assay (a topical assay compared with orally administered animal model).

Gordon et al. reported that rats were resistant to the teratogenic effects of thalidomide, but rabbits (as well as higher primates) were sensitive (Gorden et al). They speculated that differences were due to alterations in biotransformation between the species. Furthermore, they noted that after thalidomide treatment, 4- and 5-hydroxylated metabolites of thalidomide were recovered from the urine of rabbits, but not rats. The presence of phenolic derivatives of thalidomide suggests that the drug might undergo oxidative metabolism via an arene oxide intermediate. Arene oxides have

been implicated as mutagens, cytotoxins, and teratogens. The intermediate metabolite is also most likely responsible for the antiangiogenic activity. Furthermore, Gordan et al. showed that inhibiting epoxide hydrolase results in enhanced teratogenicity. Likewise, Folkman and colleagues noted that inhibition of epoxide hydrolase results in enhanced antiangiogenic properties.

Bauer et al evaluated thalidomide in two in vitro angiogenesis models (rat aorta model and human endothelial cell culture) and demonstrated antiangiogenic activity in the presence of human liver microsomes (Bauer et al. 1998b). Furthermore, they reported that rodent microsomes failed to generate the active metabolite, but rabbits did.

1.5.2.1 Preclinical Pharmacology

The biochemical mechanism of the non sedative effects of thalidomide is unclear. Very little work has been done to understand the neurotoxic action or immunomodulatory effect of the compound on a molecular basis. Considering the possible combinations of hydrolysis, hydroxylation, and optical activity, there may be more than 50 metabolites of thalidomide in vivo.

Effects of thalidomide on the endocrine system have been consistently observed in both clinical trials and animal experiments. These actions may be due to an effect of the drug on the hypothalamus (Locker et al. 1971). In humans, a tendency to normalize hyperthyroid states has been noted. Iodine uptake by the thyroid gland was slightly decreased, and myxedema was occasionally observed. Increased urinary secretion of 17-hydroxycorticosteroids associated with hypoglycemia has been reported. Drug interactions with thalidomide have not been systematically studied. Thalidomide enhances the sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine, while its sedative action is antagonized by methylamphetamine and methylphenidate. Based on our clinical experience within the Medicine Branch, we have not observed hypothyroidism in patients with metastatic prostate cancer. We are currently evaluating the effect of concurrent cytorchrome P450 enzyme inducers and inhibitors for drug interaction with thalidomide using a population pharmacokinetic system. To date, we have not identified significant drug interactions.

1.5.2.2 Preclinical Toxicology

Thalidomide is a potent teratogen. In 1961, McBride and Lenz described the association between limb defects in babies and maternal thalidomide usage. Although humans are exquisitely sensitive to the teratogenic effects of thalidomide, experiments in rodents failed to reveal similar effects. Teratogenic effects could be experimentally reproduced by the administration of thalidomide to pregnant rabbits at an oral dose of 100-300 mg/kg/day. [Over the past 30 years the mechanism of thalidomide's teratogenicity has been extensively studied, but has remained unsolved (Stephens 1988)].

1.5.2.3 Pharmacokinetics and Drug Metabolism in Animals

Studies in experimental animals showed high concentrations of the drug in the gastrointestinal tract, liver, and kidney, and lower concentrations in muscle, brain, and adipose tissue. In pregnant animals, thalidomide is able to pass across the placental barrier (Fabro et al. 1967A, Nicholls 1966; Schumacher et al. 1965a.; 1970).

In animals, the main pathway of degradation appears to be non-enzymatic hydrolytic cleavage (Fabro et al. 1967a; Schumacher et al. 1965a). Minor amounts of hydroxylated products have been detected in the urine of some species (Schumacher et al. 1965a). Hepatic metabolism of thalidomide probably involves enzymes of the cytochrome P450 family (Braun et al. 1986). Only the parent compound is enzymatically modified (Braun & Weinreb 1985; Schumacher et al. 1965a). Thalidomide itself does not cause enzyme induction (Brode 1968a), but possibly interferes with enzyme induction caused by other compounds (Brode 1968a).

1.5.3 Clinical Pharmacokinetics

The pharmacokinetics of thalidomide has not been clearly characterized in man (Piscitelli et al). Theoretically, greater than 12 different metabolites can be formed from thalidomide by hydrolysis and several others by alternative metabolic pathways (phenolic metabolites); however, the main

transformation of thalidomide in the body may be by spontaneous chemical processes and not involve enzyme reactions. Thus, it seems probable that a minor proportion of the drug is enzymatically hydroxylated.

Oral administration of thalidomide at 100 to 200 mg in humans results in maximal blood concentrations of 0.9 to 1.5 μg/mL after 4 to 6 h (Chen et al.). Absorption and elimination half-lives calculated from data of 8 healthy subjects were 1.7 ± 1.05 and 8.7 ± 4.11 h, respectively; a lag time of 0.41 ± 0. 17 h was observed in 6 individuals (Chen et al. 1989). Using a 1-compartment model, the authors calculated a volume of distribution of 120.64 ± 45.36 L, a total body clearance of 10.41± 2.04 L/h, and a renal clearance of 0.08 ± 0.03 L/h. Only 0.6 ± 0.22% of the administered dose was excreted as unchanged compound in the urine. The hydrolytic cleavage in serum (Chen et al.) is much slower than that in vitro at pH 7.4 (Schumacher et al. 1965b). This may be because thalidomide is highly bound to plasma proteins (Bakay & Nyhan 1968).

There is some controversy over the incidence of neurotoxicity associated with thalidomide. The incidence may be disease specific (patients with prurigo nodularis may have a higher incidence than patients with rheumatoid arthritis or some other disease). A group from Columbia reported treating 17 patients with arthritis with a dose of 400 to 600 mg per day of thalidomide (mean duration of therapy, 24.8 months, range 7-65 months). They found that 2 patients developed symptoms of peripheral sensory neuropathy that was reversed on discontinuation of therapy. Crawford reported that 25% of patients (n=60) receiving thalidomide for the management of chronic discoid lupus erythematosus developed neuropathies, and all patients (n=8) receiving it for nodular prurigo and aphthous stomatitis were found to have neuropathies. Sheehan reported the development of neurological complications in 2 of 5 patients receiving thalidomide for prurigo nodularis. Polyneuropathy persisted in one of those patients for greater than 12 months after the discontinuation of therapy.
Aronson et al. reported the development of sensory peripheral neuropathies (onset 2 to 12 months into therapy) in 3 of 4 patients with prurigo nodularis that were receiving thalidomide (100 to 300 mg per day). Their in vitro work went on to show that thalidomide induced primary neuronal degeneration. Schroder et al. reported that there was a reduction in myelin thickness of sural nerve fibers (reduction in sheath thickness) and a decrease in conduction velocity in thalidomide treated New Zealand white rabbits as compared to controls.

Figg and colleagues have reported on the pharmacokinetics of thalidomide in patients with prostate cancer (Figg et al 1999). They observed a slight decrease in the clearance and an estimated terminal half-life with daily

dosing of 200 mg/d to be 7.1 hours. There was a linear relationship between dose and plasma concentration using doses between 200 and 1200 mg/day.

1.5.4 Experience with Thalidomide in Prostate Cancer

We have enrolled 45 patients onto the phase II trial of thalidomide in patients with androgen independent prostate cancer. To date, approximately 30% of patients with overt metastatic disease have had some clinical benefit. One individual had improvement in bony lesions (documented on bone scan over an 8 month period) that resulted in clinical improvement and another patient had a PSA decline of >50% that corresponded with symptomatic improvement and fewer pain medications. In addition, several individuals have had minor reductions of soft tissue masses as documented by CT scan. The side effects have been relatively minor in this patient population: constipation, occasional sedation, depression, and mild peripheral neuropathy in those receiving drug for greater than 6 months. Other, more concerning side effects were Stevens Johnson Syndrome (associated with death) and clotting problems.

1.6 Rationale

It is postulated that the efficacy of anti-angiogenic agents, such as thalidomide, will be greatest in the setting of minimal disease burden. Patients found to have a rising PSA following definitive therapy for prostate cancer as their only evidence of disease are felt to have a minimal disease state. The presence of hormone responsive disease (clinical benefit to androgen ablation such as PSA declines, scan improvements, etc), as assessed by the six monthly injections of leuprolide or goserelin, implies a better prognosis than those who fail to respond to androgen ablation. It is in this setting that we propose to evaluate the clinical efficacy of thalidomide.

This trial proposes, by means of a randomized, double blind, placebo-controlled, crossover trial design, to evaluate the efficacy of an angiogenesis inhibitor, thalidomide, in patients with stage D0 androgen dependent prostate cancer. Both treatment arms will receive six monthly doses of leuprolide or goserelin (similar to intermittent androgen ablation which is widely utilized in patients with PSA only disease) followed by either thalidomide or placebo (Phase A). At the time of PSA failure, the patient will be crossed over to the other treatment arm and again receive six monthly doses of leuprolide or goserelin followed by either thalidomide or placebo (Phase B). Time to progression will be monitored for each arm and each treatment period. From a theoretical point, it is hypothesized that the ability of anti-angiogenic agents to control metastatic disease will be greatest when the burden of metastatic disease is low, as in this setting.

2.0 Eligibility Assessment and Enrollment

2.1 Inclusion Criteria

2.1.1 Patients must have PSA only androgen dependent adenocarcinoma of the prostate. All patients must have failed definitive therapy (radical prostatectomy, radiation therapy with external beam or brachytherapy, or cryosurgery).

2.1.2 Patients must have a negative CT scan and Bone Scan for metastatic prostate cancer.

2.1.3 Patients must have histopathological documentation of prostate cancer. Every attempt should be made to have slides and blocks reviewed at the NCI Pathology laboratory. The review of pathology by the NCI will not delay enrollment.

2.1.4 Patients must have progressive prostate cancer

2.1.4.1 Two consecutively rising PSAs above the nadir post-definitive therapy and an absolute value greater than 1.0 ng/ml separated by at least 2 weeks.

2.1.5 Patients must have a life expectancy of more than 12 months.

2.1.6 Patients must have a performance status of 0 to 2 according to the ECOG criteria.

2.1.7 Hematological eligibility parameters (within 2 weeks of starting therapy):

2.1.7.1 Granulocyte count $\geq$ 1, 000/mm^3

2.1.7.2 Platelet count $\geq$75, 000/mm^3

2.1.8 Biochemical eligibility parameters (within 2 weeks of starting therapy):

2.1.8.1 If the creatinine is > 2.0 mg/dL obtain a 24-hour urine collection. Creatinine clearance must be greater than 40 mL/min.

2.1.8.2 Hepatic function: bilirubin (total) $\leq$1 mg/dL (upper limit of

normal); ALT <2.5 x upper limit of normal; AST <2.5 x upper limit of normal.

Exception: Patients with Clinical Gilbert's Syndrome may have total bilirubin less than or equal to (≤) 2.5 mg/dL.

2.1.9 Patients must not have other concurrent malignancies (within the past 2 years with the exception of non-melanoma skin cancer and Rai Stage 0 chronic lymphocytic leukemia), in situ carcinoma of any site, or life threatening illnesses, including untreated infection (must be at least 1 week off intravenous antibiotic therapy before beginning thalidomide).

2.1.10 Patients with a history of unstable or newly diagnosed angina pectoris, recent myocardial infarction (within 6 months of enrollment), New York class II-IV congestive heart failure, chronic obstructive lung disease requiring oxygen therapy, uncontrolled seizure activity, or by the medical judgement of the physician, are not eligible.

2.1.11 Patients must be able to understand and sign an informed consent document.

2.1.12 Patients must be willing to travel from their home to the NIH or the participating institution (LSU, Univ. of Washington, Columbia University, Wayne State, University of Minnesota, University of Pittsburgh. Holy Cross) for follow-up visits (due to sedation associated with thalidomide it is preferred that patients not drive during the first 3 days of taking daily dosing, or if sedation appears to be a continuing complication).

2.1.13 Patients must be ≥ 18 years of age.

2.1.14 Male patients must be counseled about the possibility that thalidomide may be present in semen. Men must use a latex condom every time they have sexual intercourse with women during therapy and for 8 weeks after discontinuing thalidomide, even if they have had a successful vasectomy.

2.1.15 Late Entry

Patients may enroll as a late entry if the following criteria are met

- have received luprolide or goserelin within 3 months of starting study and
- have a PSA within two weeks of hormonal injection
- bone scan and CT scan without metastasis within 8 weeks of enrollment

2.1.16 Patients with Rai Stage 0 Chronic Lymphocytic Leukemia (lymphocytosis only) will be eligible.

2.2. Exclusion Criteria

2.2.1 Patients that have received leuprolide, DES, flutamide, bicalutamide, PC-SPES, goserelin, cytotoxic chemotherapy, finasteride, and/or nilutamide within the past year (or currently) are not eligible. Patients that received these agents for adjuvant or neoadjuvant therapy at the time of definitive therapy are eligible.

Exception: Patients enrolled under late entry criteria, who have received luprolide/goserelin within 3 months of starting study are eligible.

2.2.2 Patients with NCI/CTEP grade 2 or greater peripheral neuropathy of any cause that is clinically detectable, patients receiving anti-convulsive medications, and patients with a history of seizures within the past 10 years will not be eligible for this study.

2.2.3 Patients who are receiving sedative/hypnotic agents (i.e. benzodiazepines), which cannot be discontinued, will not be eligible for this study.

2.2.4 Patients who have had a bilateral surgical orchiectomy will not be eligible for this study.

2.2.5 Patients who have received systemic chemotherapy for prostate cancer will not be eligible.

2.2.6 Patients with a confirmed psychiatric history of a major depression consistent with American Psychiatric Association Diagnostic and Statistical Manual (DSM IIIR criteria), confirmed by a psychiatrist, will not be eligible.

2.3 Research Eligibility Evaluation (Baseline)

2.3.1 Complete history and physical examination (including weight, digital rectal exam, and ECOG score) with documentation of all prior therapies (hormonal, surgical, radio-therapeutic, and cytotoxic) will be conducted within the month prior to starting therapy.

2.3.2 Imaging Studies (Baseline)

2.3.2.1 Technetium-99 Bone Scintigraphy:

2.3.2.1.1 The baseline bone scan that will be used for the determination of disease progression as defined in

section 5.2.2. will be obtained within 8 weeks before starting therapy.

2.3.2.2 CT Scan or some other Diagnostic Imaging Method

2.3.2.2.1 The baseline CT scan of the abdomen and pelvis that will be used for the determination of disease progression as defined 5.2.2. will be obtained within 8 weeks before starting therapy.

Patients who are eligible under late entry will need a CT and bone scan within 8 weeks of commencing trial. Outside scans prior to hormonal commencement will be reviewed, if available.

2.3.3 Laboratory Evaluation (Baseline)

2.3.3.1 Laboratory Evaluation [baseline is to be obtained within 14 days prior to starting therapy]

2.3.3.1.1 Hematological Profile

2.3.3.1.1.1 CBC with differential and platelet count

2.3.3.1.2 Biochemical Profile

2.3.3.1.2.1 Acute care panel (electrolytes, BUN, creatinine)

2.3.3.1.2.2 Liver function tests (AST/ALT/Total bilirubin)

2.3.3.1.3 Testosterone and DHT levels (should be obtained within 4 weeks prior to day 1).

2.3.3.1.4 Tumor Marker Profile

2.3.3.1.4.1 PSA (baseline within 14 days prior to starting treatment)

2.3.3.1.5 Late Entry

Patients who are eligible under late entry will need lab evaluation within 14 days of starting trial and PSA within 14 days of initial hormonal injection.

2.4 Patient Randomization and Registration

2.4.1 Authorized physicians or designee from each participating institution must fax information concerning an eligible candidate to the Orkand personnel (Orkand is the current data management contract company for the Division of Clinical Sciences of the NCI) at (301) 402-0757 between the hours of 8:30am and 5:00pm East Coast Time, Monday through Friday. All participating sites must use this randomization center. Orkand will communicate directly with the Pharmaceutical Management Branch, CTEP, NCI to provide blinded study drug (i.e., thalidomide/placebo) to the registering investigator.

2.4.2 At the time of randomization, eligibility criteria will be queried. A protocol specific eligibility checklist will be developed by the Orkand staff and reviewed by the principal investigator (see Appendix C). For drug ordering purposes, the "Blinded Patient On-Study Form" (see Appendix C) will need to include the NCI protocol number (i.e., T99-0053), the NSC (i.e., 66847), and the quantity ordered (i.e., 4 bottles) and will need to collect the patient initials (i.e., the first three letters of the patient's last name), the name and NCI ID number of the registering physician, and the name and address of the registering physician's institution. It will include space to record the date of administration of the first dose of leuprolide or goserelin if the first dose was administered prior to patient registration on the protocol. It will also include space for Orkand to record the date of registration (i.e., the date the patient was actually registered on the protocol) and the unique patient identifier (e.g., 00C0080-001) assigned by Orkand at the time of registration. This form will be faxed by Orkand to the Pharmaceutical Management Branch (PMB), CTEP, NCI at the time of registration and will be used by PMB to enter the initial order for the patient.

2.4.3 NCI MOCRU (e.g. Jane Carter, RN or her designee/phone 301-435-5614 / fax 301- 402-7901) must be notified when the patient completes the first blinded treatment phase (i.e., Phase A) and when the patient completes the second blinded treatment phase (i.e., Phase B). The "Blinded Patient Crossover / Off-Study Form" (see Appendix C) will need to collect the NCI protocol number (i.e., T99-0053), the unique patient identifier (e.g., 00C0080-001), the patient initials (i.e., the first three letters of the patient's last name), the date of progression on Phase A, the date of progression on Phase B, the name and NCI ID number of the registering physician, and the name and address of the registering physician's institution. This form will be faxed by the NCI MOCRU to the PMB at the completion of Phase A (PMB will recall Phase A clinical supplies and ship Phase B clinical supplies) and at the completion of Phase B (PMB will recall Phase B clinical supplies).

3.0 Study Implementation

3.1 Study Design

The study will be conducted as a two-arm randomized double-blind placebo-controlled trial of thalidomide. Patients will be followed until PSA progression, as defined in section 5.2. Once patients have progressed, they will be retreated with leuprolide or goserelin for 6 months and then will receive the placebo if they initially received thalidomide, or thalidomide if they initially received placebo. Thus, while patients are crossed-over to the other therapy, because the time until crossover is dependent on time until progression, this differs from a classic crossover study in which patients are followed on both arms for a fixed period of time, evaluated, given a wash-out period, and then followed identically on the other agent. As such, results from the earlier placebo vs. treatment period will be used to determine the sample size, but data from periods can be evaluated in the analysis.

PSA will be monitored every month and radiographic studies will be performed at the time of PSA progression. Each patient will be evaluated every 4 weeks for the duration of the study. If at any point the patient develops objective metastatic disease (i.e., new bone lesions or soft tissue mass consistent with metastatic prostate cancer or if his PSA rises while on leuprolide or goserelin) he will be removed from the study.

3.1.1 Patients may remain on either arm of treatment, as long as they do not meet the "off study" criteria listed in section 3.7.

3.1.2 Number of Patients
140 patients will be treated on each arm of this study (i.e., total of 280 patients).

3.2 Drug Administration

Thalidomide will be initially given orally (200 mg) every evening at 2100. Each patient will be evaluated on (or about) each month. Treatment may continue indefinitely provided that there is no dose-limiting toxicity, as defined in section 3.7, or disease progression, as defined in section 5.2.3 or 5.2.4. At each monthly clinic visit, clinic staff should (1) collect all "old" bottles [i.e., empty bottle(s), partial bottle(s), full bottle(s)] of thalidomide / placebo capsules from the patient; (2) perform a capsule count and record the results on the bottom portion of the "old" Pill Count Case Report Form [i.e., the Pill Count Case Report Form started at the previous clinic visit] (see Appendix C); (3) determine the total number of capsules remaining in all "old" bottle(s) of thalidomide / placebo capsules and subtract that number from 140 … round up to the next even "100" to determine how many "new" bottle(s) of thalidomide / placebo capsules will be needed until the next clinic visit … note that the minimum number of capsules dispensed at each clinic visit should be 140 and the maximum number of capsules dispensed at each clinic visit should be 239 [Example 1: 60 capsules remaining from "old" bottle(s) … 140 – 60 = 80 … round up to 100 …

dispense 60 capsules from "old" bottle plus 100 capsules from "new" bottle for a total of 160 capsules / Example 2: 20 capsules remaining from "old" bottle ... 140 – 20 = 120 ... round up to 200 ... dispense 20 capsules from "old" bottle and 200 capsules from two "new" bottles for a total of 220 capsules]; (4) complete the upper portion of a "new" Pill Count Case Report Form and affix the tear-off label(s) from any "new" bottle(s) of thalidomide / placebo capsules; (5) dispense the partial and full bottles of thalidomide / placebo capsules to the patient.

3.3 Treatment Modifications

3.3.1 The dose may be reduced to 100 mg (2 capsules) per day for toxicity (grade ≥3 toxicity that appears to be drug related or grade ≥2 peripheral neuropathy) which resolves to grade ≤1 with interruption of treatment within a 2 month period. Since this is a double blind study the investigator will not know if he is reducing thalidomide or the placebo. If a patient requires an additional dose reduction below 100mg, then he will be crossed over to the other treatment arm or removed from study based on "off study" criteria. In addition, patients may have their dose reduced for sedation that does not meet grade 2 toxicity.

3.4 Pharmacokinetics (only for NCI patients)

The pharmacokinetic profile of thalidomide in patients with prostate cancer has been previously characterized (Figg et al. 1999). However, clear pharmacodynamic correlations have not been made. Therefore, we will obtain two green top tubes (see section 3.5.3.3.1 for handling procedure) at each clinic visit in order to assess steady state concentrations. (This pharmacokinetic analysis will be done for the NCI patients only.)

3.5 On Study Evaluation (Follow-up)

3.5.1 Clinical Evaluation (Follow-up)

3.5.1.1 Complete history and physical examination (including weight and ECOG score) will be conducted prior to starting therapy. Patients will be seen and examined (history and physical) as outlined in the schema. For those receiving the 30 day formulation of an LHRH agonist, monthly; for those receiving the 3 month formulation, at baseline, 3 month, 6 month, then monthly. EMG and nerve conduction studies may be requested as clinically indicated. Toxicity scoring for peripheral neuropathy will be based on NCI CTC toxicity criteria and not on EMG/nerve conduction studies.

3.5.1.2 Imaging Studies (Follow-up)

3.5.1.2.1 Technetium-99 Bone Scintigraphy:

3.5.1.2.1.1 The follow-up bone scans will be obtained at the time of PSA progression before receiving hormones as defined in sections 5.2.3.1 and 5.2.4.1, or if there are other clinical reasons.

3.5.1.2.2 CT Scan or some other Diagnostic Imaging Method

3.5.1.2.2.1 The follow-up scan will be obtained at the time of PSA progression before receiving hormones, or if there are other clinical reasons.

3.5.2 Laboratory Evaluation (Follow-up)

3.5.2.1 Laboratory Evaluation [at each clinic visit] For those receiving the 30 day formulation of an LHRH agonist, monthly; for those receiving the 3 month formulation, at baseline, 3 month, 6 month, then monthly.

3.5.2.1.1 Hematological Profile

3.5.2.1.1.1 CBC with differential and platelet count

3.5.2.1.2 Biochemical Profile

3.5.2.1.2.1 Acute care panel (electrolytes, BUN, creatinine)

3.5.2.1.2.2 Liver function tests (AST/ALT/Total bilirubin)

3.5.2.1.2.3 Testosterone and DHT

3.5.2.2 Tumor Marker Profile

3.5.2.2.1 PSA at each clinic visit. For those receiving the 30 day formulation of an LHRH agonist,

monthly; for those receiving the 3 month formulation, at baseline, 3 month, 6 month, then monthly.

3.5.2.3 Research Bloods

Because this is a double blind study, no sample(s) will be analyzed until that patient is taken off the trial in order to maintain the blind.

3.5.2.3.1 Two tubes of serum (two 7 ml green top tube) will be obtained at each clinic visit for pharmacokinetic analysis for the NCI patients only.

Three tubes of plasma (three 7 ml red tubes) will be obtained at each clinic visit for monitoring growth factors (i.e., bFGF, VEGF, TGFb, IGF1, etc) (only for the NCI patients).

Two buffy coat tubes (two 7 ml blue tiger top tubes) will be obtained at each visit for mRNA analysis of changes in growth factor expression (only for the NCI patients).

Send to Dr. Figg, Bldg 10, Rm 5A01; tel 402-3622 stat on ice.

3.6 Concurrent Therapies

With the exception of medications listed in the inclusion/exclusion criteria, medications may be administered as clinically indicated, or at the discretion of the investigator(s). Either the Principal Investigator, Protocol Chairperson, or an Associate Investigator should be notified of any change in the patients therapy if one is indicated. All efforts should be made to give only medications that are clearly indicated for a specific medical purpose during the trial.

3.6.1 Alcohol consumption should be discouraged.

3.6.2 Because sedation is a common side effect of thalidomide, all patients should be cautioned regarding driving and operating heavy machinery. Thalidomide related sedation may subside with continued daily dosing.

3.6.3 Since thalidomide is associated with constipation, Colace 200 mg orally every day should be administered to patients. If additional therapy is needed, then it will be provided on a case-by-case basis. Patients may also adjust the Colace dose down if their stool is too soft.

3.7 Off Study Criteria

3.7.1 PSA progression or the development of objective metastatic lesions (See section 5.2.4).

3.7.2 NCI/CTEP grade III or greater toxicity (http://ctep.cancer.gov), that does not resolve to ≤ NCI/CTEP grade II toxicity within two months, or grade 2 or greater peripheral neuropathy that does not resolve to grade I or less within two months while drug is being held.

3.7.3 Patient request.

3.7.4 Best medical judgement of the Principal or an Associate Investigator.

3.7.5 A rising PSA while on LHRH agonist (see section 5.2.4) (≥25% increase and a minimum value of 5 ng/ml increase and confirm 2 weeks later)

4.0 Supportive Care

Support care will be provided in accordance with good medical care and consistent with standard care for the individuals type of cancer.

5.0 Data Collection and Evaluation

5.1 Data Collection

5.1.1 Multi-Institutional Guidelines

5.1.1.1 IRB Approvals: The PI will provide the NCI IRB with a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NCI IRB.

5.1.1.2 Amendments and Consents: The PI will provide the NCI IRB with copies of all amendments, consents, and approvals from each participating institution.

5.1.1.3 Patient Registration: All patients from participating institutions must register patients with the DCS Central Office (ORKAND) unless alternative registration procedures are specified in the protocol. The eligibility checklist for the protocol must be FAXED to the Central Office according to standard operating procedures.

5.1.1.4 Data Collection and Toxicity Reporting: The PI will provide specific guidelines for quality assurance, data collection and format. Data is to be submitted to the coordinating center every 2 week. All adverse events from participating institutions must be submitted to the NCI IRB within 10 days.

5.1.1.5 Data and Center Audits: The PI will provide guidelines for audits of participating institutions (at least yearly). Selected patient charts should be audited as well as the participating institutions Standard Operating Procedures (SOP) at the time of the visit. Data from participating institutions should be available when the protocol is audited at the NCI.

5.1.2 Specific Guidelines for This Multi-Institutional Study

5.1.2.1 This protocol will be conducted as a joint study with the NCI-MOCRU and Univ. of Washington, LSU, Columbia University,Wayne State, Univ. of Minnesota, Univ. of Pittsburgh, Holy Cross and Portsmouth Naval Hospital as the participating institutions. The protocol will be conducted as a single research effort and data from each participating investigator will be included in the analysis of results.

5.1.2.2 The principal investigator will be the liason between the participating institutions. The principal investigator, or designee, will coordinate the submission and approval of the protocol as well as its subsequent amendments to each institution for IRB approval.

5.1.2.3 The principal investigator will be responsible for the conduct of the study and the monitoring of its progress; he will review all case report forms. The principal investigator will have ultimate responsibility for reporting the results of this trial.

5.1.2.4 All patients, whether entered at NCI-MOCRU or at Univ. of Washington, LSU, Columbia University, Wayne State, Univ. of Minnesota, Univ. of Pittsburgh, Holy Cross or Portsmouth Naval Hospital will be registered through Orkand. (See section 2.4.1)

5.1.2.5 The case report forms will be of a common format. The principal investigator from the NCI-MOCRU will review the records of all protocol patients at 3 months intervals. The pertinent diagnostic studies (CT scans, Chest radiographs, etc., record of tumor measurements on physical exam) will be reviewed for all responding patients and the response criteria will be verified by at least two co-investigators.

5.1.2.6 There will be only one version of the protocol, and each participating institution will use that document. Any modifications of the protocol will be done by the principal investigator who is solely responsible for formulating protocol amendments after IRB approval.

5.1.3 Patient Records and Quality Assurance

Quality assured complete records must be maintained on each patient treated on the protocol. These records should include primary documentation (e.g, laboratory report slips, X-ray reports, scan reports, pathology reports, physicians notes, etc.) which confirm that:

5.1.3.1 The patient met all eligibility criteria.

5.1.3.2 Signed informed consent was obtained prior to treatment.

5.1.3.3 Treatment was given according to protocol (dated notes about doses given, complications, and clinical outcomes).

5.1.3.4 Toxicity was assessed according to protocol (laboratory report slips, etc.)

5.1.3.5 Response was assessed according to protocol (X-ray, scan, lab reports, date noted on clinical assessment, as appropriate).

5.1.3.6 NCI Drug Accountability Records were kept for each patient.

5.2 Response Criteria

5.2.1 Disease Progression to switch from the first treatment period to the second:

5.2.1.1 If the PSA returns to baseline (defined as the PSA value prior to starting leuprolide or goserelin) or increases to the absolute value of 5.0 ng/ml, then the patient will be crossed over to receive six more monthly doses of leuprolide or goserelin and then start the other treatment option.

5.2.2 Off Study Progressive Disease

5.2.2.1 If the PSA returns to baseline after the second treatment arm (defined as the PSA value prior to starting the second treatment cycle of leuprolide or goserelin) or increases to the absolute value of 5.0 ng/ml, then the patient will be taken off study

5.2.2.2 Development of a new bone lesion

5.2.2.3 Development of a soft tissue mass identified on CT scan or physical exam consistent with metastatic prostate cancer. If identified on physical exam, this lesion may be biopsied to confirm the presence of prostate cancer.

5.2.2.4 Development of urethral, urethral, or spinal cord obstruction secondary to tumor.

5.2.2.5 Development of cytologically positive pleural effusion or lymphangitic spread in the lungs.

5.2.2.6 A rising PSA while on leuprolide or goserelin (A rising PSA while on LHRH agonist (see section 5.2.4) (≥25% increase and a minimum value of 5 ng/ml increase and confirm 2 weeks later)

5.2.2.7 If the patient fails to achieve a PSA value of less than 5 ng/ml at the end of a either treatment cycle of leuprolide or goserelin, he will be taken off study.

5.3 Toxicity Criteria

5.3.1 This study will utilize the CTC version 2.0 for toxicity and adverse event reporting. A copy of the CTC version 2.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTC version 2.0.

5.3.2 Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
	Unexpected and	Unex-		Unexpected with	Unexpected without	Expected with	Expected without	Unex-pected	Expected

	Expected	pected	Expected	Hospitali-zation	Hospitali-zation	Hospitali-zation	Hospitali-zation		
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**

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

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

December 15, 2004

Note: All deaths on study must be reported using expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Note 1 Telephone number available 24 hours daily (301) 230-2330 (Recorder after hours)
Note 2 See attached DCTD/NCI Common Toxicity Criteria
Note 3 Report to: Investigational Drug Branch, Post Office Box 30012, Bethesda, MD 20824. A fax number for reporting is (301) 230-0159
Note 4 A list of all known toxicities can be found in the protocol document or consent form.
Note 5 For hospitalization, any medical event equivalent to CTC Grade 3, 4, or 5, which precipitate hospitalization (or prolongation of existing hospitalization) must be reported regardless of whether it is an expected or an unexpected event, and regardless of attribution.
Note 7 Expedited reports are to be submitted using AdEERS or the paper templates available at http://ctep.cancer.gov. The NCI Guidelines for expedited

adverse event reporting are also available at this site.

5.4 Statistical Considerations

5.4.1 The principal objective of the study is to determine whether thalidomide is able to increase the time to progression of patients with stage D0 prostate cancer.

5.4.2 The study will be conducted as a two-arm randomized double-blind placebo-controlled trial of thalidomide. Patients will be followed until PSA progression, as defined in section 5.2. Once patients have progressed, they will be retreated with leuoprolide for 6 months and then will receive the placebo if they initially received thalidomide or if they initially received placebo. Thus, while patients are crossed-over to the other therapy, because the time until crossover is dependent on time until progression, this differs from a classic crossover study in which patients are followed on both arms for a fixed period of time, evaluated, given a wash-out period, and then followed identically on the other agent. As such, results from the earlier placebo vs. treatment period will be used to determine the sample size, but data from periods can be evaluated in the analysis.

5.4.3 Because the current estimate of time to progression for patients with this stage of disease treated with leuprolide or goserelin is 10 months, it would be desirable to increase this to 14 months. A one-tailed hypothesis will be used since it would be considered only interesting to see the improvement due to thalidomide compared to placebo. With 80% power, and a one-tailed alpha=0.05 in order to detect a difference in median time to progression (during the first part of the trial) between the two arms of 10 vs. 14 months, 140 patients per arm (280 total) are required, assuming 18 months to accrue patients and 18 additional months to follow-up following entry of the last patient.

5.4.4 With nine institutions participating (NCI intramural, Columbia in New York, LSU in New Orleans, Wayne State University, University of Washington, Univ. of Minnesota, Univ. of Pittsburgh, Holy Cross and Portsmouth Naval Hospital), it is expected that 16 patients per month (190 per year) can be entered onto the trial with an estimated completion of accrual expected in 18 months.

5.4.5 This trial will be monitored by the NCI/DCS Data Safety and Monitoring Board. Due to the rapid accrual projection, it is expected that only one interim look may take place of the data. Using the O'Brien-Fleming approach, if the p-value at the interim look, based on the evaluation of the first time to progression, is 0.0054 (one -tailed) then the trial should be stopped due to statistical criteria. Otherwise, at the final evaluation, a one-tailed p-value of 0.049 (essentially 0.05) will be used to declare statistical significance.

5.4.6 Time to progression between the two study arms will be compared separately for the two periods of the cross-over study: initial treatment and second (crossover) treatment. Both comparisons will be reported in order to indicate the effect of thalidomide on this endpoint. In addition, because each patient will have received both agents, comparisons of time to progression can be undertaken between both treatment conditions, employing appropriate methodology for paired subject data, in order to further interpret the findings.

6.0 Human Subjects Protections

6.1 Rationale for subject selection

Subjects treated on this study will be individuals with prostate cancer, which has recurred (or persisted) after appropriate standard treatment for local disease. Individuals of any race or ethnic group will be eligible for this study. Eligibility assessment will be based solely on the patient's medical status. Recruitment of patients onto this study will be through standard Medicine Branch mechanisms. No special recruitment efforts will be conducted.

6.2 Evaluation of benefits and risks/discomforts

The potential benefit to a patient that goes on study is a delay in the development of progressive disease. In addition, the patient may have an improved quality of life by decreasing the time on hormonal therapy. Potential risks include the possible occurrence of any of a range of side effects that are listed in the Consent Document and in Section 1.5 above. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as described in Section 3.5.

6.3 Risks to patients in relation to anticipated benefits

Patients with progressive stage D0 androgen dependent prostate cancer (i.e., rising PSA) will eventually develop metastatic disease. The potential risks are simply associated with the side effects of treatment. There is a debate about when hormonal therapy should be initiated, but some may view the lack of consistent hormonal ablation as a risk. Additional risks would be related to the side effects of thalidomide.

6.4 Participation of Children

Because prostate cancer does not occur in children, they will not be eligible for this study.

6.5 Consent and assent processes and documents

Patients will meet with an attending physician in the Prostate Cancer Clinic at the NCI or a participating site during the initial evaluation for this study. During that meeting, the attending physician will provide verbal informed consent regarding this study, as

well as provide a copy of the informed consent document that is included in this protocol manuscript (appendix B). The patient will be allowed to take as much time as they wish in deciding whether or not they wish to participate. If a prolonged period of time expires during the decision making process (several weeks, as an example), it may be necessary to re-assess the patient for protocol eligibility.

6.6 All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on the study.

6.7 Patient Records and Quality Assurance

Quality assurance records will be maintained on each patient treated on the protocol. These records should include primary documentation (e.g., laboratory report slips, X-ray reports, scan reports, pathology reports, physicians notes, etc.) which confirm that:

6.7.1 The patient met all eligibility criteria.

6.7.2 Signed informed consent was obtained prior to treatment.

6.7.3 Treatment was given according to protocol (dated notes about doses given and reasons for any modifications).

6.7.4 Toxicity was assessed according to protocol (laboratory report slips, etc.).

6.7.5 Response was assessed according to protocol (X-ray, scan, lab reports, date noted on clinical assessment, as appropriate).

7.0 Data Reporting

7.1 Any unanticipated or unknown treatment- or drug-related toxicity (ies) and life-threatening and lethal toxicity (ies) will be reported according to CTEP Guidelines for Adverse Events Reporting to the Investigational Drug Branch (301-230-2330; Fax 301-230-0159) within 24 hours, with a copy sent to the NCI-IRB. The "NCI Guidelines: Expedited Adverse Events Reporting Requirements for NCI Investigational Agents" will be followed.

Clinical associates and/or senior staff should notify the Principal Investigator, William Dahut (301) 435-8183, the protocol chairperson, William Figg (301) 402-3622, Bldg 10, Room 5A01, or an associate investigator, or one of the other associate investigators of the occurrence of such toxicity.

7.2 The first occurrence of any previously unreported toxicity, greater than or equal to grade 2, will be reported to the Drug Monitor with the Investigational Drug Branch within 24 hours.

7.2.1 Investigators at the non-NCI sites should report simultaneously adverse events to the Protocol Chair as well as to the Investigational Drug Branch of CTEP, as outlined below.

7.3 The Principal Investigator or an Associate Investigator will be responsible for completing the AdEERS and for notifying the NCI's Institutional Review Board and the IRB's of all participating sites.

7.4 A summary of the ongoing study will be submitted to the NCI's Institutional Review Board at 12 month intervals and a final report will be sent within six months of study completion at the request of the Institutional Review Board using the CTEP study summary form. The status reported will be submitted and presented at upcoming NCI meetings as requested.

7.5 This study will be monitored by the Clinical Data Update system (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

7.5.1 This study will utilize the CTC version 2.0 for toxicity and adverse event reporting. A copy of the CTC version 2.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTC version 2.0.

7.6 Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

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AdEERS 10 calendar day report:

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December 15, 2004

Note: All deaths on study must be reported using expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

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  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

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Note 5 For hospitalization, any medical event equivalent to CTC Grade 3, 4, or 5, which precipitate hospitalization (or prolongation of existing hospitalization) must be reported regardless of whether it is an expected or an unexpected event, and regardless of attribution.
Note 7 Expedited reports are to be submitted using AdEERS or the paper templates available at http://ctep.cancer.gov. The NCI Guidelines for expedited adverse event reporting are also available at this site.

7.7 Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA):

The agent(s) (hereinafter referred to as thalidomide), used in this protocol is/are provided to the NCI under a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA) between Celgene (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment, Diagnosis. Therefore, the following obligations/guidelines apply to the use of the Agent(s) in this study:

7.7.1 Thalidomide may not be used outside the scope of this protocol, nor can thalidomide be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for thalidomide are confidential and proprietary to Collaborator(s) and should be maintained as such by the investigators.

7.7.2 For a clinical protocol where there is an investigational thalidomide used in combination with (an)other investigational Agent(s), each the subject of different CTAs or CRADAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

7.7.2.1 NCI must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

7.7.2.2 Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational Agent.

7.7.2.3 Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

7.7.3 The NCI encourages investigators to make data from clinical trials fully available to Collaborator(s) for review at the appropriate time (see Clinical trial data developed under a CTA or CRADA will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate.

7.7.4 When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for cooperative group studies, or PI for other studies) of Collaborator's wish to contact them.

7.7.5 Any data provided to Collaborator(s) must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

7.7.6 Any manuscripts reporting the results of this clinical trial should be rovided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to Collaborator(s) intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator(s) for courtesy review following submission, but prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Room 718
Bethesda, Maryland 20892
FAX 301-402-1584

The Regulatory Affairs Branch will then distribute them to Collaborator(s).

8.0 Pharmaceutical Information

8.1 Thalidomide

8.1.1 Thalidomide with matching placebo will be provided to study participants free of charge by Celgene Corporation and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).Note that this study involves a crossover from thalidomide to placebo (Arm 1) or from placebo to thalidomide (Arm 2). The medication for the initial phase will be labeled as "Phase A" and the medication for the crossover phase will be labeled as "Phase B", regardless of which arm the patient is randomized to. When dispensing, please be certain that the physician has specified on the prescription which phase the patient should be receiving and be certain that the phase specified on the patient's bottle corresponds to the phase specified on the patient's prescription. If the phase is missing from the patient's prescription, please contact the physician!

Thalidomide (NSC 66847 / IND #48832) and matching placebo will be supplied in white plastic bottles each containing 100 - 50mg capsules with a child-resistant cap and a tamper-evident seal. At the starting dose of thalidomide or placebo 200mg (i.e., four capsules) orally once daily at bedtime, each bottle contains a 25-day supply of drug. Each bottle will be

labeled with the protocol number (i.e., 'T99-0053'), the patient's ID number (e.g., '00C0080-001' where '00C0080' represents the NIH Clinical Center protocol number and '001' represents a patient sequence number assigned at registration), the patient's initials (i.e., the first three letters of the patient's last name), the phase (i.e., Phase A [initial therapy] or Phase B [crossover therapy]), a blank line for the patient's name, the number of capsules (i.e., '100 capsules'), the agent identification (i.e., 'Thalidomide 50mg or Placebo'), administration instructions (i.e., 'Take ___ capsules once daily at bedtime'), storage instructions, emergency contact instructions, and a julian date. At the time the bottle is dispensed to the patient, the pharmacist should enter the patient's name and the number of capsules the patient should take in the spaces provided. The julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 1999 = 99, 2000 = 00) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 1999 would have a julian date of '99001' and a bottle labeled and shipped on December 31, 2000 would have a julian date of '00365'. The julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e., both thalidomide and placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

8.1.2 Other names: Thalomid

8.1.3 Molecular formula: $C_{13}O_4N_2H_9$

8.1.4 Molecular weight: 243

8.1.5 Formulation: Supplied by CTEP as 50 mg hard gelatin capsules.

8.1.6 Storage: Store at room temperature

8.1.7 Stability: Shelf life surveillance studies are ongoing

8.1.8 Route of administration: Oral

8.1.9 Known toxicities: Allergic/Immunology: hypersensitivity reaction (rash, fever, tachycardia, hypotension), Blood/Bone Marrow: leukopenia, neutropenia, granulocytopenia, Cardiovascular (general): postural hypotension, edema, peripheral vascular disorder, thrombosis/embolism, Cardiovascular (Arrhythmia): bradycardia, and in very rare cases there maybe sudden or unexpected death, Constitutional symptoms: fatigue (lethargy, malaise, asthenia), Dermatology/Skin: dry skin, rash/desquamation, pruritis, Stevens-Johnson Syndrome, Gastrointestinal: constipation, mouth dryness, nausea, dyspepsia/heartburn, Hepatic: increased SGOT (AST) (serum glutamic oxaloacetic transaminase),

increased SGPT (ALT) (serum glutamic pyruvic transaminase), Metabolic: hypothyroidism, Musculoskeletal: myalgia, muscle weakness (not due to neuropathy), Neurology: confusion, depressed level of consciousness, mood alterations-depression, dizziness, lightheadedness, somnolence, sensory neuropathy, motor neuropathy, seizures, tremor, Ocular: dry eye, blurred vision, fleeting blindness, Pulmonary: dyspnea (shortness of breath), Sexual/reproductive function: teratogenic effects (birth defects), thalidomide can be detected in semen. There has been a report of Amaurosis Fugax "Fleeting Blindness" temporary loss of vision to a one eye (can last up to minutes).
Also reported on NCI-sponsored trials but with the relationship to thalidomide still undetermined: vomiting, anorexia, weight loss, syncope, abdominal pain, hyperglycemia, anxiety, apnea, supraventricular tachycardia, atrial fibrillation, thrombocytopenia, and increased alkaline phosphatase, sick sinus syndrome and pancreatitis.
There have been two reports of grade 3 and grade 4 renal dysfunction in patients with multiple myeloma who were receiving thalidomide and bisphosphonates.

8.1.10 Warning: There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking thalidomide even for short periods. Therefore, this teratogenic action of thalidomide necessitates that male patients be counseled about the possibility that thalidomide may be present in semen. Men must use a latex condom every time they have sexual intercourse with a woman both during therapy and for 8 weeks after discontinuing therapy, even if they have had a successful vasectomy.

8.2 Leuprolide Acetate

8.2.1 Other names: TAP-144, Abbott-43818

8.2.2 Description: Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH or LHRH). Leuprolide and other gonadotropin-releasing agonists are characterized by substitution of a D-amino acid in the sixth position and ethylamide for glycine in the N-terminus position, resulting in greater agonistic activity at LHRH receptors than naturally occurring gonadotropin-releasing hormone.

Animal and human studies indicate that chronic leuprolide acetate administration suppresses ovarian and testicular steroidogenesis. This effect is reversible after discontinuing therapy. In humans, leuprolide acetate causes an initial increase in circulating levels of luteinizing hormone (LH), leading to a transient increase in testosterone and dihydrotestosterone in males and estrone and estradiol in premenopausal females. Among patients with prostate cancer, transient increases in

prostatic acid phosphatase levels may occur sometime early in treatment; however, by the fourth week, the elevated levels can be expected to decrease to values at or near baseline. Subsequently, continuous administration results in decreased levels of LH and follicle-stimulating hormone (FSH). In males, testosterone is reduced to castrate levels and in premenopausal females, estrogens are reduced to postmenopausal levels within 2–4 weeks after initiating treatment. Castrate testosterone levels have been maintained in patients with prostate cancer for more than five years for as long as patients continue to receive monthly injections. Normal pituitary-gonadal function is usually restored within three months after treatment is discontinued. Clinical and pharmacologic studies in adults (age ≥ 18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks.

8.2.3 Chemical Names: (1) Luteinizing hormone-releasing factor (pig), 6-D-leucine-9-(*N*-ethyl-L-prolinamide)-10-deglycinamide-, monoacetate (salt); (2) 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide monoacetate (salt)

8.2.4 Chemical Identification

Empiric formula	$C_{59}H_{84}N_{16}O_{12}$ o $C_2H_4O_2$
Molecular weight	1269.48 Daltons
CAS registry No.	74381-53-6

8.2.4 Source: Leuprolide acetate (Lupron Depot® 7.5 mg) will be purchased by the NIH Clinical Center Pharmacy Department from commercial sources.

8.2.5 Formulation: Leuprolide acetate is commercially marketed as Lupron Depot® (Tap Pharmaceuticals Inc., Deerfield, IL), a sustained-release formulation.

Lupron Depot® 7.5 mg and Lupron Depot®–3 Month 22.5 mg are packaged in vials and in a prefilled dual-chamber syringe. All four products contain sterile lyophilized microspheres, which when mixed with diluent, become a suspension which is intended for monthly intramuscular injection.

8.2.7 Preparation

Lupron Depot® 7.5 mg Single-dose Vial:
(1) Using a syringe with a 22-gauge needle, withdraw 1 mL of diluent from the ampule, and inject it into the vial. (Extra diluent is provided; any remaining should be discarded.) (2) Shake well to thoroughly disperse particles to obtain a uniform, milky suspension. (3) Withdraw the entire contents of the vial into the syringe and inject it at the time of reconstitution.

Lupron Depot®–3 Month 22.5 mg Single-dose Vial:
(1) Using a syringe with a 22-gauge needle, withdraw 1.5 mL of diluent from the ampule, and inject it into the vial. (Extra diluent is provided; any remaining should be discarded.) (2) Shake well to thoroughly disperse particles to obtain a uniform, milky suspension. (3) Withdraw the entire contents of the vial into the syringe and inject it at the time of reconstitution.

Lupron Depot® Prefilled dual-chamber syringe:
(1) Screw the white plunger into the end stopper until the stopper begins to turn. (2) Remove and discard the tab around the base of the needle. (3) Holding the syringe upright, release the diluent by slowly pushing the plunger until the first stopper is at the blue line in the middle of the barrel. (4) Gently shake the syringe to thoroughly mix the particles to form a uniform, milky suspension. (5) If the microspheres adhere to the stopper, tap the syringe against your finger, then remove the needle guard and advance the plunger to expel the air from the syringe. (6) At the time of reconstitution, inject the entire contents of the syringe intramuscularly.
NOTE: The suspension settles very quickly after reconstitution; therefore, Lupron Depot® 7.5 mg should be mixed and used immediately. Reshake the suspension to disperse the drug if settling occurs.

8.2.8 Stability: The reconstituted suspension is stable for 24 hours, but contains no preservative; therefore, it should be used promptly after reconstitution. Vials of unreconstituted drug may be stored at room temperature. Each vial bears the manufacturer's expiration dating.

8.2.9 Storage: Vials containing Lupron Depot® Injection, the diluent ampules, and the prefilled dual-chamber syringe may be stored at room temperature.

8.2.10 Dosage and Administration: Lupron Depot® Injection 7.5 mg is administered once monthly as an intramuscular injection.
The recommended dose of Lupron Depot®—3 Month 22.5 mg is 22.5 mg, administered as one injection every 3 months (or 84 days). The 3-month depot and monthly formulations (Lupron Depot® Injection 7.5 mg) are not are not equivalent and fractional dose administration using the 3-month formulation should not be attempted.
The injection sites should be varied periodically.

8.2.11 Toxicities: The major toxicities associated with LHRH agonists are those of androgens withdrawal, and include hot flashes (vasomotor flushing) which often do not decrease with continued treatment (50–70%) Vance, 1984 #229 and sweating (58.9%), penile erectile impotence (5.4%), decreased libido Vance, 1984 #229, testicular atrophy, and gynecomastia and breast tenderness.

Potential exacerbations of prostate cancer signs and symptoms during the first few weeks of treatment are a concern in patients with vertebral metastases and urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness, paresthesias of the lower limbs, and worsening urinary symptoms. Patients with vertebral lesions and potential urinary tract obstruction should be closely observed during the first few weeks of therapy.

Other adverse effects associated with leuprolide acetate treatment include edema (12.5%), nausea and vomiting (none, to up to 5.4%) Vance, 1984 #229 , dyspnea of uncertain etiology (5.4%), general pain (7.1%), asthenia (5.4%), headache (≤ 32%), peripheral neuropathy, spinal fracture ± paralysis, tenosynovitis-like symptoms, prostate pain, increased SGOT/ALT (> 2 x normal limits), increased LDH (> 2 x normal limits), increased alkaline phosphatase (> 1.5 x normal limits), increased serum triglycerides, thrombosis, pulmonary embolus, myocardial infarction, acne and skin reactions. Rarely observed adverse effects and single case reports temporally associated with leuprolide treatment include pure red cell aplasia, leukopenia, ascites, hyperphosphatemia, ovarian hyperstimulation, vaginal hemorrhage, vaginitis. Transient pain, induration, and abscess may also occur at the site of leuprolide injection.

Hazardous Drug Status (NIH Clinical Center): At the Clinical Center, leuprolide acetate will be handled and labeled as a hazardous drug. When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg to rabbits (1/600–1/6 the human dose), Lupron Depot® produced a dose-related increase in major fetal abnormalities. There were increased fetal mortality and decreased fetal weights with the two higher doses of Lupron Depot® in rabbits and with the highest dose in rats. The effects on fetal mortality are logical consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy. Two-year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6–4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities. Mutagenicity studies performed with leuprolide

acetate using bacterial and mammalian systems have demonstrated no evidence of a mutagenic potential.

8.2.12 Drug Interactions: Leuprolide acetate is a peptide that is only about 46% bound to plasma proteins and is primarily degraded by peptidase. Drug interactions are not expected to occur with leuprolide.

8.3 Goserelin Acetate

8.3.1 Other names: ICI 118,630

8.3.2 Description: Goserelin is a synthetic decapeptide analog of LHRH with agonistic activity at LHRH receptors. It initially causes stimulation and subsequently profound suppression of LH and FSH production. Goserelin is commercially available as a sustained-release, biodegradable copolymer pellet formulation (Zoladex®, ICI Pharma, Wilmington, DE). The product is marketed in a disposable syringe device fitted with a 16-gauge needle.

After initial administration, goserelin causes an increase in serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations with subsequent increases in serum levels of testosterone. Chronic goserelin administration subsequently causes profound suppression of LH and FSH production. Consequently, serum testosterone levels fall into the range normally seen in surgically castrated men approximately 21 days after initiation of therapy. In clinical trials with follow-up of > 2 years, serum testosterone suppression to castrate levels was maintained over the dosing interval in approximately 91% (145/160) of the patients studied.

Pharmacokinetics: Time to peak concentration after subcutaneous (sc) injection with the 3.6-mg depot formulation is 12–15 days in males and 8–22 days in females; and 2 hours after sc injection with the 10.8-mg depot formulation.

Distribution: The apparent volume of distribution determined after subcutaneous administration of 250 μg aqueous goserelin solution was 44.1 +13.6 L for healthy males. The total plasma protein binding of goserelin was found to be 27%; volume of distribution = 44.1 L in males and 20.3 L in females.

Metabolism: The major clearance mechanism for goserelin occurs by hydrolysis of its C-terminal amino acids. The major circulating metabolite in serum appeared to be a 1–7 fragment, and the major component present in urine in one healthy male volunteer was a 5–10 fragment. All goserelin metabolites found in humans have also been found in species studied for toxicology.

Elimination: Goserelin is 90% renally excreted; total body clearance = 163.9 mL/min (female) and 110.5 mL/min (male). Goserelin's elimination half-life ($t_{1/2}$) = 4.2 hours in males and 2.3 hours in females.

In clinical trials with a solution formulation of goserelin, subjects with impaired renal function (Cl_{cr} < 20 mL/min) had a serum elimination $t_{1/2}$ of 12.1 hours compared to 4.2 hours for subjects with normal renal function (Cl_{cr} > 70 mL/min); however, there was no evidence for an accumulation of goserelin on multiple dosing of the goserelin 10.8-mg depot to subjects with impaired renal function. In addition, there was no evidence for an increase in incidence of adverse events in renally impaired patients who received the 10.8-mg depot. There is no evidence to date, which indicates that goserelin dosage should be adjusted in patients with impaired renal or hepatic function, or in geriatric patients.

A decrease of approximately 1–2.5% in the goserelin AUC has been correlated with a kilogram increase in body weight in a patient treated with the goserelin 10.8-mg depot formulation. Consequently, testosterone levels should be closely monitored in obese patients who do not respond clinically.

8.3.3 Chemical Names: (1) Luteinizing hormone-releasing factor (pig), 6-[*O*-(1,1-dimethylethyl)- D-serine]-10-deglycinamide-, 2-(aminocarbonyl)hydrazide; (2) 1-(5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*O-tert*-butyl-D-seryl-L- leucyl-L-arginyl-L-prolyl)semicarbazide

8.3.4 Chemical Identification

Empiric formula	$C_{59}H_{84}N_{18}O_{14}$
Molecular weight	1269.44 Daltons
CAS registry No.	65807-02-5

8.3.5 Formulation: Goserelin acetate is an off-white powder that is freely soluble in glacial acetic acid. It is also soluble in water, 0.1 M hydrochloric acid, 0.1 M sodium hydroxide, dimethylformamide, and dimethyl sulfoxide. Goserelin acetate is practically insoluble in acetone, chloroform, and ether.

Monthly administration: Zoladex® Goserelin Acetate Implant is supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 3.6 mg of goserelin. Zoladex® is designed for subcutaneous injection with continuous release over a 28-day period. Goserelin acetate is dispersed in a matrix of D,L-lactic and glycolic acids copolymer (13.3–14.3 mg/dose) containing less than 2.5% acetic acid and up to 12% goserelin-related substances and presented as a sterile, white- to cream-colored cylinder, 1 mm in diameter, preloaded in a special single use syringe with a 16-gauge

needle and overwrapped in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule. Studies of the D,L-lactic and glycolic acids copolymer have indicated that it is completely biodegradable and has no demonstrable antigenic potential.

Every 3 months administration: Zoladex® 3-Month 10.8 mg Depot is supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 10.8 mg of goserelin. The product is designed for subcutaneous implantation with continuous release over a 12-week period. Goserelin acetate is dispersed in a matrix of D,L-lactic and glycolic acids copolymer (12.82–14.76 mg/dose) containing less than 2% acetic acid and up to 10% goserelin-related substances and presented as a sterile, white- to cream-colored cylinder, 1.5 mm in diameter, preloaded in a special single-use syringe with a 14-gauge needle and overwrapped in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule.

8.3.6 Storage: Store at room temperature, but do not exceed 77°F (25°C). Each syringe package bears the manufacturer's expiration date.

8.3.7 Dosage and Administration: Goserelin acetate implant 3.6 mg is administered subcutaneously (sc), once every 28 days. Goserelin acetate implant 10.8 mg is administered sc, once every 12 weeks. For both formulations, the injection site of choice is the anterior upper abdominal wall; however, the midline of the lower abdomen may also be used.

Administration Technique:

(1) Do not use the syringe if the packaging material is damaged. Examine the syringe and confirm that the drug is visible in the translucent chamber. Do not remove the sterile syringe until immediately before use. (2) After cleaning with an alcohol swab, a local anesthetic may be used to infiltrate an area of skin on the upper abdominal wall. (3) Stretching the skin with one hand, grip the barrel of the hypodermic syringe and insert the needle into the sc fat. Do not aspirate. If the needle has penetrated a large blood vessel, blood will be seen instantly within the syringe chamber. If blood is seen, withdraw the syringe and inject elsewhere with a new syringe. (4) Change the direction of the needle such that it parallels the abdominal wall. Push the needle into the skin until the needle hub touches the patient's skin. Withdraw the needle to create a space to discharge the drug, depressing the plunger fully to completely discharge the drug. (5) Withdraw the needle and bandage the site of entry. Confirm that the drug had been discharged by visualizing the tip of the plunger within the needle lumen at the tip. Dispose of the used needle and syringe in a safe manner.

8.3.8 Toxicities: The major toxicities associated with LHRH agonists are those

of androgens withdrawal, and include hot flashes (vasomotor flushing), penile erectile impotence decreased libido, breast tenderness, breast swelling or gynecomastia, vaginal spotting or 'breakthrough bleeding'. Patients have also reported transient pain, redness, and bruising at the site of injection. Other adverse effects associated with goserelin include general pain, pelvic pain, bone pain, aching testes or other testicular discomfort, vaginal dryness, dyspareunia, nausea, urticaria, and asthenia. Rarely observed adverse effects and single case reports temporally associated with goserelin treatment include deep vein thrombosis, taste disturbances, diarrhea,
gingival atrophy, abdominal pain, and rash.

Goserelin acetate, like other LHRH agonists, causes transient increases in serum testosterone. A small percentage of patients experienced a temporary worsening of signs and symptoms, usually manifested by an increase in cancer-related pain. Isolated cases of exacerbation of disease symptoms, either ureteral obstruction or spinal cord compression, occurred at similar rates in controlled clinical trials with both goserelin and surgical orchiectomy.

Hazardous Drug Status (NIH Clinical Center): At the Clinical Center, goserelin acetate will be handled and labeled as a hazardous drug.

In rats, subcutaneous implant of goserelin acetate at about 3–9 times the recommended human dose on a mg/m^2 basis has resulted in an increased incidence of pituitary adenomas. The relevance of the rat pituitary adenomas to humans has not been established. In mice, subcutaneous implants of goserelin acetate at doses up to about 70 times the recommended human dose on a mg/m^2 basis resulted in an increased incidence of histiocytic sarcoma of the vertebral column and femur. Mutagenicity tests using bacterial and mammalian systems for point mutations and cytogenetic effects have provided no evidence for mutagenic potential.In male and female rats, goserelin produces histologic changes that are consistent with gonadal suppression which are almost completely reversed within several weeks after dosing was stopped; however, fertility and general reproductive performance were reduced in the animals that became pregnant after goserelin was discontinued. Although fertile matings occurred within 2 weeks after ceasing goserelin administration, total recovery of reproductive function may not have occurred before mating took place, and the ovulation rate, the corresponding implantation rate, and number of live fetuses were reduced.

Based on histological examination, drug effects on reproductive organs seem to be completely reversible in male and female dogs when drug treatment was stopped after continuous administration for 1 year at 100 times the recommended monthly dose.

Studies in both rats and rabbits at doses of about 0.1–3 times and 2–100 times the daily maximum recommended human dose on a mg/m² basis, respectively, administered during the period of organogenesis have increased dose-related pregnancy loss.

8.3.9 Drug Interactions: No confirmed interactions have been reported between goserelin and other drugs.

8.4 Drug orders, transfers, returns, accountability/Emergency unblinding

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 301-496-5725 Monday through Friday between 8:30 am and 4:30 pm Eastern Time.

8.4.1 Drug Orders: No starter supplies will be available for this study. When a patient is registered, Orkand will notify PMB (see Section 2.4.2) and PMB will automatically ship an initial three-month (i.e., four bottles) patient-specific supply for Phase A to the registering site. Two months after the initial request (i.e., one month before needed), sites may reorder an additional four bottles (i.e., a three month supply) by completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient's ID number (e.g., '00C0080-001') and initials (i.e., the first three letters of the patient's last name) should be entered in the "Patient or Special Code" field. All drug orders should be shipped directly to the physician responsible for treating the patient.

When the patient progresses on Phase A, the NCI Medicine Branch will notify PMB (see Section 2.4.3) and PMB will again automatically ship an initial three month (i.e., four bottles) patient-specific supply for Phase B to the registering site. Any remaining supplies for Phase A should be returned immediately on receipt of supplies for Phase B (see Section 8.4.3).

8.4.2 Drug Transfers: Bottles MAY NOT be transferred from one patient to another patient, from one center to another center, or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating center to another participating center, the principal investigator at a participating center changes, etc) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 301-480-4612) a Transfer Investigational Agent Form available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The

patient's ID number (e.g.,'00C0080-001') and initials (i.e., the first three letters of the patient's last name) should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., T99-0053).

8.4.3 Drug Returns: Unopened bottles of thalidomide or placebo which have NOT been dispensed to the patient should be returned to PMB with an NCI Return Agent Form when a patient completes Phase A and again when a patient completes Phase B. This return should also be documented on the patient-specific drug accountability log. Bottles of thalidomide or placebo that have been dispensed to the patient (whether opened or unopened) are returned to the pharmacy and the return and subsequent destruction of those bottles should be logged on the patient-specific accountability log or the Pill Count Case Report Form: Protocol T99-0053/00-C-0080. When returning study drug to the PMB, use the NCI Return Agent Form available on the NCI homepage (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient's ID number (e.g., '00C0080-001') and initials (i.e., the first three letters of the patient's last name) should be entered in the "Protocol or IND No." field in addition to the protocol number (i.e., T99-0053).

8.4.4 Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. A separate NCI Investigational Agent Accountability Record must be maintained for each patient on this protocol.

8.4.5 Emergency Unblinding: In the event of an emergency, call the Prostate Cancer Attending of the Month at the NCI at 301-496-1211. Remember ... this is only in the event of an emergency! NCI Medicine Branch staff will require the protocol number (i.e., T99-0053), the patient's ID number (e.g., '00C0080-001'), the patient's initials (i.e., the first three letters of the patient's last name), and the current phase (i.e., 'Phase A' or 'Phase B') to unblind the patient.

9.0 References

Aronson IK, Yu R. West DP. Van Den Broek H. Antel J. Thalidomide-induced peripheral neuropathy. Archives of Dermatology 120: 1466-1470. 1984.

Bahmer FA Zaun H. Luszpinski P. Thalidomide treatment of recurrent erythema multiforme. Acta Dermato-Venerologica 62: 449-450. 1982.

Bakay B, Nyhan WL. Binding of thalidomide by macromolecules in the fetal and maternal rat. J Pharmacol Exp Ther 161(2): 348-60. 1968.

Bauer KC, Lush RM, Rudek MA, Figg WD. Novel Therapeutic Targets in the Development of Anticancer Agents: Angiogenesis, Cyclin Dependent Kinases, Signal Transduction, and Matrix Metalloproteinases. Highlights in Oncology Practice 1998;16:3-11.

Bauer KS, Dixon SC, Figg WD. Inhibition of Angiogenesis by Thalidomide Requires Metabolic Activation which is Species-Dependent. Biochem Pharmacol 1998;55:1827-34.

Braun AG, Weinreb SL. Teratogen metabolism: spontaneous decay products of thalidomide and thalidomide analogues are not bioactivated by liver microsomes. Terato Carcinog Mutagen 5(3): 149-58. 1985.

Braun AG. Harding FA, Weinreb SL. Teratogen metabolism: thalidomide activation is mediated by cytochrome p450. Toxicol Appl Pharmacol Jan; 82(1): 175-9. 1986.

Brode E. Experimental studies with cyclic imides. Modification of hypohyseal-adrenal axis by thalidomide. Arzneimittelforschung June; 18(6): 661-5. 1968.

Chen TL. Vogelsang GB, Petty BG. Brundrett RB, Noe DA. et al. Plasma pharmacokinetics and urinary excretlon of thalidomide after oral dosing in healthy male volunteers. Drug Metabolism and Disposition 17: 402-405. 1989.

Crawford CL. Thalidomide neuropathy. N Engl J Med. 1992 Sep 3;327(10):735.

Cude KJ, Dixon SC, Guo Y, Lisella J, Figg WD. The Androgen Receptor: Genetic Considerations in the Development and Treatment of Prostate Cancer. Mol Medicine - accepted 1/99.

D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci. USA, 91: 4082-4085. 1994.

Dixon SC, Kruger E, Bauer KS, Figg WD. Thalidomide Upregulates Prostate-Specific Antigen (PSA) Secretion from LNCaP Cells. Cancer Chemotherap Pharmacol - accepted 9/98.

Fabro S, Smith RL, Williams RT. Toxicity and teratogenicity of optical isomers of thalidomide. Nature Jul 15; 215(98): 296. 1967a.

Fabro S, Smith RL, Williams RT. The fate of the hydrolysis products of thalidomide in the pregnant rabbit. Biochem J Aug; 104(2): 570-4. 1967b.

Figg WD, Feuer J, Bauer KS. Management of Hormone-Sensative Metastatic Prostate Cancer. Cancer Practice 1997;5:258-263.

Figg WD, Reed E, Green S, Pluda JM. Thalidomide, A Prodrug Inhibits Angiogenesis. In Teicher BA (Ed) Antiangiogenic Agents in Cancer Therapy, Humana Press, Inc., Totowa, NY, 1999; 407-22.

Figg WD, Raje S, Bauer KS, Tompkins A, Dyer V, Davis P, Venzon D, Bergan R, Chen A, Hamilton M, Pluda J, Reed E. Pharmacokinetics of Thalidomide in an Elderly Prostate Cancer Population. J Pharm Sci 1999; 88:121-5.

Figg WD, Kim G. The Role of Angiogenesis Inhibition in Metastatic Prostate Cancer. Adv Prostate Cancer 1998;8:2-5.

Fine HA, Figg WD, Jaeckle K, Wen PY, Kyritsis AP, Loeffler JS, Levin VA, Black PM, Kaplan R, Pluda JM, Yung WKA. A Phase II Trial of the Anti-angiogenic Agent, Thalidomide, in Patients with Recurrent High Grade Gliomas. submitted 2/99.

Folkman J. Tumor angiogenesis: Therapeutic implications. N Engl J Med 285: 1182-1186. 1971.

Folkman J. Tumor angiogenesis in "Cancer Medicine". Holland JF, et al (Eds), Lea and Febiger, Philadelphia, PA, 1993.

Gimbrone MA, et al. Tumor dormancy in vivo by prevention of neovascularization. J Exp Med 136: 261-276. 1972.

Goldenberg SL, et al. Intermittent androgen suppression in the treatment of prostate cancer: a preliminary report. Urology. 1995 May; 45(5): 839-44.

Kruger E, Reed E, Figg WD. Thalidomide and Analogues of Thalidomide as Inhibitors of Angiogenesis. In Rubanyi GM (Ed) Angiogenesis in Health and Disease, Marcel Dekker Inc., New York, NY, in press.

Locker D, Superstine E, Sulman FG. The metabolism of the push and pull principle. Endocrine effects of thalidomide and its analogues. Arch Int pharmacodyn Ther Nov; 194(1): 39-55. 1971.

Londono F. Thalidomide in the treatment of actinic prurigo. International Journal of Dermatology 12: 326-328. 1973.

Luzzio FA, Piatt Zacherl D, Figg WD. A Facile Scheme for Phthalimide/Phthalimidine Conversion. Tetrahedron Letters - accepted 1/99.

Masiero L, Figg WD, Kohn EC. New Anti-angiogenesis Agents: Review of Experience with CAI, Thalidomide, TNP-470, and IL-12. The Angiogenesis Journal 1997;1:23-35.

McBride WG. Thalidomide and congenital abnormalities. Lancet 2: 1358. 1968.

Nicholls PJ. A note on the absorption and exretion of 14C-labeled thalidomide in pregnant mice. J Pharm PHarmacol Jan; 18(1): 46-8. 1966.

Piscitelli SC, Figg WD, Hahn B, Kelly G, Thomas S, Walker RE. Single Dose Pharmacokinetics of Thalidomide in HIV-Infected Patients. Antimicrob Agents Chemother 1997;41:2797-9.

Sartor O, Rafford W, Figg WD. Treatment Options for Advanced Prostate Cancer. In Gentiourinary Cancer, Ed Scardino. Accepted 10/98.

Schroder JM, et al. Inhibitory effects of thalidomide on cellular proliferation, endoneurial edema and myelin phagocytosis during early wallerian degeneration. Acta Neuropathol (Berl). 1995;89(5):415-9.

Schroder JM, et al. Experimental thalidomide neuropathy: the morphological correlate of reduced conduction velocity. Acta Neuropathol (Berl). 1985;65(3-4):285-92.

Schroder JM, et al. Unmyelinated nerve fibers in senile nerves and in late thalidomide neuropathy: a quantitative electron microscopic study Acta Neuropathol (Berl). 1977 Aug 31;39(3):271-80.

Schumacher H, Smith RL, Williams RT. The metabolism of thalidomide and some of its hydrolysis products in various species. Brit J Pharmacol 25: 338-351. 1965.

Sheehan NJ. Thalidomide neurotoxicity and rheumatoid arthritis. Arthritis Rheum. 1986 Oct;29(10):1296.

Simmons BR, Lush RM, Figg WD. A Reverse-Phase HPLC method using Solid Phase Extraction for Quantitating Thalidomide. Analy Chim Acta 1997;339:91-7.

Stephens TD. Proposed mechanisms of action in thalidomide embryopathy. Teratology Sept; 38(3): 229-39. 1988.

Wasson JH, et al. Androgen deprivation therapy for asymptomatic advanced prostate cancer in the prostate specific antigen era: a national survey of urologist beliefs and practices. J Urol. 1998 Jun;159(6):1993-6.

Weidner N, et al. Tumor angiogenesis and metastasis-correlation in invasive breast carcinoma. Am J Pathol 324:1-8. 1993a.

Weidner N, et al. Tumor angiogenesis correlates with metastasis in invasive prostate carcinoma. Am J Pathol 143:401-409. 1993b.

White CW, et al. Treatment of pulmonary hemangiomatosis with recombinant interferon alfa-2a. N Engl J Med 320:1197. 1989.

Appendix A - ECOG Performance Status Scale

Score	Definition	Karnofsky Equivalent
0	Asymptomatic	100
1	Symptomatic, fully ambulatory	80-90
2	Sytmptomatic, in bed less than 50% of day	60-70
3	Symptomatic, in bed more than 50% of day but not bedridden	40-50
4	Bedridden	20-30

(Zubrod CG, Schneiderman M, Frei E et al: Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. J Chron Dis 11:7-33, 1960)

Appendix B - Informed Consent Document

Appendix C - Case Report Forms