A PHASE 3 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DOCETAXEL AND PREDNISONE WITH OR WITHOUT LENALIDOMIDE IN SUBJECTS WITH CASTRATE-RESISTANT PROSTATE CANCER

STUDY DRUG: Lenalidomide

PROTOCOL NUMBER: CC-5013-PC-002

DATE FINAL: 18 June 2009

EudraCT NUMBER 2008-007969-23

[redacted]

Signature of Celgene Therapeutic Area Head

[redacted]

Printed Name of Celgene Therapeutic Area Head

Date Signed: 18 June 2009

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator **dd/mm/yy**

Printed Name of Coordinating Principal Investigator and Title

Site Number_____

By my signature, I agree to supervise and oversee the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, **and the applicable parts of the United States Code of Federal Regulations** and local regulations governing the conduct of clinical studies.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator **dd/mm/yy**

Printed Name of Site Principal Investigator and Title

Site Number_____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, **and the applicable parts of the United States Code of Federal Regulations** and local regulations governing the conduct of clinical studies.

1. STUDY CONTACT INFORMATION

Table 1: Celgene Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Study Manager	[redacted] or Designee	86 Morris Avenue Summit, NJ 07901 [redacted]
Responsible Clinical Research Physician	[redacted] or Designee	86 Morris Avenue Summit, NJ 07901 [redacted]
North America Drug Safety Contact	Clinical Trial Safety	Celgene Corporation 86 Morris Avenue Summit, NJ 07901 Phone: 908-673-9667 Fax: 908-673-9115 drugsafety@celgene.com
International Drug Safety Contact For Local Drug Safety Affiliate Office Contact Information, Please Refer to the Serious Adverse Event Report Form Completion Guidelines.	Clinical Trial Safety	Celgene International Sàrl Route de Perreux 1 2017- Boudry Neuchatel, Switzerland Tel: + 41 327 298 776 Fax: + 41 327 298 709 drugsafetyeurope@celgene.com
24-Hour Emergency Contact (Celgene Corporation)	[redacted] or Designee	86 Morris Avenue Summit, NJ 07901 [redacted]

Role in Study	Name	Address and Telephone Number
24-Hour Emergency Contact (Quintiles) Numbers also available for urgent issues: North America: 1-866-412-9970 International/Rest of world: 1-661-328-2062	[redacted]	1801 Rockville Pike, Suite 300 Rockville, MD 20852 [redacted]

Name of central clinical laboratory(ies) and other medical and/or technical department(s) and /or institutions

1. **Name** ICON Central Laboratories, Inc.
   Address 123 Smith Street, Farmingdale, NY 11735
   Phone Number 856-778-9933

2. SYNOPSIS

Name of Sponsor/Company: Celgene Corporation

Name of Investigational Product: Lenalidomide

Protocol Number: CC-5013-PC-002

Protocol Title: A Phase 3 Study to Evaluate the Efficacy and Safety of Docetaxel and Prednisone with or without Lenalidomide in Subjects with Castrate-Resistant Prostate Cancer (CRPC)

Indication: Chemo-naïve metastatic prostate cancer subjects with documented rising Prostate Specific Antigen (PSA) or documented Progressive Disease (PD) following hormonal therapy

Study Duration:	**Phase of Development:**
Up to 28 days screening Treatment with lenalidomide or placebo in combination with docetaxel until radiological progression, toxicity or any other reason Subjects will be followed after study treatment discontinuation for survival and additional treatments for prostate cancer every 90 days for up to 5 years or until all subjects have expired	Phase 3

Objectives:

Primary:

- To compare the Overall Survival (OS) benefit of docetaxel and prednisone with and without lenalidomide as first-line therapy in chemo-naïve metastatic CRPC subjects

Secondary:

- Progression-Free Survival (PFS)
- Objective Response Rate
- Safety of lenalidomide in combination with docetaxel and prednisone

Exploratory

- PSA response, PSA progression, PSA doubling time and PSA velocity
- Biomarker analysis
- Pharmacokinetic analysis
- Change in Analgesic Use
- Patient-Reported Outcomes

Study Endpoints:

Primary

- Overall Survival

Secondary

- Progression-Free Survival (PFS) is defined as time from randomization to disease progression, as determined by RECIST Version 1.1 criteria or death due to any cause, whichever occurs first. Progression criteria will be met by analysis of target and non-target lesions according RECIST Version 1.1 criteria
- Objective Response Rate of measurable and/or non-measurable disease as determined based on RECIST Version 1.1 criteria
- Safety (type, frequency, and severity of adverse events [AEs] and relationship of AEs to the Investigational Medicinal Products)

Exploratory:

- PSA reductions ≥30%, ≥50%; PSA progression; PSA velocity; and PSA doubling time will be analyzed to assess any significant correlation of PSA levels with relevant clinical benefits (e.g., OS, PFS, and Pain Endpoints)
- Exploratory analysis of biomarkers, including but not limited to CTCs will be performed to assess any significant correlation of CTC levels with relevant clinical benefits. Sample collection for this exploratory analysis may be limited to selected clinical centers
- Intensive and sparse sampling pharmacokinetics (PK) analysis of lenalidomide when administered in combination with docetaxel and prednisone will be performed on randomized subjects in selected clinical centers
- Change in Analgesic use will be evaluated over the course of the study for the interpretation of self-reported pain severity in light of concomitant analgesic use
- Patient-Reported Outcomes (PRO) will be evaluated using validated instruments for Pain Assessment and Health-Related Quality of Life Questionnaires

Study Design:

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study in chemo-naïve subjects with metastatic CRPC with documented progressive disease as determined by rising PSA levels or radiological progression following hormonal therapy. Approximately 1015 subjects meeting inclusion criteria will be randomized 1:1 into one of two treatment arms:

- *DP Treatment Arm:* docetaxel, prednisone and placebo
- *DPL Treatment Arm:* docetaxel, prednisone and lenalidomide

Subjects will begin their initial study treatment (Cycle 1, Day 1) within 3 days of randomization. Study treatment will continue until subjects experience disease progression as per RECIST Version 1.1, except bone lesions, or premature discontinuation for any other reason. Discontinuation for bone progression

will require ≥ 2 new lesions with confirmation during the next scheduled tumor assessment (9 weeks after initial observation of ≥ 2 new lesions). *NOTE: For purposes of this study PSA progression is not considered disease progression and does not mandate discontinuation from the Treatment Phase of the study.*

Subjects experiencing treatment-related toxicity will be allowed to dose reduce or discontinue either docetaxel or lenalidomide while remaining eligible to continue study treatment with the remaining drug. Complete discontinuation of both drugs will result in discontinuation of study treatment. All subjects will be contacted 28 days after last dose for AEs and concomitant medications and then followed for survival and post-study prostate cancer treatments every 90 days until death or up to 5 years following treatment phase discontinuation. Efficacy and safety assessments to be performed during the study are detailed in Table 2: Schedule of Study Assessments.

A safety assessment performed by an independent Data Monitoring Committee to ensure the safety and tolerability of the study regimen is planned after 100 randomized subjects have either completed 2 cycles of study treatment or withdrawn prematurely from the study. Ongoing safety assessments will be performed every 6 months after the first review at 100 subjects. Additional safety assessments will be performed as appropriate.

An interim efficacy analysis based on OS will be performed when 468 events have occurred. The final primary analysis for overall survival is planned once 624 events are observed.

Number of Subjects (planned):

Approximately 1015 subjects meeting inclusion criteria are to be randomized 1:1 into either the DPL or the DP treatment arm. Subject's randomization will be stratified according to Eastern Cooperative Oncology Group (ECOG) performance status, geographic region and type of disease progression following hormonal therapy.

Study Population

Key Inclusion Criteria

Subjects Must Meet All of the Following Inclusion Criteria to be Eligible for Enrollment Into The Study:

1. Understand and voluntarily sign an Informed Consent Form (ICF)
2. Males ≥ 18 years of age at the time of consent
3. Able to adhere to the study visit schedule and requirements of the protocol
4. ECOG performance status of ≤ 2
5. Life expectancy of ≥ 12 weeks
6. Willingness to participate in HRQoL and pain assessments and have ability to complete PRO and pain assessments without assistance or with minimal assistance from trained site personnel and/or caregiver
7. Effective castration (serum testosterone levels < 50 ng/dL) due to orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist

- Primary testicular androgen suppression (e.g., LHRH agonists) should be continued during study treatment for subjects who have not had a bilateral orchiectomy

8. Histologically confirmed adenocarcinoma of the prostate and:
   - Prostate cancer that is unresponsive or refractory to hormonal therapy AND
   - Metastatic disease confirmed by bone scan, Computer Tomography (CT) scan, Magnetic Resonance Imaging (MRI) or X-ray
9. Have documented disease progression while receiving or following hormonal therapy for treatment of advanced prostate cancer despite castrate levels of serum testosterone due to orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist as determined by **at least one** of the following criteria:
   - Serum PSA level ≥ 2ng/mL that has increased from a reference value on at least two consecutive PSA measurements obtained at least 1 week apart prior to randomization
   - Progression of measurable disease
     - Measurable disease is defined as at least one measurable lesion ≥ 10 mm long diameter by CT or MRI (or 20 mm by Chest X-ray) and/or lymph nodes ≥ 15 mm short axis
     - Progression of measurable disease is defined as an increase of > 20% in the sum of the diameters of target lesions from the time of maximal regression OR the appearance of ≥ 1 new lesion
   - Unequivocal progression of non-measurable disease
     - Non-measurable disease is defined as all lesions < 10mm in the longest diameter or pathological lymph nodes ≥10 mm to < 15 mm short axis
       - Unequivocal progression of existing lesions is defined as an increase in overall disease burden based on the change in non-measurable disease that is comparable in magnitude to the increase that would be required to declare disease progression for measurable disease
     - 2 or more new bone lesions as detected by bone scan
10. All subjects:[a]
    - Must be counseled about pregnancy precautions and risks of fetal exposure. See Appendices 21.6.2 (EX-EU version) or 21.7.2(EU version) Lenalidomide Risks of Fetal Exposure and Acceptable Birth Control Methods, and Appendices 21.6.3 (Ex-EU version) or 21.7.3 (EU version) Lenalidomide Education and Counseling Guidance Document
    - Must agree to use a condom (specified in the appropriate country specific appendix) during sexual contact with a female of childbearing potential (FCBPb), even if they have had a

[a] Refer to the "Lenalidomide Pregnancy Risk Minimization Program in Celgene Clinical Trials" in Appendix 21.6 (Ex-EU) or Appendix 21.7 (EU) for country specific guidelines. The Ex-EU (Appendix 21.6) version is for clinical sites in the US and all countries utilizing the US program guidelines. The EU version (Appendix 21.7) is for clinical sites in all EU countries and any country following the EU program guidelines

vasectomy, while participating in this study, during dose interruptions, and for a period of days (specified in the appropriate country specific appendix) following the last dose of study drug

- Must agree to refrain from donating semen or sperm while participating in this study and for a period of days (specified in the appropriate country specific appendix) following the last dose of study drug
- Must agree to refrain from donating blood or plasma while participating in this study and for a period of days (specified in the appropriate country specific appendix) following the last dose of study drug
- Must agree not to share study drug with anyone during participation in the study

Key Exclusion Criteria

Presence of any of the Following will Exclude a Subject from Enrollment into the Study:

1. A history of clinically significant (as determined by the investigator) medical, surgical, or psychiatric disease that would place the subject at an unacceptable risk for study entry
2. Prior therapy with thalidomide, lenalidomide (CC-5013) or pomalidomide (CC-4047)
3. Prior chemotherapy for prostate cancer
   - Treatment with estramustine will be allowed if last treatment is more than 28 days prior to randomization, and subject has recovered from side effects
   - Adjuvant and/or neoadjuvant treatment will be allowed if completed > 3 years prior to randomization and provided the regimen did not contain docetaxel
4. Use of any other experimental drug or therapy within 28 days prior to randomization
5. Prior whole pelvic radiation therapy or irradiation to ≥ 30% of Bone Marrow (see Appendix 21.3) and/or per radiation specialist
6. Any other radiation therapy within 28 days prior to randomization
   - Subjects receiving prior radiation must have recovered from acute toxicity or any side effects due to radiation treatments prior to signing the ICF
7. Prior use of Strontium-89 at any time or Samarium-153 within 56 days prior to randomization
8. Surgery within 28 days prior to randomization (minimally invasive procedures for the purpose of diagnosis or staging of the disease are permitted)
9. Concurrent corticosteroid or hormonal therapy
   - Hormonal therapy, (e.g., ketoconazole, aminoglutethimide, corticosteroids, flutamide, or megestrol) must be discontinued at least 4 weeks prior to randomization
   - Prior therapy with bicalutimide and nilutamide must be discontinued at least 6 weeks prior

[b] A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

to randomization

- Subjects without prior orchiectomy should continue treatment with LHRH agonists
- Bisphosphonates may be continued if at a stable dose for 28 days prior to enrollment
- Concurrent therapy with steroids or hormones for adrenal insufficiency or nondisease-related conditions (e.g., insulin for diabetes) are allowed

10. Any of the following laboratory values:
    - Hemoglobin < 9 g/dL (blood products and growth factors are permitted)
    - Absolute neutrophil count (ANC) < 1.5 x 10^9 cells/L
    - Platelet count < 100 x 10^9 cells/L
    - Creatinine > 1.5 x upper limit of normal (ULN)
    - Total bilirubin > 1.0 x the upper limit of normal (ULN)
    - Serum aspartate transaminase (AST)/SGOT > 1.5 x upper limit of normal (ULN) concomitant with alkaline phosphatase > 2.5 x ULN
11. Must not have had significant active cardiac disease within the previous 6 months including:
    - History of hypertension allowed provided blood pressure (BP) is controlled (i.e., BP < 160/90 mm Hg) by anti-hypertensive therapy
    - New York Heart Association class II-IV congestive heart failure
    - Unstable angina
    - Angina requiring surgical or medical intervention
    - Myocardial infarction
12. Clinically significant peripheral arterial occlusive disease (i.e., claudication on less than 1 block)
13. Thrombotic or thromboembolic events within the past 6 months, including any of the following:
    - Deep Vein Thrombosis or Pulmonary Embolism within the preceding 6 months
    - Transient ischemic attack
    - Cerebrovascular accident
    - Any other arterial thrombotic event
14. History of peripheral neuropathy of ≥grade 2
15. History of severe hypersensitivity reaction to drugs formulated with polysorbate 80
16. Paraplegia
17. History of symptomatic central nervous system (CNS) or brain metastases
    - Subjects who have remained asymptomatic for 90 days and demonstrate no active CNS involvement as shown by CT, MRI, or lumbar puncture are not excluded
    - If required, CT, MRI, or lumbar puncture should be performed during the screening process

18. History of malignancies other than prostate cancer within the past 5 years, with the exception of treated basal cell/squamous cell carcinoma of the skin
19. Concurrent use of alternative cancer therapies during study treatment. Subjects taking alternative therapies for cancer must stop taking these therapies prior to randomization. Alternative therapies are not allowed during the treatment or follow-up portions of the study. This includes alternative therapies such as, but not limited to:
    - Saw Palmetto
    - DHEA
    - Lycopene
    - PC-SPES (all types)
    - Vitamins and/or dietary supplements used at therapeutic doses for treatment of prostate cancer including:
        - Vitamin D
        - Selenium
    - Citrus pectin

Additional Criteria:

Before Starting Study Drug:

- Subjects should understand the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential
- Subjects should understand the need for the use of a condom if engaged in sexual activity with a woman of childbearing potential
- Subjects should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment

During Study Participation and for a Period of Days (as Specified in the Appropriate Appendix) Following Discontinuation from Study:

- No more than a 28-day supply of study drug will be dispensed at a time
- Subjects should be monitored during the course of the study and after the end of study therapy to:
    - Ensure they continue to use a condom during sexual contact with a FCBP
    - If a female partner of a male subject becomes pregnant she should be referred to the appropriate physician

Investigational Product, Dosage and Mode of Administration:

Celgene Corporation will supply lenalidomide (CC-5013) as 10 mg, 15 mg, 20 mg, 25 mg and matching placebo capsules for oral administration. Study drug will be packaged in bottles containing enough capsules for 14 days of dosing. All subjects will be required to take a single capsule, lenalidomide or

placebo, each day for Days 1-14 of each cycle.

Celgene Corporation will also supply commercial docetaxel and prednisone labeled as investigational medicinal product (IMP) in all non-US investigational study sites.

During the 21-day treatment period study drug will be administered as follows:

DP treatment arm: Oral placebo once each day (QD) on Days 1-14 of the treatment cycle; 75 mg/m^2 docetaxel IV on Day 1; 5 mg prednisone orally twice each day (BID) of the treatment cycle

DPL treatment arm: 25 mg lenalidomide orally once each day (QD) on Days 1-14; 75 mg/m^2 docetaxel IV on Day 1; 5 mg prednisone orally twice each day (BID) each day of the treatment cycle

Note: Subjects will receive pre-treatment for docetaxel according to institutional standards.

Subjects will be evaluated for AEs during each visit, using the NCI CTCAE Version 4.0. Refer to Section 10.2.1.2.1, Table 5 and Table 9 for instructions on dose modifications of lenalidomide.

Reference Therapy, Dosage and Mode of Administration:

The comparator arm will consist of docetaxel and prednisone in combination with identical matching placebo capsules. Docetaxel will be administered IV at 75 mg/m^2 on Day 1 of each 21-day cycle. Prednisone will be administered 5 mg orally BID each day of the 21-day treatment cycle and the placebo will be administered orally QD on Days 1-14 of the study in the DP arm. Subjects will receive prednisone prior to docetaxel administration.

Dose modifications for docetaxel will be performed as described in Section 10.2.1.3 and as per the package insert.

Assessments:

Efficacy:

- Overall Survival
- Progression-Free Survival
- Tumor assessment by RECIST Version 1.1:
  - CT, MRI, Chest X-rays and Bone scans of measurable and non-measurable lesions
- ECOG Performance Status

Safety:

- Adverse event severity by NCI CTCAE Version 4.0.
- Physical examination including but not limited to:
  - Heart, lungs, abdominal head/neck and extremities. A clinical neurological examination will be performed if clinically indicated.
- Vital signs, weight, and height (only during screening)
- Hematology laboratory evaluations
- Serum Chemistry laboratory evaluations

- Urine Dipstick
- Electrocardiogram (ECG)
- Concomitant medications/Procedures

Exploratory

- PSA reductions ≥30%, ≥50%; PSA progression; PSA velocity; and PSA doubling time will be calculated. Statistical analysis will be performed to assess any significant correlation of PSA levels with relevant clinical benefits (e.g., OS, PFS, and Pain Endpoints).
- Exploratory analysis of biomarkers, including but not limited to CTCs will be performed to assess any significant correlation of CTC levels with relevant clinical benefits. Sample collection for this exploratory analysis may be limited to selected clinical centers.
- Intensive and sparse sampling pharmacokinetics (PK) analysis of lenalidomide when administered in combination with docetaxel and prednisone will be performed on randomized subjects in selected clinical centers
- Change in Analgesic use will be evaluated over the course of the study for the interpretation of self-reported pain severity in light of concomitant analgesic use
- Patient-Reported Outcomes (PRO) will be performed using the validated instruments listed below for Pain and Health-Related Quality of Life (HRQoL) assessments
  - Pain Assessment
    - Brief Pain Inventory-Short Form (BPI-SF)
  - Health-Related Quality of Life and Prostate Cancer Symptoms
    - Functional Assessment of Cancer Therapy - Prostate Cancer (FACT-P)
    - EuroQol (EQ-5D) Questionnaire

Statistical Analysis:

Statistical Overview:

This is a multicenter, double blind, randomized Phase 3 study comparing lenalidomide (DPL) versus placebo (DP) as first-line treatment in combination with docetaxel and prednisone in chemo-naïve subjects with metastatic CRPC. Subjects will be randomized 1:1 according to the following stratification factors: baseline ECOG performance status (≤1 vs. 2), geographic region (US and Canada vs. EU countries and Australia vs. Rest of World), and type of disease progression following hormonal therapy (rising PSA only vs. tumor progression). An Interactive Voice Response System (IVRS) will be utilized to ensure a central randomization based on a permuted-block randomization method. An independent Data Monitoring Committee (DMC) will be used to monitor the study conduct.

Sample Size:

Approximately 1015 subjects will be randomized over 24 months. An interim analysis for OS will be performed when at least 468 events are observed and all 1015 subjects have been randomized. The final analysis, planned after 624 events have been observed, is expected approximately 48 months following randomization of the first subject onto the study. The O'Brien-Fleming boundary

will be used to determine the nominal significance level with overall two-sided 5% significance level. Assuming that DP treatment arm results in a median OS of 19.2 months the DPL has a targeted median OS of 25.0 months (30% improvement). This design would allow the demonstration of a statistically significant difference in the OS at a two-sided 5% significance level with at least 90% power.

Demographics, Disposition and Dosing

The baseline characteristics of all randomized subjects will be summarized. An accounting will be made of all subjects who received study drug and, in particular, the number of subjects who died or withdrew during treatment will be specified together with the reasons for withdrawal.

Safety Analysis:

Data from all subjects who receive one or more doses of study drug will be included in the safety analyses. Adverse events, physical examinations (including vital sign measurements), clinical laboratory information, ECG interpretations, and concomitant medications/procedures will be tabulated and summarized by treatment group. All toxicities will be summarized by relative and absolute frequency, severity grade based on the NCI CTCAE Version 4.0 and relationship to treatment. Study medication-related AEs, serious adverse events (SAEs), and events leading to discontinuation or death will be listed separately. Safety information obtained during the Follow-up period will be described. Graphical displays will be provided where useful in the interpretation of results.

An initial safety assessment is planned after 100 randomized subjects have either completed 2 cycles of the treatment or withdrawn prematurely in order to ensure the safety and tolerability of the study regimen. Following the initial safety assessment, further safety assessments will be performed approximately every 6 months until the final subject enrolled has completed either 2 cycles of treatment or prematurely withdrawn from the study. Additional safety assessment may be performed if recommended by the DMC.

Efficacy Analysis:

For the primary analysis, the overall survival will be compared between treatment arms based on the log rank test. The overall two-sided significance level is 5%. This 5% will be spread over 2 analyses by an O'Brien-Fleming alpha spending function. The significance of efficacy will be claimed if the p-value is less than or equal to the significance level as calculated based on the specified alpha spending function and the observed number of events.

The Kaplan-Meier method will be used to estimate the survival distribution functions for each treatment arm. The number of events, subjects censored, and the Kaplan-Meier estimates at the time points of 52, and 104 weeks, along with standard errors (Greenwood's formula, Klein and Moeschberger, 2003), will be provided. The plots of survival curves using the Kaplan-Meier method will be presented.

Kaplan-Meier product limit methods will be used to estimate the survival functions for PFS. A two-sided log-rank test will be used to compare survival functions. The medians will be estimated using Kaplan-Meier estimates with 95% confidence intervals (CI) computed using the method of Brookmeyer and Crowley. The Cox model will also be used to estimate hazard ratio and identify prognostic factors.

Categorical endpoints will be summarized in frequency tables. Percentages in the summary tables

will be rounded and may, therefore, not always sum to 100%.

Additional details will be provided in the statistical plan.

Patient-Reported Outcomes:

For the analysis of patient-reported outcomes, analyses will be completed on a PRO intent-to-treat population defined for PRO assessment as all randomized subjects who completed the baseline assessment and had at least one follow-up assessment with the BPI-SF, the FACT-P or the EQ-5D. The primary PRO analysis will focus on pain palliation during the double-blind treatment phase. Other HRQoL measures (i.e., pain interference, FACT-P, EQ-5D) will be considered secondary PRO measurements. Between group measures will be evaluated using analysis of covariance procedures (ANCOVA). A PRO Statistical Analysis plan will fully specify the between-group analysis procedures, as well as methods to assess responsiveness and minimally important differences.

Interim Analysis:

One interim analysis based on OS is planned and an independent DMC will review and give advice to the sponsor regarding the study conduct. An independent statistician will be responsible for preparation of the appropriate data and reports to provide the members of the DMC prior to their scheduled meeting. The analysis results will not be disseminated among investigators and those directly involved with the study conduct. The efficacy interim analysis will be performed when 468 events are observed and all subjects have been randomized. A final analysis is planned when 624 events are observed. The boundary of the nominal p-value based on the log-rank test statistics for declaring superiority is as follows:

Analysis stage	Boundary for nominal p-value
1	0.0193
2	0.0442

Data Monitoring Committee:

An independent DMC will be convened which will be composed of medical oncologists with experience in treating subjects with prostate cancer and a statistician, all of whom are not otherwise involved in the study as investigators or reviewers of efficacy data. During the course of the study, the DMC will review the efficacy data once in accordance with the guidelines for the pre-planned interim analysis. The committee will also review safety data on a pre-determined schedule as described above (Section 8.10.1). An independent third party will prepare the reports of aggregate data summaries and individual subject data listings, as appropriate, to provide the members of the DMC for each scheduled meeting. Operational details for the DMC will be detailed in the DMC charter.

Table 2: Schedule of Study Assessments

		Treatment Phase					Follow-Up Phase	
Procedure	**Screening (-28 Days)**	**Cycle 1 Day 1**	**Cycle 1 Day 14 [a] +/- 3 days)**	**All Cycles Day 1 (After Cycle 1) (+/- 3 days)**	**Every 3rd Cycle Day 1 (Starting Cycle 4) (+/- 3 days)**	**Treatment Phase Discontinuation (+/- 3 days)**	**28 Days after last dose (+/-7 days)**	**Every 90 days after last dose (+/- 14 days)**
Entry Assessments:								
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Complete Medical History	X							
Confirm Diagnosis	X							
Safety Assessments:								
Adverse Event Query	X	X	X	X		X	X	
Physical Examination[b]	X	X	X[a]	X		X		
Vital Signs[c]	X	X	X[a]	X		X		
Hematology Labs[d]	X	X[d]	X[a]	X		X		
Serum Chemistry Labs[e]	X [e,f]	X[e]	X[a]	X		X		
Urine Dipstick [g]	X	X		X		X		
ECG[h]	X					X		
Concomitant Medications / Procedures	X	X	X	X		X	X	
Pharmacokinetics[i]		X	X					
Efficacy Measurements:								
PSA[j]	X[j]	X		X		X		
ECOG Performance Status[k]	X	X[k]		X		X		

Table 2: Schedule of Study Assessments (Continued)

		Treatment Phase					Follow-Up Phase	
Procedure	**Screening (-28 Days)**	**Cycle 1 Day 1**	**Cycle 1 Day 14 (+/- 3 days)** [a]	**All Cycles Day 1 (After Cycle 1) (+/- 3 days)**	**Every 3rd Cycle Day 1 (Starting Cycle 4) (+/- 3 days)**	**Treatment Phase Discontinuation (+/- 3 days)**	**28 Days after last dose (+/-7 days)**	**Every 90 days after last dose (+/- 14 days)**
Tumor Assessment[l]	X				X	X[l]		
Progression-Free Survival[m]					X	X		
Analgesic Use[n]	X	X	X	X		X	X	
Biomarkers Blood Collection[o]		X			X	X		
HRQoL								
BPI-SF[p]	X	X		X		X		
FACT-P[p]		X			X	X		
EQ-5D[p]		X			X	X		
Study Drug:								
Dispense Lenalidomide/ Drug Accountability[q]		X		X		X		
Docetaxel/Prednisone Treatment and Accountibility[r]		X		X		X		
Follow-up:								
Survival[s]								X
Prostate Cancer Treatments[t]								X

[a] Safety Assessments will be performed on the first 100 subjects and any subject participating in the sparse PK sampling sub-study, during Cycle 1, Day 14 (+/ 3 days) for evaluation during the initial scheduled DMC safety assessment. Subjects participating in the sparse PK sub-study can have this visit up to 3 days prior to but no later than Cycle 1, Day 14 (the last scheduled day of lenalidomide during the cycle). Subsequent subjects (after safety assessment for the first 100 subjects) will to be evaluated during Cycle 1, Day 14 only if determined necessary due to safety concerns.

[b] Physical Examination: A complete physical exam is required including but not limited to heart, lungs, abdominal, head/neck and extremities. A clinical neurological examination will be performed if clinically indicated. The Investigator should denote any clinically significant values as Adverse Events.

[c] Vital Signs: Blood pressure, pulse, temperature and weight will be evaluated at each study visit. Height will only be assessed at screening.

[d] Hematology: Red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count and differential (including absolute neutrophil count [ANC] and platelet count). May be repeated more frequently if clinically indicated. Hematology labs assessed at screening will not be repeated on Cycle 1, Day 1 if performed within 7 days of Cycle 1, Day 1.

[e] Serum Chemistry: Sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, aspartate transaminase (AST/SGOT), alanine transaminase (ALT/SGPT), lactate dehydrogenase (LDH) and uric acid. Any or all may be repeated more frequently if clinically indicated. Serum chemistry labs assessed at screening will not be repeated on Cycle 1, Day 1 if performed within 7 days of Cycle 1, Day1.

[f] Serum Chemistry analyses during the screening visit will include measuring testosterone levels. Serum testosterone must be < 50 ng/dl to meet study inclusion criteria.

[g] Urine dipstick will be performed. If abnormal, urinalysis is to be perform for specific gravity, protein, glucose, pH, ketones, urobilinogen and occult blood. If clinically indicated microscopic analysis will be performed (as a reflex test).

[h] 12-lead ECG is performed at screening, treatment phase discontinuation and as clinically indicated.

[i] Pharmacokinetics (See Section 14.1): Subjects who sign the PK sub-study ICF will participate in either the PK Intensive Sampling or the PK Sparse Sampling. Whole blood samples (approximately 3 mls) will be collected during the PK Intensive Sampling during Cycle 1, Day 1 at 1, 1.5, 2, 3, 4 and 6-8 hours after administration of lenalidomide on Cycle 1 Day 1. Docetaxel infusion will be administered immediately following collection of the 1 hour post lenalidomide dosing PK sample. The PK Sparse Sampling will take place on Cycle 1, Day 14. Two blood samples will be collected between 4 – 10 hours after taking study drug. The Sparse PK samples can be collected at visits up to 3 days prior to and including Day 14, but not after Day 14.

[j] PSA inclusion criteria includes two consecutive rising PSA values at least one week apart from a baseline value prior to randomization. PSA measurements will not be used for assessment of PFS or Objective Response Rate calculations.

[k] ECOG performance status will be evaluated at screening, Day 1 of each cycle and at treatment phase discontinuation. ECOG Performance status will not be repeated on Cycle 1, Day 1 if performed within 14 days of Cycle 1, Day1.

[l] Tumor Assessment: CT, MRI, Chest X-ray and/or bone scans, of measurable and non-measurable lesions should be performed at screening (within 28 days prior to the first treatment dose, Cycle 1 Day 1) and then every subsequent 3rd cycle Day 1 (every 9 weeks). Response will be evaluated based on RECIST Version 1.1 criteria and as described in Section 12.2.3. To ensure comparability, baseline methods and on-study methods for response assessment must be performed using identical techniques. Tumor assessments at the Discontinuation Visit do not need to be repeated if performed ≤ 28 days prior to discontinuation.

[m] Progression-Free Survival is followed until progression of disease or death, whichever occurs first. Disease progression will be defined as per RECIST Version 1.1 criteria

[n] All analgesic use will be captured along with concomitant medications on the appropriate page of the CRF.

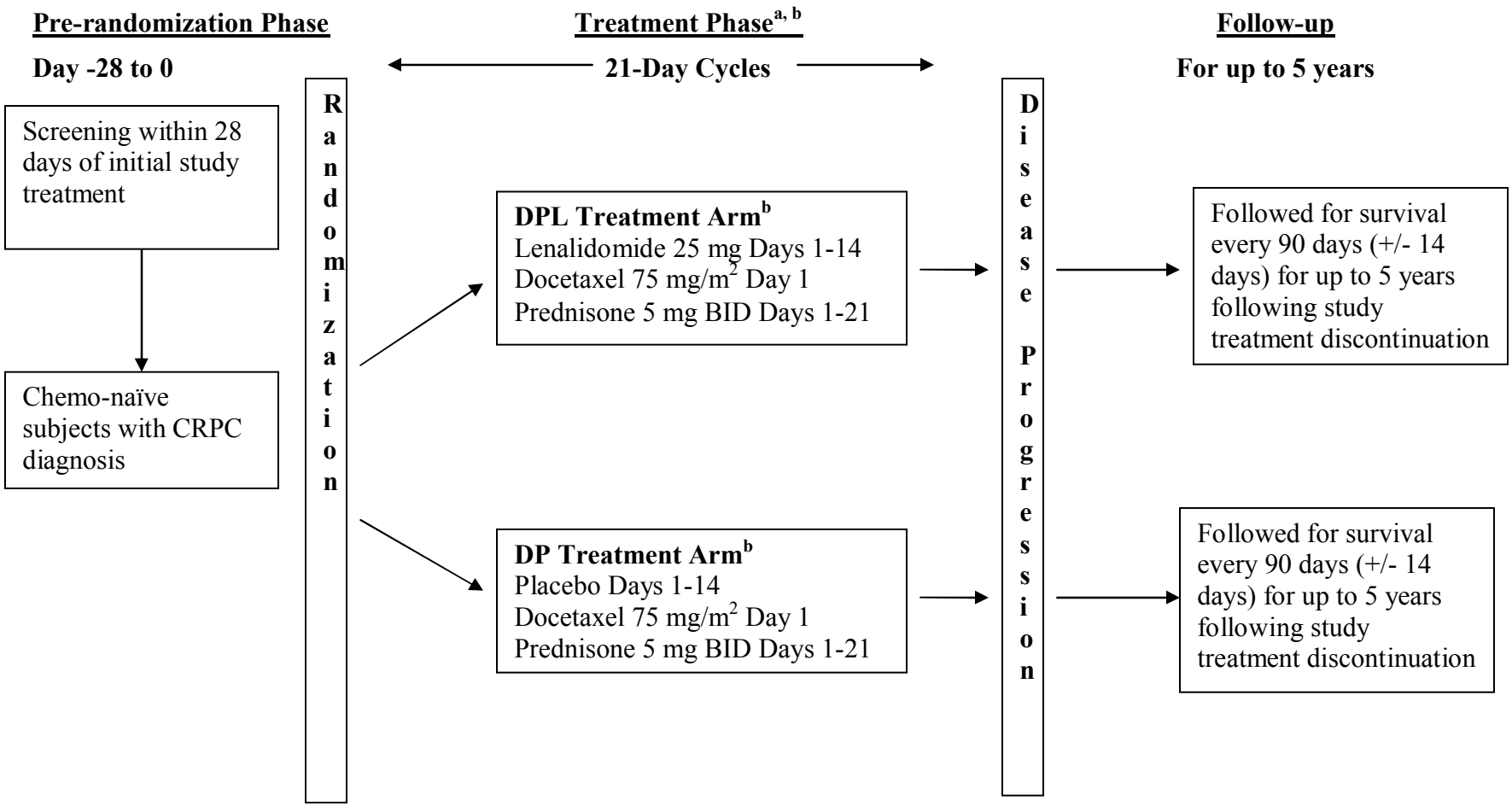
[o] Biomarker blood collection will only be performed at selected sites.

[p] Patient-Reported Outcome assessments will include HRQoL questionnaires (FACT-P, EQ-5D) and pain assessment (BPI-SF). Questionnaires will be completed during site visit prior to treatment, exams or other assessments.

[q] Dispense lenalidomide/placebo and/or perform drug accountability.

[r] Administer docetaxel Day 1 of each cycle. Dispense and/or account for prednisone.
[s] Survival data will be captured via phone contact every 90 days until death or 5 years post treatment phase discontinuation.
[t] Any post-study treatments for prostate cancer following treatment phase discontinuation will be captured and recorded every 90 days for up to five years.

Figure 1: Study Design



[a] Treatment (Cycle 1, Day 1) will begin within 3 days of randomization
[b] Treatment until disease progression or withdrawal from treatment
[c] Dose Reductions or discontinuation of either docetaxel or lenalidomide/placebo are permitted

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 3: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamic- pyruvic transaminase)
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AST (SGOT)	Aspartate amino transaminase (serum glutamic-oxaloacetic transaminase)
BID	Twice-a-day (Bis in Die)
BPI-SF	Brief Pain Inventory – Short Form
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRPC	Castrate Prostate Resistant Prostate Cancer
CT	Computerized axial tomography
CTCs	Circulating Tumor Cells
CTCAE	Common terminology criteria for adverse events
DCF	Data clarification form
DMC	Data Monitoring Committee
DP	Docetaxel, prednisone and placebo
DPL	Docetaxel, prednisone and lenalidomide
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMEA	European Agency for Evaluation of Medicinal Products
EQ-5D	EuroQoL (EQ-5D) Questionnaire

Table 3: Abbreviations and Specialist Terms (Continued)

Abbreviation or specialist term	Explanation
FACT-P	Functional Assessment of Cancer Therapy – Prostate Scale
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMiDs®	Immunomodulatory drugs
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent to treat
IV	Intravenously
LD	Longest Diameter
LDH	Lactate dehydrogenase
LHRH	Luteinizing hormone release hormone
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Drug Regulatory Activities
MM	Multiple Myeloma
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	Natural killer
OS	Overall survival
PD	Progressive disease
PK	Pharmacokinetics

Table 3: Abbreviations and Specialist Terms (Continued)

Abbreviation or specialist term	Explanation
PFS	Progression-free survival
PR	Partial response
PRO	Patient-Reported Outcomes
PSA	Prostate Specific Antigen
QD	Once a Day (Quaque Die)
RBC	Red blood cells
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
TNF	Tumor necrosis factor
TPP	Therapeutic Product Programme
TTP	Time to progression
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
WBC	White blood cells
WHO	World Health Organization

5. INTRODUCTION

5.1. Castrate-Resistant Prostate Cancer

Prostate cancer is the most common form of noncutaneous cancer diagnosed in American and European men, and was expected to account for approximately 25% of all newly diagnosed cases of cancer among men during 2008. Among American men prostate cancer is the second leading cause of death and the most common cancer-related cause of death in European men, The American Cancer Society 2009 estimates include 192,280 new cases of prostate cancer and 27,360 deaths in the US resulting from this disease. Annually more than 670,000 men are newly diagnosed worldwide including approximately 300,000 cases in Europe each year.

Although diet, race, family history, tobacco and alcohol use have all been studied for correlation with prostate cancer, age remains the strongest risk factor (National Comprehensive Cancer Network [NCCN] Guidelines, 2008). Approximately 60% of new prostate cancer cases arise in men over 60 years of age. The median age at diagnosis is 72 years for Caucasians and 70 years for African-Americans (Albertson, 2001). This represents a serious public health concern as the population ages.

Prostate cancer often follows an indolent course for the first 10 to 15 years after diagnosis (Cooperburg, 2005). Advances in early detection of prostate cancer have given rise to typically treating the disease while it is still localized. Early curative therapy includes radical prostatectomy or external beam radiation therapy. Untreated however, prostate cancer can metastasize to multiple locations including bone, soft tissues and the central nervous system resulting in a much poorer prognosis. This has led to the stratification of treatment based on the patient's life-expectancy, symptoms, and stage of disease. Unfortunately a small proportion of subjects will be diagnosed with advanced prostate cancer or go on to have advanced disease after local curative therapy. These subjects are often treated with hormonal therapy such as a Luteinizing Hormone Release Hormone (LHRH) which reduces the level of serum testosterone. Advanced prostate cancer carries a five-year overall survival of 23.6% once patients require hormonal therapy (Prostate Cancer Trialist's Collaborative Group, 2000). All patients with metastatic disease, however, eventually become refractory to hormonal therapy.

5.2. Background and Rationale

5.2.1. Non-clinical Rationale for Evaluating Lenalidomide in Prostate Cancer

Lenalidomide has been assessed for pharmacological activity in a variety of preclinical and in vitro models. Evidence that lenalidomide is both anti-angiogenic and a potent immunomodulator provides the non-clinical rationale for evaluating lenalidomide in prostate cancer. Studies in an animal model using basic fibroblast growth factor (bFGF) to induce micro-vascularization demonstrated the ability of lenalidomide to inhibit angiogenic activity (Dredge et al, 2005; Chavakis et al, 2001; Lu et al, 2008;). Lenalidomide has demonstrated enhancement of both innate and adaptive immune responses in multiple preclinical models. (Davies et al, 2001; Haslett et al, 2003; Schafer et al, 2003). In addition, lenalidomide has demonstrated immune modulation (activation) in patients with solid tumors (Bartlett et al, 2004).

Many studies have been performed to investigate the immunomodulatory activities of lenalidomide. In vitro studies have shown the ability of lenalidomide to enhance T cell activation and NK cell effector function against prostate cancer cells (Celgene study report PD466 and Zhu et al, 2008). Furthermore, lenalidomide synergistically enhanced the apoptosis-inducing effect of docetaxel on PC3 cells in this model (Zhu et al, 2008), suggesting a potential benefit for CRPC patients receiving docetaxel/prednisone therapy. Recent studies demonstrated that T-regulatory (Tregs) cells present within prostate tumor-derived infiltrating lymphocytes (TILs) are immune suppressive (Kiniwa et al, 2007). Lenalidomide has been shown to inhibit the expansion and immunosuppressive activity of Tregs in vitro (Galustian et al, 2008).

Lenalidomide has also demonstrated direct anti-tumor activity in a preclinical mouse xenograft model using the human prostate cell line DU145. Combination treatment of lenalidomide with docetaxel exhibited an additive effect resulting in a reduction in the tumor size found in three of ten mice. (Celgene Study IDD CTRC 082905).

Based on the in vitro activity and expected plasma levels at the suggested study treatment dose we expect lenalidomide to enhance T cell activation as well as reduce the immune suppressive activity of Tregs, potentially providing increased benefit for patients receiving lenalidomide in combination with docetaxel and prednisone therapy for castrate-resistant prostate cancer patients.

5.2.2. Systemic Treatment of Advanced Prostate Cancer

Systemic salvage therapy is warranted for patients with advanced prostate cancer who have become refractory to hormonal therapies. Currently only estramustine, mitoxantrone, zoledronic acid and docetaxel are approved as first-line therapy in CRPC patients. While all provide some level of symptomatic or palliative benefit, only docetaxel has been shown in clinical trials to provide a significant OS advantage in this patient population.

A docetaxel-based regimen is now the accepted standard of care for these patients (NCCN Guidelines 2008). In the Tax 327 first-line CRPC study, docetaxel and prednisone demonstrated a median survival advantage of 19.2 months vs. 16.3 months in the mitoxantrone and prednisone treatment arm (Berthold et al, 2008). Docetaxel and estramustine treatment resulted in an OS of 17.5 months in the SWOG 9916 study compared to 15.6 months in subjects treated with mitoxantrone and prednisone (Petrylak et al, 2004).

Despite the survival advantage conferred by docetaxel-based regimens, rapid disease progression and a significantly shortened lifespan exhibited by most patients with CRPC indicates the significant unmet medical need in this disease state.

5.2.2.1. Clinical Studies of Lenalidomide in Prostate Cancer

Multiple phase 1 and phase 2 clinical trials have been performed with lenalidomide, as both a single agent and combination therapies, in subjects with advanced prostate cancer. These studies have demonstrated lenalidomide to be both tolerable and active in this disease indication suggesting that lenalidomide should be further examined in larger trials of advanced prostate cancer patients.

Lenalidomide is well-tolerated in solid tumors as monotherapy and in combination treatment with other agents. Used during the first 21 days of a 28-day cycle, lenalidomide was found to be tolerated up to 35 mg in patients with various solid tumors (Tohnya et al, 2006). Another solid

tumor clinical study investigating lenalidomide in combination with docetaxel found that treatment on Day 1 with docetaxel and Days 1-14 with lenalidomide resulted in a maximum tolerated dose (MTD) of 75 mg/m^2 docetaxel and 25 mg lenalidomide (Sanborn et al, 2008).

Garcia et al, (2008) examined the combination therapy of lenalidomide and ketoconazole, with lenalidomide administered on Days 1-21 of a 28-day cycle. This treatment regimen was generally well-tolerated and showed significant activity, assessed by both reductions of PSA levels and RECIST criteria, in a majority of study subjects.

A dose escalation study investigating the combination treatment of lenalidomide with docetaxel was performed in subjects with metastatic CRPC. Subjects were administered docetaxel IV on day 1 and lenalidomide days 1-14 of a 21-day cycle. This combination treatment was well-tolerated in this population with the MTD found to be 75 mg/m^2 docetaxel and 25 mg lenalidomide. Activity of this combination therapy in 34 evaluable subjects has resulted in a PSA decline of over 50% in 15 subjects (44%) while a total of 20 subjects (59%) experienced PSA reductions of over 30%. Of 23 pts with measurable disease, 1 patient achieved a complete response, 5 patients achieved a partial response and 11 patients had stable disease (Hirsh et al, 2009).

The CC-5013-PC-002 clinical investigation proposes to evaluate lenalidomide in a Phase 3 study for the treatment of metastatic, CRPC in combination with docetaxel and prednisone in chemo-naïve patients. Pre-clinical studies suggest that lenalidomide will have clinical activity in treating prostate cancer patients. Data from Phase 1 and Phase 2 clinical studies provide evidence that lenalidomide has an activity and safety profile that warrants further study in the treatment of patients with advanced prostate cancer. Furthermore, the safety profile of lenalidomide in solid tumor studies is comparable to the acceptable safety data reported from more than 40,000 patients that have been treated with lenalidomide for various indications.

5.2.2.2. Rationale for Proposed Lenalidomide Treatment Dose

The dose and schedule proposed for this study is 25 mg lenalidomide administered once daily for days 1-14, docetaxel administered at 75 mg/m^2 on Day 1 and prednisone administered at 5 mg BID each day of a 21-day treatment cycle. Currently lenalidomide is approved as a treatment for myelodysplastic syndromes at a dose of 10 mg per day and for treatment of multiple myeloma (MM) at a dose of 25 mg once each day for Days 1-21 of a 28-day cycle. While myelosuppression is the major DLT in patients with hematologic disorders treated with lenalidomide, evidence exists that lenalidomide tolerability may be improved for patients without hematological malignancies or compromised bone marrow (Tohnya et al, 2006). Lenalidomide studies performed in prostate cancer patients have established that lenalidomide is well-tolerated at doses of at least 25 mg per day as both a single agent as well as in combination with docetaxel. The proposed dosing schedule of lenalidomide on days 1-14 of a 21-day cycle corresponds with the optimal 3 week treatment schedule of docetaxel and prednisone, the current first-line standard of care for CRPC patients. This proposed treatment dose and schedule is also directly supported by the multiple Phase 1, dose escalation studies described above (Hirsh et al, 2009; Sanborn et al, 2008).

6. STUDY OBJECTIVES

6.1. Primary Objective

- To compare the Overall Survival (OS) benefit of docetaxel and prednisone with and without lenalidomide as first-line combination therapy in chemo-naïve metastatic CRPC

6.2. Secondary Objectives

- Progression-Free Survival (PFS)
- Objective Response Rate
- Safety of lenalidomide in combination with docetaxel and prednisone

6.3. Exploratory Objectives

- PSA response, PSA progression, PSA doubling time and PSA velocity
- Biomarker analysis
- Pharmacokinetic analysis
- Change in Analgesic Use
- Patient-Reported Outcomes

7. STUDY ENDPOINTS

7.1. Primary

- Overall Survival (OS)

7.2. Secondary

- Progression-Free Survival (PFS) defined as time from randomization to disease progression or death due to any cause, whichever occurs first. Progression criteria will be met by analysis of target and non-target lesions as defined by RECIST Version 1.1 criteria according to the following definitions:

  Progression of Target Lesions

  - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters while on study or the appearance of one or more new lesions. The sum must also demonstrate an absolute increase of at least 5 mm.
  - Lymph nodes identified as target lesions (≥ 15 mm diameter in short axis) will be followed and reported by changes in diameter of short axis. (Note: the appearance of one or more new lesions is also considered progression)

  Progression of Non-target Lesions

  - Unequivocal progression of non-target lesions is defined as:
    - An increase in overall disease burden based on the change in non-measurable disease that is comparable in magnitude to the increase required to declare PD for measurable disease
    - The unequivocal appearance of one or more new non-target lesions
    - A change sufficient to warrant a change in therapy
    - Unequivocal progression is **NOT** attributable to differences in scanning technique, non-tumor findings, healing of bone lesions or flare of pre-existing lesions.

- Objective Response Rate is determined for subjects with measurable and/or non-measurable disease as defined by RECIST Version 1.1 criteria according to the following definitions:

  Response of Measurable Lesions

  - Complete Response (CR) is defined as:
    - Disappearance of all target lesions except lymph nodes
    - Lymph nodes must have a reduction in the short axis to < 10 mm
  - Partial Response (PR) is defined as:

- At least a 30% decrease in the sum of the diameters of target lesions taking as reference the baseline sum diameters

Response of Non-Measurable Lesions

- Complete Response (CR):
  - Complete resolution of all non-target lesions
  - All lymph nodes must be non-pathological (< 10 mm in the short axis)
- Non –CR/Non-PD:
  - Persistence of one or more non-target lesion(s)

- Safety (type, frequency, and severity of AEs and relationship of AEs to Investigational Medicinal Products)

7.3. Exploratory:

- PSA reductions ≥30%, ≥ 50%; PSA progression, PSA velocity and PSA doubling time will be analyzed to assess any significant correlation of PSA levels with relevant clinical benefits (e.g., OS, PFS, and Pain Endpoints)
- Exploratory analysis of biomarkers, including but not limited to CTCs will be performed to assess any significant correlation of CTC levels with relevant clinical benefits. Sample collection for this exploratory analysis may be limited to selected clinical centers
- Pharmacokinetics (PK) of lenalidomide when administered in combination with docetaxel and prednisone to be performed on randomized subjects in selected clinical centers as described in Section 14.1
- Change in Analgesic use will be evaluated over the course of the study for the interpretation of self-reported pain severity in light of concomitant analgesic use
- Patient-Reported Outcomes (PRO) will be evaluated using validated instruments for Pain and Health-Related Quality of Life Assessments
  - Pain Assessment
    - Brief Pain Inventory-Short Form (BPI-SF)
  - Health-Related Quality of Life and Prostate Cancer Symptoms
    - Functional Assessment of Cancer Therapy - Prostate Cancer (FACT-P)
    - EuroQol (EQ-5D) Questionnaire

8. OVERALL STUDY DESIGN

8.1. Discussion of Study Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study in chemo-naïve subjects with metastatic CRPC. Approximately 1015 subjects meeting inclusion criteria will be randomized 1:1 via IVRS into one of two treatment arms:

- *DP Treatment Arm:* docetaxel, prednisone and placebo
- *DPL Treatment Arm:* docetaxel, prednisone and lenalidomide

The 21-day treatment cycles will consist of docetaxel administered as an IV infusion for approximately 60 minutes (as per package insert) at a dose of 75 mg/m^2 to all subjects on Day 1 of each cycle and prednisone at a dose of 5 mg oral BID administration as per the current approved standard of care for this disease indication. Pre-treatment for docetaxel will be administered according to institutional standards.

Lenalidomide will be administered at 25 mg orally, QD for Days 1–14 of each cycle. An identical matching placebo will be administered Days 1-14 in the control arm. Neither lenalidomide nor placebo will be taken on days 15-21 in either treatment cycle. Rationale for this treatment dose selection is found in Section 5.2.2.2.

8.2. Study Population

The study population will consist of subjects with metastatic CRPC experiencing documented progressive disease as determined by either rising PSA levels or radiological progression following treatment with one or more hormonal therapies for advanced prostate cancer. The subjects will be randomized 1:1 into the DPL or DP treatment arm. Stratification of subjects will be performed based on ECOG Performance Status (≤1 vs. 2), geographical region (US and Canada vs. EU and Australia vs. Rest of World) and type of disease progression following hormonal treatment (rising PSA only vs. tumor progression).

8.3. Duration of Treatment

Subjects will be screened within 28 days of study treatment initiation. The initial study treatment (Cycle 1, Day 1) will begin within 3 days of randomization. Study treatment will continue until subjects experience disease progression as per RECIST Version 1.1, except bone lesions, or discontinue study treatment for any other reason. Discontinuation for bone progression will require ≥ 2 new lesions with confirmation during the next scheduled tumor assessment (9 weeks after initial observation of ≥ 2 new lesions). Subjects experiencing treatment-related toxicity will be allowed to dose reduce, or discontinue either docetaxel or lenalidomide/placebo, while remaining eligible to continue study treatment with the remaining drug. Complete withdrawal of both drugs will result in discontinuation of study treatment. All subjects will be contacted 28 days after last dose for AEs and concomitant medications and then followed for survival and any post-study prostate cancer related treatments every 90 days until death or up to 5 years following discontinuation.

8.4. Dose and Dose Interval

The study treatment cycle will be 21 days. Subjects meeting the inclusion criteria will be randomized 1:1 to receive 25 mg lenalidomide orally, QD on days 1-14 (DPL arm) or an identical matching placebo orally QD for days 1-14 (DP arm). All subjects will receive 75 mg/m^2 docetaxel IV on Day 1 of each cycle and 5 mg of prednisone orally BID each day of the study treatment cycle. Pre-medication for docetaxel treatment should be administered according to institutional standards.

8.5. Blinding

This study will assess the efficacy and safety of lenalidomide in combination with docetaxel and prednisone compared to docetaxel and prednisone, the current standard of care for this indication. This study will incorporate a placebo-controlled double-blinded study design to alleviate potential treatment bias.

8.6. Concomitant Medication

Anti-thrombotic medications (such as aspirin, low molecular weight heparin, or warfarin) will be allowed as prophylactic treatment in subjects with a high risk of developing deep vein thrombosis (DVT) or pulmonary embolism (PE). These medications will also be allowed for therapeutic use for any subject developing these medical problems.

Treatment with growth factors according to ASCO guidelines (such as Granulocyte-Colony Stimulating Factor [G-CSF] and Granulocyte Macrophage-Colony Stimulating Factor [GM-CSF]) are allowed during the study treatment for subjects experiencing myelosuppression. Prophylactic use of growth factors is not allowed in this study.

8.7. Efficacy

This study will assess OS as a primary efficacy endpoint. Subjects will be followed for up to five years following study discontinuation for survival and to document further treatments for prostate cancer.

Computer Tomography (CT), MRI, Chest X-Rays and/or bone scans will be performed to follow extent of disease response and progression as assessed by RECIST (Version 1.1) criteria and described in (Section 12.2.3).

8.8. Safety

Safety will be assessed according to NCI-CTC AE Version 4.0 and measured using:

- Adverse events (type, frequency, severity, and relationship of adverse events to study drug)
- Physical examination including but not limited to:
  - Heart, lungs abdominal, extremities and a clinical neurological examination will be performed if clinically indicated.
- Vital signs, weight, and height (only during screening)

- Hematology laboratory parameters
- Serum chemistry laboratory parameters
- Urine dipstick
- Electrocardiogram (ECG)
- Concomitant medications / procedures

8.9. Other Outcomes

8.9.1. Exploratory Outcomes

Exploratory outcomes will include:

- PSA reductions ≥30%, ≥50%; PSA progression; PSA velocity; and PSA doubling time will be analyzed to assess any significant correlation of PSA levels with relevant clinical benefits (e.g., OS, PFS, and Pain Endpoints)
- Exploratory analysis of biomarkers, including but not limited to CTCs will be performed to assess any significant correlation of CTC levels with relevant clinical benefits. Sample collection for this exploratory analysis may be limited to selected clinical centers
- Pharmacokinetic assessments will be performed in subjects who provide additional consent at select centers. Both intensive and sparse sampling pharmacokinetics (PK) analysis of lenalidomide when administered in combination with docetaxel and prednisone will be performed. Subjects can decide to participate in either the intensive or sparse PK blood sampling but not both.
- Change in Analgesic Use will be evaluated for changes in analgesic use over the course of the study and to be able to interpret self-reported pain severity in light of concomitant analgesic use.
- Patient-Reported Outcomes (PRO) will be evaluated using the validated instruments listed below for Pain and Health-Related Quality of Life Assessments
  - Pain Assessment
    - Brief Pain Inventory-Short Form (BPI-SF)
  - Health-Related Quality of Life and Prostate Cancer Symptoms
    - Functional Assessment of Cancer Therapy - Prostate Cancer (FACT-P)
    - EuroQol (EQ-5D) Questionnaire

8.10. Data Monitoring Committee

An Independent DMC will be convened which will be composed of medical oncologists with experience in treating subjects with prostate cancer and a statistician, all of whom are not otherwise involved in the study as investigators or reviewers of efficacy data. An independent third party will prepare the reports of aggregate data summaries and individual subject data

listings, as appropriate, to provide the members of the DMC for each scheduled meeting. Operational details for the DMC and the algorithm and its validation by an expert panel will be detailed in the DMC charter.

The independent DMC activities are planned as follows:

8.10.1. Safety Assessments:

- An initial safety assessment to ensure the safety and tolerability of the study regimen is planned after 100 randomized subjects have either completed 2 cycles of the treatment or withdrawn prematurely from study.
  - An additional site visit during Cycle 1 Day 14 for safety assessments (AEs, Physical Exam, Vital signs, Hematology Labs, and Serum Chemistry Labs) will be performed on the first 100 subjects and all subjects participating in the sparse PK sub-study. This information will be included in the initial DMC safety assessment. Subsequent subjects will not be evaluated on Cycle 1 Day 14 unless this site visit is determined necessary by the DMC due to safety concerns.
- Ongoing safety assessments will be performed every 6 months after the first review at 100 subjects. Additional assessments will be performed as appropriate.

8.10.2. Efficacy Assessments:

- A planned efficacy interim analysis will be performed when 468 events are observed and enrollment has been completed.

9. STUDY POPULATION

9.1. Subject Inclusion Criteria

Subjects Must Meet All of the Following Inclusion Criteria to Be Eligible for Enrollment Into the Study:

1. Understand and voluntarily sign an Informed Consent Form (ICF)
2. Males ≥ 18 years of age at the time of consent
3. Able to adhere to the study visit schedule and requirements of the protocol
4. ECOG performance status of ≤ 2
5. Life expectancy of ≥ 12 weeks
6. Willingness to participate in HRQoL and pain assessments and have ability to complete PRO and pain assessments without assistance or with minimal assistance from trained site personnel and/or caregiver
7. Effective castration (serum testosterone levels < 50 ng/dL) due to orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist
   - Primary testicular androgen suppression (e.g., LHRH agonists) should be continued during study treatment for subjects who have not had a bilateral orchiectomy.
8. Histologically confirmed adenocarcinoma of the prostate and:
   - Prostate cancer that is unresponsive or refractory to hormonal therapy AND
   - Metastatic disease confirmed by bone scan, CT scan, MRI, or X-Ray
9. Documented disease progression while receiving or following hormonal therapy for treatment of advanced prostate cancer despite castrate levels of serum testosterone due to orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist as determined by **at least one** of the following criteria:
   - Serum PSA level ≥ 2ng/mL that has increased from a reference value on at least two consecutive PSA measurements obtained at least 1 week apart prior to randomization
   - Progression of measurable disease
     - Measurable disease is defined as at least one measurable lesion ≥ 10 mm long diameter by CT or MRI (or 20 mm by Chest X-ray) and/or lymph nodes ≥ 15 mm short axis
     - Progression of measurable disease is defined as an increase of > 20% in the sum of the diameters of target lesions from the time of maximal regression **OR** the appearance of ≥ 1 new lesion.
   - Unequivocal progression of non-measurable disease
     - Non-measurable disease is defined as all lesions < 10mm in the longest diameter or pathological lymph nodes ≥10 mm to < 15 mm short axis

- Unequivocal progression of existing lesions is defined as an increase in overall disease burden based on the change in non-measurable disease that is comparable in magnitude to the increase that would be required to declare disease progression for measurable disease
- 2 or more new bone lesions as detected by bone scan

10. All subjects:[c]

- Must be counseled about pregnancy precautions and risks of fetal exposure. See Appendices 21.6.2 (EX-EU version) or 21.7.2 (EU version) Lenalidomide Risks of Fetal Exposure and Acceptable Birth Control Methods, and Appendices 21.6.3 (Ex-EU version) or 21.7.3 (EU version) Lenalidomide Education and Counseling Guidance Document
- Must agree to use a condom (specified in the appropriate country specific appendix) during sexual contact with a female of childbearing potential (FCBP)[d], even if they have had a vasectomy, while participating in this study, during dose interruptions, and for a period of days (specified in the appropriate country specific appendix) following the last dose of study drug
- Must agree to refrain from donating semen or sperm while participating in this study and for a period of days (specified in the appropriate country specific appendix) following the last dose of study drug.
- Must agree to refrain from donating blood or plasma while participating in this study and for a period of days (specified in the appropriate country specific appendix) following the last dose of study drug
- Must agree not to share study drug with anyone during participation in the study

9.2. Subject Exclusion Criteria

Presence of Any of the Following Will Exclude a Subject from Enrollment Into the Study:

1. A history of clinically significant (as determined by the investigator) medical, surgical, or psychiatric disease that would place the subject at an unacceptable risk for study entry
2. Prior therapy with thalidomide, lenalidomide (CC-5013) or pomalidomide (CC-4047),
3. Prior chemotherapy for prostate cancer
   - Treatment with estramustine will be allowed if last treatment is more than 28 days prior to randomization, and subject has recovered from side effects

[c] Refer to the "Lenalidomide Pregnancy Risk Minimization Program in Celgene Clinical Trials" in Appendix 21.6 (Ex-EU) or Appendix 21.7 (EU) for country specific guidelines. The Ex-EU version is for clinical sites in the US and all countries utilizing the US program guidelines. The EU version is for clinical sites in all EU countries and any country following the EU program guidelines

[d] A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

- Adjuvant and/or neoadjuvant treatment will be allowed if completed > 3 years prior to randomization and provided the regimen did not contain docetaxel

4. Use of any other experimental drug or therapy within 28 days prior to randomization.
5. Prior whole pelvic radiation therapy or irradiation to ≥ 30% of Bone Marrow (see Appendix 21.3) and/or per radiation specialist
6. Any other radiation therapy within 28 days prior to randomization
   - Subjects receiving prior radiation must have recovered from acute toxicity or any side effects due to radiation treatments
7. Prior use of Strontium-89 at any time or Samarium-153 within 56 days prior to randomization.
8. Surgery within 28 days prior to randomization (minimally invasive procedures for the purpose of diagnosis or staging of the disease are permitted).
9. Concurrent corticosteroid or hormonal therapy:
   - Hormonal therapy, (e.g., ketoconazole, aminoglutethimide, corticosteroids, flutamide, or megestrol) must be discontinued at least 4 weeks prior to randomization
   - Prior therapy with bicalutimide and nilutamide must be discontinued at least 6 weeks prior to randomization
   - Subjects without prior orchiectomy should continue treatment with LHRH agonists
   - Bisphosphonates may be continued if at a stable dose for 28 days prior to enrollment
   - Concurrent therapy with steroids or hormones for adrenal insufficiency or nondisease-related conditions (e.g., insulin for diabetes) are allowed
10. Any of the following laboratory values:
    - Hemoglobin < 9 g/dL (blood products and growth factors are permitted.)
    - Absolute neutrophil count (ANC) < 1.5 x 10^9 cells/L
    - Platelet count < 100 x 10^9 cells/L
    - Creatinine > 1.5 x ULN
    - Total bilirubin > 1.0 x the ULN
    - Serum aspartate amino transaminase (AST)/SGOT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN
11. Must not have had significant active cardiac disease within the previous 6 months including:
    - History of hypertension allowed provided blood pressure (BP) is controlled (i.e., BP < 160/90 mm Hg) by anti-hypertensive therapy
    - New York Heart Association class II-IV congestive heart failure
    - Unstable angina

- Angina requiring surgical or medical intervention
- Myocardial infarction

12. Clinically significant peripheral arterial occlusive disease (i.e., claudication on less than 1 block)
13. Thrombotic or thromboembolic events within the past 6 months, including any of the following:
    - Deep Vein Thrombosis or Pulmonary Embolism within the preceding 6 months
    - Transient ischemic attack
    - Cerebrovascular accident
    - Any other arterial thrombotic event
14. Current or history of peripheral neuropathy of ≥ grade 2
15. History of severe hypersensitivity reaction to drugs formulated with polysorbate 80
16. Paraplegia
17. History of symptomatic central nervous system (CNS) or brain metastases
    - Subjects who have remained asymptomatic for 90 days and demonstrate no active CNS involvement as shown by CT, MRI, or lumbar puncture are not excluded
    - If required, CT, MRI, or lumbar puncture should be performed during the screening process
18. History of malignancies other than prostate cancer within the past 5 years, with the exception of treated basal cell/squamous cell carcinoma of the skin
19. Concurrent use of alternative cancer therapies during study treatment. Subjects taking alternative therapies for cancer must stop taking these therapies prior to randomization. Alternative therapies are not allowed during the treatment or follow-up portions of the study. This includes alternative therapies such as, but not limited to:
    - Saw Palmetto
    - DHEA
    - Lycopene
    - PC-SPES (all types)
    - Vitamins and/or dietary supplements used at therapeutic doses for treatment of prostate cancer including:
        - Vitamin D
        - Selenium
    - Citrus pectin

9.3. Additional Criteria:

Before Starting Study Drug:

- Subjects should understand the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential.
- Subjects should understand the need for the use of a condom if engaged in sexual activity with a woman of childbearing potential.
- Subjects should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

During Study Participation and for a Period of Days (as Specified in the Appropriate Appendix) Following Discontinuation from Study:

- No more than a 28-day supply of study drug will be dispensed at a time
- Subjects should be monitored during the course of the study and after the end of study therapy to:
  - Ensure they continue to use a condom during sexual contact with a FCBP
  - If a female partner of a male subject becomes pregnant she should be referred to the appropriate physician

10. DESCRIPTION OF TREATMENT

10.1. Description of Study Drug

Celgene Corporation will supply Lenalidomide (CC-5013) 10 mg, 15 mg, 20 mg, 25 mg and their respective matching placebo capsules for oral administration. Study drug will be packaged in bottles containing enough capsules for 14 days of dosing. All subjects will be required to take a single capsule, lenalidomide or placebo, each day for Days 1-14 of each cycle.

Celgene Corporation will also supply commercial docetaxel and prednisone labeled as investigational medicinal product (IMP) for all non-US investigational study sites.

During each 21-day treatment period study drug will be administered as follows:

DP treatment arm: Identical matching oral placebo QD for Days 1-14; 75 mg/m^2 docetaxel IV on Day 1; 5 mg prednisone orally BID each day of the treatment cycle

DPL treatment arm: 25 mg lenalidomide orally QD on Days 1-14; 75 mg/m^2 docetaxel IV on Day 1; 5 mg prednisone orally BID each day of the treatment cycle

Note: Subjects will receive pre-treatment for docetaxel according to institutional standards.

10.2. Treatment Assignments

Subjects meeting inclusion criteria will be randomized 1:1 via IVRS into 1 of 2 treatment arms to receive either 25 mg/day lenalidomide for Days 1-14 (DPL) or an identical matching placebo for Days 1-14 (DP) of a 21-day cycle. All subjects will receive docetaxel via IV infusion at 75 mg/m^2 on Day 1 of each cycle and 5 mg prednisone orally BID each day of treatment cycle. Lenalidomide or placebo should be taken each morning or at approximately the same time each day. Dose adjustments for toxicities will be prescribed as defined in Section 10.2.1.

Stratification of subjects will be performed based on ECOG Performance Status (≤1 or 2), geographic region (US and Canada or EU and Australia or Rest of World) and type of disease progression following hormonal therapy (rising PSA only or tumor progression).

Treatment with docetaxel and lenalidomide or placebo will continue in 21-day cycles until disease progression as per RECIST Version 1.1, except bone lesions, unacceptable toxicity, or treatment discontinuation for any other reason. Discontinuation for bone progression will require ≥ 2 new lesions with confirmation during the next scheduled tumor assessment (9 weeks after initial observation of ≥ 2 new lesions). Subjects will be allowed to dose reduce or discontinue either docetaxel or lenalidomide while remaining eligible to continue study treatment with the remaining drug. Discontinuation of both drugs will result in treatment phase discontinuation at which time subjects will enter into the follow-up phase of the study.

NOTE: For purposes of this study PSA progression is not considered disease progression and does not mandate discontinuation from the Treatment Phase of the study.

10.2.1. Dose Modification and Interruption

10.2.1.1. Lenalidomide Dosing

An oral, daily 25 mg dose of lenalidomide will be taken Days 1-14 of each 21-day cycle each morning or at approximately the same time each day. This dose will be maintained for the duration of the study unless dose modification is necessary due to toxicity. The allowable dose reduction schedule for lenalidomide is defined in Table 4.

10.2.1.2. Missed Doses

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If the dose is missed for the entire day, the subject should not take an extra dose the next day or take an unscheduled dose.

Table 4: Lenalidomide Dose Reduction Steps

Starting Dose	**25 mg daily (Day 1-14 of 21-day cycles)**
Dose Level- 1	20 mg daily every 21 days
Dose Level- 2	15 mg daily every 21 days
Dose Level -3	10 mg daily every 21 days

[a] Subjects unable to tolerate dose level -3 will be discontinued

10.2.1.2.1. Lenalidomide Dose Modifications and Interruptions

Subjects will be evaluated for AEs at each visit, using the NCI CTCAE Version 4.0. Lenalidomide can be reduced for toxicity to a minimum dose of 10 mg/day as described in Table 4. If a 10 mg/day dose of lenalidomide is not tolerated, lenalidomide will be discontinued. Only a single dose reduction will be allowed during a 21-day cycle. No re-escalation of lenalidomide will be allowed.

Guidelines for dose modifications of lenalidomide due to toxicity are described in Table 5. Suggested dose interruptions and modifications guidelines for both lenalidomide and docetaxel based on overlapping hematological toxicities are provided in Table 9.

Table 5: Lenalidomide Dose Modification Criteria

Toxicity	Grade	Dose Level Change
Rash	2 / 3	Hold lenalidomide until resolution to ≤ Grade 1 Resume at one dose-level reduction. Further dose reductions are permitted to a minimum of 10 mg. If rash is desquamating, discontinue lenalidomide.
	4	Discontinue lenalidomide.
Sinus bradycardia, atrial fibrillation or other cardiac arrhythmias	2	Hold lenalidomide until resolution to ≤ Grade 1 Resume at one dose-level reduction. Additional dose reductions are permitted to a minimum of 10 mg.
	3 / 4	Discontinue lenalidomide.
Venous thrombosis or embolism	3	Treat according to local practice guidelines. Assess risk/benefit and continue lenalidomide if clinically indicated.
	4	If subject is on therapeutic dose of anticoagulation, discontinue lenalidomide. If subject is NOT on therapeutic dose of anticoagulation, treat according to local practice guidelines, and assess risk/benefit of continuing lenalidomide treatment. If clinically indicated, hold lenalidomide until resolution to ≤ Grade 2 Resume at same dose-level.
Allergic reaction or Hypersensitivity	2 / 3	Hold lenalidomide until resolution to ≤ Grade 1\ Resume at one dose-level reduction. Additional dose reductions are permitted to a minimum of 5 mg.
Other non-hematological toxicity assessed as lenalidomide-related	3 / 4	Hold lenalidomide until resolution to ≤ Grade 2 Resume at one dose-level reduction. Additional dose reductions are permitted to a minimum of 5 mg.

10.2.1.3. Docetaxel Dosing

Docetaxel will be administered IV at a dose of 75 mg/m^2 on the first day of each 21-day cycle. This dose will be maintained for the duration of the study unless dose modification is necessary due to toxicity. The allowable dose reduction schedule for docetaxel is defined in Table 6. A 5 mg oral dose of prednisone will be administered twice daily while the subject is receiving docetaxel treatment, however prednisone administration will be held during docetaxel interruptions.

Table 6: Docetaxel Dose Reduction Steps

Dose Level	Docetaxel Dose (mg/m^2)
Starting Level (0)	75
Level – 1	60

[a] Subjects unable to tolerate dose level -1 (60 mg/m^2) will be discontinued

10.2.1.3.1. Docetaxel Dose Modifications and Interruptions

Docetaxel should only be administered according to the guidelines in Table 7. Initial administration of docetaxel (Cycle 1, Day 1) will require ANC ≥ 1500 celll/mm^3, according to requirements for study entry.

Subjects who experience febrile neutropenia, neutrophils < 500 cells/mm^3, or severe cumulative cutaneous reactions should follow dose modification guidelines defined in Table 9. Other AE, such as moderate neurosensory signs and/or symptoms during the study should have the dosage of docetaxel reduced from 75 to 60 mg/m^2 as per package insert. If the subject continues to experience an AE at 60 mg/m^2 docetaxel treatment should be discontinued according to Table 9 or the package insert. No re-escalation of docetaxel is allowed following dose reduction.

Table 7: Hematological Criteria for Docetaxel Administration on Day 1 of Cycle

Values on scheduled day of treatment	Next treatment	Dose adjustments
ANC < 1.0 x 10^9/L (<Grade 2 Neutropenia)[1]	Delay maximum 2 wks until recovery (i.e. ANC ≥ 1.0 x 10^9/L)	Adjustment according to Overlapping Toxicities (see Table 9)
Platelets < 100 x 10^9/L (≤ Grade 1 Thrombocytopenia)	Delay maximum 2 wks until recovery (i.e. Platelets ≥ 100 x 10^9/L)	Adjustment according to Overlapping Toxicities (see Table 9)

[1]First administration of docetaxel (Cycle 1, Day 1) will require ANC ≥ 1500 celll/mm^3, according to requirements for study entry

Guidelines for management of acute hypersensitivity reactions to docetaxel are provided in Table 8. For further information regarding docetaxel-related toxicities and treatment guidelines refer to the package insert.

Table 8: Suggested Management of Acute Hypersensitivity

Severity of Symptoms	Treatment Guidelines
Mild: Localized cutaneous reactions such as mild pruritus, flushing, rash	Consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor subject, then complete docetaxel infusion at the initial planned rate
Moderate: Any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, and hypotension with systolic BP >80 mmHg	Interrupt docetaxel infusion Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor subject until resolution of symptoms Resume docetaxel infusion after recovery of symptoms; depending on the physician's assessment of the subject, docetaxel infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate, (e.g., infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, then finally, resume a 1-hr infusion rate) Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the **next cycle** of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour infusion, (e.g., infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, and finally, administer at a 1-hr infusion rate)
Severe: Any reaction such as bronchospasm, generalized urticaria, systolic BP ≤80 mmHg, angioedema	Immediately discontinue docetaxel infusion Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor subject until resolution of symptoms Follow the same treatment guidelines outlined under moderate symptoms (i.e., the third and fourth bullets)
Anaphylaxis: NCI CTCAE grade 4 reaction	No further administration of docetaxel

10.2.1.4. Dose Modifications and Interruptions for Overlapping Toxicities

Table 9 provides guidelines for dose interruptions and modifications for overlapping toxicities of both docetaxel and lenalidomide. Refer to Section 10.2.1.5 for rules governing study treatment interruptions and discontinuation.

Table 9: Suggested Dose Modifications for Overlapping Docetaxel and Lenalidomide Hematological Toxicities

Toxicity	Occurrence	Dose Reduction	
		Docetaxel	**Lenalidomide**
Grade 4 Neutropenia for >7 days **Febrile neutropenia**[1] **Grade 3-4 Neutropenic infection**[2]	1st occurrence	Hold docetaxel for a maximum of 2 weeks Resume treatment with no dose reduction[3]	Hold lenalidomide until resolution to grade < 2 Resume with no dose reduction[3]
	2nd occurrence	Hold docetaxel for a maximum of 2 weeks Resume treatment with one level dose reduction at 60 mg/m^2	Hold lenalidomide until resolution to grade < 2 Resume with no dose reduction
	3rd occurrence and subsequent occurrences	Discontinue docetaxel	Hold lenalidomide CBC weekly until resolution to < Grade 2 Resume at one dose level reduction. Additional dose reductions are permitted to a minimum of 10 mg
Grade 3 Neutropenia or Thrombocytopenia **Grade 4 Neutropenia for ≤ 7 days**	1st occurrence	Hold docetaxel Treat symptomatically Consider dose reduction	Hold lenalidomide Treat symptomatically Resume with no dose reduction
	2nd occurrence	Hold docetaxel Treat symptomatically Consider dose reduction	Hold lenalidomide Treat symptomatically Resume with no dose reduction
	3rd occurrence	Hold docetaxel Treat symptomatically Resume treatment with one level dose reduction at 60 mg/m^2	Hold lenalidomide Treat symptomatically Consider dose reduction
	Further occurrences	Discontinue docetaxel	Hold lenalidomide Resume at one dose level reduction. Additional dose reductions are permitted to a minimum of 10 mg

Table 9: Suggested Dose Modifications for Overlapping Docetaxel and Lenalidomide Hematological Toxicities (Continued)

Toxicity	Occurrence	Dose Reduction	
		Docetaxel	**Lenalidomide**
Grade 4 Thrombocytopenia	1st occurrence	Hold docetaxel CBC weekly until resolution to < Grade 2 Resume treatment with one level dose reduction at 60 mg/m^2	Hold lenalidomide CBC weekly until resolution to < Grade 2 Resume with no dose reduction
	2nd occurrence	Discontinue docetaxel	Hold lenalidomide, CBC weekly until resolution to < Grade 2 Resume at one dose level reduction. Additional dose reductions are permitted to a minimum of 10 mg
	3rd occurrence and subsequent occurrences	NA	Hold lenalidomide CBC weekly until resolution to < Grade 2 Resume at one dose level reduction. Additional dose reductions are permitted to a minimum of 10 mg

[1] Fever ≥ 38.5°C of unknown origin without clinically or microbiologically documented infection with concomitant ANC < 1.0 x 10^9/L
[2] Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L)
[3] GCS-F recommended, as per ASCO guidelines, during the next cycle with no dose reduction

10.2.1.5. Study Treatment Interruptions and Discontinuation

Treatment will be administered on a 21-day schedule, with a permitted plus or minus 3-day window for each treatment. In the event that treatment with the investigational products warrant an interruption due to toxicity, both investigational products will be held and the subject assessed weekly to determine if the AE has adequately resolved to allow further treatment. In case of an interrupted treatment due to toxicity the ensuing rules will be followed:

- Study treatment delays of ≤ 14 days in the case of unresolved toxicities are acceptable
- New cycles cannot begin until study treatment-related toxicities have been adequately resolved according to the dose modification guidelines for lenalidomide (Section 10.2.1.1 and Table 5), docetaxel administration and modification guidelines (Section 10.2.1.3 and Table 7), and the guidelines for dose modification for overlapping docetaxel and lenalidomide hematological toxicities as defined in Table 9
- Dose adjustments for continued treatment with the investigational products after a dose interruption will follow the dose modification criteria described for lenalidomide

(Table 5), docetaxel (Section 10.2.1.3.1 and the docetaxel Package Insert), and overlapping toxicities Table 9

  - If a drug is interrupted during a treatment cycle for toxicity, it cannot be restarted until start of next scheduled cycle

- Once toxicities are adequately resolved the investigator should resume treatment with either or both of the investigational products according to the appropriate dose modification guidelines (Table 5, Table 7, and/or Table 9)
  - If both lenalidomide and docetaxel are re-started, both should be restarted on same day
  - If treatment with only one drug is started the other must be held until Day 1 of next cycle
- If study drug treatment is interrupted for ≥ 14 days and cannot begin on Day 1 of next cycle, this will result in discontinuation of that investigational product
  - Subject cannot miss 2 consecutive doses of docetaxel
  - Subject cannot miss 2 consecutive cycles of lenalidomide
- If either investigational product is held due to drug-related toxicity during any part of two consecutive cycles, that investigational product will be discontinued

Following discontinuation of docetaxel and prednisone treatment the subject will remain eligible to continue study treatment with lenalidomide, until disease progression, unacceptable toxicities or withdrawal of consent. If lenalidomide is discontinued for any reason during the study, the subject remains eligible to continue study treatment with docetaxel and prednisone, until disease progression, unacceptable toxicities or withdrawal of consent. Discontinuation of both lenalidomide and docetaxel and prednisone will result in discontinuation of study treatment and subject will enter the Follow-up phase of the study.

10.3. Blinding

This is a double-blind, placebo-controlled study. Neither the study subject, investigator, nor investigative personnel will know the study treatment of individual subjects. Blinding and the use of an identical matching placebo provides a means to control potential treatment bias in this study. Subjects randomized to the lenalidomide (DPL) or the placebo (DP) arm will be required to take a single capsule once orally on Days 1-14 of each cycle.

10.4. Emergency Unblinding

The blind must not be broken during the course of the study. Exceptions include the necessity for regulatory reporting of suspected unexpected serious adverse reactions (SUSARs), or in the opinion of the investigator treatment assignment is absolutely needed to safely treat the subject.

Emergency unblinding will be via Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS). A 24-hour emergency code break service will ensure that treatment details can be accessed promptly via telephone connection from any site.

Every effort should be made to contact the Medical Monitor prior to breaking the blind. The reason for breaking the blind must be documented in the subject's CRF and in the subject's medical records. Documentation of contact or attempted contact with the Medical Monitor prior to breaking the blind must also be documented in the subject's medical records.

10.5. Prior/Concomitant Medications

All medications (prescription and non-prescription), treatments and therapies taken from signing of the ICF through the follow-up visit, must be recorded in the Case Report Form (CRF).

10.5.1. Permitted Concomitant Therapy

- Subjects should continue to receive therapy with LHRH agonists if no prior orchiectomy
- Subject may continue to receive therapy with bisphosphonates if initiated at least 28 days prior to randomization
- Hematopoietic growth factors (such as G-CSF and GM-CSF) are permitted as clinically indicated according to ASCO guidelines. Hematopoietic growth factors are NOT permitted for prophylactic use
- Subjects may receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate
- Narcotic and non-narcotic analgesics for Prostate Cancer disease-related pain
- Pre-medication for docetaxel according to institutional standards
- Subjects with a high risk of thromboembolism may use prophylactic anticoagulant therapy (e.g., aspirin, low-molecular weight heparin, warfarin) in accordance with product labeling. The investigator will assess the risk/benefit to the subject regarding the use of prophylactic anticoagulant therapy

10.5.2. Prohibited Concomitant Therapy

- Anti-cancer therapy (except for continued use of LHRH agonists and bisphosphonates)
- Treatment with hormones or other chemotherapeutic agents may not be administered except for:
  - steroids administered for non-prostate related conditions (i.e., adrenal insufficiency, asthma)
  - hormones administered for non-prostate related conditions (e.g., insulin for diabetes)
- Radiation therapy
- Use of any other experimental drug or therapy

10.6. Treatment Compliance

Study personnel will be instructed to complete pill counts of unused medication at Day 1 of each cycle and at study discontinuation. Compliance is defined as taking between 70% and 120% of study medication during any cycle. Lack of compliance may lead to discontinuation from the study at the discretion of the investigator.

10.7. Discontinuation from Treatment

The following events are considered sufficient reasons for discontinuing a subject from study drug:

- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- Disease progression, except progression attributable to a single new bone lesion
- Two or more new bone lesions with confirmation during the next scheduled tumor assessment (9 weeks after initial observation of new lesions).
- Subject withdraws consent.
- Subject lost to follow-up
- Death
- Protocol violation

The reason for discontinuation should be recorded in the CRF and in the subject's medical records. Celgene is to be notified of all discontinuations from study drug.

11. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

11.1. Supplier(s)

11.1.1. Lenalidomide

Celgene Corporation will supply lenalidomide (CC-5013) and identical matching placebo.

11.1.2. Docetaxel and Prednisone

Celgene Corporation will supply commercial docetaxel and prednisone labeled as IMP for all non-US investigational study sites.

11.2. Dosage Form

Celgene Corporation will supply lenalidomide 10 mg, 15 mg, 20 mg, 25 mg and their respective matching placebo capsules in bottles containing enough study drug for 14 days of dosing via oral administration

Docetaxel is commercially available and will be administered IV at 75 mg/m^2 or 60 mg/m^2. Prednisone 5 mg is commercially available and will be taken orally. Pre-medication for docetaxel will be administered as per institutional guidelines.

11.3. Dosage Regimen

The length of each study treatment cycle will be 21 days. Subjects meeting the inclusion criteria will be randomized 1:1 via IVRS to receive lenalidomide treatment (DPL arm) or identical placebo (DP arm). Treatment will begin within 3 days of randomization. Subjects will take a single capsule of lenalidomide or placebo orally once per day on Days 1-14.

Docetaxel will be administered as an IV infusion for approximately 60 minutes (as per package insert) at a dose of 75 mg/m^2 to all subjects on Day 1 of each cycle. Preparation, storage and administration of docetaxel will be as directed on the docetaxel package insert. Prednisone is administered at a dose of 5 mg orally, BID, each day of the study treatment. Dose adjustments of docetaxel due to toxicity will be determined according to the docetaxel label and as described in Section 10.2.1.3.1 and Section 10.2.1.4. Pre-medication for docetaxel will be provided to all subjects according to institutional standards.

11.4. Investigational Product Packaging and Labeling

The label for investigational product supplied by Celgene will bear Celgene's name, address and telephone number, the protocol number, EudraCT number (if applicable), product name, dosage form and strength, lot number, medication identification/kit number, dosing instructions, storage conditions, quantity of investigational product contained, expiration date, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as needed or applicable per local regulations.

11.5. Receipt and Storage

The Investigator is responsible for conducting an inventory of shipment of investigational products and comparing it with the accompanying shipping order form. The Investigator will verify the accuracy of the information on the shipping order form and call the IVRS to register the study medication receipt at site.

At the study site, all investigational products will be stored in a locked, safe area to prevent unauthorized access.

Investigational products should be stored as directed on the product label.

11.6. Record of Administration

Accurate recording of all investigational product administration (including dispensing and dosing) will be kept.

11.7. Investigational Product Accountability

The investigator(s) or designee(s) is responsible for accounting for all investigational product issued to and returned by the subject during the course of the study.

11.8. Investigational Product Handling and Disposal

Celgene will instruct the Investigator(s) on the return or destruction of unused investigational product. If any investigational product is lost or damaged, its disposition should be documented. Celgene will provide instructions for the return of investigational product at the end of the study.

12. ASSESSMENT OF EFFICACY

12.1. Assessments

The following efficacy assessments will be performed at scheduled intervals throughout the duration of the study as described in the Schedule of Assessments found in Table 2: Schedule of Study Assessments

- Overall Survival
- Progression-Free Survival
- Tumor assessment by:
  - CT, MRI, Chest X-rays and Bone scans of measurable and non-measurable lesions
- ECOG Performance Status

12.2. Methods and Timing of Efficacy Assessments

12.2.1. Overall Survival

Subjects will be followed for survival throughout the study treatment and every 90 days after treatment phase discontinuation via telephone contact for up to 5 years or until all subjects have expired. All post-study prostate cancer related treatments will also be documented during these follow-up telephone contacts.

12.2.2. Progression-Free Survival

Progression-free survival will be assessed on Day 1 of each third cycle (starting with Cycle 4, Day 1), and at treatment phase discontinuation. Progression-Free Survival is defined as the time from randomization to disease progression, as defined by RECIST Version 1.1 (Section 12.2.3), or death due to any cause, whichever occurs first.

12.2.3. Tumor Assessment (CT, MRI, X-Ray and Bone Scans)

Tumor assessment of measurable and non-measurable lesions will be performed to determine tumor progression and tumor response. Tumor assessments will use CT, MRI, Chest X-ray, and/or bone scans as defined by RECIST Version 1.1 guidelines and described in Section 12.2.3.1 and Section 12.2.3.2. Assessments will be scheduled for the screening visit and Day 1 of each third cycle (every 63 days), starting with Cycle 4 Day 1, and at Treatment Phase discontinuation. To ensure comparability, baseline methods and on-study methods for response assessment must be performed using identical techniques.

Disease progression attributable to new bone lesions is defined according to the RECIST Version 1.1 guidelines for non-measurable disease (appearance of ≥ 1 new lesion) for the calculation of PFS. Discontinuation from the double-blind treatment phase of the study based on new bone lesions will require ≥ 2 new bone lesions with a confirmatory tumor assessment to be performed

9 weeks after initial observation of ≥ 2 new lesions (during the next scheduled tumor assessment) and not according to RECIST Version 1.1.

While all areas of malignant disease will be monitored, subjects will be categorized into having either target lesions or non-target lesions as defined by RECIST Version 1.1.

12.2.3.1. Target Lesions

Target Lesions will be identified as up to a maximum of 5 measurable lesions with no more than 2 measurable lesions per organ. Measurable lesions are defined as those that can be accurately and reproducibly measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT (with slice thickness ≤ 5 mm) MRI, or 20 mm by chest X-ray.

Lymph nodes must be ≥ 15 mm in the short axis when assessed by CT scan (slice thickness of ≥ 5 mm) to be considered as measurable lesions.

Target lesions will be recorded and measured at baseline. A sum of the longest diameters (LD) for non-nodal target lesions and short axis for nodal target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameter will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

- Complete Response (CR) is defined as:
  - Disappearance of all target lesions except lymph nodes
  - Lymph nodes must have a reduction in the short axis to < 10 mm
- Partial Response (PR) is defined as:
  - At least a 30% decrease in the sum of the diameters of target lesions taking as reference the baseline sum diameters
- Progressive Disease (PD) is defined if **any** of the criteria below are met:
  - At least a 20% increase in the sum of diameters of target lesions taking as a reference the smallest sum of diameters in the study AND an absolute increase of ≥ 5 mm
  - The appearance of ≥ 1 new lesions
- Stable Disease (SD):
  - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking the smallest sum diameters on study as reference
  - Confirmed by follow-up measurements at least once after study entry at a minimum interval of at least 6 weeks.

The duration of overall response is measured from the time measurement criteria are met for CR and PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented.

12.2.3.2. Non-target Lesions

All lesions not identified as target lesions, including small lesions (non-nodal lesions with LD ≤ 10 mm and nodal lesions with short axis ≥ 10 mm and < 15 mm) and bone metastasis, will be identified as non-target lesions and should be recorded at baseline. Response for subjects with non-measurable disease will be evaluated primarily by changes in non-target lesions by CT, MRI or Chest X-ray, and bone scans. While some non-target lesions may be measurable, measurements are not required and these lesions will be assessed as described by RECIST Version 1.1 and as follows for non-measurable lesions.

- Complete Response (CR):
  - Disappearance of all non-target lesions
  - All lymph nodes must be non-pathological in size < 10 mm (in the short axis)
- Non –CR/Non-PD:
  - Persistence of one or more non-target lesion(s)
- Progressive Disease (PD) is defined by any of the following:
  - Unequivocal progression of existing non-target lesions defined by the following:
    - An increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease
    - The unequivocal appearance of one or more new non-target lesions
    - A change sufficient to warrant a change in therapy

  Note: Unequivocal progression is not attributable to differences in scanning technique, non-tumor findings, healing of bone lesions or flare of pre-existing lesions

12.2.4. Eastern Cooperative Group Performance Status

Each subject will be assessed according to the ECOG Performance Status at screening, Day 1 of each cycle, and at treatment phase discontinuation according to the scale found in Appendix 21.2.

13. ASSESSMENT OF SAFETY

13.1. Assessments

- Adverse event severity by NCI CTCAE Version 4.0.
- Physical examination
- Vital signs, weight, and height
- Hematology labs
- Serum Chemistry labs
- Urinalysis
- Electrocardiogram (ECG)
- Concomitant medications/Procedures
- Post-Study Prostate Cancer treatments

13.2. Methods and Timing of Safety Assessments

Serial measurements of safety will be performed at scheduled intervals throughout the duration of the study as described in the Table 2: Schedule of Study Assessments. Abnormalities will be captured as AEs. Cause of death is to be recorded in the CRF and the subject's medical record. Safety laboratory measurements will be performed centrally. Electrocardiograms will be performed locally at each study site; no central over-read will be performed.

During Cycle 1 Day 14 the following assessment will be performed on the first 100 subjects and for all subjects participating in the sparse PK (Day 14) sampling: AEs, Physical Exam, Vital signs, Hematology Labs, and Serum Chemistry Labs. The information collected from this visit will be included in the initial DMC safety assessment. Subsequent subjects will not be evaluated on Cycle 1 Day 14 unless this safety assessment is determined necessary by the DMC due to safety concerns.

13.2.1. Adverse Event Severity by NCI CTCAE Version 4.0

All subjects will have adverse event assessment performed during all visits once the ICF is signed until 28 days after last study dose.

13.2.2. Physical Examination

All subjects will have a physical examination at screening, Day 1 (pre-treatment) of each cycle and at the treatment phase discontinuation visit. Physical examinations will include but are not limited to heart, lungs, abdominal, head/neck and extremities. A clinical neurological examination will be performed if clinically indicated. Investigators are to report any clinically significant abnormal findings as adverse events.

13.2.3. Vital Signs and Height

Vital signs (including blood pressure, pulse, and temperature) and weight will be measured during screening, Day 1 of each treatment cycle and during the treatment phase discontinuation visit. Height will only be assessed during screening.

Investigators are to report any clinically significant abnormal findings as adverse events.

13.2.4. Hematology Labs

All subjects will have hematology (RBC count, hemoglobin, hematocrit, WBC count and differential, ANC, and platelet count) measurements performed during screening, Day 1 of each treatment cycle and during the treatment phase discontinuation visit.

13.2.5. Serum Chemistry Labs

All subjects with have serum chemistry (sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, LDH, and uric acid) assessments during screening, Day 1, of each treatment cycle, and during the treatment phase discontinuation visit. Serum testosterone levels will be measured during screening for inclusion criteria.

13.2.6. Urine Dip Stick

A urine dip stick will be performed during screening, Day 1 of each cycle and treatment phase discontinuation visits. If abnormal, a urinalysis will be performed that will include specific gravity, protein, glucose, pH, ketones, urobilinogen and occult blood. If clinically indicated microscopic analysis will be performed (as a reflex test).

13.2.7. Electrocardiogram (ECG)

Electrocardiograms will be performed to evaluate the overall cardiovascular health of study subjects to participate in the treatment phase of the study. After the ICF is signed an ECG will be performed during the screening and treatment phase discontinuation visits. Further ECGs will be performed during the study as clinically indicated.

13.2.8. Concomitant Medications/Procedures.

All subjects will have concomitant medication and procedure assessment performed at all visits from signing of the ICF until 28 days after last dose.

13.2.9. Post-Study Prostate Cancer Treatments

Any additional treatments for prostate cancer following study treatment discontinuation will be captured and recorded every 90 days during the five years following treatment phase discontinuation.

13.3. Recording and Reporting of Adverse Events

The recording and reporting of adverse events is described in Appendix 21.5.

14. OTHER ASSESSMENTS

14.1. Assessment of Pharmacokinetics

Pharmacokinetic assessments will be performed on subjects who provide additional consent at select centers. Subjects can participate in either the intensive or sparse PK blood sampling.

14.1.1. Intensive PK sampling

Intensive PK sampling will be performed during Cycle 1 Day 1 at select centers on approximately 100 randomized subjects who agree to sign the PK ICF and select the intensive sampling option in the PK ICF. Lenalidomide (or placebo) will be administered to these subjects in the morning during their study site visit. After administration of lenalidomide (or placebo), PK blood samples will be collected at 1, 1.5, 2, 3, 4 and 6-8 hours. Intravenous infusion of docetaxel should start immediately following collection of the 1 hour post-lenalidomide dosing PK blood sample.

The following information will be recorded for population PK analysis:

- Actual date and time for administration of lenalidomide (or placebo)
- Actual date and time of the last meal prior to administration of lenalidomide (or placebo)
- Actual date and time for any food eaten within 4 hours following administration of lenalidomide (or placebo)
- Actual date and time for the start of docetaxel infusion

14.1.2. Sparse PK sampling

Sparse PK sampling will be performed during Cycle 1 Day 14 at select centers. Randomized subjects who agree to participate in the PK sub-study and select the sparse sampling option in the PK ICF will be assessed. On Cycle 1, Day 14, subjects should take the study drug in the morning, approximately 4 hours prior to their arrival at the study site. At this visit, a total of 2 blood samples will be collected. The first blood sample will be collected upon arrival of the subject at the clinic and the second blood sample will be collected at least 1 hour (preferably 2 hours) later. All samples will be collected between approximately 4 and 10 hours following lenalidomide (or placebo) administration.

Subjects will be asked to accurately provide the following information and report them to the study staff on Day 14:

- Actual date and time for administration of lenalidomide (or placebo) on Day 13 (the day prior to PK visit) and Day 14 of Cycle 1
- Actual date and time of the last meal prior to administration of lenalidomide (or placebo) (Cycle 1 Day 14 only)
- Actual date and time for any food eaten within 4 hours following administration of lenalidomide (or placebo) (Cycle 1 Day 14 only)

14.1.3. Determination of lenalidomide concentrations in plasma

For each PK sample, blood will be collected and plasma will be prepared as described in a study manual provided in the central lab manual. During the infusion of docetaxel, PK blood should be drawn from the arm opposite to that for drug infusion. The PK samples will be unblinded by a third party (a bioanalytical lab), so that only samples from subjects on DPL Treatment Arm will be analyzed. Lenalidomide concentration in plasma will be determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

14.2. Assessment of Pharmacodynamics

NA

14.3. Assessment of Other Outcomes

14.3.1. Exploratory Assessments

14.3.1.1. PSA Correlations

Prostate Specific Antigen reductions ≥30% and ≥50%, PSA progression, PSA velocity, and PSA doubling time will be calculated. Statistical analysis will be performed to assess any significant correlation of PSA levels with relevant clinical benefits (e.g., OS, PFS, and Pain Endpoints). PSA will be measured at screening, Day 1 of each cycle and at treatment phase discontinuation. Samples for PSA evaluation during study treatment visits will be obtained prior to administration of study treatment.

- PSA Progression:

  A subject would be considered having PSA Progression based on the following criteria:

  - If subject experience's a PSA increase of:
    - ≥25 % and ≥2 ng/ml above the nadir if a PSA decline from baseline is observed or,
    - ≥25% and ≥2 ng/ml above baseline if no PSA decline from baseline is observed
  - PSA progression must be confirmed ≥ 3 weeks later by a second value to document rising trend in PSA
  - Subjects must remain on study for at least 12 weeks to be evaluated for PSA progression
  - Time to PSA Progression will be measured from the first day of treatment to first PSA increase meeting the criteria of progression (i.e., not the date of confirmation)

- PSA response: Calculations will be performed to determine the response rates of both a 30% and a 50% decline in PSA from a baseline PSA value measured twice at least 21 days apart

14.3.1.2. Exploratory analysis of biomarkers

Biomarkers including but not limited to CTCs to will be performed during Cycle 1 Day 1 and starting on Cycle 4, on Day 1 of every 3rd cycle (Cycle 4, 7, 10 etc.) to assess any significant correlation of CTC levels with relevant clinical benefits. Sample collection for this exploratory analysis may be limited to selected clinical centers.

14.3.1.3. Change in Analgesic Use

Analgesic use will be determined by gathering pain medications information from the Concomitant Medications Forms (Concomitant Medication and Analgesia-specific Concomitant Medication Form). Analgesic use will be collected at all visits from signing of the ICF until 28 days after last dose. Morphine equivalents (based upon a 10 milligram dose of morphine) will be calculated to provide a common metric (i.e., a "standard dose") for opioid-containing medications. An analgesic score will be calculated by assigning a score of 4 for a standard dose of a narcotic analgesic and a score of 1 for a standard dose of a non-narcotic analgesic (Tannock et al, 2004).

14.3.1.4. Patient-Reported Outcomes (PRO)

Health-related Patient-Reported Outcomes will be assessed using the validated instruments to measure quality of life and pain as described in Section 14.3.1.4.1 and Section 14.3.1.4.2. Subject will be required to complete these surveys without assistance or with minimal assistance from trained site personnel and/or caregiver.

Patient-reported outcome instruments will assess health-related quality of life and prostate symptoms as well as pain severity and pain interference. The PRO instruments described in the following sections are found in Appendix 21.4.

14.3.1.4.1. Pain Measures

The Brief Pain Inventory-Short Form (BPI-SF) will be completed by the subject prior to any treatment, examination or other assessments during the screening visit, on Day 1 of each cycle and at treatment phase discontinuation.

- The BPI-SF is a validated measure of pain severity and pain interference. Four questions assess pain severity on an 11-point scale ranging from "no pain" (0) to "pain as bad as you can imagine" (10). Severity subscales include worst pain, least pain, average pain, and current pain. Seven items assess pain interference with functional activities: general activity, mood, walking ability, normal work (includes both work outside the home and housework), relations with other people, sleep, and enjoyment of life. Interference items are also measured on an 11-point scale, ranging from "does not interfere" (0) to "completely interferes" (10). Validated versions of this instrument are available in many languages. The BPI takes 3-5 minutes to administer.

14.3.1.4.2. Health-Related Quality of Life and Prostate Cancer Symptoms

The FACT-P and EQ-5D questionnaires will be completed by the subject during site visits prior to any treatment, examination or other assessments. These questionnaires will be completed on

Cycle 1, Day 1 and Day 1 of each third cycle (every 63 days from Cycle 1 Day 1) and at treatment phase discontinuation.

- The Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire is a validated measure used to assess HRQoL in men with prostate cancer. The FACT–P is composed of two sections: the FACT-G (general) and the Prostate Cancer Subscale (PCS). The FACT-G is a 27-item self-report questionnaire that measures general HRQoL in cancer patients within four domains: physical, social, emotional and functional. The 12-item PCS is designed specifically to measure prostate cancer-specific quality of life. A higher overall score indicates better HRQoL. Items on all subscales are measured on a 5-point scale ranging from "not at all" (0) to "very much" (Esper, 1997). Validated versions of this instrument are available in many languages. The FACT-P takes 5-10 minutes to administer.
- The EQ-5D is a patient-completed instrument designed to assess impact on quality of life in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The scores from the five domains may be used to calculate a single index (or utility) value. Additionally, the EQ-5D contains a visual analogue scale that asks the subject to rate their current health state from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state. Validated versions of the EQ-5D are available in many languages. The EQ-5D takes 1-2 minutes to administer.

14.3.1.5. Pharmacokinetics Analysis

Pharmacokinetics analysis is an exploratory assessment that will be performed as described in Section 14.1.

15. STATISTICAL ANALYSES

15.1. Statistical Overview

This is a multicenter, double blind, randomized Phase 3 study comparing docetaxel and prednisone with (DPL) or without (DP) lenalidomide as first-line treatment in chemo-naïve subjects with metastatic CRPC. Subjects will be randomized according to the following stratification factors: baseline ECOG performance status (≤1 vs. 2), geographic region (US and Canada vs. EU countries and Australia vs. Rest of World), and type of disease progression following hormonal therapy (rising PSA only vs. tumor progression). An Interactive Voice Response System (IVRS) will be utilized to ensure a central randomization based on a permuted-block randomization method. An independent Data Monitoring Committee (DMC) will be used to monitor the study conduct.

15.2. Study Population Definitions

15.2.1. Intent-To-Treat Population

The primary efficacy analysis will be performed on the ITT population, which will include all subjects randomized.

15.2.2. Efficacy Evaluable Population

Confirmatory efficacy analysis will be performed on the efficacy evaluable population, which will include all randomized subjects who meet eligibility criteria, take at least one dose of study drug and have at least one post baseline efficacy assessment.

15.2.3. Safety Population

All randomized subjects who receive any study drug will be included in the safety analyses.

15.3. Efficacy Evaluation

15.3.1. Primary Endpoint

15.3.1.1. Overall Survival

OS is defined as the weeks between randomization and death. All deaths, regardless of the cause of death, will be included. All subjects who are lost to the follow-up prior to the end of the trial or who are withdrawn from the trial will be censored at the time of last contact. Subjects who are still receiving treatment as of the data cutoff date will be censored at the cutoff date.

15.3.2. Secondary Endpoints

15.3.2.1. Progression-Free Survival

Progression-Free Survival will be calculated as the time from randomization to disease progression, as defined by RECIST Version 1.1 (and as defined in Section 12.2.3) or death due to any cause, whichever occurs first.

Subjects who withdraw for any reason or who received another anti-tumor therapy without documented PD will be censored on the date of their last adequate efficacy response assessment (or last adequate assessment prior to receiving other prostate cancer-therapy). Subjects who are still active as of the data cutoff date and who have not progressed will be censored on the date of their last adequate efficacy response assessment.

15.3.2.2. Tumor Response

Tumor response, including PD, will be assessed according to the RECIST Version 1.1 criteria for subjects with measurable and non-measurable disease at baseline and as described in Section 12.2.3. The tumor response rate based on the best response during the treatment period and the relative proportions in each response category will be examined. Responses from subjects after they received other anti-cancer treatments will not be counted; however, these subjects will be included in the denominator.

15.3.3. Efficacy Analyses

For the primary analysis, the overall survival will be compared between treatment arms based on the log rank test. The overall two-sided significance level is 5%. This 5% will be spread over 2 analyses by an O'Brien-Fleming alpha spending function. The significance of efficacy will be claimed if the p-value is less than or equal to the significance level as calculated based on the specified alpha spending function and the observed number of events.

The Kaplan-Meier method will be used to estimate the survival distribution functions for each treatment arm. The number of events, subjects censored, and the Kaplan-Meier estimates at the time points of 52, and 104 weeks, along with standard errors (Greenwood's formula, Klein and Moeschberger, 2003), will be provided. The plots of survival curves using the Kaplan-Meier method will be presented.

Kaplan-Meier product limit methods will be used to estimate the survival functions for PFS. A two-sided log-rank test will be used to compare survival functions for time-to-event endpoints in the 2 treatment groups. Median PFS and OS will be estimated using Kaplan-Meier estimates with 95% confidence intervals (CI) computed using the method of Brookmeyer and Crowley. The Cox model will also be used to estimate hazard ratio and identify prognostic factors.

Categorical endpoints will be summarized in frequency tables. Percentages in the summary tables will be rounded and may, therefore, not always sum to 100%. Comparisons will be performed using one-sided Fisher's exact test with $\alpha = 2.5\%$.

Additional details will be provided in the Statistical Analysis Plan.

15.4. Background and Demographic Characteristics

The baseline characteristics of all randomized subjects will be summarized. An accounting will be made of all subjects who received study drug and, in particular, the number of subjects who died or withdrew during treatment will be specified together with the reasons for withdrawal.

15.5. Study Drug

Descriptive statistics will be used to summarize the duration of treatment with each study drug by treatment arm. Dosage statistics will be provided for each treatment arm. The proportion of

subjects who had dose modifications will also be summarized. Time to the first dose reduction and reasons for dose reduction will be summarized for each treatment arm. Reasons for discontinuation will be summarized. Duration of treatment will be summarized for each treatment arm.

15.6. Concomitant Therapy

All concomitant treatment usage documented during the study period will be summarized in frequency tabulations for each treatment group separately. The Anatomical Therapeutical Chemical (ATC) coding scheme of the World Health Organization (WHO) will be used to group medications into relevant categories for these tabulations.

15.7. Safety Evaluation

Data from all subjects who receive one or more doses of drug will be included in the safety analyses. Adverse events, physical examinations (including vital sign measurements), clinical laboratory information, ECG interpretations, and concomitant medications/procedures will be tabulated and summarized by treatment group. All toxicities will be summarized by relative and absolute frequency, severity grade based on the NCI CTCAE Version 4.0 and relationship to treatment. Study medication-related AEs, SAEs, and events leading to discontinuation or death will be listed separately. Safety information obtained during the Follow-up period will be described. Graphical displays will be provided where useful in the interpretation of results.

15.8. Interim Analyses

One interim analysis based on OS is planned and a DMC will review and give advice to the sponsor regarding the study conduct. An independent third party will be responsible for preparation of the appropriate data and reports to provide the members of the DMC prior to their scheduled meeting. The analysis results will not be disseminated among investigators and those directly involved with the study conduct. The efficacy interim analysis will be performed when at least 468 events are observed and all 1015 subjects are randomized. The final analysis is planned when 624 events are observed. The boundary of the nominal two-sided p-value for declaring superiority is as follows:

Analysis Stage	Boundary for Nominal p-value
1	0.0193
2	0.0442

15.8.1. Data Monitoring Committee

An independent DMC will be convened which will be composed of medical oncologists with experience in treating subjects with prostate cancer and a statistician, all of whom are not otherwise involved in the study as investigators or reviewers of efficacy data. During the course of the study, the DMC will review the efficacy data once in accordance with the guidelines for the pre-planed interim analysis. The committee will also review safety data. An independent third party will prepare the reports of aggregate data summaries and individual subject data listings, as appropriate, to provide the members of the DMC for each scheduled meeting.

Operational details for the DMC and the algorithm and its validation by an expert panel will be detailed in the DMC charter.

15.9. Other Topics

15.9.1. Stratification Parameters

Subjects will be randomized according to the following stratification factors: baseline ECOG performance status (≤1 vs. 2), geographic region (US and Canada vs. EU countries and Australia vs. Rest of World), and type of disease progression following hormonal therapy (rising PSA only vs. tumor progression). Subgroup analyses for OS and PFS will be performed by each stratification factor.

15.9.2. Exploratory Endpoints

- PSA response defined as reduction of PSA levels of ≥30% and ≥50% as described in Section 14.3.1.1; PSA progression as described in Section 14.3.1.1; PSA velocity; and PSA doubling time will be calculated. Statistical analysis will be performed to assess any significant correlation of PSA levels with relevant clinical benefits (e.g., OS, PFS, and Pain Endpoints).
- Exploratory analysis of biomarkers, including but not limited to CTCs will be performed to assess any significant correlation of CTC levels with relevant clinical benefits. Sample collection for this exploratory analysis may be limited to selected clinical centers
- Pharmacokinetic assessments will be performed in subjects who provide additional consent at select centers. Both intensive and sparse sampling pharmacokinetics (PK) analysis of lenalidomide when administered in combination with docetaxel and prednisone will be performed. Subjects can decide to participate in either the intensive or sparse PK blood sampling but not both.
- Change in Analgesic Use will be evaluated for changes in analgesic use over the course of the study and to be able to interpret self-reported pain severity in light of concomitant analgesic use.
- Patient-Reported Outcomes (PRO) will be evaluated using the validated instruments listed below for Pain and Health-Related Quality of Life Assessments. A modified ITT population defined for PRO assessment is all randomized subjects who completed the baseline assessment (Day 1) and had at least one follow-up assessment with the Brief Pain Inventory, the FACT-P or the EQ-5D.
  - Scoring for the psychometric instruments will be accomplished according to directions provided by the instrument developers. Missing values at the subscale or total scale level will be handled according to specifications provided by the instrument developers. A hierarchical procedure will be specified to handle multiplicity in the PRO endpoints, with pain severity specified as the primary PRO endpoint.

- Preliminary exploratory analyses will assess the relationship between PRO measures and selected demographic and clinical variables, as well as reliability and validity instrument characteristics in the study population. Between-group differences in change from baseline for total and subscale scores on the BPI, the FACT-P and the EQ-5D will be analyzed through specification of analysis of covariance models. A method to interpret longitudinal changes in pain severity in light of variation in pain medication usage will be pre-specified, as will methods to assess responsiveness and minimally important differences.

15.10. Sample Size and Power Considerations

Approximately 1015 subjects will be randomized over 24 months. An interim analysis for OS will be performed when at least 468 events are observed and all 1015 subject have been randomized. The final analysis, planned after 624 events have been observed, is expected approximately 48 months following randomization of the first subject. The O'Brien-Fleming boundary will be used to determine the nominal significance level with overall two-sided 5% significance level. Assuming that DP treatment arm results in a median OS of 19.2 months the DPL has a targeted median OS of 25.0 months (30% improvement), this design would allow the demonstration of a statistically significant difference in the OS at a two-sided 5% significance level with at least 90% power.

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1. Monitoring

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. Before the study is initiated at a site visit or at an investigator meeting, all aspects of the study are reviewed with the investigator(s) and the staff. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs with the Investigator(s). Monitoring will include on-site visits with the Investigator(s) and his/her staff as well as any appropriate communications by mail, fax, or telephone. At each monitoring visit, the facilities, study drug storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative for adherence to the protocol and Good Clinical Practice.

At each site visit, the monitor will review CRFs for completion and accuracy. Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRF against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator(s) and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via source data clarification forms by the Investigator(s) and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and the proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

16.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. From time to time, representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator(s) is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of subject participation for audits and inspections by IRB/IECs, regulatory authorities (e.g. FDA, EMEA, TPP) and company authorized representatives. The Investigator(s) should make every effort to be available for the audits and/or inspections. If the Investigator(s) is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

16.3. Investigator(s) Responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice and in the US Code of Federal Regulations. Celgene or a representative will contact and select all principal investigators or co-investigators who in turn will select their staff. The investigator must give the monitor access to relevant records to confirm the above.

The Investigator(s) is responsible for keeping a record of all subjects who sign an Informed Consent Form and are screened for entry into the study. For those subjects who fail screening

the reason(s) for exclusion must be recorded in the subject's source documents and on the Screening Log provided by Celgene.

No procedure/assessment/measurement/test other than those outlined here, or in the schedule of study assessments, is to be performed without the prior written approval of Celgene, or unless deemed by the investigator(s) as necessary for the subject's medical care. Investigator(s) and/or authorized designee(s) must enter study data onto CRFs supplied by Celgene. The data on the CRF will be recorded in an anonymous manner to protect the subject's identity by using a unique identifier that will prevent personal identifiable information.

The Investigator(s), or a designated member of the Investigators' staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The CRFs must be completed as soon as possible after the subject's visit but no later than prior to each monitoring visit and be made available to the Celgene representative(s) so that the accuracy and completeness may be checked.

17. REGULATORY CONSIDERATIONS

17.1. Institutional Review Board/Independent Ethics Committee Review and Approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki (see Appendix 21.8). The review of this protocol by the IRB/IEC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards. Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Celgene before the study initiation. The names and occupations of the chairman and the members of the IRB/IEC must be supplied to Celgene.

The Investigator(s) will be responsible for preparing documents for submission to the relevant IRB/IEC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

A copy of the IRB/IEC approval for the protocol and the Informed Consent is to be provided to Celgene. The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

The Investigator(s) is responsible for notifying the IRB/IEC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by Celgene and the IRB/IEC prior to use.

17.2. Protocol Amendments

Any amendment to this protocol that seems appropriate, as the study progresses (e.g. affects safety or efficacy) will be agreed upon between the coordinating and/or principal investigator(s) and the Celgene study physician. Amendments will be submitted to the IRB/IEC for written approval before the implementation of the amended version. The written signed approval from the IRB/IEC should refer specifically to the investigator(s) and to the protocol number and title and mention any amendment numbers that are applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

17.3. Informed Consent

The Investigator(s) must obtain informed consent of a subject or his/her designee prior to any study related procedures as per Good Clinical Practices (GCP) as set forth in the 21 CFR Parts 50 and 56 and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and of the informed consent process should be recorded in the subject's source documents. The original consent form, signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent must be revised. Subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent. The revised consent form signed and dated by the subject and by the person consenting the subject must be maintained in the Investigator's study files and a copy given to the subject.

17.4. Subject Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator(s) to permit Celgene's representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator(s) to obtain such permission in writing from the appropriate individual.

18. DATA HANDLING AND RECORDKEEPING

18.1. Data/Documents

The investigator(s) must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents original documents, data, and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files) and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study are complete, accurate, and filed and retain.

18.2. Data Management

Data will be entered into the clinical database as per Celgene SOPs. These data will be electronically verified through use of on-line checks during data entry, and through programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary, in the form of a Data Clarification Form (DCF). Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data. A quality control audit will be performed per Celgene SOP(s).

18.3. Retention of Records

The investigator(s) must maintain records of all study documents and supporting information relating to the conduct of the study. This documentation includes, but is not limited to, protocols, case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with health authorities and IRBs/IECs, informed consent forms, investigator(s) curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice specified below. The study monitor must be consulted if the investigator(s) wishes to assign the study files to someone else, remove them to another location or is unable to retain them for a specified period.

For studies conducted in the United States under a US IND, the investigator(s) must retain the study records for a minimum of 2 years after a marketing application for the indication is approved or for 2 years after the IND is withdrawn. If no application is filed, or if the application is not approved for the indication, the records are to be retained for two years after the investigation (i.e., the IND) is discontinued, and FDA is notified of that fact. For IND studies conducted outside the US, the investigator(s), must retain study records for the time period described above or according to local laws or requirements, whichever is longer. The monitor will inform the investigator(s) of the dates for retention. All study documents should be made available if required by relevant health authorities. For studies not conducted under the US IND, the investigator(s) records must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing

applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by other applicable regulatory requirements.

19. PREMATURE DISCONTINUATION OF THE STUDY

19.1. Single Site

The responsible clinical Investigator, as well as Celgene, has the right to discontinue a single site at any time during the study for reasonable medical or administrative reasons. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the study protocol

19.2. Study as a Whole

Celgene reserves the right to terminate this clinical study at any time for reasonable medical or administrative reasons.

Any possible premature discontinuation would have to be documented adequately with reasons being stated, and information would be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

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Celgene study report PD466

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21. APPENDICES

21.1. Summary of RECIST Version 1.1 Criteria

(Eisenhauer et al, 2009)

Table 10: Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (short axis ≥ 15 mm at baseline) must have reduction to < 10 mm short axis
Partial Response (PR)	At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum diameters recorded on study, and an absolute increase on 5 mm. The appearance of one or more new lesions is also considered progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Table 11: Evaluation of Non-target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and reduction of lymph nodes to < 10 mm
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s)
Progressive Disease (PD)	Unequivocal progression[a] of existing non-target lesions and/or appearance of one or more new lesions

[a]Unequivocal progression of existing non-target lesions defined by the following: An increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease

Table 12: Evaluation of Best Overall Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE[a]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[a]NE=inevaluable

21.2. ECOG Performance Status Scale

(Oken, 1982)

Table 13: ECOG Performance Status Scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

21.3. Percent of Normal Bone Marrow Irradiation

(Ellis, RE, et al, 1961)

Site of Irradiation	% Total Red Marrow
Skull (not Including Mandible)	**12%**
UpperLimb girdle (unilateral) (humeral head, scapulae, clavicle	**4%**
Ribs	**8%**
Ribs (hemithorax)	**4%**
Cervical vertebrae (all)	**3%**
Thoracic vertebrae (all)	**14%**
Lumbar vertebrae (all)	**11%**
Sacrum	**14%**
Pelvis (including both innominates and both femoral heads and necks	**26%**
Mantle (approximate)	**25%**
Upper para aortic nodes (approximate)	**11%**
Inverted Y (approximate)	**45%**

21.4. Patient-Reported Outcomes Assessments

21.4.1. Functional Assessment of Cancer Therapy - Prostate (FACT-P)

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

3/20/03
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FACT-P (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-P (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience significant pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

21.4.2. EuroQol (EQ-5D) Questionnaire (EQ-5D)

CELGENE CORPORATION

Protocol No.	Site No.	Subject No.	Subject Initials	Visit

Visit Date: dd mon yyyy

EQ-5D

By placing a check in one box in each group, please indicate which statements best describe your own heath state today

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems with washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities
(e.g., work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

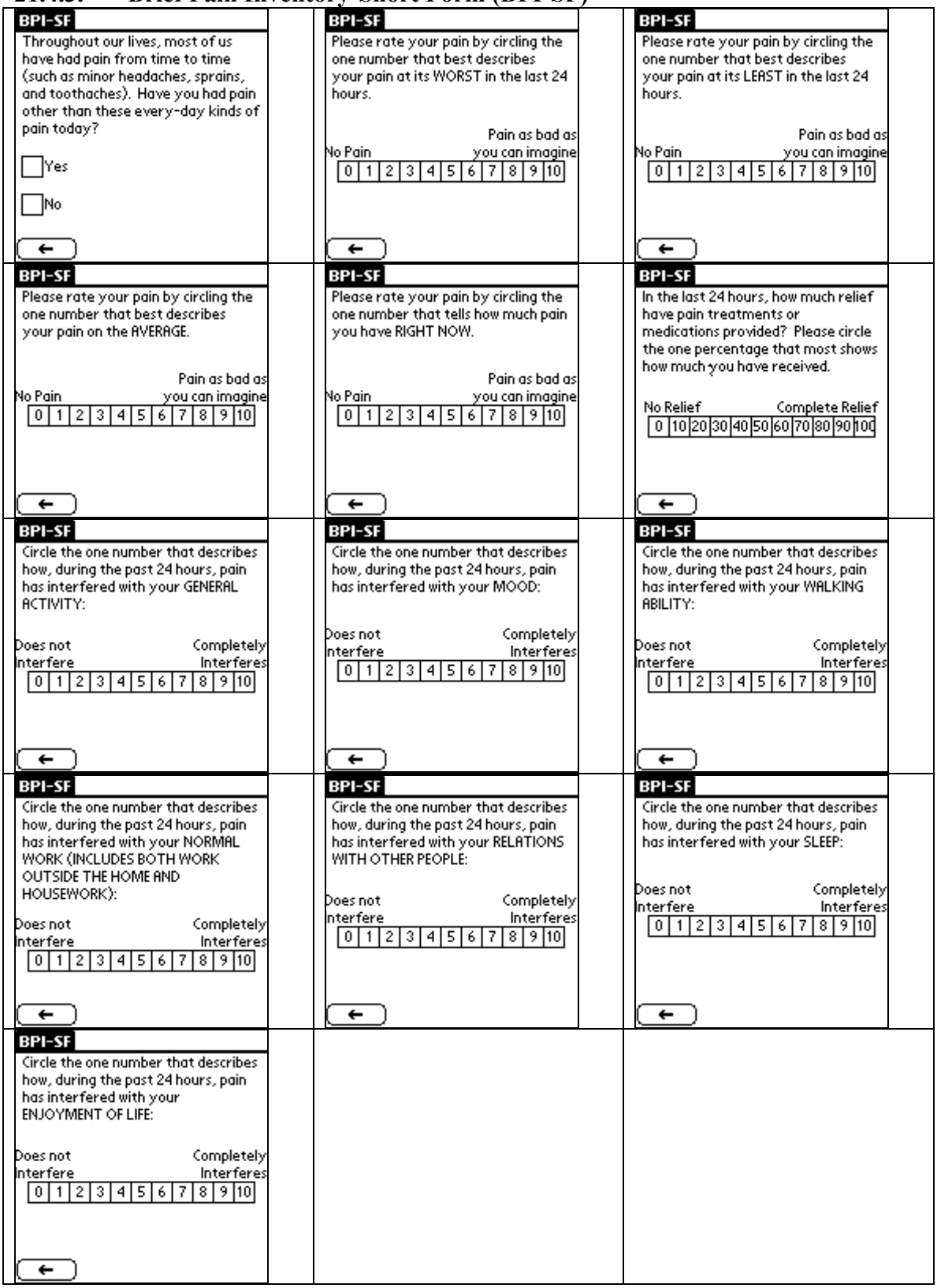
- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety / Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

Draft 15 Feb 2008

21.4.3. Brief Pain Inventory-Short Form (BPI-SF)



21.5. Adverse Event

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any medical condition that was present prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition this should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the Case Report From rather than the individual signs or symptoms of the diagnosis or syndrome.

All AEs will be recorded by the Investigator(s) from the time subject signs the ICF (up to 28 days prior to initial study treatment) until 28 days after the last dose of study drug. AEs will be recorded on the AE page of the CRF and in the subject's source documents.

Abnormal Laboratory Values Defined as Adverse Events

An abnormal laboratory value is considered to be an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study.
- Requires treatment, modification/interruption of study drug dose, or any other therapeutic intervention.
- Is judged by the Investigator(s) to be of significant clinical importance.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

Serious Adverse Event

A serious adverse event (SAE) is any AE which:

- Results in death
- Is life-threatening (i.e., in the opinion of the Investigator(s) the subject is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered to be SAEs are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition.

If an AE is considered serious, both the AE pages of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator(s) will provide information on severity, start and stop dates, relationship to study drug, action taken regarding study drug, and outcome.

Classification of Severity

For both AEs and SAEs, the investigator(s) must assess the severity of the event. The severity of AEs will be graded based upon the subject's symptoms according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0); http://ctep.cancer.gov/reporting/ctc.html. The AEs will be evaluated for severity according to the following scale:

Grade 1 = Mild

Grade 2 = Moderate

Grade 3 = Severe

Grade 4 = Life-threatening

Grade 5 = Fatal

Classification of Relationship/Causality of Adverse Events (SAE/AE) to Study Drug

The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not Suspected: The temporal relationship of the adverse event to study drug administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event

Suspected: The temporal relationship of the adverse event to study drug administration makes **a causal relationship possible,** and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

Monitoring and Reporting of Adverse Events

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms; laboratory,

pathological, radiological, or surgical findings; physical examination findings; or other appropriate tests and procedures.

Immediate Reporting of Serious Adverse Events

Any AE that meets the any criterion for a SAE requires the completion of an SAE Report Form in addition to being recorded on the AE pages of the CRF. The Investigator(s) is required to ensure that the data on these forms is accurate and consistent. This applies to all SAEs, regardless of relationship to study drug, that occur during the study, those made known to the Investigator(s) within 28 days after a subject's last dose of study drug, and those made known to the investigator(s) at anytime that are suspected of being related to study drug.

The SAE must be reported immediately (i.e., within 24 hours of the Investigators' knowledge of the event) to Celgene Drug Safety by facsimile. An initial written report (prepared by the Investigator(s) using the SAE Report Form provided by Celgene) is to be faxed to Celgene Drug Safety.

The SAE report should provide a detailed description of the SAE and include copies of hospital records and other relevant documents. If a subject has died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, and sent to Celgene.

The Investigator(s) is responsible for informing the Institutional Review Board/Ethics Committee (IRB/IEC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator(s) must keep copies of all SAE information, including correspondence with Celgene and the IRB/IEC, on file. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until either the event resolves completely, stabilizes/resolves with sequelae, or returns to baseline (if a baseline value is available).

Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female partner of a male subject occurring while the subject is on study drug, or within 28 days of the subject's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the investigator(s). The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Celgene Drug Safety immediately by facsimile using the SAE Report Form.

Female partners of males taking investigational product should be advised to call their healthcare provider immediately if they get pregnant and male subjects should notify their doctors as well.

The female should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator(s) will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety of the outcome of the pregnancy as a follow-up to the initial SAE report.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator(s) should follow the procedures for reporting SAEs (i.e., report the event to Celgene Drug Safety by facsimile within 24 hours of the Investigator's knowledge of the event).

In the case of a live "normal" birth, Celgene Drug Safety should be advised by facsimile within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator(s) suspects is related to the in utero exposure to the study drug should also be reported to Celgene Drug Safety by facsimile within 24 hours of the Investigators' knowledge of the event.

If the female is found not to be pregnant, any determination regarding the subject's continued participation in the study will be determined by the Investigator(s) and the Celgene Medical Monitor.

Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to lenalidomide based on the Investigator Brochure.

For countries within the European Economic Area (EEA), Celgene will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to the other investigational medicinal product (IMP), prednisone and docetaxel, based on the US PI for both products.

Celgene shall notify the Investigator of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected, i.e., suspected unexpected serious adverse reaction (SUSAR)
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/IEC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information, including correspondence with Celgene and the IRB/IEC, on file.

Celgene Drug Safety Contact Information:

For Local Drug Safety Affiliate Office contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines.

21.6. Ex-European Union (EU) Pregnancy Risk Management Language (for use in sites in countries following the Ex-EU Risk Management Plan)

21.6.1. Lenalidomide Pregnancy Risk Minimization Plan for Celgene Clinical Trials

Appendix 21.6.1 applies to all patients randomized to receive study treatment (Treatment Arms DPL and DP). The following Pregnancy Risk Minimization Plan documents are included in this appendix:

1. Lenalidomide Risks of Fetal Exposure and Acceptable Birth Control Methods (Section 21.6.2);
2. Lenalidomide Education and Counseling Guidance Document (Section 21.6.3);
3. Lenalidomide Information Sheet (Section 21.6.4).

The Lenalidomide Risks of Fetal Exposure and Acceptable Birth Control Methods document (Section 21.6.2) provides the following information:

- Risks to the fetus associated with lenalidomide exposure
- Acceptable birth control methods for male patients receiving Lenalidomide in the study
- Requirements for counseling of all study patients receiving Lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide

The Lenalidomide Education and Counseling Guidance Document (Section 21.6.3) must be completed and signed by either a trained counselor or the investigator at the participating clinical center prior to dispensing of each study treatment. A copy of this document must be maintained in the patient records.

The Lenalidomide Information Sheet (Section 21.6.4) will be given to each patient randomized to receive study therapy. The patient must read this document prior to starting lenalidomide study treatment.

21.6.2. Lenalidomide Risks of Fetal Exposure and Acceptable Birth Control Methods

Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Traces of lenalidomide have been found in semen. Male patients taking lenalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a woman of childbearing potential
- Understand the need for the use of a latex condom even if he has had a vasectomy, if engaged in sexual activity with a female of childbearing potential.

Before starting study drug

Male Patients:

Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation even if he has undergone a successful vasectomy or practices complete abstinence.

During study participation and for 28 days following study drug discontinuation

Male Patients:

- Counseling about the requirement for latex condom use during sexual contact with females of childbearing potential and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions:

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the Investigator at the end of treatment.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be dispensed with each cycle of therapy.

21.6.3. Lenalidomide Education and Counseling Guidance Document

Protocol Number: _____

Patient Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

MALE:

1. I counseled the Male patient regarding the following:
   - Potential fetal harm
   - Use a latex condom when engaging in sexual intercourse (including those who have had a vasectomy) with a female of childbearing potential, or engage in complete abstinence, while taking lenalidomide, during dose interruptions and for 28 days after stopping lenalidomide.
   - Female partners of males taking lenalidomide should be advised to call their healthcare provider immediately if they get pregnant and males should notify their study doctor as well.
   - NEVER share lenalidomide with anyone else.
   - Do not donate blood, semen or sperm while taking lenalidomide and for 28 days after stopping lenalidomide.
   - Do not break, chew, or open lenalidomide capsules.
   - Return unused lenalidomide capsules to the investigator.
2. Provide Lenalidomide Information Sheet to the patient.

Investigator/Counselor Name (Print): _____
(Circle applicable)

Investigator/Counselor Signature: _____ Date: _____/_____/_____
(Circle applicable)

**Maintain a copy of the Education and Counseling Guidance Document in the patient records. **

21.6.4. Lenalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Lenalidomide Information Sheet before you start taking lenalidomide and each time you get a new supply, since there may be new information. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

1. **Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Lenalidomide has not been tested in pregnant women but may also cause birth defects. Preliminary findings from a monkey study appear to indicate that lenalidomide caused birth defects in the offspring of female monkeys who received the drug during pregnancy**.**

If you are a male:

Lenalidomide is detected in trace quantities in human semen. The risk to the fetus in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time.

- Male patients, including those who have had a vasectomy, must practice complete abstinence or use a latex condom during sexual intercourse with a pregnant female or a female of child bearing potential:
  - While you are taking lenalidomide
  - During dose interruptions of lenalidomide
  - For 28 days after you stop taking lenalidomide
- **Male patients should not donate sperm or semen** while taking lenalidomide and for 28 days after stopping lenalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation.**

2. **Lenalidomide restrictions in sharing lenalidomide and donating blood:**
   - **Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
   - Do not give blood while you take lenalidomide and for 28 days after stopping lenalidomide.
   - **Do not break, chew, or open lenalidomide capsules.**

- You will get no more than a 28-day supply of lenalidomide at one time.
- Return unused lenalidomide capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

21.7. European Union Pregnancy Risk Management Information (for use in sites in countries following the EU RMP)

21.7.1. Lenalidomide Pregnancy Risk Minimisation Plan for Celgene Clinical Trials

Appendix 21.7.1 applies to all patients randomized to receive study treatment (Treatment Arms DPL and DP). The following Pregnancy Risk Minimisation Plan documents are included in this appendix:

1. Lenalidomide Risks of Foetal Exposure and Acceptable Birth Control Methods (Section 21.7.2)
2. Lenalidomide Education and Counselling Guidance Document (Section 21.7.3);
3. Lenalidomide Information Sheet (Section 21.7.4).

The Lenalidomide Risks of Foetal Exposure and Acceptable Birth Control Methods document (Section 21.6.2) provides the following information:

- Risks to the foetus associated with lenalidomide exposure
- Acceptable birth control methods for male patients receiving Lenalidomide in the study
- Requirements for counselling of all study patients receiving Lenalidomide about pregnancy precautions and the potential risks of foetal exposure to lenalidomide

The Lenalidomide Education and Counselling Guidance Document (Section 21.7.3) must be completed and signed by either a trained counsellor or the investigator at the participating clinical centre prior to the patient starting study treatment. A copy of this document must be maintained in the patient records.

The Lenalidomide Information Sheet (Section 21.7.4) will be given to each patient randomized to receive study treatment. The patient must read this document prior to starting lenalidomide study treatment.

21.7.2. Lenalidomide Risks of Fetal Exposure and Acceptable Birth Control Methods

Pregnancy warning

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofoetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimisation plan to prevent pregnancy must be observed.

The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the female partner of a male patient does not have childbearing potential.

Counselling

Traces of lenalidomide have been found in semen. Male patients taking lenalidomide must meet the following conditions (i.e., all males must be counselled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a woman of childbearing potential
- Understand the need for the use of a condom if engaged in sexual activity with a woman of childbearing potential, even if they have had a vasectomy

Precautions for Men

All male patients should use condoms throughout treatment duration, during dose interruption and for 7 days after cessation of treatment if their partner is of childbearing potential and has no contraception.

Additional precautions

Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood or semen (other than for this study) during therapy or for 7 days following discontinuation of lenalidomide.

21.7.3. Lenalidomide Education and Counselling Guidance Document

Protocol Number: _____

Patient Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

To Be Completed at Start of Lenalidomide Therapy:

Counselling for Men

Prior to the first dispense of lenalidomide, I have counselled the subject on the following

- The need to use condoms throughout treatment duration, during dose interruption, and for 7 days after cessation of treatment if partner is of childbearing potential, even if the patient has had a vasectomy.
- Not to share medication
- To return unused capsules to pharmacist
- Not to donate blood or semen (other than for this study) whilst taking Revlimid or for 7 days after stopping.

I have provided the patient booklet to the patient

Investigator's Name (Print): _____

Investigator's Signature: _____ Date: _____/_____/_____

Maintain a copy of the Education and Counselling Guidance Document in the patient records.

21.7.4. Lenalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Lenalidomide Information Sheet before you start taking lenalidomide and each time you get a new supply, since there may be new information. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

Brochure for Male Patients

- Lenalidomide may be harmful to the unborn child.
- In order to ensure that an unborn baby is not exposed to lenalidomide, you doctor will complete a Patient Card documenting that you have been informed of the requirement for your partner NOT to become pregnant during treatment with lenalidomide and for 7 days after you finish lenalidomide.
- You should never share lenalidomide with anyone else
- You should always return any unused capsules to the pharmacist
- You should not donate blood or semen (other than for this study) during treatment or for 7 days after treatment finishes
- If you experience any side effects whilst taking lenalidomide you should tell your doctor
- Traces of lenalidomide have been found in semen. If your partner is able to become pregnant, and she doesn't use effective contraception, you must use condoms, during treatment, during dose interruptions and 7 days after the end of treatment even if you have had a vasectomy.

If your partner does become pregnant whilst you are taking lenalidomide, you should inform your treating doctor immediately.

21.8. Declaration of Helsinki

Initiated: 1964 17.C

Original: English

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly

Helsinki, Finland, June 1964 and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects**.** Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic

methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. *(See footnote*)*
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, reestablishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

***FOOTNOTE:**

Note of Clarification on Paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo controlled trial and that in general this methodology should only be used in the absence

of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm. All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review. 6.10.2002