eProst # 20150402

Long-term Follow-Up and/or Continued Thalidomide (THALOMID®) Maintenance Therapy for Patients Enrolled on Clinical Trial 20030165

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Study Exempt from IND Requirements per 21 CFR 312.2(b).

INVESTIGATOR AGREEMENT

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol.

I have read and understand the information in the Investigators' Brochure (and/or other such pertinent safety information) regarding the risks and potential benefits.

I agree to inform all those who assist/collaborate with me in the conduct of this study of their responsibilities and obligations.

Once the protocol has been reviewed and approved by the Institutional Review Board (IRB) I understand that any change(s) made during the course of the study must also (first) be approved by the IRB prior to implementation, except when such modification is made to remove any immediate hazard(s) to the subject(s).

I certify that I and the study staff responsible, have received the requisite training to conduct this research protocol.

I agree to maintain adequate and accurate records in accordance with the University of Miami policies, federal, state and local laws and regulations.

I agree to maintain the confidentiality of all information received and/or developed in connection with this protocol.

eProst Number:	
Protocol Version Number:	Protocol Version Date:

Signature of Investigator:	Date:
Name of Investigator (printed):	Institution:

PROTOCOL REVISION HISTORY

Version #	Summary of Changes	Version Date

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ABBREVIATIONS & DEFINITIONS

Term	Abbreviation	Definition
Overall Survival	OS	The length of time from either the date of diagnosis or the start of treatment for a disease, that patients diagnosed with the disease are still alive.
Progression-Free Survival	PFS	The length of time during and after the treatment of a disease that a patient lives with the disease but it does not get worse.
Time to Progression	TTP	The length of time from the date of diagnosis or the start of treatment for a disease until the disease starts to get worse or spread to other parts of the body.

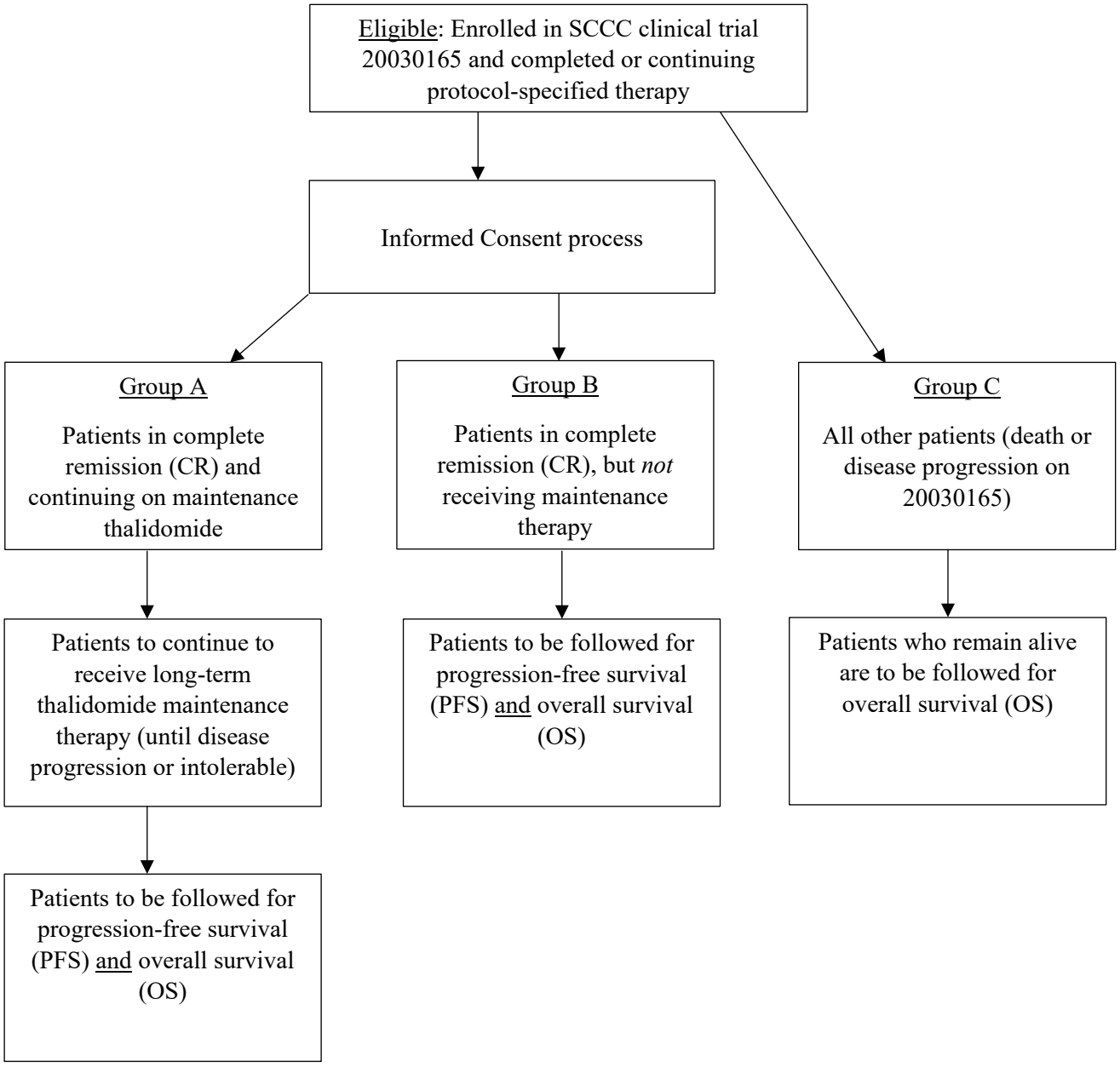
Reference: National Cancer Institute (NCI) Dictionary of Cancer Terms
http://www.cancer.gov/dictionary

PROTOCOL SYNOPSIS

Protocol Title	Long-term Follow-Up and/or Continued Thalidomide (THALOMID®) Maintenance Therapy for Patients Enrolled on Clinical Trial 20030165
Targeted Patient Population	Patients enrolled on Clinical Trial 20030165.
Study Design	The study is designed to provide long-term follow-up and/or to offer continued maintenance thalidomide (THALOMID®) therapy to those patients enrolled in 20030165. Group A: Patients who achieved CR in 20030165 and continue to receive maintenance Thalidomide. Group B: Patients who achieved CR in 20030165, but are not receiving maintenance Thalidomide. Group C: All other patients enrolled in 20030165 who expired or experienced disease progression.
Treatment Schema	Thalidomide (THALOMID®) will be administered as per standard of care guidelines to Group A; in compliance with REMS™ program requirements.
Study Duration	Patients in Group A, B and C will be followed until withdrawal of consent, or death. **Note**: All other patients in Group C who expired on 20030165 will also be included in all analyses.
Follow-up Required	All patients will be followed annually by telephone or in-person visit(s), until death or withdrawal.
Objectives	Primary Objective: To provide long-term follow-up and/or offer continued maintenance thalidomide (THALOMID®) to patients enrolled in 20030165 . Secondary Objective: To continue to evaluate objectives specified for 20030165 (please refer to 20030165 for details).
Expected Number of Patients	Group A: 2 Group B: 12 Group C: 8
Expected Number of Centers	1-Sylvester Comprehensive Cancer Center (SCCC) *Note: SCCC is inclusive of the constituent satellite sites.*

Expected Duration of the Protocol	At least 5 years.
Inclusion Criteria	1. Enrolled on the 20030165 clinical trial. 2. Ability to understand and willingness to sign a written informed consent document.
Exclusion Criteria	1. Patients who were discontinued from 20030165 for any reason prior to the completion of protocol-specified treatment (e.g. withdrawal of consent). 2. Uncontrolled, intercurrent serious illness including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, and/or cardiac arrhythmia. 3. Psychiatric illness/condition likely in the judgment of the Principal Investigator (PI) to limit compliance with clinical study requirements.

PROTOCOL SCHEMA



1.0 BACKGROUND

1.1 Study Disease

Mantle cell lymphoma (MCL), a subtype of non-Hodgkin's lymphoma (NHL) that represents a distinct disease entity. The term MCL was proposed in 1992 to unify previously defined subtypes of NHL, such as diffuse poorly differentiated lymphocytic lymphoma, intermediate differentiated lymphocytic lymphoma, centrocytic lymphoma, and diffuse small cleaved cell lymphoma, into a single disease entity (1). According to the International Lymphoma Study Group (ILSG), MCL represents 6% of all NHLs (2). MCL is derived from a subset of naive pre-germinal center cells, and may present with two cytological variants: typical (lymphocytic) or blastic (3-4). In addition, there are three possible patterns of involvement: mantle-zone, nodular or diffuse (4). It has been suggested that the treatment response and survival of the diffuse and nodular patterns are worse than those involving the mantle cell zone. Majlis et al reported 3-year survival rates for mantle-zone, nodular, and diffuse type of 100%, 50%, and 55% respectively (5). The monoclonal B-cells express CD19, CD20, CD22, HLA-DR, CD5, surface IgM and, in most cases, surface IgD. They are negative for CD23 and CD10 (CALLA) antigens (6).

The characteristic cytogenetic abnormality in MCL is the t(11;14) (q13;q32) translocation. Band 11q23 includes the BCL-1 locus, which is the site of the PRAD1 (CCND1) gene encoding for cyclin D1. This rearrangement results in translocation of the BCL-1 locus to the immunoglobulin heavy chain gene enhancer region located at 14q32, causing cyclin D1 over-expression. Cyclin D1 interacts with cyclin dependent kinases 4 and 6 to facilitate the progression of cell through G1 into S phase of proliferation (7).

MCL is one of the worst types of NHL since it incorporates some of the undesirable features of both low-grade and high-grade lymphomas, namely incurability and rapid course respectively (7). Most of the patients present with advanced stage, high international prognostic index (IPI), and extranodal involvement. The incidence of Stage III and IV varies between 75 to 90% of the patients (2, 4, 6-8). In addition, there is a high incidence of extranodal involvement, the most common sites being bone marrow (61-79%), spleen (31-60%), liver (13-30%), peripheral blood (12-30%), and gastrointestinal tract (18-20%) (6-9). Central nervous system (CNS) involvement occurs in about 4% of the patients and is associated with poor prognosis (10).

The long-term survival for patients with MCL is generally poor, with only about 27% of the patients surviving 5 years after diagnosis and 11% of the patients being disease-free after 5 years. In addition, the ILSG found no 5-year survivors with IPI index 4/5, placing MCL among the lymphomas with worse overall prognosis (2). Despite response rates of 50% to 70% to different regimens, all patients eventually develop disease progression after chemotherapy, with the mean survival around 3 years (11).

1.2 Study Agent

Patients in Group A will receive daily oral thalidomide (THALOMID®) as per standard of care and THALOMID® REMS™ guidelines (formerly known as *S.T.E.P.S.)*.

1.3 Rationale

Several studies using combination chemotherapy with or without anthracyclines (CHOP or COP) showed responses between 56% and 90%, with CR rates ranging from 9% to 58%. However, relapse-free survival was relatively short with average of 15 to 20 months. Median survival in most studies ranged from 28 to 52 months (12). Therapy with fludarabine alone or in combination with other chemotherapeutic agents has been tested in small trials. In a recent study, Cohen et al obtained response rates of 66% (30% CR) in a study involving 30 patients treated with fludarabine and cyclophosphamide. The overall survival for patients receiving this combination as first line therapy has not been reached at 43 months, although failure- free survival was 28 months (13). In another study involving 29 patients, Zinzani et al achieved a 63% overall response (28% CR) using fludarabine alone or in combination with idarubicin (14). Rituximab has also been tested in MCL. Igarashi et al treated 21 patients with refractory or relapsed MCL, achieving a 31% response rate (no CR observed) (15). Howard et al obtained a 96% response rate (48%n CR) in 25 patients with MCL, using a combination of CHOP and rituximab. 25 patients were evaluated for molecular remission, which was seen in 9 of them. However, the achievement of CR or molecular remission did not translate into a prolonged progression-free survival, which was 16.6 months (16). Khouri et al, treated patients with Hyper-CVAD, an aggressive regimen alternating cycles of cyclophosphamide, doxorubicin, vincristine, and dexamethasone and high-dose methotrexate and cytarabine. This regimen induced a 93% response rate with 82% CR. This therapy was followed by stem cell transplantation and 93% of previously untreated patients were alive at 3 years post-transplant, 73% of them disease-free (19).

Although encouraging results have been reported for stem cell transplant (SCT), its role in the treatment of patients with MCL remains unknown. Overall 3-year survival for MCL patients previously treated ranges between 24% to 59%, with one study, performed by Milpied et al, reporting 80% overall survival at 4 years (20- 22). Event-free survival (EFS) or progression-free survival (PFS) at three years however, ranges between 17% to 48% (19, 22). Stewart et al, reported a 23% overall survival for SCT in MCL patients in first remission. EFS/PFS however, was only 8% (23). There have been few small studies on the use of allogeneic SCT in MCL. The reported overall survival is 55% to 62% at 2 years (24-25).

Due to unsatisfactory results obtained with both conventional chemotherapy and SCT, it has become clear that new high-dose intense chemotherapeutic regimens are needed to improve the survival rates for patients with MCL. Similar intensity protocols have been used for treatment of Burkitt's lymphoma. Magrath treated patients with Burkitt's lymphoma using the CODOX-M protocol, which consisted of cyclophosphamide, doxorubicin, prednisone, vincristine, high-dose methotrexate and intrathecal methotrexate, alternating with IVAC (ifosfamide, etoposide, high-dose cytarabine and intrathecal methotrexate). This regimen resulted in excellent disease control and was

relatively well tolerated in both children and adults (17). Mead et al used this same regimen in 52 patients with Burkitt's lymphoma. All patients developed grade ¾ neutropenia and 64% of the patients developed grade ¾ thrombocytopenia. The only other significant side effect was mucositis, observed in about 40% of the cases (18). We have therefore developed a similar intense protocol combining most of the agents that demonstrated activity in MCL in an attempt to provide a better disease control with improved response rates and overall survival.Since a recent study has demonstrated a beneficial effect of thalidomide in patients with mantle cell lymphoma, patients were offered the option to receive maintenance thalidomide after the completion of the induction therapy as a consolidation to the aggressive chemotherapy (25a).

2.0 OBJECTIVES

2.1 Primary Objectives

To provide long-term follow-up and/or offer continued maintenance thalidomide (THALOMID®) to patients enrolled in 20030165.

2.2 Secondary Objectives

To continue to evaluate objectives specified for 20030165 (please refer to 20030165 for details).

3.0 ENDPOINTS

3.1 Primary endpoint

Progression-free survival (PFS): Patients will be evaluated at least annually and at the discretion of the treating Investigator. PFS is defined as the time from 20030165 enrollment until documented disease progression or death (by any cause, in the absence of progression). In progression-free patients, PFS will be censored at the last evaluable tumor assessment (clinical, hematologic, and/or radiographic).

3.1.1 Criteria for Evaluation

- Evaluable for PFS: Any eligible subject enrolled into the SCCC 20030165 study, who received protocol-specified therapy.

3.2 Secondary endpoints

Progression-free survival (PFS): Patients will be evaluated at least annually and at the discretion of the treating Investigator. PFS is defined as the time from 20030165 enrollment until documented disease progression or death (by any cause, in the absence of progression). In progression-free patients, PFS will be censored at the last evaluable tumor assessment (clinical, hematologic, and radiographic).

Overall survival (OS): Patients will be evaluated at least annually. OS is defined as the elapsed time from 20030165 enrollment to death or date of censoring. Patients alive or lost to follow-up will be censored at the last date of contact (or last date known to be alive).

Response rate (RR): Patients will be evaluated at least annually or more frequently as clinically indicated and at the Investigator's discretion. Response rate is defined as the percentage of patients whose cancer shrinks or disappears after treatment.

Toxicity: Monitoring of AEs including serious adverse events (SAEs). AEs will be assessed in terms of nature, grade and attribution to treatment, using the National Cancer institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3.0. Patients on maintenance thalidomide (THALOMID®) will be evaluated for adverse events (AEs) continually while on study.

3.2.1 Criteria for Evaluation

- Evaluable for PFS: Any eligible subject enrolled into the SCCC 20030165 study, who received protocol-specified therapy.
- Evaluable for OS: Any eligible subject enrolled into the SCCC 20030165 study, who received protocol-specified therapy.
- Evaluable for RR: Eligible patients enrolled into the SCCC 20030165 study, who receive protocol-specified therapy.
- Evaluable for Toxicity: Eligible patients in Group A, enrolled into the SCCC 20030165 study, who experience AEs while receiving thalidomide (THALOMID®).

4.0 SUBJECT SCREENING & RECRUITMENT

Patients enrolled on the 20030165 clinical trial are eligible for this trial and will be offered enrollment to this study.

5.0 PATIENT SELECTION

5.1 Inclusion Criteria

5.1.1 Enrolled on the 20030165 clinical trial.

5.1.2 Ability to understand and willingness to sign a written informed consent document.

5.2 Exclusion Criteria

5.2.1 Patients who were discontinued from 20030165 for any reason prior to the completion of protocol-specified treatment (e.g. withdrawal of consent).

5.2.2 Uncontrolled, intercurrent serious illness including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, and/or cardiac arrhythmia likely in the judgment of the PI to interfere with clinical study requirements.

5.2.3 Psychiatric illness/condition likely in the judgment of the PI to limit compliance with clinical study requirements.

6.0 Enrollment Procedures

To enter a patient, the Investigator or Study Team will contact the Clinical Research Services' (CRS) Representative. All eligibility requirements must be reviewed prior to the patient entering the study. The following information must be provided to the CRS Representative:

1) Completed and signed protocol-specific eligibility checklist;
2) All pages of the original signed informed consent form (ICF) including HIPAA Form B;
3) Relevant source documents *such as*: subject medical history and physical exam, admission or discharge notes, diagnostic reports, pathologic confirmation of diagnosis, and relevant subject-specific written communication.

6.1 Cancellation Guidelines

If a patient does not wish to receive protocol therapy (i.e. for those in Group A) or to be followed, the patient may withdraw. Contact the CRS Representative, or e-mail the information including the reasons for withdrawal.

6.2 Emergency Registration

If an emergency registration takes place after business hours, the items listed above must be submitted by the next business day.

7.0 STUDY DESIGN

The study is designed to provide long-term follow-up, as well as to offer continued thalidomide (THALOMID®) maintenance therapy to patients enrolled in 20030165.

There are 14 eligible patients in Groups A and B expected to rollover from 20030165. An additional Group C consisting of all other patients who expired or experienced disease progression on 20030165, will also be included in all analyses.

8.0 TREATMENT PLAN

8.1 Thalidomide (THALOMID®) for Group A

Thalidomide (THALOMID®) will be administered as per standard of care guidelines, in compliance with THALOMID® REMS™ program requirements.

For additional information on thalidomide (THALOMID®) including mechanism of action, drug metabolism, pharmacokinetics & toxicology, known side effects, composition, and storage recommendations, see [Section 9.1].

8.2 Treatment Dispensation, Compliance and Accountability of thalidomide (THALOMID®) for Group A

Thalidomide will be administered in the outpatient setting as per standard of care guidelines, in compliance with THALOMID® REMS™ program requirements.

8.3 Supportive Care Guidelines

Appropriate supportive care as per institutional guidelines should be given, as necessary.

8.4 Drug Interactions and Precautions

The use of opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants concomitantly with THALOMID® may cause an additive sedative effect and should be avoided.

Drugs which cause bradycardia or peripheral neuropathy may cause additive effects and should be used with caution.

Hormonal contraceptives increase the risk of thromboembolism.

Concomitant use of HIV-protease inhibitors, griseofulvin, modafinil, penicillins, rifampin, rifabutin, phenytoin, carbamazepine, or certain herbal supplements such as St. John's Wort with hormonal contraceptive agents may reduce the effectiveness of the contraception up to one month after discontinuation of these concomitant therapies.

8.4.1 *Concurrent Medications*

Concurrent medications will not be captured as part of this trial.

8.5 Duration of Treatment

Group A: Patients will continue with thalidomide (THALOMID®) as per standard of care guidelines, until progression of disease, discontinuation due to toxicity, death or study withdrawal. Patients who discontinue thalidomide for any reason other than death, or withdrawal of consent will continue to be followed as per Section 8.6.

See Section 12.0 for evaluations.

8.6 **Duration of Follow-Up**

Patients will be followed annually until death or withdrawal from the study. See Section 12.0 for evaluations.

9.0 **AGENTS (DRUG FORMULATION AND PROCUREMENT)**

9.1 **Thalidomide (THALOMID®)**

[Refer to the FDA-approved package insert for more information (26).]

9.1.1 THALOMID®, thalidomide

9.1.2 Mechanism of Action

The mechanism of action of THALOMID is not fully understood. THALOMID possesses immunomodulatory, antiinflammatory and antiangiogenic properties. Available data from in vitro studies and clinical trials suggest that the immunologic effects of this compound can vary substantially under different conditions, but may be related to suppression of excessive tumor necrosis factor-alpha (TNF-α) production and down-modulation of selected cell surface adhesion molecules involved in leukocyte migration. For example, administration of thalidomide has been reported to decrease circulating levels of TNF-α in patients with erythema nodosum leprosum (ENL); however, it has also been shown to increase plasma TNF-α levels in HIV-seropositive patients. Other anti-inflammatory and immunomodulatory properties of thalidomide may include suppression of macrophage involvement in prostaglandin synthesis, and modulation of interleukin-10 and interleukin-12 production by peripheral blood mononuclear cells. Thalidomide treatment of multiple myeloma patients is accompanied by an increase in the number of circulating natural killer cells, and an increase in plasma levels of interleukin-2 and interferon-gamma (T cell-derived cytokines associated with cytotoxic activity). Thalidomide was found to inhibit angiogenesis in a human umbilical artery explant model in vitro. The cellular processes of angiogenesis inhibited by thalidomide may include the proliferation of endothelial cells.

9.1.3 Drug Metabolism, Pharmacokinetics and Toxicology

In a C-radiolabel ADME study in humans, unchanged drug is the predominant circulating component. Thalidomide is not a substrate of the cytochrome P450 system. At therapeutic concentrations, thalidomide is not an inhibitor or inducer of human cytochrome P450 enzymes in vitro. Pharmacokinetic drug-drug interactions with substrates, inhibitors or inducers of CYP450 are not anticipated.

Nonclinical Toxicology: Two-year carcinogenicity studies were conducted in male and female rats and mice. No compound-related tumorigenic effects were observed at the highest dose levels of 3,000 mg/kg/day to male and female mice (38-fold greater than the highest recommended daily human dose of 400 mg based upon body surface area [BSA]), 3,000 mg/kg/day to female rats (75-fold the maximum human dose based upon BSA), and 300 mg/kg/day to male rats (7.5-fold the maximum human dose based upon BSA).

Thalidomide was neither mutagenic nor genotoxic in the following assays: the Ames bacterial (S. typhimurium and E. coli) reverse mutation assay, a Chinese hamster ovary cell (AS52/XPRT) forward mutation assay, and an in vivo mouse micronucleus test.

Fertility studies were conducted in male and female rabbits; no compound-related effects in mating and fertility indices were observed at any oral thalidomide dose level including the highest of 100 mg/kg/day to female rabbits and 500 mg/kg/day to male rabbits (approximately 5- and 25-18 fold the maximum human dose, respectively, based upon BSA). Testicular pathological and histopathological effects (classified as slight) were seen in male rabbits at dose levels ≥30 mg/kg/day (approximately 1.5-fold the maximum human dose based upon BSA).

9.1.4 Management of Agent-Specific Adverse Events

Most patients taking thalidomide can be expected to experience adverse reactions.

Teratogenicity:

The most serious toxicity associated with thalidomide is its documented human teratogenicity. The risk of severe birth defects, primarily phocomelia or death to the fetus, is extremely high during the critical period of pregnancy. The critical period is estimated, depending on the source of information, to range from 35 to 50 days after the last menstrual period. The risk of other potentially severe birth defects outside this critical period is unknown, but may be significant. Based on present knowledge, thalidomide must not be used at any time during pregnancy. Because thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex or synthetic condom during any sexual contact with females of reproductive potential, even if he has undergone a successful vasectomy.

Venous and Arterial Thromboembolism:

An increased risk of venous thromboembolism (such as deep vein thrombosis and pulmonary embolism), ischemic heart disease (including myocardial

infarction), and stroke have been reported in patients with multiple myeloma treated with thalidomide [see Venous and Arterial Thromboembolism].

Peripheral Neuropathy:

Peripheral neuropathy is a very common, potentially severe, adverse reaction of treatment with thalidomide that may result in irreversible damage. Peripheral neuropathy generally occurs following chronic use over a period of months. However, reports following relatively short-term use also exist. Incidence of neuropathy events leading to discontinuation, dose reduction or interruption increases with cumulative dose and duration of therapy. Symptoms may occur sometime after thalidomide treatment has been stopped and may resolve slowly or not at all.

Somnolence, dizziness, and rash are the most commonly observed adverse reactions associated with the use of thalidomide. Adverse event profiles from clinical trials are summarized in the sections that follow.

Adverse Reactions in Multiple Myeloma Controlled Clinical Trials

The safety analyses were conducted in two controlled clinical studies (Study 1 and Study 2). The safety analysis in Study 1 was conducted on 204 patients who received treatment. Table 1 lists the most common adverse drug reactions (≥ 10%). The most frequently reported adverse reactions were fatigue, hypocalcemia, edema, constipation, sensory neuropathy, dyspnea, muscle weakness, leukopenia, neutropenia, rash/desquamation, confusion, anorexia, nausea, anxiety/agitation , tremor, fever, weight loss, thrombosis/embolism, neuropathy-motor, weight gain, dizziness, and dry skin.

Twenty-three percent of patients (47/204) discontinued due to adverse reactions; 30% (31/102) from the THALOMID/dexamethasone arm and 16% (16/102) from the dexamethasone alone arm.

Table 1: Adverse Drug Reactions Reported in ≥10% of Patients in the THALOMID/Dexamethasone Arm

(Study 1 - Safety Population; N=204)

Organ System Class/Preferred Term	Thal + Dex * (N=102) All Grades n (%)	Grade 3/4 n (%)	Dex Alone* (N=102) All Grades n (%)	Grade 3/4 n (%)
Metabolic/Laboratory	97 (95)	33 (32)	96 (94)	30 (29)
Hypocalcemia	73 (72)	11 (11)	60 (59)	5 (5)
Neurology	92 (90)	30 (29)	76 (74)	18 (18)
Neuropathy-sensory	55 (54)	4 (4)	28 (28)	1 (1)
Confusion	29 (28)	9 (9)	12 (12)	3 (3)
Anxiety/agitation	26 (26)	1 (1)	14 (14)	3 (3)
Tremor	26 (26)	1 (1)	6 (6)	0 (0)
Neuropathy-motor	22 (22)	8 (8)	16 (16)	5 (5)
Dizziness/ lightheadedness	20 (20)	1 (1)	14 (14)	0 (0)
Depressed level of consciousness	16 (16)	3 (3)	3 (3)	3 (3)
Constitutional Symptoms	91 (89)	19 (19)	84 (82)	16 (16)
Fatigue	81 (79)	17 (17)	72 (71)	13 (13)
Fever	24 (24)	1 (1)	20 (20)	3 (3)
Weight loss	23 (23)	1 (1)	21 (21)	2 (2)
Weight gain	22 (22)	1 (1)	13 (18)	0 (0)
Blood/Bone Marrow	88 (86)	29 (29)	96 (94)	19 (19)
Leukocytes (decreased)	36 (35)	6 (6)	30 (29)	3 (3)
Neutrophils (decreased)	32 (31)	10 (10)	24 (24)	10 (10)
Gastrointestinal	83 (81)	22 (22)	70 (69)	8 (8)
Constipation	56 (55)	8 (8)	29 (28)	1 (1)
Anorexia	29 (28)	4 (4)	25 (24)	2 (2)
Nausea	29 (28)	5 (5)	23 (22)	1 (1)
Mouth dryness	12 (12)	1 (1)	6 (6)	0 (0)
Cardiovascular	70 (69)	37 (36)	60 (59)	21 (21)
Edema	58 (56)	6 (6)	47 (46)	4 (4)
Thrombosis/embolism	23 (22)	21 (21)	5 (5)	5 (5)
Pain	64 (63)	10 (10)	66 (65)	15 (15)
Myalgia	17 (17)	0 (0)	14 (14)	1 (1)
Arthralgia	13 (13)	0 (0)	10 (10)	2 (2)
Pulmonary	52 (51)	19 (19)	51 (50)	20 (20)
Dyspnea	43 (42)	13 (13)	32 (31)	15 (15)
Dermatology/Skin	48 (47)	5 (5)	35 (34)	2 (2)
Rash/desquamation	31 (30)	4 (4)	18 (18)	2 (2)
Dry skin	21 (21)	0 (0)	11 (11)	0 (0)
Hepatic	47 (46)	7 (7)	45 (44)	4 (4)
Bilirubin	14 (14)	2 (2)	10 (10)	2 (2)
Musculoskeletal	42 (41)	9 (9)	41 (40)	14 (14)
Muscle weakness	41 (40)	6 (6)	38 (37)	13 (13)

*Treatment-emergent adverse reactions reported in ≥10% of patients in THALOMID/dexamethasone arm and with a ≥1% difference in the THALOMID/dexamethasone arm compared to the dexamethasone alone arm.

The safety analysis in Study 2 was conducted on 466 patients who received treatment. Table 2 lists the most common adverse drug reactions (≥ 10%) that were observed. Table 3 lists the most common Grade 3/4 adverse drug reactions (occurring at > 2%) that were observed. The adverse reactions most often reported by patients treated with THALOMID/dexamethasone were constipation, peripheral edema, tremor, asthenia, dizziness and fatigue. Adverse reactions with a frequency at least 2-fold higher in the THALOMID/dexamethasone group than in the placebo/dexamethasone group include constipation, tremor, deep vein thrombosis and peripheral sensory neuropathy. Twenty-six percent of patients (121/466) discontinued due to adverse events; 37% (86/234) from the THALOMID/dexamethasone arm and 15% (35/232) from the placebo/dexamethasone arm.

Table 2: Adverse Drug Reactions Reported in ≥10% of Patients in the THALOMID/Dexamethasone Arm

(Study 2 - Safety Population; N=466)

MedDRA System Organ Class/Preferred Term	Thal/Dex (N=234)* n (%)	Placebo/Dex (N=232)* n (%)
Patients with at least 1 Adverse Reaction	**233 (99)**	**230 (99)**
General Disorders and Administration Site Conditions	**176 (75)**	**149 (64)**
Edema peripheral	80 (34)	57 (25)
Asthenia	56 (24)	47 (20)
Fatigue	50 (21)	36 (16)
Edema NOS	31 (13)	19 (8)
Gastrointestinal Disorders	**162 (69)**	**149 (64)**
Constipation	116 (50)	49 (21)
Nausea	30 (13)	27 (12)
Dyspepsia	27 (11)	21 (9)
Nervous System Disorders	**161 (69)**	**138 (60)**
Tremor	62 (26)	29 (12)
Dizziness	51 (23)	32 (14)
Paraesthesia	27 (12)	15 (6)
Peripheral sensory neuropathy	24 (10)	12 (5)
Infections and Infestations	**139 (59)**	**138 (60)**
Pneumonia NOS	35 (15)	28 (12)
Psychiatric Disorders	**90 (38)**	**97 (42)**
Anxiety	27 (12)	22 (10)
Depression	24 (10)	19 (8)
Metabolism and Nutrition Disorders	**96 (41)**	**89 (38)**
Hyperglycemia NOS	36 (15)	32 (14)
Vascular Disorders	**92 (39)**	**53 (23)**
Deep vein thrombosis	30 (13)	4 (2)

*All adverse reactions reported in ≥10% of patients in THALOMID/dexamethasone arm and with a ≥1% difference in proportion of patients between the THALOMID/dexamethasone arm compared to the placebo/dexamethasone arm.

MedDRA = Medical Dictionary for Regulatory Activities; NOS = not otherwise specified.

Table 3: Grade 3/4 Adverse Drug Reactions Reported in >2% of Patients in the THALOMID/Dexamethasone Arm (Study 2 - Safety Population; N=466)

MedDRA System Organ Class/Preferred Term	THALOMID/Dex (N=234)* n (%)	Placebo/Dex (N=232)* n (%)
Infections and Infestations	**50 (21)**	**36 (16)**
Pneumonia NOS	17 (7)	14 (6)
Bronchopneumonia NOS	7 (3)	3 (1)
General Disorders and Administration Site Conditions	**44 (19)**	**26 (11)**
Asthenia	11 (5)	4 (2)
Metabolism and Nutrition Disorders	**33 (14)**	**34 (15)**
Hypokalemia	7 (3)	3 (1)
Nervous System Disorders	**47 (20)**	**20 (9)**
Syncope	8 (3)	1 (<1)
Peripheral neuropathy NOS	8 (3)	0 (0)
Cerebrovascular accident	6 (3)	1 (<1)
Cardiac Disorders	**35 (15)**	**27 (11)**
Atrial fibrillation	11 (5)	8 (3)
Myocardial ischemia	6 (3)	2 (1)
Vascular Disorders	**42 (18)**	**14 (6)**
Deep vein thrombosis	27 (12)	4 (2)
Gastrointestinal Disorders	**26 (11)**	**22 (10)**
Constipation	7 (3)	2 (1)
Investigations	**21 (9)**	**21 (9)**
Weight increased	8 (3)	4 (2)
Blood and Lymphatic System Disorders	**24 (10)**	**17 (7)**
Neutropenia	8 (3)	6 (3)
Respiratory, Thoracic, and Mediastinal Disorders	**27 (12)**	**13 (6)**
Pulmonary embolism	16 (7)	4 (2)
Psychiatric Disorders	**19 (8)**	**8 (3)**
Anxiety	5 (2)	3 (1)
Confusional state	5 (2)	2 (1)
Ear and Labyrinth Disorders	**6 (3)**	**0 (0)**
Vertigo	5 (2)	0 (0)

*All Grade 3/4 adverse reactions with >2% of patients in THALOMID/dexamethasone arm and with a higher frequency in the THALOMID/dexamethasone arm compared to the placebo/dexamethasone arm.

MedDRA = Medical Dictionary for Regulatory Activities; NOS = not otherwise specified.

Less Common Adverse Drug Reactions in Multiple Myeloma Controlled Clinical Trials

In Study 2, THALOMID in combination with dexamethasone in patients with multiple myeloma, the following adverse drug reactions not described above were reported*:

Gastrointestinal disorders: Vomiting NOS, dry mouth, peritonitis, diverticular perforation

Nervous system disorders: Somnolence, hypoesthesia, polyneuropathy NOS, transient ischemic attack

Respiratory, thoracic, and mediastinal disorders: Bronchitis NOS

Psychiatric disorders: Mood alteration NOS

Vascular disorders: Hypotension NOS, orthostatic hypotension

Cardiac disorders: Bradycardia NOS

Eye disorders: Blurred vision

* All adverse reactions with ≥3% of patients in THALOMID/dexamethasone arm and with a ≥1% difference in proportion of patients between the THALOMID/dexamethasone arm compared to the placebo/dexamethasone arm. All grade 3/4 and serious adverse reactions reported >2 patients in THALOMID/dexamethasone arm and with a percentage higher in the THALOMID/dexamethasone arm compared to the placebo/dexamethasone arm have been considered for possible inclusion. In any cases medical judgment has been applied for consideration of causality assessment.

Adverse Reactions in Erythema Nodosum Leprosum (ENL) Clinical Trials

Table 4 lists treatment-emergent signs and symptoms that occurred in THALOMID-treated patients in clinical trials in ENL. The most common adverse reactions (≥10%) reported in patients with ENL were somnolence, rash, headache. Doses ranged from 50 to 300 mg/day. All adverse reactions were mild to moderate in severity, and none resulted in discontinuation.

Table 4: Summary of Adverse Events (AEs)
Reported in Celgene-sponsored Controlled Clinical Trials

Body System/Adverse Event	All AEs Reported in Patients with ENL	AEs Reported in ≥3 HIV-seropositive Patients		
		Thalidomide		Placebo
	50 to 300 mg/day (N=24)	100 mg/day (N=36)	200 mg/day (N=32)	(N=35)
Body as a Whole	**16 (66.7%)**	**18 (50.0%)**	**19 (59.4%)**	**13 (37.1%)**
Abdominal pain	1 (4.2%)	1 (2.8%)	1 (3.1%)	4 (11.4%)
Accidental injury	1 (4.2%)	2 (5.6%)	0	1 (2.9%)
Asthenia	2 (8.3%)	2 (5.6%)	7 (21.9%)	1 (2.9%)
Back pain	1 (4.2%)	2 (5.6%)	0	0
Chills	1 (4.2%)	0	3 (9.4%)	4 (11.4%)
Facial edema	1 (4.2%)	0	0	0
Fever	0	7 (19.4%)	7 (21.9%)	6 (17.1%)
Headache	3 (12.5%)	6 (16.7%)	6 (18.7%)	4 (11.4%)
Infection	0	3 (8.3%)	2 (6.3%)	1 (2.9%)
Malaise	2 (8.3%)	0	0	0
Neck pain	1 (4.2%)	0	0	0
Neck rigidity	1 (4.2%)	0	0	0
Pain	2 (8.3%)	0	1 (3.1%)	2 (5.7%)
Digestive System	**5 (20.8%)**	**16 (44.4%)**	**16 (50.0%)**	**15 (42.9%)**
Anorexia	0	1 (2.8%)	3 (9.4%)	2 (5.7%)
Constipation	1 (4.2%)	1 (2.8%)	3 (9.4%)	0
Diarrhea	1 (4.2%)	4 (11.1%)	6 (18.7%)	6 (17.1%)
Dry mouth	0	3 (8.3%)	3 (9.4%)	2 (5.7%)
Flatulence	0	3 (8.3%)	0	2 (5.7%)
Liver function tests multiple abnormalities	0	0	3 (9.4%)	0
Nausea	1 (4.2%)	0	4 (12.5%)	1 (2.9%)
Oral moniliasis	1 (4.2%)	4 (11.1%)	2 (6.3%)	0
Tooth pain	1 (4.2%)	0	0	0
Hemic and Lymphatic	**0**	**8 (22.2%)**	**13 (40.6%)**	**10 (28.6%)**
Anemia	0	2 (5.6%)	4 (12.5%)	3 (8.6%)
Leukopenia	0	6 (16.7%)	8 (25.0%)	3 (8.6%)
Lymphadenopathy	0	2 (5.6%)	4 (12.5%)	3 (8.6%)
Metabolic and Endocrine Disorders	**1 (4.2%)**	**8 (22.2%)**	**12 (37.5%)**	**8 (22.9%)**
Edema peripheral	1 (4.2%)	3 (8.3%)	1 (3.1%)	0
Hyperlipemia	0	2 (5.6%)	3 (9.4%)	1 (2.9%)
SGOT increased	0	1 (2.8%)	4 (12.5%)	2 (5.7%)
Nervous System	**13 (54.2%)**	**19 (52.8%)**	**18 (56.3%)**	**12 (34.3%)**
Agitation	0	0	3 (9.4%)	0
Dizziness	1 (4.2%)	7 (19.4%)	6 (18.7%)	0
Insomnia	0	0	3 (9.4%)	2 (5.7%)
Nervousness	0	1 (2.8%)	3 (9.4%)	0
Neuropathy	0	3 (8.3%)	0	0
Paresthesia	0	2 (5.6%)	5 (15.6%)	4 (11.4%)
Somnolence	9 (37.5%)	13 (36.1%)	12 (37.5%)	4 (11.4%)
Tremor	1 (4.2%)	0	0	0
Vertigo	2 (8.3%)	0	0	0
Respiratory System	**3 (12.5%)**	**9 (25.0%)**	**6 (18.7%)**	**9 (25.7%)**
Pharyngitis	1 (4.2%)	3 (8.3%)	2 (6.3%)	2 (5.7%)
Rhinitis	1 (4.2%)	0	0	4 (11.4%)
Sinusitis	1 (4.2%)	3 (8.3%)	1 (3.1%)	2 (5.7%)
Skin and Appendages	**10 (41.7%)**	**17 (47.2%)**	**18 (56.3%)**	**19 (54.3%)**
Acne	0	4 (11.1%)	1 (3.1%)	0
Dermatitis fungal	1 (4.2%)	2 (5.6%)	3 (9.4%)	0
Nail disorder	1 (4.2%)	0	1 (3.1%)	0
Pruritus	2 (8.3%)	1 (2.8%)	2 (6.3%)	2 (5.7%)
Rash	5 (20.8%)	9 (25.0%)	8 (25.0%)	11 (31.4%)
Rash maculopapular	1 (4.2%)	6 (16.7%)	6 (18.7%)	2 (5.7%)
Sweating	0	0	4 (12.5%)	4 (11.4%)
Urogenital System	**2 (8.3%)**	**6 (16.7%)**	**2 (6.3%)**	**4 (11.4%)**
Albuminuria	0	3 (8.3%)	1 (3.1%)	2 (5.7%)
Hematuria	0	4 (11.1%)	0	1 (2.9%)
Impotence	2 (8.3%)	1 (2.8%)	0	0

Other Adverse Events Observed in ENL Patients

THALOMID in doses up to 400 mg/day has been administered investigationally in the United States over a 19-year period in 1465 patients with ENL. The published literature describes the treatment of an additional 1678 patients. To provide a meaningful estimate of the proportion of the individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using a modified COSTART dictionary/terminology. These categories are used in the listing below. All reported events are included except those already listed in the previous table. Due to the fact that these data were collected from uncontrolled studies, the incidence rate cannot be determined. No causal relationship between THALOMID and these events can be conclusively determined at this time. These are reports of all adverse events noted by investigators in patients to whom they had administered thalidomide.

Body as a Whole: Abdomen enlarged, fever, photosensitivity, upper extremity pain.

Cardiovascular System: Bradycardia, hypertension, hypotension, peripheral vascular disorder, tachycardia, vasodilation.

Digestive System: Anorexia, appetite increase/weight gain, dry mouth, dyspepsia, enlarged liver, eructation, flatulence, increased liver function tests, intestinal obstruction, vomiting.

Hemic and Lymphatic: ESR decrease, eosinophilia, granulocytopenia, hypochromic anemia, leukemia, leukocytosis, leukopenia, MCV elevated, RBC abnormal, spleen palpable, thrombocytopenia.

Metabolic and Endocrine: ADH inappropriate, amyloidosis, bilirubinemia, BUN increased, creatinine increased, cyanosis, diabetes, edema, electrolyte abnormalities, hyperglycemia, hyperkalemia, hyperuricemia, hypocalcemia, hypoproteinemia, LDH increased, phosphorus decreased, SGPT increased.

Muscular Skeletal: Arthritis, bone tenderness, hypertonia, joint disorder, leg cramps, myalgia, myasthenia, periosteal disorder.

Nervous System: Abnormal thinking, agitation, amnesia, anxiety, causalgia, circumoral paresthesia, confusion, depression, euphoria, hyperesthesia, insomnia, nervousness, neuralgia, neuritis, neuropathy, paresthesia, peripheral neuritis, psychosis.

Respiratory System: Cough, emphysema, epistaxis, pulmonary embolus, rales, upper respiratory infection, voice alteration.

Skin and Appendages: Acne, alopecia, dry skin, eczematous rash, exfoliative dermatitis, ichthyosis, perifollicular thickening, skin necrosis, seborrhea, sweating, urticaria, vesiculobullous rash.

Special Senses: Amblyopia, deafness, dry eye, eye pain, tinnitus.

Urogenital: Decreased creatinine clearance, hematuria, orchitis, proteinuria, pyuria, urinary frequency.

Other Adverse Events Observed in HIV-seropositive Patients

In addition to controlled clinical trials, THALOMID has been used in uncontrolled studies in 145 patients. Less frequent adverse events that have been reported in these HIV-seropositive patients treated with THALOMID were grouped into a smaller number of standardized categories using modified COSTART dictionary/terminology and these categories are used in the listing below. Adverse events that have already been included in the tables and narrative above, or that are too general to be informative are not listed.

Body as a Whole: Ascites, AIDS, allergic reaction, cellulitis, chest pain, chills and fever, cyst, decreased CD4 count, facial edema, flu syndrome, hernia, thyroid hormone level altered, moniliasis, photosensitivity reaction, sarcoma, sepsis, viral infection.

Cardiovascular System: Angina pectoris, arrhythmia, atrial fibrillation, bradycardia, cerebral ischemia, cerebrovascular accident, congestive heart failure, deep thrombophlebitis, heart arrest, heart failure, hypertension, hypotension, murmur, myocardial infarct, palpitation, pericarditis, peripheral vascular disorder, postural hypotension, syncope, tachycardia, thrombophlebitis, thrombosis.

Digestive System: Cholangitis, cholestatic jaundice, colitis, dyspepsia, dysphagia, esophagitis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gum disorder, hepatitis, pancreatitis, parotid gland enlargement, periodontitis, stomatitis, tongue discoloration, tooth disorder.

Hemic and Lymphatic: Aplastic anemia, macrocytic anemia, megaloblastic anemia, microcytic anemia.

Metabolic and Endocrine: Avitaminosis, bilirubinemia, dehydration, hypercholesteremia, hypoglycemia, increased alkaline phosphatase, increased lipase, increased serum creatinine, peripheral edema.

Muscular Skeletal: Myalgia, myasthenia.

Nervous System: Abnormal gait, ataxia, decreased libido, decreased reflexes, dementia, dysesthesia, dyskinesia, emotional lability, hostility, hypalgesia, hyperkinesia, incoordination, meningitis, neurologic disorder, tremor, vertigo.

Respiratory System: Apnea, bronchitis, lung disorder, lung edema, pneumonia (including Pneumocystis carinii pneumonia), rhinitis.

Skin and Appendages: Angioedema, benign skin neoplasm, eczema, herpes simplex, incomplete Stevens-Johnson syndrome, nail disorder, pruritus, psoriasis, skin discoloration, skin disorder.

Special Senses: Conjunctivitis, eye disorder, lacrimation disorder, retinitis, taste perversion.

Postmarketing Experience

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

Cardiovascular System: Cardiac arrhythmias including atrial fibrillation, bradycardia, tachycardia, sick sinus syndrome, EKG abnormalities, myocardial infarction.

Digestive System: Intestinal perforation, gastrointestinal perforations, intestinal obstruction.

Metabolic and Endocrine: Electrolyte imbalance including hypercalcemia or hypocalcemia, hyperkalemia and hypokalemia, hyponatremia, hypothyroidism, increased alkaline phosphatase, tumor lysis syndrome.

Nervous System: Changes in mental status or mood including depression and suicide attempts, disturbances in consciousness including lethargy, syncope, loss of consciousness or stupor, seizures including grand mal convulsions and status epilepticus, Parkinson's disease, stroke.

Skin and Appendages: Erythema multiforme, toxic epidermal necrolysis.

Hemic and Lymphatic: Decreased white blood cell counts including neutropenia and febrile neutropenia, changes in prothrombin time, pancytopenia.

Respiratory System: Pleural effusion.

Reproductive System and Breast Disorders: amenorrhea, sexual dysfunction.

Immune System Disorders: Hypersensitivity, angioedema/urticaria.

Ear and Labyrinthine Disorders: Hearing impairment/deafness.

Renal and Urinary Disorders: Renal failure.

Other Adverse Events in the Published Literature or Reported from Other Sources

The following additional events have been identified either in the published literature or from spontaneous reports from other sources: acute renal failure, amenorrhea, aphthous stomatitis, bile duct obstruction, carpal tunnel, chronic myelogenous leukemia, diplopia, dysesthesia, dyspnea, enuresis, erythema nodosum, erythroleukemia, foot drop, galactorrhea, gynecomastia, hangover effect, hypomagnesemia, hypothyroidism, lymphedema, lymphopenia, metrorrhagia, migraine, myxedema, nodular sclerosing Hodgkin's disease, nystagmus, oliguria, pancytopenia, petechiae, purpura, Raynaud's syndrome, stomach ulcer, suicide attempt, interstitial lung disease and severe infections (e.g., fatal sepsis including septic shock).

9.1.5 Composition and Dosage Forms

Dosage forms and composition			
Strength	Color	Imprint	Non-medicinal ingredients
50 mg	White opaque	Do Not Get Pregnant woman logo CELGENE 50 mg	pregelatinized starch and magnesium stearate; capsule shell contains gelatin, titanium dioxide and black ink*
100 mg	Tan opaque	Do Not Get Pregnant woman logo CELGENE 100 mg	pregelatinized starch and magnesium stearate; capsule shell contains gelatin, black iron oxide, yellow iron oxide, titanium dioxide, and black ink*
200 mg	Blue opaque	Do Not Get Pregnant woman logo CELGENE 200 mg	pregelatinized starch and magnesium stearate; capsule shell contains gelatin, FD&C blue #2, titanium dioxide, and white ink

* The 50 mg and 100 mg capsule shells have black ink which contains shellac and black iron oxide.

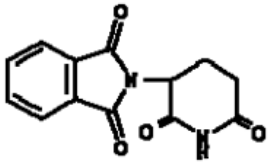
Drug Substance:

Proper name: thalidomide

Chemical name: α-(N-phthalimido) glutarimide

Molecular formula and molecular mass: $C_{13}H_{10}N_2O_4$, 258.2 g

Structural formula:



Physicochemical properties: Thalidomide is an off-white to white, odorless, crystalline powder that is soluble at 25℃ in dimethyl sulfoxide and sparingly soluble in water and ethanol. The glutarimide moiety contains a single asymmetric center and, therefore, may exist in either of two optically active forms designated S-(-) or R-(+). Thalidomide used in THALOMID® contains an equal mixture of the S-(-) and R-(+) forms and, therefore, has a net optical rotation of zero.

9.1.6 Storage Recommendations

Store at 15-30º C. Keep out of the reach of children.

9.1.7 Dispensation and Accountability

THALOMID® is only available through a controlled distribution program called THALOMID® REMS™. Under this program, only enrolled prescribers and program-certified pharmacists are able to prescribe and dispense the product. In addition, THALOMID® can only be dispensed to patients who are registered and meet all the conditions of the REMS™ program.

For more information, call the manufacturer (Celgene Customer Care Center) toll-free number at 1-888-423-5436 or log on to the www.CelgeneRiskManagement.com website.

9.1.8 SPECIAL HANDLING INSTRUCTIONS

Currently, no published data are available regarding the cutaneous absorption of thalidomide.

Most health care institutions recommend that latex gloves be worn while handling chemotherapeutic agents. Health care providers may consider wearing gloves when directly handling THALOMID® (thalidomide capsules), along with standard hand washing. Females who could become pregnant, or who plan to become pregnant can handle THALOMID® capsules if they are using latex gloves.

Repackaging of THALOMID® must only be done on exceptional circumstances. This should only be done by pharmacists.

10.0 TREATMENT/ DOSE MODIFICATIONS

10.1 Unacceptable Toxicity

Development of grade 3-4 peripheral neuropathy that is considered to be related (possibly, probably or definitely) and unacceptable (because of severity and/or irreversibility) will require THALIDOMIDE discontinuation.

10.2 Dose Modification Guidelines for Thalidomide (THALOMID®)

Thalidomide (THALOMID®) will be administered as per standard of care guidelines and in compliance with REMS™ program requirements.

11.0 STUDY/TREATMENT DISCONTINUATION

Study participation/Treatment may be discontinued for any of the following reasons:

- The patient withdraws consent from the study
- (**Group A**): The patient experiences an adverse event that in the opinion of the Investigator makes continued study treatment an unacceptable risk
- (**Group A**): The patient experiences unacceptable toxicity as described in Section 10.1
- The patient is significantly noncompliant with the requirements of the protocol

Should discontinuation of study therapy occur (for Group A patients), all efforts should be made to execute/ report End-of-Treatment and/or Follow-up Evaluations as completely as possible *and* to determine/ document the reason for discontinuation (unless the patient withdraws consent).

If a patient wishes to withdraw consent from the study, the PI must be notified. The information regarding withdrawal (i.e. subject identifiers and date of withdrawal) should be documented in the subject's record and updated within any other research database(s).

12.0 SCHEDULE OF CLINICAL & LABORATORY EVALUATIONS

12.1 Pre-Treatment Evaluations (Screening)

Prior to performing any study-specific procedures or evaluations, written informed consent and authorization for the use of protected health information (HIPAA) must be obtained in accordance with all applicable policies, regulations and laws.

12.2 Evaluations on Treatment for Group A

The following evaluations should be performed as described. Additional tests are at the discretion of the Investigator.

12.2.1 Monthly (every 4 weeks, ±5 days)

- **Additional for Women of Childbearing Potential (WoCBP) receiving thalidomide maintenance therapy (Group A):** Serum pregnancy test: (beta-HCG)
- Adverse Events (AEs): Monitoring and collection of Adverse Events (AEs) should occur throughout the study for patients in Group A.

12.2.2 Annually (every 12 months, ±30 days)

- Physical exam (PE)
- Complete Blood Count (CBC), including
  - Differential (diff) and
  - Platelet count (PLT)
- Comprehensive Metabolic Panel (CMP)
- Lactate dehydrogenase (LDH)

12.3 Evaluations on Study for Group B

The following evaluations should be performed as described. Additional tests are at the discretion of the Investigator.

12.3.1 Annually (every 12 months, ±30 days)

- Physical exam (PE)
- Complete Blood Count (CBC)
  - Differential (diff) and
  - Platelet count (PLT)
- Comprehensive Metabolic Panel (CMP)
- Lactate dehydrogenase (LDH)

12.4 Evaluations on Study for Group C

The following evaluation(s) should be performed as described until death or withdrawal of consent as described. Additional tests are at the discretion of the Investigator.

12.4.1 Annually (every 12 months, ±30 days)

- Survival: contact by telephone or in-person visit; Methods used for attempted contact must also be documented properly.

12.5 Off-Treatment Evaluations (End of Treatment or EOT) for Group A

The following assessments should be performed at the EOT visit and should occur 30-days (± 5 days) after the last dose of thalidomide.

- Physical exam (PE)
- Complete Blood Count (CBC), including
  - Differential (diff) and
  - Platelet count (PLT)

- Comprehensive Metabolic Panel (CMP)
- Lactate dehydrogenase (LDH)
- **(Additional for WoCBP)** Serum pregnancy test: (beta-HCG)

12.6 Follow-up Evaluations for All Patients

The following evaluation should be performed at least annually, until death or withdrawal of consent as described for:

- Survival: contact by telephone or in-person visit; Methods used for attempted contact must also be documented properly.

(For Group A, contact should occur after end of treatment visit; for Group B, contact should occur prior to or after disease progression; survival contact for patients in Group C should continue until death or withdrawal of consent.)

12.7 Calendar of Clinical and Laboratory Evaluations

	Baseline	**Every 4 weeks** (±5 days)	**Every 12 months** (±30 days)	**Off-Treatment [A]**	**Follow-up [B]**
(Group A) thalidomide (THALOMID®)		Once daily [A]			
Informed consent	X				
Eligibility	X				
Physical exam			X	X	
CBC w/diff, plts			X	X	
CMP			X	X	
Lactate dehydrogenase (LDH)			X	X	
Beta-HCG (WoCBP)		X [A]	X [A]	X	
Adverse event evaluation		X [A]			
Survival					X [B]

Footnote(s):
[A] To be done only for patients in Group A
[B] Contact by telephone or in-person visit until death or withdrawal of consent

13.0 MEASUREMENT OF EFFECT

For the purposes of this study, patients should be evaluated for response every as per standard or care until documented disease progression or study withdrawal (for reasons including toxicity and/or death).

13.1 Definitions

Response Category	Physical Exam	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CR (u)	Normal	Normal	Normal or >75% decrease	Normal indeterminate
PR	Normal	Normal or ≥50% decrease	Normal or ≥50% decrease	Positive or irrelevant
Relapse/ Progressive Disease	Enlarging liver, spleen or other sites	New or increased	New or increased	Reappearance

Key: CR=Complete Response; CR(u)=Complete Response/unconfirmed; PR=Partial Response

13.2 Response Criteria

13.2.1 CR requires the following:

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities (e.g. LDH) definitely assignable to NHL.

2. All lymph nodes and nodal masses must have regressed to normal size. Previously involved nodes that were between 1.1 to 1.5 cm in their greatest transverse diameter before treatment, must have decreased to ≤ 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).

3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical exam. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic sizes.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy on the same site.

13.2.2 CR/unconfirmed (CR (u)) requires the following:

1. Residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.

2. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

13.2.3 PR requires the following:

1. > 50% decrease in SPD of the six largest dominant nodes or nodal masses.

2. No increase in the size of other nodes, liver, or spleen.

3. Splenic or hepatic nodules must regress by at least 50% in the SPD.

4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.

5. Bone marrow assessment is irrelevant for the determination of a PR because it is assessable and not measurable disease.

6. No new sites of disease.

13.2.4 Stable disease (SD) is defined as less than a PR but not progressive disease.

13.2.5 Relapsed disease (PD requires the following:

1. Appearance of any new lesion or increase by ≥ 50% in the size of previously involved sites.

2. ≥ 50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

13.2.6 Progressive disease (PR or nonresponders) require the following:

1. ≥50% increase from nadir in the SPD of any previously identified abnormal node for PRs or nonresponders.

2. Appearance of any new lesion during the end of therapy.

13.3 **(Duration of Overall Response)**

(The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.)

13.4 **(Duration of Stable Disease)**

(Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.)

13.5 **Progression-Free Survival (PFS)**

Patients will be followed at a minimum of annual intervals (every 12 months, ±30 days) or as clinically indicated and at the discretion of the Investigator to document the progression-free interval.

13.6 **Overall Survival (OS)**

Patients will be followed at annual intervals to document the overall survival.

14.0 **ADVERSE EVENTS**

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for adverse event reporting.

14.1 **Purpose**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies, as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care.

14.2 **Adverse Event**

Adverse Event (AE): Can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, medical treatment, or procedure without judgment about causality. An adverse event can arise from any use and from any route of administration, formulation, or dose including an overdose. This includes any newly occurring event or a previous condition that has increased in severity or frequency since initiation of a drug, medical treatment, or procedure.

Abnormal Findings

In any clinical assessment, a value outside the normal or reference range (such as a clinical laboratory, vital sign, or ECG) will not be reported or assessed as an AE unless that value is considered to be of clinical significance by the investigator. A value of clinical significance is one that leads to discontinuation or delay in protocol treatment, dose modification, therapeutic intervention*, or is considered to be a clinically significant new finding or change from baseline by the investigator.

*Transfusion support administered to offset clinical symptoms of anemia or thrombocytopenia will not be considered therapeutic intervention.

Signs and Symptoms

Signs/symptoms resulting from an underlying clinical diagnosis should be documented as one comprehensive AE. If no underlying clinical diagnosis can be identified, each sign/symptom should be reported as a separate independent event. (A new or worsening event resulting from an underlying clinical diagnosis or a reaction to concurrent medications should be documented as a separate independent AE unless it is within the normal range of fluctuation for that patient.)

Grade Changes/Fluctuations

AEs will be reported at the maximum grade/severity experienced for the duration of the event. Should one particular event warrant further investigation, additional details may be collected at the discretion of the Principal Investigator.

Progression of Disease

Progression of disease, if documented in accordance to standard of care, should not be reported as an AE.

Tests and Procedures

Tests and procedures should not be reported as AEs. The underlying clinical diagnosis (or sign/symptom in the event an underlying clinical diagnosis is not known) requiring testing or a procedure, should be reported as an adverse event if it meets criteria for reporting.

14.3 Serious Adverse Events (see also Appendix A)

Serious AE (SAE) means any untoward medical occurrence that occurs at any dose:

1. **Results in death.**
2. **Is life-threatening.**
   The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
3. **Requires inpatient hospitalization or prolongation of present hospitalization.**
   Elective hospitalization to simplify protocol treatment/evaluations or to treat a baseline condition that did not worsen from baseline will not be considered an SAE.
4. **Results in persistent or significant disability/incapacity.**
   Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
5. **Is a congenital anomaly/birth defect**.
6. **Is a medically important event.**
   A medically important event may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between the terms *serious* and *severe* because they ARE NOT synonymous. The term *severe* is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

14.4 Adverse Event Collection Period

In this protocol, adverse events include only treatment-emergent adverse events. A treatment-emergent adverse event (TEAE) is defined as any event that begins or worsens after the start of protocol treatment. All baseline-emergent adverse events, any event that begins or worsens after completion of the informed consent but prior to the start of protocol treatment, should be reported as a Baseline/Comorbid Condition.

All adverse events that occur within ≤ 30 days of the last dose of study therapy will be reported and followed until resolution. Resolution is defined as a return to baseline status or the stabilization of an event with the expectation that it will remain chronic. (Exception: If a patient begins an alternative therapy that confounds accurate assessment of AEs within ≤ 30 days of the last dose of study therapy, all adverse event collection will stop and any ongoing events will be left open.)

14.5 Targeted Adverse Event Collection

The targeted collection of the following safety data is specified for this protocol:

- Serious adverse events (unexpected or expected); see also Appendix A
- Potentially serious adverse events, such as suicidality (suicidal ideation or thoughts) or suspected pregnancy in Group A patients
- Adverse events that cause discontinuation of treatment/intervention (e.g. Section 10.1)
- Unexpected adverse events with reasonable causality (possible, probable or definite) to the treatment/intervention

14.6 Adverse Event Reporting Requirements

The information to be reported in AEs will be assessed by and assigned severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3.0. The NCI CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the NCI CTCAE v3.0 can be

downloaded from the CTEP home page (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Information to be reported in the description of each adverse event may be included, but is not limited to:

1. Clinical Diagnosis of the event as determined by NCI CTCAE, Version 3.0 descriptive terminology. If no clinical diagnosis can be identified, each sign/symptom should be reported as a separate independent event.
2. Date of onset of the AE (start date).
3. Date of resolution of the AE (end date).
4. Severity of the event determined by NCI CTCAE, Version 3.0 grading scale.
5. Relationship of the AE to study therapy. Categorized as follows:

Definite	The adverse event is clearly related to the investigational agent(s)
Probable	The adverse event is likely related to the investigational agent(s)
Possible	The adverse event may be related to the investigational agent(s)
Unlikely	The adverse event is doubtfully related to the investigational agent(s)
Unrelated	The adverse event is clearly not related to the investigational agent(s)

6. Whether or not the AE is Serious or Not Serious as defined in Section 14.3 Serious Adverse Events.
7. Whether the AE is Suspected and/or Unexpected.

Suspected	Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE.
Unexpected	Any AE for which the nature or severity of the event is not consistent with the applicable product information, e.g., the Investigator's Brochure or Package Insert.

8. Action taken as a result of the AE.
9. Outcome.

14.7 Expedited Adverse Event Reporting Requirements

All applicable AEs, regardless if serious or not, will be described in the source documents, reported on the applicable AE log, and entered into *Velos*. However, certain adverse events must also be reported in an expedited manner for more timely monitoring of patient safety and care. Appendix A provides information about these expedited reporting requirements.

15.0 STATISTICAL CONSIDERATIONS

At this time, no formal statistical analysis is planned for this long-term follow-up study. If necessary, and as deemed by the Principal Investigator (PI), the results of this trial will be integrated with the 20030165 trial analyses.

16.0 DATA REPORTING

Data must be submitted according to the protocol requirements for all patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

16.1 Data and Safety Monitoring

The Sylvester Comprehensive Cancer Center (SCCC) Data and Safety Monitoring Committee (DSMC) will monitor this clinical trial according to the Cancer Center's DSM Plan. In its oversight capacity, the DSMC bears responsibility for suspending or terminating this study. DSMC oversight of the conduct of this trial includes ongoing review of accrual and adverse event (AE) data, and periodic review of the study therapy. The guidelines appearing in section 7.0 are offered for DSMC consideration in assessing AEs or other study endpoint(s). In addition, the DSMC will review reports from all audits, site visits, or study reviews pertaining to this clinical trial and take appropriate action. The SCCC DSM Plan to which this study is subject can also be found at www.sylvester.org.

17.0 INVESTIGATOR RESPONSIBILITIES

17.1 Investigator Responsibility/Performance

The investigator will ensure that this study is conducted in accordance with all regulations governing the protection of human subjects. The investigator will ensure that all work and services described in or associated with this protocol will be conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice.

17.2 Confidentiality

The investigator must ensure that each subject's anonymity will be maintained and each subject's identity will be protected from unauthorized parties. A number will be assigned to each subject upon study entry and the number and the subject's initials will be used to identify the subject for the duration of the study. The investigator will maintain all documents related to this study in strict confidence.

17.3 Informed Consent and Permission to Use Protected Health Information

It is the responsibility of the investigator to obtain written informed consent from each subject participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The investigator must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative conventional therapy as indicated. Prior to study participation, each subject will sign an IRB approved informed consent form and receive a copy of same (and information leaflet, if appropriate). For subjects not qualified or able to give legal consent, consent must be obtained from a parent, legal guardian, or custodian. The investigator or designee **must** explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB. It is the investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject, or if appropriate, the subjects' parent or legal guardian.

17.4 Source Documentation and Investigator Files

The investigator must maintain adequate and accurate records to fully document the conduct of the study and to ensure that study data can be subsequently verified. These documents should be classified into two separate categories: (1) investigator study file and (2) subject clinical source documents that corroborate data collected on CRFs within *Velos*. Subject clinical source documents may include hospital/clinic patient records; physician's and nurse's notes; appointment book; original laboratory, ECG, EEG, radiology, pathology, and special assessment reports; pharmacy dispensing records; subject diaries; signed informed consent forms; and consultant letters. When the CRF or any form is used as the source document, this must be clearly stated in the investigator study file. Minimally, the following be documented in source documents:

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify protocol entry criteria
- Study number, assigned subject number, and verification that written informed consent was obtained (each recorded in dated and signed notes on the day of entry into the study)
- Progress notes for each subject visit
- Documentation of treatment
- Laboratory test results
- Adverse events (action taken and resolution)
- Condition and response of subject upon completion of or early termination from the study

17.5 Recording and Processing of Data

If using hard copies of CRF's, study center personnel will complete individual CRF's in black ink. All corrections to entered data will be made by drawing a single line

through the information to be corrected without obscuring it. All corrections will be initialed, dated and explained, if necessary. The use of "white-out" or obscuring correction tape will be prohibited. A CRF is required for every patient who received any amount of study treatment. The investigator will ensure that the CRF's are accurate, complete, legible and timely. Separate source records are required to support all CRF entries except those for which use of the CRF as source document is clearly allowed per note in the investigator study file.

Data must be submitted according to the protocol requirements for ALL patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

Data will be recorded in CRFs within *Velos*. Monthly drug dispensing and annual reviews will be documented on electronic CRFs.

CRFs will be captured within *Velos*.

Basic forms should include:

- On-Study information, including patient eligibility data;
- Tumor/disease assessment forms or other forms for response assessment.
- Specialty forms for pathology, radiation or surgery when required;
- Off-Study summary sheet, including a final assessment by the treating physician;
- Follow-up forms when required

Data must be submitted according to the protocol requirements for ALL patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

A list of forms to be submitted, as well as expectation dates may be found in Appendix B.

17.6 Non-Protocol Research

No investigative procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB.

17.7 Ethics

The investigator agrees to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA) regulatory guidelines and standard of ethics.

UM Ethics Programs' Research Ethics Consultation Service (RECS) is a free resource for UM Researchers. See the website for further information: http://www.miami.edu/index.php/ethics/projects/recs/

17.8 Essential documents for the conduct of a clinical trial

Essential documents are those documents with individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. The following documents should be on file: 1) 1572 (for studies involving IND drugs or devices); 2) CV's and license of all Investigators; 3) IRB documentation/correspondance and 4) Documentation of IRB certification

18.0 **REFERENCES**

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APPENDIX A: EXPEDITED ADVERSE EVENT (AE) REPORTING REQUIREMENTS

For all AEs that meet criteria for expedited reporting, the Principal Investigator (PI) is obligated to pursue and provide follow-up reporting information until the event has resolved or until an acceptable medical endpoint has been reached (i.e. for the duration specified in the protocol), or the patient is lost to follow-up.

The PI and all applicable research study team members should become familiar with the safety profile of the investigational agent(s) and/or intervention at the start of the study and for the duration of the research, e.g. by reviewing the Investigator's Brochure (IB) and any Safety Reports released, (i.e. by the Sponsor) as applicable.

A. FDA Expedited Reporting

   a. Adverse drug experiences that are suspected to be associated and any suspected pregnancy occurring during thalidomide (THALOMID) treatment.

   b. For more information regarding reporting to the FDA, please refer to the FDA website for REPORTING GUIDELINES: http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

B. IRB Expedited Reporting

   a. All Investigators should also be aware of local Institutional requirements for AE reporting. For more information regarding the IRB policy, please refer to the UM HSRO's Investigator Manual: http://hsro.med.miami.edu/documents/HRP-103_-_INVESTIGATOR_MANUAL_4.11.2014.docx and the UM HSRO SOP on New Information (HRP-024) https://eprost.med.miami.edu/eProst/Doc/0/HLJ5OTJVQEH419E0I6QPT3B199/HRP-024%20-%20SOP%20-%20New%20Information.docx

   b. All AEs that are serious, unexpected and related or possibly related to the research and that indicate there are new or increased risks to subjects, shall be promptly reported to the IRB within ten (10) business days of the PI becoming aware of the event.

C. Sponsor Expedited Reporting

   a. Please follow reporting methods outlined by the Celgene REMS program, as applicable.

APPENDIX B: DATA SUBMISSION SCHEDULE

CASE REPORT FORM(S)	TIMEPOINT TO BE COMPLETED
ICF, including HIPAA signed/dated	Prior to registration
Eligibility Checklist	
SCCC Protocol Enrollment Form	
On-study Form	Within 30 days of registration
Treatment Form (Group A)	Due every cycle
Off Treatment Form (Group A)	Within 14 days of discontinuation/completion of protocol therapy
Follow-up Form	Every 3 months if < 2 years from study entry; Every 6 months is 2-5 years from study entry; Every 12 months if more than 5 years from study entry
Progression/Relapse	Within 4 weeks of knowledge of progression/relapse
Notice of Death Form	Within 4 weeks of knowledge of death
Subsequent Malignancy	Within 4 weeks of knowledge of another malignancy

APPENDIX C: PERFORMANCE STATUS SCALES

PERFORMANCE STATUS CRITERIA					
ECOG (Zubrod)		**Karnofsky**		**Lansky**	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
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.	80	Normal activity with effort, some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of, and less time spent in, play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to a bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.
5	Dead	0	Dead	0	Dead

As published in Am J Clin Oncol: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655. The Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair.

APPENDIX D: NYHA CLASSIFICATION OF HEART DISEASE

New York Heart Association (NYHA) classification of heart disease

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients.

APPENDIX E: INFORMATION ON THALOMID REMS™

A known teratogen, THALOMID® (thalidomide) is approved for marketing only under a restricted distribution program approved by the Food and Drug Administration (FDA). This program is called the THALOMID Risk Evaluation and Mitigation Strategy (REMS) ™ program (formerly known as the *S.T.E.P.S*® program).

Please refer to the following website(s) for more information:

www.CelgeneRiskManagement.com

www.THALOMIDREMS.com

Or call the Celgene Customer Care Center toll-free at

1-888-423-5436

Reference: Celgene Corporation. Risk Evaluation and Mitigation Strategy (REMS), THALOMID® (thalidomide). Modified: 9/2014.