

A non-interventional observational post authorisation safety study of subjects treated with lenalidomide

STUDY DRUG: Lenalidomide
PROTOCOL NUMBER: CC-5013-PASS-001
DATE FINAL: 29 November 2007

Signature of Celgene Head of EU Risk Management

Printed Name of Celgene Head of Risk Management

Date Signed _____

CONFIDENTIAL

This protocol is provided to you as an Investigator, potential Investigator, or consultant for review by you, your staff, and ethics committee/institutional review board. The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless such disclosure is required by law or regulations. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

1.	SYNOPSIS	8
2.	INTRODUCTION	16
2.1.	Multiple Myeloma.....	16
2.2.	Lenalidomide.....	16
2.3.	Clinical Studies of Lenalidomide in Multiple Myeloma	16
2.4.	Pharmacological class effects.....	19
2.5.	Lenalidomide Risk Management Programme	19
3.	STUDY OBJECTIVES	21
4.	INVESTIGATIONAL PLAN	22
4.1.	Overall Study Design.....	22
4.2.	Design Rationale	23
4.3.	Study Limitations	26
5.	STUDY POPULATION	27
5.1.	Subject Inclusion Criteria	27
6.	DESCRIPTION OF TREATMENT	28
6.1.	Description of Drug of Interest.....	28
6.2.	Treatment Assignments.....	28
6.3.	Prior/Concomitant Medications	28
6.4.	Discontinuation from Treatment.....	28
7.	STATISTICAL ANALYSES	28
7.1.	Study Population Definitions	28

7.2. **Background and Demographic Characteristics** 29

7.3. **Study Drug** 29

7.4. **Safety Evaluation** 29

7.5. **Safety Advisory Board** 30

8. QUALITY CONTROL AND QUALITY ASSURANCE 30

9. REGULATORY AND ETHICAL CONSIDERATIONS..... 31

9.1. **Regulatory Agency/Independent Ethics Committee Review and Approval**..... 31

9.2. **Protocol Amendments** 31

9.3. **Informed Consent** 31

9.4. **Subject Confidentiality**..... 31

9.5. **Payment to investigators** 31

9.6. **Reporting to Regulatory Agencies**..... 31

9.7. **Publication**..... 32

10. RESOURCE 33

11. DATA HANDLING AND RECORDKEEPING 34

REFERENCES..... 35

APPENDIX 1 37

APPENDIX 2..... 41

APPENDIX 3..... 42

AE	Adverse Event
ANC	Absolute Neutrophil Count
ASCT	Autologous Stem Cell Transplantation
CHMP	Committee for Human Medicinal Products
CR	Complete Response
CRF	Case Record Form
CTC	Common Toxicity Criteria
DLT	Dose-limiting Toxicity
DMC	Data Monitoring Committee
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Agency for Evaluation of Medicinal Products
EMG	Electromyogram
EU	European Union
ICH	International Conference on Harmonization
IMiD	Immunomodulatory drug
MAH	Market Authorisation Holder
MTD	Maximum Tolerated Dose
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
PE	Pulmonary Embolism
PR	Partial Response
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
TSH	Thyroid Stimulating Hormone
VTE	Venous Thromboembolism
WBC	White Blood Cell Count

WCBP	Women of childbearing potential
------	---------------------------------

STUDY CONTACT INFORMATION**Table 1: Celgene Emergency Contact Information**

Sponsor:	Celgene International Sarl Celgene International Sàrl Route de Perreux 1 2017 Boudry Neuchatel Switzerland
Contract Research Organization (CRO):	Parexel International Ltd The Quays, 101 to 105 Oxford Road, Uxbridge, Middlesex UB8 1 LZ United Kingdom
CRO Study Manager:	Clare Barclay Parexel International Ltd The Quays, 101 to 105 Oxford Road, Uxbridge, Middlesex UB8 1 LZ United Kingdom Tel +44 18 95 61 46 27 +44 12 73 84 12 42 Email: clare.barclay@parexel.com
Celgene Study Manager:	Dr Janine Collins Celgene International Sarl Celgene International Sàrl Route de Perreux 1 2017 Boudry Neuchatel Switzerland Tel: +41 (0) 32 729 84 61 Mobile: +41 (0) 79 360 57 32 Email: jcollins@celgene.com

Celgene Physician:

Dr Janine Collins
Celgene International Sarl
Celgene International Sàrl
Route de Perreux 1
2017 Boudry
Neuchatel
Switzerland
Tel: +41 (0) 32 729 84 61
Mobile: +41 (0) 79 360 57 32
Email: jcollins@celgene.com

1. SYNOPSIS

Name of Sponsor/Company: Celgene International Sarl	
Name of Investigational Product: Lenalidomide	
Protocol Number: CC-5013-PASS-001	
Protocol Title: A non-interventional observational post authorisation safety study of subjects treated with lenalidomide	
Study Duration: The study is anticipated to last for 4.5 years with maximum subject involvement estimated to be 4 years. Recruitment will continue until 1500 subjects have commenced the third cycle of treatment with lenalidomide and 1500 subjects have been enrolled in the background cohort arm.	Phase of development: Post-authorisation
Objectives: <u>Primary</u> <ul style="list-style-type: none"> To characterize and determine the incidence of adverse events of special interest; specifically neutropenia, thrombocytopenia, acute and opportunistic infections, bleeding events, venous thromboembolism, cardiac disorders (cardiac failure, arrhythmia, QT prolongation), neuropathy, rash, hypersensitivity, hypothyroidism and renal failure in subjects treated with lenalidomide in a naturalistic setting and placing into context with the background incidence of these adverse events in a non-lenalidomide cohort of multiple myeloma subjects who newly receive 2nd or later lines of treatment for multiple myeloma. 	
<u>Secondary</u> <ul style="list-style-type: none"> To monitor the evolution or resolution of neuropathy in subjects taking lenalidomide who have pre-existing neuropathy at baseline. Identification of new safety signals for lenalidomide treated subjects (with 95% confidence that the event does not occur at a higher frequency than 1 in 500). 	

- To monitor the compliance with the requirements for pregnancy testing and effective contraception in women of childbearing potential (WCBP) and the requirements for counselling of all subjects treated with lenalidomide.

<p>Study Design:</p> <p>Subjects will be recruited from approximately 300 haematology/oncology sites in EU countries. In all cases, the decision to treat the patient will be made prior to the decision to enter the subject into the study.</p> <p>The study will recruit a lenalidomide cohort of subjects and recruitment will continue until 1500 subjects have commenced their 3rd cycle of therapy. When this target is reached, all subjects on lenalidomide will continue to be followed over the next 21 months or for 30 days after discontinuation of treatment with lenalidomide. Subjects will be recruited consecutively and a log will be kept of subjects who do not consent for their data to be captured. This log will record age, gender and line of multiple myeloma treatment that the patient has received. The follow-up of subjects on lenalidomide who discontinue treatment due to an adverse event will not be time limited and will continue until resolution or stabilization or when, in the opinion of the investigator, no additional useful information can be obtained from the event or the subject withdraws their consent to any more data being collected.</p> <p>In order to put these adverse events into context in this disease population, the background incidence of the stated events of special interest will be determined in a background cohort of 1500 multiple myeloma subjects who are not treated with lenalidomide. Subjects will be entered into the background cohort once the decision has been made to start a new treatment. Recruitment will be consecutive. A log will be kept of subjects who do not consent for their data to be captured. This log will record age, gender and line of multiple myeloma treatment that the patient has received. Subjects in the background cohort will be followed until there are no longer any active lenalidomide subjects in the study and the study is closed. Subjects who discontinue the new therapy will be followed for 30 days after discontinuation of the therapy.</p> <p>Subjects in both cohorts will discontinue from the study if they switch to another treatment. However, if the patient in the background cohort immediately switches to lenalidomide or is prescribed lenalidomide at some point in the future, then this patient can be re-entered into the study as a new subject and their data collected for the duration of the lenalidomide treatment. If these subjects continue lenalidomide treatment to the 3rd cycle of treatment then their data will contribute towards the 1500 lenalidomide treated recruitment target for this study.</p> <p>Data from the lenalidomide cohort will also be compared with the clinical trial experience in studies MM009 and MM010</p>	
<p>Dosing Regime</p> <p>Treatment will be according to clinical</p>	<p>Study Drug Supply</p> <p>All treatments will be prescribed by the treating investigator in accordance with</p>

practice	normal clinical practice. Lenalidomide will not be supplied by Celgene
<p>Study Population Subjects must meet the following inclusion/exclusion criteria to be eligible for the study.</p> <p>Inclusion Criteria: All subjects: Understand and voluntarily sign an informed consent form. Lenalidomide cohort: Subjects who are commencing lenalidomide treatment. Background cohort: Subjects with multiple myeloma who have received at least one prior therapy and are commencing a new therapy but not lenalidomide.</p> <p>Exclusion Criteria: All subjects: Refusal to participate in the study or currently participating in an interventional clinical trial. Lenalidomide cohort: Subjects who have previously taken lenalidomide either as part of normal prescribing practice or in a clinical trial. Background cohort: Subjects commencing a new line of treatment having previously been enrolled in the study when treated with an earlier line of treatment. NB. Subjects previously enrolled into this study and subsequently prescribed lenalidomide can be recruited into this study as part of the lenalidomide cohort.</p>	
<p>Assessments</p> <p>All assessments will be made according to the normal clinical practice of the treating investigator. The investigator will not be requested to undertake any assessment which he would not normal carry out in his normal practice. Therefore if a parameter is requested on the CRF but the investigator’s normal practice is not to carry out such an assessment, then the field will not be completed.</p> <p>Safety:</p> <ul style="list-style-type: none"> • Baseline data as per schedule of assessments • Adverse Event Assessment • Dose and dose interruptions • Pregnancy testing and contraceptive status for WCBP • Renal function • VTE Prophylaxis • Neuropathy grading if neuropathy recorded at baseline • Discontinuation: Date, reasons for discontinuation. 	
<p>Statistical Analysis:</p> <p>Study Populations: Data from all subjects who receive at least one dose of treatment will be included in the safety</p>	

analyses. Data from any subject in whom lenalidomide has been used outside of the authorized use i.e. off label will also be included in the safety analysis. Data summaries will also be provided by country.

Demographic Data

For demographic and baseline characteristics data, descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be provided for continuous variables; categorical variables will be summarized using frequency tabulations.

Study Drug:

For lenalidomide, study dosing will be summarized using descriptive statistics. Duration of dosing will be similarly summarized together with a summary of dosing interruptions and reductions. Dosing in subjects who receive lenalidomide off label will be summarized separately.

Safety Analysis:

Adverse events will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI CTCAE VERSION 3.0 whenever possible.

Adverse event frequency will be tabulated by body system and MedDRA term. In the by-subject analysis, a subject having the same event more than once will be counted only once. Adverse events will be summarized by worst NCI CTCAE VERSION 3.0 grade.

Adverse events leading to death or to discontinuation from treatment, study-drug-related events, and serious adverse events will be listed separately.

Incidence density (ID) for individual adverse events together with 95% two-sided confidence intervals will be provided. ID is defined as the ratio of number of new adverse events in the calendar period over accrued population time.

Summary tables will be provided to allow a side-by-side comparison of the incidence density observed in the lenalidomide cohort, the background cohort, and the MM009 and MM010 clinical trials. Odds ratios, together with two-sided 95% confidence intervals, will be calculated to estimate the relative risk between the two cohorts in the study. Estimates will be adjusted a posteriori to control for any differences in the comparative populations.

The Kaplan-Meier procedures will be used to characterize time to onset and time to resolution for adverse events of special interest. Multivariate logistic regression will be used to determine the demographic and baseline characteristics most predictive of developing adverse events of interest. A forward selection stepwise procedure will be used to identify the subset of relevant factors.

Summary tables will also be provided for clinically relevant subgroups, e.g., based on lines of therapy and disease severity, to allow side by side comparison for the lenalidomide cohort, the background cohort, and the MM009 and MM010 clinical trials.

Analyses will be undertaken to explore the course of neuropathy for subjects taking lenalidomide who have pre-existing neuropathy at baseline. Specifically, cross-tabulations will be used to summarize changes in severity observed during lenalidomide treatment and summary statistics will be provided for other relevant variables.

Relevant summary tables will be provided by country, that is, by pooling data from all centers within a specific country.

Table 2 Schedule of Assessments

All assessments will be made according to the normal clinical practice of the treating investigator. The investigator will not be requested to undertake any assessment which he would not normally carry out in his normal practice. Therefore if a parameter is requested on the CRF but the investigator's normal practice is not to carry out such an assessment, then the field will not be completed.

Data	Baseline visit	Monthly CRF	At discontinuation
Centre Identification	Y	Y	
Subject identification Anonymised	Y	Y	
Assessment date	Y	Y	
Age/DOB	Y		
Height and weight	Y		
Gender	Y		
Smoking history	Y		
Medical history	Y		
Indication for treatment with lenalidomide	Y		
Previous treatments for indication, dates and duration	Y		
Risk factors for VTE	Y		
VTE prophylaxis	Y	Y	
Any neuropathy present at baseline	Y	Y (if present at baseline)	
Aetiology of baseline neuropathy (thalidomide, bortezomib, other drug induced, non drug induced)	Y		
Calcium	Y		
Haemoglobin	Y		
Neutrophil count	Y		
Platelet count	Y		
Serum creatinine	Y	Y	
T ₄ and TSH	Y		
Creatinine clearance (calculated or determined on 24 hour urine)	Y		
Lytic bone lesions	Y		
Baseline ECOG Performance rating	Y		
Baseline ECG (if applicable)	Y		
Baseline EMG/neurophysiological investigations (if applicable)	Y		

Woman of child bearing potential (WCBP) yes, no (lenalidomide only)	Y		
Counselling for Pregnancy Prevention (lenalidomide only)	Y		
For male subjects, counselling regarding effective contraception (lenalidomide only)	Y		
For WCBP date of negative pregnancy test (lenalidomide only)	Y	Y	
For WCBP effective contraception (lenalidomide only)	Y	Y	
Study drug dose	Y	Y	
Start date of study drug	Y		
Dose reduction		Y	
Dose interruption		Y	
Adverse events		Y	
SAE yes/no		Y	
Pregnancy yes/no		Y	
Date of discontinuation			Y
Reason for discontinuation			Y

2. INTRODUCTION

2.1. Multiple Myeloma

Multiple myeloma is an incurable disease that is characterized by the accumulation of clonal plasma cells in the bone marrow (Alexanian R. 1994). Multiple myeloma is a rare disease accounting for 1% of all malignant disease and 10% of all haematologic cancers (Cancer Research UK 2005). It is estimated that approximately 21,500 new cases of multiple myeloma are diagnosed per annum with approximately 16,000 deaths from the disease annually within the EU (EUCAN database 1998). The primary approach to the treatment of multiple myeloma is systemic antineoplastic therapy. Prior to the introduction of alkylator agents in the 1960s, the median survival for subjects with multiple myeloma was less than 12 to 17 months from the time of diagnosis (Durie B. 1982, Gregory W. 1992). Conventional chemotherapy has increased median survival to about 3 years (Alexanian R. 1980, Michiels J. 1992). High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is an alternative to conventional chemotherapy and improves survival in selected subjects (Attal M. 1996).

2.2. Lenalidomide

Lenalidomide (CC-5013, Lenalidomide[®]) is an analogue of the immunomodulatory drug (IMiD), thalidomide (Thalomid[®]) with a potentially greater potency to activate immunomodulatory effects and inhibit angiogenesis. *In vitro* studies have demonstrated that lenalidomide is one of the most potent IMiDs. These studies compared the activity and potency of lenalidomide and thalidomide and examined the effects of IMiDs on the production of cytokines and multiple myeloma cell proliferation. In all studies, lenalidomide was found to be 50 to 2000 fold more potent than thalidomide (Corral L 1999). In addition, preclinical studies of lenalidomide have demonstrated an enhancement of the anti-myeloma activity of dexamethasone (Hideshima T 2000).

2.3. Clinical Studies of Lenalidomide in Multiple Myeloma

A phase I study identified myelosuppression as the DLT of oral lenalidomide, a MTD of 25 mg daily and demonstrated a 50% paraprotein reduction in 20% of the treated subjects (Zangari M. 2001). Preliminary phase II data indicated that an interrupted schedule of administration ameliorates the marrow suppressive effects of oral lenalidomide (Barlogie B. 2002; Richardson P. 2002).

Two pivotal Phase III Special Protocol Assessment (SPA) studies, MM009 and MM010, were conducted to investigate the effectiveness and safety of lenalidomide plus dexamethasone compared with placebo plus dexamethasone in previously treated relapsed or refractory multiple myeloma subjects.

MM009, a Phase III randomized, double-blinded, placebo-controlled study enrolled 353 subjects from 47 clinical sites throughout North American with data available from 170 subjects randomized to lenalidomide plus dexamethasone and 171 subjects randomized to placebo plus dexamethasone. The median subject age was 64 years in the lenalidomide plus dexamethasone arm, compared to 62 years in the placebo plus

dexamethasone arm of the study. An Independent Data Monitoring Committee conducted the planned interim analysis and determined that the study clearly exceeded the pre-specified efficacy stopping rule of $p < 0.0015$ for the primary endpoint, time-to-disease progression. Consistent with the findings of the interim analysis, the available clinical data as of June 28, 2005 (the date of unblinding) showed:

- The median time-to-disease progression with lenalidomide plus dexamethasone was 48.1 weeks compared with the median time-to-disease progression of 20.1 weeks for placebo plus dexamethasone ($p < 0.0001$).
- Best response rate with lenalidomide plus dexamethasone was 61.0 percent, compared with a response rate of 19.9 percent for placebo plus dexamethasone.
- Complete response rate of lenalidomide plus dexamethasone was 14.1 percent, compared with 0.6 percent for placebo plus dexamethasone.

MM010, a Phase III randomized, double-blinded, placebo-controlled study enrolled 351 subjects from 50 clinical sites internationally with data available from 176 subjects randomized to lenalidomide plus dexamethasone and 175 subjects randomized to placebo plus dexamethasone. The median subject age was 63 years in the lenalidomide plus dexamethasone arm, compared to 64 years in the placebo plus dexamethasone arm of the study. An Independent Data Monitoring Committee conducted the planned interim analysis and determined that the study clearly exceeded the pre-specified efficacy stopping rule of $p < 0.0015$ for the primary endpoint, time-to-disease progression. Consistent with the findings of the interim analysis, the updated clinical data as of August 3, 2005 (the date of unblinding) showed:

- The median time-to-disease progression with lenalidomide plus dexamethasone was 48.7 weeks compared with median time-to-disease progression of 20.1 weeks for placebo plus dexamethasone ($p < 0.0001$).
- Best response rate with lenalidomide plus dexamethasone was 60.2 percent, compared with a response rate of 24.0 percent for placebo plus dexamethasone.
- Complete response rate of lenalidomide plus dexamethasone was 15.9 percent, compared with 3.4 percent with placebo plus dexamethasone.

The safety data for both clinical studies was further updated to December 31, 2005. The most significant toxicities observed in clinical studies were neutropenia and thrombocytopenia. Neutropenia reactions occurred in 39.4% of subjects in the lenalidomide/dexamethasone group compared to 6.3% in the placebo/dexamethasone group. Grade 3/4 neutropenia reactions were observed in 32.9% of subjects treated with lenalidomide/dexamethasone respectively compared to 3.4% treated with placebo/dexamethasone. Grade 3/4 thrombocytopenia reactions occurred in 11.3% of subjects in lenalidomide/dexamethasone subjects compared to 2.3% in placebo/dexamethasone subjects. Grade 3/4 infective reactions occurred in 8.8% of the lenalidomide/dexamethasone respectively compared to 5.7% in the placebo/dexamethasone group. The most frequent infection reactions were pneumonia (grade 3/4 pneumonia NOS occurred in 3.7% in the lenalidomide/dexamethasone group compared to 1.1% in the placebo/dexamethasone group). The incidence of

grade 3/4 atypical pneumonia (pneumocystis carinii pneumonia and primary atypical pneumonia) was low: there being only one report of each reaction in the lenalidomide/dexamethasone group and none in the placebo/dexamethasone group. Despite the incidence of thrombocytopenia, the incidence of bleeding reactions (specifically all bleeding reactions) was low and comparable between the two treatment arms: 1.1% in the lenalidomide/dexamethasone arm and 1.4% in the placebo dexamethasone arm.

There was a significantly higher incidence of venous-thromboembolic reactions in the lenalidomide/dexamethasone group compared to the placebo/dexamethasone group. Pulmonary embolism and deep vein thrombosis occurred in 2.5% and 7.1% respectively in the lenalidomide/dexamethasone group compared to 0.9% and 3.4% in the placebo/dexamethasone group.

In the MM population skin rashes occurred significantly more frequently in the lenalidomide/dexamethasone group than in the placebo/dexamethasone group. Those considered to be related to drug occurred in 10.2% of subjects in the lenalidomide/dexamethasone group compared to 3.4% in the placebo/dexamethasone group. These were however, non serious reactions; there being only one serious reaction of skin discoloration (0.3%). In the study population there have been no reported reactions of Steven Johnson Syndrome or Toxic Epidermal Necrolysis. There were no reports of hypersensitivity.

In the study population, the incidence of reported reactions of neuropathy was comparable between the two treatment arms. In the lenalidomide/dexamethasone arm, paraesthesia, peripheral neuropathy, and hypoaesthesia occurred in 8.5%, 5.7% and 6.2% of subjects respectively compared to 8.3%, 4.6% and 2.9% in the placebo/dexamethasone group.

Approximately 20% of multiple myeloma subjects have a degree of renal failure consequent to their disease. The predominant route of elimination of lenalidomide is through renal excretion. In the clinical study population, the incidence of renal failure as reported adverse drug reactions was low and comparable between the two treatment groups. Reactions of renal failure, acute renal failure, and renal tubular necrosis occurred in 1.4%, 0.8%, and 0.3% respectively in the lenalidomide/dexamethasone group compared to 0.3%, 0.3% and 0% in the placebo/dexamethasone group.

With the exception of atrial fibrillation, the incidence of cardiac reactions was similar across the two treatment arms. Whilst atrial fibrillation was reported as a reaction in 2.5% of the lenalidomide/dexamethasone group compared to none in the placebo/dexamethasone group, further analysis revealed that these subjects had significant co morbidity to account for the onset of atrial fibrillation.

There was one report only of QT prolongation reaction (0.3%). This was grade 1 and occurred in the len/dex group. Congestive cardiac failure and pulmonary oedema reactions occurred in 0.6% and 0.3% in the lenalidomide/dexamethasone arm respectively and 0% and 0.6% in the placebo/dexamethasone group.

Acquired hypothyroidism reactions were reported in 0.8% of the lenalidomide/dexamethasone group compared to 0.3% in the placebo/dexamethasone group.

2.4. Pharmacological class effects

Pharmacological signals indicate that the efficacy of lenalidomide is different to that of thalidomide and the results from clinical studies suggest that the safety profile is also different.

The reported rate of thromboembolism with thalidomide therapy varies in the literature from 0% to 43%. The incidence rate appears to depend on the underlying disease and concomitant application of glucocorticoids or multiagent chemotherapy (Osman et al. 2001; Zangari et al. 2001; Bowcock et al. 2002; Rajkumar et al. 2002).

The teratogenicity of thalidomide is well documented.

Hypersensitivity to thalidomide has been reported and may include the development of an erythematous macular rash sometimes associated with fever, tachycardia and hypotension. Toxic epidermal necrolysis and Steven-Johnson syndromes have been reported with thalidomide (Horowitz 1999, Thalomid™ US Product Information).

Peripheral neuropathy has a reported incidence of between 1% to 70% in thalidomide dependant upon the definition and the underlying disorder (Tseng et al. 1996). Thalidomide neuropathy remains incompletely characterized but there is general agreement that the neuropathy is poorly reversible. Reports vary as to whether or not there is a correlation between the incidence of peripheral neuropathy and the cumulative thalidomide dose (Apfel 2004). In a study by Chaudhry et al (2002) all seven subjects had electrophysiological and clinical evidence of a sensory more than motor polyneuropathy that presented as painful paraesthesiae and numbness.

Sinus bradycardia has been reported in 5% of subjects treated with thalidomide. The bradycardia was severe enough to cause syncope and pacemaker placement may be necessary (Kaur et al. 2003, Escudier et al. 2002). The mechanism of thalidomide-induced cardiovascular side effects is still not well understood.

There are reports of thalidomide therapy resulting in hypothyroidism and significant increases in serum thyroid stimulating hormone (TSH) levels in subjects with multiple myeloma. The mechanism is not clear (Badros et al 2002).

2.5. Lenalidomide Risk Management Programme

Lenalidomide is structurally related to thalidomide, a known human teratogen. As the teratogenic potential of lenalidomide cannot currently be excluded, a Pregnancy Prevention Programme has been established. All women of childbearing potential must:

- Receive counselling regarding the potential teratogenicity of lenalidomide and the need to avoid pregnancy

- Use one effective method of contraception for 4 weeks before therapy, during therapy, during dose interruptions and 4 weeks after therapy has finished, unless the woman commits to absolute and continued abstinence confirmed on a monthly basis.
- Have a medically supervised negative pregnancy test once she has been established on contraception for 4 weeks, at 4 weekly intervals during therapy and 4 weeks after the end of therapy.

It is not currently known if lenalidomide is present in semen. Therefore all male subjects should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is of childbearing potential and has no contraception.

The SmPC provides further guidance on the Pregnancy Prevention Programme including the definition of a woman of childbearing potential, counselling, effective contraception and pregnancy testing.

A complete blood count, including white blood count monitoring with differential count, platelet count, haemoglobin and haematocrit should be performed at baseline and every week for the first 8 weeks of treatment and then monthly thereafter.

A dose reduction may be required. In the case of neutropenia, the investigator should consider the use of growth factors in subject management. Co-administration of lenalidomide with other myelosuppressive agents should be done with caution.

The combination of lenalidomide and dexamethasone is associated with an increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in subjects with multiple myeloma. Concomitant administration of erythropoietic agents or previous history of DVT may also increase the thrombotic risk in these subjects. Prophylactic antithrombotic medications are recommended especially in subjects with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual subject's underlying risk factors.

3. STUDY OBJECTIVES

Objectives:

Primary

- To characterize and determine the incidence of adverse events of special interest; specifically neutropenia, thrombocytopenia, acute and opportunistic infections, bleeding events, venous thromboembolism, cardiac disorders (cardiac failure, arrhythmia, QT prolongation), neuropathy, rash, hypersensitivity, hypothyroidism and renal failure in subjects treated with lenalidomide in a naturalistic setting and placing into context with the background incidence of these adverse events in a non-lenalidomide cohort of multiple myeloma subjects who newly receive 2nd or later lines of treatment for multiple myeloma.

Secondary

- To monitor the evolution or resolution of neuropathy in subjects taking lenalidomide who have pre-existing neuropathy at baseline.
- Identification of new safety signals for lenalidomide treated subjects (with 95% confidence that the event does not occur at a higher frequency than 1 in 500).
- To monitor the compliance with the requirements for pregnancy testing and effective contraception in WCBP and the requirements for counselling of all subjects treated with lenalidomide.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

Subjects will be recruited from approximately 300 haematology/oncology sites in EU countries. In all cases, the decision to treat the patient will be made prior to the decision to enter the subject into the study.

The study will recruit a lenalidomide cohort of subjects and recruitment will continue until 1500 subjects have commenced their 3rd cycle of therapy. When this target is reached, all subjects on lenalidomide will continue to be followed over the next 21 months or for 30 days after discontinuation of treatment with lenalidomide. Subjects will be recruited consecutively and a log will be kept of subjects who do not consent for their data to be captured. This log will record age, gender and line of multiple myeloma treatment that the patient has received. The follow-up of subjects on lenalidomide who discontinue treatment due to an adverse event will not be time limited and will continue until resolution or stabilization or when, in the opinion of the investigator, no additional useful information can be obtained from the event or the subject withdraws their consent to any more data being collected.

In order to put these adverse events into context in this disease population, the background incidence of the stated events of special interest will be determined in a background cohort of 1500 multiple myeloma subjects who are not treated with lenalidomide. Subject will be entered into the background cohort once the decision has been made to start a new treatment. Recruitment will be consecutive. A log will be kept of subjects who do not consent for their data to be captured. This log will record age, gender and line of multiple myeloma treatment that the patient has received. Subjects in the background cohort will be followed until there are no longer any active lenalidomide subjects in the study and the study is closed. Subjects who discontinue the new therapy will be followed up for 30 days following that discontinuation.

Subjects in both cohorts will discontinue from the study if they switch to another treatment. However, if a patient in the background cohort immediately switches to lenalidomide or is prescribed lenalidomide at some point in the future, then this patient can be re-entered into the study as a new subject and their data collected for the duration of the lenalidomide treatment. If these subjects continue lenalidomide treatment to the 3rd cycle of treatment then their data will contribute towards the 1500 lenalidomide treated recruitment target for this study.

Data from the lenalidomide cohort will also be compared with the clinical trial experience in studies MM009 and MM010

For all subjects data will be collected as “baseline” data upon commencing lenalidomide. At monthly intervals, the investigators will complete a Case Record Form (either via a secure internet system or on paper) which will collect:

- Adverse event data
- Dosing and dose interruption data
- For WCBP, the date of last pregnancy test and confirmation that subject has effective contraception

- If neuropathy present at baseline, the severity of neuropathy (NCI CTCAE Version3.0)
- Renal function
- VTE prophylaxis

Upon discontinuation from the study, the reason for discontinuation will be documented.

Serious adverse events will be collected on an ongoing basis and entered into Celgene's global safety database (see Appendix 1).

Serious adverse events from the background cohort will be notified to the relevant MAH where applicable.

All pregnancies occurring in subjects exposed to lenalidomide will be notified immediately to Celgene and followed up (see Appendix 1).

Event specific questionnaires will be implemented to gain follow up of Serious Adverse Events of special interest.

Safety will be assessed by evaluating adverse events. Adverse event severity will be graded using the NCI CTCAE VERSION 3.0.

4.2. Design Rationale

This study will observe subjects treated in normal clinical practice i.e. in a naturalistic setting without the exclusion constraints of a clinical trial.

The study will define the incidence and characterize events of special interest.

These are events which:

- Have been identified in MM009 and MM010 as associated with lenalidomide use (neutropenia, thrombocytopenia (with potential risk of infection and bleeding reactions) venous thromboembolic disorders) or
- Have been observed in MM009 and MM010 without sufficient evidence of a causal link but which require further monitoring (cardiac failure, arrhythmias, QT prolongation) or
- Have been identified with thalidomide use and therefore should be monitored in the post-marketing setting with lenalidomide (neuropathy, toxic epidermal necrolysis and Steven-Johnson syndrome, hypothyroidism, hypersensitivity, bradycardia) or
- Have been identified for monitoring due to the pharmacokinetics/pharmacodynamics of lenalidomide and the disease condition (renal failure, acute and opportunistic infections)

Subjects from approximately 300 centres who receive treatment with lenalidomide will be enrolled and recruitment will continue until 1500 subjects on lenalidomide have commenced their third cycle of treatment. These subjects will be followed for a further period of 21 months or for 30 days after they discontinue lenalidomide treatment. Recruitment into this study is estimated to take 2 years but may stop sooner if the target is met earlier. Those subjects recruited early into the study would therefore generate around 4 years of data.

This sample size has been determined based on the known incidence of adverse events of special interest as determined in pre-approval studies and has been specifically selected to enable this study's primary objective concerned with the characterization of such events. Furthermore, sample size will permit evaluation of previously undocumented adverse drug reactions with an incidence of 1/500 to be detected with a 95% confidence interval.

The rationale for this duration of follow-up is as follows:

- Multiple Myeloma is a disease of the elderly and is managed in either tertiary or secondary care. The patient population is not therefore highly mobile. This has been confirmed in study MM010 which was carried out in Europe, where there was a 0% lost to follow up rate. A low lost to follow up rate is therefore anticipated in this study.
- Many adverse drug reactions occur during the first 3 months of therapy. Thus by ensuring that recruitment is continued until 1500 subjects have been exposed for 3 months, there is maximum opportunity to identify these events.
- Multiple myeloma is a fatal disease with an average life expectancy of 3.5 years. As the authorized use of lenalidomide is in subjects who have previously received at least one prior therapy, many subjects will have a life expectancy of less than 3.5 years upon commencing lenalidomide. Therefore a follow up period of 2 years is an appropriate duration. As of 12 April 2007, in Study MM010, 27/176 (15.3%) of subjects remain on treatment, with 49.4% having discontinued due to progression of disease and 6.3% discontinued due to death. In MM010, 76/176 (43%) of subjects were treated for at least 52 weeks; 57/176 (32%) for at least 78 weeks and only 42/176 (24%) of subjects have been on treatment for at least 2 years. By following subjects for 21 months from the time that 1500 subjects have accrued will result in some subjects being followed for a period beyond 2 years, up to a maximum potentially of 4 years.
- Data from studies MM 009 and MM010 showed that 83% of subjects completed 12 weeks or more and 24% completed 2 years of study drug. Thus it is estimated that approximately 1800 subjects will be enrolled to obtain 1500 at 3 months and that approximately 430 of these will remain on drug at 2 years.

In summary a follow-up period of 21 months from the time of accrual of 1500 lenalidomide subjects who have been on treatment for 3 months will allow an assessment of long term exposure to lenalidomide taking into account the short duration of life expectancy for these subjects who will already have received at least one prior therapy for their disease.

The data from this study will therefore supplement clinical trial data in terms of long term exposure.

Vincristine, thalidomide and bortezomib use are associated with neuropathy. This study will observe in a naturalistic setting the evolution of neuropathy in those subjects who present with neuropathy at baseline.

At baseline, subjects on lenalidomide who are women of childbearing potential will be identified. For this subset of subjects, the extent to which there has been

compliance with the Pregnancy prevention programme (PPP) in terms of completion of 4 weekly pregnancy tests and adherence to effective contraceptive methods, will be assessed. Additionally, the total number of subjects of child-bearing potential will be ascertained. In the first 6 months postmarketing experience in the US, 1.7% of the exposed population were women of childbearing potential. Assuming this to be similar in the EU, it can be expected that this study will identify approximately 25 WCBP. It is recognized that this is one tool for monitoring the effectiveness of the PPP and that other tools are being explored by the company in conjunction with National Competent Authorities. At baseline, a record will be made to reflect whether all subjects have been counseled on the need to avoid pregnancy and also whether male subjects have been specifically counseled to use condoms if their partner is a female of childbearing potential.

The authorized indication for the use of lenalidomide is for multiple myeloma subjects who have received at least one prior therapy.

In order to put the safety data collected in this study into perspective, it is beneficial to also consider the background incidence of these adverse events of special interest. Several potential available databases have been considered for this purpose but these are limited either in terms of size, use of one specific therapy, extent of adverse event data available or are databases with information from randomized controlled clinical trials in which the inclusion/exclusion criteria would not be the same as the naturalistic setting. In order to obtain background incidences, the population should be as similar as possible as the authorized indication for lenalidomide. For this reason, a background cohort of 1500 subjects who have multiple myeloma and have received at least one prior therapy will be followed. The data will be collected by the same methodology as the lenalidomide cohort.

The rationale for this background cohort can be summarised as follows:

- The subjects in the background cohort will be subjects with the same indication as the approved indication for lenalidomide.
- Size of background cohort will be the same as the lenalidomide cohort.
- The background cohort will reflect the “real world” setting and thus be comparable to the lenalidomide cohort i.e. there will not be the limitations as a result of restrictions due to inclusion/exclusion criteria as in a clinical trial.
- Data will be collected in background cohort prospectively and with the same methodology as in the lenalidomide cohort.
- The same data will be collected in both cohorts therefore allowing more meaningful assessment.
- Adverse event reporting methodology will be the same in both groups.

It is recognized that incidence of adverse events and patient morbidity may differ depending upon the line of therapy of the patient i.e. a patient who has received 3 previous lines of therapy may differ from one who is receiving second line therapy. For this reason in the analysis, subjects will be stratified by line of treatment.

Additionally, the safety profile determined from this lenalidomide cohort in this study will be considered in the context of the safety profile determined from the two pivotal phase III studies: MM009 and MM010. This will be a descriptive analysis to identify and discuss the events of special interest observed in the clinical trial and the “real world” setting.

4.3. Study Limitations

Post-authorization observational studies of a newly marketed pharmaceutical product provide the opportunity to characterize its safety profile across patient types and practice settings; generalizability is a strength of this study design. However, because subjects are not randomized to treatments, bias in the allocation of treatments to subjects may compromise study findings. Confounding by indication may occur if the decision to prescribe a particular therapy is influenced by a patient's underlying disease severity. Channeling bias may occur when drugs with similar therapeutic indications are prescribed to subjects with prognostic differences that may affect outcome. This study will collect information on disease severity, baseline prognostic factors and comorbidities, and baseline data on previous multiple myeloma treatments. These data can then be used to either demonstrate comparability between subjects on lenalidomide and those who are not, or alternatively, adjust for such baseline differences in the assessment of differences in adverse event rates.

Subjects who are participating from other interventional clinical studies will be excluded from these studies. Hence there is the possibility of bias in that more subjects meeting exclusion criteria for the clinical studies may be entered into this post authorization safety study.

Having considered all the options for obtaining background incidence data, whilst the development of a background cohort is considered to be the best approach for obtaining background incidences, it is recognized that it will also have some limitations:

- In general as the patient moves to the later lines of therapy, the disease will be more severe. Hence a 4th line patient is likely to have a greater morbidity than a 2nd line patient.
- In addition, by recruiting non-lenalidomide subjects into a background cohort, it is recognised that as these background subjects move to a later line of therapy, they may commence lenalidomide. Therefore as the background cohort is recruited at a site, the pool of subjects for the lenalidomide cohort could effectively be reduced. Therefore, whilst subjects will discontinue from the background cohort if they move to a later line of treatment, they will be allowed to be recruited to the lenalidomide cohort if the later line of treatment is lenalidomide.
- Adverse events are more likely to occur in the first three months of a treatment. For this reason, in order to more closely have a cohort in the background population as similar as possible to the lenalidomide cohort, subjects will be enrolled in the background cohort as they commence their new line of therapy. Thus, both cohorts will be starting a new treatment regime upon recruitment. Therefore the window in which adverse events are most likely to occur will be comparable in the two cohorts.

5. STUDY POPULATION

Subjects will be enrolled following launch of lenalidomide and recruitment will continue until 1500 lenalidomide subjects have commenced their third cycle of therapy.

As a condition of the Market Authorisation, all investigators who intend to prescribe lenalidomide will receive an investigator information pack detailing the controlled distribution system. Where local regulations permit, the same investigators will also receive communication in relation to this study. By ensuring a wide dissemination of this information, selection bias will be reduced.

The delivery of healthcare for Multiple Myeloma subjects differs across each country in Europe. The Applicant will attempt to get as representative sample of sites as possible to reflect the distribution of treating centres per country. Some subjects will be treated in academic tertiary centres, others in secondary care and others in an office based setting. Attempts will be made to document the categorization of sites and at intervals during the study will compare this data to available market information regarding the distribution of prescribing centres to ensure the site participation reflects the prescribing population. Furthermore, a record will be kept of those sites who have been offered the opportunity to participate in the study but who have not agreed to do so. The reason for their refusal will be documented. On a six monthly basis in the RMP, the Applicant will provide a recruitment report detailing the output of these exercises.

Consecutive subjects treated at each site will be enrolled into the study until such time as the recruitment target for that group is met. The investigator will be requested to keep a log of all subjects who are invited to enter this study. If any of these subjects are not enrolled in the study, this will be documented and the reason for non-recruitment will be documented. The investigator will be requested to additionally document the age, gender, treatment and line of therapy (i.e. 1st line, 2nd line 3rd line etc) and provide this to the sponsor as aggregate data.

The same process for recruitment of the background cohort will also be implemented, i.e. multiple myeloma subjects who have received one previous therapy will be recruited consecutively into the background cohort according to line of therapy, with a log and reasons for non recruitment documented. Aggregate data on age, gender and line of therapy of the non participating subjects will be required.

5.1. Subject Inclusion Criteria

Inclusion Criteria:

All subjects: Understand and voluntarily sign an informed consent form.

Lenalidomide cohort: Subjects who are commencing lenalidomide treatment.

Background cohort: Subjects with multiple myeloma who have received at least one prior therapy and are commencing a new therapy but not lenalidomide.

Exclusion Criteria:

All subjects: Refusal to participate in the study or currently participating in an interventional clinical trial.

Lenalidomide cohort: Subjects who have previously taken lenalidomide either as part of normal prescribing practice or in a clinical trial.

Background cohort: Subjects commencing a new line of treatment having previously been enrolled in the study when treated with an earlier line of treatment. NB. Subjects previously enrolled into this study in the non-lenalidomide cohort who discontinue treatment and who are later prescribed lenalidomide can be recruited into this study as a new subject as part of the lenalidomide cohort.

6. DESCRIPTION OF TREATMENT

6.1. Description of Drug of Interest

Subjects will be treated in accordance with normal clinical practice. All investigators participating in the study will be provided with a copy of the SmPC for lenalidomide.

Lenalidomide will be prescribed by the treating investigator in accordance with normal clinical practice. Lenalidomide will not be supplied by Celgene.

For the non-lenalidomide cohort subjects will receive treatment according to normal clinical practice.

6.2. Treatment Assignments

The investigator will make the decision to treat the patient according to clinical need before making the decision to enter the patient into the relevant cohort. As per section 5.0 consecutive subjects will be enrolled into the cohorts.

6.3. Prior/Concomitant Medications

Investigators participating in the study will be provided with a copy of the SmPC for lenalidomide and will have the discretion to use prior or concomitant medications according to his/her clinical judgment.

6.4. Discontinuation from Treatment

The investigator and/or subjects may discontinue treatment at any time as part of normal clinical practice. Subjects in both cohorts will discontinue from the study on switching to another treatment. However, if the patient in the background cohort immediately switches to lenalidomide or is prescribed lenalidomide at some point in the future, then this patient can be re-entered into the study and their data collected for the duration of the lenalidomide treatment. If these subjects continue lenalidomide treatment to the 3rd cycle of treatment then their data will contribute towards the 1500 lenalidomide treated recruitment target for this study.

7. STATISTICAL ANALYSES

Final statistical analyses will be performed when all subjects have discontinued the study.

7.1. Study Population Definitions

Data from all subjects who receive at least one dose of treatment will be analyzed.

Data from any subject in whom lenalidomide has been used outside of the authorized use i.e. off label will also be included in the safety analysis. Data summaries will also be provided by country.

7.2. Background and Demographic Characteristics

Subjects' continuous demographic and baseline variables will be summarized using descriptive statistics (mean, standard deviation, median, minimum and maximum), while categorical variables will be summarized using frequency tabulations. Individual subject listings will be provided. Background data in terms of age, gender and line of multiple myeloma therapy of enrolled subjects in the lenalidomide group will be compared to that of those who are to be treated with lenalidomide but do not consent for their data to be captured. A similar comparison will be made in the background group.

7.3. Study Drug

For lenalidomide, dosage statistics (mean, standard deviation median, minimum and maximum) will be provided for the highest dose level achieved, final dose, and the average daily dose. Duration of exposure will be similarly summarized together with a summary of dosing interruptions and reductions.

Dosing summaries will be provided for all subjects and separately for subjects in whom lenalidomide has been used outside of the authorized use i.e. off label.

7.4. Safety Evaluation

Adverse events will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI CTCAE VERSION 3.0 whenever possible.

The frequency of adverse events will be tabulated by body system and MedDRA term. In the by-subject analysis, a subject having the same event more than once will be counted only once. Adverse events will be summarized by worst NCI CTCAE VERSION 3.0 grade.

Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTCAE VERSION 3.0 grade 3 or higher, study-drug-related events, and serious adverse events will be listed separately.

Incidence density (ID) for individual adverse events together with two-sided 95% confidence intervals will be provided. ID is defined as the ratio of number of new adverse events in the calendar period over accrued population time.

Summary tables will be provided to allow a side-by-side comparison of the incidence density observed in the lenalidomide cohort, the background cohort and MM009/010. Odds ratios, together with two-sided 95% confidence intervals, will be calculated to estimate the relative risk between the two cohorts in the study for relevant adverse events. Estimates will be adjusted a posteriori to control for any differences in the comparative populations.

The Kaplan-Meier procedures will be used to characterize the time to onset and the time to resolution for adverse events of special interest.

Multivariate logistic regression will be performed in exploratory analyses to determine the demographic and baseline characteristics most predictive of developing adverse events of interest. A forward selection stepwise procedure will be used to identify the relevant factors.

Summary tables will also be provided for clinically relevant subgroups, e.g., based on lines of therapy and disease severity, to allow side by side comparison for the lenalidomide cohort, the background cohort, and the MM009 and MM010 clinical trials.

Analyses will be undertaken to explore the course of neuropathy for subjects taking lenalidomide who have pre-existing neuropathy at baseline. Specifically, cross-tabulations will be used to summarize changes in severity observed during lenalidomide treatment and summary statistics will be provided for other relevant variables.

Relevant summary tables will be provided by country, that is, by pooling data from all centers within a specific country.

7.5. Safety Advisory Board

An external Safety Advisory Board will review data on serious adverse events of special interest. The event specific questionnaires will also be reviewed and agreed by independent advisors.

8. QUALITY CONTROL AND QUALITY ASSURANCE

All data collected for the study should be recorded accurately and promptly. The individuals responsible for the integrity of the data shall have the education, training, and experience to perform the assigned tasks. In particular, all individuals will be trained in the requirements of solicited adverse event reporting and the expedited reporting procedure. Training records will be maintained in the site files.

A random selection of sites will be selected for site monitoring visits at which data will be checked against source documents for completeness. If sites do not meet the pre-determined criteria for completeness of adverse event rate reporting, that site will undergo re-training and all sites in the study will receive additional reminders of the importance of maintaining adverse event reporting standards. Further cohorts of sites will be selected for site monitoring to ensure that standards of adverse event reporting are maintained.

Security of the data will be maintained at all times in line with local applicable regulatory law and procedures. Access will be limited to authorised individuals. Controls, such as document encryption, will be used to ensure the authenticity, integrity and confidentiality of electronic records when transmitted over open systems (e.g., the internet). Adequate back up of the data will be maintained throughout the course of the study.

9. REGULATORY AND ETHICAL CONSIDERATIONS

9.1. Regulatory Agency/Independent Ethics Committee Review and Approval

This study will be performed in accordance with Volume 9 A of the Rules Governing Medicinal Products in the European Union and will also comply with Good Pharmacoepidemiology Practice.

This protocol has been approved by the CHMP. Additional approval by National Competent Authorities and National/local Ethics Committees will be obtained in accordance with local regulations.

9.2. Protocol Amendments

Any major amendment of this protocol that seems appropriate, as the study progresses, will be reported to the Rapporteur and co-Rapporteur.

9.3. Informed Consent

This study is non-interventional and by definition, no additional procedures will be carried out on the subject beyond the normal clinical practice of the treating investigator. Informed Consent will be obtained from all subjects for their clinical data to be recorded anonymously. Subjects will also be informed of their right to withdraw their consent at any time during the study.

9.4. Subject Confidentiality

All relevant legislation on Data Protection will be followed. The Subject's personal identifiers will be replaced by a code in the study documents, and only authorised persons will have access to identifiable personal details for the purposes of data verification procedures. Responsibility for the retrieval of information from personal medical records lies with the Healthcare Professional(s) responsible for the subjects' care.

9.5. Payment to investigators

Payment will be made to participating investigators in recompense for the additional time and expense incurred according to local guidelines. This will include study preparation and training time, ongoing site administration and contact with the sponsor or designated contractor as well as the additional time to record data on the data collection forms and record additional follow-up data on events of special interest and serious adverse events.

9.6. Reporting to Regulatory Agencies

Reports of all serious adverse reactions to lenalidomide arising from the study will be reported on an expedited basis (i.e. within 15 days), to the Competent Authority of the Member State on whose territory the incident occurred. All adverse reactions, i.e. including non-serious ones, will be included in the final study report in frequency tables.

Serious adverse events which are reported on the background cohort will be notified to the relevant Market Authorisation Holder where known.

The status and available results from the study will be reported in each RMP update with the PSUR and will be made available to the EMEA, CHMP and the Competent Authorities of the territories where the study is being carried out.

In each update, the following information at least will be included:

- Status of the country of the study
- Recruitment level
- Safety data as soon as it is available

9.7. Publication

It is intended to publish the results of this study.

10. RESOURCE

This study will be performed in several EU Member States. There will be local country resource for the support of the sites and also central coordination to ensure adequate communication. This will include a Project Manager, Data Management, Statistics, Medical expertise and local monitoring resource. Medical sales representatives will not be involved in recruitment of investigators or subjects. Clinical Research Associates will be used to facilitate data collection.

11. DATA HANDLING AND RECORDKEEPING

The investigator will rely upon his normal consultation practice to identify adverse events. No specific subject questionnaires will be used.

Either electronic or paper CRFs (according to investigator preference) will be used to collect baseline and interval data.

The investigator will record on the CRF verbatim adverse events experienced by subject along with an assessment of seriousness, relationship to study drug and outcome. The investigator will be required to complete a Serious Adverse Event Form for all SAEs. These will then be followed up by Celgene's Drug Safety Department and Event Specific Questionnaires will be sent to the investigator as a means of following up all events of special interest.

All data from CRFs will be entered into a secure clinical database. SAE data will be contained in Celgene's Safety Database. Periodic reconciliation will take place. Those SAEs notified to Celgene for treatments other than lenalidomide will be notified to the relevant Market Authorisation Holder where known.

REFERENCES

1. Alexanian R. Treatment of multiple myeloma. *Acta Haemat* 1980; 63: 237-240.
2. Alexanian R, Dimopoulos M. The treatment of multiple myeloma. *N Engl J Med* 1994; 330: 484-489.
3. Apfel SC, Zochodne DW. Thalidomide Neuropathy: Too much or too long. *Neurology* 2004;62: 2158-2159
4. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized, trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med* 1996; 335: 91-97.
5. Badros A, Siegel E, Bodenner D, et al. Hypothyroidism in subjects with multiple myeloma following treatment with thalidomide. *Am J Med* 2002;112: 412-3.
6. Barlogie B. Personal communication. July 2002.
7. Bowcock S, Rassam S, Ward S, et al. Thromboembolism in subjects on thalidomide for myeloma. *Hematology* 2002;7:51-3.
8. Cancer Research UK. 2005; <http://info.cancerresearchuk.org/cancerstats/types/multiplemyeloma/?a=5441>
9. Chaudhry V, Cornblath DR, Corse A, Freimer M, Simmons-O'Brien E, Vogelsang G. Thalidomide-induced neuropathy. *Neurology* 2002;59(12):1872
10. Corral LG, Haslett PAJ, Muller GW, et al. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF- α . *J Immunol* 1999; 163: 380-386.
11. Durie BGM, Salmon SE. The current status and future prospects of treatment for multiple myeloma. *Clinics Haematol* 1982; 11: 181-210.
12. Escudier B, Lassau N, Leborgne S, Angevin E, Laplanche A. Thalidomide and venous thrombosis. *Ann Intern Med* 2002;136(9):711.
13. EUCAN database. 1998; <http://www-dep.iarc.fr/eucan/eucan.htm>
14. Gregory WM, Richards MA, Malpas JS. Combination chemotherapy versus melphalan and prednisolone in the treatment of multiple myeloma: An overview of published trials. *J Clin Oncol* 1992; 10: 334-342.
15. Hideshima, T., Chauhan, D. et al. Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood* 2000; 96: 2943-2950

16. Horowitz SB, Striling AL. Thalidomide –Induced Toxic Epidermal Necrolysis. *Pharmacotherapy* 1999; 19 (10).
17. Kaur A, Yu SS, Lee AJ, Chiao TB. Thalidomide-induced sinus bradycardia. *Ann Pharmacother* 2003;37(7-8):1040-3.
18. Lewis JA 1981) Post marketing Surveillance: How many subjects. *Trends in Pharmaceutical Sciences* 2 (4): 93-94
19. Michiels JJ. Multiple myeloma: Prognostic factors and treatment modalities. *Neth J Med* 1992; 40: 254-270.
20. Osman K, Comenzo R, Rajkumar S. Deep venous thrombosis and thalidomide therapy for multiple myeloma. *N Engl J Med* 2001;344:1951-2.
21. Rajkumar S, Hayman S, Gertz M, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *J Clin Oncol* 2002;20:4319-23
22. Richardson P, Schlossman RL, Weller E, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in subjects with relapsed multiple myeloma. *Blood* 2002; 100:3063-3067.
23. Richardson P. Personal communication. July 2002.
24. Thalomid US Product Information
25. Tseng S, Pak G, Washenik K, Pomeranz MK, Shupack JL. Rediscovering thalidomide: a review of its mechanism of action, side effects, and potential uses. *J Am Acad Dermatol* 1996;35(6):969-79.
26. Zangari M, Anaissie E, Barlogie B, et al. Increased risk of deep-vein thrombosis in subjects with multiple myeloma receiving thalidomide and chemotherapy. *Blood* 2001;98:1614-5.
27. Zangari M, Tricot G, Zeldis J, Eddlemon P, Saghafifar F, Barlogie B. results of phase I study of CC-5013 for the treatment of multiple myeloma (MM) subjects who relapse after high dose chemotherapy (HDCT). *Blood* 2001; 98:775a (Abstract 3226).

APPENDIX 1

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 Form rather than the individual signs or symptoms of the diagnosis or syndrome.

All AEs will be recorded by the Investigator(s) from the first dose of study medication through the end of the last dose of study medication. 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 in subject 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 outsubject 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 Toxicity Criteria (CTCAE, Version 3.0) (<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 = Death

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.

The follow up of subjects on lenalidomide who discontinue treatment due to an adverse event will not be time limited and will continue until resolution or stabilization or when in the opinion of the investigator no additional useful information can be obtained from the event or the subject AEs that cause a subject to discontinue study participation must be followed until either the event resolves, stabilizes or returns to baseline (if a baseline assessment is available).

Immediate reporting of serious adverse events

Any AE that meets the 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 medication, that occur during the period when the subject is receiving treatment with study drug, those made known to the Investigator(s) within 30 days after a subject's last dose of medication, and those made known to the investigator(s) at anytime that are suspected of being related to medication.

The SAE must be reported immediately (i.e., within 24 hours of the Investigators' knowledge of the event) to the Celgene's Drug Safety Department using the SAE Report Form provided by Celgene (see below for contact information).

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 or will be provided in an Event Specific Questionnaire, and sent to Celgene.

All SAEs in subjects exposed to lenalidomide 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 subject or the female partner of a male subject occurring while the subject is on lenalidomide, or within 30 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Celgene's Drug Safety Department immediately using the Pregnancy Capture Form.

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 the Celgene's Drug Safety Department of the outcome of the pregnancy via the Pregnancy follow-up forms within 24 hours of the Investigators' knowledge of the event.

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.

In the case of a live “normal” birth, the Celgene Drug Safety Monitor should be informed within 24 hours of the Investigators’ knowledge of the event.

All infants born following foetal exposure should be followed up for the first 12 months after delivery.

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 the Celgene Drug Safety Monitor 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.

Celgene safety contact information

Local Celgene Office contact information will be provided with Study materials. Alternatively, contact can be made to Celgene Drug Safety Europe at:

Email: drugsafetyeurope@celgene.com

Fax: +41 327 298 409

APPENDIX 2

ECOG PERFORMANCE STATUS SCORE	
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

APPENDIX 3

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 investigators 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 investigator to promote and safeguard the health of the people. The investigator's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the investigator with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A investigator shall act only in the patient 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 investigator 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 that 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. Investigators 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. Investigators 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 investigator 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 investigator should be particularly cautious if the subject is in a dependent relationship with the investigator or may consent under duress. In that case the informed consent should be obtained by a well-informed investigator 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 investigator 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 subjects 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 investigator 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-investigator relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the investigator, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the investigator'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.