1. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company: Celgene International Sarl</td></tr>
<tr><td colspan="2">Name of Investigational Product: Lenalidomide</td></tr>
<tr><td colspan="2">Protocol Number: CC-5013-PASS-001</td></tr>
<tr><td colspan="2">Protocol Title: A non-interventional observational post authorisation safety study of subjects treated with lenalidomide</td></tr>
<tr><td>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.</td><td>Phase of development:
Post-authorisation</td></tr>
<tr><td colspan="2">Objectives:
<u>Primary</u>
• 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.</td></tr>
<tr><td colspan="2"><u>Secondary</u>
• 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).</td></tr>
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- 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.

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. 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.

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.

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

Dosing Regime	**Study Drug Supply**
Treatment will be according to clinical	All treatments will be prescribed by the treating investigator in accordance with

practice	normal clinical practice. Lenalidomide will not be supplied by Celgene

Study Population
Subjects must meet the following inclusion/exclusion criteria to be eligible for the study.

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 and subsequently prescribed lenalidomide can be recruited into this study as part of the lenalidomide cohort.

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 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.

Safety:

- 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.

Statistical Analysis:

Study Populations:

Data from all subjects who receive at least one dose of treatment will be included in the safety

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.