# PrECOG Protocol Number: PrE1003

## A Phase I/II Study of the Tolerability of Lenalidomide and Low Dose Dexamethasone in Previously Treated Multiple Myeloma Patients with Impaired Renal Function

**STUDY CHAIRS:** Joseph R. Mikhael, M.D.

**STUDY CO-CHAIRS:** [redacted]

**MEDICAL MONITOR:** [redacted]

**STUDY STATISTICIAN:** [redacted]

**PrECOG STUDY CONTACT:** Carolyn Andrews, R.N.

(Internal Use Only) Celgene Ref. ID Number: RV-MM-PrECOG-0394

**IND #:** **103014**

**NCT #:** **00790842**

**Version Number:** 6.0

**Version Date:** 3/28/2011

| Release/Revision History | |
|---|---|
| Version 1.0 December 4, 2008 | MC0885 Released to Mayo Sites only |
| MCCC Addendum 1 September 29, 2009 (Version 2.0) | MC0885 Released to Mayo Sites only |
| MCCC Addendum 2 November 24, 2009 (Version 3.0) | MC0885 Released to Mayo Sites only |
| MCCC Addendum 3 October 1, 2010 (Version 4.0) | MC0885 Released to Mayo Sites only |
| Version 5.0: November 03, 2010 | Released to Sites |
| Version 6.0: March 28, 2011 | Released to Sites |

| **Revision History** | | |
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| Version 5.0 | 11/03/2010 | **Released to sites** |
| **THE FOLLOWING AMENDMENT WAS MADE TO VERSION 5.0 OF THE PROTOCOL** | | |
| Version 6.0 | 3/28/2011 | PrECOG Study Site Contacts<br>**Added:**<br>[redacted]<br>**Associate Project Manager**<br>**PrECOG, LLC**<br>**1818 Market Suite, Suite 1100**<br>**Philadelphia, PA 19103**<br>**9:00 am-5:00 pm**<br>**Eastern Time Zone**<br>**Phone: 215-789-7001**<br>[redacted] |
| Version 6.0 | 3/28/2011 | Medical Monitor SAE Fax Number<br>**Was:**<br>SAE Fax: 888-**801-8795**<br>**Is:**<br>SAE Fax: 888-**577-9921** |
| Version 6.0 | 3/28/2011 | Schema<br>**Was:**<br>PHASE I only: Prior to discussing protocol entry with the patient, call **PrECOG at 215-789-7001** to ensure that a place on the protocol is open to the patient.<br>**Is:**<br>PHASE I only: Prior to discussing protocol entry with the patient, call **the PrECOG Project Manager** to ensure that a place on the protocol is open to the patient. **The Project Manager contact information is located in the Study Reference Manual.** |

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| Version 6.0 | 3/28/2011 | 1.7 Dosing Recommendation for Lenalidomide in Patients with Renal Impairment, Hemodialysis<br>**Was:**<br>This study originated December 22, 2008 at Mayo Clinic in Arizona and Rochester. As of November **03**, 2010, a total of **13** subjects have been enrolled.<br>**Is:**<br>This study originated December 22, 2008 at Mayo Clinic in Arizona and Rochester. As of November **09**, 2010, a total of **15** subjects have been enrolled |
| Version 6.0 | 3/28/2011 | 3.1 Eligibility Criteria<br>**Was:**<br>NOTE: Phase I Only – Prior to discussing protocol entry with the patients **AND** prior to registering in the **interactive web registration system (IWRS), call PrECOG at 215-789-7001** to ensure that a place on the protocol is open to the patient.<br>**Is:**<br>NOTE: Phase I Only – Prior to discussing protocol entry with the patients **AND** prior to registering in the **electronic data capture (eDC) system, call the PrECOG Project Manager** to ensure that a place on the protocol is open to the patient. **The Project Manager contact information is located in the Study Reference Manual.** |
| Version 6.0 | 3/28/2011 | 4. Test Schedule<br>Footnote 18 for Survival **and Malignancy Surveillance**<br>**Was:**<br>18. Follow-up every 6 months for survival x 3 years. If patient has not progressed at off-study, document date of progression.<br>**Is:**<br>18. Follow-up every 6 months for survival, **second primary malignancy diagnosis, and recurrence of any prior malignancy (if applicable)** x 3 years. If patient has not progressed at off-study, document date of progression. **This should include subjects who may have discontinued the study at any time or for any reason, who may be in a survival follow-up period, or who may have died. Following this 3 year time period, reporting of all identified cases of subsequently diagnosed second primary malignancies is voluntary by the treating physician to the manufacturer.** |

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| Version 6.0 | 3/28/2011 | 4. Test Schedule<br>Footnote 19<br>**Added:**<br>19. Bone marrow (with aspirate/FISH/cytogenetics) and skeletal survey may be used if performed ≤90 days of study enrollment. **In addition to the standard evaluation for prolonged cytopenias that do not recover after discontinuation of treatment, a bone marrow exam should be considered, in patients with the following parameters: no leukopenia at the time of multiple myeloma diagnosis, no active multiple myeloma at the time of the cytopenia, no vitamin or element deficiency to explain the cause of the cytopenia(s).** |
| Version 6.0 | 3/28/2011 | 6.31 Phase I Dose Escalation<br>**Was:**<br>Prior to discussing protocol entry with patient **AND** prior to registering a patient through the electronic **interactive web registration (IWR)** system, call **PrECOG at 215-789-7001** to ensure that a place on the protocol is open to the patient.<br>**Is:**<br>Prior to discussing protocol entry with patient **AND** prior to registering a patient through the electronic **data capture (eDC)** system, call **the PrECOG Project Manager** to ensure that a place on the protocol is open to the patient. **The Project Manager contact details can be found in the Study Reference Manual.** |
| Version 6.0 | 3/28/2011 | 6.3.11 Patients must not start protocol treatment prior to registration.<br>**Was:**<br>Upon determination that a subject meets eligibility criteria, the subject will be registered in the study by site personnel via an electronic **IWR** system. Confirmation of registration will be displayed in the **IWR** system once site personnel have verified the subject's eligibility status.<br>**Is:**<br>Upon determination that a subject meets eligibility criteria, the subject will be registered in the study by site personnel via an electronic **data capture (eDC)** system. Confirmation of registration will be displayed in the **eDC** system once site personnel have verified the subject's eligibility status. |

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| Version 6.0 | 3/28/2011 | 6.32 Phase II Patient Registration<br>**Was:**<br>Upon determination that a subject meets eligibility criteria, the subject will be registered in the study by site personnel via an electronic **interactive web registration (IWR)** system. Confirmation of registration will be displayed in the **IWR** system once site personnel have verified the subject's eligibility status.<br>**Is:**<br>Upon determination that a subject meets eligibility criteria, the subject will be registered in the study by site personnel via an electronic **data capture (eDC)** system. Confirmation of registration will be displayed in the **eDC** system once site personnel have verified the subject's eligibility status. |
| Version 6.0 | 3/28/2011 | 8.0 Dose Modification Based on Adverse Events for Phase I and Phase II<br>**Removed:**<br>***ALERT: ADR reporting may be required for some adverse events (see Section 10.0)***. |
| Version 6.0 | 3/28/2011 | 8.0 Dose Modification Based on Adverse Events for Phase I and Phase II<br>**Was:**<br>Subjects will be evaluated for AEs at each visit with the NCI CTCAE V4.0 used as a guide for the grading of severity. Refer to Tables below for specific Lenalidomide and Dexamethasone dose reduction steps. Subjects who cannot tolerate lowest dose level are to be discontinued from the treatment phase of the study. Subjects experiencing ≥grade 3 non-hematologic or grade 4 hematologic adverse events will have their study drug held per Table 8.31.<br>**Is:**<br>Subjects will be evaluated for AEs at each visit with the NCI CTCAE V4.0 used as a guide for the grading of severity. Refer to Tables below for specific Lenalidomide and Dexamethasone dose reduction steps. Subjects who cannot tolerate lowest dose level are to be discontinued from the treatment phase of the study. Subjects experiencing ≥grade 3 non-hematologic or grade 4 hematologic adverse events will have their study drug held per Table 8.31. **Held doses are not made up**. |
| Version 6.0 | 3/28/2011 | 8.0 Dose Modification Based on Adverse Events for Phase I and Phase II<br>**Removed:**<br>**Omit = The current dose(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time.**<br>**Hold = Refers to decision made at the beginning of the cycle to delay the start of the cycle until the patient meets the protocol criteria to restart drug. Held doses are not made up.** |

<table>
<tr><td>Version 6.0</td><td>3/28/2011</td><td>8.21 Hematological Requirements for Day 1 of Each Cycle<br>Was:<br>If either of these two criteria is not met, the start of the cycle should be held and CBC should be followed weekly. Once ANC and platelets have recovered to Grade 2 or less, cycle should be started at next lower dose of lenalidomide.<br>Is:<br>If either of these two criteria is not met, the start of the cycle should be held and CBC should be followed weekly. Once ANC and platelets have recovered to Grade 2 or less, cycle should be started at next lower dose of lenalidomide. Held doses are not made up.</td></tr>
<tr><td>Version 6.0</td><td>3/28/2011</td><td>Table 8.31: Dose Modification for Lenalidomide<br>Add above Table 8.3.1:<br>Please note: Held doses are not made up.</td></tr>
<tr><td>Version 6.0</td><td>3/28/2011</td><td>Table 8.31: Dose Modification for Lenalidomide<br>Was:
<table>
<tr><th>NCI CTC Toxicity Grade</th><th>Day 2-14 of Cycle</th><th>≥Day 15 of Cycle</th></tr>
<tr><td>Grade 3 neutropenia associated with fever (temperature ≥38.5ºC) or Grade 4 neutropenia</td><td>• Hold (interrupt dose).<br>• Follow CBC weekly.<br>• If neutropenia has resolved to ≤grade 2, restart at next lower dose level and continue the cycle until day 2 .</td><td>• Omit lenalidomide for remainder of cycle. Restart lenalidomide next cycle (decrease dose by one dose level)</td></tr>
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<tr><th>NCI CTC Toxicity Grade</th><th>Day 2-14 of Cycle</th><th>≥Day 15 of Cycle</th></tr>
<tr><td>Thrombocytopenia ≥Grade 3 (platelet count <50,000/mm³)</td><td>• Hold (interrupt) lenalidomide.<br>• Follow CBC weekly.<br>• If thrombocytopenia resolves to ≤grade 2, restart lenalidomide at next lower dose level and continue the cycle through Day 21.</td><td>• Omit lenalidomide for remainder of cycle. Restart lenalidomide next cycle (decrease dose by one dose level).</td></tr>
<tr><td>Non-blistering rash<br>Grade 3</td><td>• If Grade 3, hold (interrupt) lenalidomide dose. Follow weekly.<br>• If the adverse event resolves to ≤grade 1, restart lenalidomide at next lower dose level and continue the cycle through Day 21.</td><td>• Omit lenalidomide for remainder of cycle. Restart lenalidomide next cycle (decrease dose by one dose level).</td></tr>
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<tr><th>NCI CTC Toxicity Grade</th><th>Day 2-14 of Cycle</th><th>≥Day 15 of Cycle</th></tr>
<tr><td>Sinus bradycardia/other cardiac arrhythmia Grade 2</td><td>• .Hold (interrupt) lenalidomide dose. Follow at least weekly.</td><td>• Omit lenalidomide for remainder of cycle. Restart lenalidomide next cycle (decrease dose by one dose level).</td></tr>
<tr><td>Allergic reaction or hypersensitivity Grade 2-3</td><td>• Hold (interrupt) lenalidomide dose. Follow at least weekly.</td><td>• Omit lenalidomide for remainder of cycle. Restart lenalidomide next cycle (decrease dose by one dose level).</td></tr>
<tr><td>Venous thrombosis/ embolism<br>≥Grade 3</td><td>• Hold (interrupt) lenalidomide and start therapeutic anticoagulation; restart lenalidomide at investigator’s discretion (maintain dose level).</td><td>• Omit lenalidomide for remainder of cycle. See Anticoagulation Consideration (see Section 9.4). Restart lenalidomide next cycle (decrease dose by one dose level).</td></tr>
<tr><td>Hyperthyroidism or hypothyroidism ≥Grade 3</td><td>• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level)</td><td>• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level).</td></tr>
<tr><td>Other non-hematologic adverse events assessed as lenalidomide related ≥Grade 3</td><td>• Hold (interrupt) lenalidomide dose. Follow at least weekly.<br>• If the adverse event resolves to ≤grade 2, restart lenalidomide and continue through the scheduled Day 21 of current cycle. Otherwise, omit for remainder of cycle. Omitted dose are not made up. For toxicity attributed to lenalidomide, reduce by one dose level when restarting lenalidomide</td><td>• Omit lenalidomide for remainder of cycle. Restart lenalidomide next cycle (decrease dose by one dose level).</td></tr>
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| Version 6.0 | 3/28/2011 | 10.0 Adverse Event (AE) Monitoring and Reporting<br>**Removed:**<br>**10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE. Next, determine whether the event is expected or unexpected (refer to Sections 10.12 and 15.0) and if the adverse event is related to the medical treatment or procedure (see Section 10.13). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2) in addition to the routinely reported clinical data (see Section 10.31).**<br>**Expedited adverse event reporting requires submission of a written report, but may also involve telephone notifications. Telephone and written reports are to be completed within the timeframes specified in Section 10.2. All expedited adverse event reports should also be submitted to the local Institutional Review Board (IRB).**<br>**10.12 Expected vs. Unexpected**<br>• **The determination of whether an AE is expected is based on agent-specific adverse event information provided in Section 15.0 of the protocol.**<br>• **Unexpected AEs are those not listed in the agent-specific adverse event information provided in Section 15.0 of the protocol.** |
| Version 6.0 | 3/28/2011 | **Was:**<br>**10.14** When a study includes both investigational and commercial agents, the following apply:<br>• When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered investigational. **Expedited** reporting of adverse events follows the guidelines for investigational agents.<br>• **When a study includes an investigational agent(s) and a commercial agent(s) on a separate arm, follow the guidelines for investigational agents only if the event is specifically associated with the investigational agent(s). If the event is associated with a regimen containing only commercial agent(s), expedited reporting follows the guidelines for commercial agents.**<br>**Is:**<br>**10.12** When a study includes both investigational and commercial agents, the following apply:<br>• When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered investigational. **R**eporting of adverse events follows the guidelines for investigational agents. |

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<tr>
<td>Version 6.0</td>
<td>3/28/2011</td>
<td>Removed:<br>10.2 Expedited Adverse Event Reporting Requirements
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<tr><th></th><th>Grade 4 or 5[1]<br>Unexpected with Attribution of Possible, Probable, or Definite</th><th>Other Grade 4 or 5<br>or<br>Any hospitalization during treatment</th></tr>
<tr><td>Notify PrECOG[2] within 24 hours of becoming aware of event</td><td>X</td><td></td></tr>
<tr><td>Submit written report within 24 hours/1 business day[3]</td><td>X</td><td></td></tr>
<tr><td>Submit Grade 4 or 5 Non-AE Reportable Events/Hospitalization Form within 5 working days.</td><td></td><td>X[4]</td></tr>
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1. Includes all deaths within 30 days of the last dose of investigational agent regardless of attribution or any death attributed to the agent(s) (possible, probable, or definite) regardless of timeframe.<br>2. See Section 10.51 for PrECOG contact information.<br>3. PrECOG will provide SAE forms. Fax the SAE forms to PrECOG at 888-577-9921. Within 24 hours of notification, PrECOG will fax the SAE to Celgene Drug Safety at [redacted].<br>4. If expedited written report was submitted, this form does not need to be completed.</td>
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<td>Version 6.0</td>
<td>3/28/2011</td>
<td>Was:<br>10.3 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 grading unless otherwise stated in the table below:<br>Is:<br>10.2 All Adverse Events are to be graded at each evaluation and all pretreatment symptoms/conditions are to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 grading. The specific Adverse Events/Symptoms in the table below are to be collected as indicated below:</td>
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| Version 6.0 | 3/28/2011 | **Was:**<br>**10.4** Serious Adverse Event (SAE) Definition<br>A serious adverse event is one that at any dose (including overdose):<br>▪ Results in death<br>▪ Is life-threatening[1]<br>▪ Requires inpatient hospitalization or prolongation of existing hospitalization<br>▪ Results in persistent or significant disability or incapacity[2]<br>▪ Is a congenital anomaly or birth defect<br>▪ Is an important medical event[3]<br>▪ **Pregnancy**<br>**Is:**<br>**10.3** Serious Adverse Event (SAE) Definition<br>A serious adverse event is one that at any dose (including overdose):<br>▪ Results in death<br>▪ Is life-threatening[1]<br>▪ Requires inpatient hospitalization or prolongation of existing hospitalization<br>▪ Results in persistent or significant disability or incapacity[2]<br>▪ Is a congenital anomaly or birth defect<br>▪ Is an important medical event[3]<br>▪ **Diagnosis of a new second primary cancer** |

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| Version 6.0 | 3/28/2011 | **Was:**<br>**10.42** Pregnancies<br>Pregnancy of a female subject or the female partner of a male subject occurring while the subject is on lenalidomide or within 4 weeks after the subject's last dose of lenalidomide are considered expedited reportable events. If the subject is on lenalidomide, it is to be discontinued immediately and the subject is to be instructed to return any unused portion of lenalidomide to the Investigator. The pregnancy must be reported to PrECOG within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the **SAE** Form. Within 24 hours of notification, PrECOG will fax to Celgene Drug Safety the **SAE**.<br>• The Investigator will follow the pregnant female until completion of the pregnancy, and must notify PrECOG of the outcome as specified below. PrECOG will provide Celgene Drug Safety with the outcome The Investigator will provide this information as a follow-up to the initial **SAE**.<br>• If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (e.g., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for Expedited Reporting of SAEs to PrECOG (e.g., report the event to PrECOG by facsimile within **24 hours** of the Investigator's knowledge of the event). PrECOG will report the event to Celgene Drug Safety within 24 hours of the knowledge of the event.<br>**Is:**<br>**10.32** Pregnancies<br>Pregnancy of a female subject or the female partner of a male subject occurring while the subject is on lenalidomide or within 4 weeks after the subject's last dose of lenalidomide are considered expedited reportable events. If the subject is on lenalidomide, it is to be discontinued immediately and the subject is to be instructed to return any unused portion of lenalidomide to the Investigator. The pregnancy must be reported to PrECOG within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the **Pregnancy** Form. Within 24 hours of notification, PrECOG will fax to Celgene Drug Safety the **Pregnancy Form**.<br>• The Investigator will follow the pregnant female until completion of the pregnancy, and must notify PrECOG of the outcome as specified below. PrECOG will provide Celgene Drug Safety with the outcome The Investigator will provide this information as a follow-up to the initial **submission**.<br>• If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (e.g., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for Expedited Reporting of SAEs to PrECOG (e.g., report the event to PrECOG by facsimile within 24 hours of the Investigator's knowledge of the event). PrECOG will report the event to Celgene Drug Safety within **1 business day** of the knowledge of the event. |

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| Version 6.0 | 3/28/2011 | **Was:**<br>**10.42** Pregnancies<br>• Any suspected fetal exposure to lenalidomide must be reported to PrECOG within 24 hours of being made aware of the event. PrECOG will report any suspected fetal exposure to Celgene Drug Safety within **24 hours** of being aware of the event. The pregnant female should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.<br>**Is:**<br>**10.32** Pregnancies<br>• Any suspected fetal exposure to lenalidomide must be reported to PrECOG within 24 hours of being made aware of the event. PrECOG will report any suspected fetal exposure to Celgene Drug Safety within **1 business day** of being aware of the event. The pregnant female should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. |
| Version 6.0 | 3/28/2011 | **Was:**<br>**10.5 Expedited** Reporting by Investigator to PrECOG<br>**Is:**<br>**10.4 Serious Adverse Event** Reporting by Investigator to PrECOG |
| Version 6.0 | 3/28/2011 | **Was:**<br>**10.51** Serious adverse events (SAE) are defined above. The investigator should inform PrECOG of any **unexpected** SAE **that is possibly, probably or definitely related to drug** within 24 hours of being aware of the event. The date of awareness should be noted on the report. This must be documented on PrECOG SAE form. This form must be completed and supplied to PrECOG within 24 hours/1 business day at the latest on the following working day. **PrECOG will inform and submit SAE Form to Celgene Drug Safety within 24 hours/1 business day of being aware of the event.** The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up PrECOG SAE report form. A final report to document resolution of the SAE is required. **The protocol number (RV-MM-PrECOG-0394) (PrE 1003) should be included on SAE reports to PrECOG**. A copy of the fax transmission confirmation of the SAE report to PrECOG should be attached to the SAE and retained with the patient records. **PrECOG will submit final report to Celgene Drug Safety with Celgene Tracking Number RV-MM-PrECOG-0394 (PrE1003).** |

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| Version 6.0 | 3/28/2011 | **Is:**<br><br>**10.41** Serious adverse events (SAE) are defined above. The investigator should inform PrECOG of any **SAE** within 24 hours of being aware of the event. The date of awareness should be noted on the report. This must be documented on PrECOG SAE form. This form must be completed and supplied to PrECOG within 24 hours/1 business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up PrECOG SAE report form. A final report to document resolution of the SAE is required. A copy of the fax transmission confirmation of the SAE report to PrECOG should be attached to the SAE and retained with the patient records. |
| Version 6.0 | 3/28/2011 | **Was:**<br><br>**10.51** Serious adverse events (SAE) are defined above.<br>**PrECOG Drug Safety Contact Information**<br><br>PrECOG will **forward SAEs that meet expedited reporting requirements and related information received from Investigators to Celgene Drug Safety within 24 hours of receipt of SAE and related documents.**<br><br>**Is:**<br><br>**10.41** Serious adverse events (SAE) are defined above.<br>**PrECOG Drug Safety Contact Information**<br><br>PrECOG will **notify Celgene of any SAE within 1 business day of receipt from the site**. |
| Version 6.0 | 3/28/2011 | **Was:**<br><br>**10.6** Reporting of Other Second Primary **Cancers**<br><br>All cases of new primary **cancers** that occur on PrECOG protocols during or after protocol treatment must be **recorded as an AE** and **reported via the eCRF to PrECOG**. New primary **cancers** should be reported **with 30 days of diagnosis**, regardless of relationship to protocol treatment. A copy of the pathology report should be sent, if available.<br><br>*NOTE**:* Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted.** |

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| Version 6.0 | 3/28/2011 | **Is:**<br>**10.5** Reporting of Other Second Primary **Malignancies**<br>All cases of new primary **malignancies** that occur on PrECOG protocols during or after protocol treatment must be **reported as a SAE** and **documented on a PrECOG SAE form**. New primary **malignancies** should be reported **within 24 hours of being aware** of diagnosis, regardless of relationship to protocol treatment. **SAE submission process described above in Section 10.4 should be followed**. A copy of the pathology report should be sent **with SAE form**, if available.<br>*NOTE**:*** Data regarding survival and remission status, **second primary malignancies, and recurrence of prior malignancies will be followed x 3 years. This should include subjects who may have discontinued the study at any time or for any reason, who may be in a survival follow-up period, or who may have died. Data for all identified cases of subsequently diagnosed second primary malignancies after this 3 year time will be reported voluntarily by the treating physician to the manufacturer.** |
| Version 6.0 | 3/28/2011 | **Was:**<br>11.0 Treatment Evaluation<br>**Is:**<br>11.0 Treatment Evaluation **(Response is to be assessed at the end of each treatment cycle within 3 days prior to the start of the next cycle)** |
| Version 6.0 | 3/28/2011 | 11.2 Clarification of Test Indications<br>**Was:**<br>Listed below are the minimal required tests required to assess response based on the characteristics of their disease at on study.<br>**Is:**<br>Listed below are the minimal required tests required to assess response based on the characteristics of their disease at on study. **Response is to be assessed at the end of each treatment cycle within 3 days prior to the start of the next cycle.** |
| Version 6.0 | 3/28/2011 | 19.7 Electronic Case Report Form (eCRF) Information<br>**Was:**<br>The completed eCRF must be promptly reviewed, electronically signed, and dated by **a qualified physician who is an** Investigator **or Sub-investigator .**<br>**Is:**<br>The completed eCRF must be promptly reviewed, electronically signed and dated by **the Principal** Investigator. |

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| Version 6.0 | 3/28/2011 | Appendix I Informed Consent Example<br>**Was:**<br>Version Date: **November 03**, 2010<br>**Is:**<br>Version Date: **March 28**, 2011 |
| Version 6.0 | 3/28/2011 | Appendix I Informed Consent Example<br>**Added:**<br>**Second New Cancers**<br>**According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with induction therapy (treatment as first step to reducing number of cancer cells) and/or bone marrow transplant then lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then placebo (a capsule containing no lenalidomide). Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers.** |
| Version 6.0 | 3/28/2011 | Appendix I Informed Consent Example<br>What About Confidentiality?<br>**Added:**<br>**A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time**. |
| Version 6.0 | 3/28/2011 | Appendix XI Eligibility Checklist<br>**Was:**<br>**NOTE:** Phase I Only – Prior to discussing protocol entry with the patient **AND** prior to registering in **IWRS**, call PrECOG to ensure that a place on the protocol is open to the patient.<br>**Is:**<br>**NOTE:** Phase I Only – Prior to discussing protocol entry with the patient **AND** prior to registering in **eDC**, call PrECOG to ensure that a place on the protocol is open to the patient. |

| | | |
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| Version 6.0 | 3/28/2011 | Appendix XII Investigator's Statement<br>**Was:**<br>1. I have carefully read this protocol entitled "**A Phase I/II Study of the Tolerability of Lenalidomide and Low Dose Dexamethasone in Previously Treated Multiple Myeloma Patients with Impaired Renal Function, Version 5.0 dated 11/03/2010" (Protocol number PrE1003)** and agree that it contains all the necessary information required to conduct the study. I agree to conduct the study as outlined in the protocol.<br>**Is:**<br>1. I have carefully read this protocol entitled "**A Phase I/II Study of the Tolerability of Lenalidomide and Low Dose Dexamethasone in Previously Treated Multiple Myeloma Patients with Impaired Renal Function, Version 6.0 dated 3/28/2011" (Protocol number PrE1003)** and agree that it contains all the necessary information required to conduct the study. I agree to conduct the study as outlined in the protocol. |

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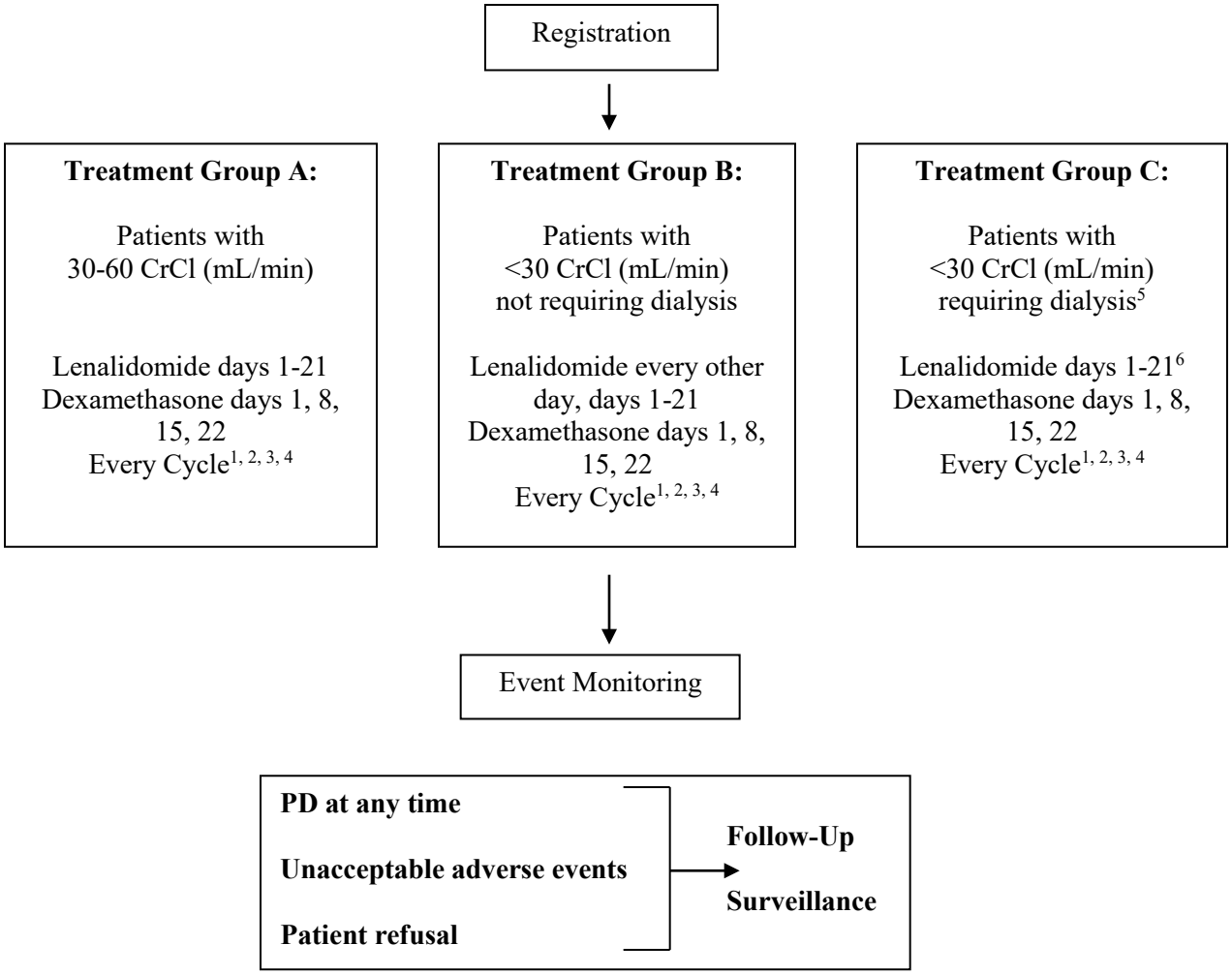
**Schema**

**PHASE I only: Prior to discussing protocol entry with the patient, call the PrECOG Project Manager to ensure that a place on the protocol is open to the patient. The Project Manager contact information is located in the Study Reference Manual.**




If a patient is deemed ineligible or never received treatment, please refer to Section 13.0 for follow-up information.

[1] Cycle = 28 days
[2] If patient is treated beyond 4 cycles, therapy may be interrupted to allow for stem cell harvest and mobilization (see Section 7.0).
[3] Patients must also be treated with anticoagulants (see Section 9.4).
[4] Refer to Section 7.21 for Dose Escalation Tables
[5] Dialysis includes hemodialysis or peritoneal dialysis
[6] When lenalidomide treatment day occurs on a dialysis day, lenalidomide must be taken after dialysis

| | |
|---|---|
| Generic name: Lenalidomide<br>Brand name(s): Revlimid®<br>Availability: Provided by Celgene | Generic name: Dexamethasone<br>Brand name: Decadron<br>Availability: Commercial |

## 1.0 Background

### 1.1 Multiple Myeloma (MM)

MM affects approximately 20,000 Americans annually[1] and remains an incurable hematologic malignancy characterized by frequent early response followed by universal treatment relapse necessitating multiple sequential therapeutic regimens.[2] Until recently, few effective therapies existed. Several novel agents for MM have now become available including the immunomodulatory drugs thalidomide,[3] lenalidomide,[4] as well as the proteasome inhibitor, bortezomib.[5] Each of these agents is undergoing extensive clinical evaluation in combination with other therapies to produce unprecedented response rates in newly diagnosed and relapsed MM. Indeed, comparative studies show these agents to be more effective than conventional chemotherapies when used as primary induction therapy prior to stem cell transplantation[6-8] and salvage therapy in patients with MM.[9-10] Lenalidomide has proven to be a highly effective treatment agent, particularly when used in combination with dexamethasone[11] but is renally excreted and little information is available about its use in myeloma patients with impaired kidney function (20% have renal failure at some time after diagnosis). Defining a safe and effective dose of lenalidomide to use is then a critical step in MM treatment.

### 1.2 Lenalidomide

The immunomodulatory drugs thalidomide (Thal) and lenalidomide especially in combination with dexamethasone have proven to be the standard for relapsed/refractory disease as well as front line MM therapy. In phase II clinical studies, single-agent thalidomide or lenalidomide therapy administered to heavily pre-treated patients with relapsed or refractory MM has resulted in response rates of 20-30%.[4, 12] Lenalidomide is a proprietary IMiD® compound of Celgene Corporation. IMiDs®, of which thalidomide is the parent compound, has both immunomodulatory and anti-angiogenic properties which could confer anti-tumor and anti-metastatic effects.[13-14]

### 1.3 Clinical Experience in Multiple Myeloma with Lenalidomide

In two phase I studies in multiple myeloma, a total of 40 patients have been treated with lenalidomide. In one study at the University of Arkansas, 15 patients who relapsed or were refractory to high dose melphalan therapy with stem cell transplant were treated for 4 weeks in an open-label safety study and were permitted to continue therapy in an extension phase of the trial.[15] Patient cohorts were treated at the following daily doses: 5 mg, 10 mg, 25 mg, and 50 mg. In a similar study at the Dana Farber Cancer Institute, 25 patients with rapidly advancing refractory multiple myeloma were treated.[16]

Anti-myeloma activity was observed in each of these two phase I studies. Decreases in neutrophil and platelet counts were the dose-limiting toxicities associated with lenalidomide. The maximum tolerated dose (MTD) was not reached within 28 days. Due to dose modifications associated with myelosuppression observed beyond Day 28 at the 25 mg and 50 mg daily dose levels, the dose schedule most widely used in future studies has been lenalidomide 25 mg on Days 1-21, repeated every 28 days.

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies.[16] Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5 mg, 10 mg, 25 mg and 50 mg). Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. No plasma accumulation was observed with multiple daily dosing. Peak and overall plasma concentrations were dose proportional over the dosing range of 5 mg to 50 mg.

A multicenter, randomized, phase II trial compared 2 syncopated dose schedules of lenalidomide used alone or in combination with dexamethasone in the treatment of relapsed or refractory multiple myeloma.[17] All patients were treated on Days 1-21 of a 28-day cycle. Patients treated with 15 mg BID experienced more myelosuppression and dose reductions compared with patients treated with 30 mg daily. Anti-myeloma activity was observed with each dose and schedule of single agent lenalidomide. The addition of dexamethasone to lenalidomide yielded responses in some patients who had not responded to lenalidomide alone.

A recent phase II trial utilizing lenalidomide plus dexamethasone for newly diagnosed multiple myeloma patients was recently reported by the Mayo Clinic.[7] Lenalidomide was given orally 25 mg daily on days 1-21 of a 28-day cycle. Dexamethasone was given orally 40 mg daily on days 1-4, 9-12, 17-20 of each cycle. Objective response was defined as a decrease in serum monoclonal protein by 50% or greater and a decrease in urine M protein by at least 90% or to a level less than 200 mg/24 hours, confirmed by two consecutive determinations at least 4 weeks apart. Thirty-one of 34 patients achieved an objective response, including 2 (6%) achieving complete response (CR), and 11 (32%) meeting criteria for both very good partial response and near complete response, resulting in an overall objective response rate of 91%. Of the 3 remaining patients not achieving an objective response, two had minor response (MR) and one had stable disease. Forty-seven percent of patients experienced grade 3 or higher non-hematologic toxicity, most commonly fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%), and rash (6%). Lenalidomide and dexamethasone is a highly active regimen with manageable side-effects in the treatment of newly diagnosed myeloma.

Celgene Corporation sponsored 2 multicenter, randomized, double-blinded, placebo-controlled phase III trials, one U.S. (MM-009)[11] and one international (MM-010),[18] in patients with relapsed or refractory multiple myeloma. More than 350 patients were enrolled into each of these studies. All patients had to be considered sensitive to dexamethasone and were treated with dexamethasone 40 mg qd, Days 1-4, 9-12 and 17-20. In addition to receiving dexamethasone, patients were randomized to lenalidomide 25 mg qd or placebo, Days 1-21. Cycles were repeated every 28 days. After 4 cycles, there was a predetermined reduction of the dexamethasone dose to 40 mg qd, Days 1-4 repeated every 28 days. In both studies, a pre-specified interim analysis conducted by an Independent Data Monitoring Committee demonstrated that subjects receiving the combination of lenalidomide plus dexamethasone had significantly longer times to progression and higher response rates than those treated with single-agent dexamethasone. These studies led to the FDA approval of lenalidomide in combination with dexamethasone for the treatment of multiple myeloma in patients that have received at least one prior therapy.

An additional subgroup analysis was performed on patients with impaired creatinine clearance (CrCl).[19] No significant difference in response rate, time to progression, or overall survival was noted for patients with CrCl above or below 50 ml/min who were treated with Lenalidomide and dexamethasone, but for 16 patients with CrCl <30 ml/min, median time to progression (TTP) and overall survival (OS) was shorter than for those with CrCl >30 ml/min, but still significantly higher than for patients treated with dexamethasone. Grade 3-4 thrombocytopenia was significantly higher in patients with impaired renal function (<50 ml/min, 13.8%; >50 ml/min 4.6%, p<.01; <30 ml/min, 18.8%, >30 ml/min, 5.5%, p<.05), but there was no difference for grade 3-4 neutropenia at either cutoff.

1.4 Lenalidomide Pharmacokinetics

Absorption: [redacted] Multiple dosing at the recommended dose-regimen does not result in drug accumulation.[20]

[redacted] In multiple myeloma patients, those with mild renal impairment had an AUC 56% greater than those with normal renal function.[21]

Distribution: In vitro (14C)-lenalidomide binding to plasma proteins is approximately 30%.[20]

Metabolism and Excretion: [redacted] Steady-state levels are achieved by Day 4.[20]

This drug is known to be substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.[22] Dysuria, renal failure, hematuria, acute renal failure, azotemia, calculus ureteric, and renal mass are listed as reported adverse events in the package insert.

1.5 Experience in Newly Diagnosed Myeloma with Renal Failure

Niesvizky et al. evaluated 58 newly diagnosed multiple myeloma patients on lenalidomide 25 mg daily on days 1-21 of a 28 day cycle, dexamethasone 40 mg weekly, and Biaxin 500 mg twice daily (BiRD).[22] Eleven of 36 patients who achieved a partial

response to therapy required a dose reduction of lenalidomide for neutropenia and/or thrombocytopenia. Ten of these 11 patients had a serum creatinine level >1.4 mg/dL ($p<0.0001$). When using the Cox proportional hazards regression model, it indicated 6.4-fold increased dose-reduction likelihood for each 1-unit increase in baseline serum creatinine level. A creatinine clearance ≤40 ml/min was similarly associated with lenalidomide dose reductions. The authors state that myelosuppression and renal dysfunction potentiate the need for lenalidomide dose reductions.

### 1.6 Experience in Relapsed/Refractory Multiple Myeloma

The combination of lenalidomide ± corticosteroid was evaluated in 69 patients with relapsed/refractory multiple myeloma.[23] Of the 69 patients, 23 had an elevated baseline creatinine (cr) level (group 1: median cr=138 umol/L, range 110-412 umol/L) and 46 had normal cr level (group 2: 80 umol/L, range 51-109 umol/L). After 3 cycles of therapy, median cr was 104 umol/L (range 61-372) in group 1 and 79 umol/L (range 53-180) in group 2. Creatinine was decreased in 39% of patients in both groups, and increased in 26% and 32% of patients in group 1 and 2, respectively ($p=0.56$). In addition, it was seen that patients with an elevated creatinine had a lower baseline platelet count, and during therapy experienced more grade 3-4 thrombocytopenia and were more likely to require platelet transfusion.

A subgroup analysis from the registration trials for patients with previously treated myeloma concluded that no significant difference was noted in response rate, time to progression or overall survival between patients whose creatinine clearance was above or below 50 ml/min. In the 16 patients with creatinine clearance below 30 ml/minute, time to progression and overall survival was shorter than for those with creatinine clearance above 30 ml/min. Grade 3-4 thrombocytopenia (but not grade 3-4 neutropenia) was also noted to be significantly higher in patients with impaired renal function.[19]

### 1.7 Dosing Recommendation for Lenalidomide in Patients with Renal Impairment, Hemodialysis

Chen et al.[21] conducted a multi-center study with lenalidomide 25 mg a day as a single oral dose in five groups of subjects defined by renal function [1] normal (CrCl >80 mL/min); [2] mild (CrCl: >50- <80 mL/min); [3] moderate (CrCl:>30- <50 mL/min); [4] severe (CrCl <30 mL/min but not on dialysis); [5] End Stage Renal Disease (requiring dialysis). Thirty subjects over the age of 35 were included in the study. Subjects with normal, mild, moderate or severe renal insufficiency received a single 25 mg oral dose of lenalidomide. Subjects with end stage renal disease (ESRD) received 2 single 25 mg doses, separated by 7-10 days: one dose on a non-dialysis day and the other dose 3 hours before a 4-hour hemodialysis. [21] Blood and urine samples were collected over 72 hours and creatinine clearance was estimated with a 24-hour urine collection (Celgene Corporation 2006). Assessments included PK and safety parameters. All subjects completed the study. Total and renal clearance of lenalidomide were strongly correlated with CrCl ($R >0.9$, $p <0.01$). As a result, $AUC\infty$ increased with decreasing CrCl. The mean difference in $AUC\infty$ between normal renal function (NRF) and mild renal insufficiency (RI) was <20%. Compared with the pooled data from NRF and mild RI groups, mean $AUC\infty$ increased approximately 140% in moderate RI, 240% in severe RI, and 360% in ESRD (off dialysis). There was no correlation between Cmax or Tmax and

CrCl. Approximately 10% of the dose was recovered in the dialysate of subjects with ESRD. Protein binding of lenalidomide was not markedly affected by RI (~35 - 44%). The drug was well tolerated. On the basis of these data, recommendations for initial starting doses were made.

The following dose recommendations were suggested by Chen et al. for patients with MM and MDS and renal dysfunction and were based on Area Under the Curve for entire exposure to the drug (AUC 0-∞). The lower doses of lenalidomide recommended for patients with renal dysfunction are derived from modeling to produce AUCs comparable to those produced by the administration of a 25 mg or 10 mg dose of lenalidomide, respectively, in patients with normal renal function. (Note: For previously treated multiple myeloma dosing is for 21 days of a 28-day cycle. Dosing is continued or modified based on clinical and laboratory findings.)

Renal Function (CrCL) Multiple Myeloma

- Mild (CrCl ≥50 mL/min) 25 mg qd (Full Dose)
- Moderate (30 ≤ CrCl <50 mL/min) 10 mg qd *
- Severe (CrCl <30 mL/min, not requiring dialysis) 15 mg q 48 hr
- ESRD (CrCl <30 mL/min, requiring dialysis) 15 mg 3x a week following each dialysis

*The dose may be escalated to 15 mg qd after 2 cycles if patient is tolerating drug well but not responding to treatment.

In summary since data on the maximum tolerated dose of lenalidomide in impaired renal function is lacking and this remains a clinically significant issue we plan to do this phase I/II trial in previously treated MM patients with varying degrees of renal impairment to clinically assess the MTD per risk group. This trial is designed after the Chen et al.[21] experience.

This study originated December 22, 2008 at Mayo Clinic in Arizona and Rochester. As of November 09, 2010, a total of 15 subjects have been enrolled. It is now being opened at multiple institutions through PrECOG with 10 sites for Phase I (including above Mayo sites) and 30 sites for Phase II.

## 2.0 Objectives

2.1 Primary Objectives

2.11 **Phase I Trial:** To establish the maximum tolerated dose of lenalidomide in each of three groups of myeloma patients with impaired renal function.

2.12 **Phase II Trial:** To assess the efficacy (response rate [CR, sCR, VGPR, PR]) of this combination across the three groups of myeloma patients with impaired renal function.

2.2 Secondary Objectives

2.21 To describe the overall survival, progression-free survival, duration of response, and time to treatment failure of myeloma patients with impaired renal function treated with lenalidomide and dexamethasone.

2.22 To evaluate the safety profile of lenalidomide given in combination with weekly dexamethasone in myeloma patients with impaired renal function.

2.23 To describe renal function over time and to evaluate the safety profile of a onetime increase in lenalidomide dose at least 2 cycles after start of treatment due to improved renal function.

2.24 To determine the pharmacokinetics of lenalidomide administration in myeloma patients with impaired renal function (pharmacokinetic analysis will be performed in up to 12 consented Mayo Clinic subjects treated during the Phase II component of the trial only).

## 3.0 Patient Eligibility

3.1 Eligibility Criteria

NOTE: Phase I Only – Prior to discussing protocol entry with the patients **AND** prior to registering in the electronic data capture (eDC) system, call the PrECOG Project Manager to ensure that a place on the protocol is open to the patient. The Project Manager contact information is located in the Study Reference Manual.

3.11 ≥18 years of age.

3.12 Diagnosed with previously treated multiple myeloma (please see Appendix II for definition of myeloma).

3.13 Patients must have measurable disease assessed by one of the following ≤21 days prior to registration:

- Serum monoclonal protein ≥1 g by protein electrophoresis*
- >200 mg of monoclonal protein in the urine on 24 hour electrophoresis*
- Serum immunoglobulin free light chain ≥10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio
- Monoclonal bone marrow plasmacytosis ≥30% (evaluable disease)

*NOTE: If both serum and urine m-components are present, both must be followed in order to evaluate response.

3.14 All previous cancer therapy including chemotherapy, radiation, hormonal therapy and surgery, must have been discontinued ≥2 weeks prior to registration.

3.15 ECOG Performance Status (PS) 0, 1, or 2 (see Appendix III).

3.16 Acceptable organ and marrow function ≤21 days prior to registration as defined below:

- Absolute neutrophil count ≥1000 cells/$mm^3$
- Platelet count ≥75,000 cells/$mm^3$
- Total bilirubin ≤2 mg/dL.
- AST (SGOT) and ALT (SGPT) ≤3 x ULN

3.17 Renal impairment at baseline as measured by serum creatinine clearance (CrCl) ≤60 mL/min ≤21 days prior to registration (see Appendix IV).

3.18 Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days and again within 24 hours prior to starting Cycle 1 of lenalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix V: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, AND also Appendix VI: Education and Counseling Guidance Document.

3.19a Able to take required prophylactic anticoagulation (see Section 9.4).

3.19b Ability to understand and the willingness to sign a written informed consent document.

3.19c Patient willing to provide blood samples for research purposes (see Sections 4.0 and 14.0). Only applies to selected subjects registered at Mayo Clinic only to the Phase II component (12 subjects total).

3.19d If previously received lenalidomide, demonstration of clinical response of any duration or stable disease with progression-free interval of ≥6 months from the start of that therapy.

3.2 Exclusion Criteria

3.21 Concurrent use of other anti-cancer agents or treatments. NOTE: Growth factors and bisphosphonates are allowed as medically indicated. Steroids may be used with an equivalency of up to 20 mg Prednisone per day as long as the dose has not been adjusted upwards in past 2 weeks prior to study registration.

3.22 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring intravenous antibiotics, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.23 Any of the following as this regimen may be harmful to a developing fetus or nursing child:

- Pregnant women
- Breast-feeding women
- Men or women of childbearing potential or their sexual partners who are unwilling to employ adequate contraception (condoms with spermicidal agent, diaphragm, birth control pills, injections, intrauterine device [IUD], surgical sterilization, subcutaneous implants, or abstinence, e.g.).

† A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (e.g., has had menses at any time in the preceding 24 consecutive months).

3.24 HIV-positive patients on combination antiretroviral therapy (because of the potential for pharmacokinetic interactions with lenalidomide. NOTE: In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated).

3.25 Known hypersensitivity to thalidomide or other immunomodulary drugs (IMiDs®).

3.26 History of Stevens-Johnson syndrome characterized by a desquamating rash while taking thalidomide or similar drugs.

3.27 Other active malignancy with the exception of non melanoma skin cancer or in situ cervical or breast cancer.

3.28 Concurrent radiation therapy, except for palliation of a single painful bone lesion or fracture.

## 4.0 Test Schedule

*Treatment should begin ≤7 working days from registration
*Variations of +/- 3 days of the scheduled visits are permitted

| | ≤21 days prior to registration | Cycle 1 only | For Each of the First Four Cycles | | | | End of Cycle 4 | Day 1 Each additional cycle[17] | Day 1 of cycle 9 or at end of treatment | Follow-Up[16,18] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 6 | Day 1 | Day 8 | Day 15 | Day 22 | | | | |
| History & Exam, Wt., PS Assessment | X | | X[12] | | | | X | X | X | |
| Height | X | | | | | | | | | |
| CBC w/differential | X | | X[13] | X | X | X | | X[13] | | |
| Chemistry Panel (Na,K,Ca,AST,ALT,Alk Phos,Total Bili, Glucose, Creatinine, Albumin) | X | | X | X[14] | X[14] | X[14] | X | X | X | |
| Serum Creatinine Clearance[1] | X | | X | | | | X | X | X | |
| LDH, Beta-2 Microglobulin, C-Reactive Protein | X | | | | | | X | | X | |
| Serum TSH[2] | X | | X | | | | | X | | |
| SPEP[3] | X | | X[12] | | | | X | X | X | |
| UPEP (24hr collection)[3] | X | | X[12] | | | | X | X | X | |
| Quantitative Immunoglobulins[3] | X | | X[12] | | | | X | X | X | |
| Serum Free Light Chains[3] | X | | X[12] | | | | X | X | X | |
| Immunofixation-Serum & Urine[4] | X | | | | | | X | | X | |
| Bone Marrow Biopsy w/aspirate | X[5] | | | | | | X[15] | | X[15] | X[19] |
| Bone Marrow-FISH, cytogenetics | X[5] | | | | | | | | | |
| Metastatic Bone Survey w/ long bones | X[5] | | | | | | X | | X | |
| Chest X-Ray | X | | | | | | | | | |

| | ≤21 days prior to registration | Cycle 1 only | For Each of the First Four Cycles | | | | End of Cycle 4 | Day 1 Each additional cycle[17] | Day 1 of cycle 9 or at end of treatment | Follow-Up[16,18] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 6 | Day 1 | Day 8 | Day 15 | Day 22 | | | | |
| ECG | X | | | | | | | | | |
| Pharmacokinetics[6, R] | | X[6] | | | | | | | | |
| INR[7] | | | X[7] | X[7] | X[7] | X[7] | X[7] | X[7] | X[7] | |
| Pregnancy Testing[8] | X[8] | | X[8] | | | | | X[8] | X[8] | |
| Education and Counseling Guidance Document[9] | | | X[9] | | | | | X[9] | X[9] | |
| Dispense Study Drug[10] | | | X[10] | | | | | X[10] | | |
| Study Drug Compliance (Medication Diary) | | | X | | | | | X | X | |
| Adverse Event Assessment[11] | | | | X | X | X | X[16] | X | X[16] | X[16] |
| Survival and Malignancy Surveillance | | | | | | | | | | X[18] |

1. Creatinine clearance will be estimated using the Cockroft-Gault formula. If the patient is >65 y/o and creatinine is <1, use 1 as serum creatinine value to calculate the creatinine clearance, see Appendix IV.
2. To be completed at baseline and then every 3 months.
3. Required at baseline, and then only required if used to assess disease response (see Section 11.2, Table 11.2).
4. Is required at study entry only if not previously performed or test results not available. If complete response is seen a 2nd immunofixation should be performed 4 weeks later to confirm. Urine immunofixation is only required if positive at study entry.
5. Bone marrow (with aspirate/FISH/cytogenetics) and skeletal survey may be used if performed ≤90 days of study enrollment.
6. Only applies to selected Mayo Clinic subjects registered to the Phase II component. Pharmacokinetics of lenalidomide: 5cc of blood is to be drawn and put into an EDTA tube at the following time points on Day 6 of Cycle 1: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 hr at all dose groups and at 48 and 72 hr for patients in Group B with severe renal impairment or in Group C on dialysis (hemodialysis or peritoneal dialysis). Please see Section 14.2 for processing procedures. Pharmacokinetic samples will be collected from up to 12 Mayo Clinic participants with a minimum of two patients in each group (Groups A, B and C) of the Phase II component.
7. Treatment with Coumadin should be used with caution. If a patient is being treated with Coumadin, close monitoring of INR is required.
8. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer

therapy does not rule out childbearing potential) for at least 24 consecutive months (e.g., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur within 10–14 days prior to initiation of Cycle 1 of lenalidomide and again within 24 hours prior to initiation of Cycle 1 of lenalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on lenalidomide therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on lenalidomide therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix V: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

9. All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done on Day 1 of each cycle (or at a minimum of every 28 days) throughout the entire duration of lenalidomide treatment, including dose interruptions, and at lenalidomide discontinuation. The Appendix VI: Education and Counseling Guidance Document must be completed by a trained Counselor (Counselors will be trained by Celgene).
10. Only enough lenalidomide for 1 cycle of therapy may be provided to the patient each cycle.
11. Refer to Section 10.2 for minimum events to be collected at baseline and each evaluation.
12. Except Day 1 of Cycle 1.
13. On Day 1of each cycle, the ANC must be ≥1,000/μL and the platelet count must be ≥50,000/μL.
14. Serum creatinine only.
15. Bone marrow aspirate and biopsy are **only** required to document or confirm CR or sCR, except for patients with evaluable disease **only**, where a bone marrow is required to document all response categories including progression (see Section 11.3). However, a second confirmatory bone marrow is **not** required to confirm response.
16. An additional safety assessment will be done 30 days (+/- 2 days) following the last dose of study drug.
17. Therapy may be interrupted to allow for stem cell harvest and mobilization for patients treated beyond 4 cycles.
18. Follow-up every 6 months for survival, second primary malignancy diagnosis, and recurrence of any prior malignancy (if applicable) x 3 years. If patient has not progressed at off-study, document date of progression. This should include subjects who may have discontinued the study at any time or for any reason, who may be in a survival follow-up period, or who may have died. Following this 3 year time period, reporting of all identified cases of subsequently diagnosed second primary malignancies is voluntary by the treating physician to the manufacturer.
19. Note: In addition to the standard evaluation for prolonged cytopenias that do not recover after discontinuation of treatment, a bone marrow exam should be considered, in patients with the following parameters: no leukopenia at the time of multiple myeloma diagnosis, no active multiple myeloma at the time of the cytopenia, no vitamin or element deficiency to explain the cause of the cytopenia(s).

R Research test. Will be charged to study and not to patient's account.

## 5.0 Stratification Factors

5.1 Renal Impairment: Group A: Moderate renal dysfunction 30-60 CrCl mL/min) vs. Group B: Severe renal dysfunction (CrCl <30 mL/min, not requiring dialysis) vs. Group C: ESRD renal dysfunction (CrCl <30 mL/min, requiring hemodialysis or peritoneal dialysis)

5.2 Component: Phase I vs. Phase II

5.3 Dose Level: 1 vs. 2 vs. 3 vs. 4

## 6.0 Registration/Randomization Procedures

### 6.1 Ethics

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with applicable US regulatory requirements and International Conference on Harmonization Good Clinical Practice (ICH GCP).

The study will be conducted in compliance with the protocol. The protocol and any Amendments and the patient informed consent will receive Institutional Review Board (IRB) approval prior to initiation of the study.

Freely given written informed consent must be obtained from every patient or their legally acceptable representative prior to clinical trial participation, including informed consent for any screening procedures conducted to establish patient eligibility for the trial.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of investigators or study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment). Investigators are responsible for the conduct of the study at their study site.

### 6.2 Regulatory Requirements

Before a site may enter patients, protocol-specific regulatory and other documents must be submitted to PrECOG representatives as noted in study materials. Detailed information regarding document submission and control is provided to each site in separate study materials.

Once all required documents are received, reviewed, and approved by PrECOG or their representative, a registration information packet will be forwarded to the site. Any changes to site regulatory documents must be submitted by the investigator to the responsible party in a timely manner. Initial study drug shipment will not occur until the regulatory packet is complete. No patients should begin protocol therapy without formal registration as per the process below.

### 6.3 Registration Procedures

6.31 Phase I Dose Escalation – Prior to discussing protocol entry with patient **AND** prior to registering a patient through the electronic data capture (eDC) system, call the PrECOG Project Manager to ensure that a place on the protocol is open to the patient. The Project Manager contact details can be found in the Study Reference Manual.

6.311 Patients must not start protocol treatment prior to registration.

Patients must meet all of the eligibility requirements listed in Section 3.0 prior to registration. Treatment should begin ≤7 working days from registration.

An eligibility checklist is included in Appendix XI and a usable version is available in separate study materials provided to the site. A confirmation of eligibility assessment by the investigator and/or site will be performed during the registration process.

Upon determination that a subject meets eligibility criteria, the subject will be registered in the study by site personnel via an electronic data capture eDC system. Confirmation of registration will be displayed in the eDC system once site personnel have verified the subject's eligibility status.

Full information regarding registration procedures and guidelines can be found in the Study Reference Manual provided to your site. All correspondence regarding patient registration must be kept in the study records.

6.32 Phase II Patient Registration

Patients must not start protocol treatment prior to registration.

Patients must meet all of the eligibility requirements listed in Section 3.0 prior to registration. Treatment should begin ≤7 working days from registration.

An eligibility checklist is included in Appendix XI and a usable version is available in separate study materials provided to the site. A confirmation of eligibility assessment by the investigator/site will be performed during the registration process.

Upon determination that a subject meets eligibility criteria, the subject will be registered in the study by site personnel via an electronic data capture (eDC) system. Confirmation of registration will be displayed in the eDC system once site personnel have verified the subject's eligibility status.

Full information regarding registration procedures and guidelines can be found in the Study Reference Manual provided to your site. All correspondence regarding patient registration must be kept in the study records.

6.321 Body Fluid Biospecimens

A mandatory translational research component for blood specimens is part of this study; the patient will be automatically registered onto this component (Sections 3.18c, 4.0 and 14.0). Only applies to select Mayo Clinic subjects registered to the Phase II component.

6.4 Pretreatment tests must be completed within the guidelines specified on the test schedule.

6.5 All required baseline symptoms must be documented and graded.

6.6 Study drug availability checked.

## 7.0 Protocol Treatment

7.1 Treatment Schedule

7.11 Phase I Component:

- Lenalidomide at assigned dose (Section 7.21, Tables 7.211, 7.212 or 7.213)
- Dexamethasone 40 mg orally on days 1, 8, 15 and 22
- Anticoagulation (see Section 9.4)

Dosing for lenalidomide for each group is per the assigned cohort; see tables in Section 7.21. Each cycle is 28 days. All groups get a 7 day rest (days 22-28) from lenalidomide. Dosing will be in the morning at approximately the same time each day. Only one cycle of study drug will be supplied to the patient each cycle. Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up (this applies to all dosing schedules). For patients in Group C, when a lenalidomide treatment day occurs on a dialysis day, lenalidomide must be taken after dialysis. Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Compliance with therapy will be assessed at the beginning of each cycle and at the end of treatment. Patients will be given a medication diary for recording of doses of study drugs as provided by each study site.

Dexamethasone will be given at a fixed dose of 40 mg by mouth once weekly on a 28 day treatment cycle. If a dose of dexamethasone is missed, it is up to the treating physician whether the dose should be made up. In addition, continuing dexamethasone if lenalidomide is stopped is also at the discretion of the treating physician.

Treatment is to be continued as tolerated until disease progression, intolerable toxicity or patient refusal.

Subjects experiencing adverse events may need study treatment modifications.

If patient is treated beyond 4 cycles, therapy may be interrupted to allow for stem cell harvest and mobilization.

7.111 Phase I Dose Assignment

We want to determine the MTD for patients with MM in three different risk groups:

- Moderate Renal Dysfunction (30-60 CrCl mL/min)
- Severe Renal Dysfunction (CrCl <30 mL/min, not requiring dialysis)
- ESRD Renal Dysfunction (CrCl <30 mL/min, requiring hemodialysis or peritoneal dialysis)

7.112 Creatinine Clearance will be estimated by using the Cockcroft and Gault equation (see Appendix IV):

**Males:**

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})}$$

**Females:**

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85$$

If the patient is >65 y/o and creatinine is <1, use 1 as serum creatinine value to calculate the creatinine clearance.

7.12 Phase II Component:

- Lenalidomide at assigned dose (as determined by studies in Phase 1 component)
- Dexamethasone 40 mg orally on days 1, 8, 15 and 22
- Anticoagulation (see Section 9.4)

The dose for lenalidomide will be determined for each group in the Phase 1 portion of the study. Each cycle is 28 days. All groups get a 7 day rest (days 22-28) from lenalidomide. Dosing will be in the morning at approximately the same time each day. Only one cycle of study drug will be supplied to the patient each cycle. Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up (this applies to all dosing schedules). For patients in Group C, when a lenalidomide treatment day occurs on a dialysis day, lenalidomide must be taken after dialysis. Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Dexamethasone will be given at a fixed dose of 40 mg by mouth once weekly on a 28 day treatment cycle. If a dose of dexamethasone is missed, it is up to the treating physician whether the dose should be made up. In addition, continuing dexamethasone if lenalidomide is stopped is also at the discretion of the treating physician.

Treatment is to be continued as tolerated until disease progression, intolerable toxicity or patient refusal.

7.2 Phase I Dose Escalation and Determination of MTD.

7.21 Dose Escalation of Lenalidomide:

**Table 7.211: Group A = Patients with a 30-60 CrCl (mL/min)¤**

| Dose Level | | Dose | Treatment Day | Rest Day | Route |
|---|---|---|---|---|---|
| 1* | Lenalidomide | 10 mg | 1-21 | 22-28 | Orally |
| 2 | Lenalidomide | 15 mg | 1-21 | 22-28 | Orally |
| 3 | Lenalidomide | 25 mg | 1-21 | 22-28 | Orally |

**Table 7.212: Group B = Patients with CrCl <30 mL/min who are NOT on dialysis⌂**

| Dose Level | | Dose | Treatment Day | Rest Day | Route |
|---|---|---|---|---|---|
| 1* | Lenalidomide | 15 mg | Every other day, days 1-21 | 22-28 | Orally |
| 2 | Lenalidomide | 25 mg | Every other day, days 1-21 | 22-28 | Orally |
| 3 | Lenalidomide | 15 mg | 1-21 | 22-28 | Orally |
| 4 | Lenalidomide | 25 mg | 1-21 | 22-28 | Orally |

**Table 7.213: Group C = Patients with CrCl <30 mL/min who are on dialysis#◊**

| Dose Level | | Dose | Treatment Day | Rest Day | Route |
|---|---|---|---|---|---|
| 1*† | Lenalidomide | 5 mg | 1-21£ | 22-28 | Orally |
| 2 | Lenalidomide | 10 mg | 1-21£ | 22-28 | Orally |
| 3 | Lenalidomide | 15 mg | 1-21£ | 22-28 | Orally |
| 4 | Lenalidomide | 25 mg | 1-21£ | 22-28 | Orally |

* Starting dose level
\# Dialysis includes hemodialysis or peritoneal dialysis.
† The starting dose for patients in Group C accrued to dose level 1 cohort (completed September 2010) was lenalidomide 15 mg post dialysis three times weekly on Days 1-21. Starting with protocol version 5.0, if a return to dose level 1 is indicated, lenalidomide 5 mg on Days 1-21 should be used according to the package insert.
£ When a lenalidomide treatment day occurs on a dialysis day, lenalidomide must be taken after dialysis.
¤ **Group A:** As of November 03, 2010, dose level 1 is completed. Dose level 2 is open.
⌂ **Group B:** As of November 03, 2010, dose level 1 is completed. Dose level 2 is open.
◊ **Group C:** As of November 03, 2010, dose level 1 is completed. Dose level 2 is open.

## 7.22 Definition of Dose-Limiting Adverse Events

Dose Limiting Adverse Events:

Dose Limiting Toxicity (DLT) will be defined as any of the following events that is determined to be possibly, probably, or definitely related to lenalidomide (as determined by the investigator) within the first cycle of therapy irrespective of whether the adverse events resolved:

- Grade 3 or higher neutropenia with fever ≥38.5ºC
- Grade 4 neutropenia ≥7 days
- Grade 4 or higher thrombocytopenia
- Other non-hematologic Grade 4 or higher adverse event not present prior to starting therapy or not due to underlying cause

Management and dose modifications associated with the above AEs are outlined in Section 8.0.

## 7.23 Dose Escalation Phase:

A standard cohort of 3 phase I design will be used where subjects will be initially enrolled in groups of three and individually assessed for safety and DLT. For a subject to be considered evaluable for dose limiting toxicity the subject must have received at least one dose of both drugs in Cycle 1 and have not been withdrawn from the study prior to Cycle 2 secondary to a drug related AE. If a subject withdraws from the study without meeting these criteria for reasons other than adverse events, the subject will be replaced in that cohort.

Doses will be escalated until the first observation of a DLT as defined in Section 7.22 in the first treatment cycle in a group of at least 3 subjects treated at that dose level. All DLTs occurring in the first 3 cycles of the Phase I and II components will be collected and considered in the overall analysis, however, only DLTs occurring in Cycle 1 will define MTD during the Phase I component. Severity grading will be defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE V4.0). A one-time dose escalation of lenalidomide after 2 cycles of treatment due to improvement of renal function is allowed within an individual patient as described in Section 8.3.

A standard 3+3 phase I design will be used to determine the recommended dose in each renal dysfunction group. Dose level 1 will be the initial dose level (see Tables in Section 7.21).

- For current dose level accrue 3 patients (accrual for the group [Group A, B, or C] will be temporarily closed while the 3 patients are evaluated for DLT).
- If exactly 0/3 experience a DLT, then proceed to the next higher dose level.

- If exactly 1/3 experience a DLT, then accrue 3 more patients at the current dose level (accrual for the group [Group A, B, or C] will be temporarily closed while the 3 additional patients are evaluated for DLT). If (out of 6 patients) there are at least 2 that experienced a DLT, the recommended dose level has been exceeded. Drop down one dose level.
- If 2 or more (out of 3) patients experience a DLT, the recommended dose level has been exceeded. Drop down one dose level.

The recommended dose level for the phase II portion of the trial is the maximum dose level that resulted in less than 2/6 patients with DLTs. Patients who experience DLTs will be dose reduced to the next lower dose level.

Dose escalation will proceed within each group [Group A, B, or C] according to the following scheme. A DLT is defined above.

| **Number of Patients with DLT at a Given Dose Level** | **Phase I Escalation Decision Rule** |
|---|---|
| 0 out of 3 | Enter 3 patients at the next dose level. |
| ≥2 | Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose. |
| 1 out of 3 | Enter at least 3 more patients at this dose level.<br>• If 0 of these 3 patients experience DLT, proceed to the next dose level.<br>• If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose. |
| ≤1 out of 6 at highest dose level below the maximally administered dose | This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose. |

**Once the MTD is reached in the Phase I component for Group A, B or C, the group with the defined MTD dose will immediately be eligible to go to the Phase II component, and will not have to wait for the MTD in the other two groups**

## 8.0 Dosage Modification Based on Adverse Events for Phase I and Phase II

Treatment modifications are based on adverse events. All adverse events should be graded according to the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE V4.0).

Subjects will be evaluated for AEs at each visit with the NCI CTCAE V4.0 used as a guide for the grading of severity. Refer to Tables below for specific Lenalidomide and Dexamethasone dose reduction steps. Subjects who cannot tolerate lowest dose level are to be discontinued from the treatment phase of the study. Subjects experiencing ≥grade 3 non-hematologic or grade 4 hematologic adverse events will have their study drug held per Table 8.31. Held doses are not made up. Grade 3 or 4 AEs must resolve to ≤grade 2 in severity prior to resumption of study medications. Administration of the next drug dose is to be continued with a one-level dose reduction of the relevant drug as indicated in dose reductions. Once a subject's dose has been reduced, no dose re-escalation is permitted except for a possible one-time dose escalation of lenalidomide in the event of improved renal function as described in Section 8.3.

### 8.1 Lenalidomide Dose Levels (Based on Adverse Events in Table 8.31)

**Table 8.11: Group A Dose Modifications[#]**

| Dose Level | | Dose | Treatment Day | Rest Day | Route |
|---|---|---|---|---|---|
| 3 | Lenalidomide | 25 mg | 1-21 | 22-28 | Orally |
| 2 | Lenalidomide | 15 mg | 1-21 | 22-28 | Orally |
| 1* | Lenalidomide | 10 mg | 1-21 | 22-28 | Orally |
| -1 | Lenalidomide | 5 mg | 1-21 | 22-28 | Orally |
| -2 | Lenalidomide | 10 mg | Every other day, days 1-21 | 22-28 | Orally |
| -3 | Lenalidomide | 5 mg | Every other day, days 1-21 | 22-28 | Orally |

**Table 8.12: Group B Dose Modifications[#]**

| Dose Level | | Dose | Treatment Day | Rest Day | Route |
|---|---|---|---|---|---|
| 4 | Lenalidomide | 25 mg | 1-21 | 22-28 | Orally |
| 3 | Lenalidomide | 15 mg | 1-21 | 22-28 | Orally |
| 2 | Lenalidomide | 25 mg | Every other day, days 1-21 | 22-28 | Orally |
| 1* | Lenalidomide | 15 mg | Every other day, days 1-21 | 22-28 | Orally |
| -1 | Lenalidomide | 10 mg | Every other day, days 1-21 | 22-28 | Orally |
| -2 | Lenalidomide | 5 mg | Every other day, days 1-21 | 22-28 | Orally |

**Table 8.13: Group C Dose Modifications[#]**

| Dose Level | | Dose | Treatment Day | Rest Day | Route |
|---|---|---|---|---|---|
| 4 | Lenalidomide | 25 mg | 1-21[£] | 22-28 | Orally |
| 3 | Lenalidomide | 15 mg | 1-21[£] | 22-28 | Orally |
| 2 | Lenalidomide | 10 mg | 1-21[£] | 22-28 | Orally |
| 1*[†] | Lenalidomide | 5 mg[†] | 1-21[£†] | 22-28 | Orally |
| -1 | Lenalidomide | 5 mg | Every other day, days 1-21[£] | 22-28 | Orally |
| -2 | Lenalidomide | 5 mg | Twice weekly[£] | 22-28 | Orally |

* Starting dose level

\# GCSF may be used beginning in cycle 2 for neutropenia. Consistent with ASCO guidelines, the recommended starting dose for G-CSF is 5 mcg/kg/d administered subcutaneously until the occurrence of an ANC of 10,000/uL or adequate neutrophil recovery is achieved.

† The starting dose for patients in Group C accrued to dose level 1 cohort (completed September 2010) was lenalidomide 15 mg post dialysis three times weekly on Days 1-21. Starting with protocol version 5.0, if a return to dose level 1 is indicated, lenalidomide 5 mg on Days 1-21 should be used according to the package insert.

£ When a lenalidomide treatment day occurs on a dialysis day, lenalidomide must be taken after dialysis.

8.2 Lenalidomide Dose Modification Based on Hematological Toxicity (see Table 8.31 below)

8.21 Hematologic Requirements for Day 1 of Each Cycle

- ANC is ≥1,000/μL
- Platelet count is ≥50,000/μL

If either of these two criteria is not met, the start of the cycle should be held and CBC should be followed weekly. Once ANC and platelets have recovered to Grade 2 or less, cycle should be started at next lower dose of lenalidomide. Held doses are not made up.

8.3 Lenalidomide Dose Modification Based On Non-Hematological Toxicity (see Table 8.31)

A one-time dose escalation in lenalidomide of one dose level is allowed at any one time point after completion of 2 cycles of treatment if one of the following conditions is met:

1. The patient was originally registered in Group C but has renal function improvement to a point that dialysis is no longer needed; or
2. The patient was originally registered in Group B but has renal function improvement to ≥30 CrCl (mL/min).

All previously established or new toxicities observed any time, are to be managed as per Table 8.31 and Table 8.4.

If drug must be discontinued, the patient comes off treatment and goes to follow-up per Section 4.0 and event monitoring per eCRF completion guidelines. If the toxicity resolves and drug is to be restarted, the dose must be reduced by dose levels as indicated in the dose reduction table.

**Please note: Held doses are not made up.**

**Table 8.31: Dose Modification for Lenalidomide**

| NCI CTC Toxicity Grade | Day 2-14 of Cycle | ≥Day 15 of Cycle |
|---|---|---|
| Grade 3 neutropenia associated with fever (temperature ≥38.5ºC) or Grade 4 neutropenia | • Hold lenalidomide.<br>• Follow CBC weekly.<br>• If neutropenia has resolved to ≤grade 2, restart at next lower dose level and continue the cycle until day 21. | • Hold lenalidomide for remainder of cycle. Restart lenalidomide next cycle (decrease dose by one dose level). |
| Thrombocytopenia ≥Grade 3 (platelet count <50,000/mm³) | • Hold lenalidomide.<br>• Follow CBC weekly.<br>• If thrombocytopenia resolves to ≤grade 2, restart lenalidomide at next lower dose level and continue the cycle through Day 21. | • Hold lenalidomide for remainder of cycle. Restart lenalidomide next cycle (decrease dose by one dose level). |
| Non-blistering rash<br>Grade 3 | • If Grade 3, hold lenalidomide dose. Follow weekly.<br>• If the adverse event resolves to ≤grade 1, restart lenalidomide at next lower dose level and continue the cycle through Day 21. | • Hold lenalidomide for remainder of cycle. Restart lenalidomide next cycle (decrease dose by one dose level). |
| Grade 4 | • Discontinue lenalidomide study drug and go to follow-up and event monitoring. | • Discontinue lenalidomide study drug and go to follow-up and event monitoring. |
| Desquamating (blistering) rash- any Grade | • Discontinue lenalidomide study drug and go to follow-up and event monitoring. | • Discontinue lenalidomide study drug and go to follow-up and event monitoring. |
| Erythema multiforme ≥Grade 3 | • Discontinue lenalidomide study drug and go to follow-up and event monitoring. | • Discontinue lenalidomide study drug and go to follow-up and event monitoring. |
| Sinus bradycardia/other cardiac arrhythmia Grade 2 | • Hold lenalidomide dose. Follow at least weekly.<br>• If the adverse event resolves to ≤grade 1, restart lenalidomide at next lower dose level and continue the cycle through Day 21. | • Hold lenalidomide for remainder of cycle. Restart lenalidomide next cycle (decrease dose by one dose level). |
| ≥Grade 3 | • Discontinue lenalidomide study drug and go to follow-up and event monitoring. | • Discontinue lenalidomide study drug and go to follow-up and event monitoring. |

| | | |
|---|---|---|
| Allergic reaction or hypersensitivity<br>Grade 2-3 | • Hold lenalidomide dose. Follow at least weekly.<br>• If the adverse event resolves to ≤grade 1, restart lenalidomide at next lower dose level and continue the cycle through Day 21. | • Hold lenalidomide for remainder of cycle. Restart lenalidomide next cycle (decrease dose by one dose level). |
| Grade 4 | • Discontinue lenalidomide study drug and go to follow-up and event monitoring. | • Discontinue lenalidomide study drug and go to follow-up and event monitoring. |
| Venous thrombosis/embolism ≥Grade 3 | • Hold lenalidomide and start therapeutic anticoagulation; restart lenalidomide at investigator's discretion (maintain dose level). | • Hold lenalidomide for remainder of cycle. See Anticoagulation Consideration (see Section 9.4). Restart lenalidomide next cycle (decrease dose by one dose level). |
| Hyperthyroidism or hypothyroidism ≥Grade 3 | • Hold lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level) | • Hold lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level). |
| Other non-hematologic adverse events assessed as lenalidomide related ≥Grade 3 | • Hold lenalidomide dose. Follow at least weekly.<br>• If the adverse event resolves to ≤grade 2, restart lenalidomide and continue through the scheduled Day 21 of current cycle. Otherwise, hold for remainder of cycle. Held doses are not made up. For toxicity attributed to lenalidomide, reduce by one dose level when restarting lenalidomide. | • Hold lenalidomide for remainder of cycle. Restart lenalidomide next cycle (decrease dose by one dose level). |

## 8.4 Dexamethasone Dose Modifications

| **Table 8.41: Dose Modifications for Dexamethasone** | | |
|---|---|---|
| **NCI CTC Category** | **Adverse Event** | **Dosage Change** |
| Gastrointestinal | Dyspepsia, gastric or duodenal ulcer, gastritis<br>Grade 1-2 (requiring medical management) | Treat with $H_2$ blockers, sucralfate, or omeprazole.<br><br>If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level. |
| | ≥Grade 3 (requiring hospitalization or surgery) | Hold dexamethasone until symptoms adequately controlled. Restart by decreasing dose by 1 dose level along with concurrent therapy with $H_2$ blockers, sucralfate, or omeprazole. |
| | Acute pancreatitis | Discontinue dexamethasone and do not resume. |
| Cardiovascular | Edema<br>≥Grade 3 (limiting function and unresponsive to therapy or anasarca) | Diuretics as needed, and decrease dexamethasone dose by 1 dose level. |
| Neurology | Confusion or Mood alteration<br>≥Grade 2 (interfering with function +/- interfering with activities of daily living) | Hold dexamethasone until symptoms adequately controlled. Restart by decreasing dose by 1 dose level. |
| Musculoskeletal | Muscle weakness<br>≥Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living) | Decrease dexamethasone dose by 1 dose level. If weakness persists decrease dose by 1 dose level as needed. |
| Metabolic | Hyperglycemia<br>≥Grade 3 or higher | Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by 1 dose level. |
| Any Other | ≥Grade 3 or higher | Hold dexamethasone until symptoms adequately controlled. Restart by decreasing dose by 1 dose level. |

| **Table 8.42: Dexamethasone Dose Levels** | | |
|---|---|---|
| | **Dosage** | **Days** |
| Starting Dose | 40 mg | Days 1, 8, 15, 22 |
| Dose Level -1 | 20 mg | Days 1, 8, 15, 22 |
| Dose Level -2 | 20 mg | Days 1,15 only |
| Dose Level -3 | 10 mg | Days 1, 15 only |
| Dose Level -4 | Discontinue Dexamethasone | |

## 9.0 Ancillary Treatment

9.1 Growth Factors:

9.11 Erythropoietin (Procrit or Aranesp) may be used to treat anemia beginning in treatment cycle 2 at the discretion of the treating physician in accordance with the published ASCO/ASH guidelines (JCO 2002, 20: 4083-4107).

9.12 G-CSF/GM-CSF: G-CSF/GM-CSF may be used beginning in treatment cycle 2 in accordance with published NCNN guidelines (see Section 8.0 Treatment Modification Based on Toxicity).

9.2 Infection Prophylaxis: Ciprofloxacin or Levofloxacin daily (or other quinolone/broad spectrum antibiotic) is allowed.

The dose of ciprofloxacin should be modified in impaired renal function as follows:
- 250 to 500 mg every 12 hours for creatinine clearance between 30 to 60 mL/min
- 250 to 500 mg every 18 hours for creatinine clearance between 5-29 mL/min

The dose of levofloxacin should be modified in impaired renal function as follows:
- 250 mg every 24 hours for creatinine clearance between 20-49 mL/min
- 250 mg every 48 hours for creatinine clearance between 10-19 mL/min

9.3 GI Toxicity: Routine prophylaxis with $H_2$ blockers or proton pump inhibitors should be considered for all patients during days of dexamethasone administration.

9.4 Anti-Coagulation: Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history of thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is combined with other agents such as steroids (e.g., dexamethasone, prednisone), anthracyclines (Doxil, Adriamycin) and erythropoietin the risk of thrombosis is increased. Prophylactic anti-coagulation with aspirin (ASA) is required for all patients at either 81 mg daily or 325 mg daily (dose per MD discretion). Heparin, low molecular weight heparin or coumadin may be utilized in patients that are intolerant to ASA. Coumadin should be used with caution and close monitoring of INR.

9.5 Any other supportive measures consistent with optimal patient care should be given throughout the study.

## 10.0 Adverse Event (AE) Monitoring and Reporting

***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient administered a medicinal product in a clinical investigation and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product (investigational or marketed), whether or not considered related to the product (investigational or marketed).

Following written consent to participate in the study, the collection of AEs/SAEs should begin at the initiation of therapy, unless related to a protocol related procedure.

10.1 Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

10.11 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

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

10.12 When a study includes both investigational and commercial agents, the following apply:

- When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered investigational. Reporting of adverse events follows the guidelines for investigational agents.

10.2 All Adverse Events are to be graded at each evaluation and all pretreatment symptoms/conditions are to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 grading. The specific Adverse Events/Symptoms in the table below are to be collected as indicated below:

| Category | Adverse Event/Symptoms | Baseline | Each Evaluation |
|---|---|---|---|
| Blood/Bone Marrow | Hemoglobin | X | X |
| | Neutrophils/Granulocytes (ANC/AGC) | X | X |
| | Platelets | X | X |
| Constitutional Symptoms | Fatigue (lethargy, malaise, asthenia) | X | X |
| Neurology | Neuropathy-Sensory | X | X |
| Dermatology/Skin | Rash/Desquamation | X | X |
| Renal/Genitourinary | Cystitis | X | X |
| Lymphatics | Edema: Limb | X | X |
| Gastrointestinal | Nausea | X | X |
| | Vomiting | X | X |
| | # of stools per day | X | |
| | Diarrhea | | X |
| Musculoskeletal/Soft Tissue | Muscle Weakness/Lower Extremity | X | X |

10.21 Submit via appropriate electronic Case Report Forms (eCRFs) the following AEs experienced by a patient and not specified in Section 10.2. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than individual symptoms. The following information should be documented for all AEs: date of onset and resolution, severity of the event; the investigator's opinion of the relationship to investigational product; treatment required for the AE; cause of the event (if known); and information regarding resolution/outcome.

- Grade 1 and 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.
- Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure
- Grade 5 AEs (Deaths)
    - Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

- Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.22 Refer to the instructions in the eCRF Study Manual regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (e.g., compliance with Test Schedule in Section 4.0).

10.3 Serious Adverse Event (SAE) Definition

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]
- Diagnosis of new second primary cancer

[1] "Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3] Medical and scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

10.31 The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

## 10.32 Pregnancies

Prior to study enrollment, women of childbearing potential (WOCBP) must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy, documented in the informed consent. In addition, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

Pregnancy of a female subject or the female partner of a male subject occurring while the subject is on lenalidomide or within 4 weeks after the subject's last dose of lenalidomide are considered expedited reportable events. If the subject is on lenalidomide, it is to be discontinued immediately and the subject is to be instructed to return any unused portion of lenalidomide to the Investigator. The pregnancy must be reported to PrECOG within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the Pregnancy Form. Within 24 hours of notification, PrECOG will fax to Celgene Drug Safety the Pregnancy Form.

- The Investigator will follow the pregnant female until completion of the pregnancy, and must notify PrECOG of the outcome as specified below. PrECOG will provide Celgene Drug Safety with the outcome The Investigator will provide this information as a follow-up to the initial submission.

- If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (e.g., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for Expedited Reporting of SAEs to PrECOG (e.g., report the event to PrECOG by facsimile within 24 hours of the Investigator's knowledge of the event). PrECOG will report the event to Celgene Drug Safety within 1 business day of the knowledge of the event.

- Any suspected fetal exposure to lenalidomide must be reported to PrECOG within 24 hours of being made aware of the event. PrECOG will report any suspected fetal exposure to Celgene Drug Safety within 1 business day of being aware of the event. The pregnant female should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

- 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 suspect is related to the *in utero* exposure to lenalidomide should also be reported.

- In the case of a live "normal" birth, PrECOG should be advised as soon as the information is available. PrECOG will advise Celgene Drug Safety as soon as the information is available.

10.4 Serious Adverse Event Reporting by Investigator to PrECOG

10.41 Serious adverse events (SAE) are defined above. The investigator should inform PrECOG of any SAE within 24 hours of being aware of the event. The date of awareness should be noted on the report. This must be documented on PrECOG SAE form. This form must be completed and supplied to PrECOG within 24 hours/1 business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up PrECOG SAE report form. A final report to document resolution of the SAE is required. A copy of the fax transmission confirmation of the SAE report to PrECOG should be attached to the SAE and retained with the patient records.

**PrECOG Drug Safety Contact Information**

All SAEs should be faxed to:

888-577-9921

as per the instructions found in study materials provided to the investigator site.

[redacted]
Medical Monitor
During Normal Business Hours
8:30 am-5:00 pm EST
Tel: 610-354-0404
After Normal Business Hours
Tel: 484-574-2367
[redacted]

Manager, Clinical Safety
During Normal Business Hours
8:30 am-5:00 pm EST
Tel: 610-354-0404 ext 143
After Normal Business Hours
Cell: 484-574-2367

PrECOG will notify Celgene of any SAE within 1 business day of receipt from the site.

Collection of complete information concerning SAEs is extremely important. Full descriptions of each event will be followed. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

All SAEs must be collected which occur within 30 days of discontinuation of dosing for lenalidomide and/or dexamethasone, whichever is the last to be received. In addition, the Investigator should notify PrECOG or designee of any SAE that may occur after this time period which they believe to be definitely, probably or possibly related to investigational product.

10.5 Reporting of Other Second Primary Malignancies

All cases of new primary malignancies that occur on PrECOG protocols during or after protocol treatment must be reported as a SAE and documented on a PrECOG SAE form. New primary malignancies should be reported within 24 hours of being aware of diagnosis, regardless of relationship to protocol treatment. SAE submission process described above in Section 10.4 should be followed. A copy of the pathology report should be sent with SAE form, if available.

*NOTE:* Data regarding survival and remission status, second primary malignancies, and recurrence of prior malignancies will be followed x 3 years. This should include subjects who may have discontinued the study at any time or for any reason, who may be in a survival follow-up period, or who may have died. Data for all identified cases of subsequently diagnosed second primary malignancies after this 3 year time will be reported voluntarily by the treating physician to the manufacturer.

## 11.0 Treatment Evaluation
**(Response is to be assessed at the end of each treatment cycle within 3 days prior to the start of the next cycle)**

11.1 Terms and Definitions

- **M-Protein:** synonyms include M-spike, monoclonal protein and myeloma protein, paraprotein, M-component.

  Serum M-protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable.

  - M-proteins migrating in the β-region (usually IgA M-proteins)
  - Cases in which the M-spike is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin (Ig) level (by greater than 1500 mg/dL) due to technical staining properties of the agarose gel
  - Cases in which there are multiple peaks of same monoclonal protein (aggregates or dimers)

  If SPEP is not available or felt to be unreliable (above examples) for routine M-protein quantitation, then quantitative immunoglobulin levels derived from nephelometry or turbidometry can be accepted. However, this must be explicitly reported at baseline, and only nephelometry can be used for that patient to assess response. SPEP derived M-spike values and quantitative nephelometric immunoglobulin values cannot be used interchangeably. In determining response, if the quantitative immunoglobulin result contradicts the M-spike result (or vice-versa), the treating physician may request permission from the PI to alter which parameter will be followed for response determination. This adjustment may be made once during a patient's course.

  Urine M-protein measurement is estimated using 24-h UPEP only. Random or 24-h urine tests measuring kappa and lambda light chain levels are not reliable and are not accepted for this study.

  Free light chain (FLC) estimation is currently carried out using the serum FLC assay (Freelite, The Binding Site Limited, UK). Patients with kappa/lambda FLC ratio <0.26 are defined as having monoclonal lambda FLC and those with ratios >1.65 as having a monoclonal kappa FLC. The monoclonal light chain isotype is considered the involved FLC isotype, and the opposite light chain type as the uninvolved FLC type.

- **Response Terms:** The following response terms will be used: stringent Complete Response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), progressive disease (PD) and relapse from CR (RFCR).

In addition, for each response category, there will be an "unconfirmed" response category, which will be for internal use, for the purpose of guiding decision making and test ordering. These designations will be applied at the time of the first measurement at which the quantitative aspect of the response category has been satisfied without the confirmation step having been satisfied. The designation "u" will precede the standard abbreviations, and will include usCR, uCR, uVGPR, uPR, uPD.

- **Measurable Disease:** Patients who have a measurable serum or urine M-protein.
  - Serum M-protein ≥1 g/dl
  - Urine M-protein ≥200 mg/24 h
  - Serum FLC assay: Involved FLC level ≥10 mg/dl provided serum FLC ratio is abnormal
  - Bone marrow plasma cells ≥30%

The serum free light chain (FLC) assay is of particular use in monitoring response to therapy in patients who have oligo-secretory or non-secretory disease and **should be used in assessing response only if the baseline serum and/or urine M proteins are not "measurable" as above, and the baseline level of the involved FLC is "measurable."** When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and in patients with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio normalizes with achievement of CR. Thus both the level of the involved and the uninvolved FLC isotype (e.g., the involved/uninvolved ratio or involved-uninvolved difference) should be considered in assessing response. ***Patients included on the study on the basis of FLC alone (e.g., no measurable serum/urine) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC results.***

- **Evaluable Disease**: Patients who do not have a "measurable" serum M-spike, serum free light chain, or urine M-spike.

- **Oligosecretory Myeloma:** Patient with multiple myeloma who has NEVER had "measurable" serum M-spike or urine M-spike, but has had a detectable monoclonal protein in his/her serum and/or urine and/or measurable serum free light chain.

- **Non-Secretory Myeloma:** Patient with multiple myeloma who has NEVER had a detectable monoclonal protein in his/her serum and/or urine.

11.2 Clarification of Test Indications

Listed below are the minimal required tests required to assess response based on the characteristics of their disease at on study. Response is to be assessed at the end of each treatment cycle within 3 days prior to the start of the next cycle.

**Table 11.2**

**Tests Required To Assess Response (Must Be Done At Each Disease Measurement Visit)**

| **On Study Baseline Value** | **SPEP** | **24 hr UPEP** | **Ig FLC** | **BM Bx** |
|---|---|---|---|---|
| Serum M-spike ≥1 g/dl, and urine M-spike ≥200 mg/24 hrs | X | X | | |
| Serum M-spike ≥1 g/dl, but urine M-spike <200 mg/24 hrs | X | | | |
| Serum M-spike <1 g/dl, and urine M-spike ≥200 mg/24 hrs | | X | | |
| Serum M-spike <1 g/dl, urine M-spike <200 mg/24 hrs, but involved Ig FLC is ≥10 mg/dL | | | X | |
| Serum M-spike <1 g/dl, urine M-spike <200 mg/24 hrs, involved Ig FLC is <10 mg/dL, bone marrow ≥30% plasma cells | | | | X[a] |
| ***Immunofixation studies of both serum and urine*** are required to document CR regardless of registration values, and in addition ***FLC*** measurement and ***bone marrow immunophenotyping*** is required to document sCR. | | | | |

[a]*Exception: bone marrow biopsy does not have to be confirmed.*

11.3 Confirmed Response

In order to be classified as a hematologic response, confirmation of serum monoclonal protein, serum immunoglobulin free light chain (when primary determinant of response) and urine monoclonal protein (when primary determinant of response) results must be made by verification on two consecutive determinations.

- Bone marrow aspirate and biopsy are **only** required to document or confirm CR or sCR, except for patients with evaluable disease **only**, where a bone marrow is required to document all response categories including progression. However, a second confirmatory bone marrow is **not** required to confirm response.
- Radiographic studies are not required to satisfy these response requirements, however, if radiographic studies were performed there should be no evidence of progressive or new bone lesions.

Appropriate tests required to document and confirm response are listed in Table 11.2 and 11.5.

11.4 Bone Progression

Caution must be exercised to avoid rating progression or relapse on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response

and may not indicate progression. When progression is based on skeletal disease alone, it should be discussed with the medical monitor before removing the patient from the study. Palliative radiation alone for bone pain during treatment does not qualify as progressive disease.

11.5 Response and Progression

Criteria for response and progression are listed in Table 11.5.

**Table 11.5**

| CATEGORY | RESPONSE CRITERIA [a] |
|---|---|
| **stringent Complete Response (sCR)** | • CR as defined below plus all of the following<br>o Normal serum FLC ratio<br>o Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence [b] |
| **Complete Response (CR)** | • Negative immunofixation of the serum and urine<br>• If at on study, the only measurable non-bone marrow parameter was FLC, normalization of FLC ratio<br>• <5% plasma cells in bone marrow<br>• Disappearance of any soft tissue plasmacytomas |
| **Very Good Partial Response (VGPR)[e]** | • PR as defined below plus all of the following:<br>o Serum and urine M-component detectable by immunofixation but not on electrophoresis or<br>o If at on study, serum measurable, ≥90% or greater reduction in serum M-component<br>o Urine M-component <100 mg per 24h |
| **Partial Response (PR)** | • One of the following:<br>▪ If at on study, serum and urine measurable, a ≥50% reduction of serum M-protein and reduction in 24h urinary M-protein by ≥90% or to <200 mg per 24h<br>▪ If at on study, only serum measurable (but urine not), a ≥50% reduction of serum M-protein<br>▪ If at on study, urine measurable (but serum not), a reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24h<br>▪ If at on study, the only measurable non-bone marrow parameter was FLC, a ≥50% decrease in the difference between involved and uninvolved FLC levels or a 50% decrease in level of involved FLC with 50% decrease in ratio<br>▪ If at on study, the bone marrow was only measurable parameter, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥30%<br>• In addition to the above criteria, if a plasmacytoma present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required |

| | |
|---|---|
| **Stable Disease (SD)** | Not meeting criteria for CR, VGPR, PR or progressive disease |
| **Progressive Disease (PD)** | Any one or more of the following:<br>• Increase of 25% from lowest confirmed response in:<br>▪ Serum M-component (absolute increase must be ≥0.5 g/dl)[c]<br>▪ Urine M-component (absolute increase must be ≥200 mg/24h)<br>▪ If at on study, only the only measurable non-bone marrow parameter was FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dl)<br>▪ Bone marrow plasma cell percentage (absolute % must be 10%)[d]<br>• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas<br>• Development of hypercalcemia (corrected serum calcium >11.5 mg/dl) that can be attributed solely to the plasma cell proliferative disorder |
| **Relapse from CR or sCR** | Patient who has achieved confirmed CR who has any one or more of the following:<br>• Reappearance of serum or urine M-protein by immunofixation or electrophoresis<br>• Development of ≥5% plasma cells in the bone marrow [d]<br>• Appearance of any other sign of progression (e.g., new plasmacytoma, lytic bone lesion, or hypercalcemia) |

[a] All response categories require two consecutive assessments made at any time before the institution of any new therapy; complete and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. Each category, except for stable disease, will have a working subcategory of "unconfirmed" [prefix 'u"] to designate first time point at which response category MAY have been achieved if confirmed.

[b] Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence require a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of >4:1 or <1:2.

[c] For progressive disease, serum M-component increases of ≥1 gm/dl are sufficient to define relapse if starting M-component is ≥5 g/dl. Positive immunofixation alone in a patient previously classified as CR will not be considered progression.

[d] Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

[e] This response category is not available for those patients being followed by either free light chain only or by bone marrow only.

## 12.0 Descriptive Factors

Below is additional data that will be collected as part of this protocol and recorded in the eCRFs.

12.1 Serum M-Spike ≥1 g/dL: Yes vs. No.

12.2 Serum Immunoglobulin Free Light Chain ≥10 mg/dL: Yes vs. No.

12.3 Urine M-Spike ≥200 mg/24 hours: Yes vs. No.

12.4 Bone Marrow Plasma Cells ≥30%: Yes vs. No.

12.5 Number of Previous Myeloma Therapies: 1 vs. 2 vs. 3 vs. 4 vs. ≥5.

12.6 Type of Dialysis: Hemodialysis vs. Peritoneal vs. None.

12.7 Beta-2 Microglobulin: <3.5 mg/L vs. ≥3.5, <5.5 mg/L vs. ≥5.5 mg/L.

12.8 Albumin: ≥3.5 g/dL vs. <3.5 g/dL.

## 13.0 Treatment/Follow-Up Decision at Evaluation of Patient

13.1 If it is determined that after registration a patient did not satisfy each and every eligibility criteria, the patient will be noted as being *ineligible.* The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the follow-up/event monitoring phase of the study.

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Follow-up per Section 4.0 and event monitoring per eCRF completion guidelines will be required.
- If the patient never received treatment, on-study material must be submitted. Follow-up per Section 4.0 and event monitoring per eCRF completion guidelines will be required.

13.2 If a required treatment/procedure in cycle 1 is not done and the violation is deemed severe, the patient will be noted as having a *major violation.* All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to follow-up/event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Follow-up per Section 4.0 and event monitoring per eCRF completion guidelines will be required.

13.3 If a patient is removed from the study for any reason before any study treatment is given, the patient will be noted as having been *cancelled.* On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.4 Criteria for Patient Withdrawal

Patients may be withdrawn from the study for the following reasons:

- Progressive multiple myeloma
- Patient withdraws consent to continue in the trial
- Patient develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment
- The Investigator withdraws the patient in the patient's best interests
- Patient is lost to follow-up (defined as the inability to contact the patient on 3 separate occasions over a period of 2 weeks)
- Administrative reasons (e.g., the patient is transferred to hospice care)
- An adverse event, which in the opinion of the Investigator, precludes further trial participation
- Pregnancy
- Closure of study by PrECOG

13.5 All attempts should be made to complete the End of Study procedures if a patient withdraws from the trial early.

13.6 **Phase I:** If a patient fails to complete one cycle of treatment for reasons other than toxicity, the patient will be regarded as inevaluable and will be replaced.

13.7 Patients who develop progressive disease while receiving therapy will go to the event-monitoring phase.

13.8 Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase.

13.9 Patients who are in sCR, CR, VGPR, PR, or SD (or usCR, uCR, uVGPR, uPR) may have stem cells harvested at any time after 4 cycles at the discretion of the Investigator. If the patient is continued on therapy, lenalidomide and dexamethasone may be discontinued during the harvest period and the dates of cessation and resumption recorded.

## 14.0 Body Fluid Biospecimens

**(Mandatory only for Mayo Clinic subjects registered onto the Phase II component). Biospecimens will be collected from at least two patients in each patient group on the Phase II component (Groups A, B and C) for a total of 12 patients.**

14.1 Rationale: To determine the pharmacokinetics of lenalidomide in impaired renal function.

14.2 Blood Sample Collection, Processing and Storage

14.21 Fill ice bucket with enough ice before drawing blood.

14.22 Collect 5 mL of whole blood into 5 mL EDTA tube. Gently invert the tube 3-5 times and immerse it into the ice immediately to prevent possible compound degradation at room temperature. (Record drawing time immediately).

14.23 Within 15 min of blood collection, sample will be processed by centrifuging at 1500g for 10 min at 4$^{o}$C to obtain plasma. A refrigerated desktop centrifuge should be used.

14.24 The plasma (approx. 2 mL) will then be separated and put into 2 clean pre-labeled polypropylene tube. (Note – each tube should contain at least 0.8 mL of plasma).

14.25 Store all plasma samples (within 1 hr of collection) in -70$^{o}$C freezer until shipping to the bioanalytical laboratory.

14.26 The samples can be batched (weekly or monthly) and sent to the bioanalytical Lab (pending arrangement). Additional information will be provided in separate study materials.

14.27 Sampling Labeling: The label should contain at minimum the following information:

1. Subject number
2. Subject initials
3. Treatment Dose group
4. Lenalidomide in plasma
5. Sampling date and time (hr/mm)
6. Study ID Number (PrECOG1003, Celgene study number RV-MM-PrECOG-0394)
7. Date of drug administration
8. Primary sample or secondary sample

14.3 Packaging and Shipping of Biological Samples

14.31 Shipping to QPS Laboratories, Inc.

- Biological samples should be shipped on dry ice.
- Samples should be shipped only on a Monday, Tuesday, or Wednesday, to minimize the possibility of them being in transit over a weekend.

- If duplicate samples are being shipped, please send one set of samples and await confirmation of arrival at QPS Laboratories before shipping the second set.

14.32 Sample Packing

- Arrange the sample collection, with your courier.
- Use a styrofoam box, for example 19" x 19" x 12". Use a larger one if you are shipping many samples.
- Obtain 20 lbs. of dry ice pellets. Use as much dry ice as possible, to help safeguard against any possible delays.
- Place a 4" layer of dry ice in the bottom of the styrofoam box.
- Samples should be identified using self-adhesive labels that should be applied prior to freezing the samples.
- Wrap the frozen samples in bundles using an elastic band and place the sample bundles in a plastic freezer bag.
- Use newspaper or other similar material to insulate the bagged sample bundles from direct contact with the dry ice.
- Place the sample bundles in the styrofoam box and fill the excess space with the remaining dry ice pellets.
- Record the estimated weight of the dry ice used per box.
- Place the lid on the styrofoam box and seal completely with tape.
- Tape a list of the samples contained inside the box, to the lid (e.g., plasma, subjects 1 – 6 pre-dose, 30 min., and 1hr). In order to protect this paperwork insert it into a plastic bag.
- Place the Styrofoam box in a cardboard shipping carton, seal securely with tape.

14.33 Labeling on Shipping Containers

- Label the cardboard box as follows:

    1. Mark the outside of the cartons with tally number e.g., 1 of 3, 2 of 3, and 3 of 3.

2. Affix an address label, with the information below, to the outside of each box:

   Please ship the samples via Fed Ex to:

   [redacted]

- Affix the following labels on each box:
- 1 x carbon dioxide label with the weight included. Example:

**Carbon Dioxide Solid UN-1845**

**Class 9 PKG GR III**

**KG _____**

- 2 x internationally recognized dry ice symbols (Class 9) - one on either side of the box. Example:


- 1 x **KEEP FROZEN** label

14.34 Paperwork to Accompany Shipment

These human biological samples are not known to be infectious or hazardous. For laboratory use only.

Beginning with the first shipment:

The following information must accompany all shipments:

- Subject Identification
- Time Point Identification
- Protocol Number
- Sponsor Name

Any missing information may cause a delay in analysis.

Notify QPS Lab, by email or fax immediately after the courier has collected the samples. Please provide the following information:

- Name of courier or transport company.
- Date and time the shipment left your premises.
- The airway bill number.

14.35 QPS Lab Shipping Contacts

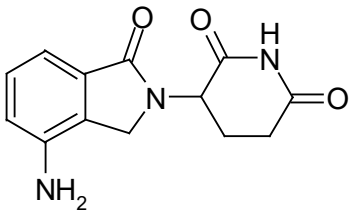
The contact person at QPS Lab for all shipments is:

If the shipment labeling and documentation are not completed correctly, the shipment may be delayed. Upon arrival at QPS Lab, the shipment will be unpacked and you will be advised of its safe arrival.

## 15.0 Background Drug Information

15.1 Lenalidomide (REVLIMID®), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

**Chemical Structure of Lenalidomide**




3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

15.11 Clinical Pharmacology

Mechanism of Action:

[redacted]

15.12 Pharmacokinetics and Drug Metabolism:

Absorption: [redacted] Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic [redacted]

15.13 Pharmacokinetic Parameters:

Distribution: In vitro ($^{14}$C)-lenalidomide binding to plasma proteins is approximately 30%.

15.14 Metabolism and Excretion:

[redacted]

15.15 Supplier(s)

Supplied: Celgene Corporation will supply Revlimid® (lenalidomide).

Dosage Form: Lenalidomide will be supplied as 5 mg and 25 mg capsules for oral administration.

Packaging: Lenalidomide will be shipped to the pharmacy at the study site in individual bottles. Bottles will contain a sufficient number of capsules to last for one cycle of dosing. Study drug must be dispensed in the original packaging with the label clearly visible. Only enough lenalidomide for 1 cycle of therapy may be provided to the patient each cycle.

Labeling: Lenalidomide investigational supplies are dispensed to the patients in individual bottles of capsules. Each bottle will identify the contents as study medication. In addition, the label will bear Celgene's name, quantity contained and the standard caution statement as follows: Caution: New drug - Limited by Federal law to investigational use. The study drug label must be clearly visible. For appropriate drug

accountability, it is recommended that each bottle be marked with the institutional or Celgene protocol number (RV-MM-PrECOG-0394) upon receipt. Additional labels must not cover the Celgene label.

Receipt of Study Drug: The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to PrECOG or its representative.

Storage: At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. The study drug should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

Unused Study Drug Supplies: PrECOG will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by PrECOG. Patients will be instructed to return empty bottles or unused capsules.

Drug Dispensing Requirements: In investigational studies, lenalidomide will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). These healthcare professionals will be trained by Celgene in requirements specific to counseling of subjects. Once trained these healthcare staff will counsel subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with lenalidomide. This step will be documented with a completed Education and Counseling Guidance Document (Appendix VI), and no drug will be dispensed until this step occurs. Counseling includes verification with the patient that required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet (Appendix VII) will be supplied with each medication dispense.

15.16 Human Toxicology:

Complete and updated adverse events are available in the Investigational Drug Brochure and the IND Safety Letters.

Likely Risks: Neutropenia; thrombocytopenia; fatigue; constipation; diarrhea.

Less Likely Risks: anemia; fever; itching and dry skin; back or joint pain; headache; dizziness, cough; shortness of breath or difficulty catching your breath; upper respiratory infection; decreased appetite; difficulty sleeping, nausea; muscle cramps; peripheral edema; rash; lack or loss of strength.

Rare Cases of the following have been reported: Tumor Lysis syndrome (TLS) which is a metabolic disorder that results from the rapid killing of tumor cells most often connected with cancers of the blood and can lead to increased levels of phosphorous, potassium, uric acid and low levels of calcium which can lead to kidney failure; angioedema; Stevens-Johnson syndrome and toxic epidermal necrolysis – serious allergic skin reactions that begin as a rash in one area and later cover more of the body; rhabdomyolysis, a serious condition involving the destruction of skeletal muscle that can lead to kidney failure; anaphylaxis; tumor flare reaction; increase in blood levels of lipase due to inflammation of pancreas gland.

Serious Risks: Neutropenia associated with fever; pulmonary embolism in or around the lungs; deep vein thrombosis in a larger blood vessel, atrial fibrillation; progression of the disease; pneumonia; sepsis; dehydration; kidney failure; myocardial infarction; congestive heart failure.

Other Risks: Patients should be instructed to inform the study staff if any physician other than the study doctor prescribes medication for them for another condition or if they are taking any over-the-counter medications or vitamins.

Lenalidomide has been shown to increase the level of digoxin in the blood in some patients; please instruct patients to inform the study staff if they are taking digoxin.

15.17 Nursing Implications:

1. The most common side effects are neutropenia and thrombocytopenia.

2. Due to the highly teratogenic potential of the closely related thalidomide, it is highly recommended that all women of childbearing age group and all men use effective contraception during therapy (see Appendix V for required birth control and other information related to the risks of fetal exposure). All staff who are pregnant or who can become pregnant should not handle this drug outside of its original packaging.

3. Instruct patient to report any rash immediately to the study team.

4. Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.

5. If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

6. Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

15.2 Dexamethasone

15.21 Other Names: Decadron, Dexameth, Dexon, DXM, Hexadrol

15.22 Classification: Adrenal Corticosteroid

15.23 Mode of Action:
Dexamethasone is a potent synthetic glucocorticoid that affects almost every body system. It has anti-inflammatory, immunosuppressant, antineoplastic, and antiemetic properties and very little mineralocorticoid activity. As an antineoplastic agent, Dexamethasone may bind to specific proteins (receptors) within the cell forming a steroid-receptor complex. Binding of the receptor-steroid complex with nuclear chromatin alters mRNA and protein synthesis within the cell.

15.24 Storage and Stability: The drug is stored at room temperature in a dry place.

15.25 Dose Specifics: 40 mg/day orally on days 1, 8, 15 and 22 each 28 day cycle
Route of Administration: Oral.

15.26 Availability: Commercially available in 0.25, 0.5, 0.75, 1, 1.5, 2, 4, and 6 mg tablets.

15.27 Main Side Effects:
1. Gastrointestinal: Nausea, vomiting, anorexia, increased appetite, weight gain; aggravation of peptic ulcers.
2. Dermatologic: Rash, skin atrophy, facial hair growth, acne, facial erythema, ecchymoses.
3. Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities).
4. Neurologic: Insomnia, euphoria, headache, vertigo, psychosis, depression, seizures, and muscle weakness.
5. Cardiovascular: Fluid retention and edema, hypertension; rarely, thrombophlebitis.
6. Ocular: Cataracts, increased intraocular pressure, exophthalmos.
7. Metabolic: Hyperglycemia, decreased glucose tolerance, aggravation or precipitation of diabetes mellitus, adrenal suppression (with Cushinoid features), hypokalemia.
8. Hematologic: Leukocytosis.
9. Other: Osteoporosis (and resulting back pain), appearance of serious infections including herpes zoster, varicella zoster, fungal infections, Pneumocystis carinii, tuberculosis; muscle wasting; delayed wound healing; suppression of reactions to skin tests.

15.28 Nursing / Patient Implications:
1. When administered orally, give with food or milk.
2. Observe for signs of hyperglycemia.
3. Observe for subtle signs of infection (fever, pain).

## 16.0 Statistical Considerations and Methodology

16.1 Study Design: This phase I/II study involves three single arm phase I trials designed to determine the MTD and toxicity of lenalidomide in the treatment of multiple myeloma in three groups of patients defined by renal dysfunction. Once an MTD is determined within a group, an additional 15 patients will be accrued within the group and treated with the MTD as part of the phase II study to assess efficacy of lenalidomide and dexamethasone in the treatment of multiple myeloma. The 6 phase I patients treated at the MTD plus 15 additional patients accrued in each group will be combined (total = 63 patients) to assess efficacy using a one-stage design.

The first phase I study enrolls patients with moderate renal dysfunction (Group A); the second one enrolls patients with severe renal dysfunction (Group B); and the third one enrolls patients with ESRD renal dysfunction (Group C). Groups A, B, and C have a maximum of 3, 4, and 4 dose levels respectively. The MTD for each group will be determined concurrently.

16.11 Sample Size: **Phase I**: For Group A, the study may involve a maximum of 18 patients (6 for each of the 3 dose levels) but would likely require 15 patients (3 at the first dose level, 6 for the dose level prior to the MTD, and 6 at the MTD). For Group B, the study may involve a maximum of 24 patients (6 for each of the 4 dose levels) but would likely require 18 patients (3 at the first 2 dose levels, 6 for the dose level prior to the MTD, and 6 at the MTD). For Group C, the study may involve a maximum of 24 patients (6 for each of the 4 dose levels) but would likely require 18 patients (3 at the first 2 dose levels, 6 for the dose level prior to the MTD, and 6 at the MTD). **Phase II**: Each group will accrue an additional 15 patients at the MTD. **Overall**: Therefore, overall, the study needs a maximum of 111 patients, and an expected number of 96 patients.

In addition, the protocol allows replacement of patients in phase I who withdraw before completing cycle 1 for reasons other than toxicity.

16.12 MTD Determination: MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity in at least one-third of patients (at least 2 of a maximum of 6 new patients). MTD will be determined independently for each group as outlined in Section 7.2.

16.13 Accrual and Study Duration: We expect a 3-month period at the beginning of the study during which IRB approvals will be obtained. Then, given accrual history from PrECOG sites and assuming equal accrual to all three cohorts, it is estimated that 1.15 patients per week in each group will be accrued to this trial. Maximum total time per dose/group cohort of 6 patients will be:

2.5 weeks to enroll the first 3 patients
4 weeks to treat the first 3 patients through one cycle
1 week to assemble data and evaluate the outcome

2.5 weeks to enroll the second 3 patients
4 weeks to evaluate their outcome
1 week to assemble data and evaluate the outcome

This corresponds to a maximum requirement of approximately 15 weeks to enroll, treat, and evaluate 6 patients. Therefore, the accrual time for Groups A, B, and C will be 45 weeks, 60 weeks, and 60 weeks, respectively (note- these occur concurrently so the total duration of the phase I component is maximally 60 weeks with expected duration of 45 weeks) and the overall study duration will be 60 weeks (phase I component) + 15 weeks (accrual for 15 additional patients per group at 1 patient per group per week) + 24 weeks (6 cycles to treat and evaluate patients in the phase II component) = 99 weeks (about 23 months).

16.14 Operating Characteristics: The following table gives the probability of dose escalation at a single dose level as a function of the true probability of DLT at that level using the cohorts of 3 design described in Section 7.2.

| **True Rate of DLT (%)** | **Probability of Dose Escalation** |
|---|---|
| 10 | 0.91 |
| 20 | 0.71 |
| 30 | 0.49 |
| 40 | 0.31 |
| 50 | 0.17 |

16.2 Phase I Analysis Plans: Data will be analyzed separately within the three patient groups with the exception of the additional 15 patients per group accrued at the MTD (e.g., patients included in the phase II component). However, the analysis procedures, described below, are the same for the three groups. All the relevant phase I results pertaining to toxicity, MTD, response, timed endpoints and laboratory correlates will be examined in an exploratory and hypothesis-generating fashion.

16.21 Adverse Events Profile

The number and severity of all adverse events (overall and by dose-level) will be tabulated and summarized within the three patient groups. The grade 3+ adverse events will also be described and summarized in a similar fashion. This will provide an indication of the level of tolerance for this treatment combination in the three patient groups.

16.22 Toxicity Profile

As per NCI CTCAE V4.0, the term “toxicity” is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Non-hematologic toxicities will be evaluated via the ordinal CTCAE standard toxicity grading. Hematologic toxicity measures of thrombocytopenia, neutropenia, and leukopenia will be

assessed using continuous variables as the outcome measures (primarily nadir) as well as categorization via CTCAE standard toxicity grading.

Overall toxicity incidence as well as toxicity profiles by dose level will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

Further, the overall toxicity profiles and the MTD will be compared in an exploratory fashion among the three groups for any possible differences.

Lastly, the duration of treatment, dose level and total dose per agent each cycle will be summarized using descriptive statistics overall per group and by dose level per group.

16.23 Timed Endpoints

The data on time-related variables will be summarized descriptively. These include time until any treatment related toxicity, time until treatment related grade 3+ toxicity, time until hematologic nadirs (WBC, ANC, platelets), time to progression and time to treatment failure, where time to treatment failure is defined as the time from registration to documentation of progression, unacceptable toxicity, or refusal to continue participation by the patient.

16.3 Phase II Design and Analysis

16.31 Primary Endpoint and Estimation: The primary endpoint is the proportion of patients who have at least a partial response to treatment. Throughout Section 16.3, partial response or better will be considered synonymous with "success", unless specified otherwise. The 6 patients treated at the recommended dose level (MTD) within each group will be included in the analysis for this portion of the study. The efficacy population will include the 63 patients across groups and include all patients meeting eligibility criteria who signed a consent form and began treatment.

The proportion of successes will be estimated by the number of successes divided by the total number of patients in the efficacy population. Eligible, treated patients who are unevaluable for response will be included in the denominator when estimating the proportion of successes. Confidence intervals for the true success proportion will be calculated according to the properties of the binomial distribution. Secondary analyses include estimation of the proportion of successes with confidence intervals for each group.

16.32 Statistical Design: The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 40%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 55%. The following one-stage design based on the binomial distribution uses 63 patients to test the null hypothesis that the true success proportion in a given patient population is at most 40%.

The success rate of 40% is based on the results of two phase III studies of lenalidomide plus dexamethasone versus dexamethasone alone in relapsed or refractory multiple myeloma (MM-009, North America, 353 patients; MM-010, Europe, Australia, and Israel, 351 patients). The overall response (≥PR) rates associated with lenalidomide and dexamethasone were 61% and 59.1% in MM-009 and MM-010, respectively, and the overall response rates associated with dexamethasone (plus placebo) were 20.5% and 24% in MM-009 and MM-010, respectively, with a median follow-up of 17.1 months (MM-009) and 16.5 months (MM-010) as reported by Weber et al[19]. An additional pooled subgroup analysis was reported by Weber et al[19] investigating renal dysfunction groups. Overall response rate to lenalidomide and dexamethasone was not significantly different between patients with creatinine clearance above 60 ml/min and patients with creatinine clearance below 60 ml/min. However, for 16 patients with creatinine clearance below 30 ml/min, median time to progression and overall survival were significantly shorter than for those with creatinine clearance above 30 ml/min. Further, the median time to progression and overall survival of patients with creatinine clearance below 30 ml/min was significantly greater than patients with creatinine clearance below 30 ml/min on the dexamethasone (and placebo) arm. Results for overall response rate in the <30 ml/min group were not reported. Based on this, it is reasonable to anticipate that the overall response rate in (at least) Group B and Group C of the current study will be less than 60%. However, the study chairs felt that an overall response rate of 40% would be the minimum acceptable in this context.

16.33 Decision Rule: Enter 63 patients into the study. If 30 or fewer successes are observed in 63 eligible, treated patients, we will consider this regimen ineffective in this patient population and terminate this study. If 31 or more successes are observed among 63 eligible, treated patients, we may recommend further testing of this regimen in subsequent studies in this population.

16.34 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process but will be included in all final point estimates.

16.35 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is ≥10% and the probability of declaring that this regimen warrants further studies (e.g., statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

| If the true success proportion is . . . . . | 0.4 | 0.45 | 0.5 | 0.55 | 0.6 |
|---|---|---|---|---|---|
| then the probability of declaring that the regimen warrants further studies is . . . . . | 0.09 | 0.29 | 0.60 | 0.85 | 0.97 |

16.36 Analysis Plan: The analysis for this trial will commence at planned time points and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair, in accord with PrECOG Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and

the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is 24 months.

16.37 Definitions and Analyses of Secondary Endpoints:

Survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier.

Progression-free survival time is defined as the time from registration to the earliest date of documentation of disease progression. If a patient dies without a documentation of disease progression the patient will be considered to have had disease progression at the time of their death. If the patient is declared to be a major treatment violation, the patient will be censored on the date the treatment violation was declared to have occurred. In the case of a patient starting treatment and then never returning for any evaluations, the patient will be censored for progression on day 1 post-registration. The distribution of progression-free survival time will be estimated using the method of Kaplan-Meier.

Duration of response is defined for all eligible, treated patients who have achieved a partial response or better as the date at which the patient's earliest objective status is first noted to be either a partial response or better to the earliest date progression is documented.

Time to treatment failure is defined to be the time from registration to the date at which the patient is removed from treatment due to progression, adverse events, or refusal. If the patient is considered to be a major treatment violation or is taken off study as a non-protocol failure, the patient will be censored on the date they are removed from treatment.

Adverse Events: All eligible patients who began treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration. The duration of treatment, dose level and total dose per agent each cycle will also be summarized using descriptive statistics. Lastly, renal function over time will be described using descriptive statistics.

16.38 Pharmacokinetic Analysis:

Pharmacokinetic (PK) analysis will be performed in consented subjects administered a dose during the "Phase II" portion of the trial.

The following pharmacokinetic parameters will be determined using the non-compartmental methods:

- Maximum observed plasma concentration ($C_{max}$)
- Time to maximum plasma concentration ($t_{max}$)
- Area under the plasma concentration-time curve from Time 0 to the last measurable time point (AUC)

- Area under the plasma concentration-time curve from Time 0 to infinity ($AUC_{\infty}$)
- Apparent total body clearance when dosed orally (*CL/F*)
- Apparent volume of distribution when dosed orally ($V_z/F$)
- Terminal elimination half-life in plasma ($t_{½,z}$)

The relationship between renal function (CrCl) and PK parameters will be explored.

The results will be summarized by descriptive statistics.

16.4 Data & Safety Monitoring:

Study Monitoring: PrECOG, LLC will be responsible for study monitoring. Refer to Section 19.5 for details.

Adverse Event Stopping Rule: The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to a group if at any time we observe events considered at least possibly related to study treatment (e.g., an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy the following:

- If 7 or more patients in the first 20 treated patients (or 33% of patients after 20 have been accrued) experience a grade 4 or higher non-hematologic adverse event.

We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event. The adverse event rule will be evaluated for each group using all patients in the group who initiate treatment (e.g., will include patients in the phase I and phase II components).

16.5 Inclusion of Women and Minorities

This study will be available to all eligible patients regardless of race, gender, or ethnic group.

There is no information currently available regarding differential agent effects of this regimen in subsets defined by gender, race, or ethnicity, and there is no reason to expect such differences exist. Therefore, although the planned analyses will, as always, look for differences in treatment effect based on gender and racial groupings, the samples sizes are not increased in order to provide additional power for such subset analyses.

To predict the characteristics of patients likely to enroll in this trial we have reviewed the Mayo registration classified by race and gender. This revealed that roughly 3% of patients registered into cancer trials during the past five years could be classified as minorities and about 50% of patients were women. Expected sizes of racial by gender subsets are shown in the following table:

| Ethnic Category | Sex/Gender | | | |
|---|---|---|---|---|
| | **Females** | **Males** | **Unknown** | **Total** |
| Hispanic or Latino | 2 | 2 | | 4 |
| Not Hispanic or Latino | 53 | 54 | | 107 |
| **Ethnic Category: Total of all subjects*** | 55 | 56 | | 111 |
| **Racial Category** | | | | |
| American Indian or Alaskan Native | 0 | 0 | | 0 |
| Asian | 0 | 0 | | 0 |
| Black or African American | 1 | 1 | | 2 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | | 0 |
| White | 54 | 55 | | 109 |
| **Racial Category: Total of all subjects*** | 55 | 56 | | 111 |

**These totals must agree. Enter actual estimates (**not percentages**)*

| | |
|---|---|
| **Ethnic Categories:** | **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."<br>**Not Hispanic or Latino** |
| **Racial Categories:** | **American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.<br>**Asian –** a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)<br>**Black or African American –** a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."<br>**Native Hawaiian or other Pacific Islander –** a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.<br>**White –** a person having origins in any of the original peoples of Europe, the Middle East, or North Africa. |

## 17.0 Pathology Considerations: None

## 18.0 Budget Considerations

18.1 Costs Charged to Patient:

18.11 Tests and clinical visits considered part of standard care will be charged to the patient. Patient will also be charged for the cost of dexamethasone and associated preparation charges.

18.12 Lenalidomide will be provided complimentary by Celgene.

18.13 Patients randomized to the pharmacokinetic portion of the study will not be charged for the pharmacokinetic samples.

## 19.0 Administrative

### 19.1 Protocol Compliance

The study shall be conducted as described in this protocol. All revisions to the protocol must be discussed with, and be prepared by PrECOG and/or representatives. The Investigator should not implement any deviation or change to the protocol or consent without prior review and documented approval/ from PrECOG and/or representatives and the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

If a deviation or change to the approved protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB approval, notification will be submitted to the IRB for review and approval as soon as possible afterward. Documentation of approval signed by the chairperson or designee of the IRB(s) should be in the study records. If PrECOG and/or representatives provides an amendment that substantially alters the study design or increases the potential risk to the patient; the consent form must be revised and submitted to the IRB(s) for review and approval; the revised form must be used to obtain consent from patients currently enrolled in the study if they are affected by the amendment; and the new form must be used to obtain consent from new patients prior to study entry. Information as to who investigators should send correspondence will be provided in additional study documents.

### 19.2 Institutional Review Board

Before study initiation, the Investigator must have written and dated approval from their respective IRB for the protocol, consent form, patient recruitment materials/process and any other written information to be provided to patients. The Investigator should also provide the IRB with a copy of the Investigator Brochure or product labeling, and any updates.

The Investigator should provide the IRB with reports, updates, and other information (e.g., Safety Updates, Amendments, and Administrative Letters) according to regulatory requirements, IRB or study site procedures.

### 19.3 Informed Consent Procedures

Investigators must ensure that patients who volunteer for clinical trials or their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other information.

A protocol specific informed consent form (ICF) template will be provided to sites. Preparation of the site-specific consent form is the responsibility of the site Investigator and must include all applicable regulatory and IRB requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. All changes to the ICF template will be approved by PrECOG and/or their representatives prior to implementation.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the consent process will also include written authorization by patients to release medical information to allow PrECOG and/or its agents, regulatory authorities, and the IRB of record at the study site for access to patient records and medical information relevant to the study, including the medical history. This will be documented in the informed consent form or other approved form obtained at the time of informed consent per institutional policies. This form should also be submitted to PrECOG and/or its agents for review prior to its implementation.

The Investigator must provide the patient or legally acceptable representative with a copy of the consent form and written information about the study in the language in which the patient is most proficient. The language must be non-technical and easily understood. The Investigator should allow time necessary for patient or patient's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the patient or the patient's legally acceptable representative and by the person who conducted the informed consent discussion. The patient or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study patients prior to patient's participation in the trial. The investigator is responsible for assuring adequate documentation of this process and for storage and maintenance of the original signed consent form for each patient/subject.

The informed consent and any other information provided to patients or the patient's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the patient's consent, and should receive IRB approval prior to use. The Investigator, or a person designated by the Investigator should inform the patient or the patient's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue participation in the study. This communication should be documented in the patient record. During a patient's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the patient.

## 19.4 Safety Communication

Investigators will be notified of all AEs that are serious, unexpected, and certainly, probably, or possibly related to the investigational product. Upon receiving such notices, the Investigator must review and retain the notice with the Investigator Brochure and submit a copy of this information to the Institutional Review Board (IRB) according to local regulations. The Investigator and IRB will determine if the informed consent requires revision. The Investigator should also comply with the IRB procedures for reporting any other safety information. All revisions should be submitted to PrECOG and/or agents for review.

## 19.5 Monitoring

Representatives and agents of PrECOG and, as applicable to the study, the manufacturer of Investigational Product must be allowed to visit all study site locations periodically to assess the data, quality and study integrity. The purpose of this visit is to review study records and directly compare them with source documents and discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

The study may be evaluated by other auditors and government inspectors who must be allowed access to eCRFs, source documents and other study files. The investigator must notify PrECOG of any scheduled visits by regulatory authorities, and submit copies of all reports. Information as to who investigators should notify of an audit or where to address questions will be provided in additional study materials.

19.6 Study Records

An Investigator is required to maintain adequate regulatory files with corresponding communication and approvals, accurate histories, observations and other data on each individual treated. Full details of required regulatory documents will be provided in additional study materials. Data reported on the CRF must be consistent with the source documents as part of the patient record.

The confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

A study specific signature record will be maintained to document signatures and initials of all persons at a study site who are authorized to make entries and/or corrections on eCRFs as well as document other study-specific roles.

19.7 Electronic Case Report Form (eCRF) Information

Additional information regarding eCRF instructions, timelines for data entry/ submission and query completion can be found in supplemental materials provided to the site. Sites will be expected to complete eCRFs as per the schedule provided and submit all relevant data as per the specified timelines. All items recorded on eCRFs must be found in source documents.

The completed eCRF must be promptly reviewed, electronically signed, and dated by the Principal Investigator.

**Instructions for management of patients who do not receive any protocol therapy:**
If a patient is registered and does not receive any assigned protocol treatment, baseline, Serious Adverse Event and End of Active Treatment/Cancel Notification Form will still be entered and must be submitted according to the eCRF instructions. Document the reason for not starting protocol treatment on the appropriate eCRF.

19.8 Records Retention

FDA Regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents for the periods described below for studies performed under a US IND:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

The Investigator must retain investigational product disposition records, copies of eCRFs (or electronic files), and source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, whichever is longer. The Investigator must contact PrECOG and/or representatives prior to destroying any records associated with the study.

Information as to who investigators should contact for questions will be provided in additional study documents. PrECOG and/or representatives will notify the Investigator when the trial records for this study are no longer needed.

## 20.0 References

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## Appendix I Informed Consent Example

# PrECOG 1003: A Phase I/II Study of the Tolerability of Lenalidomide and Low Dose Dexamethasone in Previously Treated Multiple Myeloma Patients with Impaired Renal Function

Version Date: March 28, 2011

This is a clinical trial, a type of research study. Your doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision after getting the information you need. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your doctor for more explanation. The information in this form is part of a process called informed consent, which will allow you to make a decision about whether you want to volunteer for this clinical trial. Please take your time to make your decision and discuss it with your friends and family.

Once all of your questions have been answered, if you still wish to take part, you will be asked to sign this form. Your study doctor and/or a member of the study team will also sign the form. You will receive a copy of the form to keep. If you have any questions at any time during the research study, you should feel free to ask them. You will receive answers to your questions in a way that you will be able to understand. You are not giving up any of your legal rights by volunteering for this research study or signing this consent form.

### WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS STUDY?

You are being asked to take part in this research study to find out what is the best way to give the drug lenalidomide (Revlimid®) in patients with previously treated multiple myeloma and kidney problems. It is designed to find out the correct dose of the drug and its effect on multiple myeloma when patients have kidney damage.

### WHO IS DOING THIS STUDY?

This study is being conducted by PrECOG LLC, in conjunction with Celgene Corporation. Your study doctor has agreed to participate in this study as a study investigator and will receive payments to cover some research costs such as the cost of performing research tests and collecting and reporting study information.

### WHY IS THIS STUDY BEING DONE?

This study is divided into 2 phases. Phase I will establish the maximum tolerated dose of the combination of lenalidomide with dexamethasone therapy in patients with previously treated multiple myeloma with kidney damage. Phase II will study how effective the treatment is against previously treated multiple myeloma in patients who have kidney damage.

Lenalidomide is approved by the Food and Drug Administration (FDA) for the treatment of specific types of myelodysplastic syndrome (MDS) and in combination with dexamethasone for patients with multiple myeloma (MM) who have received at least one prior therapy. MDS and MM are cancers of the blood. Lenalidomide is currently being tested in a variety of cancer conditions.

**HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?**

Approximately 111 patients from 30 different study centers will be entered into the study.

**WHAT IS INVOLVED IN THIS STUDY?**

Before you are enrolled in the study, you will undergo certain tests to ensure that it is safe for you to go on the study and that your enrollment in the study will provide important information towards answering the question that the study is addressing. You will have a full medical history and physical examination along with blood, urine, bone marrow tests and x-rays as shown below. Some of these tests would be done even if you do not take part in this study.

If you meet all of the criteria for being in the study, you will receive the study treatment. The study is broken down into three periods: screening, treatment and post-treatment. The screening period includes a number of procedures to evaluate your cancer and overall health. The treatment period consists of the time that you will take the medication. Post-treatment is when you have follow-up testing.

Below is a description of the procedures and study visits:

**Screening Procedures**

- Medical History
- Physical Exam, including height and weight
- Routine blood and urine tests
- Bone marrow biopsy and aspirate (removal of bone marrow with a needle and syringe)
- EKG (Electrocardiogram-a measurement of your heart's electrical activity)
- Chest x-ray and Bone survey (x-ray)
- Pregnancy test (only for females of childbearing potential) 10-14 days prior to and again within 24 hours of starting lenalidomide therapy.

**Treatment Procedures**

If you are found to be eligible, you will start treatment. During the treatment period, you will be asked to come to the hospital/outpatient clinic/MD office to receive a supply of the study medicine. Before receiving each treatment, you will be asked about any new problems that may have occurred since your last visit.

While on this study you will receive at least two cycles of treatment unless it causes too many bad side effects. Each cycle is 28 days. If your disease stays the same or is helped you will continue to receive study treatment and if your disease gets worse you will be taken off study treatment. You will take lenalidomide by mouth on specified days each cycle as indicated by your study doctor. You will also take dexamethasone once weekly and aspirin daily or another form of anticoagulation medication as prescribed by your study doctor. Swallow lenalidomide capsules whole with water at the same time each day. Do not break, chew or open the capsules.

If you miss a dose of the medications, take them as soon as you remember on the same day. If you miss taking your dose for the entire day, take your regular dose the next scheduled day (do NOT take double your regular dose to make up for the missed dose). Please contact the study staff right away if you inadvertently take more than your usual dose of either drug.

If you take more than the prescribed dose of lenalidomide you should seek emergency medical care if needed and contact study staff immediately.

Females of childbearing potential that might be caring for you should not touch the lenalidomide capsules or bottles unless they are wearing gloves.

You will be given a diary to record when you take your study drugs. Between each cycle of treatment you will be seen by your physician to check if the treatment is having any benefit or whether you are having any bad effects from the treatment. During each of these visits, you will have blood and urine tests.

Day 1 of Cycles 1-4:

- Physical Exam
- Routine blood and urine tests
- Counseling about pregnancy precautions, risks of fetal exposure and other risks
- Pregnancy test (only for females of childbearing potential)

Day 6 of Cycle 1 (For select participants in Phase II part of study only):

- 5cc (about 1 teaspoon) of blood will be drawn at the following time points after you have taken your medication on Day 6 of Cycle 1: 0 (pre-dose), 30 minutes, 1 hour, 1 and ½ hours, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, and 24 hours at all dose groups. Blood may also be drawn at 48 hours and 72 hours for participants with severe renal impairment or on dialysis.

Weekly during Cycles 1-4:

- Pregnancy test every week for the first 28 days (only for females of childbearing potential)
- Routine blood work

At the End of Cycle 4:

- Physical Exam
- Routine blood and urine tests
- Bone marrow biopsy and aspirate (removal of bone marrow with a needle and syringe)
- Bone survey (x-ray)

Day 1 of Each Additional Cycle:

- Physical Exam
- Routine blood and urine tests
- Counseling about pregnancy precautions, risks of fetal exposure and other risks
- Pregnancy test every 28 days while on therapy (only for females of childbearing potential)

Day 1 of Cycle 9 or End of Treatment:

- Physical Exam
- Routine blood and urine tests
- Bone survey (x-ray)
- Bone marrow biopsy and aspirate (removal of bone marrow with a needle and syringe)
- Counseling about pregnancy precautions, risks of fetal exposure and other risks
- Pregnancy test every 28 days while on therapy, the end of your treatment with lenalidomide, and 28 days after the last dose of lenalidomide (only for females of childbearing potential)

**Post-Treatment Procedures**

Once you are no longer receiving study medication, or if you withdraw from the study at any time, you will be asked to return to be followed. You will be asked about new problems that have happened since your last visit.

**HOW LONG WILL I BE IN THE STUDY?**

You may get treatment as long as your disease continues to respond. You will be followed every 6 months once you have stopped treatment. We would like to keep track of your medical condition for up to 3 years from the time you begin treatment on this study so researchers can watch your health status and look at the long-term effects of the treatment.

Your doctor may decide to take you off this study if your multiple myeloma does not improve or if side effects of treatment would make it unsafe to continue. You will be informed of new developments that might affect your participation in the study.

You may stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

**WHAT ARE THE RISKS OF THE STUDY?**

While on this study, you are at risk for the side effects listed below. Everything possible will be done to prevent or reduce any discomfort or risk. Your doctor may alter schedules and doses of your therapy if necessary to reduce side effects. You may experience all, some or none of the side effects listed. There also may be other side effects that the researchers cannot predict. Side effects may appear shortly after receiving the drug or may appear years later. Many side effects may disappear after the drugs are stopped. Other side effects may be long lasting, permanent or fatal.

Other drugs may be given to make side effects less serious and uncomfortable. You will be asked to contact your study doctor for any problems or questions that arise at any time during your treatment, so that treatment can be started to prevent or decrease serious problems.

Risks and side effects related to the drugs you will be given in this study include:

**Lenalidomide (Revlimid®)**

**Likely risks of lenalidomide** *(events occurring greater than 20% of the time)*

- Fatigue or feeling tired
- Neutropenia or a decrease in white blood cells that can make you more prone to infections
- Thrombocytopenia or a decrease in platelets which can cause you to bruise or bleed easily and/or may require platelet transfusion
- Constipation or difficulty moving your bowels
- Diarrhea or loose/frequent bowel movements

**Less likely risks of lenalidomide** *(events occurring in between 3 to 20% of the time)*

- Anemia or a decrease in red blood cells that can cause tiredness which may require red blood cell transfusion
- Nausea
- Loss of appetite
- Back pain
- Joint pain
- Muscle cramps
- Swelling of the arms and legs
- Problems falling asleep or staying asleep

- Fever
- Cough
- Shortness of breath or difficulty catching your breath
- Upper respiratory infection
- Rash
- Itching and dry skin
- Lack or loss of strength
- Dizziness
- Headache

**Serious side effects** *(events occurring less than 3% of the time)*

- Neutropenia associated with a fever
- Pulmonary embolism or blood clot in or around the lungs
- Deep vein thrombosis or blood clots in a larger blood vessel
- Atrial fibrillation or irregular heartbeat
- Progression of the disease being studied including multiple myeloma
- Pneumonia or an infection of the lungs
- Sepsis or an infection of the blood
- Dehydration
- Kidney failure which can cause changes in the amounts of chemicals in your blood which can cause irregular heartbeats, muscle twitching, seizures, and/or death.

**Rare cases of the following events have been reported** *(events occurring less than 1% of the time)*

- Angioedema – an allergic skin disease characterized by patches of swelling involving the skin and/or the lining of your nose, mouth, and gastrointestinal tract.
- Anaphylaxis- serious potentially life-threatening type of allergic reaction that may cause breathing difficulty, dizziness, low blood pressure, and loss of consciousness.
- Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis – serious allergic skin reactions that begin as a rash in one area and later cover more of the body leading to detachment of the top layer of skin (could be body-wide). Medical journals have reported patients with allergic skin reaction with thalidomide who also developed the same type of reaction with lenalidomide.
- Tumor Lysis Syndrome (TLS) – metabolic problems can occur during or without treatment of cancer. These complications are caused by the break-down products of dying cancer cells and include hyperkalemia (high potassium), hyperphosphatemia (high phosphorus), hyperuricemia and hyperuricosuria (high uric acid in the blood and urine), hypocalcemia (low calcium), and consequent acute uric acid nephropathy and acute renal failure (kidney damage).
- Tumor Flare Reaction – a condition that can involve increase in the size of the cancerous lymph nodes, rash and slight fever.
- Rhabdomyolysis – a serious condition involving the destruction of skeletal muscle that can lead to kidney failure. Signs and symptoms include dark, red, or cola-colored urine and muscle tenderness, stiffness, aching (myalgia) or weakness.
- Increase in blood levels of lipase due to inflammation of pancreas gland.

Occasional adverse events such as atrial fibrillation (irregular heartbeat), myocardial infarction (heart attack), and congestive heart failure (condition where the heart becomes weak and cannot pump enough blood to the rest of the body) have been reported with the use of lenalidomide.

**Hematological Toxicity**

Lenalidomide is associated with significant neutropenia (decrease in white blood cells that help fight infection) and thrombocytopenia (decrease in platelets that help with blood clotting). You will have your blood counts checked frequently when starting treatment with lenalidomide.

**Deep Vein Thrombosis and Pulmonary Embolism**

Lenalidomide has demonstrated an increased risk of deep vein thrombosis [DVT (blood clot in a larger blood vessel)] and pulmonary embolism [PE (a blood clot in or around the lungs)] in some people with certain medical conditions. The study staff will ask you about any risk factors you may have. [If you have a history of blood clots your doctor will prescribe either heparin or coumadin for the first four months of the study treatment. The doctor may continue to prescribe the medication or aspirin for the remainder of your course of study treatment. All other patients will receive (at the discretion of the treating physician) either oral low–dose aspirin or another treatment to prevent blood clotting during study participation.] Patients unable or unwilling to undergo treatment for prevention of blood clots will not be eligible to participate in this study. You will be instructed on the signs and symptoms of DVT and PE and if symptoms occur you should contact your study doctor promptly.

**Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)**

Reports of progression to Acute Myeloid Leukemia (AML) have been received in MDS studies. It is unclear whether lenalidomide increases the risk of AML or if progression merely reflects the natural course of the disease. AML is the rapid multiplication of abnormal cells which accumulate in the bone marrow and interfere with the production of normal blood cells. AML is a very serious condition which may result in death.

**Second New Cancers**

According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with induction therapy (treatment as first step to reducing number of cancer cells) and/or bone marrow transplant then lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then placebo (a capsule containing no lenalidomide). Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers.

**Dexamethasone (DXM)**

**Likely risks of dexamethasone** *(events occurring greater than 20% of the time)*

- Stomach and throat ulcers or worsening of any ulcers you had before treatment
- Swelling and pain of the pancreas
- Weight gain around the stomach
- Puffiness (especially in the face)
- Build-up of fluids and a rise in blood pressure
- Possible rise in your blood sugar
- Changes in the blood levels of potassium
- Infection

**Less likely risks of dexamethasone** *(events occurring in between 3 to 20% of the time)*

- Muscle weakness
- Brittle bones
- Menstrual changes
- Itching, and other allergic reactions, some severe

**Rare risks of dexamethasone** *(events occurring less than 3% of the time)*

- Mood swings
- Depression
- Trouble sleeping
- Changes in personality
- Seizures
- Dizziness
- Patients who are more likely to get heart disease may have heart failure

**Other Risks and Discomforts**

If any physician other than the study doctor prescribes medication for you for another condition or you are taking any over-the-counter medications or vitamins, you must inform the study staff. This is important because the interaction of some medications may cause serious side effects.

Lenalidomide has been shown to increase the level of digoxin in the blood in some patients; please tell your doctor if you are taking digoxin.

The risks of having blood drawn include fainting, bleeding, bruising at the place on your arm where the blood was drawn or needle inserted, pain, swelling and rarely, infection or nerve damage. Imaging scans such as chest x-ray and bone survey will expose you to low doses of radiation.

**Risks from a Bone Marrow Biopsy**

A bone marrow aspirate is a procedure in which an area of the hip is numbed and a small sample of bone marrow is withdrawn. When the local anesthesia (numbing medicine) is given, you may initially feel a burning sensation in your skin and bone surface for several seconds. During the procedure, you may temporarily feel pressure and/or pain of varying degrees. If necessary, you may ask your doctor for additional local anesthesia or a medication to ease your stress. You also may experience bleeding, and/or bruising after the procedure is completed and you may experience soreness in the area for a few days afterwards. Rarely, infection can develop.

**Risks Associated with Pregnancy**

Lenalidomide is related to thalidomide. Thalidomide is known to cause severe life-threatening human birth defects. Findings from a monkey study indicate that lenalidomide caused birth defects in the offspring of female monkeys who received the drug during pregnancy. If lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Females must not become pregnant while taking lenalidomide. If you are female, you agree not to become pregnant while taking lenalidomide. Lenalidomide is present at very low levels in human semen of healthy men for three days after stopping the drug according to a study. For some men, such as men with kidney problems, lenalidomide may be present in semen for more than three days. Because of the

risk of birth defects, all patients taking lenalidomide must read the following statements that apply to them according to gender and menopausal status.

**NOTE: If your study utilizes the pregnancy counseling (LCP): All patients must receive, read and agree to what is stated in the Lenalidomide Information Sheet.**

Because of this risk, all participants taking lenalidomide must read the following statements that apply to them according to gender and menopausal status.

**FOR FEMALES WHO *ARE ABLE* TO BECOME PREGNANT***

*(Sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (not having menstrual cycles due to cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (for example, has had menses at any time during the preceding 24 consecutive months).

**Please read thoroughly and initial each space provided if you understand each statement**

_____: I understand that birth defects may occur with the use of lenalidomide. I have been warned by my doctor that my unborn baby may have birth defects and can even die, if I am pregnant or become pregnant while I am taking lenalidomide.

_____: I understand that I must NOT take lenalidomide if I am pregnant, breast-feeding a baby or able to get pregnant and not using 2 reliable methods of birth control.

_____: If I am having sexual relations with a man, my uterus and/or both ovaries have not been removed, I have had at least one menstrual period in the past 24 months and/or my menses stopped due to treatment of my disease, I understand that I am able to become pregnant. I must use one highly effective method of birth control plus one additional effective method of birth control (contraception) at the SAME TIME.

| Highly Effective Methods | Additional Effective Methods |
|---|---|
| Intrauterine device (IUD) | Latex condom |
| Hormonal (birth control pills, injections, implants) | Diaphragm |
| Tubal ligation | Cervical Cap |
| Partner's vasectomy | |

_____: These birth control methods must be used during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide therapy; 2) throughout lenalidomide therapy, including interruptions in therapy and 3) for at least 28 days after lenalidomide has been stopped. I must use these methods unless I completely abstain from heterosexual sexual contact. If a hormone (birth control pill, injection, patch or implant) or IUD method is not medically possible for me, I may use another highly effective method or two barrier methods AT THE SAME TIME.

_____: I know I must have a pregnancy test done by my doctor within 10 – 14 days and again within 24 hours prior to starting lenalidomide therapy, even if I have not had my menses due to treatment of my disease or had as little as one menstrual period in the past 24 months. If I have regular or no menstrual cycles, I will then have pregnancy tests every week for the first 28 days, then every 28 days while I am taking lenalidomide, again when I have been taken off of lenalidomide therapy and then 28 days after I have stopped taking lenalidomide. If I have irregular menstrual cycles, I will have pregnancy tests every week for the first 28 days, then every 14 days while I am taking lenalidomide, again when I have been taken off of lenalidomide therapy, and then 14 days and 28 days after I have stopped taking lenalidomide.

_____: I know I must immediately stop taking lenalidomide and inform my doctor, if I become pregnant while taking the drug, if I miss my menstrual period or have unusual menstrual bleeding, if I stop using 2 reliable forms of birth control, or if I think for any reason that I may be pregnant. I must talk to my doctor before changing any birth control methods.

_____: I am not now pregnant, nor will I try to become pregnant for at least 28 days after I have completely finished taking lenalidomide.

_____: I understand that lenalidomide will be prescribed only for me. I must not share it with ANYONE, even someone that has similar symptoms to mine. It must be kept out of reach of children and should never be given to females who are pregnant or able to have children.

_____: I agree any unused drug supply will be returned to the research site at each visit.

_____: I know that I cannot donate blood while taking lenalidomide and for 28 days after stopping lenalidomide.

Study patients who become pregnant will be monitored throughout the pregnancy and will continue to be monitored for 30 days after delivery (premature delivery, aborted fetus, full-term pregnancy, or no longer pregnant).

**FOR ALL MALES**

**Please read thoroughly and initial each space provided if you understand each statement:**

_____: I understand that birth defects may occur with the use of lenalidomide. I have been warned by my doctor that an unborn baby may have birth defects and can even die, if a female is pregnant or becomes pregnant while taking lenalidomide.

_____: I have been told by my doctor that I must NEVER have unprotected sexual contact with a female who can become pregnant. Because lenalidomide is present in semen, my doctor has explained that I must completely abstain from sexual contact with females who are pregnant or able to become pregnant, or I must use a latex condom every time I engage in any sexual contact with females who are pregnant or may become pregnant. I must do this while I am taking lenalidomide, including during times when lenalidomide is temporarily stopped, and for 28 days after I permanently stop taking lenalidomide, even if I have had a successful vasectomy.

_____: I know I must inform my doctor if I have unprotected sexual contact with a female who is pregnant or can become pregnant or if I think, for ANY REASON, that my sexual partner may be pregnant. Female partners of male patients taking lenalidomide should be advised to call their own physician immediately if they get pregnant.

_____: I understand that lenalidomide will be prescribed only for me. I must not share it with ANYONE, even someone that has similar symptoms to mine. It must be kept out of reach of children and should never be given to females who are able to have children.

_____: I agree any unused drug supply will be returned to the research site at each visit.

_____: I know that I cannot donate blood, sperm or semen while taking lenalidomide and for 28 days after stopping lenalidomide.

**FOR FEMALES THAT ARE *NOT* ABLE TO BECOME PREGNANT**

**Please read thoroughly and initial each space provided if you understand each statement.**

_____: I understand that birth defects may occur with the use of lenalidomide. I have been warned by my doctor that an unborn baby may have birth defects and can even die, if a female is pregnant or becomes pregnant while taking lenalidomide.

_____: I certify that I am not now pregnant, nor am I of child bearing potential as I have been in a natural menopause for at least 24 months (been through the change in life without even 1 menstrual period for the past 24 months); or I had my uterus removed (hysterectomy) or had both my ovaries removed (bilateral oophorectomy).

_____: I understand that lenalidomide will be prescribed only for me. I must not share it with ANYONE, even someone that has similar symptoms to mine. It must be kept out of reach of children and should never be given to females who are pregnant or able to have children.
_____: I agree any unused drug supply will be returned to the research site at each visit.
_____: I know that I cannot donate blood while taking lenalidomide and for 28 days after stopping lenalidomide.

**ALL PATIENTS**

You will be counseled at least every 28 days during lenalidomide treatment and again one last time when you stop taking lenalidomide about not sharing lenalidomide (and other study drugs), the potential risks of fetal exposure, abstaining from blood and other donations, and you will be reminded not to break, chew or open lenalidomide capsules. You will be provided with the "Lenalidomide Information Sheet for Patients Enrolled in Clinical Research Studies" with each new supply of lenalidomide as a reminder of these safety issues.

**ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with multiple myeloma in the future.

**WHAT OTHER OPTIONS ARE THERE?**

You do not have to be in this study to receive treatment for your condition. Your other choices may include:

- Alternative chemotherapy treatments
- Treatment with lenalidomide off study.
- Comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by cancer. It does not treat cancer directly, but instead tries to improve how you feel.

You should talk to the researcher and your regular physician about each of your choices before you decide if you will take part in this study.

**HOW WILL I KNOW IF THERE IS NEW INFORMATION LEARNED THAT MIGHT AFFECT MY DESIRE TO CONTINUE TO PARTICIPATE IN THIS STUDY?**

During the course of the study, your study doctor will let you know about any new information that may affect your willingness to remain in the study. If new information is learned that may affect you after the study has been completed, you will be contacted by the study doctor.

**WHAT ABOUT CONFIDENTIALITY?**

This study is being conducted by PrECOG, LLC. PrECOG is a not for profit organization that conducts research for the Eastern Cooperative Oncology Group (ECOG) Research and Education Foundation. Your doctor has agreed to participate in this study as an investigator.

You have a right to privacy. All information gathered in this study that can be identified with your name would remain confidential by state and federal law. Your initials and the study number assigned will be used to identify your records specific to the study. Your name will not be placed on any of your blood samples. Your name will not be made public in any reports or publications resulting from this study.

This study requires the use of your medical information. National data protection regulations give you the right to control the use of your medical information. Therefore, by signing this form you specifically authorize your medical information to be checked, transferred and processed as follows: the study monitors, auditors and inspectors may review your medical information by direct access to your medical records. Study data, including your anonymous medical information, may be processed, which means it will be collected, entered into computer databases, verified, analyzed, printed and reported as necessary for legitimate scientific purposes. Authorization to access your medical records will end upon completion of this clinical trial. You may access your medical information as allowed by national law.

By signing this consent you are hereby authorizing the use and/or disclosure of protected health information to certain individuals, including:

- The study investigator (doctor) and study staff at the office/hospital
- PrECOG and/or their authorized representatives
- Government regulatory agencies and/or their authorized representatives (such as the FDA)
- Celgene and/or their authorized representatives

This may include your original medical record plus any additional specific information recorded or generated during the study.

Your original medical records, plus any additional, study specific information, related to your participation in the study, may be required in order to verify study data. Any inspection will be done only under the permitted federal and local laws and regulations. These records will not be available to the public.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

**WHAT ABOUT COSTS?**

You and/or your health plan will need to pay for all tests and procedures that are part of this study because they are needed for your regular medical care. The study drug, lenalidomide, will be provided to you at no cost, and the blood samples collected on day 6 of cycle 1 will also be completed at no cost to you for the selected participants in the phase II arm of study. However, you or your health care plan will need to pay for the dexamethasone. You or your health plan will have to pay for other drugs or treatments which are given to help you control side effects. Before you take part in this study, you should call your health insurer to find out if the cost of these tests and/or procedures will be paid for by the plan. Some health insurers will not pay for these costs. You will have to pay for any costs not covered by your health insurer.

In the event of injury or illness resulting from this study, emergency medical treatment is available, but it will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

**WILL I BE PAID TO PARTICIPATE IN THIS STUDY?**

You will receive no payment for taking part in this study.

**BLOOD SAMPLES FOR FUTURE RESEARCH (PHASE II IN SELECTED PATIENTS)**

Your blood samples will be sent to a central laboratory. The central laboratory can use your blood samples solely for research purposes as described in the research study. Your blood samples may be destroyed upon termination or expiration of the research study. Your sample will be sent to the central laboratory in a coded format, which protects your identity.

These tests are only for research purposes. You will be told the results of tests that are part of your clinical care, but you will not be told the results of the research tests.

**WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?**

It is important that you tell your doctor, *[investigator's name(s)];* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

**WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study, or choosing not to take part, will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study, including new information about the safety of the study medications or treatment for your disease.

**WHAT IF I HAVE QUESTIONS OR PROBLEMS?**

For questions about the study or a research-related injury, contact your cancer doctor, at

*Name(s)* *Telephone Number(s)*

For questions about your rights as a research participant, contact the [NAME OF CENTER] Institutional Review Board, which is a group of people who review the research to protect your rights) at _____.

*If available, also list a patient representative or other individual who is not on the research team or IRB.*

**WHERE CAN I GET MORE INFORMATION?**

You will get a copy of this form. You may talk to your study doctor at any time regarding your participation in the study or your treatment. More information on cancer clinical trials can be found through resources of the National Cancer Institute (1-800-4-CANCER) or http://www.cancer.gov/clinicaltrials and the National Clinical Trials Registry at clinicaltrials.gov.

**CONSENT STATEMENT**

I have read and understand the information describing this medical research study in this consent form. The study doctor or study staff have explained this information and answered all of my questions to my satisfaction. I voluntarily consent to take part in this study. I authorize the release of my medical records related to this study, including my signed consent form, to the Sponsor and their representatives, the Food and Drug Administration (FDA), and the IRB. By signing this form I have not given up any of my legal rights as a research participant. I understand that, on the day I sign this consent form, I will receive a signed copy of this consent form for my records.

_____

Printed Name of Participant

_____ _____

Signature of Participant or Legal Representative Date

_____

Printed Name of Person Explaining Consent

_____ _____

Signature of Person Explaining Consent Date

**PRINCIPAL INVESTIGATOR'S STATEMENT**

I attest that my representative or I discussed this study with the above named participant or legal representative. This person had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to participate in this study.

_____ _____

Signature of Principal Investigator Date

## Appendix II Multiple Myeloma Diagnostic Criteria

Standard criteria for a diagnosis of multiple myeloma are as follows (Kyle et al *British Journal of Haematology. 121(5):749-57, 2003)*

**Multiple Myeloma**
Monoclonal protein present in serum ≥3 g/dl
and/or
Bone marrow clonal plasma cells ≥10%

**Myeloma-related organ or tissue impairment (ROTI)**
Calcium 1 mg/dL (0.25 mmol/L) above the upper limit of normal
Creatinine >2 mg/dL (173 mmol/L)
Anemia: hemoglobin 2 g/dL below the lower limit of normal
or hemoglobin <10 d/gL
Lytic bone lesions or osteoporosis

**Asymptomatic myeloma**
Multiple myeloma and absence of ROTI

**Symptomatic myeloma**
Multiple myeloma and presence of any ROTI that can be attributed to myeloma.

## Appendix III ECOG Performance Status Scale

| SCORE | DESCRIPTION |
|---|---|
| **0** | Fully active, able to carry on all pre-disease performance without restriction. |
| **1** | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, 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. |

(Source: Eastern Cooperative Oncology Group, Robert Comis, M.D., Group Chair)

## Appendix IV Cockcroft-Gault Estimation of Creatinine Clearance (CrCl)

(Cockcroft, 1976; Luke 1990)

**Males:**

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})}$$

**Females:**

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85$$

If the patient is >65 y/o and creatinine is <1, use 1 as serum creatinine value to calculate the creatinine clearance.

## Appendix V Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

### Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Criteria for Females of Childbearing Potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (e.g., has had menses at any time in the preceding 24 consecutive months).

Counseling

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (e.g., all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting lenalidomide, throughout the entire duration of lenalidomide treatment, including dose interruptions, and for 28 days after the end of lenalidomide treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as lenalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol.
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that:

- Females of childbearing potential comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding, and acknowledge the aforementioned requirements
- Females NOT of childbearing potential acknowledge that she understands the hazards and necessary precautions associated with the use of lenalidomide
- Male patients taking lenalidomide acknowledge that he understands that traces of lenalidomide have been found in semen, that he understands the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential, and that he understands the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

**Before starting lenalidomide**

*Female Patients:*

FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10-14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The patient may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

*Male Patients*:

Must agree to practice complete abstinence or agree to use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

**During study participation and for 28 days following lenalidomide discontinuation**

*Female Patients:*

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 28 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 14 and Day 28 following lenalidomide discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control at each visit during the time that birth control is required.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days throughout the entire duration of lenalidomide treatment, including dose interruptions.
- If pregnancy or a positive pregnancy test does occur in a study patient, lenalidomide must be immediately discontinued.

- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be temporarily discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after lenalidomide discontinuation.

*Male Patients:*

- Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.
- Counseling about the requirement for condom use during sexual contact with females of childbearing potential and the potential risks of fetal exposure must be conducted at a minimum of every 28 days throughout the entire duration of lenalidomide treatment, including dose interruptions.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

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

## Appendix VI Education and Counseling Guidance Document

Protocol Number: PrE1003_____

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

Female: □

If female, check one:

FCBP (Female of Childbearing Potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (**amenorrhea following cancer therapy does not rule out childbearing potential**) for at least 24 consecutive months (e.g., has had menses at any time during the preceding 24 consecutive months)

□ NOT FCBP

Male: □

**To be completed prior to each dispensing of lenalidomide.**

**Do Not Dispense lenalidomide if:**

- **The patient is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual intercourse) [at least 28 days prior, during dose interruption, and 28 days after discontinuation of lenalidomide].**

**FCBP:**

1. I verified that the required pregnancy tests performed are negative.

2. I counseled FCBP regarding the following:

   - Potential fetal harm: If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. The teratogenic potential of lenalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking lenalidomide.

   - Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual intercourse [at least 28 days prior, during dose interruption and 28 days after discontinuation of lenalidomide].

   - Continuation of TWO reliable methods of birth control or complete abstinence if therapy is interrupted.

   - **That even if she has amenorrhea she must comply with advice on contraception**

- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - Highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy
  - Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap
- Pregnancy tests before and during treatment, even if the patient agrees not to have reproductive heterosexual intercourse. Two pregnancy tests will be performed prior to receiving study drug, one within 10-14 days and the second within 24 hours of the start of lenalidomide.
- Frequency of pregnancy tests to be done:
  - Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
  - If the patient missed a period or has unusual menstrual bleeding.
  - When the patient is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.
- Stop taking lenalidomide immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share lenalidomide with anyone else.
- Do not donate blood while taking lenalidomide and for 28 days after stopping lenalidomide.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open lenalidomide capsules.
- **Return unused lenalidomide to the investigator.**

3. Provide Lenalidomide Information Sheet to the patient.

**FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):**

1. I counseled the female NOT of child bearing potential regarding the following:
   - Potential fetal harm (Refer to item #2 in FCBP)
   - NEVER share lenalidomide with anyone else.
   - Do not donate blood while taking lenalidomide and for 28 days after stopping lenalidomide.
   - Do not break, chew, or open lenalidomide capsules
   - **Return used lenalidomide capsules to the Investigator.**
2. Provide Lenalidomide Information Sheet to the patient.

**MALE:**

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

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

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

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

August 2009 (Global PPP version date)

## Appendix VII Lenalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

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

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

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

   **If you are a female who is able to become pregnant:**

   - **Do not take lenalidomide if you are pregnant or plan to become pregnant**
     - for 28 days before starting lenalidomide
     - while taking lenalidomide
     - during dose interruptions of lenalidomide
     - for 28 days after stopping lenalidomide
   - **Stop taking lenalidomide if you become pregnant during lenalidomide treatment**
   - **Do not breastfeed while taking lenalidomide**
   - **You must have pregnancy testing done at the following times:**
     - within 10 – 14 days and again 24 hours prior to the first dose of lenalidomide
     - weekly for the first 28 days
     - every 28 days after the first month or every 14 days if you have irregular menstrual periods
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of lenalidomide (14 and 28 days after the last dose if menstrual periods are irregular)

- **You must practice complete abstinence or use two reliable, separate forms of effective birth control at the same time:**
  - for 28 days before starting lenalidomide
  - while taking lenalidomide
  - during dose interruptions of lenalidomide
  - and for 28 days after stopping lenalidomide
- The study doctor will be able to advise you where to get additional advice on contraception.
- If you suspect you are pregnant at any time during the study, you must stop lenalidomide immediately and immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation.

**If you are a female not of childbearing potential:**

**In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant.**

**If you are a male:**

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

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

**2. Lenalidomide restrictions in sharing lenalidomide and donating blood:**

- **Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
- **Do not give blood** while you take lenalidomide and for 28 days after stopping lenalidomide.

- **Do not break, chew, or open lenalidomide capsules.**
- You will get no more than a 28-day supply of lenalidomide at one time.
- **Return unused lenalidomide capsules to your study doctor.**

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

Name _____
PrECOG Patient ID Number: _____
Cycle No. _____

**Appendix VIII Lenalidomide Days 1 to 21 MEDICATION DIARY**

Please complete this diary on a daily basis. Write in the amount of the dose of lenalidomide, dexamethasone and aspirin that you took in the appropriate "Day" box.

On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time. Do **not** make up any missed doses of lenalidomide or dexamethasone.

If you are on dialysis, on the days you undergo dialysis take lenalidomide and/or dexamethasone after your dialysis treatment.

*Warfarin or low molecular weight heparin can be substituted in place of Aspirin at MD discretion. Discuss with your doctor.

Week of: _____

| Study Drug | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|---|---|---|---|---|---|---|---|
| Lenalidomide | | | | | | | |
| Dexamethasone | | | | | | | |
| Aspirin* | | | | | | | |

Week of: _____

| Study Drug | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 |
|---|---|---|---|---|---|---|---|
| Lenalidomide | | | | | | | |
| Dexamethasone | | | | | | | |
| Aspirin* | | | | | | | |

Week of: _____

| Study Drug | Day 15 | Day 16 | Day 17 | Day 18 | Day 19 | Day 20 | Day 21 |
|---|---|---|---|---|---|---|---|
| Lenalidomide | | | | | | | |
| Dexamethasone | | | | | | | |
| Aspirin* | | | | | | | |

Week of: _____

| Study Drug | Day 22 | Day 23 | Day 24 | Day 25 | Day 26 | Day 27 | Day 28 |
|---|---|---|---|---|---|---|---|
| Lenalidomide | | | | | | | |
| Dexamethasone | | | | | | | |
| Aspirin* | | | | | | | |

**My next scheduled visit is:** _____
If you have any questions, please call: _____
**Patient Signature: _____ Date: _____**

Name _____
PrECOG Patient ID Number: _____
Cycle No. _____

**Appendix IX Lenalidomide Every Other Day MEDICATION DIARY**

Please complete this diary on a daily basis. Write in the amount of the dose of lenalidomide, dexamethasone and aspirin that you took in the appropriate "Day" box.

On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time. Do **not** make up any missed doses of lenalidomide or dexamethasone.

If you are on dialysis, on the days you undergo dialysis take lenalidomide and/or dexamethasone after your dialysis treatment.

*Warfarin or low molecular weight heparin can be substituted in place of Aspirin at MD discretion. Discuss with your doctor.

Week of: _____

| Study Drug | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|---|---|---|---|---|---|---|---|
| Lenalidomide | | | | | | | |
| Dexamethasone | | | | | | | |
| Aspirin* | | | | | | | |

Week of: _____

| Study Drug | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 |
|---|---|---|---|---|---|---|---|
| Lenalidomide | | | | | | | |
| Dexamethasone | | | | | | | |
| Aspirin* | | | | | | | |

Week of: _____

| Study Drug | Day 15 | Day 16 | Day 17 | Day 18 | Day 19 | Day 20 | Day 21 |
|---|---|---|---|---|---|---|---|
| Lenalidomide | | | | | | | |
| Dexamethasone | | | | | | | |
| Aspirin* | | | | | | | |

Week of: _____

| Study Drug | Day 22 | Day 23 | Day 24 | Day 25 | Day 26 | Day 27 | Day 28 |
|---|---|---|---|---|---|---|---|
| Lenalidomide | | | | | | | |
| Dexamethasone | | | | | | | |
| Aspirin* | | | | | | | |

**My next scheduled visit is:** _____
If you have any questions, please call: _____
**Patient Signature: _____ Date: _____**

Name _____
PrECOG Patient ID Number: _____
Cycle No. _____

**Appendix X Lenalidomide Two Times Weekly MEDICATION DIARY**

Please complete this diary on a daily basis. Write in the amount of the dose of lenalidomide, dexamethasone and aspirin that you took in the appropriate "Day" box.

On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time. Do **not** make up any missed doses of lenalidomide or dexamethasone.

If you are on dialysis, on the days you undergo dialysis take lenalidomide and/or dexamethasone after your dialysis treatment.

*Warfarin or low molecular weight heparin can be substituted in place of Aspirin at MD discretion. Discuss with your doctor.

Week of: _____

| Study Drug | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|---|---|---|---|---|---|---|---|
| Lenalidomide | | | | | | | |
| Dexamethasone | | | | | | | |
| Aspirin* | | | | | | | |

Week of: _____

| Study Drug | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 |
|---|---|---|---|---|---|---|---|
| Lenalidomide | | | | | | | |
| Dexamethasone | | | | | | | |
| Aspirin* | | | | | | | |

Week of: _____

| Study Drug | Day 15 | Day 16 | Day 17 | Day 18 | Day 19 | Day 20 | Day 21 |
|---|---|---|---|---|---|---|---|
| Lenalidomide | | | | | | | |
| Dexamethasone | | | | | | | |
| Aspirin* | | | | | | | |

Week of: _____

| Study Drug | Day 22 | Day 23 | Day 24 | Day 25 | Day 26 | Day 27 | Day 28 |
|---|---|---|---|---|---|---|---|
| Lenalidomide | | | | | | | |
| Dexamethasone | | | | | | | |
| Aspirin* | | | | | | | |

**My next scheduled visit is:** _____
If you have any questions, please call: _____
**Patient Signature:** _____ **Date:** _____

## Appendix XI Eligibility Checklist

| | |
|---|---|
| | **Pt Initials: ___ ___ ___** **Study Personnel: _____**<br>**F M L** **Date of Evaluation: ___/___/____** |
| | **NOTE:** Phase I Only – Prior to discussing protocol entry with the patient **AND** prior to registering in eDC, call PrECOG to ensure that a place on the protocol is open to the patient. |
| | **INCLUSION CRITERIA** |
| | Age ≥18.<br>Birth Date: _____/_____/_____ ☐ Documentation in patient record |
| | Diagnosed with previously treated multiple myeloma (please see Appendix II for definition of myeloma).<br>Date of Diagnosis: _____/_____/_____ ☐ Documentation in patient record |
| | Patients must have measurable disease assessed by one of the following ≤21 days prior to registration:<br>☐ Serum monoclonal protein ≥1 g by protein electrophoresis<br>☐ >200 mg of monoclonal protein in the urine on 24 hour electrophoresis<br>☐ Serum immunoglobulin free light chain ≥10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio<br>☐ Monoclonal bone marrow plasmacytosis ≥30% (evaluable disease).<br>**NOTE:** If both serum and urine m-components are present, both must be followed in order to evaluate response.<br>☐ Documentation in patient record |
| | All previous cancer therapy including chemotherapy, radiation, hormonal therapy and surgery, must have been discontinued ≥2 weeks prior to registration.<br>Type of treatment: _____<br>☐ End date of treatment: _____/_____/_____<br>☐ Documentation in patient record |
| | ECOG Performance Status 0, 1 or 2 (see Appendix III).<br>PS ☐ 0 ☐ 1 ☐ 2 (must document in patient record) |
| | Acceptable organ and marrow function ≤21 days prior to registration as defined below:<br>Laboratory test date __ __/__ __/__ __ __ __.<br>• Absolute neutrophil count ≥1000 cells/mm³. Absolute neutrophil count = _____.<br>• Platelet count ≥75,000 cells/mm³. Platelet count = _____.<br>Laboratory test date __ __/__ __/__ __ __ __.<br>• Total bilirubin ≤2 mg/dL. Total bilirubin = _____.<br>• AST (SGOT) and ALT (SGPT) ≤3 x ULN.<br>AST (SGOT) = _____. AST (SGOT) ULN = _____.<br>ALT (SGPT) = _____. ALT (SGPT) ULN = _____.<br>Laboratory test date __ __/__ __/__ __ __ __._<br>• Renal impairment at baseline as measured by serum creatinine clearance (CrCl) ≤60 mL/min ≤21 days prior to registration (see Appendix IV). CrCl = _____. |

| | |
|---|---|
| | **Pt Initials: ___ ___ ___** **Study Personnel: _____**<br>**F M L** **Date of Evaluation: ___/___/____** |
| | ☐ Females of childbearing potential (FCBP)* must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days and again within 24 hours prior to starting Cycle 1 of lenalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing.<br><br>☐ Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy.<br><br>All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix V: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, AND Appendix VI: Education and Counseling Guidance Document.<br><br>☐ Not a woman of childbearing potential or male.<br>☐ Woman of childbearing potential - Negative pregnancy test date __ __/__ __/__ __ __ __<br><br>* A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (e.g., has had menses at any time in the preceding 24 consecutive months). |
| | Able to take required prophylactic anticoagulation (see Section 9.4).<br>☐ Documentation in patient record |
| | Ability to understand and the willingness to sign a written informed consent document.<br>Consent Date: _____/_____/_____ ☐ Consent in patient record |
| | **Only applies to selected subjects registered at Mayo Clinic to the Phase II component.**<br>Patient willing to provide blood samples for research purposes (see Sections 4.0 and 14.0).<br>NA ☐ **OR** Phase II Mayo Subject ☐ Yes ☐ NA (required # of pts already met). |
| | If previously received lenalidomide, demonstration of clinical response of any duration or stable disease with progression-free interval of ≥ 6 months from the start of that therapy.<br>☐ N/A –or-<br>☐ Previously received lenalidomide with clinical response of: _____<br><br>☐ Start date of treatment: _____/_____/_____ ☐ End date of treatment: _____/_____/_____<br>☐ Documentation in patient record |

| | **EXCLUSION CRITERIA** |
|---|---|
| | Concurrent use of other anti-cancer agents or treatments.<br>**NOTE:** Growth factors and bisphosphonates are allowed as medically indicated. Steroids may be used with an equivalency of up to 20 mg Prednisone per day as long as dose has not been adjusted upwards in past 2 weeks prior to study registration.<br>☐ N/A ☐ Documentation in patient record |
| | Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring intravenous antibiotics, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.<br>☐ N/A ☐ Documentation in patient record |
| | Any of the following as this regimen may be harmful to a developing fetus or nursing child:<br>• Pregnant women<br>• Breast-feeding women<br>• Men or women of childbearing potential or their sexual partners who are unwilling to employ adequate contraception (condoms with spermicidal agent, diaphragm, birth control pills, injections, intrauterine device [IUD], surgical sterilization, subcutaneous implants, or abstinence, e.g..)<br>☐ N/A ☐ Documentation in patient record |
| | HIV-positive patients on combination antiretroviral therapy (because of the potential for pharmacokinetic interactions with lenalidomide).<br>**NOTE:** In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.<br>☐ N/A ☐ Documentation in patient record |
| | Known hypersensitivity to thalidomide or other immunomodulary drugs (IMiDs®).<br>☐ N/A ☐ Documentation in patient record |
| | History of Stevens-Johnson syndrome characterized by a desquamating rash while taking thalidomide or similar drugs.<br>☐ N/A ☐ Documentation in patient record |
| | Other active malignancy with the exception of non melanoma skin cancer or in situ cervical or breast cancer.<br>☐ N/A ☐ Documentation in patient record |
| | Concurrent radiation therapy, except for palliation of a single painful bone lesion or fracture.<br>☐ N/A ☐ Documentation in patient record |

## Appendix XII Investigator's Statement

1. I have carefully read this protocol entitled "**A Phase I/II Study of the Tolerability of Lenalidomide and Low Dose Dexamethasone in Previously Treated Multiple Myeloma Patients with Impaired Renal Function, Version 6.0 dated 3/28/2011" (Protocol number PrE1003)** and agree that it contains all the necessary information required to conduct the study. I agree to conduct the study as outlined in the protocol.

2. I agree to conduct this study according to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the principles of GCP as described in 21 CFR and any applicable local requirements.

3. I understand that this trial will not be initiated without approval of the appropriate Institutional Review Board, and that all administrative requirements of the governing body of the institution will be complied with fully.

4. Informed written consent will be obtained from all participating patients in accordance with institutional and FDA requirements as specified in Title 21, Code of Federal Regulations, Part 50.

5. I understand that my signature on the electronic Case Report Form indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.

6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from PrECOG, LLC unless this requirement is superseded by the Food and Drug Administration.

**Principal Investigator:**

**PI Name:** _____

**Site Name:** _____

**Signature of PI:** _____

**Date of Signature:** _______________
MMM DD YYYY