Mayo Clinic Cancer Center

Phase I/II Double Blind Randomized Trial of Lenalidomide/ Dexamethasone/ Anakinra vs. Lenalidomide/Dexamethasone/Placebo in Patients with Early Stage Multiple Myeloma and High Plasma Cell Growth Rate

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√Study contributor(s) not responsible for patient care

Drug Availability
Commercial Agents: Dexamethasone
Drug Company Supplied: Lenalidomide; Anakinra or placebo

Document History	Effective Date
Activation	15Apr2016
MCCC Addendum 1	June 2, 2016
MCCC Addendum 2	November 30, 2016
MCCC Addendum 3	July 20, 2017
MCCC Addendum4	August 8, 2018
MCCC Addendum 5	December 19, 2018

Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted] Quality Assurance Specialist Phone: [redacted] E-mail: [redacted]
Forms completion and submission	[redacted] Clinical Research Coordinator Phone: [redacted] Email: [redacted]
Protocol document, consent form, regulatory issues	See Protocol Catalog for current RPS assignment: [redacted]
Serious Adverse Events	[redacted] SAE Coordinator Phone: [redacted] E-mail: [redacted]

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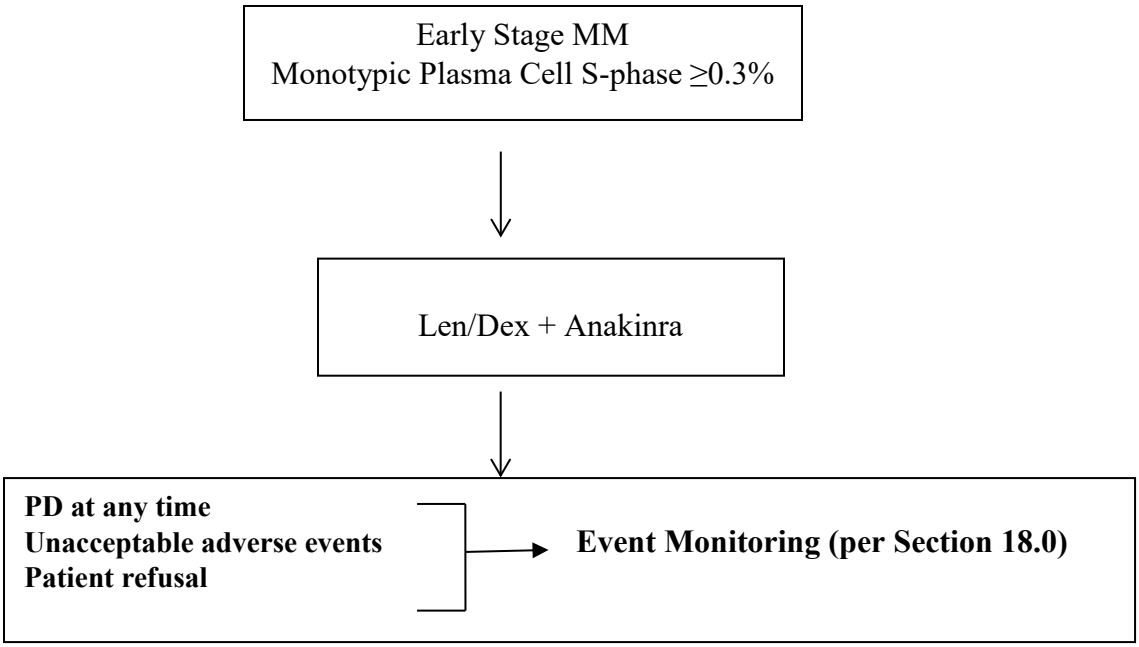
Schema: Phase I Dose Escalation

Prior to discussing protocol entry with the patient, call the MCCC Registration Office [redacted] for dose level and to insure that a place on the protocol is open to the patient.

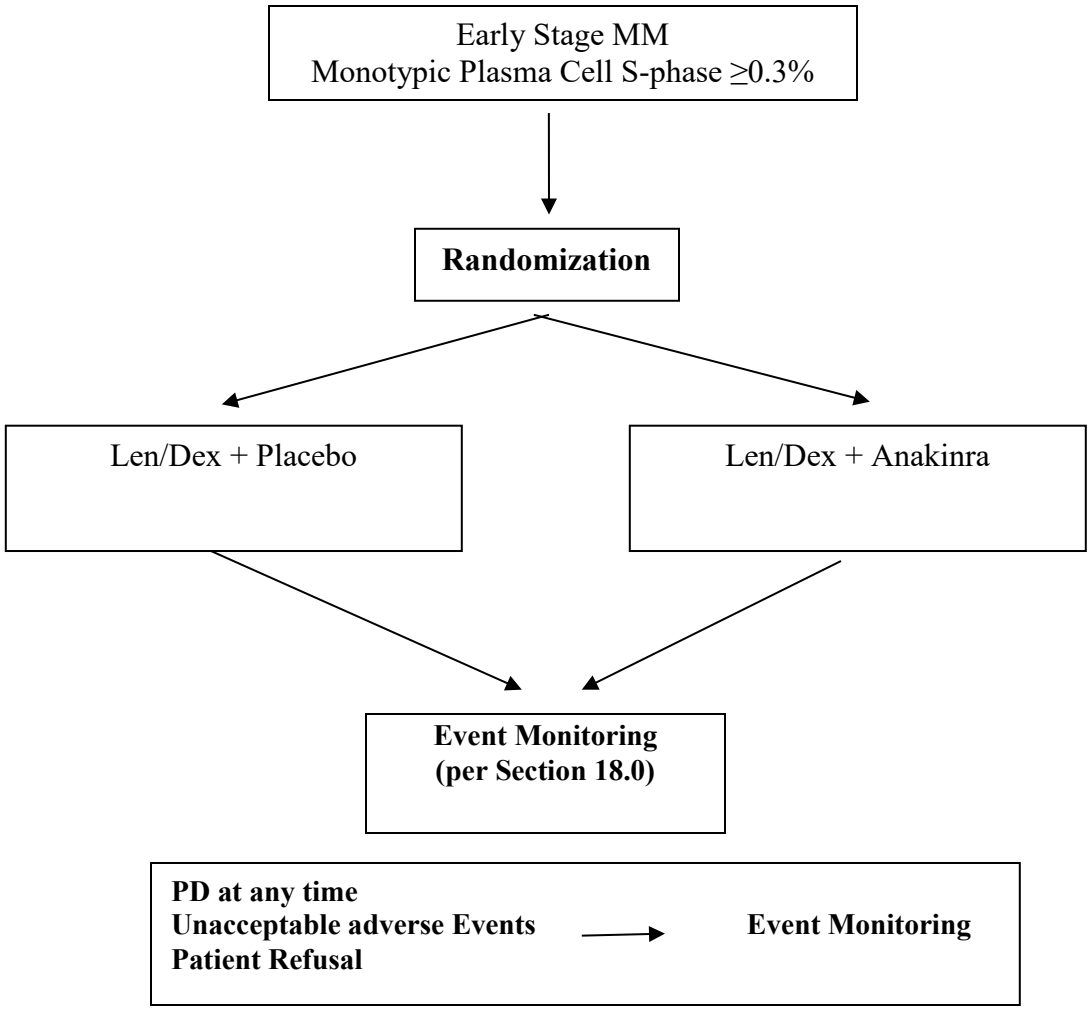


NOTE (Phase I Only): As of Addendum 5, Anakinra will no longer be provided and all patients will go off study treatment. Event monitoring will no longer be required. Patients may obtain Anakinra commercially and be treated off study.

If a patient is deemed ineligible or a cancel, please refer to Section 13.0 for follow-up information.
Cycle length=28 days

Generic name: Lenalidomide Brand name(s): Revlimid® Mayo Abbreviation: CC5013 Availability: via Revlimid REMS	Generic name: Anakinra Brand name(s): Kineret® Mayo Abbreviation: ANAKIN Availability: As of October 31, 2018: Commercially available (Previously provided by SOBI, AB)	Generic Name: Dexamethasone Brand Name: Decadron® Mayo Abbreviation: DXM Availability: Commercial

Schema: Phase II



If a patient is deemed ineligible or a cancel, please refer to Section 13.0 for follow-up information.
Cycle length=28 days

Generic name: Lenalidomide Brand name(s): Revlimid® Mayo Abbreviation: CC5013 Availability: via Revlimid REMS	Generic name: Anakinra Brand name(s): Kineret® Mayo Abbreviation: ANAKIN Availability: TBD	Generic Name: Dexamethasone Brand Name: Decadron® Mayo Abbreviation: DXM Availability: Commercial

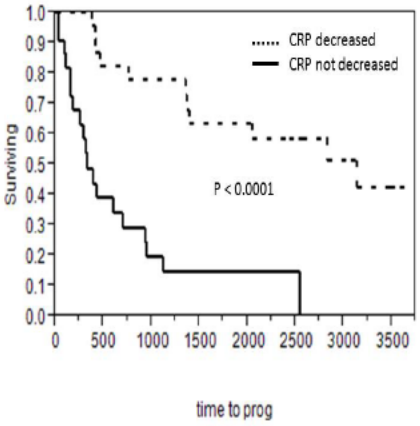
1.0 Background

1.1 Treatment options for multiple myeloma have expanded over the last decade with the introduction of thalidomide, lenalidomide, and bortezomib and has resulted in improved survival[1,2]. In a large group of 2981 patients with newly diagnosed myeloma, those diagnosed in the last decade had a 50% improvement in overall survival because of the effectiveness of these novel therapies compared with patients diagnosed earlier (44.8 vs. 29.9 months; $p<0.001$)[2].

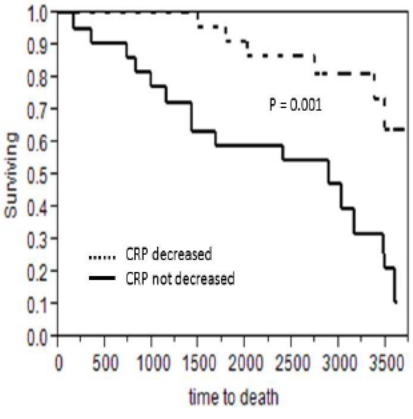
1.2 MM has clinically benign precursor conditions termed monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM; bone lesions absent), and indolent multiple myeloma (IMM; bone lesions present)[3,4]. Individuals with SMM and IMM are often referred to as asymptomatic MM patients. SMM patients with ≥20% bone marrow plasma cells have a median time to progression to active myeloma of 26 months and IMM patients have an even shorter time to progression of 8-10 months [5-9]. The current standard of care for patients with SMM and IMM has been observation; however patients and many physicians are uncomfortable with this approach due to the high likelihood of progression[3]. A recent study published in the New England Journal of Medicine showed fewer myeloma related events and better progression-free and overall survival among patients with high risk SMM who were treated with lenalidomide and dexamethasone compared to observation[10]. With the current use of effective biologic agents in myeloma treatment that have acceptable toxicity, it is appropriate to consider utilizing these therapies in the management of patients with SMM/IMM in an attempt to delay or prevent progression to active myeloma.

1.3 Controlling the myeloma proliferative component is critical in active myeloma. Greipp et al. have shown the importance of measuring the plasma cell labeling index (PCLI), a marker of plasma cell growth, as a prognostic factor in several myeloma studies[11-15]. It has been hypothesized that myeloma remains incurable because the stem cell/proliferative component

Progression Free Survival grouped by CRP Decrease



Overall Survival grouped by CRP Decrease



is not adequately eliminated by current therapies[16]. Interleukin-6 has been demonstrated to be a central growth factor for myeloma cells[17-20] and animal studies utilizing IL-6 knockout mice have shown that IL-6 is an essential requirement for the development of

myeloma[21]. Although many cytokines can stimulate IL-6 production, in myeloma interleukin-1β (IL-1β) appears to be one of the major cytokines responsible for the paracrine production of IL-6 by marrow stromal cells[22-25]. The aberrant IL-1β produced by the myeloma cells induces IL-6 production by bone marrow stromal cells which in turn supports the growth and survival of the myeloma cells[22]. The results of a recent clinical trial using IL-1 receptor antagonist (IL-1Ra) confirmed that IL-1Ra *in vivo* targeted the myeloma proliferative component. The median progression free survival (PFS) for the entire group of 47 patients was 37 months. The median PFS for patients without (n=22) and with (n=25) a decrease in their baseline hsCRP was 11 months and 103 months respectively ($p<0.0001$). The median overall survival (OS) for the 47 patients was 9.5 years. The median OS for patients without and with a decrease in their baseline hsCRP was 7.9 years and has not been reached, respectively ($p=0.001$). In SMM/IMM patients at high risk for progression to active myeloma, treatment with IL-1 inhibitors (IL-1Ra ± Dex) results in an increased PFS and OS in patients that demonstrate a ≥40% reduction in the baseline CRP compared to those who do not show this decrease. Toxicity included injection site reactions during the first month of therapy and asymptomatic neutropenia[26]. The importance of IL-1 lies in the fact that small amounts of IL-1β can induce large amounts of IL-6 in a paracrine fashion[22,27]. Since IL-6 is a central myeloma growth factor, it appears that the myeloma proliferative component can be inhibited with IL-1Ra in early stage disease.

1.4 Patient and physicians desire a way to delay progression in patients with early stage MM. Patients with ≥10% BMPCs and ≥3 g/dL M-protein have a median time to progression to active MM of 2 years and patients with a high growth rate have an even shorter time to progression[28]. Lenalidomide and dexamethasone (len/dex) are useful at targeting the non-proliferative myeloma compartment however patients with a high growth rate often relapse quickly on lenalidomide/dexamethasone. Since IL-1R inhibitors are effective at inhibiting the proliferative myeloma subset, early stage myeloma patients with an elevated growth rate (≥1%) may benefit from a combination of lenalidomide/dexamethasone and IL-1 receptor antagonist which is the focus of this trial.

1.5 There is a large body of literature describing the dosing of lenalidomide with dexamethasone and one publication describing the dosing of anakinra with dexamethasone[26] however the use of all three in a clinical trial has not been previously reported. Therefore, we will perform a Phase I Safety Run increasing doses of anakinra with lenalidomide and dexamethasone.

1.6 This study will be conducting in accordance with the Declaration of Helsinki and Good Clinical Practices Guidelines (GCP).

2.0 Goals

2.1 Primary Objective

2.11 Phase I: To determine the MTD/MAD of anakinra that can be combined with lenalidomide and dexamethasone.

2.12 Phase II: The primary goal of this trial is to compare the time to progression of the standard treatment arm (lenalidomide/dexamethasone) to the experimental arm (lenalidomide/dexamethasone + anakinra).

2.2 Secondary Objectives

2.21 To compare the response rate of the standard treatment arm (lenalidomide/dexamethasone) to the experimental arm (lenalidomide/dexamethasone + anakinra).

2.22 To compare the toxicity of the standard treatment arm (lenalidomide/dexamethasone) to the experimental arm (lenalidomide/dexamethasone + anakinra).

2.23 To compare the overall survival of the standard treatment arm (lenalidomide/dexamethasone) to the experimental arm (lenalidomide/dexamethasone + anakinra).

3.0 Patient Eligibility

Phase I only: Prior to discussing protocol entry with the patient, call the MCCC Registration Office [redacted])for dose level and to insure that a place on the protocol is open to the patient.

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 The following laboratory values obtained ≤7 days prior to registration.

- Absolute neutrophil count (ANC) ≥1700/mm^3
- Platelet count ≥100,000/mm^3
- Hemoglobin ≥8.0 g/dL
- SGOT (AST) ≤3 x upper limit of normal (ULN)
- Creatinine clearance ≥30 mL/min (as determined by Cockroft-Gault equation*)

*Cockcroft-Gault Equations:

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age})(\text{actual body weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$$

$$\text{Creatinine clearance for females} = \frac{(140 - \text{age})(\text{actual body weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$$

Example: A woman aged 75, weight 50 kg and creatinine of 1.35 mg/dL has a calculated clearance of 28.

3.13 Diagnosis of multiple myeloma according to International Myeloma Working Group criteria and one of the following:

- SMM
- IMM
- newly diagnosed MM

Note: Patients with lytic disease and anemia are eligible

3.14 High risk disease defined by all of the following:

- ≥10% bone marrow plasma cells
  AND
- Abnormal serum free light chain (FLC) ratio (<0.26 or >1.65) by serum FLC assay
  AND
- Monotypic Plasma Cell S-phase ≥0.3%

3.15 Measureable level of M-protein >1 g/dL on serum protein electrophoresis or >200 mg of M-protein on a 24 hour urine protein electrophoresis.

3.16 Negative tuberculosis (TB) testing (Quantiferon – TB blood test or skin test) ≤7 days prior to registration.

3.17 ECOG performance status (PS) 0, 1 or 2 (Appendix I).

3.18 Provide signed informed consent.

3.19a Negative (serum or urine) pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

NOTE: A second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

3.19b Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.19c Willing and able to comply with the requirements of the Revlimid REMS™ program.

3.19d Females of childbearing potential must be willing to adhere to the scheduled pregnancy testing as required by the Revlimid REMS™ program.

3.2 Exclusion Criteria

3.21 Prior treatment with any other agent that may affect M-protein ≤30 days prior to registration.

3.22 Acute/chronic infections, open wounds, or any active infection requiring intravenous antibiotic therapy ≤12 weeks prior to registration.

3.23 Other active malignancy (≤3 years) prior to registration.
Exceptions: Basal cell skin cancer or carcinoma-in-situ of the cervix or low-risk prostate cancer after curative therapy

3.24 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.25 NYHA Class 3 or 4 CHF symptoms

3.26 Other concurrent chemotherapy, radiotherapy, or any ancillary therapy considered investigational.

NOTE: Bisphosphonates are considered to be supportive care rather than therapy, and are thus allowed while on protocol treatment.

4.0 Test Schedule

Tests and Procedures	Active Monitoring				
	≤7 Days Prior to Registration	End of Cycles 1-3 then end of every third cycle and end of treatment[7]	Pre-treatment every cycle[5]	Mid-cycle eyery cycle[10]	End of Cycle 6 and Cycle 12, then yearly
Complete medical history	X				
Adverse Event monitoring	X	X[9]	X		
Physical exam, including weight and vital signs	X	X			
Height	X				
Performance status (ECOG scale)	X	X			
EKG	X				
Hematology group (WBC, ANC, Hgb, PLT)	X	X[10]	X[5]	X	
Chemistry group (glucose, alkaline phosphatase; total bilirubin; SGOT (AST); serum creatinine, creatinine clearance, calcium, LDH and TSH[6])	X	X			
$Beta_2$-microglobulin, high sensitivity C-reactive protein	X	X			
SPEP and UPEP (24 hours collection)	X	X			
Circulating plasma cells (PBLI/PCLI)	X	X			
Immunofixation serum and urine	X[2]	X[4]			
Immunoglobulin free light chain (MML)	X	X			
Involved Immunoglobulin (IgA, IgG, IgM)	X	X[3]			
X-ray skeletal survey (incl long bones) or low dose full body CT	X[2]				X
Bone marrow aspirate and biopsy, myeloma FISH, metaphase cytogenetics, Plasma cell proliferation assay and flow cytometry	X[2]	X[4]			X
Serum or urine pregnancy test	X[1]	X[1]	X[1,5]		
Tuberculosis testing (Quantiferon blood test or skin testing)	X				
Register patient into Revlimid REMS® program	X				
Prescribe lenalidomide via Revlimid REMS		X[5,8]	X		
Research per IRB 521-93, optional[R]	X[R]				X[R]

1) 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 for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur ≤7 days prior to registration and again within 24 hours prior to initiation of lenalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 4 weeks and then every 28 days while on 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 4 weeks and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix VI: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

2) ≤30 days prior to registration
3) Specific testing required only if used to assess disease response
4) Required to document complete response; if response, repeat (mail-in acceptable) to confirm response at ≥4weeks. Bone marrow biopsy does not need confirmation. (Bone marrow biopsy will occur one time as clinically indicated.)
5) Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle. After the first 3 months, the drug may be mailed out to the patient if clinical evaluation and blood tests can be obtained per test schedule and mailed/faxed to Mayo Clinic, and patient can return at least every 3 months for follow up to Mayo Clinic. In place of physical exam, RNs will phone patient for adverse event assessment. All unused study drug must be returned to Mayo Clinic and all study drug must be accounted for. CBC and pregnancy testing may be done at local clinic.
6) TSH to be repeated every three months, for patients on active treatment.
7) ±7 days
8) Lenalidomide must be prescribed through and in compliance with Celgene's Revlimid REMS program. Prescriptions must be filled within 7 days.
9) The patient should be contacted by a nurse 30 days (±2 days) after the last dose of study treatment (or at the time of initiation of subsequent treatment if started before 30 days) to check if the patient has experienced any late adverse events. Grade 3 or higher adverse events and all serious adverse events (SAEs) at least possibly related to study treatment and deaths due to any cause should be reported as a late adverse event on the event monitoring form if they were not already reported on the nadir/AE form for the last cycle and they occurred prior to any subsequent treatment.
10) CBC should be done weekly during Cycle 1. After Cycle 1, CBC should be done pre-treatment and mid-cycle every cycle. CBC should also be done at the end of treatment. CBC testing may be done at local clinic.

R Research funded (see Section 19.0). Will be charged to study and not to patient's account.

5.0 Grouping/Stratification Factors:

5.1 Grouping Factors

5.11 Phase: I vs. II

5.2 Stratification Factors (Phase II Only)

5.21 Diagnosis of Active Myeloma: Yes vs. No

5.22 Presence of Myeloma Bone Lesions: Yes vs. No

5.23 Disease Stage (ISS Staging System) > 1: Yes vs. No

6.0 Registration Procedures

6.1 Phase I Registration Procedures

Prior to discussing protocol entry with the patient, call the MCCC Registration Office [redacted] for dose level and to insure that a place on the protocol is open to the patient.

To register a patient, fax (507-284-0885) a completed eligibility checklist to the Mayo Clinic Cancer Center (MCCC) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.2 Phase II Registration Procedures

6.21 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/ randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at (507) 284-2753 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted] If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.22 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted]. If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.3 Phase I and II

6.31 Prior to accepting the registration, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form

- Existence of a signed authorization for use and disclosure of protected health information

6.32 Treatment on this protocol must commence at Mayo Clinic Rochester under supervision of a hematologist

6.33 Treatment cannot begin prior to registration.

6.34 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.35 All required baseline symptoms (see Section 10.6) must be documented and graded.

6.36 Study drug is available on site

6.4 Phase II Randomization Procedures

6.41 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.42 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups

- Len/Dex + Placebo
- Len/Dex +Anakinra

6.5 Procedures for Double-Blinding the Treatment Assignment

6.51 After the treatment assignment has been ascertained by the registration/randomization application, the patient's study medication code number will be displayed on the confirmation of registration screen

6.52 The data manager/nurse/pharmacist at the patient's institution must contact the MCCC Registration Office for a code number when additional study product is needed for the patient.

6.53 The number of the syringe will be recorded on the dosing form.

6.54 MCCC Registration Office personnel will monitor the supply of coded bottles at each participating institution

7.0 Protocol Treatment

7.1 Treatment Schedule - Cycle length = 28 days

7.11 Phase I - Dose Escalation

Agent	Dose	Route	Days
Lenalidomide	25 mg	PO	Days 1-21
Dexamethasone	20 mg (SMM and IMM); 40 mg (Active MM)	PO	Days 1, 8, 15, and 22
Anakinra	As assigned by MCCC Registration Office	SQ	Days 1-28
Aspirin	325 mg/day with food	PO	Days 1-28

7.12 Phase II Study at MTD/MAD

Agent	Dose	Route	Days
Lenalidomide	25 mg	PO	Days 1-21
Dexamethasone	20 mg (SMM and IMM); 40 mg (Active MM)	PO	Days 1, 8, 15, and 22
Anakinra or Placebo	Based on phase I results	SQ	Days 1-28
Aspirin	325 mg/day with food	PO	Days 1-28

7.2 Determination of Maximum Tolerated Dose (MTD)/Maximum Allowable Dose (MAD)

7.21 Dose Escalation

Dose Level	Dose of anakinra
1*	100 mg SQ every 3rd day
2	100 mg SQ every other day
3	100 mg SQ daily

*Starting dose

7.211 For this protocol, the patient must return to the consenting institution for evaluation at least every 28 days during treatment (Active Monitoring Phase).

7.212 Treatment by a local medical doctor (LMD) is not allowed.

7.213 Three patients will be treated at each dose level and observed for a minimum of 4 weeks (i.e. one full cycle), to assess toxicities, before new patients are treated. Doses will not be escalated in any individual patient.

7.214 Investigators are to contact the Study Chair as soon as any dose-limiting toxicity (DLT) occurs.

7.22 Definition of DLT – See Section 16.22 for additional information

For this protocol, DLT will be defined as an adverse event during Cycle 1 of treatment at least possibly related to the study medication and meeting the following criteria:

Toxicity*	***DLT Definition***
Blood and lymphatic system disorders	Grade 3 Febrile neutropenia: ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour
Investigations	Grade 4 neutropenia (ANC <500/mm$^{3)}$ for ≥7 days or Grade 4 thrombocytopenia (<25,000/mm$^{3)}$ for ≥7 days
Infection and infestations	Grade 4
Other Non-hematologic	Grade 4 as per NCI Common Terminology Criteria for Adverse Events v 4.0**
Dose Delay	Any toxicity that causes a dose delay of >2 weeks of the next intended dose.***
Dose Reduction	Any dose reduction within cycle 1.***

*Adverse event at least possibly related to the study medication.
**Grade 4 vomiting or diarrhea with maximal supportive treatment(s) will be considered dose limiting.
***Except dose reductions and delays due to rash associated with lenalidomide. These patients will be replaced with another study patient.

7.3 Lenalidomide supply

Patients will receive lenalidomide every 28 days. All unused study drug must be returned to Mayo Clinic to be recorded. Study drug is to be handed back to the patient to return as per Revlimid REMS. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.**

7.4 Stem cell collection

Treatment can be interrupted for the purpose of collecting stem cells. Patients can be restarted on protocol therapy after stem cell collection as long as criteria for initiation of a next cycle are met at the time of therapy initiation (Section 8.11).

7.5 Stable plateau

Patients that achieve a stable plateau after 2 years of therapy may be tapered to lower doses of lenalidomide and/or dexamethasone at the discretion of the treating physician

When the patient discontinues all study medication, the MCCC Registration Office must be called (507-284-2753) to find out which study therapy the patient was receiving. Appropriate procedures for gradually reducing the doses of lenalidomide and/or dexamethasone should then be followed.

7.6 Return to Mayo Clinic

For this protocol, the patient must return to the Mayo Clinic for evaluation for Cycles 1-3 and then at least every 3 cycles. After the first 3 cycles, clinical evaluation and blood tests

can be obtained per test schedule and mailed/faxed to Mayo Clinic and patient can return at least every 3 cycles for follow up to Mayo Clinic. Adverse events will be collected at the end of each cycle by telephone call.

Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle. All study participants must be registered into the mandatory REVLIMID REMS™ program, and be willing and able to comply with the requirements of REVLIMID REMS™.

After the first 3 cycles, lenalidomide and anakinra may be mailed out monthly to the patient if clinical evaluation and blood tests can be obtained per test schedule. Patient can return at least every 3 cycles for follow up to Mayo. Prescription for dexamethasone will be provided.

7.7 Breaking Codes in Double–Blinded Studies

Situations requiring codes to be broken: There are three distinct situations in which it is appropriate to break the codes for individual patients enrolled in double-blind trials:

(1) In the event of an emergency for an individual patient.

(2) In the event that it would be helpful for the future clinical care of an individual patient after she/he has completed participation in the trial.

(3) When it is necessary to know the specific treatment assignment of each patient in the trial in order to manage them all appropriately after they have completed participation in the trial. Example: There is a blinded arm that contains a steroid, narcotic, or other medication that must be carefully reduced in order to prevent physiological damage. [This one is rare--there are no currently active protocols of this type.]

In the event of an emergency, call the MCCC Registration Office at [redacted] to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. Central Time. If the code must be broken after hours, assume the patient was assigned to active treatment and treat accordingly. Place a call to the MCCC Registration Office and leave a message informing them of the need to un-blind a patient. Provide your contact information so that MCCC Registration Office personnel can return the call the next business day.

If, in the judgment of the attending physician, it would be helpful for the future clinical care of the individual patient, the code may be broken *after* the patient has completed the study. That is, after the patient has been fully evaluated and all evaluation information has been recorded by the attending physician and the patient (if appropriate), the MCCC Registration Office may be called [redacted] to find out which study therapy the patient was receiving.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Dose Levels (Based on Adverse Events in Tables 8.2)

Dose Level	**Lenalidomide**
Starting Dose	25 mg days 1-21 every 28 days
-1	15 mg days 1-21 every 28 days
-2	10 mg days 1-21 every 28 days
-3	5 mg days 1-21 every 28 days

Dose Level	**Anakinra**
Starting Dose	100 mg SQ daily
-1	100 mg SQ every other day
-2*	100 mg SQ every 3rd day

*If patients unable to tolerate -2 they will go off treatment to event monitoring

8.11 Instruction for initiation of a new cycle of therapy

A new course of treatment may begin on the scheduled day 1 of a new cycle if:

- The ANC is ≥1,500/µL;
- The platelet count is ≥75,000/µL;
- Any drug-related injection site reaction or peripheral sensory neuropathy that may have occurred has resolved to ≤Grade 1 severity;
- Any other drug-related adverse events that may have occurred have resolved to ≤Grade 2 severity;
- If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. If lenalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. **If lenalidomide dosing was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled Day 1**, then the new cycle will be started with a one-level dose reduction of lenalidomide.

8.2 Dose Modifications of Lenalidomide during a Cycle of Therapy

Dose reductions of one drug and not the other may be done at the investigators discretion based on attribution of adverse events except neutropenia in which lenalidomide should be decreased first before anakinra.

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified*** ← ←

CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION** Days 2-14 of cycle**	**ACTION** Day ≥15 of cycle**
Blood and lymphatic system disorders	Febrile neutropenia associated with fever (temperature ≥38.5ºC)	Lenalidomide	Omit lenalidomide dose. Follow CBC weekly. If neutropenia has resolved to ≤Grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained	Omit lenalidomide for remainder of cycle. See Section 8.11 for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained for the next cycle at the investigator's discretion.
Investigations	Platelet count decreased ≥ Grade 3 (platelet count <50,000/mm³)	Lenalidomide	Omit lenalidomide dose Follow CBC weekly Hold anticoagulation until platelets >50,000 If thrombocyte-penia resolves to ≤Grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21	Omit lenalidomide for remainder of cycle See Section 8.11, Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level

CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	AGENT	ACTION** Days 2-14 of cycle	ACTION** Day ≥15 of cycle
Skin and subcutaneous tissue disorders	Rash maculo papular Grade 2 or 3.	Lenalidomide	Omit lenalidomide dose Follow weekly If the event resolves to ≤Grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21	Omit lenalidomide for remainder of cycle See Section 8.11, Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level
	Any rash Grade 4	Lenalidomide	Discontinue lenalidomide	Discontinue lenalidomide
Nervous System Disorders	Peripheral sensory neuropathy Grade 3	Lenalidomide	Omit lenalidomide dose Follow at least weekly If the event resolves to ≤Grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21	Omit lenalidomide for the remainder of the cycle. See Section 8.11 Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level
	Peripheral sensory neuropathy Grade 4	Lenalidomide	Discontinue lenalidomide	Discontinue lenalidomide
Immune system disorders	Allergic reaction Grade 2-3	Lenalidomide	Omit dose Follow at least weekly If the toxicity resolves to ≤Grade 1 prior to Day 15 restart at next lower dose level and continue the cycle until Day 21	Omit lenalidomide for the remainder of the cycle If the adverse event resolves to ≤Grade 1, reduce dose 1 level in next cycle If adverse event recurs, discontinue therapy
	Grade 4	Lenalidomide	Discontinue lenalidomide	Discontinue lenalidomide
Vascular disorders	Thromboembolic event ≥Grade 3	Lenalidomide	Omit dose and start anticoagulation; restart at investigator's discretion (maintain dose level)	Omit lenalidomide for remainder of cycle and start anticoagulation. Maintain dose level in next cycle

CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	AGENT	ACTION** Days 2-14 of cycle	ACTION** Day ≥15 of cycle
Endocrine disorders	Hyperthyroidism or Hypothyroidism ≥Grade 2	Lenalidomide	-Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. -See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level	Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. See Section 8.11, Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level
Other non-hematologic adverse event	Other non-hematologic toxicity ≥Grade 3	Lenalidomide	-Omit lenalidomide dose. Follow at least weekly. If the toxicity resolves to ≤Grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21	Omit lenalidomide for remainder of cycle. See Section 8.11, Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.

8.3 Dose Modifications of Anakinra/Placebo during a Cycle of Therapy

Dose reductions of one drug and not the other may be done at the investigators discretion based on attribution of adverse events except neutropenia in which lenalidomide should be decreased first before anakinra.

CTCAE System/organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION ** (each cycle)
Blood and lymphatic system disorders	Febrile Neutropenia ≥Grade 3	Anakinra/ Placebo	For ANC <1000, omit anakinra/placebo until ANC ≥1500. Then restart anakinra or placebo with the dose reduced one dose level.
Infections and Infestations	Infection/Febrile Neutropenia ≥Grade 2		Omit until infection resolved; then restart at same dose
	Infection/Febrile Neutropenia ≥Grade 3		Omit until infection resolved; then restart anakinra or placebo with the dose reduced one dose level
Other non-hematologic adverse event	Any adverse event ≥Grade 3		Omit until toxicity reduces to ≤grade 2; then restart anakinra or placebo with the dose reduced one dose level

8.4 Dose Modifications of Dexamethasone during a Cycle of Therapy

CTCAE System/organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION ** (each cycle)
Gastrointestinal Disorders	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL)	Dexamethasone	Treat with H2 blockers, sucralfate, or omeprazole If symptoms persist despite above measures, decrease dexamethasone dose by 50%
	Dyspepsia, gastric or duodenal ulcer, gastritis ≥Grade 3 (Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self-care ADL; disabling)		Omit dexamethasone until symptoms adequately controlled Restart one dose level below along with concurrent therapy with H2 blockers, sucralfate, or omeprazole If symptoms persist despite above measures, decrease dex by 50%
	Pancreatitis ≥Grade 3 (severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support))		Discontinue dex, and begin event monitoring
General Disorders	Edema ≥Grade 3 (limiting function and unresponsive to therapy or anasarca)		Decrease dex by 50%; use diuretics prn
Psychiatric Disorders	Confusion or Mood alteration ≥Grade 2 (Severe disorientation; limiting self-care ADL)		Omit until symptoms resolve; Decrease dex by 50%
Musculoskeletal and connective tissue disorders	Muscle weakness ≥Grade 2 Weakness limiting self-care ADL; disabling		Decrease dex by 50%; if symptoms persist then decrease 50% prn
Eye Disorders	Blurred vision ≥Grade 3		Decrease dex by 50%; if symptoms persist then decrease 50% prn
Metabolism and nutrition disorders	Hyperglycemia Grade 3 or higher, (>250 - 500 mg/dL; >13.9 - 27.8 mmol/L); hospitalization indicated		Treat with oral hypoglycemic agent or insulin prn; decrease by 50% prn

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- Discontinue = The specified drug(s) are totally stopped.

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle. If that cycle is

completed with no further adverse events >Grade 2, then the dose may be increased, at the investigator's discretion, one level at a time, in the following cycles.

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the two dose-reduction steps (levels –1 and –2) will be at the discretion of the treating physician, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data.

NOTE: Patients in whom one or more of the study treatment agents have been discontinued will remain on study unless all study treatment agents are discontinued. Patients in whom all study treatment agents were discontinued will proceed to event monitoring (see Section 18.0).

9.0 Ancillary Treatment/Supportive Care

9.1 Patients may receive concurrent treatment with a bisphosphonate.

9.2 Patients may continue on low level/stable steroid doses for replacement or inhalation therapy.

9.3 The following medications are not permitted during the trial:

- Any other investigational treatment
- Any cytotoxic chemotherapy
- Any other systemic anti-neoplastic therapy including, but not limited to, immunotherapy, hormonal therapy or monoclonal antibody therapy.
- Any external beam radiotherapy

9.4 Antiemetics may be used at the discretion of the attending physician.

9.5 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. ASCO 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guidelines Journal of Clinical Oncology 2006; 24:3187-3205.

9.6 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.7 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.8 Use of colony stimulating factors is allowed as detailed in the dose modification table for lenalidomide

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

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 version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Important: Expedited adverse event reporting requires submission of a MedWatch 3500A report(s). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.52 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI.

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected

- The determination of whether an AE is expected is based on the agent-specific information provided in Section 15.0 of this protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of this protocol.

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

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

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.4 Expedited Reporting Requirements for Studies using Commercial Agent(s) ONLY:

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Imaging Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

NOTE Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.41 of the protocol.

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via MedWatch within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions:

1. An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
2. Submit form 3500A to the FDA, MedWatch, [redacted]

   Mayo Clinic Cancer Center (MCCC) Institutions: Use MCCC SAE Reporting Form [redacted]

   Provide copies of MedWatch and SOBI SAE forms to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist [redacted]) who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator.

10.41 Special Situations for Expedited Reporting and Submission of Notification Forms

Exceptions to Expedited Reporting and Submission of Notification Forms: EXPECTED Serious Adverse Events

An expedited report or notification form may not be required for specific Serious Adverse Events where the AE is **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supersede the standard Expedited Adverse Event Reporting Requirements (Note: These adverse events must still be reported through the routine reporting mechanism [i.e. Nadir/Adverse Events form]; see Footnote 1):

System Organ Class (SOC)	Adverse event/Symptoms	CTCAE Grade at which the event will not be expeditedly reported[1]
Blood and lymphatic system disorders	Anemia	3 or 4
Investigations	Platelet count decreased	3 or 4
	Neutrophil count decreased	3 or 4
	Lymphocyte count decreased	3 or 4
	White blood cell decreased	3 or 4

[1] This exception only applies if the adverse event does not result in hospitalization ≥24 hours. If this adverse event results in hospitalization ≥24 hours, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

10.42 Expedited Reporting by Investigator to Celgene

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to lenalidomide based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day Fax: [redacted] The initial report must be as complete as possible, including 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 report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-CL-MM-PI-004334) and the institutional protocol number (MC138B) should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

10.43 Expedited Reporting by Investigator to SOBI AB

The research staff must inform Swedish Orphan Biovitrum (SOBI) in writing using a SOBI SAE or a MEDWATCH 3500A form of any SAE. The written report must be completed and supplied to SOBI by e-mail or facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. 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 report. A final report to document resolution of the SAE is required. A copy of the email transmission of the SAE report to SOBI [redacted] should be attached to the SAE and retained with the patient records.

SOBI Safety Reporting contact information:
Drug Safety Swedish Orphan Biovitrum
[redacted]

The reporting of serious adverse events to SOBi does not relieve the sponsor from other regulatory reporting responsibilities.

SOBi Safety Reporting contact information:
Fax: [redacted]

10.5 Other Required Reporting

10.51 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.52 Death

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death:

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur following treatment with an agent under an IND/IDE must be reported. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.55 Pregnancy

Females of reproductive potential must adhere to scheduled pregnancy testing as required in the Revlimid REMS™ program.

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or email using the Pregnancy Initial Report Form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE report form, or approved equivalent form.

Pregnancy reporting is also required for SOBi according to the same guidelines.

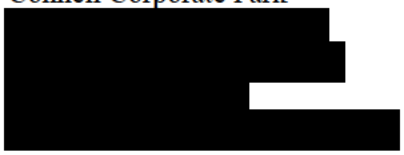
10.551 Neonatal deaths

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

10.552 Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

10.553 Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park


10.554 SOBi Drug Safety Contact Information:

SOBi Safety Reporting contact information:

[redacted]

10.56 Overdose

Overdose, as defined for this protocol, refers to lenalidomide and anakinra dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of lenalidomide or anakinra assigned to a given patient, regardless of any associated adverse events or sequelae.

Method of administration	Amount that constitutes overdose
PO	any amount over the protocol-specified dose
IV	10% over the protocol-specified dose
SC	10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

10.561 Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park

[redacted]

10.562 SOBi Drug Safety Contact Information:

SOBi Safety Reporting contact information:

[redacted]

10.6 Required Routine Reporting

Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

SYSTEM ORGAN CLASS	Adverse event/Symptoms	Baseline	Each evaluation
Investigations	Creatinine increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
	Lymphocyte count decreased	X	X
	White blood cell decreased	X	X
	Anemia	X	X
General disorders and administration site conditions	Fatigue	X	X
	Injection site reaction		X
Gastrointestinal Disorders	Nausea	X	X
	Vomiting	X	X
	Diarrhea		X
	Constipation		X
	Number of stools	X	
Renal and urinary disorders	Chronic kidney disease (decreased creatinine clearance)	X	X
Skin and subcutaneous tissue disorders	Rash, maculopapular	X	X
Nervous system disorders	Peripheral sensory neuropathy	X	X
Constitutional Symptoms	Insomnia	X	X
Vascular Disorders	Thromboembolic event	X	X

10.61 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6 (above):

10.611 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.612 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.613 Grade 5 AEs (Deaths)

10.6131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6132 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.

10.62 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.7 All serious adverse events (SAEs) will be followed until resolution or death.

11.0 Treatment Evaluation

The International Myeloma Working Group (IMWG) uniform response criteria (Rajkumar et al, 2011) will be used to assess response to therapy

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-protein is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin 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 M-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-protein values and quantitative nephelometric immunoglobulin values cannot be used interchangeably.

  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 recommended.

  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), Minimal Response (MR), stable disease (SD), and progressive disease (PD).

  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 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, uMR, uPD.

- **Measurable disease:** Patients who have a measurable serum or urine M-protein.
  - serum M-protein >1 g/dL OR urine M-protein >200 mg/24 hr

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.

Table 11.2

Tests Required To Assess Response (Must Be Done At Each Disease Measurement Visit except as indicated[1,2])

On Study Baseline Value	SPEP[3]	24 hr UPEP[2]	Ig FLC	BM Bx
Serum M-protein ≥3 g/dl, and urine M-protein ≥500 mg/24 hrs	X	X		
Serum M-protein ≥3 g/dl, but urine M-protein <500 mg/24 hrs	X			
Serum M-protein <3 g/dl, and urine M-protein ≥500 mg/24 hrs		X		

[1] **SPEP, UPEP, Immunofixation studies of both serum and urine, and Bone marrow biopsy** are required to document CR regardless of registration values, and in addition **FLC** measurement and **bone marrow immunophenotyping** is required to document sCR. SPEP and UPEP are required to document VGPR regardless of registration values.

[2] For serum measurable patients, 24 hour urine does not need to be confirmed (i.e. repeated after documented response) for any response category

[3] If serum M-protein is being followed by quantitative immunoglobulin levels derived from nephelometry or turbidometry, quantitative immunoglobulins are required. SPEP is only required to document CR or VGPR.

11.3 Confirmed response

In order to be classified as a hematologic response, confirmation of serum M- protein, serum immunoglobulin free light chain (when primary determinant of response) and urine M- 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 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 in any case.
- 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

11.4 Bone progression

Caution must be exercised to avoid rating progression 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 Study Chair before removing the patient from the study.

11.5 Response and Progression

Criteria for response and progression are listed in Table 11.5. Progressive disease for all patients as defined in Table 11.5.

Table 11.5

CATEGORY	RESPONSE CATEGORY [a]
Stringent Complete Response (sCR) [b]	• CR as defined *plus* • Normal FLC ratio *and* • Absence of clonal PCs by immunohistochemistry or 2- to 4- color flow cytometry [h]
Complete Response (CR) [b]	• Negative immunofixation of serum and urine [c] *and* • Disappearance of any soft tissue plasmacytoma *and* <5% PCs in Bone Marrow
Very Good Partial Response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis [c] *or* • ≥90% reduction in serum M-protein and urine M-protein <100 mg/24 h [c]
Partial Response (PR)	• If present at baseline, ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24hrs [c] • If present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas
Minor Response (MR)	• If present at baseline, ≥25% but ≤ 49% reduction of serum M protein *and* reduction in 24-hour urine M-protein by 50-89% which still exceeds 200mg/24 hours [c] *and* • If present at baseline, 25-49% reduction in the size of soft tissue plasmacytoma *and* • No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response)
Progressive Disease (PD) [b, g]	Increase of 25% from lowest value in any of the following [e, f]: • Serum M-protein (absolute increase must be ≥ 0.5 g/dL) *and/or* • Urine M-protein (absolute increase must be ≥ 200 mg/24 hrs) *and/or* Or any one or more of the following: • Development of new bone lesion or soft tissue plasmacytoma or definite increase in the size of existing bone lesions or soft tissue plasmacytoma • Development of hypercalcemia (corrected serum calcium > 11.5mg/dL) that can be attributed solely to the PC proliferative disorder
Stable Disease (SD)	Not meeting criteria for sCR, CR, VGPR, PR, MR or PD

[a] All response categories require two consecutive assessments (sCR, CR, VGPR, PR, MR, PD) made at any time before the institution of any new therapy; sCR, CR, VGPR, PR, MR 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] CR patient will need to progress at the same level as VGPR and PR patients to be considered a PD. A positive immunofixation alone is not sufficient.

[c] If more than one M protein spike meets the criteria for measurable disease at baseline, then both need to be followed for response. Otherwise, only follow the measurable M protein spike for response.

[d] In patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26-1.65 in addition to the CR criteria listed above.
[e] A "25% increase" refers to M protein, FLC and bone marrow results and does not refer to bone lesions, soft tissue plasmacytoma or hypercalcemia. The lowest value does not need to be a confirmed value. If the lowest serum M-protein is ≥ 5 g/dL, an increase in serum M-protein of ≥ 1 g/dL is sufficient to define disease progression.
[f] In the case where a value is felt to be a spurious result per physician discretion (for example, a possible lab error), that value will not be considered when determining the lowest value.
[g] Progressive disease should be confirmed. However, treatment may be discontinued for progressive disease that is unconfirmed per physician discretion. In this case, an objective status of PD should be entered on the measurement form and progressive disease should be reported on the event monitoring form.
[h] Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of 4:1 or 1:2.

12.0 Descriptive Factors

12.1 Prior treatment: Yes vs. no.

12.2 Durie Salmon Stage of myeloma at diagnosis: I vs. II vs. IIIa vs. IIIb

12.3 ISS Stage of myeloma at diagnosis: I vs. II vs. III

12.4 Parameters followed for hematologic response (pick one): serum M- protein >1 g/dL and urine M-protein >200 mg/24 hours vs. serum M-protein >1 g/dL only vs. urine M-protein >200 mg/24 hours only.
NOTE: Distinguish between SPEP measurements versus quantitative IgA measurements for serum M-protein

12.5 Diagnosis: Smoldering multiple myeloma (SMM) vs. indolent multiple myeloma (IMM) vs. newly diagnosed multiple myeloma

12.6 Dose Level: 1 vs. 2 vs. 3

13.0 Treatment/Follow–up Decision at Evaluation of Patient

NOTE (Phase I Only): As of Addendum 5, Anakinra will no longer be provided and all patients will go off study treatment. Event monitoring will no longer be required. Patients may obtain Anakinra commercially and be treated off study

13.1 Responding to treatment
Patients who are sCR, CR, VGPR, PR, or SD (or usCR, uCR, uVGPR, uPR) will continue treatment per protocol.

13.2 Treatment continuation
In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

13.21 Progression requiring treatment for active myeloma

13.22 Unacceptable toxicity and ineligibility for retreatment.

13.23 Patient refusal of continued treatment.

All attempts should be made to complete the End of Study procedures if a patient withdraws from the trial early. The patient will then go to event monitoring per Section 18.0.

13.3 Ineligible patients

A patient is deemed ineligible if at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. 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 event-monitoring phase of the study.

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per section 18.0 of the protocol.
- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.4 Major Violation

A patient is deemed a major violation, if protocol requirements regarding treatment in Cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. Event monitoring will be required per Section 18.0 of the protocol.

The patient may continue treatment with lenalidomide and dexamethasone off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.5 Cancel

A patient is deemed a cancel if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted.

13.6 Phase I only: Failure to complete the first cycle of treatment

If a patient fails to complete the first cycle of treatment for reasons other than toxicity, the patient will be regarded as inevaluable and will be replaced. If a patient has a dose reduction to <70% of the expected dose or dose delay of more than 3 weeks during Cycle 1 for reasons other than DLT, the patient will be replaced by an additional patient.

14.0 Body Fluid Biospecimens: None

15.0 Drug Information

15.1 Lenalidomide (Revlimid®, CC-5013, CDC-501)

Please consult the most current Investigator's Brochure and package insert for complete drug information.

15.11 **Background**: Lenalidomide has a wide range of effects, including the inhibition of hematopoietic tumor cell proliferation, the enhancement of T cells and natural killer (NK) cell activity, the modulation of stem cell differentiation, the inhibition of angiogenesis, and the inhibition of inflammation.

15.12 **Formulation**: For clinical study, lenalidomide is provided as 10, 15, and 25 mg as capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

The lenalidomide capsules are supplied in push-through blister foil or tamper-evident, child-resistant, opaque, high-density polyethylene (HDPE) containers with HDPE caps.

15.13 **Preparation and storage**: Lenalidomide should be stored at room temperature, between 59 and 86ºF (15-30ºC). Store drug away from direct sunlight.

15.14 **Administration:** Capsules are administered by mouth daily with water. Patients should not break, chew or open the capsules.

15.15 **Pharmacokinetic information**:

a) Absorption – Lenalidomide is rapidly absorbed following oral administration to subjects with multiple myeloma or MDS, with maximum plasma concentrations occurring between 0.5 and 1.5 hours post-dose. Co-administration with a high-fat and high-calorie meal in healthy subjects reduced the extent of absorption, resulting in an approximately 20% decrease in AUC and 50% decrease in C_{max} in plasma.

In the pivotal MM and MDS registration trials where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Multiple dosing (up to 100 mg BID) did not cause marked drug accumulation.

b) Distribution – In vitro (14C)-lenalidomide binding to plasma proteins is approximately 30%.

c) Metabolism – Lenalidomide undergoes limited metabolism. Unchanged lenalidomide is the predominant circulating component in humans. Two identified metabolites are hydroxy-lenalidomide and N-acetyl-lenalidomide; each constitutes less than 5% of parent levels in circulation.

d) Excretion – Elimination is primarily renal. Approximately 65% to 85% of lenalidomide is eliminated unchanged through urinary excretion in subjects with normal renal function. The half-life of elimination is approximately 3 to 4 hours (2 to 3 hours in patients 5 to 21 years) at the clinically relevant doses (5 to 50 mg/day). Steady-state levels are achieved within 4 days.

15.16 **Potential Drug Interactions**: In vitro studies demonstrate that lenalidomide is not a substrate of CYP enzymes. In addition, lenalidomide shows little inhibitory or induction potential towards the CYP enzymes in vitro. Hence, coadministration of CYP substrates, inhibitors, or inducers with lenalidomide is not likely to result in clinically relevant drug-drug interactions in humans.

In vitro, lenalidomide is not a substrate of BCRP, MRP1, MRP2, MRP3, OAT1, OAT3, OATP1B1, OCT1, OCT2, MATE1, OCTN1, or OCTN2. Thus, it is unlikely that substrates or inhibitors of these transporters would affect lenalidomide disposition in humans.

Lenalidomide is not an inhibitor of BSEP, BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2. Thus, lenalidomide is not anticipated to cause any significant drug-drug interactions due to inhibition of these transporters.

Lenalidomide is not an inhibitor of UGT1A1 and is not anticipated to cause any significant drug-drug interactions due to UGT1A1 inhibition.

In vitro, lenalidomide is a weak substrate, but not an inhibitor of P-glycoprotein (P-gp).

Erythropoietic agents or other agents that may increase the risk of thrombosis, such as hormone replacement therapy and oral contraceptives, should be used with caution in patients with multiple myeloma receiving lenalidomide with dexamethasone.

Periodic monitoring of digoxin plasma levels is recommended due to increased C_{max} and AUC with concomitant lenalidomide therapy. Close monitoring of PT and INR is recommended in multiple myeloma patients taking concomitant warfarin.

15.17 **Known potential toxicities**:

Pregnancy Warning: Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, a teratogenic effect of lenalidomide in humans cannot be ruled out. Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

Very Common AEs (≥10%): anemia, febrile neutropenia, granulocytopenia, leukopenia, lymphopenia, neutropenia, thrombocytopenia, cataracts, blurred vision, abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting, asthenia, chills, edema including peripheral, fatigue, pyrexia, abnormal liver function tests, bronchitis, gastroenteritis, influenza, nasopharyngitis, sinustitis, pneumonia, rhinitis, upper respiratory tract infection, urinary tract infection weight decreased, decreased appetite, hyperglycemia, hypocalcemia, hypokalemia, arthralgia, back pain, bone pain, muscle spasms, musculoskeletal pain, myalgia, pain in extremity, dizziness, dysgeusia, headache, hypoesthesia, neuropathy peripheral, neuropathy, paresthesia, tremor, depression, insomnia, renal failure, cough, dyspnea, epistaxis, pharyngitis, pulmonary embolism, dry skin, pruritus, rash, and deep vein thrombosis.

Common (≥1% and <10%): hemolytic anemia, pancytopenia, acute myocardial infarction, atrial fibrillation, cardiac failure, congestive heart failure, myocardial

ischemia, tachycardia, vertigo, upper abdominal pain, dry mouth, toothache, chest pain, fall, cholestasis, arthritis infective, bacteremia, cellulitis, erysipelas, herpes simplex, herpes zoster, lower respiratory infection, lung infection, meningitis, ophthalmic herpes zoster, respiratory infection, sepsis, contusion, alanine aminotransferase increased, c-reactive protein increased, gamma-glutamyltransferase increased, dehydration, diabetes mellitus, gout, hypercalcemia, hyperuricemia, hypophosphatemia, hypomagnesemia, hyponatremia, iron overload, muscular weakness, acute myeloid leukemia, basal cell carcinoma, myelodysplastic syndrome, squamous cell carcinoma of skin, T-cell type acute leukemia, tumor flare, tumor lysis syndrome, cerebrovascular accident, lethargy, peripheral sensory neuropathy, syncope, mood altered, respiratory distress, erythema, hyperhidrosis, night sweats, hematoma, hypertension, hypotension, thrombosis, and vasculitis.

Uncommon, limited to important or life-threatening (< 1%): appendicitis, bursitis infective, clostridium difficile colitis, infective exacerbation of chronic obstructive airways disease, pyelonephritis, hypersensitivity, Graft vs Host Disease, viral reactivation (such as hepatitis B virus or herpes zoster), DRESS.

The following additional adverse reactions have been reported in Celgene-sponsored clinical studies and are considered by the company to be at least possibly related to the administration of lenalidomide: pneumonitis, transient abnormal liver laboratory tests, hyperthyroidism, hypothyroidism, viral reactivation (such as hepatitis B virus or herpes virus) acute graft-versus-host disease following allogeneic transplant, solid organ rejection, TLS, TFR, and allergic conditions (including angioedema, SJS, TEN, and DRESS). These reactions are reported voluntarily from a population of uncertain size, so it is not possible to reliably estimate their frequency.

Lenalidomide may have minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence, vertigo and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

Please refer to the Investigator's Brochure for a more comprehensive list of treatment-emergent adverse events.

15.18 **Drug procurement:** Lenalidomide (Revlimid®) will be provided directly to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers in accordance with the REVLIMID REMS™ program. Per standard Revlimid REMS® program requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the Celgene REVLIMID REMS® program. Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. Prescriptions must be filled within 7 days. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.**

Any unused lenalidomide should be returned for disposition in accordance with the REVLIMID REMS® program.

15.19 **Nursing Guidelines:**

15.191 Myelosuppression is dose-dependent and reversible with treatment interruption and/or dose reduction. Monitor CBC w/diff regularly.

Instruct patient to report any unusual bruising or bleeding (thrombocytopenia); signs and symptoms of infection (neutropenia); and energy conserving lifestyle (anemia).

15.192 Lenalidomide can have thrombotic adverse events (i.e DVT and PE). Instruct patient to report any limb swelling or pain, and to seek medical attention for shortness of breath or chest pain.

15.193 Because of the potential for birth defects patients should be instructed in effective methods of birth control. Female patients should use 2 forms of birth control during treatment and for 4 weeks after discontinuing therapy. Males must be instructed to use a latex condom during any sexual contact with a woman of child bearing potential (even if they have had a vasectomy), because it is unknown if lenalidomide is present in semen.

15.194 Patents may experience pruritus, rash and dry skin. Because of the rare risk of Steven's Johnson Syndrome, patients should immediately report any rash to their provider.

15.195 Drug may cause hyperglycemia. Patients with diabetes or impaired fasting glucose may need to have their glucose levels monitored more closely.

15.196 Gastrointestinal side effects (diarrhea, constipation, nausea, dyspepsia, anorexia, etc) are commonly seen. Manage patent symptomatically and monitor for effectiveness.

15.197 Patients may experience myalgias, arthralgias, parasthesias, and other generalized pain. Administer analgesics as ordered and monitor for their effectiveness. Rarely infective bursitis and arthritis have been reported. Instruct patients to report and joint pain or redness to study team immediately

15.198 Upper respiratory symptoms (nasopharyngitis, cough, epistaxis, etc.) can be seen. Manage symptomatically and monitor for effectiveness

15.199a Agent may cause fatigue, dizziness, vertigo or blurred vision. Instruct patients to use caution when driving or operating machines.

15.199b Monitor LFT's and report any elevations to the study team. Instruct patient to report abdominal pain and/or jaundice to the study team.

15.199c All prescribers and patients must be enrolled into the REVLIMID REMS program. Only enough Lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

15.199d Rarely secondary malignancies have been seen after lenolidamide therapy, including MDS, squamous/basal cell carcinomas of the skin, T-cell type acute leukemia.

15.199e Monitor Renal function, renal failure has been reported.

15.2 **Dexamethasone for Oral Administration (DXM)**

15.21 **Background**: Dexamethasone is an adrenal corticosteroid compound. Dexamethasone decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response. Dexamethasone's mechanism of antiemetic activity is unknown.

15.22 **Formulation**: Commercially available for oral administration as:
Tablets [scored]: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg,

15.23 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature between 20ºC to 25ºC (60ºF to 77ºF). Protect from moisture. Dispense in a well-closed, light-resistant container as defined in the USP/NF. Store oral liquid at room temperature, do not freeze. Do not use if solution contains a precipitate. Refer to commercial package for drug expiration date.

15.24 **Administration:** Refer to the treatment section for specific administration instructions. May be taken with meals to decrease GI upset.

15.25 **Pharmacokinetic information**:
Onset of action: Prompt
Duration of metabolic effect: 72 hours
Metabolism: Hepatic
Half-life elimination: Normal renal function: 1.8-3.5 hours; **Biological half-life:** 36-54 hours
Time to peak, serum: Oral: 1-2 hours
Excretion: Urine and feces

15.26 **Potential Drug Interactions**:
Cytochrome P450 Effect: Substrate of CYP3A4 (major); **Induces** CYP2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 3A4 (strong)
Increased Effect/Toxicity: Aprepitant, azole antifungals, calcium channel blockers, cyclosporine, estrogens, and macrolides may increase the serum levels of corticosteroids. Corticosteroids may increase the hypokalemic effects of amphotericin B or potassium-wasting diuretics (loop or thiazide); monitor. Refer to the package insert for a listing of other drugs.
Decreased Effect: Antacids and bile acid sequestrants may reduce the absorption of corticosteroids; may reduce the absorption of corticosteroids; separate administration by 2 hours. Aminoglutethimide, barbiturates, and CYP3A4 inducers may reduce the serum levels/effects of dexamethasone and dexamethasone may decrease the levels/effects of other CYP3A4 substrates. Serum concentrations of isoniazid may be decreased by corticosteroids. Corticosteroids may lead to a reduction in warfarin effect. Corticosteroids may suppress the response to vaccinations.
Ethanol/Nutrition/Herb Interactions:
Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).
Food: Dexamethasone interferes with calcium absorption. Limit caffeine.
Herb/Nutraceutical: Avoid cat's claw, Echinacea (have immunostimulant properties)

15.27 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Common known potential toxicities, frequency not defined:
Fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection, exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances,

convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia.

15.28 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 **Nursing Implications**:

15.291 Monitor regularly for hypertension, CHF and other evidence of fluid retention.

15.292 Advise patient of possible mood or behavioral changes, i.e., depression, euphoria, insomnia, even psychosis. Instruct patient to report any suspected changes to healthcare team.

15.293 Assess for symptoms of gastric ulcer, heartburn, or gastritis. Suggest antacids. Instruct patient to report symptoms to healthcare team if unable to control.

15.294 Evaluate signs of infection, particularly local candidal infections and treat appropriately**.**

15.295 Monitor blood glucose frequently.

15.296 Instruct patient to report frequent, unrelenting headaches or visual changes to healthcare team.

15.297 Advise patient that easy bruising is a side effect.

15.3 **Anakinra (Kineret®) or Placebo**

15.31 **Background**: Anakinra is an interleukin-1 (IL-1) receptor agonist. Interleukin-1 (IL-1) is a key mediator of immune and inflammatory responses. This cytokine promotes fever, hypotension, and anorexia as well as mediates inflammation by increasing neutrophils, activating macrophages, and initiating T-cell and B-cell growth and differentiation. Production of IL-1 is induced in response to inflammation, immunologic reactions, microbial invasion, and tissue injury and may lead to acute or chronic inflammation. Acute and chronic inflammatory diseases that have been linked to IL-1 activity include rheumatoid arthritis (RA), osteoarthritis (OA), multiple sclerosis (MS), Lyme arthritis, graft-versus-host disease, acute and chronic myelogenous leukemia (AML and CML, respectively), multiple myeloma, stroke, head trauma, ulcerative colitis, Crohn's disease, septic shock or sepsis syndrome, asthma, and diabetes mellitus.

15.32 **Formulation**: Injection: 100 mg/0.67 mL solution in a single-use prefilled syringe for subcutaneous injection. Graduated syringe allows for doses between 20 mg and 100 mg.
Placebo is provided as 0.67 mL 0.9% NaCL in a single-use syringe for subcutaneous injection.

15.33 **Preparation and storage**: Kineret is supplied in single-use preservative free, prefilled glass syringes with 29 gauge needles. Each prefilled glass syringe contains 100 mg of anakinra per 0.67 mL. The full syringe contains 100 mg anakinra. Kineret is dispensed in a 4 x 7 syringe dispensing pack containing 28 syringes. Kineret is also dispensed in a 1 x 7 syringe dispensing pack containing 7 syringes.
Storage: Kineret should be stored in the refrigerator at 2ºC to 8ºC (36ºF to 46ºF). **DO NOT FREEZE OR SHAKE.** Protect from light..

15.34 **Administration:** Instructions on appropriate use should be given by the healthcare provider to the patient or caregiver. The prescribed dose of anakinra or placebo should be administered according to the instructions for use and any unused portions discarded. After administration of anakinra or placebo it is essential to follow the proper procedure for disposal of syringes and any residual drug. Rotate injection sites between areas including the thigh, abdomen, upper arm, buttocks. The injection should be given at least 1 inch away from the previous injection site. Allow solution to warm to room temperature prior to use (60-90 minutes); do not shake.

15.35 **Pharmacokinetic information**: The absolute bioavailability of Kineret after a 70 mg subcutaneous bolus injection in healthy subjects (n = 11) is 95%. In subjects with RA, maximum plasma concentrations of Kineret occurred 3 to 7 hours after subcutaneous administration of Kineret at clinically relevant doses (1 to 2 mg/kg; n = 18); the terminal half-life ranged from 4 to 6 hours. In RA patients, no unexpected accumulation of Kineret was observed after daily subcutaneous doses for up to 24 weeks. The influence of demographic covariates on the pharmacokinetics of Kineret was studied using population pharmacokinetic analysis encompassing 341 patients receiving daily subcutaneous injection of Kineret at doses of 30, 75, and 150 mg for up to 24 weeks. The estimated Kineret clearance increased with increasing creatinine clearance and body weight. After adjusting for creatinine clearance and body weight, gender and age were not significant factors for mean plasma clearance.
Patients With Renal Impairment: The mean plasma clearance of Kineret in

subjects with mild (creatinine clearance 50-80 mL/min) and moderate (creatinine clearance 30-49 mL/min) renal insufficiency was reduced by 16% and 50%, respectively. In severe renal insufficiency and end stage renal disease (creatinine clearance <30 mL/min1), mean plasma clearance declined by 70% and 75%, respectively. Less than 2.5% of the administered dose of Kineret was removed by hemodialysis or continuous ambulatory peritoneal dialysis. Based on these observations, a dose schedule change should be considered for subjects with severe renal insufficiency or end stage renal disease.

Patients with Hepatic Dysfunction: No formal studies have been conducted examining the pharmacokinetics of Kineret administered subcutaneously in patients with hepatic impairment.

15.36 **Potential Drug Interactions (USPI Section Drug Interactions)**:
Warnings and Precautions

Serious Infections – Kineret has been associated with an increased incidence of serious infections (2%) vs Placebo (<1%) in clinical trials in RA. Administrations of anakinra should be discontinued if a patient develops a serious infection. Treatment should not be initiated in patients with active infections. The safety and efficacy of anakinra in immunosuppressed patients or in patients with patients with chronic infections have not been evaluated.

Drugs that affect the immune system by blocking TNF have been associated with an increased risk of reactivation of latent tuberculosis (TB). It is possible that taking drugs such as anakinra that blocks IL-1 increases the risk of TB or other atypical or opportunistic infections. (Section 5.1 of the USPI)

Hypersensitivity reactions – Hypersensitivity reactions, including anaphylactic reactions and angioedema have been reported with anakinra. If a severe hypersensitivity reaction occurs, administration of anakinra should be discontinued and appropriate therapy initiated. (Section 5.3 of the USPI)

Immunosuppression – The impact of treatment with anakinra on active and / or chronic infections and the development of malignancies is not known. (Section 5.4 of the USPI)

15.37 **Known potential toxicities**:
>10% of patients:
Local: Injection site reaction (majority mild, typically lasting 14-28 days, characterized by erythema, ecchymosis, inflammation, and pain). Infection (Upper respiratory infections were 14% in the combined studies while serious infections were only 2%).

1% to 10% of patients: Hematologic: neutropenia
Miscellaneous: Headache, Immunogenicity to Anakinra.

<1% of patients (limited to important or life-threatening):
Hypersensitivity reactions (including anaphylaxis, angioedema, pruritus, rash, urticarial)

15.38 **Drug procurement:** As of October 31, 2018. Avavailable from commercial supply. Note: Previously provided by SOBI, AB.

15.39 **Nursing Guidelines:**

15.391 Instruct patients on self-administration of anakinra and monitoring of injection sites. Be sure to instruct patient on rotating injection sites - injection sites should be at least 1 inch away from previous injections.

15.392 Allow solution to warm to room temperature over 60-90 minutes. Do not shake.

15.393 Patients should not receive live vaccines while on agent.

15.394 Instruct patient about injection site reactions which can last anywhere from 14-28 days. Instruct patient to contact PI if they have concerns about injection site reactions.

15.395 Warn patients of infection risk. Instruct patients to report any fever, or other signs/symptoms of infection to the study team.

15.396 Patients may experience headache. Treat symptomatically and monitor for effectiveness.

15.397 Although less common, gastrointestinal side effects (diarrhea and nausea), may be seen. Treat symptomatically and monitor for effectiveness.

15.398 Neutropenia may be seen. Monitor CBC w/diff as per protocol and instruct patients to report signs and symptoms of infection to the study team.

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a phase I/II study. The phase I portion is designed to determine the maximally tolerated dose (MTD) and toxicity profile of lenalidomide in combination with dexamethasone plus anakinra in patients with high risk SMM, IMM, or newly diagnosed multiple myeloma using the standard cohort 3+3 design. The MTD may not be reached and therefore the maximum administered dosage (MAD) will be obtained. The phase II portion is a randomized study designed to compare time to disease progression (TTP) of lenalidomide and dexamethasone plus placebo (standard treatment arm) versus lenalidomide and dexamethasone plus anakinra (experimental arm) in patients with high risk (monotypic plasma cell S-phase≥0.3%) SMM, IMM, or newly diagnosed multiple myeloma. Approximately one third of newly diagnosed multiple myeloma patients are expected to be high risk.

16.11 Primary Endpoint

The primary endpoint of the phase I portion is toxicity, and more specifically, MTD determination. The primary endpoint of the phase II portion of this study is time to disease progression (TTP), which will be compared between the two arms. Time to progression is defined as the time from registration until 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 unless there is sufficient documented evidence to conclude no progression occurred prior to death. If a patient receives subsequent treatment before disease progression, they will be censored on the date of the last disease assessment. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for the primary endpoint.

16.12 Sample Size

The phase I portion of the trial is expected to require at least 12 patients and as many as 18 patients to determine the MTD. The phase II portion of this study is expected to accrue a maximum of 45 evaluable patients in each arm unless undue toxicity is encountered. We anticipate accruing 12 additional patients (2 phase I, 5 phase II in each arm) to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, this study is expected to accrue a maximum of 120 patients overall.

16.13 Accrual Rate and Study Duration

The anticipated accrual rate is 4 patients per month assuming that approximately one third of newly diagnosed patients will be high risk. At this rate, it will likely take about 2.5 months to enroll, treat, and evaluate each cohort in the phase I portion of this study. The phase I portion is expected to take between 10 and 15 months. The phase II portion of this study is expected to accrue in 2 years. The total study duration is expected to be approximately 5.5 years, or until the last patient accrued has been observed for at least 2 years.

Phase I Portion

16.2 Study Design

The phase I study is designed to determine the maximally tolerated dose (MTD) and toxicity profile of lenalidomide in combination with dexamethasone and anakinra in patients with high risk SMM, IMM, or newly diagnosed multiple myeloma using the

standard cohort 3+3 design. Three patients will be treated at each dose level and observed for a minimum of four weeks (i.e. one full cycle) before new patients are treated. Doses will not be escalated in any individual patient.

16.21 MTD Definition

MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity (DLT) in at least one-third of patients (at least 2 of a maximum of 6 new patients). A total of 6 patients treated at the MTD will be sufficient to identify common toxicities at the MTD. For instance, those toxicities with an incidence of at least 25% will be observed with a probability of at least 82% ($1-(1-0.25)^6$).

If all dose levels are determined to be safe, then the maximum administered dosage (MAD) will be the dose level selected to be brought forward to the phase II portion of the study.

Refer to Section 7.22 for definition of dose-limiting toxicity (DLT).

16.22 MTD Determination

Dose Escalation: The phase I portion of this study will utilize a standard cohort-of-three design. The dose levels to which patients will be assigned in sequential cohorts are described in Section 7.21. The first cohort of three patients will be treated at dose level 1. Decisions on when and how to dose escalate are described below.

16.221 Three patients will be treated at a given dose level combination and observed for one (1) cycle to assess toxicity.

16.222 If DLT is not seen in any of the 3 patients, 3 new patients will be accrued and treated at the next higher dose level. If DLT is seen in 2 or 3 of 3 patients treated at a given dose level, then the next 3 patients will be treated at the next lower dose level, if only 3 patients were enrolled and treated at this lower dose level.

16.223 If DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional three patients (≥2 of 6), the MTD will have been exceeded and further accrual will cease to this cohort. If dose-limiting toxicity (DLT) is not seen in any of the three additional patients, 3 new patients will be accrued and treated at the next higher dose level.

16.224 After enrolling 6 patients on a specific dose level, if DLT is observed in at least 2 of 6 patients, then the MTD will have been exceeded and defined as the previous dose unless only 3 patients were treated at the lower dose level. In that case, 3 additional patients will be treated at this lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.

16.225 Dose de-escalation: If dose-limiting toxicity meets the stopping boundaries set by the above dose escalation algorithm at dose level 1 (for example, more than 1 out of 3 patients or more than 1 out of 6 patients), the study will be temporarily closed. Further dose re-escalation will depend on the toxicity profile observed, and re-evaluation of the regimen by the study team may be done.

16.226 If a patient fails to complete the first cycle of treatment for reasons other than toxicity, the patient will be regarded as inevaluable and will

be replaced. If a patient has a dose reduction to <70% of the expected dose or dose delay of more than 3 weeks during Cycle 1 for reasons other than DLT, the patient will be replaced by an additional patient.

16.227 Operating Characteristics for standard cohort of 3 design: 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 above.

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

16.23 Analysis Plans

All the relevant results pertaining to toxicity, MTD, response, timed endpoints and laboratory correlates will be examined in an exploratory and hypothesis-generating fashion. The small sample size and the heterogeneous patient population associated with phase I studies restricts the generalizability of the results. Any notable statistical result should only be viewed as preliminary evidence for further study in Phase II trials rather than a definitive finding in and of itself. Data will continue to be collected on patients as long as they are trial participants.

16.231 Adverse Events Profile

The number and severity of all adverse events (overall and by dose-level) will be tabulated and summarized in this patient population. 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 this patient group.

16.232 Toxicity Profile

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 CTC 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 CTC standard toxicity grading.

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

16.233 Response Profile

A response is defined to be a sCR, CR, VGPR, or PR noted as the objective status. Response will be evaluated using all cycles of treatment. All patients meeting the eligibility criteria who have signed

a consent form and have begun treatment will be evaluable for response.

Responses will be summarized by simple descriptive summary statistics delineating complete and partial responses as well as stable and progressive disease in this patient population.

Phase II Portion

16.3 Statistical Considerations

16.31 **Study Design**:

In a study of consecutive patients treated with lenalidomide and dexamethasone as initial therapy for symptomatic multiple myeloma at Mayo Clinic, the TTP for 16 high risk patients (defined as presence of hypodiploidy, del(13q) by metaphase cytogenetics, del(17p), IgH translocations [t(4; 14), or t(14;16)] or PCLI ≥3%) was approximately 18 months (Kapoor et al, 2009). However, that definition of high risk may not be inclusive of all patients that will be accrued to this study. In addition, a second study of patients treated with lenalidomide and dexamethasone at Mayo Clinic estimated that 29 high risk patients (defined as PCLI ≥1%) had a median TTP of approximately 29 months (unpublished). This study will define high risk as monotypic plasma cell S-phase≥0.3%. PCLI and monotypic plasma cell S-phase are both assays that measure plasma cell proliferation, where a cutoff of ≥0.3% for monotypic plasma cell S-phase would give a similar patient population as using a cutoff of ≥1% for PCLI. Thus, estimates of TTP from previous studies that defined high risk using PCLI would still be relevant. However, due to the small sample sizes and inconsistency in TTP estimates for high risk patients in these prior studies, the lenalidomide and dexamethasone arm of this study will be used to better estimate TTP in high risk myeloma patients (defined as monotypic plasma cell S-phase≥0.3% for this study). We estimate that the median TTP in the lenalidomide and dexamethasone plus placebo arm will be 20 months. We are interested in testing the alternative hypothesis that the median TTP in the lenalidomide and dexamethasone plus Anti-IL-1 antibody arm will be at least 40 months. This translates into an improvement in the 2-year TTP from 43% to 66% assuming an exponential survival model.

The primary goal of this trial is to compare the time to progression of the standard treatment arm (Arm A) to the experimental arm (Arm B). We will conduct a randomized trial comparing the experimental arm against the standard treatment arm. We will enter 45 evaluable patients to each arm of the study using a 1:1 randomization scheme (Pocock et al, 1975). The stratification factors that will be used are listed in Section 5.0. The primary analysis will be a comparison of Arm A to Arm B using a one-sided log-rank test between the two Kaplan-Meier curves. This final analysis will take place after an approximate 24-month accrual period and after 52 total progressions have occurred or the last patient has been followed for at least 2 years (whichever occurs first). Additionally, we assume a constant accrual rate over the course of the study and that we will not have a significant lost to follow-up issue, as historically lost to follow-up rates in Mayo clinic trials have been <1%. A sample size of 45 evaluable patients per arm (90 total) provides 80% power to detect an improvement in median time to progression from 20 months to 40 months (a hazard ratio of 2.0), using a 1-sided log-rank test at a significance level of 0.05. A final decision regarding the level

of promise for the experimental regimen will take all factors into account including TTP, response rate, OS, adverse events, and other relevant factors. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for the primary endpoint.

16.32 **Interim Monitoring**

An interim analysis with a futility rule will be performed to permit the decision regarding inactivity if there is strong evidence that the proposed treatment is inactive. The interim analysis will be performed after one-half of the required number of events for the primary analysis, or specifically, after 26 events (progressions) are observed on study. At the interim analysis, we will compare the distribution of TTP in the experimental arm (Arm B) to the standard treatment arm (Arm A). If the observed hazard rate of Arm B divided by the observed hazard rate on Arm A ≥1, we will conclude that an advantage for Arm B has not been established and the trial will be terminated early for futility. Termination of the trial for futility at the interim analysis using this rule results in minimal loss of power (<2%) (Wieand et al, 1994).

16.33 **Secondary Outcome Analyses**

The secondary endpoints listed below will be evaluated in each arm independently and will also be compared between the two arms in an exploratory manner.

16.331 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 within each arm and compared between the arms using a one-sided log-rank test.

16.332 Overall response rate: The overall response rate will be estimated by the number of patients with an objective status of sCR, CR, VGPR, or PR divided by the total number of evaluable patients. All evaluable patients will be used for this analysis. Exact binomial 95% confidence intervals for the true overall response rate will be calculated within each arm and compared between the arms using Fisher's exact test.

16.34 Adverse Events

All eligible patients that have intitiated 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.

16.35 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 processes; however, they will be included in final point estimates and confidence intervals.

16.36 Data & Safety Monitoring:

16.361 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible

for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.362 Adverse Event Stopping Rules (These rules apply to Arm A and Arm B independently for patients in the randomized phase II portion of the study): The stopping rules specified below are 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 both arms if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy either of the following:

- if 3 or more patients in the first 12 treated patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.
- if after the first 12 patients have been treated, 25% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment

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.

16.4 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 5.5 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 2 years.

16.5 Inclusion of Women and Minorities

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

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

16.53 The geographical region served by MCCC has a population which includes approximately 5% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 5% of patients will be classified as minorities by

race and about 45% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race for All Phase 2 and 3 Studies

Ethnic Category	Sex/Gender			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	1	1	0	2
Not Hispanic or Latino	53	65	0	118
Unknown	0	0	0	0
Ethnic Category: Total of all subjects	54	66	0	**120**
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	2	2	0	4
Native Hawaiian or other Pacific Islander	0	0	0	0
White	52	64	0	116
More than one race	0	0	0	0
Unknown	0	0	0	0
Racial Category: Total of all subjects	54	66	0	**120**

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."

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.

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.)

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."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens: None

18.0 Records and Data Collection Procedures

NOTE (Phase I Only): As of Addendum 5, Anakinra will no longer be provided and all patients will go off study treatment. Event monitoring will no longer be required. Patients may obtain Anakinra commercially and be treated off study.

18.1 Submission Timetables

18.11 Initial Material(s)

Case Report Form (CRF)	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study	≤14 days after registration
Adverse Event - Baseline	
Measurement – Baseline	
SPEP, UPEP, FLC, Immunofixation, FISH, Cytogenetics, PCLI reports	
Bone marrow biopsy report	
Skeletal survey report	
End of Active Treatment/Cancel Notification	Submit ≤14 days after registration if withdrawal/refusal occurs prior to beginning protocol therapy

18.12 Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Evaluation/Treatment	X	X
Nadir/Adverse Event	X	X
Hematology Interval Laboratory	X	
Measurement	X	X
End of Active Treatment/Cancel Notification		X
ADR/AER	At each occurrence (see Section 10.0)	
SPEP, UPEP, FLC, Immunofixation, FISH, Cytogenetics, PCLI reports	X[2]	X[2]
Bone marrow biopsy report	X[1]	X[1]
Skeletal survey report	X[1]	X[1]
Stem Cell Harvest (optional)	X[3]	

1. Only when required by the Test Schedule (see Section 4.0).
2. Submission of these reports is only required for documentation of CR (including sCR) or progression. For documentation of CR, submit all of these reports at the first confirmation of CR. For documentation of progression, submit one report for one of the measures where progression was seen. Submit reports to the QAS for MC138B.
3. May interrupt therapy for stem cell collection at any time per Section 7.4. Submit the Stem Cell Harvest Form after stem cell collection has been completed.

18.13 Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	q. 6 months until PD[2]	At PD[2]	After PD q. 12 mos.	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 3 years after registration, no further follow-up is required.
2. Submit copy of documentation of response or progression to the MCCC Operations Office, Attention: QAS for MC138B.

19.0 Budget

19.1 Costs charged to patient: Routine clinical care

19.2 Tests to be research funded: Lenalidomide will be provided by Celgene. As of October 31, 2018 Anakinra will no longer be provided (previously provided by SOBI, AB. .

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Appendix I ECOG Performance Status Scale

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix II Mayo Risk Stratification

High Risk

FISH deletion 17p

FISH t(4:14)

FISH t(14:16)

Metaphase cytogenetic del 13

Hypodiploidy

PCLI >3%

Appendix III NYHA Classification

Class I: NO Symptoms with ordinary activity

Class II: Symptoms with ordinary activity

Class III: Symptoms with minimal activity

Class IV: Symptoms at rest

Appendix IV 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)
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 V PATIENT MEDICATION DIARY

Patient name _____ Study ID _____

Please complete this diary on a daily basis. Write in the amount of the dose of lenalidomide, anakinra/placebo, 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.

If you experience any health/medical complaints or take any medication other than listed drugs, please record this information on the next page or a separate sheet of paper.

Medication(s)	Dose
#1 Lenalidomide	**mg**
#2 Dexamethasone	**mg**
#3 Anakinra	**mg**
#4 Aspirin	**mg**

Week of: _____

Study Drug	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Lenalidomide							
Anakinra/placebo							
Dexamethasone							
Aspirin							

Week of: _____

Study Drug	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Lenalidomide							
Anakinra/placebo							
Dexamethasone							
Aspirin							

Week of: _____

Study Drug	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Lenalidomide							
Anakinra/placebo							
Dexamethasone							
Aspirin							

Week of: _____

Study Drug	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**	**Day 28**
Lenalidomide							
Anakinra/placebo							
Dexamethasone							
Aspirin							

Patient Signature _____ **Date** _____

My next scheduled visit is: _____
If you have any questions, please call: _____
Bring *all* bottles and any unused study medication along with this diary when you return for your next appointment.

Other Medications:

Comments:

Area Below Only to be Completed by Coordinator

Number of pills returned_____ **Study Coordinator Initials_____**

Number of vials returned_____

Date **Discrepancy Yes No**

Appendix VI 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. The risks to a fetus are not known. However, because lenalidomide is related to thalidomide, and thalidomide is known to cause severe birth defects, the following requirements must be observed.

Females of childbearing potential (FCBP)[†] 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 study drug; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.

Before starting study drug:

Female Subjects:

- FCBP must have two negative pregnancy tests (sensitivity of at least 50 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 subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.
- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure..
- Must agree to abstain from donating blood during study participation and for at least 28 days after discontinuation from the study.

Male Subjects:

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.
- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure,

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

- Must agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation from the study.

During study participation and for 28 days following discontinuation from the study:

All Subjects:

- Only enough lenalidomide for one cycle of therapy may be dispensed with each cycle of therapy.
- If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, lenalidomide must be immediately discontinued.

Female Subjects:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following discontinuation from the study.
- In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use two reliable methods of birth control at each visit.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood, .

Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.

- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after discontinuation from the study.

Male Subjects:

Counseling about the requirement for latex condom use during sexual contact with females of childbearing potential and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood, sperm, or semen