

MAYO CLINIC CANCER CENTER

Phase 2 trial of LDE225 and lenalidomide maintenance post autologous stem cell transplant for multiple myeloma

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Drug Availability

Novartis Supplied Investigational Agent: LDE225

Commercial Agent: Lenalidomide (CC-5013, Revlimid®)

√Study contributor(s) not responsible for patient care.

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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]
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*No waivers of eligibility per NCI

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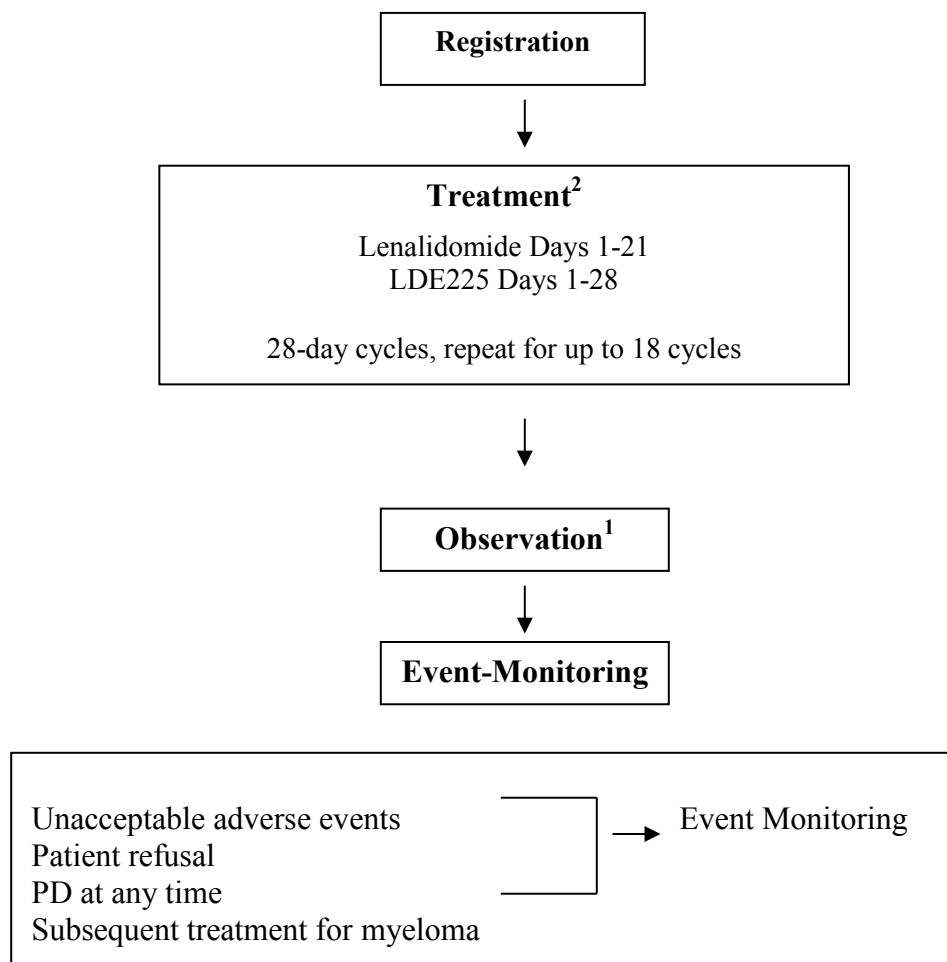
Consent Form

Appendix I – Prohibited concomitant medications

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Schema

1. Every 90 days for up to 3 years from the time of registration, or until progression or subsequent treatment for myeloma
2. Patients will be seen prior to each cycle for the first 6 cycles, after that they can be seen every 3 months (3 cycles)

Generic name: LDE225 Brand name(s): Mayo Abbreviation: LDE225 Availability: Novartis	Generic name: Lenalidomide Brand name(s): Revlimid® Mayo Abbreviation: REVLIMID Availability: Commercial via Revlimid REMS
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1.0 Background

- 1.1 ***Role of autologous stem cell transplantation in myeloma:*** High dose therapy and stem cell transplantation (SCT) remain the standard of care for patients with multiple myeloma (MM) who are eligible to undergo the procedure.(Attal, Harousseau et al. 1996; Child, Morgan et al. 2003; Kumar 2009) It is an effective therapy, with improvement in overall survival and quality of life (time without symptoms and treatment) compared to conventional therapies. However, patients with MM undergoing SCT invariably suffer disease relapse after a median duration of 24 to 30 months. This is not surprising given that only a third of the patients achieve a complete response following induction therapy and SCT. Patients with high proliferative rates of tumor cells, those with high International Staging System (ISS) stage and those with adverse cytogenetic profile, such as presence of t(4;14) and t(14;16) are at a higher risk.(Gertz, Lacy et al. 2005) Strategies to improve the duration of response to SCT can contribute to improved patient wellbeing and potentially improve survival, and become an integral part of the therapeutic approach to MM. The high dose chemotherapy allows significant tumor control and the ability to overcome drug resistance.
- 1.2 ***Depth of response and outcome:*** Several lines of evidence suggest that the depth of response achieved with various treatments, especially in the context of SCT, is a powerful determinant of the response duration. In multiple studies it has been noted that achievement of CR post SCT predicts the duration of response and in some studies the overall survival of these patients.(Rajkumar, Fonseca et al. 2000; Harousseau, Palumbo et al. 2010) However, in nearly half of the patients with a clinical CR residual myeloma cells can be detected using more sensitive methods such as multicolor flow cytometry or PCR based techniques. In the setting of MM, we know that MRD is an important predictor of outcome in patients undergoing aggressive therapy. Rawstron et al used a sensitive flow cytometry assay that quantitated normal and neoplastic plasma cells (PCs) to monitor the bone marrow (BM) of 45 patients undergoing autologous stem cell transplant (ASCT).(Rawstron, Davies et al. 2002) Among the 42% of patients in whom monoclonal PCs were detectable 3 months after ASCT, the median PFS was 20 months compared to 35 months for those with undetectable PCs. Even among those with negative immunofixation studies, considered the hallmark of “CR”, a third had detectable PCs and had a poorer outcome. Bakkus et al examined the utility of detecting MRD using a quantitative allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) assay at 3–6 months post-transplant in 67 patients.(Bakkus, Bouko et al. 2004) Using specific cutoffs for the quantitative PCR results, the authors identified patients with residual disease and a short time to relapse. Lipinski et al retrospectively analyzed the tumor load in peripheral blood (PB) and BM samples of 13 patients at time of remission after ASCT and at the time of progression using ASO-qPCR(Lipinski, Cremer et al. 2001). Progression was detected early by this method compared to monoclonal protein estimation demonstrating sensitivity of the technique. Galimberti et al examined the prognostic value of PCR based monitoring of MRD in 20 patients after ASCT by non-myeloablative allogeneic transplant (NMT).(Galimberti, Benedetti et al. 2005) After ASCT, only 3 patients (15%) achieved PCR-negativity, versus 12 (60%) after NMT. 76% of patients with no MRD were still alive at 2 years versus 34% of PCR positive patients.

- 1.3 ***Maintenance strategies after autologous stem cell transplantation:*** The concept of maintenance therapy has been tested mostly in the setting of high dose therapy and autologous stem cell transplantation. Patients invariably relapse after initial treatment strategies including SCT and various trials have attempted to maintain the SCT response through maintenance approaches. Initial trials prior to the availability of the new drugs have examined steroids or interferon, and a small randomized clinical trial of interferon- $(3 \times 10^6 \text{ units/m}^2)$ subcutaneously 3 times weekly, following initial ASCT, suggested a modest improvement in EFS.(Cunningham, Powles et al. 1998) The IFM99-02 trial randomized patients with standard-risk MM (Beta₂-microglobulin [B2M] <3, no deletion 13), : to receive no maintenance, pamidronate, or pamidronate plus thalidomide after tandem SCT.(Attal, Harousseau et al. 2006) Thalidomide was associated with higher response rates, improved EFS (52% vs. 36% with no maintenance) and improved overall survival (4-year estimated survival from diagnosis with thalidomide (87%) compared with no maintenance (77%). At least 5 different randomized trials have examined the role of thalidomide as a maintenance therapy post-SCT.(Lokhorst, van der Holt et al. 2009; Spencer, Prince et al. 2009; Stewart, Trudel et al. 2010) A meta-analysis of these trials support improved progression-free survival, but remains equivocal in terms of overall survival improvement. In addition a, high discontinuation rate has been noted in all these studies due to toxicity. In particular the Canadian study showed worsening of QoL parameters among patients getting thalidomide maintenance.(Stewart, Trudel et al. 2010)

A phase 3 study from the IFM enrolled 614 patients < 65 years, with non-progressive disease, within 6 months after upfront ASCT.(Attal, Lauwers et al. 2010) Patients received 2 cycles of consolidation with lenalidomide 25 mg daily for 3 of 4 weeks followed by a randomization to lenalidomide 10-15 mg/day until relapse or to placebo (n=307 in each arm). Patients were stratified according to Beta-2M, del13, and VGPR to initial therapy. There was an improvement in the PFS with maintenance therapy, with a median PFS of 42 months for lenalidomide vs. 24 months for the placebo. The improvement in the PFS was seen in all the subgroups based on stratification. With the current follow-up, overall survival (OS) remains identical in the two groups. In a very similar trial, McCarthy and colleagues randomized patients 70 years or younger, who attained a stable disease or better with their induction therapy and underwent ASCT within one year of diagnosis, to lenalidomide (5-15 mg/day) or placebo until relapse.(McCarthy, Owzar et al. 2010) Patients were stratified based on Beta-2M and use of thalidomide or lenalidomide therapy during induction. Patients were enrolled prior to the ASCT, with 19% of the 568 enrolled dropping out before randomization. As expected, grade 3 and 4 adverse events were significantly higher lenalidomide arm during in the maintenance arm compared to the placebo, with hematological toxicities being the common events. The median time to progression was 42 months with lenalidomide compared to 21.8 months with the placebo, results very similar to the French study. More recent updates suggest an improvement in the overall survival for the lenalidomide arm in the CALGB study. There are differences, however, between the two trials in terms of the design as well as duration of therapy. Patients in the IFM trial received uniform induction therapy unlike the CALGB trial. Patients in the IFM study received 2 cycles of consolidation with lenalidomide before starting maintenance. In addition, the IFM trial limited maintenance to approximately 24 months based on concerns regarding second malignancies and did not allow cross over. However, the CALGB trial allowed cross over

from placebo arm to lenalidomide maintenance based on interim analysis and also allowed maintenance until progression.

So the bulk of evidence points to the importance of exploring continued treatment approaches in the majority of patients with myeloma post-SCT, preferable in the context of clinical trials. In vitro studies suggest that the major obstacle to eradicating the tumor clone of myeloma is the result of the protective tumor microenvironment that exists in the marrow. Clearly novel approaches need to be examined in the context of SCT for eradication of residual disease. This is even more relevant today, with the deep responses we are able to obtain with new agents pre-SCT, thus enabling the use of experimental approaches in the context of minimal residual disease.

- 1.4 ***Hedgehog signaling in myeloma:*** In multiple myeloma, the abnormal proliferation of plasma cells is very much dependent on the bone marrow microenvironment.(Podar, Richardson et al. 2007) Hedgehog (Hh) signaling is a highly conserved pathway that plays an important role in development in both vertebrates and invertebrates (Ingham and McMahon 2001). Aberrant functioning of the Hh pathway has been reported in several tumors including prostate and lung cancers. To summarize the Hh pathway, Hh ligands secreted by the stromal cells, namely indian (Ihh), sonic (Shh) and desert (Dhh) bind to their receptor, patched (PTCH) on tumor cells. This binding alleviates the inhibition of PTCH on its downstream target, smoothened (Smo), thereby activating it. This activation leads to activation of the cubitus interruptus-like transcription factor involved in glioma formation (Gli) which promotes the transcription of its target genes leading to tumor development and progression (Xie and Abbruzzese 2003). In the myeloma setting it has been found that Hh pathway is essential for maintaining a subset of tumor causing stem cells. Blocking the Hh pathway by inhibiting Smo activation by treatment with cyclopamine, an inhibitor of Smo, did minimize the clonal expansion of the subset of tumor causing stem cells by enabling them to differentiate terminally (Peacock, Wang et al. 2007). When MM cell cultures were treated with cyclopamine and cell viability was examined, it was found that the MM cells were less viable in the presence of cyclopamine than in the absence of it (Dierks, Grbic et al. 2007). More recently, Blotta et al demonstrated that plasma cells from MGUS patients express higher levels of Ihh/Shh, Smo and Ptch1 receptors, as well as Gli1 and Gli2 transcription factors, but lower levels of the repressor genes Ptch2 and Gli3 compared with normal plasma cells.(Blotta, Jakubikova et al. 2012) Similarly, plasma cells from patients with MM showed up-regulation of Ptch1, Gli1 and Gli2 and down-regulation of Ptch2 and Gli3, again supporting a role of this pathway in myeloma pathogenesis. In contrast, these changes were less obvious in cell lines and plasma cell leukemia likely reflecting the lack of microenvironment dependence in these situations. The investigators were also able to show activation of both ligand dependent (canonical) as well as independent (non-canonical) mechanisms for the up regulation of Hh pathway seen in MM. Finally, these studies confirmed prior observations regarding the stromal cells being a major source of Shh that can drive proliferation of myeloma cells as well as afford protection against anti-myeloma drugs.

- 1.5 ***LDE225:*** LDE225 is a potent, selective and orally bioavailable Smo antagonist. LDE225 is a high-affinity ligand for human and mouse Smo, as shown by its ability to displace radiolabeled Smo agonists, with an IC50 of 11 nM for human Smo and 12 nM for mouse

Smo. In multiple cell-based assays, LDE225 is a potent antagonist of Hh-dependent pathway activation. It inhibits Hh-mediated Gli1 activation in mouse TM3 and human HEPM cells with an IC50 of 7 nM and 13 nM, respectively. LDE225 potently inhibits proliferation and Gli1 expression of freshly isolated mouse MB tumor cells in vitro with an IC50 of 7 nM. Treatment with LDE225 results in tumor regression in vivo in several genetically defined animal models. Efficacy in these tumor models is dose-related and correlates with inhibition of Hh pathway signaling, as measured by decreased Gli1 mRNA. Treatment with LDE225 also shows in vivo efficacy in models of pancreatic cancer and SCLC. In vivo studies in the myeloma setting have shown significant efficacy of LDE225, particularly in combination with bortezomib.(Blotta, Jakubikova et al. 2012)

LDE225 was well tolerated in mice with no significant body weight loss at all doses (up to 160 mg/kg QD) investigated. In vivo PK/PD analysis in MB models showed a good correlation between the given dose, the measured blood and tissue levels, the effects on the Hh pathway as measured by Gli1 mRNA expression and the anti-tumor activity. It appeared that almost complete and sustained Gli1 mRNA inhibition (above approximately 95%) is required to yield tumor regression in the animal models studied. LDE225 was well absorbed with Tmax occurring within 0.5 to 24 hours post-dose. The clearance was low to moderate and the volume of distribution was always greater than the total body water in all species investigated. The majority of adverse effects of LDE225 observed in toxicity studies in rats and dogs can be attributed to the pharmacologic mechanism of action on developmental pathways. The most striking of these pharmacologic effects were on growing bones and teeth (growing incisors in rodents). The bone effects included thinning or closure of the bone growth plates in the sternum and femur. Effects on the reproductive systems were seen in rats and dogs. GI toxicity was likely dose limiting in the animal studies. In the GLP juvenile rat study minimal to slight degeneration of nerve fibers was found in the sciatic nerve and, less commonly, in the thoracic spinal cord, but not in the cervical or lumbar spinal cord or optic nerve. Effects on nerves were not seen in any of the toxicity studies on more mature rats or dogs.

We have examined the activity of LDE in combination with lenalidomide in myeloma, especially in the context of bone marrow derived stromal cells or tumor microenvironment. In in vitro experiments, LDE225 treatment of myeloma cell lines resulted in a modest inhibition of cell proliferation at increasing doses (**Figure 1**).

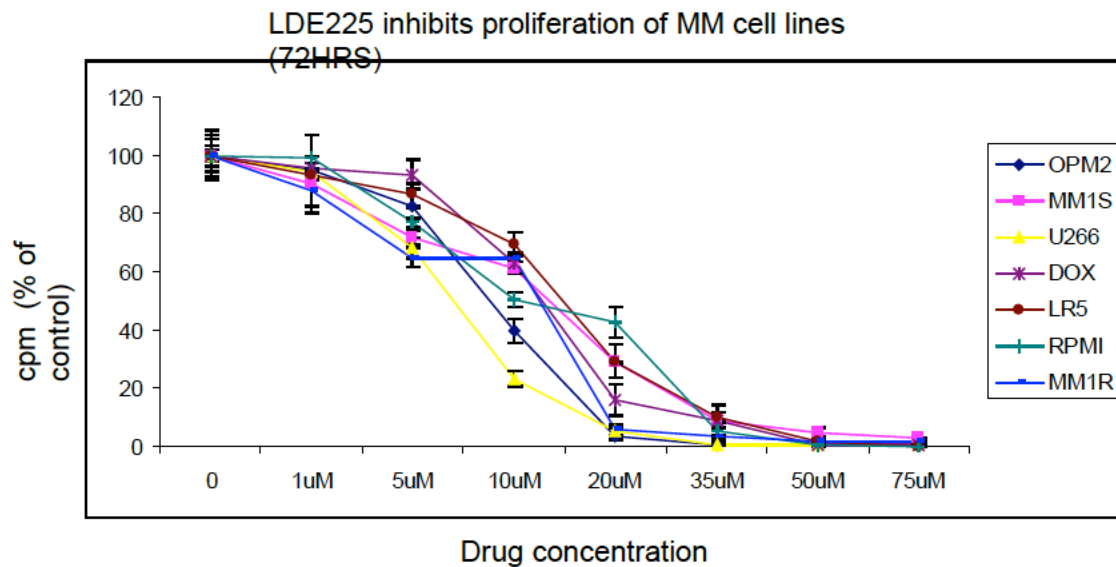
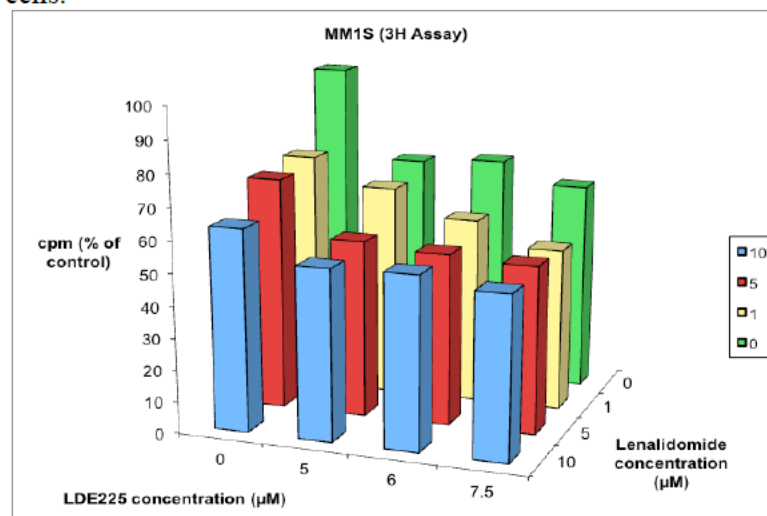


Figure 1: Various myeloma cell lines were incubated with the indicated concentrations of LDE225 for 72 hours and cell viability was measured by thymidine incorporation. Y-axis represents the thymidine uptake as counts per min. standardized to the control.

When LDE225 was combined with lenalidomide, a more than additive effect was observed in terms of myeloma cell proliferation, an effect that was more pronounced in the context of myeloma cell lines growing in co-culture with marrow derived stromal cells.



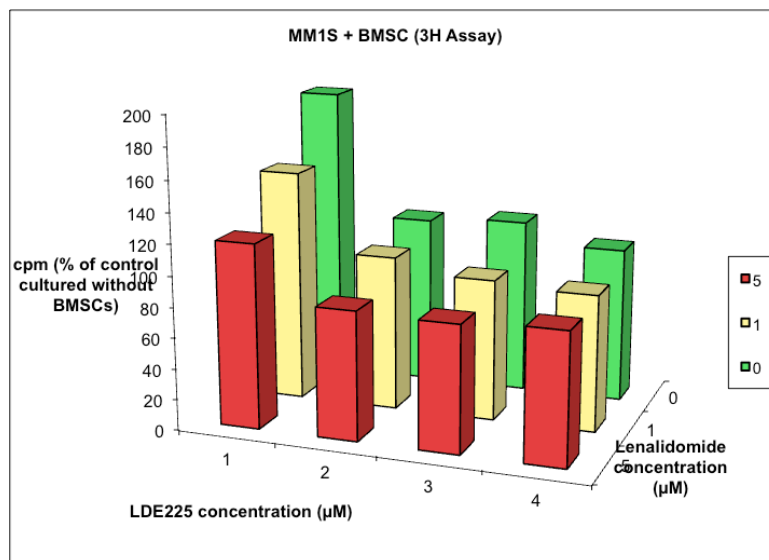


Figure 2: MM1.s myeloma cell line was incubated with the indicated concentrations of LDE225 and lenalidomide for 72 hours and cell viability was measured by thymidine incorporation. Y-axis represents the thymidine uptake as counts per min. standardized to the control.

- 1.6 **Clinical experience with LDE225:** LDE225 is currently undergoing evaluation in three Phase I clinical trials (CLDE225X2101, CLDE225X1101 and CLDE225X2104) and one Phase II trial (CLDE225A2201) to assess the safety, tolerability, PK, PD and potential efficacy of continuous daily oral administration in patients with malignant solid tumors. As of October, 2011, data were available on 103 patients with cancer who have been treated with LDE225 at dose levels of 100, 200, 400, 800, 1000, 1500, and 3000 mg once daily (QD) and 250, 400 and 750 mg twice daily (BID). Based on the available data, the recommended phase II of LDE225 in adults is 800 mg once daily. DLTs that are characterized by CTC grade 3 or 4 increases in plasma creatine phosphokinase (CK) observed at once daily doses ≥ 800 mg and twice daily doses ≥ 250 mg. The majority of the DLT events occurred during the initial 4-6 weeks of treatment with LDE225. None of the patients experienced impairment of renal function as a result of this toxicity. The DLTs resolved following discontinuation of LDE225 therapy. Across all the doses studied, the commonly ($>10\%$) reported CTCAE grade 1 or 2 adverse events that are suspected to be treatment-related include: nausea, vomiting, dysgeusia, decreased appetite, myalgia, muscle spasms, blood CK increased, alopecia, asthenia and fatigue.
- 1.7 **Study Rationale:** These findings form the basis of evaluation of HH inhibition as a strategy to enhance the activity of lenalidomide in the post-transplant maintenance setting. The minimal residual state post SCT provides the most optimal situation for evaluation of a drug that is likely to work by inhibiting the interaction between tumor cells that escaped the high dose therapy with the help of protection by the microenvironment.

2.0 Goals**2.1 Primary**

2.11 To assess the CR rate with lenalidomide and LDE225 maintenance following an upfront single autologous SCT

2.2 Secondary

2.21 To assess the toxicity of lenalidomide and LDE225 when used as maintenance therapy in patients post autologous SCT.

2.22 To determine the progression-free survival rate at 1 and 2 years post autologous SCT

2.23 To evaluate progression-free survival and overall survival

2.3 Correlative Research

2.31 To determine the proportion of patients achieving a minimal residual disease (MRD) negative status

3.0 Patient Eligibility**3.1 Inclusion Criteria**

3.11 Age ≥ 18 years

3.12 The following laboratory values obtained ≤ 14 days prior to registration:

- Absolute neutrophil count $\geq 1500/\mu\text{L}$
- Platelet count $\geq 80,000/\mu\text{L}$
- Hemoglobin ≥ 9.0 g/dL
- Serum total bilirubin $\leq 1.5 \times \text{ULN}$ (upper limit of normal)
- AST and ALT $\leq 2.5 \times \text{ULN}$ or $\leq 5 \times \text{ULN}$ if liver involvement
- Plasma creatine phosphokinase (CK) $< 1.5 \times \text{ULN}$
- Serum creatinine $\leq 1.5 \times \text{ULN}$ or 24-hour clearance $\geq 50\text{ml/min}$

3.13 Diagnosis of symptomatic MM

3.14 Patients should have received single autologous stem cell transplantation 60-120 days prior to enrollment to the trial.

3.15 Patients should have received the autologous SCT within 12 months of their diagnosis of myeloma to be eligible for the study.

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

- 3.17 Recovered from toxicity of previous chemotherapy (excludes grade 1 neurotoxicity and hematological toxicity)
- 3.18 Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that the subject may withdraw consent at any time without prejudice to future medical care
- 3.19a Willingness to return to the Mayo Clinic enrolling institution for follow-up
- 3.19b Measurable disease of multiple myeloma at the time of baseline values for disease assessment (see section 11.11) as defined by at least one of the following:
- Serum monoclonal protein ≥ 1.0 g/dL (see Section 11.1 for definition)
 - ≥ 200 mg of monoclonal protein in the urine on 24 hour Electrophoresis
 - Serum immunoglobulin free light chain (involved FLC) ≥ 10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio.

NOTE: For patients with no relapse prior to transplant, measurable disease at the time of diagnosis.

NOTE: For patients who have had a disease relapse prior to transplant, measurable disease at the time of the most recent relapse immediately prior to transplant. NOTE: If the patient had treatment for the relapsed disease prior to transplant, the patient must have measurable disease at the time of relapse prior to this therapy.

- 3.19c Patients may have a history of current or previous deep vein thrombosis or pulmonary embolism but must be willing to initiate prophylaxis with low molecular weight heparin.
- 3.19d Females of childbearing potential (FCBP)[†] must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting lenalidomide and LDE225 and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide and LDE225. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure.

† A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 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).

- 3.19e Sexually active males must be willing to use a condom (even if they have undergone a prior vasectomy) while having intercourse, while taking lenalidomide and for 4 weeks after stopping treatment.
- 3.19f Patient enrolling to this study must agree to register to the mandatory **REVLIMID REMS™** program, and be willing and able to comply with the requirements of (**REVLIMID REMS™**)
- 3.19g Patients must be willing to provide biological samples as required by the study (Section 14).

3.2 Exclusion Criteria

- 3.21 Prior allogeneic bone marrow/peripheral blood stem cell transplant
- 3.22 Patients with evidence of disease progression post SCT at the time of consideration for the study enrollment will not be included.
- 3.23 Impaired cardiac function or clinically significant heart disease, including any one of the following:
 - Angina pectoris within 3 months
 - Acute myocardial infarction within 3 months
 - QTcF > 450 msec for males and > 470 msec for females on the screening ECG
 - A past medical history of clinically significant ECG abnormalities or a family history of prolonged QT-interval syndrome
 - Other clinically significant heart disease (e.g. congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
- 3.24 Seroreactivity for HIV, HTLV I or II, HBV, HCV
- 3.25 Other active malignancy requiring therapy. **EXCEPTIONS:** Non-melanotic skin cancer or carcinoma-in-situ of the cervix.
- 3.26 Any of the following:
 - Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).

- Patients who are not willing to apply highly effective contraception during the study and through the duration as defined below after the final dose of study treatment.
 - **Women of child-bearing potential**, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and through **6 months** after the final dose of study treatment. Highly effective contraception is defined as either:
 1. Total abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
 2. Sterilization: Patient has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
 3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female study patients, the vasectomised male partner should be the sole partner for that patient]
 4. Use a combination of the following (both a+b):
 - a. Placement of a non-hormonal intrauterine device (IUD) or non-hormonal intrauterine system (IUS)
 - b. Barrier method of contraception: Condom or Occlusive cap (diaphragm or cervical vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Note: Hormonal contraception methods (e.g. oral, injected, implanted) are not allowed as it cannot be ruled out that the study drug decreases the effectiveness of hormonal contraception

Note: Woman are considered post-menopausal and not child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL and estradiol < 20 pg/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential
 - **Male patient** must use highly effective (double barrier) methods of contraception (e.g., spermicidal gel plus condom) for the entire duration of the study, and continuing using contraception and refrain from fathering a child for 6 months following the study drug. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the study treatment via seminal fluid

- Sexually active males who are unwilling to use a condom during intercourse while taking drug and for 6 months after stopping investigational medications and agree not to father a child in this period..
- 3.27 Other co-morbidity, which would interfere with patient's ability to participate in the trial, e.g. uncontrolled infection, uncompensated lung disease.
- 3.28 Concurrent chemotherapy, radiotherapy, or any ancillary therapy for treatment of multiple myeloma.
NOTE: Bisphosphonates are considered to be supportive care rather than therapy, and are thus allowed while on protocol treatment.
- 3.29 Known allergies to any of the components of the investigational treatment regimen or required ancillary treatments
- 3.30 Major surgery within 4 weeks prior to registration.
- 3.31 Patients with concurrent uncontrolled medical conditions that may interfere with their participation in the study or potentially affect the interpretation of the study data.
- 3.32 Patients unable to take oral drugs or with lack of physical integrity of the upper gastrointestinal tract or known malabsorption syndromes.
- 3.33 Patients who have previously been treated with systemic LDE225 or with other hedgehog pathway inhibitors.
- 3.34 Patients who have neuromuscular disorders (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis and spinal muscular atrophy) or are on concomitant treatment with drugs that are recognized to cause rhabdomyolysis, such as HMG CoA inhibitors (statins), clofibrate and gemfibrozil, and that cannot be discontinued at least 2 weeks prior to starting LDE225 treatment. NOTE: If it is essential that the patient stays on a statin to control hyperlipidemia, only pravastatin may be used with extra caution.
- 3.35 Patients who have taken part in an experimental drug study \leq 4 weeks prior to registration.
- 3.36 Patients who are receiving treatment with medications known to be moderate and strong inhibitors or inducers of CYP3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 that have narrow therapeutic index, and that cannot be discontinued before starting treatment with LDE225.
- 3.37 Patients unwilling or unable to comply with the protocol.
- 3.38 Requirement for anticoagulation with warfarin

4.0 Test Schedule

	Active Monitoring ¹					
	Days Prior to Registration		Prior to each cycle ^{11 ©}	Day 15, Cycles 1 and 2 ¹³	End of Cycle 18	Observation every 90 days ⁵
	≤30 days	≤14 days				
Complete medical history	X					
Adverse Event monitoring		X	X ^d		X	X
Physical exam, including weight and vital signs		X	X ^b		X	X
Height		X				
Performance status (ECOG scale)		X	X		X	X
CBC with differential		X	X	X	X	X
Prothrombin time (PT)	X					
Chemistry group to include sodium, potassium, glucose, alkaline phosphatase; total and direct bilirubin; SGOT (AST); serum creatinine, calcium, albumin, plasma creatinine phosphokinase (CK), ALT		X	X		X	X
sTSH		X	X ⁴		X	
LDH, Beta ₂ -microglobulin, C-reactive protein	X					
Electrophoresis of serum and urine		X	X ¹²		X ¹²	X ¹²
Affected serum immunoglobulin		X	X ⁷		X ⁷	X ⁷
Immunofixation serum and urine	X		X ²		X ²	X ²
Immunoglobulin serum free light chains		X	X ⁶		X ⁶	X ⁶
Metastatic skeletal survey	X		X ⁴		X ⁴	X ⁴
Bone marrow aspirate and biopsy, myeloma FISH, metaphase cytogenetics, and flow cytometry	X		X ¹⁰		X ⁸	X ^{10, 8}
Research blood sample as per 521-93, optional ^R		X	X ¹⁰		X	X ¹⁰
Research bone marrow aspirate (see Section 14.0) ^R		X	X ⁹		X	X ⁹
Chest x-ray, ECG	X					
Serum pregnancy test		X ³				

- 1) All scheduled visits will have a window of ± 7 days, unless otherwise stated
- 2) Immunofixation (IF) needed only in the absence of M-protein to document sCR or CR.
- 3) For women of childbearing potential only. Must be done ≤ 7 days prior to registration.
- 4) Every 6 cycles
- 5) For up to 3 years from the time of registration, or until progression or subsequent treatment for myeloma, whichever occurs first
- 6) Immunoglobulin free light chain required only if used to assess disease response.
- 7) Affected immunoglobulin refers to the baseline M-protein type, that is, IgM, IgG, IgA, or IgD. Not applicable if patient “non-secretory”, or if patient has no heavy chain, i.e. light chain MM. Affected immunoglobulin is required after baseline only if it used for disease monitoring instead of SPEP (for e.g. IgA myeloma)
- 8) No FISH or cytogenetics required unless clinically indicated
- 9) At the time of suspected CR

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- 10) Only required to document CR or sCR.
- 11) Does not need to be repeated at Cycle 1 Day 1. Baseline values can be used for Cycle 1.
- 12) Urine Electrophoresis required only if used to assess disease response.
- 13) Can be completed at local MD
- R Research funded (see Section 19.0). Will be charged to study and not to patient's account.
- b) After 6 cycles of follow up this will be done every 3 months (3 cycles)
- c) Routine blood work and urine tests can be done at home or by mail in kit if patient is not being seen at Mayo clinic prior to each cycle.
- d) Nurse will call patient for adverse event monitoring prior to each cycle if patient is not being seen at Mayo Clinic that cycle.

5.0 Grouping Factor:

None

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the remote registration/randomization application. The remote 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 a [REDACTED] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday). The instructions for remote registration 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 remote system can be confirmed in any of the following ways: 1) Contact the MCCC Registration Office [REDACTED]. If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration. 2) Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about a registered subject".

- 6.2 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 Prior to accepting the registration/randomization, the remote 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
- 6.4 Treatment on this protocol must commence at a Mayo Clinic institution under the supervision of a member of the hematology group.
- 6.5 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.
- 6.6 Pretreatment tests/procedures must be completed within the guidelines specified on the test schedule.
- 6.7 All required baseline symptoms must be documented and graded.
- 6.8 A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19g, 14.1).

7.0 Protocol Treatment

Treatment should start before 180 days from the day of transplant.

7.1 Treatment Schedule

Cycle 1

Agent	Dose	Route	Day	Cycle length
Lenalidomide	10 mg	PO	1-21	28 days
LDE225	400 mg	PO	1-28	

- 7.2 The study will be temporarily closed to accrual after the first six patients have been accrued. Patients will be evaluated for toxicity after they have completed 3 months of therapy. If the level of toxicity in the first 6 patients is acceptable per Section 16.351, then the study will reopen for accrual.
- 7.3 For this protocol, the patient must return to the Mayo Clinic every 28 days for the first 6 cycles. After this if patients do not have ongoing toxicity issues, they may return to the Mayo Clinic every 3 months (3 cycles).

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 Table 8.2),

Dose Level	Lenalidomide
0*	10 mg PO QD Days 1-21
-1	5 mg PO QD Days 1-21
-2	5 mg PO QD Days 1-7, 15-21
-3	Discontinue

Dose Level	LDE225
0*	400 mg PO QD Days 1-28
-1	200 mg PO QD Days 1-28
-2	200 mg PO QD Days 1-21
-3	Discontinue

*Dose level 0 refers to the starting dose. All cycles are 28 days in length.

If patients cannot tolerate dose level – 2 of BOTH drugs they will go to event monitoring.

8.11 Instruction for initiation of a new cycle of therapy

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

- The ANC is $\geq 1000/\mu\text{L}$
- The platelet count is $\geq 50,000/\mu\text{L}$
- Any other drug-related adverse event that may have occurred has resolved to \leq grade 1 or baseline 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 therapy will be held until the toxicity has resolved as described above.

If any drug 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 any drug dosing was omitted for the remainder of the previous cycle or if the new cycle is held due to known hematologic toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction. If a new cycle of therapy cannot be restarted within 4 weeks of the scheduled day 1, the patient will be removed from protocol therapy and will go to event monitoring.

8.2 Dose modifications based on adverse events during a cycle

Table 0-1 Recommended Dose Modifications and Dose Delays for suspected treatment-related toxicities

→ → 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
BASED ON INTERVAL ADVERSE EVENT **			
Blood and lymphatic system disorders	Febrile neutropenia Grade 3 or 4	LDE225	Omit dose until resolved, then decrease dose by 1 step
Investigations	Platelet count decreased \geq Grade 3 (platelet count $< 50,000/\text{mm}^3$)	LDE225	Omit dose until resolved to \leq grade 1, then: <ul style="list-style-type: none"> • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then decrease dose by 1 step
	Neutrophil count decreased \geq grade 3 (ANC $< 1,000/\text{mm}^3$)	LDE225	Omit dose until resolved to \leq grade 1, then: <ul style="list-style-type: none"> • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then decrease dose by 1 step

→ → 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
	<p>CPK increased</p> <p>Grade 1 or 2 CPK increased and asymptomatic myalgia (no new-onset myalgia or worsening of pre-existing myalgia)</p> <p>Grade 1 or 2 CPK increased and symptomatic myalgia (new-onset myalgia or worsening of pre-existing myalgia)</p> <p>Grade 3 or 4 CPK increased (with or without myalgia)</p>	LDE225	<ul style="list-style-type: none"> For CTCAE grade 1 CPK increased, continue treatment on same dose and continue monitoring as per schedule of assessments For CTCAE grade 2 CPK increased, consider performing a muscle biopsy; continue on same dose level of LDE225. CPK should be measured weekly until resolution to \leq grade 1. For CTCAE grade 1 CPK with myalgia \geq CTCAE grade 1, continue treatment at same dose and measure CPK weekly until CPK returns to normal or baseline value or myalgia resolves For CTCAE grade 2 CPK with myalgia \geq CTCAE grade 1, continue treatment at same dose level of LDE225. CPK should be measured weekly until CPK is \leq CTCAE grade 1 Omit LDE225 dose, check blood myoglobin and monitor renal function. Measure CPK weekly until resolution to grade \leq 1 Consider performing electromyography, MRI scan of symptomatic muscle group(s) and muscle biopsy If renal function is not impaired and resolution to \leq CTCAE grade 1 occurs within 21 days, consider resuming treatment at a reduced dose; CPK should be measured weekly for 2 months after re-

→ → 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
			administration of LDE225 <ul style="list-style-type: none"> Patients who experience renal impairment (serum creatinine > 2x ULN) should be permanently discontinued from treatment. Patient goes to event monitoring per section 18.0
	Creatinine increased Grade 2 (1.5-3 x ULN) Grade 3 (>3.0 – 6.0 x ULN) Grade 4 (>6.0 x ULN)		Omit dose until resolved to ≤ grade 1, then: <ul style="list-style-type: none"> If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then decrease dose by 1 step (consider checking serum CPK, if not already done) Omit dose until resolved to ≤ grade 1, then decrease dose by 1 step Omit dose and discontinue patient from treatment. Patient goes to event monitoring per section 18.0
	Blood bilirubin increased Grade 2 (1.5- 3 x ULN) Grade 3 (>3.0 – 10.0 x ULN)		Omit dose until resolved to ≤ grade 1, then: <ul style="list-style-type: none"> If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then decrease dose by 1 step (consider checking serum CPK, if not already done) Omit dose until resolved to ≤ grade 1, then decrease dose by 1 step

→ → 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
	Grade 4 (>10.0 x ULN)		Omit dose and discontinue patient from treatment. Patient goes to event monitoring per section 18.0
	Aspartate aminotransferase increased or alanine aminotransferase increased Grade 3 (>5.0 – 20.0 x ULN) Grade 4 (>20.0 x ULN)		Omit dose until resolved to ≤ grade 1 or baseline, then: <ul style="list-style-type: none"> • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then decrease dose by 1 step Omit dose until resolved to ≤ grade 1 or baseline, then decrease dose by 1 step
	Electrocardiogram QT corrected interval prolonged ≥ grade 3		First Occurrence: <ul style="list-style-type: none"> • Omit dose • Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed. • Perform a repeat ECG within one hour of the first QTc of > 500 ms • If QTc remains > 500 ms, repeat ECG as clinically indicated but at least once a day until the QTc returns to < 480 ms. • Once QTcF prolongation has resolved, study treatment may be restarted at a reduced dose level Second Occurrence: Discontinue patient from further study treatment. Patient goes to event

→ → 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
			monitoring per section 18.0.
Musculoskeletal and connective tissue disorders	Myalgia Grade 2 Grade 3	LDE225	Measure CPK weekly until myalgia resolves to ≤ grade 1. If CPK is elevated, follow guidance for CPK elevation as described above. Continue treatment with LDE225 For new-onset CTCAE grade 3 myalgia, interrupt LDE225. Check CPK measurement at the time of dose interruption. Provide symptomatic treatment. Measure CPK weekly until the myalgia resolves to ≤ grade 1 and resume therapy at a reduced dose. Measure CPK weekly for 2 months after re-administration.
Respiratory, thoracic and mediastinal disorders	Dyspnea ≥ grade 3		Omit dose and discontinue the patient from treatment. Patient goes to event monitoring per section 18.0
	Pulmonary edema ≥ grade 3		Omit dose and discontinue the patient from treatment. Patient goes to event monitoring per section 18.0
Cardiac disorders	Palpitations ≥ grade 2 Myocarditis grade ≥ 2		Omit dose and discontinue the patient from treatment. Patient goes to event monitoring per section 18.0 Omit dose and discontinue the patient from treatment. Patient goes to event monitoring per section 18.0
Other non-hematologic adverse events	Grade 3 Grade 4		Omit dose until resolved to ≤ grade 1, then decrease dose by 1 step Omit dose and discontinue patient from treatment. Patient goes to event monitoring per section 18.0.

Rescue medication

The use of rescue medication/ procedures, such as any surgery or radiation therapy during the study is not permitted. The patient will be discontinued if such procedures are required.

→ → 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
BASED ON INTERVAL ADVERSE EVENT			
Blood and lymphatic system disorders	Febrile neutropenia associated with fever (temperature $\geq 38.5^{\circ}\text{C}$)	Lenalidomide	<ul style="list-style-type: none"> • Omit lenalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to \leq grade 2 prior to Day 21 and fever has resolved, restart lenalidomide at next lower dose level and continue the cycle through Day 21. If febrile neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained.
Investigations	Grade 3 neutrophil decreased and sustained for 7 days or Grade 4 neutropenia	Lenalidomide	<ul style="list-style-type: none"> • Omit lenalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to \leq grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21. Restart next cycle at the lower 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.
	Platelet count decreased \geq Grade 3 (platelet count $< 50,000/\text{mm}^3$)	Lenalidomide	<ul style="list-style-type: none"> • Omit lenalidomide dose. • Follow CBC weekly • Hold anticoagulation until platelets $> 50,000$ • If platelet count resolves to \leq grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21.

→ → 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
Skin and subcutaneous tissue disorders	Rash maculo papular Grade 2 or 3.	Lenalidomide	<ul style="list-style-type: none"> • Omit lenalidomide dose. Follow weekly. • If the toxicity resolves to \leq grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21. Restart next cycle at the lower dose level.
	Any rash Grade 4	Lenalidomide	Discontinue lenalidomide. Remove patient from study. Go to event monitoring.
Nervous system disorders	Peripheral sensory Neuropathy Grade 3	Lenalidomide	<ul style="list-style-type: none"> • Omit lenalidomide dose. Follow at least weekly. • If the toxicity resolves to \leq grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21. Restart next cycle at the lower dose level.
	Grade 4	Lenalidomide	<ul style="list-style-type: none"> • Discontinue lenalidomide. • Remove patient from study. • Go to event monitoring.
Immune system disorders	Allergic reaction Grade 2-3	Lenalidomide	Omit dose. Follow at least weekly. If the toxicity resolves to \leq grade 1 prior to Day 15 restart at next lower dose level and continue the cycle until Day 21. Restart next cycle at the lower dose level.
	Grade 4	Lenalidomide	Discontinue lenalidomide study drug. Go to event monitoring.
Vascular disorders	Thromboembolic event \geq Grade 3	Lenalidomide	Omit dose and start anticoagulation; restart at investigator's discretion (maintain dose level).
	Hyperthyroidism or Hypothyroidism	Lenalidomide	<ul style="list-style-type: none"> • Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. <p>See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.</p>

→ → 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
	Other non-hematologic toxicity ≥ Grade 3	Lenalidomide	Omit (interrupt) 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. Restart next cycle at the lower dose level.

* 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 toxicity can be attributed to either lenalidomide or LDE225, both drugs must be omitted, and once toxicity has resolved to the level allowing restarting the drugs, lenalidomide should be reintroduced first at the same dose level and if no toxicity is observed for the rest of the cycle, LDE can be reintroduced at one lower dose level. If the toxicity recurs, lenalidomide stopped and restarted at one lower dose level once toxicity resolves to the required grade. In this situation, LDE225 can be restarted at the same level.

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: If one of the drugs have to be discontinued, the patient can continue on the other drug.

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:

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- 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. The use of growth factors should follow published guidelines of the ASCO 2006 Update of Recommendation for the Use of White Blood Cell Growth Factors: An Evidence-based Clinical Practice Guideline Journal of Clinic Oncology, Vol. 24, No 19 (July 1), 2006” pp. 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 Prophylactic full dose aspirin (325 mg once daily) is mandatory to protect against thrombosis. If patients are intolerant to aspirin, substitution with low molecular weight heparin (LMWH) is recommended.
- 9.9 Patients who are planning on embarking on a new strenuous exercise regimen after initiation of study treatment. NB: Muscular activities, such as strenuous exercise, that can result in significant increases in plasma CK levels should be avoided while on LDE225 treatment.

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):

(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 10.5). With this information, determine whether the event must be reported as an expedited report (see Section 10.31). 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 10.6 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 Events

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

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.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME Arm

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting-

Routine Reporting

- Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is stated in the protocol. See Section 10.6.
- Routine AE reporting for Phase 3 clinical studies using an investigational agent/intervention and a commercial agent in combination must be reported as defined by the general guidelines provided by sponsors, Groups, Cancer Centers, or Principal Investigators. See Section 10.6.

Expedited Reporting

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for investigational agents/interventions in Section 10.4, and where indicated, an expedited report must be submitted.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to Section 10.4 for specific AE reporting requirements or exceptions.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch.
- An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the

commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

10.4 Expedited Reporting Requirements for IND/IDE Agents

10.41 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention^{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
 - 1) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
 - 2) A congenital anomaly/birth defect.
 - 3) 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.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days			24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		7 Calendar Days	

NOTE Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.42 of the protocol.

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported 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

10.42 Expedited Reporting Requirements for 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 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:

- 7) Death
- 8) A life-threatening adverse event
- 9) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- 10) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 11) A congenital anomaly/birth defect.
- 12) 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.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days			24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		7 Calendar Days	

NOTE Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.42 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.

¹Serious 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.

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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 to the FDA, MedWatch, 5 [REDACTED]

10.43 Special Situations for Expedited Reporting

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events

An expedited report may not be required for specific Grade 1, 2 and 3 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

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

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

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 abnormalities 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 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 be reported. Three options are available to describe the event:
 - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic 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 Special reporting requirements for Novartis

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E)

Reporting procedures

The investigator must complete the FDA MedWatch 3500a form and Novartis SAE coversheet in English, assess the relationship to study treatment and send the initial completed MedWatch form and Novartis SAE coversheet by fax 1.888.299.4565 within 24 hours to the local Novartis Clinical Safety & Epidemiology (CS&E) Department. The investigator must then ensure that the form and coversheet are accurately and fully completed with follow-up information and fax those to Novartis CS&E Department within 2 to 3 calendar days for deaths or life-threatening events and 5 calendar days for other serious adverse events. The original and the duplicate copies of the FDA MedWatch form, Novartis SAE coversheet, and the fax confirmation sheet must be kept with the case report forms at the study site.

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or discontinued study participation. The MedWatch form, Novartis SAE coversheet, and fax confirmation sheet must be retained. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

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 (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Investigations	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
General disorders	Edema limbs	X	

and administration site conditions			
	Fatigue	X	X
Gastrointestinal Disorders	# of Stools per day	X	
	Diarrhea		X
	Constipation		X
	Vomiting	X	X
Pain	Myalgia	X	X
Infections and infestations	Sepsis	X	X
Blood and lymphatic system disorders	Febrile neutropenia	X	X
Skin and subcutaneous tissue disorders	Rash maculo-papular	X	X
Nervous system disorders	Peripheral sensory neuropathy	X	X
Vascular	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:

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).

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 Multiple Myeloma Patients

11.11 Determination of Baseline values for disease assessment

- **Baseline values for disease assessment:** All disease response measurements will be based on the values obtained at the time of diagnosis if there has been no relapse prior to transplant. If patients had a disease relapse prior to transplant, the baseline values will be those obtained at the time of relapse immediately prior to the transplant. If patient had treatment for the relapsed disease prior to transplant, the values will be from prior to this therapy, ie, the time of relapse.

Clinical relapse is defined using the definition of clinical relapse in the IMWG criteria. In the IMWG criteria, clinical relapse is defined as requiring one or more of the following direct indicators of increasing disease and/or end-organ dysfunction that are considered related to the underlying plasma cell proliferative disorder:

1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging
2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
3. Hypercalcemia (>11.5 mg/dL; >2.875 mM/L)
4. Decrease in hemoglobin of more than 2 g/dL (1.25 mM) or to less than 10 g/dL
5. Rise in serum creatinine by more than or equal to 2 mg/dL (≥ 177 mM/L)
6. Hyperviscosity

NOTE: If the patient does not meet the IMWG criteria for clinical relapse but the patient has increasing M protein leading to a change in clinical management, this will also be considered a relapse at the discretion of the treating physician.

11.12 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 be applied at the time of the first measurement at which the quantitative aspect of the response category has been satisfied without the confirmation step having been satisfied. The designation “u” will precede the standard abbreviations, and will include usCR, uCR, uVGPR, uPR, uMR, uPD.

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

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

- **Evaluable disease:** Patients who do not have a “measurable” serum M-protein, serum free light chain, or urine M-protein.
- **Oligosecretory myeloma:** Patient with multiple myeloma who has NEVER had “measurable” serum M-protein or urine M-protein, but has had a detectable M-protein in his/her serum and/or urine and/or measurable serum free light chain.
- **Non-secretory myeloma:** Patient with multiple myeloma who has NEVER had a detectable M-protein in his/her serum and/or urine.

11.2 Clarification of test indications

Listed below are the minimal required tests required to assess response based on the characteristics of their disease at on study.

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	SPEP⁴	24 hr UPEP²	Ig FLC	BM Bx
Serum M-protein ≥ 1 g/dl, and urine M-protein ≥ 200 mg/24 hrs	X	X		
Serum M-protein ≥ 1 g/dl, but urine M-protein < 200 mg/24 hrs	X			
Serum M-protein < 1 g/dl, and urine M-protein ≥ 200 mg/24 hrs		X		
Serum M-protein < 1 g/dl, urine M-protein < 200 mg/24 hrs, but involved Ig FLC is ≥ 10 mg/dL			X	

Serum M-protein < 1 g/dl, urine M-protein < 200 mg/24 hrs, involved Ig FLC is <10 mg/dL, bone marrow \geq 30% plasma cells				X ³
--	--	--	--	----------------

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 *At a minimum, a bone marrow biopsy should be repeated every 3 months until documented response. Bone marrow biopsy results do not need to be repeated after documented response.*

⁴ *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	<ul style="list-style-type: none"> • CR as defined <i>plus</i> • Normal FLC ratio <i>and</i> • Absence of clonal PCs by immunohistochemistry or 2- to 4- color flow cytometry ⁱ
Complete Response (CR) ^{b, j}	<ul style="list-style-type: none"> • Negative immunofixation of serum and urine ^c <i>and</i> • Disappearance of any soft tissue plasmacytoma <i>and</i> • <5% PCs in Bone Marrow <i>and</i> • If the only measurable disease is FLC, a normal FLC ratio ^d
Very Good Partial Response (VGPR)	<ul style="list-style-type: none"> • Serum and urine M-protein detectable by immunofixation but not on electrophoresis ^c <i>or</i> • ≥90% reduction in serum M-protein and urine M-protein <100 mg/24 h ^c • If the only measurable disease is FLC, a ≥90% reduction in the difference between involved and involved FLC levels
Partial Response (PR)	<ul style="list-style-type: none"> • 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 the only measurable disease is FLC, a ≥50% reduction in the difference between involved and involved FLC levels • If the only measurable disease is BM, a ≥ 50% reduction in BM PC's (provided the baseline PC's was ≥ 30%) • If present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas
Minor Response (MR)	<ul style="list-style-type: none"> • If present at baseline, ≥25% but < 49% reduction of serum M protein <i>and</i> reduction in 24-hour urine M-protein by 50-89% which still exceeds 200mg/24 hours ^c <i>and</i> • If present at baseline, 25-49% reduction in the size of soft tissue plasmacytoma <i>and</i> • No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response)
Progressive Disease (PD) ^{b, h}	<p>Increase of 25% from lowest value in any of the following ^{f, g}:</p> <ul style="list-style-type: none"> • Serum M-protein (absolute increase must be ≥ 0.5 mg/dL) <i>and/or</i> • Urine M-protein (absolute increase must be ≥ 200 mg.24 hrs) <i>and/or</i> • If the only measurable disease is FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) <i>and/or</i> • If the only measurable disease is BM, bone marrow PC percentage (absolute increase must be > 10%) ^e <p>Or any one or more of the following:</p> <ul style="list-style-type: none"> • Development of new bone lesion or soft tissue plasmacytoma or definite increase in the size of existing bone lesions or soft tissue

	plasmacytoma <ul style="list-style-type: none"> • 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 Bone marrow criteria for PD are only to be used in patients without measurable disease by M protein and by FLC;

^f 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.

^g 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.

^h 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.

ⁱ 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.

^j If a patient has already achieved a complete response prior to registration as a result of the induction therapy or stem cell transplant, the patient will be considered a continued complete response if they continue to meet the complete response criteria at the next assessment. Reconfirmation of complete response is not required.

12.0 Descriptive Factors**12.1 Prior treatment(s) types and number**

12.1.1 Immunomodulatory agents (IMiDs)

12.1.2 Alkylators

12.1.3 Proteasome inhibitors

12.2 Response to last treatment prior to SCT: Yes vs. no**12.3 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 vs. serum immunoglobulin free light chain (involved FLC) ≥ 10 mg/dL vs. Distinguish between SPEP measurement versus quantitative IgA measurement for serum M-protein. All measurements are based on those at the time of Baseline values for disease assessment as defined in Section 11.11.****13.0 Treatment/Follow-up Decision at Evaluation of Patient****13.1 Patients who are sCR, CR, VGPR, PR, MR, or SD (or usCR, uCR, uVGPR, uPR, uMR) will continue treatment per protocol.****13.2 Observation: At the completion of 18 cycles of treatment, the patient will be observed every 90 days for up to 3 years from the time of registration. If the patient develops progressive disease or receives subsequent treatment for myeloma while in observation then the patient will go to the event-monitoring phase per Section 18.0.****13.3 Criteria for Patient Initiation of Event Monitoring:**

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

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

- 13.4 A patient is deemed *ineligible* if after registration, it is determined that 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 (or off study, if applicable).
- 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.
- 13.5 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.
- 13.6 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. No further data submission is necessary.
- 13.7 Criteria for Study Discontinuation

The study may be temporarily or permanently discontinued at any site and at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- Safety concerns
- Poor enrollment
- Non-compliance with the protocol, Good Clinical Practice guidances or other regulatory requirements by the Investigator(s)
- Request to discontinue the trial by a regulatory or health authority or an IRB
- Manufacturing difficulties/concerns

All Investigators and the requisite regulatory authorities will be notified if the study is suspended or terminated for safety reasons. In the case of such termination, the Investigator will notify the IRB.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected for this Protocol

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Visit 1: Study Entry	Visit 2: End of cycle 18	Visit 3: At suspected CR	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Minimal residual disease	Mandatory	Bone marrow aspirate	EDTA (lavender)	3 mL (1)	X	X	X	No	Ambient
Flow cytometry for early myeloma cell (myeloma stem cell)	Mandatory	Bone marrow aspirate	EDTA (lavender)	3 mL (1)	X	X	X	No	Cool Pak
Gene expression profiling	Optional	Bone marrow aspirate	EDTA (lavender)	3 mL (2)	X	X	X	No	Cool Pak

14.2 Collection and Processing

14.21 Minimal residual disease evaluation: This will be performed on bone marrow aspirate following a wash no lyse method on fresh samples.

14.22 Gene expression profiling: This will be performed on CD138 sorted plasma cells from the bone marrow aspirate.

14.3 Shipping and Handling

14.31 Minimal Residual Disease

Draw 1-2 mLs of bone marrow aspirate into one 2 mL lavender top EDTA tube. It is important to thoroughly mix the blood with the anticoagulant agent by gently inverting the tube not less than five times. Carefully unstop the EDTA tube and using the pipette provided transfer 1 mL of aspirate into the provided 1 mL Cyto-Check tube. Gently invert vial by hand 3 times to mix. Immediately ship ambient via overnight delivery to the address below. A kit will be shipped to the participating site.

Please plan to obtain samples for bone marrow aspirates on Monday through Thursday only.

14.32 Gene expression profiling

No special instructions

14.33 Shipping Specimens: Samples can be shipped on ice. They should be shipped overnight taking care to avoid Friday collection and shipping.

Please notify Mayo Clinic by email [REDACTED] or phone, [REDACTED] 5 to ensure that samples are received.

[REDACTED]
Mayo Clinic
[REDACTED]
200 First Street SW
Rochester, MN 55905

14.4 Background and Methodology

14.41 Minimal residual disease evaluation: Currently 30-40% of patients achieve a CR with initial therapy. In most cases, patients classified as CR in reality have minimal residual disease (MRD) since (i) many such patients relapse, and (ii) residual clonal disease is detectable in most by more sensitive techniques such as multiparameter flowcytometry and PCR based techniques.(Sarasquete, Garcia-Sanz et al. 2005; Mateo, Montalban et al. 2008; Paiva, Vidriales et al. 2009). We will determine minimal residual disease positivity at various stages of treatment, among patients achieving a conventional complete response. Bone marrow

aspirates will be evaluated for presence of clonal plasma cells as well as the ratio of clonal to non-clonal plasma cells after 3 cycles and whenever a CR is suspected and a marrow is done.

MRD detection will be done on BM samples as previously described³². Plasma cells are identified by their characteristic CD45/CD38/CD138 staining pattern with light chain restriction and CD19/CD56 phenotype on each case. One ml (milliliter) of BM (bone marrow) is subjected to flow cytometry on a Cantos Flow Cytometer. Samples are collected ungated, up to one million events per tube.

- 14.42 Gene expression profiling. CD138-sorted MM tumors cells, and CD138 negative tumor microenvironment cell compartment, obtained from clinical bone marrow sampling, will be banked before and after 12 cycles of therapy as well as at the time of documented CR (CD138- only); high-resolution array-based gene expression studies of paired (before/after) samples will be undertaken. Samples will be analyzed using high-density oligonucleotide microarrays containing probes for 50,000 transcripts and variants including 14,500 known genes (U133 Plus 2- array; Affymetrix, Santa Clara, CA) using standard methods.
- 14.421 Sample Preparation, Fragmentation, Array Hybridization, and Scanning: The purified cDNA is used as the template for *in vitro* transcription reaction for synthesizing biotinylated complementary RNA (cRNA) using an RNA transcript labeling reagent (Affymetrix). The quality of the fragmented biotin-labeled cRNA in each experiment is evaluated before hybridizing by both gel electrophoresis and hybridizing (fraction of the sample) onto test-3 microarray and analyzing as a measure of quality control. Appropriate amounts of labeled cRNA and control oligonucleotide B2 are added along with control cRNA (BioB, BioC, BioD), herring sperm DNA, and bovine serum albumin to the hybridization buffer. The hybridization mixture is heated at 99°C for 5 minutes followed by incubation at 45°C for 5 minutes before applying the sample onto the GeneChip. Hybridization is performed at 45°C for 16 hours with mixing, following which the solutions are removed, and arrays washed and stained with streptavidin-phycoerythrin (Molecular Probes, Portland, OR). After washes, probe arrays are scanned using the gene chip system confocal scanner. All samples will run individually with no pooling.
- 14.422 Data Analysis and Interpretation: The arrays will be scanned using a Genechip 300 scanner and GeneChip 5.0 software (Affymetrix) will be used to quantitatively analyze the scanned image. Algorithms in the software use probe cell fluorescence intensities to calculate an average intensity for each set of probe pairs representing a gene, which directly correlates with the amount of mRNA. The plasma cell gene expression from different patient groups as described before will be compared using Genespring. The selection criteria for all genes reported as differentially expressed will be as follows: (1) in absolute analysis, a detection call of present; (2) a change either increased or decreased; (3) signal of greater than 1,000; and (4) greater than 2-fold differences in expression in all

pair wise comparisons. Only genes with transcript levels that satisfied all 4 criteria will be considered as significantly differentially expressed. Average differences in mean expression (as measured by fluorescence intensity) of transcripts that met all of these criteria are compared across groups using the 2-sided Student's *t* test. *P* values for differences between means of *P* less than .05 are considered statistically significant.

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 1.25-, 2.5-, 5-, 10-, 15-, 20-, and 25-mg 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.

Placebo capsules for the 1.25-, 2.5-, 5-, 10-, 15-, 20-, and 25-mg lenalidomide capsules are available for use in blinded studies. Each placebo capsule visually matches the drug product.

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

A lenalidomide formulation for constitution to oral suspension is available for subjects who cannot swallow capsules and for subjects who participate in clinical studies; however, it is not commercially available. It is provided in an individually sealed 10 mL polyethylene terephthalate glycol (PETG) vial with a chlorobutyl stopper sealed with an aluminum crimp seal and a flip-off cap. Each vial contains 80 mg of lenalidomide powder with no inactive ingredients. The lenalidomide powder in each vial is constituted with 8 mL of suspending vehicle (Flavor Blend flavored) to create a lenalidomide suspension with a final concentration of 10 mg/mL.

15.13 **Preparation and storage:** Lenalidomide should be stored at room temperature, between 59 and 86°F (15-30°C). 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.

The suspension formulation is administered by mouth.

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.

The bioavailability of the lenalidomide oral suspension (10 mg/mL, active pharmaceutical ingredient in Flavor Blend flavored suspending vehicle) was also evaluated in healthy subjects. The study demonstrated that the lenalidomide oral suspension is bioequivalent to the approved 25-mg capsule formulation at the 25-mg dose. A high-fat meal reduced the rate and extent of lenalidomide suspension absorption, resulting in an approximate 20% decrease in AUC, 57% decrease in C_{max} , and 1.9-hour delay in t_{max} .

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 ($\geq 10\%$): 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, sinusitis, 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 ($\geq 1\%$ 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-glutamyl

ltransferase increased, dehydration, diabetes mellitus, gout, hypercalcemia, hyperuricemia, hypophosphatemia, hypomagnesemia, hyponatremia, iron overload, muscular weakness, acute myeloid leukemia, basal cell carcinoma, T-cell type acute leukemia, Myelodysplastic syndrome, squamous cell carcinoma of skin, 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 hematopoietic 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 in accordance with the REVLIMID REMS™ program. Per standard 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. 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 Patients 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 patient 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 any 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.
- 15.199 Agent may cause fatigue, dizziness, vertigo or blurred vision. Instruct patients to use caution when driving or operating machines.
- 15.200 Monitor LFT's and report any elevations to the study team. Instruct patient to report abdominal pain and/or jaundice to the study team.
- 15.201 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.

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

15.203 Monitor Renal function, renal failure has been reported.

15.2 LDE225 Sonidegib (LDE225, Odomzo®)

15.21 **Background:** Sonidegib (LDE225) is a potent antagonist of Hedgehog (Hh)- and Smoothened (Smo)-dependent signaling. Smo is a G protein-coupled receptor (GPCR)-like molecule that positively regulates the Hh signal transduction pathway. Hh pathway activation at or upstream of Smo is linked to the pathogenesis of several types of cancer .

In particular, activating mutations in Hh pathway genes have been identified in patients with medulloblastoma (MB), basal cell carcinoma (BCC), and rhabdomyosarcoma. Aberrant upregulation of the Hh pathway without known mutation is linked to the pathogenesis of many other cancer types including pancreatic breast, esophageal, gastric, colorectal, glioblastoma, ovarian, sarcoma, acute and chronic leukemias, multiple myeloma, lymphoma and small-cell lung cancer (SCLC). Antagonists of Smo are hypothesized to block the growth of tumors that are dependent on Hh pathway activation. Furthermore, preclinical and emerging clinical data suggests Hh signaling may play an important role in many hematological cancers, such as acute and chronic leukemia, multiple myeloma and lymphomas.

15.22 **Formulation:** Hard gelatin capsules contain LDE225 drug substance at dose strength of 200 mg, with the following excipients: crospovidone, lactose monohydrate, magnesium stearate, poloxamer 188, silica colloidal anhydrous/colloidal silicon dioxide and sodium laurilsulfate/sodium lauryl sulfate. The capsule uses a size 00 pink (“Swedish Orange”) opaque capsule shell with either no imprint or with “NVR” imprinted in black ink on the cap and “SONIDEGIB 200MG” in black ink on the body. The capsule shell contains gelatin, red iron oxide and titanium dioxide.

Immediate-release film-coated tablets contain 200 mg sonidegib drug substance (based on free base content), with the following excipients for the tablet core: cellulose, microcrystalline cellulose, crospovidone, hypromellose, magnesium stearate, colloidal silicon dioxide, silicon dioxide, sodium lauryl sulfate, sodium starch glycolate and talc. The film-coating contains black, red, and yellow iron oxides, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide. The tablets are reddish to pale red in color with an ovaloid shape, a beveled edge, and “CC” engraved on one side and “NVR” on the other side.

An oral suspension has been established at the dose strength of 50 mg sonidegib per mL (based on free base content) for adult and pediatric use in the medulloblastoma indication (refer to Study CLDE225A2114 for relative

bioavailability relative to the capsule in healthy volunteers and Study CLDE225C2301 for patient experience). The oral suspension is prepared in-situ at the clinical sites, yielding a white homogenous suspension. The clinical sites are supplied with sonidegib powder for oral suspension, which is packaged in amber glass bottles with a white child-resistant cap. The white to practically white powder contains sonidegib drug substance with the following commonly used compendial grade excipients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, sucralose (or E955) and Tutti Frutti dry flavor. Additionally, 80 ml of a Solvent for oral suspension (a clear solution of medium-chain triglycerides) is supplied packaged in amber glass bottles with a white child-resistant cap. (Each bottle contains a 20 ml overfill to permit the complete withdrawal of the 60 ml nominal volume from the bottle). Oral dosing syringes are provided to enable accurate preparation and dispensing of the reconstituted suspension. The packaging materials employed are commonly used in commercial products.

- 15.23 **Preparation and storage:** The capsules are packaged in high density polyethylene (HDPE) bottles with an induction seal and child-resistant closure, with desiccant. Please refer to the clinical label for the current shelf-life, in-use period and storage conditions.

Novartis provides a kit composed of an amber bottle with sonidegib powder for oral suspension, an amber glass bottle with solvent for oral suspension, and a dosing syringe to prepare the oral suspension. The instructions for use describe reconstitution of the powder at the study site by site personnel. Patients receive reconstituted oral suspension in multiple-use bottles, and dosing syringes for daily administration. A second instruction for use describes drug dosing at home. As the shelf-life and storage conditions of both the sonidegib powder and the solvent for oral suspension will be continually assessed based on accelerated and long term stability data, please refer to the clinical label for current shelf-life, in-use and storage conditions.

Sonidegib is considered a teratogenic agent. Great care must be taken when handling dosage forms of sonidegib, especially while pregnant. Due to the physical properties of sonidegib drug substance and dosage forms, sonidegib can neither be inhaled nor absorbed through the skin. Therefore hands should be washed thoroughly with soap and water upon direct exposure to sonidegib.

- 15.24 **Administration:** LDE225 capsules should be taken once daily, at approximately the same time each day.
LDE225 should be taken as follows:
Patients should be instructed to take their once-a day dose at approximately the same time each day 2 hours after a light breakfast (eg. juice, toast and jam). Food intake should be avoided for at least 1 hour after study drug administration.

Patients should follow the administration instructions on the clinical label and the instructions for use that accompany the sonidegib suspension.

- On days where PK samples need to be collected prior to taking study drug, that day's dose should be taken in the clinic (study site)
- Each daily dose of LDE225 should be taken with a glass of water and consumed over as short a time as possible (e.g. 1 capsule every 2 minutes)
- Patients should be instructed to swallow capsules whole and to not chew or open them
- Each daily dose of LDE225 (including days which involve PK blood sampling) should be taken **2 hours after** a light breakfast (e.g., consisting of juice, toast and jam). If breakfast was completed at 08:00 a.m., then study drug administration should occur at 10:00 a.m. Food intake should be avoided for at least 1 hour after study drug administration
- Patients must avoid grapefruit, pomegranate, star fruit and Seville (sour) oranges during the entire study. The juices and products containing these fruits may also be avoided.
- If vomiting occurs during the course of the treatment, then no re-dosing of the patient is allowed before the next scheduled dose
- If the patient forgets to take his/her daily morning dose, then he/she should take LDE225 within 6 hours after the missed dose. If more than 6 hours have passed, then that day's dose should be omitted and the patient should continue treatment with the next scheduled dose
- Patients should inform the investigational site staff of any missed or delayed dose

15.25 **Pharmacokinetic information:**

Absorption and Distribution – Median time to T_{max} occurs at 2-4 hours (range 1-48 hrs). T_{max} appeared to be independent of dose. Steady state for sonidegib is anticipated to be reached after 8-12 weeks of dosing in most patients. The 2nd generation tablet variants provided bioavailability similar to the capsule formulation. The oral suspension provided higher bioavailability compared with the capsule formulation, with a 600 mg oral suspension dose yielding a similar AUC_{0-14d} to that of 800 mg capsule dose. A large positive food effect was observed, with 8-fold C_{max} and 7-fold AUC, compared with fasting conditions. In anticipation of a food effect, food consumption will continue to be restricted around the time of dosing for clinical studies. Sonidegib is highly bound (>97%) to human plasma proteins.

Metabolism: The metabolite profile in plasma shows unchanged sonidegib as the major circulating component (36%). The main circulating metabolite (M48) is pharmacologically inactive as an inhibitor of Smoothed receptor. Sonidegib is primarily metabolized by CYP3A4 in the liver.

Excretion – Excretion is almost exclusively through feces (88.7% of dose and as unchanged), with no detectable levels in the urine. The median half-life is approximately 28 days.

- 15.26 **Potential Drug Interactions:** LDE225 is shown to potently inhibit CYP2B6 and CYP2C9. Because of the potential risk for drug-drug interactions, using concomitant medications known to be metabolized by these enzymes with low therapeutic index (CYP2B6: bupropion, efavirenz, cyclophosphamide, ifosfamide, thiotepa, procarbazine; CYP2C9: celecoxib, diclofenac, tolbutamide, warfarin, tamoxifen, phenytoin) should be carefully monitored or excluded, in accordance with protocol-specific guidelines.

Precaution should be taken when LDE225 is administered with any known potent CYP3A4 inhibitors and inducers, as these have the potential to influence the biotransformation and clearance of LDE225. See 3.37 tables for more information.

LDE225 is an inhibitor of breast cancer resistance protein (BCRP) in vitro. Therefore substrates, especially those with a narrow therapeutic range, should be used with caution. BCRP substrates include zidovudine, pantoprazole, cimetidine, sulfasalazine, nitrofurantoin, mitoxantrone, methotrexate, topotecan, imatinib, and irinotecan or “statins”.

- 15.27 **Known potential toxicities:** Based on its mechanism of action and the results of the pre-clinical toxicology studies, the major potential toxicities of LDE225 in humans are anticipated to be the following: thinning or early closure of growth plates, in growing children; disruption of gametogenesis and impairment of the development of reproductive organs with resultant infertility; and gastrointestinal irritation with potential mucosal damage. LDE225 is a teratogen, as are other Smo inhibitors, in view of the role of Hh signaling in embryo-fetal development. In addition, the emerging clinical data has revealed dose-limiting toxicities characterized by elevated plasma CK associated with muscle pain and/or muscle spasms, rhabdomyolysis being a serious adverse event.

The following adverse reactions occur at a frequency of $\geq 10\%$:
Metabolism and nutrition disorders: decreased appetite, weight decreased
Nervous system disorder: Dysgeusia, headache, insomnia, dizziness
Gastrointestinal disorders: Nausea, diarrhea, abdominal pain, vomiting
Skin and subcutaneous tissue disorders: Alopecia, pruritus
Musculoskeletal and connective tissue disorders: Muscle spasms, musculoskeletal pain, myalgia, asthenia
Reproductive system and breast disorders: amenorrhea
General disorders: Fatigue, pain, cough, UTI, lethargy, pain in extremity, pyrexia, dyspnea, lipase increased

The following adverse reactions occur at a frequency of 1-10%:
Metabolism and nutrition disorders: Dehydration
Gastrointestinal disorders: Dyspepsia, constipation, gastroesophageal reflux disorder
Skin and subcutaneous tissue disorder: Rash, abnormal hair growth
Musculoskeletal and connective tissue disorders: myopathy (muscular fatigue and muscular weakness)

Other reported serious adverse reactions include febrile neutropenia, anemia, blood glucose increased, gastritis, myositis, myoglobin blood increased, hypersensitivity, and acute renal failure. Adverse events occurred based on lab abnormalities: hemoglobin decreased, lymphocyte count decreased, serum creatinine increased, serum creatine phosphokinase (CK) increased, blood glucose increased, lipase increased, alanine amino transaminase (ALT) increased, aspartate amino transaminase (AST) increased, amylase increased.

Routine safety monitoring will include physical examinations (including vital signs), hematology, serum chemistries, coagulation tests, urinalyses, cardiac monitoring, as well as bone monitoring in pediatric patients. In particular, the main dose-limiting toxicities observed in the clinic relate to muscle toxicity that is characterized with plasma CK elevation, increased plasma myoglobin, muscle spasms, myalgia and muscular weakness. Therefore, close monitoring of plasma CK levels during the first 8 weeks of LDE225 therapy is recommended.

- 15.28 **Drug procurement:** Drug will be provided free of charge to study participants by Novartis.
- 15.29 **Nursing Implications:**
 - 15.291 Agent is considered teratogenic. Warn patients that they should not become pregnant or father a child while on this agent. Adequate birth control measures should be exercised. Caution should be used for health care workers that are administering the agent especially if pregnant. If direct exposure to LDE225 powder occurs, the hands should be washed thoroughly with soap and water.
 - 15.292 Assess patient's concomitant medications. Care should be exercised when administering with agents that utilize the CYP2B6, CYP2C9, and CYP3A4 pathways as there is the potential for drug-to drug interactions, especially those with a low therapeutic index (see section 15.16).
 - 15.293 Given the very early investigational nature of this agent, not all side effects can be known at this time. Assess patients regularly and report side effects to the study team.
 - 15.294 Based on preclinical studies, there is the possible risk of infertility, warn patients of this possibility.
 - 15.295 Gastrointestinal side effects (nausea, decreased appetite, vomiting, diarrhea and constipation) have all been reported. Manage symptomatically and monitor for effectiveness.
 - 15.296 Muscle spasms and myalgias have been seen. Treat symptomatically and monitor for effectiveness.
 - 15.297 Monitor LFT's.
 - 15.298 Alopecia has been reported. Warn patients of this possibility.
 - 15.199a Instruct patient to take medication at the same time each day, 2 hours after a light breakfast and to avoid food intake for 1 hour after taking medication.

- 15.199b Fever can be seen. Treat symptomatically with antipyretics and monitor for effectiveness.
- 15.199c Monitor CBC w/diff. Instruct patient to report any fever, signs or symptoms of infection, unusual bruising or bleeding to the study.

16.0 Statistical Considerations and Methodology

16.1 Overview:

This is a Phase II study designed to assess the proportion of complete responses as well as the toxicity associated with Lenalidomide and LDE225 used as maintenance therapy following autologous stem cell transplantation.

16.11 Primary Endpoint:

The primary endpoint of this trial is the rate of complete response. Throughout Section 16.0, complete response will be considered synonymous with “success”, unless specified otherwise. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for complete response, with the exception of patients who are determined to be a major treatment violation.

16.2 Statistical Design:

16.21 Decision Rule:

In a Mayo Clinic database study that captured data prospectively into a continuously updated database, 178 multiple myeloma patients received a stem cell transplant within 12 months of diagnosis.(Kumar, Lacy et al. 2011) The complete response rate to stem cell transplant was 35%. Since patients in this study will receive a stem cell transplant within 12 months of diagnosis, an increase in complete response rate to greater than 35% with the addition of maintenance therapy with lenalidomide and LDE225 would be of interest.

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 35%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 55%. The following one-stage binomial design uses 39 evaluable patients to test the null hypothesis that the true success proportion in a given patient population is at most 35%.

16.211 Final Decision Rule: If 17 or fewer successes are observed in the first 39 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 18, this will be considered evidence of promising activity, and the treatment may be recommended for further testing in subsequent studies.

16.212 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.34.

16.22 Sample Size:

The single stage study design to be used is fully described in section 16.21. A maximum of 39 evaluable patients will be accrued onto this phase II study unless undue toxicity is encountered. We anticipate accruing an additional 4 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Maximum projected accrual is 43 patients.

16.23 Accrual Rate and Study Duration:

The anticipated accrual rate is approximately 2-3 patients per month. Therefore, the accrual period for this phase II study is expected to be about 1.5 years. The final analysis can begin approximately 2 years after the trial begins, i.e. as soon as the final patient accrued to this trial has been followed for at least 6 months.

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

If the true success proportion is...	0.35	0.40	0.45	0.50	0.55
Then the probability of declaring that the regimen is promising and warrants further study is...	0.10	0.27	0.50	0.74	0.90

16.25 Other Considerations: Toxicity, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan: The analysis for this trial will commence at planned timepoints (see 16.2) and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair, in accord with CCS Standard Operating Procedures, availability of data for secondary endpoints (eg, laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when last patient has been followed for at least 6 months.

16.31 Primary Endpoint:

16.311 Definition: The primary endpoint of this trial is the rate of complete response. A complete response is defined as a CR noted as the objective status on 2 consecutive evaluations. Complete response will be evaluated using all cycles. Note that a patient may have already achieved a complete response prior to registration as a result of the induction therapy or stem cell transplant. In this case, a continued complete response will be considered a complete response for the primary endpoint. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, with the exception of patients who are determined to be a major treatment violation.

16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success proportion will be calculated.

16.32 Definitions and Analyses of Secondary Endpoint:

16.321 Overall survival: Survival time is defined as the time from SCT to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier (Kaplan and Meier, 1958). All evaluable patients will be included in this analysis. In addition, overall survival time from the time of registration will also be evaluated.

16.322 Progression-free survival: The progression-free survival time is defined as the time from SCT to progression or death due to any cause. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier (Kaplan and Meier 1958). The progression-free survival rates at 1 year and 2 years post SCT will be assessed. In addition, progression-free survival from the time of registration will also be evaluated.

16.323 Adverse Events: The maximum grade for each type of adverse event, regardless of causality, will be recorded and reported for each patient, and frequency tables will be reviewed to determine adverse event patterns. Adverse events will continue to be recorded and reported through the observation period, or up to 30 days after the last day of study drug treatment for patients who do not proceed to observation.

16.33 Correlative Analyses

16.331 Minimal residual disease will be assessed on bone marrow aspirate in all patients achieving CR. The proportion of patients who achieve MRD negative status will be estimated by the number of patients who are MRD negative divided by the total number of evaluable patients who achieve a CR. Exact binomial 95% confidence intervals for the true MRD negative rate will be calculated.

16.34 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals.

16.35 Data & Safety Monitoring

16.351 Safety Analysis: The trial will initially open to only 6 evaluable patients that will be included in a safety analysis. The study will temporarily close while these patients are evaluated for toxicity during the first 3 months of treatment.

Safety Analysis Stopping Rule: If 0 or 1 patients experience a DLT, the study will be reopened to accrual. If 2 or more patients experience a DLT, the study team will review all adverse events and determine whether study will be closed or reopened with adjustments to the starting dose levels as outlined in Table 8.1.

For this protocol, dose-limiting toxicity (DLT) will be defined as an adverse event attributed (definitely, probably, or possibly) to the study treatment during the first 3 cycles of treatment and meeting the following criteria:

Toxicity (CTCAE v4.0) DLT Definition

<u>Toxicity (CTCAE v3.0)</u>	<u>DLT Definition*</u>
Hematologic	Grade 4 ANC for ≥ 7 days or PLT $< 25,000$ for ≥ 7 days
Infection	Grade 4
Febrile Neutropenia	Defined as fever $\geq 38.5^{\circ}\text{C}$ ($38 > 1$ hour) with grade ≥ 3 neutropenia
CK elevation	\geq Grade 3 CK elevation
Other Non-hematologic	\geq grade 3 as per NCI Common Terminology Criteria for Adverse Events v4.0**.

*Any toxicities that caused dose delay of > 2 weeks of the intended next dose will also be considered dose-limiting.

**Grade 3 nausea, vomiting, or diarrhea with maximal supportive treatment(s) will be considered dose-limiting. Fatigue and mouth sores that are considered Grade 3 with an attribution of definitely, probably, or possibly related to treatment will be reviewed by the study team to determine if they were due to other causes (i.e. disease progression or infection) or treatment. If it is determined that the fatigue or mouth sores were due to other causes they would not be considered a DLT and if they were due to treatment they would be considered a DLT.

- 16.352 The principal investigator(s) and the study statistician will review the study at least every quarter 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.
- 16.353 Adverse Event Stopping Rule: The stopping rule specified below is based on the knowledge available at study development. We note that the 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 treatments 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 this study 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 4 or more patients in the first 15 treated patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.
- if after the first 15 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 “ClinicalTrials.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 2 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 6 months.

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 or gender, 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 Mayo, has a population which includes approximately 3% minorities. Based on prior Mayo studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and about 33% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	0	1	1
Not Hispanic or Latino	14	28	42
Ethnic Category: Total of all subjects	14	29	43
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	13	28	41
Racial Category: Total of all subjects	14	29	43

Ethnic Categories: **Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rican, 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 N/A

18.0 Records and Data Collection Procedures**18.1 Submission Timetable****Initial Material(s) -**

Case Report Form (CRF)	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
On-Study Form	≤2 weeks after registration		
Baseline Adverse Event Form			
Pretreatment Measurement Form (registration values)			
Myeloma pretreatment measurement form baseline values for disease assessment (see Section 11.11)			
Myeloma Pretreatment Measurement Form Baseline Values at Time of Diagnosis			
On-study lab reports ¹ : SPEP, UPEP, Serum FLC, Serum and Urine Immunofixation, Serum Immunoglobulins, Bone Marrow biopsy and aspirate, X-Ray skeletal survey, Cytogenetic, FISH.			
Bone Marrow Aspirate Submission Form			
Lab reports for baseline values for disease assessment ¹ as defined in Section 11.11: SPEP, UPEP, Serum FLC and Immunoglobulins			
End of Active Treatment/Cancel Notification Form	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy		

1. Submit copy of lab reports to the MCCC Operations Office, Attention: [REDACTED]

[REDACTED] 200 First Street SW, Rochester, MN 55905.

Test Schedule Material(s) -

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Evaluation/Treatment Form	X ²	X	
Evaluation/Observation Form			X ¹
Nadir/Adverse Event Form	X	X	X

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Treatment Measurement Form	X	X	X
SPEP, UPEP, FLC , Serum and Urine Immunofixation, Bone Marrow biopsy and aspirate, X-Ray skeletal survey	X ³	X ³	X ³
End of Active Treatment/Cancel Notification Form		X	
Notification Form – Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form	At each occurrence (see Section 10.0)		
ADR/AER	At each occurrence (see Section 10.0)		
Bone Marrow Aspirate Submission Form	X (See Section 14.0)	X	X (See Section 14.0)

1. Complete at each evaluation during Observation (see Section 4.0).
2. Complete at each evaluation during Active Treatment (see Section 4.0).
3. Submission of these reports is only required for documentation of CR 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 to MCCC Operations Office, Attention: [REDACTED] 200 First Street SW, Rochester, MN 55905 .

Follow-up Material(s) -

CRF	Event Monitoring Phase¹				
	q. 3 months until PD or subsequent treatment for myeloma ²	At PD or subsequent treatment for myeloma ²	q. 6 mos. after PD or subsequent treatment for myeloma	Death	New Primary
Event Monitoring Form	X	X	X	X	At each occurrence

1. If a patient is still alive 5 years after registration, no further follow-up is required.
2. For documentation of progression, submit one report for one of the measures where progression was seen (SPEP or UPEP or FLC or X-Ray) to MCCC Operations Office, Attention: [REDACTED] 200 First Street SW, Rochester, MN 55905.

19.0 Budget

19.1 Costs charged to patient: routine clinical care, study drug lenalidomide

19.2 Tests to be research funded: study drug LDE225

19.3 Other budget concerns:

20.0 References

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Prohibited concomitant medications

Strong CYP3A inhibitors and inducers

No clinical studies have been performed to confirm if LDE225 is a sensitive CYP3A4 substrate, hence concomitant use of strong CYP3A4 inhibitors and inducers is not permitted. Patients receiving concomitant medications known to strongly inhibit and/or induce CYP3A4/5 that are deemed medically necessary should be excluded from the study. A partial list of drugs that are inducers, and inhibitors of CYP3A4/5 is included in [the table below](#). The above list of medications has been generated by Novartis Oncology Clinical Pharmacology (OncCP) (DDI database document: last update August 2010) that is compiled by using information listed under “draft guidance for industry, drug interaction studies, CDER 2006”, Indiana University School of Medicine drug interaction tables at <http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable>, and “drug interaction from University of Washington. Patients should be instructed not to take grapefruit, St John Wort or Seville (sour) orange juice while receiving LDE225 treatment throughout the study due to potential CYP3A4/5 inhibition. The other drugs without an asterisk should be carefully used as concomitant therapy.

Table	Medications that are CYP3A4/5 inducers or inhibitors
Medications	
Inhibitors	<p>HIV antivirals: indinavir, nelfinavir, ritonavir*, saquinavir</p> <p>Antibiotics: azithromycin, ciprofloxacin, chloramphenicol, clarithromycin, erythromycin*, fluconazole^{&}, itraconazole*, ketoconazole*, voriconazole*, telithromycin, posaconazole, norfloxacin</p> <p>Calcium channel blockers: diltiazem^{&}, verapamil^{&}</p> <p>Antidepressants: , fluvoxamine, nefazodone[*]</p> <p>Miscellaneous: amiodarone, cimetidine, delavirdine, diethyl-dithiocarbamate (chlorzoxazone), interleukin-10*, mifepristone, mibefradil , grape fruit juice^{&}, isoniazid^{&}, aprepitant^{&}</p>
Inducers	<p>HIV antivirals: efavirenz, nevirapine</p> <p>Anticonvulsants: barbiturates**, carbamazepine**, Oxcarbazepine**, phenytoin**, phenobarbital**</p> <p>Systemic glucocorticoids: dexamethasone^{&}, glucocorticoids, hydrocortisone, prednisolone, prednisone</p> <p>Antibiotics: rifabutin**, rifampicin**, rifapentine**</p> <p>Antidiabetics: pioglitazone, troglitazone</p> <p>Miscellaneous: modafinil, hormone replacement therapy, oral contraceptives, St John's wort**</p>
<p>*- Known strong inhibitors of CYP3A4 are estimated to cause a ≥ 5 fold increase in the AUC values or a ≥80% decrease in clearance of a CYP3A4 substrate;</p> <p>& -a moderate inhibitor is estimated to cause a ≥2-but < 5 fold increase in the AUC values or a 50-80% decrease in the clearance of a sensitive substrate when the inhibitor is given at the highest approved dose.</p> <p>** -Known strong inducers of CYP3A4/5 (AUC decrease by 50-80%)</p>	

Medications that are CYP2B6 and CYP2C9 substrates (narrow therapeutic index)

LDE225 is a potent inhibitor of drugs metabolized by the cytochromes CYP2B6 and CYP2C9 *in vitro*. Because of the potential risk for drug-drug interactions, using concomitant medications known to be metabolized by these enzymes that have low therapeutic index (see [table below](#)) is not permitted in the study. The other drugs without an asterisk should be carefully used as concomitant therapy.

Table	Drugs metabolized by CYP2B6 and CYP2C9
CYPs	Drugs metabolized by CYPs
CYP2B6	Bupropion, cyclophosphamide, efavirenz, ifosfamide, methadone
CYP2C9	NSAIDs: diclofenac, ibuprofen, lornoxicam, meloxicam, naproxen, piroxicam, suprofen Oral hypoglycemic agents: tolbutamide, glipizide Angiotensin II blockers: losartan, irbesartan Sulfonylureas: glyburide/glibenclamide, glipizide, glimepiride, tolbutamide Miscellaneous: amitriptyline, celecoxib, fluoxetine, pravastatin ^{&} , glyburide, nateglinide, phenytoin, rosiglitazone, tamoxifen, torsemide, warfarin*, quinidine*
<p>* -narrow therapeutic index: drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g. Torsade de Pointes) are not allowed</p> <p>&- statins – If it is essential that the patient takes a statin to control hyperlipidemia [see Section 5.1.7.5], then only pravastatin may be used with extra caution. Pravastatin has the lowest potential of cause rhabdomyolysis compared with other statins (3 cases/ 6 millions of prescription from 1994 to 2002) (Evans et al. 2002) and the lowest risk for drug-drug interactions with LDE225, as it is primarily transformed in the liver cytosol by sulfonation, not by CYP2C9 or CYP3A4. (Evans et al. 2002)</p>	

Warfarin and coumadin derivatives

Therapeutic doses of warfarin sodium (Coumadin®) or any other coumadin-derivative anticoagulants are not permitted since LDE225 is a competitive inhibitor of CYP2C9 based on the *in vitro* data. An alternative, therapeutic anticoagulation may be accomplished using low-molecular weight heparin.

Drugs that may increase risk of rhabdomyolysis when used concomitantly with LDE225

Selected drugs that may increase risk of myopathy and rhabdomyolysis when used concomitantly with LDE225 should be avoided. Such drugs should be discontinued for at least 2 weeks prior to initiation of LDE225 and it must be ensured the plasma CK is within the normal range at baseline. The list compiled below is based on reported association of the individual drugs with muscle toxicity and in addition to the potential risk of clinically relevant PK drug-drug interaction with LDE225 through inhibitory effects on CYP3A4

(enzyme metabolized LDE225) or the inhibitory effect on CYP2C9 by LDE225 of drugs that may induced rhabdomyolysis.

- Azoles antifungals: Itraconazole, ketoconazole, fluconazole, voriconazole
- Macrolides: azithromycin, clarithromycin, erythromycin, telitromycin
- Fibrates: gemfibrozil
- 3-hydroxy-3 methyl-glutaryl (HMG) CoA reductase inhibitors (Statins): Atovastatin, Fluvastatin, Fluvastatin XL, Lovastatin, Pravastatin*, Rosuvastatin- and Simvastatin
- Antiretrovirals: Indonavir and ritonavir

Others: phenobarbital, barbiturates, phenytoin and isoniazid

* If it is essential that the patient stays on a statin to control hyperlipidemia [see [Section 5.1.7.5](#)], only pravastatin may be used with extra caution; CK should be monitored weekly during the first 8 weeks on concomitant treatment with LDE225 and then bi-weekly thereafter for 8 weeks and then every four weeks

ECOG Performance Status Scale

SCORE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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

Name _____

Mayo Clinic No. _____

PATIENT MEDICATION DIARY

Please complete this diary on a daily basis. Write in the amount of the dose of lenalidomide and LDE225 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 lenalidomide or LDE225, please record this information.

Week of: _____

Study Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Lenalidomide							
LDE225							

Week of: _____

Study Drug	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Lenalidomide							
LDE225							

Week of: _____

Study Drug	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Lenalidomide							
LDE225							

Week of: _____

Study Drug	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Lenalidomide							
LDE225							

Patient Signature _____

Date: _____

My next scheduled visit is: _____
If you have any questions, please call: _____
