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TITLE: Denosumab for Smoldering Multiple Myeloma

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IND Number: **Denosumab:**

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Study Title	**Denosumab for Smoldering Multiple Myeloma**
Principle Investigator and Study Chair	Brea Lipe, MD Wilmot Cancer Institute, University of Rochester, Rochester NY USA
Study Site & Enrollment	University of Rochester Medical Center 20 evaluable patients
Study Rationale	Smoldering multiple myeloma (SMM) is a premalignant condition conveying a variable risk of progression to multiple myeloma, but with a median time to progression of 2 years for high risk patients [1]. While the exact mechanisms of transformation from SMM to multiple myeloma (MM) are not known, alterations in bone metabolism are seen in both patients with SMM and MM and are in part mediated through altered bone metabolism leading to increased bone destruction [2]. Recently, changes in markers for bone-turnover have been associated with disease progression from monoclonal gammopathy of undetermined significance (MGUS) to MM [3]. As MM remains an incurable disease, therapies aimed to prevent disease progression of SMM are needed. Denosumab is a monoclonal antibody targeting receptor activator of nuclear factor kappa-B ligand (RANKL) that correlates to improved bone microarchitecture and strength [4], but whose biologic effects also make denosumab of particular interest in SMM and MM. In patients with MM, RANKL is up regulated while OPG is suppressed. This dysregulation correlates with clinical disease activity, severity of bone disease, and decreased survival [5]. In patients with MGUS and SMM, RANKL, and the RANKL/OPG ratio are increased compared to healthy controls, but to a lesser extent than in patients with frank MM [5]. Through actions via RANKL, denosumab also causes a reduction in DKK1 levels which is implicated in disease progression and skeletal dysregulation and provides further rationale for the use of denosumab in patients with SMM who are both at risk for skeletal events and disease progression [6]. We therefore propose to study the impact of denosumab on bone architecture and markers of bone metabolism in patients with SMM.

Study Objectives	**Primary objective:** • To determine the change in risk for progression to MM in patients with SMM treated with denosumab for one year. **Secondary objectives:** • To measure the change in monoclonal (M) serum protein or free light chain (FLCs) as appropriate to assess response per IMWG criteria listed in Appendix A. • Determine the rate of skeletal related events (SREs) • To assess the rate of disease progression to MM • Determine the progression free survival (PFS) • Define the rate of adverse events (AEs) • Determine the change in bone mineral density **Exploratory objectives:** • To determine the impact of denosumab on soluble factors of bone activity including MIP-1α, DKK1, Notch signaling, sclerostin, RANKL, and OPG. • To describe the changes in mesenchymal and osteolineage populations and osteoprogenitor function • To determine the impact of denosumab discontinuation on markers of bone turnover and bone formation including serum bone alkaline phosphatase, total osteocalcin, procollagen type 1 N-terminal propeptide, serum C-terminal cross-linked telopeptides, and urinary N and C-terminal cross-linked telopeptides.
Inclusion Criteria	Patients must meet all of the following inclusion criteria to be eligible for participation in this study: 1. Patient has confirmed SMM according to the definition of the International Myeloma Working Group (IMWG) definition: serum M-protein ≥3 g/dL or BMPC >10% but less than 60%, or both, along with no plasma-cell related abnormal organ and marrow function (CRAB related to a plasma cell disorder) within 24 weeks prior to baseline, without new evidence of disease progression to multiple myeloma. • C: Absence of hypercalcemia, evidenced by a calcium ≤11 mg/dL, • R: Absence of renal failure, evidenced by a creatinine ≤ 2.0mg/dL, • A: Absence of anemia, evidenced by a hemoglobin ≥10 g/dL • B: Absence of lytic bone lesions per IMWG recommendations: One of either PET-CT, low-dose whole-body CT (LDWBCT) or MRI of the whole body or spine. Increased uptake on PET-CT alone is not adequate for the diagnosis of multiple myeloma; evidence of underlying

	osteolytic bone destruction is needed on the CT portion of the examination.

	2. One of the risk factors below that portends for an increased risk of progression to MM: • An abnormal free light chain ratio • M-spike ≥ 2 g/dL • ≥ 20% bone marrow plasma cells • Immunoparesis ≥ 20% less than the institutional normal standard of the uninvolved immunoglobulins 3. Serum calcium or albumin-adjusted serum calcium ≥ 2.1 mmol/L (8.4 mg/dL) and ≤ 2.9mmol/L (11.5 mg/dL) (Reference range 8.5-10.8 mg/dL) 4. Able to tolerate daily supplementation of calcium and vitamin D 5. Must have a vitamin D level ≥ 30 ng/mL or have a level 12ng/mL to 30ng/mL and be on active repletion with cholecalciferol 50,000 IU po weekly or equivalent. 6. Participants must have normal organ as defined below: • Total bilirubin ≤ 2.0 x institutional upper limit of normal (ULN); patients diagnosed with Gilbert's syndrome can enroll with a total bilirubin > 2 after review of the principal investigator • AST(SGOT) ≤2.5 × institutional ULN • ALT(SGPT) ≤2.5 × institutional ULN 7. Age ≥ 18 years. 8. ECOG PS ≤1 9. Life expectancy greater than 12 months 10. Subjects with reproductive potential must be willing to use, in combination with his/her partner, 2 highly effective methods of effective contraception or practice sexual abstinence throughout the study and continue for 5 months after the study duration. Subjects who are surgically sterile (e.g. history of bilateral tubal ligation, hysterectomy) or whose sexual partner is sterile (e.g. history of vasectomy) are not required to use additional contraceptive measures. 11. Ability to understand and the willingness to sign a written informed consent document. 1. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up. 12. Statement on Inclusion of Women and Minorities • Men and women of all ethnicities and racial backgrounds are eligible for this study.

Exclusion Criteria	Patients who meet any of the following exclusion criteria are not to be enrolled to this study: 1. Prior administration of denosumab. 2. Any history of IV bisphosphonate use prior to or during the study 3. Prescription oral fluorides or bisphosphonate usage > 3 months within the past 2 years 4. Systemic corticosteroids > 10mg prednisone per day 5. Patient has symptomatic MM, as defined by any of the following related to the plasma cell disorder: • Lytic lesions or pathologic fractures. • Anemia (hemoglobin <10 g/dL) • Hypercalcemia (corrected serum calcium > 11.0 mg/dL) • Renal insufficiency (creatinine > 2.0 mg/dL). • Clonal bone marrow plasma cells > 60% • An involved serum free light chain (kappa or Lambda) > 100mg/L with the ratio of the involved/uninvolved free light chains also > 100 mg/L • One or more osteolytic lesions on radiography, but more than one lesion is required if < 10% marrow plasma cells. From MRI imaging, there must be more than one lesion of > 5mm in size. 6. Other: symptomatic hyperviscosity, amyloidosis, plasma cell leukemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein) 7. Prior history or current evidence of osteonecrosis/osteomyelitis of the jaw. 8. Active dental or jaw condition that requires oral surgery, including tooth extraction. 9. Non-healed dental/oral surgery, including tooth extraction. 10. Planned invasive dental procedures during the course of study. 11. Evidence of any of the following conditions per subject self-report or medical chart review: • Any prior invasive malignancy within 3 years of enrollment that may affect outcome of study • Any non-invasive malignancy not treated with curative intent or with known active disease within 3 years before enrollment that may affect outcome of study • Major surgery or significant traumatic injury occurring within 4 weeks before enrollment • Active infection with Hepatitis B virus or Hepatitis C virus

	• Known infection with human immunodeficiency virus (HIV) requiring IV anti-infective therapy 13. Subject is pregnant or breast feeding, or planning to become pregnant within 5 months after the end of treatment. 14. Female subject of child-bearing potential is not willing to use, in combination with her partner, 2 methods of highly effective contraception during treatment and for 5 months after the end of treatment. 15. Clinically significant hypersensitivity to denosumab or any components of denosumab 120mg. 16. Known sensitivity to any of the products to be administered during the study (e.g., calcium, or vitamin D). 17. Subject is receiving or is less than 14 days since ending other experimental drug (no marketing authorization for any indication). 18. Any major medical or psychiatric disorder that, in the opinion of the investigator, might prevent the subject from completing the study or interfere with the interpretation of the study results.
Efficacy Endpoints	The primary objective of the study is to determine the rate of downgraded risk for the progression to multiple myeloma as defined by a reduction in the risk category for progression. The risk categories will be identified as in section 7.1.6 using the Mayo clinic and PETHEMA criteria [7, 8].
Study Design	Single center, open label, Phase II single-arm trial of denosumab in patients with smoldering multiple myeloma. The trial will aim to enroll 10 patients per year with 2 years of follow up after completion of therapy for a total study duration of 5 years.
Dosing Regimen & Treatment Study Visits	All cycles will be 28 days. Denosumab: 120mg will be administered subcutaneously once every 4 weeks, +/- one week. **SCHEMA**

	
Correlative Experiments	Study labs (peripheral blood and urine) will be collected at baseline, 13 months, 24 months, and 36 months. A bone marrow biopsy and DXA scan will be collected at baseline and at 13 months, 24 months, and 36 months. Study labs will be analyzed in the laboratory of Brea Lipe.

1 . BACKGROUND

1.1 SMM

Plasma cell dyscrasias exist as a spectrum of diseases, from the asymptomatic precursors monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) to the malignancy multiple myeloma (MM). MM is relatively rare with 30,000 new cases estimated in 2018 [9],and with 14% of those patients expected to have SMM [10]. MGUS is a relatively common finding with increasing incidence with age, seen in up to 3% of patients over age 50 and 5% of patients over age 70 [11]. MM is an incurable cancer causing significant morbidity and mortality characterized by hypercalcemia, renal insufficiency, anemia, and lytic bone lesions (CRAB criteria), and is felt to be preceded by precursor plasma cell dyscrasias in the form of MGUS or SMM [12]. Most patients with MGUS or SMM do not develop MM, providing an opportunity to both study and understand who is at risk to progress and to investigate strategies aimed at preventing the devastating consequences for the patients destined to get MM.

SMM requires the absence of myeloma defining events related to the plasma cell disorder; CRAB criteria (hypercalcemia, anemia, renal insufficiency, bone lesions, and an involved serum light chains< 100mg/L and a light chain ratio < 100), and the presence of between 10%-60% clonal plasma cells in the bone marrow, and/ or a serum M protein level ≥3 g/dL, and /or a urine monoclonal protein level ≥500 mg/24 hours [13]. While patients with SMM are by definition, asymptomatic, they carry a lifelong risk of progressing to the incurable malignancy, multiple myeloma (MM). The average risk of progression to MM from SMM is 10% per year for the first five years, and the risk decreases with the passage of time to a maintained risk of 1% per year [14]. Amongst patients with SMM, risk factors that predispose a higher than average risk of progression have been identified and include a serum monoclonal protein level ≥ 4g/dL, a bone marrow plasma cell percentage > 50% or between 20-50%, immunoparesis, and an abnormal free light chain ratio of involved to uninvolved chains of >8 or elevated from normal [1, 7]. A more recent risk stratification system was presented at ASCO, 2019 and predicts a higher risk of disease progression to MM for patients with a paraprotein of at least 2g/ dL and at least 20% bone marrow plasma cells [60]. Stratification of SMM using risk factors for progression has allowed greater precision in identifying patients more likely to get MM. This is an exploratory study and will include any patient with SMM with an increased risk of progression to MM.. SMM is differentiated from MGUS by a higher plasma cell burden and increased risk of progression to MM [11]. Patients with MGUS have clonal bone marrow plasma cells < 10%, an M-protein < 3g/dL, urine monoclonal proteins < 500 mg/24 hours, and the absence of myeloma defining events or CRAB criteria and an average risk of progression to MGUS of 1% per year [15].

*Risk factors included in the model include monoclonal protein levels ≥3g/dL, Bone marrow plasma cells ≥10%, and having an abnormal free light chain ratio

The current standard of care for patients with SMM or MGUS is observation without active treatment because early trials for the treatment of SMM did not demonstrate a survival advantage and demonstrated toxicity [16, 17]. Initial results with thalidomide demonstrated response rates, but widespread adaptation of early treatment was limited by the risks involved with treating patients who may never develop an active disease[18, 19]. A randomized trial of thalidomide + zoledronic acid versus zoledronic acid alone showed improved PFS, but no difference in the rate of PFS as defined by CRAB criteria or OS [20]. More recently, the PETHEMA group reported results on the treatment of patients with SMM at high risk for disease progression who were randomized to treatment with lenalidomide and dexamethasone versus observation alone. Patients on the treatment arm had improvements in the 3-year overall survival and lower rates of disease progression [21]. However, generalizability of the PETHEMA study has been questioned based on the use of flow markers for risk stratification, and on the choice of salvage therapy in the observation arm that did not include lenalidomide, and the way the trial dealt with biochemical progression. Despite this, the PETHEMA study has regenerated interest in the optimal management of patients with SMM and has lead the way for multiple ongoing clinical trials, including this proposed study supported by Amgen.

1.2 BONE DISEASE

While the exact mechanisms of transformation from MGUS to MM are not known, alterations in bone metabolism are seen in patients with MGUS and MM and are in part mediated through altered bone metabolism leading to increased bone destruction [2]. Throughout life, bone remodeling is an ongoing balance between cells that make and breakdown bone, namely osteoblasts, osteoclasts, and osteocytes. In patients with MM, the balanced coupling of bone modeling cells is disrupted and leads to increased osteoclast activity and subsequent bone destruction [22]. The increased bone turnover seen in myeloma is also thought to contribute to disease pathogenesis and can be correlated with advanced disease stage

and an increased risk of death [23]. Recently, changes in markers for bone-turnover have been associated with disease progression from MGUS to MM [3]. A meta-analysis has also demonstrated an increased risk of fracture and lower bone mineral density in patients with MGUS, demonstrating that alterations in bone metabolism precede the malignant disease phase and further supports a contributory role [24].

The perturbations of bone metabolism seen amongst patients with plasma cell dyscrasias are mediated in part through the Receptor Activator of Nuclear Factor- κB (RANK) and RANK Ligand (RANKL) pathway. RANKL is a membrane bound protein expressed on cells of osteoblast lineage that binds the RANK receptor on osteoclast precursors to induce osteoblastic resorption and increase osteoclast survival [2]. Osteoprotegrin (OPG), is a decoy receptor for RANK and limits osteoclastogenesis. In patients with MM, RANKL is up regulated while OPG is suppressed. This dysregulation correlates with clinical disease activity, severity of bone disease, and decreased survival [5]. In patients with MGUS, RANKL, and the RANKL/OPG ratio are increased compared to healthy controls, but to a lesser extent than in patients with frank MM [5]. MM cells are felt to directly participate in the bone dysregulation as MM cells can directly produce both RANKL and degrade OPG [25-27].

Clinically, the RANK/RANKL/OPG pathway has been exploited to alter bone modeling and decrease tumor burden. In the SCID-hu-MM mouse model of human MM, a RANKL antagonist limited bone destruction and reduced tumor burden [28]. Another study demonstrated the ability of OPG to decrease serum paraprotein levels and inhibit bone destruction in mouse models using the 5T2MM cell line [29]. In humans, targeting bone remodeling with bisphosphonates decreases skeletal related events [30, 31]. In vitro, bisphosphonates have a direct cytotoxic effect [32, 33]. It has been suggested as well that more potent bisphosphonates can improve overall survival rates [34, 35]. Overall, the animal and human experience demonstrates the therapeutic potential in targeting bone remodeling to modulate myeloma disease activity.

Given the early perturbations in bone modeling seen in patients with MGUS and SMM, bisphosphonates have been studied. Bisphosphonates are pyrophosphate analogs that bind bone hydroxyapatite and inhibit osteoclast function and bone resorption during remodeling [36]. In pamidronate and zoledronic acid, the most commonly used bisphosphonates for plasma cell disorders, the mechanism of action is through inhibition of the enzyme farnesyl pyrophosphate synthase, causing cytoskeleton abnormalities in osteoclasts [37]. The action of bisphosphonates translates to improvement in bone mineral density in patients with MGUS when given zoledronic acid [38]. However, randomized studies have evaluated the impact of bisphosphonates on SMM and found that while bisphosphonates decrease the risk of skeletal events, the progression free survival was not improved with the use of a bisphosphonate [39, 40].

1.3 EXPLORATORY ENDPOINTS

In patients with MGUS, altered bone architecture has also been linked to elevated DKK1, sclerostin, and MIP-1a levels [41]. DKK1 is a key regulator of osteoblast activity thought to play a role in myeloma bone disease through action via the Wnt pathway on RANKL and OPG [42]. DKK1 is also thought to play a role in disease progression and relapse in MM. Therapies targeting DKK1 (BHQ880) are in development for the treatment of MM and SMM [43, 44]. Denosumab causes a reduction in DKK1 levels and further study

into correlation of the clinical impact of denosumab with DKK1 levels and osteoprogenitors evaluation are needed [6]. Notch signaling is also implicated in the progression of MM from precursor states through upregulation of RANKL and alterations in the bone marrow stromal environment [45]. The impact of denosumab on bone signaling pathways requires further study given the importance of these signaling pathways at the interface between bone RANKL expression, bone health, and MM disease pathogenesis.

In addition to altered bone modeling, MM involved alterations in bone cell function. Patients with MM have decreased osteocytes and impaired ability of bone marrow stromal cells to differentiate into osteoblasts [46, 47]. Cell to cell interactions within the bone marrow stromal compartment are important for MM cell homing and these altered stromal compartments in myeloma are important for disease pathogenesis [48]. The impact of denosumab on the precursor stromal environment is not known, but the importance of osteoprogenitors and the stromal compartment in MM pathogenesis make further study of potential denosumab impacts of particular importance. We therefore propose to study the impact of denosumab on bone architecture and markers of bone metabolism in patients with MGUS and SMM.

1.4 STUDY DRUG

Denosumab is a fully human monoclonal IgG2 antibody targeting RANKL in soluble and membrane bound forms. Denosumab binds with high affinity and specificity without binding to other related proteins of the TNF family [52]. A key difference between denosumab and bisphosphonates is that denosumab can exert effect within the extracellular milieu versus requiring internalization, allowing a more broad impact for denosumab on the development and survival of osteoclasts [53]. Furthermore, the activity of circulating denosumab allows for broader impact on bone versus at the bone mineral surface [54, 55]. Clinically, the differences between bisphosphonates and denosumab have been observed. In women with low bone mineral density, denosumab increased bone mineral density compared to a bisphosphonate [56] . Another study demonstrated the ability of denosumab to increase bone mineral density in patients already treated with a bisphosphonate [57]. In malignancy, a randomized phase 3 study demonstrated non-inferiority of denosumab compared to zoledronic acid in delaying time to first skeletal related event, but showed denosumab had greater ability to suppress bone turnover [58]. A phase 3 trial in MM also showed non-inferiority of denosumab compared to zoledronic acid, but demonstrated an improvement in progression free survival for patients treated on the denosumab arm [50]. Overall, the preclinical and clinical data suggests that denosumab exerts a fundamentally different impact on bone remodeling via a different mechanism of action from bisphosphonates and offers a novel opportunity to further explore the impact of RANKL inhibition in patients with plasma cell dyscrasias.

Case reports have suggested a rare risk of multiple vertebral fractures in women who discontinue denosumab[49]. The described case reports demonstrate the risk of multiple vertebral fractures in women undergoing treatment for breast cancer or with a history of osteoporosis, with longer duration of use seeming to correlate with the increased risk. There are no reports of multiple vertebral fractures in women treated with denosumab for multiple myeloma [50]. The exact mechanism of this increased risk is not known, but a rebound increase in bone resorption and resultant decrease in bone mineral density is thought to be the likely culprit [51]. In this study, we propose to follow markers of bone resorption

and DXA scans for 2 years after the discontinuation of denosumab to determine the long-term effects of denosumab withdrawal in patients with SMM.

Denosumab is currently FDA approved for the prevention of skeletal-related events in patients with multiple myeloma. Additional and updated information can be found in the Investigator's Brochure for additional and updated information on safety, background, and clinical experience.

1.4.1 PHARMACOKINETICS

Denosumab displays dose-dependent, nonlinear pharmacokinetics at doses below 60mg in healthy patients and patient populations evaluated. However, dose-proportional increases in exposure (based on area under the serum concentration-time curve and maximum serum denosumab concentration) are seen at higher doses. Bioavailability is 62%. In patients with newly diagnosed MM, 120 mg denosumab subcutaneously every 4 weeks (Q4W), up to 2.8-fold accumulation in serum denosumab concentrations was observed at steady-state (at 6 months) and these steady-state exposures were maintained with continued dosing. These results are consistent with a lack of change in pharmacokinetics with time upon multiple dosing. The mean elimination half-life was 28 days. Median reductions in uNTx/Cr of approximately 75% were observed by week 5. Reductions in bone turnover markers were maintained, with median reductions of 74% to 79% for uNTx/Cr from weeks 9 to 49 of continued 120mg q4w dosing.

1.4.2 DENOSUMAB DOSE SELECTION

As mentioned above, multiple phase 3 studies have demonstrated the efficacy and safety of the 120 mg SC Q4W dose regimen, with non-inferiority in the risk of SREs compared with zoledronic acid observed in subjects with advanced malignancies involving bone. In addition, this dose regimen led to significantly greater ($p < 0.0001$) suppression of uNTx/Cr when compared to zoledronic acid; this result and the robust SRE data for denosumab suggest that targeting maximal suppression of uNTx/Cr is an appropriate strategy for dose selection.

Denosumab administered at a dose of 120 mg SC Q4W has been well tolerated in the pivotal phase 3 studies. Therefore, 120 mg SC Q4W has been selected as the dose in subjects with SMM in this study

1.5 HYPOTHESIS

Current standard of care for patients with SMM is close observation despite the risk of developing an incurable malignancy. While the exact mechanisms for disease progression from SMM to MM are not known, perturbations in bone modeling are linked to disease progression biologically and clinically. Specifically, the RANKL pathway is postulated to play a role in the development of MM and inhibition of this pathway has led to tumor reduction in animal models. Denosumab is an FDA approved agent that has proven safe and effective in modulating bone modeling and preventing skeletal related events in

patients with MM. The unique mechanism of action and strong safety profile make denosumab an ideal drug to target disease progression in SMM. We therefore hypothesize that denosumab will result in reduced disease activity and a decreased risk of progression to MM. We further hypothesize that the alterations in bone remodeling will lead to increased bone mineral density, and lower than expected rates of disease progression and prolonged progression free survival when compared to historical averages. Additionally, the ultimate effects of denosumab on osteoprogenitor numbers, function and the impact on modulators of MM disease activity as it interacts with the bone marrow stromal compartment are not known but bear further investigation.

2 OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

- To determine the change in risk for progression to MM in patients with SMM treated with denosumab for one year.

2.2 SECONDARY OBJECTIVES

- To measure the change in monoclonal (M) serum protein or free light chain (FLCs) as appropriate to assess for disease response per the IMWG criteria in Appendix A.
- Determine the rate of skeletal related events (SREs)
- To assess the rate of disease progression to MM
- Determine the progression free survival (PFS)
- Define the rate of adverse events (AEs)
- Determine the change in bone mineral density as measured by bone densitometry (DXA scanning)

Exploratory objectives:

- To determine the impact of denosumab on soluble factors of bone activity including MIP-1α, Notch signaling, DKK1, sclerostin, RANKL, and OPG.
- To describe the changes in mesenchymal and osteolineage populations and osteoprogenitor function
- To determine the impact of denosumab discontinuation on markers of bone turnover and bone formation including serum bone alkaline phosphatase, total osteocalcin, procollagen type 1 N-terminal propeptide, serum C-terminal cross-linked telopeptides, and urinary N and C-terminal cross-linked telopeptides.

3 ELIGIBILITY CRITERIA

Patients must meet all of the following inclusion criteria and none of the exclusion criteria to be eligible for participation in this study.

3.1 INCLUSION CRITERIA

Patients must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Patient has confirmed SMM according to the definition of the International Myeloma Working Group (IMWG) definition: serum M-protein ≥3 g/dL or BMPC >10% but less than 60%, or both, along with no plasma-cell related abnormal organ and marrow function (CRAB related to a plasma cell disorder) within 24 weeks prior to baseline, without new evidence of disease progression to multiple myeloma.
   C: Absence of hypercalcemia, evidenced by a calcium ≤11 mg/dL.
   R: Absence of renal failure, evidenced by a creatinine ≤ 2.0mg/dL
   A: Absence of anemia, evidenced by a hemoglobin ≥10 g/dL.
   B: Absence of lytic bone lesions per IMWG recommendations:
   One of either PET-CT, low-dose whole-body CT (LDWBCT) or MRI of the whole body or spine. Increased uptake on PET-CT alone is not adequate for the diagnosis of multiple myeloma; evidence of underlying osteolytic bone destruction is needed on the CT portion of the examination.
2. One of the risk factors below that portends for an increased risk of progression to MM:
   - An abnormal free light chain ratio
   - M-spike ≥ 2 g/dL
   - ≥ 20% bone marrow plasma cells
   - Immunoparesis ≥ 20% less than the institutional normal standard of the uninvolved immunoglobulins
3. Serum calcium or albumin-adjusted serum calcium ≥ 2.1 mmol/L (8.4 mg/dL) and ≤ 2.9mmol/L (11.5 mg/dL) (Reference range 8.5-10.8 mg/dL)
4. Able to tolerate daily supplementation of calcium and vitamin D
5. Must have a vitamin D level ≥ 30 ng/mL or have a level 12ng/mL to 30ng/mL and be on active repletion with cholecalciferol 50,000 IU po weekly or equivalent.
6. Participants must have normal organ as defined below:

   Total bilirubin ≤ 2.0 x institutional upper limit of normal (ULN); patients diagnosed with Gilbert's syndrome can enroll with a total bilirubin > 2 after review of the principal investigator

   AST (SGOT) ≤2.5 × institutional ULN

   ALT (SGPT) ≤2.5 × institutional ULN
7. Age ≥ 18 years.
8. ECOG PS ≤1
9. Life expectancy greater than 12 months
10. Subjects with reproductive potential must be willing to use, in combination with his/her partner, 2 highly effective methods of effective contraception or practice sexual abstinence throughout the study and continue for 5 months after the study duration. Subjects who are surgically sterile

(e.g. history of bilateral tubal ligation, hysterectomy) or whose sexual partner is sterile (e.g. history of vasectomy) are not required to use additional contraceptive measures.

11. Ability to understand and the willingness to sign a written informed consent document.
12. Patient must be willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
13. Men and women of all racial and ethnic origins are eligible for this study.

3.2 EXCLUSION CRITERIA

Patients who meet any of the following exclusion criteria are not to be enrolled to this study:

1. Prior administration of denosumab.
2. Any history of IV bisphosphonate use prior to or during the study
3. Prescription oral fluorides or bisphosphonate usage > 3 months within the past 2 years
4. Systemic corticosteroids > 10mg prednisone per day
5. Known secondary cause for osteopenia or osteoporosis
6. Patient has symptomatic MM, as defined by any of the following related to the plasma cell disorder:
    - Lytic lesions or pathologic fractures.
    - Anemia (hemoglobin <10 g/dL)
    - Hypercalcemia (corrected serum calcium > 11.0 mg/dL)
    - Renal insufficiency (creatinine > 2.0 mg/dL).
    - Clonal bone marrow plasma cells > 60%
    - An involved serum free light chain (kappa or Lambda) > 100mg/L with the ratio of the involved/uninvolved free light chains also > 100 mg/L
    - One or more osteolytic lesions on radiography, but more than one lesion is required if < 10% marrow plasma cells. From MRI imaging, there must be more than one lesion of > 5mm in size.
7. Other: symptomatic hyperviscosity, amyloidosis, plasma cell leukemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein)
8. Prior history or current evidence of osteonecrosis/osteomyelitis of the jaw.
9. Active dental or jaw condition that requires oral surgery, including tooth extraction.
10. Non-healed dental/oral surgery, including tooth extraction.
11. Planned invasive dental procedures during the course of study.
12. Evidence of any of the following conditions per subject self-report or medical chart review:
    - Any prior invasive malignancy within 3 years of enrollment that may affect outcome of study
    - Any non-invasive malignancy not treated with curative intent or with known active disease within 3 years before enrollment that may affect outcome of study
    - Major surgery or significant traumatic injury occurring within 4 weeks before enrollment
    - Active infection with Hepatitis B virus or Hepatitis C virus
    - Human immunodeficiency virus (HIV) requiring IV anti-infective therapy
13. Subject is pregnant or breast feeding, or planning to become pregnant within 5 months after the end of treatment.
14. Female subject of child-bearing potential is not willing to use, in combination with her partner, 2 methods of highly effective contraception during treatment and for 5 months after the end of treatment.
15. Clinically significant hypersensitivity to denosumab or any components of denosumab 120mg.
16. Known sensitivity to any of the products to be administered during the study (e.g., calcium, or vitamin D).
17. Subject is receiving or is less than 14 days since ending other experimental drug (no marketing authorization for any indication).

18. Any major medical or psychiatric disorder that, in the opinion of the investigator, might prevent the subject from completing the study or interfere with the interpretation of the study results.

4 STUDY DESIGN

4.1 OVERVIEW OF STUDY DESIGN

This is an open label, Phase II trial of denosumab 120mg subcutaneous (SC) for patients with smoldering multiple myeloma (SMM). Subjects will be recruited from the James P. Wilmot Cancer Center, University of Rochester in Rochester, New York. Patients seen in the inpatient or outpatient setting with histologically confirmed SMM will be evaluated for this study.

20 patients will be treated as follows:

Denosumab: day 1 = 120mg SC every 4 weeks for 12 cycles. Cycles will be 28 days in length. Patients will be followed after completion of the study per standard of care for progression free survival for an additional 2 years after the last dose of denosumab. All patients will take daily vitamin D and calcium supplements of at least 1200mg elemental calcium and 800IU of vitamin D unless documented hypercalcemia develops on study. Pre-existing hypocalcemia must be corrected prior to initiating therapy with denosumab.

Serum vitamin D levels will be checked during screening and patients with hydroxyvitamin D level < 30ng/mL prior to denosumab administration must take at least 50,000 IU cholecalciferol weekly during treatment or equivalent until hydroxyvitamin D level ≥ 30ng/mL at which time patients can continue 800IU vitamin d daily. Hydroxyvitamin D levels < 30ng/mL will be repeated at least every 12 weeks or more frequently at investigator's discretion.

Correlates:

Clinical labs including CBC, CMP, and SPEP with IFE, FLC, quantitative immunoglobulins, and phosphorous levels will be collected at baseline, monthly during treatment, and at 13 months. A UPEP with IFE will be collected at baseline and at 13 months and additionally as per clinically indicated. Other clinical labs will be collected during the study per standard of care of the investigator.

Investigational Labs (peripheral blood and urine) to be collected at baseline, 13 months, 24 months, and 36 months will be analyzed in the laboratory of Brea Lipe

DXA scans will be conducted at baseline, 13 months, 24 months, and 36 months

Bone marrow and aspirate samples will be analyzed for baseline disease assessment and disease response in the clinical pathology laboratory at the University of Rochester Medical Center with additional aspirate samples to be analyzed in the Lipe laboratory.

Patients may discontinue therapy early for unacceptable toxicity or withdrawal from the study due to investigator decision or other reasons.

4.2 REGISTRATION

4.3 PATIENTS MUST NOT START ANY PROTOCOL INTERVENTION PRIOR TO REGISTRATION THROUGH THE WILMOT CANCER INSTITUTE. REGISTRATI ONS ARE CAPTURED IN THE WILMOT CANCER INSTITUTE REDCAP DATABASE AT THE UNIVERSITY OF ROCHESTER. SITE PERSONNEL WILL BE RESPONSIBLE FOR ENTERING THE PATIENT DATA INTO REDCAP WITHIN 24 HOURS OF THE SIGNING OF INFORMED CONSENT.

DISCONTINUATION FROM STUDY TREATMENT

Patients will be discontinued from study treatment for any of the following reasons:

- Partial withdrawal of consent meaning that a patient declines further denosumab, but consents to continued data and sample collection.
- Full withdrawal of consent meaning a patient does not wish to receive further denosumab and does not wish to continue any further study participation.
- Pregnancy in a female patient
- Inability of the patient to comply with study requirements
- Use of bisphosphonates or commercial use of denosumab
- Non-compliance/lost to follow-up
- Investigator discretion
- Study termination

Patients who discontinue from study treatment will continue to be followed for progression and late toxicities for one year. After withdrawal from protocol treatment, patients will be followed for AEs for 30 calendar days after their last dose of study drug. All new AEs occurring during this period will be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case the investigator must record his or her reasoning for this decision in the patient's medical records. All patients who have CTCAE Grade 3 or 4 laboratory abnormalities at the time of withdrawal should be followed until the laboratory values have returned to Grade 1 or 2, unless in the opinion of the investigator, it is not likely that these values are to improve because of the underlying disease. In this case, the investigator must record his or her reasoning for making this decision in the patient's medical records.

4.4 CRITERIA FOR STUDY T ERMINATION

This study will be considered terminated when 1 of the following conditions are met:

- All subjects have completed all required study visits;
- All subjects have discontinued from the study;

- The University of Rochester Data Safety Monitoring Committee or Institutional Review Board (IRB) discontinues the study because of safety considerations.

5 STUDY ASSESSMENTS AND TREATMENT SCHEDULE

Table 5.1 below lists all of the required assessments that should be performed at the corresponding study visit.

TABLE 5.1: STUDY ASSESSMENTS AND TREATMENT SCHEDULE

Procedure	Pre-study[1]	Study Day 1[2]	Weeks 2-4	C2-C12	Off Treatment[16]	24 months	36 months
Informed Consent	X						
Inclusion/Exclusion Criteria	X	X					
Medical and Treatment History	X						
Physical Exam[3]	X	X		X	X		
Oral Examination[4]	X	X		X	X		
ECOG Performance Status	X	X		X	X		
CBC with diff[3]	X			X	X		
Serum Chemistries[3,5]	X			X	X		
Serum Calcium[6]	X		X	X	X		
[7]sCTX, MIP-1α, DKK1, sclerostin, NOTCH RANKL, and OPG[7]	X				X		
[7]Markers of bone resorption and turnover	X				X	X	X
uNTX[8]	X				X	X	X
SPEP with IFE	X			X	X		
UPEP with IFE[9]	X				X		
Free light chain testing	X			X	X		
Vitamin D level	X				x		
Pregnancy Test[10]	X						
Bone marrow biopsy/ aspirate [11]	X				X		
PET-CT, low-dose whole-body CT or MRI of the whole body or spine	X						
Denosumab (SC)[12]		X		X			
DXA	X				X	X	X
Adverse Event Evaluation[13]		X		X	X		
Skeletal Event Recording[14]		X		X	X		
Concomitant Meds/Treatment[15]	X	X		X	X		

[1]**Screening**: All screening assessments must be completed and results obtained (e.g., chemistry, hematology) before entry into the study. Assessments conducted as standard of care do not require informed consent and may be provided as screening data. Imaging tests done as standard of care within the 12 months prior to enrollment will be considered within the screening window. Other screening assessments will have a 30 day window.

[2]**Study Day 1**: The first day that disease-related treatment is administered will be study day 1.
[3]**Physical Exam, Vital Signs, Hematology and Chem:** visit days have - 8 day window

[4]**Oral Examination:** A visual examination of the oral cavity, including teeth, mucosa to establish baseline oral health conditions and to identify any new abnormalities or changes in pre-existing conditions.
[5]**Serum Chemistries:** To include Na, K, CL, CO2, Mg, Phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST, ALT
[6]**Serum Calcium:** Monitored weekly for first 4 weeks then every cycle thereafter with a +/-3 day window. Calcium level willbe assessed prior to the administration of denosumab.

[7]**Soluble markers of bone turnover:** to be drawn after fasting to be analyzed in the laboratory of Brea Lipe, MD
[8]**Urinary markers:** to be collected from second morning void and to be analyzed in the laboratory of Brea Lipe, MD

[9]**UPEP:** Twenty-four hour urine samples for quantitation of M-protein and assessment of M-protein by immunofixation are to be requested from all patients during screening and will be analyzed in the local laboratory. Patients may refuse to provide urine samples.

[10]**Serum pregnancy test:** prior to Cycle 1 / Day 1 for females of childbearing potential. If patient has experienced menopause or no longer has uterus / ovaries this can be omitted.
[11]**Bone marrow biopsy and aspirate:** routine processing per pathology with aspirate and marrow samples sent to the laboratory of Brea Lipe, MD. Baseline bone marrow biopsy/aspirate not needed if recent sample within 3 months.
[12]**Treatment administration:** +/- 8 day window, but must have a minimum of 3-week intervals for administration of denosumab.

[13]**Adverse event reporting:** Adverse events must be assessed and documented at each scheduled clinic visit. Subjects must be followed for adverse events for 30 days after the last dose of denosumab, or until all denosumab-related toxicities and ongoing serious adverse events have resolved or are considered stable, whichever is later.

[14]**Skeletal event (SE) recording:** SEs will include all pathologic fractures, radiation to bone, surgery to bone for fracture or stabilization. SEs will be confirmed by imaging.
[15]**Concomittant medications:** Type and timing of concomitant medications will be collected. Calcium and vitamin D supplementation will be recorded.
[16]**Off treatment:** 4 weeks + 30 days following completion of cycle 12 or upon discontinuation of therapy. Follow AEs for 30 days after discontinuation of protocol treatment; after 30 days only AEs related to protocol must be followed. Follow-up survival and safety data will be collected per routine of care clinic visits for 2 years after the last dose of denosumab.

6 AGENT ADMINISTRATION

6.1 DENOSUMAB

- Denosumab is a human IgG2 monoclonal antibody that binds to human RANKL. Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.
- Onset of action: Decreases markers of bone resorption by ~85% within 3 days; maximal reductions observed within 1 month
- Duration: Markers of bone resorption return to baseline within 12 months of discontinuing therapy
- Bioavailability: SC: 62%
- Half-life elimination: ~25-28 days
- Time to peak, serum: 10 days (range: 3-21 days

6.1.1 FORM

- Denosumab will be provided as a sterile, clear, colorless to slightly yellow, preservative free liquid, in single-use 3.0 mL glass vials containing a deliverable dose of 1.7mL
- Denosumab will be packaged in boxes containing single-use vials of denosumab of 120mg/ 1.7mL (70mg/mL).

6.1.2 STORAGE AND STABILITY

- Store denosumab in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once removed from the refrigerator, denosumab must not be exposed to temperatures above 25°C/77°F or direct light and once removed from the refrigerator must be used within 24 hours. Discard denosumab if not used within 24 hours. Do not use denosumab after the expiry date printed on the label. Avoid vigorous shaking.

6.1.3 PREPARATION

- Each box of denosumab will contain one 1.7 mL vial. A single use syringe should be used to prepare the dose. There are no other special preparations required prior to denosumab administration.

6.1.4 ADMINISTRATION

- Subcutaneous injections are to be given at different locations. There are no other special preparations required prior to denosumab administration.

6.1.5 ORDERING

- Denosumab will be shipped to the responsible investigational pharmacist at the University of Rochester, who will check the amount and condition of the drug and enter these data into the Proof of Receipt Form. If any abnormality on the bottles is observed, the Pharmacist or the appropriate person must document that on the acknowledgement of receipt and contact that Sponsor and/or Sponsor designee. The Proof of Receipt Form should then be returned to Amgen Inc., and the original retained at the site.

6.1.6 SAFETY

A complete list of the adverse events and potential risks associated with the denosumab administered in this study can be found at http://pi.amgen.com/united_states/xgeva/xgeva_pi.pdf

- **Hypocalcemia:** Denosumab can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Hypocalcemia needs to be corrected prior to initiating denosumab. Monitor calcium levels and administer calcium, magnesium, and vitamin D as necessary. Calcium levels have to be monitored weekly for the first 4 weeks of treatment then every cycle thereafter. All subjects need to be adequately supplemented with calcium and vitamin D (see Section 5.1). If hypocalcemia occurs, additional short-term calcium supplementation may be necessary.
- **Osteonecrosis of the jaw (ONJ):** can occur in patients receiving denosumab, manifesting as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. The risk of ONJ is associated with the length of the exposure and risk factors for ONJ. Subjects should be monitored for ONJ as part of routine clinical practice. Subjects should be instructed to maintain good oral hygiene while on treatment with denosumab.

  A dental examination with appropriate preventive dentistry should be considered prior to treatment with denosumab in subjects with risk factors for ONJ. Subjects who are suspected of having or who develop ONJ while on denosumab should receive care by a dentist or an oral surgeon. Expert evaluation of patients with potential ONJ cases should be based on the American Association of Oral and Maxillofacial Surgeons (AAOMS) guidelines for ONJ. In subjects who develop ONJ during treatment with denosumab 120 mg, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves. While on treatment with denosumab, subjects should be instructed to avoid invasive dental procedures, if possible. For subjects in whom invasive dental procedures cannot be avoided, the clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

  In three phase III active-controlled clinical trials in subjects with advanced malignancies involving bone, ONJ was conformed in 1.8% of patients in the denosumab group treated with 120 mg subcutaneously every 4 weeks. The trials in patients with breast and prostate cancer included denosumab extension treatment phase (median overall exposure of 14.9 months; range

0.1 – 67.2). The patient-year adjusted incidence of confirmed ONJ was 1.1% during the first year of treatment and 4.1% thereafter. The median time to ONJ was 20.6 months (range: 4-53).

- **Atypical femoral fracture (AFF):** has been reported with denosumab. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. AFF most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. During denosumab treatment, subjects should be advised to report new or unusual thigh, hip, or groin pain. Subjects presenting with such symptoms should be evaluated for an incomplete femoral fracture, and the contralateral femur should also be examined. Expert evaluation of patients with potential AFF cases should be based on the American Society for Bone and Mineral Research (ASBMR) guidelines for A FF.
- **Hypersensitivity:** Clinically significant hypersensitivity including anaphylaxis has been reported with use of denosumab. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritus, and urticaria. Clinically significant hypersensitivity has been identified as a contraindication for treatment with denosumab. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue denosumab therapy permanently
- **Multiple vertebral fractures:** There is a risk of multiple vertebral fractures (MVF) following denosumab discontinuation. When denosumab is discontinued, evaluate the individual patient's risk for vertebral fractures.
- **Musculoskeletal pain**: Including severe cases, has been identified as an adverse drug reaction based on data from the post-marketing setting.

6.1.7 DESTRUCTION AND RETURN

A Denosumab Accountability Record for the denosumab mandated by the protocol must be kept current and should contain:

- Dates and quantities of denosumab received from Amgen Inc.
- Manufacturing lot number AND box numbers for product received
- Subject's identification (subject number and initials)
- Date and box number of denosumab dispensed
- Initials of the dispenser

Used vials will not be returned to Amgen. Any partial or remaining drug at the time of use will be discarded per institutional safe handling procedure. Drug accountability will be maintained within the institutional system.

At the end of the study, or as directed, all denosumab supplies will be discarded per institutional standards. For each medication destroyed, documentation will be filed and kept in the appropriate protocol file. Documentation will include, medication destroyed, quantity, protocol number, and date drug is placed in Biohazard container.

6.1.8 DOSAGE ADJUSTMENTS AND DISCONTINUATION OF DENOSUMAB

- There will be no dose adjustments for the SC denosumab.
- Administration of SC denosumab will be withheld for any subject who experiences a grade 3 or 4 adverse event (refer to Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0) reported by the investigator as related to denosumab**, or** osteonecrosis of the jaw (ONJ) as determined by the investigator or by an independent expert panel. Denosumab will be held for albumin-adjusted serum calcium levels less than 8.4 mg/dL. Re-exposure to denosumab may occur only when the event resolves to grade 1 or less or to the subject's baseline and if the investigator and sponsor agree subject safety will not be compromised.
- If any scheduled dose after study day 1 is delayed for more than 8 calendar days from the scheduled visit date, this will be considered a missed dose and recorded as such on the case report form (CRF). The next dose is to be given on the next scheduled visit date (based on study day 1). There must be a minimum of a 3-week interval between administrations of denosumab. If subjects are delayed for more than 5 weeks, then subjects will be removed from study at the treating physician's discretion.
- Administration of the denosumab is recommended to be withheld 30 days prior to any elective invasive oral/ dental procedure. Denosumab administration is recommended to be withheld until documented evidence of complete mucosal healing following any invasive oral/dental procedure.
- Invasive dental procedures should be avoided, if possible. If a subject undergoes an invasive dental procedure while on study, a clinical decision to continue the subject on the denosumab must be documented in the medical chart.

6.2 CONCOMITANT/ EXCLUDED MEDICATIONS

- Calcium and vitamin D supplements will not be provided as part of the trial, but will be prescribed by the investigator as a concomitant medication per standard of care as described previously.
- No formal drug –drug interaction trials have been conducted with denosumab.

- Bisphosphonates (oral or IV) are not permitted during the study period or until the end of study assessments are completed.

7 MEASUREMENT OF EFFECT

7.1 METHOD OF ASSESSMENT

In addition to clinical examination, laboratory-based evaluation will be used in this study for all patients enrolled.

7.1.1 SERUM

Blood samples for quantitation of Ig (IgA, IgG, and IgM are required; IgD and IgE are optional) and M-protein and assessment of M-protein by immunofixation in serum are to be collected from all patients during Screening. Such samples also are to be collected at the time points designed in Table 5.1.
All samples will be analyzed by the local laboratory.

7.1.2 FREE LIGHT CHAIN TESTING

Serum samples for FLC testing are to be collected from all patients during screening and at the time points designed in Table 5.1. The free kappa/lambda ratio is to be recorded in the eCRF.
A serum sample for FLC testing also is to be collected in order to confirm stringent complete response (sCR).
All samples will be analyzed by the local laboratory.

7.1.3 URINE

Twenty-four hour urine samples for quantitation of M-protein and assessment of M-protein by immunofixation are to be requested from all patients during screening. Patients may refuse to provide urine samples.

All samples will be analyzed by the local laboratory.

7.1.4 BONE MARROW EXAMINATION

Bone marrow aspiration and trephine biopsy per institution standard are to be performed for all patients during screening prior to study treatment administration and the end of study. If a bone marrow biopsy has been done within 3 months before screening, this does not need to be repeated. Bone marrow aspiration and biopsy are to be repeated during treatment as clinically indicated, at the

Investigator's discretion, in order to confirm complete response (CR).

A portion of the pre-treatment sample and the end of treatment sample will be used for correlative studies.

7.1.5 DXA SCANS

DXA scans are to be performed during screening and at the end of study. All scans will be performed at the local radiology facility. Bone density will be measured at the lumbar spine, femoral neck, total hip, and distal 1/3 of the radius.

7.1.6 ASSESSMENT OF RESPONSE

Patients will be assigned a baseline category of SMM risk for progression as below in Table 7.1.6. Patients will be determined to have a downgraded risk of progression if the risk category decreases. Patients with low risk SMM will have a downgraded risk if they no longer meet the criteria for SMM, but have MGUS instead. MGUS will be defined per IWMG criteria as an M-protein < 3g/dL and clonal bone marrow plasma cells < 10% and urine monoclonal protein < 500mg/24 hours [14].

Table 7.1.6

Risk Factors	**Low risk**	**Low-intermediate risk**	**High-intermediate risk**	**High risk**
BM plasma cell % ≥50	Patient has SMM, but none of the listed risk factors	1 risk factor is present	2 risk factors are present	3 risk factors are present
M-protein ≥ 3g/dL				
Involved/uninvolved free light chains ≥ 8				
Immunoparesis	Not present	Present without other risk factors		

Disease progression and the response rate will be determined by the International Myeloma Working Group Criteria (IMWG) [13] (Appendix A). Investigators will assess response and progression on the basis of analyses of M-protein in serum or urine that will be performed locally and according to methods and frequencies consistent with local standard of care. It is recommended to monitor serum (or urine) M-protein every 4 weeks until first progression.

Disease progression in bone and outside of the bone (extra osseous) will be determined by the investigator based on local review of images and/or clinical observations according to methods and frequencies consistent with local standard of care. The criteria for disease progression are described herein. Disease progression will be documented on the CRF.

Changes in bone mineral density will be determined by bone densitometry (DXA).

8 STATI STIC AL CON SID E R ATION S

8.1 DESIGN

This is a single center, single-arm prospective open-label trial of denosumab in patients with smoldering multiple myeloma (SMM). We aim to establish preliminary estimates of downgrade rate after denosumab treatment in this population. The downgrade rate will be estimated from twenty enrolled subjects. Exact binomial methods will be used to calculate an associated 90% two-sided confidence interval. The maximum possible width of a 90% two-sided confidence interval using 20 subjects is 0.396, when the rate is 0.50. We anticipate a downgrade rate much lower than 0.50. If the downgrade rate were 0.10, the resulting 90% two-sided confidence interval would have a width of 0.265 (from 0.018 to 0.283). Table 8.1 highlights 90% confidence interval limits based on the number of downgrades seen in twenty enrolled patients. Despite the wide confidence intervals produced due to limited sample size, this information is still critical to obtain prior to investigating this regimen in a larger definitive trial. This study will produce pilot data that will be used to plan future larger definitive studies. 2 or more downgrade events will be considered sufficient rationale for moving forward with a larger trial.

Table 8.1: 90% Confidence Intervals for a range of possible event counts

Number of downgrade events	90% confidence interval limits
1	(0.003, 0.216)
2	(0.018, 0.283)
3	(0.042, 0.344)
4	(0.071, 0.401)
5	(0.104, 0.456)

8.2 EARLY STOPPING RULE FOR SAFETY

This study will be continuously monitored for grade 4 or higher adverse events (AEs) related (possibly, probably or definitely) to denosumab using a Pocock-style boundary for repeated testing. {Ivanova, 2005 #1764}Using the table below, the trial will be stopped and data reviewed if the boundary number of related grade 4 or higher AE events is reached or exceeded. Only points where stopping is possible are listed. If the true rate of such events is 5% (maximum-tolerated rate), there is a 7% chance of early termination (type I error). If the true rate is as high as 25%, there is an 86% chance of stopping the trial early.

Table 8.2: Early Stopping Boundary

# Patients	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
# Events	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	4	4	4	4

8.3 PATIENT DISPOSITION

The disposition of patients includes the number and percentage of patients for the following categories: patients enrolled, patients treated (safety population), patients in the intent to treat population, and patients discontinued from the study. The reasons for study discontinuation will also be summarized in this table. Only one primary reason for study discontinuation will be reported in the summary. However, all reasons will be presented in the listing. A listing will present data concerning patient disposition.

8.4 PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline demographic and clinical characteristics will be summarized as medians and interquartile ranges (IQR) for continuous variables, and as counts and proportions for categorical variables.

8.5 EXTENT OF EXPOSURE

The dose (mg) of study drug administered, the total number of doses of study drug, and the duration of treatment (number of study cycles) will be summarized with descriptive statistics. The number and percentage of patients whose dose is modified at any time will be summarized by each type of modification by cycle and overall. The proportion of patients completing each cycle of treatment will be summarized.

8.6 STATISTICAL ANALYSES

The treated population is defined as all enrolled subjects who received at least 1 dose of denosumab. Efficacy and safety analysis will be based on this population. The downgrade rate (DR) is defined as the proportion of patients for whom risk of progression from SMM to MM is lower after denosumab treatment. The criteria defining risk are defined in Table 7.1.6. Patients who cannot be assessed for any reason will be considered not downgraded and will be included in the denominator when calculating the DR.

Secondary endpoints will be analyzed as follows. Medians and interquartile ranges (IQR) will be reported for continuous variables and counts and proportions will be reported for categorical variables. The non-parametric Wilcoxon signed rank test will be used to compare pre- and monthly measures of monoclonal (M) serum protein levels, free light chain (FLC) levels, and bone mineral density (baseline and each post-treatment point). If the normality assumption is valid or can be met with transformation, linear mixed models will be used compare changes in each measure across all time points simultaneously, and will include a subject-specific intercept to account for correlations in data coming from the same subject. Time will be treated as a categorical fixed effect. A separate model will be fit for each outcome: M serum protein levels, FLC levels and bone mineral density. Rates of skeletal related events will be calculated and

presented with associated 95% two-sided exact binomial confidence intervals. Cumulative incidence for progression to MM from treatment initiation (Study Day 1 in Table 5.1) through 1 year will be calculated, treating death as a competing risk. PFS is defined as the time to progression or death from any cause, whichever occurs first. PFS from treatment initiation (Study Day 1 in Table 5.1) through 3 years will be summarized using the Kaplan-Meier method. Safety and toxicity data will be summarized at the event level and at the subject level. Adverse event level data will be tabulated and summarized as frequency, type and severity of each adverse event. Subject level data will be tabulated and summarized as subject incidence of each adverse event. The safety population includes all subjects who received at least 1 dose of denosumab.

9 SAFETY REPORTING

Study Investigators will conduct continuous review of data and patient safety. The Investigator will submit semi-annual progress reports of these data to the Data Safety Monitoring Committee for review. The review will include: the number of patients enrolled, withdrawals, significant toxicities as described in the protocol, serious adverse events both expected and unexpected, dose adjustments, and responses observed. The PI maintains a database of all adverse events with toxicity grade and information regarding treatment required, complications, or sequelae. The Investigator will submit a copy of the AE spreadsheet along with a Progress Report to the Data Safety Monitoring Committee (DSMC) for review. Actual review dates will be assigned when the 1st patient is accrued.

The DSMC at the Wilmot Cancer Institute, University of Rochester provides oversight of study progress and safety by review of accrual and adverse events at semi-annual meetings or more often if concerns arise. Any adverse event requiring expedited review per protocol, will be submitted to the Safety Coordinator of the DSMC at the University of Rochester for determination as to whether further action is required. When patient safety is of concern, an interim meeting may be called

- Any serious adverse event that is serious, related AND unexpected must be reported within 5 calendar days to both the DSMC Safety Coordinator and the RSRB (see RSRB guidelines). The DSMC Chair will determine whether further action is required, and when patient safety is of concern, an interim meeting may be called.
- Serious adverse events that are related AND expected or unrelated AND unexpected will be reported to the DSMC for review. SAE reports are expected to include sufficient detail so that the DSMC can determine the severity, toxicity grade, expectedness, treatment required, and a follow up report documenting resolution or if there are sequelae. Serious adverse events that require detailed reports (but not necessarily expedited) are expected, related, non-hematologic toxicities of grades 3, 4 or 5.
- Safety data and aggregate reports will be reported to Amgen as in section 9.7.

The Safety Coordinator administratively coordinates reports and data collection and prepares documents for the DSMC Chair and committee review. The Safety Coordinator will administratively monitor adverse

event rates utilizing the report from the study database. If any study has had two or more of the same SAE's reported in a month or more than six of the same SAE's in six months, the DSMC will review the summary of SAEs, discuss events with Study Chair, and conduct a more detailed review with the Study Chair. The Data Safety Monitoring Chair will determine if further action is required.

9.1 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 5.0 will be utilized for AE reporting. All investigators should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only. Please refer to the denosumab prescribing information for a listing of expected AEs.

9.2 DEFINITIONS OF ADVER SE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product. An AE does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0 is to be used for the grading of severity of symptoms and abnormal findings. For adverse events not covered by the NCI-CTCAE Version 5.0 grading system, the following definitions will be used:

- **Grade 1**: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local or non-invasive intervention indicated.
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated.
- **Grade 4**: Life-threatening consequences; urgent intervention indicated.
- **Grade 5**: Death related to AE.

9.3 ADVERSE EVENTS (AES) AND TREATMENT EMERGENT ADVERSE EVENTS (TEAES)

All AEs and SAEs occurring on study will be listed by patient. The frequency and percentages of patients with treatment-emergent adverse events (TEAEs) will be tabulated by system organ class (SOC) and preferred term (PT), where treatment-emergent is defined as any AE that:

- Occurs after first dosing of study medication and through the end of the study or up through 30 days after the last dose of study treatment, or
- Is considered treatment-related regardless of the start date of the event, or
- Is present before first dosing of study medication but worsens in intensity or the investigator subsequently considers treatment-related.

TEAEs that are considered at least possibly related to study treatment will be tabulated as well as deaths, SAEs, and events resulting in treatment discontinuation.

At each level of summarization, a patient will be counted only once for each AE, SOC, or PT experienced within that level. In the summation for AE severity, within each level of AE, SOC, or PT experienced, the one with the highest severity will be included. In the summation for AE's relationship to the study drug, within each level of AE, SOC, or PT experienced, the one with the closest relationship to the study drug will be included.

9.4 ADVERSE EVENTS/SERIOUS ADVERSE EVENT CAUSALITY ASSESSMENT

The Investigator must also assess the relationship of any adverse event to the use of study drugs based on available information, using the following guidelines:

- **Not Related**: Clear-cut temporal and/or mechanistic relation to a cause other than the study drug(s).
- **Doubtful**: There is no reasonable possibility that the event is related to the study drug(s) but a definite cause cannot be ascertained.
- **Possible**: There is still a reasonable possibility that the cause of the event was the study drug(s) but there exists a more likely cause of the event such as complications of progressive disease.
- **Probable**: The most likely cause of the event is the study drug(s) but other causes cannot be completely excluded.
- **Definite:** Clear cut temporal and/or mechanistic relation to the study drug(s). All other causes have been eliminated. Events classified as definite will often be confirmed by documenting resolution on discontinuation of the study drug and recurrence upon resumption.

9.4.1 HANDLING OF ADVERSE EVENTS

All adverse events resulting in discontinuation from the study will be followed until resolution or stabilization. Patients will be followed for AEs for 30 calendar days after discontinuation or completion of protocol-specific treatment. All new AEs occurring during this period will be reported and followed until

resolution unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigator will record or her reasoning for this decision in the patient's medical record and as a comment on the CRF. After 30 days, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

9.5 SERIOUS ADVERSE EVENTS

9.5.1 DEFINITIONS OF SERIOUS ADVERSE EVENTS

The definitions of serious adverse events (SAEs) are given below. The investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

An SAE or reaction is defined as any untoward medical occurrence that:

- Results in death, is immediately life-threatening,
- Requires at least a 24-hour in-patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, and/or
- Causes a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per IWCLL Hallek et al. 2008, should not be reported as a serious adverse event.

A suspected unexpected serious adverse reaction (SUSAR) is defined as an SAE that is suspected to be at least possibly related to study medication(s) and is an unexpected event.

Treatment within or admission to the following facilities does not meet the criteria of "in-patient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the study for a pre-planned surgical or a medical procedure (one which was planned prior to entry in the study), does not require reporting as a serious adverse event.

9.5.2 SERIOUS ADVERSE EVENT REPORTING BY INVESTIGATORS

It is important to distinguish between serious and severe adverse events, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs and SAEs on the CRF.

Adverse events classified by the treating investigator as serious require expeditious handling and reporting to the Sponsor in order to comply with regulatory requirements. Serious adverse events may occur at any time from the signing of the informed consent form through the 30-day follow-up period after the last study treatment. Sponsor or designee should be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.

All SAEs (regardless of causality assessment) occurring on study or within 30 days of last study treatment should be immediately reported to the sponsor as SAEs within the CRF and followed until resolution (with autopsy report if applicable).

SMM progression or death due to SMM progression should be reported by the investigator as a serious adverse event only if it is assessed that the study drugs caused or contributed to the SMM progression (i.e. by a means other than lack of effect). Unrelated events of SMM progression should be captured on the appropriate CRF.

The investigator must review and sign off on the SAE data on the SAE report. The SAE should be reported to the Sponsor.

When an SAE is reported to the sponsor or designee, the same information should be entered on the CRF within 24 hours (1 business day).

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the sponsor or designee as soon as it is available; these reports should be submitted using the appropriate SAE form, MedWatch3500A.

The sponsor is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, and/or local regulatory requirements.

The sponsor is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drugs to the regulatory agencies and competent authorities within 7 calendar days after being notified of the event. The Sponsor will report all related but unexpected SAEs including non-

death/non-life-threatening related but unexpected SAEs (SUSAR) associated with the use of the study medications to the regulatory agencies and competent authorities by a written safety report within 15 calendar days of notification. Following the submission to the regulatory agencies and competent authorities, Investigators and trial sites will be notified of the SUSAR. Investigators must report SUSARs and follow-up information to their responsible Institutional Review Board (IRBs)/Independent Ethics Committee according to the policies of the responsible IRB (Research Ethics Committee).

SUSARs and pregnancy or lactation will be reported to Amgen per section 9.7.

9.6 RECORDING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the SAE Report Forms and AE CRF. Avoid colloquialisms and abbreviations.

All AEs, including those that meet SAE reporting criteria, should be recorded on the AE CRF; AEs that meet the definition of an SAE should additionally be reported.

9.6.1 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE CRF. If a persistent AE becomes more severe (changes from a Grade 1 or 2 AE to a Grade 3 or 4 AE) or lessens in severity (changes from a Grade 3 or 4 AE to a Grade 1 or 2 AE), it should be recorded on a separate SAE Report Form and/or AE CRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF for each recurrence.

9.6.2 DEATHS

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of the patient's SMM for up to 30 days post the last dose of study drug will be recorded on the appropriate study CRF and reported on the Adverse Event page of the CRF, i.e. are exempted from expedited reporting. All other on-study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the Sponsor.

When recording a serious adverse event with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event page of the CRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the CRF Adverse Event page.

9.6.3 HOSPITALIZATION, PROLONGED HOSPITALIZATION, OR SURGERY

Any AE that results in hospital admission of >24 hours or prolongs hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE.

9.7 SAFETY REPORTING TO AMGEN

The Sponsor/Investigator is responsible for compliance with expedited reporting requirements for serious, unexpected and related adverse events (SUSARs), for generation of SAE reports including narratives, and for periodic reporting to Amgen of SAEs as outlined in Table 9.7.1 and Table 9.7.2 below. Individual safety reports (Table 9.7.1) should be accompanied by the Safety Fax Cover Form and sent to Amgen Global Safety, utilizing the fax or email information provided on the cover page. Aggregate safety reporting (Table 9.7.2) including listings, tabulations and summary reports should be scanned and accompanied by the Data Reconciliation Fax Cover Form, and sent to Amgen NASCR, utilizing the email information provided on the cover page.

Table 9.7.1. Expedited Reporting Requirements for Interventional Studies

Safety Data	Timeframe for Submission to Amgen
Suspected Unexpected Serious Adverse Reaction (SUSARs)	Individual reports sent to Amgen at time of expedited reporting to IRB and/or FDA.
Pregnancy/Lactation	Individual reports sent within 10 calendar days of Sponsor/Investigator awareness.

Individual reports should be faxed to [redacted] or scanned and sent via email to [redacted]

Table 9.7.2. Aggregate Reports

Safety Data	Timeframe for submission to Amgen
US IND Annual Safety Report	Annually
Other Aggregate Analyses (any report containing safety data generated during the course of a study)	At time of ISS sponsor submission to any body governing research conduct (eg, FDA, IRB, etc)

Final (End of Study Report), including: • Unblinding data for blinded studies • Reports of unauthorized use of a marketed product	At time of ISS sponsor submission to any body governing research conduct (eg, FDA, IRB, etc) but not later than 1 calendar year of study completion

Aggregate reports should be submitted via email to the Amgen NASCR manager, accompanied by the Data Reconciliation Fax Cover Form

10 CLINICAL DATA COLLECTION

10.1 AMENDMENTS TO THE PROTOCOL

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

All amendments require review and approval of the Principal Investigator. The written amendment must be submitted to the IRB at the investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB.

The amendment will be submitted formally to the FDA or other regulatory authorities by the investigator as applicable, and specifically when an increase to dosing or patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

10.2 FINANCIAL DISCLOSURE S AND ETHICAL CONSIDERATIONS

This study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

10.3 IRB AND REGULATORY APPROVAL

The study protocol, ICF, IB, available safety information, patient documents, patient recruitment procedures, information about payments and compensation available to the patients and documentation

evidencing the PI's qualifications must be submitted to the IRB for ethical review and approval prior to the study start and in accordance with institutional guidelines.

The PI/Sponsor and/or designee will follow all necessary regulations to ensure initial and ongoing, IRB study review. The PI must submit and, when necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB. Sites must follow institutional IRB guidelines for submission requirements.

If applicable, the PI will notify the IRB within 90 days of the end of the study, or if the study terminates early, the PI must notify the IRB within 15 days of the termination. A reason for the early termination must be provided (as defined in Directive 2001/20/EC).

10.4 INFORMED CONSENT

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the responsible regulatory authority, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the study. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this study, the candidate will be asked to give consent to participate in the study by signing an informed consent form. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the informed consent form, to include the patient's signature, will be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study must be obtained.

10.5 CONFIDENTIALITY

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and national data protection laws. HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization from the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study;
- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study;
- Whether the authorization contains an expiration date; and
- The rights of a research patient to revoke his or her authorization. In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period. In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of the Sponsor, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify patients on the CRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the CRF or database. No material bearing a patient's name will be kept on file by the Sponsor. Patients will be informed of their rights within the ICF.

10.6 STUDY DOCUMENTATION AND STORAGE

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the CRFs are to be included on this document. All entries in the patient's CRF are to be supported by source documentation where appropriate. Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the patient's CRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, EKG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The PI and study staff are responsible for maintaining a comprehensive and centralized filing system (Site Study File/SSF or ISF) of all study-related (essential) documentation, suitable for inspection at any time by

representatives from the Sponsor and/or applicable regulatory authorities. The ISF/SSF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF/SSF should contain as a minimum all relevant documents and correspondence, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain PI name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the CRF must be maintained and be readily available.

The IRB shall maintain adequate documentation / records of IRB activities for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories and any other study-related records for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., medical records), all original, signed informed consent forms, and copies of all CRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Sponsor or its representative will notify the investigator(s)/institutions(s) when the study-related records are no longer required.

10.7 DATA COLLECTION AND SAFETY

The study CRF is the primary data collection instrument for the study. An electronic case report form will be utilized for the collection of all data and all data will be entered into the RedCap database using the English language and should be kept current to enable review of the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, initials, and date of birth will identify the patient in the CRF. If the patient's name appears on any other document (e.g. laboratory report), it must be obliterated on the copy of the document to be supplied to the investigator site and replaced instead with the patient number and patient's initials. The investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be

identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

The University of Rochester Data and Safety Monitoring Committee (DSMC) will be the data safety monitoring committee of record for the conduction of this study. Please refer to the Wilmot Cancer Institute (WCI) University of Rochester Policy and Procedures for Data and Safety Monitor document for details.

10.8 PUBLICATION POLICY

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential.

A clinical study report will be prepared upon completion of the study. The PI will disclose the study results, in the form of a clinical study report synopsis, to the applicable regulatory authorities within one year of the end of the study.

11 PLANNED CORRELATIVE ANALYSES

At URMC, peripheral blood will be collected from fasting patients within 30 days of the first treatment and at the end of treatment at the times of a regularly scheduled blood draw. The second morning void will be collected for assessment of uNTx measurements via immunoassay at the time of a regularly scheduled lab collection. These assays will include measurement of sRANKL, sCTx, NOTCH signals, sclerostin, DKK1, MIP-1α, and OPG via enzyme-linked immunosorbent assay (ELISA). These specimens will be collected, processed and analyzed by the Lipe laboratory as below.

Peripheral blood:

1. 10 mL of Whole blood will be collected in 2 green top tubes
2. Centrifuge at 1800xg for 30 minutes in a swing bucket centrifuge (not a fixed angle) within 24 hours of collection
3. 10mL of Whole blood will be collected in 2 red top tubes
4. Blood will be allowed to clot prior to centrifugation at 4000 x g for 10 minutes
5. Blood will be stored at -80 degrees centigrade until analysis

Bone marrow:

1. 40mL of Bone marrow aspirate will be collected first in 2 Sodium Heparin (green top with 10mL each) and then 2 lavender top collection tubes (10mL each).
    a. Samples will undergo Ficoll separation for the collection of mononuclear cells. Mononuclear cells will be grown and analyzed in the Lipe laboratory.
2. Bone marrow samples will be collected and processed in the Lipe laboratory.

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13 APPENDIX A : IMWG RESPONSE CRITERIA

INTERNATIONAL MYELOMA WORKING GROUP (IMWG) UNIFORM RESPONSE CRITERIA FOR MULTIPLE MYELOMA

Response	***IMWG criteria***
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[3] by immunohistochemistry or immunofluorescence[4]
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow3
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
PR	> 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable,[5] a >50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M- protein, provided baseline bone marrow plasma cell percentage was > 30% In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
MR	NA
No change/Stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease
Plateau	NA

Progressive Disease[5]	Increase of ≥ 25% from lowest response value in any one or more of the following: Serum M-component and/or (the absolute increase must be >0.5 g/dL)[6] Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h) Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL Bone marrow plasma cell percentage; the absolute percentage must be > 10%[7] Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[6] It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice Development of new soft tissue plasmacytomas or bone lesions 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

	Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] Decrease in hemoglobin of ≥ 2 g/dL [1.25 mmol/L] Rise in serum creatinine by 2 mg/dL or more [177 mmol/L or more]
Relapse from CR[5] (To be used only if the end point studied is DFS)[8]	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of > 5% plasma cells in the bone marrow7 Appearance of any other sign of progression (i.e., new plasmacytomas, lytic bone lesion, or hypercalcemia)

1 BGM Durie et al. International uniform response criteria for multiple myeloma. Leukemia (2006) 1-7.

Adapted from Durie BGM, et al. Leukemia 2006; 20: 1467-1473; and Kyle RA, Rajkumar SV. Leukemia 2008;23:3-9.

Note: A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.

[3] Confirmation with repeat bone marrow biopsy not needed.

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

[5] All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.

[6] For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

[7] Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

[8] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

14 APPENDIX B: ABBREVIA TIONS

Abbreviation	Unabbreviated
AE	Adverse events
BMPC	Bone marrow plasma cell
Cbc	Complete blood chemistry
Cmp	Comprehensive metabolic profile
Cr	Creatinine
CR	Complete response
CRF	Case report form
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DKK1	Dickkopf-related protein 1
dL	Deciliter
DR	Downgrade rate
DSMC	Data safety monitoring committee
DXA	Dual energy x-ray abrorptiometry scan
FLC	Free light chain
G	Gram
HIV	Human immunodeficiency virus
IFE	Immunofixation
IMWG	International myeloma working group
IQR	Interquartile range
kDa	kilodaltons
L	liter
M	monoclonal

Mg	Milligram
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
Mmol	millimoles
Ng	Nanograms
ONJ	Osteonecrosis of the jaw
OPG	osteoprotegrin
PFS	Progression free survival
PS	Performance status
Q4w	Every 4 weeks
RANK	Receptor activator of nuclear factor kappa-B
RANKL	Receptor activator of nuclear factor kappa-B ligand
SAE	Serious adverse events
SC	subcutaneous
sCR	Stringent complete response
SMM	Smoldering multiple myeloma
SPEP	Serum protein electrophoresis
SRE	Skeletal related events
SUSAR	suspected unexpected serious adverse reaction
ULN	Upper limit of normal
uNTx	Urinary N-telopeptide
UPEP	Urine protein electrophoresis