CLINICAL STUDY PROTOCOL

A Collaborative Research Project with the Multiple Myeloma Research Consortium (MMRC)

Study Title: A Phase 1/2 Trial of Linsitinib (OSI-906) in Combination with Bortezomib and Dexamethasone for the Treatment of Relapsed or Relapsed/Refractory Multiple Myeloma

Lead Principal Investigator: Suzanne Trudel, M.D.
Sponsor/IND holder:

Princess Margaret Cancer Centre/University Health Network
McLaughlin Centre for Molecular Medicine
610 University Ave, Room 10-721
Toronto, ON M5G 2M9

IND No.: 115550

Protocol ID: PMHOSI906-MM001

Project Manager: Engin Gul
University Health Network
416 946 4501 ext.: 2608

Medical Monitor: Dr. Suzanne Trudel

Protocol Version/Date:
Original: Version 1.0
Date: April 23, 2012

Version 2.0 / June 19, 2012
Version 3.0 / October 22, 2012
Version 4.0 / August 15, 2013
Version 5.0 / March 1, 2014

Dr. Suzanne Trudel, M.D., Investigator

Princess Margaret Cancer Centre, University Health Network,
Member of the Multiple Myeloma Research Consortium

610 University Avenue

Toronto, Ontario Canada M5G 2M9

STUDY ACKNOWLEDGMENT

A Phase 1/2 Trial of Linsitinib (OSI-906) in Combination with Bortezomib and Dexamethasone for the Treatment of Relapsed or Relapsed/Refractory Multiple Myeloma

Protocol Version 5.0
March 1, 2014

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study in compliance with all applicable regulations and guidelines as stated in the protocol and other information supplied to me. I will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision with copies of the protocol and access to all information for the conduct of this trial. I will discuss this material with them to ensure that they are fully informed about the drug(s) and the study.

Signature of Principal Investigator	Date
Print Name	Site Number

TABLE OF CONTENTS

PROTOCOL SYNOPSIS

Protocol –PMHOSI906-MM001

Title of Study:	A Phase 1/2 Trial of Linsitinib in Combination with Bortezomib and Dexamethasone for the Treatment of Relapsed or Relapsed/Refractory Multiple Myeloma
Objectives:	The primary objective of this study is: • Phase 1: To determine the maximum tolerated dose (MTD) of Linsitinib administered in combination with the recommended dose and schedule of bortezomib and dexamethasone. • Phase 2: To evaluate the antitumor activity of Linsitinib in combination with bortezomib and dexamethasone at their MTD established from the Phase 1 component. The antitumor activity will be determined by overall response rate (ORR) including stringent complete response (sCR), complete response (CR), very good partial response (VGPR) and partial response (PR) according to the International Myeloma Working Group (IMWG) criteria [32]. The rate of minimal response (MR) and progressive disease (PD) will also be observed. The secondary objectives of this study are: Phase 1: • To evaluate the safety and tolerability of Linsitinib in combination with bortezomib and dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma (MM). • To evaluate the pharmacokinetic (PK) profile of single agent Linsitinib when administered to patients with multiple myeloma in combination with bortezomib and dexamethasone. Phase 2: • To evaluate the progression-free survival (PFS) and overall survival (OS) in patients receiving Linsitinib in combination with bortezomib and dexamethasone at the MTD determined in Phase 1. • To further evaluate the safety and tolerability and evaluate the incidence of toxicities for these regimens in this patient population at the MTD. • To evaluate PK of Linsitinib as single-agent in patients with MM and in combination therapy with bortezomib and dexamethasone. Exploratory • To seek biomarkers, IGF-1R+ and CD45-, predictive of drug responsiveness and to demonstrate successful target inhibition in correlative studies. One subgroup of MM patients (IGF-1R+/CD45-) is hypothesized to have a greater potential for response to IGF-1R inhibition.
Study Design:	This is a multi-center, open-label, non-randomized study.

Patients will receive Linsitinib in combination with bortezomib and dexamethasone. Phase 1 involves dose escalation of the combination, whereas Phase 2 involves the expansion of Linsitinib combined with bortezomib and dexamethasone at the MTD to establish the ORR. This trial will accrue patients with relapsed or relapsed/refractory MM – a disease state for which bortezomib is approved to treat by the FDA and Health Canada. The combination of Linsitinib with bortezomib is supported by pre-clinical work in MM in which the combination with an IGF1-R inhibitor enhances anti-tumor activity of bortezomib.

The Phase 1 portion of the study will determine the MTD and DLTs of bortezomib administered on days 1, 4, 8 and 11 of a 21-day cycle combined with Linsitinib dosed twice daily orally continuously. The combination of Linsitinib with bortezomib has not previously been tested. The active agent bortezomib will be used during Cycle 1 – 8 at the recommended treatment dose of 1.3 mg/m2 days 1, 4, 8 and 11 and Cycles 9+ on days 1, 8, 15 and 22 of a 5-week cycle and Linsitinib will be dose escalated as detailed in section 3.1 and as outlined below:

Dose Levels			
Cohort	Linsitinib PO	Bortezomib IV or S/Q	Dexamethasone PO or IV
1	75 mg BID	1.3 mg/m2	20 mg on days 1,4,8,11(C1 – 8) Days 1,8,15 and 22 (C9+)
2	100 mg BID	1.3 mg/m^2	
3	125 mg BID	1.3 mg/m^2	
4	150 mg BID	1.3 mg/m^2	

The Phase 1 portion of this trial will utilize a modified 3+3 design. Four dose levels will be evaluated followed by an expansion cohort at the MTD. The 150 mg dose will be the maximum dose evaluated and will be the RP2D if the MTD is not exceeded. The MTD will be based on the assessment of DLTs during the first cycle of therapy, and will be defined as the highest dose at which fewer than one-third of patients in a cohort experiences DLT to the combination. DLT is a clinically significant toxicity that occurs during the first treatment cycle
(i.e., 21 days). For the purposes of this study, DLT will be defined as:

- Grade 4 or higher hematologic toxicity that does not resolve within 7 days (except for lymphopenia). Patients are allowed platelet transfusion to manage bortezomib related thrombocytopenia. A platelet count that cannot be maintained at grade 3 or better for a minimum of 72h from the last platelet transfusion is a DLT. Grade 3 or Grade 4 thrombocytopenia with bleeding is a DLT.
- Febrile neutropenia (fever > 38.5) or documented infection that persists > 48 hours despite adequate treatment with

antibiotics and/or antifungal/antiviral agents is considered a DLT;

- Grade 3 or higher non-hematological toxicity possibly or probably related to any study drug except a) alopecia, b) grade 3 nausea, vomiting or diarrhea if not premedicated or adequately treated, c) fatigue or d) hyperglycemia/hypoglycemia – (see below);
- Prolongation of QTcF > 480 msec or absolute increase >60msec from baseline;
- Grade 2 elevation in liver function tests: ALT/AST ≥ 3X ULN, total bilirubin 2.0 X ULN (isolated bilirubin >2.0 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%);
- Treatment delay of cycle 2 for more than 14 days due to unresolved toxicity;

Hyperglycemia will be assessed as follows:

Patients will monitor their blood glucose levels at home via hand-held glucometer. Early intervention and treatment of hyperglycemia should be initiated to prevent a DLT. Hyperglycemia will NOT be considered a DLT if:

- Isolated non-fasting glucose values are grade 3 and the patient is asymptomatic and glucose levels return to normal values without interruption in therapy.
- Blood glucose and ketone values obtained via a home glucose monitor will not be considered DLT until confirmed by laboratory serum tests.

Hyperglycemia will be considered a DLT if:

- Fasting glucose ≥ Grade 3 (> 250 mg/dL or 13.9 mmol/L)
- non-fasting Grade 3 hyperglycemia associated with symptoms of glucose intolerance (polydipsia, polyuria, and weight loss) that interferes with activity of daily living or positive blood ketones (> ULN) not attributable to another cause;
- Hyperglycemia ≥ Grade 4 (glucose > 500 mg/dL or 27.8 mmol/L)
- Ketoacidosis as evidenced by serum bicarbonate of ≤ 15 mmol/L or venous pH < 7.3 with serum ketones present and anion gap > 12, in the presence of hyperglycemia of Grade 3 or higher (fasting blood glucose > 250 mg/dL; >13.9 mmol/L).
- Electrolyte ≥ grade 3 (Na, K, Ca, Mg, Cl, phosphate, and bicarbonate) abnormalities due to glucose intolerance and not attributable to another cause.

Hypoglycemia will be considered a DLT if:

- Symptomatic grade 2 hypoglycemia not resolved in one hour to Grade 1 or less with dietary supplement or any Grade 3 hypoglycemia.

	Dose escalation rules: • If 0 of three patients experience a DLT in Cycle 1, dose escalation will continue. • If 1 of three patients experiences a DLT in Cycle 1, three additional patients will be added to that dose level. • If 2 of three or 2 of 6 patients experience a DLT in Cycle 1, dose escalation will stop and the previous dose level will be declared the MTD. If only 3 patients were evaluated at that dose level, 3 additional patients will be added to fully evaluate the cohort. • The MTD will be the highest dose level at which ≤ 1 of 6 patients experienced a DLT following 1 cycle of therapy. The first 12 patients in Phase 2 will be considered the PK cohort and will receive a 7 day run-in (Cycle 0) with single agent Linsitinib at the MTD prior to adding the bortezomib and dexamethasone combination therapy to allow PK analysis of single agent Linsitinib and combination PK analysis. For purposes of scheduling or other hardships, exceptions may be made for individual patients that are unable to enroll into the 7 day run in, in consultation with the PI. With this exception, consecutive recruitment into the PK cohort will continue until 12 patients, who fulfill all PK requirements, are enrolled. The Phase 2 portion of this study is designed to assess the ORR compared to historical controls. The sample size calculation based on a Simon's Minimax two stage design will be used. The two-stage design will permit early stopping of the trial if there is strong evidence that the study regimen is inactive.
Number of Patients Planned:	In Phase I, approximately 24 patients will be treated with escalating doses of Linsitinib and fixed dose of bortezomib to determine the MTD. For the Phase II portion of the trial, approximately 35 evaluable patients (12 in the PK cohort and 23 in the non-PK cohort) are required. An evaluable patient is defined as a patient who has a baseline myeloma assessment and at least one follow-up assessment performed on or after day 21 on study (one cycle of therapy). In the exploratory analysis of this study, should less than 13 patients be evaluable in the IGF-1R+/CD45- subgroup or if a higher response rate be observed in this subgroup out of the 59 evaluable Phase I and II patients, an additional 8 IGF-1R+/CD45- patients may be enrolled. Non-evaluable patients (approximately 4) will be replaced for a total planned accrual of approximately 71 patients.
Target Population:	Patients with relapsed or relapsed/refractory MM.
Duration of	Patients will be treated until progression of disease, unacceptable

Treatment:	toxicity, withdrawal of consent, Investigator decision, death or study termination. For phase 1 and phase 2, patients may receive up to 8 cycles of bortezomib. After 8 cycles, the schedule of bortezomib may be reduced to once weekly on days 1, 8, 15 and 22 of a 5 week cycle. In the event that bortezomib is not tolerated after cycle 4 or patients do not have access to bortezomib after cycle 8, Linsitinib may be continued as single agent as long as there is clinical benefit.
Diagnosis and Main Eligibility Criteria:	**INCLUSION CRITERIA** Eligible patients will be considered for inclusion in this study if they meet all of the following criteria: 1. Males or females, age 18 years or older. 2. A diagnosis of MM and documentation of relapsed or relapse/refractory status following at least 1 prior line of therapy for phase 1 and 1 to 5 prior lines of therapy for phase 2. 3. Patients with measurable disease defined as at least one of the following (these baseline laboratory studies for determining eligibility must be obtained within 21 days prior to enrollment): a. Serum M-protein ≥ 0.5 g/dl (≥ 5 g/l) b. Urine M-protein ≥ 200 mg/24 h c. Serum free light chains (FLC) assay: Involved FLC level ≥ 10 mg/dl (≥ 100 mg/l) and an abnormal serum free light chain ratio (< 0.26 or > 1.65) d. Biopsy proven plasmacytoma. Prior biopsy is acceptable e. If the serum protein electrophoresis is unreliable for routine M-protein measurement, quantitative immunoglobulin levels on nephrolometry or turbidometry will be followed 4. Patient has an Eastern Cooperative Oncology Group (ECOG) ≤ 2 OR Karnofsky ≥ 60% performance status (PS) (Appendix 12-2) 5. Predose mean QTc ≤ 450 msec or mean QTc Fridericia's Correction (QTcF) on Day 1 (cycle 1 or cycle 0 if applicable) must be ≤ 450 msec. (see Appendix 12-1for details on screening and Day 1 QTC evaluations) 6. Females of childbearing potential (FCBP): a female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months). Pregnancy status in women of childbearing potential must be confirmed by serum β-hCG at screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women. FCBP must use acceptable forms of birth control or agree to abstain from

heterosexual intercourse while participating in the study and for 90 days following the last dose of study drug. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy while participating in the study and for 90 days following the last dose of study drug

7. Voluntary, written informed consent before performance of any study-related procedure not part of routine medical care with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care
8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations)
9. Must be able to take and retain oral medications
10. Inclusion Clinical Laboratories Criteria
    The following laboratory results must be met within 21 days of first study drug administration. (Patients must meet the below criteria within 24 hours of the first dose to start their treatment):
    a. Absolute neutrophil count (ANC) $\geq$ 1,000 cells/dL (1.0 x 10^9/L) (Growth factors cannot be used within 14 days of first study drug administration)
    b. Platelet count $\geq$ 50,000 cells/dL (50 x 10^9/L);
    c. Hemoglobin $\geq$ 8.0 g/dL (4.96 mmol/L)
    d. Serum AST or ALT $\leq$1.2 x ULN
    e. Total bilirubin within normal limits
    f. Creatinine clearance $\geq$ 30 mL/min (Cockcroft-Gault calculation)
    g. Serum creatinine $\leq$1.5 x ULN (correction with hydration and re-testing is permitted)(values $\geq$ 1.5 X ULN may be acceptable if improved to < 1.5 x ULN, with hydration and/or attributable to progressing MM)
    h. Serum calcium (ionized or corrected for albumin) $\geq$ 2.0 mmol/L (8.0 mg/dL or 1.0 mmol/L ionized calcium) to $\leq$1.2 x ULN. Treatment of hypercalcemia or hypocalcemia is allowed and patient may enroll if serum calcium returns to $\geq$ 2.0 mmols/L to $\leq$1.2 x ULN with standard treatment (See Appendix 12-13 for calcium correction formula)
    i. Serum potassium, and magnesium within normal limits (correction with supplementation is permitted).
    j. HgbA1c of $\leq$ 7% (within 21 days only, not required on within 24 h of first dose)
    k. Troponin I or T within normal limits (patients with abnormal values may be enrolled with sponsor approval

after full cardiac evaluations are done to determine that the abnormality is non-cardiac)

l. BNP or NT-proBNP within normal limits (patients with abnormal values may be enrolled with sponsor approval after full cardiac evaluations are done to determine that the abnormality is non-cardiac)

m. Fasting glucose of ≤126 mg/dL (7.0 mmol/L). A diagnosis of Type II diabetes mellitus is permitted if > 8 weeks since diagnosis and well controlled. Concurrent non-insulinotropic antihyperglycemic therapy is permitted if the dose has been stable for 8 weeks

11. Resolution of prior toxicities associated with a prior treatment to ≤ grade 1

EXCLUSION CRITERIA

Patients will be ineligible for this study if they meet any one of the following criteria:

1. Patients refractory or intolerant to bortezomib are not permitted (Refractory = non-responsive/progressed on therapy or within 60 days of last dose of bortezomib) on the Phase 2 part of the study only.
2. Diagnosed or treated for another malignancy within 3 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy
3. Patient has received other investigational drugs or chemotherapy within 21 days or approved anti-myeloma therapy including steroid therapy within 14 days prior to first study drug administration
4. History (within the last 6 months) of significant cardiovascular disease unless the disease is well-controlled. Significant cardiac disease includes but is not limited to second/third degree heart block; clinically significant ischemic heart disease; superior vena cava (SVC) syndrome; poorly controlled hypertension; congestive heart failure of New York Heart Association (NYHA) Class II or worse. History of arrhythmia (multifocal premature ventricular contractions [PVCs], bigeminy, trigeminy, ventricular tachycardia, or uncontrolled atrial fibrillation) that is symptomatic or requires treatment (≥ grade 3), left bundle branch block (LBBB), or asymptomatic sustained ventricular tachycardia are not allowed. Patients with atrial fibrillation controlled by medication are not excluded
5. Mean QTcF interval > 450 msec at screening

6. Prior autologous, peripheral stem cell transplant within 12 weeks of the first dose of study drug
7. Daily requirement for corticosteroids (except for inhalation corticosteroids)
8. Patients with evidence of mucosal or internal bleeding and/or platelet transfusion refractory (i.e., unable to maintain a platelet count ≥ 50,000 cells/dL)
9. Known active infection requiring parenteral or oral anti-infective treatment
10. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse follow-up evaluation
11. Use of any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient Examples of such conditions include any pre-existing kidney disease (acute or chronic, unless renal insufficiency is felt to be secondary to MM), hypertension, active seizure disorder or pulmonary diseases that would impose excessive risk to the patient
12. Patient has hypersensitivity to any of the components of study drugs
13. Known HIV or active hepatitis B or C viral infection;
14. Diabetes mellitus currently requiring insulin or insulinotropic therapy or prior history of steroid induced diabetes (See appendix 12-10)
15. History of cerebrovascular accident (CVA) within 6 months prior to registration or that is not stable
16. Prior therapy with an IGF-1R inhibitor
17. Use of drugs that have a risk of causing QT interval prolongation and/or have a known risk of causing Torsades de Pointes (TdP) before 14 days or the recommended 5 half-life washout period elapses (as indicated in Appendix 12-6), whichever is longer prior to Cycle 1 Day 1 dosing;. Drugs that have a known risk of causing TdP can be found on (www.azcert.org/medical-pros/drug-lists/bycategory.cfm)
18. Use of strong/moderate CYP1A2 inhibitors such as ciprofloxacin and fluvoxamine. Other less potent CYP1A2 inhibitors/inducers are not excluded (see appendix 12-9)
19. Gastro-intestinal abnormalities, including bowel obstruction, inability to take oral medication, requirement for intravenous (IV) alimentation, active peptic ulcer or prior surgical procedures or bowel resection or other poorly controlled gastrointestinal disorders that could affect the absorption of study drug (eg, Crohn's disease or ulcerative colitis).
20. Peripheral neuropathy ≥ grade 2
21. Significant liver disease or metastatic disease to the liver
22. History of amyloid, plasma cell leukemia or CNS

involvement

23. Prior radiation therapy or major surgical procedure within 4 weeks of the first dose of study treatment (this does not include limited course of radiation used for management of bone pain)

Study Procedures/ Frequency:

See Schedule of Procedures (Appendix 12-1).

Test Product, Dose, and Mode of Administration:

PHASE 1:

Dose Levels			
Cohort	Linsitinib PO	Bortezomib IV or S/Q	Dexamethasone PO or IV
1	75 mg BID	1.3 mg/m2	20 mg on days 1,4,8,11(C1 –8) Days 1,8,15 and 22 (C9+)
2	100 mg BID	1.3 mg/m^2	
3	125 mg BID	1.3 mg/m^2	
4	150 mg BID	1.3 mg/m^2	

- Treatment Cycle is 21 days for cycles 1 – 8 and 35 days for cycle 9+
- Bortezomib IV or SQ on days 1, 4, 8 and 11 every 21 days and dexamethasone (PO or IV) pre bortezomib dose Cycles 1 - 8. Cycle 9+ bortezomib once weekly on days 1, 8, 15 and 22 every 5 weeks and dexamethasone pre bortezomib dose. Linsitinib = orally BID daily.

All toxicities, in addition to the hyperglycemia rules will be used to evaluate the MTD as outlined in the definition of DLT.

For Phase 2: 12 patients will begin therapy with a 7 day run-in (Cycle 0) of single agent Linsitinib prior to the initiation of combination therapy to allow for single agent PK analysis of Linsitinib in addition to combination PK assessment. Linsitinib and dexamethasone will be administered at the MTD as determined in Phase 1 with the standard dose and schedule of bortezomib. Phase II will enroll 35 additional patients (12 in the PK cohort and 23 in the non-PK cohort).

For Phase 1 and Phase 2: patients may continue on therapy until progression. After Cycle 8 the schedule of bortezomib will be reduced to once weekly on days 1, 8, 15 and 22 of a 5 week cycle. In the event that bortezomib is not tolerated after cycle 4 or patients do not have access to bortezomib after cycle 8, Linsitinib may be continued as single agent as long as there is clinical benefit.

Reference Therapy, Dose, and Mode of

Linsitinib is provided as tablets in strengths of 25 mg, 100 mg and 150 mg. It is to be taken orally twice daily (BID). Astellas

Administration:	Pharma Global Development, Inc. (APGD), will supply Linsitinib for use in this study. Bortezomib for injection is supplied as individually cartoned 10 mL vials containing 3.5 mg of bortezomib as a white to off-white cake or powder. Commercial supplies of bortezomib will be used in this study. Dexamethasone is commercially available. Commercial supplies of both IV and oral formulation will be used for this study.
Criteria for Evaluation:	
Safety:	All patients will be evaluated for safety analysis if they receive at least one dose of Linsitinib and or bortezomib. Adverse events will be recorded. Safety will be assessed through physical examinations including vital signs, laboratory testing (complete blood count (CBC) with differential and platelets, serum chemistries, and coagulation parameters), blood glucose monitoring and electrocardiograms. ECGs will be obtained to monitor for changes in QT interval; ECGs will be locally read. The UHN DSMB committee will evaluate the safety of the trial after completion of enrollment of the first 12 patients and/or biannually during phase II. If greater than 20% of subjects experience hyperglycemia, liver toxicity or QTc prolongation that meets the DLT criteria, a detailed review of these toxicities will be performed by an independent safety committee to determine whether the trial should be stopped.
Efficacy:	**Phase 1:** No formal statistical analysis of efficacy will be performed in this investigation. Myeloma response data will be reported by descriptive statistics. **Phase 2:** The response rate (defined as partial response or better by IMWG criteria) will be calculated as the number of patients achieving a response divided by the number of evaluable patients. All patients meeting the eligibility criteria, who have signed a consent form, and have begun treatment, will be evaluable for the estimation of confirmed response rate. The rate of Minor Response (MR), adapted from the EMBT criteria will also be reported. Responses are determined by the Site Investigator according to the IMWG response criteria guidelines provided in Appendix 12-5 [32]. Confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner[1].
Pharmacokinetics/ Pharmacodynamics/ Exploratory Biomarkers:	**Pharmacokinetics** **Phase 1**: On all patients, on day 21, single agent PK will be collected pre Linsitinib dose, 30 min, 1hr, 2hrs, 3hrs, 4hrs, 6hrs, 8hrs with the 24 hour collection on cycle 2/day1 pre bortezomib infusion. Combination PK will be collected on day 8 pre Linsitinib and bortezomib dose, 30 min, 1hr, 2hrs, 3hrs, 4hrs,

6hrs, 8hrs post dose with the 24 hour collection on cycle 1 day 9 pre Linsitinib and bortezomib dose.

Phase 2: The first 12 patients only during the 7 day lead in (cycle 0), will have single agent PK samples drawn on day 7 pre Linsitinib dose, 30 min, 1hr, 2hrs, 3hrs, 4hrs, 6hrs, 8hrs post dose with the 24 hour collection on cycle 1 day 1 pre bortezomib infusion. Combination PK will be collected on Cycle 1 Day 8 pre Linsitinib and bortezomib dose and 2 and 4 hours post dose.

Details on sample handling are provided in Appendix 12-3.

Biomarker Studies

Expression of IGF-1R and CD45

Although IGF-1R is widely expressed in MM tumors with some studies reporting its presence in 30-70% of newly diagnosed MM cases and in 90% of human myeloma cell lines [2,3,4] it is clear that its expression is not universal. CD45 expression is estimated in various reports to be approximately 20-80% by flow cytometry [5, 6,7]. Further, pre-clinical studies indicate that CD45 negative but not CD45 positive myeloma tumors are sensitive to IGF-1R inhibition [8]. Expression of CD45 and IGF-1R will be determined by flow cytometry on all screening bone marrow samples (Phase 1 and 2 samples). Briefly, an aliquot of bone marrow will be subjected to red cell lysis. We will use a quadruple antibody combination (anti-CD138-APC/cy7, anti-CD38-FITC, anti-IGF-1R-PerCP and a pan-anti-CD45-PE) combined with side scatter and forward scatter properties to evaluate the expression of CD45 and IGF-1R on the myeloma cell population. Flow cytometry will be done using a LSR II flow cytometer (BDIS), and offline listmode analysis will done using FlowJo software. Correlation of expression with response will be reported.

Pharmacodynamics (Phase 2 only)

As a companion study to the proposed clinical trial, we will conduct studies aimed at identifying predictors of response and pharmacodynamic (PD) studies to demonstrate target inhibition. For the purposes of the current trial, we will obtain a research BM aspirate at study screening and follow up BM samples

on Cycle 1 day 21 (- 3 days) at 3-4 hours following single-agent Linsitinib, and at progression

Flow Cytometry/ Pharmacodynamic Studies

Myeloma cells from bone marrow samples will be evaluated for target modulation and the effects of Linsitinib on downstream signaling targets of IGF-1R. Flow cytometry is a highly developed technique for the diagnosis of hematological malignancies, based on the correlated measurements of multiple surface immunophenotypic markers plus forward and orthogonal light scattering characteristics of cell subpopulations. However,

the recent introduction of techniques that measure the activation states of signaling pathways using phosphospecific antibodies, the scope of flow cytometry now extends into molecular therapeutic monitoring in the clinic. By using flow cytometry applications, we will determine whether the IGF-1R target AKT is activated in myeloma cells pre-treatment and whether administration of Linsitinib in primary cells. Effects of Linsitinib on the tyrosine phosphorylation of IRS-1 will also be determined. Correlation with CD45 expression, patient response, dose and available drug plasma levels will be determined. The results will be analyzed on an exploratory basis.

Flow Cytometry Protocol

We will use a quadruple antibody combination (anti-CD138, anti-CD38, anti-CD45 and anti-pAKT) to analyze PI3K signaling in myeloma cells. Bone marrow samples will be subjected to red cell lysis and quality of the sample will be assessed by flow cytometry measurements of forward and side scatter, CD138/CD38/CD45 and PI staining. Cells will be resuspended in stem span H3000 defined serum free medium and aliquoted to FACS tubes. To one set of tubes, 50 μM LY294002 (inhibitor of PI3K) or solvent control will be added and incubated at 37^0C for 30 min. By comparing with the solvent control we can establish whether there is constitutive activation of AKT in myeloma cells. To second set of tubes we will add 50 ng/mL IGF-1 (to activate IGF-1R signaling) or solvent for 12 minutes. As a control the cells will also be stimulated with 50 ng/mL IL-6 and the cells will be labeled with anti-pERK and anti-pSTAT3, this will demonstrate that signaling is intact in the cells as this pathway should not be affected by Linsitinib. The cells will then be fixed and permeabilized using our recently developed protocol that optimizes the preservation of phenotypic features and intracellular phosphorylated epitopes. Briefly, samples are removed from the dry bath, fixed by adding methanol-free formaldehyde to give a final concentration of 4% for 10 min. The cells will be washed in cold wash buffer and then resuspended in 1 mL of cold freezing medium consisting of 10% glycerol, 20% fetal bovine serum in RPMI tissue culture medium, and stored at -20^0C and patched for antibody staining so that paired samples are analyzed together.

For intracellular phospho-specific antibody staining, thawed cells will be washed and 0.1 million cell aliquots will be resuspended and permeablilized in 1 mL of 50% methanol in 0.9% NaCl and incubated on ice for 10 min. Cells will then be washed and the cell pellet resuspended and labeled with an antibody mix containing primary conjugated phospho-specific antibodies described above and incubated at room temperature for 15 min. Approximately, 10,000 ungated events will be collected for each sample on a LSR II flow cytometer.

Pharmacogenomic Studies

Plasma cells will be isolated from bone marrow mononuclear cells (PBMCs) by immunobead selection with anti-CD138

antibodies using the AutoMACs automated separation system. PC cell purity will be confirmed by immunofluorescence staining for intracellular staining for kappa and lambda. Cells will be sorted in TRIZOL and banked for future RNA extraction for pharmacogenomic studies. If sufficient material is recovered from patients gene expression analysis will be obtained for the purpose of addressing three groups of biomarkers (i) expression profiles associated with response to the agents (ii) expression profiles associated with specific toxicities of the agents and (iii) understanding the cellular actions of the drug in myeloma cells (iv) molecular mechanisms of acquired resistance. Alternatively, real-time PCR will be performed using an APGD proprietary gene signature to be performed by standard methods. In addition, gene expression analysis will be analyzed for adverse prognostic cytogenetic abnormalities such as t(4;14) and t(4;16).

Sample Procurement

Good laboratory practice SOPs developed by the MM Research Consortium (MMRC) will be employed throughout collection, shipping and processing. Samples from all participating centers will be shipped overnight to Princess Margaret Cancer Centre. In brief, mononuclear cells from unpurified fresh marrow will be aliquoted for flow cytometry. In addition, bone marrow aspirates will be processed as described for pharmacogenomic studies above. See Appendix 12-4.

Statistical Methods:

Phase 1: The dose escalation Phase 1 portion of this study will evaluate up to 4 dose levels in order to determine the MTD. This portion of the trial will require approximately 24 patients.

Phase 2: The Phase 2 portion of this study is designed to assess the ORR compared to historical controls .[9,10,11] The sample size calculation based on a Simon's Minimax two stage design will be used. The two-stage design will permit early stopping of the trial if there is strong evidence that the study regimen is inactive.

For Linsitinib plus bortezomib and dexamethasone, assuming Ho: ORR=0.6 vs. Ha: ORR=0.8, power=80%, alpha (type I error) =0.05. In the first stage, 13 evaluable patients will be enrolled. The trial will be terminated if the number of patients responding is <=8. Otherwise, additional 22 evaluable patients will be enrolled to the second stage of Phase 2. A total of 35 evaluable patients are required. The treatment hypothesis is rejected if fewer than 25 patients responded in total.

Exploratory analysis: Pre-clinical studies suggest that myeloma cells lacking CD45 may predict for IGF-1R sensitivity. Based on published literature, the incidence of IGF-1R protein expression (IGF-1R+) is estimated to be 30-70% [2,3,4]); the incidence of CD45 negativity (CD45-) is estimated to be 30-80% [5,6,7]. The large

	variation in the reported incidence maybe related to stage of disease with a higher percentage of patients reportedly expressing IGF-1R or lacking CD45 in more advanced disease. Patients will be stratified, and overall response by IMWG criteria will be assessed in the following 3 groups: IGF-1R, IGF-1R+/CD45+ and IGF-1R+/CD45- for patients in Phase 1 and 2. This sample size is estimated to include ~11-43 patients with IGF-1R+ and ~11-49 patients with CD45- evaluable for myeloma response. The IGF-1R+/CD45- subgroup is estimated at 6-34 patients should accrual go to the end of the second stage. The IGF-1R+/CD45- group is hypothesized to have a greater potential for response to IGF-1R inhibition, Linsitinib may be considered worthy of further study should the addition of Linsitinib to bortezomib and dexamethasone produce a 20% higher response in this subgroup out of the 59 enrolled patients. Should a higher response rate be observed in this subgroup or less than 13 patients with IGF-1R+/CD45- MM be evaluable, up to 8 IGF-1R+/CD45- patients would be enrolled in addition to the planned sample size in Phase 1 and Phase 2. This number is based on an exploratory objective and is not determined by statistical power considerations. Non-evaluable patients (up to 4) will be replaced for a total planned accrual of approximately 71 patients. No formal comparative statistical testing of efficacy will be performed in this investigation. The ORR and safety data will be reported by descriptive statistics. The PFS and OS will be evaluated using the Kaplan-Meier method.
Protocol Date:	March 1, 2014

GLOSSARY OF ABBREVIATIONS

ACC	adrencortical carcinoma
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANC	absolute neutrophil count
APGD	Astellas Pharma Global Development, Inc.
AST	aspartate aminotransferase (SGOT)
AUC24h	Area-under-the-curve for 24 hours
bHCG	beta human chorionic gonadotropin
BMA	bone marrow aspirate
BID	twice daily dosing
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
°C	degrees Celsius
CA	Compentent Authority
C_{AVG}	average plasma concentration
CBC	complete blood count
CI	confidence interval
CL	Clearance
C_{max}	maximum plasma concentration
CRA	Clinical Research Associate
CR	complete response
CRF	case report form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CT scan	computerized tomography scan
DLT	dose-limiting toxicity DVT deep venous thrombosis
EBMT	European Group for Blood & Marrow Transplantation
ECG	electrocardiogram
eCRF	Electronic CRF
EGFR	epidermal growth factor receptor
ECOG	Eastern Cooperative Oncology Group
EOT	end-of-treatment
°F	degrees Fahrenheit
FCBP	Female of child-bearing potential
FDA	Food and Drug Administration
FLC	Free light chains
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HCC	hepatocellular cancer
hERG	Human Ether-à-go-go Related Gene
HIV	Human immunodeficiency virus
HMCL	Human myeloma cell lines
HPLC	high performance liquid chromatography
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonization
IEC	independent ethics committee
IGF-1	insulin-like growth factor-1
IGF-2	insulin-like growth factor-2
IGF-1R	insulin-like growth factor-1 receptor
IMWG	International Myeloma Working Group
IND	Investigational New Drug application
INR	international normalized ratio
IR	Insulin receptor
IRB	Institutional Review Board
IST	Investigator sponsored trial
IV	intravenous
K	potassium
kg	kilogram
LD	lethal dose
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	monoclonal gammopathy of unknown significance
mL	milliliter
MM	Multiple myeloma
MMRC	Multiple Myeloma Research Consortium
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
Na	sodium
NCI	National Cancer Institute
NOEAL	no-observed-adverse effect level
NSCLC	non-small cell lung cancer
NOS	not otherwise specified
ORR	objective response rate
PD	progressive disease
PE	physical examination
PFS	progression-free survival
PK	Pharmacokinetics
PO	Oral administration
PR	partial response
PS	performance status
QA	quality assurance
QD	Once daily administration
QT	time for ventricular depolarization and repolarization
QTc	QT interval corrected for heart rate
QTcF	QTc Fridericia's Correction
REC	Research Ethics Committee
RR	relapsed/refractory
RP2D	Recommended phase 2 dose
RTK	Receptor tyrosine kinase
sCR	stringent complete response
SAE	serious adverse event
SD	stable disease
SOC	system organ class
SPEP	serum protein electrophoresis
SQ	subcutaneous
T1/2	Elimination half-life
T_{max}	time to maximum concentration
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States

Vd	volume of distribution
Vss	volume of distribution at steady-state
WHO	World Health Organization

1 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The trial is an Investigator Sponsored Trial to be conducted at sites in both Canada and the United States. The trial will be administered and monitored by the Investigator/Sponsor and or a designee.

The Sponsor and Lead Principal Investigator

Suzanne Trudel, M.D.
Princess Margaret Cancer Centre/University Health Network
McLaughlin Centre for Molecular Medicine
610 University Ave, Room 10-721
Toronto, ON M5G 2M9

Sponsor's Agent in the United States

Andrzej Jakubowiak, M.D
University of Chicago Medical Center
5841 S. Maryland Avenue, MC2115
Chicago, IL 60637-1470

Project Manager

Engin Gul
Princess Margaret Cancer Centre/University Health Network
Hydro Building
700 University Avenue, 35-2nd Floor North
Toronto, ON. M5G 1X6

2 INTRODUCTION

Linsitinibis a potent and selective dual tyrosine kinase inhibitor of both the insulin-like growth factor 1 receptor (IGF-1R) and the insulin receptor (IR). Linsitinib inhibits IGF and insulin-stimulated downstream signaling pathways and shows corresponding antiproliferative activity against a broad panel of human tumor cell lines. Data from *in vitro* studies have shown that Linsitinib caused partial growth inhibition in cisplatin-resistant ovarian cancer tumor cell lines such as OVCAR5 and MDAH2774 and that this inhibition correlated with blockade of phospho-AKT. When administered orally once daily to mice bearing xenografted GEO human colorectal cancer tumors or tumors from 3T3/huIGF-1R fibroblasts expressing human IGF-1R, Linsitinib caused dose-dependent inhibition of tumor growth with some tumor regressions evident during the dosing period. Within a panel of three multiple myeloma (MM) cell lines, all were found to be sensitive to Linsitinib, with IC_{50} values (proliferation) < 1 μM. Treatment of MM cell lines with Linsitinib resulted in inhibition of phosphorylation of both AKT and ERK. Multiple myeloma cell lines demonstrated expression and activation of both IGF-1R and IR and Linsitinib inhibited both IGF-1R and IR signaling with greater down-regulation of AKT phosphorylation compared to a specific IGF-1R neutralizing antibody, suggesting that inhibition of both IGF-1R and IR may provide greater efficacy in (MM).

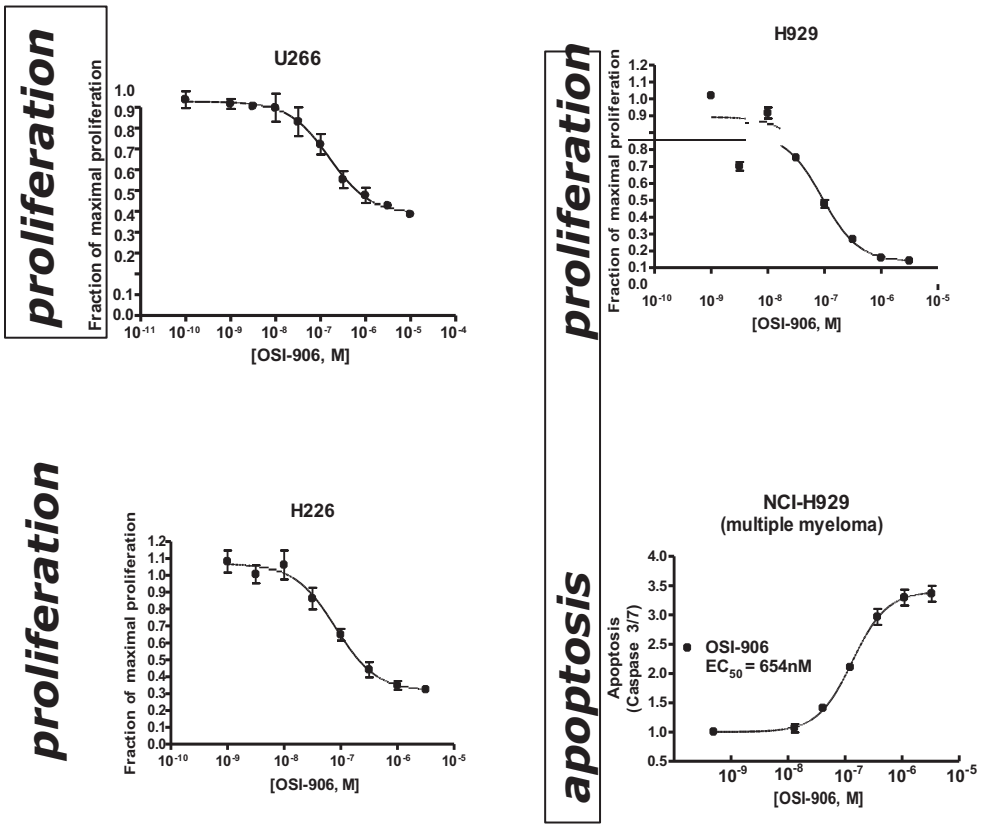
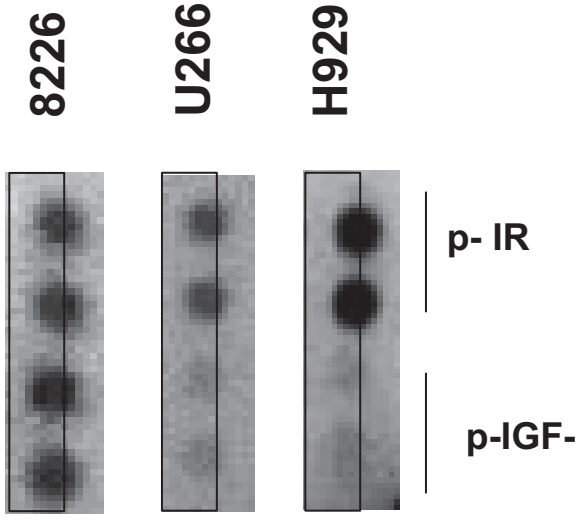


Figure 1: Shows that Linsitinib potently inhibits the proliferation of MM tumor cell lines in vitro. Additionally, Linsitinib can induce apoptosis, as evidenced by increased caspase 3/7 activity, activity in H929 myeloma cells.



MM tumor cell lines exhibit dual phosphorylation of IGF-1R and IR.

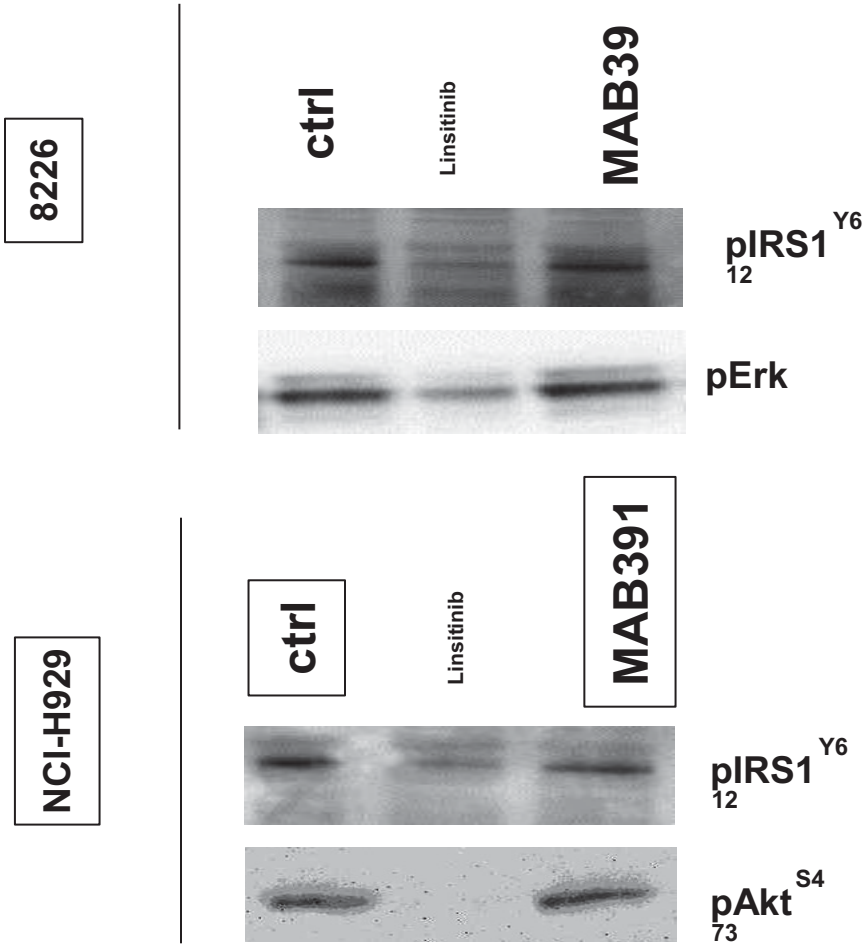


Figure 2: Shows that both IGF-1R and IR are phosphorylated in MM tumor cell lines. Further, while Linsitinib, a dual inhibitor of IGF-1R and IR fully suppresses the phosphorylation of IRS-1-Y612 and ERK, this is not observed with a specific neutralizing antibody targeting IGF-1R alone (MAB391).

A comprehensive review of Linsitinib is contained in the most recent version of the Investigator's Brochure[12]. This document must be reviewed by the Investigator prior to initiating the study.

2.1 Background Therapeutic Information

MM is a malignancy of plasma cells, and is the second most common hematological malignancy in adults. Approximately 20,000 cases of MM are diagnosed each year in the United States (U.S.), with over 11,000 reported deaths due to MM annually. While the advent of autologous stem cell transplantation and advances novel biological agents have improved patient outcomes from a 3-year median life expectancy to 5 years, MM remains incurable [13]. During the past decade, insights into the biology, genetics, and molecular

pathology of the disease have provided a platform upon which novel therapeutic strategies that target the myeloma cell and/or the bone-marrow microenvironment more specifically and effectively are being fashioned. One such target that has emerged is the insulin-like growth factor-1 receptor (IGF-1R).

IGF-1R is a receptor tyrosine kinase widely expressed in normal tissues where it functions in growth regulation. The primary ligands are insulin-like growth factors 1 (IGF-1) and 2 (IGF-2) and, to a much lesser extent, insulin. Receptor activation has been shown to stimulate proliferation, survival, transformation, migration, and angiogenesis in various cell types and contexts [14,15]. Increased expression of IGF-1, IGF-2 and/or their corresponding receptor, IGF-1R, has been shown in a broad range of solid tumors and hematopoietic neoplasias, and increased levels of circulating IGF-1 are associated with colon, prostate, breast, lung, and bladder cancers. Increased expression of IGF-2 is also observed for many types of tumors, driven at least in part by loss of imprinting for the IGF2 locus. Given its prominent role as a pleiotropic factor in so many tumor types, several approaches have been taken to inhibit IGF-1R signaling, including antisense [16], anti-IGF-1R antibodies [17, 18, 19]dominant-negative IGF-1R [20], and small molecule inhibitors [21].

When considering these various targeted approaches it is important to recognize the ability for one receptor tyrosine kinase (RTK) to compensate for another to maintain growth and survival signaling in tumor cells. This has emerged as a common mechanism of resistance to anti-tumor agents that selectively target individual RTKs. IGF-1R is structurally and functionally related to the insulin receptor (IR), and IR can also activate tumor cell AKT signaling and cellular transformation. In human tumor cells selective inhibition of IGF-1R has been shown to promote a compensatory increase in IR activity, and dual IGF-1R and IR inhibition can achieve enhanced and broader anti-tumor activity in preclinical models. These data indicate that agents targeting both IGF-1R and IR as may provide superior efficacy compared to an agent that selectively target only IGF-1R.

In addition to its well-documented role in solid tumors, many studies have highlighted the ability of IGF-1R to stimulate the proliferation and survival of MM cells [22, 23]. Despite the clinical and genetic heterogeneity of MM, IGF-1R is widely expressed in primary patient samples (30-70%) and in human myeloma cell lines (90%), and stromal cells are known to secrete IGF-1[2,3,4]. Another major MM growth factor, IL-6, has been shown to act in part via recruitment of IGF-1R [24]. Ligand binding by IGF-1 or IGF-2 induces IGF-1R autophosphorylation and subsequent activation of the IRS/PI-3K/Akt/mTOR and

Shc/Sos/Raf/MEK/MAPK signaling pathways, which leads to increased survival and proliferation, respectively [25]. These effects are negatively regulated by the phosphatase CD45, which is variably expressed (25-30%) in MM [5,6,7]. It is postulated that IGF-1R signaling remains unrestrained in CD45 negative cells making them sensitive to IGF-1R inhibition. Pre-clinical studies support this hypothesis demonstrating that CD45- but not CD45+ myeloma cell lines are sensitive to inhibition of IGF-1 signaling [8]. IGF-1 has also been shown to have an important role in myeloma cell migration, adhesion, and invasion. Furthermore IGF-1R expression is associated with poor prognosis MM subtypes, in particular t(4;14) and t(14;16) translocation groups, and abnormal IGF-1 expression has been linked to progression from monoclonal gammopathy of unknown significance (MGUS) to MM[3,4] . Given the well-established role of IGF-1R in MM, several preclinical studies have been conducted with a variety of IGF-1R inhibitors with encouraging results[35,36]. Studies with the small molecule inhibitor picropodophyllin have been conducted using primary patient samples, human myeloma cell lines (HMCLs), and murine models [26]. Picropodophyllin was found to induce apoptosis and to inhibit proliferation, angiogenesis, and osteolysis, and notably to dramatically increase survival in mice [27,28]. The small molecule inhibitor NVP-AEW541 has been studied in combination with agents currently being used for MM treatment and has been found most effective in combination with dexamethasone and bortezomib and in combination with an mTOR inhibitor [29]. Similarly, treatment with the anti-IGF-1R antibody, AVE1642, was most effective in combination with bortezomib producing synergistic responses [30].

2.2 Nonclinical Studies with Linsitinib

2.2.1 Nonclinical Pharmacology

Linsitinib is a potent inhibitor of IGF-1R and IR tyrosine kinase signaling in biochemical and cellular assays. Additionally, Linsitinib inhibits IGF-stimulated downstream signaling pathways and shows corresponding antiproliferative activity against a broad panel of human tumor cell lines. Among a panel of >100 human protein kinases, Linsitinib was determined to be a selective inhibitor of only IGF-1R and IR. Pharmacokinetic/pharmacodynamic studies indicate that a trough plasma Linsitinib concentration of approximately 4 μM is necessary in mice to maintain maximal inhibition of tumor IGF-1R phosphorylation in xeografted human tumors. When administered orally once daily to mice bearing GEO human colorectal cancer xenografts or tumors from 3T3 fibroblasts overexpressing human IGF-1R, Linsitinib caused dose-dependent inhibition of tumor growth with some tumor regressions evident during the dosing period.

These data indicate that, when administered orally, Linsitinib has the potential to provide efficacy in a range of human cancers that depend on the IGF-1R/IR pathway for tumor growth and survival.

Linsitinib did not cause effects on the CNS, respiratory, or gastric systems, but a preclinical signal to potentially prolong the QT interval was observed in the hERG channel assay and dog IV cardiovascular study.

Linsitinib did not cause significant inhibition at expected therapeutic concentrations for radio-ligand binding to a series of G-protein coupled receptors, steroid receptors, ion channels, and transporters. The IC_{50} in the in vitro hERG assay was 0.188 μM.

QTc prolongation was seen in anesthetized dogs when Linsitinib was administered by intravenous infusion. The relevance of this intravenous infusion study in anesthetized dogs to the intended oral route in patients is not clear. The low pH of the infusion solution and the effects on several clinical chemistry parameters (glucose, pH, and lactate) together with anesthetics used may have contributed to the effects seen on cardiac function in this study. In the definitive cardiovascular safety study in conscious, telemetered rhesus monkeys, no effects on cardiovascular or electrophysiological parameters were seen when Linsitinib was administered orally at doses up to 60 mg/kg. In a 28-day toxicity study in rhesus monkeys, a single oral dose of 60 mg/kg resulted in C_{max} values ranging from 1.99 to 12.2 μM. Mean plasma protein binding of Linsitinib in rhesus monkeys was 94.4%, leading to a free plasma concentration at C_{max} between 0.111 and 0.659 μM, suggesting that free plasma exposure in rhesus monkeys was in the range of the IC_{50} in the hERG channel assay. No effects were observed on vital functions of the CNS and respiratory systems. Gastric emptying was not affected by single or multiple doses of Linsitinib.

2.2.2 Nonclinical Pharmacokinetics

Linsitinib is rapidly absorbed following oral administration in rats, and the bioavailability after oral administration in 25 mM tartaric acid vehicle ranged from 76.9 to 109%. Food did not alter the bioavailability of Linsitinib in rats. Although the exposure of Linsitinib increased with dose up to 750 mg/kg in rats, it was not proportional to the dose and absorption appears to be rate-limited at higher doses. The exposure of Linsitinib in female rats was > 2-fold higher compared with males, which could be due to gender differences in enzymes involved in the metabolism of Linsitinib. The oral bioavailability in rhesus monkeys was variable and dose-dependent. The exposure of Linsitinib in rhesus monkeys increased with dose up to 100 mg/kg. There was no significant accumulation of

Linsitinib in rats and monkeys following once-daily oral administration for 28 days. The relative bioavailability of Linsitinib in rats after dosing with prototype capsules similar to those in clinical use was essentially equivalent to the bioavailability of Linsitinib when dosed as a solution in 25 mM tartaric acid vehicle. The Vss values indicate that Linsitinib distributes into various tissues and appears to undergo phase 1 and/or 2 metabolism. The primary route of metabolism is via CYP1A2.

2.2.3 Nonclinical Toxicology

A series of studies have been conducted to develop a toxicology profile for Linsitinib. Repeat-dose 28-day oral dosing studies were conducted in rats and monkeys to assess toxicity with subchronic administration of Linsitinib. The rhesus monkey was selected as a nonrodent species based on its comparable metabolic profile to that of humans and the large intra-animal exposure variability observed in dogs. The possible genotoxic potential of Linsitinib was investigated in vitro and in vivo. Target organs for toxicity were identified in the 28-day studies in both species, and the NOAEL and MTD were established. All studies were conducted using the freebase of Linsitinib with once-daily administration, except that twice-daily administration was used in 2 dose levels in the monkey dose-range-finding study and in one 14-day study in rats.

The primary dose-limiting toxicities of Linsitinib were acute symptoms of weakness and lethargy in rhesus monkeys, rapid body weight loss in rats, and tremors in dogs. In the most severe cases, animals were found laterally recumbent and lethargic. While most animals recovered between daily doses, 2 of 12 rhesus monkeys that received 60 mg/kg/day developed hypothermia during the fourth and sixth days of dosing and were sacrificed in moribund conditions.

Examination of individual animals from the dose-range-finding experiments indicates that symptoms were seen at an exposure (AUC24h) of approximately 30 μg*hr/mL depending on individual animal susceptibility. Clinical symptoms were observed in 1 dog with exposure of 40.3 μg*hr/mL after a single dose of 50 mg/kg and in 1 monkey with exposure of 30.0 μg*hr/mL after 5 days of 50 mg/kg BID dosing. There were also several animals with similar exposure that did not show any symptoms (29.9 μg*hr/mL in monkey 13365 on Day 1 at 100 mg/kg QD, 28.7 μg*hr/mL in monkey 13366 after 5 days of 50 mg/kg BID). This level of exposure also corresponds to the median AUC24h of the 60 mg/kg dose group on Day 1 of the 28-day toxicity study in monkeys, in which symptoms of lethargy were observed (28.1 μg*hr/mL). After dose reduction from 60 to

40 mg/kg, no clinical symptoms were seen in any of the monkeys for the remainder of the 28-day GLP toxicity study.

The main adverse effects appear to be related to interference with glucose metabolism, as indicated by an increase in glucose and insulin concentrations. The elevation in glucose despite high concentrations of insulin is also indicative of insulin receptor inhibition. Data from the 28-day GLP study in monkeys indicated that glucose and insulin concentrations returned to normal in parallel with the elimination curve of Linsitinib. Therefore, the measurement of clinical chemistry parameters at 24 hours postdose did not reflect the changes that occurred in the hours following Linsitinib administration. The only toxicologically relevant chemistry effect seen in rats at 24 hours postdose was an increase in urinary glucose, suggesting serum glucose may also have been elevated at earlier time points.

Histopathological changes were limited to a decrease in zymogen granules at 40 mg/kg in the exocrine pancreas in rhesus monkeys and hepatocellular cytoplasmic vacuolation, consistent with glycogen depletion in the liver of rats at 20 mg/kg. Hepatocellular cytoplasmic vacuolation, to a lesser degree, was also present in control rats.

With the exception of a mild increase in liver weight in rats, all parameters showed reversibility within the 28-day postdose recovery period in both rats and rhesus monkeys.

Linsitinib given BID is less well tolerated than when given QD; however, the effects observed were the same independent of the dosing schedule used and appear to be related to interference with glucose metabolism.

Based on the low IC_{50} seen in the hERG channel assay and data obtained from an exploratory intravenous infusion study in dogs, it is concluded that Linsitinib showed a preclinical signal for potential QT prolongation. However, in the definitive cardiovascular safety study, no adverse effects on cardiovascular or electrocardiographic parameters were observed after a single oral 60 mg/kg dose in rhesus monkeys. Furthermore, Linsitinib did not cause any effects on vital functions in the respiratory and central nervous systems.

Linsitinib is genotoxic in the chromosome aberration test in Chinese hamster ovary cells after metabolic activation and in the in vivo rat bone marrow micronucleus test, suggesting that 1 or more metabolites are responsible for this effect.

2.3 Clinical Experiences with Linsitinib

Linsitinib is being studied in multiple phase 1 through phase 3 studies. A comprehensive review of the clinical safety of Linsitinib is contained in the Investigator's Brochure[12].

2.3.1 Phase 1 Experience

Two phase 1 dose-escalation studies have defined the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for continuous and intermittent schedules of single agent Linsitinib in patients with solid tumors (OSI-906-101 and OSI-906-102). These studies are complete and were designed to evaluate the safety and pharmacokinetics of Linsitinib in various subgroups of patients with advanced solid tumors.

Linsitinib has been evaluated as a single agent in two phase 1 dose escalation studies. In study OSI-906-101 the drug was given on either a QD or BID schedule. The MTD/RP2D for the QD schedule was determined to be 400 mg QD and the MTD/RP2D for the BID schedule was determined to be 150 mg BID..

DLTs in Patients in OSI-906 -101

Dose	Event	Grade
450 qd	Hyperglycemia	3
450 qd	Abdominal pain †	2
450 qd	Nausea †	2
150 bid	Aspartate aminotransferase increased	3
400 qd	Electrocardiogram QT corrected interval prolonged	3
200 bid	Hyperglycemia	3
200 bid	Aspartate aminotransferase increased ‡	4
200 bid	Alanine aminotransferase increased ‡	4
200 bid	Blood bilirubin increased ‡	3

† Events occurred in the same patient
‡ Events occurred in the same patient

Study OSI-906 -102 explored three schedules of intermittent daily dosing: Schedule 1 (QD Days 1 – 3 every 14 days); Schedule 2 (QD Days 1 – 5 every 14 days) and Schedule 3 (QD Days 1 – 7 every 14 days). 79 patients were enrolled and treated across 9 Schedule 1 dose levels (10 – 750 mg/day), 1 Schedule 2 dose level (450 mg/day), and 2 Schedule 3 dose levels (450 – 600 mg/day). For schedule 1 and 3, 600 mg QD has been identified as the RP2D, schedule 2 was stopped at 450 mg/day with no DLTs as it was thought to add little advantage over schedules 1 and 3.

DLTs in Patients in OSI-906-102

Dose	Event	Grade
600 S1	Hyperglycemia	3
750 S1	Hyperglycemia	3
750 S1	Vomiting	2
750 S1	Electrocardiogram QT corrected interval prolonged	3
600 S3	Fatigue	4
600 S1	Hyperglycemia	3
600 S3	Hyperglycemia	3

S1: schedule 1; S3: schedule 3

Study OSI-906-103 is a multicenter, open-label, dose-escalation, phase 1 study of Linsitinib in combination with erlotinib in patients with advanced solid tumors. 91 patients were treated across three schedules, starting with Schedule 1 (S1) Linsitinib once daily, days 1 through 3 every 7 days and erlotinib on day 2 through day 21). After observation of clinically significant related toxicity ≥ Grade 2 in any patient on S1 or after ≥ 2 dose levels in S1 had been examined without evidence of DLT, Schedule 2 (S2) was initiated, with both Linsitinib and erlotinib administered daily (erlotinib starting on day 2) through day 21. After observation of clinically significant related toxicity ≥ Grade 2 in any patient on S2 or after ≥ 2 dose levels in S2 had been examined without evidence of DLT, Schedule 3 (S3) was initiated, with Linsitinib administered twice daily and erlotinib once daily (erlotinib starting on day 2) through day 21.

DLTs in Patients in OSI-906-103

Dose	Event	Grade
600 S1	Hyperglycemia	3
600 S1	Aspartate aminotransferase increased †	3
600 S1	Blood alkaline phosphatase increased †	3
600 S1	Alanine aminotransferase increased †	2
450 S1	Liver function test abnormal	3
400 S2	Electrocardiogram QT corrected interval prolonged	3
150 S3	Anorexia	3
450 S1	Electrocardiogram QT corrected interval prolonged	3
400 S2	Electrocardiogram QT corrected interval prolonged	3

S1: schedule 1; S2: schedule 2; S3: schedule 3

† Events occurred in the same patient.

Study OSI-906-202 is an on-going multicenter, randomized, open-label, phase 1/2 study in patients with recurrent epithelial ovarian cancer and other solid tumors. The phase 1 dose escalation portion was to establish the MTD of either intermittent (Arm A) or continuous (Arm B) Linsitinib in combination with weekly paclitaxel in patients with advanced solid tumors. Dose escalation for the intermittent and continuous arms began concurrently and proceeded in parallel and independently of dose escalation within the other schedule. All patients in an existing cohort were followed for at least 28 days for assessment of DLTs prior to the opening of subsequent dose levels/cohorts unless patients are discontinued due to DLT within 28 days of treatment. Thereafter, patients are allowed to continue to receive Linsitinib and/or paclitaxel in the absence of disease progression or unacceptable toxicity. Based on the observation that Linsitinib exposure was reduced on the day of paclitaxel infusion in Arm B, 2 investigational subgroups for Arm B were evaluated. Arm B2 included additional Linsitinib pharmacokinetic sampling following paclitaxel infusion. Arm B3 separated Linsitinib administration and paclitaxel infusion.

58 patients were enrolled and treated in the phase 1 portion across 3 dose levels in Arm A and 2 dose levels in Arm B. Six DLTs have been observed in 6 patients [see Table 1]. The MTD/RP2D for Arm B is 150 mg BID continuous dosing and the MTD/RP2D for Arm A is 600 mg QD intermittent dosing.

Table 1 DLTs in Patients in OSI-906 -202

Dose	Event	Grade
150 bid	Pulmonary embolism	4
150 bid	Fatigue	3
450 qd	Neuropathy peripheral	2
450 qd	Neutropenia	3
150 bid	Hyperglycemia	3
450 qd	Deep Vein Thrombosis	3

With the RP2D for Arm A and Arm B determined in the phase 1 portion, the phase 2 portion began to enroll. One-hundred forty-one (141) patients with relapsed/recurrent epithelial ovarian cancer will be randomized 1:1:1 to 3 treatment groups:

- **Arm A** – Intermittent Linsitinib once daily on days 1 through 3 every 7 days with weekly paclitaxel
- **Arm B** – Continuous Linsitinib twice daily with weekly paclitaxel
- **Arm C** – Weekly paclitaxel

To summarize, common adverse events that have been considered related to Linsitinib include nausea, vomiting, rash and diarrhea. Across the four phase 1 studies, there have been 31 DLTs related to Linsitinib in 26 patients: 8 events of fasting hyperglycemia, 6 events of elevated liver function tests (AST and/or ALT), 5 events of prolonged QTc, 2 events of fatigue, 1 event of vomiting, 1 event of nausea, 1 event of anorexia, 1 event of

neutropenia, 1 event of neuropathy, 1 event of bilirubin increase, 1 event of blood alkaline phosphatase increase, 1 event of pulmonary embolism, 1 event of deep vein thrombosis and 1 interruption of dosing due to toxicity (abdominal cramping and nausea). With the exception of these DLTs, most adverse events have been mild to moderate in severity. As of 18 January 2013, one Grade 5 adverse events/deaths related to Linsitinib has been reported.

The preliminary pharmacokinetics data in cancer patients indicated that median time to reach peak plasma concentrations of Linsitinib was 1.1 to 6.0 hours after twice daily oral administration. The exposure of Linsitinib was approximately dose proportional and the median terminal half-life of Linsitinib in cancer patients was 1.65 to 10.4 hours. The exposure of Linsitinib was not altered significantly after co-administration with erlotinib or paclitaxel.

2.3.2 Phase 2/3 Experience

A double-blind phase 3 study to evaluate the efficacy of single agent Linsitinib versus placebo in patients with locally advanced/metastatic adrenocortical carcinoma (ACC) was completed and did not show improvement on overall survival (primary endpoint) and was un-blinded. Two phase 2 studies in non-small cell lung cancer (NSCLC) 1 including maintenance with erlotinib, (OSI-906-205) the other for first-line in EGFR activating mutation NSCLC (OSI-906-207), globally enrolled a total of 200 and 88 patients respectively. The OSI-906-205 study was discontinued for lack of efficacy after DMC formal review of PFS. The OSI-906-207 study is ongoing. A phase 2 study of Linsitinib in hepatocellular cancer (HCC) was voluntarily terminated by the Sponsor after identifying fatal safety events in 2 patients with advanced HCC and cirrhosis.

2.4 Bortezomib and Dexamethasone

Bortezomib is currently approved by Health Canada and the United States Food and Drug Administration for the treatment of MM patients who have received at least one prior therapy.

The safety and efficacy of bortezomib in patients with MM were investigated in two phase 2 clinical trials, including M34100-024 (patients treated after first relapse) and M34100-025 (patients treated after second or greater relapse and refractory to their latest therapy). In M34100 025, 202 patients with refractory multiple myeloma after at least two failed previous treatments received bortezomib, 1.3 mg/m2 on Days 1, 4, 8, and 11 of a 21-day treatment cycle. The Blade Criteria from the European Group for Blood and

Marrow Transplant (EBMT)[31] were utilized to determine disease response. CR was observed in 4% of subjects, with an additional 6% of patients meeting all criteria for CR except they had a positive immunofixation test. PR or better was achieved by 27% of subjects. The overall response rate, CR, PR and MR combined was 35%. Seventy percent of subjects experienced stable disease or better.

In a phase 2 open-label study of bortezomib, 54 patients with MM who had relapsed after or were refractory to frontline therapy were randomized to receive intravenous 1.0 or 1.3 mg/m(2) bortezomib twice weekly for 2 weeks, every 3 weeks for a maximum of eight cycles.[10] Responses were determined using modified European Group for Blood and Marrow Transplantation criteria. The CR + PR rate for bortezomib alone was 30% and 38% in the 1.0 mg/m2 (8 of 27 patients) and 1.3 mg/m2 (10 of 26 patients) groups respectively. The CR + PR rate for patients who received bortezomib alone or in combination with dexamethasone was 37% and 50% for the 1.0 and 1.3 mg/m2 cohorts respectively.

In an international, open-label, phase 3b trial, 638 patients with relapsed or refractory MM (median 3 prior therapies) received bortezomib 1.3 mg/m2 on days 1, 4, 8, and 11 of a maximum of eight 3-week cycles (median 5 cycles). Dexamethasone 20 mg/d was added the day of and day after each bortezomib dose for progressive disease after ≥2 cycles or for stable disease after ≥4 cycles. Responses were assessed based on M-protein changes. Overall response rate was 67%, including 11% complete (100% M-protein reduction), 22% very good partial (75–99% reduction), 18% partial (50–74% reduction), and 16% minimal response (25–49% reduction). Dexamethasone was added in 208 patients (33%), of whom 70 (34%) showed improved response.[11]

The phase 3 study (M34101-039), also referred to as the APEX study, was designed to determine whether bortezomib provided benefit (time to progression, response rate, and survival) to patients with relapsed or refractory MM relative to treatment with high-dose dexamethasone. The study was also designed to determine the safety and tolerability of bortezomib relative to high-dose dexamethasone, and whether treatment with bortezomib was associated with superior clinical benefit and quality of life relative to high-dose dexamethasone. A total of 669 patients were enrolled and 663 patients received study drug (bortezomib: 331; dexamethasone: 332). Patients randomized to bortezomib received 1.3 mg/m2 I.V. push twice weekly on days 1, 4, 8, and 11 of a 3-week cycle for up to eight treatment cycles as induction therapy, followed by 1.3 mg/m2 bortezomib weekly on days 1, 8, 15, and 22 of a 5-week cycle for three cycles as maintenance

therapy. Patients randomized to dexamethasone received oral dexamethasone 40 mg once daily on days 1 to 4, 9 to 12, and 17 to 20 of a 5-week cycle for up to four treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on days 1 to 4 of a 4-week cycle for five cycles as maintenance therapy. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade,[31] were utilized to determine disease response. There was a 78% increase in TTP for the bortezomib arm. Median TTP was 6.2 months for the bortezomib arm and 3.5 months for the dexamethasone arm (P<.0001). CR + PR was 38% with bortezomib vs. 18% with dexamethasone (P<.0001). CR was 6% with bortezomib vs. <1% with dexamethasone (P<.0001). The CR + nCR rate was 13% with bortezomib vs. 2% with dexamethasone. In patients that had received 2 prior regimens, the CR + PR rate was 34% in the bortezomib arm vs. 13% in the dexamethasone arm. In patients who had received only one prior line of treatment (bortezomib: 132; dexamethasone: 119), CR + PR was 45% with bortezomib vs. 26% with dexamethasone (P=.0035). With a median 8.3 months of follow-up, overall survival was significantly longer (P=.0013) for patients on the bortezomib arm vs. patients on the dexamethasone arm. The probability of survival at one year was 80% for the bortezomib arm vs. 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with bortezomib (P=.0005). In patients who had received only one prior line of treatment, the probability of survival at one year was 89% for the bortezomib arm vs. 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with bortezomib (P=.0098)[9].

2.5 Rationale for the Current Study

Many studies have also shown that IGF-1R stimulates the proliferation and survival of MM cells as well as their migration, adhesion, and invasion[22,23]. Despite the clinical and genetic heterogeneity of MM, IGF-1R is widely expressed in primary patient samples and its expression is associated with high-risk clinical subtypes[2-4]. Several pre-clinical studies have demonstrated anti-myeloma activity of IGF-1R inhibition against myeloma cell lines, primary patient samples and myeloma xenograft models[26-2835,36,]. Further, it has previously been reported that IGF-1R inhibition enhances the in vitro activities of dexamethasone and bortezomib, suggesting that agents targeting this pathway may improve the clinical efficacy of drugs employed in the treatment of myeloma[29,35,36,]. These pre-clinical data therefore supports the evaluation of IGF-1R inhibitors as single-agent therapy and in combination with bortezomib/dexamethasone in MM. The potent in

vitro activity of dual IGF-IR and IR inhibition in human myeloma cell lines forms the basis for clinical evaluation of Linsitinib in patients with myeloma.

In this phase 1/2 clinical trial, Linsitinib will be evaluated as single-agent therapy and in combination with bortezomib/dexamethasone as we anticipate that this class of drug will be most effective when used in combination in myeloma and cancers in general. Bortezomib has been approved by the FDA, Health Canada and other health authorities for treatment of relapsed and refractory MM [33], including patients in first relapse [9,10]. The combination of bortezomib with Linsitinib is supported by pre-clinical work in myeloma in which the combination of an IGF-1R inhibitor with bortezomib is synergistic. Given the potential of high dose dexamethasone to cause hyperglycemia, its use will be first explored in phase 1. Blood glucose levels will be closely monitored for both phases 1 and 2 patients in this study.

The phase 2 component of the study will explore the anti-myeloma activity of Linsitinib in relapsed and relapsed-refractory multiple myeloma, treating patients who have received at least one but no more than 4 prior anti-myeloma regimens.

2.6 Study Objectives

The primary objective of this study is:

- Phase 1: To determine the maximum tolerated dose (MTD) of Linsitinib administered in combination with the recommended dose and schedule of bortezomib and dexamethasone;
- Phase 2: To evaluate the antitumor activity of Linsitinib in combination with bortezomib and dexamethasone at the MTD established from the Phase 1 component. The antitumor activity will be determined by the overall response rate (ORR) including stringent complete response (sCR), complete response (CR), very good partial response (VGPR) and partial response (PR) according to the International Myeloma Working Group (IMWG) criteria. The rate of minimal response (MR) and progressive disease (PD) will also be evaluated.

The secondary objectives of this study are:

- Phase 1:
  - To evaluate the safety and tolerability of Linsitinib in combination with bortezomib and dexamethasone in patients with relapsed or refractory MM.
  - To evaluate the PK profile of Linsitinib when administered to patients with MM in combination with bortezomib and dexamethasone.
- Phase 2:

- To evaluate the progression-free survival (PFS) and overall survival (OS) in patients receiving Linsitinib in combination with bortezomib and dexamethasone.
- To further evaluate the safety and tolerability and the incidence of toxicities of this regimen at the MTD in this patient population.
- To evaluate the PK profile of Linsitinib when administered to patients with MM as single-agent and in combination with bortezomib and dexamethasone.

  Exploratory: to seek biomarkers, IGF-1R+ and CD45-, predictive of drug responsiveness and to demonstrate successful target inhibition in correlative studies. One subgroup of MM patients (IGF-1R+ and CD45-), is hypothesized to have a greater potential for response to IGF-1R inhibition.

3 STUDY DESIGN AND PLAN

This is a multi-center, open-label, non-randomized study. Patients will receive Linsitinib in combination with bortezomib and dexamethasone. Phase 1 involves dose escalation of the combination, whereas Phase 2 involves the expansion of Linsitinib combined with bortezomib and dexamethasone at the MTD to establish the ORR of the combination. This trial will accrue patients with relapsed or relapsed/refractory MM – a disease state for which bortezomib is approved to treat by FDA and Health Canada. The combination of Linsitinib with bortezomib is supported by pre-clinical work in MM in which the combination with an IGF-1R inhibitor enhances anti-tumor activity of bortezomib.

The Phase 1 portion of the study will determine the MTD and DLTs of bortezomib administered on days 1, 4, 8 and 11 of a 21 -day cycle combined with Linsitinib dosed twice daily orally continuously. The combination of Linsitinib with bortezomib has not previously been tested. The active agent bortezomib will be used during Cycle 1 – 8 at the recommended treatment dose of 1.3 mg/m2 days 1, 4, 8 and 11 and Cycles 9+ on days 1, 8, 15 and 22 of a 5-week cycle and Linsitinib will be dose escalated as detailed in section 3.1 of the protocol.

The Phase 1 portion of this trial will utilize a modified 3+3 design. Up to four dose levels will be evaluated followed by an expansion cohort at the MTD (Table 3-1). The MTD will be based on the assessment of DLTs during the first cycle of therapy, and will be defined as the highest dose at which fewer than one-third of patients in a cohort experiences DLT to the combination.

The first 12 patients in the Phase 2 will receive a 7 day run-in with single agent Linsitinib at the MTD prior to adding the bortezomib and dexamethasone combination therapy to allow PK analysis of single agent Linsitinib and combination PK analysis. For purposes of scheduling or other hardships, exceptions may be made for individual patients that are unable to enroll into the 7 day run in, in consultation with the PI. With this exception, consecutive recruitment into the PK cohort will continue until 12 patients, who fulfill all PK requirements, are enrolled. The Phase 2 portion of this study is designed to assess the ORR compared to historical controls.

3.1 Treatment Plan and Regimen

3.1.1 Treatment Plan

The previously determined, recommended phase 2 dose of single-agent Linsitinib is 150 mg BID (continuous dosing) in a solid tumor population. Based on current clinical and nonclinical toxicity data, the starting dose of 75 mg BID was selected for this study, together with bortezomib at its recommended dose and schedule (1.3 mg/m^2 on Days 1, 4, 8 and 11 every 21 days), in combination with dexamethasone. Four dose levels of Linsitinib will be tested (75mg, 100mg, 125 mg, 150 mg) in 4 dosing cohorts. The 150 mg dose will be the maximum dose evaluated and will be the RP2D if the MTD is not exceeded. See **Table 3-1** for the proposed phase 1 dosing cohorts.

Table 3-1: Phase 1 Dose Escalation Cohorts

Cohort	Linsitinib (mg) oral	Bortezomib (mg/m^2) IV or SQ	Dexamethasone (mg) oral or IV
1	75 BID	1.3	20 mg on days 1,4,8,11(C1 – 8) Days 1,8,15 and 22 (C9+)
2	100 BID	1.3	
3	125 BID	1.3	
4	150 BID	1.3	

CYCLE 1 - 8 = 21 days. C 9+ = 35 days.

Phase 2: Once the MTD has been established in Phase 1, an additional 29 (6 at MTD plus 29 for a total of 35) patients will be enrolled at the MTD. 12 patients will be begin therapy with a 7 day run in cycle (Cycle 0) of single agent Linsitinib prior to the initiation of the combination to allow for single agent PK analysis. Linsitinib will be administered at the MTD as determined in Phase 1.

For Phase 1 and Phase 2: patients may receive up to 8 cycles of therapy. After 8 cycles, the schedule of bortezomib will be reduced to once weekly on days 1, 8, 15 and 22 of a 5 week cycle. In the event that bortezomib is not tolerated after cycle 4 or patients do not have access to bortezomib after cycle 8, Linsitinib may be continued as single agent as long as there is clinical benefit and after discussion with Lead Principal Investigator and APGD medical lead as appropriate.

3.1.2 Dose-limiting Toxicities

The Phase 1 portion of this trial will utilize a modified 3+3 design. Up to four dose levels will be evaluated followed by an expansion cohort at the MTD. The 150 mg dose will be the maximum dose evaluated and will be the RP2D if the MTD is not exceeded. The MTD will be based on the assessment of DLTs during the first cycle of therapy, and will be defined as the highest dose at which fewer than one-third of patients in a cohort experiences DLT to the combination. DLT is a clinically significant toxicity that occurs during the first treatment cycle (ie, 21 days). For the purposes of this study, DLT will be defined as:

- Grade 4 or higher hematologic toxicity that does not resolve within 7 days (except for lymphopenia). Patients are allowed platelet transfusion to manage bortezomib related thrombocytopenia. A platelet count that cannot be maintained at grade 3 or better for a minimum of 72h from the last platelet transfusion is a DLT. Grade 3 or Grade 4 thrombocytopenia with bleeding is a DLT.
- Febrile neutropenia (fever > 38.5) or documented infection that persists > 48 hours despite adequate treatment with antibiotics and/or antifungal/antiviral agents is considered a DLT
- Grade 3 or higher non-hematological toxicity possibly or probably related to any study drug except a) alopecia, b) grade 3 nausea, vomiting or diarrhea if not premedicated or adequately treated, c) fatigue or d) hyperglycemia – (see below)
- Prolongation of QTcF > 480 msec or absolute increase > 60msec from baseline
- Grade 2 elevation in liver function tests: ALT/AST ≥ 3X ULN, total bilirubin 2.0 X ULN (isolated bilirubin >2.0 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
- Treatment delay of cycle 2 for more than 14 days due to unresolved toxicity
- Hyperglycemia will be assessed as follows:

Patients will monitor their blood glucose levels at home via hand-held glucometer. Early intervention and treatment of hyperglycemia should be initiated to prevent a DLT. Hyperglycemia will NOT be considered a DLT if:

- Isolated non-fasting grade 3 glucose values will not be considered a DLT if the patient is asymptomatic and glucose levels return to normal values without interruption in therapy.
- Blood glucose and ketone values obtained via a home glucose monitor will not be considered DLTs until confirmed by laboratory serum tests.

Hyperglycemia will be considered a DLT if:

- ≥Grade 3 fasting glucose (> 250 mg/dL or 13.9 mmol/L)
- non-fasting Grade 3 hyperglycemia associated with symptoms of glucose intolerance (polydipsia, polyuria, and weight loss) that interferes with activity of daily living or positive blood ketones (> ULN) not attributable to another cause;
- ≥Grade 4 hyperglycemia (glucose > 500 mg/dL or 27.8 mmol/L)
- Ketoacidosis as evidenced by serum bicarbonate of ≤ 15 mmol/L or venous pH < 7.3 with serum ketones present and anion gap > 12, in the presence of hyperglycemia of Grade 3 or higher (fasting blood glucose > 250 mg/dL; >13.9 mmol/L).
- ≥ grade 3 electrolyte (Na, K, Ca, Mg, Cl, phosphate, and bicarbonate) abnormalities due to glucose intolerance and not attributable to another cause;

Hypoglycemia will be considered a DLT if:

- Symptomatic grade 2 hypoglycemia not resolved to Grade 1 or less in one hour with dietary supplement or any Grade 3 hypoglycemia.

Toxicity will be graded using NCI CTCAE v4.03. Refer to the following website for the CTCAE manual for the document:

http://ctep.cancer.gov/reporting/ctc.html

3.1.3 Phase 1 Assessment of Cohort Toxicity

In the Phase 1 portion of the study, 3 patients in a given dose cohort must have received at least 75% of Linsitinib dosing and completed 21 days (Cycle 1) of therapy or have been removed from treatment for toxicity and successfully replaced before the next cohort may enroll. The incidence of DLT (as defined in Section 4.1.2) will be based on toxicity encountered during Cycle 1. A minimum of 3 and a maximum of 6 evaluable patients will be entered within each cohort for purposes of MTD identification. An "evaluable patient" for Cycle 1 DLT determination is a patient who has completed 21 days (Cycle 1) of therapy and has received at least 75% of the planned Linsitinib /bortezomib doses OR a patient who has been removed from treatment for toxicity.

Dose escalation rules are provided in Table 3-2.

Table 3-2: Dose Escalation for Sequential Cohorts

Number of Patients with Drug-related DLT in a Given Cohort	Dose Escalation*
0 of 3	Proceed to next dose cohort level
1 of 3	3 more patients treated at the same dose level
≥ 2 of 3	Dose escalation stops; MTD is next lower dose level (assuming 6 patients have been treated*)
1 of 6	Proceed to next dose cohort level
≥ 2 of 6	Dose escalation stops; MTD is next lower dose level (assuming 6 patients have been treated*)
≤ 1 of 6 at the highest dose level	MTD

*If only 3 patients were evaluated in the cohort 4 additional patients will be added to fully evaluate that cohort to meet the Maximum Tolerated Dose per section 3.1.4.

3.1.4 Definition of Maximum Tolerated Dose

The maximum tolerated dose of the combination of Linsitinib and bortezomib is the dose level below that at which DLT is observed in ≥ 33% (ie, ≥ 2 of 6) of evaluable patients in a cohort.

3.1.5 Dose Modification

Dose modifications to Linsitinib, bortezomib and dexamethasone are permitted. Adjustments of each drug should be based on assessed attribution of toxicity related to the specific drug. If attribution is unknown or uncertain, adjustments to both drugs should be made according to the guidelines outlined below.

Therapy may be delayed for up to 3 weeks following cycle 2 to allow recovery from all Linsitinib related toxicity. Re-initiation of therapy for a patient who has missed more than 3 weeks of therapy may only occur following approval from the Lead Principal Investigator.

3.1.5.1 Linsitinib Dose Adjustments

To date, DLT of Linsitinib occurring in more than one patient has included Grade 3 or higher episodes of fasting hyperglycemia, elevated AST and/or ALT and prolonged QTc interval. In addition, individual patients have noted DLTs of severe fatigue, vomiting and abdominal cramping/nausea. The proposed schedule for oral Linsitinib is twice daily continuously. Dose reductions of Linsitinib will occur in 25 mg decrements to a minimum dose of 75 mg.

Table 3-3: Dose Reduction Steps for Linsitinib specific related toxicities

Starting Dose	1ST Dose Reduction	2ND Dose Reduction	3RD Dose Reduction
Linsitinib 150 mg BID	Linsitinib 125 mg BID	Linsitinib 100 mg BID	Linsitinib 75 mg BID
Linsitinib 125 mg BID	Linsitinib 100 mg BID	Linsitinib 75 mg BID	Discontinue therapy
Linsitinib 100 mg BID	Linsitinib 75 mg BID	Discontinue therapy	
Linsitinib 75 mg BID	Discontinue therapy		

3.1.5.2 Linsitinib Dose Modification Guidelines

Initiation of subsequent therapy may be delayed for up to 3 weeks to allow recovery from all Linsitinib related toxicity. Re-initiation of therapy for a patient who has missed more than 3 weeks of therapy may only occur following approval from the Lead Principal Investigator. Only 2 weeks are permitted for resolution of Linsitinib related prolonged QTc.

Linsitinib dose that is reduced due to study drug side effect may be re-escalated with study sponsor's written approval only during phase 2. Requests for re-escalation will be evaluated on a case by case basis to ensure participant safety. Patients enrolled in lower dose levels may be escalated to next dose level if next dose level is cleared and active patients have completed at least 3 cycles of treatment.

3.1.5.2.1 Drug related toxicity ≥ Grade 3

Linsitinib dosing should be interrupted if a patient experiences ≥ Grade 3 non-hematologic toxicity related to Linsitinib, with the exception of Grade 3 nausea, vomiting, or diarrhea if not pre-medicated or adequately treated and other events as described below. Linsitinib dosing should also be interrupted if a patient experiences a Grade 3 hematologic toxicity related to Linsitinib that is associated with symptoms such as bleeding or febrile neutropenia or Grade 4 hematologic toxicity with the exception of Grade 4 lymphopenia. Upon resolution of the toxicity to ≤ Grade 1 or no more than 1 grade above baseline, Linsitinib may be reintroduced at the next lower dose level.

3.1.5.2.2 Hyperglycemia

In case of hyperglycemia that meets the definition of a DLT (See section 3.1.2), related to Linsitinib and/or dexamethasone, Linsitinib and dexamethasone dosing should be interrupted. The primary treatment should include supportive management with fluids

and electrolytes. If a patient's blood glucose remains elevated for ≥ 24 hours despite interruption of Linsitinib, metformin may be introduced at the Investigator's discretion in order to reduce the blood glucose (see Section 5.6.2 and Appendix 12-8). Upon resolution of the blood glucose to Grade 1 (≤ 160 mg/dL or 8.9 mmol/L), Linsitinib and dexamethasone may be reintroduced both at the next lower dose level at the Investigator's discretion and provided that the patient is receiving clinical benefit. Metformin should be discontinued for ≥ 48 h prior to the reintroduction of Linsitinib and dexamethasone. For a repeat episode of hyperglycemia meeting the DLT definition metformin use may be continued however with caution and monitoring for hypoglycemia. Alternatively, metformin use can be restricted to the day of and day after dexamethsone if the episode of hyperglycemia was associated with dexamethasone use. If hypoglycemia does occur, metformin should be discontinued. If the hyperglycemia has not resolved to < grade 2 within 14 days, then Linsitinib should be discontinued. Bortezomib dosing may continue throughout any Linsitinib interruption due to hyperglycemia. Dexamethasone doses should be interrupted.

Table 3-4: Dose Modification Guidelines for Linsitinib-Related Hyperglycemia

NCI CTCAE V4.02	Dose Interruption	Dose Reduction
Grade 1 > ULN – 160 mg/dL or > ULN – 8.9 mmol/L	No change (Refer to **Appendix 12-8**)	
Grade 2 161 – 250 mg/dL or 8.9 – 13.9 mmol/L		
≥ Grade 3 (> 250 mg/dL or > 13.9 mmol/L)	Hold until ≤ grade 1 If glucose > grade 1 after 24 hours, metformin may be introduced.	1st episode – reduce to level -1 2nd episode – reduce to level -2 3rd episode or 2nd episode and no resolution in 14 days to <grade 2 – discontinue Linsitinib

Care needs to be taken with insulin as it may not be effective and there may be a risk of rebound hypoglycemia when the Linsitinib/placebo levels drop and the exogenous insulin is still active.

Preclinical data suggests metformin may be useful in the setting of hyperglycemia after interruption of Linsitinib. Any decision to reintroduce Linsitinib after interruption must be made by a study investigator and according to the protocol. No data exist regarding concomitant administration of Linsitinib and metformin or the ability of other antihyperglycemic medications to reverse Linsitinib-induced

hyperglycemia. Sulphonylureas are metabolized through the CYP2C9 enzyme, which may be inhibited by Linsitinib, and so these drugs should not be used.

Use of insulin to treat Linsitinib induced hyperglycemia is expected to be of limited value. Insulin should only be considered if the patient is experiencing diabetic ketoacidosis (DKA) or if hyperglycemia (≥ Grade 3) persists despite Linsitinib interruption and metformin has been tried without result. It is to be used with extreme caution, and the patient should be carefully monitored in anticipation of possible rebound hypoglycemia.

No data exist regarding the ability of other anti-diabetic medications to reverse Linsitinib induced hyperglycemia. (See also Appendix 12-8 for an algorithm of hyperglycemia management)

3.1.5.2.3 Hypoglycemia:

The investigator must follow local institution specific guidelines in the event hypoglycemia is experienced by a patient on treatment with Linsitinib in this study. Consultation with the appropriate specialist (e.g., Endocrinologist, etc.) is recommended. Patients on treatment with Linsitinib who demonstrate hypoglycemia must have their blood glucose levels and any associated symptoms closely monitored until blood glucose values return to normal.

Below is meant as guidance to the investigator and is not to supersede any local country or institution specific guidelines in the event they are more stringent in the management of hypoglycemia.

Grade 1 (glucose <ULN-55mg/dL or 3.1 mmol/L)

- Repeat glucose value. If second level is above 55mg/dL or 3.1 mmol/L, continue dosing Linsitinib.
- If below 55mg/dL or 3.1 mmol/L see algorithm below
- Consider increase in glucose monitoring frequency

Grade 2 (Glucose <55-40 mg/dL or 3.1-2.2 mmol/L)

- Repeat glucose level then advise the patient to drink a glass of orange juice or other drink containing glucose and discontinue Linsitinib. If the patient is taking oral hypoglycemics these should be held as well.
- After first documented episode, monitor glucose every 24 hrs until it returns to normal on 2 consecutive days

- Once glucose levels return to normal in less than 1 hour resume Linsitinib at the current dose, otherwise (more than 1 hour) decrease dose of Linsitinib by one level and resume dosing
- If the subject has repeat episode of Grade 2 hypoglycemia, decrease dose by another level and repeat glucose monitoring every 24 hrs until it returns to normal on 2 consecutive days
- After 3rd episode of Grade 2 hypoglycemia permanently discontinue study drug

Grade 3 (glucose <40-30 mg/dL or 2.2-1.7 mmol/L) –

- Repeat glucose level then advise the patient to drink a glass of orange juice or other drink containing glucose and discontinue Linsitinib, if the patient is taking oral hypoglycemics these should be held as well.
- After first documented episode, monitor glucose every 24 hrs until it returns to normal on 2 consecutive days
- Inform the study medical monitor
- Once glucose levels have returned to normal decrease dose of Linsitinib by one level and resume dosing
- If the subject has repeat episode of Grade 3 or 4 hypoglycemia permanently discontinue study drug

Grade 4 (Glucose <30 mg/dL or <1.7 mmol/L) –

- Advise the patient to stop taking Linsitinib and go to the hospital or emergency room for monitoring*
- Repeat glucose value then advise the patient to drink a glass of orange juice or other drink containing glucose and permanently discontinue Linsitinib
- Inform the study medical monitor
- Continue to monitor glucose every 24 hrs until it returns to normal on 2 consecutive days

* If there are no available beds in the site hospital, advise the patient to go to the nearest emergency room. Contact the emergency room physician to provide background regarding the patient and clinical trial. Fax these guidelines to him/her with the provision that the guidelines are to be used as advice only and should not replace clinical assessment.

Any hypoglycemic event of grade 4 or higher per NCI CTCAE v4.03, regardless of the presence or absence of symptoms and causality to study drug, must be reported as a serious adverse event (SAE) within 24 hours. Hypoglycemic events of grade 1 to grade 3 per NCI CTCAE v4.03 must be recorded as an adverse event (AE) on the appropriate CRF page, and if the event meets any other criteria of seriousness must be reported as an

SAE. All events of hypoglycemia, regardless of causality or grading, will be reviewed on a regular basis. In addition, the Data Monitoring Committee (DMC) will also have access to SAE and AE data relative to blood glucose during their regular safety review.

3.1.5.2.4 QTc Prolongation:

ECG monitoring will be conducted in this study as part the safety monitoring. Triplicate 12-lead ECGs will be obtained for all patients at screening and pre and post dose on day1 of cycle 0, 1 and 2 and 2 to 4 hours post dose on days 8 and 15 of cycle 1. If clinically significant abnormalities are observed, patients will be required to do triplicate ECGs pre and post dose on day 1 of each subsequent cycle. Patients with normal ECGs will have single 12-lead ECG pre dose and 2 to 4 hours post dose on day 1 of cycle 3 and subsequent cycles (Appendix 12-1). For single ECG monitoring, if the QTc is > 450 msec then triplicate ECGs will be required and the mean QTc value will be used for the assessment. A digital ECG machine will be used that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTc and/or QTcF intervals. Additional ECGs may be done as agreed by the Investigator, or clinically indicated. At each assessment a 12-lead ECG will be performed by qualified personnel at the site at least 2 minutes apart after at least a five-minute rest with the subject in a semi-recumbent or supine position. Mean QTc values greater than 450 msec as confirmed by the machine must be confirmed manually using the Fridericia's formula given below:

The Fridericia's formula is $QTcF=QT \times (1/RR)^{1/3}$

Patients with a confirmed calculated mean QTcF > 450 msec will be excluded from the study. Patients with QTc or QTcF≤ 450 will be eligible for the study. Linsitinib dosing should be discontinued for any patient with a confirmed (triplicate reads repeated within 2 hours) mean QTcF ≥ 501 msec (≥ grade 3) or change > 60 msec from baseline, regardless of when the event occurs or possible relationship to Linsitinib.

Linsitinib dosing will be interrupted for any patient with a mean QTcF value of > 481 msec mean QTcF ≤ 500 msec (grade 2), and a repeat ECG (in triplicate) must be obtained in 24 -48 hours. If the original QTc interval prolongation is confirmed, Linsitinib should be withheld until the mean QTcF returns to ≤ 480 msec (≤ grade 1). In the meantime, ECGs and electrolytes should be checked as clinically indicated, but at a minimum of once a week. If the prolongation is related to electrolyte abnormalities or drugs known to prolong the QT interval, then Linsitinib can be restarted at the same dose once electrolyte values return to normal and the mean QTcF interval is ≤ 480 msec (≤ grade 1). If the prolongation is not related to electrolyte abnormalities (ie, electrolytes levels are within

normal limits), then Linsitinib can be restarted at dose level reduction upon resolution of the mean QTcF to ≤ 480 msec (≤ grade 1). If Linsitinib is restarted after the QTc prolongation has resolved, ECGs and monitoring of electrolytes should, at a minimum, be performed at 1, 2, and 3, weeks after Linsitinib is restarted and then at the every 3-week treatment period frequency while the patient is receiving Linsitinib.

If the QTc interval prolongation does not resolve (mean QTcF ≤ 480 msec, ≤ grade 1) within 14 days, then Linsitinib should be discontinued.

Table 3-5: Dose Modification Guidelines for Linsitinib-Related QTcF abnormalities

NCI CTCAE V4.03	Dose Interruption	Dose Reduction
QTcF Prolongation		
Grade 1 **450 – 480 msec**	No mandatory change	
Grade 2 **481 – 500 msec**	Hold until grade 1 or lower. Check electrolytes and ECGs (at least weekly) until at normal levels[a]	1st episode – Reduce by one dose level if not related to electrolyte abnormality, and monitor electrolytes[a]. 2nd episode – Reduce by an additional dose level (if feasible), if not related to electrolyte abnormality, and monitor electrolytes[a]. No reduction if related to corrected electrolyte abnormality.
Grade 3+ **≥ 501 msec**	Discontinue Linsitinib	

a. ECGs and monitoring of electrolytes should, at a minimum, be performed at 1, 2, and 3, weeks after Linsitinib is restarted, and then at the every 3-week treatment period frequency while the patient is receiving Linsitinib.

3.1.5.2.5 Elevated Liver Function Tests:

If laboratory testing for a patient enrolled in study and receiving study drug reveals an increase of serum aminotransferases (AT) to > 3X ULN, or bilirubin > 2X ULN, then serum gamma-glutamyltransferase (GGT) and PT/INR should be drawn and at least all four of the usual serum hepatic measures (ALT, AST, ALP, and TBL) should be repeated. Testing should be repeated within 48-72 hours of notification of the test results. Patients should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities:

Confirmed abnormalities will be characterized as moderate and marked where ULN:

		ALT or AST		Total Bilirubin
Moderate		> 3 x ULN)	or	> 2 x ULN
Marked		> 3 x ULN	and	> 2 x ULN

In addition, the patient should be considered to have marked hepatic abnormalities for any of the following:

- ALT or AST > 8X ULN
- ALT or AST > 5X ULN for more than 2 weeks
- ALT or AST > 3X ULN and INR > 1.5
- ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or marked abnormalities and require additional monitoring and follow-up.

Follow-up Procedures:

Moderate and marked abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF). Patients with confirmed abnormal liver function testing should be followed as described below.

- Moderately abnormal LFTs should be repeated 2-3 times weekly then weekly or less (no less than weekly for the first 2 cycle) if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.
- Marked hepatic liver function abnormalities, in the absence of another etiology, may be considered an important medical event and reported as a Serious Adverse Event (SAE). The Principal Investigator should be contacted and informed of all patients for whom marked hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as 'adverse events' on the AE page of the CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of the CRF. Information on alcohol, other substance use, and diet should be entered on the LA-CRF.
- Obtain a history of exposure to environmental chemical agents
- Based on the subject's history, other testing may be appropriate including:
    - acute viral hepatitis (A, B, C, D, E or other infectious agents).
    - ultrasound or other imaging to assess biliary tract disease
    - other laboratory tests including INR, direct bilirubin
- Consider gastroenterology or hepatology consultations
- Submit results for any additional testing and possible etiology.

Study Discontinuation

In the absence of an explanation for increased LFTs, such as viral hepatitis, pre-existing or acute liver disease or exposure to other agents associated with liver injury, the patient may be discontinued from the study. The investigator may determine that it is not in the patient's best interest to continue study enrollment. In addition to the protocol criteria for discontinuation of treatment may be considered if:

- ALT or AST > 8X ULN
- ALT or AST > 5X ULN for more than 2 weeks despite dosing interruption > 14 days
- ALT or AST > 3X ULN and (TBL > 2X ULN or INR > 1.5) despite dosing interruption >14 days

- ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

In addition, if close monitoring for a subject with moderate or marked hepatic laboratory tests is not possible, drug should be discontinued. If a subject is identified has a Hy's law case, the subject will be discontinued from the study.

In the event of a confirmed, marked hepatic abnormality, it is the investigator's responsibility to ensure contact with the Principal Investigator and APGD immediately (i.e. within 24 hours of awareness or at the earliest possible time point).

Additional information regarding drug induced liver injury may be reviewed in the FDA document issued July 2009: Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation".

3.1.5.3 Bortezomib Dose Adjustments

Bortezomib-related toxicities may require dose reduction and/or dose omission. Common toxicities are hematologic (primarily thrombocytopenia and neutropenia) and non-hematologic (neurological, gastrointestinal, constitutional and more rarely hepatic and/or renal toxicity). If a patient experiences a Grade 3 or higher toxicity that is considered by the Investigator to be related to bortezomib (during either phase 1 or 2 of the clinical trial), reduction and/or omission of the bortezomib dose may occur at the discretion of the Investigator per Table 3-6 specific dose modification guidelines for these toxicities are outlined below in table 3-7.

Table 3-6: Dose Reduction Steps for Bortezomib specific related toxicities

Starting Dose	1ST Dose Reduction	2ND Dose Reduction *	3RD Dose Reduction**	4TH Dose Reduction**	5TH Dose Reduction
Bortezomib 1.3 mg/m^2 Days 1, 4, 8 and 11	Bortezomib 1.3 mg/m^2 Days 1, 8 and 15	Bortezomib 1.0 mg/m^2 Days 1, 8 and 15	Bortezomib 0.7 mg/m^2 Days 1, 8 and 15	Bortezomib 0.5 mg/m^2 Days 1, 8 and 15	Discontinue therapy

* Except for neuropathy; see Table 3-8

** Dose reduction will apply only if standard institutional practice otherwise patient may discontinue bortezomib after 2nd dose reduction

Table 3-7: Bortezomib dose modification guidelines

Description	Recommended Action
Grade 3 Thrombocytopenia ($< 50 \times 10^9$/L)	Additional platelet counts should be performed at the discretion of the Investigator.
Grade 4 Thrombocytopenia ($< 25 \times 10^9$/L)	Platelet transfusions and post-transfusion platelet counts should be performed. Patients may be dosed on the same day and at the same dose level if platelets recover to grade 3. Otherwise hold bortezomib. If platelet count recovers to Grade 3 or higher within 7 days no dose reduction is required.
Grade 3 or higher thrombocytopenia associated with bleeding.	Hold bortezomib then resume at next lower dose level when toxicity resolves to ≤ Grade 2 *
Grade 4 Neutropenia (ANC $< 0.5 \times 10^9$/L) or febrile neutropenia (ANC $< 1.0 \times 10^9$/L, fever ≥ 38.5°C)	Hold bortezomib. When neutropenia returns to Grade 2 (ANC $> 1.0X\ 10^9$/L) and/or fever resolves Resume therapy at next lower dose level of bortezomib*
Peripheral Neuropathy	Patients who experience bortezomib-related neuropathic pain and/or peripheral sensory neuropathy should be managed according to table 3-8.
Other bortezomib related toxicity ≥ Grade 3	Hold therapy until resolved to ≤ Grade 2

* If thrombocytopenia can be managed with platelet transfusions and neutropenia can be managed with the use of growth factors, dose reductions of bortezomib are not required but can be made at the investigators discretion.

3.1.5.3.1 Bortezomib related Neuropathy

For patients who experience neuropathic pain and/or peripheral sensory or motor neuropathy related to bortezomib, dose adjustment will be based on the severity of the event as indicated in Table 3-8.

Table 3-8: Recommended Dose Modifications for Bortezomib-Related Neuropathic Pain and/or Peripheral Sensory Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms	Bortezomib Dose Modification
Grade 1 (paresthesias, weakness, and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce one dose level
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate with reduced two dose levels
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue from the Treatment Phase of the study

Linsitinib dosing may continue throughout any interruption of bortezomib dosing. Dexamethasone doses should be omitted.

Following cycle 2, initiation of subsequent cycles of therapy may be delayed for up to 3 weeks to allow recovery from all bortezomib-related toxicity. Re-initiation of therapy for a patient who has missed more than 3 weeks of therapy may only occur following approval from the Lead Principal Investigator (the 3-week interval is dated from the anticipated first dose of bortezomib in a subsequent cycle, not from last dose of bortezomib).

3.1.5.3.2 Combined or unknown attribution:

Any other drug related toxicity ≥ Grade 3	Assess attribution if possible: • Linsitinib attribution, hold drug until resolved to ≤ Grade 2. Resume at one level dose reduction • Bortezomib attribution, hold drug until resolved to ≤ Grade 2. Resume at one level dose reduction • Dexamethasone attribution, hold drug until resolved to ≤ Grade 2. • For multiple drug attribution, take required action for each drug.

3.1.5.4 Dexamethasone Dose Adjustments

For patients taking dexamethasone: If a patient experiences a toxicity or adverse experience related to dexamethasone, that in the opinion of the investigator requires a dose reduction, the dose will be modified as indicated in Table 3-9. If dexamethasone is not tolerated at the lowest dose of 10 mg on the day of each dose of bortezomib, dexamethasone may be discontinued. Dexamethasone dose may continue throughout any interruption of bortezomib dosing at investigator discretion. Dexamethasone should be administered once weekly when bortezomib is administered once weekly.

Table 3-9: Dexamethasone Dose De-Escalation Schedule

Dexamethasone		
Dose Level	**Dose Reduction 1**	**Dose Reduction 2**
20 mg on the day of dose of bortezomib	10 mg on the day of dose of bortezomib	Discontinue dexamethasone

4 PATIENT POPULATION

The target population for this trial includes patients with relapsed or relapsed/refractory multiple myeloma.

Questions about eligibility criteria should be addressed with the Lead Principal Investigator PRIOR to registration. The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to assure that patients who enter this study are medically appropriate candidates for this therapy.

4.1 Inclusion Criteria

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

1. Males or females, age 18 years or older.
2. A diagnosis of MM and documentation of relapsed or relapse/refractory status following at least 1 prior line of therapy for phase 1 and 1 to 5 prior lines of therapy for phase 2.
3. Patients with measurable disease defined as at least one of the following (these baseline laboratory studies for determining eligibility must be obtained within 21 days prior to enrollment):

a. Serum M-protein ≥ 0.5 g/dl (≥ 5 g/l)
b. Urine M-protein ≥ 200 mg/24 h
c. Serum free light chains (FLC) assay: Involved FLC level ≥ 10 mg/dl (≥ 100 mg/l) and an abnormal serum free light chain ratio (< 0.26 or > 1.65)
d. Biopsy proven plasmacytoma. Prior biopsy is acceptable.
e. If the serum protein electrophoresis is unreliable for routine M-protein measurement, quantitative immunoglobulin levels on nephrolometry or turbidometry will be followed.

4. Patient has an Eastern Cooperative Oncology Group (ECOG) ≤ 2 OR Karnofsky ≥ 60% performance status (PS) (Appendix 12-2).
5. Predose mean QTc≤ 450 msec or QTc Fridericia's Correction (QTcF) on Day 1(cycle 1 or cycle 0 if applicable) must be ≤ 450 msec. (see Appendix 12-1 for details on screening and Day 1 QTC evaluations).
6. Females of childbearing potential (FCBP): a female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bildateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months). Pregnancy status in women of childbearing potential must be confirmed by serum β-hCG at screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women. FCBP must use acceptable forms of birth control or agree to abstain from heterosexual intercourse while participating in the study and for 90 days following the last dose of study drug. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy while participating in the study and for 90 days following the last dose of study drug.
7. Voluntary, written informed consent before performance of any study-related procedure not part of routine medical care with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).
9. Must be able to take and retain oral medications.
10. *Inclusion Clinical Laboratories Criteria*
    The following laboratory results must be met within 21 days of first study drug administration. (Patients must meet the below criteria within 24 hours of the first dose to start their treatment):
    a. Absolute neutrophil count (ANC) ≥ 1,000 cells/dL (1.0 x 10^9/L) *(Growth factors cannot be used within 14 days of first study drug administration);*
    b. Platelet count ≥ 50,000 cells/dL (50 x 10^9/L)
    c. Hemoglobin ≥ 8.0 g/dL (4.96 mmol/L)
    d. Serum AST or ALT ≤ 1.2 x ULN
    e. Total bilirubin within normal limits
    f. Creatinine clearance ≥ 30 mL/min (Cockcroft-Gault calculation)
    g. Serum creatinine ≤ 1.5 x ULN (correction with hydration and re-testing is permitted)(values ≥ 1.5 X ULN may be acceptable if improved with hydration and/or attributable to progressing MM)

h. Serum calcium (ionized or corrected for albumin) ≥ 2.0 mmol/L (8.0 mg/dL or 1.0 mmol/L ionized calcium) to ≤ 1.2 x ULN. Treatment of hypercalcemia or hypocalcemia is allowed and patient may enroll if serum calcium returns to ≥ 2.0 mmols/L to ≤ 1.2 x ULN with standard treatment (See Appendix 12-13 for calcium correction formula)
i. Serum potassium, and magnesium within normal limits (correction with supplementation is permitted)
j. HgbA1c of ≤ 7% (within 21 days only, does not need to be repeated 24 h pre-dose)
k. Troponin I or T within normal limits (patients with abnormal values may be enrolled with sponsor approval after full cardiac evaluations are done to determine that the abnormality is non-cardiac)
l. BNP or NT-proBNP within normal limits (patients with abnormal values may be enrolled with sponsor approval after full cardiac evaluations are done to determine that the abnormality is non-cardiac)
m. Fasting glucose of ≤126 mg/dL (7.0 mmol/L). A diagnosis of Type II diabetes mellitus is permitted if > 8 weeks since diagnosis and well controlled. Concurrent non-insulinotropic antihyperglycemic therapy is permitted if the dose has been stable for 8 weeks.

11. Resolution of prior toxicities associated with a prior treatment to ≤ grade 1

4.2 Exclusion Criteria

Patients are to be excluded for safety concerns, lack of suitability, or administrative reasons. Patients who meet *any* of the following exclusion criteria are not eligible for enrollment.

1. Patients refractory or intolerant to bortezomib are not permitted (Refractory = non-responsive/progressed on therapy or within 60 days of bortezomib) on the Phase 2 part of the study only.
2. Diagnosed or treated for another malignancy within 3 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.
3. Patient has received other investigational drugs or chemotherapy within 21 days or approved anti-myeloma therapy including steroid therapy within 14 days prior to first study drug administration.
4. History (within the last 6 months) of significant cardiovascular disease unless the disease is well-controlled. Significant cardiac disease includes but is not limited to second/third degree heart block; clinically significant ischemic heart disease; superior vena cava (SVC) syndrome; poorly controlled hypertension; congestive heart failure of New York Heart Association (NYHA) Class II or worse. History of arrhythmia (multifocal premature ventricular contractions [PVCs], bigeminy, trigeminy, ventricular tachycardia, or uncontrolled atrial fibrillation) that is symptomatic or requires treatment (≥ grade 3), left bundle branch block (LBBB), or asymptomatic sustained ventricular tachycardia are not allowed. Patients with atrial fibrillation controlled by medication are not excluded.

5. Mean QTcF interval > 450 msec at screening.
6. Prior autologous, peripheral stem cell transplant within 12 weeks of the first dose of study drug.
7. Daily requirement for corticosteroids (except for inhalation corticosteroids).
8. Patients with evidence of mucosal or internal bleeding and/or platelet transfusion refractory (*i.e.,* unable to maintain a platelet count ≥ 50,000 cells/dL).
9. Known active infection requiring parenteral or oral anti-infective treatment.
10. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse follow-up evaluation.
11. Use of any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient. Examples of such conditions include any pre-existing kidney disease (acute or chronic, unless renal insufficiency is felt to be secondary to MM), hypertension, active seizure disorder or pulmonary diseases that would impose excessive risk to the patient.
12. Patient has hypersensitivity to any of the components of study drugs.
13. Known HIV or active hepatitis B or C viral infection.
14. Diabetes mellitus currently requiring insulin or insulinotropic therapy or prior history of steroid induced diabetes (see Appendix 12-10).
15. History of cerebrovascular accident (CVA) within 6 months prior to registration or that is not stable.
16. Prior therapy with an IGF-1R inhibitor.
17. Use of drugs that have a risk of causing QT interval prolongation and/or have a known risk of causing Torsades de Pointes (TdP) before 14 days or the recommended 5 half-life washout period elapses (as indicated in Appendix 12-6) whichever is longer, prior to Cycle 1 Day 1 dosing. Drugs that have a known risk of causing TdP can be found on www.azcert.org/medical-pros/drug-lists/bycategory.cfm).
18. Use of strong/moderate CYP1A2 inhibitors such as ciprofloxacin and fluvoxamine. Other less potent CYP1A2 inhibitors/inducers are not excluded.
19. Gastro-intestinal abnormalities, including bowel obstruction, inability to take oral medication, requirement for intravenous (IV) alimentation, active peptic ulcer or prior surgical procedures or bowel resection or other poorly controlled gastrointestinal disorders that could affect the absorption of study drug (eg, Crohn's disease or ulcerative colitis).
20. Peripheral neuropathy ≥ grade 2.
21. Significant liver disease or metastatic disease to the liver
22. History of amyloid, plasma cell leukemia or CNS involvement.
23. Prior radiation therapy or major surgical procedure within 4 weeks of the first dose of study treatment (this does not include limited course of radiation used for management of bone pain).

5 STUDY DRUG(S) AND CONCOMITANT MEDICATIONS

Linsitinib (cis-3-[8-amino-1-(2-phenyl-quinolin-7-yl)-imidazo[1,5-a]pyrazin-3-yl]-1-methyl-cyclobutanol) is an investigation drug and will be supplied by Astellas Pharma Global Development, Inc. (APGD) for this clinical trial.

Bortezomib (Velcade®) is an approved drug for the treatment of patients with relapsed and relapsed/refractory MM and will be obtained from commercial supplies within each investigative site.

Dexamethasone is a commonly administered, generically available drug for the treatment of patients with relapsed and relapsed/refractory MM; dexamethasone (either intravenous or oral) will be obtained from commercial supplies within each investigative site.

5.1 Description and Handling of Linsitinib

5.1.1 Formulation

The drug product is available as immediate-release, film-coated tablets in 3 dosage strengths: 25, 100, and 150 mg. The 25 and 100 mg tablets are white, round and biconvex and the 150 mg tablets are white, biconvex and capsule-shaped.

Linsitinib is formulated with standard excipients including mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, and magnesium stearate. The film-coating of the tablets includes Opadry® White.

5.1.2 Packaging and Labeling

Linsitinib tablets are provided in 60cc HDPE bottles with an induction sealed liner and child resistant closure. Each bottle contains 30 tablets of either 25, 100 or 150 mg.

5.1.3 Storage and Handling

The available stability data support storage of Linsitinib film-coated tablets not above 25°C (77°F). Assignment of the expiry date is per the product labeling, as it is continuously evaluated and extended as supportive stability data are generated concurrent with the clinical trials.

5.2 Dispensation and Administration of Linsitinib

5.2.1 Dispensation and Administration

Linsitinib is available as film-coated tablets for oral administration in doses of 25, 100, and 150 mg. For this clinical trial, Linsitinib is dosed at a fixed daily dose (it is not

adjusted based on body weight or body surface area). The tablets should be taken with food and up to 200 mL of water twice daily at approximately 12-hour intervals. Doses should be taken at approximately the same time each day. On the days when PK levels are to be done Linsitinib should be taken in clinic within 30 minutes of the bortezomib dose and the time of the dose recorded.

For the Phase 1: patients will received either 75 mg BID, 100 mg BID, 125 mg BID or 150 mg BID in 21-day cycles. Depending on which dose level cohort the patient has been assigned to, a sufficient number of tablets should be dispensed to patients for dosing (number of days multiplied by the number of tablets per dose) on an out-patient basis between clinic visits. Full bottles may be dispensed for the exact number of tablets calculated for a 21-day cycle. More than one bottle may be dispensed, as required.

- Dose Level #1: only the 25 mg tablets should be dispensed.
- Dose Level #2: only the 100 mg tablets should be dispensed.
- Dose Level #3: both 25 mg tablets and 100 mg tablets should be dispensed.
- Dose Level 4: only the 150 mg tablets should be dispensed.

For the Phase 2: patients will receive the MTD of Linsitinib as determined by the phase 1 stage of this trial.

On PK sampling days, the first daily dose of Linsitinib must be taken in the clinic within 30 minutes of the bortezomib dose.

Dose modification based on observed toxicities will occur as outlined in Section 3.1.5.

5.2.2 Adverse Events Associated with Linsitinib Administration

As of 05 January 2012, 534 patients had enrolled in clinical trials investigating Linsitinib. Common adverse events that have been considered related to Linsitinib include nausea (27.5%), fatigue (26.4%), diarrhea (25.2%), vomiting (14.6%), anorexia (8.8%), hyperglycemia (8%), rash (6.2%), headache (5%), lethargy (3.4%), peripheral neuropathy (3.4%), prolonged QTc interval (2.4%), renal failure (1.1%), liver toxicity (0.2%), and hypoglycemia (0.4%). Preclinical toxicology and safety pharmacology studies have identified 3 safety considerations: prolonged QT/QTc interval, induction of glucose intolerance (hyperglycemia and hyperinsulinemia), and lethargy/weakness/asthenia. Phase 1 clinical studies utilizing home glucose monitoring indicated that 34% of patients had hyperglycemia (blood glucose > 160 mg/dL) at some time while receiving Linsitinib treatment; the duration of hyperglycemia was usually brief (< 12 hours). Although CTCAE grading refers to serum glucose values, when CTCAE criteria are applied to

home glucometer results, 8% of these patients had Grade 3 (> 250 to 500 mg/dL) hyperglycemia and no patient had Grade 4 (> 500 mg/dL) hyperglycemia. Therefore, significant hyperglycemia is possible in patients treated with Linsitinib . Monitoring of blood glucose levels will be incorporated into this clinical study. Results of phase 1 clinical studies utilizing home glucose monitoring indicated that Linsitinib treatment was associated with hypoglycemia in 29% of patients. Most hypoglycemia was mild to moderate; however, when CTCAE criteria are applied to home glucose monitoring results, Grade 3 (< 40-30 mg/dL) hypoglycemia occurred in 4% of patients and Grade 4 (< 30 mg/dL) hypoglycemia occurred in 6% of patients. The possible mechanism is related to Linsitinib inhibition of insulin receptors and hyperinsulinemia. Therefore, hypoglycemia episodes may be more likely to occur shortly after carbohydrate-rich meals and be of brief duration. The hypoglycemia detected by home glucose monitoring was often not associated with clinical symptoms.

Preliminary phase 1 clinical study results indicated that prolonged QTc interval was reported as an adverse event in 2.4% of patients treated with Linsitinib. Generally, patients with significant heart disease, patients with a baseline QTc > 450 msec, and patients receiving concurrent drugs that may prolong the QTc interval will be excluded from study participation.

Cases of renal failure and creatinine increases have been reported infrequently in patients receiving Linsitinib treatment. These cases have been confounded by prior history of renal failure, prior or concurrent treatment with drugs known to be nephrotoxic (eg, chemotherapy or vancomycin), dehydration, obstruction of the urinary system, and urinary tract infection.

Liver toxicity

Hy's Law cases have the following three components:

- hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST
- Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
- No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

As of 02 Dec 2011, 537 patients on the 906 program had been exposed to drug. The preliminary data of the aforementioned review identified one case of Hy's law and 6 patients that potentially met Hy's law criteria but had confounding factors and/or alternative explanations for the liver enzyme changes. The temporal pattern of drug exposure to liver function (LFT) changes that identify a possible Hy's law case would indicate that these events occur prior to day 40 of being on study, that there is no clear association with drug dose administered and the occurrence of LFT changes, and that patients with liver metastasis or HCC prior to entering study - i.e., conditions that may indicate a reduced liver function, may be at a higher risk of developing these LFT changes.

In the ongoing Linsitinib studies (i.e., (OSI-906) -202; -205; 207) and in this study, safety will be assessed via physical examination, vital signs, clinical laboratory tests (hematology and biochemistry), ECGs (including assessment of QT duration) and adverse events. The safety monitoring plan is designed to detect potential early changes in hepatic and renal function and blood glucose levels, i.e., weekly monitoring of liver and renal function as well as changes in blood glucose levels for the first 6 weeks of being on study. This should allow for an identification of early potential changes in liver and renal function as well as glucose blood levels and will permit for an early study termination if indicated. Following that first 6 week period, the monitoring will continue on a 3 weekly basis, i.e., at the start of any new treatment cycle, for the duration that the patient is receiving Linsitinib. With this close monitoring, there does not appear to be an unmanageable risk to subjects receiving Linsitinib in these studies at this time.

The primary route of metabolism of Linsitinib involves CYP1A2. The metabolism and consequently overall pharmacokinetics of Linsitinib could be altered by inhibitors and/or inducers or other substrates of CYP1A2. Table 5-1 lists medications which are commonly inhibited by CYP1A2.

Across the four phase 1 studies, there have been 31 DLTs related to Linsitinib in 26 patients: 8 events of fasting hyperglycemia, 6 events of elevated liver function tests (AST and/or ALT), 5 events of prolonged QTc, 2 events of fatigue, 1 event of vomiting, 1 event of nausea, 1 event of anorexia, 1 event of neutropenia, 1 event of neuropathy, 1 event of bilirubin increase, 1 event of blood alkaline phosphatase increase, 1 event of pulmonary embolism, 1 event of deep vein thrombosis and 1 interruption of dosing due to toxicity (abdominal cramping and nausea). With the exception of these DLTs, most adverse events have been mild to moderate in severity. As of 18 January 2013, no Grade 5 adverse events/deaths related to Linsitinib have been reported.

5.3 Administration of Bortezomib/Dexamethasone

5.3.1 Bortezomib

Bortezomib is available as single-use vials as a lyophilized powder in the form of a mannitol boronic ester. Each vial contains 3.5 mg bortezomib. Each vial must be reconstituted with (0.9%) sodium chloride for injection. Dissolution is completed in less than 2 minutes. The reconstituted solution is clear and colorless, with a final pH of 4 to 7. The reconstituted solution must be inspected visually for particulate matter and discoloration prior to administration. If any discoloration or particulate matter is observed, the reconstituted product must be discarded.

Bortezomib should be administered within 30 minutes post the Linsitinib dose. Dexamethasone should be given within 15 minutes prior to the bortezomib dose.

Different volumes of 0.9% sodium chloride are used to reconstitute the drug for the different routes of administration IV or SQ as indicated in the table below. Either the 1mg/ml or the 2.5 mg/ml concentrations can be administered SQ depending on institutional policy. Caution should be used when calculating the reconstituting volume and final concentration depending on the route of administration. Refer to the Package Insert for complete details on drug preparation and administration.

Route of Administration	Bortezomib (mg/vial)	Diluent (0.9% Sodium Chloride	Final bortezomib concentration (mg/ml)
Intravenous (IV)	3.5 mg	3.5 ml	1 mg/ml
Subcutaneous (SQ)	3.5 mg	3.5 ml	1 mg/ml
Subcutaneous (SQ)	3.5 mg	1.4 ml	2.5 mg/ml

5.3.2 Stability of Reconstituted Bortezomib

The reconstituted solution of bortezomib should be used immediately after preparation. Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 25°C stored in the original vial and/or a syringe prior to administration, with a maximum of 8 hours in the syringe. Institutional guidelines for

storage and in-use stability of reconstituted bortezomib may be followed if different from above.

5.3.3 Administration of Bortezomib and Dexamethasone

Bortezomib will be administered intravenously or subcutaneously, twice weekly on Day 1, 4, 8 and 11 of a 21-day cycle or if dose reduced for toxicity, then weekly on days 1, 8 and 15 of every 21 day cycle for cycle 1 – 8 and on Days 1, 8, 15 and 22 of a 35 day cycle in cycles 9 +. There must be at least 72 hours between each dose of bortezomib. The dose of bortezomib will be 1.3 mg/m^2 administered as a rapid (3-5 second) injection. When administering by subcutaneous injection, sites for injection (thigh or abdomen) should be rotated. New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous or indurated. Refer to the bortezomib package insert for complete drug preparation and administration guidelines for subcutaneous administration. The dose may be reduced per section 3.1.5.3, but may not be escalated as this dose represents its recommended dose for single-agent therapy in this population. The amount of bortezomib in milligrams to be administered will be determined based on body surface area. Body surface area will be calculated based on body weight using a standard nomogram.

The dose will be calculated on Day 1 of each cycle; the dose administered will remain the same throughout each cycle but will be recalculated at Day 1 of the next cycle. Dose reductions based on observed toxicities will occur as outlined in Section 3.1.5.3.

Dexamethasone should be administered within 15 minutes prior to the bortezomib dose. The dose of bortezomib will be administered 30 minutes after the dose of Linsitinib according to local practice and in accordance with the most recent Package Inserts/Data Sheets. Hydration should occur if indicated by local institutional guidelines.

5.3.4 Dexamethasone Administration

Dexamethasone should be administered as ordered by the Investigator (either intravenous or oral dosing may occur). The dose of dexamethasone should occur on the day of bortezomib administration within 15 minutes prior to bortezomib.

5.3.5 Adverse Events Associated with Bortezomib Administration

In the initial phase 2 trials of bortezomib (n=228), the most commonly reported Adverse Events were asthenia (including fatigue, malaise, weakness, fatigue aggravated and lethargy) (65%), nausea (64%), diarrhea (including loose stools) (55%), appetite decreased (including anorexia) (43%), constipation (43%), thrombocytopenia (43%),

peripheral neuropathy (including peripheral sensory neuropathy and peripheral neuropathy aggravated) (37%), pyrexia (36%), vomiting (36%), and anemia (32%).

Fourteen percent of patients (14%) experienced at least one episode of Grade 4 toxicity, with the most common toxicity being thrombocytopenia (3%) and neutropenia (3%). The most commonly reported Serious Adverse Events included pyrexia (7%), pneumonia (7%), diarrhea (6%), vomiting (5%), dehydration (5%) and nausea (4%).

Use of bortezomib has been associated with the development of certain pulmonary and cardiac toxicity, specifically acute diffuse infiltrative pulmonary disease and pericarditis.

Refer to the full prescribing information for bortezomib:
http://www.millennium.com/PDF/VelcadePrescribingInformation.pdf

5.3.6 Adverse Events Associated with Dexamethasone Administration

Toxicities associated with the use of dexamethasone include:

- Gastrointestinal (stomach upset, increased sensitivity to stomach acid to the point of ulceration of esophagus, stomach, and duodenum);
- Increased appetite leading to significant weight gain;
- Glucose intolerance;
- Immunosuppression;
- Psychiatric disturbances, including personality changes, irritability, euphoria, mania;
- Hypertension, fluid and sodium retention, edema, worsening of heart insufficiency (due to mineral corticoid activity);
- Increased intraocular pressure, certain types of glaucoma, cataract (serious clouding of eye lenses) ;
- Dermatologic: acne, allergic dermatitis, dry scaly skin, ecchymoses and petechiae, erythema, impaired wound-healing, increased sweating, rash, striae, suppression of reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria;
- Allergic reactions

Toxicities secondary to chronic dexamethasone therapy also include:

- Osteoporosis under long term treatment, pathologic fractures;
- Muscle atrophy, negative protein balance (catabolism);
- Elevated liver enzymes, fatty liver degeneration (usually reversible);
- Cushingoid syndrome;
- Depression of the adrenal gland.

5.4 Drug Accountability

Drug accountability logs for Linsitinib must be maintained (see **Section 10.3.1**). These logs must record quantities of Linsitinib received from APGD and quantities dispensed to

patients, including lot number, date dispensed, patient identifier number, patient initials, protocol number, dose, quantity returned, balance forward, and the initials of the person dispensing the study drug.

5.5 Treatment Compliance

Compliance with Linsitinib dosing should be checked by review of the patient diary card and by returned/unused tablet count. Any dose error should be reported immediately.

5.6 Concomitant Medications

All medications will be recorded in an appropriate section of the case report form (CRF). Concomitant medications will be captured from 30 days prior to first study drug administration to the end of treatment evaluation, including herbal and over-the-counter medications.

5.6.1 Permitted Concomitant Medications

Administration of antiemetics (such as aprepitant or lorazepam) may be used at the discretion of the Investigator only after documented nausea or vomiting following Linsitinib and/or bortezomib therapy without antiemetics. High-dose steroids should not be used as antiemetic therapy, as steroids will be administered in a controlled manner in this trial. Serotonin antagonists (Kytril® or equivalent) should be used as a secondary option due to their potential to contribute to QTc prolongation. Otherwise, centers can follow their standard practice for antiemetic therapy.

Use of antidiarrheals such as loperamide and diphenoxylate/atropine is permitted at the discretion of the Investigator after documented diarrhea has occurred without these medications having been used.

Following cycle 1, use of erythropoietin or darbepoetin (Aranesp®) is permitted at the discretion of the Investigator. Red blood cell transfusions while on study are permitted at the discretion of the Principal Investigator.

Use of granulocyte colony-stimulating factor (G-CSF, filgrastim, Neupogen®; pegfilgrastim; Neulasta®) in a patient who is experiencing recurrent difficulties with neutropenia is permitted at investigator discretion except during cycle 0.

Platelet transfusions are permitted during study treatment at the discretion of the Investigator.

Concomitant therapy with any marketed bisphosphonate is acceptable.

Stable steroid therapy for inhalation therapy is acceptable.

Allopurinol may be used for prevention of tumor lysis syndrome.

Prophylactic antibiotics, antifungal agents can be instituted at the Investigator's discretion depending on the clinical situation. Antibiotics with potential to contribute to QTc prolongation should be avoided.

Lansoprazole or other oral proton-pump inhibitor to prevent peptic disease for the duration of treatment may be instituted at the Investigator's discretion. Proton Pump inhibitors should not be taken within 4 hours before or after Linsitinib.

Note: Caution should be used with inhibitors of CYP1A2, see Appendix 12-9.

The use of or antiviral (herpes zoster) prophylaxis is highly recommended during therapy with bortezomib unless the patient is intolerant of such medications.

Any other medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator. No other investigational agents are permitted during the entire duration of the study (from 14 days before the first administration until the end-of-treatment evaluation).

5.6.2 Antihyperglycemic Therapies

Due to the short half-life of Linsitinib, drug interruption of Linsitinib may be expected to alleviate any transient hyperglycemia. If a patient's blood glucose remains elevated for ≥ 24 hours despite supportive management of fluids and electrolytes and an interruption of Linsitinib dosing, metformin may be introduced at the Investigator's discretion in order to reduce the blood glucose. Upon resolution of the blood glucose to Grade 1 (≤ 160 mg/dL or 8.9 mmol/L), Linsitinib and dexamethasone may be reintroduced both at the next lower dose level at the Investigator's discretion and provided that the patient is receiving clinical benefit. Metformin should be discontinued for ≥ 48 h prior to the reintroduction of Linsitinib and dexamethasone. For a repeat episode of hyperglycemia meeting the definition of DLT, metformin may be continued however with caution and monitoring for hypoglycemia. Alternatively, metformin use can be restricted to the day of and day after dexamethsone if hyperglycemia is associated with dexamethasone use. At this time there are no clinical data on the concomitant administration of metformin and Linsitinib. Any metformin use must be exercised with caution and patients must be monitored for hypoglycemia. If hypoglycemia occurs discontinue the use of metformin. Given that tubular secretion is the major route of metformin elimination, caution should

be exercised with the use of metformin in patients with prior exposure to platinum compounds or renal insufficiency. Bortezomib dosing may continue throughout any Linsitinib interruption due to hyperglycemia; dexamethasone doses should be omitted.

Use of insulin to treat Linsitinib-induced hyperglycemia is expected to be of limited value. Insulin should only considered if the patient is experiencing diabetic ketoacidosis or if hyperglycemia (≥ Grade 3) persists despite Linsitinib interruption and metformin has been tried without result. Only then should it be used with extreme caution, and the patient should be carefully monitored in anticipation of possible rebound hypoglycemia.

No data exist regarding the ability of other antihyperglycemic medications to reverse Linsitinib -induced hyperglycemia. Refer to Appendix 12-8 for the algorithm for management of hyperglycemia.

5.6.3 Prohibited Concomitant Medications

Throughout a patient's time of participation in this clinical trial a patient may not receive investigational therapy (for any indication) or any other anticancer therapy except for palliative radiotherapy, as outlined in Section 5.6.4. For entry into the study patients may not have received chemotherapy within 21 days or approved anti-myeloma therapy including steroids within 14 days prior to first study drug administration. For entry into this clinical trial, patients must demonstrate adequate blood counts without the use of growth factor in 14 days of first study drug administration. Concurrent use of non-insulinotropic antihyperglycemic therapy is permitted however sulfonylurea and meglitinides should not be used after study initiation unless the subject has been on these agents prior to study entry and stable for 8 weeks then these agents may be continued. . Patients on insulin or insulinotropic medications are prohibited from being enrolled and concurrent use of these drugs with Linsitinib are prohibited. If hypoglycemia occurs then these agents should be discontinued. Metformin may be used with caution to control hyperglycemia.

5.6.3.1 Drugs that affect the QTc interval or with a known risk for Torsades de Pointes.

Appendix 12-6 presents a list of concomitant medications with QTc effects or with a known risk for Torsades de Pointes, that are excluded; or for these medications, Linsitinib may be administered after a 5 half-life washout period elapses following the use of these drugs.

5.6.3.2 Drugs that affect CYP1A2

The primary route of metabolism of Linsitinib is via CYP1A2. A potential for drug-drug interaction exists when Linsitinib is co-administered with drugs that are CYP1A2 inhibitors/inducers. Table 5-1 lists medications which are commonly inhibited by CYP1A2. These medications may be continued but the Investigator should be cautious in their use. Strong inhibitors of CYP1A2 however such as verapamil, ciprofloxacin and fluvoxamine are prohibited (see Appendix 12-9)

Table 5-1: CYP1A2 Inhibitors

Inhibitors				
Weak	Cimetidine			
Others	Amiodarone	Fluoroquinolones	Furafylline	Interferon
	Methoxsalen	Mibefradil		

5.6.4 Palliative Radiotherapy

Localized radiation therapy for the treatment of cancer complications, if required in the Investigator's opinion, is permitted. If the patient develops a definite increase in the size of existing bone lesions or soft tissue plasmacytomas, treatment must be discontinued for progressive disease regardless of whether radiation therapy is initiated. Use of radiotherapy must be recorded on the CRF.

6 STUDY PROCEDURES

The study procedures to be conducted for each patient enrolled in the study are presented in **Appendix 12-1** and detailed in the text that follows. Additional information on the study procedures for PK and PD sampling processing are provided in section 8.

6.1 Patient Enrollment and Treatment Assignment

Before recruitment of patients into the study, written IRB/REC approval of the protocol, informed consent, and any additional patient information must be obtained.

The Investigator is responsible for verifying that the patient is eligible before requesting registration. If any of the inclusion criteria are not met, or any of the exclusion criteria are met, the patient should not be enrolled.

The screening period for a particular patient commences when the patient signs the informed consent. Consent must be signed before any study-specific tests may be performed. A separate consent will be provided for patients in Phase 2 that agree to the

optional additional bone marrow biopsy. After a patient has been screened and has successfully met all eligibility criteria, the site representative will email the inclusion/exclusion checklist and all other required documentation to the Project Manager listed below:

Project Manager: Engin Gul

E-mail : engin.gul@uhnresearch.ca

Telephone: 416-946-4501 Ext: 2608

Fax: 416-946-2969

A unique patient number will be assigned at that time that will be used to identify the patient throughout the clinical study and must be used on all study documentation related to that patient. Patients will be assigned to a dose cohort at enrollment. Prior to accepting the registration, the Project Manager or representative will verify the following:

- IRB/REC approval at the registering institution
- Patient eligibility (enrolment package must include the signed eligibility check list along with screening ECGs, 2D-Echo, CBC, Chemistry, myeloma assessment documenting progression, and documentation of prior lines of therapy.)
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information (US sites only)

Study drug treatment may not begin prior to registration and must begin within 10 days after registration. Pretreatment tests/procedures must be completed within the guidelines specified on the Study Procedures Table, Table 6-2 (also see Schedule of Assessments table in appendix 12-1).

At the site, the Investigators must maintain a patient log for all screened (including patients who failed screening) and enrolled patients.

6.2 Baseline Assessments

Cycle 1/Day 1 may be the same as screening/baseline assessments and may not need to be repeated. To allow for flexibility in timing of assessments, each Day 1 visit should occur within ± 4 days.

Patients will be evaluated to determine if they meet the eligibility criteria specified in **Section 4**. The baseline evaluations will include investigations as outlined in the schedule of events (Appendix 12-1).

6.3 Study Assessments

The ongoing treatment and evaluations will include investigations as outlined in Appendix 12-1.

6.3.1 Clinical Laboratory Tests

Clinical laboratory tests will be performed in order to assess eligibility for enrolment and repeated on-study as indicated in Appendix 12-1. Tests can be repeated more frequently, if clinically indicated.

CBCs are required prior to dosing of bortezomib on Days 1 and 8 every cycle and Day 15 of cycle 1 and 2 and at the End of Study Visit. Institutional guidelines that require more frequent CBC assessment may be followed. For dose modification and dose interruptions, see Section 3.1.5.3. For patients enrolled in Phase 2, Cycle 0, repeat CBC on day 1 of Cycle 0.

Fasting biochemistry is required pre-dose on Day 1 of every Cycle, pre-dose on Days 8 and 15 of Cycle 1 and 2 and at the post-treatment visit. In the event of ≥ Grade 3 toxicity, repeat testing is required (refer to Appendix 12-8 for the algorithm for hyperglycemia management). For patients enrolled in Phase 2, Cycle 0, obtain fasting chemistry on day 1 of Cycle 0. See additional requirements for liver safety monitoring, assessment and reporting, section 3.1.5.2.5).

6.3.2 Glucose Monitoring

In addition to the fasting glucose monitoring by serum chemistry performed at the clinic on day one of each cycle, patient monitoring of serum glucose and urinary ketones will occur using a home glucose monitor and urine reagent strips. Patients will be instructed to measure their blood glucose and ketone levels twice daily (pre-breakfast and pre-evening meal) during (cycle 0 if applicable) and cycle 1 of Linsitinib treatment in combination with bortezomib and dexamethasone. Assessments beyond the first cycle will be done at the Investigator's discretion.

For signs or symptoms related to glucose intolerance (e.g., frequent urination, excessive thirst, extreme hunger, unusual weight loss, increased fatigue, irritability, and blurred vision), patient will also be instructed to use urine reagent strips to test for urinary ketones. If abnormalities are reported by the patient, patients will be instructed to call and go in to the site to have tests repeated at the site laboratory. Only results obtained at the site laboratory will be used for adverse event determination.

6.3.3 Performance Status and Symptom/Adverse Event Assessment

The performance status, symptoms and adverse events of all patients will be graded at scheduled intervals according to either the ECOG or Karnofsky PS and the NCI CTCAE, v4.03.

Patients will be monitored continually throughout the study for the occurrence of adverse events. All adverse events that occur from the time of study drug administration until the completion of the study will be recorded on the CRF as an adverse event, regardless of the potential relationship to any study drug. The date of onset, severity, and Investigator's opinion of potential relationship of the event to protocol therapy will be recorded.

6.3.4 ECG Monitoring:

ECG monitoring will be conducted in this study as part the safety monitoring. Triplicate 12-lead ECGs will be obtained for all patients at screening and pre and post dose on Day1 of Cycle 1 and 2 and 2 to 4 hours post dose on Days 8 and 15 of Cycle 1. If clinically significant abnormalities are observed, patients will be required to do triplicate ECGs pre and post dose on Day 1 of each subsequent Cycle. Patients with normal ECGs will have single 12-lead ECG pre dose and 2 to 4 hours post dose on Day 1 of cycle 3 and subsequent cycles and End of Study Visit (Appendix 12-1). For single ECG monitoring, if the QTc is > 450 msec then triplicate ECGs will be required and the mean QTc value will be used for the assessment. A digital ECG machine will be used that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTc and/or QTcF intervals. Additional ECGs may be done as agreed by the Investigator, or clinically indicated. At each assessment a 12-lead ECG will be performed at least 2 minutes apart by qualified personnel at the site after at least a five-minute rest with the subject in a semi-recumbent or supine position. Mean QTc values greater than 450 msec as confirmed by the machine must be confirmed manually using the Fridericia's formula given below:

The Fridericia's formula is $QTcF=QT \times (1/RR)^{1/3}$

Patients with a confirmed calculated mean QTcF > 450 msec will be excluded from the study. Patients with QTc or QTcF$\leq$ 450 will be eligible for the study. Linsitinib dosing should be discontinued for any patient with a confirmed (triplicate reads repeated within 2 hours) mean QTcF $\geq$ 501 msec ($\geq$ grade 3) or change > 60 msec from baseline, regardless of when the event occurs or possible relationship to Linsitinib.

Triplicate ECG (12-Lead) should be performed at screening, and should be repeated within 24 hours prior to Day 1 dosing regardless of when the screening evaluation was performed. The QTc or QTcF of the ECG tracing will be used as the baseline assessment. Patients with confirmed QTc≥ 450 msec will have QTcF values calculated. Patients are excluded if the confirmed mean QTcF ≥ 450 msec (based on triplicate values).

Table 6-1: Cardiac Assessment Monitoring

Cycle	Day of Cycle	ECG Monitoring
Screening		Triplicate 12-lead ECG
Cycle 0	1	Triplicate ECGs pre and 2 to 4 post dose
Cycle 1	1	Triplicate ECGs pre and 2 to 4 post dose
	8	Triplicate ECGs 2 to 4 post dose
	15	Triplicate ECGs 2 to 4 post dose
Cycle 2	1	Triplicate ECGs pre and 2 to 4 post dose
Cycle 3+	1	Single 12-lead ECG pre and post dose if previous ECGs are normal otherwise triplicate pre and prost dose ECGs

Study drug dosing should be discontinued for any patient with a confirmed (repeated within 2 hours) mean QTcF value ≥ 501 msec. Study drug must be withheld for QTcF 481 – 500 msec and repeat ECG (in triplicate) must be obtained in 24 – 48 hours. The QTc or QTcF of ECG tracings should be used for all treatment decisions. The frequency of ECGs will be increased to weekly assessments in cases of mean QTcF interval 481 – 500 msec. Additional ECG's will be performed in the event of prolonged QTcF. Also see protocol guidelines for management and reporting of prolonged QTcF.

For Phase 2 patients enrolled into Cycle 0, ECGs will be performed prior to day 1 dosing and 2 – 4 hours post dose on day 1 in addition to the evaluations outlined above.

Information on ECGs will be put in tabular form. Incidences of patients with changes from normal ECG findings at baseline to abnormal during the study will be generated as appropriate. Summary of mean/median changes in ECG intervals will be generated. ECG intervals will be correlated with pharmacokinetic data where appropriate. QTcF analysis will be performed to identify those patients who have had a 60 msec increase in QTcF and/or patients who have a QTcF > 500 msec.

6.3.5 Echocardiogram

Echocardiogram monitoring will be conducted in this study as part the safety monitoring at screening, cycle 3 day 1 and as clinically indicated during phase 1 and for the first 10

patients enrolled at the MTD before study drug administration. Echocardiogram monitoring will not be required beyond this if cardiac toxicity is not observed in these patients.

6.3.6 Myeloma Assessment

Patients will be evaluated under local Investigator review for disease response according to the International Myeloma Working Group (IMWG) uniform response criteria (see Appendix 12-5; Rajkumar 2011)

Table 6-2: Tests Required To Assess Response

Tests Required To Assess Response (Must Be Done At Each Disease Measurement Visit)				
On Study Baseline Value	**SPEP**	**24 hr UPEP**	**Ig FLC**	**Plasmacytoma assessment**
Serum M-spike ≥1 g/dl, and urine M-spike≥ 200 mg/24 hrs	X	X		
Serum M-spike ≥ 1 g/dl, but urine M-spike < 200 mg/24 hrs	X			
Serum M-spike<1 g/dl, and urine M-spike≥ 200 mg/24 hrs		X		
Serum M-spike < 1 g/dl, urine M-spike < 200 mg/24 hrs, but involved Ig FLC is ≥10 mg/dL			X	
Plasmacytoma				X[a]
Immunofixation studies of both serum and urine are required to document CR regardless of registration values, and in addition **FLC** measurement and **bone marrow immunophenotyping** is required to document sCR. [a] Complete evaluations done at baseline with same technique Q 12 weeks.				

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

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

- Imunofixation is only required at screening and then to confirm CR or sCR only.
- Bone marrow aspirate and biopsy are **only** required to document or confirm CR or sCR, except for patients with evaluable disease **only**, where bone marrow

assessment is required to document all response categories including progression. However, a second confirmatory bone marrow is **not** required to confirm response.

- Radiographic studies are not required to satisfy these response requirements, however, if radiographic studies were performed there should be no evidence of progressive or new bone lesions.
- Progression does not require confirmation, but treating physician may continue an additional cycle to confirm progression if clinically indicated.

Bone progression: Caution must be exercised to avoid rating progression or relapse on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response and may not indicate progression. When progression is based on skeletal disease alone, it should be discussed with the Principal Investigator before removing the patient from the study.

6.3.7 Post-treatment Assessments

Every attempt should be made to evaluate all patients after the last treatment with study drug. Any adverse events related to study drug that are ongoing at this point should be followed until resolution, until severity returns to baseline, or until the start of subsequent anticancer therapy. Appropriate arrangements for follow-up or confirmation of responses should be made, if required. Evaluations will be performed according to the Schedule of Assessments table in **Appendix 12-1**.

All serious adverse events occurring more than 30 days after last study drug administration and considered at least possibly study drug-related must be reported. See Section 7.6 for serious adverse event reporting requirements.

6.3.8 Long-term Follow-up

Every attempt should be made to follow patients every 3 months to determine disease progression, additional therapy, and long-term survival, and to collect information on any new or ongoing drug-related adverse events.

6.4 Assessments for Premature Discontinuation from Study

If a patient discontinues study medication dosing, every attempt should be made to keep the patient in the study and continue to perform the required study-related follow-up procedures. If this situation is not possible or acceptable to the patient or Investigator, the patient may be withdrawn from the study.

6.5 Criteria for Study Discontinuation

Patients may withdraw from the study at any time. Patients who withdraw will be monitored for adverse events (AEs), as described in Section 7. The Principal Investigator may elect to discontinue the study at any time.

The Investigator may remove a patient from the study for the following reasons:

- Progressive myeloma
- Noncompliance with study procedures
- Requirement for alternative therapy
- Patient no longer consents to participate in the study
- Intercurrent illness that interferes with study assessments
- Incidence or severity of AEs that indicates a potential health hazard to the patient
- Patient is lost to follow-up (defined as the inability to contact the patient on 3 separate occasions over a period of 2 weeks)

The Lead Principal Investigator or designee must be notified within 24 hours if a patient is withdrawn from the study by the participating site Investigator or designee.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first. All serious adverse events (SAEs) occurring from the time of informed consent through 30 days after the last administered dose of study drug will be reported. All SAEs regardless of relationship to study drug must be followed to resolution or to stabilization if improvement or resolution is not expected.

7 ADVERSE EVENTS

7.1 Safety Assessment

Assessments will consist of monitoring and recording of adverse events and serious adverse events, physical examination, measurement of protocol-specific laboratory variables and vital signs, ECG, as well as other tests deemed important for this trial. The specific procedures and intervals for assessment are described in Section 6 and summarized in the Schedule of Assessments table (**Appendix 12-1**). Circumstances in which these assessments should be reported as adverse events are described in Section 7.8. All patients who have received at least one dose of study drug will be evaluated for safety of the study drug.

7.2 Definition of Adverse Event

An adverse event or adverse experience is any untoward medical occurrence in a study patient who is administered a study drug that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug.

Pre-existing conditions that increase in frequency or severity or worsen in nature during or as a consequence of use of a drug in human clinical trials will also be considered adverse events. Adverse events may also include pre- or post-treatment complications that occur as a result of protocol-mandated procedures (eg, invasive procedures such as biopsies).

Any continuing medical condition or clinically significant laboratory abnormality with an onset date before the first date of study drug administration should be considered pre-existing and should be documented on the appropriate CRF page.

An adverse event that persists from one treatment period (cycle) to another should only be reported once unless the grade becomes more severe in a subsequent treatment period. An adverse event, which resolves and then recurs during a different treatment period (cycle), must be reported each treatment period (cycle) it recurs.

An adverse event **does not** include:

- Relapse or progression of the underlying malignant disease; however, the associated signs, symptoms, or diagnoses should be recorded as adverse events (eg, “jaundice”

due to new or increasing liver metastases, or "tumor pain" or "bone pain" due to progressive disease);

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is the adverse event;
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions);
- Overdose of either study drug or concomitant medication without any signs or symptoms unless the patient is hospitalized for observation;
- Pregnancy (see **Section 7.10**).

7.3 Definition of Serious Adverse Event

A serious adverse event is defined as any adverse event occurring at any dose that results in any of the following outcomes:

- Death;
- Life-threatening situation (patient is at immediate risk of death);
- Inpatient hospitalization or prolongation of an existing hospitalization (excluding those for study drug administration, protocol-related procedures, elective surgery, palliative or hospice care, or placement of an indwelling catheter, unless associated with other serious events);
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect in the offspring of a patient who received study drug;
- Other: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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;
  - Development of drug dependency or drug abuse.

In addition, if any of the following adverse events occur during the study drug treatment period or up to 30 days after the last dose of Linsitinib study drug treatment, they should be considered as serious adverse events and reported as such.

- acute liver failure
- acute renal failure
- acute respiratory failure
- agranulocytosis
- anaphylaxis
- any secondary malignancy

- aplastic anemia
- confirmed or suspected endotoxin shock
- confirmed or suspected transmission of infectious agent by marketed product
- congenital anomalies
- liver necrosis
- malignant hypertension
- pulmonary fibrosis
- pulmonary hypertension
- sclerosing syndromes
- seizure (only central neurological seizure)
- torsade de pointes
- toxic epidermal necrolysis
- ventricular fibrillation
- Note – A Hy's Law case is considered an SAE (see section 3.1.5.2.5 and 5.2.2).

Clarification of Serious Adverse Events

- Death is an outcome of a serious adverse event and not a serious adverse event in itself. When death is an outcome, the event(s) resulting in death should be reported (eg, "pulmonary embolism" with a fatal outcome). The appropriate diagnosis or term should be recorded and assigned severity Grade 5;
- In instances of death due to "Disease Progression" the cause of death should be indicated as the event or condition resulting in death to the extent possible (eg, "respiratory failure" due to progressive lung cancer). If no appropriate term with a Grade 5 severity in the CTCAE can be identified, then a term should be selected from the CTCAE category "Death";
- The term "Disease Progression" should be avoided in situations in which a patient is admitted for management of conditions that are secondary to disease progression. Instead, the medical condition should be recorded (eg, "seizure" secondary to brain metastases);
- "Occurring at any dose" does not imply that the patient is receiving study drug at the time of the event. Dosing may have been administered as treatment cycles or interrupted temporarily prior to the onset of the serious adverse event, but may still have contributed to the event;
- "Life-threatening" means that the patient was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity. Grade 4 events (eg, thrombocytopenia) are not always serious unless they have life-threatening consequences or result in hospitalization;
- Complications that occur during hospitalization are adverse events. If a complication prolongs the hospitalization, it is a serious adverse event;

- "Inpatient hospitalization" means the patient has been formally admitted to a hospital for medical reasons, for any length of time. Presentation and care within an emergency department does not necessarily constitute a serious adverse event;
- The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. If a diagnosis is unavailable at the time of initial reporting, a follow-up report should be submitted once a diagnosis is made or when the discharge summary is available.
- All deaths, regardless of causality, must be reported for patients on study (within 30 days of last study drug administration);
- All serious adverse events occurring after the last study drug administration and considered at least possibly related must also be reported.

7.4 Adverse Event Reporting Period

Any adverse event (ie, a new event or an exacerbation of a pre-existing condition) that occurs after the first dose of study medication up to 30 days after the last study drug administration must be recorded as an adverse event or serious adverse event on the appropriate page(s) of the CRF and Serious Adverse Event form, as applicable. Serious Adverse Event collection should start from the time the subject signs the informed consent and continue up to 30 day after the last study drug administration. Should a patient discontinue from or complete the study and commence subsequent anticancer therapy within 30 days of the last study drug administration, adverse events attributable to this subsequent therapy should **not** be recorded. Any serious adverse event that occurs more than 30 days after the last study drug administration should be reported if considered related to study drug. All deaths, regardless of cause, must be reported for patients on study (within 30 days of the last study drug dose). The evaluation of an adverse event should continue until the adverse event resolves, until the start of subsequent anticancer therapy, or until the Investigator determines the patient's condition is stable.

7.5 Adverse Event Assessment and Documentation

A consistent methodology for eliciting adverse events should be adopted. Examples of nondirective questions include: "How have you felt since your last clinical visit?" or "Have you had any new or changed health problems since you were last here?" New findings on physical examination or clinically significant changes in ECGs may qualify as an adverse event. See **Section 7.8** for guidelines on reporting Clinical Laboratory Abnormalities.

All adverse events will be assessed by the Investigator and recorded on the appropriate CRF page, including the dates of onset and resolution, severity, relationship to study drug, seriousness, and the action taken with the study drug. Any medication necessary for treatment of an adverse event must be recorded on the concomitant medication section of the patient's CRF and, if applicable, on the Serious Adverse Event Report Form.

Correct medical terminology/concepts should be used when recording adverse event terms. Abbreviations should be avoided. A diagnosis is preferred rather than individual signs and symptoms (eg, record pneumonia rather than fever, cough, pulmonary infiltrate). An adverse event that meets serious criteria should be recorded **both** on the Adverse Event CRF and on the Serious Adverse Event Report Form. The adjectives "severe" and "serious" are not synonymous. Serious is a regulatory definition (see **Section 7.3**), while severity describes the intensity of the adverse event. Severity should be recorded and graded according to the NCI CTCAE, v4.0 (refer to the following website for the CTCAE manual or the CTCAE document):

http://ctep.cancer.gov/reporting/ctc.html

The relationship to study drug therapy should be assessed using the following definitions:

- **Not Related:** Evidence exists that the adverse event has an etiology other than the study drug (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication). This includes events that are considered remotely or unlikely related to study drug.
- **Related:** A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective study drug treatment should not be considered as causally related in the context of adverse event reporting. This includes events that are considered possibly, probably, or definitely related to study drug.

These criteria, in addition to good clinical judgment, should be used as a guide for the Investigator determining the causality assignment.

7.6 Serious Adverse Event Reporting Requirements

The conduct of the study will comply with all FDA safety reporting requirements.

All adverse experience reports must include the patient number, age, sex, weight, event diagnosis (if known) or signs/symptoms, severity of reaction (mild, moderate, severe), relationship to study drug (probably related, unknown relationship, definitely not related),

date and time of administration of test medications and all concomitant medications, and medical treatment provided. The Investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined below are present.

The Sponsor must be notified by email or fax of the occurrence of any SAE as well as to APGD Drug safety within 24 hours of the Investigator, designee, or site personnel's knowledge of the event. To report an SAE, the site representative must complete the SAE forms in the EDC system, fax or email an SAE form to:

University Health Network

Phone: 416- 946-4501 ext. 2608

Fax Number: 416-946-4419 E-mail: engin.gul@uhnresearch.ca

Astellas Drug Safety	
Fax SAE worksheets and supporting documentation to:	
North America	Europe & ROW
Fax: +1 303-546-7706	Fax: +44 800-471-5263
Or you may email to:	
World-wide email:	safety-us@us.astellas.com

Telephone reports must be followed by a written report within 24 hours. Follow up reports must be submitted within 24 hours as additional information becomes available.

The Investigator is responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local regulations, of all SAEs. The Sponsor is responsible for reporting SAE's to Astellas Pharma Global Development, Inc. (APGD), Health Canada and the FDA. The Project Manager or the Lead Principal Investigator may request additional source documentation pertaining to the SAE. If a patient is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report form as well as the Study Discontinuation report form.

All SAEs occurring from the time that the patient signs consent for study participation through but prior to the initial dose of the investigational product will be collected only if they are considered by the Investigator to be causally related to study required

procedures. All SAEs occurring from the time of initial dose of investigational product through 30 days after the last administered dose of study drug will be reported. All SAEs regardless of relationship to study drug must be followed to resolution or to stabilization if improvement or resolution is not expected.

7.7 Adverse Events Leading to Discontinuation from the Study

Non-serious adverse events resulting in permanent discontinuation from the study must be recorded and the discontinuation reported to the Lead Principal Investigator. Serious adverse events resulting in permanent discontinuation must be reported according to section 7.6. This form must be reported within 24 hours of the Investigator's knowledge of the event.

7.8 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities are usually not recorded as adverse events; however, signs and/or symptoms that are associated with laboratory findings requiring study withdrawal, dose modification, or medical intervention (eg, anemia requiring transfusions or hyperglycemia requiring treatment) or other abnormal assessments (eg, ECG, radiographs, vital signs) must be recorded as adverse events (or serious adverse events) if they meet the definition of an adverse event (or serious adverse event) as described in **Section 7.2** and **7.3**. In addition, laboratory abnormalities equating to DLT or any laboratory abnormalities marked as clinically significant should also be recorded as adverse events. The Investigator will record the grade of the clinically significant laboratory abnormality and will evaluate its relationship to the study drug and clinical condition. All clinically significant abnormal laboratory results will be followed until they return to normal or stabilize.

7.9 Expected Adverse Events

The most recent version of the Linsitinib Investigator's Brochure contains a complete description of the safety information for this investigational drug. The most recent version of the botezomib Package Insert should be used to determine expectedness of adverse events related to bortezomib.

An unexpected adverse event or adverse drug reaction (ADR) is any event for which the nature or severity is not consistent with the information contained in the Investigator's Brochure.

7.10 Pregnancy and Breast-feeding

Linsitinib should not be used during pregnancy or while breastfeeding. Premenopausal women of childbearing potential must use one of the following forms of birth control (ie, barrier methods, condom or diaphragm with spermicide) or agree to abstain from heterosexual intercourse while participating in the study and for 90 days following the last dose of study drug. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy.

Pregnancy and breast feeding are exclusion criteria. If a female patient or partner of a male patient becomes pregnant while receiving study drug or within 120 days after the last dose of study drug, the pregnancy must be reported. The pregnancy must be followed during the entire course, with perinatal and neonatal outcomes recorded even if completely normal and without an adverse event.

7.11 Data Monitoring Committee and Safety Monitoring Plan

For the phase 1 portion of the trial, monitoring of toxicities and accrual will occur at three levels.

- The Principal Investigator at each site will review the toxicities as they occur and/or are reported. Serious adverse events will be reported within 24 hours of the Investigator being made aware of the event.
- Prior to dose escalation, a conference call will be held between the Lead Principal Investigator and the Investigators at participating sites. Prior to the conference call, sites should make every effort to enter data into the eCRF database. Available safety data (laboratory data, adverse events with severity, onset, duration and an assessment of whether possibly related to study drug) will be reviewed. Available pharmacokinetic and pharmacodynamic data may also be considered in analysis of toxicity.
- Following review, decisions will be made regarding whether the safety profile has been altered, whether an update to the risks section of the template Informed Consent is required (together with recommended language), whether any protocol amendment is required (either entry criteria or safety monitoring procedures) and whether enrollment should safely continue.

For the phase 2 portion of the trial, monitoring of toxicities and accrual will occur at regular intervals by the UHN DSMB. The UHN DSMB committee will evaluate the safety of the trial after completion of enrollment of the first 12 patients and/or biannually during phase II. If greater than 20% of subjects experience hyperglycemia, hepatoxicity or increase QTc prolongation that meets the DLT criteria, a detailed review of toxcities

will be performed by an independent safety committee to determine whether the trial should be stopped.

8 PHARMACOKINETIC SAMPLING AND ANALYSIS

Details on sample collection, handling and shipping are provided in Appendix 12-3.

Phase I: on all patients, on day 21, single agent PK will be collected pre Linsitinib dose, 30 min, 1hr, 2hrs, 3hrs, 4hrs, 6hrs, 8hrs with the 24 hour collection on cycle 2/day1 pre bortezomib infusion. Combination PK will be collected on day 8 pre Linsitinib dose, 30 min, 1hr, 2hrs, 3hrs, 4hrs, 6hrs, 8hrs post dose with the 24 hour collection on cycle 1 day 9 pre bortezomib dose.

Phase 2: The first 12 patients only during the 7 day lead in (cycle 0), will have single agent PK samples drawn on day 7 pre Linsitinib dose, 30 min, 1hr, 2hrs, 3hrs, 4hrs, 6hrs, 8hrs post dose with the 24 hour collection on cycle 1 day 1 pre bortezomib infusion. Combination PK will be collected on Cycle 1 Day 8 pre OSI and bortezomib dose and 2 and 4 hours post dose.

8.1 Exploratory Biomarker Sampling and Analysis

An exploratory objective of this clinical trial is to seek markers predictive of drug responsiveness and to demonstrate successful target inhibition in correlative studies

As a companion study to the proposed clinical trial, patients will be approached for consent to conduct studies aimed at identifying predictors of response, mechanisms of resistance and PD studies to demonstrate target inhibition. For the purposes of the current trial, a research bone marrow aspirate (BMA) and blood sample will be obtained at baseline and one follow-up BMA sample:

- Phase 2 only: on Cycle 1 day 21 (+/- 3 days) at 3-4 hours following Linsitinib but prior to the initiation of bortezomib.
- At progression

Two BMA samples should be collected at baseline. The first sample (first pull) should be forwarded to the central analytical laboratory for this study (PMCC, Toronto Canada). The second sample is forwarded to local hematopathology laboratory for assessment of cellularity and percentage CD138+ cells (FISH should be performed if standard of care at the institution).

Details on sample handling are provided in Appendix 12-4.

9 STATISTICAL METHODS

This is a multi-center, open-label, Phase 1/2 study in which patients with relapsed or relapsed/refractory multiple myeloma requiring treatment will receive single agent Linsitinib and/or combination treatment with Linsitinib and bortezomib and dexamethasone

This study consists of two phases. Phase 1 involves the evaluation of sequential cohorts in which Linsitinib is escalated in combination with fixed doses of bortezomib and dexamethasone to establish the MTD of Linsitinib and bortezomib in combination with dexamethasone. A phase 2 portion will be conducted in order to determine the efficacy of the combination of Linsitinib (OSI-906), bortezomib and dexamethasone.

9.1 Objectives and Design

The primary objective of this study is:

- Phase 1: To determine the maximum tolerated dose (MTD) of Linsitinib administered in combination with the recommended dose and schedule of bortezomib and dexamethasone;
- Phase 2: To evaluate the antitumor activity of single-agent Linsitinib in combination with bortezomib and dexamethasone at the MTD established from the Phase 1 component. The antitumor activity will be determined by the overall response rate (ORR) including stringent complete response (sCR), complete response (CR), very good partial response (VGPR) and partial response (PR) according to the International Myeloma Working Group (IMWG) criteria. The rate of minimal response (MR) and progressive disease (PD) will also be evaluated.

The secondary objectives of this study are:

- Phase 1:
  - To evaluate the toxicity of Linsitinib in combination with bortezomib and dexamethasone in patients with relapsed or refractory MM.
  - To evaluate the PK profile of Linsitinib when administered to patients with multiple myeloma in combination with bortezomib and dexamethasone.
- Phase 2:
  - To evaluate the progression-free survival (PFS) and overall survival (OS) in patients receiving Linsitinib in combination with bortezomib and dexamethasone.
  - To further evaluate the safety and tolerability and the incidence of toxicities of this regimen at the MTD in this patient population.

- To evaluate the PK profile of Linsitinib when administered to patients with multiple myeloma as single-agent and in combination with bortezomib and dexamethasone.
- Exploratory: to seek biomarkers, IGF-1R+ and CD45-, predictive of drug responsiveness and to demonstrate successful target inhibition in correlative studies. One subgroup of MM patients (IGF-1R+ and CD45-), is hypothesized to have a greater potential for response to IGF-1R inhibition.

9.2 Sample Size

Phase I: The dose escalation Phase I portion of this study will evaluate up to 4 dose levels in order to determine the MTD. This portion of the trial will require approximately 24 patients.

Phase 2: The Phase 2 portion of this study is designed to assess the ORR compared to historical controls.[9, 10,11] The sample size calculation based on a Simon's Minimax two stage design will be used. The two-stage design will permit early stopping of the trial if there is strong evidence that the study regimen is inactive.

For Linsitinib plus bortezomib and dexamethasone, assuming Ho: ORR=0.6 vs. Ha: ORR=0.8, power=80%, alpha (type I error) =0.05. In the first stage, 13 evaluable patients will be enrolled. The trial will be terminated if the number of patients responded was <=8. Otherwise, additional 22 evaluable patients will be enrolled to the second stage of Phase II. A total of 35 evaluable patients are required. The treatment hypothesis is rejected if fewer than 25 patients responded in total.

Exploratory analysis: Pre-clinical studies suggest that myeloma cells lacking CD45 may predict for IGF-1R sensitivity. Based on published literature, the incidence of IGF-1R protein expression (IGF-1R+) is estimated to be 30-70%[2-4]; the incidence of CD45 negativity (CD45-) is estimated to be 30-80%[5-7]. The large variation in the reported incidence maybe related to stage of disease with a higher percentage of patients reportedly expressing IGF-1R or lacking CD45 in more advanced disease. Patients will be stratified, and overall response by IMWG criteria will be assessed in the following 3 groups: IGF-1R-, IGF-1R+/CD45+ and IGF-1R+/CD45- for patients in Phase I and II. This sample size is estimated to include ~11-43 patients with IGF-1R+ and ~11-49 patients with CD45- evaluable for myeloma response. The IGF-1R+/CD45- subgroup is estimated at 6-34 patients should accrual go to the end of the second stage. The IGF-1R+/CD45- group is hypothesized to have a greater potential for response to IGF-1R inhibition, Linsitinib may be considered worthy of further study should the addition of Linsitinib to bortezomib and dexamethasone produce a 20% higher response in this

subgroup out of the 59 enrolled patients. Should a higher response rate be observed in this subgroup or less than 13 patients with IGF-1R+/CD45- MM be evaluable, up to 8 IGF-1R+/CD45- patients would be enrolled in addition to the planned sample size in Phase I and Phase II. This number is based on an exploratory objective and is not determined by statistical power considerations.

Non-evaluable patients (up to 4) will be replaced for a total planned accrual of approximately 71 patients.

No formal comparative statistical testing of efficacy will be performed in this investigation. The ORR and safety data will be reported by descriptive statistics. The PFS and OS will be evaluated using the Kaplan-Meier method.

9.3 Study Endpoints

9.3.1 Efficacy

For the phase 2 portion of the study, the primary efficacy endpoint will be objective response rate (ORR, as evidenced by confirmed response rate, defined as partial response or better) by IMWG criteria. All patients meeting the eligibility criteria, who have signed a consent form, and have begun study drug treatment, and had at least one follow-up assessment or progressive disease, will be evaluable for the estimation of confirmed objective response rate.

9.3.1.1 Definition of Response

A patient will be classified as having had a response if he/she has a confirmed response per the definitions in Appendix 12-5 (i.e., a stringent complete response, or complete response or near complete response or very good partial response or partial response noted as the objective status of two consecutive assessments).

9.3.1.2 Time to Response

Time to response is defined as the time from date of first study drug administration to first objective documentation of response. Patients who drop out of the study prior to an assessment of response or progression, or who die from unrelated causes, will be censored at the date on which they were last known not to be either a responder or to have tumor progression.

9.3.1.3 Response Duration

Duration of response is defined as the time from the first objective documentation of response to the first objective documentation of tumor progression or to death due to multiple myeloma. For patients with responding tumors who do not have objective evidence of tumor progression and are either removed from study treatment or who are given antitumor treatment other than the study treatment or who die from non-disease causes, duration of response will be censored.

9.3.1.4 Survival

Survival is defined as the time from date of first study drug administration to date of death. In the absence of confirmation of death, survival time will be censored at the last date of follow-up when the patient was known to be alive.

9.3.1.5 Progression-Free Survival

Progression free survival (PFS) is defined as the time from first study drug administration to first objective documentation of tumor progression or to death due to any cause. For patients who are not known to have died and who do not have objective evidence of tumor progression, and who are either removed from study treatment or who are given antitumor treatment other than the assigned study treatment, PFS will be censored at the last complete disease assessment. Patients who complete the study and have not progressed at the cut-off date for final analysis will be censored at the last complete disease assessment. Patients with two or more missing assessments immediately prior to the next visit with a documented progression will be censored for PFS at the last assessment with documentation of no progression.

9.3.2 Safety

All patients will be evaluable for safety analysis if they receive at least one dose of Linsitinib and/or bortezomib. Safety analyses will review adverse events, electrocardiogram results, laboratory tests (hematology, clinical chemistry and coagulation tests), vital signs and physical examinations.

For phase 1, incidence of DLT per dose level will be summarized. For the purposes of this protocol, DLT is defined as occurring in Cycle 1 only. An “evaluable patient” for Cycle 1 DLT determination is a patient who has completed 21 days (1 cycle) of therapy and has received at least 75% of the planned Linsitinib and bortezomib dose or has been removed from treatment for toxicity.

9.4 Planned Analysis

9.4.1 Baseline Characteristics and Dosing

Patient characteristics at study entry will be summarized. Information will be collected concerning patient demographics, including baseline performance status, type of myeloma disease (immunoglobulin type, cytogenetic and FISH data at diagnosis and baseline if available), baseline beta-2 microglobulin, gender, age, time since initial diagnosis, sites of extramedullary disease, baseline laboratory parameters, duration from initiation of first treatment for myeloma, prior transplant and prior treatment (including prior bortezomib). For prior therapy: the following information will be collected: regimen; duration (start/stop dates) for each prior agent; dose; best response; reason for discontinuation (for example, progression of disease, treatment intolerance, complete response, etc.); and details regarding prior transplantation (conditioning regimen, source of transplant, and whether maintenance therapy was initiated).

Study drug administration will be described (for phase 1 by dose level; for phase 2 overall) in terms of the total number of cycles administered; the median (range) of cycles administered; dose intensity; relative dose intensity; dose modifications, dose delays, and dose omissions; and reasons for deviations from planned therapy.

9.4.2 Efficacy

For the phase 2 primary efficacy analysis, the objective response rate (defined as partial response or better by IMWG criteria) will be calculated as the number of patients achieving a response divided by the number of evaluable patients. All patients meeting the eligibility criteria, who have signed a consent form, and have begun treatment, will be evaluable for the estimation of confirmed response rate. Responses are determined by the Site Investigator according to the IMWG response criteria guidelines provided in Appendix 12-5. Confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner.

Response by IMWG criteria will be separately assessed in various groups (IGF-1R(+) and (-) myeloma; CD45 (+) and (-) myeloma, and finally IGF-1R(+) and CD45 (-) myeloma). An estimate of response rate in any of these groups is not known at this time. As one subgroup (such as IGR-1R(+) and CD45(-) with an estimated 10-12 patients likely to have enrolled in this study, should accrual go to the second stage), Linsitinib may also be considered worthy of further study should Linsitinib in combination with bortezomib and dexamethasone produce a higher response in patients in this subgroup.

9.4.3 Safety

All patients who receive at least 1 dose of Linsitinib or bortezomib will be considered evaluable for all safety analyses.

Descriptive statistics will be used to summarize safety data. Adverse events will be graded using CTCAE version 4.03 and summary tables for all adverse events will be generated. Incidence rates will be summarized for each preferred term and body system. Additional summary tables will be generated for the following population subsets: patients with serious adverse events, patients with related adverse events, patient deaths, and patients who discontinue due to adverse events. Adverse events will also be summarized by dose level. Severity, Investigator-attributed relationship to study drug, duration, and outcome of events will also be recorded.

All Adverse events and abnormal laboratory variables will be assessed according to the NCI CTCAE (v 4.03) grading system. Adverse events will be summarized by worst NCI CTCAE grade.

9.4.3.1 Adverse Events

The frequency of patients experiencing a specific AE will be tabulated by body system, dose level, phase 1 or phase 2, and (for phase 2) by Linsitinib single-agent therapy (Cycle 0) and Linsitinib /bortezomib/dexamethasone combination therapy. In the by-patient analysis, a patient having the same event more than once will be counted only once.

All adverse events will be evaluated by incidence, serious adverse events, deaths, and discontinuation due to adverse events. Severity, Investigator-attributed relationship to study drug, duration, and outcome of the events will also be recorded. The number and percent of each event will be computed and summarized by body system.

9.4.3.2 Laboratory Data

Myeloma laboratory, chemistry, hematology and coagulation data will be put in tabular form.

Hematological data will be summarized by patient and by cycle. Hematological data will be graded according to NCI CTCAE (v 4.03) severity grade. The frequencies of the worst severity grade observed will be displayed for each parameter for each study treatment.

Selected chemistry data will be summarized by patient and by cycle. Blood chemistry will be graded according to NCI CTCAE (v 4.03) severity grade, when applicable. For

blood chemistry variables graded according to NCI CTCAE (v 4.03) severity grade, the frequencies of the worst severity grade observed will be summarized.

9.4.3.3 Physical Examination/ Vital Signs/ Performance Status/ ECGs

Clinically significant changes in vital signs and new findings on PE will be recorded as adverse events. Incidences of patients with changes from normal PE findings at baseline to abnormal during the study will be generated.

Descriptive statistics will be used to summarize ECOG/KPS performance status. Vital signs will be reported in listings.

ECGs will be read locally. Data on QTc interval and heart rate will be collected. QTcF will be analyzed for changes > 60 msec and any observation of QTcF > 500 msec will be reported.

10 STUDY CONDUCT

10.1 Adherence to the Protocol

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

Deviations from the protocol shall not be made without discussion with the Lead Principal Investigator except in a medical emergency, when the intent is to reduce immediate risk to the patient. In such cases, the Lead Principal Investigator, IRB/REC, regulatory authorities, and insurance company, as appropriate, should be notified in accordance with local requirements.

Changes to the protocol may be made only when a written protocol amendment provided by the Lead Principal Investigator has been signed by the Investigator and approved by the IRB/REC and applicable regulatory agencies in accordance with local requirements.

10.2 Recording and Collecting of Data

10.2.1 Case Report Forms

The Sponsor will be responsible for the data management of this clinical trial. The Sponsor or its designee will be responsible for the design and monitoring of the electronic case report forms (eCRFs). The Sponsor or its designee will generate queries in the event of incomplete or inconsistent data to be reconciled by the study site.

For each patient enrolled, an eCRF must be completed and signed by the Principal Investigator or authorized delegate from the study staff. An electronic signature from the Principal Investigator or authorized designee will suffice (the system will comply with 21 CRF Part 11, Electronic Records, Electronic Signatures).

10.2.2 Study Files and Patient Source Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents include Investigators' Study Files and original patient clinical source documents generated at the study site. The term "original" means the first recording of the data.

The Investigator will ensure the Study Files are maintained, including the protocol/amendments, IRB/REC and regulatory approvals with associated

correspondence, informed consents, study drug records, staff curriculum vitae, all correspondence, and other appropriate documents.

Patient clinical source documents may include, but are not limited to, patient hospital/clinic records, physicians' and nurses' notes, appointment books, laboratory reports, ECGs, radiographs, pathology and special assessment reports, and consultant letters. The Investigator must assure that all original source documents are available to support monitoring activities.

10.3 Monitoring

The Sponsor of this study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded in the eCRFs. The Sponsor or its designee is responsible for reviewing the eCRFs at regular intervals throughout the study, verifying adherence to the protocol, assuring completeness, consistency, and accuracy of the data, and reviewing study files and drug accountability (see **Section 10.3.1**). The original medical records and laboratory results will be reviewed as part of source document verification to ensure validity of the data. The Investigator's responsibility is to ensure that any issues detected in the course of a monitoring visit are resolved.

10.3.1 Drug Accountability

As outlined in **Section 5.4**, the Investigator is responsible for ensuring adequate accountability of all used and unused Linsitinib study drug. All drug supplies, used and unused, and associated documentation will be reviewed and verified by the Sponsor or its designee. Used and unused material cannot be disposed of until approval is obtained from the Sponsor. The study site is responsible for the disposal and/or destruction of all unused study drug supplies, according to the site's standard operating procedures.

10.3.2 Biological Materials Accountability

The Investigator is responsible for collecting and maintaining all tissue, blood, plasma, urine, spinal fluid, or other biological materials required for the study (collectively, "biological materials") and will transfer biological materials as directed in the study reference manual. Unused biological materials may not be utilized for any purpose other than the uses described in the study.

10.4 Retention of Records

According to C.05.012 of the Food and Drug Regulations in Canada, the sponsor shall maintain all records for a period of 25 years. The Investigator must retain protocols, amendments, IRB/IEC approvals, copies of the Form FDA 1572 and/or Canadian QIU, signed and dated consent forms, medical records, case report forms, drug accountability records, all correspondence, and any other documents pertaining to the conduct of the study.

10.5 Inspection

Following pre-qualification and initiation of the study site, periodic monitoring visits will be made by the Sponsor and/or a monitor from its designated representative. The Investigator must provide sufficient space and allocate sufficient time for the monitor to inspect patient source records, case report forms, drug accountability records, and regulatory documents. The purpose of trial monitoring is to verify the following:

- The rights and wellbeing of human patients are protected.
- The reported data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol, amendment(s), ICH GCP, FDA CFR, and any other applicable regulatory requirements.

The monitor shall submit a written report after each trial site visit or trial-related communication. Reports shall include a summary of what the monitor reviewed and significant findings, deviations and deficiencies, conclusions, actions taken or to be taken to ensure site compliance.

The Investigator must also permit trial-related audits, IRB/IEC review, and regulatory inspections providing direct access to data and source documents pertaining to this study if so requested.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Routine study site monitoring
- eCRF review against source documents
- Data management quality control checks
- Medical review

The Sponsor or its designee will be responsible for the design and monitoring of the electronic case report forms. Queries may be generated in the event of incomplete or inconsistent data to be reconciled by the study site.

10.6 Legal and Ethical Requirements

10.6.1 Good Clinical Practice/Regulatory Approval

The study will be conducted in accordance with Health Canada, U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, any applicable local health authority requirements, and IRB or IEC requirements.

10.6.2 Institutional Review Board/Research Ethics Committee Approval

The Investigator must submit this protocol, the informed consent form(s), and any accompanying material that will be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) to the IRB/REC. Approval from the board/committee must be obtained **before** starting the study and documented in writing to the Investigator specifying the protocol number, protocol version, documents reviewed, and date on which the committee met and granted the approval. Written evidence of the approval must be made available. Any modifications made to the protocol after receipt of IRB/REC approval must also be submitted to the board/committee for approval prior to implementation.

The Investigator or designee will be responsible for obtaining annual IRB/IEC re-approval throughout the duration of the study. Copies of the Investigator's annual report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be submitted to the Lead Principal Investigator or designee.

10.6.3 Informed Consent

The Investigator is responsible for obtaining written, informed consent(s) from each patient interested in participating in this study prior to conducting any study-related procedures. Written informed consent should be obtained after adequate, thorough, and clear explanation of the aims, methods, objectives, potential risks and benefits of the study, as well as any use of the patient's genetic information from the study. The Investigator must use the most current IRB/REC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the patient and the person obtaining consent. The investigational site must retain the

original signed consent and provide a copy to the patient. Documentation of the consent process should be documented in the patient's medical record.

Significant new safety information received by the Investigator should be provided to current and future study patients at the first available opportunity.

10.6.4 Study Termination

The Sponsor, the Investigator, Astellas Pharma Global Development, Inc. (APGD) and/or the regulatory authorities reserve the right to terminate the study at any time. Should termination be necessary, all parties will formulate and coordinate termination procedures. In terminating the study, the Sponsor and the Investigator will assure that patients' safety and rights are carefully protected.

10.7 Confidentiality and Data Protection

Patient medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The patient may request in writing that medical information be given to his/her personal physician.

The Investigator/Institution will permit direct access to source data and documents by the Sponsor, its designees, the Health Canada, the FDA, and other applicable regulatory authorities and APGD the supplier of Linsitinib. The access may consist of trial-related monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

11 REFERENCE LIST

1. Duffy D, Santner T. Confidence intervals for a binomial parameter based on multistage tests. Biometrics 1987;43:81-93.

2. Bataille R, Robillard N, Avet-Loiseau H, Harousseau JL, Moreau P.

   CD221 (IGF-1R) is aberrantly expressed in multiple myeloma, in relation to disease severity. Haematologica 2005;90: 706-7.

3. Sprynski AC, Hose D, Caillot L, Réme T, Shaughnessy JD Jr, Barlogie B, Seckinger A, Moreaux J, Hundemer M, Jourdan M, Meissner T, Jauch A, Mahtouk K, Kassambara A, Bertsch U, Rossi JF, Goldschmidt H, Klein B. The role of IGF-1 as a major growth factor for myeloma cell lines and the prognostic relevance of the expression of its receptor. Blood. 2009 7;113(19):4614-26.

4. Chng WJ, Gualberto A, Fonseca R. IGF-1R is overexpressed in poor-prognostic subtypes of multiple myeloma. Leukemia. 2006;20(1):174-6.

5. Menke DM, Horny HP, Griesser H, Atkinson EJ, Kaiserling E, Kyle RA.

   immunophenotypic and genotypic characterisation of multiple myelomas with adverse prognosis characterised by immunohistological expression of the T cell related antigen CD45RO (UCHL-1). J Clin Pathol. 1998;51(6):432-7.

6. Lin P, Owens R, Tricot G, Wilson CS. Flow cytometric immunophenotypic analysis of 306 cases of multiple myeloma. Am J Clin Pathol. 2004;121(4):482-8.

7. Kumar S, Rajkumar SV, Kimlinger T, Greipp PR, Witzig TE. CD45 expression by bone marrow plasma cells in multiple myeloma: clinical and biological correlations. Leukemia. 2005;19(8):1466-70.

8. Descamps G, Wuilleme-Toumi S, Trichet V, Venot C, Debussche L, Hercend T, et al. CD45neg but not CD45 pos human myeloma cells are sensitive to the inhibition of IGF-1 signaling by a murine anti-IGF-1R monoclonal antibody mAVE1642. J Immunol 2006;177: 4218-23.

9. Richardson, P.G., P. Sonneveld, M. Schuster et al. (2005) Bortezomib or high-dose dexamethasone for relapsed, refractory myeloma. N Engl J Med 352(24), 2487-98

10. Jagannath S, Barlogie B, Berenson J, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. Br J Haematol. 2004 Oct;127(2):165-72.

11. Mikhael, J. R., Belch, A. R., Prince, H. M., et al, High response rate to bortezomib with or without dexamethasone in patients with relapsed or refractory multiple myeloma: results of a global phase 3b expanded access program. British Journal of Haematology, 144: 169–175. doi: 10.1111/j.1365-2141.2008.07409.x

12. Linsitinib Investigator's Brochure Global Edition 3, dated 28 May 2013.

13. Raab MS, Podar K, Breitkreutz I, Richardson PG, Anderson KC. Multiple Myeloma. Lancet 2009;374: 324-39.

14. Pollack MN, Schernhammer ES, Hankinson SE et al. Insulin-like growth factors and neoplasia. Nat Rev Cancer 2004; 4(7):505-18.

15. Wang Y, Sun Y. Insulin-like growth factor receptor-1 as an anti-cancer target: blocking transformation and inducing apoptosis. Curr Cancer Drug Targets 2002; 2(3):191-207.

16. Resnicoff M, Tjuvajev J, Rotman HL, Abraham D, Curtis M, Aiken R et al. Regression of C6 rat brain tumors by cells expressing an antisense insulin-like growth factor I receptor RNA. J Exp Ther Oncol 1996; 1(6):385-9.

17. Cohen BD, Baker DA, Soderstrom C, Tkalcevic G, Rossi AM, Miller PE et al. Combination therapy enhances the inhibition of tumor growth with the fully human anti-type 1 insulin-like growth factor receptor monoclonal antibody CP-751,871. Clin Cancer Res 2005: 11(5):2063-73.

18. Garaber K. IGF-1: old growth factor shines as new drug target. J Natl Cancer Inst 2005; 97(11):790-2.

19. Goetsch L, Gonzalez A, Leger O, Beck A, Pauwels PJ, Haeuw JF et al. A recombinant humanized anti-insulin-like growth factor receptor type I antibody (h7C10) enhances the antitumor activity of vinorelbine and anti-epidermal growth factor receptor therapy against human cancer xenografts. Int J Cancer 2005; 113(2):316-28.

20. Sachdev D, Hartell JS, Lee AV, Zhang X, Yee D. A dominant negative type I insulin-like growth factor receptor inhibits metastasis of human cancer cells. J Biol Chem 2004; 279(6):5017-24.

21. Garcia-Echeverria C, Pearson MA, Marti A, Meyer T, Mestan J, Zimmermann J et al. In vivo antitumor activity of NVP-AEW541- A novel, potent and selective inhibitor of the IGF-IR kinase. Cancer Cell 2004; 5(3):231-9.

22. Menu E, van Valckenborgh E, van Camp B, Vanderkerken L. The role of insulin-like growth factor 1 receptor in multiple myeloma. Arch Pysiol Biochem 2009;115: 49-75.

23. Ge NL, Rudikoff S. Insulin-like growth factor I is a dual effector of multiple myeloma cell growth. Blood 2000;96: 2856-61.

24. Abroun S, Ishikawa H, Tsuyama N, et al, Receptor synergy of interleukine-6 (IL-6) and insulin-like growth factor-1 in myeloma cells that highly express IL-6 receptor alpha. Blood 2004;103 :2291-8

25. Tu Y, Gardner A, Lichtenstein A. The phosphatidylinositol 3-kinase/AKT kinase pathway on multiple myeloma plasma cells: roles in cytokine-dependant survival and proliferative rsponses. Cacer Res 2000;06 :6763-70

26. Stromberg T, Ekman S, Girnita L, et al. IGF-1 receptor tyrosine kinase inhibition by the cyclolignan PPP induces G2/M-phase accumulation and apoptosis in multiple myeloma cells. Blood 2006;107: 669-78.

27. Menu E, Jernberg-Wiklund H, De Raeve H, et al. Targeting the IGF-1R using picropodophyllin in the therapeutical 5T2MM mouse model of multiple myeloma: beneficial effects on tumor growth, angiogenesis, bone disease and survival. Int J Cancer 2007;121: 1857-61.

28. Menu E, Jernberg-Wiklund H, Stromberg T, et al. Inhibiting the IGF-1 receptor tyrosine kinase with the cyclolignan PPP: an in vitro and in vivo study in the 5T33MM mouse model. Blood 2006;107: 655-60.

29. Maiso P, Ocio EM, Garayoa M, et al. The insulin-like growth factor-I receptor inhibitor NVP-AEW541 provokes cell cycle arrest and apoptosis in multiple myeloma cells. Br J Haematol 2008;141: 470-82.

30. Baumann P, Hagemeier H, Mandl-Weber S, Franke D, Schmidmaier R.

Myeloma cell growth inhibition is augmented by synchronous inhibition of the insulin-like growth factor-1 receptor by NVP-AEW541 and inhibition of mammalian target of rapamycin by Rad001. Anticancer Drugs 2009;20:

259-66.

31. Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol. 1998;102:1115-1123.

32 Rajkumar SV, Harousseau J-L, Durie B, e al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood First Edition Paper, pre-published online February 3, 2011;DOI 10.1182/blood-2010-10-299487

33 Richardson, P.G., B. Barlogie, J. Berenson et al. (2003) A phase 2 study of BZ in relapsed, refractory myeloma. N Engl J Med 348, 2609-17

34 Durie et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-73.

35 Mitsiades CS, Mitsiades NS, McMullan CJ, Poulaki V, Shringarpure R, Akiyama M, Hideshima T, Chauhan D, Joseph M, Libermann TA, García-Echeverría C, Pearson MA, Hofmann F, Anderson KC, Kung AL. Inhibition of the insulin-like growth factor receptor-1 tyrosine kinase activity as a therapeutic strategy for multiple myeloma, other hematologic malignancies, and solid tumors. Cancer Cell. 2004;5(3):221-30.

36 Liang SB, Yang XZ, Trieu Y, Li Z, Zive J, Leung-Hagesteijn C, Wei E, Zozulya S, Coss CC, Dalton JT, Fantus IG, Trudel S. Molecular target characterization and antimyeloma activity of the novel, insulin-like growth factor 1 receptor inhibitor, GTx-134. Clin Cancer Res. 2011;17(14):4693-704.

12 APPENDICES

Appendix 12-1: Table of Assessments

PROCEDURES	Screen	Cycle 0**	Cycle 1 (cycle = 21 days)					Cycle 2-8 (cycle = 21 days)					Cycle 9 + Cycle = 35 days	End of Treatment	Post Study Follow Up[16]
	-21d to -1d	Day 1	Day 1	Day 4	Day 8	Day 11	Day 15	Day 1	Day 4	Day 8	Day 11	Day 15	Day 1		
Informed Consent	X														
Medical History,	X		X												
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X		X	X	X
PE[1], Height[1], Weight, BSA[1], KPS/ECOG	X		X					X					X	X	
Toxicity Evaluation (AE/SAE)[2]	X	X	X[2]	X	X	X	X	X[2]	X	X	X		X[2]	X	X
Vital Signs (HR, Temp, BP)	X		X					X					X	X	
ECG[3]	X[3]	X	X		X		X	X					X	X	
2D Echo	X							X							
CBC[4]	X	X	X		X		X	X		X		X	X	X	
Fasting Serum Chemistry[5]	X	X	X		X		X	X		X		X	X	X	
Glycosulated Hemoglobin (HbA1c)[15]	X							X					X	X	
Glucose Monitoring(home)[6]		X													
PT/PTT (INR)[17]	X														
Creatinine Clearance	X													X	
Pregnancy test [FCBP only]	X	X						X					X	X	
Extramedullary disease[7]	X							X						X	
Skeletal Survey[8]	X														
BMB_X (Aspiration/Biopsy)[9]	X						(DAY 21)							X	
Myeloma specific lab tests	X[10]		X[10]					X[10]					X	X[10]	
Pharmacokinetics (Phase 1/2)[12]		X[12]	X		X		(DAY 21)	X[12]							
Dexamethasone administration[11]			X	X	X	X		X	X	X	X		X		
Bortezomib Administration[13]			X	X	X	X		X	X	X	X		D1, 8, 15, 22		
Linsitinib Administration[14]		X	X--------BID D1-21--------->					X-------BID D1 - 21--------->					BID daily		
Long term follow-up[16]															X

Linsitinib + Bortezomib/Dexamethasone

1) Height measured at screening only. BSA to be calculated at the start of each cycle prior to bortezomib administration. Cycle 1 - 8 is 21 days. Cycle 9+ is 35 days. Full physical exam (PE) excluding genitourinary exam but including cardiopulmonary assessments (auscultation) will be done at baseline. A symptom directed physical exam including cardiopulmonary assessments will be done on day 1 of each cycle.

2) Toxicity (AE/SAE) evaluation: Baseline physical assessment (excludes genitourinary exam), signs, symptoms and toxicities and baseline FACT-GOG-NTx; Day 1 of each cycle includes a brief symptom directed physical assessment and neurological assessment FACT-GOG-NTx prior to the administration of bortezomib. Continuous AE/SAE assessments must be done at each study visit.

3) Triplicate 12-lead ECGs will be obtained for all patients at screening and pre and 2-4 hours post dose on Day1 of Cycles 0, 1and 2. Additionally, 2 to 4 hours post dose triplicate ECGs on Days 8 and 15 of Cycle 1 are required. If clinically significant abnormalities are observed, patients will be required to do triplicate ECGs pre and 2-4 hours post dose on day 1 of each subsequent cycle. Patients with normal ECGs will have single ECG pre dose and 2 to 4 hours post dose on Day 1 of Cycle 3 and subsequent cycles. An ECG at the end of treatment visit will be required as well. Triplicate ECGs must be digitally recorded and at least 2 minutes apart. ECGs should be performed within 24 hours prior to Day 1 dosing regardless of when the screening evaluation was performed. The QTc or QTcF of ECG tracings will be used as the baseline assessment. Patients with QTc> 450 will require QTcF calculations done. Patients with confirmed QTcF ≥ 450 msec (based on triplicate values) are excluded. Prior to performing ECGs, patients should rest in the supine position for at least 2 minutes and triplicate ECGs must be at least 2 minutes apart. See protocol guidelines for management and reporting of prolonged QTcF.

4) CBC should be performed and reviewed by clinician within 24 hours of Linsitinib and bortezomib dosing Day 1 and weekly during Cycle 1 and 2 and then Day 1 and 8 of each subsequent Cycle up to cycle 8. CBC is to be performed and reviewed by clinician within 24 hours of bortezomib on Day 1 of Cycle 9 and each subsequent Cycle. If platelet count < 25 X 109/L prior to bortezomib dosing patients may be transfused platelets and the CBC repeated thereafter. Patients maybe dosed with bortezomib on the same day at the same dose level if the platelet count ≥ 25 X109/L on repeat testing

5) Fasting Serum Chemistry to be performed and reviewed by the Investigator within 24 hours of Linsitinib and bortezomib dosing (Day 1 and weekly for Cycle 1 and 2 then Day 1 of each cycle). Chemistry includes: FASTING glucose, calcium, albumin, total protein, sodium, potassium, Mg, CO2, chloride, BUN, creatinine, ALK Phos, ALT, AST, total bilirubin . Direct and indirect bilirubin, (GGT, PT/INR are required only where liver function abnormalities of Grade 2 or higher is observed), Troponin I or T and BNP or NT-proBNP (Troponin I or T must be done at screening and day 1 of each cycle excluding cycle 0, BNP or NT-proBNP must be done at screening and day 1 of every third cycle (3, 6, 9)), and uric acid. Weight and serum creatinine will be used to calculate creatinine clearance (eGFR and eCCr). Also see protocol guidelines for patient management and reporting of elevated liver function tests.

6). Monitoring of serum glucose and urinary ketones: Fasting glucose is required at screening, within 24 hours of pre-dose on Day 1 Cycle 1 and Cycle 0 if applicable, then pre-dose on Days 8 and 15 of Cycle 1 and 2 and at more frequent intervals for episodes of grade 3 hyperglycemia or at the investigators discretion, and at the End of Study Visit. Patients should monitor serum glucose and urinary ketones using a home glucose monitor and urine reagent strips. Patients will be instructed to measure their blood glucose and ketone levels with the provided supplies twice daily (pre-breakfast and pre-evening meal) during Cycle 1 and Cycle 0 if applicable. Assessments beyond the cycle 1 will be done at the Investigator's discretion. For signs or symptoms related to glucose intolerance (e.g., frequent urination, excessive thirst, extreme hunger, unusual weight loss, increased fatigue, irritability, and blurred vision), patient will also be instructed to use urine reagent strips to test for urinary ketones. If abnormalities are reported by the patient, patients will be instructed to call the site to have tests repeated at the site laboratory. See protocol guidelines for management and reporting of hyper or hypoglycemia.

7) Extramedullary disease: prior to study and every 12 weeks or upon clinical suspicion of progressive disease. This may include CT scan of the abdomen/pelvis, CT or x ray of the chest, ultrasound of the liver/spleen or abdomen. To ensure comparability, the baseline radiographs/scans and subsequent radiographs/scans to assess response should be performed preferably using identical techniques. The same method, radiological or physical, should be employed and assessed by the same individual on each occasion if possible.

8) Skeletal survey (including skull, all long bones, pelvis and chest) required if previous survey >12 weeks from study entry and at any time when clinically indicated.

9) BMA and/or biopsy and serum sample is required at screening. 2 BMA samples should be collected at baseline. The first BMA samples (first pull) along with serum should be sample forwarded to the central analytical laboratory (PMCC, Toronto). The second sample is forwarded to local hematopathology laboratory for assessment of cellularity and percentage CD138+ cells (FISH should be performed if standard of care at the institution; recommended probes include t(4;14), t(14;16), del13, del17 and 1q21 abnormalities. Details on sample handling are provided in Appendix 12-4. The Cycle 1 day 21 (+/- 3 day) BMA and serum sample is optional for consenting patients in Phase 2 only and is considered a research sample and must be done 3-4 hours following single-agent Linsitinib. Repeat bone marrow aspirate if nCR, CR, sCR is suspected to confirm achievement of response (aspirate only—biopsy not required). BMA and serum sample is also required for all patients at time of relapse.

10) Myeloma lab tests: ß2Microglobulin (collected at screening only); serum immunoelectrophoresis, immunoglobulin assay, M band confirmation by immunofixation and quantitation by SPEP, free light chain and 24 hour urine collection for Bence Jones protein to be performed at baseline prior to study, prior to each cycle thereafter and at time of study discontinuation (if last tests were > 4 weeks). FreeLyte test should occur if indicated by the Investigator. Not all tests may be required at each assessment time point.

11) Dexamethasone is administered at 20 mg PO or IV prior to each bortezomib dose. See protocol details for dosing and dose modifications based on toxicity.

12) Patients should be advised to ingest Linsitinib in the clinic on the PK days.

Phase 1: on all patients, on day 21, single agent PK will be collected pre Linsitinib dose, 30 min, 1hr, 2hrs, 3hrs, 4hrs, 6hrs, 8hrs with the 24 hour collection on cycle 2/day1 pre bortezomib infusion. Combination PK will be collected on day 8 pre bortezomoib and Linsitinib dose, 30 min, 1hr, 2hrs, 3hrs, 4hrs, 6hrs and 8hrs post dose with the 24 hour collection on cycle 1 day 9 pre Linsitinib and bortezomib dose.

Phase 2: The first 12 patients only during the 7 day lead in (Cycle 0) on day 7 pre Linsitinib dose, 30 min, 1hr, 2hrs, 3hrs, 4hrs, 6hrs, 8hrs post dose with the 24 hour collection on Cycle 1 Day 1 pre bortezomib infusion. Combination PK will be collected on Cycle 1 Day 8 pre Linsitinib and bortezomib dose and 2 and 4 hours post dose.

13) Bortezomib is administered IV or SQ starting in Cycle 1 on days 1, 4, 8 and 11 of a 21 Day Cycle for Cycles 1 – 8. Bortezomib is administered on Days 1, 8, 15 and 22 of a 35 Days Cycle for Cycles 9+. Bortezomib is held during the “run in” week (Cycle 0) of Phase 2. Patients who do not have access to bortezomib beyond Cycle 8 or difficulty remaining on bortezomib treatment may continue the trial on single agent Linsitinib with Sponsor approval for as long as there is clinical benefit.

14) Daily continuous therapy at approximately 12 hours at the same time of the day. Tablets should be taken with a large glass of water. Missed or vomited tablets should be not re-administered. Tablets should be taken in the clinic on days of pharmacokinetic/pharmacodynamic draws.

*Additional tests to be performed at the beginning of each cycle and at any reasonable time point during treatment if indicated for monitoring of drug profile/safety or, for disease/health status at the discretion of the Investigator.

15) Glycosylated hemoglobin is required at screening, day 1 of cycles 3, 6, 9 and every third cycle and at the end of treatment visit

16) Long-term follow-up: Every attempt should be made to follow patients every 12 weeks to determine long-term survival, disease progression (if not observed on study), and to collect information on any drug-related serious adverse events.

17) PT/PTT (INR) must be done at screening and on the days where liver function abnormalities of Grade 2 or higher is observed.

18) Echocardiogram will be done at screening, cycle 3 Day 1 and as clinically indicated during phase 1 and for the first 10 patients enrolled at the MTD.

**Cycle 0 = Run-In cycle of single agent Linsitinib is for Phase 2 patients only.

Appendix 12-2: ECOG / Karnofsky Performance Status Scale

Karnofsky Scale		ECOG Scale	
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activity; minor signs or symptoms of disease	90		
Normal activity with effort	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., office work or light house work)
Unable to carry on normal activity or perform active work; cares for self	70		
Requires occasional assistance but is able to care for most own needs	60	2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	50		
Disabled; requires special medical care and assistance	40	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Severely disabled; hospitalization indicated although death not imminent	30		
Very sick; hospitalized and active	20	4	Completely disabled; cannot perform any self-care; totally confined to bed or chair
Moribund; fatal processes progressing rapidly	10		
Dead	0		

Appendix 12-3: Pharmacokinetic Analysis

12-3.1 Plasma Samples for Pharmacokinetic Analysis

Phase 1 and Phase 2 patients will undergo PK sampling on one or two time points. This section describes the collection and preparation of plasma samples for pharmacokinetic analysis.

12-3.1.1 Time Points for Plasma Sample Collections

A 5-6 mL blood sample will be collected from each patient at each time point according to the schedule in the following table.

Phase Cycle/Day	Sample	Planned Time[1]	Note
Phase 1 Combination PK sample collection			
Phase 1 Cycle 1Day 8	1	Pre-dose	Immediately prior to Linsitinib and bortezomib dose
	2	30 minutes	
	3	1 hour	
	4	2 hours	
	5	3 hours	
	6	4 hours	
	7	6 hours	
	8	8 hours	
Phase 1 Day 9	1	24 hours	
Phase 1 Single Agent LinsitinibPK sample collection			
Phase 1 Cycle 1 Day 21	1	**Pre-dose**	**Immediately prior to Linsitinib dose**
	2	**30 minutes**	
	3	**1 hours**	
	4	**2 hours**	
	5	**3 hours**	
	6	**4 hours**	
	7	**6 hours**	
	8	**8 hours**	
Cycle 2 day 1	1	**24 hours**	Immediately prior to Linsitinib dose and prior to bortezomib administration
Phase 2 single agent PK sample collection			
Phase 2 Cycle 0 (lead in) day 7	1	**Pre-dose**	Pre-single agent dose of Linsitinib
		30 minutes	Post single agent Linsitinib dose
		1 hour	

12 patients only		**2 hour**	
		3 hour	
		4 hour	
		6 hour	
		8 hour	
Phase 2 Cycle 1 Day 1		**24 hour**	Prior to Linsitinib and bortezomib administration
Phase 2 combination therapy PK sample collection			
Phase 2 Cycle 1 day 8	201	**Pre-dose**	**Immediately prior to Linsitinib and bortezomib dose.**
	202	**2 – 4 hours post dose**	**Following the Linsitinib and bortezomib dose.**
[1] All times are indicated as the number of hours following the first dose of that day (or of the previous day in the case of 24-hour samples).			

The exact blood collection times will be recorded for each sample, as well as dose time on day of PK sampling. All sample times will be determined by the start time of the Linsitinib administration. In addition the dose time on the day prior to the day of PK sampling will be recorded.

For any PK sampling day, patients must ingest the Linsitinib tablet under nursing supervision in the clinic

12-3.2 Pharmacokinetic Analysis

Plasma concentration versus time profiles of Linsitinib and bortezomib will be obtained from the analysis of plasma samples. Pharmacokinetic parameters will be calculated for each patient. Parameters will include but are not limited to AUC, C_{max}, T_{max}, $T_{1/2\lambda z}$, clearance (CL/F), and volume of distribution (Vz/F).

12-3.3 Plasma Pharmacokinetic Samples

This section describes the collection and preparation of plasma samples for Pharmacokinetic (PK) analysis. :

- K_2EDTA tubes;
- Cryovials;
- Transfer pipettes;
- Pre-printed labels with protocol number; and
- Plastic Ziploc bags for shipping frozen samples.

12-3.4 Plasma PK Sample Collection

Blood samples will be collected according to the following procedure:

1. Label all sample collection tubes and cryovials with the patient number, patient initials, and date and time of collection. Details of exact times and dates the samples were drawn must be accurately recorded on sample collection form, "Pharmacokinetics Sampling – Plasma" and in the patient's electronic case report form (eCRF).
2. Collect a venous blood sample of 5 mL into a K_2EDTA tube for each time point specified. Each sample will be collected with a 20-gauge (or smaller gauge/larger bore) needle into the K_2EDTA tubes. If a catheter with a heparin lock is used, a 0.5 mL blood sample will be drawn and discarded prior to the collection of the study sample.
3. After collection, mix the samples by gently inverting the tubes 8 – 10 times (do not shake).
4. **Immediately refrigerate or place the sample on wet ice. Processing for each sample described below must occur within 30 minutes.**

12-3.5 Plasma PK Sample Processing

1. To separate the plasma: within 30 minutes of collection, each blood sample must be centrifuged at 1500 – 2000 g for 10 minutes in a refrigerated centrifuge (2 – 8°C) or in a cold room of 2 – 8°C. The appropriate revolutions per minute (RPM) required to generate the specified centrifugal force (1500 – 2000 g) for each centrifugation step will vary depending on the particular rotor used on the centrifuge. RPM values must be calculated in each laboratory based on the rotor in use.

2. Using a pipette, dispense 2 aliquots of plasma (each approximately 0.75 mL) into 2 labeled cryovials. Do not disturb the red blood cell or buffy coat layers. **Adequate space between the plasma and the tube cap should be provided for expansion upon freezing.**

3. Check each cryovial for the correct label requirements including: the protocol number, patient number, patient initials, and date and time of collection.

    - One of the 2 samples will be shipped to:

Chris Tucker
Principal Scientist, Bioanalysis US
Astellas Pharma Global Development, Inc.
8045 Lamon Ave. Skokie, IL 60077
Office: 847-933-7489

Fax: 847-933-7482
E-mail: chris.tucker@us.astellas.com

4. The remaining sample will be retained in the site's freezer as a back-up sample and shipped as part of the next quarterly shipment.

5. **Freeze all samples at -70°C immediately upon completion of processing.**

12-3.6 Plasma PK Sample Storage

All plasma PK samples must be frozen immediately until shipment. The back-up plasma samples should be retained at the site in a freezer at -70°C until the next quarterly shipment from the site.

FLOW DIAGRAM OF PLASMA PK PROCEDURES

Label all collection tubes and cryovials before proceeding below

Draw 5mL venous blood into provided K_2EDTA tube

Mix by gently inverting 8-10 times
Immediately refrigerate or place samples on wet ice

Within 30 minutes

Centrifuge at 1500-2000g for 10 minutes at 2-8°C

Dispense 2 aliquots of plasma (0.75 mL each) into 2 labeled cryovials

Freeze all at -70°C *

Store 1 PK sample cryovial as back-up until directed to ship by APDG/designee

Ship the remaining PK sample cryovial, when directed by APGD/designee

12-3.7 Shipping Instructions

Shipment Preparation

Frozen Samples (Plasma PK)

ALL PK samples should be stored at -70°C until shipped.

1. All samples will be shipped as outlined below.
   - PK samples will be batch shipped
   - PK samples should be shipped quarterly (every 3 months) beginning with the patient's registration date.
   - PK primary and corresponding back-up samples are required to be shipped separately. Back-up samples are held and shipped at the next quarterly shipment.
2. All samples must be shipped in accordance with local biohazard requirements. Please refer to your institutional policy for biohazard labeling and packaging for shipment of hazardous and infectious human samples.
3. PK shipments should **not** be made on Thursday, Friday, or any day prior to a holiday. Preferred shipping days are Monday, Tuesday, and Wednesday.
4. Packaging the PK samples:
   - Group PK samples all in one bundle. Place the PK sample bundle for each patient in individual pre-labeled Ziploc freezer bags. Complete each of the respective labels with the corresponding patient information.
5. A copy of the worksheet for each patient's samples in the shipment must be included in the Ziploc freezer bag with the samples. The following information must be completed in the worksheet(s) for each sample shipped:
   - Linsitinib dose any dosing modifications between treatment periods must be documented in the "Comments" section of that treatment period in the form;
   - Patient number and initials;
   - Date and time of dosing;
   - Sample collection date and time;
   - Initials of person completing worksheet(s); and
   - Date of shipment.
6. Copy the worksheet(s) and place a copy of the worksheet(s) in a separate Ziploc freezer bag sealed for protection. Then, place the sealed Ziploc bag with worksheet(s) in the freezer bag with bundled samples.

7. Place the Ziploc freezer bag of samples and completed worksheet back in the freezer until the courier arrives.

12-3.7 Phase I PK Shipping Form

Patient Number:_____ Patient Initials:_____

Site:_____ Date:_____

A Phase 1/2 Trial of Linsitinib in Combination with Bortezomib and Dexamethasone for the Treatment of Relapsed or Relapsed/Refractory Multiple Myeloma **PMHOSI906-MM001**				
Phase 1 Combination PK sample collection Form				
Phase Cycle/Day	**Sample**	**Planned Time[1]**	**Actual Time**	**Note**
Phase 1 Cycle 1Day 8	1	Pre-dose : Immediately prior Linsitinib and bortezomib dose		
	2	30 minutes		
	3	1 hour		
	4	2 hours		
	5	3 hours		
	6	4 hours		
	7	6 hours		
	8	8 hours		
Phase 1 Day 9	9	24 hours		
Phase 1 Single Agent LinsitinibPK sample collection				
Phase 1 Cycle 1 Day 21	1	**Pre-dose: Immediately prior to Linsitinibdose**		
	2	**30 minutes**		
	3	**1 hours**		
	4	**2 hours**		
	5	**3 hours**		
	6	**4 hours**		
	7	**6 hours**		
	8	**8 hours**		
Cycle 2 day 1	1	**24 hours:** Immediately prior to Linsitinib)dose and prior to bortezomib administration		

12-3.8 Phase 2 PK Shipping Form

Patient Number:_____Patient Initials:_____
Site:_____Date:_____

A Phase 1/2 Trial of Linsitinib in Combination with Bortezomib and Dexamethasone for the Treatment of Relapsed or Relapsed/Refractory Multiple Myeloma **PMHOSI906-MM001** **Phase 2 single agent PK sample collection Form**				
Phase 2 **Cycle 0 (lead in) day 7** **12 patients only**	1	**Pre-dose**	Pre-single agent dose of Linsitinib	
		30 minutes	Post single agent Linsitinib dose	
		1 hour		
		2 hour		
		3 hour		
		4 hour		
		6 hour		
		8 hour		
Phase 2 Cycle 1 Day 1		**24 hour:** Prior to Linsitinib and bortezomib administration		
Phase 2 combination therapy PK sample collection				
Phase 2 Cycle 1 day 8	201	**Pre-dose: Immediately prior to Linsitinib and bortezomib dose.**		
	202	**2 – 4 hours post dose: Following the Linsitinib and bortezomib dose.**		
[1] All times are indicated as the number of hours following the first dose of that day (or of the previous day in the case of 24-hour samples).				

Appendix 12-4: Pharmacogenomic/Pharmacodynamic Analysis

As a companion study to the proposed clinical trial, patients will be approached for consent to conduct studies aimed at identifying predictors of response, mechanisms of resistance and PD studies to demonstrate target inhibition.

For the purposes of this trial, research BMA and blood sample will be obtained at baseline and at progression for all patients enrolled in Phase 2 and a follow-up optional blood sample and BMA obtained on Cycle 1/Day 21 (+/- 3 days), approximately 3 - 4 hours after the dose of Linsitinib.

Two BMA samples should be collected at baseline. The first BMA sample collected (first pull) at baseline should be forwarded to the central analytical laboratory for this study (PMCC, Toronto Canada). The second sample is forwarded to local hematopathology laboratory for assessment of cellularity and percentage CD138+ cells (FISH should be performed if standard of care at the institution; recommended probes include those to detect t(4;14), t(14;16), del13, del17 and 1q21 abnormalities).

Expression of IGF-1R and CD45

Although IGF-1R is widely expressed in MM tumors with some studies reporting its presence in 30-70% of newly diagnosed MM cases and in 90% of HMCLs, it is clear that its expression is not universal. CD45 expression is estimated in one series to be approximately 47% by flow cytometry. Further, pre-clinical studies indicate that CD45 negative but not CD45 positive myeloma tumors are sensitive to IGF-1R inhibition. Expression of CD45 and IGF-1R will be determined by flow cytometry on all screening BMA. Briefly, an aliquot of bone marrow will be subjected to red cell lysis. A quadruple antibody combination (anti-CD138-APC/cy7, anti-CD38-FITC, anti-IGF-1R-PerCP and a pan-anti-CD45-PE) will be combined with side scatter and light scatter properties to evaluate the expression of CD45 and IGF-1R on the myeloma cell population. Flow cytometry will be done using a LSR II flow cytometer (BDIS), and offline listmode analysis will done using FlowJo software. Correlation of expression with response will be reported.

Serum Levels of IGF ligands and related peptides

Serum IGF-I and IGF-II levels as well as levels of IGF binding proteins will be evaluated by ELISA at baseline and after one cycle of treatment and correlated with response to treatment.

Pharmacogenomic Studies

Gene expression analysis will be obtained for the purpose of addressing three groups of biomarkers (i) expression profiles associated with response to the agents (ii) expression profiles associated with specific toxicities of the agents (iii) understanding the cellular actions of the drug in myeloma cells and (iv) molecular mechanisms of acquired resistance. In addition, expression of genes related to IGF/insulin signaling may be assessed by quantitative PCR. Gene expression profiling (GEP) may also be performed to analyze for adverse prognostic cytogenetic abnormalities such as t(4;14) and t(14;16). Determination of

mutations for genes within the IGF/insulin signal transduction pathway will also be determined. Mutations in genes related to the IGF/insulin signal transduction pathway, for example, the mutational or wild type status for KRAS, BRAF, PIK3CA, and PTEN, will also be evaluated.

Flow Cytometry Pharmacodynamic Studies

Myeloma cells from bone marrow samples will be evaluated for target modulation and the effects of Linsitinib with or without bortezomib on downstream signaling targets of IGF-1R. Flow cytometry is a highly developed technique for the diagnosis of hematological malignancies, based on the correlated measurements of multiple surface immunophenotypic markers plus forward and orthogonal light scattering characteristics of cell subpopulations. However, the recent introduction of techniques that measure the activation states of signaling pathways using phosphospecific antibodies, the scope of flow cytometry now extends into molecular therapeutic monitoring in the clinic. By using flow cytometry applications, we will determine whether the IGF-1R target AKT is activated in myeloma cells pre-treatment and whether administration of Linsitinib with or without bortezomib inhibits AKT in primary cells. Effects of Linsitinib on the tyrosine phosphorylation of IRS-1 will also be determined. Correlation with CD45 expression, patient response, dose and available drug plasma levels will be determined. The results will be analyzed on an exploratory basis.

Flow Cytometry Protocol

A quadruple antibody combination (anti-CD138, anti-CD38, anti-CD45 and anti-pAKT or pIRS-1) will be used to analyze PI3K signaling in myeloma cells. Bone marrow samples will be subjected to red cell lysis and quality of the sample will be assessed by flow cytometry by measurements of forward and side scatter, CD138/CD38/CD45 and PI staining. Cells will be resuspended in stem span H3000 defined serum free medium and aliquoted to FACS tubes.

To one set of tubes, 500 μM LY294002 (inhibitor of PI3K) or solvent control will be added and incubated at 370°C for 30 min. By comparing with the solvent control we can establish whether constitutive activation of AKT. To second set of tubes will be activated with 50 ng/ml IGF-1 or solvent for 12 minutes. As a control the cells will also be stimulated with 50ng/ml IL-6 and the cells will be labeled with anti-pERK and anti-pSTAT3, this will demonstrate that signaling is intact in the cells as this pathway should not be affected by Linsitinib. The cells will then be fixed and permeabilized using our recently developed protocol that optimizes the preservation of phenotypic features and intracellular phosphorylated epitopes. Briefly, samples are removed from the dry bath, fixed by adding methanol-free formaldehyde to give a final concentration of 4% for 10 min. The cells will be washed in cold wash buffer and then resuspended in 1 ml of cold freezing medium consisting of 10% glycerol, 20% fetal bovine serum in RPMI tissue culture medium, and stored at –200C and patched for antibody staining so that paired samples are analyzed together.

For intracellular phospho-specific antibody staining, thawed cells will be washed and 0.5 million cell aliquots will be resuspended and permeablilized in 1 ml of 50% methanol in 0.9% NaCl and incubated on ice for 10 min. Cells will then be washed and the cell pellet resuspended and labeled with an antibody mix containing primary conjugated phospho-

specific antibodies described above and incubated at room temperature for 15 min. Approximately 10,000 ungated events will be collected for each sample on a LSR II flow cytometer.

12-4.1 Biologic Sample Collection, processing, storage and shipping

Refer to the following instructions on collection, handling, processing, storage and shipping of specimens for pharmacokinetic as well as bone marrow aspirate samples for pharmacodynamics and pharmacogenomics.

1) Ensure that consent has been obtained from participant

2) Collect the FIRST 2-5 ml of bone marrow in heparinized tubes (aliquot into 2 tubes). The second pull should be sent to the local pathology lab if indicated. Check expiry dates on tubes before use.

3) Label tubes as marrow or peripheral blood and include the subjects study number and indicate whether these are screening, cycle 1 day 21 or progression samples

4) Complete the sample collection log sheet to be included in shipment package

5) Keep the foam refrigerant pack at room temperature for at least 4 hours (preferred) prior to the expected time of packaging otherwise place the foam refrigerant pack at the bottom of the shipping box, place pads on top before placing samples to protect the samples from freezing.

6) Put the labeled tubes inside the biohazard shipping bags and place samples on top of the pads along with the sample collection log sheet

7) Ship specimens to:

Zhi Hua Li
Princess Margaret Cancer Centre
610 University Ave, Rm 10-721
Toronto, ON
CANADA
M5G 2M9
Phone 416-946-4501 ext 6486
zli@uhnres.utoronto.ca

Note: all samples should be shipped by priority shipment on the day of collection on Monday to Thursday only. Please also do not ship for arrival on Canadian Holidays . Please e-mail Zhi Hua Li to notify her of shipment and provide her with the tracking number.

A Phase 1/2 Trial of Linsitinib (OSI-906) in Combination with Bortezomib and Dexamethasone for the Treatment of Relapsed or Relapsed/Refractory Multiple Myeloma

Bone Marrow (BM) and Peripheral Blood (BP) Identification and Processing Documentation *

Subject number: _____ Principal Investigator: _____

Subject Initials: _____

Indicate:

Screening Sample ☐

Cycle 1 Day 21 ☐

Time of Relapse ☐

	Date (dd-mmm-yy)	Time (24 hr clock)
Linsitinib dosed (only for C1 Day 21)		
BM samples taken		
PB samples taken		
Samples shipped		

Shipped by: _____ on _____ Signature: _____
(Print Name + Title) (dd-mmm-yy)

Received by: _____ Signature: _____
(Print Name + Title)

1. Ensure samples are in an insulated package with refrigerant pack and shipped via overnight courier.
   a. IATA guidelines should be followed for shipping of dangerous goods.
   b. Customs Declaration Form should be included when shipping across Canadian border (indicate $1 value).

2. NOTIFY UHN via email the DAY OF shipment as follows:
   Email: zli@uhnres.utoronto.ca Tel: (416) 946-4501 ext 6486
   Ship to:
   Zhihua Li
   Princess Margaret Cancer Centre
   610 University Ave. 10-721
   Toronto, Canada M5G 2M9

Appendix 12-5 IMWG Response Criteria

Response categories include sCR, CR, nCR, VGPR, PR, SD, and PD. In addition, minimal response (MR) will be evaluated as an alternate response.

Response	*IMWG criteria* [32,34]
sCR	CR as defined below plus: • normal FLC ratio and • absence of clonal cells in bone marrow by immunohistochemistry or 2 – 4 color flow cytometry
CR	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow. • In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
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. • In patients with only FLC disease, >90% decrease in the difference between involved and uninvolved FLC levels is required.
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,[3] 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
Stable Disease	• Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive disease	• Increase of ≥ 25% from lowest response value in any one of the following: • Serum M-component (the absolute increase must be ≥ 0.5 g/dL)[4] and/or • Urine M-component (the absolute increase must be ≥ 200 mg/24 h) and/or • Only in patients without measurable serum and urine M-protein, the difference between involved and uninvolved FLC levels. The absolute

	increase must be > 10 mg/dL • Only in patients without measurable serum and urine M-protein and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥ 10%) • 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) that can be attributed solely to the plasma cell proliferative disorder

All response categories (CR, sCR, VGPR, PR, and PD) require two consecutive assessments made at any time before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥ I gm/dl are sufficient to define response if starting M-component is ≥ 5 g/dl.

IMWG clarification for coding PD: Clarified that Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels. Clarified that 25% increase refers to M protein, FLC, and bone marrow results and does not refer to bone lesions, soft tissue plasmacytomas or hypercalcemia. Note the lowest response value does not need to be a confirmed value.

Additional response criteria for specific disease states

Minor response in patients with relapsed and refractory myeloma adapted from the EMBT criteria[3]	≥ 25% but < 49% reduction of serum M protein *and* reduction in 24 hour urine M protein by 50 – 89%, which still exceeds 200 mg/24hrs. In addition to above; if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required No increase in size or number of lytic bone lesions (development of compression fractures does not exclude response)
Immunophenotypic CR	Stringent CR plus Absence of phenotypic abarrent PC (clonal) in bone marrow with a minimum of one million of total BM cells analyzed by miltiparamtric flow cytometry (with ≥4 colors)
Molecular CR	Stringent CR plus negative ASO-PCR (sensitivity 10^{-5})

Appendix 12-6 Drugs that Affect the QTc Interval and those known to cause Torsades de Pointes

EXCLUDED CONCOMITANT MEDICATIONS			
Compound	**Compound Half Life**	**Washout Period - HOURS**	**Washout Period - DAYS**
Amiodarone	58 days (15-142) 36 days (active metabolite)		180
Arsenic trioxide	Not characterized; estimated at 90 hours; Anderson et al; Cancer J 2002 8(1):12-15		21
Bepridil	42 hr (26-64)		10
Chloroquine	Prolonged (days to weeks)		28
Chlorpromazine	30 +/- 7 hours		7
Cisapride	6 – 12 hour, up to 20 hour	60	
Clarithromycin	Non linear PK3-4 hr (250mg Q12) 5-7 hr (500mg Q12)	36	
Disopyramide	6.7 hr (4-10)	36	
Dofetilide	10 hr	48	
Domperidone	7-8 hr	48	
Droperidol	2.2 hours	10	
Erythromycin	Each salt form has different Half life		7
Halofantrine	6-10 days (variable among individual)		45
Haloperidol	18 +/-5 hr		5
Ibutilide	6 hours (range 2-12)	36	
Levomethadyl	Multiple compartment PK with active metabolite. 2.6 day for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM		20
Mesoridazine	24-48 hours (animal study)		10
Methadone	15-30 hours		7
Pentamidine	6.4+/-1.3 hours	36	
Pimozide	55 hours		10
Procainamide	3-4 hour for PA and NAPA (active metabolite)	24	
Quinidine	6-8 hours in adult; 3-4 hours in children	36	
Sotalol	12 hours	72	
Sparfloxacin	20 hours (16-30)		4
Thioridazine	20-40 hours		7

Drugs With a Known Risk of Torsades de Pointes (Excluded Medications)			
amiodarone	clarithromycin	haloperidol	probucol
arsenic trioxide	disopyramide	ibutilide	procainamide
astemizole	dofetilide	levomethadyl	quinidine
bepridil	domperidone	mesoridazine	sotalol
chloroquine	droperidol	methadone	sparfloxacin
chlorpromazine	erythromycin	pentamidine	terfenadine
cisapride	halofantrine	pimozide	thioridazine

Refer to the following website for a complete list:

http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm# -

Appendix 12-7 The Stages of Heart Failure - NYHA Classification

Class	**Patient Symptoms**
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Appendix: 12 -8 Guidance for Hyperglycemia and Hypoglycemia Management and Reporting Algorithm

This algorithm may be used to manage hyperglycemia resulting from Linsitinib. These guidelines are to be used as advice only and should not replace clinical assessment or protocol instructions.

1. **If fasting glucose > ULN and ≤ 8.9 mmol/L (160 mg/dL) (grade 1)**
   - Continue Linsitinib
   - Consider increase in glucose monitoring frequency
2. **If fasting glucose is > 8.9 mmol/L (160 mg/dL) and ≤ 13.9 mmol/L (250 mg/dL) (grade 2)**
   - Advise the patient to continue Linsitinib and have the patient stay hydrated.
   - Repeat fasting glucose after 4-6 hours
     - → If glucose ≤ 8.9 mmol/L (160 mg/dL):
       - Continue Linsitinib
       - Repeat fasting glucose after 24 hours
     - → If glucose > 13.9 mmol/L (250 mg/dL):
       - Stop Linsitinib and go to #3
     - → If glucose > 8.9 mmol/L (160 mg/dL) and ≤ 13.9 mmol/L (250 mg/dL):
       - Patient is asymptomatic:
         - Continue Linsitinib
         - Repeat fasting glucose after 24 hours.
       - Patient is symptomatic:
         - Stop Linsitinib
         - Repeat fasting glucose after 24 hours
           - If glucose ≤ 8.9 mmol/L (160 mg/dL):
             - Reintroduce Linsitinib at the same or the next lower dose
             - Repeat fasting glucose after 24 hours
           - If glucose > 13.9 mmol/L (250 mg/dl):
             - Stop Linsitinib and go to #3
           - If glucose > 8.9 mmol/L (160 mg/dL) and ≤ 13.9 mmol/L (250 mg/dL):
             - Consider dose reduction to the next lower dose or addition of metformin
             - Repeat fasting glucose after 24 hours
3. **If the fasting glucose is > 13.9 mmol/L (250 mg/dL) (grade 3 & 4)**
   - Advise the patient to stop taking Linsitinib and go to the hospital or emergency room for monitoring*

- Repeat fasting glucose at minimum every 2 hours, until glucose ≤ 13.9 mmol/L (250 mg/dL); then at minimum every 6 hours, until ≤ 8.9 mmol/L (160 mg/dL)
- Check ketones and electrolytes once every 24 hours until normal or return to baseline
- Start normal saline with aggressive hydration. Replace potassium, phosphate, bicarbonate, etc., as appropriate.
- Consider administration of metformin 500 mg BID if glucose is still elevated ≥ 24 hours after Linsitinib dosing was interrupted
- Consider insulin if the patient is experiencing diabetic ketoacidosis or if hyperglycemia persists despite Linsitinib interruption and metformin is ineffective.
  - → Administer insulin with caution after discussion with the Principal Investigator
  - → Avoid long-acting insulin and large boluses of short-acting insulin
  - → Inform study Medical Monitor
  - → Monitor for rebound hypoglycemia due to the short duration of action of Linsitinib

* If there are no available beds in the site hospital, advise the patient to go to the nearest emergency room. Contact the emergency room physician to provide background regarding the patient and clinical trial. Fax these guidelines to him/her with the provison that the guidelines are to be used as advice only and should not replace clinical assessment.

Recommended Hypoglycemia Management and Reporting

The investigator must follow local country and institution specific guidelines in the event hypoglycemia is experienced by a patient on treatment with Linsitinib in this study. Consultation with the appropriate specialist (e.g. Endocrinologist, etc.) is recommended. Patients on treatment with Linsitinib who demonstrate hypoglycemia must have their blood glucose levels and any associated symptoms closely monitored until blood glucose values return to normal.

Below is meant as guidance to the investigator and is not to supersede any local country or institution specific guidelines in the event they are more stringent in the management of hypoglycemia.

Grade 1 (glucose <ULN-55mg/dL or 3.1 mmol/L)

- Repeat glucose value. If second level is above 55mg/dL or 3.1 mmol/L, continue dosing Linsitinib.
- If below 55mg/dL or 3.1 mmol/L see algorithm below
- Consider increase in glucose monitoring frequency

Grade 2 (Glucose <55-40 mg/dL or 3.1-2.2 mmol/L)

- Repeat glucose level then advise the patient to drink a glass of orange juice or other drink containing glucose and discontinue Linsitinib. If the patient is taking oral hypoglycemics these should be held as well.
- After first documented episode, monitor glucose every 24 hrs until it returns to normal on 2 consecutive days
- Once glucose levels return to normal in less than 1 hour resume Linsitinib at the current dose, otherwise (more than 1 hour) decrease dose of Linsitinib by one level and resume dosing
- If the subject has repeat episode of Grade 2 hypoglycemia, decrease dose by another level and repeat glucose monitoring every 24 hrs until it returns to normal on 2 consecutive days
- After 3rd episode of Grade 2 hypoglycemia permanently discontinue study drug

Grade 3 (glucose <40-30 mg/dL or 2.2-1.7 mmol/L) –

- Repeat glucose level then advise the patient to drink a glass of orange juice or other drink containing glucose and discontinue Linsitinib, if the patient is taking oral hypoglycemics these should be held as well.
- After first documented episode, monitor glucose every 24 hrs until it returns to normal on 2 consecutive days
- Inform the study medical monitor
- Once glucose levels have returned to normal decrease dose of Linsitinib by one level and resume dosing

- If the subject has repeat episode of Grade 3 or 4 hypoglycemia permanently discontinue study drug

Grade 4 (Glucose <30 mg/dL or <1.7 mmol/L) –

- Advise the patient to drink a glass of orange juice or other drink containing glucose and stop taking Linsitinib and go to the hospital or emergency room for monitoring*
- Repeat glucose value then advise the patient to drink a glass of orange juice or other drink containing glucose and permanently discontinue Linsitinib
- Inform the study medical monitor
- Continue to monitor glucose every 24 hrs until it returns to normal on 2 consecutive days

*if there are no available beds in the site hospital, advise the patient to go to the nearest emergency room. Contact the emergency room physician to provide background regarding the patient and clinical trial. Fax these guidelines to him/her with the provison that the guidelines are to be used as advice only and should not replace clinical assessment.

Any hypoglycemia event of grade 4 or higher per NCI CTCAE v43.02, regardless of the presence or absence of symptoms and causality to study drug, must be reported as a serious adverse event (SAE) within 24 hours (see **Section 7.6**). Hypoglycemia events of grade 1 to grade 3 per NCI CTCAE v43.02 must be recorded as an adverse event (AE) on the appropriate CRF page, and if the event meets any other criteria of seriousness must be reported as an SAE. All events of hypoglycemia, regardless of causality or grading, will be reviewed by APGD Product Safety and Pharmacovigilance on a regular basis. In addition, the Data Monitoring Committee (DMC) will also have access to SAE and AE data relative to blood glucose during their regular safety review.

Appendix:12-9 Strong/Moderate CYP1A2 Inhibitors and Inducers

CYP1A2 Inhibitors	CYP1A2 Inducers
Excluded ciprofloxacin fluvoxamine verapamil	beta-naphthoflavone insulin methylcholanthrene modafinil nafcillin omeprazole tobacco

Strong inhibitors of CYP1A2 are prohibited. CYP1A2 inducers may be continued but should be used with caution.

Refer to the following website for a complete list:
http://medicine.iupui.edu/flockhart/table.htm

Appendix: 12-10 Excluded Insulinotropic/Insulin Drugs

Patients on insulin or insulinotropic medications are prohibited from being enrolled in this study and concurrent use of these drugs with Linsitinib is prohibited. The list of excluded insulinotropic/insulin drugs are presented below:

Excluded Insulinotropic/Insulin Drugs
All of the following drugs are excluded, whether given alone or in combination: • Insulin (any form); • Incretin mimetics (eg, exenatide).

Sulfonylurea and meglitinides (eg, nateglinide, repaglinide); are prohibited to be added on after starting on study but patients on these agents that are stable for 8 weeks are allowed on study and can continue on these agents. If hypoglyemia occurs then they should be discontinued. Metformin may be used with caution.

Appendix 12-11 FACT/GOG Neurotoxicity Questionnaire

FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
I have numbness or tingling in my hands……	0	1	2	3	4
I have numbness or tingling in my feet……	0	1	2	3	4
I feel discomfort in my hands…….	0	1	2	3	4
I feel discomfort in my feet……	0	1	2	3	4
I have joint pain or muscle cramps……	0	1	2	3	4
I feel weak all over……	0	1	2	3	4
I have trouble hearing……	0	1	2	3	4
I get a ringing or buzzing in my ears……	0	1	2	3	4
I have trouble buttoning buttons……	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand……	0	1	2	3	4
I have trouble walking……	0	1	2	3	4

Sources: Cella DF, Tulsky DS, Gray G, Sarafian B, Lloyd S, Linn E, et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. *J Clin Oncol* 1993;11(3):570-79.

Appendix 12-12 Diaries

12-12.1 Glucose/Ketone Diary

Subject Initials: _____ Subject #: _____
Cycle #:_____

Day	Date Day Month Year	Time of measurement		Glucose level (mmol/L)	Urinary Ketones
e.g: **1**	**30 JUN 11**	Pre- Breakfast	**07:30**	**4.9**	**Absent**
		Pre-Evening Meal	**16:00**	**5.5**	**Absent**
		Pre- Breakfast	:		
		Pre-Evening Meal	:		
		Pre- Breakfast	:		
		Pre-Evening Meal	:		
		Pre- Breakfast	:		
		Pre-Evening Meal	:		
		Pre- Breakfast	:		
		Pre-Evening Meal	:		
		Pre- Breakfast	:		
		Pre-Evening Meal	:		
		Pre- Breakfast	:		
		Pre-Evening Meal	:		
		Pre- Breakfast	:		
		Pre-Evening Meal	:		

12-12.2 Study Drug Diary

Once Weekly Velcade Schedule

Protocol #	Subject #	Subject Initials	Cycle #	Cycle Start Date (mm/dd/yyyy)	Linsitinib Dose

Dexamethasone Dose: _____

- Please complete this diary on a daily basis. Enter the time (AM/PM) you take your dexamethasone in the appropriate box. If you forget to take your scheduled dose, leave the box blank, but remember to take your next dose at the regularly scheduled time.
- Shaded boxes represent the days when you do not take your prescribed dose of dexamethasone.

Week 1 Date: _____ month/day		**Day 1** mm/dd	**Day 2** mm/dd	**Day 3** mm/dd	**Day 4** mm/dd	**Day 5** mm/dd	**Day 6** mm/dd	**Day 7** mm/dd
Time								
Dexamethasone		:						
Linsitinib	**AM**	:	:	:	:	:	:	:
	PM	:	:	:	:	:	:	:

Week 2 Date: _____ month/day		**Day 8** mm/dd	**Day 9** mm/dd	**Day 10** mm/dd	**Day 11** mm/dd	**Day 12** mm/dd	**Day 13** mm/dd	**Day 14** mm/dd
Time								
Dexamethasone		:						
Linsitinib	**AM**	:	:	:	:	:	:	:
	PM	:	:	:	:	:	:	:

Week 3 Date:		**Day 15** _____ month/day	**Day 16** mm/dd	**Day 17** mm/dd	**Day 18** mm/dd	**Day 19** mm/dd	**Day 20** mm/dd	**Day 21** mm/dd
Dexamethasone		Time :						
Linsitinib	**AM**	:	:	:	:	:	:	:
	PM	:	:	:	:	:	:	:

Week 4 Date:		**Day 22** _____ month/day	**Day 23** mm/dd	**Day 24** mm/dd	**Day 25** mm/dd	**Day 26** mm/dd	**Day 27** mm/dd	**Day 28** mm/dd
		Time						
Dexamethasone		:						
Linsitinib	**AM**	:	:	:	:	:	:	:
	PM	:	:	:	:	:	:	:

Week 5 Date:		**Day 29** _____ month/day	**Day 30** _____ mm/dd	**Day 31** _____ mm/dd	**Day 32** _____ mm/dd	**Day 33** _____ mm/dd	**Day 34** _____ mm/dd	**Day 35** _____ mm/dd
Dexamethasone								
Linsitinib	**AM**	:	:	:	:	:	:	:
	PM	:	:	:	:	:	:	:

Twice Weekly Velcade Schedule

Protocol #	Subject #	Subject Initials	Cycle #	Cycle Start Date (mm/dd/yyyy)	Linsitinib Dose

Dexamethasone Dose: _____

- Please complete this diary on a daily basis. Enter the time (AM/PM) you take your dexamethasone in the appropriate box. If you forget to take your scheduled dose, leave the box blank, but remember to take your next dose at the regularly scheduled time.
- Shaded boxes represent the days when you do not take your prescribed dose of dexamethasone.

Week 1 Date:		**Day 1** _____ month/day	**Day 2** _____ mm/dd	**Day 3** _____ mm/dd	**Day 4** _____ mm/dd	**Day 5** _____ mm/dd	**Day 6** _____ mm/dd	**Day 7** _____ mm/dd
Dexamethasone		Time :			Time :			
Linsitinib(	**AM**	:	:	:	:	:	:	:
	PM	:	:	:	:	:	:	:
Week 2 Date:		**Day 8** _____ month/day	**Day 9** _____ mm/dd	**Day 10** _____ mm/dd	**Day 11** _____ mm/dd	**Day 12** _____ mm/dd	**Day 13** _____ mm/dd	**Day 14** _____ mm/dd
Dexamethasone		Time :			Time :			
Linsitinib	**AM**	:	:	:	:	:	:	:
	PM	:	:	:	:	:	:	:
Week 3 Date:		**Day 15** _____ month/day	**Day 16** _____ mm/dd	**Day 17** _____ mm/dd	**Day 18** _____ mm/dd	**Day 19** _____ mm/dd	**Day 20** _____ mm/dd	**Day 21** _____ mm/dd
Dexamethasone								
Linsitinib	**AM**	:	:	:	:	:	:	:
	PM	:	:	:	:	:	:	:

Appendix 12-13 Serum Calcium Correction Formula

Serum Calcium Corrected for Albumin

As calcium binds to albumin and only the unbound (free) calcium is biologically active, the serum calcium level must be adjusted for abnormal albumin levels ("corrected serum calcium"). The formula[1] for adjustment is given below.

If calcium is expressed in mg/dL and albumin is expressed in g/dL:

Corrected calcium (mg/dL) =

Serum calcium (mg/dL) + 0.98*(4 - serum albumin [g/dL])

If calcium is expressed in mmol/L and albumin is expressed in g/L:

Corrected calcium (mmol/L) =

Serum calcium (mmol/L) + 0.0246* (40 – serum albumin [g/L])

Measurement of free ionized calcium is an acceptable alternative to corrected serum calcium for determination of hypercalcemia. Free ionized calcium levels greater than the upper limit of normal (local laboratory reference ranges) are considered to be hypercalcemic for this study.

Reference:

1. Payne RB, Little AJ, Williams RB, Milner JR. Interpretation of serum calcium levels in patients with abnormal serum proteins. Br Med J 1973;4:643–646.