A Phase II, Open-Label, Pharmacokinetic Study of Propylene Glycol-Free Melphalan HCl for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation (IIS-MEL-MCW-001)

Investigational Product:	Melphalan Hydrochloride (HCl) for Injection (Propylene Glycol Free)
Indication Studied:	Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation
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This is an investigator-initiated study. Parameswaran Hari, the principal investigator who may also be referred to as the sponsor-investigator, is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

Protocol Approval Signature Page

Protocol: IIS-MEL-MCW-001

Protocol Title: A Phase II, Open-Label, Pharmacokinetic Study of Propylene Glycol-Free Melphalan HCl for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation

_____ _____

Date

Clinical Study Protocol Agreement

Protocol IIS-MEL-MCW-001

Protocol Title: A Phase II, Open-Label, Pharmacokinetic Study of Propylene Glycol-Free Melphalan HCl for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation

I have carefully read this protocol and agree that it contains all of the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, International Conference on Harmonization Guidelines for Good Clinical Practices, and all applicable regulatory requirements.

Investigator's Signature Date

Name (Print)

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1 SYNOPSIS

Protocol Number	IIS-MEL-MCW-001
Title	A Phase II, Open-Label, Pharmacokinetic Study of Propylene Glycol-Free Melphalan HCl for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation
Investigators/ Study Sites	This is a single-center study that will be conducted at the Medical College of Wisconsin.
Study Duration and Dates	This study is expected to start October 2015 and will take approximately six months to enroll 24 patients.
Phase	Phase II
Objectives	**Primary** To assess the pharmacokinetics (PK) of Melphalan HCl for injection (propylene glycol free) at a single-day dose of 200 mg/m^2 in multiple myeloma (MM) patients undergoing autologous stem cell transplant (ASCT). **Secondary** 1. To determine complete response (CR) rates at day 100 of MM patients receiving Melphalan HCl for injection (propylene glycol free) at a single dose of 200 mg/m^2. 2. To determine the TRM, myeloablation and subsequent neutrophil engraftment in MM patients receiving high-dose Melphalan HCl for injection (propylene glycol free) followed by ASCT. 3. To describe the overall safety of Melphalan HCl for injection (propylene glycol free) at a single dose of 200 mg/ m^2.
Number of Patients	Twenty-four patients, who have symptomatic MM (per International Working Group Criteria), and qualify for ASCT.
Planned Number of Sites	One (1) (Medical College of Wisconsin)
Study Design	This study will be a single center, open-label study of high-dose Melphalan HCl for injection (propylene glycol free Melphalan) conducted in 24 patients, who have symptomatic MM and qualify for ASCT. There will be three distinct evaluation periods in this trial: a pretreatment period, a study period, and a follow-up period. The specific tests performed during each period are described below.

Study Design (continued)	**Pretreatment Period Evaluations (Days -30 to -3)** The following baseline assessments should be collected within 30 days of dosing with Melphalan HCl for injection (propylene glycol free), after the patient has signed the informed consent: • Medical history and physical examination, including prior MM treatments and the response. • Prior and concomitant medications. • Eastern Cooperative Oncology Group (ECOG) performance status. • Infectious disease testing: Serum titers for cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), hepatitis panel, West Nile Virus (WNV), rapid plasma regain (RPR) for syphilis, human immunodeficiency virus (HIV) and human T-lymphotropic virus (HTLV1) antibodies. • Hematology (CBC with manual differential and reticulocyte count). • Urine analysis • Serum chemistry (sodium, potassium, chloride, magnesium, bicarbonate, glucose, total protein, albumin, calcium, phosphate, uric acid, BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, SGOT, SGPT and creatinine clearance [measured or calculated/estimated]). • Creatinine clearance (calculated/estimated or collected). • Chest X-ray. • Vital signs (systolic and diastolic blood pressures, heart rate, respiration rate and body temperature), including height, weight and body surface area (BSA). • Serum pregnancy test for women of childbearing potential. Women are considered to be of childbearing potential unless they have had no menses for at least 12 months. **Study Period (Day -2 to Day 0)** During the study period, patients will receive 200 mg/m^2 of Melphalan HCl for injection (propylene glycol free) as a one-time infusion on day -2. Blood samples for the pharmacokinetic (PK) evaluation of melphalan will be collected after melphalan dosing (day -2). Following one day of rest after the myeloablative Melphalan conditioning (day -1), patients will receive an autologous graft with a minimum cell dose of 2×10^6 CD34+ cells/kg of patient body weight (day 0). Cryopreservation and thawing of product will be consistent with Foundation for the Accreditation of Cellular Therapy (FACT) standards and local institutional practice. The graft will be infused per institutional protocol. Per institutional autologous transplant protocol guideline, Filgrastim will be administered daily starting day +5 after transplant for patients receiving transplant as in-patient. For outpatient transplantation, per institutional protocol PEG-filgrastrim will be administered on day +1 as a single dose. All patients will receive antiemetics, hydration and infection prophylaxis according to institutional guidelines.

Study Design (continued)	The following PK, efficacy and safety evaluations will be performed at the following time points during the study period: • Ten (10) blood samples at specific time points (see PK assessments) for the PK evaluation will be collected immediately prior to and after receiving Melphalan HCl for injection (propylene glycol free) on day -2. • Vital signs (systolic and diastolic blood pressures, heart rate and respiration rate) will be recorded prior to dosing and hourly during the first four hours after receiving Melphalan. • Physical examination will be performed prior to dosing of Melphalan HCl for injection (propylene glycol free) on day -2. • CBC with differential will be performed prior to dosing of Melphalan on day -2. • Full serum chemistry panel (sodium, potassium, chloride, magnesium, bicarbonate, glucose, total protein, albumin, calcium, phosphate, uric acid, BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, SGOT, SGPT and creatinine clearance [measured or calculated/estimated]) will be performed prior to Melphalan dosing. • Toxicity grading and evaluation for AEs/SAEs according to National Cancer Institute Common Toxicity Criteria for AEs Version 4.0 (CTCAE v4.0) grade will occur during the entire study period. • Concomitant medications will be recorded during the entire study period. **Follow-Up Period (ASCT Day +1 until Day+100)** During the follow-up period, patients will return for daily laboratory tests (hematology and basic serum chemistry) and will be evaluated weekly by their physicians until the engraftment date, with the final end-of-study evaluation occurring up to seven days after engraftment date. During the follow-up period, the following tests will be performed weekly until engraftment (unless otherwise specified) and the data captured in the CRF: • Basic serum chemistry panel daily until neutrophil engraftment. • CBC with manual differential daily until neutrophil engraftment. • Physical examination. • Vital signs (systolic and diastolic blood pressures, heart rate, respiration rate and body temperature) and body weight. • Full serum chemistry panel (sodium, potassium, chloride, magnesium, bicarbonate, glucose, total protein, albumin, calcium, phosphate, uric acid, BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, SGOT, SGPT and creatinine clearance [measured or calculated/estimated]) at least twice weekly until day 21 or engraftment, whichever is later. • Multiple myeloma panel • Bone marrow biopsy • Toxicity grading and evaluation for AEs/SAEs according to NCI-CTC AE Version 4.0 will occur until study discharge or AE follow-up is complete. • Concomitant medications.

Study Population	**Study Population and Main Criteria for Inclusion/Exclusion** Inclusion • Patients with symptomatic MM requiring treatment at diagnosis or anytime thereafter. • Patients with MM, who qualify for ASCT therapy and have received pretransplant therapy for transplantation. • Adult patients (≥18 years of age) meeting institutional criteria to receive a total melphalan dose of 200 mg/m^2 as a conditioning regimen, as approved by institutional PI. • Patients with an adequate autologous graft, which is defined as an unmanipulated, cryopreserved, peripheral blood stem cell graft containing at least 2 × 10^6 CD34+ cells/kg, based on patient's actual weight. • Patients with adequate organ function as measured by: – Cardiac: Left ventricular ejection fraction at rest >40% (documented within 30 days prior to day -3). – Hepatic: Bilirubin <2 × the upper limit of normal (ULN) and ALT/AST <3 × ULN. – Renal: Creatinine clearance >40 mL/min (measured or calculated/estimated). – Pulmonary: Adjusted DLCO, FEV_1, FVC ≥50% of predicted value (corrected for Hgb) (documented within 30 days prior to day -3) Exclusion • Patients with systemic AL amyloidosis. • ECOG performance status ≥2. • Patients with uncontrolled hypertension. • Patients with an active bacterial, viral or fungal infection. • Patients with prior malignancies, except resected basal cell carcinoma or treated cervical carcinoma *in situ*. Cancer treated with curative intent >5 years previously will be allowed. • Female patients who are pregnant (positive ß-HCG) or breastfeeding.

Study Population	• Female patients of childbearing potential, who are unwilling to use adequate contraceptive techniques during and for one month following study treatment with Melphalan HCl for injection (propylene glycol free). • Patients seropositive for HIV. • Concurrent clinical trials for post-transplant therapy of myeloma are permitted provided such studies do not involve conditioning therapy. • Patients who are unwilling to provide informed consent. • Patients who are hypersensitive or intolerant to any component of the study drug formulation.
Study Treatments	During the study period, patients will receive 200 mg/m^2 of Melphalan HCl for injection (propylene glycol free) on day -2 prior to ASCT. Melphalan HCl for injection (propylene glycol free) will be diluted with normal saline to a concentration of no greater than 2 mg/mL and infused over 30 minutes via a central venous catheter. For the BSA calculation, actual body weight should be used for patients who weigh less than or between 100 and 130% of their ideal body weight (IBW). For patients who weigh more than 130% of their IBW, BSA should be calculated based on adjusted body weight.
Pharmacokinetic Assessments	Seven mL venous blood samples for the PK analysis of melphalan will be withdrawn through an indwelling peripheral intravenous cannula at 0 (predose), 10, 20, 30, 60, 90, 120, 180, 240 and 360 minutes (±5 minutes) after the completion of infusion. The predose blood sample will be collected within 60 minutes prior to the dose of Melphalan HCl for injection (propylene glycol free). These blood samples will be used to measure concentrations of total melphalan. PK evaluation will be based on the determination of the following parameters for total melphalan, including (but not limited to): AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, and k_{el}. (Blood samples for PK analysis should not be drawn from the same IV line used to administer the melphalan.)

Efficacy Assessments	The efficacy end points collected are rates of myeloablation, engraftment and myeloma response. Collection of hematology parameters (RBC, hemoglobin, hematocrit, platelet count, WBC with manual differential and reticulocyte count) daily until engraftment will be used to determine these using the following definitions: Myeloablation is defined as any one of the following: • ANC < 0.5×10^9/L. • Platelet count < 20,000/mm^3. The first of two consecutive days for which cell counts drop below these cut-off levels will be recorded as the myeloablation date. Engraftment: ANC recovery is defined as an absolute neutrophil count (ANC) of ≥ 0.5 x 10^9 /L (500/mm3) for three consecutive laboratory values obtained on different days. Date of ANC recovery is the date of the first of three consecutive laboratory values where the ANC is ≥ 0.5 x 10^9 /L. Platelet recovery is reported when the recipient's platelet count is ≥ 20 x 10^9 /L seven days after platelet transfusion and is maintained for three consecutive lab values obtained on different days. International Myeloma Working Group-defined uniform response criteria will be used to assess myeloma response at day 100.
Safety Assessments	Safety measures collected during the **Pretreatment Period (Day -30 to Day -3)** will include: physical examination, ECOG performance status, infectious disease testing (serum titers for CMV, HSV, EBV, WNV, RPR for syphilis, hepatitis panel, and HIV and HTLV1 antibodies), clinical laboratory tests (hematology, serum chemistry), chest X-ray, vital signs (including height, weight and BSA). Safety measures collected during the **Study Period (Day -3 to Day 0)** will include: SAEs, AEs, vital signs, clinical laboratory assessments (hematology, serum chemistry), physical examination findings, ECOG performance status. These tests will be performed prior to administration of Melphalan HCl for injection (propylene glycol free) on day -2. Safety measures collected during the **Follow-Up Period (Day + 1 to Day +100)** will include: physical examination findings, ECOG performance status, AEs/SAEs, vital signs (including body weight, hematology, serum chemistry and urinalysis.

Statistical Procedures	**Analysis Populations** The PK evaluable population is defined as all patients who completed dosing and adequate subsequent PK blood draws for the calculation of AUC and C_{max}. PK analyses will be performed on the evaluable population. The population is defined as all patients who are enrolled and received study drug. All safety and efficacy analyses will be performed on patients who received study drug. **Sample Size Justification** A sample size of 24 patients is planned for this study. The mean ± SD results of AUC0-t and Cmax of 100 mg/m^2 Melphalan dose from a previously conducted study were 376,577±93,401 min·ng/mL and 4374 ± 1050 ng/mL respectively. Twenty-four patients will provide ±10% width for the 90% CI around the point estimates of AUC0-t and Cmax in this study. A study size of 24 patients would also provide for a 95% confidence interval having a width of ±20% to estimate an AE incidence rate for common AEs occurring at a frequency of 25 -30%. **Pharmacokinetic Analyses** PK parameters will be determined by nonparametric PK data analysis techniques. PK parameters computed from plasma drug concentration-time data will include, but not necessarily be limited to, the following: • C_{max} derived from the individual raw data. • t_{max} derived from the individual raw data. • Apparent terminal first-order elimination rate constant (k_{el}). • Apparent elimination $t_{1/2.}$ • Area under the plasma concentration time curve to the last measurable time point (AUC_{0-t}) calculated by the trapezoidal rule. • Area under the plasma concentration time curve to infinity ($AUC_{0-\infty}$): AUC_{0-t} + area under the plasma concentration time curve from the last measurable time point extrapolated to infinity determined from the concentration at the last measurable time point divided by the k_{el}

Statistical Procedures (continued)	The plasma concentrations and PK parameters for Melphalan HCl for injection (propylene glycol free) will be summarized using descriptive statistics: arithmetic means, standard deviations and coefficients of variation will be calculated for all PK parameters and geometric means calculated for AUC_{0-t}, $AUC_{0-\infty}$ and $C_{max.}$. **Efficacy Analyses** Rates of TRM, myeloablation and engraftment will be summarized descriptively. Efficacy analysis will be performed on the enrolled patients. Time to myeloablation and engraftment will be summarized using Kaplan-Meier estimates. **Myeloma Response Analyses** Myeloma specific response for each patient will be evaluated between days 90 – 100 after transplant, using uniform response criteria (IMWG). Responses for the patients will be summarized, using response rates stratified by depth of response. **Safety Analyses** Safety analyses will be performed on the population. These include any patient who received at least one dose of study medication. The following safety analyses will be performed for this study and will include all collected data through the final study visit: • Incidence of all treatment-emergent AEs and drug-related treatment-emergent AEs by system organ class and preferred term. • Incidence of all treatment-emergent AEs by system organ class, preferred term and severity. • Incidence of all treatment-emergent AEs and treatment-emergent drug-related AEs by CTCAE v4.0 grade. • Incidence of treatment-emergent AEs, treatment-emergent drug-related AEs and treatment-emergent CTCAE v4.0 Grade 3 or 4 AEs by preferred term in descending frequency. • Incidence of all AEs that led to discontinuation of study medication. • Incidence of acute propylene glycol toxicities (metabolic acidosis and lactic acidosis). • Incidence of all SAEs and drug-related SAEs, including deaths. • Summary of changes in laboratory parameters from baseline to postdose time points. • Laboratory parameters summarized by CTCAE v4.0 Grade (frequency and shifts). • Summary of vital sign changes in vital signs from baseline to postdose time points.

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ANC	absolute neutrophil count
ANOVA	analysis of variance
ASBMT	American Society for Blood and Marrow Transplantation
ASCT	autologous stem cell transplant
AUC_{0-t}	area under the plasma concentration time curve to the last measurable time point
$AUC_{0-\infty}$	area under the plasma concentration time curve extrapolated to infinity
ß-HCG	beta human chorionic gonadotropin
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
C_{max}	maximum concentration
CFR	Code of Federal Regulations
CMV	cytomegalovirus
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
DLCO	carbon monoxide diffusing capacity
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in one second
FVC	forced expiratory vital capacity
GCP	Good Clinical Practice
HDC	high dose chemotherapy
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HSV	herpes simplex virus
HTLV1	human T-lymphotropic virus

IBW	ideal body weight
ICF	informed consent form
ICH	International Conference on Harmonization
IRB	institutional review board
k_{el}	elimination rate constant
LD_{50}	median lethal dose
LDH	lactic dehydrogenase
LV	left ventricular
MedDRA	Medical Directory for Regulatory Activities
MM	multiple myeloma
MRI	magnetic resonance imaging
MUGA	multigated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI-CTC	National Cancer Institute Common Toxicity Criteria
PK	pharmacokinetic
RBC	red blood cell
RPR	rapid plasma regain
SAE	serious adverse event
SAP	statistical analysis plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
T_{max}	time to maximum concentration
$t_{1/2}$	half life
TBI	total body irradiation
ULN	upper limit of normal
WBC	white blood cell
WNV	West Nile Virus
TRM	Transplant related mortality

3 INTRODUCTION

3.1 Background

Melphalan is an antineoplastic agent formulated for parenteral use as a sterile, nonpyrogenic, freeze-dried powder. It is manufactured by Cardinal Health for GlaxoSmithKline and distributed by Celgene as Alkeran® for injection (Alkeran®). Spectrum Pharmaceuticals, Inc. (Spectrum), developed Melphalan Hydrochloride (HCl) for injection (propylene glycol free), a reformulation of Alkeran® that incorporates the Captisol® brand of β-cyclodextrin sulfobutyl ether and sodium salts (also known as $(SBE)_{7m}$-β-CD) into the freeze-dried product. Captisol® is present to facilitate the use of an aqueous diluent (normal saline) for reconstituting the freeze-dried product instead of the cosolvent diluent necessary for the reconstitution of Alkeran®, and Captisol® improves stability, allowing for longer infusion times.

A major concern with melphalan therapy, other than its intrinsic cytotoxicity and biocompatibility, arises from its marginal solubility and limited chemical stability upon reconstitution and dilution. Cosolvents are used in the marketed two-vial formulation, which is believed to contribute to therapy side effects. The commercially available lyophilized formulation of melphalan is marketed in a single-dose vial that contains melphalan hydrochloride equivalent to 50 mg melphalan and 20 mg povidone. The product is reconstituted with a sterile cosolvent diluent, containing propylene glycol and ethanol, by rapidly injecting 10 mL of diluent directly into the vial of lyophilized powder, and then, shaking immediately and vigorously until a clear solution is obtained. Following these steps exactly is important for proper reconstitution. The resulting solution (at 5 mg/mL) must then be immediately further diluted to a concentration not greater than 0.45 mg/mL with normal saline in order to deliver the proper dose. Intravenous administration (in a minimum of 15 minutes) of the fully diluted product (110 mL) must be completed within 60 minutes of reconstitution due to instability of the solution (a citrate derivative of melphalan can form in as little as 30 minutes). Additionally, upon further dilution with normal saline, nearly 1% of the labeled strength of melphalan hydrolyzes every 10 minutes. Furthermore, reconstituted Alkeran® solutions cannot be refrigerated because a precipitate may form when the solutions are stored at 5 degrees Celsius (ºC).

The solubilizing agent used in intravenous Alkeran® is propylene glycol, which is also used as a solubilizing excipient in other water insoluble drugs. Propylene glycol at high doses has been reported to cause renal dysfunction, hyperosmolality, increased anion gap metabolic acidosis, and sepsis-like syndrome (Zar, 2007; Wilson, 2005; Yaucher, 2003). It has been reported that propylene glycol injected at doses above 69 g/day may produce toxicities. Propylene glycol is metabolized rapidly in the body, so it is also believed that the propylene glycol toxicity is related to intravenous infusion rate. Therefore, the maximum recommended infusion rate of propylene glycol is 2.9 g/h. Propylene glycol in Alkeran® is greater than 6 g per 50 mg Alkeran®. A typical dose of Alkeran® (200 mg/m^2) contains 24 g/m^2 propylene glycol. This dose of Alkeran® would include a propylene glycol dose of about 45 g for a 70-kilogram (154-pound) patient. If this Alkeran® dose is infused into the body for myeloablative conditioning in as little time as 15 minutes, as limited by the product stability after reconstitution, then the propylene glycol infusion rate is very high at 180 g/h, or nearly 60 times faster than the recommended rate.

Melphalan HCl for injection (propylene glycol free) is formulated as a sterile, nonpyrogenic, freeze-dried cake (made from melphalan hydrochloride and containing Captisol® in place of povidone) to be reconstituted initially with normal saline and either used piggyback or further diluted with normal saline for intravenous administration. The substitution of Captisol® in Melphalan HCl for injection (propylene glycol free) for the excipients found in Alkeran® directly overcomes the formulation limitations (such as the final concentration of 0.45 mg/ml for Alkeran) and provides a potentially safer melphalan formulation for administration at the high doses used in the myeloablative conditioning regimens. Moreover, Melphalan HCl for injection (propylene glycol free) has been shown to be stable for 10 to 24 hours once reconstituted. It may be refrigerated (which extends the use time).

3.2 Nonclinical Experience

Melphalan

Spectrum conducted one nonclinical study to support the use of Melphalan HCl for injection (propylene glycol free). The only difference between the Alkeran® for injection formulation and the proposed Melphalan HCl for injection (propylene glycol free) is Captisol®. Therefore, the pharmacokinetics (PK) of melphalan were evaluated following intravenous administration in Sprague-Dawley® rats of a nominal 2 mg/kg melphalan dose prepared in either a Captisol® or non-Captisol® (propylene glycol) formulation. There were no significant differences in the mean whole-blood and plasma AUC profiles or in the urinary excretion of melphalan following intravenous administration, suggesting that the change from a propylene glycol to Captisol® formulation does not affect melphalan PK.

Melphalan is an older drug with a history of clinical use since the 1960s. Approved labeling for both the oral and intravenous formulations of melphalan (Alkeran®) support the relatively low clinical doses of melphalan used in multiple cycles of induction chemotherapy for MM. While Alkeran® for injection has not been approved for high-dose (200 mg/m^2 or 100 mg/m^2/day for two days) conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation, it has been successfully used and is the standard of care in the clinic for this indication. The nonclinical data in the paragraphs below are excerpted from the current Alkeran® labeling.

Melphalan is a bifunctional (interstrand and intrastrand) alkylating agent that is non-cell-cycle specific. Melphalan is actively transported into cells by the high-affinity L-amino acid transport system. It exerts an intracellular cytotoxic effect through the formation of interstrand or intrastrand DNA cross-links or DNA-protein cross-links via the two chlorethyl groups of the molecule (alkylation), which leads to impairment of DNA replication and mitotic division and eventually cell death. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumor cells.

Melphalan acute toxicity following intravenous administration was evaluated in the rat and following oral and intraperitoneal administration in mouse and rat. The intravenous median lethal dose (LD_{50}) was determined to be 5.1 and 6.6 mg/kg in male and female rats, respectively. These doses are equivalent to 30.6 and 39.6 mg/m^2 in the male and female rat, respectively, indicating that in animal studies melphalan cannot be administered at doses high enough to support melphalan high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell

transplantation in humans. Melphalan has been shown to cause chromatid or chromosome damage in humans and was considered to be carcinogenic because chronic administration by intraperitoneal injection produced lymphosarcomas and dose-related increase in lung tumors in mice and peritoneal tumors in rats. Melphalan was embryolethal and teratogenic in rats following oral and intraperitoneal administration. It has been reported that Alkeran® for injection may cause local tissue damage should extravasation occur, and melphalan was determined to be a mild irritant following topical application.

The acute LD_{50} and chronic administration data indicate that nonclinical species demonstrate toxicity consistent with that seen in humans but at lower doses. Nonclinical studies could not be conducted at dose levels equivalent to the anticipated daily human dose of 100 mg/m^2, based on the observed intravenous LD_{50} values of 5.1 and 6.6 mg/kg (equivalent to 30.6 and 39.6 mg/m^2) in male and female rats, respectively. The primary dose-limiting toxicity of therapy relates to the myeloablative pharmacological effect of melphalan — the desired pharmacological activity in the clinical patient population. The high-dose melphalan clinical data found in the public domain support the conduct of well-controlled clinical trials with melphalan for high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with MM.

Captisol®

Captisol® is the major excipient in the Melphalan HCl for injection (propylene glycol free) formulation. There was no mortality or other evidence of toxicity observed in the single-dose intravenous toxicity studies in which 2,000 mg/kg Captisol® was administered over 10 or 20 seconds in the mouse and rat, respectively. In repeat-dose toxicity studies, vacuolation of renal tubular epithelium cells was observed in rats, dogs, and monkeys. This type of vacuolation is commonly seen in animals given substituted ß-cyclodextrins. There was no evidence of degeneration, necrosis or pseudocrystal formation in the epithelial cells at doses ≤1,000 mg/kg/day for one month in rats, ≤1,500 mg/kg/day for one month in dogs or ≤5,600 mg/kg/day for 14 days in monkeys. There was no evidence to suggest a deterioration of renal function, and vacuolation was largely reversible. There was no evidence of mutagenicity and no effects on the reproductive function of rats or rabbits were observed in the studies conducted with Captisol®. In conclusion, intravenous toxicity studies with Captisol® doses as high as 1,000 mg/kg/day (equivalent to 6000 mg/m^2/day) in rats, 1,500 mg/kg/day (equivalent to 30,000 mg/m^2/day) in dogs and 5,600 mg/kg/day (equivalent to 67,200 mg/m^2/day) in monkeys did not produce toxicologically significant findings suggestive of a risk to humans. The recommended dose for the Melphalan HCl for injection (propylene glycol free) is 200 mg/m^2, which is equivalent to 5,400 mg/m^2/day, based on a 70-kilogram patient with a BSA of 1.8 m^2).

3.3 Previous Clinical Experience

Melphalan

Melphalan is an alkylating chemotherapeutic agent that has been used alone or in combination with other drugs in the treatment of MM. For decades, the mainstay of therapy for MM has been oral chemotherapy with melphalan plus prednisone. Subsequently, the discovery that high-dose chemotherapy (HDT), coupled with ASCT, could overcome tumor resistance and prolong

survival compared with conventional chemotherapy led to the routine incorporation of HDT, as part of the front-line treatment of patients early in the disease course or at the time of relapse (Attal, 1996). Treatment regimens have included intravenous infusion of melphalan at doses ranging from 140 to 220 mg/m^2, often combined with total body irradiation (TBI) or other chemotherapeutic agents, followed by stem cell rescue.

During the past 10 years, MM treatment has evolved into a two-stage treatment approach. The first stage consists of induction therapy, consisting of conventional chemotherapy in a variety of combinations (Kyle, 2004). The goal of the first therapy stage, in patients eligible for transplant, is to maximize the number of healthy stem cells that can be collected; therefore, alkylating agents (such as melphalan) are avoided. Following conclusion of the first stage (usually multiple treatment cycles), peripheral blood stem cells are collected from the patient and the second treatment stage is initiated (NCCN, 2015; Kyle, 2004).

The second stage consists of consolidation treatment with HDT, followed by ASCT for selected patients. The most commonly used HDT agent is intravenous melphalan, which is termed a conditioning agent in this context (Bensinger, 2008; Facon, 2007; Niesvizky, 2008). The second stage goal is to maximize myeloablation, while providing ASCT to reduce the hematological toxicity of the conditioning agent. This two-stage HDT-ASCT treatment approach is a Category 1 recommendation by the National Comprehensive Cancer Network (NCCN, 2015). The American Society for Blood and Marrow Transplantation (ASBMT) also recommends the HDT-ASCT approach for newly diagnosed MM patients, based on consensus reached by an expert panel, following an evidence-based literature review (Hahn, 2003, Shah et al 2015). Patients, who are not candidates for transplant due to poor performance status or comorbidities/complications, continue to receive induction agents, as appropriate. This evolution in MM treatment has led to clinically relevant improvements in responses during the last decade (Bensinger, 2008; Kumar, 2008; Kyle, 2008; Pant, 2007).

Because Alkeran® is only approved at lower doses (16 mg/m^2), the data from the Alkeran® label are not always relevant to the use of high-dose melphalan; however, the major toxicities are expected to be similar for both the high- and low-dose uses of melphalan. The major acute toxicities associated with melphalan treatment are related to bone marrow suppression, hypersensitivity reactions, gastrointestinal toxicities, and pulmonary toxicity. The major long-term side toxicities are related to infertility and secondary malignancies (Alkeran® for Injection PI, 2008)

Safety data regarding a single high-dose treatment of melphalan (doses ranging from 140 to 220 mg/m^2), followed by ASCT, are not fully described in the literature, because high-dose melphalan toxicities are well-understood among transplant physicians. A number of studies designed to assess the efficacy of high-dose melphalan, followed by autologous bone marrow transplant or ASCT, have included information regarding dose-limiting toxicities but not necessarily information about common adverse effects. These clinical studies showed that an increasing melphalan dose results in a better response; however, with increasing the dose, there is an increasing incidence and severity of side effects (Moreau, 1999; Kühne, 2007).

Despite blood or marrow stem cell rescue, myelosuppression with neutropenia and thrombocytopenia occur in all patients (Moreau, 1996; Sarosy, 1988). Both the severity and

duration of myelosuppression are dose dependent. Gastrointestinal toxicity is the major nonhematological toxicity of high-dose melphalan and includes mucositis, nausea, vomiting and diarrhea. Although melphalan doesn't appear to be cardiotoxic like other alkylating agents, atrial fibrillation has been reported after high-dose melphalan administration, particularly in elderly patients who are prone to atrial fibrillation. In addition, pulmonary toxicities, such as pulmonary fibrosis, are a rare and late complication of melphalan therapy.

Melphalan HCl for injection (propylene glycol free) has been studied in humans in two studies to date. The Phase II, open-label study was the only one where 200 mg/m^2 dose of Melphalan HCl for injection (propylene glycol free) was administered to MM patients (Hari 2015). This study enrolled 61 MM patients, who received 200 mg/m^2 of CE-Melphalan (100 mg/m^2/day x 2) followed by ASCT. The majority of the subjects were male (57%) with a median age of 62.0 years (range 32-73), and included 56 (92%) subjects receiving upfront AHCT and five (8%) after relapse. Median lines of prior therapy were three (range 2-16). All subjects achieved myeloablation, followed by successful engraftment. Median time to neutrophil engraftment was 12 days postAHCT (range: 10–12); time to platelet engraftment was 13 days (range 10–28). There was no mortality by day 100, and as expected the most common Grade 3 and 4 toxicities were hematologic. Severe mucositis was reported in few patients (Grade 3/4; 10%). At day 100 postAHCT, all patients (100%) had a response with 82% of subjects achieving a >= very good partial response (VGPR) response, including stringent CR in 13%, CR in 8% and VGPR in 61%. Notably, the dosage schema reported did not use the more common approach of a single infusion of melphalan of 200 mg/m2.

Captisol®

Captisol® is currently used in four approved human parenteral products in the United States. Exposure data from FDA-approved package inserts for these products are summarized in *Table 1*.

Table 1. FDA-Approved Drug Products Containing Captisol®						
			Captisol® Concentration		Captisol® Exposure	
Drug Product	Indication	Route	In Drug Product	For Dosing	Maximum Rate of Intravenous Infusion[a]	Maximum Total Daily Dose (Duration)
VFEND® I.V.	Treatment of fungal infections	iv	160 mg/mL (after reconstitution)	80 mg/mL (after dilution)	56 mg/min[b] (over 1–2 h)	192 mg/kg (Day 1), then 128 mg/kg (maintenance dosing[c])
NEXTERONE® Injection	Acute treatment of ventricular arrhythmias	iv	225 mg/mL	6.55 mg/mL	67.5 mg/min (for 10 min; initial loading dose)[d]	68 mg/kg (over first 24 h of therapy, then repeat as needed for up to 3 weeks)
GEODON® Injection	Acute agitation in schizophrenia	im	294 mg/mL (after reconstitution)	294 mg/mL	NA	8.4 mg/kg (NMT 3 days)
ABILIFY® Injection	Acute agitation in schizophrenia or bipolar mania	im	150 mg/mL	150 mg/mL	NA	8.6 mg/kg (Day 1)

[a] = Based on an average patient (e.g., weight = 70 kilogram, BSA = 1.8 m^2).
[b] = Equivalent to 48 mg/kg/h for a 70-kilogram patient.
[c] = Duration of therapy, based on disease severity, recovery from immunosuppression and clinical response.
[d] = Followed by additional infusions at lower rates.
NMT = Not more than.

Based on the concentration of Captisol® contained in these marketed products, the amount of Captisol® contained in the Melphalan HCl for injection (propylene glycol free) is comparable to the amount of Captisol® administered in these approved products on a daily basis. Captisol® has also been administered intravenously to humans in investigational products at infusion rates greater than those expected with Melphalan HCl for injection (propylene glycol free).

3.4 Rationale for Study and Dose Selection

Currently, the higher doses of melphalan being used in ASCT patients are not approved by FDA; however, they have been used off label for this purpose for a number of years. The current commercial formulation of Alkeran® for injection has been used for HDT but has several limitations, based on marginal solubility. These prevent the solution from being administered as a longer infusion and are believed to contribute to therapy side effects. The commercial product must be reconstituted with a sterile diluent that contains propylene glycol, a substance that has been associated with certain side effects. After reconstitution, an impurity (citrate derivative of

melphalan) can develop in less than 30 minutes and, when further diluted, melphalan's potency is lost over time.

The substitution of Captisol® in Melphalan HCl for injection (propylene glycol free) for the excipients found in Alkeran® for injection directly overcomes these formulation limitations. Captisol® is a substituted ß-cyclodextrin that serves as the major functional excipient in Melphalan HCl for injection (propylene glycol free). Captisol® performs as a solubilizing and stabilizing agent by forming reversible complexes with melphalan in the formulation. When the formulation is administered intravenously, the complex rapidly dissociates due to its dilution by blood and the distribution and binding of melphalan to body tissues and blood components.

This study is being conducted as a Phase II, PK study of Melphalan HCl for injection (propylene glycol free) for myeloablative conditioning in MM patients undergoing autologous transplantation. It is anticipated that this study's PK data will be used define the PK-directed dosing for Melphalan HCl for injection (propylene glycol free). There has only been one large-population pharmacokinetic study on melphalan pharmacokinetics in patients with multiple myeloma receiving HDM (Nath 2010). This study used a standard melphalan preparation (Alkeran®) and not the propylene glycol-free product studied in this protocol. Factors that were found to be important determinants of clearance of melphalan included creatinine clearance, fat-free mass and hematocrit. Importantly, total and unbound melphalan exposure had significant associations with melphalan-related transplant toxicity and myeloma response to transplant. Patients, who achieved an overall deep-disease response of CR or VGPR, had significantly ($P < 0.05$) higher unbound AUC than those who did not. There is considerable variability in melphalan pharmacokinetics and current knowledge of its pharmacodynamics is very limited (Shaw 2014). The current study will establish the PK this new melphalan formulation in order to establish a safe and effective conditioning therapy platform.

The doses of study drugs selected for this study (200 mg/m^2 of Melphalan HCl for injection [propylene glycol free] on day -2) was chosen, based on current clinical practice of melphalan (Alkeran®) dosing among transplant physicians. The study drug will be infused over 30 min via a central venous catheter during this study, thus allowing for a PK comparison valid based on current clinical practice.

3.5 Rationale for Autologous Transplant; Myeloablation

Based on published data, 100% of all patients receiving Propylene Glycol-Free Melphalan HCl at a dose of 200 mg/m2 achieve myeloablation (Harr, 2015). In fact myeloablation is universal in patients receiving this drug dose. The reason autologous stem cells are used after this treatment is because irreversible myeloablation follows this dose.

The rationale for autologous transplant itself is to utilize the steep dose-response curve of tumors to cytotoxic therapy, i.e., small increments in dose of drug or radiation markedly increase the number of cancer cells killed. Effective disease control depends on delivering intensive doses of chemotherapy and/or radiation therapy. This intensity often exceeds the tolerance of bone marrow, necessitating restoration of hematopoietic marrow function in patients receiving such high-dose therapy (HDT), to prevent irreversible and fatal myeloablation. This is accomplished by restoring blood production, using autologous ("self") cells (i.e. autologous HCT). Thus,

myeloablation is a side effect of the dose administered and in fact is an undesirable aspect in one sense. Therefore, we do not have lack of myeloablation as a futility measure. In fact, if myeloma control could be achieved without myeloablation, such treatment would not require autologous cell support. Finally, a melphalan product that allows patients to recover with shorter period of myeloablation but with similar anti MM effect, would be a significant improvement, because the shorter myeloablation period will be safer for the patient. (Hari, 2014)

The equivalent bioavailability of standard melphalan and PG free Melphalan has been established and since standard melphalan at 200 mg/m2 causes myeloablation universally, we expect PG free Melphalan to do the same.

4 STUDY OBJECTIVES

4.1 Objectives

4.1.1 Primary Objective

This study's primary objective is to assess the PK of Melphalan HCl for injection (propylene glycol free) when administered as single 200 m/m^2 dose in MM patients undergoing ASCT.

4.1.2 Secondary Objective(s)

This study's secondary objectives are:

- To determine the rates of complete response (CR) at day 100 of MM patients receiving Melphalan HCl for injection (propylene glycol free) at a single dose of 200 mg/m^2.
- To determine the TRM, myeloablation and subsequent neutrophil engraftment in MM patients receiving high-dose Melphalan HCl for injection (propylene glycol free), followed by ASCT.
- To describe the overall safety of Melphalan HCl for injection (propylene glycol free) at a single dose of 200 mg/m^2.

4.2 Study End Points

4.2.1 Primary End Point

This study's primary end point is to define PK data for Melphalan HCl (propylene glycol free) when administered as a single 200 mg/m^2 dose in MM patients undergoing ASCT.

4.2.2 Secondary End Points

4.2.2.1 CR Rates, TRM, Myeloablation and Engraftment

The following efficacy end points will be measured in this trial:

- MM response rates between days 90–100 after ASCT (IMWG Uniform Response Criteria; Appendix I).
- Treatment-related mortality (death within 100 days without relapse).

- Myeloablation rate during the study
- Engraftment rate during the study
- Time to myeloablation
- Time to engraftment

These end points will be measured through collection of hematology parameters (CBC with differential) daily until neutrophil engraftment.

4.2.2.2 Safety Assessments

Safety assessments will include: SAEs, AEs, vital signs, clinical laboratory assessments (hematology, serum chemistry, urinalysis, creatinine clearance, physical examination findings, ECOG performance status).

5 STUDY DESIGN

5.1 Overall Study Design and Plan

This study will be a single center, open-label, study of high-dose Melphalan HCl for injection (propylene glycol free) in 24 patients, who have symptomatic MM and qualify for ASCT.

There will be three distinct evaluation periods in this trial: a pretreatment period, a study period, and a follow-up period.

5.1.1 Pretreatment Period (Day -30 to Day -3)

The pretreatment period will include collection and recording of baseline assessments. The baseline assessments will include physical examination; ECOG performance status; infectious disease testing (serum titers for CMV, HSV, EBV, WNV, RPR for syphilis, hepatitis panel, and HIV and HTLV1 antibodies); clinical laboratory tests (hematology, serum chemistry); chest X-ray; vital signs, including height, weight, and BSA; and any transplant-related tests that ensure that the patient has adequate organ function.

5.1.2 Study Period (Day -2 to Day 0)

During the study period, patients will receive 200 mg/m^2 of Melphalan HCl for injection (propylene glycol free) day -2. Blood samples for PK evaluation will be withdrawn through an indwelling intravenous cannula the day of melphalan dosing (day -2). (Blood samples for PK analysis should not be drawn from the same IV line used to administer the melphalan.)

Following one day of rest after the myeloablative conditioning (day -1), patients will receive an autologous graft with a minimum cell dose of 2×10^6 CD34+ cells/kg of patient body weight (Day 0). Cryopreservation and thawing of product will be consistent with FACT standards and local institutional practice. The graft will be infused per institutional protocol.

During the study period, postdose vital signs and laboratory assessments (electrolyte panel, BUN, creatinine, liver function panel) will be taken on day -2 to monitor for propylene glycol-related toxicities.

5.1.3 Follow-up Period (Day +1 to day+100)

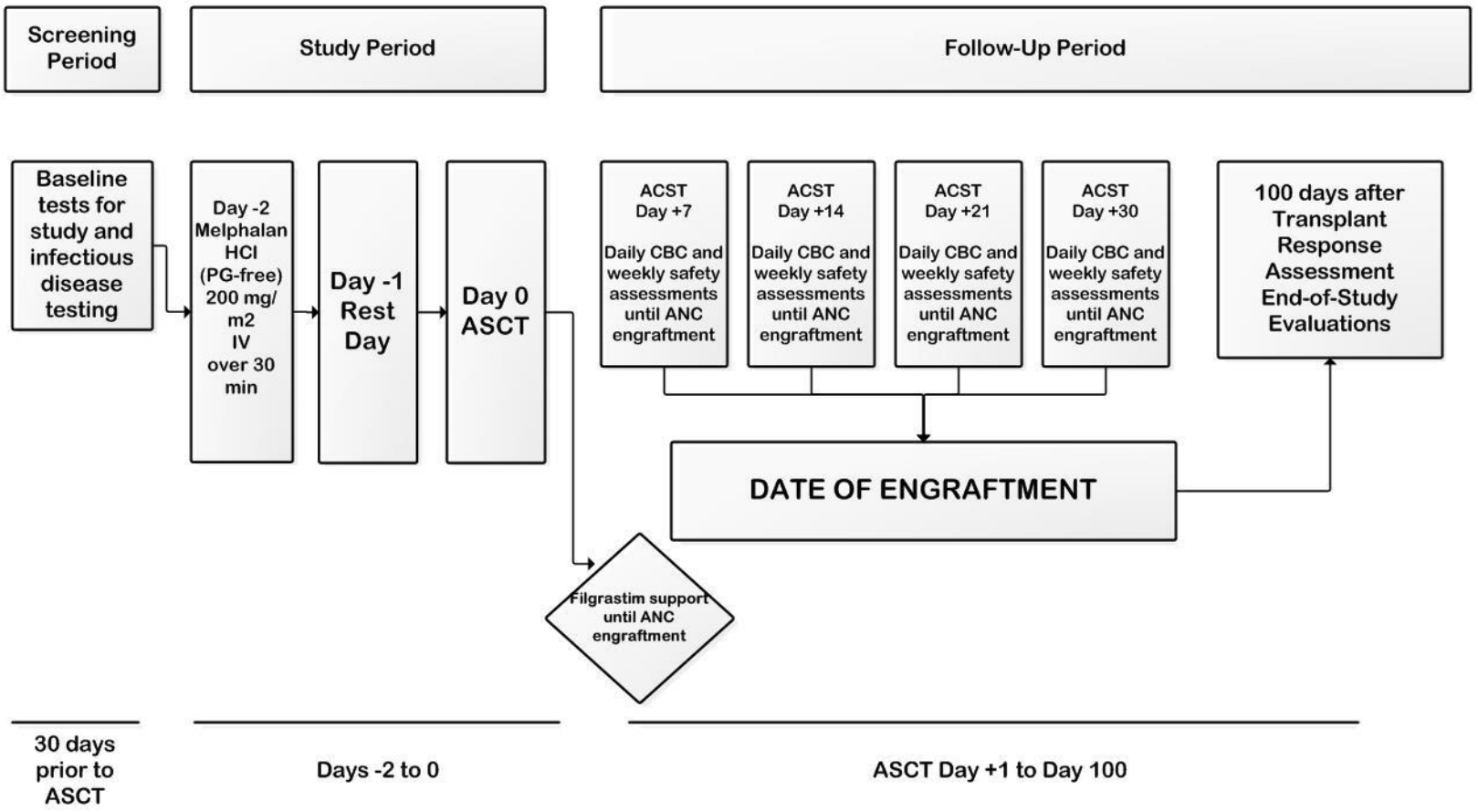
During the follow-up period, patients will return for daily laboratory tests (basic chemistry and hematology panels) and will be evaluated weekly by their physician until the date of engraftment, with the final end-of-study evaluation occurring up to seven days after the date of engraftment.

Filgrastim or pegfilgrastim will be administered as described in Section 7.7.2. Engraftment is defined per CIBMTR criteria (Section 8.3.2.1.) All patients will receive antiemetics, hydration and infection prophylaxis according to institutional guidelines. Weekly safety assessments (physical examination findings, ECOG performance status, AEs/SAEs, vital signs, hematology, serum chemistry) will be taken until the patient has achieved engraftment. After engraftment, the patient will be followed every 2 weeks with CBC and every 4 weeks with multiple myeloma

panel. Bone marrow biopsy and multiple myeloma panel will be done at day +100 to assess the post transplant disease evaluation.

5.2 Study Schema

The following study schema summarizes the treatment design for the three evaluation periods.


Screening Period
Study Period
Follow-Up Period
Baseline tests for study and infectious disease testing
Day -2 Melphalan HCl (PG-free) 200 mg/ m2 IV over 30 min
Day -1 Rest Day
Day 0 ASCT
ACST Day +7
Daily CBC and weekly safety assessments until ANC engraftment
ACST Day +14
Daily CBC and weekly safety assessments until ANC engraftment
ACST Day +21
Daily CBC and weekly safety assessments until ANC engraftment
ACST Day +30
Daily CBC and weekly safety assessments until ANC engraftment
100 days after Transplant Response Assessment End-of-Study Evaluations
DATE OF ENGRAFTMENT
Filgrastim support until ANC engraftment
30 days prior to ASCT
Days -2 to 0
ASCT Day +1 to Day 100

5.3 Stopping Rules

High dose therapy and cell transplantation is associated with hospitalization and risk of treatment related mortality. As such, grade 3-4 non hematological toxicities are expected in this program, similar to standard of care autologous transplantation. Modern published data on treatment related mortality has ranged from 1-4%. The data and safety monitoring committee (dsmc) will have authority to stop study for any unexpected treatment related mortality events during the entire course of the study. In the event of adverse events leading to treatment related mortality in 3 or more (out of 24) patients treated at phase 2 dosing, the study will be suspended. The dsmc will also be asked to review all non-hematologic grade 4-5 events and make a final determination of safety. See section 11.6.1 for more details.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion Criteria

- Patients with symptomatic MM requiring treatment at or following diagnosis.
- Patients with MM, who qualify for ASCT therapy, and have received pretransplant therapy prior to transplantation.
- Adult patients (≥18 years of age) meeting local institutional criteria to receive a total Melphalan dose of 200 mg/m^2 as a conditioning regimen.
- Patients with an adequate autologous graft, which is defined as an unmanipulated, cryopreserved, peripheral blood cell graft containing at least 2×10^6 CD34+ cells/kg, based on patient's actual body weight.
- Patients with adequate organ function, as measured by:
  - Cardiac: Left ventricular ejection fraction at rest >40% (documented within 30 days prior to Day -3).
  - Hepatic: Bilirubin <2 × ULN and ALT/AST <3 × ULN.
  - Renal: Creatinine clearance >40 mL/min (measured or calculated/estimated).
  - Pulmonary: Adjusted DLCO, FEV_1, FVC >50% of predicted value (corrected for Hgb) and documented within prior to day -3.

6.2 Exclusion Criteria

- Patients with systemic AL amyloidosis.
- ECOG performance status ≥2.
- Patients with uncontrolled hypertension.
- Patients with a serious active bacterial, viral or fungal infection.
- Patients with prior malignancies except resected basal cell carcinoma or treated cervical carcinoma *in situ*. Cancer treated with curative intent >5 years previously will be allowed.

Cancer treated with curative intent <5 years previously will not be allowed unless approved by the medical monitor.

- Female patients who are pregnant (positive ß-HCG) or breastfeeding.
- Female patients of childbearing potential, who are unwilling to use adequate contraceptive techniques during and for one month following study treatment with Melphalan HCl for injection (propylene glycol free).
- Patients seropositive for HIV.
- Concurrent clinical trials for post-transplant therapy of myeloma are permitted provided such studies do not involve conditioning therapy
- Patients who are unwilling to provide informed consent.
- Patients who are hypersensitive or intolerant to any component of the study drug formulation.
- Prior ASCT (tandem ASCT) is not permitted. Only single autologous transplant is allowed.

6.3 Withdrawal Criteria

The subject has the right to withdraw from the study at any time.

The subject will be withdrawn from the study if:

- There is deterioration in the subject's signs/symptoms and/or the subject develops a disease or condition that, in the opinion of the Investigator, would compromise the subject's safety by continuing in the study.
- In the investigator's judgment, it is in the subject's best interests.
- There is a violation of the protocol inclusion and exclusion criteria as deemed relevant by the investigator and discussed with the investigator.
- The subject begins to take any medication(s) that is excluded by the protocol.
- Any of the conditions are met in Section 5.3, "Stopping Rules."

If a subject withdraws prematurely from the trial due to the above criteria or any other reason, study staff should make every effort (at withdrawal) to complete the full set of evaluations scheduled for the end-of-study evaluation. The reason for subject withdrawal must be documented in the CRF.

If a subject withdraws from the study due to an AE (e.g., clinical signs, symptoms or clinically significant laboratory abnormality), the subject will be asked to return to the clinic for the evaluations scheduled for the posttreatment follow-up period, at a minimum. If the AE has still not resolved, additional follow-up will be performed, as appropriate, and documented in the subject's medical records. As a minimum requirement, AEs should be followed for seven days after the date of engraftment or until any treatment-emergent AE or laboratory abnormality has resolved or is otherwise explained.

In the case of a subject lost to follow-up, attempts to contact the subject must be made and documented in the subject's medical records.

Withdrawn subjects will not be replaced.

7 TREATMENTS, CONCOMITANT THERAPY, AND DOSE MODIFICATIONS

7.1 Treatments Administered

During the study period, patients will receive 200 mg/m^2 of Melphalan HCl for injection (propylene glycol free) prior to ASCT. Melphalan HCl for injection (propylene glycol free) will be diluted with normal saline to a concentration of no greater than 2 mg/mL and infused over 30 minutes via a central venous catheter. For the calculation of BSA, actual body weight should be used for patients, who weigh less than or between 100 and 130% of their IBW. For patients who weigh more than 130% of their IBW, BSA should be calculated based on adjusted body weight. For calculation of body surface area, the most recent height and weight available on day -2 will be used.

BSA = ($W^{0.425}$ x $H^{0.725}$) x 0.007184, where W=weight and H=height

Adjusted body weight= IBW + 0.4(actual weight - IBW)

Institutional standards of care rounding policies may be followed for calculating the final dose of melphalan.

7.2 Identity of Study Product(s)

7.2.1 Investigational Product

Melphalan HCl for injection (propylene glycol free) is a white lyophilized powder containing 56 mg of Melphalan HCl (equivalent to 50 mg of melphalan free base) and 2,700 mg sulfobutylether-beta-cyclodextrin Captisol®. There is also sodium hydroxide and hydrochloric acid, if necessary, present in the product that is used to adjust the pH of the solution prior to lyophilization to a physiologically well-tolerated range of pH 5.0 ± 1.0.

Normal saline solution (0.9% sodium chloride injection, USP) is used to reconstitute (8.6 mL) and dilute (for infusion) the product prior to clinical use. After reconstitution with 0.9% normal saline, the concentration of the diluted vial is 5mg/mL. Immediately further dilute with 0.9% normal saline to a final concentration equal to 2 mg/mL. Melphalan HCl for injection (propylene glycol free) is stable at room temperature for at least four hours after reconstitution, if followed by immediate dilution.

Melphalan HCl for injection (propylene glycol free) will be supplied in a 20 mL glass vial, Type I, with a 20-mm finish, a 20-mm lyophilization type rubber stopper and a crimp seal. Melphalan HCl for injection (propylene glycol free) vials should be stored protected from light and at a controlled room temperature of 20–25 °C (68–77 °F) with excursions permitted between 15 and 30 °C (59 and 86 °F).

Below is an example of the information that may appear on the label of the study medication:

- Spectrum

- Melphalan HCl for injection (propylene glycol free), lyophilized powder containing 56 mg Melphalan HCl (equivalent to 50 mg Melphalan free base)
- Each vial contains Melphalan HCl, Captisol® and sodium hydroxide
- Reconstitute with normal saline prior to infusion
- Protocol Number IIS-MEL-MCW-001
- Lot number
- Manufacture date
- Manufactured by DSM Pharmaceuticals, Inc., Greenville, North Carolina, U.S.A; for Spectrum Pharmaceuticals, Inc., USA
- Storage conditions

7.3 Assigning Subjects to Treatment Group

All patients will receive 200 mg/m^2 of either Melphalan HCl for injection (propylene glycol free) on day -2 prior to ASCT administered over 30±5 minutes as a 2mg/ml solution.

7.4 Study Medication Accountability

The investigator/pharmacist must maintain accurate records of study drug disposition, patient administration (including date and time), in addition to noting any accidentally destroyed drugs. Spectrum will supply a specific drug accountability form. At the end of the study, information describing study drug supplies (e.g., lot numbers) and disposition of supplies for each patient must be provided, signed by the investigator. If any errors or irregularities in any shipment of study medication to the site are discovered at any time, Spectrum must be contacted immediately.

At the end of the study, all medication not dispensed or administered and packaging materials will be collected with supervision of the monitor and returned to Spectrum or destroyed onsite, as dictated by the appropriate SOP at this institution.

7.5 Blinding/Masking of Treatments

This is an open-label study. All patients enrolled in the study will receive 200 mg/m^2 of Melphalan HCl for injection (propylene glycol free) on day -2 prior to ASCT. No blinding or masking of study drug will occur.

7.6 Treatment Compliance

Melphalan HCl for injection (propylene glycol free) will be infused over 30±5 minutes in a 2mg/mL solution via a central venous catheter by a trained healthcare professional. Records of study medication administered (date, time, and dose administered relative to reconstitution time) will be recorded in the patient's CRF.

7.7 Prior and Concomitant Therapies

All medications used during this study must be documented in the patient CRF.

7.7.1 Experimental Anticancer Therapy

No other anticancer therapies (including chemotherapy, radiation, hormonal treatment, antibody therapy, immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, matrix metalloprotease inhibitors or other experimental drugs) of any kind will be permitted while the subject is participating in the pretreatment period, study period, or follow-up period. Other supportive care studies using FDA approved agents are permitted.

7.7.2 Hematopoietic Growth Factors

Filgrastim is required. Pegylated filgrastim will be administered based on institutional practice. For inpatient transplantation, administer filgrastim 5 micrograms/kg/day SC (may be rounded to the nearest vial), based on actual body weight, beginning on Day +5. In the absence of toxicity, continue filgrastim until the post-nadir ANC is ≥ 500 / μL on three consecutive measurements over different days. Alternatively, for outpatient transplantation, administer pegfilgrastim 6 mg SC once on Day + 1.

7.7.3 Prophylactic Treatment for Opportunistic Infections

All patients will receive prophylaxis against bacterial, fungal and viral infections during the peritransplant period, according to institutional guidelines.

7.7.4 Antiemetics

Patients will receive antiemetics prior to high-dose melphalan administration in accordance with institutional guidelines.

7.7.5 Antidiarrheals

Use of antidiarrheal medications (e.g., loperamide) is permitted at the discretion of the investigator, but this must be documented in the CRF.

7.7.6 Blood Products

Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

7.7.7 Other Concomitant Medications

Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator and should be documented in the CRF. Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medical conditions or agents required for life-threatening medical problems.

7.8 Dose Modifications for Drug-Related SAEs and/or Toxicities

There will be no dose modifications of Melphalan HCl for injection (propylene glycol free) during this study.

8 STUDY CONDUCT

8.1 Overview of Data Collection

The schedule of study activities is presented in Table 2.

	Pretreatment Period	**Follow-Up Period (Shaded Visits are Optional Visits)**								
; s;	**Day -30 to Day -3**	**Day -2 HDM**	**Day -1 Rest Day**	**Day 0 ASCT**	**Daily Until Date of Engraft-ment**	**Week 1 Day +7 ±2 Days**	**Week 2 Day +14 ±2 Days**	**Week 3 Day +21 ±2 Days**	**Week 4 Day +28 ±2 Days**	**End-of-Study Evaluation until day + 100**
Informed Consent	√									
Confirm MM Diagnosis and Stage	√									
Review Entry Criteria	√									
Medical History	√									
Urine analysis	√									
Chest X-Ray	√									
Infectious Disease Screen	√									
Serum Pregnancy Testing for WCBP	√									
ECOG Performance Status	√	√				√	√	√	√	√
Prior/Concurrent Medications	√	√	√	√		√	√	√	√	√
AEs		√	√	√		√	√	√	√	√
Vital Signs, Height, Weight, and BSA	√	√				√	√	√	√	√
Physical Examination	√	√				√	√	√	√	√
Hematology	√	√			√	√				√
Full Serum Chemistry Panel	√	√				√	√	√	√	√
Electrolytes, LFTs, BUN, creatinine		√	√	√						
Basic Serum Chemistry Panel					√					
Multiple myeloma panel										√
Bone marrow biopsy										√
PK Assessment		√								
PG free MEL 200 mg/m^2 IV		√								
Autologous Stem Cell Graf[a]				√						

a. Followed by filgrastim or pegfilgrastim support as described in Section 7.7.2.

8.2 Description of Study Days

8.2.1 Pretreatment Period (Day -30 to Day -3)

Patient Registration:

The patient registration will be done by the principal investigator based on the eligibility criteria as defined in the protocol. Any questions regarding the registration will be answered by the principal investigator Parameswaran Hari or the research coordinator Debra Pastorek (414-805-6837).

The following baseline assessments should be collected within 30 days of dosing with Melphalan HCl for injection (propylene glycol free), after the patient has signed the informed consent:

- Review and confirm study entry criteria.
- Confirm MM diagnosis and stage (using ISS criteria).
- Medical history and physical examination, including prior MM treatments and the response.
- Prior and concomitant medications.
- ECOG performance status.
- Infectious disease testing: Serum titers for CMV, HSV, EBV, hepatitis panel, WNV, RPR for syphilis, HIV and HTLV1 antibodies.
- Hematology (RBC, hemoglobin, hematocrit, platelet count, WBC with manual differential, and reticulocyte count).
- Full serum chemistry panel (sodium, potassium, chloride, magnesium, bicarbonate, glucose, total protein, albumin, calcium, phosphate, uric acid, BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, SGOT, SGPT and creatinine clearance).
- Chest X-ray.
- Urine analysis
- Vital signs (systolic and diastolic blood pressures, heart rate, respiration rate and body temperature), height, weight and BSA.
- Serum pregnancy test for women of childbearing potential. Women are considered to be of childbearing potential unless they have had no menses for at least 12 months.
- Toxicity grading and evaluation for AEs/SAEs, according to NCI-CTC AE Version 4.0 after signing the informed consent.

8.2.2 Study Period (Day -3 to Day 0)

During the study period, patients will receive 200 mg/m^2 of Melphalan HCl for injection (propylene glycol free) as a single intravenous dose on Day -2. Following one day of rest after the myeloablative conditioning (Day -1), patients will receive an autologous graft with a minimum cell dose of 2×10^6 CD34+ cells/kg of patient body weight (Day 0).

8.2.2.1 Day -2

The following will be performed on day -2:

- Full serum chemistry panel (sodium, potassium, chloride, magnesium, bicarbonate, glucose, total protein, albumin, calcium, phosphate, uric acid, BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, SGOT, SGPT]) will be collected/calculated prior to dosing of Melphalan HCl for injection (propylene glycol free).
- Hematology (RBC, hemoglobin, hematocrit, platelet count, WBC with manual differential, and reticulocyte count) will be performed prior to dosing of Melphalan HCl for injection (propylene glycol free).
- Physical examination will be performed prior to dosing of Melphalan HCl for injection (propylene glycol free) or Alkeran® for injection.
- ECOG performance status will be recorded prior to dosing of Melphalan HCl for injection (propylene glycol free).
- Body weight will be measured and BSA calculated prior to dosing of Melphalan HCl for injection (propylene glycol free).
- Administration of 200 mg/m^2 of Melphalan HCl for injection (propylene glycol free) in a 2mg/mL solution over 30 minutes via a central venous catheter.
- Blood samples of Melphalan HCl for injection (propylene glycol free) for PK evaluation will be withdrawn through an indwelling peripheral intravenous cannula separate from the infusion site at 0 (predose), 10, 20, 30, 60, 90, 120, 180, 240 minutes after the completion of infusion. The predose blood sample will be collected within 60 minutes prior to administration of Melphalan HCl for injection (propylene glycol free).
- Vital signs (systolic and diastolic blood pressures, heart rate, and respiration rate) will be recorded prior to dosing and hourly during the first four hours after receiving either Melphalan HCl for injection (propylene glycol free).
- Toxicity grading and evaluation for AEs/SAEs according to NCI-CTC AE Version 4.0.
- Concomitant medications will be recorded.

8.2.2.2 Day -1

The following will be performed on day -1:

- Hematology (RBC, hemoglobin, hematocrit, platelet count, WBC with manual differential, and reticulocyte count) and electrolyte panel (sodium, potassium, chloride, bicarbonate), BUN, creatinine.
- Toxicity grading and evaluation for AEs/SAEs according to NCI-CTC AE Version 4.0.
- Concomitant medications will be recorded.

8.2.2.3 Day 0

The following will be performed on Day 0:

- Autologous graft with a minimum cell dose of 2×10^6 CD34+ cells/kg of patient body weight.
- Hematology (RBC, hemoglobin, hematocrit, platelet count, WBC with manual differential, and reticulocyte count) and electrolyte panel (sodium, potassium, chloride, bicarbonate), BUN, creatinine, liver function panel (SGOT, SGPT, alkaline phosphatase and total bilirubin).
- Toxicity grading and evaluation for AEs/SAEs according to NCI-CTC AE Version 4.0.
- Concomitant medications will be recorded.

8.2.3 Follow-up Period (ASCT Day +1 to day+100)

During the follow-up period, patients will return for daily laboratory tests (hematology and basic chemistry panel) and will be evaluated weekly by their physician until the date of engraftment, with the final end-of-study evaluation occurring up to seven days after the date of engraftment.

Engraftment is defined as ANC $>0.5 \times 10^9$/L $\times$ 3 consecutive daily assessments. The date of engraftment is the first day of the three consecutive days that a patient's ANC is $>0.5 \times 10^9$/L.

8.2.3.1 Week 1 (Day +7 ± 2 Days)

The following assessments will be performed daily until engraftment:

- Hematology (RBC, hemoglobin, hematocrit, platelet count, WBC with manual differential, and reticulocyte count).
- Basic serum chemistry panel (sodium, potassium, chloride, glucose, creatinine, bicarbonate, and BUN) daily until neutrophil engraftment.
- PEG-Filgrastim may be administered according to institutional practice until ANC is >500 mm^3.

The following assessments will be performed at the Week 1 (Day +7 ± 2 Days) Visit:

- Physical examination.
- ECOG performance status.
- Vital signs (systolic and diastolic blood pressures, heart rate, respiration rate, and body temperature) and body weight.
- Full serum chemistry panel (sodium, potassium, chloride, magnesium, bicarbonate, glucose, total protein, albumin, calcium, phosphate, uric acid, BUN, creatinine, CPK, total bilirubin, alkaline phosphatase, LDH, SGOT, SGPT and creatinine clearance).
- Toxicity grading and evaluation for AEs/SAEs according to NCI-CTC AE Version 4.0.

- Record concomitant medications.

8.2.3.2 Week 2 (Day +14 ± 2 Days), Week 3 (Day +21 ± 2 Days) and Week 4 (Day +28 ± 2 Days) (*Optional Visits Dependent on Date of Engraftment*)

The study visits at Week 2, Week 3 and Week 4 are *optional* visits and are dependent on the date of engraftment. If a patient meets the criteria for engraftment, he or she may proceed directly to the end-of-study evaluation visit. For those patients who have not met the criteria for engraftment, the following assessments will be performed daily until engraftment:

- Hematology (RBC, hemoglobin, hematocrit, platelet count, WBC with manual differential, and reticulocyte count).
- Basic serum chemistry panel (sodium, potassium, chloride, glucose, creatinine, bicarbonate, and BUN) daily until neutrophil engraftment.
- PEG-Filgrastim may be administered according to institutional practice for neutropenia.

For those patients who have not met the criteria for engraftment, the following assessments will be performed at weekly intervals from Week 2 (Day +14 ± 2 Days) through Week 4 (Day +28 ± 2 Days) or until the date of engraftment, whichever occurs first:

- Physical examination.
- ECOG performance status.
- Vital signs (systolic and diastolic blood pressures, heart rate, respiration rate and body temperature) and body weight.
- Full serum chemistry panel (sodium, potassium, chloride, magnesium, bicarbonate, glucose, total protein, albumin, calcium, phosphate, uric acid, BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, SGOT, SGPT, and creatinine clearance).
- Toxicity grading and evaluation for AEs/SAEs according to NCI-CTC AE Version 4.0.
- Record concomitant medications.

8.2.3.3 End of Study Evaluation (Day 100) or Study Discontinuation/Early Termination

The end-of-study Evaluations are to be performed between days 90 to 100. The end-of-study evaluation may be performed up to seven days after study discontinuation/early termination. The following evaluations will be performed at the end-of-study evaluation:

- Physical examination.
- ECOG performance status.
- Vital signs (systolic and diastolic blood pressures, heart rate, respiration rate, and body temperature) and body weight.
- Hematology (RBC, hemoglobin, hematocrit, platelet count, WBC with manual differential, and reticulocyte count).

- Full serum chemistry panel (sodium, potassium, chloride, magnesium, bicarbonate, glucose, total protein, albumin, calcium, phosphate, uric acid, BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, SGOT, SGPT, and creatinine clearance).
- Multiple myeloma panel
- Bone marrow biopsy
- Toxicity grading and evaluation for AEs/SAEs according to NCI-CTC AE Version 4.0.
- Concomitant medications.

8.3 Methods of Data Collection

8.3.1 Pharmacokinetic Evaluations

Blood samples will be collected at the time points indicated in Table 2 (within ±5 min). The concentration of "total" melphalan in these samples will be analyzed by a bioanalytical laboratory, using a validated LC/MS/MS method (Davies 2000). Full details of the methodology will be presented in the bioanalytical report, which will be appended to the clinical study report. PK evaluation will be based on the determination of the following parameters, including (but not limited to): AUC_{0-t}, $AUC_{t\text{-}inf}$, C_{max}, T_{max}, $t_{1/2}$, and k_{el}.

8.3.1.1. Pharmacokinetic Blood Sampling

Serial blood samples for the PK of Melphalan HCl for Injection (Propylene Glycol-Free) will be collected on Day -2. Pharmacokinetic samples will not be collected on subsequent patient visits. Sampling will require a peripheral intravenous catheter separate from the infusion site.

Seven-milliliter venous blood samples for PK analysis of Melphalan HCl for injection (propylene glycol free) will be withdrawn through an indwelling peripheral intravenous cannula separate from the infusion site at 0 (pre-dose), 10, 20, 30, 60, 90, 120, 180,240 and 360 minutes within after the completion of Melphalan infusion. The predose blood sample will be collected within 60 minutes prior to dose of Melphalan HCl for injection (propylene glycol free). The actual blood sample collection times will be recorded. Blood collection times for 10 minutes through 60 minutes must be obtained within ± 5 minutes. Blood samples will be collected in blood collection tubes containing K_2 EDTA as an anticoagulant. Immediately following collection, the blood specimen should be put on ice and centrifuged within 20 minutes of the collection time. The blood specimen must be centrifuged at 4 °C at 3000 × g for 10 minutes to obtain the plasma supernatant. Two equal aliquots of plasma will be transferred to polypropylene tubes and immediately frozen in a -20 °C freezer.

All plasma samples will be stored frozen (less than approximately -20 °C), until they are shipped to the analytical facility. Prior to shipping, the samples will be packed into thermal insulated containers and packed in sufficient dry ice to assure they remain frozen for a minimum of 72 hours and protected from breakage during shipment. Samples will be shipped by overnight priority courier. The samples will be divided into two shipments, each containing one aliquot of plasma for each time point. After receipt of verification that the first shipment was received by the analytical facility, the second shipment will be sent.

All samples will be shipped to:

KCAS Bioanalytical Services
12400 Shawnee Mission Parkway
Shawnee, KS 66216 USA

Phone: (913) 248-3000

8.3.2 Efficacy Evaluations

8.3.2.1 Hematology Parameters for Myeloablation and Engraftment

Efficacy evaluations (myeloablation and engraftment) will be measured through the collection of hematology parameters (RBC, hemoglobin, hematocrit, platelet count, WBC with manual differential, and reticulocyte count) daily until engraftment.

Engraftment: ANC recovery is defined as an absolute neutrophil count (ANC) of ≥ 0.5 x 10^9 /L (500/mm3) for three consecutive laboratory values obtained on different days. Date of ANC recovery is the date of the first of three consecutive laboratory values where the ANC is ≥ 0.5 x 10^9 /L. Platelet recovery is reported when the recipient's platelet count is ≥ 20 x 10^9 /L seven days after platelet transfusion and is maintained for three consecutive lab values obtained on different days.

8.3.2.2 Day 100 Myeloma Response

Myeloma-specific response evaluation will be performed between days 90 to 100 through the collection of bone marrow, hematology and urine parameters (protein electrophoresis, immunofixation, free light chain, marrow aspirate cytology, flow cytometry and immunohistochemistry). Responses will be assigned based on IMWG Uniform Response criteria (Appendix I; Kyle RA, Rajkumar SV et al. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia 2009; 23:3).

8.3.3 Safety Evaluations

8.3.3.1 Adverse Event Assessment

The investigator has the responsibility for assessing the safety of the subjects and study integrity. Subjects will be monitored for AEs during study participation (beginning at the time informed consent is obtained) and until Day 100. Any abnormal laboratory test result that on confirmation the investigator considers clinically significant should be recorded as an AE, even if the subject reports no symptoms compatible with such laboratory findings. AEs will be classified according to the Medical Directory for Regulatory Activities (MedDRA) and AEs and laboratory abnormalities will be graded according to the NCI CTCAE grading system and recorded on CRFs. (See http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf for a complete description of NCI CTCAE Grading).

Complete details of reporting adverse events, including the definition of drug-related AEs, are provided in Section 9.

8.3.3.2 Clinical Laboratory Investigations

Institutional CLIA-certified laboratories will perform all study-related clinical laboratory tests. Blood samples for hematology analytes, clinical chemistry analytes, serum pregnancy tests and urine samples for urinalysis will be prepared using standard procedures. The panels of laboratory tests to be performed at the visits indicated in Table 2 are shown below:

Hematology:	RBC, hemoglobin, hematocrit, platelet count, WBC with manual differential and reticulocyte count
Full Serum Chemistry:	Sodium, potassium, chloride, magnesium, glucose, bicarbonate, total protein, albumin, calcium, phosphate, uric acid, BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, SGOT, SGPT, creatinine clearance (measured or calculated).
Basic Serum Chemistry:	Sodium, potassium, chloride, glucose, creatinine, bicarbonate, and BUN.
Electrolyte Panel:	Sodium, potassium, chloride, bicarbonate.
Liver Function Panel:	SGOT, SGPT, alkaline phosphatase and total bilirubin.
Urinalysis:	Specific gravity, pH, protein, glucose, ketones, nitrite, RBCs and WBCs.
Serology:	Serum titers for CMV, HSV, EBV, hepatitis panel, WNV, RPR for syphilis HIV antibodies.

For females, a serum pregnancy test will be performed during the pretreatment period.

Creatinine clearance may be calculated, using the Cockgraft-Gault equation:

$$\text{Males: } \frac{(140 - \text{age})\,(\text{lean body weight in kg})}{\text{serum creatinine} \times 72}$$

$$\text{Females: } \frac{(140 - \text{age})\,(\text{lean body weight in kg})\,(0.85)}{\text{serum creatinine} \times 72}$$

Laboratory reports should be reviewed by the investigator or delegated physician. The investigator will assess clinical significance for out-of-range parameters.

8.3.3.3 ECOG Performance Status

ECOG performance status will be assessed at pretreatment, prior to administration of Melphalan HCl for injection (propylene glycol free) day -2, weekly during the follow-up period (as per Section 8.2.3.2) and at the end-of-study evaluation as follows:

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

8.3.3.4 Body Weight, Height, and Body Surface Area

Height without shoes in inches and body weight in kg will be recorded during the pretreatment period. BSA will be calculated immediately prior to dosing. Body weight will be measured during the pretreatment period, prior to administration of Melphalan HCl for injection (propylene glycol free), weekly during the follow-up period (as per Section 8.2.3.1), and at the end-of-study evaluation.

8.3.3.5 Physical Examinations

Physical examinations will include examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities and nervous system. Physical examinations will be performed during the pretreatment period, prior to administration of Melphalan HCl for injection (propylene glycol free) on day -2, weekly during the follow-up period (as per Section 8.2.3.1), and at the end-of-study evaluation.

8.3.3.6 Vital Signs

Vital signs will include systolic and diastolic blood pressures, radial pulse rates and respiratory rates. All vital signs will be obtained after the patient has been in the supine position for at least five minutes. Vital signs will be taken prior to administration of Melphalan HCl for injection (propylene glycol free) and every hour after infusion for the first 4 hours. Vital signs, including body temperature, will be taken during the pretreatment period, weekly during the follow-up period (as per Section 8.2.3.1), and at the end-of-study evaluation.

9 ADVERSE EVENT MANAGEMENT

9.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject administered a medicinal product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the CRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that does not represent a clinically significant exacerbation or worsening need not be considered AEs.

It is the investigator's responsibility to document all AEs that occur during the study. AEs will be elicited by asking the subject a nonleading question, for example, "Have you experienced any new or changed symptoms since we last asked/since your last visit?" AEs should be reported on the appropriate page of the CRF.

9.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that occurs at any dose (including after informed consent is given and prior to dosing) which either:

1. Results in death.
2. Is life threatening (subject is at immediate risk of death from the event as it occurred).
3. Requires in-subject hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization.
4. Results in persistent or significant disability/incapacity.
5. Results in a congenital anomaly/birth defect.

Important medical events that may not result in death, are not life threatening, or do not require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-subject hospitalization, or the development of drug dependency or drug abuse.

Hospitalizations for elective surgery or other medical procedures that are not related to a treatment-emergent AE are not considered SAEs.

9.3 Recording of Adverse Events and Serious Adverse Events

Any AE is to be recorded in the CRF. In order to avoid vague, ambiguous or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words. Whenever possible, the investigator should combine signs and symptoms that constitute a single diagnosis.

The existence of an AE may be concluded from a spontaneous report of the subject; from the physical examination; or from special tests like ECG, laboratory assessments, or other study-specified tests (source of AE).

AEs may occur in the specified follow-up period. All AEs, whether drug-related or not, regardless of the interval since the last administration of the study medication, should be treated as any other AE occurring during the treatment with study medication.

Each AE is to be evaluated for duration, severity, seriousness and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

9.4 Intensity of Adverse Events

The severity of the AE will be graded according to the NCI CTCAE Grading Scale (See the NCI CTCAE web page at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf for details). For AEs not covered by NCI CTCAE, the severity will be characterized as "mild, moderate or severe" according to the following definitions:

1. Mild events are usually transient and do not interfere with the subject's daily activities.
2. Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.
3. Severe events interrupt the subject's usual daily activities.

9.5 Relationship of Adverse Events to Study Drug

The investigator will make a judgment regarding whether or not the AE was related to study drug, as outlined in the following table:

None:	*The AE must definitely be caused by the subject's clinical state, or the study procedure/conditions (i.e., it has no association with the study drug).*
Improbable:	*The temporal association between the AE and the study drug is such that the study drug is not likely to have any reasonable association with the AE.*
Possible:	*The AE follows a reasonable temporal sequence from the time of drug administration, but could have been produced by the subject's clinical state or the study procedures/conditions.*

Probable: *The AE follows a reasonable temporal sequence from the time of study drug administration, abates upon discontinuation of the study drug and cannot be reasonably explained by the known characteristics of the subject's clinical state.*

Definite: *The AE follows a reasonable temporal sequence from the time of study drug administration, abates upon discontinuation of the study drug and reappears when the study drug is introduced.*

9.6 Follow-Up of Adverse Events and Serious Adverse Events

All Adverse events will be followed for seven days after the date of engraftment or until any treatment-emergent adverse event or laboratory abnormality has resolved or is otherwise explained.

9.7 Post-study Adverse Events and Serious Adverse Events

All unresolved AEs should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify Spectrum of any death or AE occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. Spectrum should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

9.8 Regulatory Aspects of Adverse Event Reporting

SAEs must be reported to the IRB and FDA within 24 hours of first knowledge of the event by study personnel, followed by a fax of the SAE Form (which can be found in the Regulatory Office documents file). It is important that the investigator provide his/her assessment of relationship to study drug at the time of the initial report.

The investigator is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the FDA according to 21 CFR 312.32. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their Institutional Review Board (IRB).

10 STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (*n*), mean, median, standard deviation, minimum and maximum for continuous data, and frequencies and percentages for categorical data.

All statistical analyses will be conducted with the SAS® System, Version 9.1.3 or higher.

10.1 Data Collection Methods

The data will be recorded on the Oncore-CRF. The Investigator must submit a completed CRF for each subject who signs an informed consent form (ICF), regardless of duration. All documentation supporting the CRF data, such as laboratory or hospital records, must be readily available to verify entries in the CRF.

Documents (including laboratory reports, hospital records subsequent to SAEs, CT scan results, etc.) should not carry the subject's name. This will help to ensure subject confidentiality.

10.2 Statistical Analysis Plan

A statistical analysis plan (SAP) will be created prior to the review of any data. This document will provide a more technical and detailed description of the proposed data analysis methods and procedures.

10.3 Sample Size Estimates

A sample size of 24 patients is planned for this study. The mean±SD results of AUC_{0-t} and C_{max} of 100 mg/m^2 melphalan dose from a previously conducted study were 376,577±93,401 min·ng/mL and 4374 ± 1050 ng/mL respectively. Twenty-four patients will provide ±10% width for the 90% CI around the point estimates of AUC_{0-t} and C_{max} in this study. A study size of 24 patients would also provide for a 95% confidence interval having a width of ±20% to estimate an AE incidence rate for common AEs occurring at a frequency of 25 -30%.

10.4 Analysis Populations

The PK evaluable population is defined as all patients, who completed dosing and adequate subsequent PK blood draws for the calculation of AUC and C_{max} for Melphalan HCl for injection (propylene glycol free). PK analyses will be performed on the evaluable population.

AllA enrolled patients receivingMelphalan HCl for injection (propylene glycol free) will be defined as the population for analyses. All safety and efficacy analyses will be performed on all patients who received study medication.

10.5 Interim and End-of-Study Analyses

Interim Analysis

An independent DSMB at the Medical College of Wisconsin will review safety data on an ongoing basis (see Section 11.6.1). Safety analyses will be presented in a manner consistent with the presentations intended for the final analysis according to CTCAE v 4.0 criteria

End-of-Study Analysis

A final analysis is planned after the last subject completes or discontinues the study and the resulting clinical database has been cleaned, quality checked, and locked.

10.6 Pharmacokinetic Analyses

PK parameters will be determined by nonparametric PK data analysis techniques. PK parameters computed from plasma drug concentration time data will include, but not necessarily be limited to the following parameters:

- C_{max} derived from the individual raw data.
- T_{max} derived from the individual raw data.
- Apparent terminal first-order elimination rate constant (k_{el}).
- Apparent elimination $t_{1\backslash 2}$.
- Area under the plasma concentration-time curve to the last measurable time point (AUC_{0-t}) calculated by the trapezoidal rule.
- Area under the plasma concentration-time curve to infinity ($AUC_{0-\infty}$): AUC_{0-t} + area under the plasma concentration-time curve from the last measurable time point extrapolated to infinity determined from the concentration at the last measurable time point divided by the k_{el}.

The plasma concentrations and pharmacokinetic parameters for Melphalan HCl for injection (propylene glycol free) will be summarized in the following manner:

Descriptive Statistics

Arithmetic means, standard deviations and coefficients of variation will be calculated for the parameters listed above. Additionally, geometric means will be calculated for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}.

10.7 Efficacy Analyses

10.7.1 Efficacy Endpoints

The rates of myeloablation and engraftment will be determined based on the following definitions:

Myeloablation is defined as any one of the following:

- ANC $<0.5 \times 10^9$/L.
- Platelet count <20,000/mm^3 or bleeding requiring transfusion.

The first of two consecutive days for which cell counts drop below these cut-off levels will be recorded as the date of myeloablation.

Engraftment is defined as per Section 8.3.2.1 as:

ANC recovery is defined as an absolute neutrophil count (ANC) of ≥ 0.5 x 10^9 /L (500/mm3) for three consecutive laboratory values obtained on different days. Date of ANC recovery is the date of the first of three consecutive laboratory values where the ANC is ≥ 0.5 x 10^9 /L. Platelet

recovery is reported when the recipient's platelet count is ≥ 20 x 10^9 /L seven days after platelet transfusion and is maintained for three consecutive lab values obtained on different days. Time to myeloablation will be calculated as the time from receiving Melphalan for injection (propylene glycol free) to the date of myeloablation.

Time to engraftment will be calculated as the time from transplant to the date of engraftment.

10.7.2 Analysis of Efficacy Endpoints

Efficacy analyses will be performed on allall patients who received study medication.

The rates of myeloablation and engraftment during the study will be calculated and will be summarized descriptively.

Time to myeloablation and time to engraftment will be calculated for each patient and summarized, using Kaplan-Meier / cumulative incidence.

Myeloma responses will be calculated for each patient and summarized.

10.8 Safety Analyses

Safety analyses will be performed all patientsalls who received study medication. The following safety analyses will be performed for this study and will include all collected data through the final study visit:

- Incidence of all treatment-emergent AEs and drug-related treatment-emergent AEs by system organ class and preferred term.
- Incidence of all treatment-emergent AEs by system organ class, preferred term, and severity.
- Incidence of all treatment-emergent AEs and treatment-emergent drug-related AEs by CTCAE v4.0 grade.
- Incidence of treatment-emergent AEs, treatment-emergent drug-related AEs, and treatment-emergent CTCAE v4.0 Grade 3 or 4 AEs by preferred term in descending frequency.
- Incidence of all AEs that led to discontinuation of study medication.
- Incidence of all SAEs and drug-related SAEs, including deaths.
- Summary of changes in laboratory parameters from baseline to postdose time points.
- Laboratory parameters summarized by CTCAE v4.0 Grade (frequency and shifts).
- Summary of changes in vital signs from baseline to postdose time points.

10.9 General Issues for Statistical Analysis

10.9.1 Multiple Comparisons and Multiplicity

There are no planned adjustments for multiplicity.

10.9.2 Subgroups

There are no planned subgroup analyses.

10.9.3 Missing Data

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been enrolled. There will be no imputation for missing data.

11 STUDY ADMINISTRATION

11.1 Regulatory and Ethical Considerations

11.1.1 Regulatory Authority Approvals

This study will be conducted in compliance with the protocol, GCPs including ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines, FDA regulatory requirements, and in accordance with the ethical principles of the Declaration of Helsinki.

The investigator should submit written reports of clinical study status to the IRB annually or more frequently, if requested by the IRB. A final study notification should also be forwarded to the IRB within 15 days after the study is completed or in the event of premature termination of the study. Copies of all contact with the IRB should be maintained in the study documents file. Copies of the clinical study status reports (including termination) should be provided to Spectrum.

11.1.2 Institutional Review Board Approvals

Before initiation of the study at each investigational site the protocol, informed consent form, subject information sheet, and any other relevant study documentation will be submitted to the appropriate IRB. Written approval of the study must be obtained before the study center can be initiated or the investigational medicinal product is released to the investigator. Any necessary extensions or renewals of IRB approval must be obtained, in particular, for changes to the study, such as modification of the protocol, informed consent form and/or written information provided to subjects and/or other procedures.

The investigator will report promptly to the IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. On study completion, the investigator will provide the IRB with a study outcome report.

11.1.3 Subject Informed Consent

Signed informed consent must be obtained from each subject (or legally acceptable representative when appropriate) prior to performing any study related procedures. Each subject should be given both verbal and written information describing the nature and duration of the clinical study. The informed consent process should take place under conditions where the subject has adequate time to consider the risks and benefits associated with his/her participation

in the study. Subjects will not be screened or treated until the subject has signed an approved ICF written in a language in which the subject is fluent.

The ICF used must be approved both by Spectrum and by the reviewing IRB. The informed consent should be in accordance with the current revision of the Declaration of Helsinki, current ICH and GCP guidelines, and Spectrum policy.

The investigator must explain to potential subjects or their legal representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the trial and any discomfort it may entail. Subjects will be informed that they are free not to participate in the trial and that they may withdraw consent to participate at any time. They will be told that refusal to participate in the study will not prejudice future treatment. They will also be told that their records may be examined by regulatory authorities and authorized persons but that personal information will be treated as strictly confidential and will not be publicly available. Subjects must be given the opportunity to ask questions. After this explanation and before entry into the trial, consent should be appropriately recorded by means of the subject's or his/her legal representative's dated signature. If a subject and his/her legal representative are unable to read, an impartial witness must be present during the entire informed consent discussion. The signature of the impartial witness will certify the subject's consent. The subject should receive a signed and dated copy of the ICF. The original signed informed consent should be retained in the study files. The investigator shall maintain a log of all subjects, who sign the ICF, and indicate if the subject was enrolled into the study or reason for failure.

11.2 Study Monitoring

During trial conduct, the investigator will ensure that the protocol and GCPs are being followed. The investigator is responsible to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Spectrum monitors or its designees and appropriate regulatory authorities direct access to source documents to perform this verification.

11.3 Quality Assurance

The trial site may be subject to review by the IRB, and/or to quality assurance audits performed by Spectrum or its designee, and/or to inspection by appropriate regulatory authorities.

11.4 Study Termination and Site Closure

Spectrum reserves the right to discontinue the trial prior to inclusion of the intended number of subjects but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating subjects immediately after notification. All study materials must be collected and all CRFs completed to the greatest extent possible.

11.5 Records Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records,

case report forms and hospital records), all original signed informed consent forms, copies of all case report forms and detailed records of treatment disposition. The records should be retained by the investigator according to local regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the investigator relocates, retires or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator, another institution. The investigator must obtain Spectrum's written permission before disposing of any records.

11.6 Study Organization

11.6.1 Data and Safety Monitoring Board

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data and Safety Monitoring Committee (MCWCC DSMC). A summary of the MCWCC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety
- Review all unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol. Grade 4 & 5 events must be reported to the DSMC within 5 calendar days of study staff's knowledge.
- Review all DSM reports
- Submit a summary of any recommendations related to study conduct
- Terminate the study if deemed unsafe for patients

The DSMC will review safety data at a minimum of every month (based on the accrual rate). (If there are fewer than one patient enrolled/accrued, there is no basis for review.)

A copy of the MCWCC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

11.7 Confidentiality of Information

Spectrum affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by Spectrum**.** However, in compliance with federal regulations, Spectrum requires the investigator to permit Spectrum's representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study.

Spectrum will ensure that the use and disclosure of protected health information obtained during a research study comply with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. The rule provides federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of subjects participating in sponsored Clinical Trials. "Authorization" is required from each research subject, i.e., specified permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information. A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization may be combined in the informed consent document (approved by the IRB) or it may be a separate document, (approved by the IRB/IEC) or provided by the investigator or sponsor (without IRB approval). It is the responsibility of the investigator and institution to obtain such waiver/authorization in writing from the appropriate individual.

11.8 Study Publication

All data generated from this study are the property of Spectrum and shall be held in strict confidence along with all information furnished by Spectrum. Independent analysis and publication of these data by the investigator or any member of his/her staff are not permitted without prior written consent of Spectrum. Written permission to the investigator will be contingent on the review by Spectrum of the statistical analysis and manuscript and will provide for nondisclosure of Spectrum confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties 30 days prior to submission. This will enable all parties to protect proprietary information and to provide comments, based on information that may not yet be available to other parties.

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13 APPENDIX I

Response criteria in Multiple myeloma:

CR : Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow; in patients for whom only measurable disease is by serum FLC level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required; two consecutive assessments are needed.

sCR: CR as defined plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or two- to four-color flowcytometry; two consecutive assessments of laboratory parameters are needed.

vGPR: Serum and urine M component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M component plus urine M component <100 mg/24 h; in patients for whom only measurable disease is by serum FLC level, > 90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required; two consecutive assessments are needed.

PR: ≥ 50% reduction of serum M protein and reduction in 24-hour urinary M protein by ≥ 90% or to < 200 mg/24 h. If serum and urine M protein are not measurable, ≥50% decrease in difference between involved and uninvolved FLC levels is required in place of M protein criteria. If serum and urine M protein and serum FLC assay are not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was ≥30%. In addition, if present at baseline, ≥50% reduction in size of soft tissue plasmacytomas is required. Two consecutive assessments are needed; no known evidence of progressive or new bone lesions if radiographic studies.

SD: Not meeting criteria for CR, VGPR, PR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed.

PD: Increase of 25% from lowest response value in any of following: Serum M component with absolute increase ≥ 0.5 g/dL; serum M component increases ≥1 g/dL are sufficient to define relapse if starting M component is ≥ 5 g/dL and/or; Urine M component (absolute increase must be ≥200 mg/24 h) and/or; Only in patients without measurable serum and urine M protein levels: difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL);Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC level, bone marrow plasma cell percentage (absolute percentage must be ≥ 10%) .Development of new or definite increase in size of existing bone lesions or soft tissue plasmacytomas. Development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder. Two consecutive assessments before new therapy are needed.

Source: Paulmbo et al. Journal Of Clinical Oncology 2014; 32:587-600 for International Myeloma Working group.